Abstract 1492

Telomere-Targeting Agent THIO in Sequential Combination with Cemiplimab Demonstrates Long Term Therapeutic Benefits Beyond Treatment Cessation. A Phase 2 Trial in Advanced Immune Checkpoint Inhibitor Resistant Non-Small Cell Lung Cancer Patients

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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.

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.
- An expansion cohort is planned based on data from Part B (n=100).

Baseline characteristics

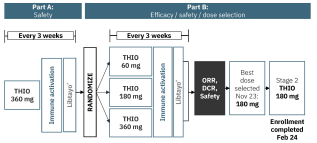
- At the time of data cut-off (16 September 2024), 79 patients with advanced NSCLC had received ≥1 dose of THIO.
- All patients had previously failed ≥1 prior line of ICI ± chemotherapy in the advanced setting and had documented disease progression at study entry.
- 34% of patients had ≥2 prior treatment 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



- **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(0.0%)	4 (5.1%)
Anemia	0(0.0%)	2 (4.9%)	1 (7.1%)	3 (3.8%)
Pyrexia	0(0.0%)	2 (4.9%)	1 (7.1%)	3 (3.8%)
Decreased appetite	0(0.0%)	1 (2.4%)	2 (14.3%)	3 (3.8%)
Blood alkaline phosphatase increased	1 (4.2%)	1 (2.4%)	0(0.0%)	2 (2.5%)
Blood bilirubin increased	0(0.0%)	1 (2.4%)	1 (7.1%)	2 (2.5%)
Gamma-glutamyltransferase increased	0(0.0%)	2 (4.9%)	0(0.0%)	2 (2.5%)
Leukopenia	1 (4.2%)	0(0.0%)	1 (7.1%)	2 (2.5%)
Asthenia	0(0.0%)	2 (4.9%)	0(0.0%)	2 (2.5%)
Erythema	0(0.0%)	2 (4.9%)	0(0.0%)	2 (2.5%)
Hypothyroidism	0(0.0%)	2 (4.9%)	0(0.0%)	2 (2.5%)
Infusion related reaction	0(0.0%)	2 (4.9%)	0(0.0%)	2 (2.5%)

Table 3. Related Grade ≥3 TEAEs

Preferred Term	60mg (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(0.0%)	3 (3.8%)
Blood alkaline phosphatase increased	0(0.0%)	1 (2.4%)	0(0.0%)	1 (1.3%)
Gamma-glutamyltransferase increased	0(0.0%)	1 (2.4%)	0(0.0%)	1 (1.3%)
Lipase increased	1 (4.2%)	0(0.0%)	0(0.0%)	1 (1.3%)
Weight decreased	0(0.0%)	1 (2.4%)	0(0.0%)	1 (1.3%)
Nausea	0(0.0%)	0(0.0%)	1 (7.1%)	1 (1.3%)
Hyperkalaemia	1 (4.2%)	0(0.0%)	0(0.0%)	1 (1.3%)
Cerebellar stroke*	0(0.0%)	1 (2.4%)	0(0.0%)	1 (1.3%)
Ischaemic stroke*	0(0.0%)	1 (2.4%)	0(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=8)*

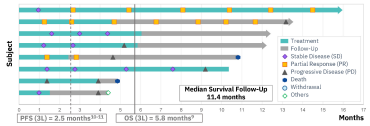


Figure 3. Patients receiving THIO as 3L treatment, all dose levels (n=20)*

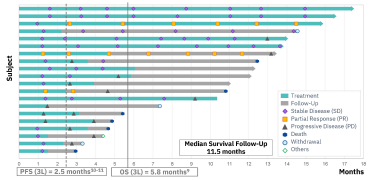
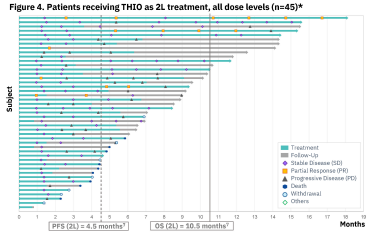


Figure 4. Patients receiving THIO as 2L treatment, all dose levels (n=45)*



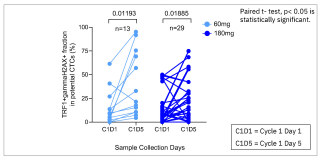
*Includes all patients with ≥1 post-baseline response assessment.

- 69 evaluable patients had completed ≥1 post-baseline assessment at the time of data cut-off (45 in 2L, 20 in 3L, 4 in 4L+).
- 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).
- 19 patients with survival follow-up above 12 months:
  - 9 in 2L, 9 ongoing follow-up
  - 10 in 3L, 8 ongoing follow-up
  - 1 patient has received 25 cycles of therapy
- In the 3L setting (n=20):
  - DCR was 85% for THIO vs. standard of care 25–35% for chemotherapy.[6]
  - 14/20 (70%) patients crossed the 5.8-month OS threshold.[9]
  - 17/20 (85%) patients crossed the 2.5-month PFS threshold.[10-11]
  - The median survival follow-up time is currently 11.5 months (n=20).
- In the 3L setting with THIO at 180 mg (n=8):
  - Median PFS: 5.5 months (24.1 weeks); OS rate at 6 months: 75%.
  - ORR 38% (3/8) vs. standard of care 6–10% for chemotherapy.[9]
  - 6/8 (75%) patients crossed the 5.8-month OS threshold.[9]
  - 7/8 (88%) patients crossed the 2.5-month PFS threshold.[10-11]
  - The median survival follow-up time is currently 11.4 months (n=8).

Biomarker findings

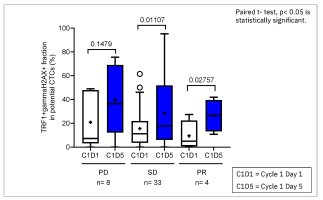
- Telomere dysfunction-Induced foci (TIF)-positive CTCs were characterized as TRF1+/gammaH2AX+fraction in CD326+/PanKRT+ CTCs.
- TIF (Telomere dysfunction-Induced Foci) analysis demonstrated the intended on-target mechanism of action: modification of telomeres in circulating tumor cells (CTCs) by THIO (Figure 5).
- On average, patients in the Stable Disease (SD) and Partial Response (PR) groups showed increased levels of TIF biomarker, whereas the Progressive Disease (PD) group did not demonstrate a statistically significant increase in the TIF biomarker (Figure 6).
- Additionally, TIF formation in CTCs was shown to be a good biomarker of on-target activity.

Figure 5. TIFs fraction in CTCs (paired samples at each dose level)



- 42 paired samples are represented in the graph.
  - 5 patients excluded (>85% TIFs at baseline)

Figure 6. TIFs fraction in CTCs (Patient Status)



- 45 patients' status represented in the graph.
  - 4 patients excluded (>85% TIFs at baseline)
  - 4 patients' status not available (1/4 baseline TIFs>85%).

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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).**
- **The ORR in the 3L setting with the 180 mg dose is 38% (3/8), which compares favorably with response rates reported of ~6% for other currently available treatments for heavily pre-treated patients.**
- **Median survival follow-up in the 3L setting has surpassed 11.5 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.**
- **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 in November 2023. The 180 mg dose 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.**

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