A Phase 1/2 First-in-Human Study of TH9619 in Patients With Advanced Refractory Solid Tumours (ODIN)

TPS3165

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BACKGROUND & RATIONALE:

Cancer cells depend on one-carbon metabolism to sustain rapid DNA synthesis and survival. Two key enzymes in this pathway - MTHFD1 (cytoplasmic) and MTHFD2 (mitochondrial/nuclear) - are highly and consistently overexpressed in solid tumours compared to normal tissues.[1,2] This creates a cancer-specific dependency that TH9619 is designed to exploit with high selectivity.

MTHFD2 is one of the most overexpressed genes in cancer[1] and consistently associated with significantly worse overall survival across multiple cancers.[1,2]

This supports MTHFD1/2 as actionable therapeutic targets in the refractory tumor settings.

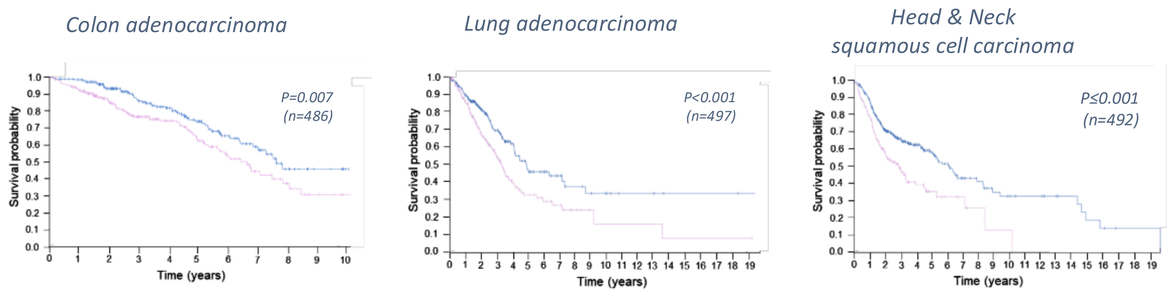

Figure legend: Kaplan-Meier survival analysis of MTHFD2 mRNA expression across three solid tumor types from TCGA cohorts. High MTHFD2 expression is associated with significantly worse overall survival in all three indications (P≤0.007).[2]

TH9619 MECHANISM OF ACTION

TH9619 is a first-in-class potent small molecule MTHFD1/2 inhibitor (intravenous administration), that selectively kills cancer through folate trapping.[3,5]

- In cancer cells, high MTHFD2 expression drives the release of formate from mitochondria into the cytosol, to generate 10-CHO-THF (formylfolate).
- Inhibition of MTHFD1 by TH9619 prevents further use of 10-CHO-THF for downstream thymidylate synthesis.
- This creates a folate trap, depleting the folate (THF) necessary for thymidylate production, resulting in nucleotide shortage, DNA damage, and cancer cell death.
- Normal cells lack MTHFD2 expression and the formate overflow needed to create this trap.

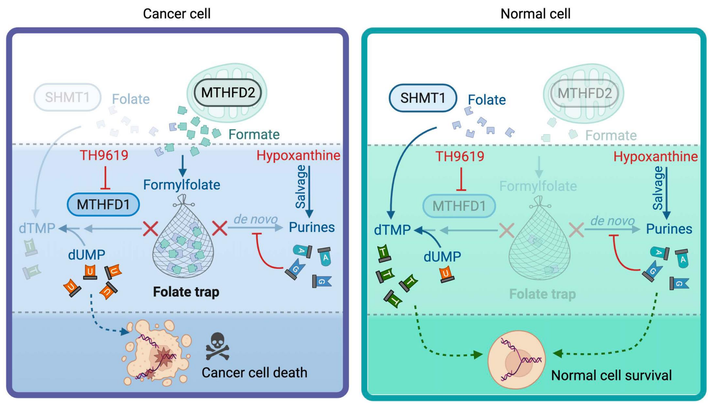

Figure legend: Proposed mechanism of action of TH9619. Selective MTHFD1/2 inhibition disrupts one-carbon metabolism in cancer cells while sparing normal cells that rely on SHMT1 and salvage pathways. Adapted from Bonagas et al., Nature Cancer 2022[3].

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ODIN STUDY DESIGN — NCT07151040

Flexible study design allowing for early signal detection[6]

PHASE 1A
Dose escalation (N up to 80)

PHASE 1B
Expansion (N up to 60)

PHASE 2
(N up to 200)

KEY ELIGIBILITY CRITERIA

- Histopathologically confirmed advanced cancer
- Indications in focus: NSCLC, HNSCC, CRC, GC, GEJC
- Prior treatment with at least one line of cytotoxic systemic therapy for metastatic and/or unresectable cancer
- Adult patients (≥18 years of age)
- Must be willing to comply with study procedures
- No history or presence of any clinically significant disorders as judged by the Investigator

STUDY TREATMENT

TH9619 i.v.
Starting dose
500 mg/m^2
28-day cycle until disease progression and/or unacceptable toxicities

Pick the best indication(s)

Confirm signal from Phase 1a

Specifics about trial design under discussion

STUDY SITES

GB **United Kingdom**	1. Northern Centre for Cancer Care, Newcastle	FR **France**	2. Institut Gustave Roussy, Villejuif	ES **Spain**	3. START Madrid – FJD; 4. Hospital Universitari Vall d'Hebron, Barcelona

PRECLINICAL DATA

TH9619 is a small molecule inhibitor with high selectivity and nM potency designed to increase cancer specificity.[3,4]

SINGLE-AGENT EFFICACY: Demonstrated in CRC and NSCLC *in vivo* models

OUTPERFORMS SoC and active in SoC-resistant lines

POTENT TUMOR KILLING in patient-derived organoids while sparing normal tissue vs SoC

FAVORABLE THERAPEUTIC INDEX versus SoC

FAVORABLE TOX PROFILE: No MTD reached in GLP toxicology studies (dog)

nM POTENCY: MTHFD2 IC_{50} = 47 nM | MTHFD1 IC_{50} = 16 nM

OBJECTIVES & ENDPOINTS & KEY ELIGIBILITY CRITERIA— PHASE 1

Primary objectives:

To assess the safety, tolerability and MTD and recommended dose(s)) of TH9619 as monotherapy in patients with selected solid tumors

Key Endpoints of the Phase 1a:

- Primary endpoints: frequency, severity and causality of adverse events; tolerability of TH9619
- Secondary endpoints: pharmacokinetics, antitumor activity/efficacy per RECIST 1.1 (such as ORR, DoR, PFS)
- Exploratory: ctDNA and biomarkers

OVERALL STUDY STATUS

- Study initiated (first patient dosed) in September 2025
- Dose escalation is ongoing
- 4 active sites in UK, France, Spain
- European site expansion planned
- Clinical data expected to be published in 2027
- Biomarkers being explored in parallel

NOTES

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Lead Author Disclosures Victor Moreno: Employee of START. Consulting fees from: Abbvie, Roche, Bayer, BMS, Janssen, Syneos, Affimed, Astra Zeneca,Merck, Ellipses Pharma. Pharmamar, ViroFend, Miltenyi, Pan-Cancer T Contact details for presenting author: victor.moreno@startmadrid.com

References: 1. Nilsson R et al. Nature Communications 2014; 5:3128; 2. Adapted from The Human Protein Atlas (proteinatlas.org), Pathology Atlas. Survival analysis based on TCGA data; 3. Bonagas et al. Nature Cancer 2022; 3;156-172; 4. Gustafsson R et al. Cancer Research 2017; 77:937–948; 5. Green et al. Nature Metabolism 2023; 5(4):642-659; 6. CT.gov ID NCT07151040

ABBREVIATIONS

CRC, colorectal cancer; ctDNA, circulating tumor DNA; DNA, deoxyribonucleic acid; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GC, gastric cancer; GEJC, gastroesophageal junction cancer; GLP, Good Laboratory Practice; HNSCC, head and neck squamous cell carcinoma; IC_{50}, half-maximal inhibitory concentration; i.v., intravenous; MTD, maximum tolerated dose; MTHFD1/2, methylenetetrahydrofolate dehydrogenase 1/2; N, number of patients; nM, nanomolar; NSCLC, non-small cell lung cancer; ODIN, study name; ORR, objective response rate; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria version 1.1; SHMT1, serine hydroxymethyltransferase 1; SoC, standard of care; THF, tetrahydrofolate