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CORRELATES OF POOR RESPONSE TO NEOADJUVANT ANTI-PD-1 THERAPY IN HEPATOCELLULAR CARCINOMA (HCC) INCLUDE WNT PATHWAY ACTIVATION AND LOSS OF HLA EXPRESSION

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Background Although anti-PD-1/PD-L1 therapy has improved patient outcomes in the past decade, only a subset of patients shows clinical benefit.¹ Furthermore, many responders develop acquired resistance after initial responses.² Therefore, understanding baseline correlates of response and mechanisms of resistance is necessary for improving anti-PD-1/PD-L1 efficacy. In a neoadjuvant Phase 2 study (NCT03916627), patients with resectable hepatocellular carcinoma (HCC) were treated with cemiplimab, a PD-1 antibody. Pathologic Tumor Necrosis (PTN) of at least 50% at resection was used as the exploratory endpoint. Here we review possible biomarkers to identify responders and explore potential underlying mechanisms of resistance.

Methods Tumor samples collected at baseline and time of resection were analyzed by multiplex immunohistochemistry. Nucleic acid isolates from tumor, adjacent normal tissue, and matched blood were analyzed by RNA and whole exome DNA sequencing. OptiType was used to infer HLA haplotype. Loss of heterozygosity (LOH) was calculated by a custom workflow.

Results At baseline, higher levels of tumor-infiltrating T cells were present in Responders with PTN (N=5) compared with Non-responders to cemiplimab (N=15). The trend was consistent and amplified when measured at resection. However, clinical responses were also observed in patients with low levels of baseline T cell infiltration. Clinical efficacy was associated with presence of HLA-A*24:02 allele (N=5; 4 Responders and 1 Non-responder). Response to cemiplimab was independent of baseline tumor mutation burden, underlying viral etiology, or PD-L1 expression in the tumor. WNT pathway activating mutations, a previously reported mechanism of immunotherapy resistance,³ were enriched in Non-responders (6 Non-responders vs. 1 Responder; mutations in 4 baseline and 5 resection samples) and correlated with low CD8 T cell infiltration at baseline and low CD8 and CD4 T cell infiltration at resection. Loss of WNT pathway mutations were observed on treatment in one Responder and one Non-responder. The Responder displayed LOH at the HLA locus during treatment and subsequently relapsed. On-treatment acquired WNT pathway mutations were identified in 3 out of 7 patients that relapsed.

Conclusions Preliminary analyses suggest that high levels of baseline tumor-infiltrating T cells is associated with clinical response to cemiplimab in HCC. The presence of WNT pathway activating mutations is indicative of low T cell infiltration and may be a potential negative predictor of clinical benefit with cemiplimab. One patient showed LOH at the HLA locus associated with clinical progression, suggesting potential alternative disease escape. Additional mechanisms of resistance are under investigation.

Trial Registration ClinicalTrials.gov identifier (NCT number): NCT03916627

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Ethics Approval Samples were obtained from specimens of patients undergoing resection at Mount Sinai Hospital (New York, NY) after obtaining informed consent in accordance with a protocol reviewed and approved by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai (RUTH Human Subjects Electronic Submission System 18-00407 and 20-04150) and in collaboration with the Biorepository and Department of Pathology.

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