Abstract #564

A Phase 3 Study of Ateganosine (THIO) Sequenced with Immune Checkpoint Inhibitor (ICI) versus Standard of Care Chemotherapy in ICI-Resistant Advanced NSCLC: THIO-104 Trial in Progress

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MAIA BIOTECHNOLOGY

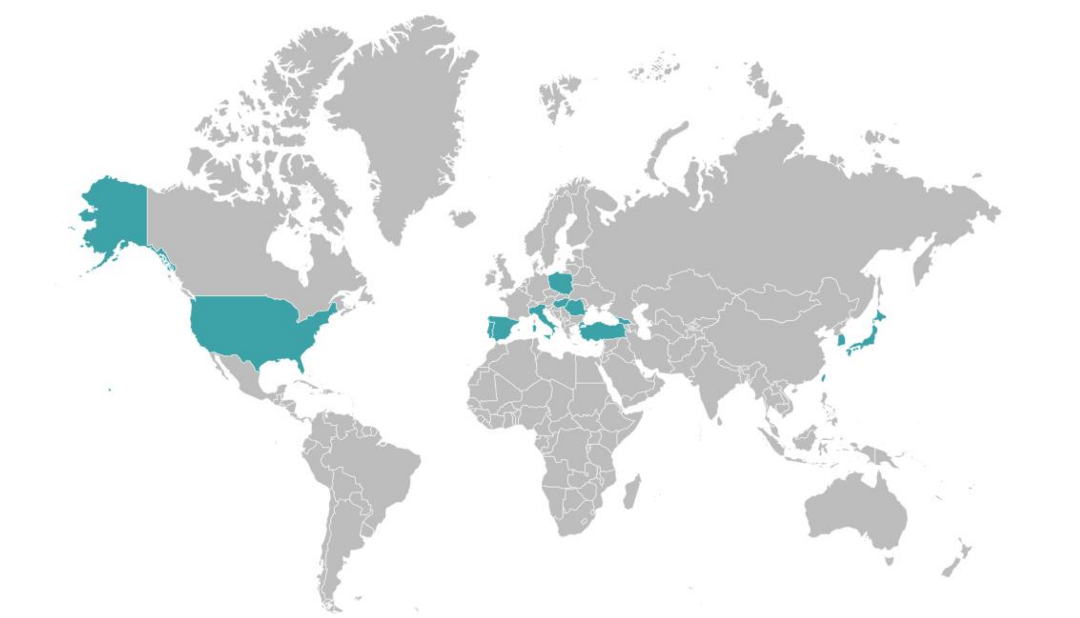
01 Introduction

- Although advances have been made in the management of advanced non-small cell lung cancer (NSCLC), therapeutic options remain limited for patients who develop resistance to immune checkpoint inhibitors (ICIs).
- Long-term outcomes are poor, with a 5-year overall survival rate of approximately 28%[1]. Patients with refractory or resistant disease following ICI therapy face particularly limited treatment alternatives.
- Ateganosine (THIO; 6-thio-2'-deoxyguanosine) is a first-in-class, telomere-targeting agent that is selectively recognized by telomerase and incorporated into telomeric DNA. This incorporation disrupts telomere integrity, resulting in telomere uncapping, activation of DNA damage responses, and rapid induction of tumor cell apoptosis.
- Preliminary findings from the THIO-101 trial (NCT05208944) in NSCLC suggest that administration of low-dose Ateganosine prior to ICIs enhances tumor sensitivity to checkpoint blockade in otherwise resistant or non-responsive tumors.

02 Methods

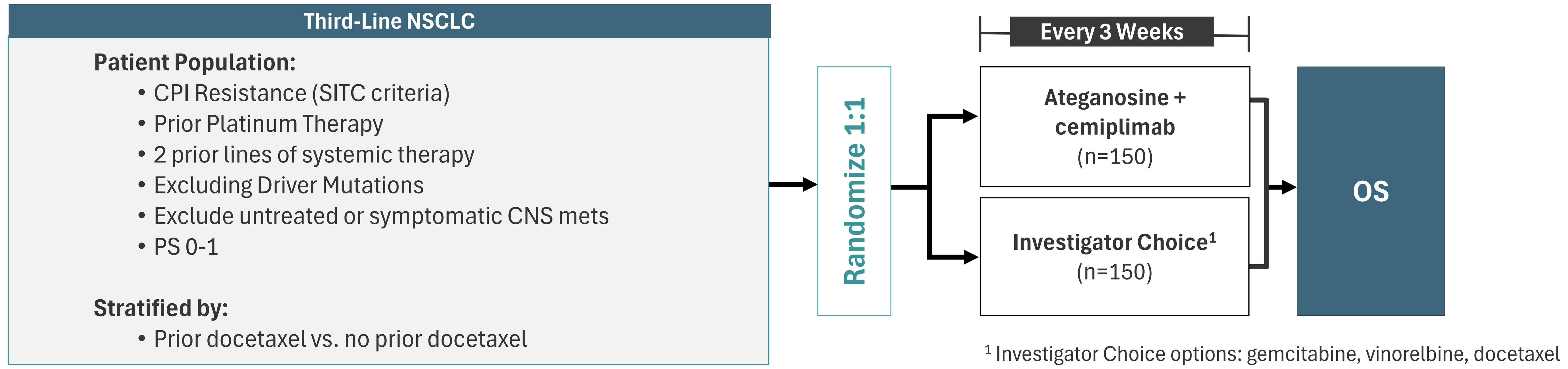
- THIO-104 is a multicenter, open-label, randomized Phase 3 study enrolling approximately 300 subjects with histologically confirmed advanced/metastatic NSCLC (NCT06908304).
- Eligible participants must have received two prior lines of systemic treatment, including at least one line of ICIs and platinum-based chemotherapy
- Participants will be randomized 1:1 to receive either Ateganosine 180 mg per cycle (60 mg IV on Days 1-3 of a 3-week cycle) followed by cemiplimab 350 mg IV on Day 5, or single-agent chemotherapy (vinorelbine, gemcitabine, or docetaxel).
- The primary endpoint is overall survival (OS). Secondary endpoints include objective response rate (ORR), progression-free survival (PFS) and duration of response (DoR).
- Preliminary safety data and efficacy outcomes will be assessed through scheduled interim analysis as the study develops.
- The trial is planned to enroll patients globally, including the USA and countries in Europe and Asia. Final list of sites may vary depending on regulatory approvals.

Figure 1. THIO-104 planned enrollment geographies



03 Study Design

Figure 2. THIO-104 study schema.



[1] Investigator Choice options: gemcitabine, vinorelbine, docetaxel

Primary endpoints: Target OS: 9.3m v. 5.8m (HR 0.62); Minimum OS: 7.8m v. 5.8m (HR 0.74)

Secondary endpoints: DCR; ORR; DoR; PFS; Safety

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

Objective: To evaluate the efficacy and safety of Ateganosine (180 mg per cycle) sequenced with fixed dose cemiplimab (350 mg per cycle) compared to Investigator's choice of single-agent chemotherapy as third-line treatment in subjects with advanced/metastatic NSCLC.

Experimental Arm: Ateganosine(THIO) + cemiplimab

- Ateganosine 60 mg administered by 30-minute intravenous (IV) infusions once daily on Days 1-3 of every 3-week cycle (for a total of 180 mg per cycle), followed by a fixed dose of cemiplimab (350 mg IV) on Day 5 every 3 weeks (Q3W)

Control Arm: Single-Agent Chemotherapy

- Standard of Care (for example vinorelbine, gemcitabine, or docetaxel chemotherapy, if not previously exposed, per Investigator's Choice) in 3-week cycles
  - ❑ **Option 1:** Vinorelbine (30 mg/m2 IV on D1, D8, and D15 Q3W)
  - ❑ **Option 2:** Gemcitabine (1250 mg/m2 IV on D1 and D8 Q3W)
  - ❑ **Option 3:** Docetaxel (75 mg/m2 IV on D1 Q3W) (Docetaxel 60-65 mg/m2 permitted based on country-specific approvals).

*D = day (within a 21-day cycle); IV = intravenous; Q3W = every 3 weeks (21-day cycles)

04 Pharmacodynamics (PD) and Pharmacokinetics (PK)

Pharmacokinetic parameters (PK):

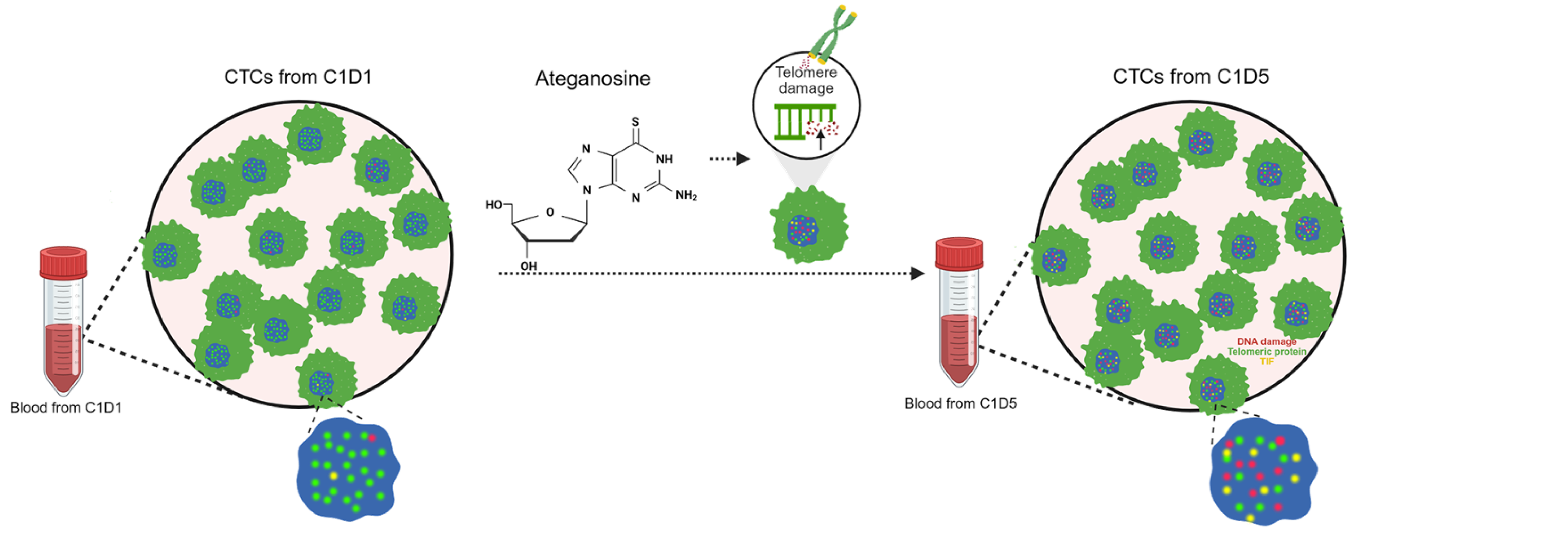
- Ateganosine concentration levels and PK parameters (Limited PK collection)

Pharmacodynamic parameters and Biomarkers (PD):

- TIF (Telomere dysfunction-induced foci) formation in CTCs
- CTCs evaluation of PDL1 expression
- Tumor telomerase TERT (+) status (via expression of telomerase mRNA), by ISH-TERT (in situ hybridization for TERT) of paraffin-embedded tumor samples.
- Hematology and Clinical Chemistry:
- Interleukin- 6 (IL-6)
- C-Reactive Protein (CRP)
- Carcinoembryonic Antigen (CEA)
- Lactate dehydrogenase (LDH)
- Neutrophil-lymphocyte ratio (NLR)
- Platelet-lymphocyte ratio (PLR)

05 Pharmacodynamic biomarker Telomere dysfunction-Induced foci (TIF)

Figure 3. PD biomarker Telomere dysfunction-Induced foci (TIF) demonstrates the on-target effect of Ateganosine in circulating tumor cells (CTCs). C1D1= Cycle 1 Day 1, C1D5= Cycle 1 Day 5. Red color represents DNA damage, green color represents telomeric protein and yellow color represents the colocalization of DNA damage and telomeric protein, referred to as TIF.



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06 Conclusions

- **THIO-104 is expected to provide critical insights into the potential role of telomere-targeting agents in restoring tumor sensitivity to ICIs in NSCLC.**
- **Based on the previously conducted studies[2], Ateganosine has been found to lead to a significant induction in TIF formation in CTCs, which is considered a primary biomarker for Ateganosine. The study will also explore key biomarkers to further characterize Ateganosine's mechanism of action and it's potential to predict patient response to therapy.**
- **The current response trend observed in the Phase 2 THIO-101 trial is expected to persist as the study progresses, paving the way for further exploration in the Phase 3 THIO-104.**
- **The selected dose of Ateganosine 180mg in the Phase 2 THIO-101 study has shown as of the data cut-off (June 30, 2025) a median observed Overall Survival (OS) of 17.8 months in advanced third-line NSCLC patients who are resistant to prior treatment with ICI and chemotherapy.**
- **An expansion of THIO-101 study to further validate the safety and efficacy observed was warranted with the completion of Parts A and B of the study.**

References

1. https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics
2. Mender I, et al. Cancer Disc 2015 Jan;5(1):82-95.

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Author disclosures

- Veronika Müller has no conflict of interest.

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