INTERIM ANALYSIS OF A PHASE 1 STUDY USING IL12-F_HAB WITH OPTIMIZED PHARMACOKINETICS

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Abstract

Objective: 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-gamma (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 immunomodulator(s) linked to a Fully-Human, Albumin Binding scFv domain (F_HAB®). The platform provides enhanced tumor targeting and retention through albumin binding to over-expressed FcRn, GP60, and SPARC, which results in an improved PK profile, in addition to a dose-sparing effect that decreases the toxicity risk, and provides a broader therapeutic index. Excellent tumor growth inhibition was seen using a "cold" immunosuppressive B16F10 melanoma model for comparing the efficacy of IL12-F_HAB with rIL-12, resulting in significant increases in activated NK, NKT, Th1, and cytotoxic CD8 T cells.

Methods: We are conducting a first-in-human, dose-escalation trial, SB101, to evaluate the safety and tolerability of SON-1010 (IL12-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 IL-12 with the introduction of a desensitizing first dose to allow administration of higher maintenance doses.

Results: No dose-limiting toxicities have been encountered in the first 3 dose cohorts and the MTD is at least 300 ng/kg. While some adverse events are similar to those reported in other studies of IL-12 at these doses, they have been transient and tolerable, allowing further dose escalation. Increases in IFN-γ 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 drug-related increase was seen with IL-1β, IL-6, IL-8, or TNF-α and there has been no evidence of cytokine release syndrome. The preliminary geomean elimination half-life ($T_{½}$) was 113 hours with single-compartment kinetics, compared with 12 hrs for SC rhIL-12. Interestingly, two-compartment kinetics were seen in a parallel single-ascending dose (SAD) study of SON-1010 in healthy volunteers. The accumulation estimates are within the margin of error and are not likely to be physiologically significant with subcutaneous dosing of SON-1010 every 3 weeks. Nine of 15 patients had stable disease at the first follow-up CT, 4 of whom were progressing at study entry. Five patients were stable at 4 months (36% clinical benefit) and 2 had unconfirmed progressive disease; 1 patient remains stable after 12 months on SON-1010 with evidence of tumor regression.

Conclusion: SON-1010 has been tolerated well with a delayed PK profile and causes a controlled and prolonged elevation of IFN-γ. The PK comparison with dosing in healthy volunteers suggests that SON-1010 is being retained in tumor tissue, as the F_HAB platform was designed to do. This monofunctional immunotherapeutic drug candidate may have a positive synergistic effect with an immune checkpoint inhibitor (ICI), particularly with 'cold' tumors that over-express SPARC like sarcoma and ovarian cancer. 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.

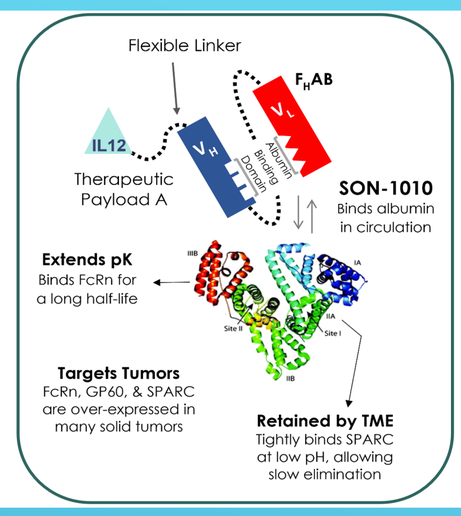
STRUCTURE/FUNCTION

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).

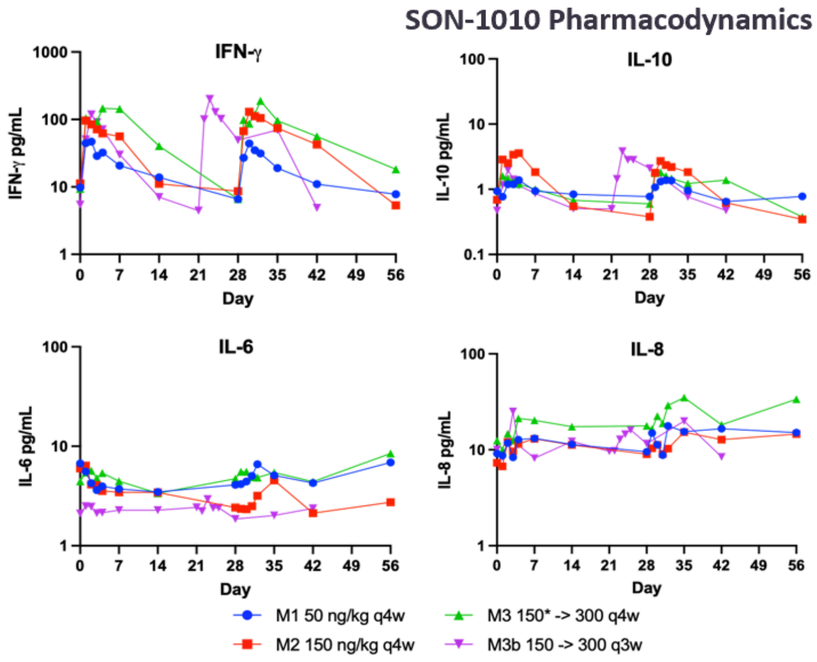
SON-1010 (Cini 2019) is recombinant, single-chain, unmodified human IL-12 joined by a flexible linker to a proprietary fully-human A10m3-Albumin Binding Domain (A10m3-ABD or F_HAB) that is being developed by Sonnet as an extended PK IL-12 molecule. Currently, SON-1010 is being studied in healthy volunteers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

SB101 Clinical Results

Safety

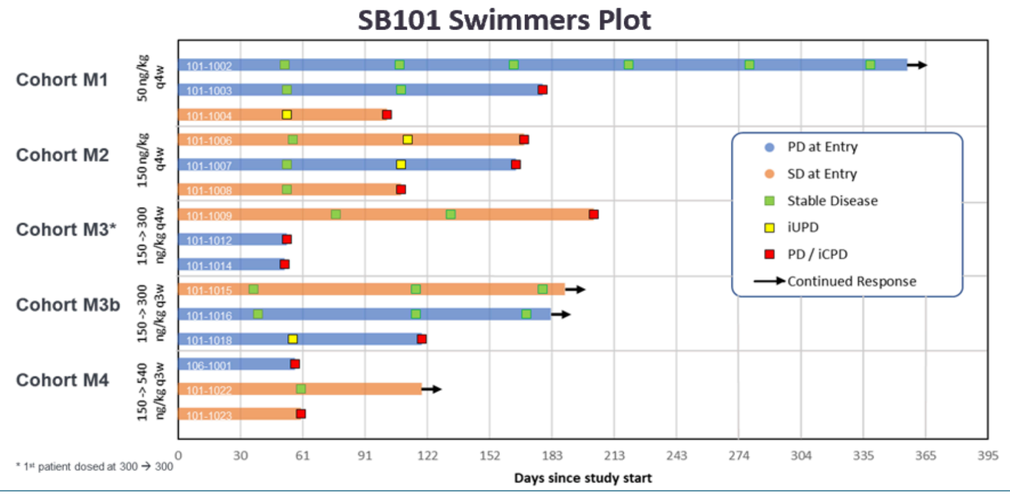
Related TEAEs by Grade	50 ng/kg q4w (N=3)	150 ng/kg q4w (N=3)	150 → 300 ng/kg q4w (N=3)	150 → 300 ng/kg q3w (N=3)	150 → 540 ng/kg q3w (N=3)
Tachycardia (Grade 1)		1 (33.3)			
Nausea (Grade 1)	1 (33.3)				
Chills (Grade 1)		1 (33.3)		1 (33.3)	
Fatigue (Grade 1)		1 (33.3)		1 (33.3)	
Injection site pain (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



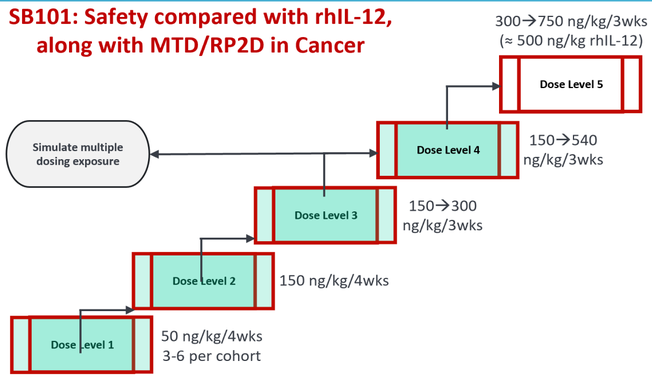
- The IFNγ response was dose-related, controlled, and prolonged after 1st and 2nd doses in all pts. Levels peaked at 24-48 hrs and returned to baseline after 2-4 wks.
- Low amounts of IL-10 were induced with each dose, likely a response to the IFNγ response .
- No consistent response was seen with IL-1β,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

SB101 Swimmers Plot



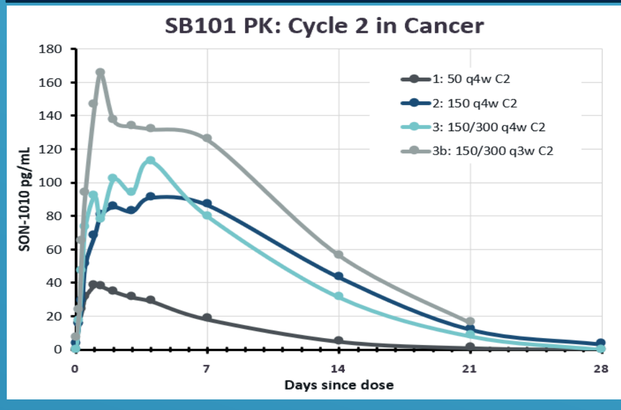
9 of 15 patients had SD at the first follow-up, 5 of whom were progressing at study entry. 5 of 14 (36%) remained stable at 4mo, suggesting clinical benefit. Mean PFS is 141 days.

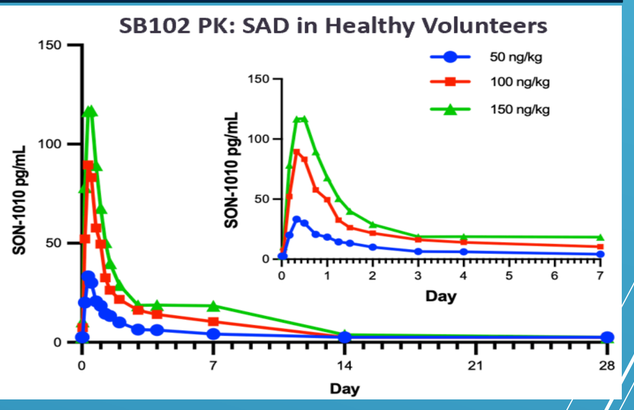
SB101: Safety compared with rhIL-12, along with MTD/RP2D in Cancer



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).

SON-1010 PK in 2 Populations





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.

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 combine SON-1010 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 and are transient
  - 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 and induces an IL-12 effect without CRS

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