Peripheral Immune Phenotyping Reveals T Cell Dynamics and Predictors of Immunotherapy Response following TACE in Hepatocellular Carcinoma Patients

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Background:
Transarterial chemoembolization (TACE) is standard for the locoregional therapy of carcinoma (HCC) and works via dual ischemic and direct cytotoxic effects, possibly enhancing immunogenic tumor cell death. Immune Checkpoint Inhibitor (ICI) therapy is now widely used in advanced HCC. In the prospective phase 1b PETAL study, safety and preliminary activity of TACE plus pembrolizumab combination therapy was analyzed. If the TACE anti-PD-1 therapy sequence is connected to changes in the peripheral immune compartment and if they may be connected to therapeutic efficacy, remains unclear.

Methods:
Patients received up to 2 rounds of TACE followed by pembrolizumab (200 mg every 21 days) for up to 1 year. Peripheral blood mononuclear cells (PBMCs) from 20 patients were sampled at key timepoints: screening (pre-TACE), pre-pembrolizumab, cycle 5 of pembrolizumab, and at the end of treatment (EOT). PBMCs were analyzed using mass cytometry by time of flight (CyTOF). 13 patients with known clinical outcome were evaluable for analysis by gating of 30 predefined immune cell populations and an unbiased data-driven clustering pipeline.

Results:
Dynamic changes in immune subpopulations correlated with radiological response at 12 weeks. CD8+ CXCR5-CCR4+CXCR3-CCR6- Tc2 cells with features of precursor exhausted T cells significantly increased at the end of treatment (EOT) compared to

baseline. Screening for predictors of immunotherapy response revealed a significant representation of CD8+ CXCR5-CCR4-CXCR3+CCR6- Tc1 cells in non-responder patients pre-initiation of ICI. At EOT, non-responders exhibited a significant increase in CD3-CD19+ B cells. High-dimensional data analysis revealed 12 distinct T cell subsets, with clusters c07 and c08 connected to patient outcomes. Cluster c08, a TH1-like CD4 T cell subset, was enriched in responders, while c07, an early differentiated memory CD4+ T cell cluster, was enriched in non-responders.

Conclusion:
Our findings suggest that the presence of a TH1-polarized T cell response prior to anti-PD-1 checkpoint therapy is associated with a favorable response. This study provides insights into the immune dynamics of TACE plus pembrolizumab combination therapy, suggesting that monitoring T cell dynamics may serve as a biomarker for efficacy.