



December 2021

NASDAQ: **IDYA**

# **IDEAYA Biosciences**

Improving Lives  
Through Transformative  
Precision Medicines

# Safe Harbor Statement

Certain statements in this presentation and the accompanying oral commentary are forward-looking statements. These statements relate to future events or the future financial performance of IDEAYA Biosciences, Inc. (the "Company") and involve known and unknown risks, uncertainties and other factors that may cause the actual results, levels of activity, performance or achievements of the Company or its industry to be materially different from those expressed or implied by any forward-looking statements. In some cases, forward-looking statements can be identified by terminology such as "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "potential" or other comparable terminology. All statements other than statements of historical fact could be deemed forward-looking, including any expectations regarding the Company's target discovery platform or new target validation efforts as creating opportunities for research and development initiatives; any projections of financial information, market opportunities, cash runway or profitability; any statements about historical results that may suggest trends for the Company's business; any statements of the plans, strategies, and objectives of management for development programs or future operations; any statements about the timing of preclinical research, clinical development, regulatory filings, manufacturing or release of data; any statements of expectation or belief regarding future events, potential markets or market size, technology developments, or receipt of cash milestones, option exercise fees or royalties; and any statements of assumptions underlying any of the items mentioned. The Company has based these forward-looking statements on its current expectations, assumptions, estimates and projections. While the Company believes these expectations, assumptions, estimates and projections are reasonable, such forward-looking statements are only predictions and involve known and unknown risks and uncertainties, many of which are beyond the Company's control. These and other important factors may cause actual results, performance or achievements to differ materially from those expressed or implied by these forward-looking statements. The forward-looking statements in this presentation are made only as of the date hereof. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of the Company in general, see the Company's periodic filings with the Securities and Exchange Commission (the "SEC"), including its Quarterly Report on Form 10Q for the quarter ended September 30, 2021, and any current and periodic reports filed thereafter. Except as required by law, the Company assumes no obligation and does not intend to update these forward-looking statements or to conform these statements to actual results or to changes in the Company's expectations.

This presentation concerns anticipated products that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). It is currently limited by Federal law to investigational use, and no representation is made as to its safety or effectiveness for the purposes for which it is being investigated.

# IDEAYA Biosciences Highlights

**Leading Synthetic Lethality (SL) focused biotechnology company** advancing transformative precision medicine therapies for cancer patients

- **Broad Pipeline for Key Emerging Targets** including clinical stage IDE397 (MAT2A) and darovasertib (PKC), and development candidate selection for PARG and Pol Theta
- **Pharma Collaborations** with GSK (over ~\$3 billion in potential milestones) and Pfizer
- **Strong Balance Sheet** with ~\$386 M in cash anticipated to fund operations into 2025<sup>1, 2</sup>
- **NASDAQ:** IDYA

- **Target Catalysts**

- IDE397 Phase 1
  - Cohort Expansions (H1 2022)
  - GSK Option Package & Clinical Data Update (H1 2022)
- PARG Development Candidate Lead Nominated
- Pol Theta Development Candidate (December 2021)
- Darovasertib (IDE196) Phase 1/2
  - Clinical Update on mPFS for Daro + Crizotinib (H1 2022)
  - Regulatory Guidance for Daro + Crizotinib (H1 2022)

(1) IDEAYA Form 10Q and Q2 2021 Financials filed with the U.S. Securities and Exchange Commission on November 15, 2021

(2) Includes cash, cash equivalents and marketable securities as of September 30, 2021

# Synthetic Lethality

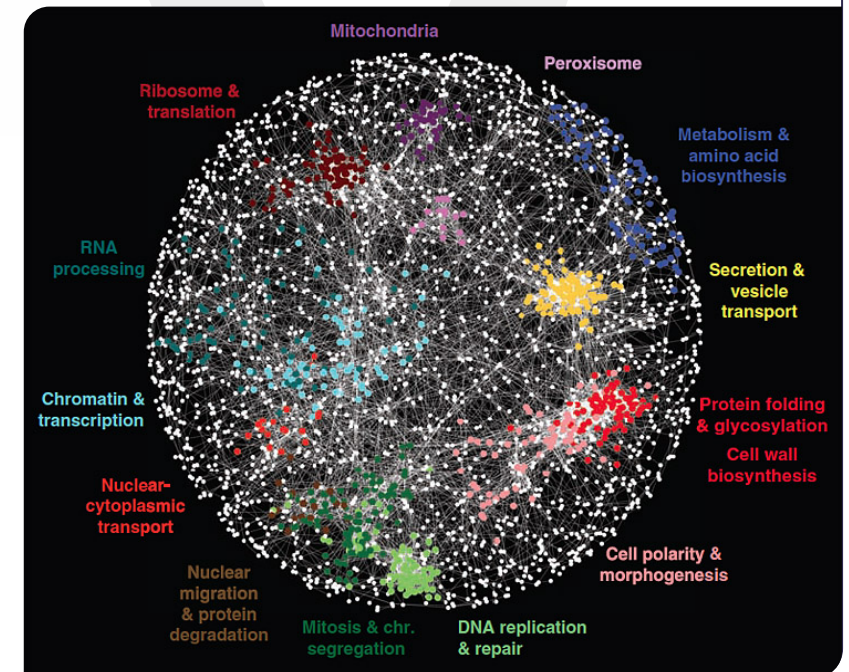
## The Next Frontier in Precision Medicine Oncology

**Synthetic Lethality** provides a powerful approach to discover novel precision medicine therapies with patient biomarkers, including MTAP-deletion (~15% of solid tumors), BRCA/HRD (Breast, Prostate, Ovarian), and high-MSI (15% GI Cancers)

**nature**  
REVIEWS GENETICS

- **Synthetic lethality** occurs when the simultaneous perturbation of two genes results in cell death
- Synthetic lethality provides a novel approach to target several historically undruggable loss of function mutations
- Large-scale screening for synthetic lethal targets has progressed through advances in molecular biology (e.g., RNA interference, CRISPR-Cas9 editing) and bioinformatics

Nature Reviews Genetics, Vol. 18, 2017, Hieter, et al., as edited by IDEAYA



Reference: Charles Boone

# IDEAYA's Precision Medicine Oncology Pipeline

Building the Industry Leading Synthetic Lethality Focused Biotechnology Company

## Precision Medicine Pipeline

	Modality/Indication	Biomarker	Preclinical	IND Enabling	Phase 1	Phase 2	Program Goals	Collaborations	Commercial (IDEAYA)
<b>IDE397</b> <i>MAT2A</i>	Monotherapy Solid Tumors	MTAP	[Progress Bar]				Cohort Expansion H1 2022 Option Package & Clin Data Update H1 2022	(1)	US 50/50 Profit Share Ex-US Royalties
	Combinations Solid Tumors	MTAP	[Progress Bar]				Preclinical Data to enable Combos (Taxanes, PRMTi, Others)		
<b>PARG</b>	Ovarian, Gastric, Breast Cancers	HRD	[Progress Bar]				Development Candidate Lead Selected	(2)	WW Commercial Rights
<b>Pol Theta</b>	Small Molecule Protein Degraders	HRD	[Progress Bar]	[Target Milestone]			Select Small Molecule Helicase Inhibitor Development Candidate December 2021	(1)	Global Royalties
<b>WRN</b>	GI Cancers	High-MSI	[Progress Bar]				Chemistry Lead Optimization	(1)	US 50/50 Profit Share Ex-US Royalties
<b>MTAP-SL</b>	Solid Tumors	MTAP	[Progress Bar]				Lead Series		WW Commercial Rights
<b>SL Platform</b>	Solid Tumors	Defined Biomarker	[Progress Bar]				Lead Series New Target / Biomarker Validation		WW Commercial Rights
<b>Darovasertib</b> <i>PKC</i>	Monotherapy MUM, UM Adjuvant	GNAQ/11	[Progress Bar]				Expand to UM Adjuvant - IST H1 2022	(3)	WW Commercial Rights
	+MEK, +cMET Combos MUM	GNAQ/11	[Progress Bar]				Daro + Crizo mPFS Update H1 2022 Regulatory Guidance H1 2022		
	GNAQ/11 Basket Skin, Mucosal	GNAQ/11	[Progress Bar]				Enhance enrollment of GNAQ/11 Basket		

- (1) Pursuant to GSK Collaboration, Option and License Agreement: MAT2A and WRN: 50/50 US Profits + ex-US Royalties; Polθ: Global Royalties  
 (2) Pursuant to CRUK Evaluation, Option and License Agreement, with ongoing Collaborative Research; IDEAYA controls all Commercial Rights  
 (3) Pursuant to Pfizer Clinical Trial Collaboration and Supply Agreement for MEK and cMET Combinations; IDEAYA retains all IDE196 Commercial Rights

[Dashed Box] = Target Program Milestone

MAT2A=methionine adenosyltransferase 2a, MTAP=methylthioadenosine phosphorylase, PARG= poly (ADP-ribose) glycohydrolase, DDT = DNA Damage Target, WRN = Werner Helicase, Polθ = DNA Polymerase Theta, HRD = homologous recombination deficiency, MSI = microsatellite instability, PKC = protein kinase C, MUM = metastatic uveal melanoma, MEK = binimetinib, cMET = crizotinib, SWS = Sturge Weber Syndrome, PWS = Port Wine Stain, WW = worldwide



# IDEAYA Leadership Team and Scientific Advisory Board

Experienced Team & Scientific Thought Leaders in Precision Medicine Oncology

## IDEAYA Executives & R&D Leadership



**Yujiro Hata, M.B.A.**  
President, Chief Executive Officer, Director



**Michael White, Ph.D.**  
SVP, Chief Scientific Officer, Head of Research



**Paul Stone, J.D.**  
SVP, Chief Financial Officer



**Mark Lackner, Ph.D.**  
SVP, Head of Biology & Translational Sciences



**Matthew Maurer, M.D.**  
VP, Head of Clinical Oncology & Medical Affairs



**Mick O'Quigley, M.B.A.**  
VP, Development Operations



**Paul Barsanti, Ph.D.**  
SVP, Head of Drug Discovery



**Jason Throne, J.D.**  
SVP, General Counsel



## IDEAYA Scientific Advisory Board



**William Sellers, M.D.**  
Broad Institute, Dana Farber, and Harvard, Professor  
Novartis, Former Head Oncology Research,  
SL Project Drive initiative



**Frank McCormick, Ph.D.**  
UCSF, Professor and former Director,  
Helen Diller Cancer Center  
Former President AACR; Founder and CSO, Onyx



**Trey Ideker, Ph.D.**  
UCSD, Professor, Co-Director Cancer Genomes & Networks  
Program, Research in Dual-CRISPR and SL interaction maps



**Brian Daniels, M.D.**  
Bristol Myers Squibb, Former SVP Global Development  
& Medical Affairs



**Elizabeth Swisher, M.D.**  
University of Washington, Professor; Co-Leader, Breast and  
Ovarian Cancer Research Program, Seattle Cancer Care Alliance  
Principal Investigator on multiple PARP inhibitor trials



**Jeffrey Hager, Ph.D.**  
Former Chief Technology Officer, IDEAYA

# IDEAYA and GSK Strategic Partnership

## Landmark Partnership in Synthetic Lethality



### Transformative Strategic Partnership

- Validates IDEAYA Synthetic Lethality platform
- Creates strategic combination opportunities
- Advancing small molecules and protein degraders

### Key Partnership Terms

- \$100M cash upfront
- \$20M equity investment as direct private placement
- \$50M option exercise fee for MAT2A
- Over \$3 billion in potential Milestone Payments, including approximately \$1 billion per program
- 50/50 US profit share for MAT2A and Werner Helicase
- 20% cost share allocated to IDEAYA for MAT2A, Werner
- Royalties tiered high single-digit to sub-teen double digit %

### MAT2A (MTAP Deletion)

- \$50M Option Fee, 50/50 US Profit Share & ex-US Royalties
- Option Data Package based on Clinical Dose Escalation Data
- ~\$1B potential Milestone Payments
- Evaluating multiple clinical combination opportunities

### Werner Helicase (MSI High)

- 50/50 US Profit Share and ex-US Royalties
- ~\$1B potential Milestone Payments
- Potential Combination with GSK's Dostarlimab, a PD-1 IO Agent

### Pol Theta (BRCA/HRD)

- GSK covers all Costs
- Global Royalties and ~\$1B potential Milestone Payments
- Potential Combination with GSK's Zejula™, a PARP Inhibitor

# IDEAYA Synthetic Lethality Platform

Fully-Integrated Target, Biomarker, Drug Discovery and Translational Capabilities

## SL Target & Biomarker Discovery and Validation



Bioinformatics, including AI Algorithms  
Dual CRISPR, CRISPR, siRNA  
Genetically Engineered Models

- Key emerging SL targets identified, such as Werner Helicase, Pol Theta and PARG
- DECIPHER™ - Dual CRISPR SL Library in DDR in collaboration with UCSD
- PAGEO™ - Paralogous Gene Evaluation in Ovarian in collaboration with Broad Institute

## Drug Discovery and Pharmacological Validation



Structure Based Drug Design  
Small Molecule Chemistry  
Protein Degradation Capabilities

- Crystal structures for five SL programs obtained to enable structure-based design
- Differentiated candidate compounds discovered, including IDE397
- Protein degraders advancing for selected targets, including Pol Theta

## Translational Research and Opportunity Expansion



Genomics – DNA and RNA Analysis  
Proteomics – Protein Expression Profiling  
Tissue (IHC, IF) and Liquid Biopsies Analysis

- Translational research to define clinical biomarkers
- Opportunity expansion through broad cell panel screening
- Pharmacodynamic biomarker analysis to confirm target modulation and correlation with clinical activity



# IDEAYA Synthetic Lethality Platform

## Synthetic Lethality Target and Biomarker Discovery and Validation



### Synthetic Lethality Target Discovery & Validation Platform

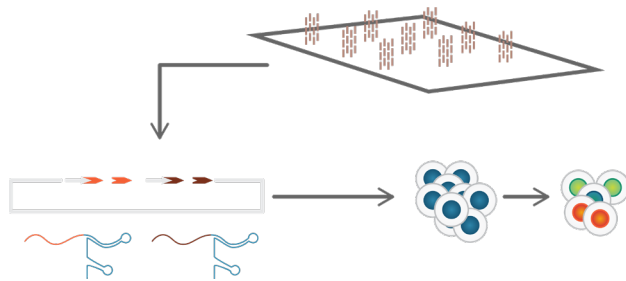
IDEAYA SL Platform integrates extensive proprietary and public data sets with orthogonal and complementary content

Bioinformatic analysis enables identification and validation of synthetic lethal target / biomarker interactions across vast datasets

Robust SL interactions validated genetically (Dual CRISPR, paralogues, isogenic pairs, CRISPR/siRNA), pharmacologically, & *in vivo*

#### DECIPHER™

#### Dual CRISPR SL Library in DNA Damage Repair (2)

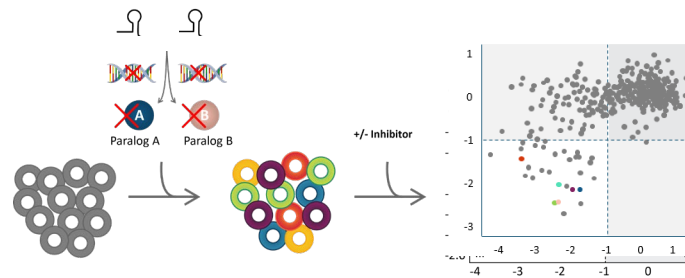


Evaluation of DNA Damage Targets synthetic lethal with tumor suppressor or oncogenes

>20 Novel Drug Targets Identified  
Target Validation Ongoing

#### PAGEO™

#### Paralogous Gene Evaluation in Ovarian Cancer (1)



Evaluation of SL targets in context of functionally redundant paralogous genes in ovarian cancer

#### Partnership Datasets

Cancer Dependency Map – Broad Institute  
Foundation Insights™ – Foundation Medicine



#### Public Databases

IDEAYA data mining and analysis across data sets



# IDEAYA's Synthetic Lethality Pipeline Strategy

Building the Industry Leading Synthetic Lethality Focused Biotechnology Company

## Focus on Potential *First-in-Class* Synthetic Lethality Programs to Deliver Patient Breakthroughs

Patient Impact: Potential First-in-Class / Best-in-Class

Significant Opportunities: Large Target Patient Populations

Precision Medicine: Compelling Patient Selection and Pharmacodynamic Biomarkers

Synthetic Lethality Platform: Deep and rich Target Pipeline with ongoing Target Identification and Validation

MTAP Deletion

IDE397 (Ph1)  
MTAP-SL (PC)

HRD / BRCA

PARG (DC)  
Pol Theta (Late PC)  
Pol Theta Degradar (PC)

MSI-High

Werner (PC)

GNAQ/11

Daro + cMET (Ph2)  
(SL Combination)

SL Platform

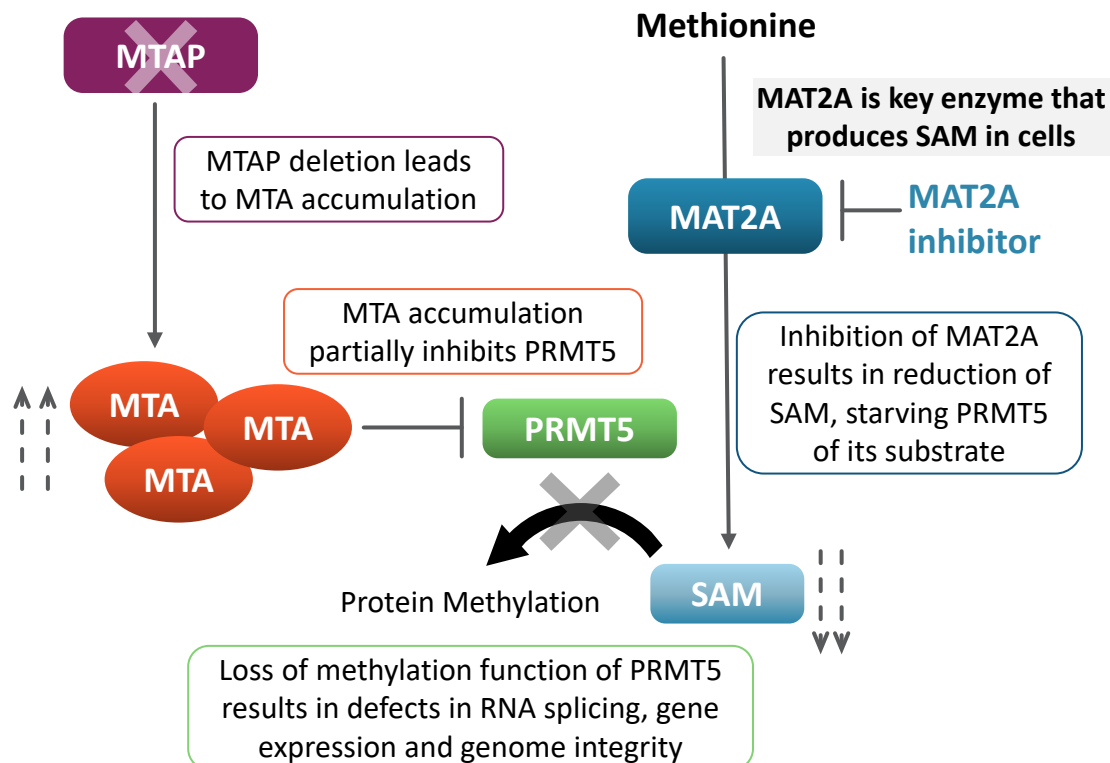
Novel Targets



# MAT2A Inhibition is Synthetic Lethal with MTAP Deletion

MTAP Deletion Prevalence ~15% of all Solid Tumors

## MTAP-MAT2A Synthetic Lethality Biology



## MTAP Deletion Prevalence

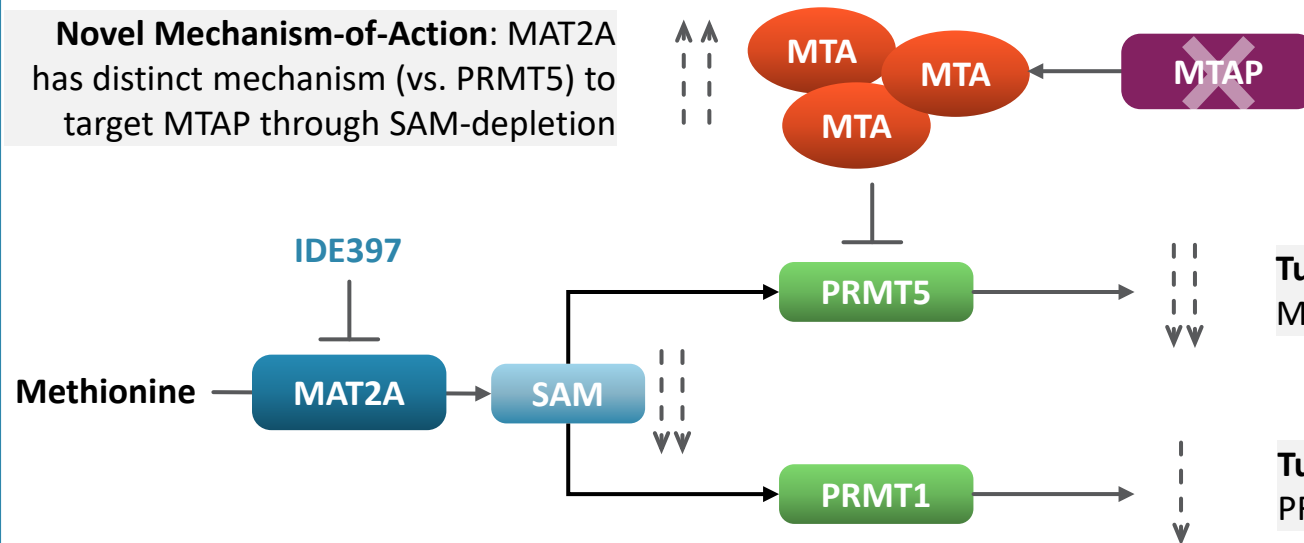
Cancer Type	N	MTAP Deletions (%)
Glioblastoma	592	41
Mesothelioma	87	32
Esophageal	95	28
Bladder	411	26
Pancreatic	184	22
Melanoma	448	16
Lung Cancer (NSCLC)	1053	15
Head and Neck	523	14
Sarcoma	255	10
Esophagogastric	514	10
Diffuse Glioma	513	9
Breast	1084	3
Ovarian	585	3
Adrenocortical	92	3
Thymic	123	3
Hepatocellular	369	3
Renal non-clear cell	348	2

Data from The Cancer Genome Atlas in cBioPortal

# MAT2A Has Novel Mechanism vs PRMT5 to Target MTAP Deletion Through SAM Depletion and Inhibition of a Selective-Essential Gene

## MAT2A Mechanism and Biology

**Novel Mechanism-of-Action:** MAT2A has distinct mechanism (vs. PRMT5) to target MTAP through SAM-depletion

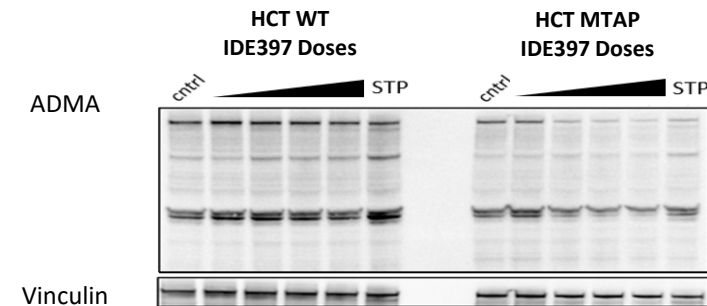


**MTAP Biomarker:** MAT2A is a Selective Essential Gene in presence of MTAP (vs PRMT5 = Pan Essential Gene), which may enhance Therapeutic Index and Combination Potential vs. PRMT5

**Tumor SDMA:** PD biomarkers preclinically correlate with efficacy; MAT2A inhibition shows robust modulation of specific SDMA substrates

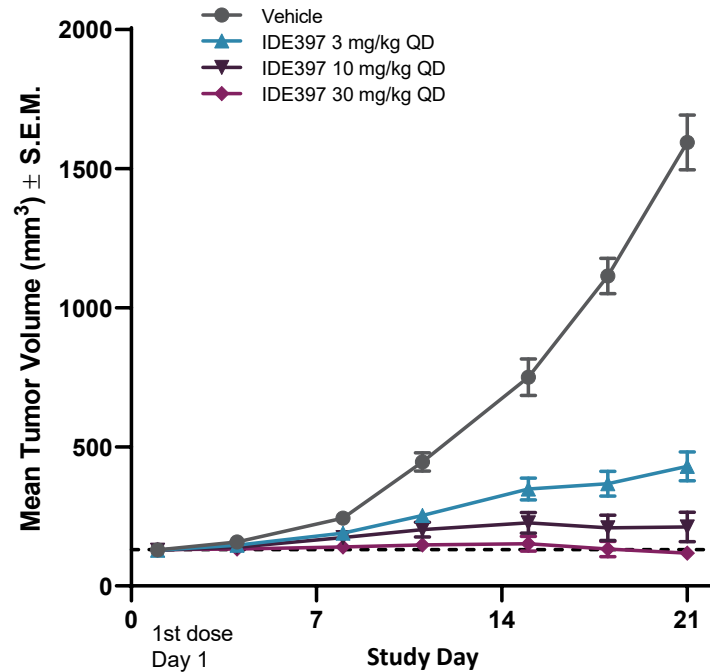
**Tumor ADMA:** downstream PD biomarker reduced in preclinical studies PRMT5 mechanistically not anticipated to reduce ADMA-levels

**Pharmacodynamic Biomarkers:** IDE397 reduction of proximal plasma and tumor SAM demonstrates robust target engagement preclinically



# IDE397 Monotherapy Demonstrates Tumor Regressions and Robust SAM and SDMA Tumor PD Modulation in CDX Xenograft models

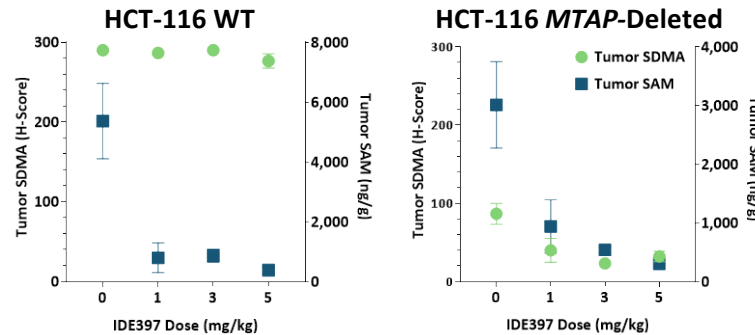
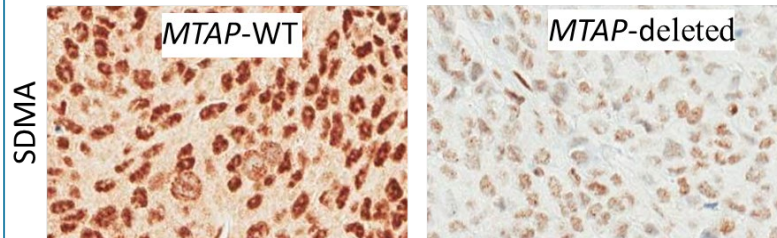
## NSCLC Endogenous MTAP-/- CDX Model



IDEAYA Data

## SDMA and SAM are Proximal PD Biomarkers of MAT2A inhibition

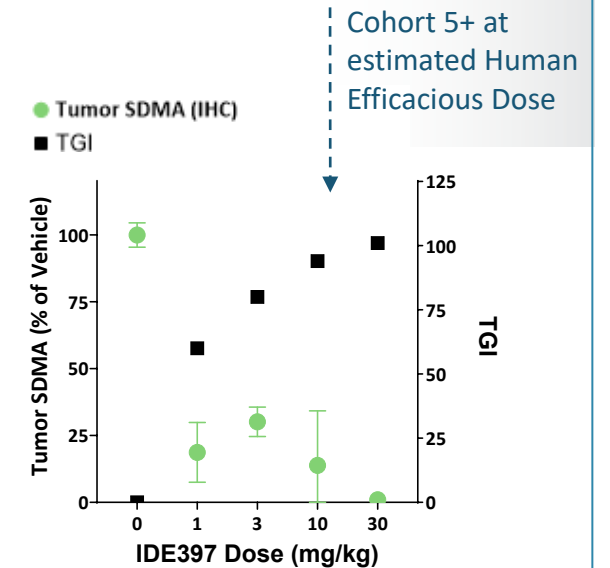
### IDE397 modulates SDMA and SAM



IDEAYA Data: Fischer et. al., AACR 2021

### SDMA modulation correlates to TGI

#### NCI-H838 MTAP-/- CDX Model



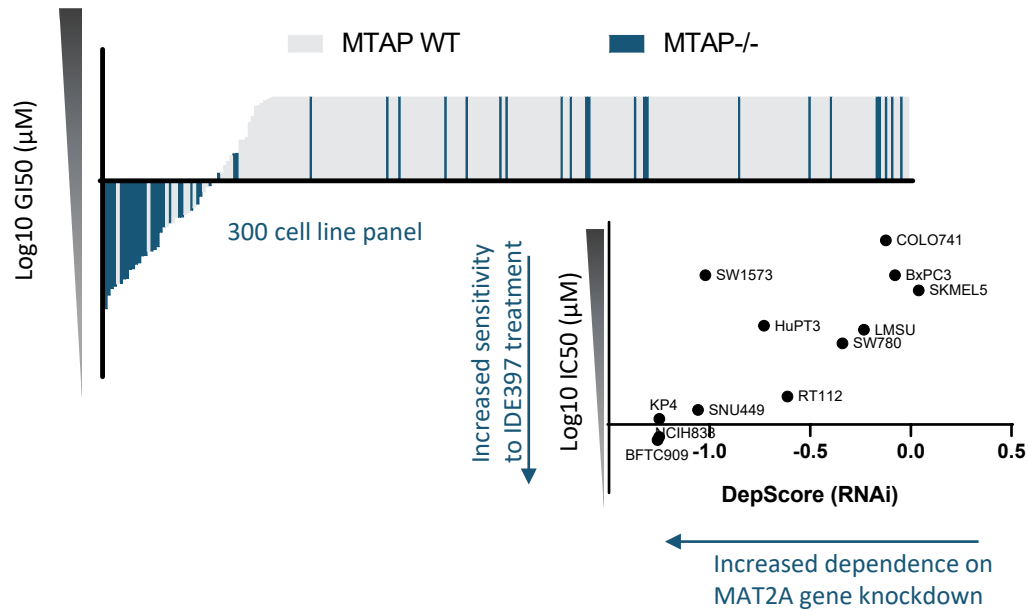
IDEAYA Data

Robust dose-dependent efficacy and PD modulation observed in NSCLC CDX Model

# IDE397: MAT2A Development Candidate *in vitro* Profile

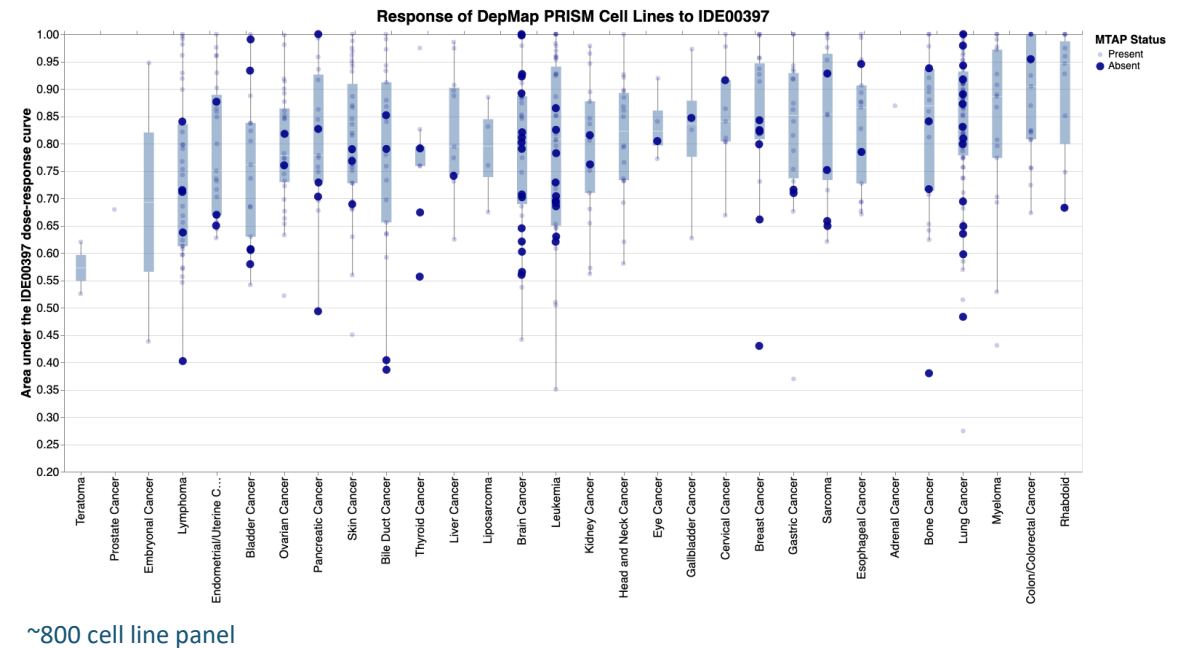
IDE397 is selective for MTAP<sup>-/-</sup> Cell Lines

## IDE397 is Selective for MTAP<sup>-/-</sup> Cell Lines



MTAP<sup>-/-</sup> cell lines are sensitive to IDE397  
 MTAP WT cell lines are generally insensitive  
 Pharmacological inhibition correlates with MAT2A genetic knockdown

## IDE397 has Broad Activity across Tumor Types



Differential sensitivity across tumor types; potential for discovery of additional predictive biomarkers  
 MTAP gene expression and copy number loss emerge as top predictors of sensitivity across cell lines

# IDE397: MAT2A Inhibitor

## Preclinical Evaluation of IDE397 – Differentiated Profile and Selective for MTAP-/- Cell Lines

### IDE397 Target Product Profile

**IDE397 demonstrates superior cellular potency and selectivity compared to AG-270**

**IDE397 has not caused preclinical liver injury or increased bilirubin**

- Not an inhibitor of UGT1A1 (AG-270 noted to inhibit UGT1A1)<sup>1</sup> or BSEP transporters at relevant concentrations
- Liver injury not observed in preclinical tox studies

**IDE397 has favorable physical properties, including solubility**

- AG-270 observed non-linear exposure >200mg QD (GI absorption)

**IDE397 demonstrates *in vivo* efficacy and PD modulation at 5 to 30mg/kg**

- AG-270 published preclinical dose typically 200mg/kg QD <sup>1</sup>

### Biochemical and *in vitro* Potency and Selectivity

	IDE397	AG-270
MAT2A biochemical IC <sub>50</sub> (nM)	7	12
KP4 EC <sub>50</sub> cellular (nM) MAT2A dependent	15	731
BXPC3 cellular EC <sub>50</sub> (nM) MAT2A independent	13200	1630
HuCCT1 cellular EC <sub>50</sub> (nM) MAT2A independent	>20000	1400

### Differentiating ADME/Physicochemical Properties

	IDE397	AG-270
BSEP inhibition @10μM (%)	1	25.2
UGT1A1 inhibition (%)	34	83
PXR Emax @30 μM (%)	9	35
Solubility @pH 7.4 (μM)	>100μM	BLOQ*

IDEAYA Data

\*BLOQ = below limit of quantitation

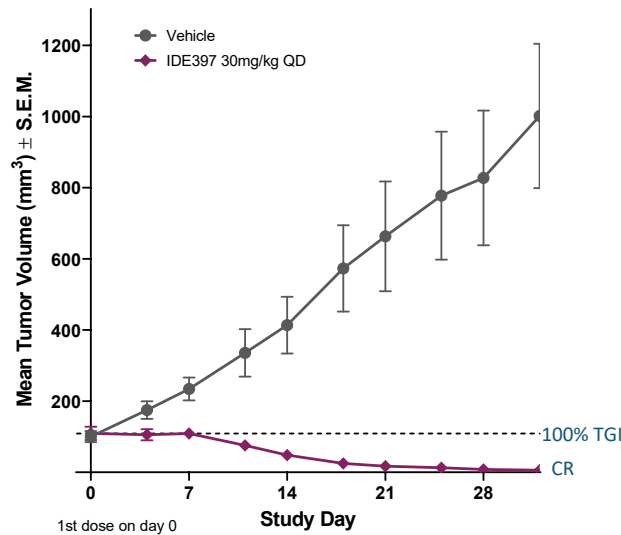
(1) Agios, AACR 2019, Keystone 2019, Triple Meeting 2019 (Webcast Call Q&A), J Med Chem 2021

# IDE397: PDX Study of >40 MTAP-/- Models in Multiple Indications

## Monotherapy Tumor Regressions & Significant TGI Across Multiple Solid Tumor Types

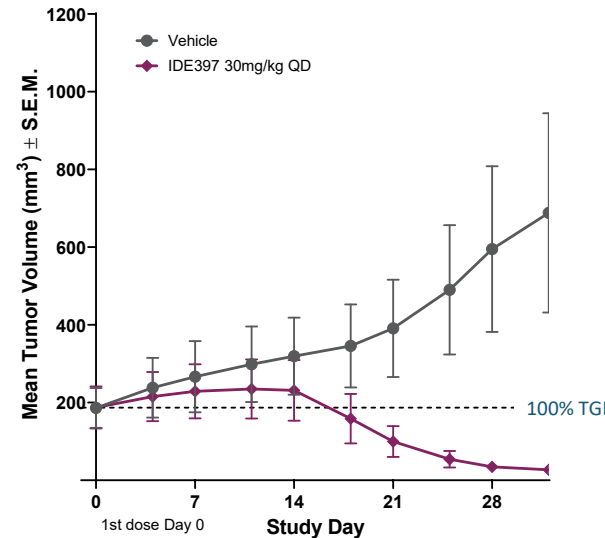
### NSCLC and Bladder Cancer MTAP-/- PDX Models

NSCLC PDX Model

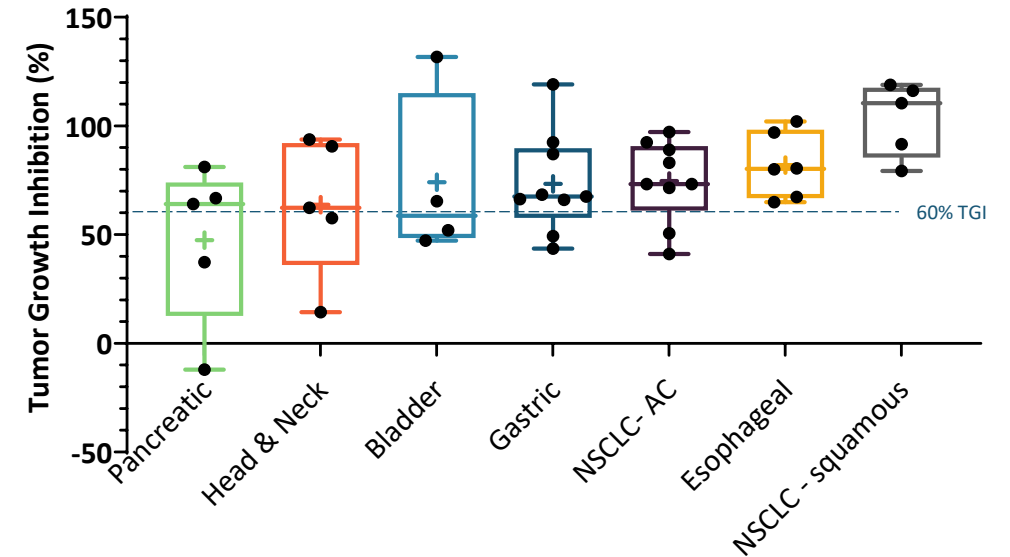


IDEAYA Data

Bladder PDX Model



### Panel Study of >40 MTAP-/- PDX Models



IDEAYA Data: Fischer et. al., AACR 2021

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

- Tumor Regressions ( $\geq 100\%$  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

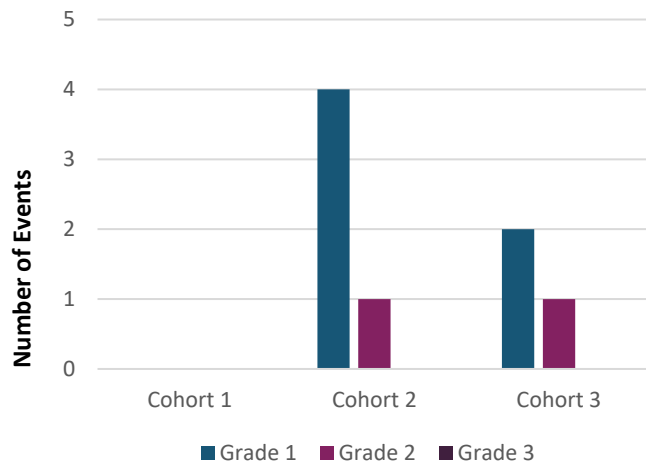


# Observed Preliminary IDE397 Clinical Activity and Tolerability

## Plasma PD Reduction and Tumor Shrinkage in MTAP Deletion Patients

### IDE397 Safety / Tolerability

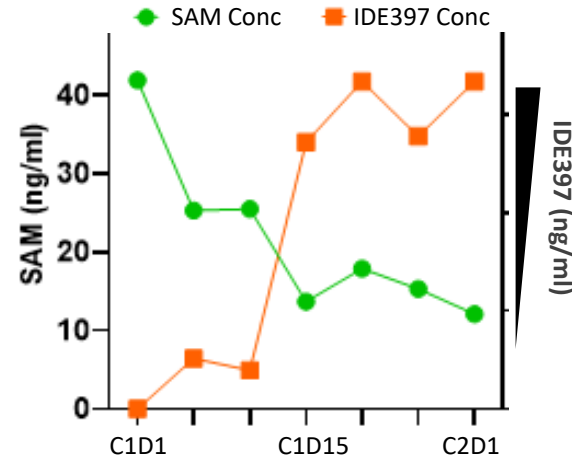
#### Drug Related Adverse Events



Cohorts 1 thru 3

### IDE397 Plasma SAM PD

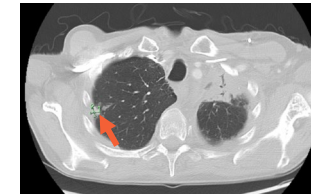
#### PK / PD Analysis Plasma SAM vs IDE397 Concentration



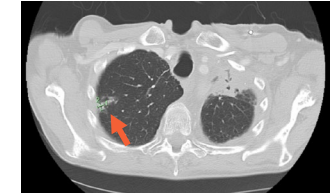
Cohort 3 Patient

### Observed Tumor Shrinkage

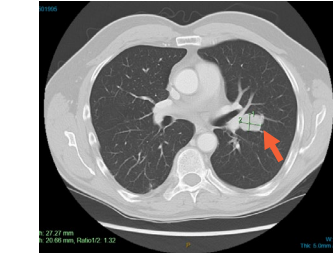
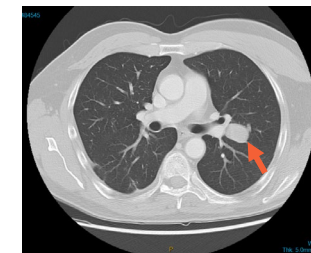
#### Baseline CT Scan



#### Early Treatment Scan



Cohort 2 NSCLC: 15% Reduction\*



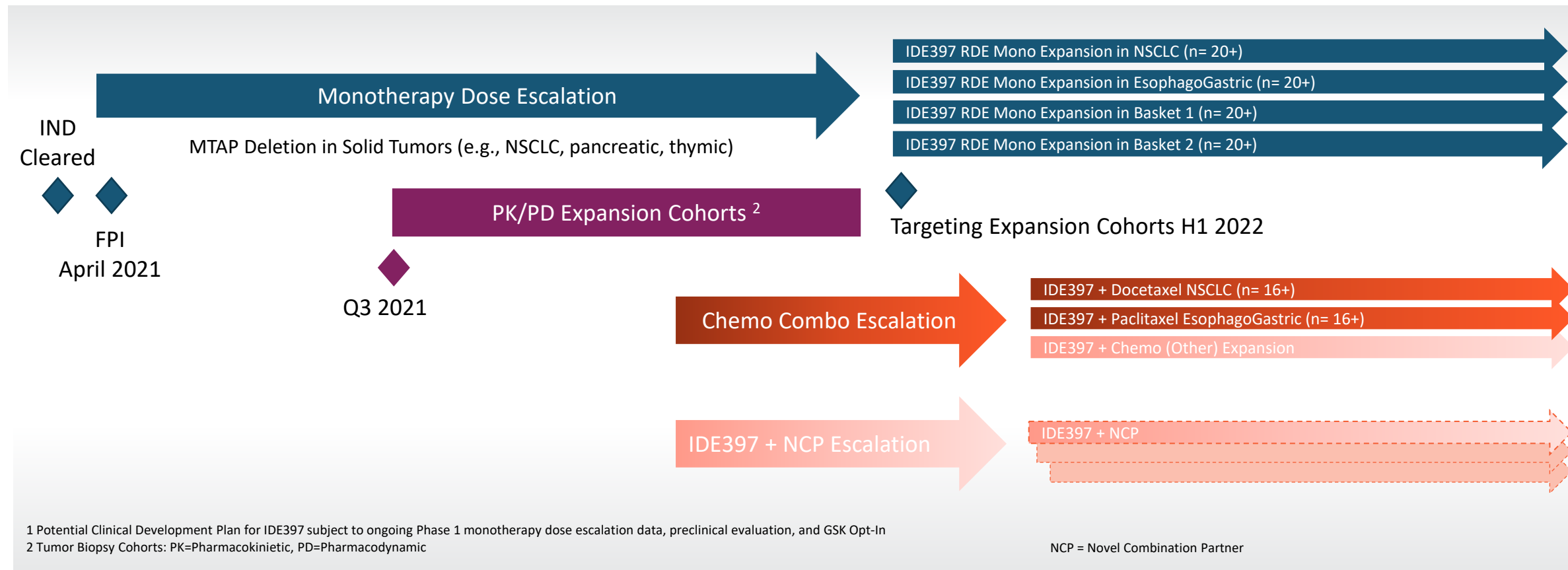
Cohort 3 ACC with Lung Mets: 11% Reduction\*

- No drug-related Serious Adverse Events: drug-related adverse events have been Grade 1/2, with no reported myelosuppression or liver toxicity
- Observed plasma SAM PD reduction in early dose escalation Cohorts 1 thru 3, achieving predefined target  $\geq 60\%$  plasma SAM suppression
- Observed tumor shrinkage in MTAP-deletion patients in early dose escalation Cohorts 2 and 3
- 80+ year-old Cohort 2 patient with large thymic carcinoma mediastinal remains on treatment after almost 6 months
- Enrolling Cohort 5; Maximum Tolerated Dose (MTD) has not yet been established

# IDE397 Phase 1 Clinical Trial

## Comprehensive Approach for Concurrent Evaluation of Monotherapy and Combinations

### Phase 1 Dose Escalation and Expansion Strategy <sup>1</sup>



Addressable Patient Population of ~75,000 estimated in US, EU5 and JP across six indications, including NSCLC, head and neck, bladder, gastric, pancreatic and esophageal cancers

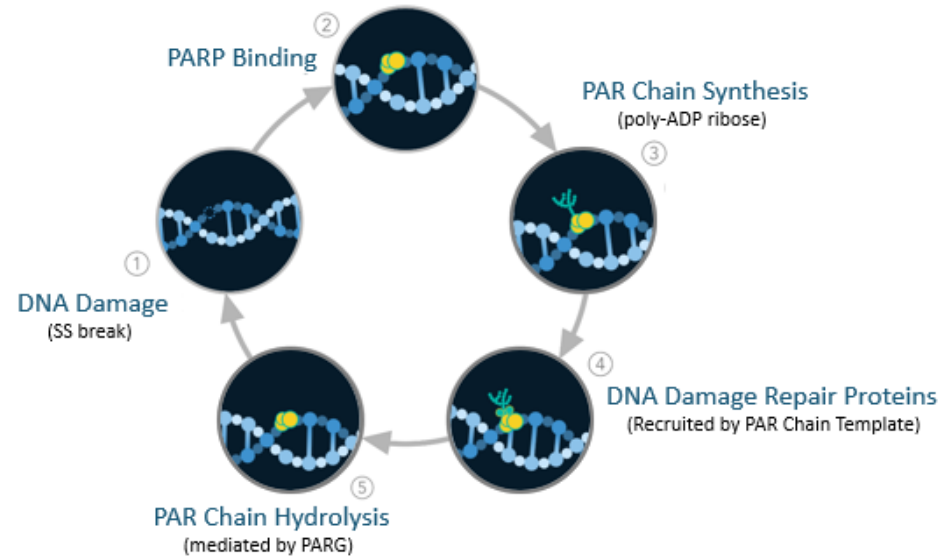
# PARG Synthetic Lethality Program

## Development Candidate Lead Selected

### PARG Biology

#### Novel target in Clinically Validated Pathway

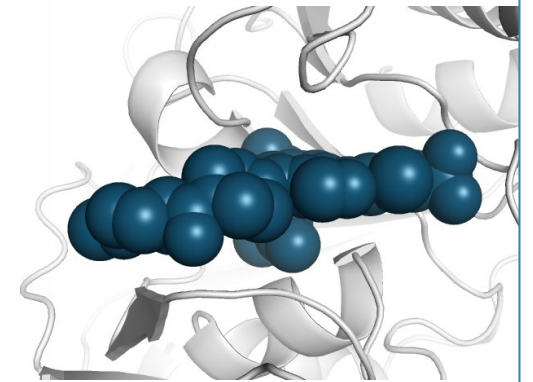
Poly(ADP-ribose) glycohydrolase (PARG) regulates DNA repair by hydrolyzing PAR chains in final step of DDR cycle



Cancer Research (Aug 2019), Cancer Research (Jul 2019), Cancer Cell (Mar 2019)

### PARG Drug Discovery Program

**Key Emerging Target with lead optimization program guided by structure-based drug design to identify potent, selective candidates**



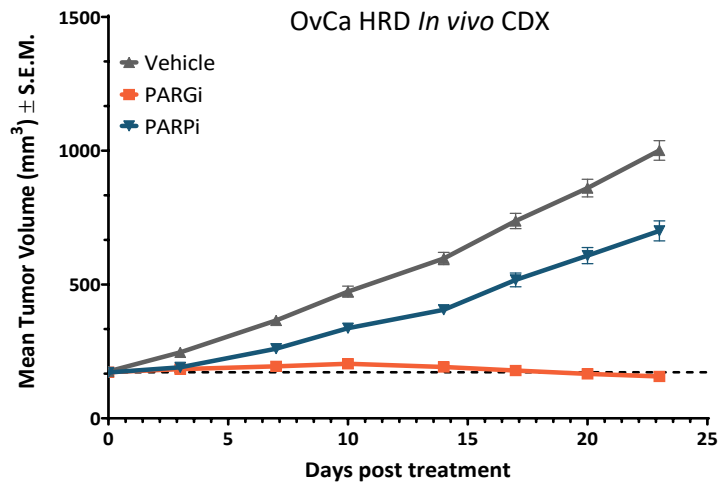
- Multiple potent cellularly active compounds demonstrate *in vitro* and *in vivo* PAR accumulation (PD) and *in vivo* efficacy in defined biomarker setting
- Collaboration with Bill Sellers lab (Broad) established to identify additional genetic sensitizers to PARGi

IDEAYA Data

# Biomarker Selected *in vitro* & *in vivo* Models are Sensitive to IDEAYA PARGi

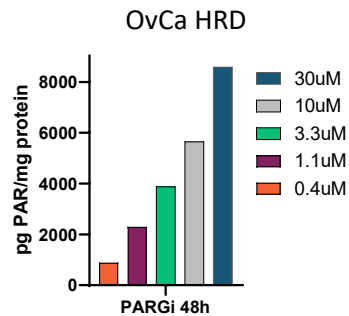
## Differentiated Activity to PARP inhibition in Ovarian, Gastric and Breast Cancer Models

### Ovarian Cancer HRD Cell Line Models

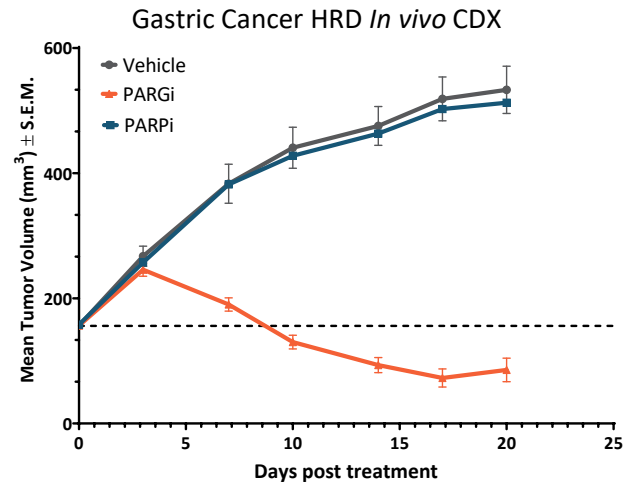


PARGi Tumor Regression and enhanced TGI relative to PARPi

Dose-dependent poly-PAR (PD) accumulation

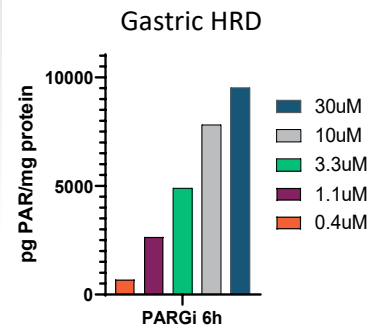


### Gastric Cancer HRD Cell Line Models

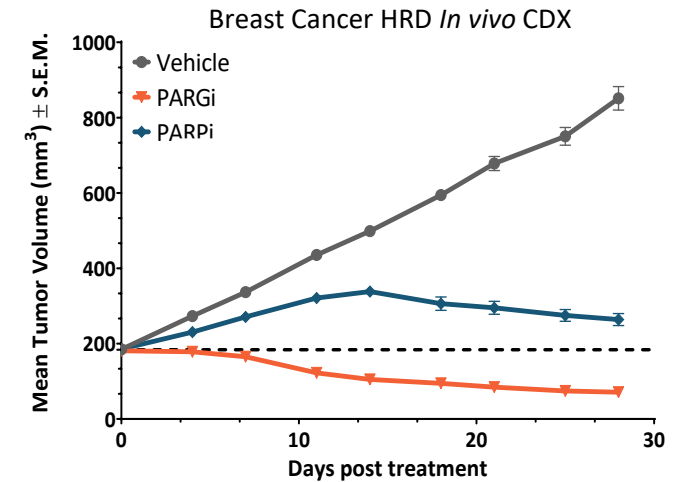


PARGi Tumor Regression in PARPi Refractory Setting

Dose-dependent poly-PAR (PD) accumulation

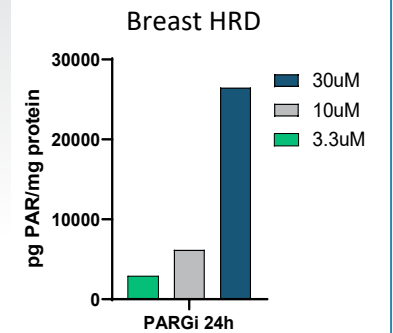


### Breast Cancer HRD Cell Line Models



PARGi Tumor Regression and enhanced TGI relative to PARPi

Dose-dependent poly-PAR (PD) accumulation





# Pol Theta Synthetic Lethality Program

## Targeting Development Candidate in December 2021

### Pol Theta Synthetic Lethality with BRCA/HRD

DNA polymerase theta (Pol Theta) promotes DNA repair by Microhomology-Mediated End-Joining (MMEJ) an error-prone mutagenic DNA repair pathway

MMEJ is active, and Pol Theta is overexpressed, in HRD cancer cells (e.g. BRCA1/2) making Pol Theta a SL target in HRD cancers

PARP1 & Pol Theta are both involved in MMEJ mediated DNA repair supporting a synergistic effect

IDEAYA Pol Theta inhibitors show selective cell viability effects in DLD1 BRCA2<sup>-/-</sup> vs. wildtype cell lines

Advancing both small molecule inhibitors and protein degraders

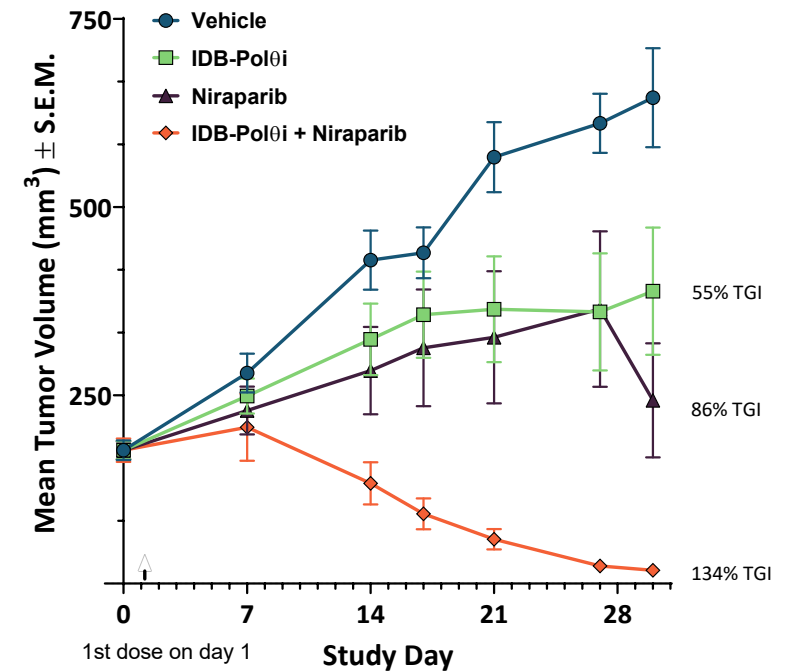
IDEAYA Data

### Pol Theta ATPase inhibitor *In Vivo* Activity

**Pol Theta inhibitor in combination with niraparib demonstrates significant tumor regression in DLD1 BRCA2<sup>-/-</sup> xenograft model**

Regressions observed for all animals dosed within combination study

IDEAYA Data





# Werner Helicase Synthetic Lethality Program

Candidate Biomarker: High-MSI (15% GI Cancers and 16% CRC)<sup>1</sup>

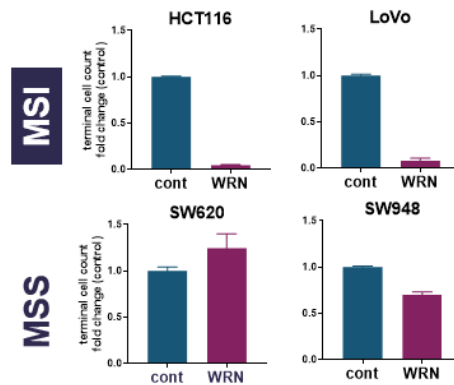
## Werner Helicase Synthetic Lethal with High-MSI



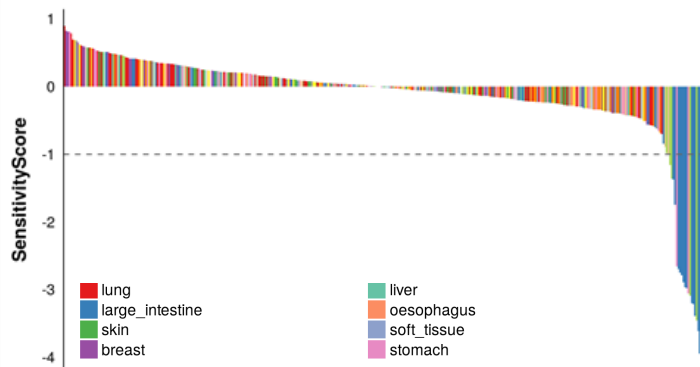
Werner Syndrome Helicase is Required for the Survival of Cancer Cells with Microsatellite Instability

IDEAYA Publication

Cell Press, iScience, March 2019, Hager et al



Project Drive: WRN is essential in MSI-High cancer cell lines



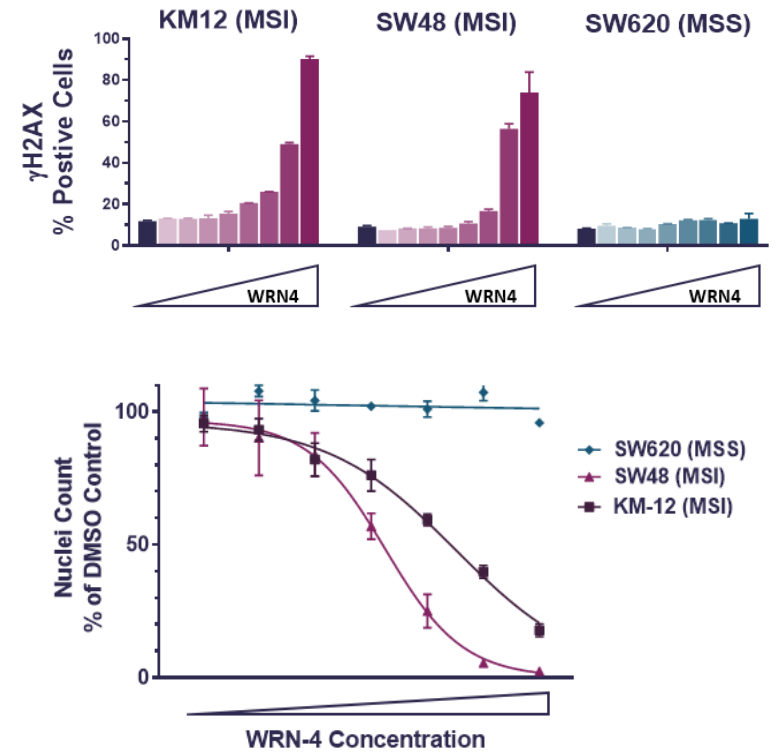
Project Drive

## Werner Inhibitor Cellular PD and Viability

PD-marker: dose dependent increase of DNA damage marker  $\gamma$ H2AX

Cell viability: MSI-high specific cell viability effect; no effect in MSS cell lines

In vivo efficacy: Preliminary WRN inhibitor in vivo PD and efficacy



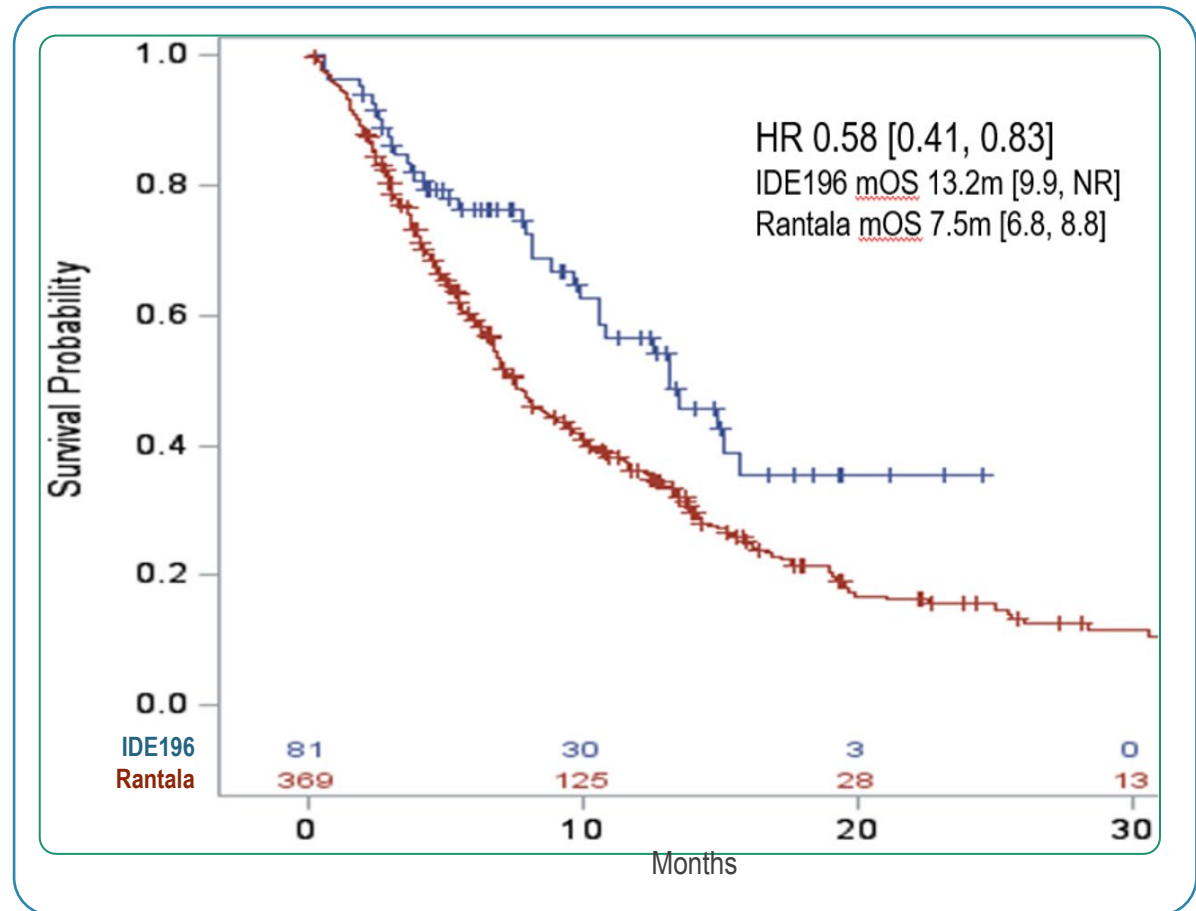
IDEAYA Data

<sup>1</sup> Cancer Res., November 1998

# Darovasertib Monotherapy Overall Survival in Heavily Pre-Treated MUM

Overall Survival favorable compared to Historical Pretreated Synthetic Control Arm <sup>1,2</sup>

Baseline Characteristics		N=81 (%)
Age	< 65	57 (70.4)
	>=65	24 (29.6)
Sex	F	41 (50.6)
	M	40 (49.4)
ECOG PS	0	61 (75.3)
	1	20 (24.7)
Baseline LDH	Normal	26 (32.1)
	>ULN	54 (66.7)
	Missing	1 (1.2)
Number of Prior Regimens	0	12 (14.8)
	1	30 (37.0)
	>=2	39 (48.1)
Tumor Burden (mm) (Sum of Target Lesions)	Median	82
	Min, Max	11, 301



<sup>1</sup> IDEAYA Data (based on preliminary analysis of unlocked database, including: pooled IDEAYA and Novartis BID monotherapy clinical data as of Apr 13, 2021)

<sup>2</sup> Synthetic Control Arm based on Rantala 2019 (meta-analysis of overall survival of patients with metastatic uveal melanoma over 1980 to 2017 evaluated by treatment modality and lines of treatment)

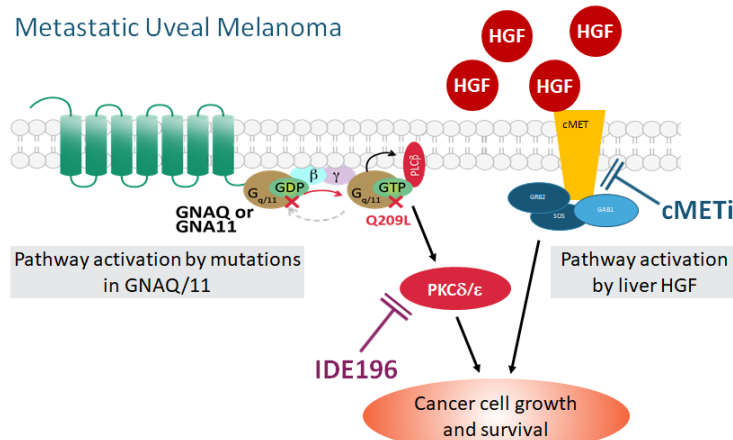
# Synthetic Lethal Combination: Darovasertib (PKC) + Crizotinib (cMET)

cMET inhibitor reduces HGF activation of cMET signaling to Synergize with Darovasertib

## PKC + cMET Synthetic Lethal Discovery

High cMET expression is associated with metastatic progression

Metastatic Uveal Melanoma

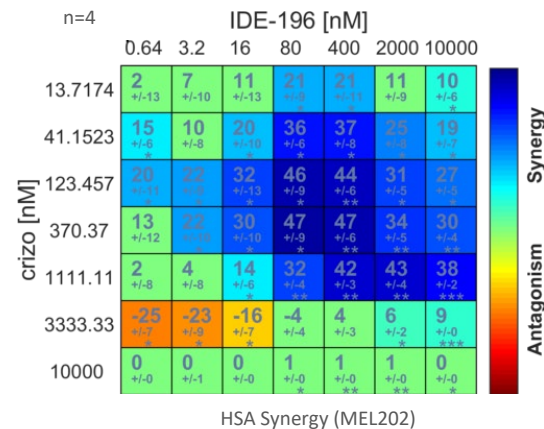


- HGF promotes cancer cell growth and survival
- Translational Research hypothesis: HGF-induced cMET signaling in the liver microenvironment activates an alternative pathway for MUM tumor progression

IDEAYA Darovasertib Investor Day, 2021

## Preclinical Synergy

Darovasertib + Crizotinib synergy exhibited in Mel202 (MUM) cell line

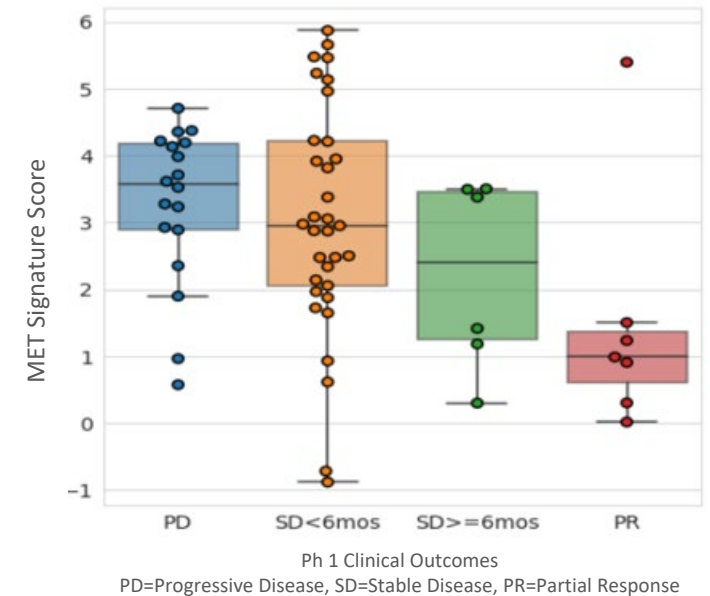


IDEAYA Data AACR 2021

## Clinical Phase 1 Data Association

Clinical response to Darovasertib monotherapy associates with low cMET activity

### Darovasertib Monotherapy Ph 1



IDEAYA Data

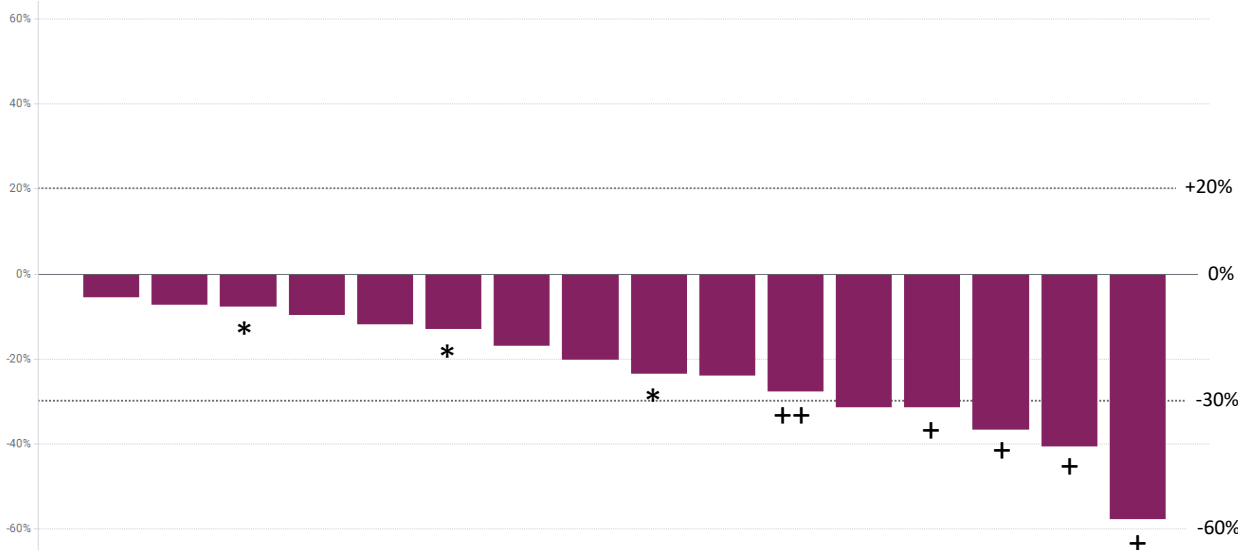


# Preliminary Darovasertib + Crizotinib Phase 2 Expansion Dose Efficacy

## Encouraging Clinical Activity in heavily pretreated Metastatic Uveal Melanoma

Daro + Crizo Expansion Dose Cohort, n=16 with  $\geq 1$  post-BL scan

**100% of patients observed tumor shrinkage (100% DCR)**  
**31% ORR in patients with  $\geq 2$  post baseline scans**



+ Confirmed partial response by investigator or central review  
 ++ Unconfirmed partial response by central review awaiting follow-up scans  
 \* Has had only 1 post baseline scan  
 3 of 4 responders were pretreated with immunotherapy

### Early Clinical PoC of PKC + cMET Synthetic Lethal

- 100% of patients show tumor reduction in target lesions (n=16 evaluable patients with  $\geq 1$  scan)
  - 100% Disease Control Rate
- Encouraging ORR% in heavily pre-treated MUM patients with  $\geq 2$  post-baseline scans (n=13)\*
  - 4 patients with confirmed PRs (31% ORR)
  - 6 patients (46%) demonstrate >30% tumor reduction, including 1 uPR awaiting follow-up scan(s)
  - IMC-GP100/IMCR: 4.7% ORR; Pembro: 5% ORR\*\*
- Baseline Characteristics of n=22 total patients, including 6 patients awaiting 1<sup>st</sup> scan
  - LDH > ULN in 65% of patients
  - 91% with prior therapies
  - 59% with 2 or more prior therapies
- Program Goal: ORR >20%
  - \* No patients off-treatment prior to 2<sup>nd</sup> scan

# Darovasertib + Crizotinib Combination Preliminary Efficacy

## Examples of Responses with significant Anti-Tumor Activity

### Patient Example 1

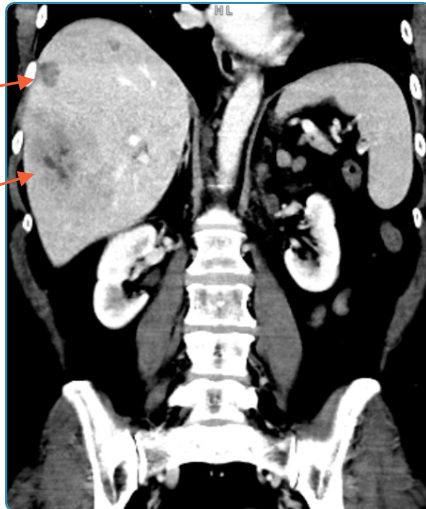
- 70+ year old patient with ongoing response at 6 months
- Priors: Ipi+Nivo, Chemoembolization, Radioembolization
- Diffuse disease in liver, lung, LN, subcut and elevated LDH

Baseline

5 months

One of many lesions

Large necrotic confluence distorting liver



### Patient Example 2

- 60+ year old patient with ongoing response at 4 months
- Priors: Ipi+Nivo
- Numerous liver lesions, normal LDH

Baseline

4 months



Multiple lesions in the dome of the liver



Markedly improved

# Darovasertib + Crizotinib SL Combination Therapy

## Differentiated Novel Treatment Mechanism in MUM

	Darovasertib + Crizotinib	Cabozantinib	Selumetinib + Dacarbazine	Tebentafusp
<b>Target / Mechanism</b>	PKC + cMET	cMET	MEK + Chemotherapy	HLA-A2-0201 Bi-Specific Ab
<b>Study Name</b>	NCT03947385	Alliance A091201 <sup>^</sup>	SUMIT (NCT01974752)	IMCgp100-102
<b>Population</b>	2L/3L+ MUM (n=16 eval)	1L+ MUM (n=31 eval)	1L+ MUM (n=97)	2L+ MUM (n=127)
<b>Patient Selection</b>	N/A (100% of MUM)	N/A (100% of MUM)	N/A (100% of MUM)	HLA-A2-0201 (~40-50% of MUM)
<b>Drug Form</b>	Oral Tablets (BID)	Oral Capsules (QD)	Oral Capsules (BID) plus chemo	IV Infusion (Weekly)
<b>Tolerability (Grade ≥3 Drug-Related AE)</b>	27%	51.6%	63% <sup>^^^</sup> (All Cause)	46.5%
<b>% of Pts with Tumor Shrinkage</b>	100%*	23% <sup>^^</sup>	35% <sup>^^</sup>	44% <sup>#</sup>
<b>Overall Response Rate (ORR)</b>	31%*	0%	3% <sup>^^^</sup>	4.7% <sup>#</sup>
<b>Progression Free Survival (PFS)</b>	Targeting mPFS update in H1 2022	2 m	2.8 m <sup>^^^</sup>	2.8 m <sup>#</sup>
<b>Overall Survival (OS)</b>	[ TBD ]	6.4 m	Not reported	16.8 m <sup>#</sup>

\* IDEAYA Ph 1/2 (ongoing): based on preliminary analysis of unlocked database as of 11/25/2021 by investigator or central review

<sup>#</sup> Based on Immunocore reported 2L+ study data (to reflect comparative patient population) and by independent review

<sup>^</sup> Randomized Phase II Trial and Tumor Mutational Spectrum Analysis from Cabozantinib versus Chemotherapy in Metastatic Uveal Melanoma (Alliance A091201); Clin Cancer Res 2020;26:804–11

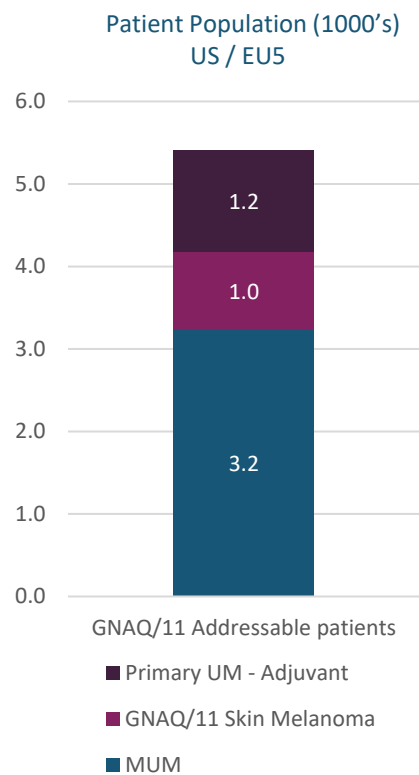
<sup>^^</sup> Estimated from Waterfall plot

<sup>^^^</sup> Journal of Clinical Oncology, Carjaval, et. al, 2018; 1232-1239

# Darovasertib Patient Population Analysis

## GNAQ/GNA11 Melanoma & Additional MET-Amplified / High Expression Tumors

### Addressable GNAQ/11 Patients



IDEAYA Analysis

### MUM, Adjuvant UM and GNAQ/11 Skin Melanoma

- No FDA Approved Therapies for MUM or GNAQ/11-Tumors
- Evaluating opportunities in Adjuvant Uveal Melanoma (Ph 1 IST) and GNAQ/11 Skin Melanoma (Ph1)
- Total Addressable Patient Population = ~5.4K pts/year

### Evaluating Additional MET-Amplified / High Expression Tumors

- Patient selection based on CLIA-validated assays for MET-amplification (e.g., NGS, FISH) or high MET expression (e.g., IHC)
- HCC focus on refractory / resistant patients based on hypothesis of constitutively active cMET/HGF axis

	MET-amplification	High MET Expression
NSCLC	~1-5% <sup>1,2</sup>	~3-4% <sup>2</sup>
CRC	-	~3-9% <sup>2</sup>
Gastric Cancer	-	~9-20% <sup>2</sup>
HCC	~9% <sup>3</sup>	~27% <sup>3</sup>

<sup>1</sup> Drilon et al., Journal of Thoracic Oncology Jan 2017, 12 (1) 15-26

<sup>2</sup> Sierra et al., Therapeutic Advances in Medical Oncology Nov 2011, 3 (S1) S21-S35

<sup>3</sup> Lee et al., Anticancer Research November 2013, 33 (11) 5179-5186

# Building a Premier Synthetic Lethality Focused Precision Medicine Oncology Biotech in 2021 and Beyond

## Focus on Potential *First-in-Class* Synthetic Lethality Programs to Deliver Patient Breakthroughs

Patient Impact: Large addressable patient populations in major solid tumor types

Potential First-in-Class / Best-in-Class: Optimized small molecule and protein degrader development candidates

Precision Medicine: Compelling patient selection and pharmacodynamic biomarkers

Synthetic Lethality Platform: Deep and rich target pipeline with ongoing target identification and validation

SL Degraders: Pol Theta Protein Degraders demonstrate degradation in cell models; additional SL degrader opportunities

### MTAP-Deletion

#### IDE397 (MAT2A)

Cohort Expansions - H1'22  
GSK Option Package - H1'22  
Clinical Data Update - H1'22

#### MTAP-SL Target

Lead Series ID

### HRD/BRCA

#### PARG

DC Lead Nominated

#### Pol Theta

DC Nomination - Dec'21  
Advance Protein Degraders

### MSI-High

#### Werner Helicase

Lead Optimization

### GNAQ/11

#### SL Combo: PKC + cMET

mPFS Update – H1'21  
Registration Trial - H1'22

### SL Platform

Novel Targets  
Chemistry Optimization

*Target Milestones to Advance Industry Leading Synthetic Lethality Pipeline*