

Exploratory endpoints are potential correlations between biomarkers and efficacy. A stratified Cochran Mantel Haenszel method will be used to assess binary endpoints. A Kaplan-Meier method, a stratified log-rank test and a stratified Cox proportional hazards model will be used to assess survival endpoints. Planned enrollment is 406 patients. The study is actively enrolling at 52 Chinese sites.

**Results** N/A

**Conclusions** N/A

**Acknowledgements** N/A

**Trial Registration** The Clinical trials. gov no NCT04158440

**Ethics Approval** This study was approved by the Ethics Board of all the involved sites; Approval number of Shanghai Chest Hospital: LS1936

**Consent** N/A

## REFERENCES

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### A PHASE 1/1B DOSE-ESCALATION STUDY OF INTRAVENOUSLY ADMINISTERED SB 11285 ALONE AND IN COMBINATION WITH ATEZOLIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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**Background** Activation of the Stimulator of Interferon Genes (STING) pathway within immune and tumor cells of the tumor microenvironment (TME) results in durable anti-tumor effects via induction of innate and adaptive immunity. SB 11285 is a next-generation immunotherapeutic cyclic dinucleotide that activates the STING pathway leading to stimulation of tumor-resident APCs, NK cells and priming of tumor antigen specific CD8+ T cells. In preclinical studies using multiple tumor-derived cell lines, SB 11285 induced cytokines, such as IFN- $\alpha$  and - $\beta$ , TNF- $\alpha$  and others consistent with engagement of TBK1 downstream of STING activation. Exposure of SB 11285 directly to tumor also induces cell death by STING-mediated apoptosis. SB 11285 reduced tumor volumes in multiple rodent tumor models when administered intravenously, intraperitoneally or intratumorally, as monotherapy and with amplified effect in combination with CTLA-4 or PD-1 antibodies. The novel properties of SB 11285 facilitate systemic administration which may facilitate trafficking of newly activated CD8+ T cells from the periphery into the TME.

**Methods** This open-label, multicenter phase 1/1b clinical trial (NCT04096638) will enroll approximately 110 patients in the dose escalation (Part 1) and expansion cohorts (Part 2). Part 1 will include parallel dose escalations evaluating ascending doses of intravenously administered SB 11285 via 3+3 design with respect to dose-limiting toxicities, maximum tolerated dose, recommended phase 2 dose (RP2D) and the pharmacokinetic/pharmacodynamic profile. Part 2 Expansion Cohorts of the study will explore initial efficacy via overall response rate in pre-specified tumor types (such as Melanoma, Head and Neck

Squamous Cell Carcinoma) at the RP2D in combination with atezolizumab. SB 11285 will be administered as monotherapy weekly on Days 1, 8, 15, and 22 of repeated 28-day cycles in escalating doses and in combination with atezolizumab administered Q4W. Biological effects of SB 11285 will be evaluated via changes in immune cell types, serum cytokines, and gene expression patterns indicative of activation of the peripheral and TME immune compartments.

**Results** ‘N/A’

**Conclusions** ‘N/A’

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### REVEAL: PHASE 1 DOSE-ESCALATION STUDY OF NKTR-262, A NOVEL TLR7/8 AGONIST, PLUS BEMPEGALDESLEUKIN: LOCAL INNATE IMMUNE ACTIVATION AND SYSTEMIC ADAPTIVE IMMUNE EXPANSION FOR TREATING SOLID TUMORS

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**Background** NKTR-262 is a small-molecule agonist of toll-like receptors (TLR) 7/8. Given by intratumoral (IT) injection, NKTR-262 is retained within the tumor microenvironment (TME) and promotes an immunostimulatory milieu and tumor antigen release. Bempegaldesleukin (BEMPEG) is a CD122-preferential IL-2 pathway agonist, which increases proliferation and tumor infiltration of CD8+ T cells and natural killer (NK) cells. Preclinically, NKTR-262 plus BEMPEG combined innate immune signaling and enhanced antigen presentation, with sustained T-cell activation, resulting in tumor growth inhibition of treated and abscopal lesions.

**Methods** This phase 1 dose-escalation study enrolled patients with relapsed/refractory, advanced/metastatic solid tumors (REVEAL; NCT03435640). Patients received escalating doses of NKTR-262 (0.03 mg to 3.84 mg IT) followed 3 weeks later by BEMPEG (0.006 mg/kg IV) q3wk utilizing a 3+3 design. The primary endpoint was safety and tolerability, including definition of the recommended phase 2 dose (RP2D). Other endpoints included antitumor activity, pharmacodynamics, and pharmacokinetics.

**Results** As of June 15, 2020, 36 patients were enrolled. One dose-limiting toxicity, transient transaminase elevation, was observed at the highest NKTR-262 dose (3.84 mg). The most frequent treatment-related adverse events were flu-like symptoms, fatigue, nausea, and pruritus, consistent with the known profile of BEMPEG. Early evidence of clinical activity was observed in patients with metastatic melanoma, with a disease control rate (partial response [PR] + stable disease) of 41.2% (7/17 patients), including two patients with PRs after progression on two prior immunotherapy regimens. Preliminary analyses showed dose-dependent induction of CXCL10 and type 1 interferon genes, consistent with TLR7/8 engagement. CD11c+ target cells were significantly more abundant in baseline melanoma biopsies than other tumor types (p<0.001). Induction

of TLR7/8-responsive genes correlated with CD11c<sup>+</sup> 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<sup>+</sup>, CD8<sup>+</sup>, 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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#### 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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#### 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<sup>+</sup> 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<sup>2</sup>) and proliferation (Ki67) of CD8<sup>+</sup> T cells measured by immunohistochemistry (IHC), and change in