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 γ-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 sushii+ 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 1/1b 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/NCT04234113?term=sotio&draw=12

The study was approved to proceed by FDA – IND 140011 - and by the sites ECs.

Ethics Approval: The NCT04234113 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 angiopoietin (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 correlative 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 patients with clinical benefit (CB) and patients with no clinical benefit (NCB).

CD8+ T cell subset analysis by cycle and clinical benefit
Detection of T cell subsets at C1D1, C3D1, and C9D1. (A) CD3+ T cells decrease in patients with no clinical benefit from C1D1 to C3D1 (p=0.009, n=16). CD3+ T cells are significantly lower 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).
Abstract 808 Figure 2 Myeloid cell subset analysis by cycle and clinical benefit
Detection of myeloid cell subsets at C1D1, C3D1, and C9D1. (A) Myeloid cells increase significantly from C1D1 to C3D1 in patients with no clinical benefit (p=0.01, n=16). (B) Monocytic myeloid-derived suppressor cells increase significantly in patients with no clinical benefit from C1D1 to C3D1 (p=0.003, n=16). (C) Dendritic cells are significantly higher at C1D1 (p=0.02, n=26) and C3D1 (p=0.02, n=16) in patients with no clinical benefit. (D) Total monocytes significantly increase in patients with no clinical benefit from C1D1 to C3D1 (p=0.003, n=16). (E) Classical monocytes increase in patients with no clinical benefit from C1D1 to C3D1 (p=0.01, n=16). (F) M2 macrophages trend higher in patients with no clinical benefit at C3D1 (p=0.07, n=16).

Abstract 808 Figure 3 NK cell subset analysis by cycle and clinical benefit
Figure 3: Detection of NK cell subsets at C1D1, C3D1, and C9D1. (A) There is a trend towards increased CD56dim/CD16- cells in NCB patients compared to CB patients at C3D1 (p = 0.08). (B) CD56dim/CD16+ cells are significantly higher in CB patients compared to NCB patients at C3D1 (p=0.04). (C) There were no significant differences in CD56bright cells according to cycle or clinical benefit. (D) CD3-/CD19-/CD56+ cells are significantly higher in CB patients compared to NCB patients at C3D1. There is a trend towards decrease of this cell subset from C1D1 to C3D1 in NCB patients (p=0.06). (E) NKp30+/CD56+ cells are significantly higher in CB patients compared to NCB patients at C1D1, but this was not significant at C3D1 (p=0.23). and CD8+ T effector memory cells (p=0.03) while no significant changes in these T cell populations were observed in CB patients (figure 1). In NCB patients, mononcytic myeloid-derived suppressor cells (p=0.003) and classical monocytes increased from C1D1 to C3D1 (p=0.01) while there was no significant change in this population in CB patients (figure 2). Interestingly, CB patients had higher activated CD56+NKp30+ at baseline (p= 0.03) with increased cytotoxic CD56 dim CD16+ population from C1D1 to C3D1 (p= 0.04) compared to NCB patients (figure 3).

Conclusions Our findings suggest that the activity of anti-PD-1 and anti-angi-2 peptibody (trebananib) combination is hindered by an increase in immunosuppressive myeloid cells leading to decrease in memory and effector T cell populations. The association between baseline activated NK cell and the expansion of cytolytic NK cells with favorable outcomes should be further explored.

Trial Registration NCT033239145

Ethics Approval The study was approved by the Institutional Review Board (IRB) at Dana-Farber Cancer Institute for NCT033239145.

Consent Written informed consent was obtained from the patient for participation in this study and publication of data.

REFERENCES

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