COMPREHENSIVE SINGLE CELL SEQUENCING ANALYSIS OF PAIRED TISSUE AND BLOOD SAMPLES FROM HCC PATIENTS TREATED WITH NEOADJUVANT ANTI-PD-1 THERAPY REVEALS TREATMENT-INDUCED CLONAL T CELL DYNAMICS

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Background While immune checkpoint blockade (ICB) therapy has provided benefit to many cancer patients, the characteristics of anti-tumor T cell responses in non-tumor tissues and in circulation are not fully understood. Neoadjuvant ICB therapy provides a unique opportunity to deeply characterize pre- and post-therapy biomarker samples and identify features of drug activity across matched patient tissues. In a single-arm, open label phase 2 study, 21 patients with resectable (stage Ib, II, and IIIb) hepatocellular carcinoma (HCC) were treated with anti-PD-1 antibody, cemiplimab, in the neoadjuvant setting. Patients were treated with two cycles of cemiplimab (350 mg Q3W) prior to resection (median time to resection = 29 days), and 6/21 patients experienced pathologic response to therapy at the time of resection (Responders).

Methods Single cell RNA (scRNA) and T cell receptor (TCR) sequencing were performed on tumor, normal adjacent tissues (NAT), tumor draining lymph node (tdLN), and blood from 20/21 patients at the time of resection. Additionally, blood samples from all patients were analyzed by scRNA- and TCR-sequencing at baseline, during neoadjuvant therapy, at resection, and during adjuvant therapy. The characteristics of all tumor-expanded T cells were compared across tissues and longitudinally in the periphery.

Results We identified several populations of PD-1+ T cells that were enriched in patient tumors compared to other tissues. Responder tumors contained significantly more PD-1+ Effector T cells than Non-responders, and TCR clonality was greater in tumors of Responders. Using TCR sequence as a fingerprint, we tracked tumor TCR clones across tissues, including longitudinal blood samples. Interestingly, NAT and tdLN had more shared T cell clones with the tumors of Responders relative to Non-responders. The most clonally-expanded TCRs identified in Responders’ resection tumors were present in baseline tumor biopsies. Additionally, tumor-expanded TCRs were found to be expanded in the circulation of Responders at baseline and multiple treatment timepoints, including just one week following initiation of anti-PD-1 therapy.

Conclusions Our analyses revealed significant tumor-expanded TCR sharing across the tdLN and NAT at the time of resection in patients who responded to neoadjuvant anti-PD-1 therapy. These clones were present in tumors at baseline, indicating that pre-existing T cell clones expanded in response to treatment and were also more expanded in circulation of Responders as early as one week into therapy. Our study suggests that tumor-expanded T cells are frequently found in the periphery, and peripheral expansion might correlate with response to neoadjuvant anti-PD-1 therapy.

Trial Registration NCT03916627

REFERENCE


Ethics Approval The study protocol and all amendments (available in the appendix pp 10–261) were approved by the institutional review board at Mount Sinai Hospital, and the study was done in accordance with the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines. All patients provided written informed consent before enrolment.