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331 IMMUNOTHERAPY WITH Y90-RADIOEMBOLIZATION FOR METASTATIC COLORECTAL CANCER (IRE-C)

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Background For patients with microsatellite stable or mismatch repair proficient (MSS/pMMR) metastatic colorectal cancer, immune checkpoint blockade does not work. Strategies are being devised where immunotherapy is being combined with other novel agents or radiotherapy to enhance PD-L1 expression, alter the tumor microenvironment (turning 'cold' tumors 'hot') and/or release neoantigens to enhance efficacy of immune checkpoint blockade. We chose Yttrium-90 radioembolization (Y90-RE) in combination with a fixed dose of immunotherapy given pre- and post-Y90-RE as a treatment strategy to be examined as part of a clinical trial for those patients with metastatic colorectal cancer who have liver-predominant or liver-only metastases.

Methods This clinical trial will be conducted as a single-center, open-label, Phase I/2 trial to evaluate the feasibility and safety of Yttrium-90 radioembolization (Y90-RE) in combination with a fixed dose of immunotherapy (durvalumab - 750 mg) in subjects with liver-predominant, metastatic colorectal cancer (mCRC), which is mismatch repair proficient/microsatellite stable (pMMR/MSS). As noted on clinicaltrials.gov, the purpose of this clinical trial is to find out more about the side effects of immunotherapy with a form of radiation treatment for the cancer in the liver called Yttrium-90 RadioEmbolization (Y90-RE). An immunotherapy drug, durvalumab, will be given intravenously every 2 weeks. We are studying what doses of durvalumab are safe for people in combination with this form of radiation treatment. Patients in this study will receive durvalumab, which is experimental and not approved by the U.S. Food and Drug Administration (FDA) for metastatic colorectal cancer. Microscopic radioactive particles (TheraSphere®) will be used for radioembolization to deliver the Y90 drug to the liver. The number of doses of the immunotherapy drug (range: 2 to 5) will depend on the cohort patients are assigned to. There is no placebo. Everyone on the study is treated with immunotherapy alongside the Y90-RadioEmbolization (table 1). Primary objective is to look at safety and feasibility of this approach.

Abstract 331 Table 1 Dose escalation cohort of durvalumab.

Dose level	Immunotherapy (Durvalumab) Administrations*		Y90 Radio-embolization	Post-Y90 doses			Number of Administration of Durvalumab
	Pre-Y90 doses	Week0		Week2	Week4	Week6	
-2						X	1
-1					X	X	2
1 (start)**	X	X					2
2	X	X			X		3
3	X	X			X	X	4
4	X	X		X	X	X	5

Once the recommended phase-2 dose is determined through an acceleration titration design, a total of 18 patients are being planned to be treated on this study at the University of Iowa Holden Comprehensive Cancer Center. The study has strong correlational components from a tumor microenvironment (pre- and post-biopsies) as well as 'liquid biopsies' - circulating tumor DNA (ctDNA) testing already integrated into the protocol. This would provide an opportunity to understand better the changes to the tumor microenvironment from such an approach in addition to understanding mechanisms of immune evasion/resistance.

Results N/A

Conclusions N/A

Trial Registration NCT04108481

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332 NOVEL TGF-β SIGNATURES IN METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH VACTOSERTIB IN COMBINATION WITH PEMBROLIZUMAB

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Background Dual inhibition of transforming growth factor beta (TGF-β) signaling and PD-1 is a promising strategy to reverse immunosuppressive tumor microenvironment and poor responses to immunotherapy. Based on preliminary clinical data with vactosertib, a highly selective and potent inhibitor of TGF-β receptor type 1, in combination with pembrolizumab, this study aimed to explore a biomarker with predictive value for this regimen in metastatic microsatellite stable (MSS) colorectal cancer (CRC).

Methods Tumor biopsy samples were obtained from 24 CRC patients at baseline and cycle 2 in the ongoing MP-VAC-204 study and analyzed by RNAseq and DNAseq. Consensus molecular subtype (CMS), TGF-β responsive gene signatures, IFN-γ signatures, and tumor mutation burden (TMB) were analyzed. Clinically benefited patients were defined by those

who achieved objective response assessed by RECIST v1.1/iRECIST or progression free survival more than 24 weeks. Vactosertib responsive gene signature (VRGS) that showed significantly different expression among previously identified TGF- β responsive gene signature and IFN- γ signature in responders than in non-responders was identified and VRGS score was calculated by a mean value of VRGS filtered-in gene expressions divided by 6 house-keeping gene expressions.

Results As of July 1, 2020, of the total evaluable 24 patients, 71% were CMS4 subtype and 33% were with high TMB (≥ 10 mut/Mb). Clinical benefit rate was 33.3% including 3 PR and 1 iPR patients. No significant associations in response rate were observed with CMS subtypes or TMB status. VRGS score was significantly enriched in responders than in non-responders (P value = 0.006; AUC = 0.836). A preliminary cut-off value of 2.179 resulted in 94% specificity and 75% sensitivity with 85.7% patients correctly classifying as a responder. After treatment of vactosertib plus pembrolizumab, TGF- β -related VRGS was significantly decreased and the extent of decrease was greater in responders, compared to non-responders.

Ethics Approval The study was approved by Ethics Board of Asan Medical Center, Yonsei University College of Medicine, Samsung Medical Center, and Seoul National University Bundang Hospital with approval number 2018-1215, 4-2018-0728, SMC 2018-07-146-006, and B-1808/487-003, respectively.

Conclusions Development of VRGS as a predictive biomarker for this combination treatment with vactosertib and pembrolizumab is ongoing and its potential clinical utility for patient selection will be explored.

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TARGETING THE APICAL INTRACELLULAR CHECKPOINT CISH UNLEASHES T CELL NEOANTIGEN REACTIVITY AND EFFECTOR PROGRAM

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Background Neoantigen-specific T cells isolated from tumors have shown promise clinically but fail to consistently elicit durable tumor regression. Expression of the intracellular checkpoint CISH is elevated in human tumor infiltrating lymphocytes (TIL) and has been shown to inhibit neoantigen reactivity in murine TIL.

Methods To explore CISH function in human T cells we developed a CRISPR/Cas9-based strategy to knockout (KO) CISH in human T cells with high-efficiency (>90%) and without detectable off-target editing.

Results CISH KO in peripheral blood T cells enhanced proliferation, cytokine polyfunctionality, and cytotoxicity in vitro. To determine if CISH KO similarly enhances TIL function, we developed a clinical-scale, GMP-compliant manufacturing process for CISH disruption in primary human TIL. In process validation runs we achieved CISH KO efficiencies >90% without detectable off-target editing while maintaining high viability and expansion. Compared to WT controls, CISH KO in patient-derived TIL demonstrated increased proliferation, T cell receptor (TCR) avidity, neoantigen recognition, and unmasked reactivity to common p53 mutations. Hyperactivation in CISH KO TIL did not increase differentiation, suggesting that CISH KO may uncouple activation and differentiation pathways. Single cell profiling identifies a pattern of CISH expression inverse to key regulators of activation, and CISH KO in human TIL increases PD1 expression. Adoptive transfer of Cish KO T cells synergistically combines with PD1 inhibition resulting in durable tumor regression in mice, highlighting orthogonal dual cell surface and intracellular checkpoint inhibition as a novel combinatorial approach for T cell immunotherapy.

Conclusions These pre-clinical data offer new insight into neoantigen recognition and serve as the basis for a recently initiated human clinical trial at the University of Minnesota (NCT04426669) evaluating inhibition of the novel intracellular immune checkpoint CISH in a CRISPR-engineered, neoantigen-specific T cell therapy for solid tumors. Updates from the clinical trial will be highlighted.

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PHASE II STUDY EVALUATING A CHEMOKINE-MODULATORY (CKM) REGIMEN IN PATIENTS WITH COLORECTAL CANCER (CRC) METASTATIC TO THE LIVER

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Background CRC remains the 2nd most common cause of cancer-related death in the US. Hepatic metastases develop in 20–50% of CRC patients.¹ Median overall survival (OS) of patients with metastatic CRC is poor, even with the advent of biologics. A high density of CRC-infiltrating effector cytotoxic T lymphocytes (Teff; CTL) is known to predict long-term outcomes and the responsiveness of tumors to immune checkpoint inhibitors (ICI). In our ex vivo tumor explant models and CRC-bearing experimental animals, the combination of toll-like receptor-3 (TLR3) ligands with interferon (IFN)- α with cyclooxygenase (COX)-2 inhibitors resulted in increased production of Teff attracting chemokines CXCL10 and CCL5, along with suppression of regulatory T cells (Treg) attracting chemokine, CCL22 in the tumor microenvironment.^{2,3} A combination of all three factors was needed to uniformly elevate the desirable chemokines and counteract CCL22 induction. Based on these studies and on prior clinical safety data, we developed this phase IIa study combining IFN α 2b, celecoxib (COX-2 inhibitor) and rintatolimod (selective TLR3 agonist) as a chemokine-modulating (CKM) regimen for CRC patients with unresectable liver-metastatic disease. We aim to study the immunological impact, potential clinical efficacy and safety