**Abstract**

**Background:** Recombinant interleukins (rIL) have had limited clinical success due to inefficient tumor targeting and short PK, requiring frequent dosing that leads to aberrant immunostimulation and toxicity. IL-12 potently activates T and NK cells to produce IFNγ and kill tumor cells, yet dosing strategies have failed to provide adequate therapeutic benefit in humans. We developed a novel platform that delivers immunomodulator(s) linked to a fully-human albumin binding (F₃AB®) domain (Cini, Front Immunol 2023). Single-chain native IL-12 genetically linked to the F₃AB provides enhanced tumor targeting and retention through albumin binding to over-expressed FcRn, GP60, and SPARC in the tumor microenvironment (TME), with an improved PK profile, a dose-sparing effect that decreases the toxicity risk, and a broader therapeutic index. Tumor growth inhibition in an immunologically ‘cold’ B16-F10 mouse melanoma model showed the efficacy of IL12-FHAB compared with rIL-12, resulting in significant increases in activated NK, NKT, Th1, and cytotoxic CD8 T cells. SON-1010 is being studied clinically as monotherapy (study SB101) in advanced solid tumors and in healthy volunteers (study SB102) (Chawla, AACR 2023). Atezolizumab (Tencentriq®), an anti-PD-L1 immune checkpoint inhibitor (ICI), has shown preliminary clinical activity in Phase 1 studies of patients with platinum-resistant ovarian cancer (PROC) (Liu, Gyn Onc 2019; Moroney, Clin Canc Res 2020). SON-1010 may ‘warm up’ the TME to improve ICI effectiveness in these immunologically-active tumors that have high levels of SPARC.

**Methods:** Study SB221 is a Phase 1b/2a multicenter, dose-escalation and proof-of-concept study to assess the safety, tolerability, PK, PD, and efficacy of SON-1010 administered SC, either alone or in combination with a fixed dose of atezolizumab given IV (NCT05756907). The study is designed in Part 1 to rapidly establish the maximum tolerated dose (MTD) of the combination in patients with advanced solid tumors with up to 5 dose-escalation groups and to expand the dataset using patients with PROC to establish the Recommended Phase 2 Dose (RP2D). Once the likelihood of efficacy is shown in a Simon 2-stage design, this will be followed in Part 2 by an assessment in patients with PROC of the potential for improved efficacy of the combination over SON-1010 alone or the standard of care (SOC). The first dose-escalation cohorts have been enrolled and additional sites are being added to help with recruitment of patients with PROC. Combination of SON-1010 with an ICI offers a unique opportunity to use this extended PK version of IL-12 to augment the potential for tumor control in PROC, which represents a significant unmet medical need.

**Background:**

- Recombinant interleukins (rIL) have had limited clinical success due to inefficient tumor targeting and short PK, requiring frequent dosing that leads to aberrant immunostimulation and toxicity. IL-12 potently activates T and NK cells to produce IFNγ and kill tumor cells, yet dosing strategies have failed to provide adequate therapeutic benefit in humans.
- We developed a novel platform that delivers immunomodulator(s) linked to a fully-human albumin binding (F₃AB®) domain (Cini, Front Immunol 2023).
- Single-chain native IL-12 genetically linked to the F₃AB provides enhanced tumor targeting and retention through albumin binding to over-expressed FcRn, GP60, and SPARC in the tumor microenvironment (TME), with an improved PK profile, a dose-sparing effect that decreases the toxicity risk, and a broader therapeutic index.
- Tumor growth inhibition in an immunologically ‘cold’ B16-F10 mouse melanoma model showed the efficacy of IL12-FHAB compared with rIL-12, resulting in significant increases in activated NK, NKT, Th1, and cytotoxic CD8 T cells.
- SON-1010 is being studied clinically as monotherapy (study SB101) in advanced solid tumors and in healthy volunteers (study SB102) (Chawla, AACR 2023).
- Atezolizumab (Tencentriq®), an anti-PD-L1 immune checkpoint inhibitor (ICI), has shown preliminary clinical activity in Phase 1 studies of patients with platinum-resistant ovarian cancer (PROC) (Liu, Gyn Onc 2019; Moroney, Clin Canc Res 2020).
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**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 pH 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

**Structured Framework**

- **Sonnet’s Fully Human Albumin Binding (F₃AB) 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 F₃AB-derived candidates bind to and “hitch-hike” on endogenous human serum albumin (HSA) for transport to target tissues.
- F₃AB 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.
- **Flexible Linker**
- **Therapeutic Payload A**
- **SON-1010 binds albumin in circulation**
- **Targets Tumors**
  - FcRn, GP60, & SPARC are over-expressed in many solid tumors.
- **Retained by TME**
  - Tight binding SPARC at low pH, allowing slow elimination.
- **Extend pK**
  - binds FcRn for a long half-life.

**Cohorts E1-E3 have been completed without DLTs and E4 is fully enrolled. We are currently enrolling patients with PROC in Cohort E5 at any time after their 1st recurrence following a bevacizumab regimen ± mirvetuximab. Contact Swati Atole (swati.atole@novotech-cro.com) for trial registration.**

**Part 1** (N=30-51): Advanced solid tumors → PROC; **Part 2** (N=80, Interim @ 32 events): PROC, defined as ovarian cancer recurrence within 6 months following the last dose of a platinum-containing regimen. Tumor types include epithelial, fallopian tube, or 1st peritoneal carcinoma. Refractory patients, defined as disease that failed to achieve at least a PR to a platinum-containing regimen (i.e., SD or PD), are eligible, provided that outcome was to a 2nd line or later repeated platinum regimen (not 1st line).

**Part 1: 3+3’ MTD design in patients with advanced solid tumors (AdvST)**

- **E1**
  - SON1 + ICI (AdvST)
  - 150/300
  - 100/150*

- **E2**
  - SON1 + ICI

- **E3**
  - SON3 + ICI (AdvST)
  - 300/450

- **E4**
  - SON4 + ICI (AdvST)
  - 300/600

- **E5**
  - SON5 + ICI (AdvST)
  - 300/850

**Part 2: POC in patients with platinum-resistant ovarian cancer (PROC)**

- **SB221 RP2D Expansion (PROC)**
  - SB221: 33 AdvST (MAD/Simon) 18 @ SON-1010 RP2D in PROC
  - SON1010 + ICI @ Part 1 RP2D

- **R1**
  - Randomized Ovarian (PROC)

- **R2**
  - SOC (paclitaxel, PDL, topotecan)

- **Download:**...