

## Editorial Note on NASH limits Anti-Tumour Surveillance Treated HCC

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Hepatocellular carcinoma (HCC) can have viral or non-viral causes. Non-alcoholic steatohepatitis (NASH) is a crucial driver of HCC. Immunotherapy has been approved for treating HCC, but biomarker-based stratification of patients for optimal response to therapy is an unmet need. Here we report the progressive accumulation of exhausted, unconventionally activated CD8+PD1+ T cells in NASH-affected livers. In preclinical models of NASH-induced HCC, therapeutic immunotherapy targeted at programmed death-1 (PD1) expanded activated CD8+PD1+ T cells within tumours but didn't cause tumour regression, which indicates that tumour immune surveillance was impaired.

Potentially curative treatments for HCC, like liver transplantation, tumour resection, or ablation, are limited to early-stage tumours. Multikinase inhibitors and anti-VEGF-R2 antibodies are approved to be used in advanced HCC. Immunotherapy, which is assumed to activate T cells or reinvigorate immune surveillance against cancer, showed response rates of 15–30% in patients with HCC. Nivolumab and pembrolizumab (PD1-directed antibodies) are approved for treatment of HCC<sup>3,4</sup>, although phase III clinical trials did not reach their primary endpoints to extend survival. A mixture of atezolizumab (anti-PDL1) and bevacizumab (anti-VEGF) demonstrated increased overall and progression-free survival during a phase III clinical trial, making it a first-line treatment for advanced HCC<sup>5</sup>. The efficacy of immunotherapy could be suffering from different underlying HCC aetiologies, with diverse hepatic environments distinctly regulating HCC induction and immune responses. Hence, we lack biomarkers that correlate with treatment response to permit patient stratification. Non-alcoholic liver disease (NAFLD) is an HCC-causing condition that affects quite 200 million people worldwide<sup>14</sup>. Approximately 10–20% of people with NAFLD progress over time from steatosis to NASH. Innate and adaptive immune-cell activation together with increased metabolites and endoplasmic reticulum stress are believed to steer to a cycle of hepatic necro-inflammation and regeneration that potentially results in HCC. NASH has become an emerging risk factor for HCC, which led us to research the consequences of

immunotherapy in NASH–HCC.

To investigate the mechanisms that drive the increased NASH–HCC transition within the preventive anti-PD1 treatment-setting, we treated NASH-affected mice with combinations of treatments. Both anti-CD8–anti-PD1 and anti-TNF–anti-PD1 antibody treatments ameliorated liver damage, liver pathology and liver inflammation and decreased the incidence of cancer of the liver compared to anti-PD1 treatment alone. Against this anti-CD4–anti-PD1 treatment didn't reduce the incidence of cancer of the liver, the NAFLD activity score (NAS), or the amount of TNF-expressing hepatic CD8+ or CD8+PD1+CXCR6+ T cells. However, both the amount of tumours per liver and tumour size were reduced, suggesting that depletion of CD4+ T cells or regulatory T cells might contribute to tumour control (Extended Data Fig. 8a, b). The incidence of tumours was directly correlated with anti-PD1 treatment, alanine aminotransferase (ALT), NAS, number of hepatic CD8+PD1+ T cells, and TNF. Extended Data Fig. 8c suggested that CD8+PD1+ T cells lacked immune-surveillance and had tissue-damaging functions<sup>27</sup>, which were increased by anti-PD1 treatment, possibly contributing to the unfavourable effects of anti-PD1 treatment on HCC development in NASH.

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