Conclusions With this set of 7 novel CT-specific TCRs we expand the arsenal of tumor specific TCRs. With this expanding library of TCRs it would be possible to select in future for each cancer patient, based on HLA typing and gene expression, a useful TCR to generate a personalized TCR-gene therapy products. In addition, patients could be treated with multiple TCRs to enhance the efficacy and increase the durability of clinical responses by reducing the likelihood of tumor escape.


Poster Presentations

P01 Emerging concepts/new agents

P01.01 SAFETY AND EFFICACY STUDY OF PEMBROLIZUMAB IN COMBINATION WITH LENVATINIB IN PARTICIPANTS WITH HEPATOCELLULAR CARCINOMA (HCC) BEFORE LIVER TRANSPLANT AS NEOADJUVANT THERAPY — PLENTY RANDOMIZED CLINICAL TRIAL

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Background Patients with hepatocellular carcinoma (HCC) who exceed standard Milan criteria suffered from high post-transplant recurrence rate. This study will evaluate the safety and efficacy of pembrolizumab in combination with lenvatinib as neoadjuvant therapy in participants with HCC exceeding Milan criteria before liver transplant.

Materials and Methods Participants would be randomly assigned (1:1) to experimental or Comparator/Control by computer-generated allocation based on the envelope method and the hierarchical block randomization method (hierarchy: BCLC stage and AFP level). The envelopes are sealed opaque, and sequentially numbered. Randomization is performed by the trial coordinator. The random number table and the block assignment number table will be kept confidential by the full-time secretary of this project. Center-stratified block-permutated randomization is used in this trial. Then permuted block randomization is used for each stratum with a block size of 4.

Results The first initial patient was recruited in August 2020, the primary hypothesis of this study are that neoadjuvant pembrolizumab plus lenvatinib is superior to regularly waiting in the list with respect to: 1) recurrence-free survival (RFS) as assessed by blinded independent central review (BICR); and 2) Objective Response Rate (ORR). The investigators design a clinical study to explore whether the combination above as a neoadjuvant treatment in patients with advanced HCC before liver transplant could reduce postoperative recurrence and to analyze potential immune biomarker of therapeutic response.

Conclusions The study is still ongoing and the preliminary short-term outcome was positive. HCC patients who exceeded milan criteria may benefit from neoadjuvant immunotherapy combined with TKI before liver transplantation.

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TARGETING DIACLYGLYCEROL KINASE ALPHA AND ZETA BY SELF DELIVERING RNAI TO OPTIMIZE TLYMPHOCYTES FOR ADOPTIVE THERAPY OF SOLID TUMORS

Background Evidence indicates that diacylglycerol kinases (DGKs) are promising targets for the optimization of T cell activity, for example in the setting of adoptive cell therapy (ACT). The tumor microenvironment (TME) of human renal cell carcinoma (RCC) is an immunosuppressive setting where T and NK cell functionality is blocked. DGK-α is a negative regulator of TCR signaling, functioning by metabolizing diacylglycerol to phosphatidic acid and thereby limiting the activation of MAPK/ERK1/2 signaling pathway. DGK-α is found increased in tumor-infiltrating lymphocytes (TIL) from RCC patients and also in adoptively transferred T cells after infiltrating into the TME. We previously reported that inhibition of DGK-α restored functionality of unresponsive CD8 T cells and NK cells from RCC-TIL. Other studies demonstrated that knockdown or pharmacologic inhibition of DGK-α and DGK-ζ alone or together increased target cell killing and cytokine production, and protected T cells from inhibitory factors in the TME. However, there are no inhibitors for DGK-ζ and available DGK-α inhibitors have undesired pharmacokinetic/pharmacodynamic properties and are highly toxic precluding their clinical application. Here, we present data using a novel RNA interference (RNAi) technology that can specifically target each DGK isoform.

Materials and Methods INTASYL™ compounds incorporate drug-like properties into RNAi, resulting not only in enhanced cellular uptake in the presence of serum but also eliminating the need for further transfection reagents. Toxicity of compounds applied alone or in combination was assessed by 7-AAD flow cytometry analysis and WST assay. Silencing of mRNA and protein was analyzed by RT-qPCR and SimpleWestern. Downstream signaling pathways and T cell function were analyzed to demonstrate pharmacological efficacy.

Results Two DGK-ζ compounds and one DGK-α compound were analyzed using Jurkat T cells and primary human TCR-transduced T cells. No effects were seen on cell viability for the compounds applied alone or in combination. On-target knockdown was achieved in Jurkat T cells evidenced by RT-qPCR and SimpleWestern. Silencing of mRNA and protein occurred quickly after 24h, peaked between 48h and 72h and lasted at least for 96h. Stimulation under DGK-targeting INTASYL treatment resulted in enhanced levels of phosphorylated ERK1/2 and enhanced secretion of IL-2.

Conclusions INTASYL™ self-delivering RNAi compounds represent a promising approach to target intracellular immune checkpoints such as DGKs. The good toxicity profile allows for combined application of several compounds enabling targeting of multiple checkpoints, which likely is necessary to counteract the complex and heterogeneous inhibitory influences of the TME. The technology enables the anti-tumor activity of T and NK cells for immunotherapy, and can be used in ACT and direct therapeutic applications towards the TME.

REFERENCES


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