Abstract 8601

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

T. Jankowski,[1] T. Csoszi,[2] L. Urban,[3] T. Nagy,[4] N. Chilingirova,[5] M. Cholakova,[6] R. Joshi,[7] M. Moore,[8] R. Ramlau,[9] S. Soter,[10] M. Kotlarski,[11] K.D. Koynov,[12] A. Mruk,[13] B. Seidl,[14] V. Minchev,[15] V. Muller,[16] V. Vitoc,[17] S. Gryaznov,[17] O. Tudos,[17] V. Zaporojan[17]

[1]Medical University Lublin, Lublin, Poland; [2]Hetenyi Geza Korhaz, Onkologiai Kozpont, Szolnok, Hungary; [3]Matrai Gyogyintezet, Matrahaza, Hungary; [4]Orszagos Onkologiai Intezet, Budapest, Hungary; [5]Medical Oncology Clinic, Heart & Brain Hospital, Pleven, Bulgaria; [6]Synexus Medical Center, Sofia, Bulgaria; [7]Cancer Research of South Australia; Adelaide, SA, Australia; [8]St. Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [9]Oncology Department Poznan University of Medical Sciences, Poland; [10]Koranyi National Institute of Pulmonology, Budapest, Hungary; [11]Centrum Medyczne Pratia, Poznan, Poland; [12]MHAT Serdika, Sofia, Bulgaria; [13]Centrum Medyczne Mrukmed, Rzeszow, Poland; [14]University of Sunshine Coast Queensland, Australia; [15]UMHAT Sofiamed, Sofia, Bulgaria; [16]Semmelweis Egyetem Pulmonologiai Klinika Budapest, Hungary; [17]MAIA Biotechnology, Chicago, IL, USA

MAIA BIOTECHNOLOGY

Introduction

- Despite recent approvals 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).
- 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]
- Sequential treatment of THIO and ICIs showed a potent and durable antitumor activity in preclinical models.[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.

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 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).

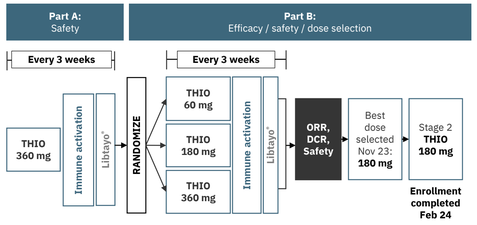
Baseline characteristics

- At the time of data cut-off (30 April 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)

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	60 mg (n=24)	180 mg (n=41)	360 mg (n=14)	Total (N=79)
Aspartate aminotransferase increased	6 (25.0%)	10 (24.4%)	4 (28.6%)	20 (25.3%)
Alanine aminotransferase increased	6 (25.0%)	8 (19.5%)	3 (21.4%)	17 (21.5%)
Nausea	1 (4.2%)	1 (2.4%)	7 (50.0%)	9 (11.4%)
Anemia	0 (0.0%)	2 (4.9%)	1 (7.1%)	3 (3.8%)
Neutropenia	2 (8.3%)	1 (2.4%)	0 (0.0%)	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	60 mg (n=24)	180 mg (n=41)	360 mg (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%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
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%)
Nausea	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.3%)
Hyperkalemia	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (1.3%)

- THIO + cemiplimab has so far been 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 (11.4% overall and 2.4% at the 180 mg dose) and decreased appetite (5.1% overall and 2.4% at the 180 mg dose).
- No study drug-related Grade 5 events have been reported.
- No study drug-related Grade 4 events have been reported 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.
- With currently available chemotherapy in this patient population, Grade 5 events are expected in 5% of cases, Grade 4 events in 23.8% and Grade 3 in 42.4%.[6,7]

Conclusions

- The combination of THIO + cemiplimab is very active 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%, 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 9.1 months.
- TIF in CTCs shows on-target effect.
- THIO + cemiplimab has so far been well-tolerated in a heavily pre-treated population.
- The safety profile of THIO has the potential to be far better than chemotherapy. 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. There were no reported related Grade 4 and 5 AEs in the 180 mg dose.

Efficacy findings

- 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) per RECIST 1.1 were observed in 9 patients (6 in 2L, 3 in 3L), with 6 PRs confirmed (3 in 2L, 3 in 3L) by a 2nd scan per Investigators' assessment.
- 5 patients have survival follow-up for >12 months (3 with treatment ongoing).
- In the 3L setting:
  - DCR was 85% for THIO vs. standard of care 25–35% for chemotherapy.[8]
  - 13/20 (65%) 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 9.1 months (n=20).
- In the 3L setting with THIO at 180 mg:
  - 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 9.1 months (n=8).

Biomarker findings

- TIF (Telomere dysfunction Induced Foci) analysis demonstrated the intended on-target mechanism of action: modification of telomeres in circulating tumor cells (CTCs) by THIO (see Figures 4 and 5).

Figure 2. Patients receiving THIO as 2L treatment (n=45)*

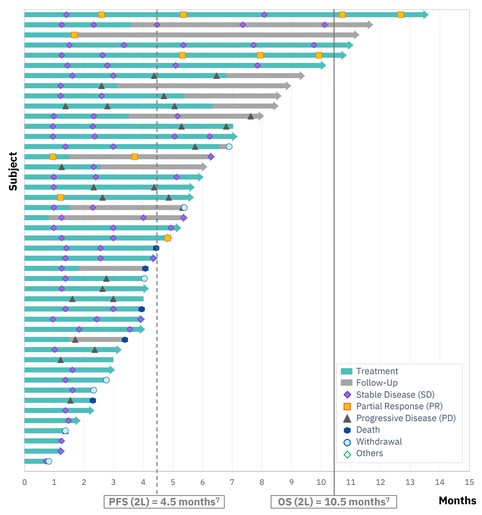


Figure 3. Patients receiving THIO as 3L treatment (n=20)*

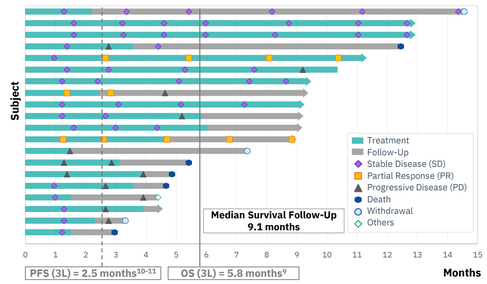
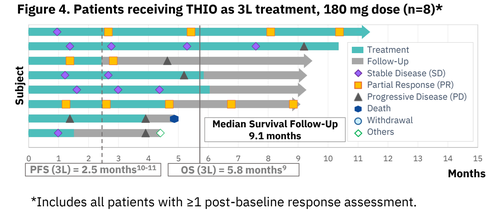


Figure 4. Patients receiving THIO as 3L treatment, 180 mg dose (n=8)*



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

Figure 5. Cumulative TRF1

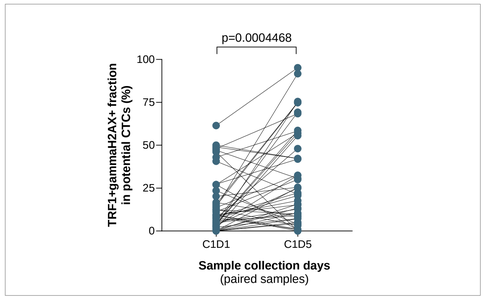
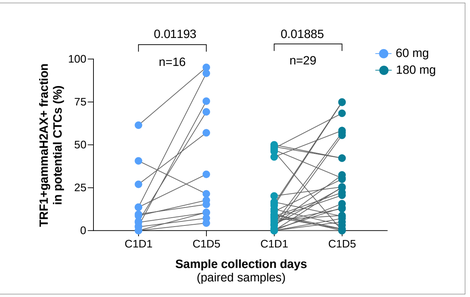


Figure 6. TRF1 by dose level



References

1. https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics
2. Shay JW, Bacchetti S. Eur J Cancer 1997;33:787–91.
3. Tahara H, et al. Cancer Res 1995;55:2734–6.
4. Mender I, et al. Cancer Disc 2015 Jan;5(1):82-95.
5. Mender I, et al. Cancer Cell 2020;38:400–11.
6. https://www.cyramza.com/hcp/nsclc-treatment/revel-trial-safety
7. https://clinicaltrials.gov/study/NCT01168973?tab=results
8. Matsumoto H, et al. Transl Lung Cancer Res 2021;10:2278–89.
9. Girard N, et al. J Thorac Onc 2009;12:1544-1549.
10. Shepherd F, et al. N Engl J Med 2005;353:123-132.
11. Fossella F, et al. J Clin Oncol 2000;18(12):2354-62.

Acknowledgements

- This study is sponsored by MAIA Biotechnology, Inc.
- The authors would like to thank the patients and research staff who contributed to this study.
- The sponsor would like to send a special thanks to REGENERON, CROMOS and NOVA-CLIN for their exceptional contribution to this study.

Presenting author contact

Tomasz Jankowski, M.D. (e-mail: tjankowski.onkolog@wp.pl)

Scan QR Code to access our presentation and a digital version of the poster

2024 ASCO ANNUAL MEETING
May 31 – June 4, 2024
Chicago, IL & Online