Project title: An artificial intelligence-based approach to identify immunologic predictors of outcome to immunotherapy in hepatocellular cancer using digital pathology.

Project Summary: Immune checkpoint inhibitors (ICI) improve outcomes in hepatocellular carcinoma (HCC), a highly lethal tumour with a <20% 5-year survival. Atezolizumab plus bevacizumab (A+B) ICI combination has revolutionised management of HCC by affording a median overall survival (OS) of 19.2 months. However, <30% of patients respond. High costs, heterogeneity in response and risk of life-threatening toxicity from treatment limit clinical benefit. While no available tissue biomarker can identify ICI responders, evidence suggests that ICI benefit is particularly enhanced in 20-30% of HCC patients harbouring a spontaneously immunogenic tumour microenvironment (TME), characterised by high T-cell infiltration.

Using machine-learning of routine hematoxylin and eosin (H&E)-stained images, we have developed an AI-based computational pathology pipeline reflective of Tumour Infiltrating Lymphocyte (TILs) and Tertiary Lymphoid Structure (TLS) enrichment as predictor of outcome in lung cancer (Rakaee M, JAMA Oncol 2022). Preliminary experiments in 102 A+B recipients with HCC demonstrated TIL-high patients (n=67) to achieve significantly longer OS compared to TIL-low: 20.9 (95%CI: 13.8-27.9) vs. 15.3 months, (6.0-24.6, p=0.026), with TIL status remaining a strong independent multivariable predictor (aHR: 2.02, 95%CI: 1.03-3.96, p=0.040).

The experimental plan will satisfy the following primary objectives:
1) To evaluate the capacity of the pre-optimised AI-based model to provide an accurate estimate of TILs and TLS in digital HCC tissue sections and to identify characteristics of T-cell exhaustion using paired immunohistochemistry and targeted transcriptomics.
2) To evaluate the predictive ability of AI-based measurement of TILs and TLS in estimating overall response rates (ORR), progression-free (PFS) and overall survival (OS) in a cohort of □100 patients treated with standard of care atezolizumab plus bevacizumab combination immunotherapy in HCC (AB-real study).
3) To externally validate the association between the AI-based TIL and TLS models and clinical outcomes in: A. An independent cohort of patients treated with A+B in routine clinical practice (USA, Europe n=□100) B. The IMBrave150 sample cohort to determine true predictive value by analysing A+B versus sorafenib (Zhu A, Nat Med. 2022.Aug;28(8):1599-1611).

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