of this CKM regimen in a non-randomized, single-arm prospective phase II trial.

**Methods** Eligible patients have recurrent/metastatic unresectable CRC with hepatic metastases that are amenable to biopsy. Enrolled patients have prior treatment with or contra-indication to a fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF treatment, and an anti-EGFR targeted therapy (if RAS wt), as well as a PD-1 or PD-L1 targeted drug if MSI-H/dMMR. Patients receive celecoxib (200 mg orally PO BID), IFNα2b IV (20 million units/m2 IV QD), and rintatolimod (200 mg IV QD) on days 1, 2, 3, 8, 9, 10, 15, 16 and 17 in the absence of disease progression or unacceptable toxicity. Response assessment via liver biopsies (pre-treatment and on D20) and CT imaging (RECIST v1.1) on D46. If stable disease/response is demonstrated during repeat CT imaging, patients will continue to follow-up with CT imaging q8 weeks until progression, clinical deterioration, or withdrawal from the study. Primary endpoint assessment compares the change in CD8+ T-cells before treatment, with that seen post-treatment (measured by quantitative RT-PCR and expressed as a ratio of CD8+ to a housekeeping gene). Secondary endpoints include objective response rate and safety profile. Subjects are monitored continuously for safety, based on Bayesian analysis. Exploratory endpoints include progression-free survival and overall survival. With a sample size of n=12 evaluable pts, the study design has a 90% power to detect a 0.77 standard deviation increase (pre- to post-treatment) at a significance level of 0.1.

**Results** N/A

**Conclusions** N/A

**Trial Registration** ClinicalTrials.gov Identifier: NCT03403634.

**Ethics Approval** The study was approved by Roswell Park Comprehensive Cancer Center’s Institutional Review Board, approval number: MOD000067221/I-52917.

**Consent** N/A

**REFERENCES**


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**335 NOVEL COUPLEDCAR™ TECHNOLOGY FOR TREATING COLORECTAL CANCER**

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**Background** Chimeric antigen receptor (CAR) T cell therapy has made significant progress in the treatment of blood cancers such as leukemia, lymphoma, and myeloma. However, the therapy faces many challenges in treating solid tumors. These challenges include physical barriers, tumor microenvironment immnosuppression, tumor heterogeneity, target specificity, and limited reactive cell expansion in vivo. Conventional CAR T cell therapy has thus far shown weak cell expansion in solid tumor patients and achieved little or no therapeutic responses. Here, we developed CAR T cells based on a novel CoupledCAR® technology to treat solid tumors. In contrast to conventional CAR T cells, CoupledCAR T cells significantly improved the expansion of the CAR T cells in vivo and enhanced the CAR T cells’ migration ability and resistance to immunosuppression by the tumor microenvironment. The enhanced migration ability and resistance allow the CAR T cells to infiltrate to tumor tissue sites and increase anti-tumor activities.

**Methods** We designed a ‘CoupledCAR’ lentivirus vector containing a single-chain variable fragment (scFv) targeting human TSHR. The lentivirus was produced by transfecting HEK-293T cells with ‘CoupledCAR’ lentiviral vectors and viral packaging plasmids. Patient’s CD3 T cells were cultured in X-VIVO medium containing 125U/mL Interleukin-2 (IL-2), and transduced with ‘CoupledCAR’ lentivirus at certain MOI. Transduction efficiency and was evaluated at 7 to 9 days after ‘CoupledCAR’ lentivirus transduction, and quality controls for fungi, bacteria, mycoplasma, chlamydia, and endotoxin were performed. After infusion, serial peripheral blood samples were collected, and the expansion and the cytokine release of CART cells were detected by FACS and QPCR. The evaluation of response level for patients were performed at month 1, month 3, and month 6 by PET/CT.

**Results** Specifically, we engineered CoupledCAR T cells with lentiviral vectors encoding an anti-GCC (guanylate cyclase 2C) CAR molecule. Furthermore, anti-GCC CAR T cells showed anti-tumor activities in vitro and in vivo experiments. To verify the safety and efficacy of CoupledCAR T cells for treating solid tumors, we conducted several clinical trials for different solid tumors, including seven patients with colorectal cancer. These seven patients failed multiple rounds of chemotherapy and radiotherapy. In the clinical trial, the patients were infused with autologous anti-GCC CoupledCAR T cells range from 4.9 × 10^6/ kg to 2.9 × 10^6/ kg. All patients using anti-GCC CoupledCAR T cells showed rapid expansion of CoupledCAR T cells and killing of tumor cells. Specifically, we observed that CoupledCAR T cells expanded significantly in the patients and infiltrated tumor tissue sites, demonstrating enhanced anti-tumor activities. PET/CT showed significant tumor shrinkage and SUV max declined, and the ongoing responses were monitored. Patient 3 achieved complete response and the best overall response rate (ORR, include complete remission, complete metabolic response, partial response, and partial metabolic response) was 71.4% (5/7), complete remission (CR) rate was 14.3% (1/7).

**Conclusions** The clinical data demonstrated that CoupledCAR T cells effectively expanded, infiltrated tumor tissue sites, and kill tumor cells in patients with colorectal cancer. We used immunotherapy to achieve complete remission in patients with advanced colorectal cancer for the first time. We are recruiting more colorectal cancer patients to further test the safety and efficacy of anti-GCC CoupledCAR T cells. Since our CoupledCAR® technology is a platform technology, we are expanding it to treat other solid tumors using different target tumor markers.

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