Pharmacodynamic Signatures and Correlatives of Response in Patients With Relapsed/Refractory Multiple Myeloma Treated With Talquetamab or Teclistamab Plus Daratumumab and Pomalidomide

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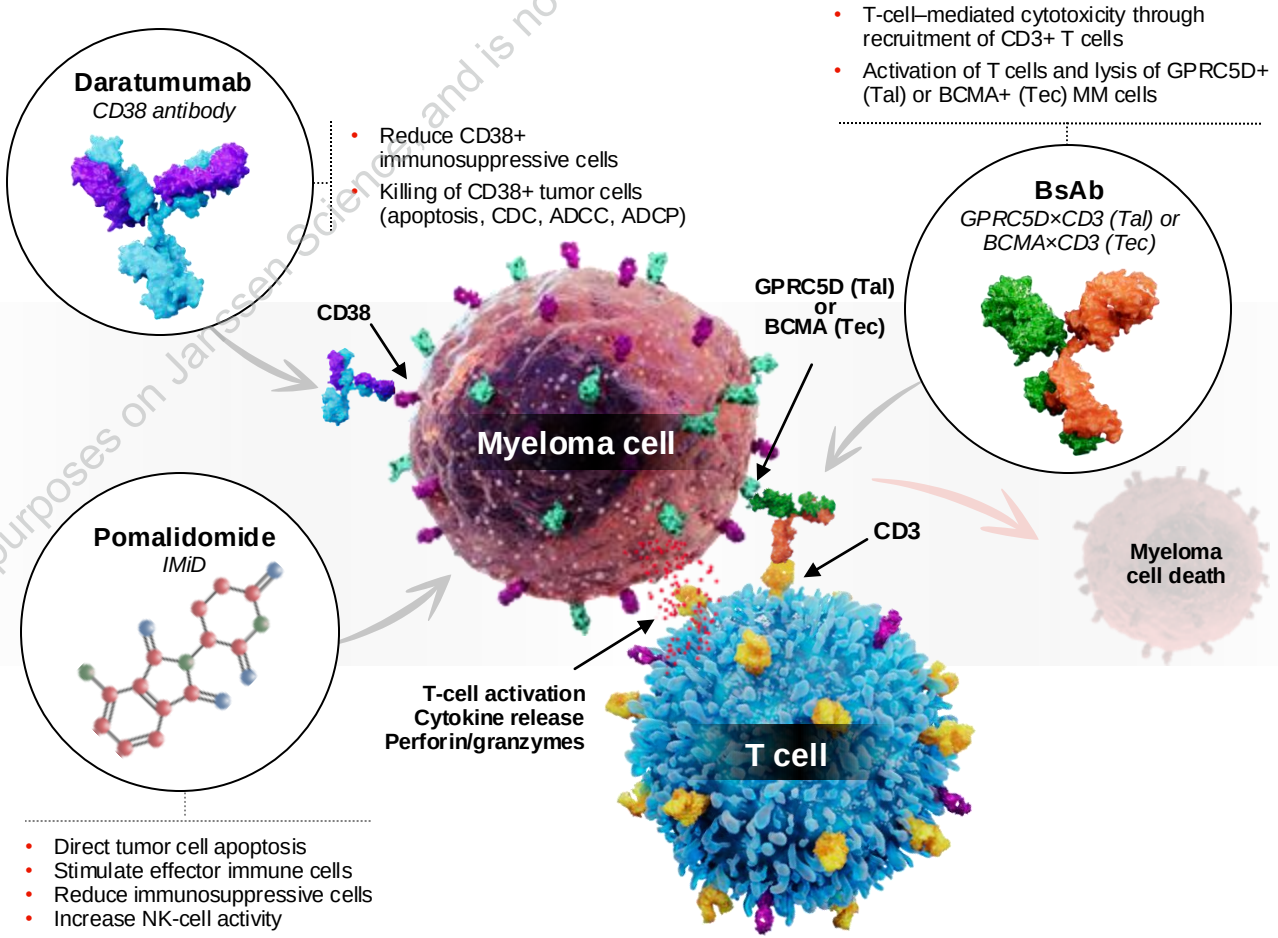
Targeting Multiple Antigens With Tal or Tec Combination Therapies May Enhance Antimyeloma Activity

- First-in-class BsAbs **talquetamab** and **teclistamab** have shown **deep, durable responses** in RRMM as mono and combination therapies[1-8]
- Combining Tal or Tec with Dara and an IMiD may enhance antimyeloma activity and overcome resistance mechanisms through multiple MOAs
  - Tal-Dara-Pom and Tec-Dara-Pom have shown promising efficacy and manageable safety across all lines of therapy in patients with RRMM[7,8]
- We assess **immunologic PD profiles and correlatives of response** in patients from the TRIMM-2 and MajesTEC-2 studies to better understand the contributions of Tal, Tec, Dara, and Pom in combination regimens in patients with RRMM



TRIMM-2 ClinicalTrials.gov identifier: NCT04108195. MajesTEC-2 ClinicalTrials.gov identifier: NCT04722146. ADCC, antibody-dependent cellular cytotoxicity; ADCP; antibody-dependent cellular phagocytosis; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CDC, complement-dependent cytotoxicity; Dara, daratumumab; GPRC5D, G protein-coupled receptor class C group 5 member D; IMiD, immunomodulatory drug; MOA, mechanism of action; NK, natural killer; PD, pharmacodynamics; Pom, pomalidomide; RRMM, relapsed/refractory multiple myeloma; Tal, talquetamab; Tec, teclistamab. 1. TALVEY (talquetamab). Prescribing information. Horsham, PA: Janssen Biotech, Inc.; 2023. 2. TALVEY (talquetamab). Summary of product characteristics. Leiden, Netherlands: Janssen Biologics BV; 2023. 3. TECVAYLI (teclistamab-cqyv). Prescribing information. Horsham, PA: Janssen Biotech, Inc.; 2022. 4. TECVAYLI (teclistamab). Summary of product characteristics. Leiden, Netherlands: Janssen Biologics BV; 2022. 5. Rasche L, et al. Presented at EHA; June 13–16, 2024; Madrid, Spain. 6. Garfall AL, et al. *J Clin Oncol* 2024;42(suppl 16):7540. 7. Bahlis N, et al; Presented at IMS; September 25–28, 2024; Rio de Janeiro, Brazil. 8. D'Souza A, et al. Presented at ASH; December 7–10, 2024; San Diego, CA, USA.

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PD Signatures and Correlatives of Response to Tal-Dara-Pom or Tec-Dara-Pom

Key inclusion criteria and baseline characteristics

TRIMM-2 (Tal-Dara-Pom)

≥3 prior LOT, including a PI and IMiD, or double-refractory to a PI and IMiD

Patients (n [%]) **refractory to**
Anti-CD38 (64 [83.1])
Pomalidomide (58 [75.3])

MajesTEC-2 (Tec-Dara-Pom)

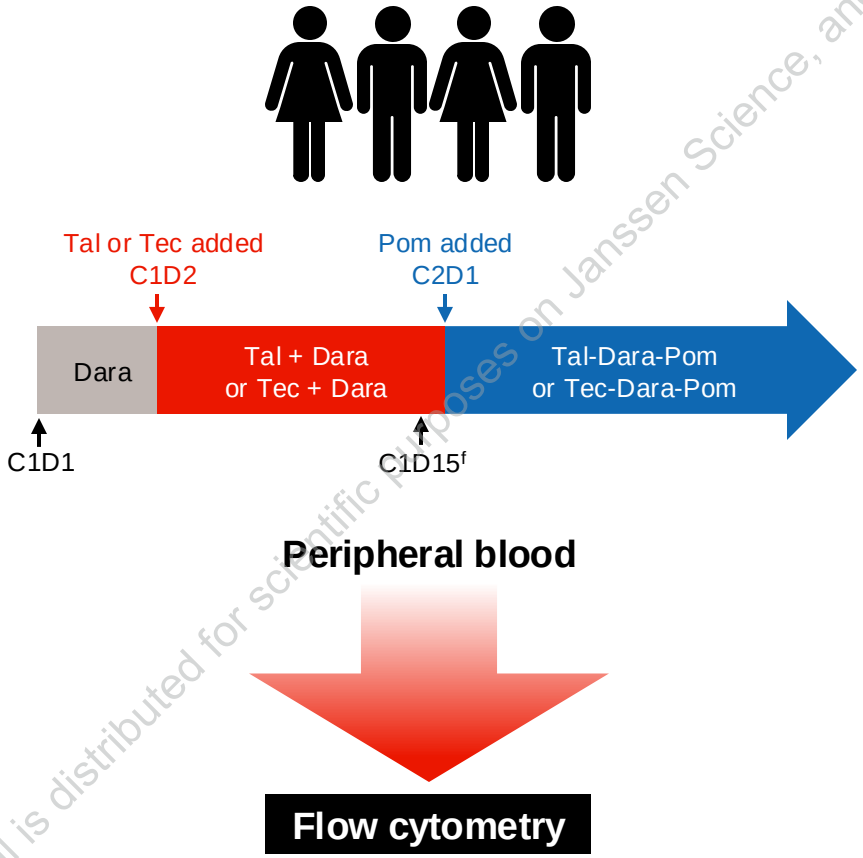
1–3 prior LOT, including a PI and lenalidomide

Patients (n [%]) **refractory to**
Anti-CD38 (1 [5.9])
Pomalidomide (1 [5.9])

Prior BsAb exposure was permitted in both studies[a]

Patients (n [%]) **refractory to BsAbs**
Tal-Dara-Pom: (29 [37.7])
Tec-Dara-Pom: (0 [0])

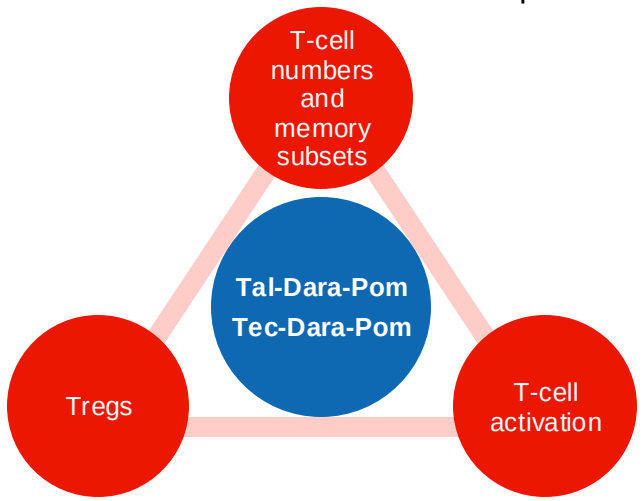
TRIMM-2[b,c] (N=77) or MajesTEC-2[d,e] (N=17)



Analyses

PD:
Immune profiling demonstrating the added effects of Dara + Pom to Tal or Tec

Mechanisms of depth and DOR:
Assessment of immune-cell profiles correlating with deep and durable responses



Tal-Dara-Pom data presented first, followed by Tec-Dara-Pom

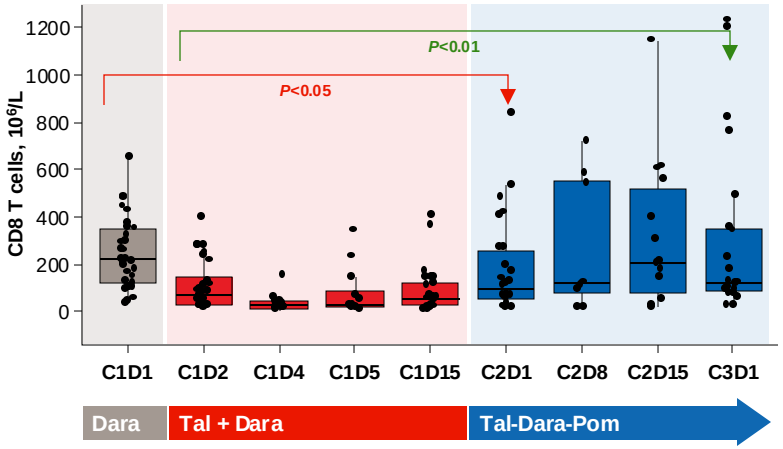
[a]Prior treatment with BCMA-targeted therapy was not permitted in MajesTEC-2. [b]Tal SC 0.4 mg/kg QW or 0.8 mg/kg Q2W after SUD, with approved schedules of Dara 1800 mg and Pom 2 mg. [c]TRIMM-2 (Tal-Dara-Pom) clinical cut-off: July 29, 2024. [d]Tec SC 0.72 or 1.5 mg/kg QW after SUD, with approved schedules of Dara 1800 mg and Pom 2 or 4 mg. [e]MajesTEC-2 (Tec-Dara-Pom) clinical cut-off: April 15, 2024. [f]First full dose of Tal or Tec.
BsAb, bispecific antibody; C, cycle; D, day; Dara, daratumumab; DOR, duration of response; IMiD, immunomodulatory drug; LOT, line of therapy; PD, pharmacodynamics; PI, proteasome inhibitor; Pom, pomalidomide; Q2W, every other week; QW, weekly; SC, subcutaneous; SUD, step-up dose; Tal, talquetamab; Tec, teclistamab; Treg, regulatory T cell.

Complementary PD Effects Observed With Tal + Dara, Which Was Synergized by Pom

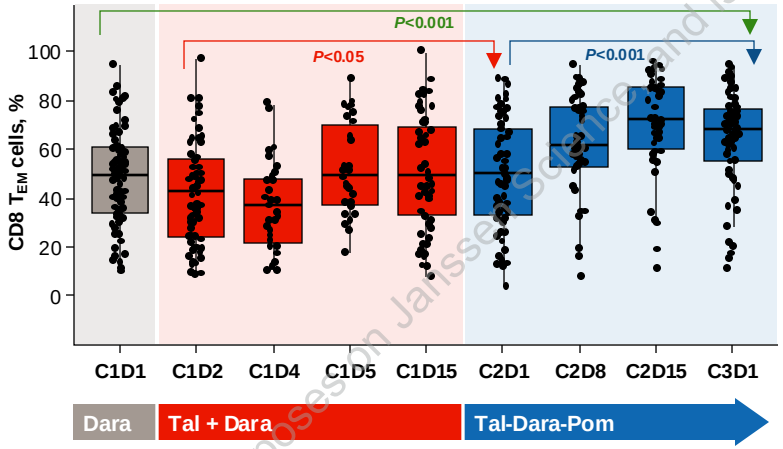
Tal-Dara-Pom

T-cell dynamics

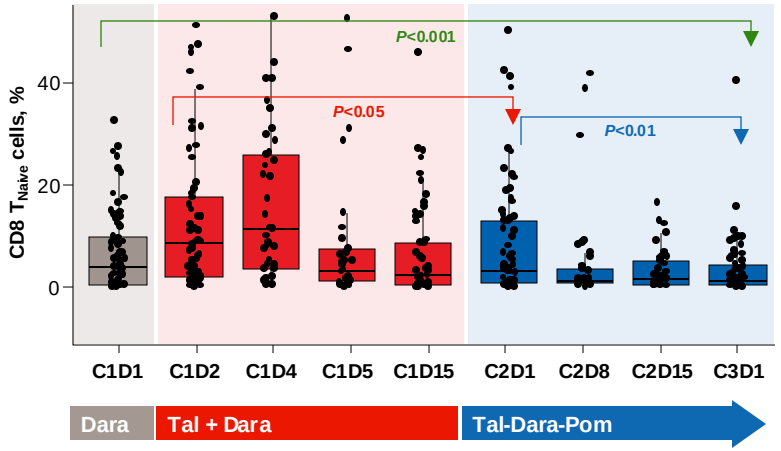
Tal-Dara-Pom–mediated recovery of absolute counts of CD8 T cells[a]



Tal-Dara-Pom–mediated CD8 T_{EM} cell expansion



Tal-Dara-Pom–mediated CD8 T_{Naive} cell reduction[a]



[a]Data points removed for visualization: top left (4), top right (10), bottom left (2), bottom middle (4). C, cycle; D, day; Dara, daratumumab; PD, pharmacodynamics; Pom, pomalidomide; Tal, talquetamab; T_{EM}, effector memory CD8 T cell.

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Complementary PD Effects Observed With Tal + Dara, Which Was Synergized by Pom

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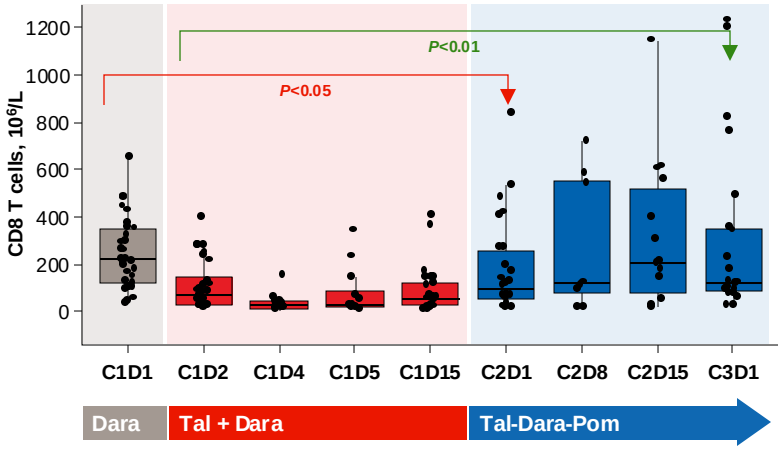
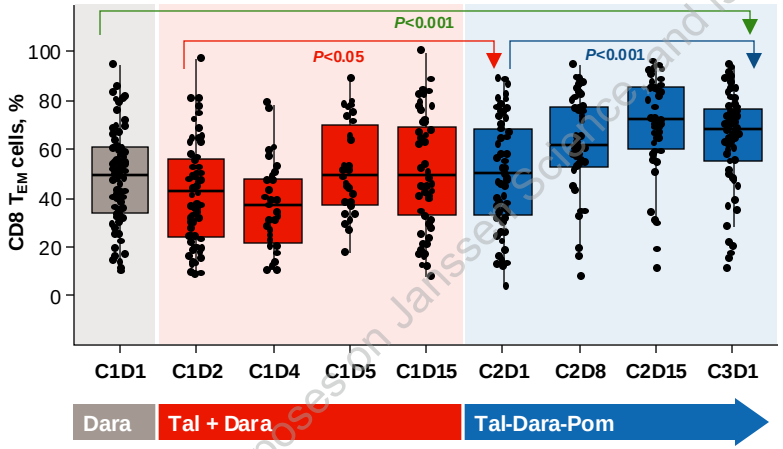
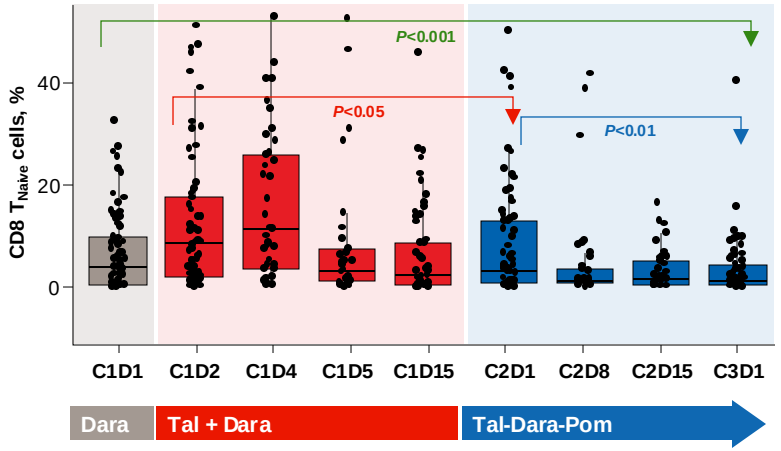


Tal-Dara-Pom–mediated CD8 T_{EM} cell expansion

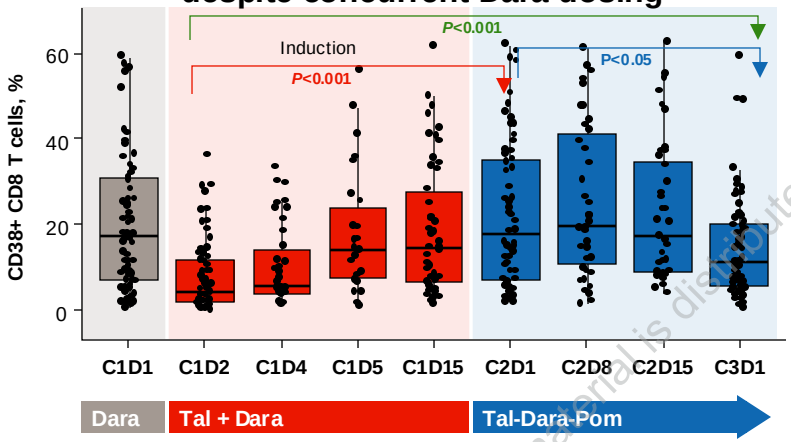


Tal-Dara-Pom–mediated CD8 T_{Naive} cell reduction[a]



CD38+ populations

Tal + Pom-mediated CD38+ CD8 T-cell induction despite concurrent Dara dosing[a]



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Tal-Dara-Pom

T-cell dynamics

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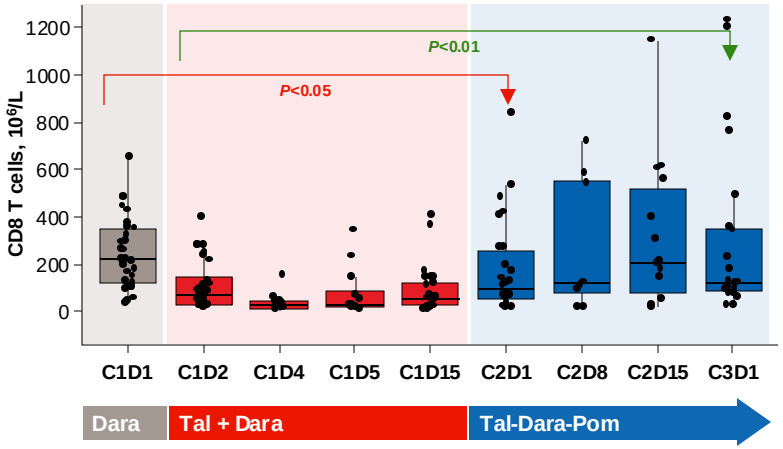
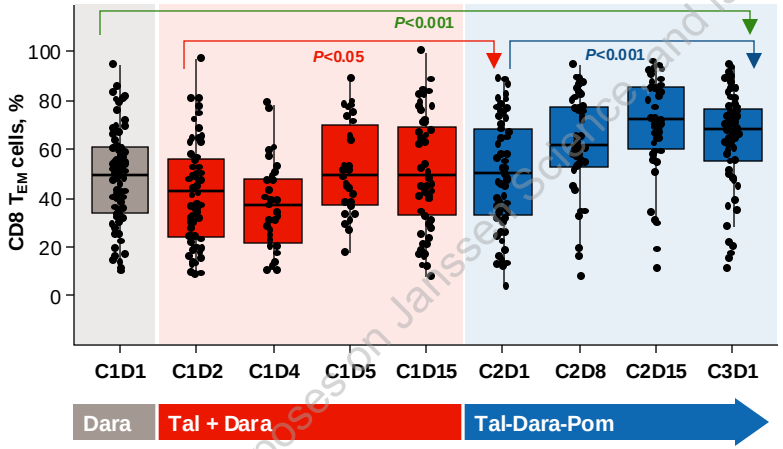
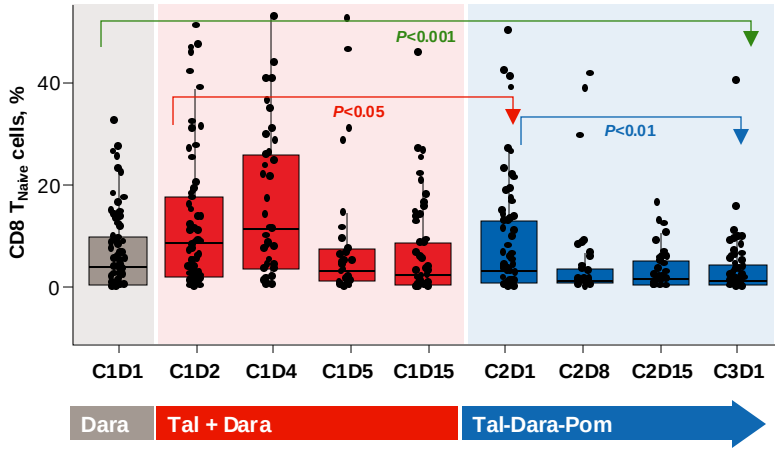


Tal-Dara-Pom–mediated CD8 T_{EM} cell expansion

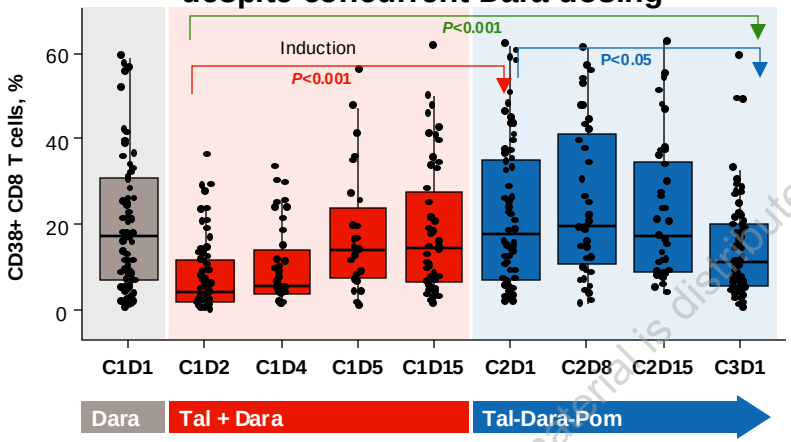


Tal-Dara-Pom–mediated CD8 T_{Naive} cell reduction[a]

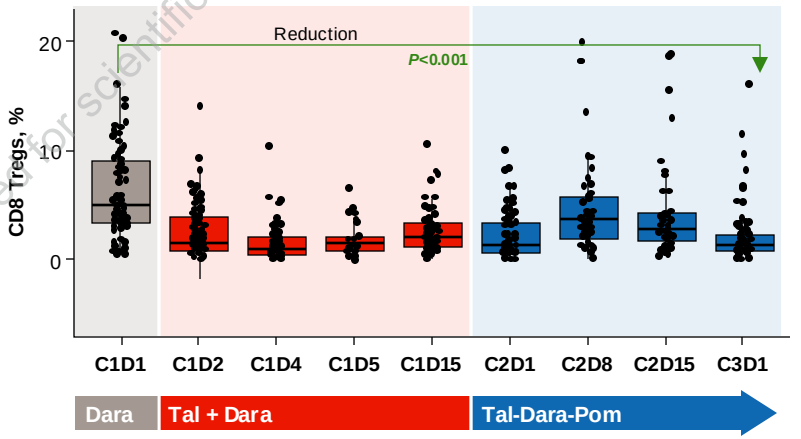


CD38+ populations

Tal + Pom-mediated CD38+ CD8 T-cell induction despite concurrent Dara dosing[a]



Dara-mediated CD38+ Treg reduction[a]



[a]Data points removed for visualization: top left (4), top right (10), bottom left (2), bottom middle (4). C, cycle; D, day; Dara, daratumumab; PD, pharmacodynamics; Pom, pomalidomide; Tal, talquetamab; T_{EM}, effector memory CD8 T cell.

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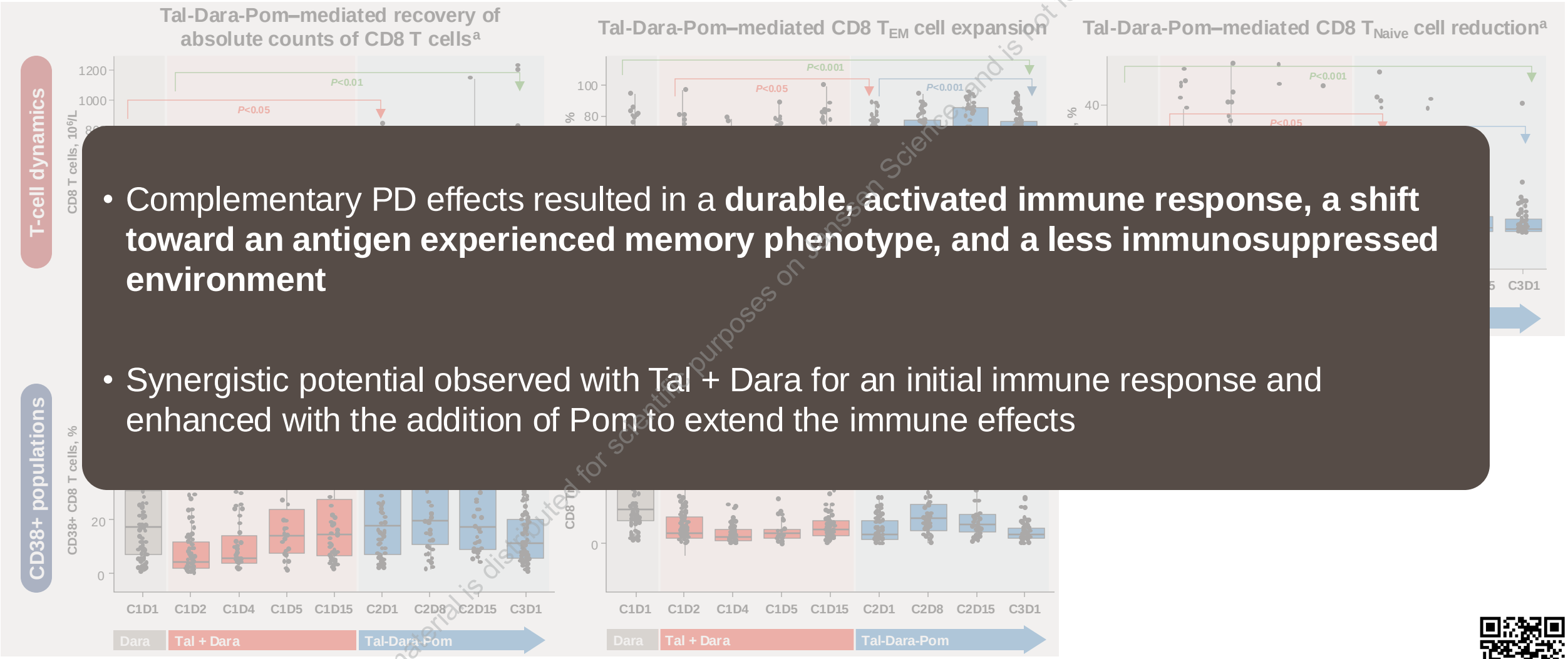
Complementary PD Effects Observed With Tal + Dara, Which Was Synergized by Pom



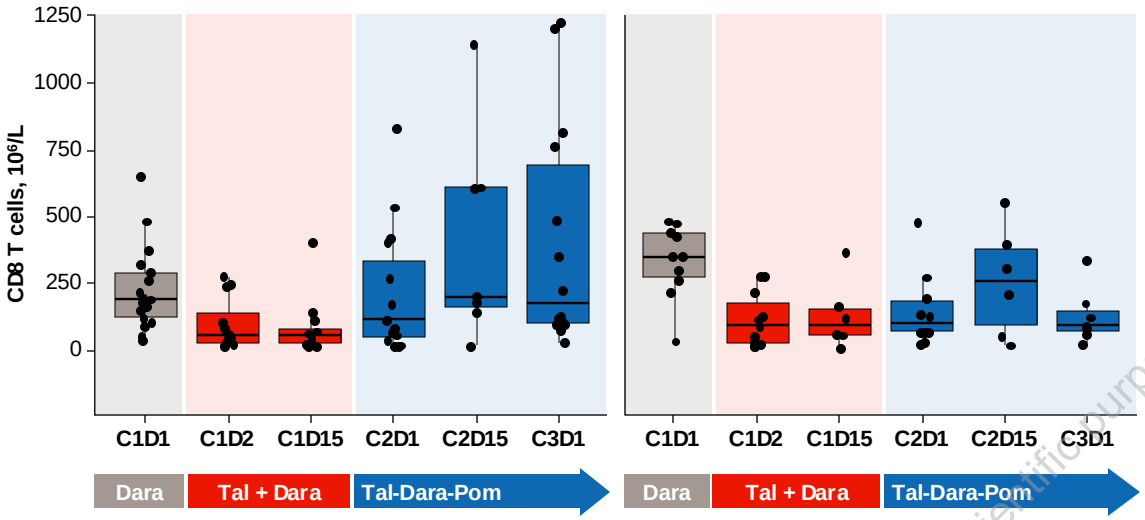
- Complementary PD effects resulted in a **durable, activated immune response, a shift toward an antigen experienced memory phenotype, and a less immunosuppressed environment**
- Synergistic potential observed with Tal + Dara for an initial immune response and enhanced with the addition of Pom to extend the immune effects

[a]Data points removed for visualization: top left (4), top right (10), bottom left (2), bottom middle (4). C, cycle; D, day; Dara, daratumumab; PD, pharmacodynamics; Pom, pomalidomide; Tal, talquetamab; T_{EM}, effector memory CD8 T cell.

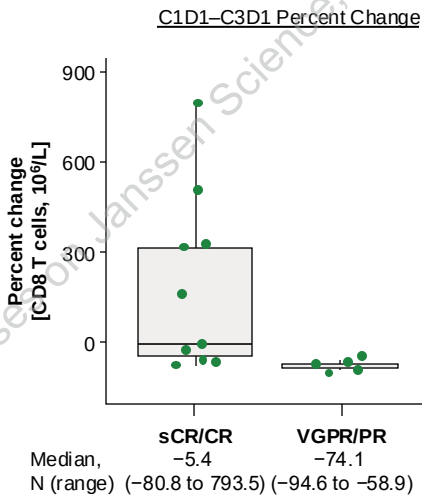
Durable Recovery of CD8 T Cells Observed in Deep Responders to Tal-Dara-Pom and Correlated Significantly With Longer DOR

Deep responders: sCR/CR[a]

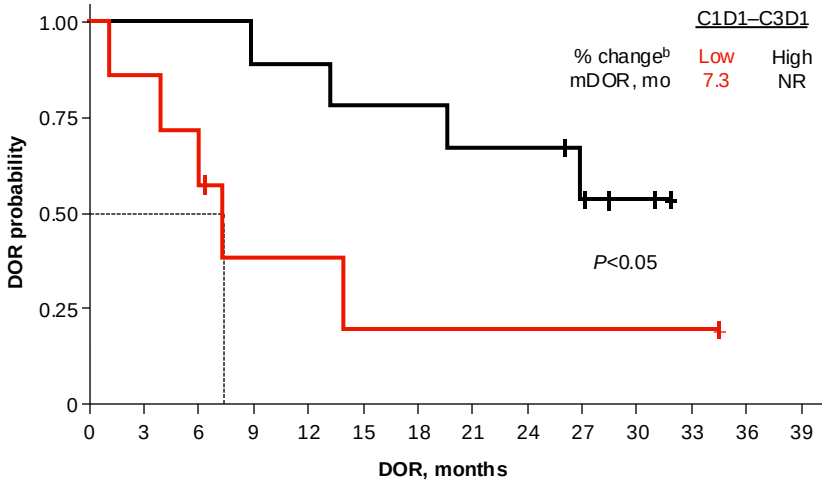
Less deep responders: VGPR/PR



Trend for greater CD8 T-cell recovery in deep responders



Higher % change in CD8 T-cell recovery significantly correlated with DOR



- Following T-cell margination, **a more durable recovery of CD8 T cells was observed in deeper responders (sCR/CR vs VGPR/PR)** and correlated with longer DOR

[a]2 data points removed for visualization. [b]DOR % change to cut low vs high = –56.8. Low % change indicates < median, and high % change indicates > median % change in absolute counts of CD8 T cells.
CR, complete response; C, cycle; D, day; Dara, daratumumab; DOR, duration of response; mDOR, median duration of response; NR, not reached; Pom, pomalidomide; PR, partial response; sCR, stringent complete response; Tal, talquetamab; VGPR, very good partial response.

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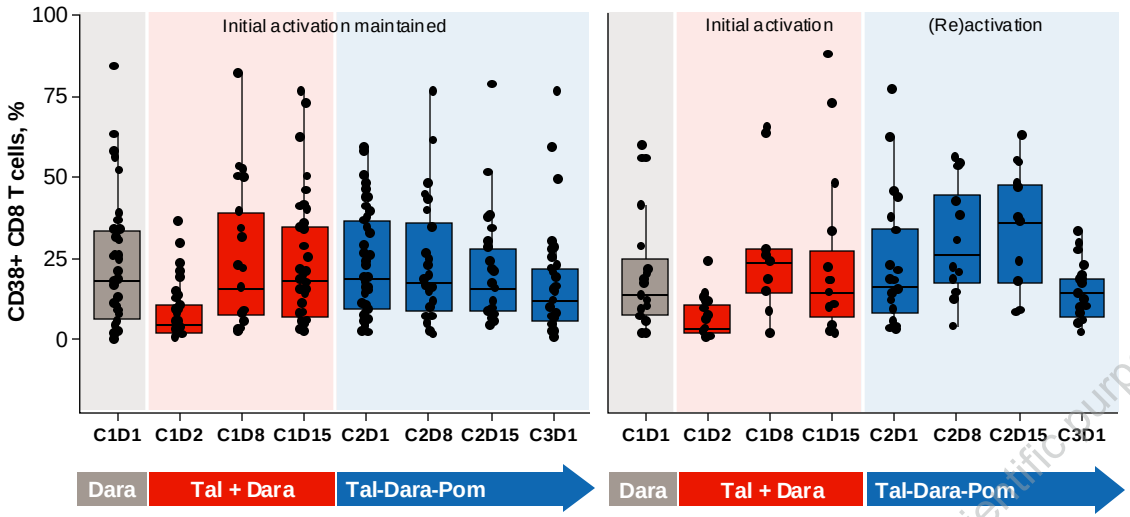
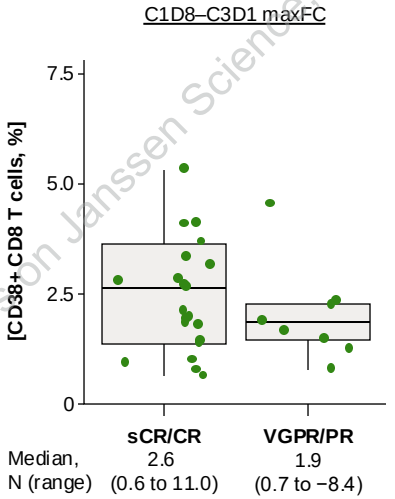
CD38+ CD8 T-cell Activation Observed in Responders to Tal-Dara-Pom and Correlated Significantly With Longer DOR

Deep responders: sCR/CR[a]

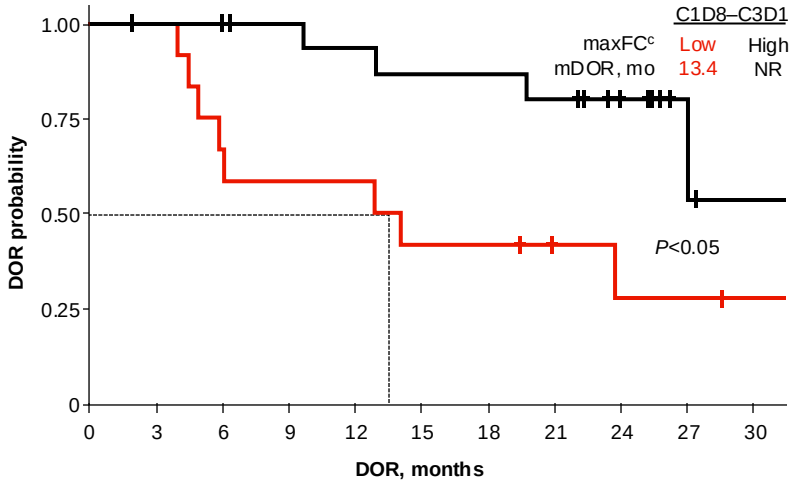
Less deep responders: VGPR/PR



Comparable CD38+ CD8 T-cell induction across all responders[b]



Higher maxFC CD38+ CD8 T-cell induction significantly correlated with DOR



- **A comparable level of CD38+ induction on CD8 T cells was observed across all responders** to Tal-Dara-Pom in early treatment cycles that correlated with longer DOR

If *P* value is not depicted in figures, the difference is not statistically significant.
[a]1 data point removed for visualization. [b]3 data points removed for visualization. [c]DOR FC to cut low vs high = 1.7. Low maxFC indicates < median, and high maxFC indicates > median maxFC in CD38+ CD8 T cells.
C, cycle; CR, complete response; D, day; Dara, daratumumab; DOR, duration of response; FC, fold change; max, maximum; mDOR, median duration of response; NR, not reached; Pom, pomalidomide; PR, partial response; sCR, stringent complete response; Tal, talquetamab; VGPR, very good partial response.

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Improved T-cell Signatures Observed in Patients With Prior BsAb Exposure Treated With Tal-Dara-Pom vs Talquetamab Monotherapy

Tal-Dara-Pom

MonumenTAL-1[1] (Tal mono)

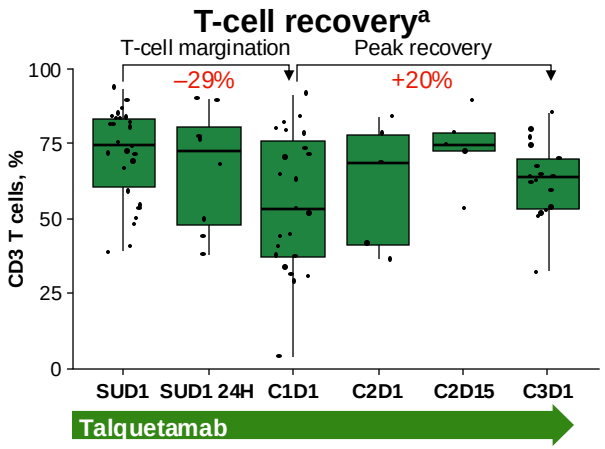
Prior BsAb n=26 (25 refractory)

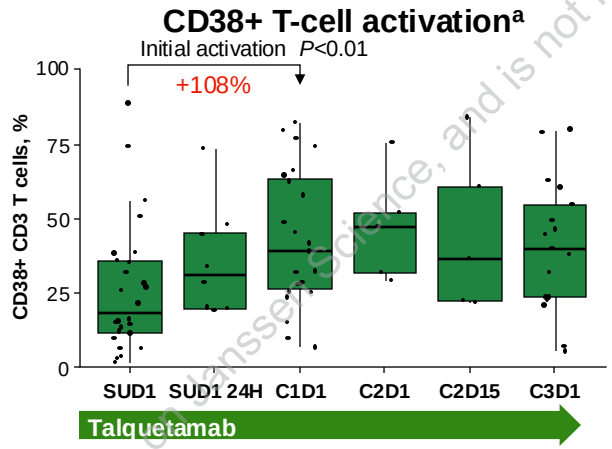
ORR: 57.7%

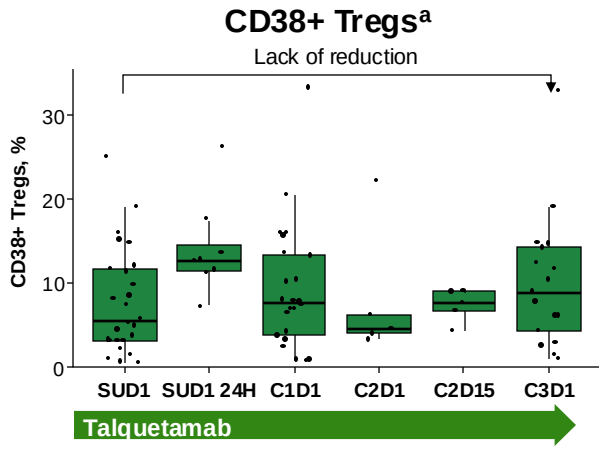
TRIMM-2[2] (Tal-Dara-Pom)

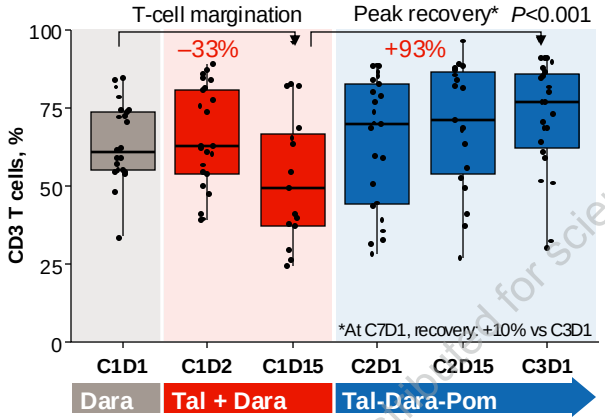
Prior BsAb n=29 (all refractory)

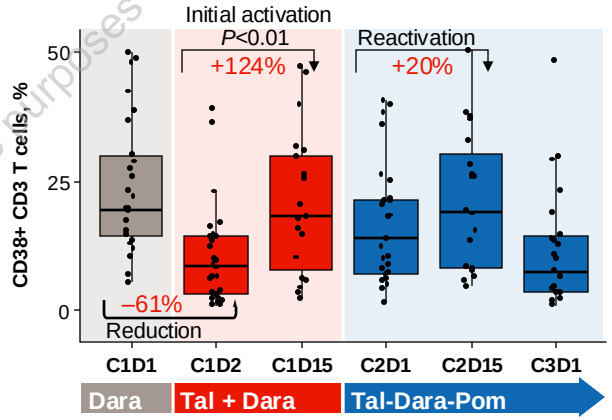
ORR: 82.8%

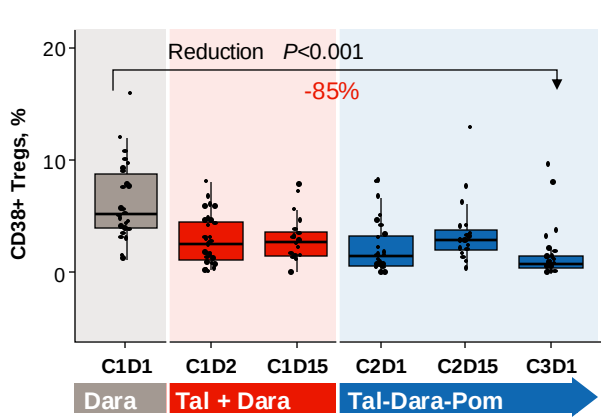












- Patients with prior exposure to bispecifics exhibited increased proportions of activated T cells, T cells expressing checkpoints, and Tregs at baseline on MonumenTAL-1[3–5]
- Compared with Talquetamab monotherapy, **markedly** greater T-cell recovery, (re)activation of T cells, and reduction of CD38+ Tregs were observed, suggesting potential for T-cell reinvigoration, which may contribute to improved responses in prior BsAb-exposed patients treated with Tal-Dara-Pom

If *P* value is not depicted in figures, the difference is not statistically significant.

[a]Data points removed for visualization: top middle (7), top right (5), bottom middle (1), bottom right (4). BsAb, bispecific antibody; C, cycle; D, day; Dara, daratumumab; mono, monotherapy; ORR, overall response rate; Pom, pomalidomide; SUD1, stepup dose 1; SUD1 24h, 24 hours after first step-up dose; Tal, talquetamab; Treg, regulatory T cells.

1. Rasche L, et al. Presented at EHA; June 13–16, 2024; Madrid, Spain. 2. Bahlis N, et al. Presented at IMS; September 25–28, 2024; Rio de Janeiro, Brazil. 3. Chari A, et al. *N Engl J Med* 2022;387:2232-44. 4. Vishwamitra D, et al. Presented at ASH; December 9–12, 2023; San Diego, CA, USA. Poster #1933. 5. Jakubowiak A, et al. Presented at ASH; December 9–12, 2023; San Diego, CA, USA. Poster #3377.

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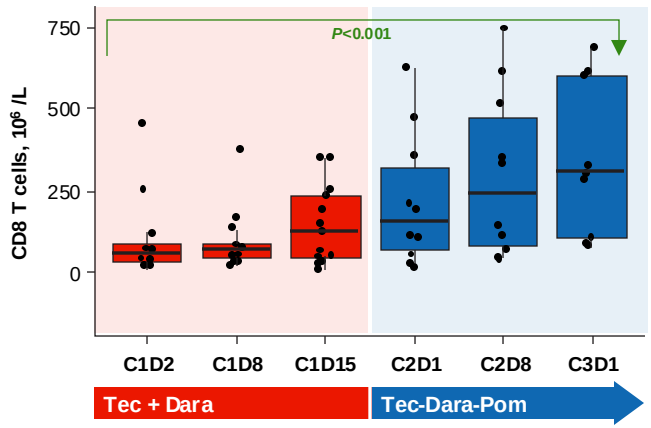
Complementary PD Effects of Tec + Dara Were Enhanced by Pom, Supporting Clinical Findings in 1–3 Prior LOT

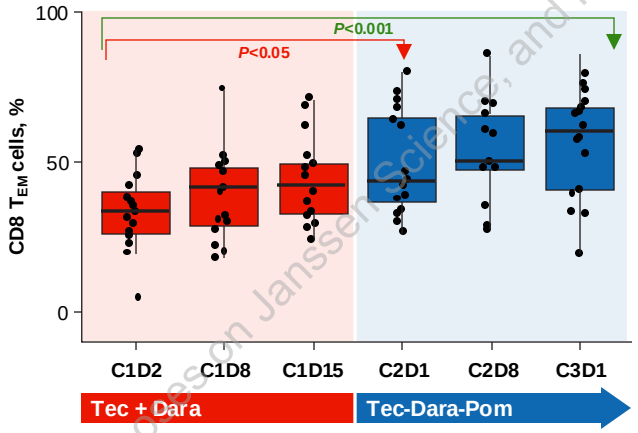
Tec-Dara-Pom

T-cell dynamics

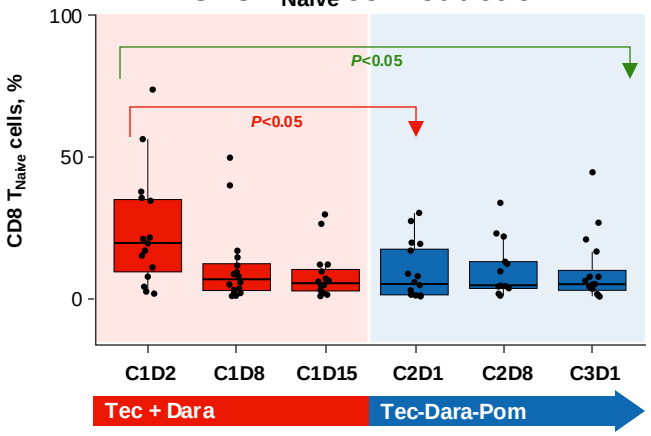
Tec-Dara-Pom–mediated T-cell recovery[a]



Tec-Dara-Pom–mediated T_{EM} cell expansion

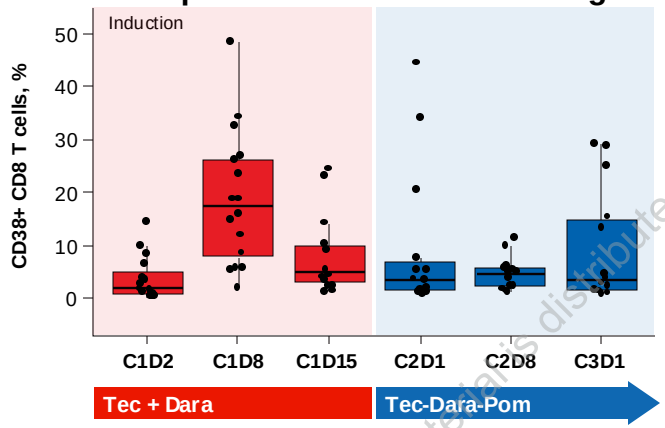


Tec-Dara-Pom–mediated CD8 T_{Naive} cell reduction

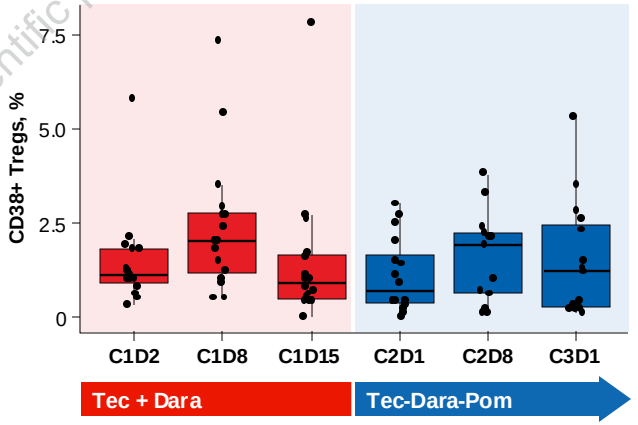


CD38+ populations

Tec + Pom-mediated CD38+ T-cell induction despite concurrent Dara dosing[a]



Dara-mediated CD38+ Treg reduction[a]



- Complementary PD effects resulted in a **durable activated immune response, a shift toward an antigen experienced memory phenotype, and a less immunosuppressed environment** with Tec + Dara that was enhanced with Pom and supports the high ORR observed clinically in these less heavily pretreated patients

[a]Data points removed for visualization: top left (1), bottom left (4), bottom middle (1).
C, cycle; D, day; Dara, daratumumab; LOT, line of therapy; PD, pharmacodynamics; Pom, pomalidomide; Tec, teclistamab; T_{EM}, effector memory CD8 T cells.

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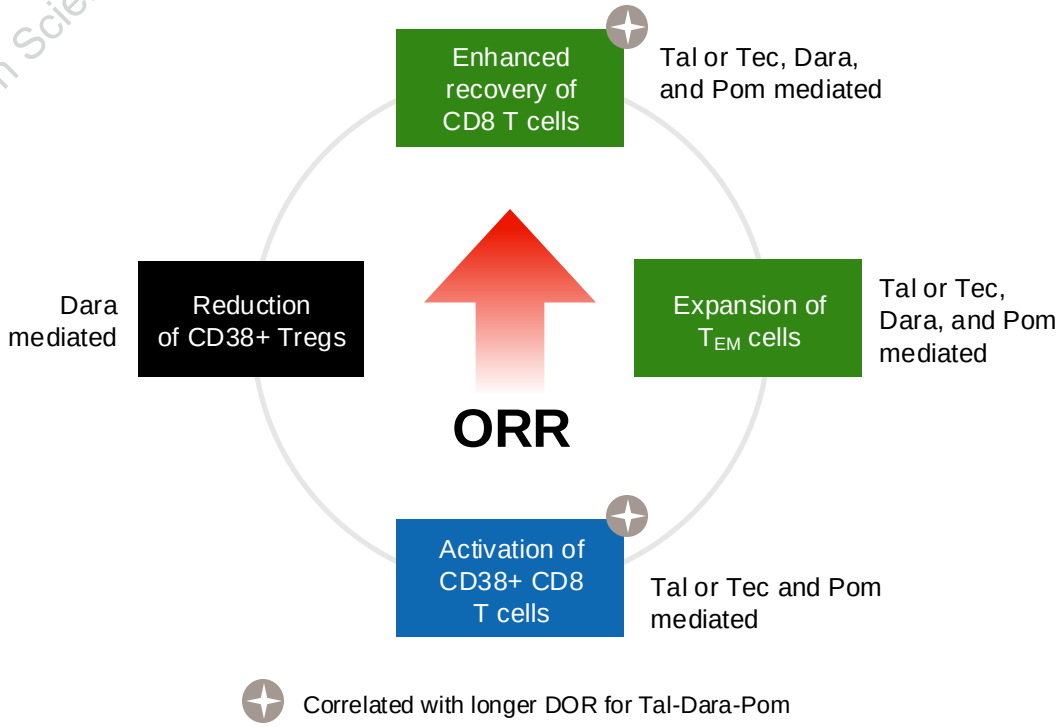
Summary and Conclusions

Synergistic, immunomodulatory MOAs of Tal-Dara-Pom and Tec-Dara-Pom regimens contribute to deep responses and beneficial long-term outcomes in patients with RRMM

- PD effects that **significantly correlated with DOR** for Tal-Dara-Pom **contributed to long-term efficacy**
- Tal-Dara-Pom showed **improved T-cell signatures longitudinally** in patients with **prior BsAb exposure** vs talquetamab monotherapy
- **PD effects observed with Tec-Dara-Pom** in 1–3 prior lines **supported the improved ORR in earlier lines** of therapy
- These data underline the **promising efficacy of these regimens in a broad RRMM population** and support further evaluation[1,2]

Tec-Dara-Pom clinical data (oral #495) in RRMM presented at ASH on Sunday, Dec 8, 2024, at 10:00 AM



BsAb, bispecific antibody; Dara, daratumumab; DOR, duration of response; MOA, mechanism of action; ORR, overall response rate; PD, pharmacodynamics; Pom, pomalidomide; RRMM, relapsed/refractory multiple myeloma; Tal, talquetamab; Tec, teclistamab; T_{EM}, effector memory CD8 T cells; Treg, regulatory T cell.

1. Bahlis N, et al; Presented at IMS; September 25–28, 2024; Rio de Janeiro, Brazil. 2. D'Souza, et al; Presented at ASH 2024; December 7–10, 2024; San Diego, CA, USA.

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Ongoing Efforts

- Translational correlatives for **Tal-** and **Tec-Dara-IMiD combinations** will be explored further in larger datasets from phase 3 registrational studies
  - **Tal + Dara and Tal-Dara-Pom in MonumenTAL-3**
  - **Tec + Dara in MajesTEC-3**
  - **Tal-Dara-Len and Tec-Dara-Len in MajesTEC-7**

MonumenTAL-3 ClinicalTrials.gov identifier: NCT05455320. MajesTEC-3 ClinicalTrials.gov identifier: NCT05083169. MajesTEC-7 ClinicalTrials.gov identifier: NCT05552222.
Dara, daratumumab; IMiD, immunomodulatory drug; Len, lenalidomide; Pom, pomalidomide; Tal, talquetamab; Tec, teclistamab.

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https://www.congresshub.com/ASH2024/Oncology/Teclistamab/Vishwamitra

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