# 429TiP: A Phase 1 Study of Synthetic Lethal, IDE397 (MAT2A Inhibitor) as a Monotherapy and in Combination with Chemotherapy in Advanced Solid Tumors Harboring MTAP Deletion

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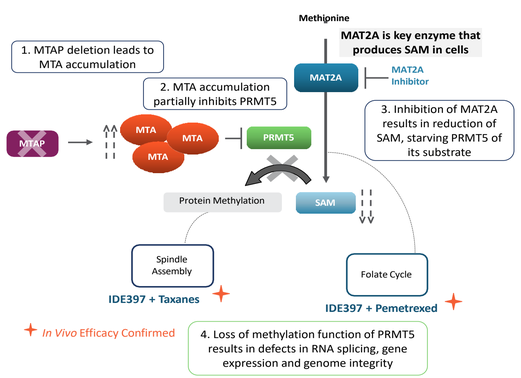
## Background

- Methylthioadenosine phosphorylase (MTAP) deletion occurs in ~15% of solid tumors in the setting of 9p21 loss and is associated with poor survival (Nature Communications; 2021; 12:5606; Han G)
- Loss of MTAP results in methylthioadenosine (MTA) accumulation and partial inhibition of protein arginine methyltransferase-5 (PRMT5)
- Inhibition of methionine adenosyltransferase-2a (MAT2A) results in reduction of s-adenosyl methionine (SAM), starving PRMT5 of its methylation substrate with resulting selective sensitivity of MTAP null cancer cells
- IDE397 is a novel MAT2A inhibitor being evaluated in cancer patients harboring a MTAP deletion. IDE397 has superior cellular potency, selectivity, and drug properties, including lack of predicted liver toxicity and high solubility, compared to compounds under clinical investigation
- In PDX models, IDE397 has been shown to exploit the synthetic lethal relationship between MTAP deletion and MAT2A with broad activity and regressions of tumors with MTAP loss when administered as a single agent and in combination with other agents such as taxanes, pemetrexed and MTA-cooperative PRMT5 inhibitors across multiple solid tumor indications
- IDE397 shows robust pharmacodynamic modulation of the proximal and distal biomarkers SAM and symmetric dimethylarginine (SDMA)
- Currently enrolling into monotherapy expansion and combination cohorts, with ongoing dose escalation arm to determine a MTD

## MAT2A Inhibition is Synthetic Lethal In Tumors with MTAP Deletion




## Key Takeaways

***IDE397*** *is a potential best-in-class* ***MAT2A inhibitor****, exploits* ***synthetic relationship between MAT2A/MTAP*** *and has the potential to be the best-in-class, novel therapy that is anticipated to be highly efficacious with a* ***superior tolerability*** *profile than existing non-targeted treatments.*

*IDE397-001 offers Monotherapy and key tumor types with innovative combination*

- *IDE397 Monotherapy*
- *IDE397 +* ***Pemetrexed***
- *IDE397 +* ***Docetaxel***
- *IDE397 +* ***Paclitaxel***
- *IDE397 +* **Gemcitabine/Nab-paclitaxel**

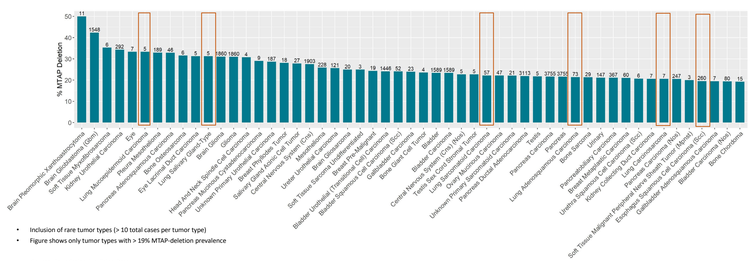
**ClinicalTrials.gov Identifier: NCT04794699**

**QR code (NCT)**

**QR Code (Contact)**

Dr. Matt Maurer

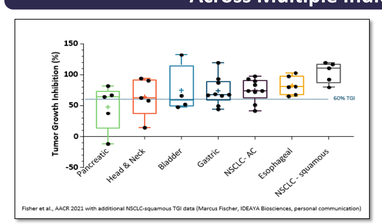
## MTAP deletion is common across diverse tumor types




- Inclusion of rare tumor types (> 10 total cases per tumor type)
- Figure shows only tumor types with > 15% MTAP-deletion prevalence

Source: Foundation Medicine Data

## Monotherapy Tumor Regressions & Significant TGI Across Multiple Indication in PDX models



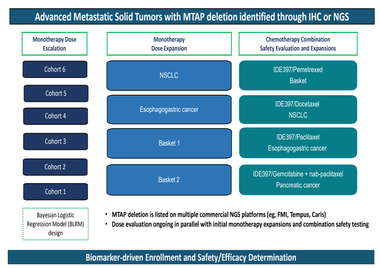

Fisher et al., AACR 2021 with additional NSCLC-squamous TGI data (Marcus Fischer, IDEAYA Biosciences, personal communication)

12 TGI = Tumor Growth Inhibition, CR = Complete Response

**IDE397 evaluation in Patient Derived Xenograft (PDX) models with homozygous MTAP deletions in Solid Tumors**

- Tumor Regressions (≥ 100% TGI) observed in multiple PDX models / indications, including in 3 of 5 NSCLC squamous models, with 1 CR
- Observed > 60% TGI in 12 of 14 NSCLC PDX models, including in 7 of 9 adenocarcinoma and in 5 of 5 squamous carcinoma PDX models
- Observed 95%-100% tumor SDMA reduction in multiple MTAP-/- PDX models, with 9 of 12 models showing 80-100% reduction in SDMA

## Study Design




## Objectives and Endpoints

| Objectives | Outcome Measures |
|---|---|
| • To evaluate the safety profile of IDE397 as a single agent and in combination with taxanes, gemcitabine/nab-paclitaxel and pemetrexed | • Dose-limiting Toxicity<br>• Maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D)<br>• Adverse events |
| • To characterize the pharmacokinetic (PK) profile of IDE397 as a single agent and combination | • Plasma Concentrations of IDE397 and combination partners over time |
| • To evaluate the anti-tumor activity of single agent IDE397 and combination | • Overall response rate (ORR) per RECIST v1.1<br>• Duration of response (DOR) per RECIST v1.1 |

Exploratory analyses with tumor and peripheral biomarkers will also be assessed

## Inclusion/Exclusion Criteria

**Inclusion Criteria**

- Patient must be ≥18 years of age
- Participants with a histologically confirmed diagnosis of an advanced or metastatic solid tumor that has progressed on at least one prior line of treatment
- Have evidence of homozygous loss of MTAP or MTAP deletion at the DNA or protein level in the participant's tumor tissue (central or local testing in a CAP- and CLIA-certified laboratory is permitted).
- Measurable disease
- Eastern Cooperative Oncology Group ≤1 or 2
- Adequate organ function

**Exclusion Criteria**

- Known CNS malignancy
- Impaired GI function
- Human immunodeficiency virus, acquired immunodeficiency syndrome related illness, hepatitis B virus, or hepatitis C virus
- Recent surgery or radiotherapy
- Females who are pregnant or breastfeeding
- Impaired cardiac function

## References

Han G, Yang G, Hao D, et al. 9p21 loss confers a cold tumor immune microenvironment and primary resistance to immune checkpoint therapy. Nat Commun. 2021;12(1):5606.

## Author Disclosure

This study is sponsored by IDEAYA Biosciences, South San Francisco, CA.

Disclosure: The first author (Dr. Melissa Johnson) declares the following real or perceived conflicts of interest: Genentech/Roche, Boehringer Ingelheim, AstraZeneca, Calithera Biosciences, Merck, Sanofi, Mirati Therapeutics, Ribon Therapeutics, Abbvie, GlaxoSmithKline, Gritstone Bi, Janssen Oncology, Lilly, Amgen, Bristol-Myers Squibb, Daiichi Sankyo, EMD Serono, G1 Therapeutics, WindMIL, Eisai, Axelia Oncology, Black Diamond Therapeutics, EcoR1 Capital, Editas Medicine, Genmab, IDEAYA Biosciences, iTeos Therapeutics, Oncorus, Regeneron, Turning Point Therapeutics, Astellas Pharma, Incyte, Pfizer, Kadmon, Stem CentRx, Novartis, Checkpoint Therapeutics, Array BioPharma, Hengrui Pharmaceutical, Lycera, BeiGene, Tarveda Therapeutics, Loxo, Guardant Health, Dynavax Technologies, Corvus Pharmaceuticals, Genocea Biosciences, Adaptimmune, Syndax, Neovia Oncology, Acerta Pharma, Takeda, Shattuck Labs, Apexigen, Atreca, OncoMed, Immunocore, Jounce Therapeutics, University of Michigan, TCR2 Therapeutics, Arcus Biosciences, BerGenBio, Tmunity Therapeutics, Inc., Seven and Eight Biopharmaceuticals, Rubius Therapeutics, Curis, Silicon Therapeutics, Dracen, PMV Pharma, Artios, BioAtla, Elicio Therapeutics, Erasca, Inc, Harpoon, Helsinn Healthcare, Hutchison MediPharma, IGM Biosciences, Memorial Sloan-Kettering Cancer Center, NeoImmuneTech, Numab, RasCal, Relay Therapeutics, Revolution Medicines, Tempest Therapeutics, Tizona Therapeutics, Inc., Vyriad, Y-mAbs Therapeutics, Exelixis, Fate Therapeutics, Merus, Kartos Therapeutics, Carisma Therapeutics, Rain Therapeutics, Nuvalent, Inc., Palleon Pharmaceuticals, Impact Therapeutics.