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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 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 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.

	Immunotherapy (Durvalumab) Administrations*					
	Pre-Y90 doses		Y90-Radio-embolization	Post-Y90 doses			Number of Administration of Durvalumab
Dose level	Week-2	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