Open-label phase I/Ib study of SO-C101 as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors

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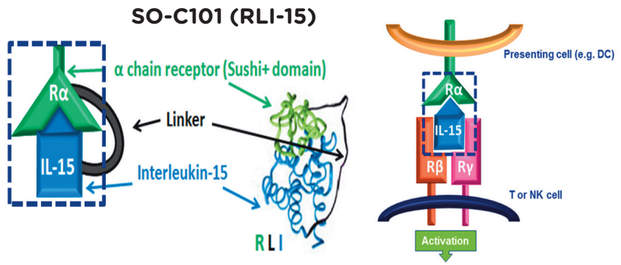
Background

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 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. A 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 administered SC as monotherapy; Part B - dose escalation of SO-C101 administered SC 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.

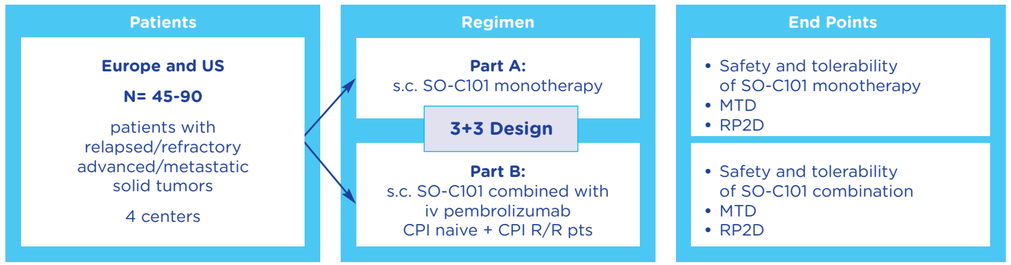
Key Inclusion criteria

- Histologically or cytologically confirmed advanced and/or metastatic solid tumors who are refractory or intolerant to existing therapies
- Have recovered from the side effects from prior treatments to grade ≤1 toxicity
- Adequate hematological, cardiovascular, hepatic and renal functions
- Adequate laboratory parameters
- Accessible tumor tissue available for fresh biopsy
- ECOG Performance Status 0-1
- Measurable disease per iRECIST

Key Exclusion criteria

- Patient with untreated CNS metastases and/or lepto-meningeal carcinomatosis
- Any active autoimmune disease (AD) or history of syndrome that required systemic steroids (except of allowed doses) or immunosuppressive medication
- Prior exposure to the drugs that are agonist of IL-2 or IL-15

Study design



N, number; CPI, checkpoint inhibition; R/R, relapsed/refractory; MTD, maximum tolerated dose; RP2D, recommended phase II dose

Dosing schedule:
Part A (SO-C101 monotherapy): SO-C101 s.c. on day 1, 2, 8 and 9 of each 21 day cycle;
Part B (SO-C101 in combination with pembrolizumab): SO-C101 s.c. on day 1, 2, 8 and 9 and pembrolizumab i.v. 200 mg on day 1 of each 21 Day cycle

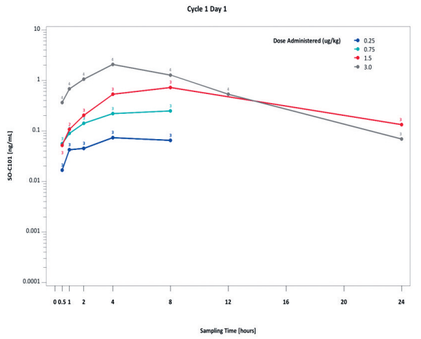
Preliminary results

- **Part A** by the cut-off date, enrollment at dose level 6 with 9 µg/kg was completed, 20 patients were treated in total in 6 cohorts, 3 patients are ongoing, no DLT was observed by the cut-off date.
- **Part B** by the cut-off date 3 patients treated at dose level 1; 1 patient is ongoing; no DLT was observed by the cut-off date.
- Patients were aged between 31 and 80 years at enrollment.
- Duration of treatment ranged from 14 days to 133 days at cut-off date.
- SO-C101 was well tolerated. No DLT was observed. No evidence of immune-mediated AEs or organ-related inflammation (e.g. colitis, dermatitis, hepatitis, pneumonitis and dermatitis).
- Preliminary PK results showed the PK profile to be dose-proportional, with a Tmax of approximately 5 – 6 hours after administration and T½ approximately 4 hours.
- Preliminary PD analysis showed dose dependent NK and CD8⁺ T cell activation.

Treatment emergent AEs (Part A), assessed as suspected to be related to SO-C101 (cohorts 1-5)

Adverse event	Number of patients	Severity CTCAE v5.0	Resolved / ongoing
Injection site reaction	10/16	1	Resolved
Localized rash	2/16	1	Resolved
Pruritus	1/16	2->1	Ongoing
Fever, chills, flu-like syndrome	9/16	1-2	Resolved
Hypotension	2/16	2	Resolved
Bilirubin increased	1/16	2->1	Gilbert Syndrome
Nausea, Vomiting	3/16	1	Resolved
Myalgia	1/16	1	Resolved
Asthenia	4/16	1-2	Resolved/Resolving
Dyspnea	1/16	1	Resolved
Generalized tremor	1/16	2	Resolved
Lymphopenia (transient)	6/16	1-2 (2pts) 3-4 (4pts)	Resolved
Neutropenia	1/16	3	Resolved
Thrombocytopenia	1/16	3->1	Resolved

Preliminary PK results, Part A cohorts 1-4*

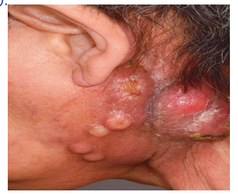


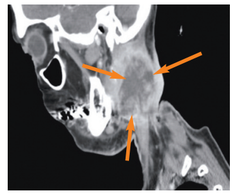
* *Time point 12 h measured from cohort 4 ;*
Time points 16 and 20 h measured from cohort 5

Preliminary efficacy

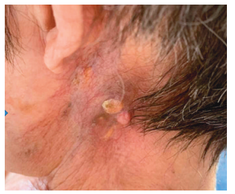
A preliminary efficacy signal has been observed in patient 62 y.o., female with **skin squamous cell carcinoma** in Part A (monotherapy with SO-C101), initial diagnosis from 2014, refractory to anti-PD1 therapy. Previous treatments: Radiotherapy 2014; Docetaxel, Cisplatin, and Cetuximab (03 – 06/2019), Cemiplimab (01– 04/2020).

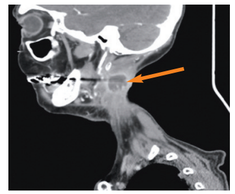
Screening



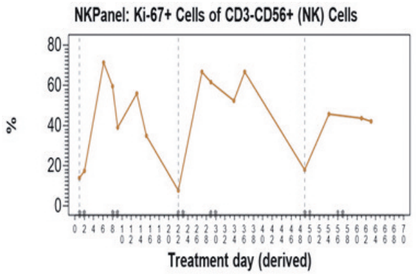


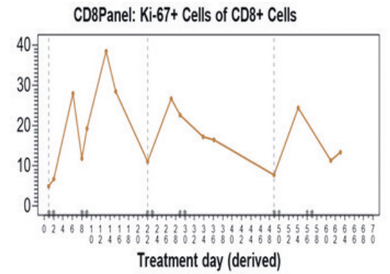
12 weeks





Patient started treatment with 6µg/kg on 04 June 20.
- CT at screening: Target lesion: 50 mm ø (3 non target lesions: left and right cervical lymphadenopathy and liver segment III)
- CT at 6 weeks: 40 mm ø, Stable disease (-20%)
- CT at 12 weeks: 26 mm ø, Partial response (-49%)
- Reduced need for pain killers and opioids after 2 treatment cycles
- 71% of activated NK cells, 38% activated CD8⁺ T cells





Results

To date, 20 patients were treated in 6 escalating dose levels in Part A and 3 patients in Part B. Current dose level in Part A is 6 and 2 - in Part B. So far treatment was safe, no DLTs observed. MTD or RP2D dose not yet reached. SO-C101 has been well tolerated, no specific side effects, e.g. no signs of vascular leakage, no systemic skin reactions. The study will proceed to reach a RP2D in both monotherapy and combination with pembrolizumab. Expansion of the study in selected indications is warranted.

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