

10416 - Immune Escape via Myeloid-Derived Suppressor Cells in Solid Tumor Cancer Patients Treated with Anchored IL-12 (Tolododekin Alfa)

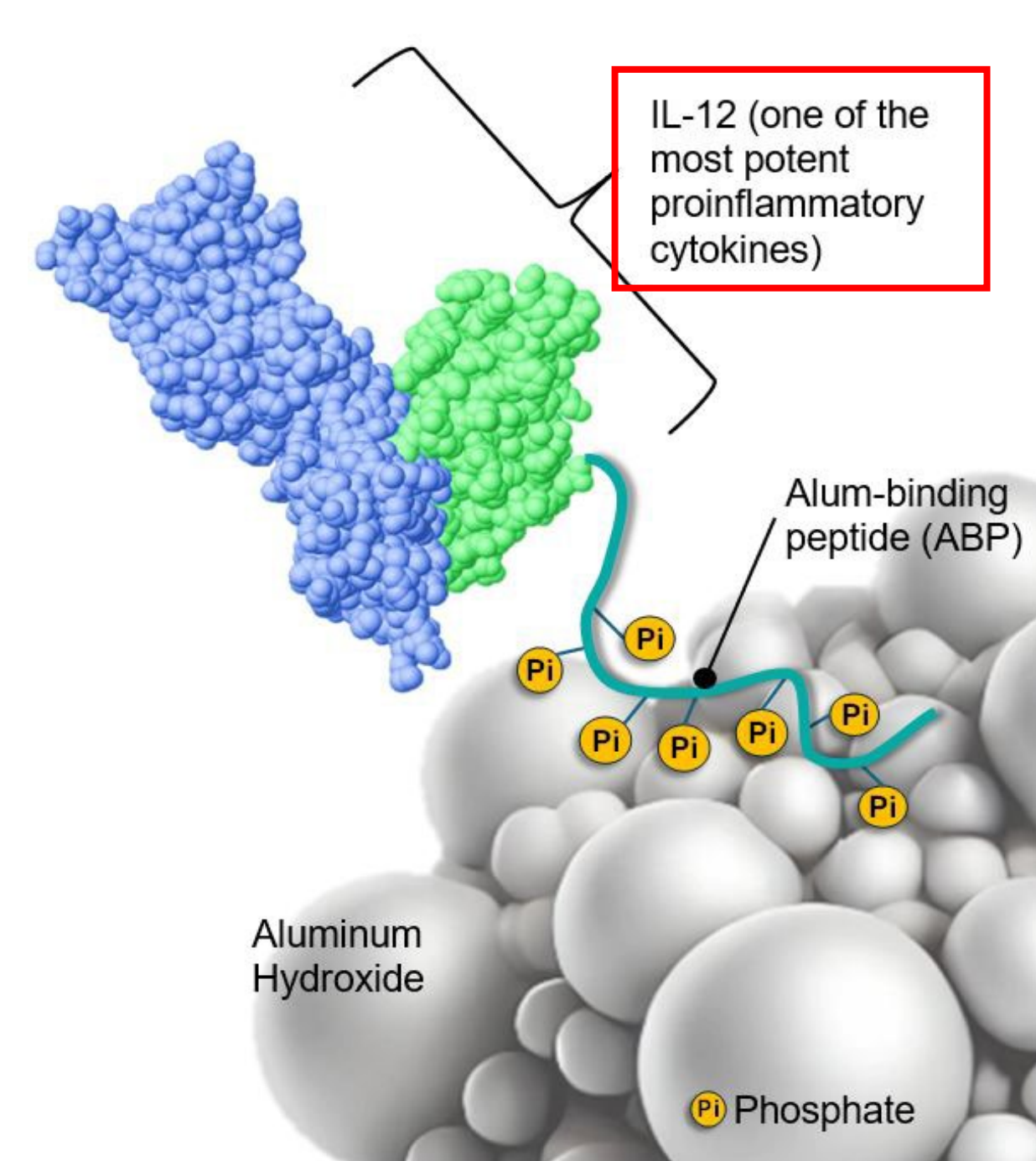
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BACKGROUND

- Tolododekin alfa (ANK-101) is a first-in-class, aluminum-anchored interleukin-12 (IL-12) engineered for prolonged intratumoral retention. In a Phase 1 trial (NCT06171750), patients with accessible advanced solid tumors received intratumoral injections every 3 weeks and demonstrated acceptable safety and biological activity, with 60% achieving disease control and two patients with an objective partial response¹.
- We showed increased CD8⁺ T-cell tumor infiltration and PD-L1 expression increased and were found associated with clinical response to ANK-101 treatment.
- To better characterize mechanisms of response and resistance to ANK-101 monotherapy, we further evaluated intratumoral changes in total as well as subsets of myeloid-derived suppressor cells (MDSCs).

METHODS



- Tolododekin alfa was designed to extend IL-12 anti-tumor activity in tumors and reduce systemic exposure.
- Optimized phosphorylation of alum-binding peptide (ABP) leads to stable anchoring of IL-12.
- It shows potent therapeutic activity after a single dose in multiple murine tumor models.
- It has good safety profile in mice, dogs and non-human primates.

Figure 1: Tolododekin alfa (ANK101) designed by Ankyra therapeutics.

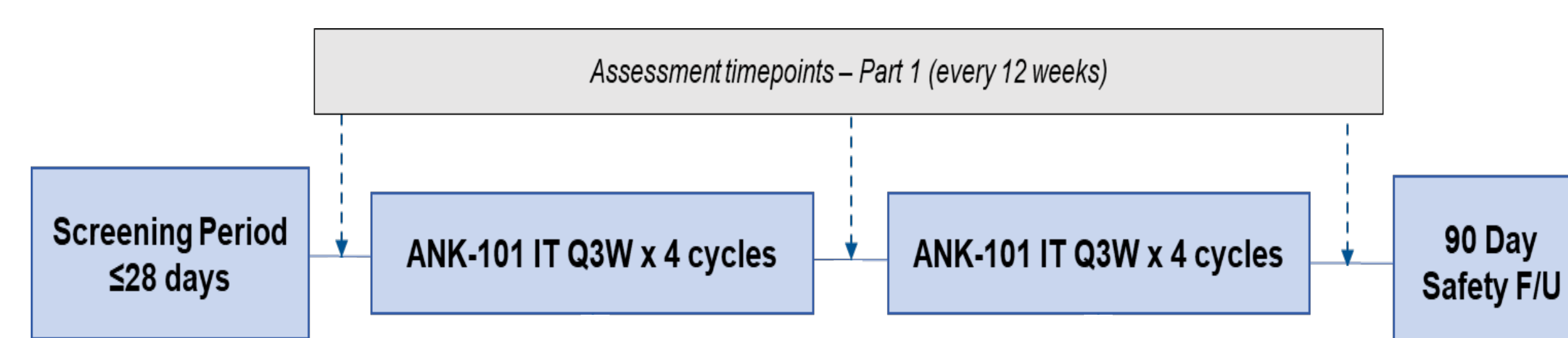


Figure 2: Clinical trial design

- Matched baseline (C1D1) and post-treatment (C2D1, day 21) biopsies from 10 patients with melanoma, head and neck squamous cell carcinoma, breast cancer, or bladder cancer were analyzed.
- FFPE sections underwent immunohistochemistry, multiplex immunofluorescence (CD11b, CD14, CD15, HLA-DR, and CK or S-100), and quantitative pathology to assess CD8⁺ T cells, PD-L1⁺ cells, monocytic MDSCs (M-MDSCs), and polymorphonuclear MDSCs (PMN-MDSCs).
- Nanostring gene expression analysis was performed on mRNA extracted from paired FFPE tumor biopsies following tumor macro-dissection.
- Statistical analysis was done using Wilcoxon matched-pairs signed rank test.

RESULTS

- ANK-101 was detected in some treated samples using IHC.
- IL-12RB2 gene expression was found to be lower in patients with PD.

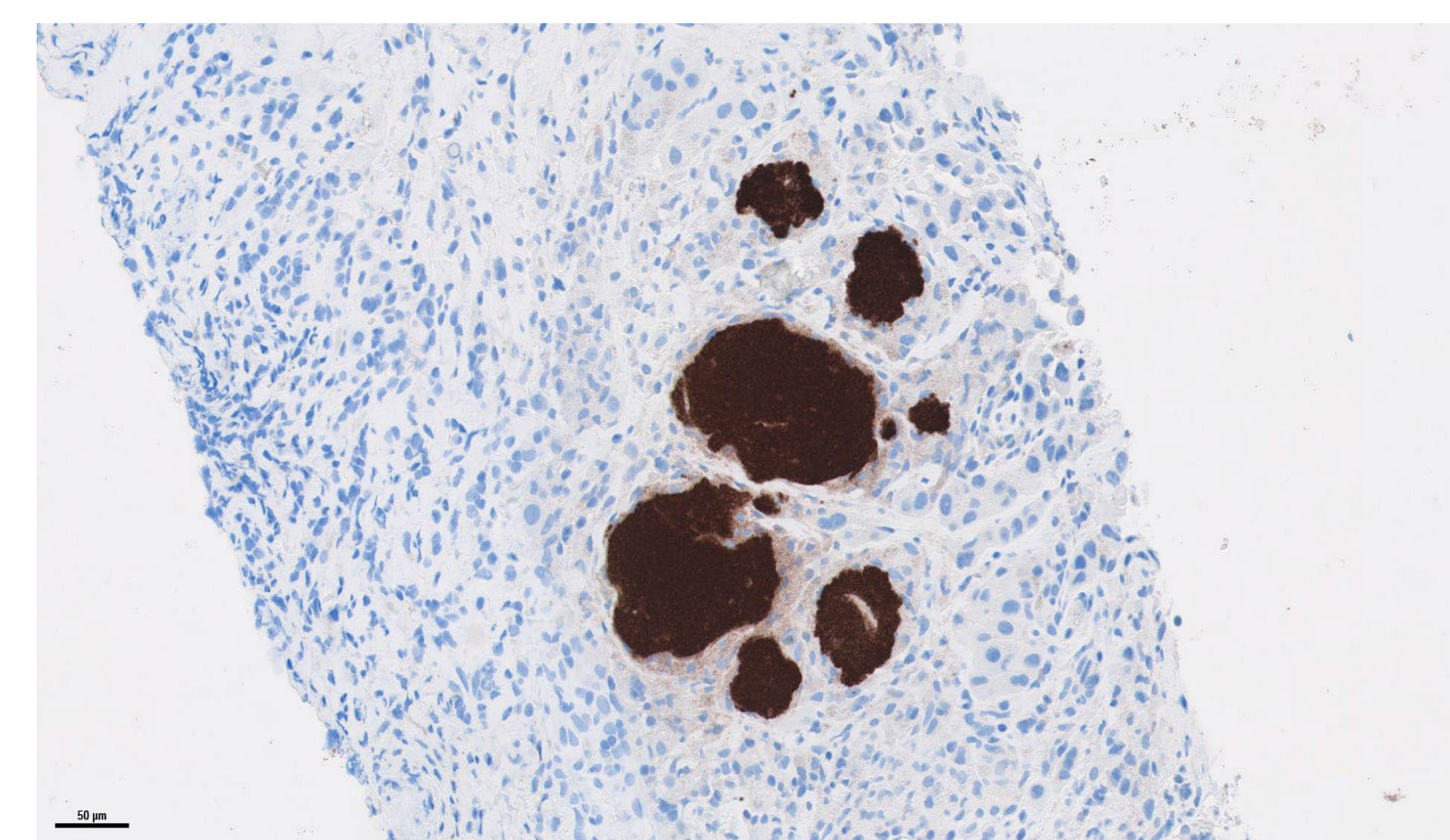
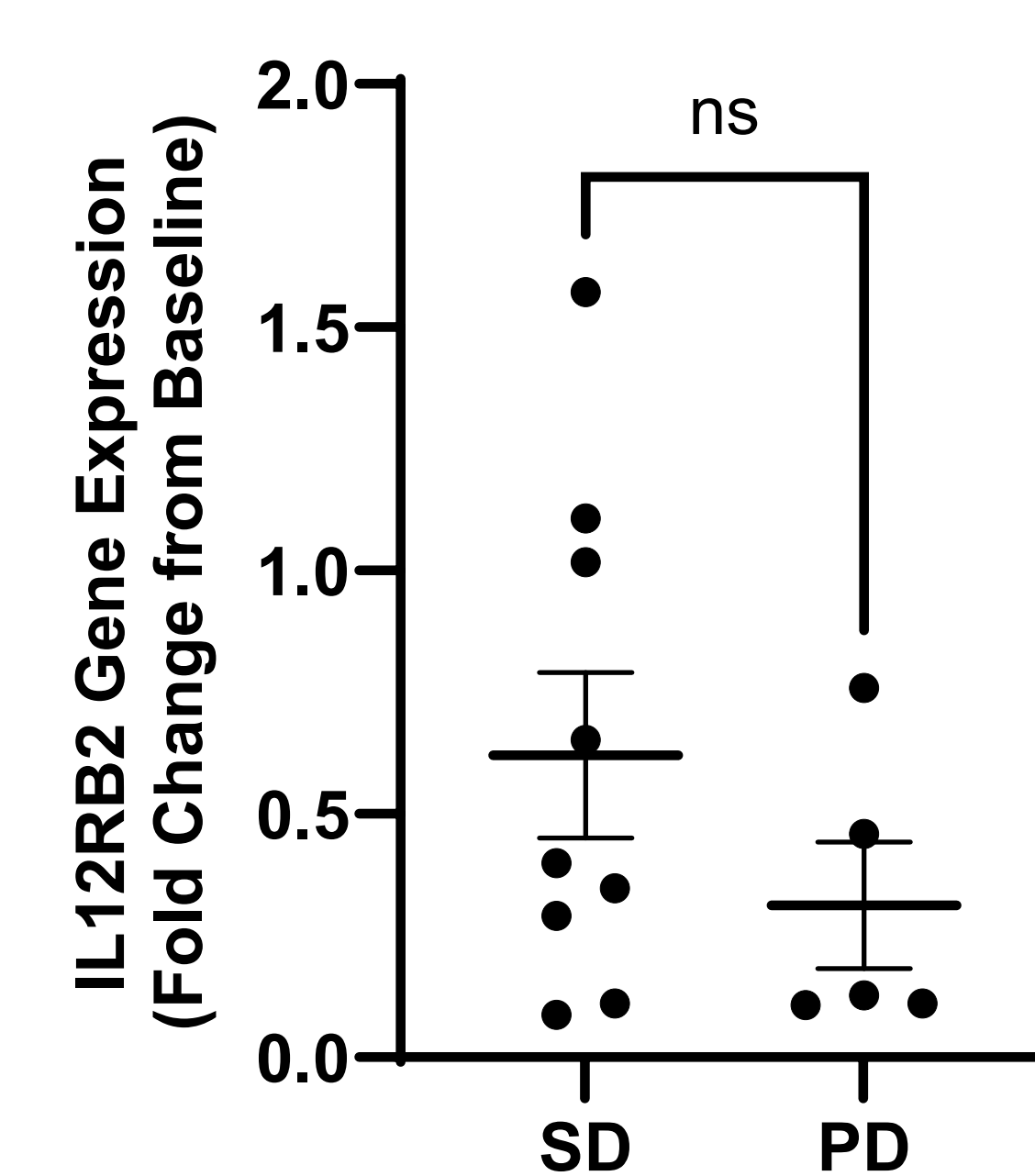
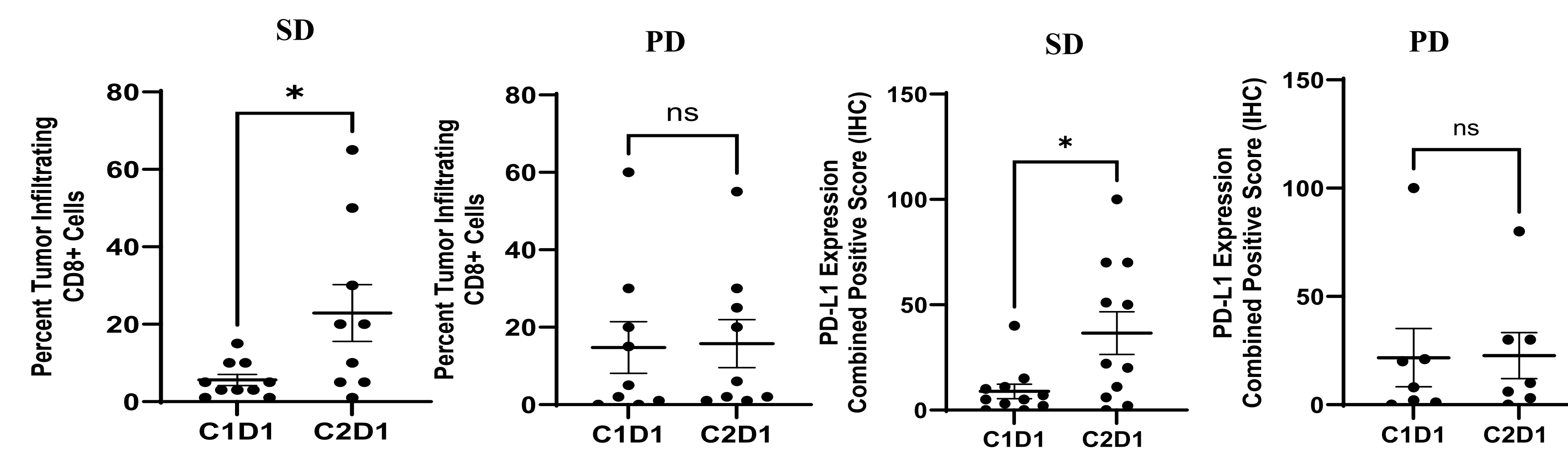


Figure 3: Representative image (40x) showing ANK101-IHC staining in a treated melanoma sample, using an anti-ABP antibody.



- Across all samples, densities of CD8⁺ T-cell and PD-L1⁺ cells increased after 1 cycle of treatment with ANK-101, with more pronounced increases in patients with disease control.



- Total MDSCs increased after ANK-101 by a significant expansion of M-MDSCs while PMN-MDSCs remained stable.

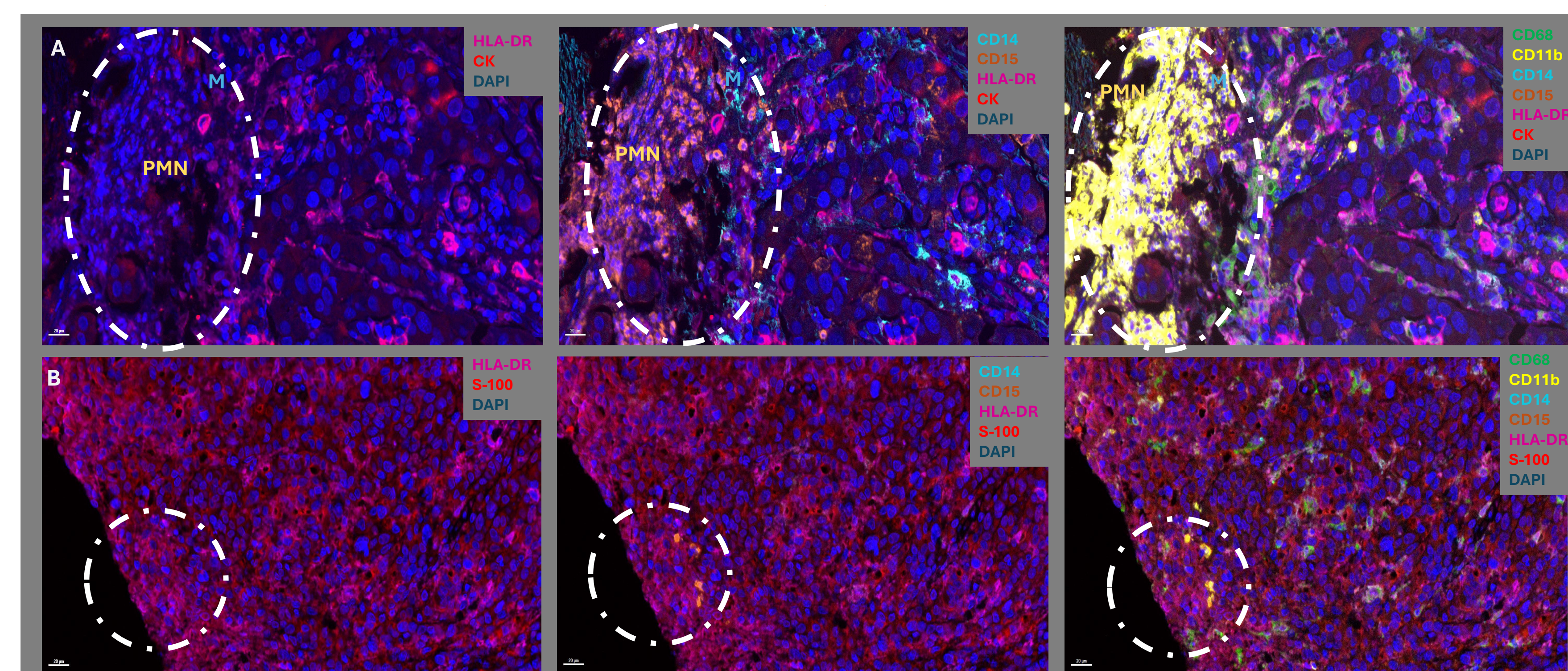
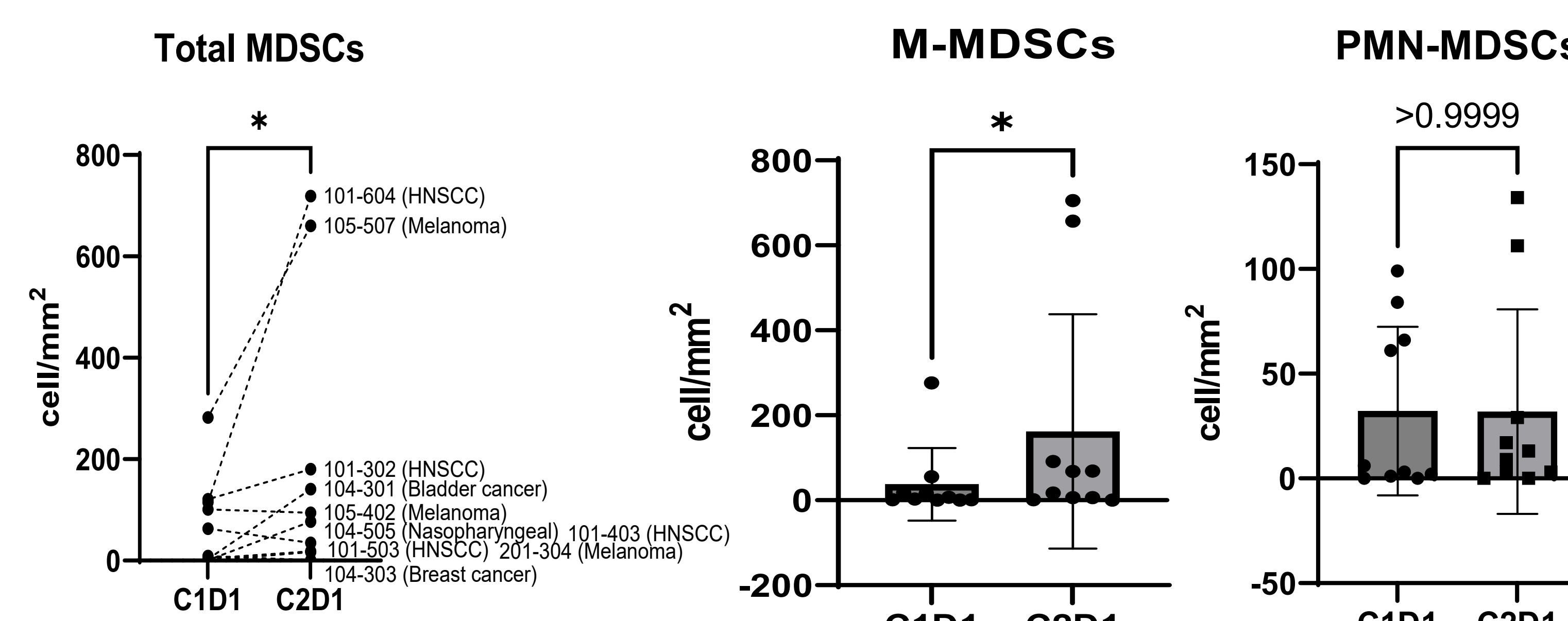
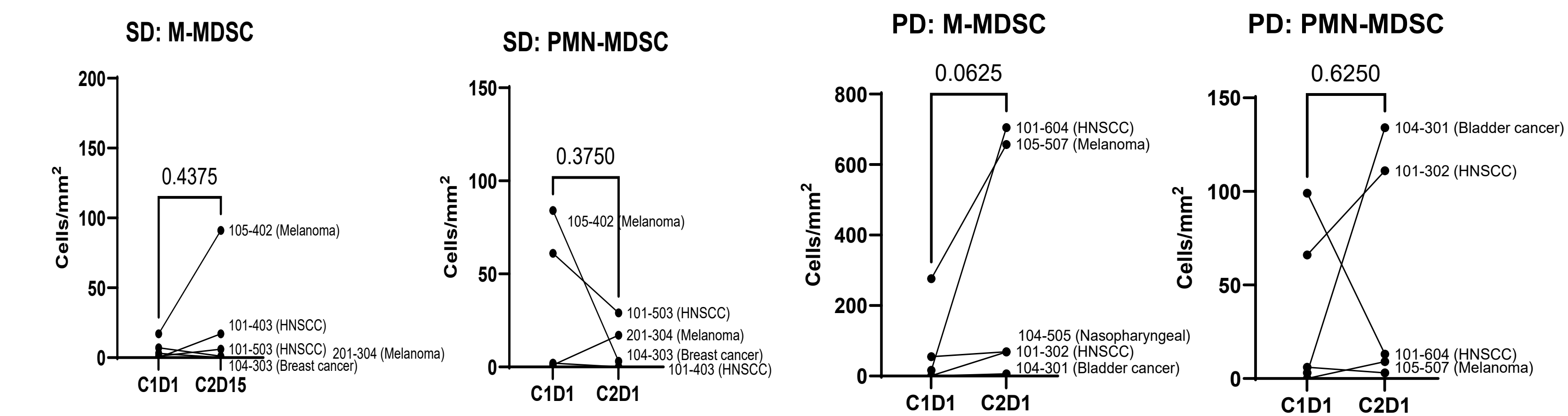


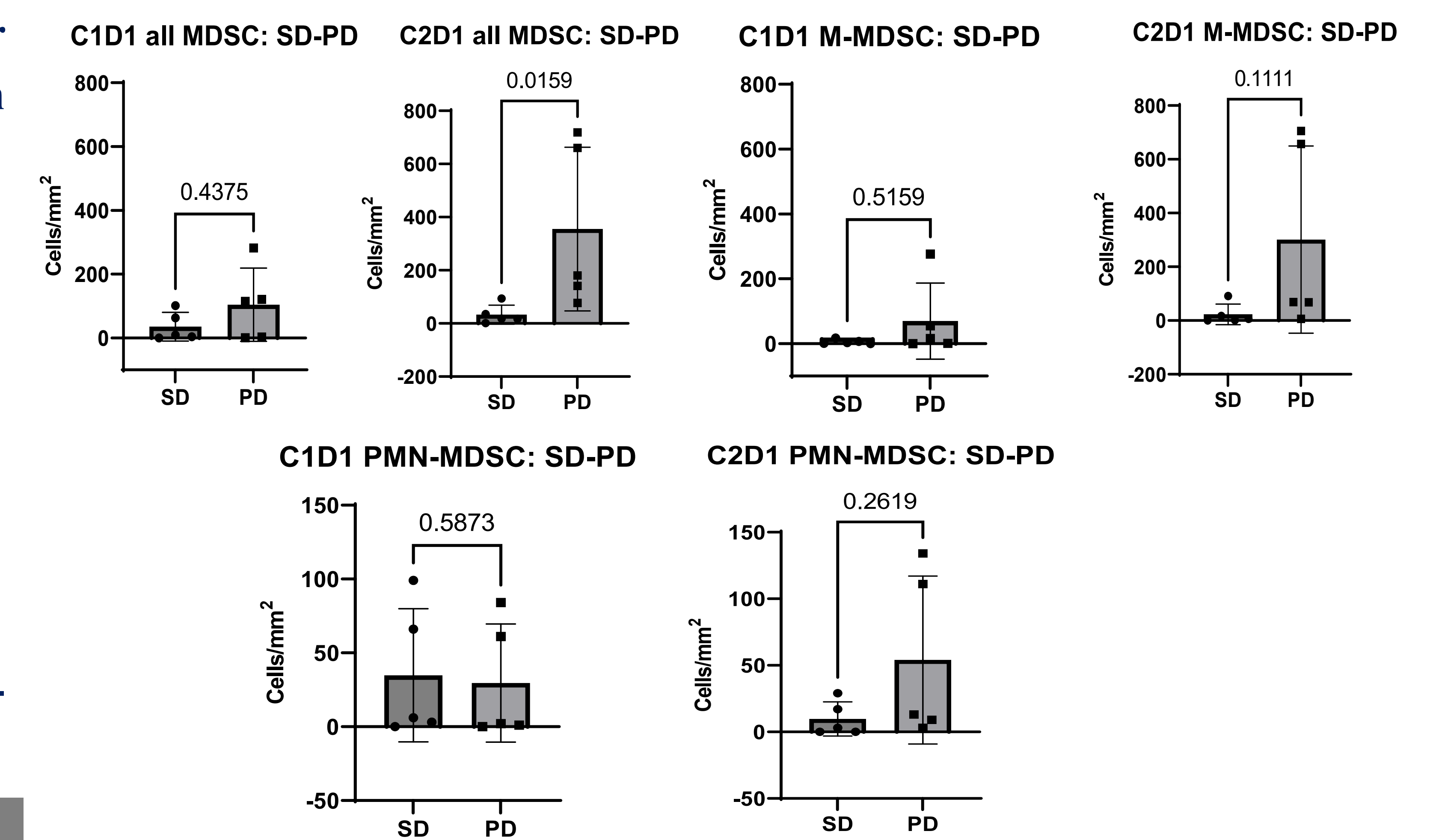
Figure 4: Representative images of HNSCC tissue (A) and melanoma (B) immuno-stained with Mx-IF panel that includes CD68, CD11b, CD14, CD15, HLA-DR, CK/S-100 and DAPI (40x). Image analysis was performed using inform (Akoya Biosciences). Statistics were done using Prism GraphPad. M-MDSC: CD11b+/CD14+/CD15-/HLA-DR low or neg -- PMN-MDSC: CD11b+/CD14-/CD15+/HLA-DR low or neg



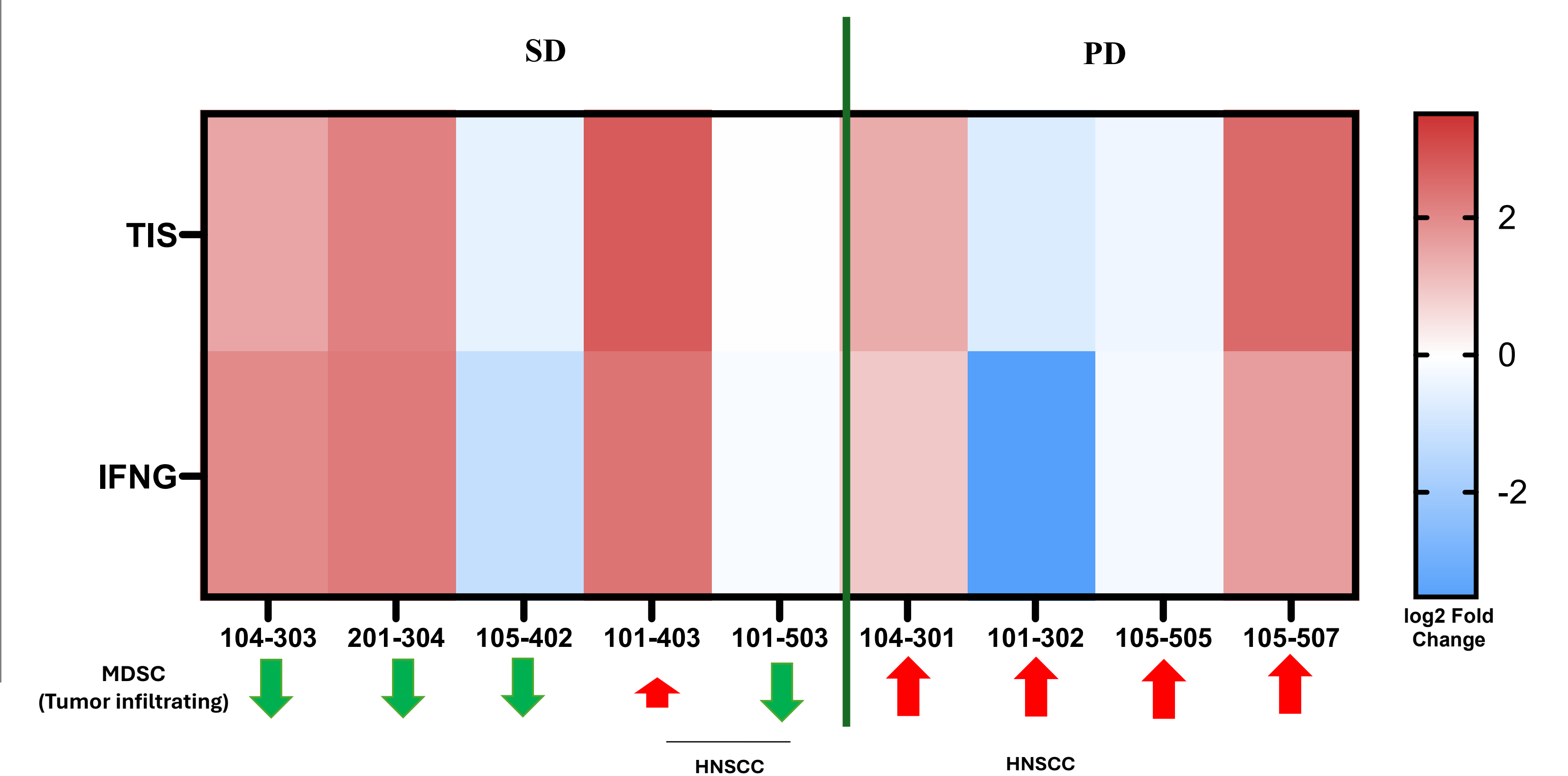
- Patients with SD showed decreased PMN-MDSCs and moderate increases in M-MDSC compared with those with PD.



- Stratification of samples by timepoint and clinical outcome: Total MDSCs was found to be significantly higher in ANK-101 treated patients with PD.



- Transcriptomic analyses showed higher tumor inflammation signature score (TIS) and lower MDSC (4/5) in responding patients.



CONCLUSIONS

Tolododekin alfa promotes intratumoral infiltration of CD8⁺ T cells, more prominently in patients who achieved disease control with anchored IL-12. Conversely, there is a compensatory recruitment of MDSCs, particularly M-MDSCs, in patients with progressive disease. MDSC expansion as a mechanism of immune escape merits additional mechanistic studies to define drivers of MDSC recruitment and inform rational therapeutic combinations.