Long-Term Efficacy, Safety and PK Data of TH1902 (Sudocetaxel Zendusortide) in Solid Tumors: A Novel SORT1-Targeting Peptide-Drug Conjugate (PDC)

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Introduction

SORT1+ Technology™
First-in-Class Peptide-Drug Conjugate (PDC) Platform Targeting Sortilin (SORT1) Receptors for Cancer
Multimodal Mechanism of Action (MOA) to Sustained Clinical Benefit

Targets SORT1
- Scavenger receptor that rapidly internalizes proteins across cell membrane via endocytosis
- Rapid internalization half life of natural ligand, 4 minutes
- Highly expressed in many types of cancer compared to healthy tissues
- Associated with poor prognosis and decreased survival
- Efficient targeted delivery to cancer cells with rapid internalization of payload
- Minimal amount of cytotoxic in circulation minimizes exposure of cytotoxic agent to healthy cells, reducing toxicity

Sudocetaxel zendusortide (TH1902)
- Lead PDC with a docetaxel payload and cleavable linker
- FDA fast track designation to be developed as a single agent or treatment of patients with SORT1+ recurrrent advanced solid tumors that are refractory to standard therapy

Multimodal mechanism of action (MOA): *Anti-tumor effects*
- Inhibits vasculogenic mimicry (VM) formation
- Efficiently targets and kills chemo therapy-resistant cancer stem cells
- Induces immune cell infiltration (even in " cold " tumor models) and activation of cGAS/sting pathway
- Bypasses the MDR1 efflux pump
- Induces apoptosis and cell cycle arrest (G2/M)
- Inhibits cell migration

Study Design

Characterize the safety and tolerability of TH1902. Part 1 (modified intra-patient dose escalation) included patients with recurrent/refractory advanced solid tumors (all comers) with no limit on number of previous therapies, including taxanes. Part 2 (dose expansion) included patients with known high SORT1 expression (e.g., ovarian and endometrial cancers, TNBC, melanoma).

Phase I Multi-Center, Open Label

Part 1: Dose escalation (n=18) (completed)

Advanced solid tumors relapsed/ refractory to standard therapy/no known effective therapies exist (all comers) (n=15-25)

30 mg/m² Q3W TH1902 starting dose

Intra-patient dose escalation scheme until maximum tolerated dose (MTD) is reached
Dose escalated to 420 mg/m²/Q3W (n=18)

Part 2: Expansion phase (basket trial) (n=18) (completed)

SORT1+ patients with:
HR+ BC (n=10)
TNBC (n=10)
Endometrial cancer (n=10)
Ovarian cancer (n=10)
Melanoma (n=10)
Thyroid (n=5)
SCLC (n=5)
Prostate (n=5)
Others (n=5-10)

Recommended dose from Part 1
300 mg/m2 Q3W

- Safety
- Tolerability
- Preliminary anti-tumor activity
- PK

1 2 3 4 5 6

Figure 1. Study Design for Parts 1 and 2

Enrollment in Part 3 (Dose Optimization) is ongoing. TH1902 is administered on Days 1, 8 and 15 of a 28-day cycle, and in patients with high grade serous ovarian cancer.

► Clinicaltrials.gov ID: NCT04706962.

Results: Subanalysis Female Cancers (TNBC, Ovarian and Endometrial) PP set (n=16)

DEMOGRAPHICS

PATIENTS		CANCER TYPE		PRIOR REGIMENS	
PART 1 (n)	6	Ovarian	9	Mean (Std. Dev)	6.4 (3.5)
PART 2 (n)	10	TNBC	4	Median	5.5
Total	16	Endometrial	3	Min; Max	3; 16
AGE		**ECOG**			
Mean (Std. Dev)	58.3 (11.0)	0	4		
Median	61	1	12	**PRIOR TAXANES**	
Min; Max	34; 74	**BSA (m²)**		Mean (Std. Dev)	2.1 (1.4)
RACE		Mean (Std. Dev)	1.8 (0.3)	Median	2
White	11	Median	1.7	Min; Max	1; 6
Other or Unknown	5	Min; Max	1.5; 2.3		

Table 1. Demographics in female cancers (TNBC, Ovarian & Endometrial) PP subset (n=16)

The Per-Protocol (PP) Set includes all enrolled patients in Parts 1 and 2 of the study who received at least two cycles of TH1902, who complete at least one post-treatment tumor assessment and have no major protocol deviation during the study

The Safety Set includes all enrolled patients in Parts 1 and 2 of the study who received at least one dose of TH1902.

EFFICACY (Duration of Response)

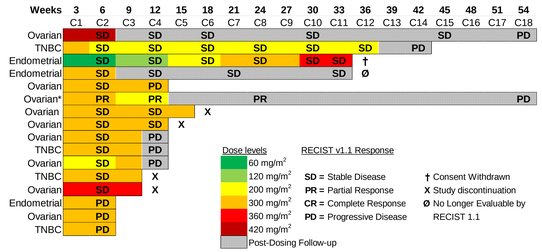

Figure 2. Duration of Response. Parts 1 & 2, All Doses, Female Cancers, PP Set (n=16)
Dosing Every 3 weeks (Q3W) on Day 1 of a 28-day cycle
*: The patient is being externally monitored and is not adhering to the standard scan schedule.

EFFICACY (Best Objective Response BOR)

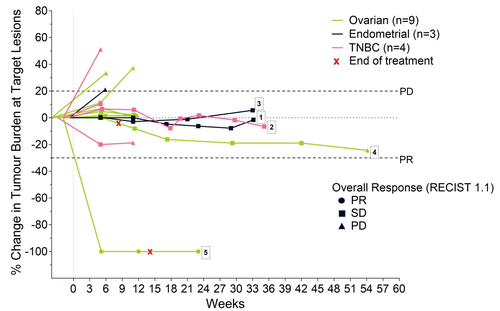

Figure 3. Long-Term Efficacy per RECIST 1.1, Study Parts 1 & 2, All Doses, Female Cancers Per Protocol (PP) Set (n=16)
1: Part 1 – Received 11 treatments with TH1902 ranging from 60 mg/m² to 360 mg/m².
2: Part 2 – Received 2 treatments with TH1902 of 300 mg/m².
3: Part 2 – Received 12 treatments with TH1902 C1: 300 mg/m²,C2-C12: 200 mg/m².
4: Part 1 – Received 2 treatments with TH1902 of 420 mg/m².
5: Part 2 – Received 4 treatments with TH1902 C1-C2: 300 mg/m²,C3-C4: 200 mg/m².

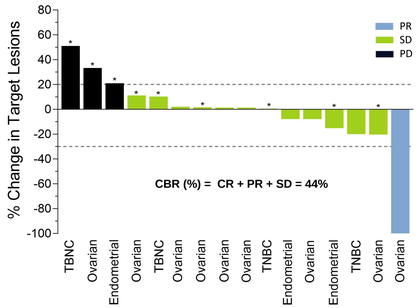

Figure 4. Best Overall response (BOR) per RECIST 1.1 Study Parts 1 & 2, All Doses, Female Cancers, PP Set (n=16)
*: Patient did not have a confirmatory scan or progressed at the time of the confirmatory scan
RECIST 1.1 confirmed response was obtained for 7/16 subjects.

SAFETY

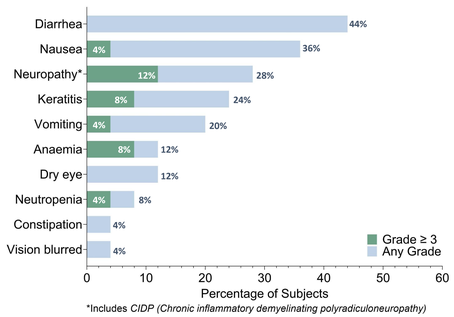

Figure 5. Most Frequent TRAEs of Interest, 300 mg/m² Group, Safety Set (n=25)

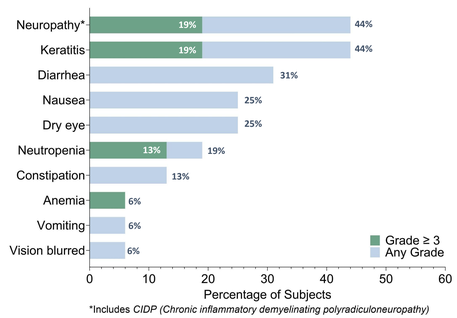

Figure 6. Most Frequent TRAEs of Interest Parts 1 & 2, All Doses, Female Cancers, PP Set (n=16)

Pharmacokinetic Results: PK Set Parts 1&2 (n=36)

PHARMACOKINETICS

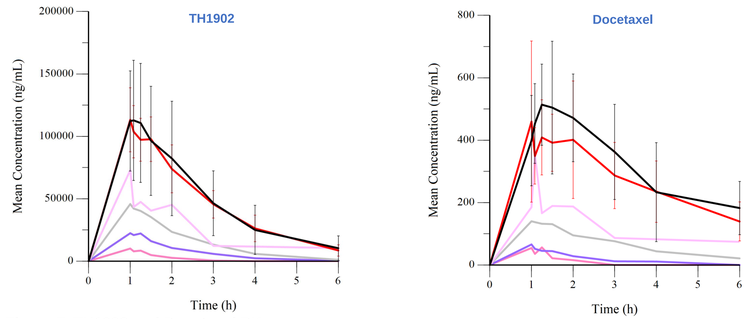

Figure 7. TH1902 and Docetaxel PK curves

- Cmax = 0.58 µM for free docetaxel vs 30.4 µM for TH1902
- AUC24 = 3.1 h.nmol/mL for free docetaxel vs 74.8 h.nmol/mL for TH1902.
- PK data were collected for both TH1902 and docetaxel up to 48 hours post dose in Part 1 and up to 4 hours post dose in part 2.
- Non-compartmental analyses (NCA) were conducted.
- PK set is defined as all patients who received at least one dose of TH1902 and who have sufficient plasma concentration data for PK evaluations

Summary of main PK parameters

At 300 and 420 mg/m² Q3W doses:
- TH1902 half-life is ≈1h10 min
- Free docetaxel/TH1902 AUC ratios <1% up to 300 mg/m², suggesting that most docetaxel remains associated with the peptide over period of analysis
- AUC & Cmax of both analytes increases in a generally dose proportional manner between 300-420 mg/m² Q3W.

Overall Conclusions

- TH1902 induces clinically significant long lasting disease stabilization (up to 45 weeks) that extends beyond treatment completion, suggesting a unique, multimodal MOA that differs from other anti-cancer treatments.
- A sub-analysis in female cancers (OVC, EC, TNBC) (n=16) demonstrated a RECIST 1.1 confirmed CBR (CR+PR+SD) in 7/16 subjects (44%).
- TH1902 has a manageable safety profile at 300mg/m² with few Gr3 AEs compared to the published literature for unconjugated docetaxel. Low levels of free docetaxel may partially explain the lower incidence/severity of AEs seen with TH1902 compared to docetaxel alone.
- Part 3 of the study involves dose optimization, in ovarian cancer patients no longer responsive to platinum, who have only one previous taxane failure and who are not expected to gain clinical benefit from current approved therapies. Weight-based dosing with lower doses given weekly for 3 weeks q 28 days, will be used to further limit toxicity and improve efficacy.

[1]Roy G et al. EORTC-NCI-AACR-2022, abstract #328.
[2]Roy G et al. AACR-2023, abstract #3942 .
[3] Demeule M et al. *Pharmaceutics.* 2022;14(9):1910.
[4]Charfi C et al. *Front. Oncol.* 2021;11:760787.
[5]Demeule M et al. *Cancer Sci.* 2021;112(10):4317-4334.
[6]Currie JC et al. *Cancers (Basel)*. 2022;14(8):1877.
[7]Simon R et al. *J National Cancer Institute.* 1997;89(15):1138-1147.
[8]Demeule M et al. Front Immunol. 2024; 15:1355945.