Sudocetaxel Zendusortide (TH1902), a Novel Sortilin-Receptor (SORT1)-Targeting Peptide-Drug-Conjugate (PDC) in Patients (pts) with Advanced Solid Tumors: Results from Part 1 (Dose-Escalation) of a Phase 1, Open-Label Study

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Introduction

- TH1902 is a first-in-class PDC which consists of 2 molecules of docetaxel conjugated to the TH19P01 peptide via a cleavable succinyl linker.
- TH1902 was granted FDA fast track designation in Feb. 2021.
- SORT1 is overexpressed in many solid tumors as compared to normal tissues[1,2].
- TH1902 demonstrated anti-cancer effects in triple-negative breast cancer (TNBC), ovarian (OVC), and endometrial cancer animal models.[3-6]
- Here we report results from Part 1 (and preliminary results for Part 2) of the First in Human (FIH), multicenter, phase 1 study, designed to characterize the safety and tolerability of TH1902 in advanced solid tumors.

Methods

- Part 1 of the study used a modified intra-patient dose escalation design.[7] The starting dose of 30 mg/m^2 Q3W of TH1902 was based on TH1902 preclinical data. Part 2 objectives were to determine the safety and efficacy of the RD dose from Part 1.
- Key Inclusion Criteria:
  - Adults with confirmed diagnosis of metastatic or advanced-stage solid tumor that is refractory to standard therapies
  - No limit on previous lines of therapy
  - Pts with measurable disease according to the RECIST 1.1
  - Life expectancy of at least 3 months; ECOG performance status of 0 to 1
  - No evidence of persistent ≥Grade 2 neurotoxicity or ocular toxicity
- Trial design:

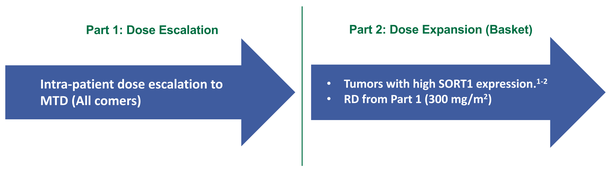

Figure 1. Trial Design for Phase 1 (Part 1 and Part 2)

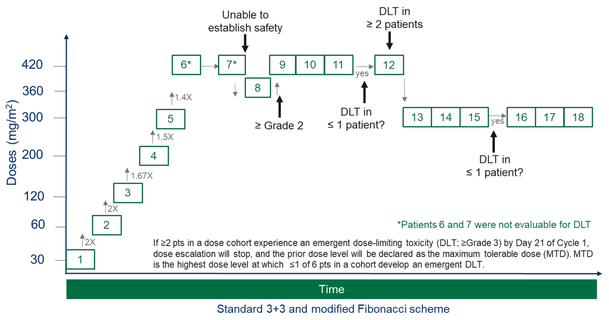

Figure 2. Dose Escalation Scheme Part 1 (18 patients)

- 1 pt enrolled per dose cohort at 30, 60, 120, 200, and 360 mg/mg^2 Q3W
- 7 pts enrolled at 300 mg/m^2 Q3W
- 6 pts enrolled at 420 mg/m^2 Q3W

Results

A. ENROLLMENT

The study was conducted in 4 sites (USA).

Patients		BSA (m^2)		Cancer Type	
N	18	Mean (Std. Dev)	1.78 (0.24)	Ovarian	6
Sex		Median	1.72	Endometrial	1
Male	6	Min, Max	1.40, 2.19	Cervical	1
Female	12			HR+ Breast	3
Age		**No. Prior Regimens**		Prostate	3
Mean (Std. Dev)	60.8 (8.7)	Mean (Std. Dev)	7.8 (4.8)	Melanoma	3
Median	62.5	Median	6.5	NSCLC	1
Min, Max	38, 76	Min, Max	3, 20		
Race		**No. Prior Taxanes**		**ECOG**	
White	15	Mean (Std. Dev)	1.8 (1.8)	0	3
Other or unknown	2	Median	1	1	15
Black or African American	1	Min, Max	0, 6		

Table 1. Demographics and Profile of Patients Enrolled (Part 1)

B. SAFETY

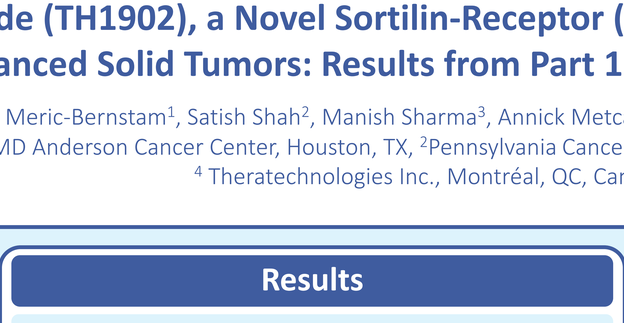

Figure 3. Most Common Treatment-Related Adverse Events (TRAEs) Part 1 (Safety Set)

- No TRAEs at <300 mg/m^2 except for a pt enrolled at 60 mg/m^2 who had Gr 2 neuropathy when escalated to 360 mg/m^2 (Cycle 10).

C. PRELIMINARY PK, IMMUNOGENICITY and SORT1 EXPRESSION

- **Pharmacokinetic (PK)**
  - AUC and Cmax of both TH1902 and docetaxel increased generally in a dose proportional manner between 30 to 420 mg/m^2.
  - TH1902 half-life is ≈1h-1h30 for 300 and 420 mg/m^2 doses.
  - The docetaxel / TH1902 AUC ratio was <1% at all doses.
- **Anti-drug antibodies (ADA)**
  - No ADA against TH1902 were detected in all 18 patients of Part 1 including patients receiving multiple doses (up to 11 treatment cycles).
- **SORT1 expression**
  - Moderate to strong expression of SORT1 (H score ≥100) was observed in ~60% of the available patient biopsies. Data are insufficient at this time to correlate efficacy with SORT1 expression

Results (cont'd)

D. EFFICACY

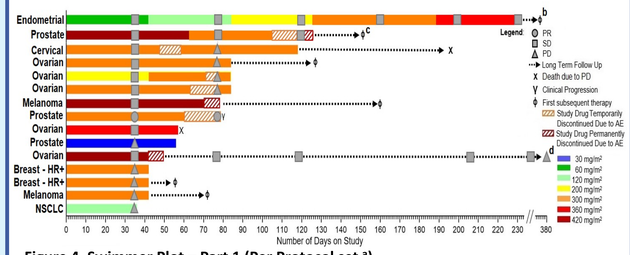

Figure 4. Swimmer Plot – Part 1 (Per Protocol set [a])

[a] The PP set consisted of all enrolled pts who received at least 2 cycles of TH1902 and who completed at least 1 post-treatment tumor assessment.
[b] Confirmed SD lasted for a total of 233 days (33 weeks). First subsequent therapy started 111 days (16 weeks) after the End of Treatment (EOT) visit.
[c] Confirmed SD lasted for a total of 119 days (17 weeks).
[d] Confirmed SD lasted for a total of 295 days (42 weeks).

E. PART 1 DOSE ESCALATION CONCLUSIONS

- TH1902 doses <300 mg/m^2 were well tolerated.
- Preliminary PK data suggest that the toxicity at ≥300 mg/m^2 is exposure-dependent.
- The MTD and DLT were established at 360mg/m^2 and 420 mg/m^2, respectively.
- At doses ≥300mg/m^2 (n=14 pts) the following ≥Gr 3 TRAEs were reported: Gr 3 neuropathy (n=2), Gr 3-4 neutropenia (n=3), Gr 3-4 leukopenia (n=2), Gr 3 anemia (n=1), and Gr 3 punctate keratitis (n=1).
- Preliminary efficacy was observed in Part 1 with 1 PR (prostate) and 3 prolonged SD (endometrial and ovarian and prostate).
- A dose of 300 mg/m^2 (i.e. below the MTD) was selected for Part 2 of the study (dose expansion).

F. PART 2 EXPANSION INTERIM SAFETY AND EFFICACY DATA

- 18 additional pts were enrolled into the 300 mg/m^2 expansion cohort.
- An interim efficacy and safety analysis from Parts 1 and 2 was performed.

TRAEs by System Organ Class	Dose 300 mg/m^2 (N = 25)	
	All	Grade ≥ 3
Blood and lymphatic system disorders	16%	12%
Eye Disorders	32% [a]	8%
Gastrointestinal disorders	52%	4%
General disorders and administration site	36%	0%
Metabolism and nutrition disorders	20%	8%
Musculoskeletal and connective tissue disorders	36%	0%
Nervous system disorders	28% [b]	8%
Respiratory, thoracic, and mediastinal disorders	4%	0%
Skin and subcutaneous tissue disorders	12%	0%
Vascular disorders	4%	0%

Table 2. Most Common TRAEs in Pts Enrolled in 300 mg/m^2 Dose Cohort (Parts 1 &2)

[a] Includes dry eyes, keratitis, punctate keratitis, blurred vision and photophobia.
[b] Includes neuropathy (20%) and other TRAEs like headache, dizziness, paresthesia and hypoesthesia.

Results (cont'd)

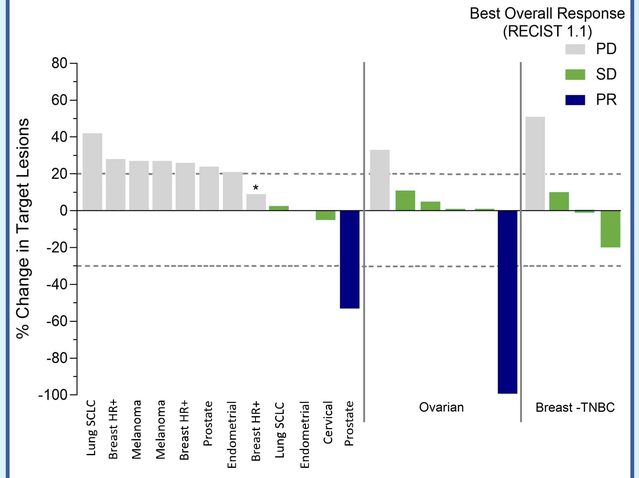

Figure 5. Best Radiological Response (RECIST 1.1) – 300 mg/m^2 dose cohort (Parts 1 & 2)

* BOR is PD due to a progression of the Non-Target Lesions.

- 2 RECIST confirmed PRs: in 1 prostate cancer pt and 1 OVC pt
- OVC (n=6): 83% of OVC pts had BOR of either PR (n=1) or SD (n=4)
- TNBC (n=4): 75% of TNBC pts had BOR of SD (1 pt for at least 4 cycles, who remains on treatment with continued clinical benefit for at least 8 cycles)
- Endometrial (n=2): 1 pt had BOR of SD (233 days or 33 weeks)

Overall Conclusions

- Based on Part 1 results, the 300 mg/m^2 Q3W dose level was selected for Part 2 basket expansion across multiple tumor types.
- At 300 mg/m^2, the most common TRAEs (>20%) were ocular changes, neuropathy, GI disturbances, and MSK complaints, with ≥Gr 3 toxicities at a frequency of ≤12%.
- Preliminary signs of efficacy were noted in 9 (36%) heavily pretreated pts in Parts 1 & 2 (n=25): 2 PRs and 7 prolonged SD or clinical benefit (≥4 cycles). However, the risk-benefit profile was deemed insufficient to proceed with the 300 mg/m^2 Q3W dosing regimen.
- In order to improve the therapeutic window of TH1902, an amendment to the study protocol reflecting changes in patient selection (ovarian cancer) and alternative dosing regimens is currently under FDA review.
- Clinicaltrials.gov ID: NCT04706962.

[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.