844 COMBINED IMMUNOTHERAPY EFFICACY ON A MULTIFOCAL HEPATOCELLULAR CARCINOMA MODEL BASED ON HYDRODYNAMIC ONCOGENE TRANSFER

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Background Immunotherapy based on checkpoints inhibitors has become a conventional treatment of advanced hepatocellular carcinoma (HCC) and is under clinical investigation as a strategy to improve the efficacy of locoregional interventions such as transarterial chemoembolization and radiofrequency. In advanced disease, the combination of nivolumab and ipilimumab has resulted in more frequent and durable objective responses as compared to nivolumab monotherapy. Important aspects are pending for these developments, such as reliable and predictive preclinical models, as well as biomarker discovery.

Methods A model based on mice bearing multifocal HCC as a result of hydrodynamic gene transfer to hepatocytes of c-myc and CRISPR/CAS9 disruption of p53 was used. This model was sophisticated to induce coexpression of luciferase, EGFP and the melanosomal antigen gp100 to permit incisive immunological mechanistic experimentation. This genetic approach attains traceability of the tumor and sufficient levels of antigenicity in order to test immunotherapy agents such as anti-CTLA-4, antiPD-1 and anti-CD137 monoclonal antibodies, IL-2 or adoptive Pmel-1 $CD8^+$ T cell therapy and their combinations. Survival assays, as well as multiplex immunofluorescence and intravital microscopy were performed to study the efficacy and mechanism of action of the therapies.

Results In this tumor setting, combinations of anti-CTLA-4 + anti-PD1 mAbs attained partial efficacy that was markedly augmented by combination with either recombinant IL-2 or an anti-CD137 mAb to deploy triplet regimens. As shown by multiplex tissue immunofluorescence and intravital microscopy, treatments enhanced T-cell infiltration and antitumor immune responses.

Conclusions We provide a relatively simple, reproducible and reliable spontaneous HCC mouse model that enabled us to test various immunotherapies. With it, we have investigated clinically feasible combinatorial regimens including triplets.

Ethics Approval All animal procedures were approved by the animal experimentation ethics committee of the regional government of Navarra (protocol 108-19).

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0844