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A Phase 2, Multi-Center, Open-Label, Dose-Optimization Study Evaluating Telomere Targeting Agent THIO Sequenced with Cemiplimab in Patients with Advanced NSCLC - Preliminary Results

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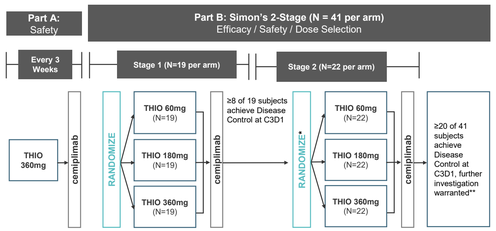
INTRODUCTION

- Resistance to immunotherapy develops in most advanced non–small-cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICI) with very limited treatment options for patients who progress. Ramucirumab and docetaxel combination in 2L showed an improvement in Disease Control Rate (DCR) (64%) and Overall Response Rate (ORR) (23%) compared to docetaxel (DCR (53%) and ORR (14%) respectively). In addition, ramucirumab-docetaxel combination showed OS improvement of 1.4 months (10.5 vs 9.1 months) and PFS improvement of 1.5 months (4.5 vs 3.0 months) over docetaxel single agent. However, 79% of patients treated in the combination arm developed Grade ≥ 3 TEAE[1], therefore there's a high need for new safer and more active treatments.
- In 3L, currently there is no SoC, various chemotherapy agents are being utilized, with reported DCRs in the 25-35% range[2]. In NSCLC 1L with PD-L1 expression >50%, Keytruda reported 71% DCR in KEYNOTE-024[3].
- DCR has been demonstrated to be a better predictor of OS advantage compared to ORR in NSCLC post first line of therapy[2].
- THIO (6-thio-2'-deoxyguanosine) is a small molecule, first-in class direct cancer telomere targeting agent which selectively kills cancer cells that are telomerase positive (TERT+). Over 80% of all cancers are TERT+ and approximately 85% of all NSCLC types[4,5].
- THIO is incorporated de novo in synthesized telomeres leading to chromatin uncapping, DNA damage signals generation and rapid apoptosis
- Preclinical data[6] in NSCLC indicates that low doses of THIO induce sensitivity to immune check point inhibitors when administered prior to an ICI in tumors which otherwise are resistant or do not respond to an ICI
- THIO targets and selectively kills cancer cells through 2 key mechanisms[6]:
  - Induction of DNA damage pathway results in the formation of Telomere Dysfunction Induced Foci (TIF), followed by rapid G2/M arrest or cell death of telomere-positive cancer cells.
  - Activation of cGAS-STING-dependent innate and adaptive immune responses upon release of intracellular and extracellular THIO-containing telomeric DNA fragments.
- Sequential treatment of THIO and immune check point inhibitors showed a potent and durable antitumor activity in preclinical models[6].

METHODS

- THIO-101 is a Phase 2, randomized, dose-optimization clinical study in adults with advanced NSCLC who either progressed or relapsed after 1L treatment with ICI alone or in combination with chemotherapy (NCT05208944)[7].
- Using a modified 3+3 design, the safety lead-in (Part A) enrolled 10 patients who received THIO, 360 mg IV [120 mg QD, D1–3], followed by 350 mg cemiplimab on D5, Q3W
- Following completion of Part A, enrollment was opened in the dose-finding portion of the study (Part B)
- Using a Simon 2-stage design, a total of 123 patients (41 patients/arm) will be assigned to one of the THIO doses: 360, 180, or 60 mg followed by cemiplimab Q3W for up to 1 year
- Disease status is assessed at Cycle 3 Day 1, Cycle 5 Day 1 and every 9 -12 weeks thereafter
- We report here data from the first 49 patients enrolled on the study

FIGURE 1. Study Schema (NSCLC 2L+)



*Stage 2 arms based on results from stage 1
**Based on data from Part B, planned expansion cohort to be completed with dose selected (N=100-120)

Primary Endpoints: Safety, ORR, DCR (CR, PR and SD)

Secondary Endpoints: DoR; PFS; OS

Exploratory Endpoints: PK and PD (activity of THIO in circulating tumor cells measured by specific biomarkers)

BASELINE CHARACTERISTICS

- 49 subjects with advanced NSCLC received at least one dose of the study drug (cutoff date 13-Sep-2023)
- All subjects had previously failed at least 1 prior line of ICI +/- chemotherapy in the advanced setting and had documented disease progression at study entry
- 51% of patients had 2 or more prior treatments lines at study entry

TABLE 1. Study Baseline Characteristics

Characteristic	60mg, N = 17[1]	180mg, N = 18[1]	360mg, N = 14[1]	Total, N = 49[1]
Age				
Mean (SD)	68 (7)	69 (7)	66 (7)	68 (7)
Median (IQR)	70 (64, 72)	70 (65, 73)	68 (60, 71)	68 (64, 72)
Range	56, 85	58, 81	50, 75	50, 85
Sex				
Female	7 / 17 (41%)	4 / 17 (24%)	7 / 14 (50%)	18 / 48 (38%)
Male	10 / 17 (59%)	13 / 17 (76%)	7 / 14 (50%)	30 / 48 (63%)
Number of Prior Lines				
1	12 / 17 (71%)	7 / 18 (39%)	5 / 14 (36%)	24 / 49 (49%)
2	4 / 17 (24%)	10 / 18 (56%)	6 / 14 (43%)	20 / 49 (41%)
3	1 / 17 (5.9%)	0 / 18 (0%)	2 / 14 (14%)	3 / 49 (6.1%)
4	0 / 17 (0%)	1 / 18 (5.6%)	1 / 14 (7.1%)	2 / 49 (4.1%)
ECOG				
0	5 / 17 (29%)	4 / 18 (22%)	7 / 14 (50%)	16 / 49 (33%)
1	12 / 17 (71%)	14 / 18 (78%)	7 / 14 (50%)	33 / 49 (67%)
Histology				
Non-Squamous	7 / 12 (58%)	10 / 15 (67%)	8 / 14 (57%)	25 / 41 (61%)
Squamous Cell Carcinoma	5 / 12 (42%)	5 / 15 (33%)	6 / 14 (43%)	16 / 41 (39%)
Brain Metastases at Baseline	0 / 15 (0%)	0 / 16 (0%)	2 / 14 (14%)	2 / 45 (4.4%)
Liver Metastases at Baseline	3 / 15 (20%)	3 / 16 (19%)	3 / 14 (21%)	9 / 45 (20%)

[1]n / N (%)

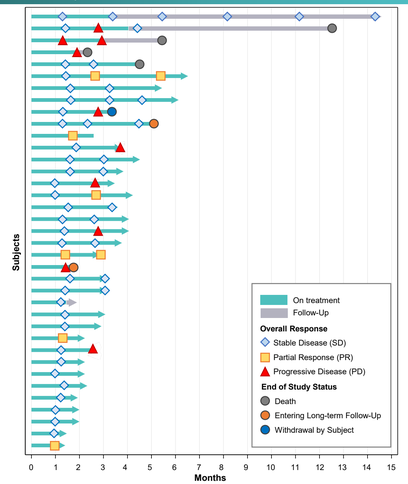
CONCLUSIONS

- **In this ongoing Phase 2 study, THIO has been investigated in sequence with cemiplimab in doses ranging from 60 – 360 mg/cycle in 49 subjects in 2L+ NSCLC who have failed prior treatment with an ICI. Enrollment is ongoing to assess preliminary safety and efficacy of THIO + cemiplimab by dose level.**
- **DCR across all dose levels met the pre-determined statistical requirements to proceed to Stage 2, dose expansion cohorts.**
- **DCR in 2L (100%) and 3L (88%) is very encouraging and may give an insight on future OS benefit.**
- **Evidence of clinical activity with PRs recorded in both 2L and 3L patients.**
- **60 and 180 mg/cycle THIO administered in sequence with 350 mg cemiplimab every 3 weeks was well tolerated. The most frequently reported related Grade 3+ AEs were ALT Increase (9.1%) and AST Increased (9.1%), none of which were associated with clinical symptoms, and all resolved to baseline.**
- **Potential to re-evaluate 360 mg dose once Stage 2 enrollment is completed at both 60 mg/cycle and 180 mg/cycle doses (41 subjects/dose) and safety evaluation across all subjects is completed.**
- **Induction of DNA damage effect measured by Telomeric Dysfunction Induced Foci (TIF) in CTC shows on target effect.**

EFFICACY

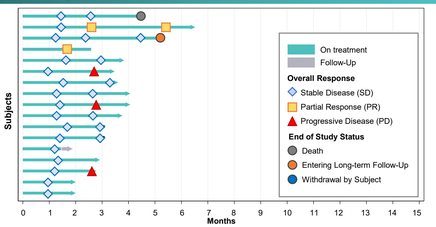
- 37 subjects completed at least 1 post baseline assessment completed at time of cut-off
- At the time of cut-off, the median duration of treatment for patients with at least 1 post baseline assessment was 12.4 weeks (range 3.4 – 28.4 weeks) with 26 of 37 subjects (70%) ongoing
- Partial Responses (PRs) per RECIST 1.1 were reported for 6 subjects, with 2 PRs confirmed by a 2nd scan (per Investigators' assessment)
- The first 2 subjects dosed on trial (both receiving 3rd line of treatment) reported long term survival of 14.6 and 12.5 months respectively at the time of the cut-off with no new anti-cancer treatment initiated. Follow up was ongoing for the first subject

FIGURE 2. All Subjects*



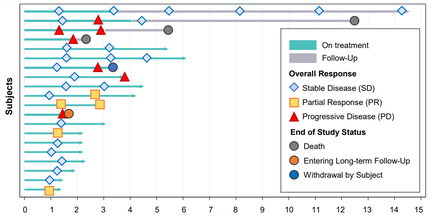
*Includes all subjects with at least 1 post baseline response assessment (n=37)

FIGURE 3. Subjects 2L*



*Includes all subjects with at least 1 post baseline response assessment (n=17)

FIGURE 4. Subjects 3L+*



*Includes all subjects with at least 1 post baseline response assessment (n=20)

DISEASE CONTROL RATES

- DCR, [defined as CR, PR, or SD per RECIST 1.1 at Cycle 3 Day 1 (6 weeks)] met the pre-determined statistical requirements per protocol to proceed to Stage 2. However, the data is not mature yet to assess the ORR
- Disease control was reported in 34 of 37 subjects (92%) with at least one post baseline assessment, including 19 of 19 subjects (100%) in 2nd line and 14 of 16 subjects (88%) in 3rd line
- By dose level, Disease control was reported in 11 of 13 subjects (85%) assigned THIO 360 mg/cycle, 11 of 11 subjects (100%) assigned THIO 180 mg/cycle, and 12 of 13 subjects (92%) assigned THIO 60 mg/cycle
- All dose levels being tested already met DCR required in Stage 1 to warrant further investigation (DCR ≥8 of 19 subjects)

TABLE 2. Study Disease Control Rates by Line of Treatment

Treatment Line*	Disease Control**	Total***	DCR
2L	19	19	100%
3L	14	16	88%
4L	1	2	50%
Total	**34**	**37**	**92%**

*All study entry
**CR/PR/SD at 1st Post Baseline Scan
***Includes all subjects with at least 1 post baseline assessment at the time of the cut-off. No subjects discontinued due to disease progression prior to first scan

SAFETY

- All and Grade 3+ related Adverse Events (AE) by dose level and total per CTCAE v5.0

TABLE 3. Related* Treatment Emergent Adverse Events - All Grades

AE Preferred Term	60mg (N=15)	180mg (N=15)	360mg (N=14)	Total (N=44)
Aspartate aminotransferase increased	3 (20%)	3 (20%)	4 (28.6%)	10 (22.7%)
Alanine aminotransferase increased	3 (20%)	3 (20%)	3 (21.4%)	9 (20.5%)
Nausea	1 (6.7%)	0 (0.0%)	7 (50%)	8 (18.2%)
Anaemia	0 (0.0%)	1 (6.7%)	1 (7.1%)	2 (4.5%)
Blood alkaline phosphatase increased	1 (6.7%)	1 (6.7%)	0 (0.0%)	2 (4.5%)
Decreased appetite	0 (0.0%)	0 (0.0%)	2 (14.3%)	2 (4.5%)
Leukopenia	1 (6.7%)	0 (0.0%)	1 (7.1%)	2 (4.5%)
Neutropenia	1 (6.7%)	1 (6.7%)	0 (0.0%)	2 (4.5%)

*All AEs reported as at least possibly related to either THIO or cemiplimab by PI in at least 2 subjects

TABLE 4. Related* Treatment Emergent Adverse Events - Grade 3+

AE Preferred Term	60mg (N=15)	180mg (N=15)	360mg (N=14)	Total (N=44)
Alanine aminotransferase increased	0 (0.0%)	2 (13.3%)	2 (14.3%)	4 (9.1%)
Aspartate aminotransferase increased	1 (6.7%)	1 (6.7%)	2 (14.3%)	4 (9.1%)
Blood alkaline phosphatase increased	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (2.3%)
Gamma-glutamyltransferase increased	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (2.3%)
Neutropenia	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Nausea	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (2.3%)

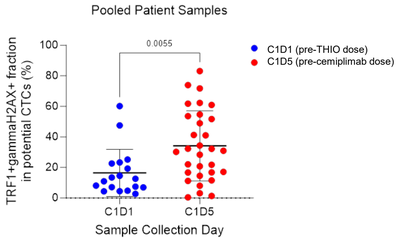
*All Grade 3+ AEs reported as at least possibly related to either THIO or cemiplimab by PI

- Overall, THIO + cemiplimab has been generally well-tolerated to date in a heavily pre-treated population, with the majority of events being Grade 1-2.
- Of the 49 patients who received at least one dose of THIO, 5 subjects were recently enrolled with less than 1 full cycle of treatment and no AEs were entered in the database. They were removed from the safety analysis to not underestimate the AE incidence.
- Related Grade 3+ ALT increase has been reported in 4 subjects (9.1%), with 2 subjects at 360 mg/cycle and 180 mg/cycle, respectively. Related Grade 3+ AST increase has been reported in 4 subjects (9.1%), with 2 subjects at 360 mg/cycle, and 1 subject at 180 mg/cycle and 60 mg/cycle, respectively. No clinical symptoms were associated with the elevated lab values, and all returned to baseline without sequela. No other related Grade 3+ event has been reported in more than 1 subject.
- Following an event of Grade 4 LFT elevation in a patient receiving 360 mg/cycle in Part B, enrollment into the 360 mg/cycle arm was paused. Enrollment is ongoing in Part B at 60 mg/cycle and 180 mg/cycle, and further enrollment into 360 mg/cycle will be evaluated following completion of Stage 2.

BIOMARKERS

- THIO is expected to induce Telomere Damage Induced Foci (TIF) in circulating tumor cells (CTCs) in whole blood patient samples as evidence of on target effect
- Aggregate data from all 3 dose-levels demonstrated statistically significant increase in TIF levels at C1D5 (prior to cemiplimab administration) as compared to baseline (pre-dose C1D1)

FIGURE 5. Treatment with THIO induces TIFs formation in patient-derived CTCs



Proprietary flow cytometry-based assay (with EpCAM (+), gH2AX(+), TRF1(+) gating strategy) was used for the TIFs detection and quantification in CTCs from patient samples.

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AUTHOR DISCLOSURES

- Tomasz Jankowski, M.D. has no conflicts of interest to declare

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