A MULTICENTER OPEN-LABEL PHASE I/LB STUDY OF SO-C101 AS MONOTHERAPY AND IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH SELECTED ADVANCED/METASTATIC SOLID TUMORS

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Background IL-15 is a member of the common y-chain family of cytokines that shares functional activities with IL-2. SO-C101 is a superagonist fusion protein of IL-15 and the IL-15 receptor α (sushi+ domain). SO-C101 stimulates the proliferation and the cytotoxic activity of NK cells and memory CD8+ T cells.

In pre-clinical studies SO-C101 promoted expansion and activation of human, murine and cynomolgus monkey NK and CD8+ T cells. NK and CD8+ T cell activation correlated with potent monotherapy anti-cancer activity of SO-C101 in metastatic and solid tumor models. The combination of an anti-PD-1 or of anti-cancer monoclonal antibodies with SO-C101 augmented the anti-tumor responses in mouse models. First clinical study was initiated in June 2019 to investigate SO-C101 as monotherapy and in combination with pembrolizumab.

Methods

The phase 1/1 b study currently on-going is a multicenter, open-label, dose escalation study for patients with selected advanced/metastatic solid tumors. The study consists of 2 parts: Part A - dose escalation of SO-C101 as monotherapy; Part B - dose escalation of SO-C101 in combination with pembrolizumab. Study objectives are to define the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of SO-C101 in both parts.

Results

As of September 22nd, 19 subjects were treated in part A in 6 escalating dose levels, and 3 subjects were treated in part B, at dose level 1.

SO-C101 was well tolerated. No DLT was observed, the main AEs related to SO-C101 were injection site reactions, fever, chills, flu-like syndrome, all G1- G2, and transient lymphopenia in 5 subjects, Grade 2 to 4, all resolved within few days.

Preliminary PK results showed the PK profile to be dose-proportional, with a Tmax of approx. 5 – 6 hours after administration and T½ approx. 4 hours.

Preliminary PD analysis showed dose dependent NK and CD8+ T cell activation.

A preliminary efficacy signal has been observed in a patient refractory to anti-PD1 therapy, who showed a RECIST PR with initial 20% shrinkage of target lesions at 6 weeks and 49% shrinkage at 12 weeks on CT-scans.

Conclusions

To date, SO-C101 has been well tolerated, with a manageable toxicity and encouraging signs of clinical activity. The study will proceed to reach a RP2D in both monotherapy and combination with Pembrolizumab. Expansion of the study in selected indications is warranted.

Trial Registration https://clinicaltrials.gov/ct2/show/NCT04243113

Ethics Approval

The NCT04239145 clinical trial was approved by each investigational site health agency and ethical committee.

Consent

Written informed consent of patients was obtained prior enrollment in the NCT04234113 clinical trial.

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EXPLORING RESISTANCE MECHANISM TO PEMBROLIZUMAB AND ANG-2 INHIBITOR TREBANANIB (NCT03239145) USING HIGH-DIMENSIONAL SINGLE-CELL MASS CYTOMETRY (CyTOF)

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Background

Angiogenesis is mediated by both the vascular endothelial growth factor (VEGF) family and the angiopeptin (Ang1-2)/Tie-2 pathway.1-3 We demonstrated that increased soluble VEGF and ang-2 is associated with decreased benefit to immune checkpoint inhibitors (ICIs).4 We then initiated a clinical trial combining pembrolizumab and ang-1/2 inhibitor (trebananib) (NCT03239145) with expansion cohorts in microsatellite stable (MSS) colorectal cancer (CRC), ovarian and renal cell cancer.5 We present the correlation analysis using high-dimensional single-cell mass cytometry (CyTOF) to characterize the effects of the combination therapy and examine differences between patients according to clinical benefit.

Methods

We used two separate CyTOF panels to monitor 48 markers of innate and adaptive immune populations in 26 evaluable patients who received the PR2D of trebananib (30mg/kg). Mass cytometry assay was performed on peripheral blood mononuclear cells of 26 patients at baseline (C1D1), 16 patients at cycle 3 day 1 (C3D1), and 4 patients at cycle 9 day 1 (C9D1). We compared immune cell markers between patients with clinical benefit (CB) and patients with no clinical benefit (NCB).

Results

Of 26 patients (16 CRC, 8 ovarian, 2 RCC), 11 patients had confirmed PR (3) or SD (8) resulting in CB of 42.3% while 15 patients had NCB. Independent of CB, there were statistically significant decreases from C1D1 to C3D1 in naïve CD8+ T cells (p=0.03), CD4+ T central memory cells and combination with Pembrolizumab.

CD8+/CXCR3+ cells decrease significantly from C1D1 to C3D1 in patients with no clinical benefit (p=0.02, n=16). (F) CD4+/CXCR3+ cells decrease significantly in patients with no clinical benefit between C1D1 and C9D1 (p=0.03, n=16). (E) CD4+/CXCR3+ cells decrease significantly in patients with no clinical benefit from C1D1 to C3D1 (p=0.02, n=16). (D) CD8+ T effector memory cells decrease significantly from C1D1 to C3D1 in patients with no clinical benefit from C1D1 to C3D1 (p=0.02, n=16). (C) CD8+ T cells decrease in patients with no clinical benefit from C1D1 to C3D1 (p=0.03, n=16). (B) CD4+ T cells decrease from C1D1 to C3D1 in patients with no clinical benefit (p=0.02, n=16). (A) CD3+ T cells decrease from C1D1 to C3D1 in patients with no clinical benefit (p=0.009, n=16). CD3+ T cells are significantly higher at C3D1 in patients with clinical benefit (p=0.02, n=16). (B) CD4+ T cells decrease in patients with no clinical benefit from C1D1 to C3D1 (p=0.01, n=16). (C) CD8+ T cells decrease in patients with no clinical benefit from C1D1 to C3D1 (p=0.03, n=16). (D) CD8+ T effector memory cells decrease significantly in patients with no clinical benefit between C1D1 and C3D1 (p=0.03, n=16). (E) CD4+/CXCR3+ cells decrease significantly in patients with no clinical benefit from C1D1 to C3D1 (p=0.02, n=16). (F) CD8+/CXCR3+ cells decrease significantly from C1D1 to C3D1 in patients with no clinical benefit (p=0.02, n=16).

Abstract 808 Figure 1 T cell subset analysis by cycle and clinical benefit

Detection of T cell subsets at C1D1, C3D1, and C9D1. (A) CD3+ T cells decrease from C1D1 to C3D1 in patients with no clinical benefit (p=0.009, n=16). CD3+ T cells are significantly higher at C3D1 in patients with clinical benefit (p=0.02, n=16). (B) CD4+ T cells decrease in patients with no clinical benefit from C1D1 to C3D1 (p=0.01, n=16). (C) CD8+ T cells decrease in patients with no clinical benefit from C1D1 to C3D1 (p=0.03, n=16). (D) CD8+ T effector memory cells decrease significantly in patients with no clinical benefit between C1D1 and C3D1 (p=0.03, n=16). (E) CD4+/CXCR3+ cells decrease significantly in patients with no clinical benefit from C1D1 to C3D1 (p=0.02, n=16). (F) CD8+/CXCR3+ cells decrease significantly from C1D1 to C3D1 in patients with no clinical benefit (p=0.02, n=16).