of TLR7/8-responsive genes correlated with $CD11c^+$ baseline density ($p<0.05$). Minimal TLR7/8-dependent changes in immune cell subsets or inflammatory cytokines were observed in peripheral blood, reflecting favorable TME modifications driven by retention of NKTR-262. Increased activation of $CD4^+$, $CD8^+$, and NK cells in blood were observed, consistent with BEMPEG mechanism of action.

Conclusions NKTR-262 plus BEMPEG led to engagement of the entire immune activation cascade required for systemic tumor clearance. Robust TLR7/8 engagement supported the NKTR-262 mechanism of action, while the minimal toxicity profile underscored the benefit of local delivery of NKTR-262, and the BEMPEG combination induced systemic activation of T and NK cells. These data support the RP2D of NKTR-262 (3.84 mg IT) plus BEMPEG (0.006 mg IV) q3w, and the initiation of the phase 1b dose-expansion phase, which is exploring concurrent dosing, with or without nivolumab, in relapsed/refractory metastatic melanoma patients.

Trial Registration NCT03435640

Ethics Approval The study was approved by the institutional review board of each participating site.

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369 SAFETY AND PHARMACODYNAMIC ACTIVITY OF ATOR-1015, A CTLA-4 X OX40 BISPECIFIC ANTIBODY, IN A PHASE 1 DOSE ESCALATION STUDY OF PATIENTS WITH ADVANCED SOLID MALIGNANCIES

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Background ATOR-1015 is a human CTLA-4 x OX40 targeting IgG1 bispecific antibody developed as a first in class tumor-localizing CTLA-4 antibody for improved efficacy and reduced toxicity.

Methods The study (NCT03782467) is a first-in-human dose escalation study followed by an expansion part. In the dose escalation patients with refractory solid malignancies are enrolled and the expansion part will enroll patients with cutaneous or mucosal malignant melanoma. Patients receive ATOR-1015 intravenously Q2W as a single agent until confirmed progressive disease, unacceptable toxicity or withdrawal of consent. Intra-patient dose escalation is allowed. The primary objective is to assess the safety and tolerability of ATOR-1015. Secondary objectives include pharmacokinetics, immunogenicity, pharmacodynamics, and clinical efficacy as assessed by iRECIST. Pharmacodynamic analyses include serum cytokines, immunophenotyping of peripheral blood mononuclear cells. Tumor biopsies before and after ATOR-1015 will be analyzed.

Results As of June 26, 2020, 23 patients have been exposed to ATOR-1015. The median age of the patients is 54 years (range 40–72). Patients have received a median of 5 prior lines of therapy (range 1–16). Most common cancer type is colorectal cancer.Dose levels from 0.043 mg to 600 mg have been evaluated and declared safe. Dose escalation is ongoing, and currently two patients have been enrolled at 750 mg dose level. The median time on study was 8.4 weeks (range 0.1–34.3). Five patients are on study and 18 patients have discontinued. Reasons for discontinuation included clinical deterioration (n=10), disease progression (n=5), death due to disease progression (n=2), and investigator's decision (n=1). Twelve of the 23 patients experienced a drug-related adverse event (AE). Two patients experienced a grade 3 drug-related AE, for all other patients AEs were grade 1 or 2. Infusion-related reactions (IRR) were reported in nine patients. Predominant symptoms of the IRR were chills, rash and pain. Potentially immune-related AEs grade 1 were reported in three patients: one patient had rash, one vitiligo, and one exanthema and eczema. No dose-limiting toxicities have occurred. Best response is stable disease. Pharmacokinetic data show dose proportional kinetics up to 600 mg. Preliminary biomarker analysis shows pharmacodynamic activity of ATOR-1015.

Conclusions ATOR-1015 has been safe and well-tolerated up to 600 mg. Currently 750 mg is under evaluation. Best response is stable disease. Following the dose escalation phase, an expansion cohort for patients with advanced malignant melanoma will be initiated.

Ethics Approval The study is approved by the Ethic Boards in Sweden and Denmark.

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370 PHARMACODYNAMIC ASSESSMENT OF A NOVEL FAP-TARGETED 4–1BB AGONIST, ADMINISTERED AS SINGLE AGENT AND IN COMBINATION WITH ATEZOLIZUMAB TO PATIENTS WITH ADVANCED SOLID TUMORS

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Background RO7122290 (RO) is a bispecific antibody-like fusion protein that simultaneously targets FAP, abundantly expressed by cancer-associated fibroblasts in most solid tumors, and 4-1BB, transiently expressed on activated T cells. Pre-clinical experiments revealed strong intra-tumoral CD8+ T cells infiltration in FAP-positive tumors, cytokines induction and significant anti-tumor activity mediated by RO (signal 2 of T cell activation), upon TCR/CD3 engagement (signal 1) or in combination with atezolizumab (ATZ). In this first-in-human study, the pharmacodynamic (PD) effects of RO were assessed, both as single agent (SA) (Part A) and in combination with ATZ (Part B).

Methods Pts with advanced and/or metastatic solid tumors were eligible for this ongoing Phase 1/1b trial (EUDRACT 2017-003961-83). RO was administered intravenously, weekly (QW) at escalating dose levels (DLs). In Part A, 62 pts were treated at 13 DLs of RO, dose range 5–2000 mg. In Part B, 39 pts were treated at 8 DLs of RO, dose range 45–2000 mg, with ATZ 1200 mg Q3W. Secondary biomarker objective was characterization of PD effects in tumor tissue and blood. The endpoints were change from baseline in intra-tumoral density (cell/mm^2) and proliferation (Ki67) of CD8+ T cells measured by immunohistochemistry (IHC), and change in

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, 16S 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 poor progression-free survival (HR=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_Fusicatenibacter in benefiters whereas f_Veillonellaceae enriched in non-benefiters. 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 201801261B0.

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 data[1] 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