

00125 **Discovery of Biomarkers for Clinical Response to Radiotherapy in HCC via Deep Immunoprofiling of Peripheral Blood**

Valerie Chew

Translational Immunology Institute (TII)

Aims: Yttrium-90 (Y90)-radioembolisation (RE) significantly regresses locally advanced hepatocellular carcinoma and delays disease progression. The current study is designed to deeply interrogate the immunological impact of Y90-RE, which elicits a sustained therapeutic response.

Methodology: Time-of-flight mass cytometry and next-generation sequencing (NGS) were used to analyse the immune landscapes of tumour-infiltrating leucocytes (TILs), tumour tissues and peripheral blood mononuclear cells (PBMCs) at different time points before and after Y90-RE.

Result: TILs isolated after Y90-RE exhibited signs of local immune activation: higher expression of granzyme B (GB) and infiltration of CD8+ T cells, CD56+ NK cells and CD8+ CD56+ NKT cells. NGS confirmed the upregulation of genes involved in innate and adaptive immune activation in Y90-RE-treated tumours. Chemotactic pathways involving CCL5 and CXCL16 correlated with the recruitment of activated GB+CD8+ T cells to the Y90-RE-treated tumours. When comparing PBMCs before and after Y90-RE, we observed an increase in tumour necrosis factor- α on both the CD8+ and CD4+ T cells as well as an increase in percentage of antigen-presenting cells after Y90-RE, implying a systemic immune activation. Interestingly, a high percentage of PD-1+/Tim-3+CD8+ T cells co-expressing the homing receptors CCR5 and CXCR6 denoted Y90-RE responders. A prediction model was also built to identify sustained responders to Y90-RE based on the immune profiles from pre-treatment PBMCs.

Conclusion: High-dimensional analysis of tumour and systemic immune landscapes identified local and systemic immune activation that corresponded to the sustained response to Y90-RE. Potential biomarkers associated with a positive clinical response were identified and a prediction model was built to identify sustained responders prior to treatment.