#301: Phase 1 dose escalation study of DSP107, a first-in-class CD47 and 4-1BB targeting multifunctional immune-recruitment protein, in patients with advanced solid tumors

Jason J. Luke[1], Anwaar Saeed[2], Babar Bashir[3], Yaffa Shwartz[4], Rinat Tabakman[4], Adam Foley-Comer[4], Antonio Jimeno[5]

Introduction:

- DSP107 is a bi-functional, trimeric, fusion protein composed of sequences from the extracellular domains of SIRPα and 4-1BBL.
- The SIRPα arm targets CD47 overexpressed on tumor cells, blocking the "don't eat me" checkpoint and triggering tumor cell phagocytosis. The trimeric 4-1BBL arm, once cross-presented and immobilized by SIRPα binding to CD47, interacts with 4-1BB expressed on activated immune cells, mainly T- and NK cells in the tumor microenvironment, and stimulates their proliferation and activation. Thereby, DSP107 triggers both an innate and an adaptive immune response.

Figure 1: Trimeric Structure Design For Tumor Selectivity and Improved Safety

Trimeric ligand ends designed to enable:

1. Cancer selective binding to overexpressed CD47 on tumor cells, minimizing RBC binding and associated toxicities
2. Conditional 4-1BB mediated T cell activation dependent on trimeric binding to CD47 on cancer cells

Methods:

- Adult patients with advanced solid tumors (N=23) were treated in escalating dose cohorts with intravenous DSP107 (0.01 - 10 mg/kg QW) during 3-week treatment cycles.
- Patients were treated in single patient cohorts (dose levels 0.01, 0.03 and 0.1 mg/kg) followed by a standard 3 + 3 design at doses 0.3, 1, 3 and 10 mg/kg.
- **Primary study objective:** To determine the safety, tolerability and pharmacokinetic (PK) parameters. When possible, paired biopsies were collected at screening and after 6 weeks (cycle 2).
- Here we report data from the completed DSP107 monotherapy dose escalation portion of study NCT04440735.

Results:

Table 1: Patient Baseline Characteristics

Characteristics	
Total number of patients	N = 23 (cohorts 1 – 7)
Sex	10 (43%) ♀; 13 (57%) ♂
Age	Median 63 (Range 29-78)
Previous lines of therapy	Median 3 (Range 2-8)
PD1/PD-L1 experienced	11 (48%)

Conclusions:

- DSP107 is a novel, CD47 and 4-1BB targeting fusion protein with a differentiated safety, binding and pharmacodynamic profile compared to other CD47 and 4-1BB targeting agents.
- DSP107 showed excellent safety profile with full receptor occupancy and no binding to RBCs.
- Treatment with DSP107 induced increased tumor necrosis and infiltration of T and NK cells at the tumor and tumor margin.
- Fifty percent of the DSP107 treated patients showed stable disease.

[1]Cancer Immunotherapeutic Center, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; [2]University of Kansas Cancer Center, Westwood, KS; [3]Sarah Cannon Research Institute and Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; [4]Kahr Medical Ltd., Jerusalem, Israel; University of Colorado Comprehensive Cancer Center, Aurora, CO[5]

Safety:

- DSP107 doses up to and including 10 mg/kg were safe and well tolerated
- No DLTs and no treatment-related SAEs
- No binding to RBCs, no hematological toxicities, and no hepato-toxicities

Treatment-Related Adverse Events

- Grade 1-2 treatment-related AEs were observed in 70% of patients (16/23)
- Two related Grade 3 AEs – transient hypertension and fatigue (at EOT visit)

Table 2: DSP107 Related AEs

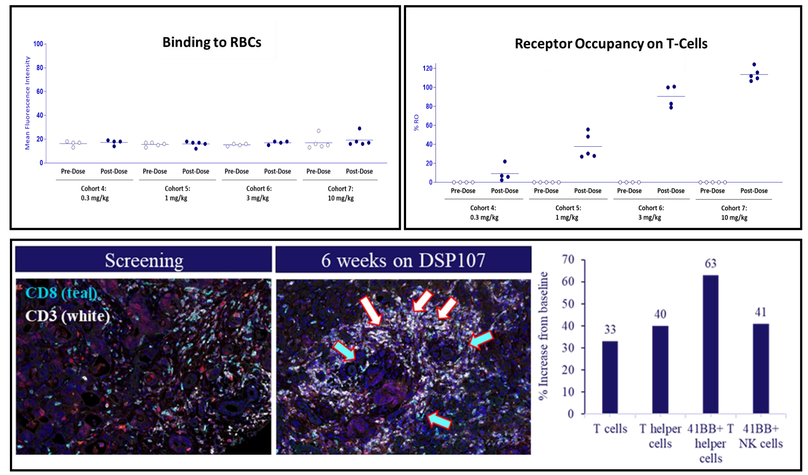
Treatment-Related AEs in ≥ 2 Patients Total No. of Patients N=23 (Cohorts 1-7)	Treatment-related AEs (any grade) n (%)	0.01 mg/kg	0.03 mg/kg	0.1 mg/kg	0. 3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg
Any	16 (70)							
Diarrhea	4 (17)	1	0	0	2	1	0	0
Fatigue	4 (17)	0	1	0	2	0	0	1
Constipation	2 (9)	0	0	0	1	1	0	0
Nausea	3 (13)	0	0	0	1	1	1	0
IRR*	7 (30)	0	0	0	1	3	0	3

*IRRs Grade 1-2 in severity. Easily abrogated (except 10-004 and 11-012 who withdrew consent) in subsequent infusions by reduced rate of infusion and concomitant IV fluids.

Pharmacokinetics and Target Engagement:

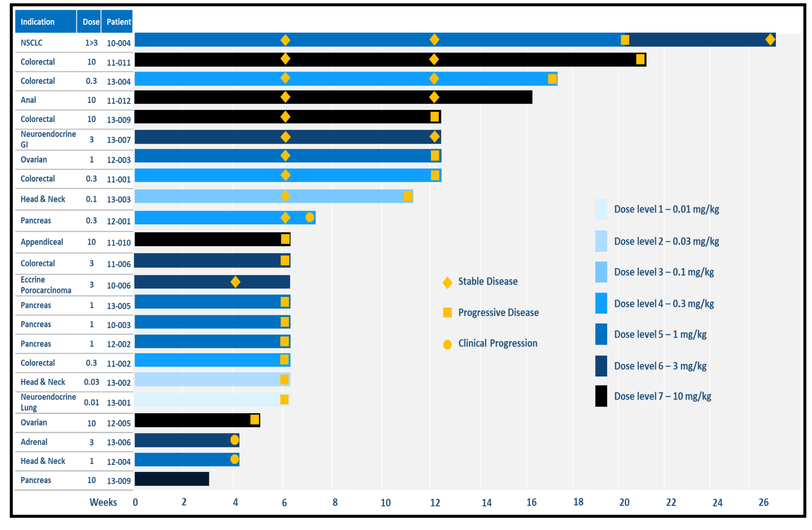
- Greater than dose-proportional exposure at 3 and 10 mg/kg.
- Duration of exposure, C_{max} and AUC increased with dose reaching C_{max} ~100 – 500 times higher than the EC_{50} concentration at 3 and 10 mg/kg, respectively.
- Exposure levels above the EC_{50} at doses ≥ 0.3 mg/kg
- Dose dependent target engagement with 100% receptor occupancy on circulating immune cells
- No binding to RBCs at any dose level.
- DSP107 increased tumor necrosis and triggered T and NK-cell infiltration into tumor microenvironment.

Figure 2: Differential Target Engagement and Immune Cell Infiltration



Response:

- Best response of Stable Disease observed in 11/22 patients with treatment duration up to 26 weeks.



Best Overall Response After DSP107 Monotherapy

- **SD = 11 (50%)**
- PD = 11 (50%) incl. 2 pts withdrawn before 1st CT scan (clinical progression)