Poster nr. 675

VICTORIA-01: A multicenter, open-label, phase 1 study to evaluate the safety and preliminary efficacy of SOT201 in patients with advanced or metastatic solid tumors

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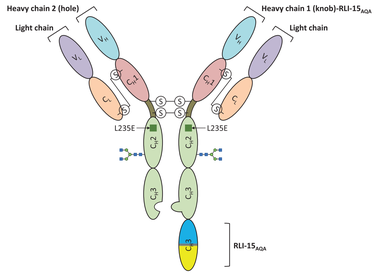
Background

- SOT201 is an immuno-cytokine consisting of a humanized monoclonal antibody against PD-1 and a low-activity variant of receptor-linker-interleukin-15 (RLI-15). RLI-15 is fused to the C-terminus of the antibody heavy chain without a linker.
- The asymmetric design of the antibody heavy chains is achieved by the knob-in-hole technology that catalyzes and stabilizes the asymmetric heavy chain assembly. The Fc part of the IgG4 antibody contains the L235E mutation that reduces binding to Fcγ receptors.

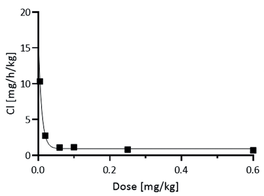


- RLI-15 is a fusion protein of the N terminal sushi+ domain of human IL 15 receptor α covalently coupled via a linker of 20 amino acids to human IL-15. It promoted the mobilization, expansion, and activation of human NK and CD8⁺ T cells in humanized mice and murine NK and CD8⁺ T cells in syngeneic mice [1-3]. RLI-15 in SOT201 (RLI-15$_{AQA}$) carries two mutations that reduce the heterogeneity of the molecule (G78A and N79Q) and a mutation that reduces the immune cell proliferation potency of the protein (N65A).

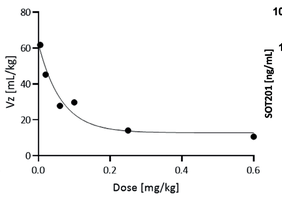
Preclinical data

- SOT201 activated and induced proliferation of human blood-derived CD8⁺ T cells and NK cells *in vitro*.
- The activity of SOT201 was enhanced when PD-1 was expressed on CD8⁺ T cells, supporting a *cis*-acting mechanism.
- SOT201 demonstrated activation of mouse CD8⁺ T cells and NK cells *in vivo* and anti-tumor activity in human PD-1-expressing transgenic mice carrying a human PD-1 ligand-expressing mouse tumor. Intravenous (IV) administration to cynomolgus monkeys promoted activation and expansion of CD8⁺ T cells and NK cells.
- SOT201 treatment showed strong anti-tumor efficacy in PD-1 responsive and resistant tumor models *in vivo* and was shown to be superior to mouse PD-1-IL-2Rβγ agonist.
- SOT201 has the potential to target dysfunctional tumor-infiltrating lymphocytes via PD-1 binding and to reinvigorate/reprogram their activity via RLI-15-mediated IL-15 receptor βγ signaling. This is intended to deblock anti-tumor responses via activating PD-1⁺CD8⁺ T cells and NK cells.
- Based on the predicted PK in humans and the correlation between PD response, PK, and dose observed in cynomolgus monkeys, the starting dose is 5 µg/kg of SOT201. This dose is predicted to promote 13% to 18% activation of NK and PD-1⁺CD8⁺ T cells.

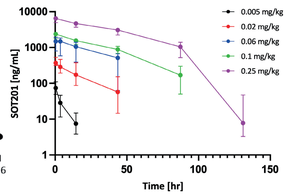
Predicted human clearance



Predicted human volume of distribution



Predicted human concentration-time profiles



Study design

- VICTORIA-01 is a multicenter, open-label, phase 1, Bayesian optimal interval (BOIN) trial assessing the safety, tolerability, and preliminary efficacy of escalating SOT201 doses in patients with advanced/metastatic solid tumors lacking standard treatment options.
- Dose escalation and de-escalation decisions will be made after each cohort completion, evaluating all patients cumulatively by BOIN model and based on dose-limiting toxicity (DLT) criteria and dose escalation rules, with the Dose Escalation Committee considering any adjustments to dose levels and dose increments.
- The trial will start with a cohort of n=1 to limit low dose exposure. After the first DLT or from dose level 2, at least 3 patients per cohort will be included as per BOIN design. A total of 40 patients are expected to be recruited.

Dose level	Dose
1	5 µg/kg
2	10 µg/kg
3	20 µg/kg
4	40 µg/kg
5	80 µg/kg
6	160 µg/kg

Key eligibility criteria

- Histologically or cytologically confirmed advanced or metastatic solid tumors
- Intolerance to or ineligibility for all available therapies
- Measurable disease per RECIST 1.1
- Tumor tissue accessible for biopsy
- Eastern Cooperative Oncology Group performance score 0-1
- Wash-out of previous anti-PD1 therapy at least 8 months
- Exclusion of patients with primary resistance against previous anti-PD1 therapy

Study treatment
SOT201 in escalating doses administered IV once every 21 days

Disease progression or unacceptable toxicity

Primary objectives

- To assess the safety and tolerability of SOT201
- To determine the effective dose, maximum administered dose (MAD) and/or the dose nearing the maximum tolerated dose (MTD) and recommended phase 2 doses (RP2Ds) of SOT201

Primary endpoints

- Type, frequency and severity of treatment-emergent AEs, clinical laboratory parameters, vital signs, and ECG
- Incidence of DLTs
- Effective dose: MAD and/or dose nearing the MTD (DLT rate >0.298)
- RP2Ds determined by safety, tolerability, PK, PD and preliminary anti-tumor activity

Secondary endpoints

- Serum concentration-time profile and calculated PK parameters of SOT201 after single and multiple dose
- Efficacy according to RECIST 1.1 and iRECIST measured as:
  - ✔ Objective response rate
  - ✔ Duration of response
  - ✔ Clinical benefit rate
  - ✔ Progression-free survival
- Minimally reproducibly active dose defined as a dose with more than one patient with clear tumor shrinkage
- Detection of anti-drug antibodies

Exploratory endpoints

- Immune response in tumor tissue and in blood as characterized by changes from baseline of immune cell subsets and immune markers
- Baseline level of the immune-, molecular-, disease-related and other exploratory biomarkers in peripheral blood and archival and/or freshly obtained tumor tissue
- Immune response in blood characterized by changes from baseline in the percentage of immune cell subsets (e.g., CD8⁺ T cells, including PD-1⁺CD8⁺ T cells, NK cells) and immune markers (cytokines and other serum proteins and immune modulators) using peripheral blood mononuclear cells

Statistics

- No formal testing of statistical hypotheses is planned. All analyses will be descriptive. Exploratory analyses will include immune and molecular biomarkers.

Trial status

- The trial is conducted at 6 sites in the US, Belgium, Spain, and the Czech Republic.
- Four patients have been treated as of today, one in dose level 1 and three in dose level 2

References: 1. Bessard A et al. High antitumor activity of RLI, an interleukin-15 (IL-15)-IL-15 receptor alpha fusion protein, in metastatic melanoma and colorectal cancer. Mol Cancer Ther. 2009; 8(9): 2736-2745. 2. Desbois M et al. IL-15 trans-signaling with the superagonist RLI promotes effector/memory CD8⁺ T cell responses and enhances antitumor activity of PD-1 antagonists. J Immunol. 2016; 197(1): 168-178. 3. Desbois M et al. IL-15 superagonist RLI has potent immunostimulatory properties on NK cells: implications for antimetastatic treatment. J Immunother Cancer. 2020; 8(1): e000632.

Abbreviations: AE, adverse event; BOIN, Bayesian optimal interval; CD, cluster of differentiation; DLT, dose-limiting toxicity; ECG, electrocardiography; Fc, fragment crystallizable; Ig, immunoglobulin; IL, interleukin; iRECIST, Response Evaluation Criteria in Solid Tumors for immune-based therapeutics; IV, intravenous; MAD, maximum administered dose; MTD, maximum tolerated dose; NK, natural killer; PD, pharmacodynamic(s); PD-1, programmed cell death protein 1; PK, pharmacokinetic(s); RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RLI-15, receptor-linker-interleukin-15; RP2D, recommended phase 2 dose