Abstract

T cells targeting neoepitopes derived from mutations exclusive to the tumor are one of the main drivers of cancer immunotherapy efficacy. Tracking these neoepitope (neo)-specific T cells during cancer immunotherapy has been hampered by the impracticality of repeated sampling from the tumor, and by the low frequency of neo-specific T cells in peripheral blood. An ultra-sensitive and high-throughput technology (imPACT™) has been developed for the identification and isolation of neo-specific T cells from peripheral blood. Subjects with pMMR colorectal cancer (which are not generally responsive to anti-PD1), endometrial adenocarcinoma and other solid tumors were treated with AB122 (anti-PD1 antibody) as part of an ongoing dose-escalation clinical trial to evaluate the safety of the drug. Pre-treatment blood samples were analyzed to identify the baseline repertoire of neo-specific T cells. Evolution of this repertoire during AB122 treatment was monitored to enable correlation of immune phenotyping with clinical outcomes. These data enable us to analyze T cells targeting neoEs and identify driver mutations that correlate with, and may be responsible for therapeutic benefit. In addition, monitoring changes of the neo-specific T cell repertoire in response to immunotherapy can inform next steps of treatment. More broadly, this platform technology promises to significantly advance our understanding of T cell-mediated mechanisms of cancer immunotherapy.

Methods

imPACT™ is an isolation technology – Capturing Neo-specific T cells from Patient Blood

imPACT™ technology - ultra-sensitive (i.e. capture neo-specific T cells at frequencies as low as 1 target CD8 T cell per 5M PBMC) and capable of monitoring the dynamics of neo-specific T cell profiles in peripheral blood for patients undergoing immunotherapy.

imPACT technology also assesses the phenotype of neo-specific T cells - informing that these T cells in blood are antigen-experienced & have trafficked to the tumor before.

Longitudinal immune monitoring holds potential to establish when and how patients benefit from treatment.

The robust drug-induced neo-specific T cell expansion in patients (such as that seen with PACT131) could be used to identify pseudo-progressors, which might otherwise be deemed to be non-responders.

Results

Figure 1: Landscape of neo-specific T cells captured from blood of trial subjects using imPACT™. Patients with colorectal cancer (PACT157, long stable disease, left; PACT132, progressive disease, middle) and endometrial adenocarcinoma (PACT131, right) were treated with AB122 (anti-PD1 antibody) as part of an ongoing dose-escalation clinical trial to evaluate the safety of the drug. PBMC were collected at different time points and analyzed by imPACT technology to monitor the on-treatment evolution of mutation-targeted T cell repertoires.

(Top) Longitudinal evolution of neo-specific T cells in peripheral blood during treatment. (Bottom) neoClonality and predicted neo-HLA binding affinity. Green dot indicates a clonal mutation, while red dot indicates a sub-clonal mutation. Please refer to abstract #1995 for additional data of receptor occupancy for these patients.

Figure 2: Phenotype characterization of neo-specific T cells from PACT131. CD8+ T cells are antigen-experienced. CD39+CD103+ positivity suggests that T cells have trafficked through the tumor compartment.

Figure 3: Functional T cell characterization & affinity of 3 TCR clones against the same PWRSA neo target captured from PACT131 blood. T cell cytokine release was detectable against non-cognate neoEs.