A PHASE 1B KEYNOTE-B79 TRIAL EVALUATING NON-GENE EDITED ALLOGENEIC CAR T-CELLS, CYAD-101, POST FOLFOX PRECONDITIONING, FOLLOWED BY PEMBROLIZUMAB, IN REFRACTORY METASTATIC COLORECTAL CANCER PATIENTS

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Background The peptide-based allogeneic chimeric antigen receptor (CAR) T-cell treatment CYAD-101 utilizes an NKG2D receptor that targets eight ligands expressed on tumor cells and non-malignant stromal cells of many cancer types. CYAD-101 also co-expresses a peptide intended to eliminate the potential of graft versus host disease (GvHD). In the phase 1 alloSHRINK study (NCT03692429), CYAD-101 was administered with FOLFOX preconditioning chemotherapy to 15 patients with metastatic colorectal cancer (mCRC). The treatment was well tolerated with no evidence of GvHD, no treatment-related adverse events $\geq$ Grade 3 and only two patients who presented a cytokine release syndrome grade 1. By contrast, encouraging clinical activity was observed including two partial responses. Evidence of changes in the TCR repertoire and modulation of the cytokine profile four months post-treatment with CYAD-101 were also observed implying that the NKG2D CAR T may also be modulating the immune suppressive environment in patients reflecting that seen in pre-clinical models (ASCO GI 2021 abstract #74). Given the expansion of the T cell repertoire after CYAD-101 therapy, we considered that employing a checkpoint inhibitor to release this expanded T cell population may drive more durable clinical responses beyond that currently seen with the CAR T alone.

Methods The KEYNOTE-B79 trial evaluates the safety and clinical activity of multiple infusions of CYAD-101, administered post FOLFOX preconditioning chemotherapy, then followed three weeks after CYAD-101 by a pembrolizumab consolidation treatment (200 mg every three weeks for a maximum two years total treatment duration) in microsatellite stable/mismatch-repair proficient mCRC patients with recurrent/progressing disease after at least one metastatic line of therapy which must include FOLFOX chemotherapy. The schedule of administration of three CYAD-101 infusions at the dose 1×10^9 cells/infusion Q2W post-FOLFOX preconditioning chemotherapy are based on the alloSHRINK study. This sequencing of checkpoint inhibitor at a timepoint after CYAD-101 therapy ensures that the modulated endogenous immune response is enabled by pembrolizumab. This study is not focused on impacting the CAR T cell itself largely since CYAD-101 cells at the time of manufacture show negligible expression of PD-1 and that this sequencing ensures no overlap of potential toxicities that could arise from the CAR T or checkpoint inhibitor therapies. The KEYNOTE-B79 study is planned to be initiated in Q4-2021.

Ethics Approval The study was approved by all relevant authorities and submitted to Institution's Ethics Boards for their approval before study initiation.

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