584 PHASE I/II STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF AVELUMAB IN COMBINATION WITH OTHER ANTI-CANCER THERAPIES IN PATIENTS WITH ADVANCED MALIGNANCIES

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Background Checkpoint agonists OX40 and 4–1BB can augment the effector function of T cells in cancers, which is counterbalanced by the upregulation of programmed death-ligand 1 (PD-L1) on cancer cells.[1] Preclinical studies suggest that combining utomilumab (4–1BB agonist) and ivuxolimab (OX40 agonist) with avelumab (an anti-PD-L1 monoclonal antibody) can potentially synergize to enhance T cell function and simultaneously overcome the effects of upregulation of PD-L1 resulting in clinical benefit.[2–4] Additionally, the tissue abscopal effect of radiation therapy can improve antigen presentation and complement PD-L1 blockade.[5] Therefore, we conducted a single institution, open-label, multi-arm, non-randomized, phase 1/2 clinical trial of avelumab in combination with utomilumab, ivuxolimab or radiation therapy in patients with advanced cancer. (Clinicaltrial.gov identifier NCT03217747)

Methods We present a subgroup analysis in patients with gastrointestinal (GI) tumors (pancreatic, colon, gastric and hepatocellular (HCC). The study arms included: Arm B with avelumab plus ivuxolimab; Arm C with avelumab plus utomilumab and ivuxolimab; Arm E with avelumab and ivuxolimab plus radiation therapy; And arm F with avelumab, utomilumab and ivuxolimab plus radiation therapy. The primary objectives of this study were to establish safety, tolerability and dose-limiting toxicities of these treatment combinations and the secondary objectives were to evaluate efficacy including response rate, progression free survival, and overall survival.

Results Thirty-one patients with pancreatic (n=21), colorectal (n=8), HCC (n=1) and gastric (n=1) cancers were included in this study. The most common treatment-related adverse events (TRAEs) were chills (12.9%), diarrhea (9.7%), colitis (9.7%), fatigue (6.5%), and fever (6.5%). There were 3 instances of grade 3 diarrhea and colitis each (9.7%) without any other treatment related grade 3, 4 or 5 AEs based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Among the 24 patients evaluable for response, 9 (37.5%) had immune-related stable disease (irSD) and 14 (58.3%) had immune-related progressive disease (irPD) by immune related Response Evaluation Criteria in Solid Tumors (irRECIST). One patient had clinical progression of disease. The median progression free survival (mPFS) was 2 months per irRECIST and the median overall survival (mOS) was 5.6 months. Correlative studies are ongoing.

Conclusions Combining immune checkpoint inhibitors with checkpoint agonists produces modest activity without added safety concerns in patients with advanced GI malignancies. The findings from this study can provide insights for future investigations in this field of research.

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Trial Registration NCT03217747

REFERENCES

1. Peng Q, Qiu X, Zhang Z, *et al*. PD-L1 on dendritic cells attenuates T cell activation and regulates response to immune checkpoint blockade. *Nature Communications*. 2020;**11**(1):4835
2. Wei H, Zhao L, Li W, *et al*. Combinatorial PD-1 blockade and CD137 activation has therapeutic efficacy in murine cancer models and synergizes with cisplatin. *PloS One.* 2013;**8**(12):e84927.
3. Guo Z, Wang X, Cheng D, Xia Z, Luan M, Zhang S. PD-1 blockade and OX40 triggering synergistically protects against tumor growth in a murine model of ovarian cancer. *PloS One.* 2014;**9**(2):e89350.
4. Hamid O, Chiappori AA, Thompson JA, *et al*. First-in-human study of an OX40 (ivuxolimab) and 4–1BB (utomilumab) agonistic antibody combination in patients with advanced solid tumors. *Journal for immunotherapy of cancer.* 2022;**10**(10): e005471.
5. Seyedin SN, Schoenhals JE, Lee DA, *et al*. Strategies for combining immunotherapy with radiation for anticancer therapy. *Immunotherapy.* 2015;**7**(9):967–980

Ethics Approval The protocol was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. This study was conducted in accordance with current U.S. Food and Drug Administration (FDA) regulations, Good Clinical Practice (GCP), the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, the ethical principles stated in the Declaration of Helsinki, and all local ethical and legal requirements.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal

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