Abstract 997

Phase 2 Study of Telomere-Targeting Agent THIO Sequenced by Cemiplimab in Immune Checkpoint Inhibitor-Resistant Advanced NSCLC: Interleukin-6 as a Potential Predictive Biomarker

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Introduction

- Despite recent advances for the first-line treatment of advanced Non-Small Cell Lung Cancer (NSCLC), long-term prognosis remains poor with a 5-year survival rate of 28%[1] and limited options exist in patients' refractory or resistant to immune checkpoint inhibitors (ICI).
- Biomarkers assessing telomere damage in cancer cells are becoming increasingly important for accurately determining efficacy following treatment.
- THIO (6-thio-2'-deoxyguanosine, also known as 6-thio-dG) is a small molecule, first-in-class direct cancer telomere targeting agent that selectively kills telomerase positive (TERT+) cancer cells:
  - Over 80% of all cancers and approx. 78-83% of all NSCLC types are TERT+.[2,3]
  - THIO is incorporated into de novo synthesized telomeres leading to chromatin uncapping, generation of DNA damage signals, and rapid apoptosis.[4]
- In preclinical models, sequential treatment of THIO and ICIs overcame ICI resistance and showed a potent and durable antitumor activity.[5]
- Preliminary trial results in NSCLC indicates that low doses of THIO induce sensitivity to ICIs when administered prior to an ICI in tumors which otherwise are resistant or do not respond to an ICI.
- Here we describe a phase 2 dose-optimization study (NCT05208944) for adult patients with advanced NSCLC who progressed or relapsed after 1–4 prior treatment lines including first-line ICI alone or in combination with platinum chemotherapy and new biomarker findings.
- Treatment options for immune checkpoint inhibitor (ICI)-resistant patients are limited. THIO, a telomere-targeting agent, modifies telomeres in cancer cells, Including circulating tumor cells (CTCs), confirming its mechanism of action and demonstrating efficacy independent of PD-L1 expression.

Methods

- 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, 79 patients were assigned to one of the THIO doses: 360, 180, or 60 mg followed by cemiplimab Q3W for up to 1 year in Part B.
- Disease status is assessed at Cycle 3 Day 1, Cycle 5 Day 1 and every 9 -12 weeks thereafter.
- The trial completed enrollment for Parts A and B in February 2024. We report here data from the 79 patients enrolled on the study, who received at least one dose of the treatment.
- CTCs were labeled with TRF1 and γH2AX to detect telomere dysfunction-induced foci (TIFs). Samples from 12 patients treated with THIO (60, 180, or 360 mg) were analyzed at baseline (C1D1) and post-treatment (C1D5). TIF and PDL1 fraction in potential CTCs were measured using flow cytometry and averaged for consistency.

Baseline characteristics

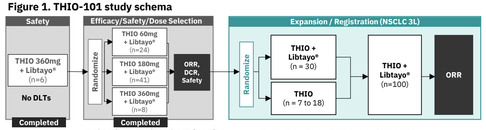
- At the time of data cut-off (15 January 2025), 79 patients with advanced NSCLC had received ≥1 dose of THIO.
- All patients had previously failed ≥1 prior line of ICI ± chemotherapy in the advanced setting and had documented disease progression at study entry.
- 34% of patients had ≥2 prior treatment lines at study entry.

Table 1. Baseline characteristics

Characteristic	60 mg (n=24)	180 mg (n=41)	360 mg (n=14)	Total (N=79)
Median age (range), years	67 (52–85)	68 (45–81)	68 (50–75)	67 (45–85)
Sex, n (%)				
Female	10 (42)	11 (27)	7 (50)	28 (35)
Male	14 (58)	30 (73)	7 (50)	51 (65)
Number of prior lines, n (%)				
1	17 (71)	30 (73)	5 (36)	52 (66)
2	6 (25)	10 (25)	6 (43)	22 (28)
3	1 (4)	0 (0)	2 (14)	3 (4)
4	0 (0)	1 (2)	1 (7)	2 (3)
ECOG PS, n (%)				
0	6 (25)	8 (20)	7 (50)	21 (27)
1	18 (75)	33 (80)	7 (50)	58 (73)
Histology, n (%)				
Non-Squamous cell carcinoma	15 (63)	25 (61)	8 (57)	48 (60)
Squamous cell carcinoma	9 (37)	16 (39)	6 (43)	31 (40)
Brain metastases, n (%)	1 (4)	1 (2)	2 (14)	4 (5)
Liver metastases, n(%)	4 (17)	5 (12)	3 (21)	12 (15)

Study Design

Figure 1. THIO-101 study schema



- Modified 3+3 design
- Completed
- Simon's 2-stage in each arm (N=41):
  - ✓ Stage 1 (n=19)
  - ✓ Stage 2 (n=22)
- Best dose THIO 180mg - selected on Nov'23
- Enrollment completed Feb'24
- Up to 148 patients – Enrollment to start Q1'25
- Patient population:
  - CPI Resistance (SITC)
  - Chemotherapy Resistance

- **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).

Safety findings

Table 2. Related TEAEs by dose level reported in ≥2 patients

Preferred Term	60mg (N=24)	180mg (N=41)	360mg (N=14)	Total (N=79)*
Aspartate aminotransferase increased	6 (25%)	11 (26.8%)	4 (28.6%)	21 (26.6%)
Alanine aminotransferase increased	6 (25%)	9 (22%)	3 (21.4%)	18 (22.8%)
Nausea	2 (8.3%)	1 (2.4%)	7 (50%)	10 (12.7%)
Neutropenia	2 (8.3%)	2 (4.9%)	0(0%)	4 (5.1%)
Anaemia	0(0%)	2 (4.9%)	1 (7.1%)	3 (3.8%)
Pyrexia	0(0%)	2 (4.9%)	1 (7.1%)	3 (3.8%)
Decreased appetite	0(0%)	1 (2.4%)	2 (14.3%)	3 (3.8%)
Blood alkaline phosphatase increased	1 (4.2%)	1 (2.4%)	0(0%)	2 (2.5%)
Blood bilirubin increased	0(0%)	1 (2.4%)	1 (7.1%)	2 (2.5%)
Gamma-glutamyltransferase increased	0(0%)	2 (4.9%)	0(0%)	2 (2.5%)
Leukopenia	1 (4.2%)	0(0%)	1 (7.1%)	2 (2.5%)
Asthenia	0(0%)	2 (4.9%)	0(0%)	2 (2.5%)
Erythema	0(0%)	2 (4.9%)	0(0%)	2 (2.5%)
Hypothyroidism	0(0%)	2 (4.9%)	0(0%)	2 (2.5%)
Infusion related reaction	0(0%)	2 (4.9%)	0(0%)	2 (2.5%)

Table 3. Related Grade ≥3 TEAEs

Preferred Term	060mg (N=24)	180mg (N=41)	360mg (N=14)	Total (N=79)
Alanine aminotransferase increased	3 (12.5%)	4 (9.8%)	2 (14.3%)	9 (11.4%)
Aspartate aminotransferase increased	5 (20.8%)	2 (4.9%)	2 (14.3%)	9 (11.4%)
Neutropenia	2 (8.3%)	1 (2.4%)	0(0%)	3 (3.8%)
Blood alkaline phosphatase increased	0(0%)	1 (2.4%)	0(0%)	1 (1.3%)
Gamma-glutamyltransferase increased	0(0%)	1 (2.4%)	0(0%)	1 (1.3%)
Lipase increased	1 (4.2%)	0(0%)	0(0%)	1 (1.3%)
Weight decreased	0(0%)	1 (2.4%)	0(0%)	1 (1.3%)
Nausea	0(0%)	0(0%)	1 (7.1%)	1 (1.3%)
Multiple organ dysfunction syndrome	0(0%)	1 (2.4%)	0(0%)	1 (1.3%)
Hyperkalaemia	1 (4.2%)	0(0%)	0(0%)	1 (1.3%)
Ischaemic stroke	0(0%)	1 (2.4%)	0(0%)	1 (1.3%)

*Cerebellar and ischaemic strokes reported refer to the same event. The medical monitor assessment was unrelated.

- THIO + cemiplimab has been generally well tolerated in a heavily pre-treated population, with most events being Grade 1–2 in severity.
- Most TEAEs were laboratory value elevations, except nausea (12.7% overall and 2.4% at the 180 mg dose) and decreased appetite (3.8% overall and 2.4% at the 180 mg dose).
- No DLTs have been reported in the Part A safety lead in.
- A related Grade ≥3 ALT increase was reported in 9 patients (11.4%), including 2 patients receiving 360 mg, 4 at 180 mg, and 3 at 60 mg. No clinical symptoms were associated with the elevated laboratory values, and all returned to baseline or normal without sequelae.
- All other related Grade ≥3 events occurred in <5% of patients.
- Following an event of Grade 4 LFT elevation in a patient receiving 360 mg in Part B, enrollment into the 360 mg arm was paused.
- Enrollment was completed in Part B at the selected dose of 180 mg/cycle in February 2024.
- THIO mechanism of action allows for more selective targeting of cancer cells, potentially reducing the frequency of adverse events relative to non-targeted therapies.[6,7]

Efficacy findings

Figure 2. Patients receiving THIO as 3L treatment, 180 mg dose (n=10)*

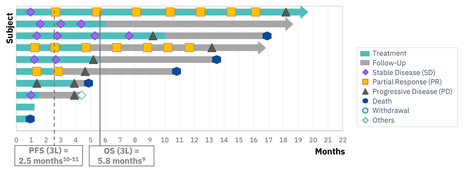


Figure 3. Patients receiving THIO as 3L treatment, all dose levels (n=22)*

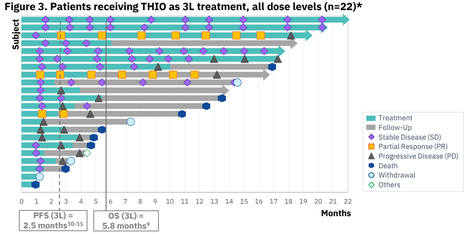
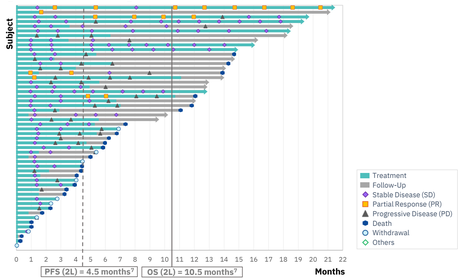


Figure 4. Patients receiving THIO as 2L treatment, all dose levels (n=52)*



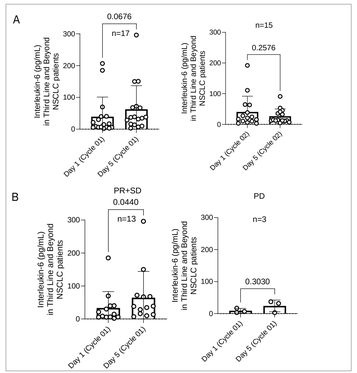
*Includes all patients who received at least one dose of THIO.

- 79 subjects received at least one dose of THIO as of 15 January 2025
- Partial Responses (PRs) RECIST 1.1 were reported for 9 subjects (6 in 2L, 3 in 3L), with 7 PRs confirmed by a 2nd scan per Investigators' assessment (4 in 2L, 3 in 3L)
- 33 patients with survival follow-up above 12 months:
  - 20 in 2L, 19 ongoing
  - 13 in 3L, 7 ongoing
  - 1 patient completed 29 cycles of therapy, ongoing
- In the 3L setting (n=22):
  - 22 subjects received at least 1 dose of THIO
  - Estimated Median Overall Survival (OS) is at 16.9 months
  - 95% CI lower bound of 12.5 months and 99% CI lower bound of 10.8 months
  - 14/22 (63%) patients crossed 5.8 months OS threshold[9]
  - 17/22 (77%) crossed 2.5 months PFS threshold[10-11]
  - DCR 77% vs 25-35% chemotherapy

Biomarker findings

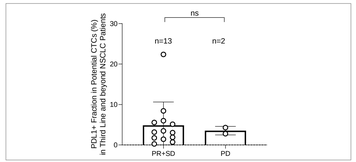
- Interleukin-6 (IL-6) was evaluated to assess the immune response to THIO in NSCLC patients receiving third line and beyond treatment (Figure 5A).
- IL-6 is elevated in cycle 1 day 5 after THIO treatment in patients responding to THIO and cemiplimab treatment (partial response (PR) and stable disease (SD)) (paired t- test, p< 0.05 is statistically significant (Figure 5B).
- This indicates that the initial elevation of IL-6 appears to be associated with immune response to THIO and cemiplimab treatment, suggesting its potential as a biomarker to predict treatment response.

Figure 5. Interleukin-6 levels (paired samples)



- Circulating tumor cells (CTCs) were marked by PDL1 to evaluate PDL1 status at cycle 1 day 1 (C1D1, baseline) in NSCLC patients receiving sequential treatment of THIO and cemiplimab as third line and beyond treatment.
- The response to THIO and cemiplimab, demonstrated by PR+SD, is independent of baseline PDL1 status (unpaired t- test, p< 0.05 is statistically significant) (Figure 6).

Figure 6. PDL1+ fraction in CTCs (Patient Status)



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Conclusions

- **The combination of THIO + cemiplimab has durable activity in this hard-to-treat patient population (CPI resistant and chemotherapy resistant progressors).**
- **Current data in third-line indicates that as of 15-Jan-2025, estimated Median Overall Survival (OS) is at 16.9 months with a 95% CI lower bound of 12.5 months and 99% CI lower bound of 10.8 months.**
- **Induction of TIFs in CTCs from patients treated with THIO + cemiplimab shows on-target effect. These findings suggest a potential link between biomarker TIF positivity and more favorable clinical outcomes.**
- **THIO + cemiplimab has so far been generally well-tolerated in a heavily pre-treated population, with most events being Grade 1-2 in severity and very few Grade ≥3, mostly ALT increase reported in 9 patients (11.4%).**
- **Treatment has the potential to be given for longer, which usually translates into longer survival.**
- **The ongoing Phase 2 study selected the best dose of THIO 180 mg which has shown better safety and superior efficacy compared with other doses: to date, 9.8% of patients receiving the 180 mg dose reported related Grade ≥3 AEs.**
- **An initial elevation of IL-6 may be associated with the immune response to THIO and cemiplimab, indicating its potential as a predictive biomarker for treatment efficacy.**

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