Combination immunotherapy with an albumin-binding interleukin-12 fusion protein that extends cytokine half-life, targets the tumor microenvironment, and enhances therapeutic efficacy

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ABSTRACT

IL-12 is a potent multifunctional regulator of cell-mediated immunity that activates T and NK cells to stimulate IFNγ production and can suppress tumor growth. Recombinant interleukins have generally had limited clinical success due to inefficient tumor targeting, short half-lives, and off-target toxicity. While IL-12 seemed promising in Phase 1, it failed Phase 2 due to unexpected tachyphylaxis. Dosing strategies were eventually optimized but none have provided adequate therapeutic benefit in humans. To address these issues, we developed a novel platform that delivers either mono- or bifunctional immunomodulators linked to a Fully-Human, Albumin Binding scFv domain (F_HAB®) to provide enhanced targeting to the TME and prolonged retention in the tumor. Albumin binding to FcRn, GP60, and SPARC results in an improved PK profile, decreased toxicity risk, and a broader therapeutic index preclinically, with significant increases in activated NK, NKT, Th1, and cytotoxic CD8 T cells, as well as marked reporalization of pro-tumor M2 MDSCs to inflammatory M1 APCs.

Monotherapy dose escalation showed the safety and tolerability of SON 1010 (IL12-F_LAB) in patients with advanced solid tumors, along with clinical benefit in 48%, including a partial response at the highest dose in a patient with clear cell sarcoma. The first dose is capped to take advantage of IL-12 tachyphylaxis, which allows administration of higher maintenance doses up to the MTD of 1200 ng/kg (the molar equivalent of 800 ng/kg IL-12). The preliminary geomean elimination half-life ($t_{1/2}$) was 122 hrs with first-order kinetics, compared with 12 hrs for SC rhIL-12. PK comparisons with lower single doses in healthy volunteers vs. patients showed target-mediated drug distribution, suggesting SON-1010 binding in tumor tissue. IFNγ responses were dose-related, controlled, and prolonged, with low induction of IL-10 and no IL-1β, IL-6, IL-8, or TNFα. There was no evidence of cytokine release syndrome.

SON-1010 is being evaluated in combination with atezolizumab (in collaboration with Genentech, a member of the Roche Group), which has shown clinical activity in patients with platinum-resistant ovarian cancer (PROC). The extended PK of SON-1010, along with its ability to induce IFNγ in the TME that causes upregulation of PD-L1, creates an excellent opportunity for synergistic activity. Dose escalation is ongoing to establish the MTD in this combination. Another trial studying dose escalation of SON-1210 (IL12-F_LAB-IL15), followed by its combination with NALIRIFOX in patients with metastatic pancreatic cancer, will begin later this year.

Finally, SON-1010 may have a positive synergistic effect in alternating doses with trabectedin in first-line patients with unresectable liposarcoma or leiomyosarcoma, which are 'cold' tumors that over-express SPARC. In addition to its ability to block DNA transcription, trabectedin has potent immunomodulatory effects that could synergize with IL-12 APC reporalization in the TME. The first 4 patients have been dosed safely with this combination in the ongoing trial.

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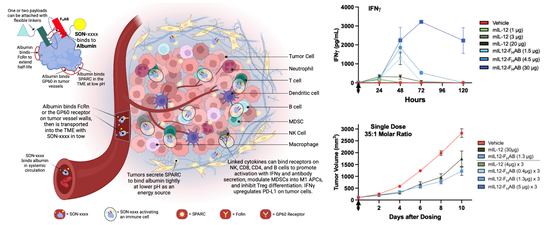
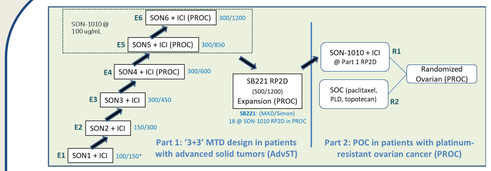
INTRODUCTION

Albumin has been exploited as a carrier for small therapeutic proteins, like IFNα linked directly to albumin to make albinterferon alfa-2B, to increase serum half-life due to its larger molecular weight (> 60 kDa). Albumin is also known to accumulate in inflamed and angiogenic tissues, such as in the TME. We screened for a scFv domain that binds albumin at normal and acidic pH and have developed this F_HAB protein as a platform for cytokine delivery to make 'cold' tumors immunologically 'hot'.

One or two payloads can be linked to this scFv and significant tumor accumulation was shown in mice. Linking IL-12 resulted in a dose-dependent increase in circulating IFNγ with a prolonged half-life, a 35x increase in therapeutic index with minimal toxicity, and an increase in survival in the B16F10 melanoma model (1). Linking IL-15 too led to a marked increase in IFNγ, even better tumor suppression, and activation of NK and CD8⁺ T cells (2).



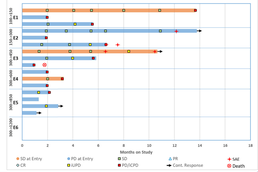
SB221: SON-1010 with Atezolizumab in PROC



The first combination strategy focuses on patients with platinum-resistant ovarian cancer (PROC), which are often immunogenic tumors capable of stimulating host anti-tumor immune responses. However, the recruitment of M2-polarized tumor-associated macrophages (TAMs) contribute to an immunosuppressive TME. IL-12 helps convert M2 to an M1 phenotype and the increased IFNγ upregulates PD-L1 expression. Atezolizumab (Tecentriq®), which blocks PD-L1, has shown clinical activity in patients with OC, although a Ph3 combination with chemotherapy missed its endpoints. We expect SON-1010 to improve the immune environment and enhance the ICI effect of atezolizumab.

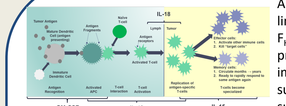
- SB221 is a dose-escalation and POC study designed in Part 1a to rapidly establish the MTD of the combination with atezolizumab (in collaboration with Genentech, a member of the Roche Group)
- Patients with advanced solid tumors or PROC currently being studied in 6 dose-escalation groups
- We will expand the dataset in PROC to establish the RP2D (and first dose safety) moving forward
- The likelihood of efficacy is shown in a Simon 2-stage design (≥1 responder in 1st 7, then ≥4 responders in up to 18 patients) in Part 1b
- Part 2 is a randomized assessment in patients with PROC of the potential for improved efficacy of the combination over the SOC

Related AE	Cohort E1 (100 → 150) N=3	Cohort E2 (150 → 300) N=3	Cohort E3 (300 → 450) N=3	Cohort E4 (300 → 600) N=3	Cohort E5 (300 → 850) N=3	Cohort E6 (300 → 1200) N=TBD	Overall (in 3+) N=16 (%, nr)
Fatigue	1	2	1	2	3		9 (56%, 11)
Pyrexia			1	3	1		5 (31%, 6)
Myalgia	1			1			2 (12%, 2)
Dizziness		1			1		2 (12%, 2)
Chills		1			1		2 (12%, 2)
Nausea		1	1	1	1		4 (25%, 5)
Vomiting		1 (Gr2)	2				3 (19%, 4)
Diarrhea				1	1		2 (12%, 2)
Anorexia					2		3 (19%, 3)
Pneumonitis		1 (Gr3)					1 (Gr3)

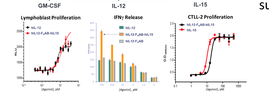


The same dosing strategy from SB101 was used to push the SON-1010 maintenance dose high enough to get the maximal effect. No dose-limiting toxicities or related SAEs have occurred. The swimmers plot shows 7 of 14 patients had SD at the first follow-up CT, 4 of whom were progressing at entry. 4 of 13 (31%) remained stable at 4mo, suggesting clinical benefit.

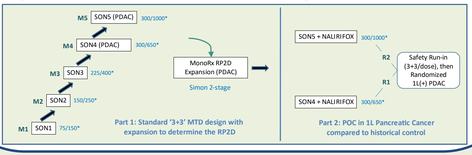
SOC-241: SON-1210 with NALIRIFOX in PDAC



A third combination approach links two cytokines in *cis* to the F_HAB. This greatly increases IFNγ production and was shown to improve tumor growth suppression, with increased survival in B16F10 mice (2).

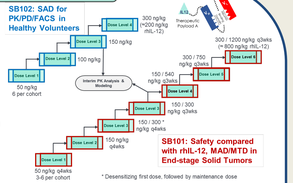


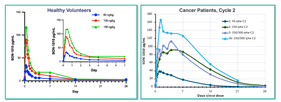
- Dose escalation is planned in Part 1a, which also incorporates the desensitizing dose concept, to establish safety at the MTD in patients with advanced solid tumors or pancreatic ductal adenocarcinoma (PDAC).
- The study will be expanded to find an RP2D in the same population in Part 1b using a Simon 2-stage design.
- Part 2 is designed to activate the TME immune response, alternating in combination with standard NALIRIFOX (liposomal irinotecan [Onivyde®], 5-FU, leucovorin, and oxaliplatin).
- The two highest doses will be randomly compared in 1st line (or higher) PDAC in Part 2 with a safety run-in.

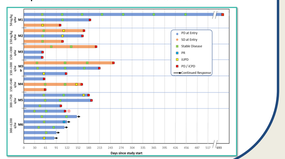


SB101 & SB102: SON-1010 Ph1 Monotherapy

SON-1010 was first introduced in SB101 in patients with advanced solid tumors at the MABEL dose, based on the IL-12 content, to establish the MTD. It was also studied in HVs in SB102 to understand the PK without interference from cancer physiology (3). Typical 2-compartment excretion was seen in HVs but not in cancer, where the PK curve appeared to show 1-compartment kinetics. This is target-mediated drug disposition (TMDD) and suggests both delivery to and retention of SON-1010 in tumors.

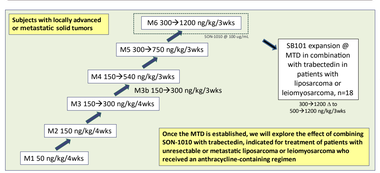


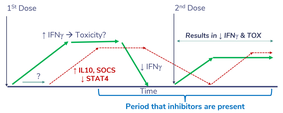




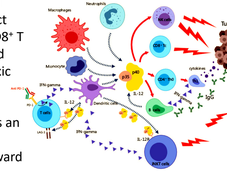
- PK modeling suggests $t_{½}$ in humans is ~120 hours
- Mostly mild AEs and no DLTs to date
- IFNγ response dose-related, controlled, & prolonged
- 10 of 21 patients (48%) have evidence of clinical benefit (SD@4mo)
- One patient in Cohort M6 had a PR.

SB101 Exp: SON-1010 with Trabectedin in Sarcoma



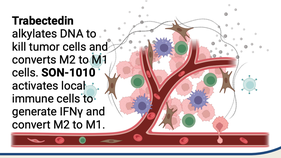


Interleukin-12 bridges innate and adaptive immune responses to act directly on NK, NKT, CD4⁺, and CD8⁺ T cells, stimulating proliferation and IFNγ secretion, increasing cytotoxic functions, and reprogramming immunosuppressive TAMS and MDSCs. Trabectedin (Yondelis®) is an alkylating drug, also known to activate human macrophages toward a pro-inflammatory phenotype.



- SB101 started with dose escalation as monotherapy to establish the MTD
- Currently expanding the study in a second combination strategy using SON-1010 alternating with trabectedin to augment its proinflammatory effects, M2 → M1
- A relatively low 'desensitizing' first dose of SON-1010 is used to benefit from IL-12's known tachyphylaxis through induction of SOCS proteins
- This protects the subsequent doses from causing IFNγ-related toxicity and allows a higher maintenance dose that may expand the therapeutic range.

Given the overlapping mechanisms of action, trabectedin should synergize with SON-1010 to serve as an effective immunotherapeutic combination in patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have been previously treated with doxorubicin, whether the first-line treatment was given alone or with trabectedin. As the risk of this combination may add to the underlying toxicity of either component, the starting dose of trabectedin has been reduced slightly from 1.5 to 1.2 mg/m². The most common (≥20%) adverse reactions for trabectedin are nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. We have initiated the treatment of 5 sarcoma patients with this combination with no unexpected side effects.



CONCLUSIONS

A platform strategy was developed that links cytokines to the F_HAB as mono- or bifunctional fusions to bind native albumin at both physiologic and acidic pH, taking advantage of the latter's long serum half-life and concentration in tumors, allowing delivery to and accumulation of the drug in the TME. IL-12 is a potent cytokine that stimulates the innate and adaptive immune responses, functioning in combination with other cytokines like IL-15 and IL-18. Several combination approaches are currently being studied in humans, such as:

- Co-administration with a checkpoint inhibitor (atezolizumab) to activate local immune cells and upregulate PD-L1 in the TME,
- Alternating administration with an immunoreactive chemotherapy drug (trabectedin) to enhance its ability to activate a pro-inflammatory phenotype in the TME, and
- Alternating administration with a potent chemotherapeutic regimen (NALIRIFOX) in front-line patients to enhance their response.

Each setting has the potential to augment the effects of the licensed therapy in populations that continue to have high unmet needs for an improved outcome. Immunotherapy allows great flexibility in selecting potentially synergistic combinations for rational implementation. SON-1010 and SON-1210 address paramount safety and tolerability factors, which have traditionally hindered the use of therapeutic cytokines in the treatment of solid tumors, by improving the therapeutic index that may result in better patient outcomes.

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