PF709

Exploratory Biomarkers Associated with Talquetamab Resistance and Relapse in the MonumenTal-1 China 400 Cohort by Data-driven Unsupervised Clustering Analysis

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Key Takeaway

The unsupervised clustering approach identified unique T cell populations with a potential exhaustion phenotype in association with Tal resistance and relapse.

Conclusions

T cell populations expressing TIM3 and CD38, were elevated in non-responders as well as upon relapse post Tal treatment.

These findings suggest that T cell exhaustion was associated with Tal resistance and relapse and support a combination strategy with other drugs (e.g. Dara).

The unsupervised clustering approach identified distinct T cell populations which were not captured by conventional gating, highlighting its value as a complementary method for flow cytometry data analysis.

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Poster

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Disclosures

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Introduction

Talquetamab (Tal, GPRC5DxCD3) is the first approved bispecific antibody targeting GPRC5D in patients with refractory or relapsed multiple myeloma (RRMM)[1,2]. The MonumenTAL-1 China 400 Cohort (TAL-1 China 400 Cohort) is a phase 2 study of Tal (400 ug/kg QW) in Chinese patients with RRMM[3]. As of Jan 24, 2024, 29 Chinese patients were enrolled, achieving a clinical response rate of 69% (20/29). With a median follow-up of 13.4 months, median duration of response was 16.6 months and median progression-free survival was 8.3 months. To better understand the mechanisms underlying resistance to Tal, and relapse after treatment, flow cytometry was utilized to analyze immune signatures in the TAL-1 China 400 Cohort.

Methods

Baseline and on-treatment blood samples were analyzed by flow cytometry (Q2 Solutions) to assess immune profiles. Correlative analyses of clinical outcomes with flow cytometry were performed with results from the conventional prespecified and validated gating method.

To expand upon these analysis, raw Flow Cytometry Standard (FCS) files were used for the data-driven approach[4]. Statistical tests were performed using nonparametric Wilcoxon test for 2-group comparisons and Pearson correlation for correlation analysis.

Figure 1. Correlative analyses of exploratory biomarkers with Tal resistance and relapse from the TAL-1 China 400 Cohort

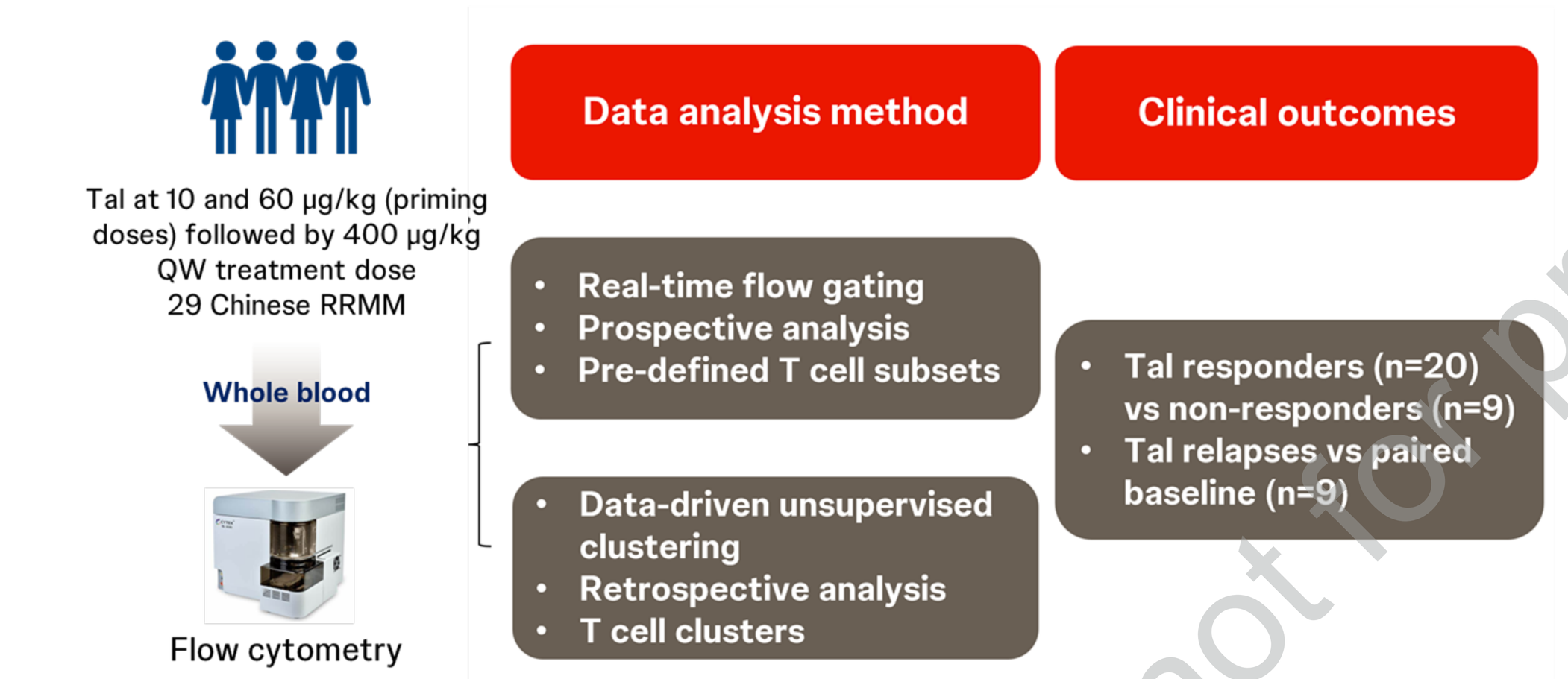
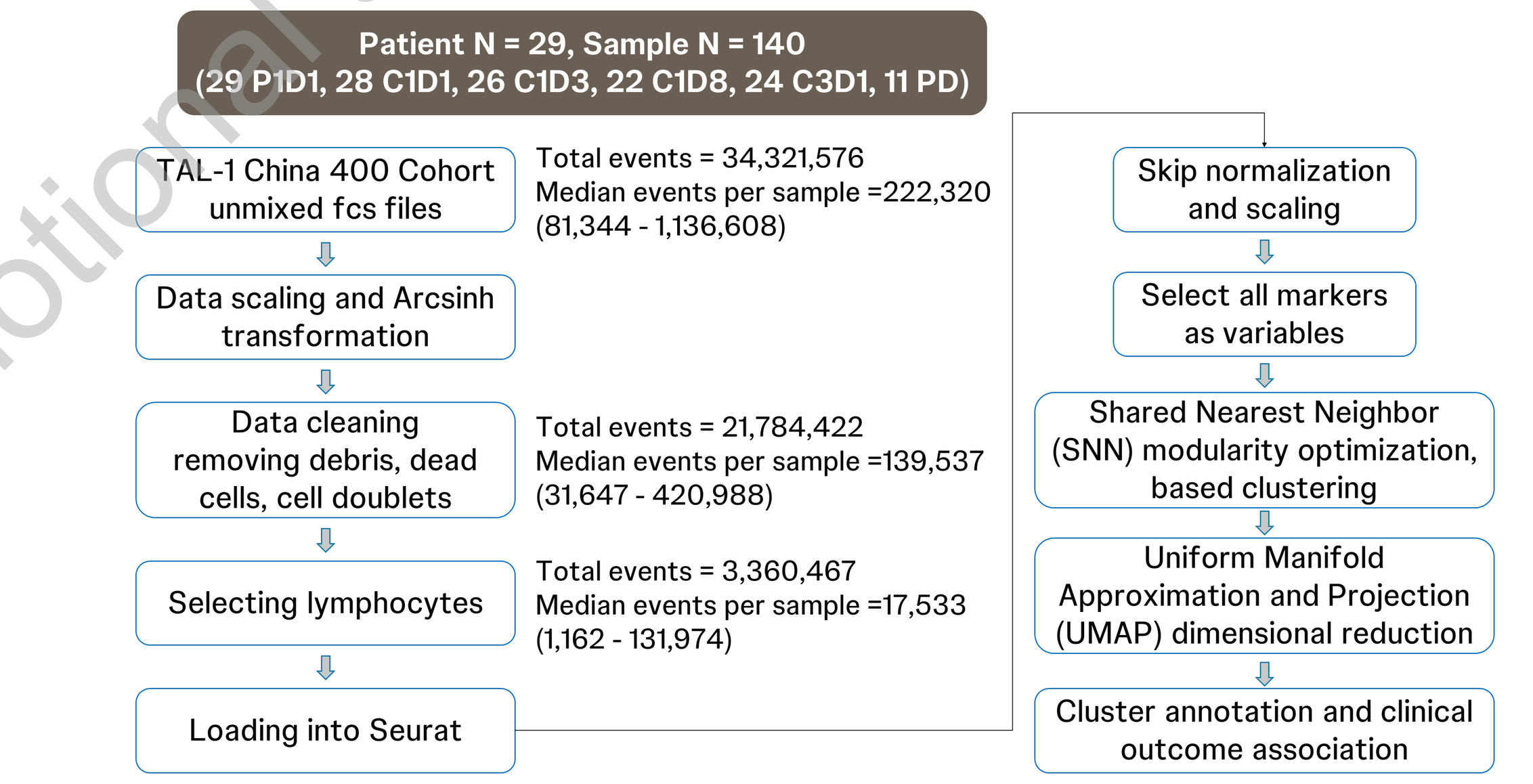


Figure 2. Overview of unsupervised clustering and dimensional reduction data analysis workflow



P: priming dose; C: cycle; D: day

Results

Figure 3. Association of immune profiles with Tal response and resistance using traditional gating analysis

- Non-responders showed a trend of higher baseline proportions of CD4⁺T cells expressing CD38 or TIM3 (data not shown).
- Trends of higher peak induction of LAG3 and TIM3 on T cells in responders during the first cycle of Tal treatment (A).
- In non-responders, a trend showing higher proportions of LAG3⁺ CD4⁺T cells at C3D1 post Tal treatment (B), indicating a T-cell exhaustion phenotype at the later point.

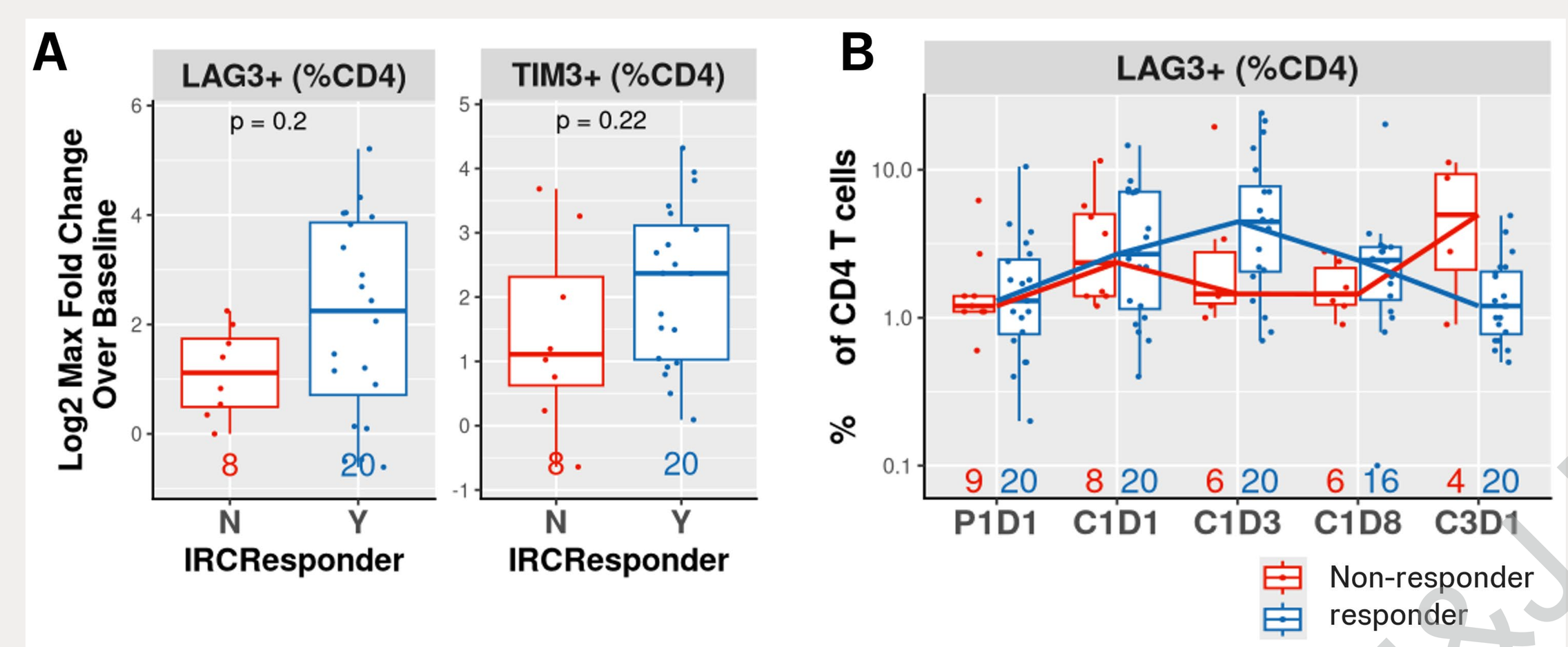


Figure 4. Identification of total CD4 and CD8 T cell clusters through unsupervised clustering and their correlation with conventional gating results

- A total of 25 cell clusters were identified by unsupervised clustering (A), including the CD4⁺T cell cluster (B) and the CD8⁺T cell cluster (C). A heatmap of the CD4⁺ and CD8⁺T cell clusters was shown in (D).
- High concordance was observed between unsupervised clustering and conventional gating regarding the proportion of total CD4⁺ and CD8⁺ T cell populations (E).

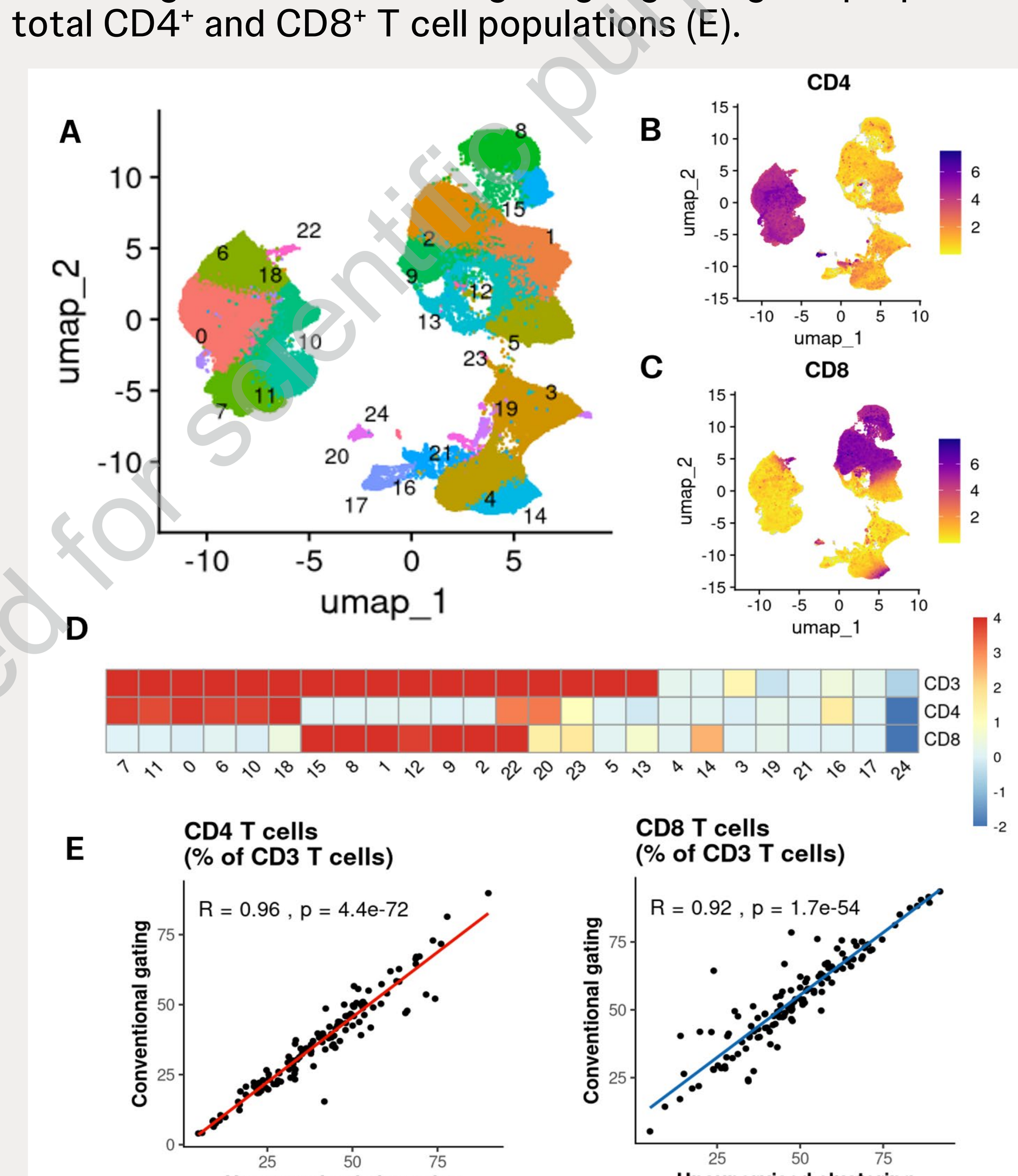
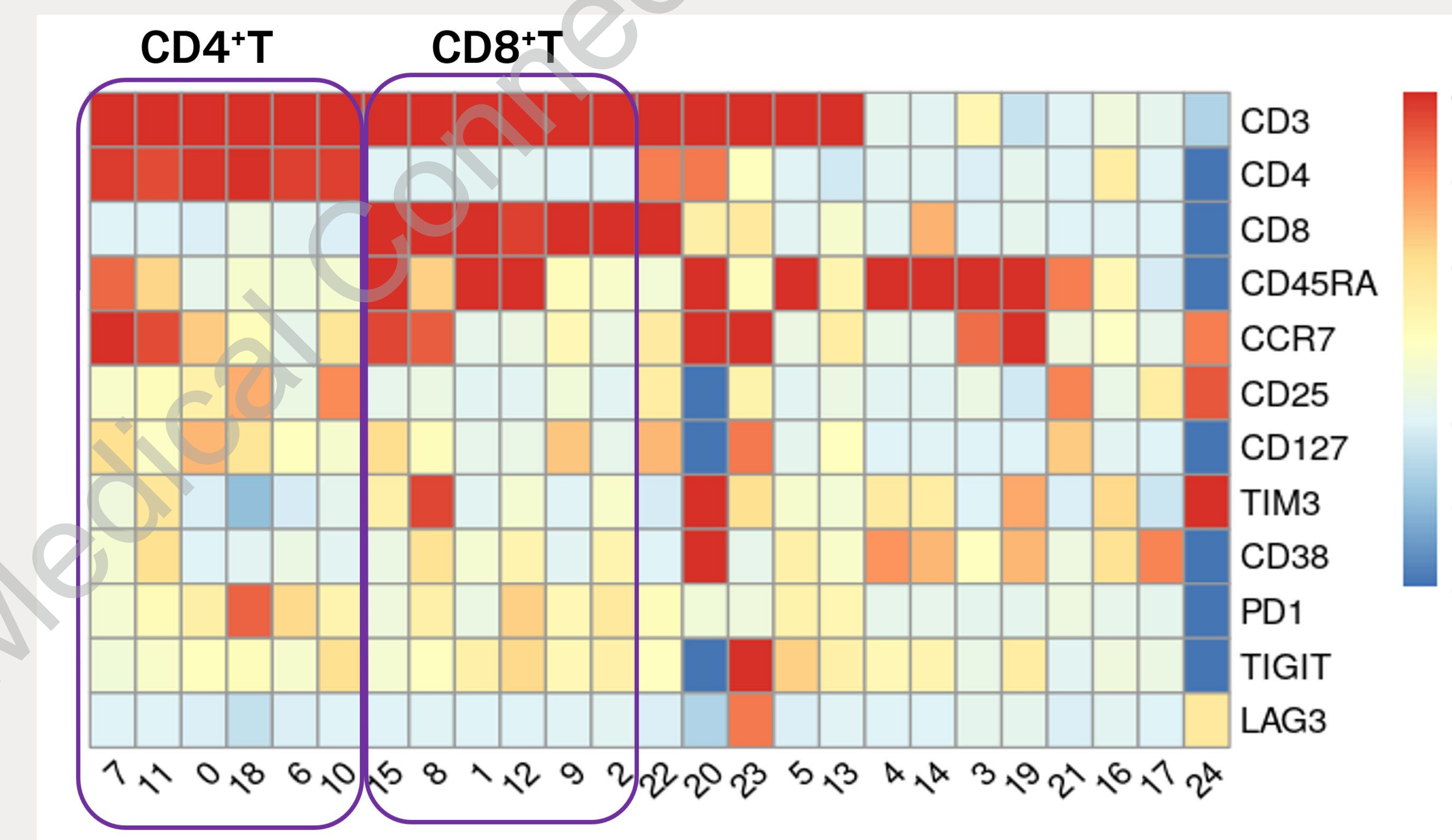


Figure 5. 12 clusters of T cells were further annotated based on their immunophenotypes

- CD4⁺T cell clusters: C7: Tnaive; C11: TIM3⁺ CD38⁺ Tnaive-like; C0: Tcm; C18: PD1⁺ Tcm; C6: Tem; C10: Treg.
- CD8⁺T cell clusters: C15: Tnaive; C8: TIM3⁺CD38⁺ Tnaive-like; C1: Temra; C12: PD1⁺TIGIT⁺CD38⁺ Temra; C9: Tcm; C2: Tem.



C: cluster; Tcm: T central memory; Tem: T effector memory; Temra: T effector memory re-expressing CD45RA; Treg: T regulatory cells.

Figure 6. Increase in a subset of Tnaive-like expressing TIM3 and CD38 during the first cycle of Tal treatment

- U-Map (A) demonstrated an increase in cluster-11 (a subset of CD4⁺Tnaive-like expressing TIM3 and CD38) and cluster-8 (a subset of CD8⁺Tnaive-like expressing TIM3 and CD38) after Tal treatment compared to baseline.
- A significant increase in cluster-11 (B) and cluster-8 (C) cell populations at C1D3 compared to baseline.

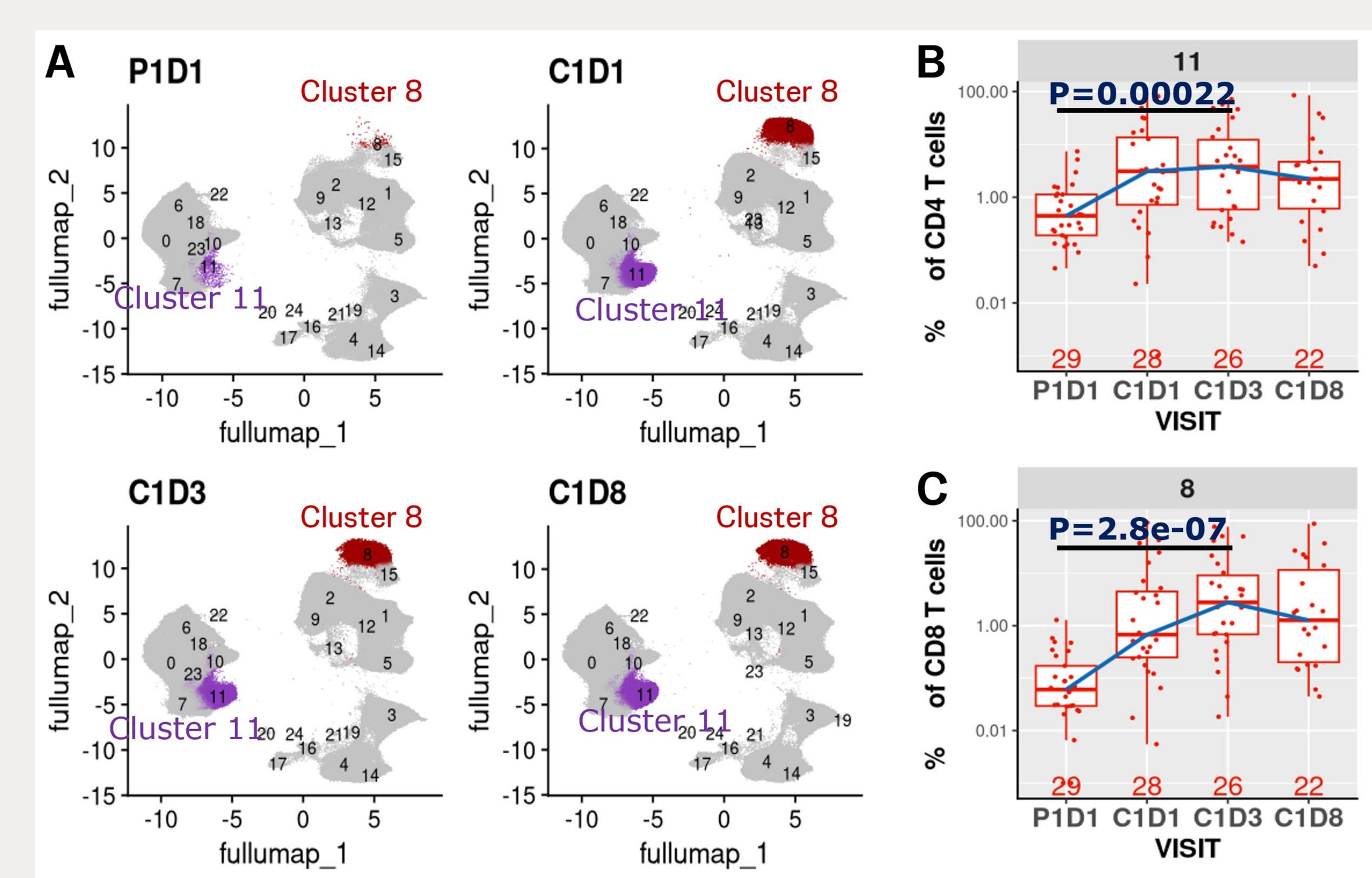


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Figure 7. Sustained higher proportion of a subset of CD4⁺Tnaive-like expressing TIM3 and CD38 observed in non-responders at C3D1

- Trends indicated higher baseline of the CD4⁺Tnaive-like subset expressing TIM3 and CD38 (cluster-11, A) and the CD8⁺Tnaive-like subset expressing TIM3 and CD38 (cluster-8, B) in non-responders.
- Cluster-11 population was more prevalent in non-responders at C3D1 (C-D), with a significant increase (p=0.018, E) compared to responders, despite the limited sample size.

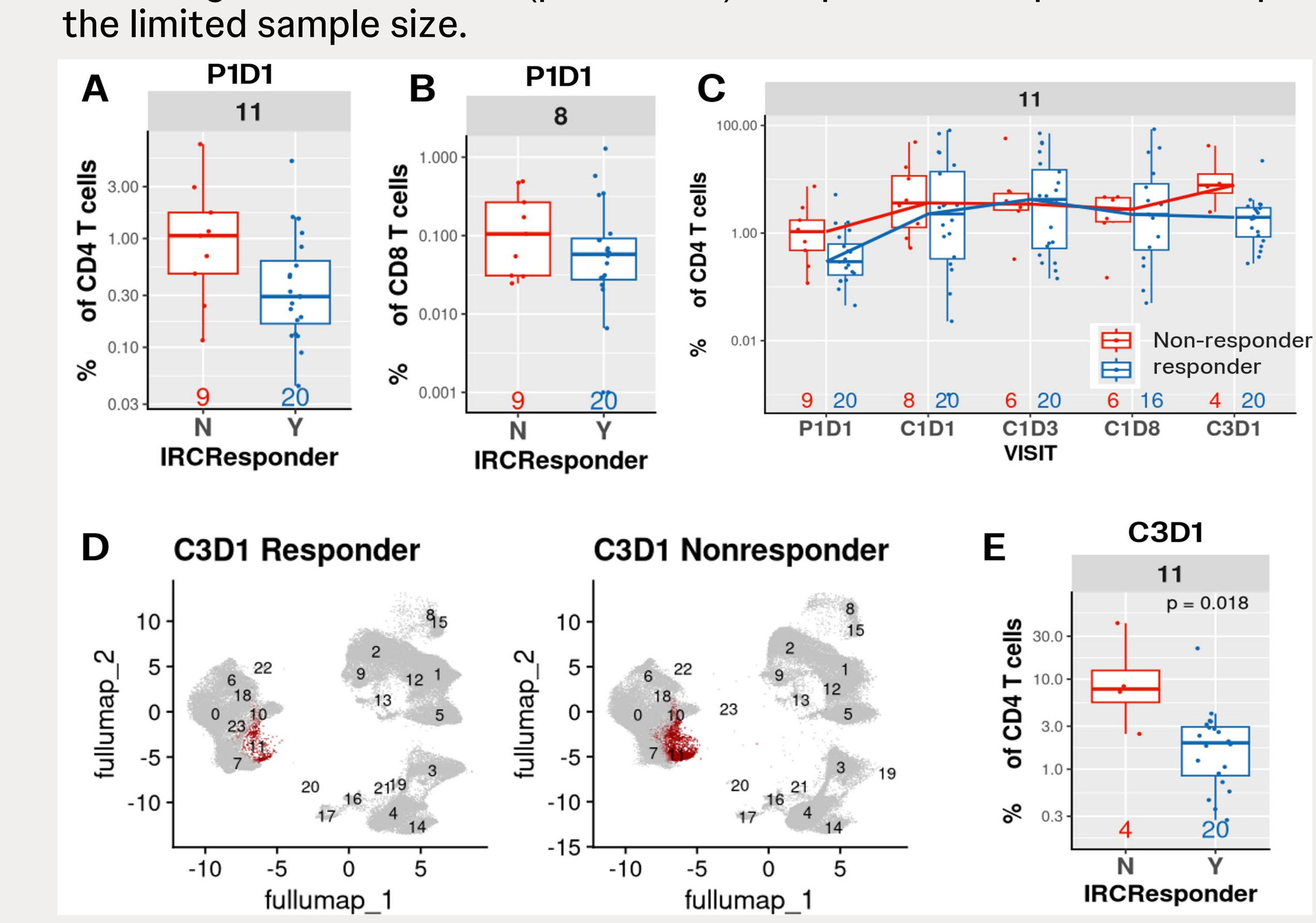

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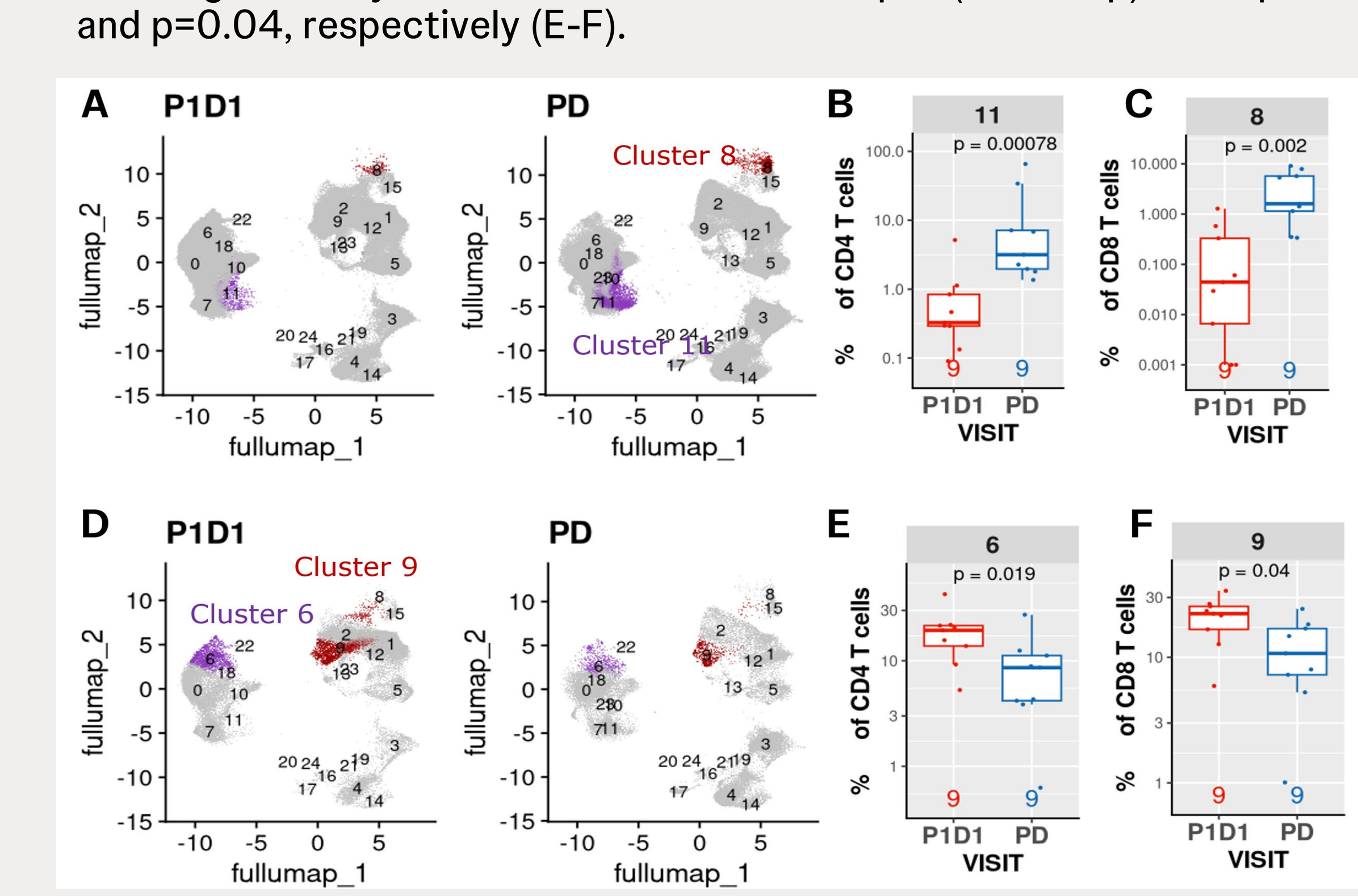
Figure 8. The subsets of CD4⁺Tnaive-like expressing TIM3 and CD38 (cluster-11) as well as the CD8⁺Tnaive-like expressing TIM3 and CD38 (cluster-8) associated with Tal relapse

- The cluster-11 and cluster-8 were significantly elevated in relapsed patients as shown by the U-map (A), with p=0.00078 and p=0.0033, respectively (B-C), compared to baseline.
- In contrast, the CD4⁺Tem-like (cluster-6) and CD8⁺Tcm-like (cluster-9) populations, which exhibited low levels of TIM3 and CD38 expression, were significantly reduced at the time of relapse (D, U-map) , with p=0.019 and p=0.04, respectively (E-F).



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Multiple Myeloma

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