Poster nr. 510

SO-C101, a high-affinity IL-15Rβγ agonist, induces safe and potent anti-tumor immune activities in patients with solid tumors and supports further clinical investigations

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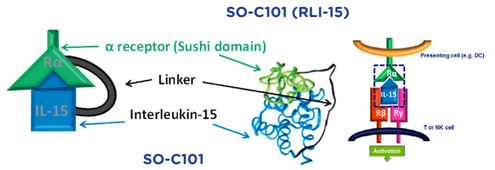
Introduction

Background: SO-C101 (future compound code: SOT101) is a high affinity superagonist fusion protein of interleukin (IL)-15 and the IL-15 receptor α (IL-15Rα) sushi+ domain, representing a promising clinical candidate for the treatment of cancer. SO-C101 specifically stimulates natural killer (NK) cells and memory CD8+ T cells with no significant expansion and activation of regulatory T cell compartment. [1,2]



Methods: Blood and tumor samples from patients with advanced/metastatic solid tumors included in Phase clinical I study (NCT04234113) were analysed by flow cytometry, immunohistochemistry and NanoString analyses for the activation of immune cells induced by SO-C101 monotherapy or in combination with Pembrolizumab.

Results: SO-C101 showed a dose-dependent activity in blood of all patients with no clear correlation between the increase of immune cell proliferation and counts in blood and recruitment of immune cells into the tumor tissue. SO-C101 as a monotherapy or in combination with Pembrolizumab increases immune cell infiltration in tumors in clinically responsive patients in Phase clinical I study (NCT04234113) which is accompanied by NK and CD8+ T cell activation and cytotoxicity, increased proinflammatory chemokines and IFN-γ signaling genes signatures.

Conclusions: All patients showed dose-dependent pharmacodynamic responses in blood, however SO-C101 activity in the tumor microenvironment might be pivotal for the therapeutic success. Favorable safety profile and potent anti-tumor immune activities in patients with solid tumors support further clinical investigations.

Methods

Study design

- The currently on-going phase 1/1b study is a multi-center, open-label, dose escalation study for patients with selected advanced/metastatic solid tumors

Dosing schedule

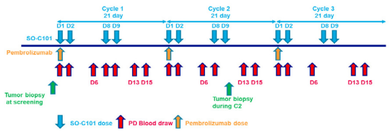
Part A (SO-C101 monotherapy)

- SO-C101 0.25-15.0 μg/kg s. c. injection on day 1, 2, 8 and 9 of each 21 day cycle

Part B (SO-C101 in combination with pembrolizumab)

- SO-C101 1.5-9.0 μg/kg s. c. injection on day 1, 2, 8 and 9
- Pembrolizumab i. v. 200 mg on day 1 of each 21 day cycle

Blood and tumor biopsy collection and analysis



Blood Analysis
- Flow cytometry
- Cytokines
- PK
- ADA

Tumor analysis
- IHC
- NanoString analysis

Figure 1: Time on study and the best overall response

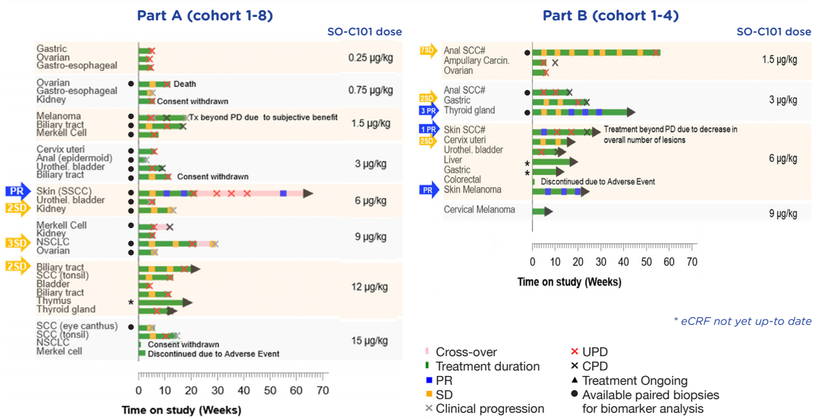


Figure 2: Increased proliferation of CD8+ T cells and NK cells following treatment with SO-C101 and SO-C101+Pembrolizumab in peripheral blood

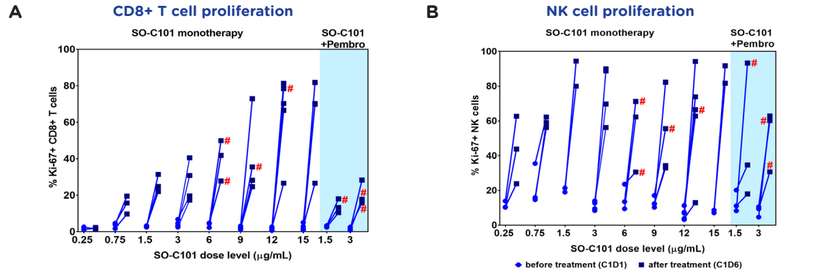


Figure 2. PBMCs were obtained from 26 patients treated with SO-C101 monotherapy and 6 patients treated with SO-C101+Pembrolizumab before treatment on day 1, cycle 1 (C1D1) and after treatment on day 6, cycle 1 (C1D6). **(A)** Percentage of Ki-67+ cells within CD8+ T cells and **(B)** NK cells was analyzed by flow cytometry. Maximum level of NK cell and CD8+ T cell activation was reached at 12 μg/kg. Clinically responsive patients (PR or ≥2SD) are marked #.

Figure 3: Increased density of CD3+ and CD8+ T cells and increased ratio of CD8+T cells/ Treg upon treatment with SO-C101 and SO-C101+Pembrolizumab in tumor tissue

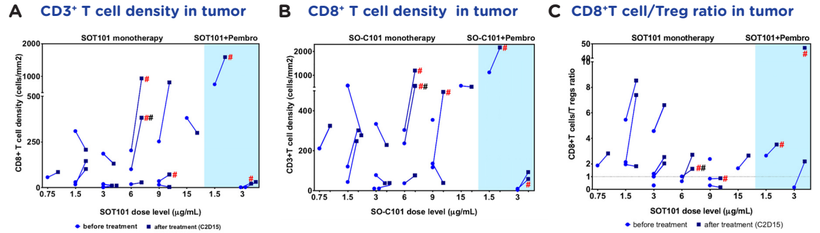


Figure 3. IHC analysis from tumor tissue. (A) Enhanced infiltration of CD3+T cells was observed in 10 out of 18 patients (55%), **(B)** enhanced infiltration of CD8+ T cells in 10 out of 18 patients (55%) **(C)** and increased CD8+ T cell/Treg ratio in 11 out of 18 patients (61%). Tumor biopsies were taken at baseline and after treatment (Cyclus 2, day 15; C2D15) from 18 patients (15 treated with SO-C101 monotherapy, 3 with SO-C101+ Pembrolizumab). Clinically responsive patients (PR or ≥ 2SD) are marked #. # Biopsy collected at week 20.

Figure 4: SO-C101 induces genes involved in T cells and NK cell activation and immune-mediated tumor regression

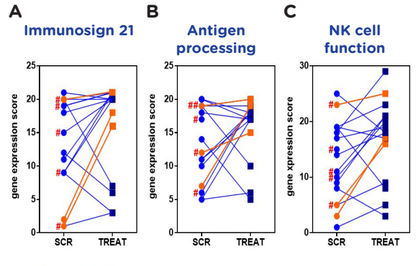


Figure 4. NanoString analysis from tumor tissue. (A) SO-C101 increases Immunosign 21 gene signature score (HalioDX) profiling pre-defined set of genes reflecting T cell activation, attraction, cytotoxicity and T cell orientation in 11 out of 18 patients (61%). **(B)** SO-C101 increases expression of genes linked to antigen processing and presentation in 11 out of 18 patients (61%). **(C)** SO-C101 increases expression of genes linked to NK cell functions in 13 out of 18 patients (72%).

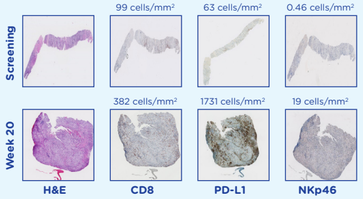
Each dot represents a different patient. Out of 18 patients, 15 were treated with SO-101 monotherapy (in blue), 3 were treated with SO-C101 in combination with Pembrolizumab (in orange). NanoString analysis was performed on matched screening and on-treatment (cycle 2 day 15) biopsies.

Clinically responsive patients (PR or ≥2SD) are marked #.

Figure 5: SO-C101 and SO-C101+Pembrolizumab induces robust immune cell infiltration in clinically responsive patients with various tumor microenvironment

Case study 1, tumor with mild immune infiltrate
Patient with sSCC, CPI refractory, confirmed PR achieved upon SO-C101 monotherapy and SO-C101+Pembrolizumab therapy

Pharmacodynamic changes on SO-C101 therapy



Patient
Female, age 62, with cutaneous Squamous Cell Carcinoma

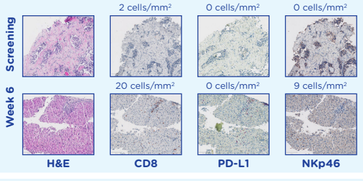
Treatment history
- 3 prior lines
- Most recent: Cemiplimab (01/2020-04/2020)

On-study benefit
- SO-C101 monotherapy 6 μg/kg started 4 Jun 2020
- PR (-58 % at target lesions) at Cycle 8 (28 Oct 2020)
- Crossover to SO-C101 1.5 μg/kg + Pembrolizumab 200 mg Q3W on 26 Nov 2020
- PR (-63 % at target lesions) at Cycle 4 (5 Feb 2021)
- 5 May 2021: PET-CT showed no „hot spots"

- Prior to SO-C101 treatment, mild infiltration of tumor with CD8+ T cells and almost no NK cells were observed. PD-L1 was expressed mainly on tumor cells.
- Following treatment, high level of CD8+T cells, robustly increased PD-L1 expression on malignant as well as immune cells and increased NK cell level were observed.

Case study 2, cold tumor
Patient with Thyroid Carcinoma, CPI naïve, confirmed PR achieved upon SO-C101+Pembrolizumab therapy

Pharmacodynamic changes on SO-C101 therapy



Patient
Female, age 47, with Thyroid Gland Carcinoma

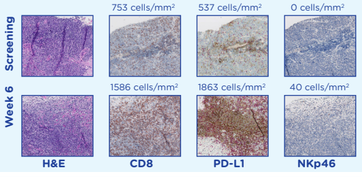
Treatment history
- 3 prior lines
- Most recent: Vandetanib (2014-2018)

On-study benefit
- SO-C101 combination 3 μg/kg + Pembrolizumab 200 mg Q3W started 20 Nov 2020
- confirmed PR (- 31%) after 8 cycles
- PR (- 36%) after 10 cycles
- Current status: Tx discontinued due to PD after 18 cycles

- Cold tumor prior to SO-C101+Pembrolizumab treatment.
- Following treatment with SO-C101+Pembrolizumab, CD8+ T cells started to accumulated in stroma and were also scattered throughout the tumor nest. NK cells were scattered throughout the intratumoral stroma and tumor nests. Highly likely that this immune infiltration was deepening over time to explain the PR observed after 8 cycles of treatment.

Case study 3, hot tumor
Patient with Anus Carcinoma, CPI refractory, achieved long-term SD upon SO-C101+ Pembrolizumab therapy

Pharmacodynamic changes on SO-C101 therapy



Patient
Female, age 49, with squamous Cell Carcinoma of Anus

Treatment history
- 2 prior lines
- Most recent: Retinfanlimab (11/2019-04/2020)

On-study benefit
- SO-C101 combination 1.5 μg/kg + Pembrolizumab 200 mg Q3W started 9 May 2020
- Best response: SD (-9 %) after 8 cycles
- Current status: Tx discontinued due to PD after 18 cycles

- Hot tumor prior to SO-C101+Pembrolizumab treatment with high intratumoral PD-L1 density
- Following treatment with SO-C101+Pembrolizumab, markedly increased infiltration of CD8+ T cells and PD-L1+ cells was observed in stroma as well as tumor nests. NK cells were scattered throughout the intratumoral stroma and tumor nest

H&E-hematoxylin and eosin

Conclusions

- **SO-C101 mode-of-action includes activation of both innate as well as adaptive immunity**
- **SO-C101 and SO-C101 + Pembrolizumab showed a dose-dependent pharmacodynamic responses in blood of all patients, however clinically responsive patients showed also an increased CD8+ T cell and NK cell infiltration in the tumor**
- **SO-C101 induces robust immune-stimulatory response in various types of tumor microenvironment**
- **SO-C101 restores the sensitivity to CPI in CPI refractory/resistant patients**
- **Further analyses are planned in phase II combination trials in 2022**

Download the poster:

References

1. Desbois M, et al. J Imm Ther Cancer 2020;8:e000632
2. Desbois M, et al. J Immunol. 2016 Jul 1;197(1):168-78

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