

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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Introduction

- Analysis of immune profiles may reveal patient populations that could benefit from novel therapies and combination therapies in MM
- The first-in-class bispecific antibodies teclistamab (Tec; targeting BCMA) and talquetamab (Tal; targeting GPRC5D) have demonstrated deep, durable responses as monotherapies in patients with RRMM¹⁻⁴
- Tec or Tal in combination with daratumumab (Dara; anti-CD38 mAb) and lenalidomide (Len; IMiD), may further augment T-cell cytotoxic activity, enhance efficacy, and improve patient outcomes, through complementary mechanisms of action⁵⁻⁹
- Here, we report differential immune signatures between patients with NDMM vs RRMM treated with Tec-Dara-Len in MajesTEC-2 or Tal-Dara-Len in MonumenTAL-2

MajesTEC-2 ClinicalTrials.gov identifier: NCT04722146 and MonumenTAL-2 ClinicalTrials.gov identifier: NCT05050097.

1. Moreau P, et al. *N Engl J Med* 2022;387:495-505. 2. van de Donk NWCJ, et al. Presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual. 3. Chari A, et al. *N Engl J Med* 2022;387:2232-44. 4. Rasche L, et al. Presented at EHA 2024 Hybrid Congress; June 13–16, 2024; Madrid, Spain. 5. Quach H, et al. *Leukemia* 2010;24:22-32. 6. Facon T, et al. *N Engl J Med* 2019;380:2104-15. 7. Krejci J, et al. *Blood* 2016;128:384-94. 8. Rodriguez-Otero P, et al. Presented at ASH; December 11–14, 2021; Atlanta, GA, USA & Virtual. 9. Dholaria B, et al. Presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual. BCMA, B-cell maturation antigen; Dara, daratumumab; GPRC5D, G protein-coupled receptor family C group 5 member D; IMiD, immunomodulatory drug; Len, lenalidomide; mAb, monoclonal antibody; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/refractory multiple myeloma; Tal, talquetamab; Tec, teclistamab.



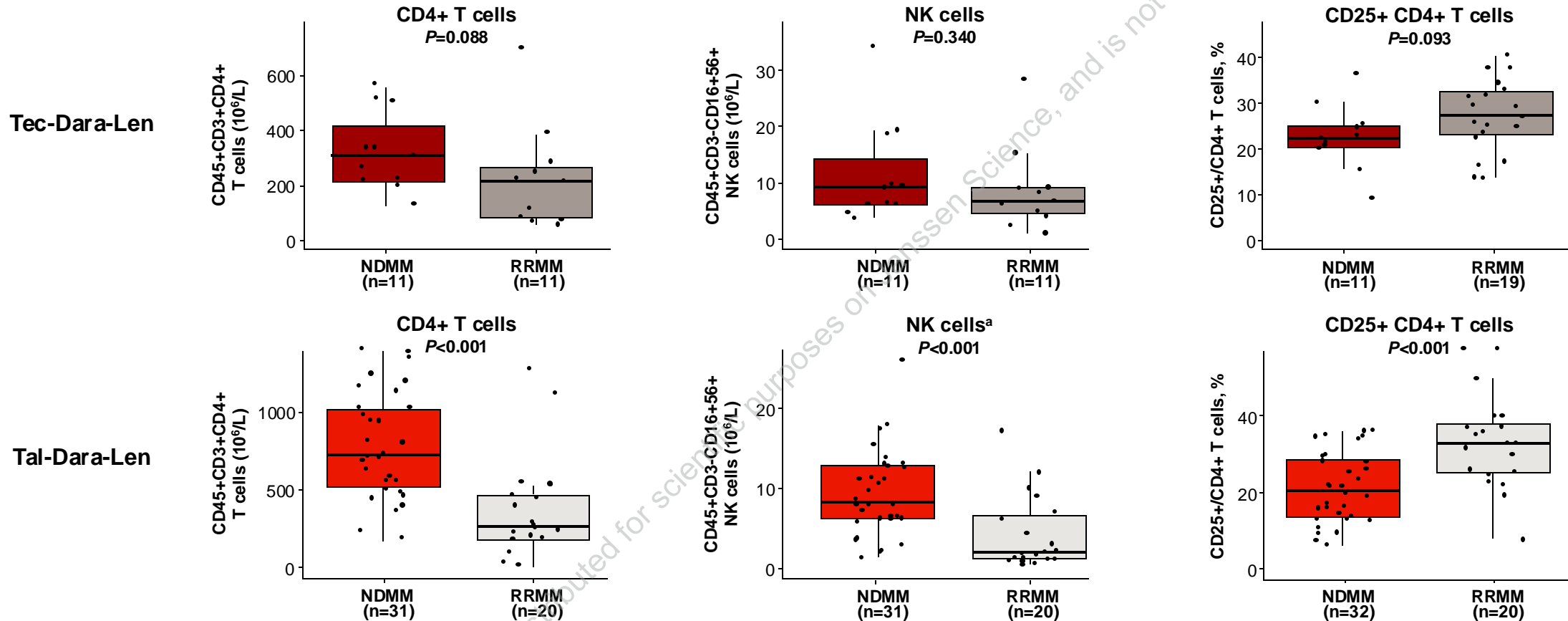
MajesTEC-2 (Tec-Dara-Len) and MonumenTAL-2 (Tal-Dara-Len): Treatment Regimens

<p>Patients</p> <ul style="list-style-type: none"> • NDMM • RRMM^a 	<p>MajesTEC-2</p>	<p>NDMM</p> <p>Tec 1.5 mg/kg SC QW^b + Dara 1800 mg SC^c + Len 25 mg PO^d (n=11)</p>	<p>Analyses on peripheral blood^g</p> <ul style="list-style-type: none"> • Immunophenotyping of: <ul style="list-style-type: none"> o T-cell numbers o T-cell activation/exhaustion markers by flow cytometry • TCR-seq^h
		<p>RRMM</p> <p>Tec 1.5 mg/kg SC QW^b + Dara 1800 mg SC^c + Len 25 mg PO^d (n=19)</p>	
	<p>MonumenTAL-2</p>	<p>NDMM</p> <p>Tal 0.6 mg/kg SC Q2W or 0.8 mg/kg SC Q4W^e + Dara 1800 mg SC^c + Len 25 mg PO^d (n=32)</p>	
		<p>RRMM</p> <p>Tal 0.3 mg/kg QW^f + Dara 1800 mg SC^c + Len 25 mg PO^d (n=20)</p>	

^aIn MajesTEC-2, patients with RRMM had 1–3 prior LOT, including a PI and an IMiD. In MonumenTAL-2, patients with RRMM had 1–3 or ≥3 prior LOT, including a PI and an IMiD. ^bAfter step-up doses (0.06 and 0.3 mg/kg). ^cAdministered QW during cycles 1 and 2, Q2W during cycles 3–6, and once (on day 1) during each subsequent 28-day cycle. ^dAdministered 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. ^eAfter step-up doses (0.01, 0.06, and 0.4 mg/kg). ^fAfter step-up doses (0.01 and 0.06 mg/kg). ^gSamples were collected for analyses at baseline and post treatment at cycle 2 and/or cycle 3. Statistical significance was determined by the Wilcoxon test. ^hOnly available for MonumenTAL-2. Dara, daratumumab; IMiD, immunomodulatory drug; Len, lenalidomide; LOT, line of therapy; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; PO, orally; Q2W, every other week; Q4W, every 4 weeks; QW, weekly; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; Tal, talquetamab; TCR-seq, T-cell receptor sequencing; Tec, teclistamab.



MajesTEC-2 (Tec-Dara-Len) and MonumenTAL-2 (Tal-Dara-Len): Baseline Immune Fitness in NDMM vs RRMM



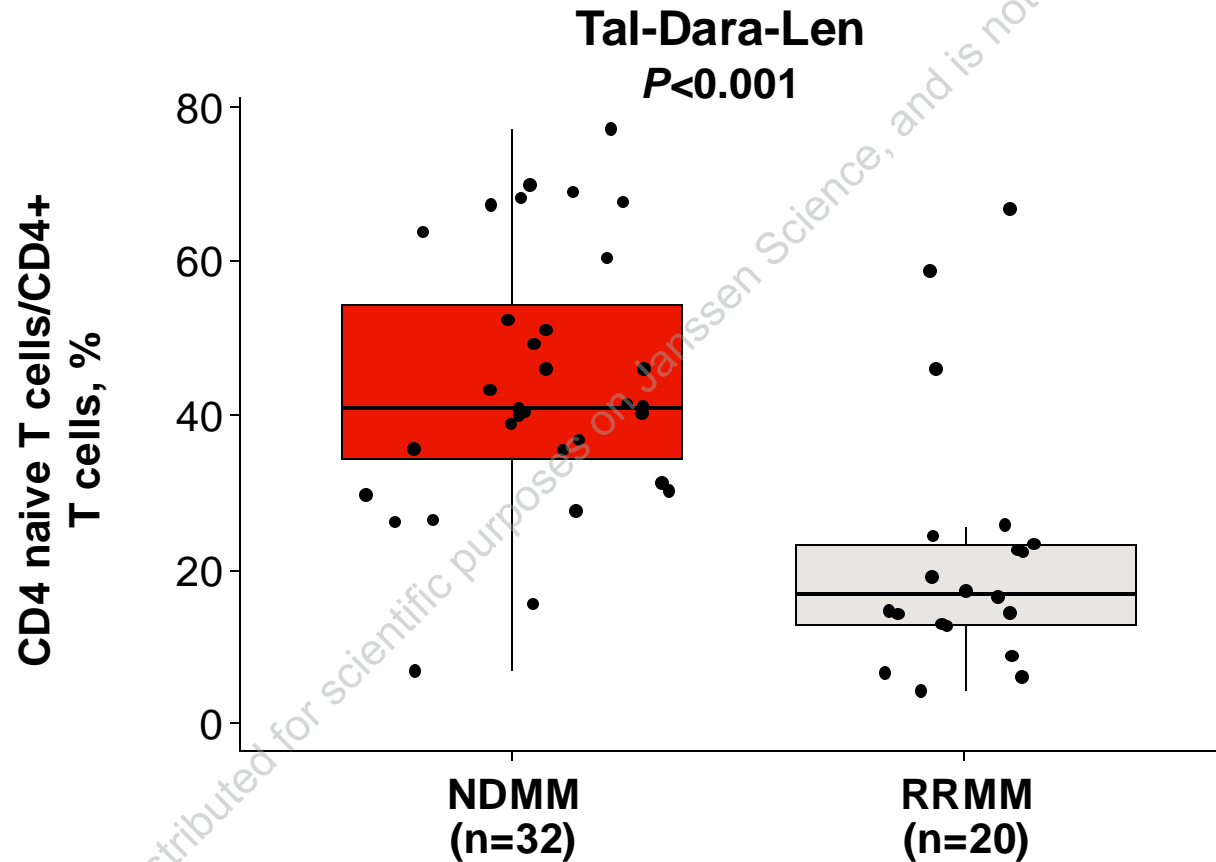
Higher peripheral T-cell and NK-cell counts and lower proportions of T cells expressing activation markers (CD25) indicate a more favorable baseline immune fitness profile in NDMM vs RRMM

^a1 outlier in the NDMM group ($y=45.581$) is not shown.

Dara, daratumumab; Len, lenalidomide; NDMM, newly diagnosed multiple myeloma; NK, natural killer; RRMM, relapsed/refractory multiple myeloma; Tal, talquetamab, Tec, teclistamab.



MonumenTAL-2 (Tal-Dara-Len): Baseline Immune Fitness in NDMM vs RRMM

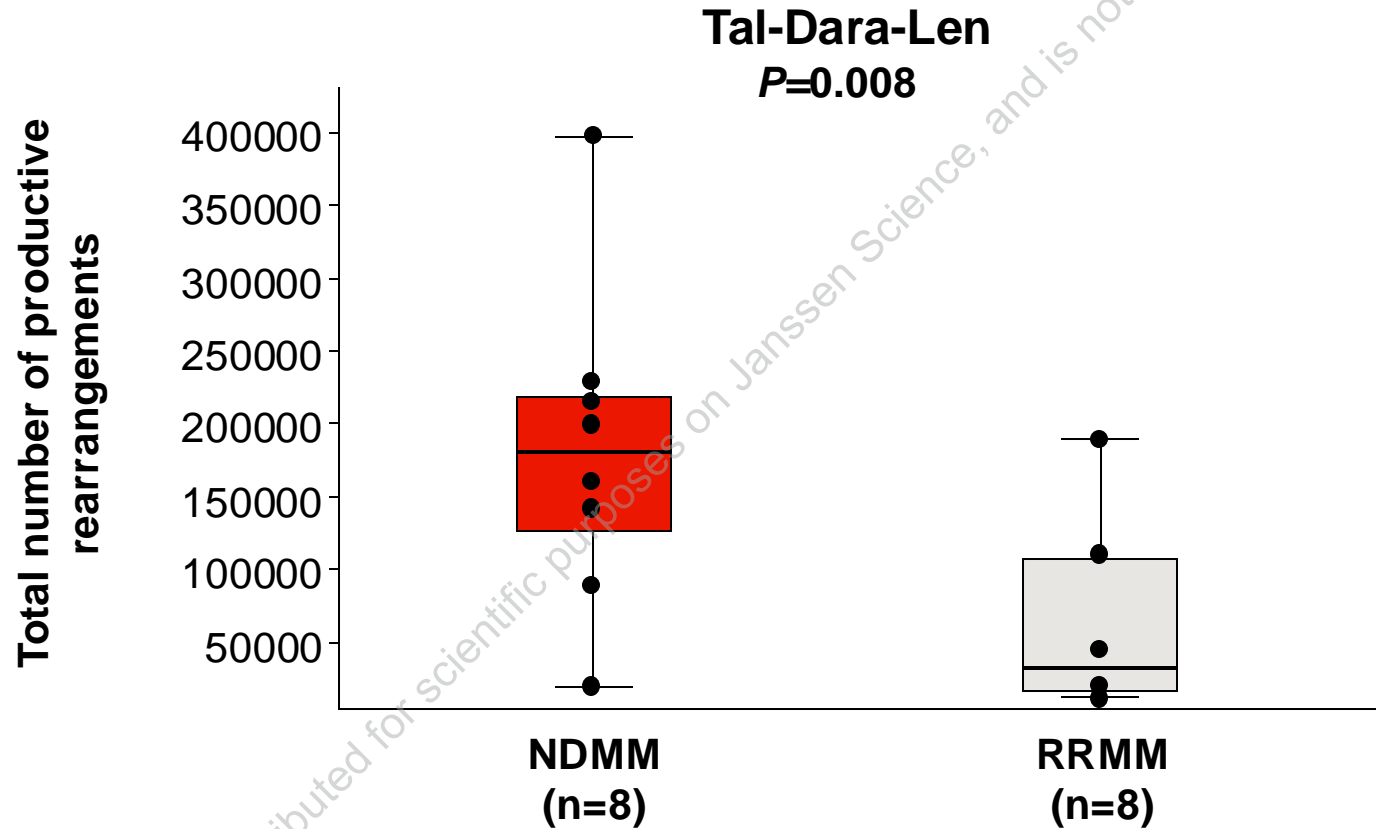


A higher proportion of naive CD4+ T cells at baseline suggest a fitter immune status in NDMM vs RRMM

Assessed by flow cytometry. Corresponding Tec-Dara-Len data with similar results shown in **Supplement 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 in **Supplemental Figure 3**. Dara, daratumumab; Len, lenalidomide; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/refractory multiple myeloma; Tal, talquetamab; Tec, teclistamab.



MonumenTAL-2 (Tal-Dara-Len): Baseline T-Cell Repertoire in NDMM vs RRMM



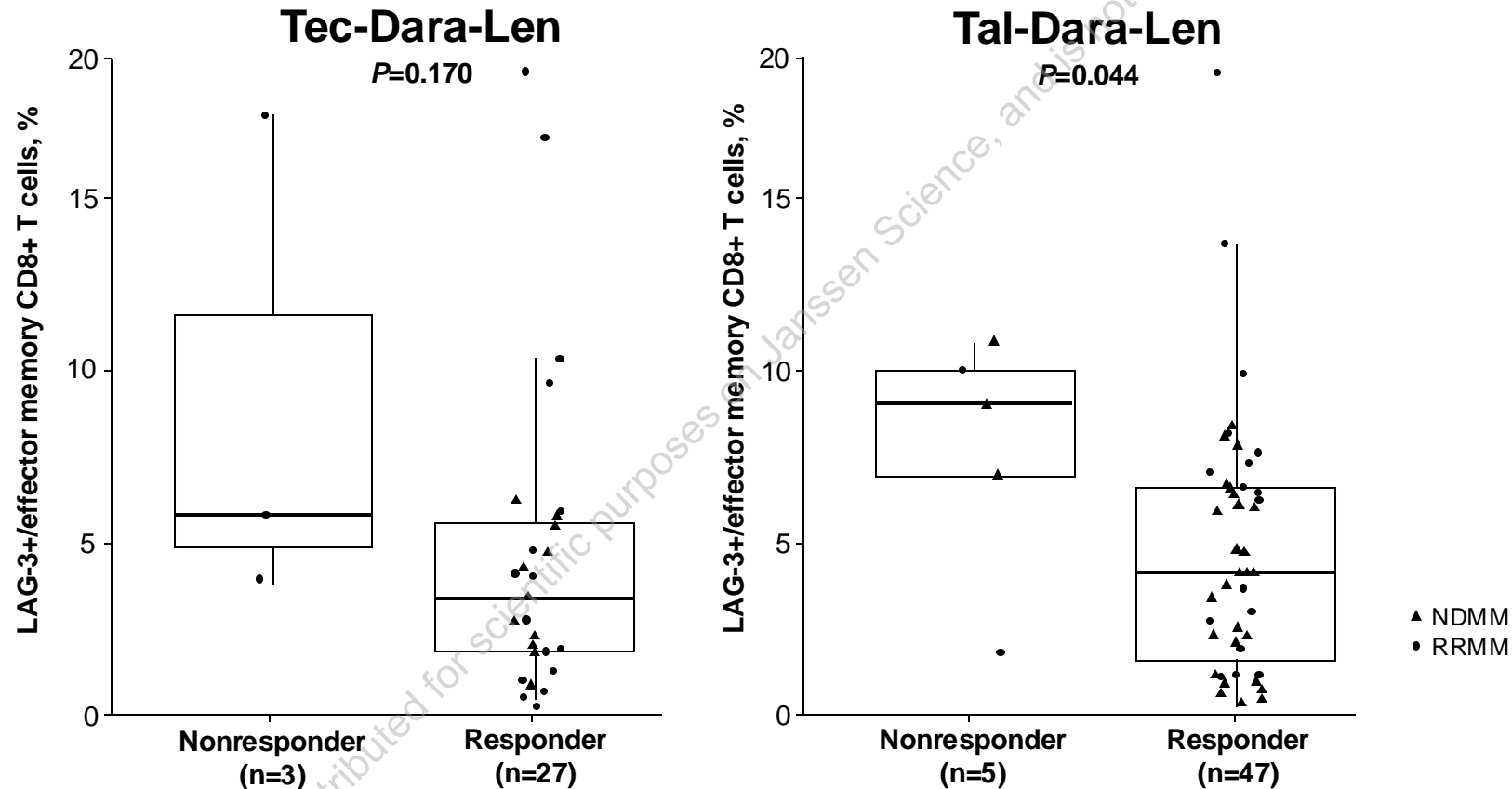
An increase in the total number of productive rearrangements indicates a more diverse T-cell repertoire at baseline, suggestive of a fitter immune status in NDMM vs RRMM

Assessed by T-cell receptor sequencing; only available for MonumenTAL-2. Similar results were observed during assessment of down-sampled rearrangements. Dara, daratumumab; Len, lenalidomide; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/refractory multiple myeloma; Tal, talquetamab.

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MajesTEC-2 (Tec-Dara-Len) and MonumenTAL-2 (Tal-Dara-Len): Baseline Proportion of LAG-3+ Effector Memory T Cells in Association With Clinical Response



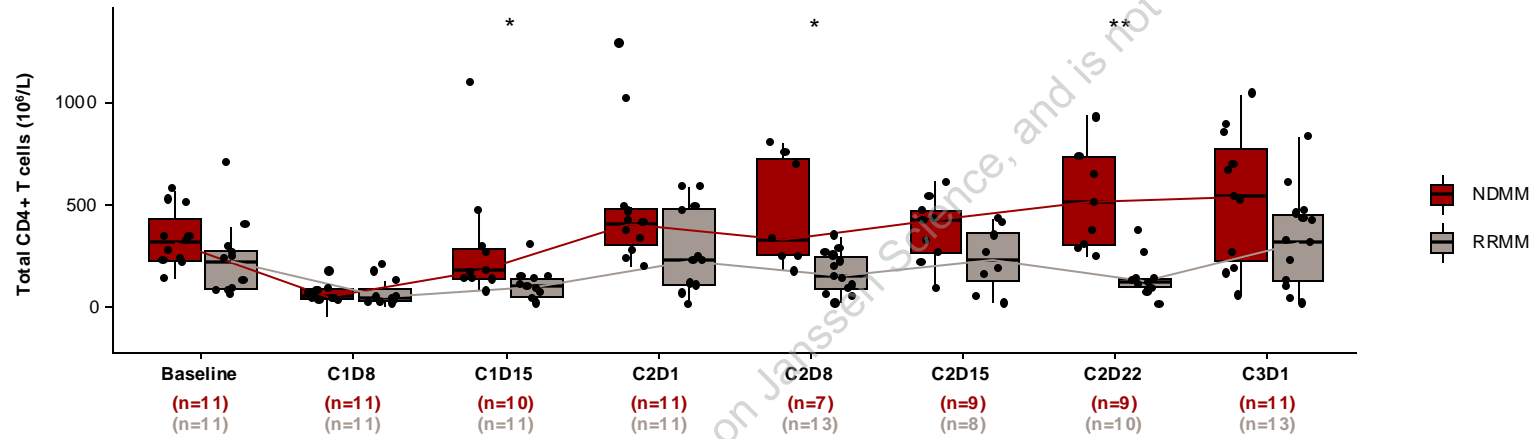
Lower proportions of effector memory CD8+ T cells expressing LAG-3, which can be a marker of T-cell exhaustion or immune suppression, associates with response in NDMM and RRMM

^aLAG-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. Dara, daratumumab; LAG-3, lymphocyte activation gene-3; Len, lenalidomide; NDMM, newly diagnosed multiple myeloma; PD-1, programmed cell death protein-1; RRMM, relapsed/refractory multiple myeloma; Tal, talquetamab; Tec, tectistamab.

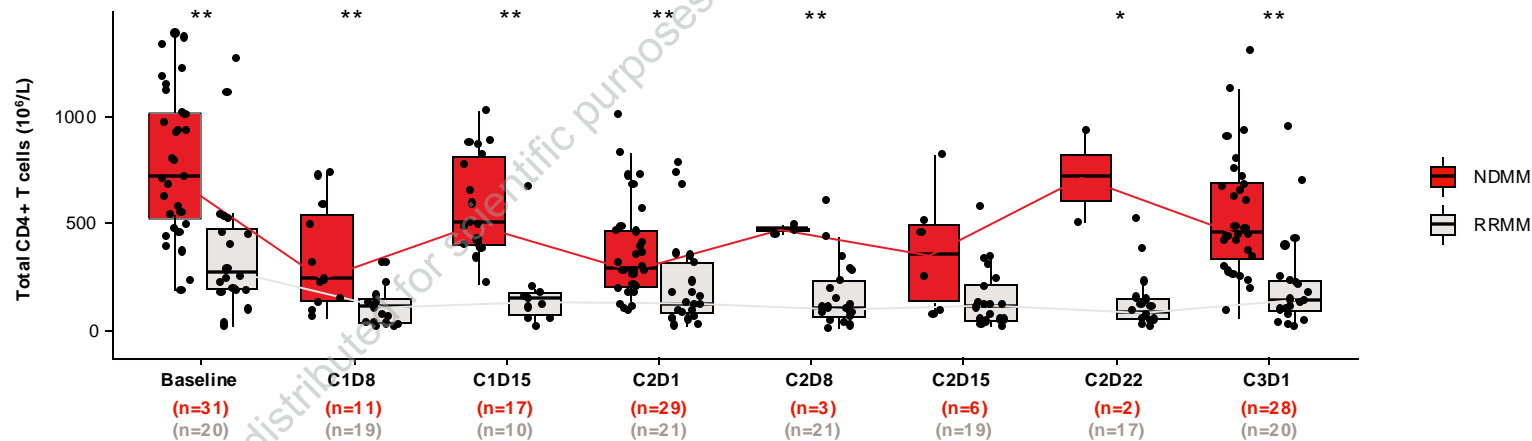


MajesTEC-2 (Tec-Dara-Len) and MonumenTAL-2 (Tal-Dara-Len): Longitudinal Analysis of CD4+ T Cells in NDMM vs RRMM

Tec-Dara-Len



Tal-Dara-Len

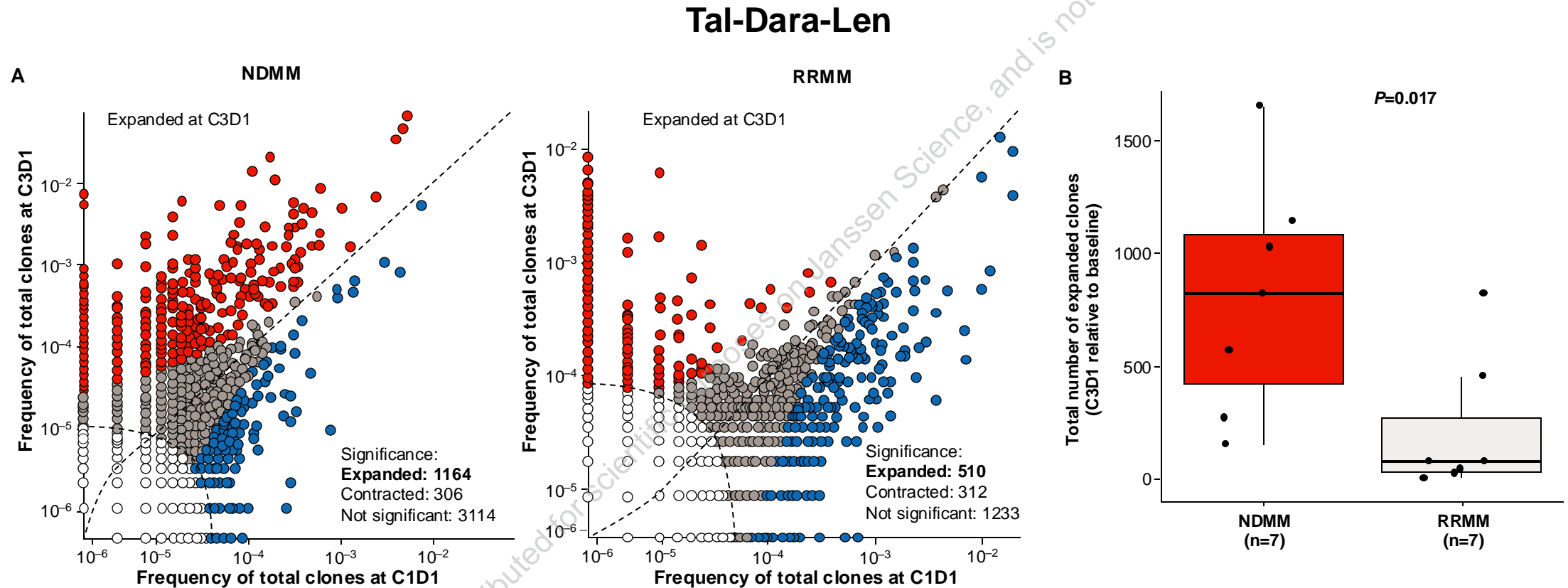


Greater T-cell recovery after C1D15 suggests a more beneficial and functional immune profile in NDMM vs RRMM

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; Dara, daratumumab; Len, lenalidomide; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/refractory multiple myeloma; Tal, talquetamab; Tec, teclistamab.



MonumenTAL-2 (Tal-Dara-Len): Longitudinal Analysis of T-Cell Clonal Expansion in NDMM vs RRMM



Greater T-cell clonal expansion suggests a more beneficial and functional immune profile, and therapy-induced T-cell expansion, in NDMM vs RRMM

Assessed by T-cell receptor sequencing; only available for MonumenTAL-2. Panel A shows a representative patient with NDMM (left) or RRMM (right). Panel B shows all patients with NDMM and RRMM and represents all unique, expanded (higher in C3D1) clones that were detected in the other sample. Greater T-cell clonal expansion shown here, together with greater T-cell recovery, 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).
 C, cycle; D, day; Dara, daratumumab; Len, lenalidomide; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/refractory multiple myeloma; Tal, talquetamab; Tec, teclistamab.



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

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

