activation (4-1BB) and proliferation (Ki67) of peripheral CD8+ T cells measured by flow cytometry. Exploratory objectives were characterization of PD effects in plasma/serum and measurement of intra-tumoral immune activation. The endpoints were change in peripheral cytokines (TNF-alfa, IFN-gamma, IL-6) and soluble(s) factors (sCD25, s4-1BB) concentration measured by ELISA, and intra-tumoral changes in gene expression measured by RNAseq.

Results In the periphery, we observed transient expression of 4-1BB on CD4+ and CD8+ T cells, along with secretion of s4-1BB and inflammatory cytokines, suggesting 4-1BB targeting and potent T cell activation. The concomitant induction of proliferating T cells indicated the potential association to priming and formation of tumor-reactive T cells. In the tumor, we detected increased CD8+ T cells infiltration and proliferation, in both Parts. Proliferating CD8+ T cells increased in both tumor nests and surrounding stroma, with a preferential accumulation in the latter. RNAseq analysis revealed induction of 4-1BB, PD-1 and IFN-gamma, indicating intra-tumoral T cells activation in Part B.

Conclusions PD activity was consistent with the postulated MoA, confirming RO to be a potent tumor-targeted 4-1BB agonist in the clinical setting. Our observations suggest that RO can synergize with endogenous T cell receptor stimulation, both as SA and in combination with ATZ.

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371 THE ASSOCIATION OF THE GUT MICROBIOTA AND CLINICAL RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH ADVANCED CANCER

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Background The gut microbiome is associated with the immune function of the host. No consensus has been reached regarding to the association between microbiota and the treatment response to immune checkpoint inhibitor (ICI). This study is designed to explore the relationship between gut microbiome composition and clinical outcomes in patients with advanced cancer treated with ICI.

Methods Fifty patients were enrolled in this study. Fecal samples were collected at the baseline, 3 months after treatment and when disease progression was noted. To explore the gut microbiota as a potential predictive biomarker for immunotherapy, 165 ribosome RNA gene sequencing was used to analyze the gut microbiota profiles. Peripheral immunity parameters were determined by multicolor flow cytometry and cytokine array. Alpha-diversity of healthy individuals was used as a cut-off.

Results When subgrouping patients into benefiter and non-benefiter according to the clinical response assessed, non-benefiter patients harbored lower alpha-diversity of gut microbiome at the baseline. Patients with low microbiome diversity had decreased CD4+/CD25+ (p=0.569, p=0.219) when compared to those with high diversity. Compositional difference was observed between the two groups as well with the enrichment of g_Fusocatibacter in benefiter whereas f_Veillonellaceae enriched in non-benefiter. Analysis of immune responses using multicolor flow cytometry revealed that patients with a high diversity of gut microbiota had decreased CD4+/CD25+ FoxP3+ regulatory T cells in response to ICI. After ICI treatment the CD4/CD8 ratio of PBMCs was decreased in clinical benefiter. The serum MIF and CXCL12 levels were decreased in clinical benefiter.

Conclusions Low alpha diversity of the gut microbiota is associated with poor response to immune checkpoint inhibitors in patients with advanced cancer. Further confirmation in the clinical trials is warranted.

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Ethics Approval The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, approval number 20180126B0.

Consent Written informed consent was obtained from the patients 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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372 SINGLE-AGENT ANTI-TUMOR ACTIVITY IN RELAPSED/ REFRACTORY SOLID TUMORS: INTERIM DATA FROM THE PHASE 1 SOLID TUMOR TRIAL OF AMV564, A NOVEL T-CELL ENGAGER

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Background Overcoming the immune-suppressive tumor environment induced by myeloid-derived suppressor cells (MDSC) is a major challenge in immune therapy. AMV564 is a potent conditional agonist that engages T cells to selectively deplete target cells such as MDSC while promoting T cell polarization and activation. Whereas CD33 plays an insignificant role in differentiated myeloid cells, CD33 signaling in immature myeloid cells promotes expansion of MDSC and production of immune-suppressive factors. Preferential binding of AMV564 to areas of high CD33 density enables selective targeting of MDSC. Ex vivo data1 as well as data from a clinical trial in acute myeloid leukemia (NCT03144245) demonstrate the ability of AMV564 to selectively deplete MDSC while sparing monocytes and neutrophils.2,3

Methods NCT04128423 is a multi-center Phase 1 study to determine the safety and tolerability, define the maximum-tolerated or pharmacologically active dose, and assess the preliminary efficacy of AMV564. In this 3+3 dose escalation study, patients with advanced solid tumors receive AMV564 once daily via subcutaneous (SC) injection on Days 1–5 and 8–12 of a 21-day cycle. Primary endpoints include incidence, nature and severity of adverse events (AEs). Secondary endpoints include assessment of pharmacokinetics and pharmacodynamics.

Results As of June 30, 2020, 11 patients have been dosed across 3 dose cohorts (15 mcg – 75 mcg). The tumor types enrolled were: colorectal (n=2), GE junction (n=2), pancreatic (n=2), squamous cell carcinoma (n=2), small intestine, ovarian, and endometrial cancer. AMV564 has been well tolerated with no dose-limiting toxicities. The most common
treatment-related AEs were fever/pyrexia (Grade 1: n=3; Grade 2: n=8) and injection site reactions (Grade 1: n=1; Grade 2: n=9). Preliminary estimate of median plasma half-life for AMV564 after SC injection was >48 hours, with dose-related increases in peak plasma concentration (Cmax). Tumor responses were evaluable in 9 patients; 1 patient had not reached their first assessment and 1 patient was not efficacy evaluable due to a non-treatment-related AE resulting in study discontinuation. Single-agent activity has been observed including a complete response by RECISTv1.1 criteria in 1 patient with ovarian cancer refractory to all standard therapies and anti-PD-1 therapy, and stable disease in 4 additional patients.

Conclusions AMV564 has been well tolerated across multiple dose levels, with good plasma exposure and evidence of anti-tumor activity when administered subcutaneously. Single-agent anti-tumor activity was observed in an ovarian cancer patient.

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Trial Registration NCT04128423

Ethics Approval The study was approved by the Institutional Review Board at each center where the study is being conducted.

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