Clinical Development of a Novel Form of Interleukin-12 with Extended Pharmacokinetics

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Abstract CT245

Recombinant interleukins (IL) have had limited clinical success due to inefficient tumor targeting and short pharmacokinetics (PK), requiring frequent dosing that leads to aberrant immunostimulation and toxicity. IL-12 is a promising cancer treatment due to its activation of T and natural killer (NK) lymphocytes to produce interferon (IFN)-γ, yet dosing strategies have failed to provide adequate therapeutic benefit in humans. To address these issues, we developed a novel platform that delivers either mono- or bifunctional immuno-modulator(s) linked to a Fully-Human, Albumin Binding scFv domain (F_HAB®), which provides enhanced tumor targeting and retention through albumin binding to over-expressed FcRn, GP60, and SPARC, an improved PK profile, a dose-sparing effect that decreases the toxicity risk, and a broader therapeutic index. Excellent tumor growth inhibition was seen using a "cold" immunosuppressive B16F10 melanoma model for comparing the efficacy of mIL12-F_HAB with rIL-12, resulting in significant increases in activated NK, NKT, Th1, and cytotoxic CD8 T cells.

We are conducting a first-in-human, dose-escalation trial to evaluate the safety and tolerability of SON-1010 (hIL12-F_HAB) and to determine the maximum tolerated dose (MTD) in patients with advanced solid tumors (NCT05352750). The study has a traditional 3+3 design, modified to take advantage of the known tachyphylaxis of rIL-12 with the introduction of a desensitizing first dose to allow administration of higher maintenance doses. No dose-limiting toxicities have been encountered in the first 3 dose cohorts and the MTD is at least 300 ng/kg. While adverse events seen in other studies of rIL-12 have occurred, they have been transient and tolerable, allowing further dose escalation. Increases in IFNγ were dose-related, controlled, and prolonged. The levels peaked at 24 to 48 hours and returned to baseline after 2 to 4 weeks. Low levels of IL-10 were induced in a dose-dependent manner. No dose-related increase was seen with IL-1β, IL-6, IL-8, or TNF-α and there was no evidence of cytokine release syndrome at these doses.

The preliminary geomean elimination half-life ($T_{½}$) was 122 hours with first-order kinetics, compared with 12 hours for SC rhIL-12. The accumulation estimates are within the margin of error and are not likely to be physiologically significant with SC dosing of SON-1010 every 3 weeks. Eight of 11 patients had stable disease at the first follow-up CT, 4 of whom were progressing at study entry. Two patients were stable at 4 months and 2 had unconfirmed progressive disease; 1 patient remains stable after 8 months on SON-1010 with evidence of tumor regression.

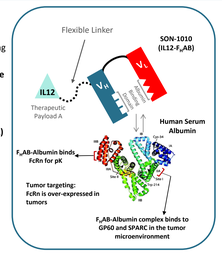
SON-1010 may have a positive synergistic effect with an immune checkpoint inhibitor (ICI), particularly with 'cold' tumors that over-express SPARC. The next stage of development will be to explore the MTD of SON-1010 in combination with an ICI, then to compare that approach with the standard of care in Phase 2.

Sonnet's Fully Human Albumin Binding (F_HAB) technology utilizes a single chain antibody fragment (scFv) capable of delivering one or two active drug compounds

- Therapeutic payloads attached via **flexible linker peptides**

Following administration, Sonnet's F_HAB-derived candidates **bind to and "hitch-hike" on endogenous human serum albumin (HSA)** for transport to target tissues

- F_HAB has been designed to **bind, unbind and rebind to albumin** in an on-and-off fashion through a physical bonding mechanism, obviating the need for chemical conjugation



KEY FEATURES

Fully Human Construct
- Low/No immunogenicity
- Single- or Bi-specific design

Targeted Delivery
- High efficacy with low side effects
- GP60- and SPARC-driven uptake
- Accumulation in lymphatic nodes

Enhanced pK Characteristics
- Extended dosing intervals
- FcRn binding

Small Size with Linear Flexibility
- Optimized tumor penetration

Mammalian Cell Production (CHO)
- Glycosylated

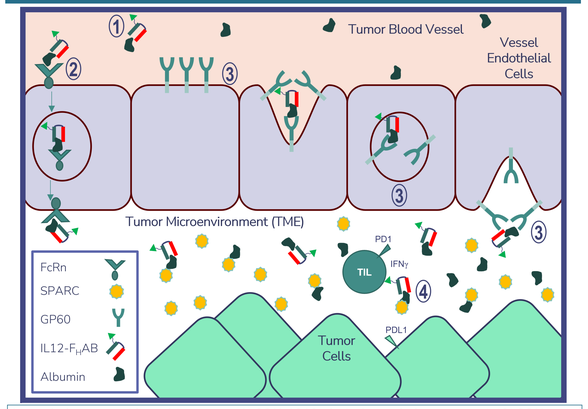
Modular
- Off-the-shelf system
- Rapid asset development

Introduction

First discovered in the late 1980's, NK-cell stimulatory factor, eventually renamed interleukin-12 (IL-12), is a pro-inflammatory cytokine produced by activated phagocytes and dendritic cells and a key regulator of cell-mediated immunity (Aste-Amezaga 1994). IL-12 bridges innate and adaptive immune responses to act directly on NK and NK T cells, as well as $CD4^+$ and $CD8^+$ T cells, stimulating proliferation and increasing cytotoxic functions. IL-12 has been shown to: (i) induce Th1 cell differentiation; (ii) increase activation and cytotoxic capacities of T and NK cells; and (iii) inhibit or reprogram immunosuppressive cells, such as tumor associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). IL-12 also induces the production of large amounts of IFNγ, which itself is cytostatic/cytotoxic, anti-angiogenic, and can upregulate MHC I and II expression on tumor cells for enhanced recognition and lysis (Nguyen 2020).

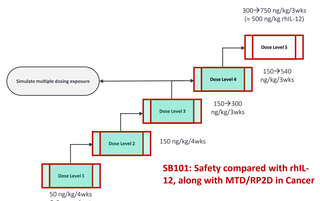
SON-1010 (Cini 2019) is recombinant, single-chain, unmodified human IL-12 joined by a flexible linker to a proprietary fully-human A10m3-Albumin Binding Domain (A10m3-ABD or F_HAB) that is being developed by Sonnet as an extended PK IL-12 molecule. Currently, SON-1010 is being studied in healthy volunteers using a SAD design in SB102 and in patients with advanced solid tumors using a MAD design in SB101.

SON-1010 Structure/Function



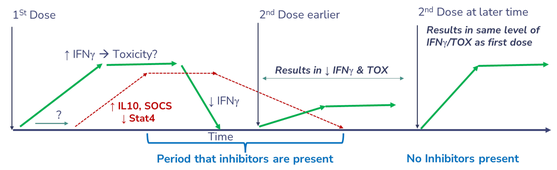
Albumin is elevated in solid tumors. (1) SON-1010 binds Albumin in the blood. (2) SON-1010/Albumin binds to the FcRn resulting in transport from blood to TME. (3) SON-1010/Albumin binds to GP60, resulting in transport from blood to TME. (4) SON-1010/Albumin binds to SPARC. IL-12 activates local immune cells, causing increase in IFNγ and PD-L1 in the tumor cells. This MOA results in SPARC retaining SON-1010 in the TME.

SB101 Study Design



SB101 uses a modified 3+3 design during escalation of SON-1010 across 5 groups, followed by expansion at the MTD to enroll up to 18 patients with platinum-resistant ovarian cancer (PROC) at the RP2D to help characterize safety and the tumor response. Simon's two-stage design will be used to classify subjects as responders if they obtain a CR, PR, or clinical benefit (SD at 4 months).

Tachyphylaxis is Used to Minimize Toxicity



Early efforts to advance rhIL12 into the clinic showed that starting 2 weeks after a test dose, a dose level up to 500 ng/kg daily could be given safely. However, in the first Phase 2 study 12 of 17 patients were hospitalized and 2 patients died (Leonard 1997). Investigation of this unexpected toxicity failed to identify any reason that could have accounted for the difference in outcomes.

A tachyphylaxis effect was found to exist with IL-12, as a single injection of rhIL-12 can have a profound abrogating effect on subsequent IL-12-induced toxicity, associated with a reduction in both Th1 (IFNγ) and Th2 (IL-10) cytokine production with the 2nd dose. This is likely due to the induction of suppressors of cytokine signaling (SOCS) proteins that normally regulate inflammatory responses (Sobah 2021). Since that Phase 2 study, numerous additional studies have been conducted to determine the potential utility of various forms of rhIL12, both in patients with cancer and in at least 19 studies in healthy volunteers, including one with over 90 subjects (Gokhale 2014).

SB101 Demographics

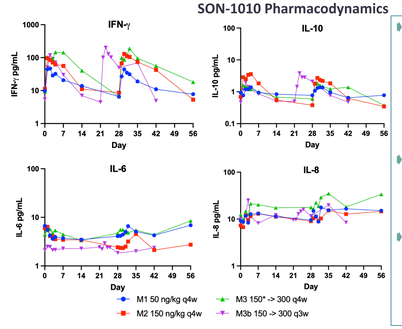
Characteristic, n (%)	50 ng/kg q4w (N=3)	150 ng/kg q4w (N=3)	150 → 300 ng/kg q4w (N=3)	150 → 300 ng/kg q3w (N=3)	150 → 540 ng/kg q3w (N=3)
Tumor Type					
Sarcoma	3 (100.0)	3 (100.0)	3 (100.0)	2 (66.7)	2 (66.7)
Eccrine Porocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Colorectal adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
Age (Mean ± SD)	54.0 ± 9.0	58.7 ± 14.5	58.0 ± 15.4	51.7 ± 9.1	48.0 ± 23.4
Sex					
Male	0 (0.0)	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)
Female	3 (100.0)	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
Race, n(%)					
White	3 (100.0)	2 (66.7)	1 (33.3)	3 (100.0)	2 (66.7)
Black or African American	0 (0.0)	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)
Height (Mean ± SD)	152.4 ± 13.4	168.5 ± 3.9	176.1 ± 10.6	157.5 ± 7.2	168.5 ± 1.5
Weight (Mean ± SD)	89.1 ± 14.7	85.3 ± 10.7	76.8 ± 21.1	77.8 ± 3.5	69.9 ± 12.8
Tumor Stage at Enrollment					
Stage III	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
Stage IV	3 (100.0)	3 (100.0)	2 (66.7)	3 (100.0)	3 (100.0)

SB101 Clinical Results

Safety

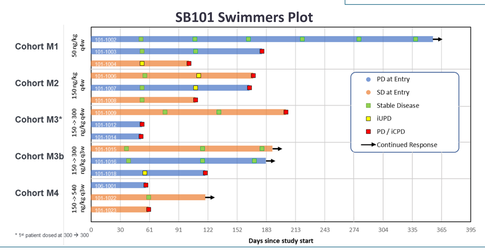
Related TEAEs by Grade	50 ng/kg q4w (N=3)	150 ng/kg q4w (N=3)	150 → 300 ng/kg q4w (N=3)	150 → 300 ng/kg q3w (N=3)	150 → 540 ng/kg q3w (N=3)
Tachycardia (Grade 1)		1 (33.3)			
Nausea (Grade 1)	1 (33.3)				
Chills (Grade 1)		1 (33.3)		1 (33.3)	
Fatigue (Grade 1)		1 (33.3)		1 (33.3)	
Injection site pain (Grade 1)	1 (33.3)	3 (100.0)			
Pain (Grade 1)	1 (33.3)				
Pyrexia (Grade 1)		1 (33.3)	1 (33.3)		1 (33.3)
Decreased appetite (Grade 1)	1 (33.3)				
Oedema peripheral (Grade 1)	1 (33.3)	1 (33.3)			
Arthralgia (Grade 1)	1 (33.3)				
Limb discomfort (Grade 1)	1 (33.3)				
Muscular weakness			1 (33.3)		
Myalgia (Grade 1)	2 (66.7)			1 (33.3)	1 (33.3)
Pain in extremity (Grade 1)	1 (33.3)	1 (33.3)			
Headache (Grade 1)		1 (33.3)		1 (33.3)	
Night sweats (Grade 1)		1 (33.3)			
Rash pruritic (Grade 1)	1 (33.3)			1 (33.3)	
Hot flush (Grade 1)	1 (33.3)				
Abdominal Pain (Grade 1)				1 (33.3)	
Eyelid swelling (Grade 1)				1 (33.3)	
Dysphonia (Grade 1)				1 (33.3)	
Oropharyngeal pain (Grade 1)					1 (33.3)
Lymphadenitis (Grade 1)				1 (33.3)	
Fatigue (Grade 2)	3 (100.0)		1 (33.3)		
Pruritis (Grade 2)				1 (33.3)	
ALT increased (Grade 2)		1 (33.3)			
AST increased (Grade 2)		1 (33.3)			
Lipase Increased (Grade 3)			1 (33.3)		

SON-1010 Pharmacodynamics



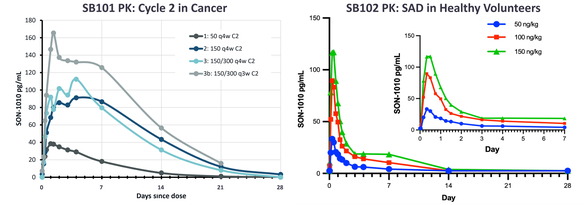
- The IFNγ response was dose-related, controlled, and prolonged after 1st and 2nd doses in all pts. Levels peaked at 24-48 hrs and returned to baseline after 2-4 wks.
- Low amounts of IL-10 were induced with each dose, likely a response to the IFNγ response .
- No consistent response was seen with IL-1β, IL-2, IL-4, IL-6, IL-8, or TNFα and no evidence of cytokine release syndrome (CRS).

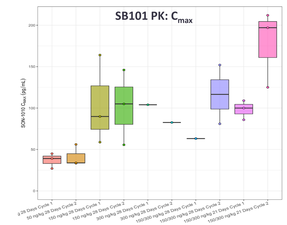
SB101 Swimmers Plot



9 of 15 patients had SD at the first follow-up, 5 of whom were progressing at study entry. 5 of 14 (36%) remained stable at 4mo, suggesting clinical benefit. Mean PFS is 141 days.

SON-1010 PK in 2 Populations





- Typical dose-related increases were seen with SC SON-1010, with 1st order elimination kinetics in cancer, 2nd order in HV
- The preliminary geomean elimination half-life ($T_{½}$) was 113 hours in SB101
- C_{max} was 39 to 197 pg/mL, and the geomean exposure ($AUC_{0\text{-}inf}$) was 8,620 to 43,600 h*pg/mL
- Accumulation estimates are not likely to be physiologically significant with dosing of SON-1010 every 3 weeks

Discussion

SON-1010 appears to be safe and well tolerated in healthy volunteers (NCT05408572) in single doses up to 300 ng/kg and in patients with advanced cancer in repeated doses up to at least 540 ng/kg. Incorporation of a desensitizing first dose at 150-300 ng/kg and dosing every 3 weeks has been implemented to capitalize on the potential benefits of tachyphylaxis with rhIL-12. The pharmacologic effect may be related to the temporary induction of SOCS proteins that can protect from toxicity due to high levels of IFNγ (Sobah 2021), so the timing between doses is important.

The potential benefits of IL-12 antitumor and antimetastatic activities have been extensively shown in murine models. The main limiting factor for the clinical application of IL-12 monotherapy in solid tumors has been the low level of IL-12 infiltration in the TME. SON-1010 targets the TME by binding to albumin, which then accumulates in tumors through binding to the FcRn, GP60, and SPARC.

Surprisingly, the PK curves in the cancer patients compared to those in HVs show a slower pattern of elimination, perhaps due to retention of SON-1010 in tumor tissue. This mimics the results observed in mice, suggesting the potential for a local response in the TME that could be more effective than prior efforts with systemic immunotherapy using rhIL-12. Based on the PK, a dose interval of 3 weeks produces little to no accumulation of SON-1010 and any accumulation of drug is not likely to be physiologically significant. The IFNγ PD response was dose-related, controlled, and prolonged, which is likely to be required to initiate tumor control, without stimulation of a more toxic immune response.

Even though there is a reasonable chance that SON-1010 will inhibit tumor growth at higher doses due to its improved targeting of the TME, SON-1010 may have its greatest effect in treating cancer in combination with some other immunomodulator, such as an immune checkpoint inhibitor (ICI). The next development step is to determine the SON-1010 MTD when combined with an ICI in patients with platinum-resistant ovarian cancer, which continues to be a high unmet need indication and is typically high in SPARC. Proof-of-concept will be assessed in combination with atezolizumab compared with SON-1010 alone or Standard of Care (SOC) therapy (NCT05756907).

Conclusions

- Preliminary PK modeling suggests the $t_{½}$ in humans is >120 hrs
  - Compares favorably with rhIL-12 $t_{½}$ of 5-12 hrs
- No Dose Limiting Toxicities to date in 15 patients
- Mostly mild with very few more significant AEs
  - AEs consistent with published literature for IL-12
  - All have been transient in nature
  - AEs are less numerous and less intense after the first dose
- The IFNγ response was dose-related, controlled, and prolonged
- 5 of the first 14 patients (36%) have evidence of clinical benefit (SD@4mo)
- Cytokine results suggest SON-1010 has extended PK, with induction of an IL-12 effect without CRS

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