



Opening Remarks

David Schenkein, M.D., Chief Executive Officer



Forward Looking Statements

This presentation and various remarks we make during this presentation contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Agios' plans, strategies and expectations for its and its collaborator's preclinical, clinical and commercial advancement of its drug development programs including IDHIFA®, TIBSOVO® (ivosidenib), AG-881, AG-348, AG-270 and AG-636; the potential benefits of Agios' product candidates; its key milestones for 2018; its plans regarding future data presentations; its financial guidance regarding the period in which it will have capital available to fund its operations; and the potential benefit of its strategic plans and focus. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "prepare," "project," "would," "could," "potential," "possible," "hope," "strategy," "milestone," "will," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from Agios' current expectations and beliefs. For example, there can be no guarantee that any product candidate Agios or its collaborator, Celgene, is developing will successfully commence or complete necessary preclinical and clinical development phases, or that development of any of Agios' product candidates will successfully continue. There can be no guarantee that any positive developments in Agios' business will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this presentation and various remarks we make during this presentation could also be affected by risks and uncertainties relating to a number of other important factors, including: Agios' results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. FDA and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; Agios' ability to obtain and maintain requisite regulatory approvals and to enroll patients in its planned clinical trials; unplanned cash requirements and expenditures; competitive factors; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to maintain key collaborations, such as its agreements with Celgene; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in Agios' public filings with the Securities and Exchange Commission. Any forward-looking statements contained in this this presentation and various remarks we make during this presentation speak only as of the date hereof, and Agios expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

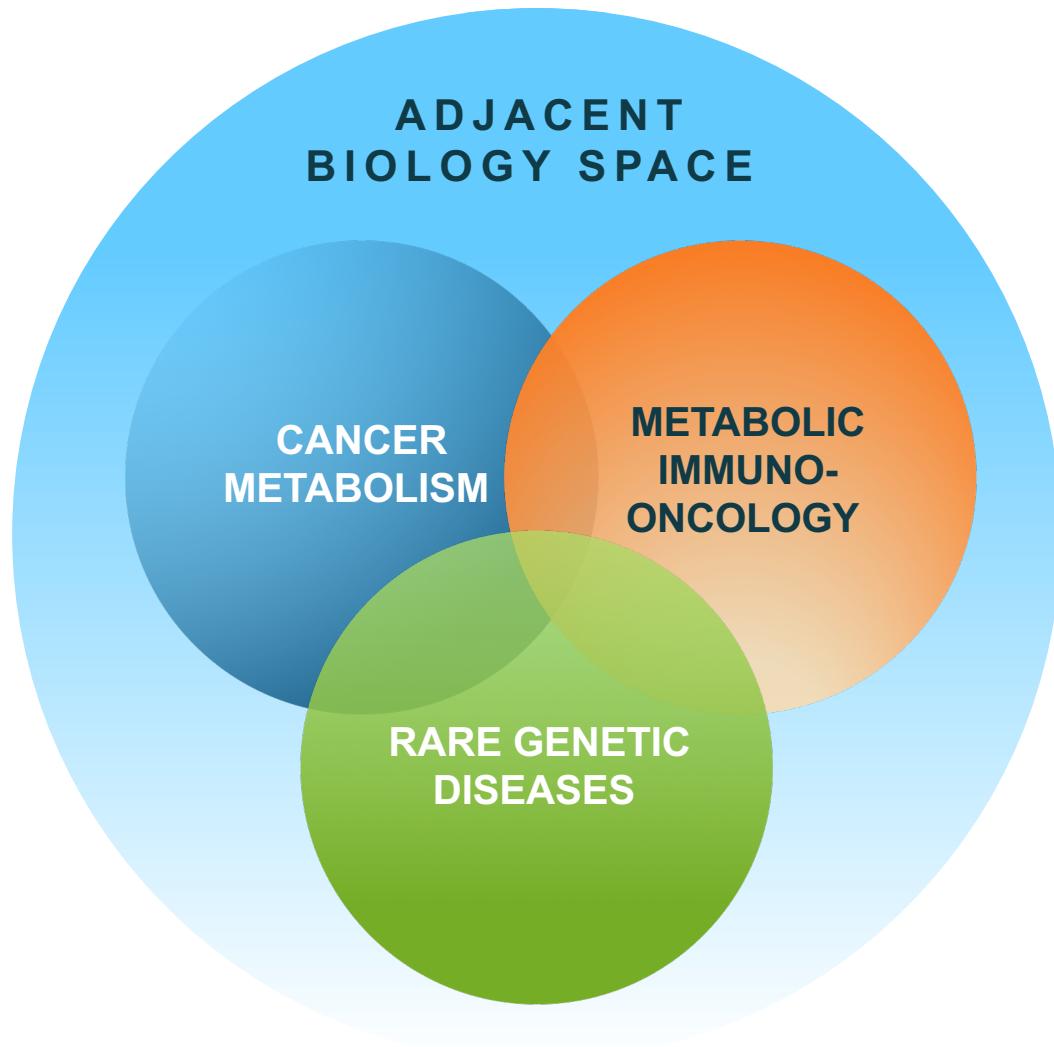


Today's Agenda

Time	Speaker
8:00 - 8:15 a.m.	Opening Remarks – David Schenkein, M.D. , Chief Executive Officer
Research	
8:15 - 9:00 a.m.	Discovery Strategy & Research Portfolio – Scott Biller, Ph.D. , Chief Scientific Officer & Kevin Marks, Ph.D. , Senior Director, Head of Cancer Biology
9:00 - 9:20 a.m.	Q&A Part 1
Clinical Development, Commercial & Finance	
9:20 - 10:00 a.m.	Ivosidenib Clinical & Commercial Strategy in Acute Myeloid Leukemia – Darrin Miles , Vice President, IDH Program Management & Steve Hoerter , Chief Commercial Officer
10:00 - 10:30 a.m.	Opportunity for IDH1 Inhibition in Solid Tumors – Susan Pandya, M.D. , Senior Medical Director, Clinical Development & Maeve Lowery, M.B., B.Ch., B.A.O. , Trinity College Dublin
10:30 - 11:00 a.m.	AG-348 Clinical Development in Pyruvate Kinase Deficiency & Rare Hemolytic Anemias – Chris Bowden, M.D. , Chief Medical Officer
11:00 - 11:15 a.m.	Financial Overview & Q1 Results – Andrew Hirsch , Chief Financial Officer & Head of Corporate Development
11:15 - 12:00 p.m.	Q&A Part 2 & Buffet Lunch



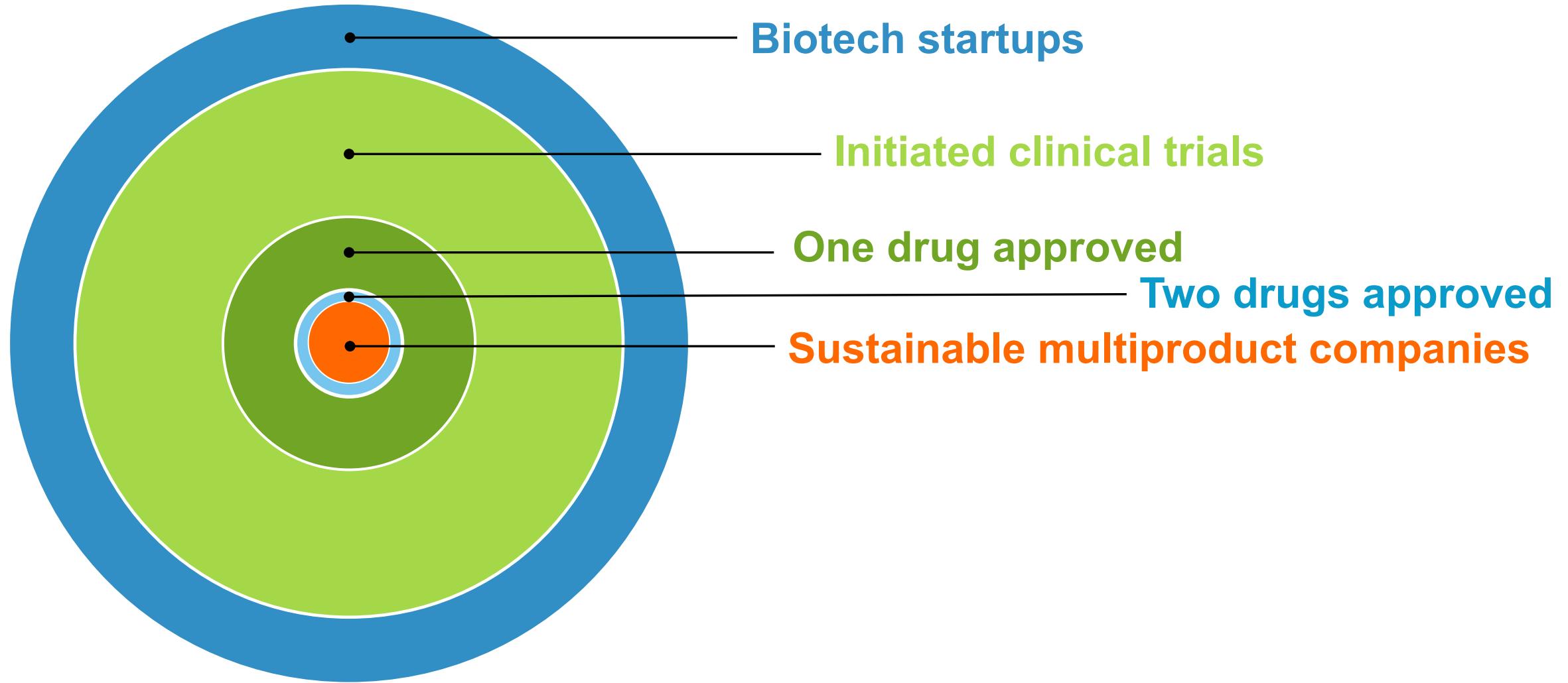
Driven By a Clear Vision and Values



AgiOS is passionately committed to applying our scientific leadership in the field of cellular metabolism to transform the lives of patients with cancer and rare genetic diseases.



Building One of the Next Great Pharmaceutical Companies



Agios' Scientific Platform Demonstrates Remarkable, Reproducible Productivity

DISCOVERY

\$50-60M

INVESTED IN DRUG DISCOVERY ANNUALLY



SCIENCE

40+

PEER-REVIEWED PUBLICATIONS



CULTURE

400+ EMPLOYEES

1 VISION



10+

CLINICAL TRIALS IN

6 DISEASES

1,000+



PATIENTS TREATED IN CLINICAL TRIALS

6



INDs

1ST MEDICINE APPROVED



2ND NDA ACCEPTED



3 ADDITIONAL COMPOUNDS IN CLINICAL DEVELOPMENT



IN 4 YEARS SINCE FIRST PATIENT DOSED



Current Clinical Portfolio Has Potential to Benefit Large Number of Patients

**ACUTE MYELOID
LEUKEMIA**

**~10,000 IDHm Patients
AML Opportunity ~\$2B**

**CHOLANGIO-
CARCINOMA**

**~3,000 IDH1m
Patients**

**PYRUVATE KINASE
DEFICIENCY**

**~3,000 to ~8,000
Patients**

LOW GRADE GLIOMA

**~9,000 IDH1m
Patients**

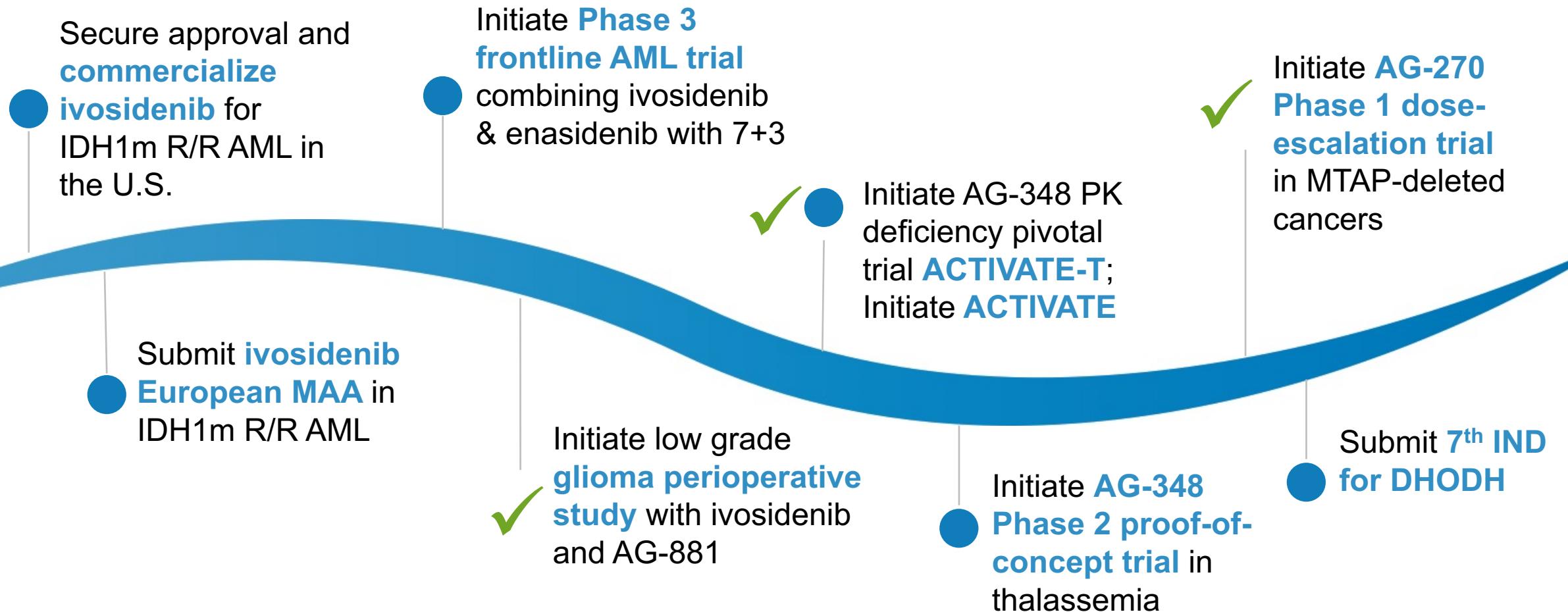
**MTAP-DELETED
TUMORS**

**>100,000 MTAP
Deletion Patients**

**Oncology patient numbers represent annual U.S. and EU incidence;
PK deficiency represent U.S. and EU prevalence**



2018 Key Milestones



2018 Goals Set Stage for Building Long-Term Value

2018 GOALS

Secure approval and commercialize ivosidenib for R/R AML in the U.S.

Initiate Phase 3 frontline AML trial combining ivosidenib & enasidenib with 7+3

✓ Initiate AG-348 PK deficiency pivotal trial (ACTIVATE-T)

✓ Initiate AG-270 Phase 1 dose-escalation trial

Submit ivosidenib European MAA

✓ Initiate glioma perioperative study

Initiate AG-348 Phase 2 trial in thalassemia

Submit 7th IND for DHODH

**Vision for
2018 &
Beyond**

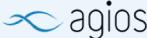
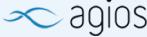
At least 3 approved medicines

Multibillion dollar commercial opportunity across clinical portfolio

Research engine primed to potentially deliver multiple INDs over next 24 months



Our Pipeline

CLINICAL PROGRAMS	INDICATION	DRUG DISCOVERY	EARLY STAGE CLINICAL DEVELOPMENT	LATE STAGE CLINICAL DEVELOPMENT	APPROVED	PRIMARY COMMERCIAL RIGHTS
IDHIFA® <i>Enasidenib</i> (IDH2m Inhibitor)	R/R AML				●	  Agios U.S. Co-promotion and Royalty
	Frontline AML		●			
Ivosidenib (IDH1m Inhibitor)	R/R AML			●	NDA accepted	
	Frontline AML			●		
	Cholangio			●		
	Glioma		●			
AG-881 (pan-IDHm Inhibitor)	Glioma		●			 
AG-348 (PK (R) Activator)	PK Deficiency			●		
AG-270 (MAT2A Inhibitor)	MTAP-deleted Tumors		●			 
RESEARCH PROGRAMS						
AG-636 (DHODH)			●			
CM Research Programs		●				
RGD Research Programs		●				
Metabolic IO Research Programs		●				 

What You Will Hear and See Today

- Research engine poised to deliver next wave of development candidates
 - Several new programs highlighted
 - 9 programs currently in drug discovery
- Robust clinical development plans in place across our early and late-stage programs
- Ready to launch our 2nd commercial product
- Well capitalized to execute on our business plan
- Culture focused on science and patient impact



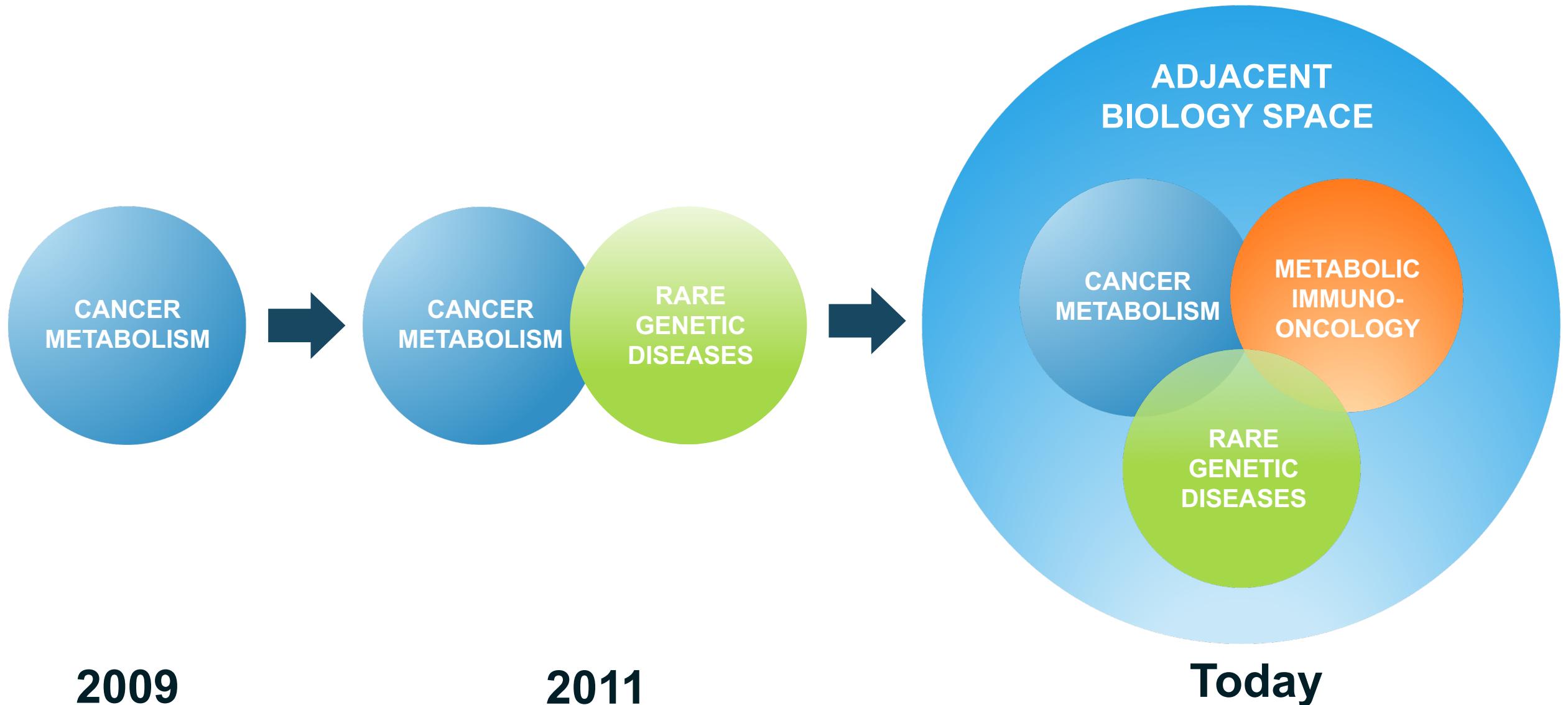


Discovery Strategy & Research Portfolio

Scott Biller, Ph.D., Chief Scientific Officer

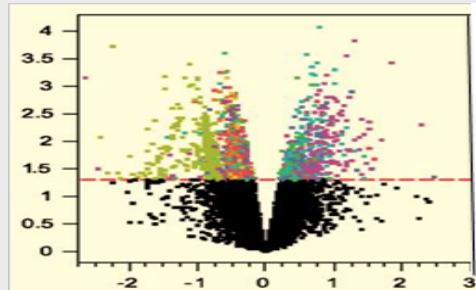


Evolving the Agios Research Portfolio Into Adjacent Biologic Areas



Evolving our Technology Platform from our Historic Strength in Metabolism to a Cutting-Edge, Systems Biology Approach

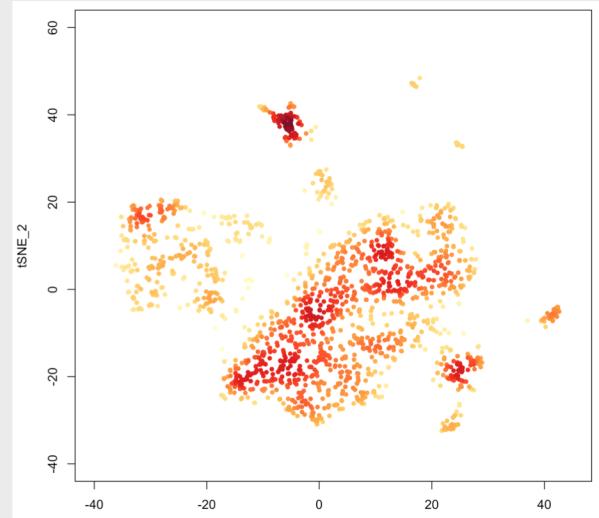
Metabolomics + Informatics + Modeling



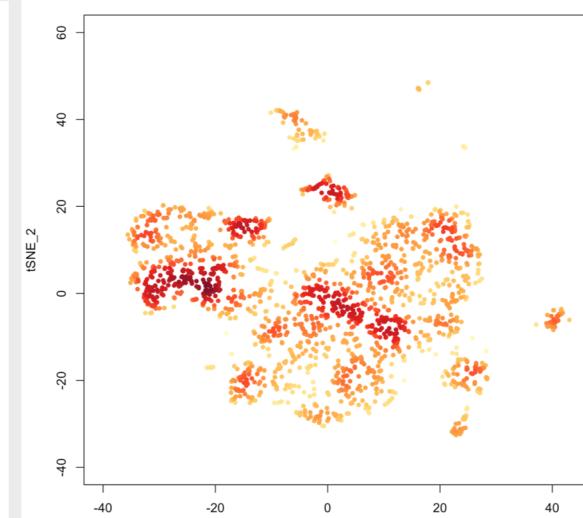
Multi-Omics + Imaging + Data Integration → New Knowledge

Single Cell RNA Sequencing

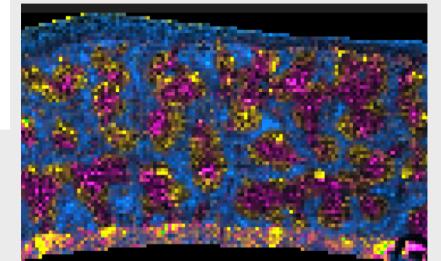
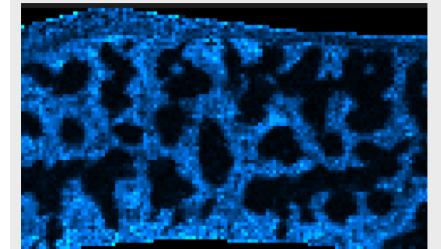
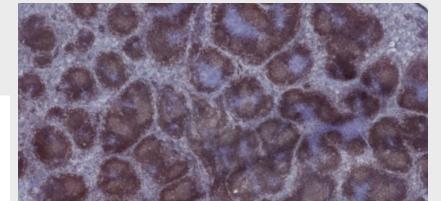
Day 5 Drug



Day 5 Vehicle



Tissue Imaging



Deep understanding of biology with a translational focus



High Probability of Success for Agios Drug Discovery

Program Criteria

**Proof of
therapeutic
strategy
in vivo**

*Animal model target
validation*

**Patient
selection
strategy**

*Genetic and
metabolic
biomarkers*

**Robust
chemical
starting
points**

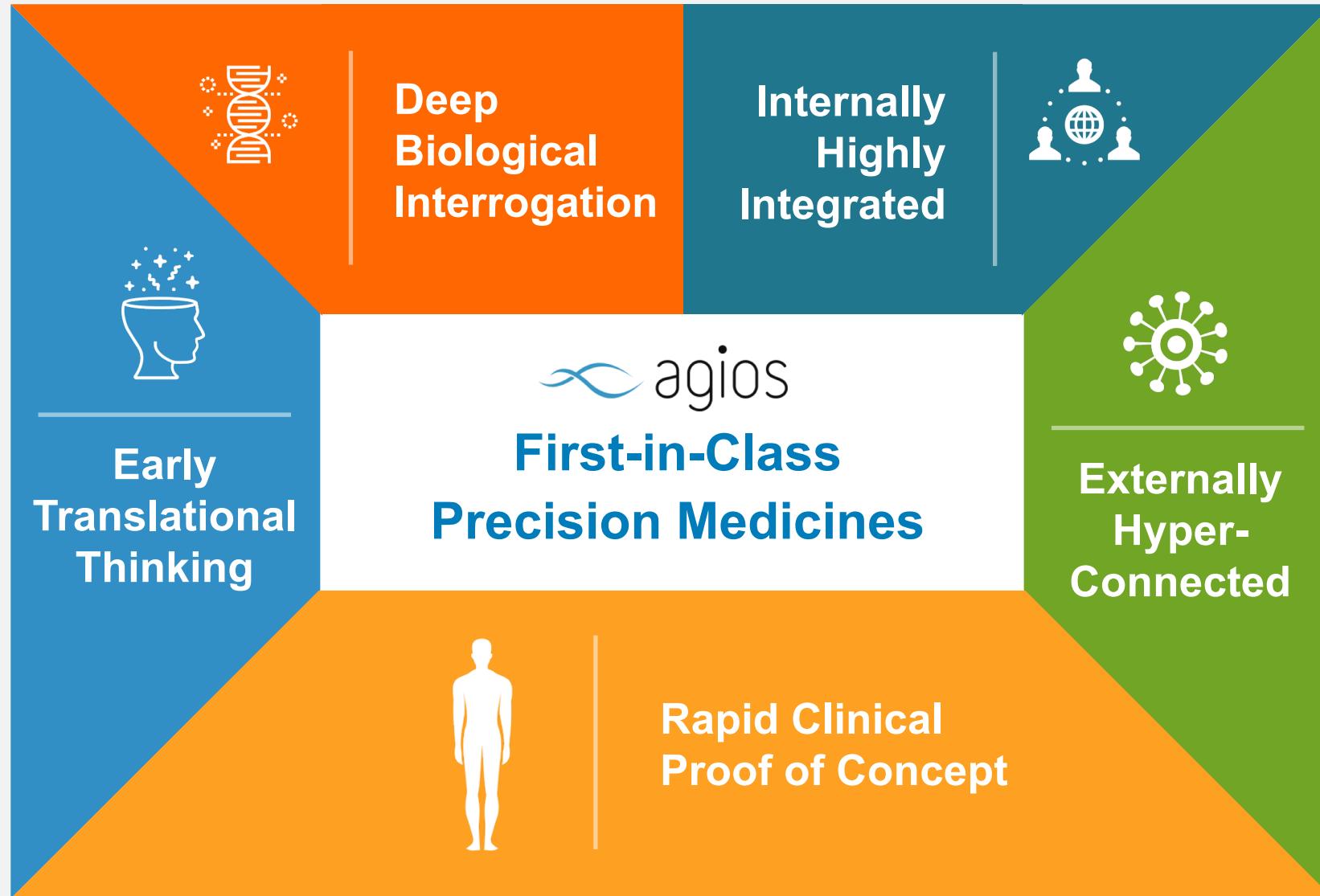
*High confidence
in druggability*



Precision Medicine



What Differentiates Agios Research Strategy?



Agios Preclinical Pipeline

Program	Target Discovery	Target Validation	Drug Discovery	Drug Candidate
Oncology				
Heme Lineage: AG-636 DHODH				●
MAT2A Follow-Ons			●	
PTEN-mutant Solid Tumors			●	
Genetically Defined Heme Target			●	
Genetically Defined Heme Target		●		
Other Exploratory Programs	●	●		
Rare Genetic Diseases				
Pyruvate Kinase Activator Follow-Ons			●	
Phenylketonuria (PKU)			●	
Erythroid Porphyrria			●	
Friedreich's Ataxia			●	
Other Exploratory Programs	●	●		
Metabolic Immuno-Oncology (Celgene Collaboration)				
T-cell and Tumor Target			●	
Macrophage Target			●	
Macrophage Target		●		
Tumor Target		●		
Other Targets (T-cell, Macrophage, Tumor)	●	●		

● Metabolic Target
 ● Non-Metabolic Target
 Metabolic and Non-Metabolic Targets
 Celgene Collaboration



Dysregulated Metabolism and Adjacent Areas of Biology

Cancer Metabolism

- Inhibit key enzymes in cancer cell specific metabolic pathways to disrupt tumor cell proliferation & survival

Rare Genetic Diseases

- Restore defective metabolic pathways in disease cells that cause rare genetic diseases of metabolism

Metabolic Immuno-oncology

- Alter immune or cancer cell metabolism to enhance the body's anti-tumor response



Translational Systems Biology Platform



Dysregulated Metabolism and Adjacent Areas of Biology

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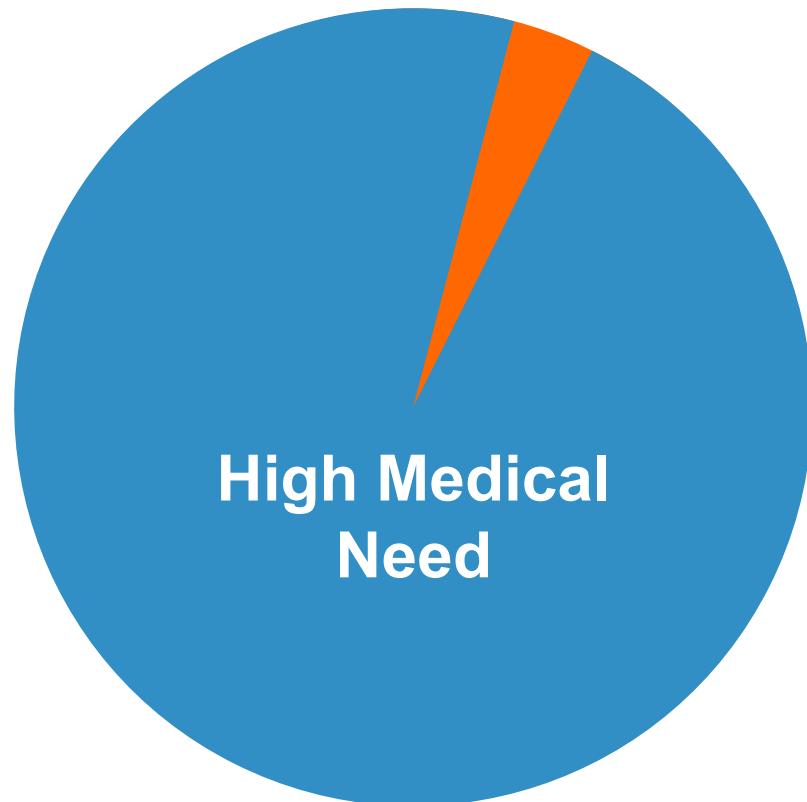


Translational Systems Biology Platform

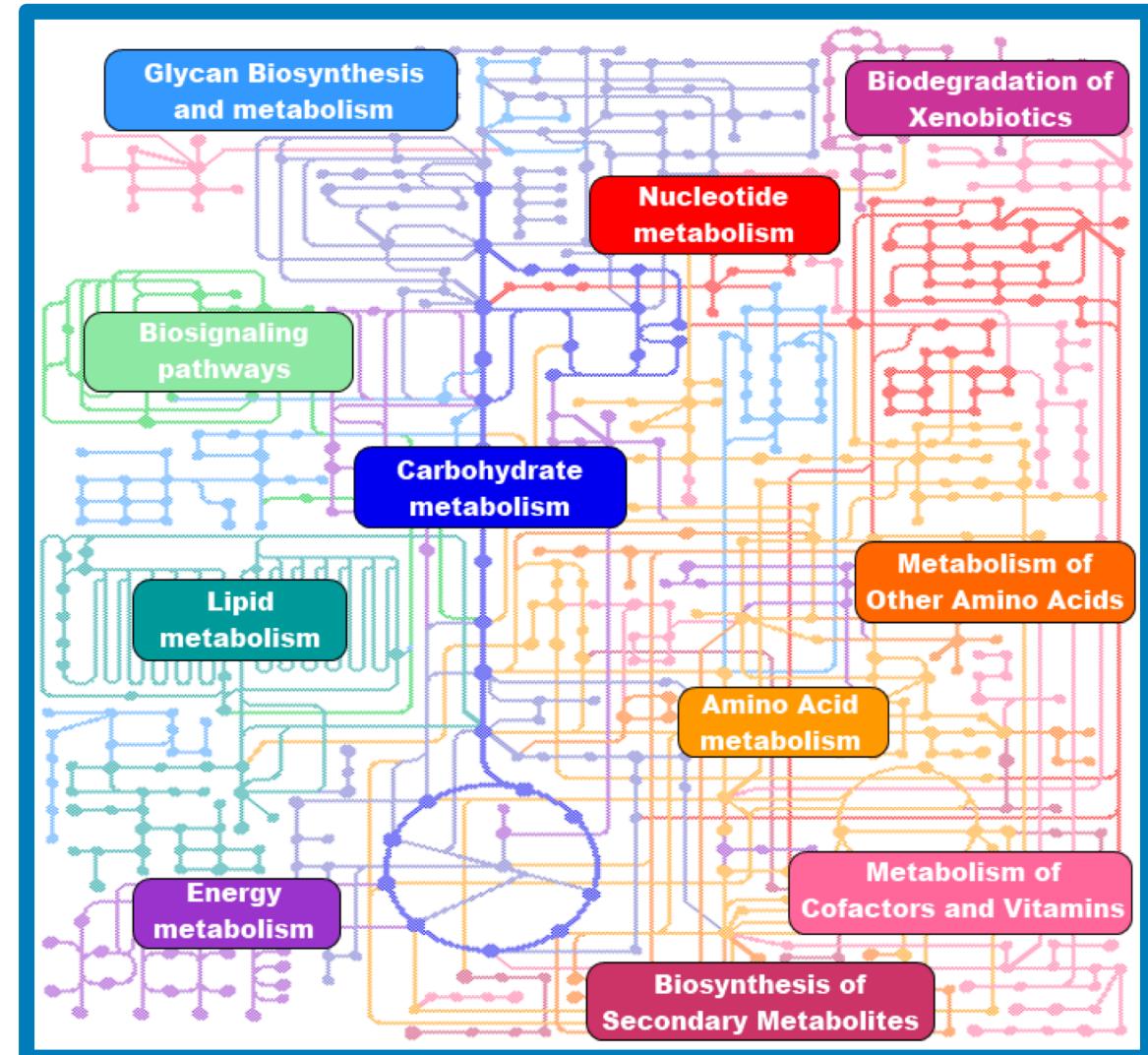


Expanding the Playing Field in Rare Genetic Diseases (RGD)

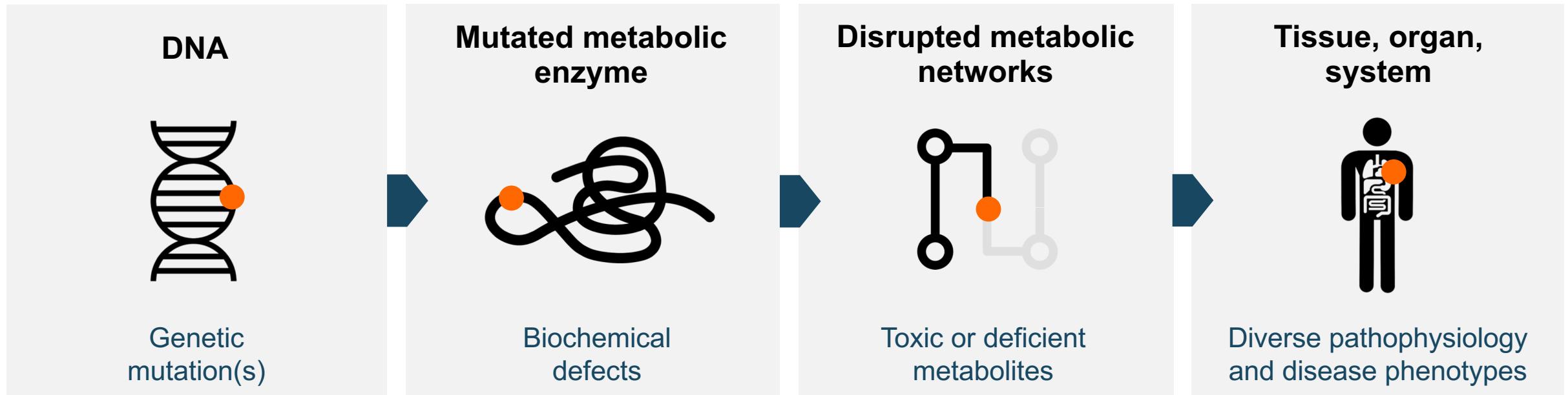
~5% of Rare Diseases have approved drugs



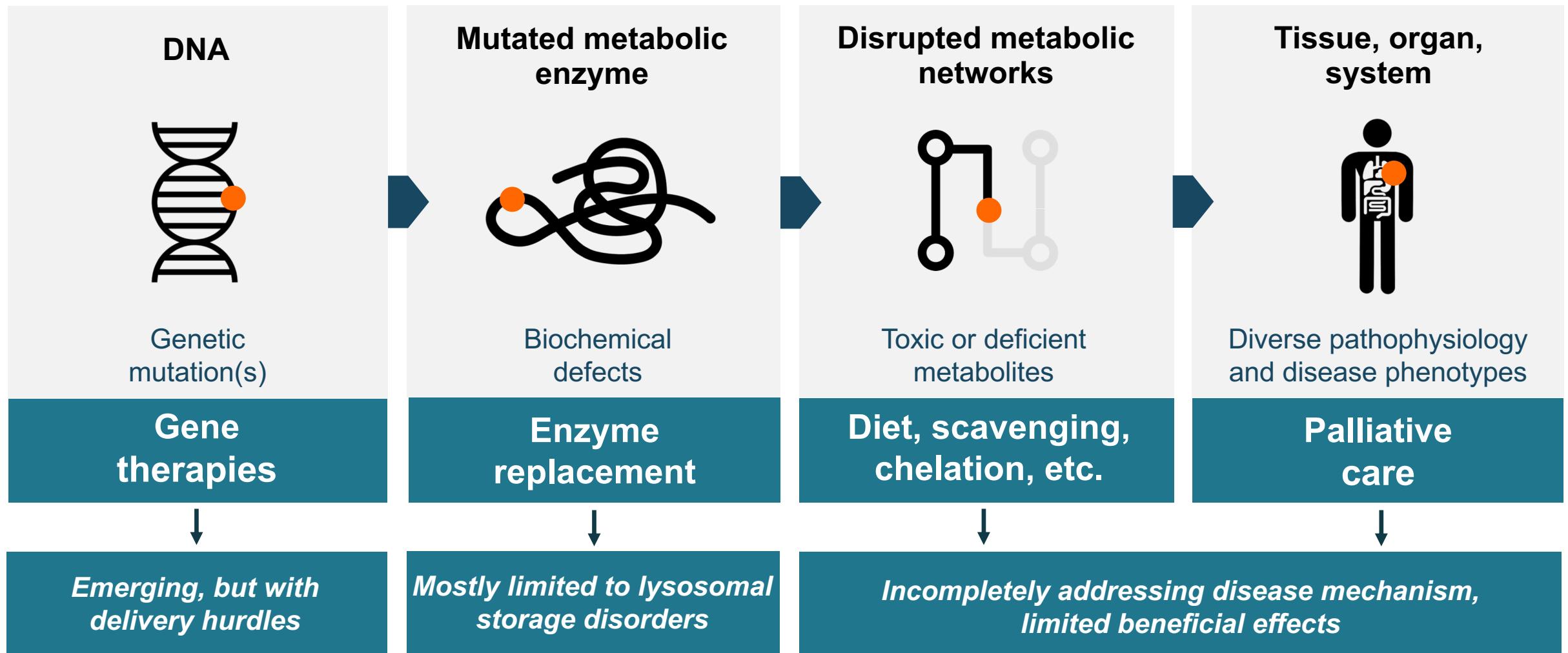
~500 Rare Diseases of Metabolism



Rare Genetic Disease Pathogenesis

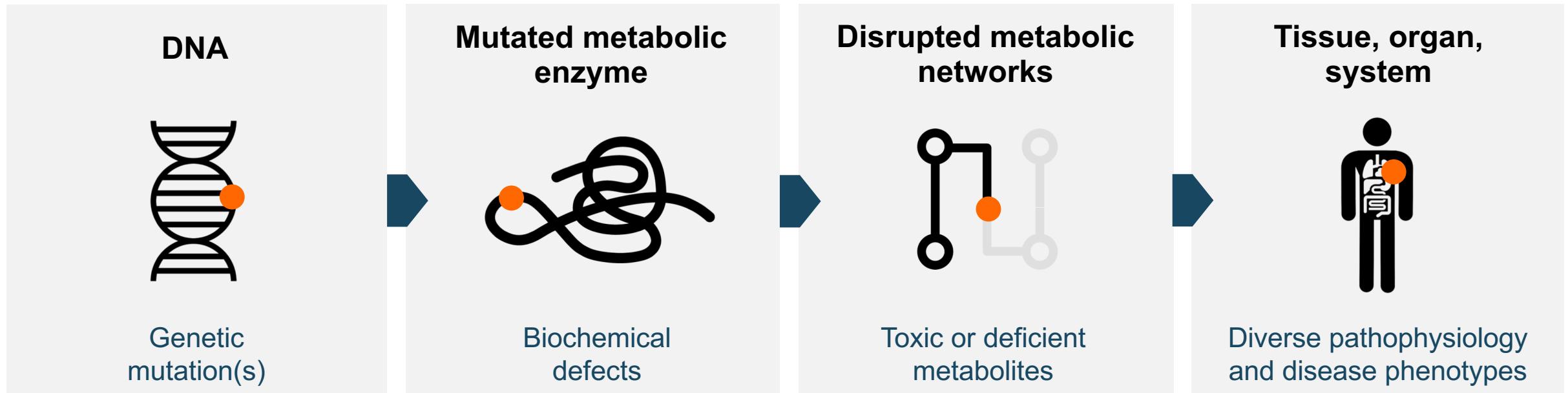


The Current Therapeutic Landscape



Creating a New Wave of Transformational Therapies

Understanding and correcting the root cause of the disease



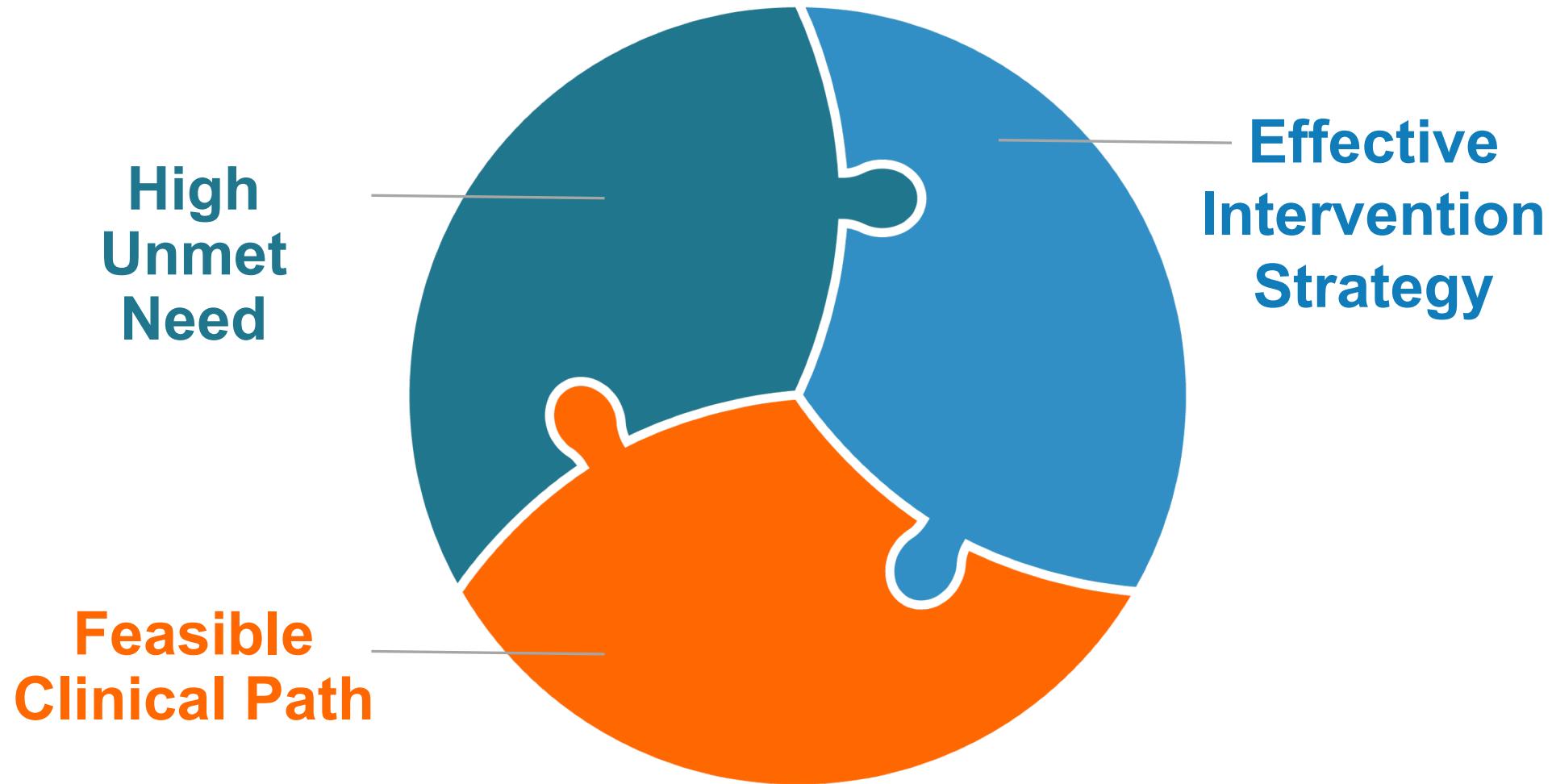
Agios Approach

*Disease-modifying small molecules
targeting intracellular pathways
leading to transformative outcomes
for patients*

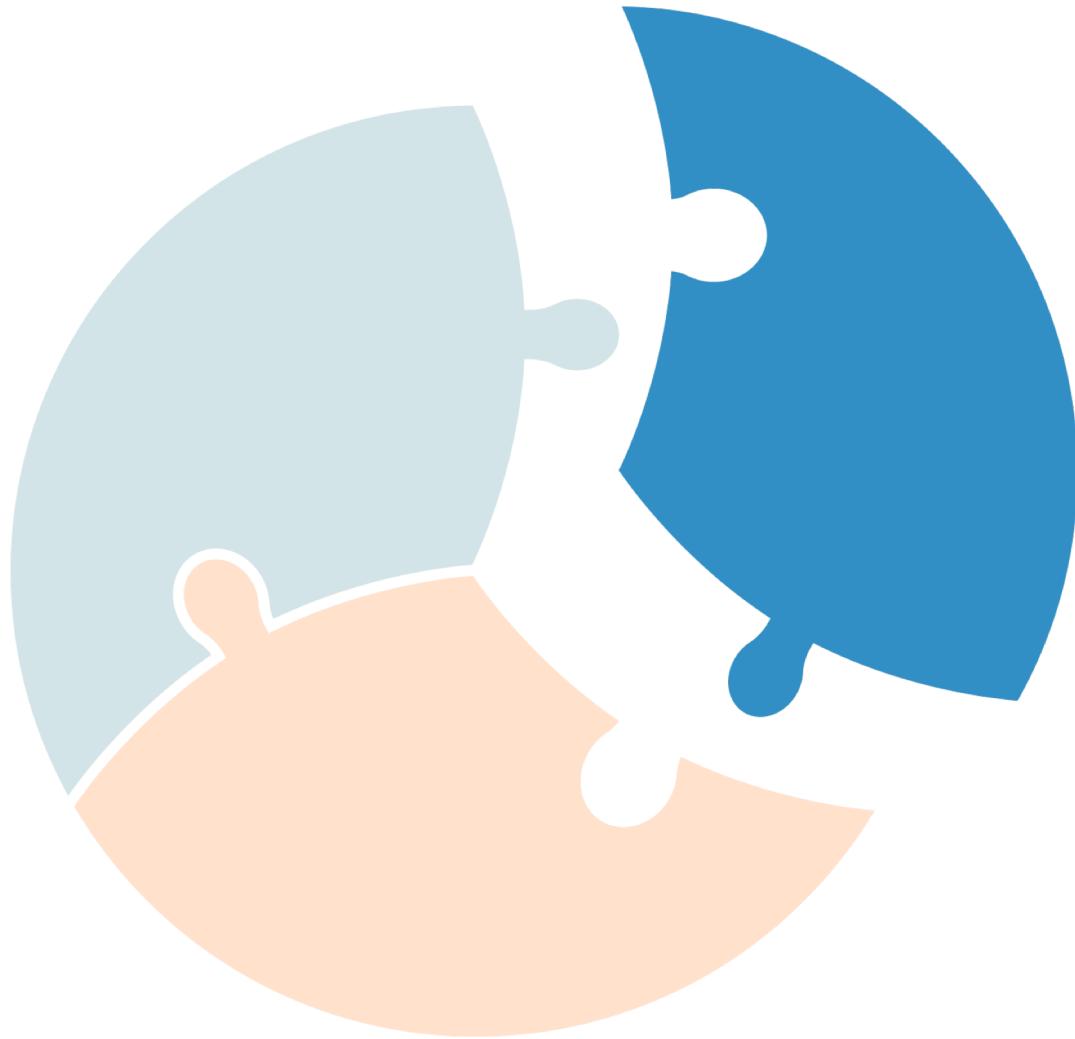


Agios RGD Disease Selection Attributes

Disease Selection Criteria and Differentiated Therapeutic Strategies



Defining Novel Therapeutic Strategies: *Agios' Competitive Advantage*

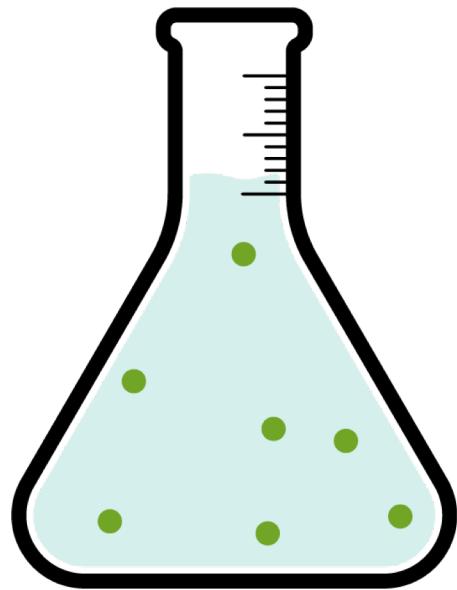


Effective Intervention Strategy

- Develop deep insight into mechanism of disease pathophysiology
- Validate therapeutic strategies in disease models
 - Patient derived cell models and genetically engineered animal models
- Design small molecule drugs using a combination of all-available technologies
- Discover pharmacodynamic and mechanistic biomarkers for rapid proof-of-concept in humans

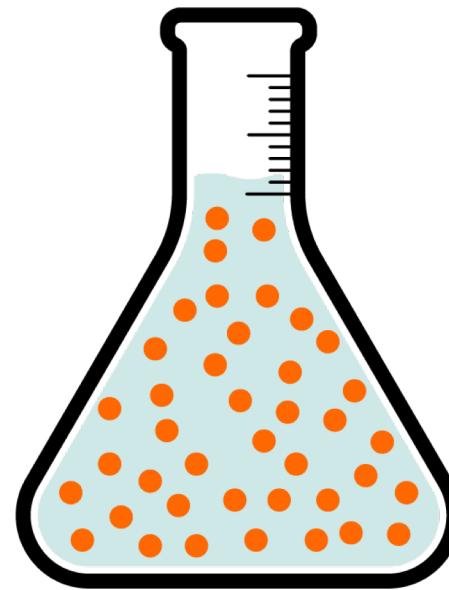


Small Molecule Strategies to Correct Disease Pathology



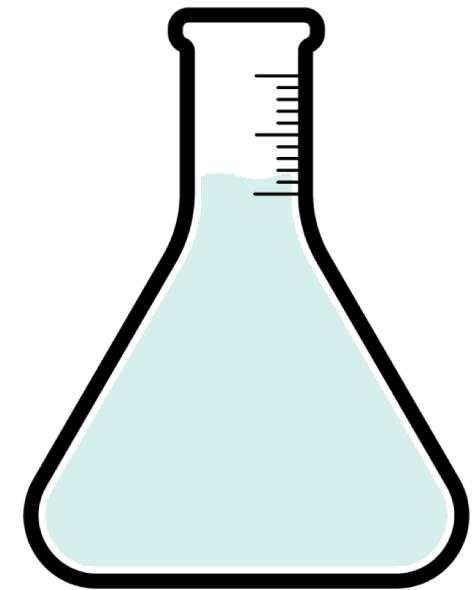
Metabolite A

Enzyme 1



Metabolite B

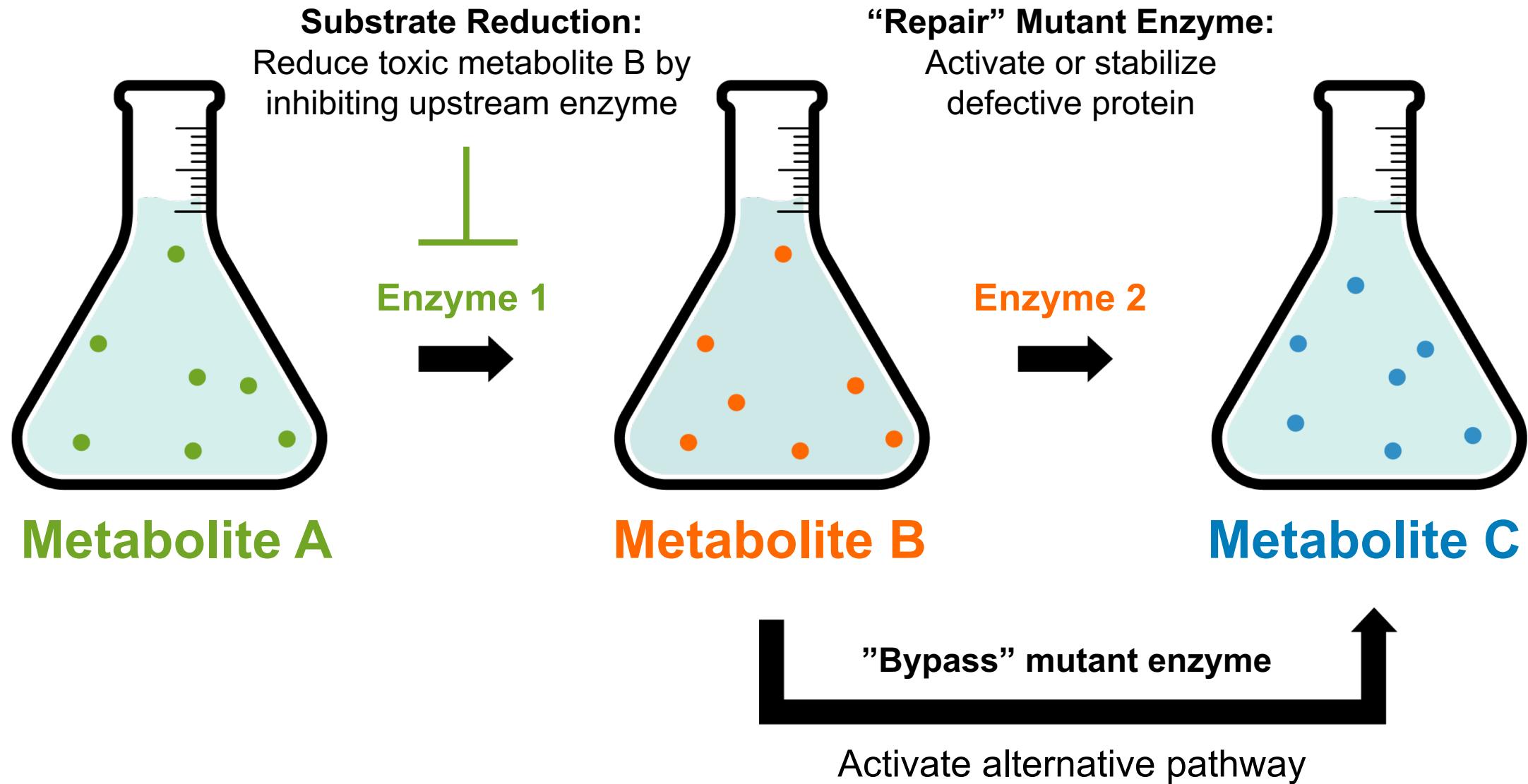
Enzyme 2



Metabolite C



Small Molecule Strategies to Correct Disease Pathology



Phenylketonuria (PKU): Mutations in Phenylalanine Hydroxylase (PAH)

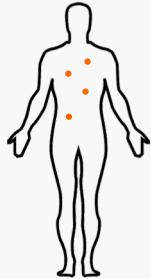


- ~16,000 PKU patients in U.S.
- ~60% of patients have severe disease
- Severity of disease correlates with extent of phenylalanine **elevation**
- Phenylalanine **elevation** causes neurocognitive defects, demyelination and intellectual disability
- High unmet medical need remains:
 - Highly restricted diet is key part of SOC
 - No effective approved treatment for severe patients



Phenylketonuria (PKU): Mutations in Phenylalanine Hydroxylase (PAH)

1.



Normal Protein Diet

A mixed diet provides your body **Phe**



Phe

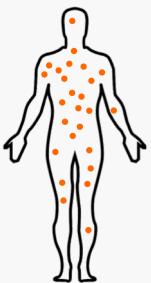
2.

Defective PAH enzyme

PAH fails to process the Phe to Tyr

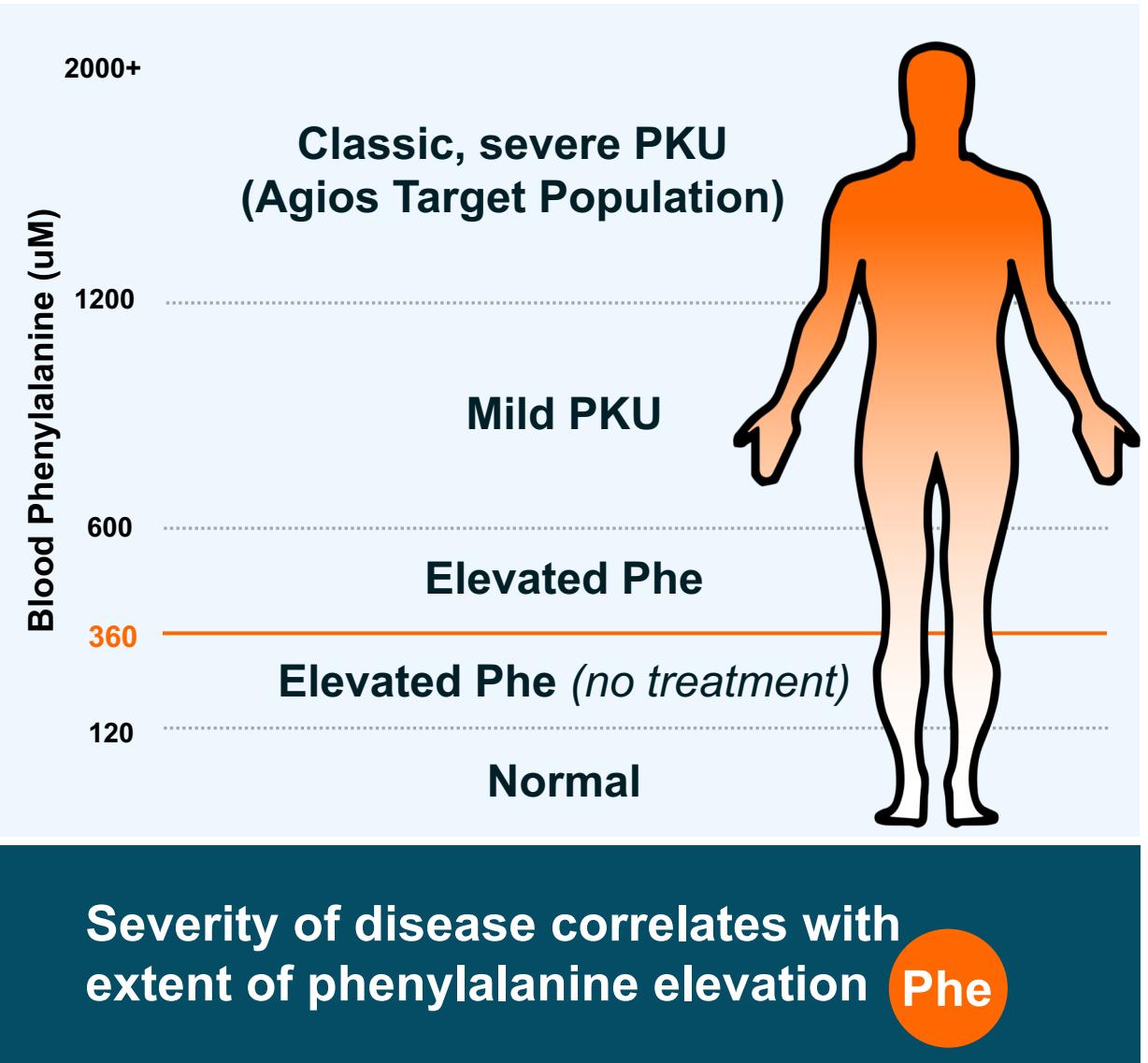


3.

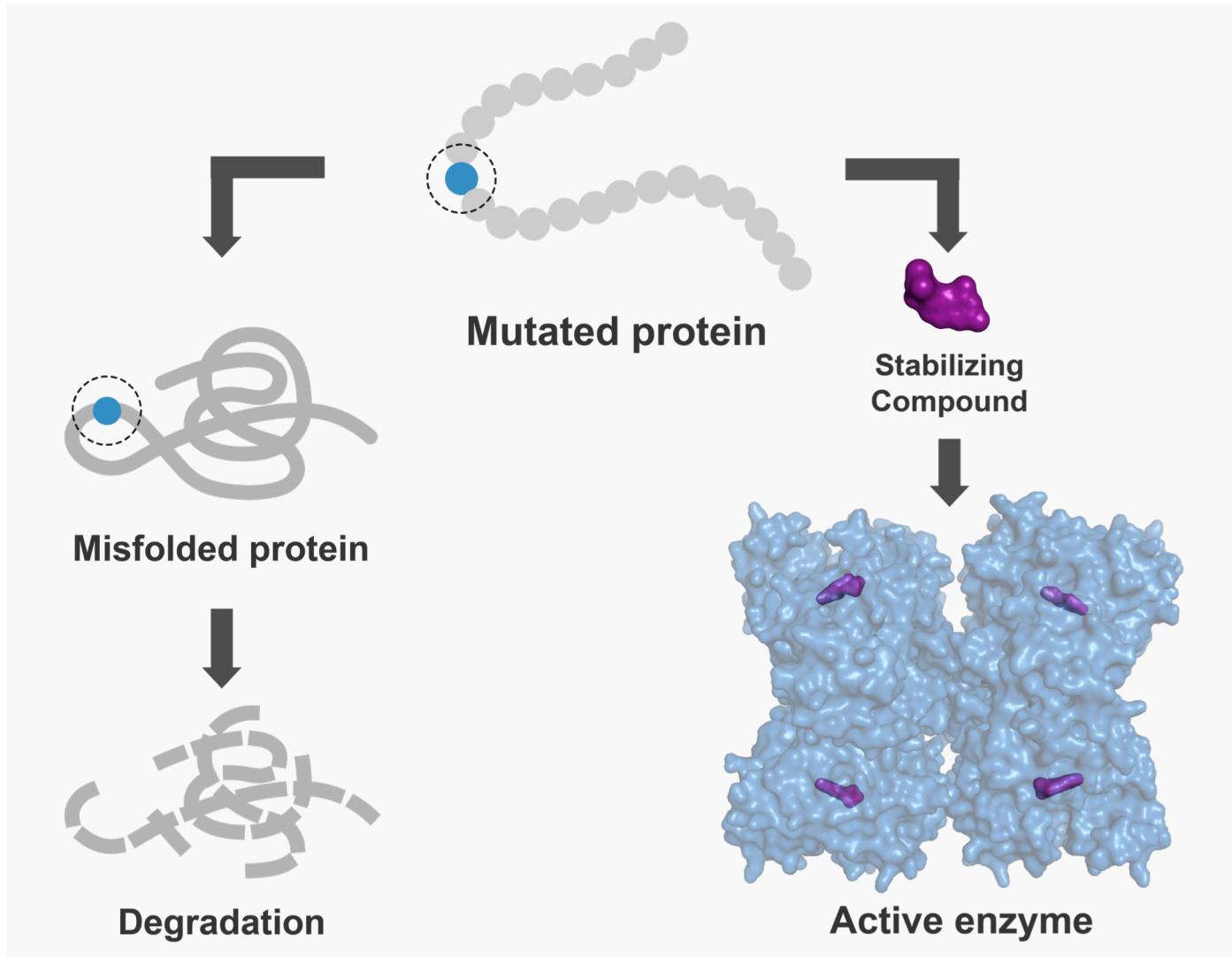


Increase in Phenylalanine

This leads to high **Phe** levels in the blood which results in neurocognitive defects



Therapeutic Strategy: Stabilize Mutant PAH to Rescue Enzyme Activity



> 900 different mutations found in PAH

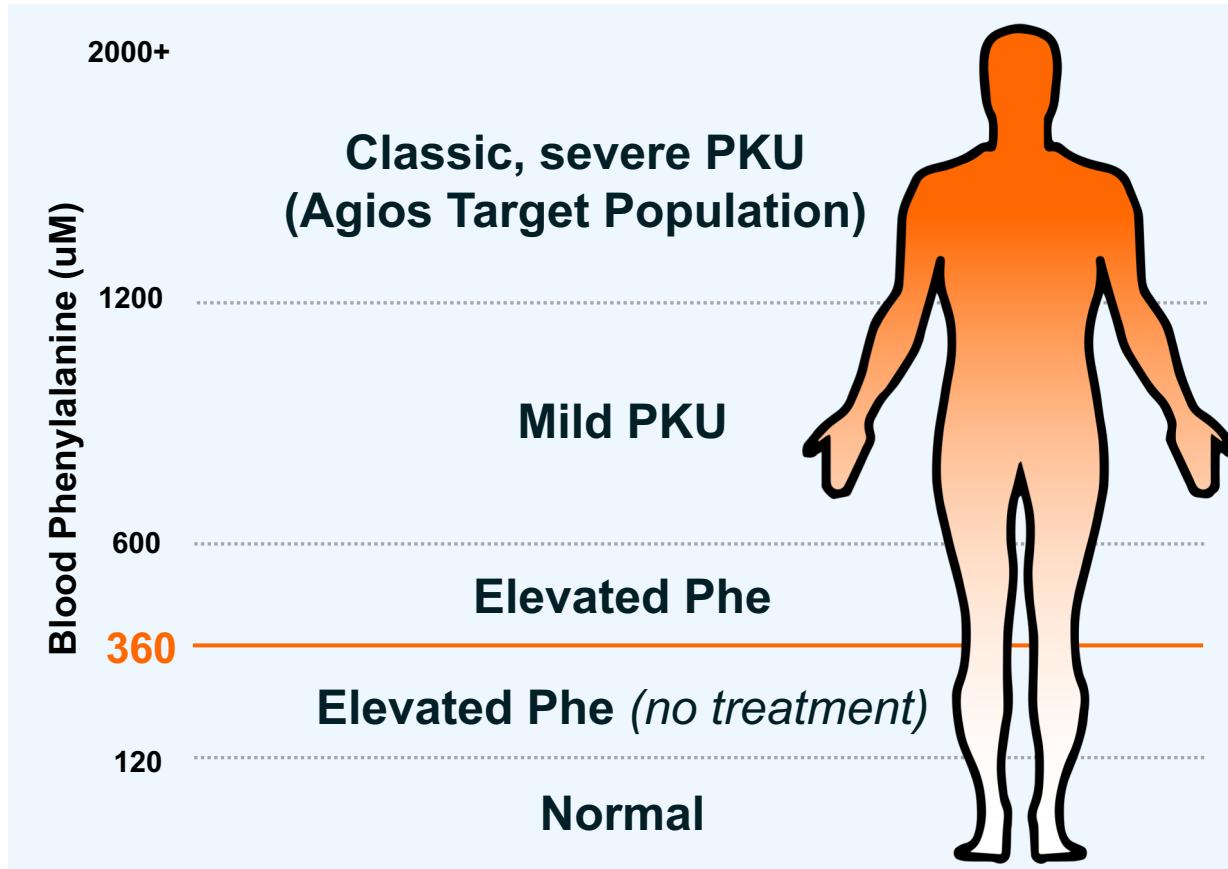
Majority result in misfolded protein leading to degradation

Agios approach is to stabilize mutant PAH

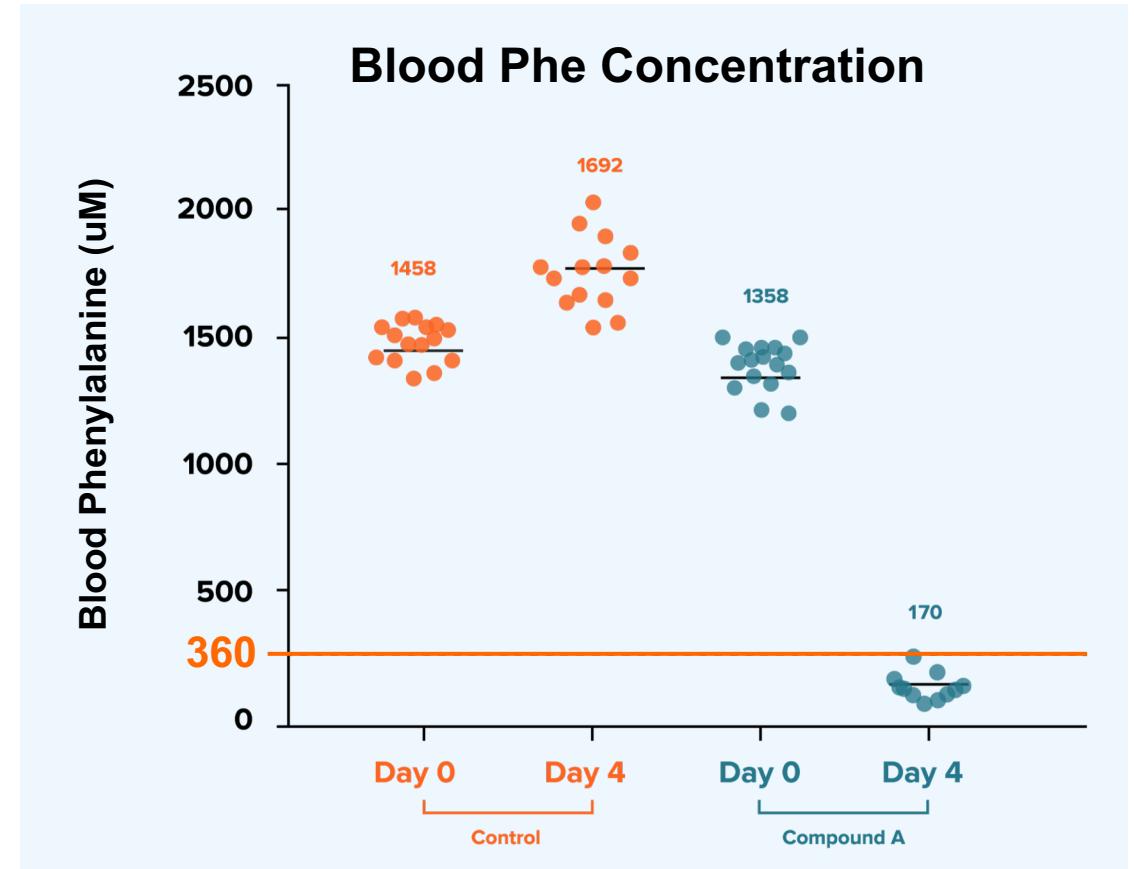
Stabilization leads to increase in active protein levels, leading to lower Phe levels



Agios Lead Molecule Dramatically Decreases Blood Phenylalanine Levels in Severe PKU Mouse Model



Severity of disease correlates with extent of phenylalanine elevation **Phe**

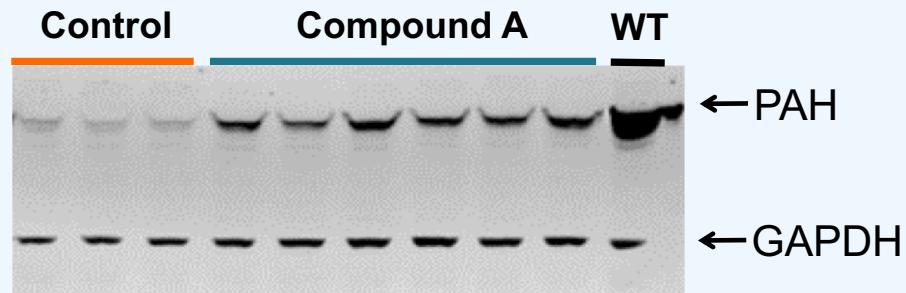


Blood Phe concentrations of treated mice **normalized**



Agios Lead Molecule Increases PAH Protein Levels in the Liver of Severe PKU Mouse

Stabilization of mutant PAH protein in knock-in mouse model of severe PKU

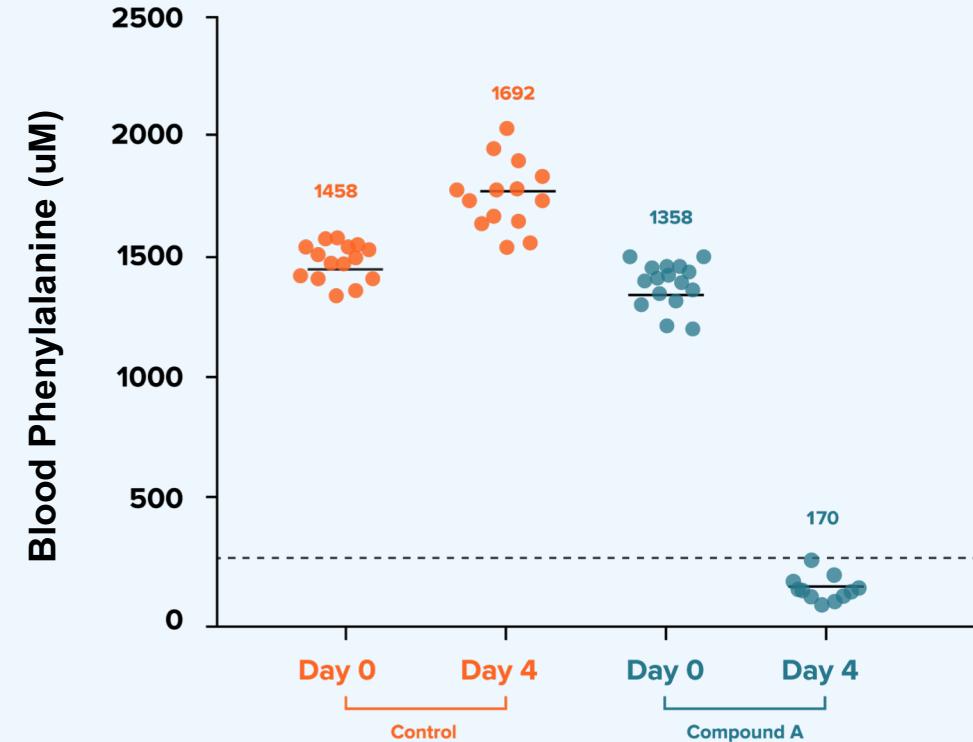


Western blot, 6 hours after final dose



PAH protein levels in livers of treated mice **increased**

Blood Phe concentration



Blood Phe concentrations of treated mice **normalized**



Emerging Portfolio of First-in-Class RGD Programs

Program	Target Discovery	Target Validation	Drug Discovery	Development Candidate
Pyruvate Kinase Activator Follow-Ons			●	
Phenylketonuria			●	
Erythroid Porphyrria			●	
Friedreich's Ataxia			●	
Exploratory (Multiple Diseases)	●	●		

● Metabolic Target
 ● Non-Metabolic Target
 ● Metabolic and Non-Metabolic Targets



Dysregulated Metabolism and Adjacent Areas of Biology

Cancer Metabolism

- Inhibit key enzymes in cancer cell specific metabolic pathways to disrupt tumor cell proliferation & survival

Rare Genetic Diseases

- Restore defective metabolic pathways in disease cells that cause rare genetic diseases of metabolism

Metabolic Immuno-oncology

- Alter immune or cancer cell metabolism to enhance the body's anti-tumor response

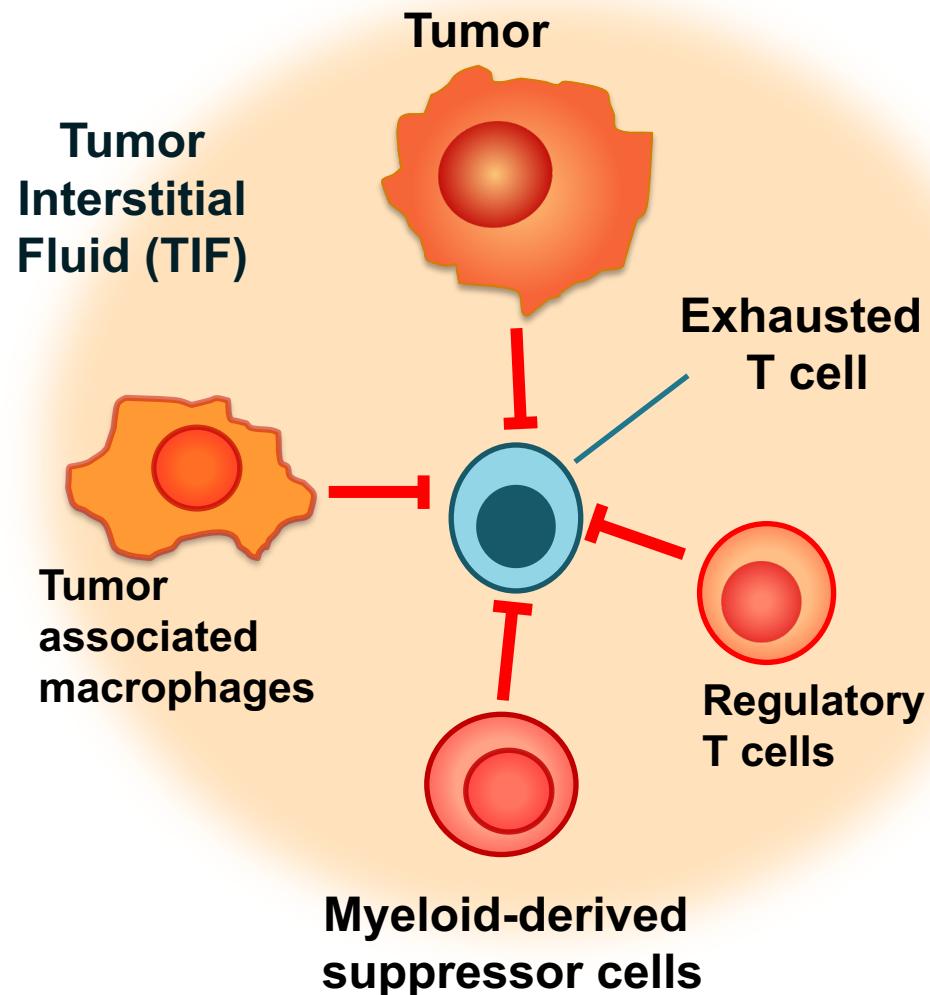


Translational Systems Biology Platform



Metabolic Immuno-Oncology (IO)

Immunosuppressive Tumor Microenvironment

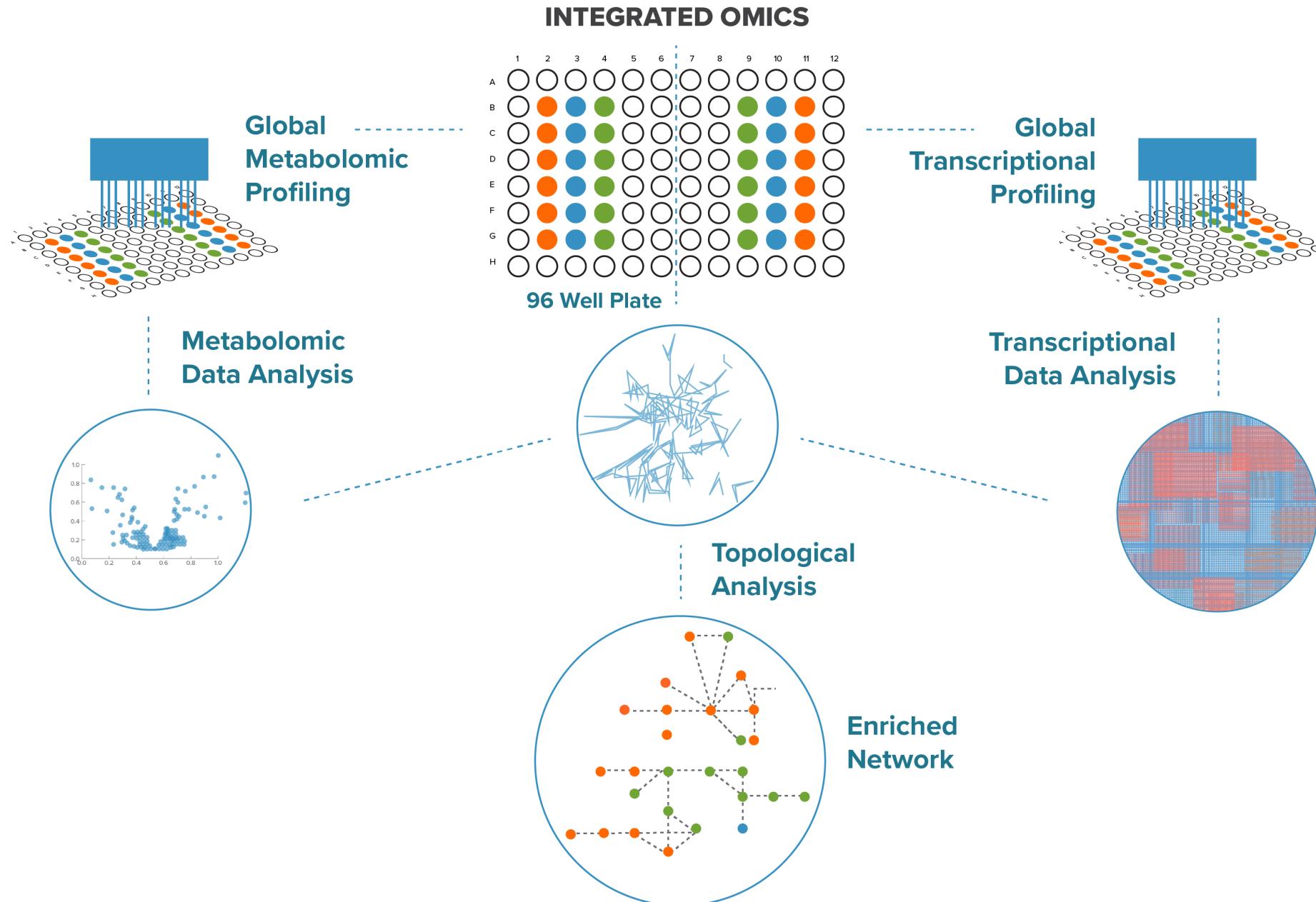


Agios Metabolic IO Strategy

- Discover targets with potential for single agent activity
- Increase response rates by utilizing patient selection strategies
- Identify mechanism based combination therapies

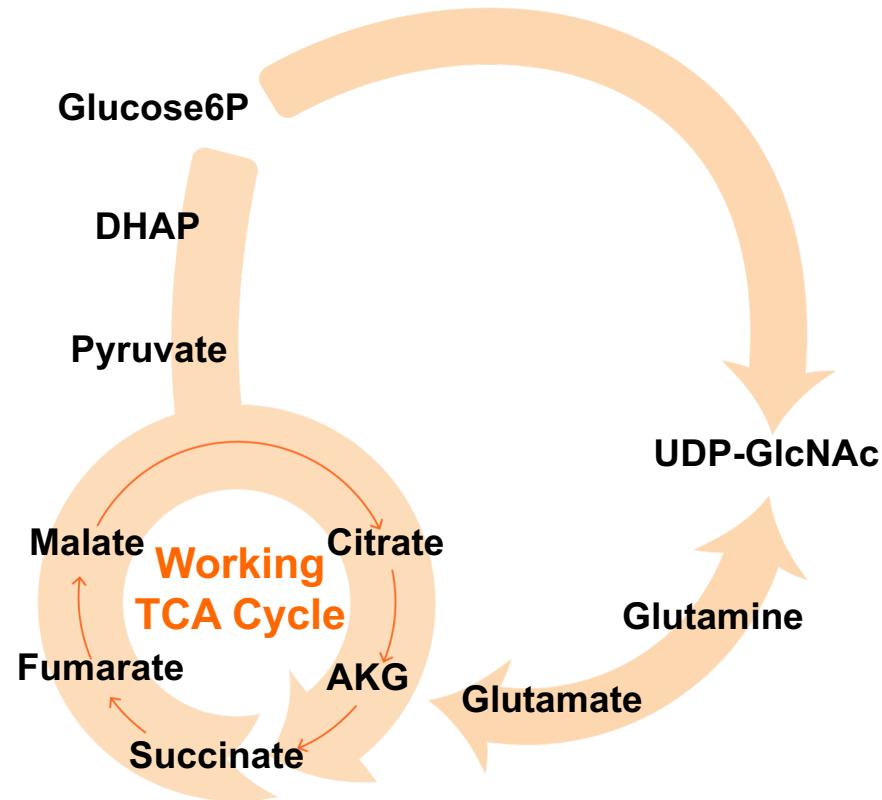


Integrated Metabolomics and Gene Expression Profiling

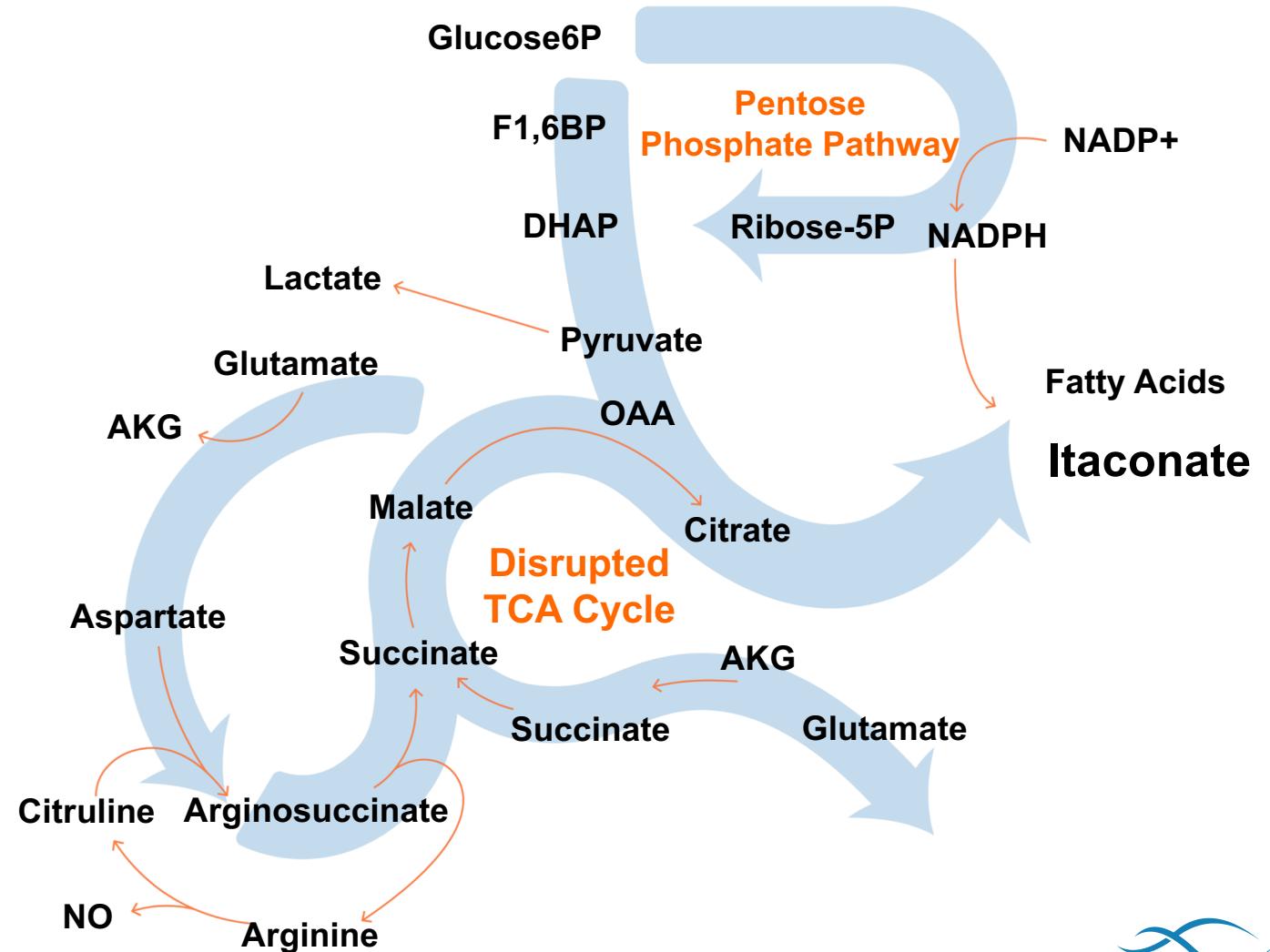


Inflammatory and Immunosuppressive Macrophages Have Dramatically Different Metabolic Programs

Immunosuppressive Macrophage



Inflammatory Macrophage

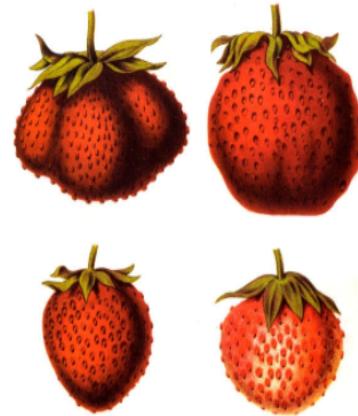


Building a Comprehensive Translational Platform to Deeply Interrogate the Tumor Microenvironment

Whole Tissue Analysis



Single Cell Analysis



Whole Tissue Imaging

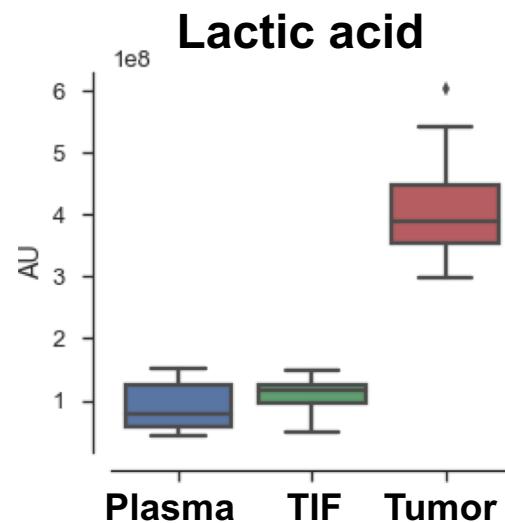
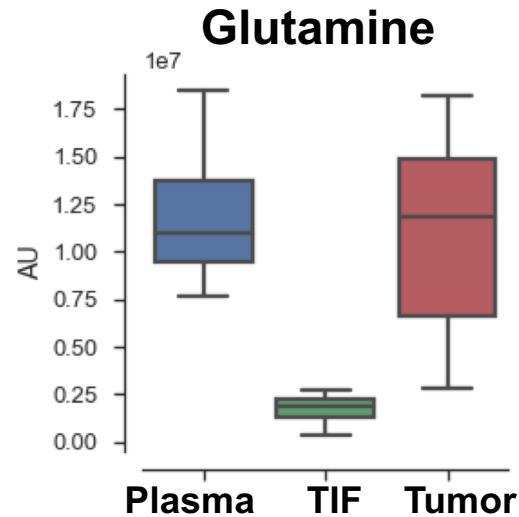


Understanding the tumor microenvironment in mouse models and human tumors to:

- Uncover novel therapeutic mechanisms
- Discover new strategies for patient stratification

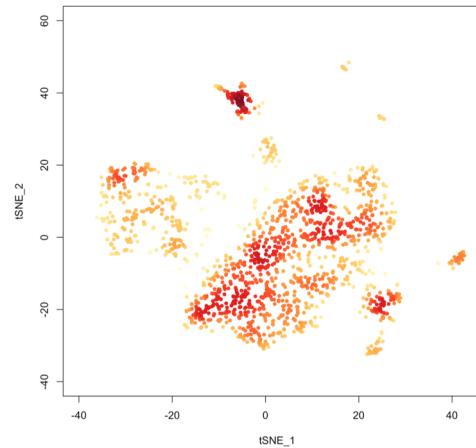
Building a Comprehensive Translational Platform to Deeply Interrogate the Tumor Microenvironment

Tumor Interstitial Fluid

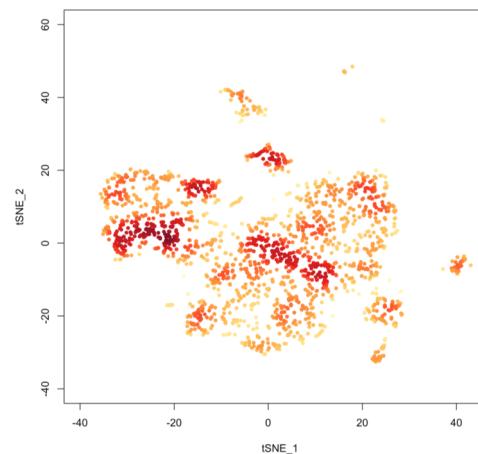


Single Cell Analysis

Treated

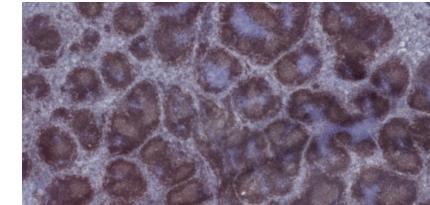


Vehicle

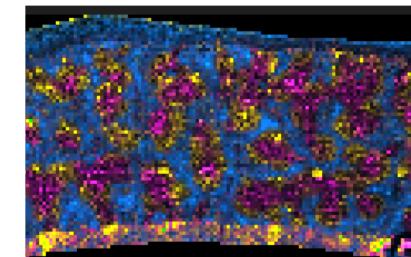


Whole Tissue Imaging

Tissue Architecture



MALDI Mass Spectroscopic Imaging



Pink = T-Cell metabolite
Yellow = B-Cell metabolite
Blue = Macrophage metabolite



Building a Network of Collaborators on Novel Targets and Technologies

Ongoing collaborations with 16 leading investigators in immunology and metabolism



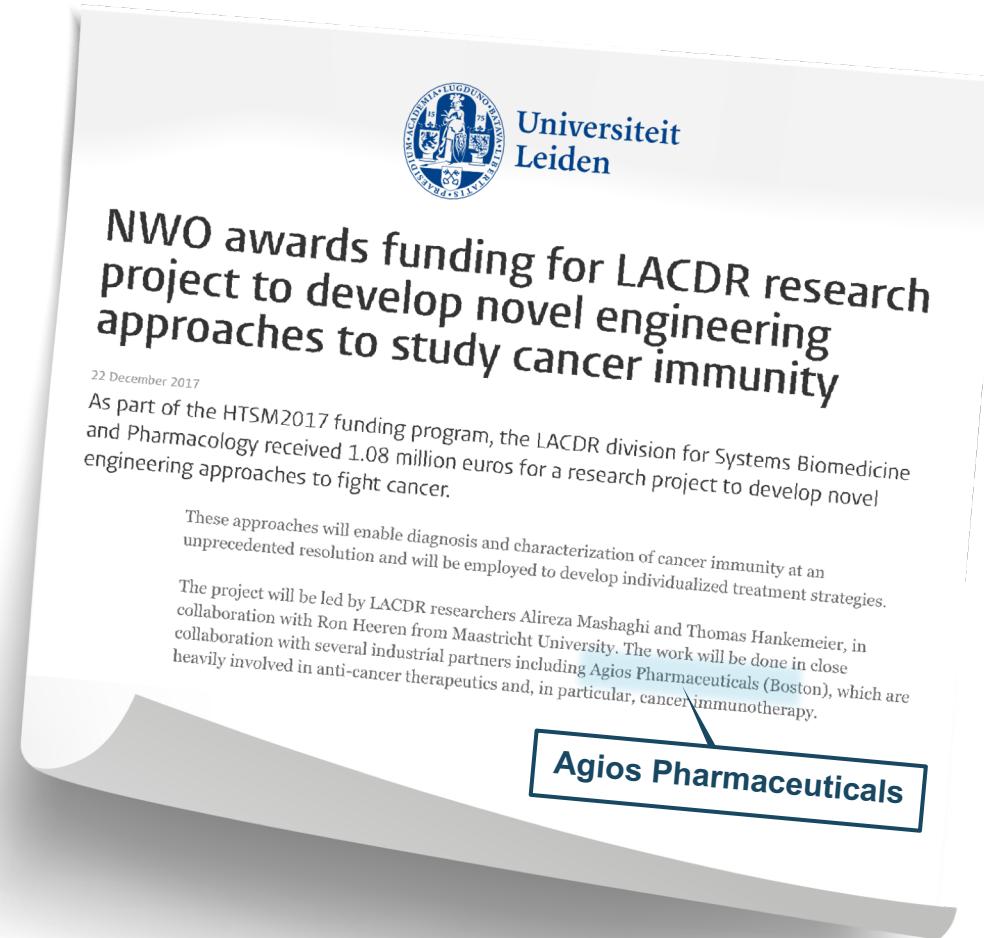
- In vivo immune cell metabolism & T cell exhaustion



- Metabolomic analysis of MCA tumor microenvironment



- Identification of cancer-cell intrinsic immunotherapy targets



Collaboration Structure:

- 1.1 MM € total matching grant from NWO
- Collaboration between Agios, Leiden University and Maastricht University

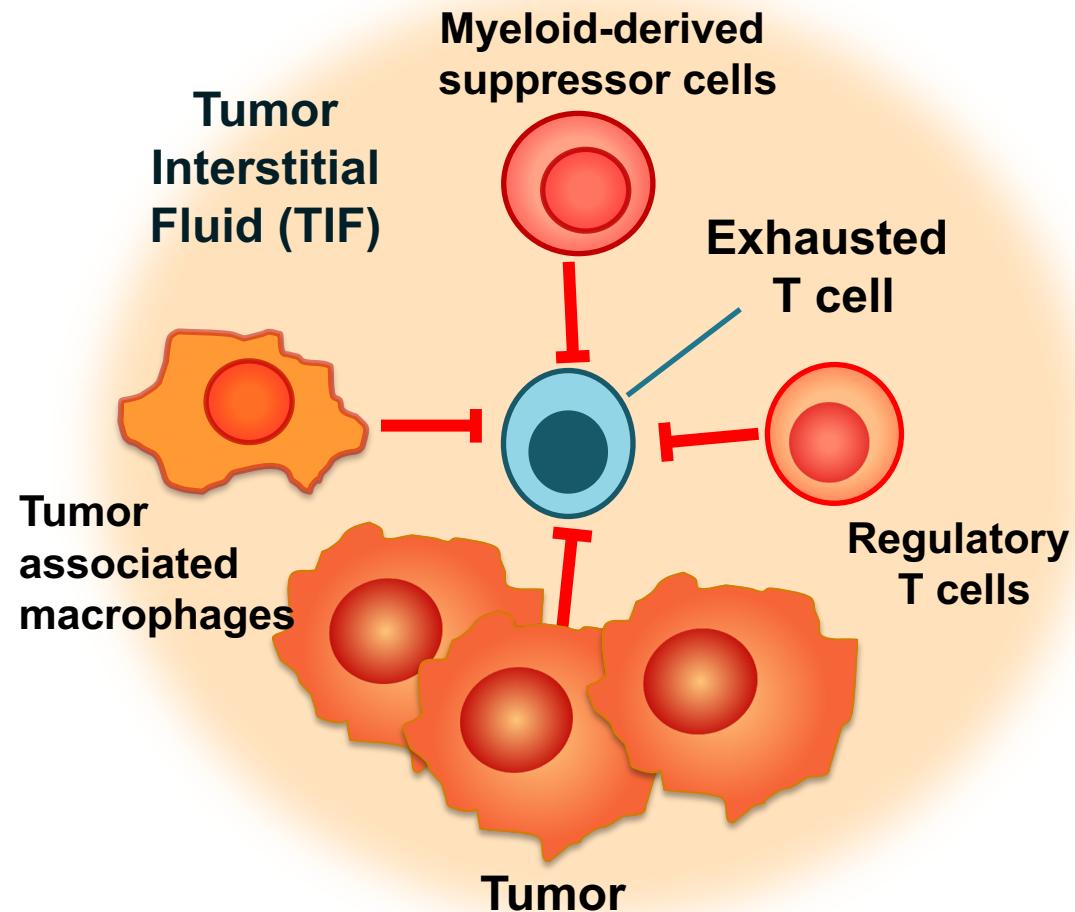
High resolution metabolic analysis of immune cells

- Development of an ultrasensitive robotic platform
- 3D cell culture screening techniques for high throughput screening of T-cells
- Single cell resolution of metabolites and tracers in cells with MS imaging

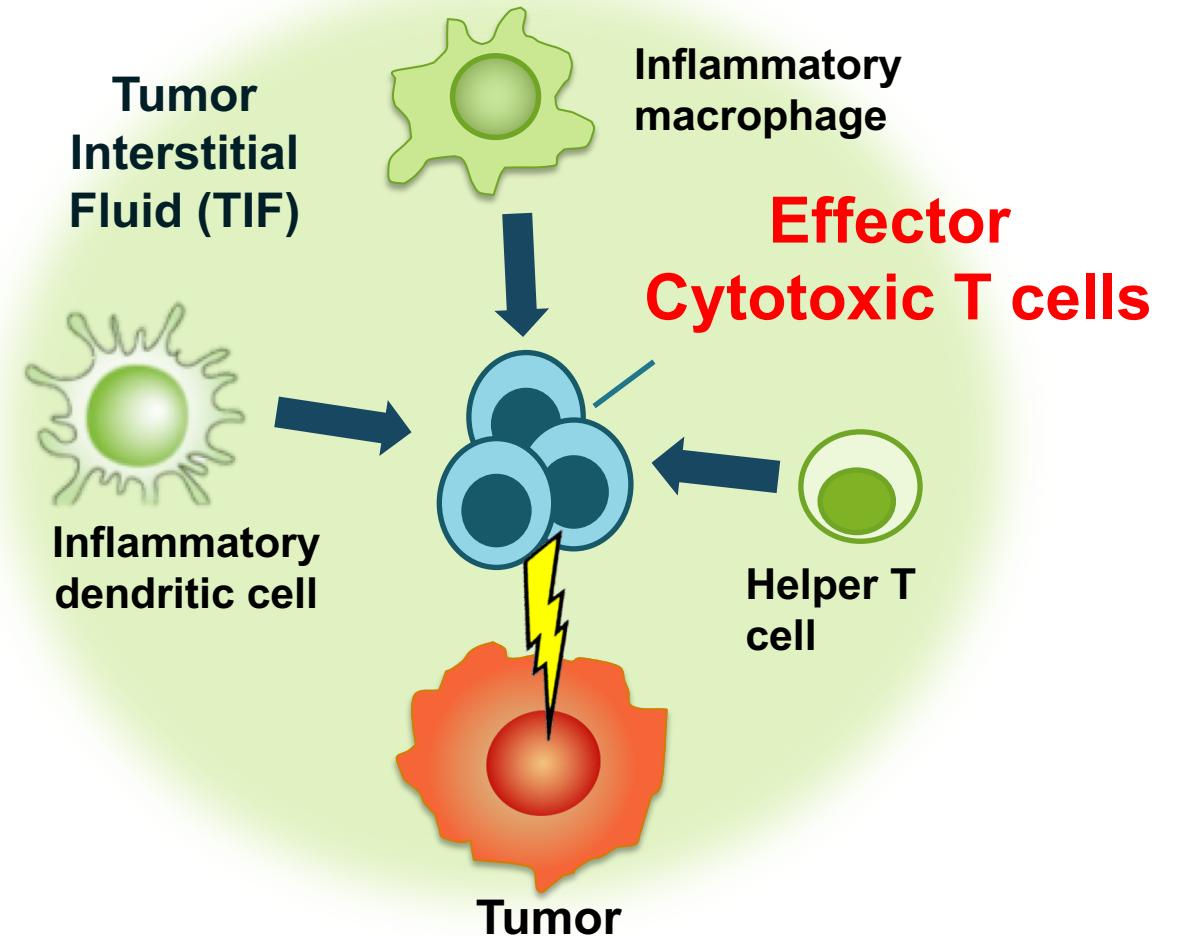


A Growing Portfolio of Metabolic Strategies to Activate Immune Cell Killing of Tumor Cells

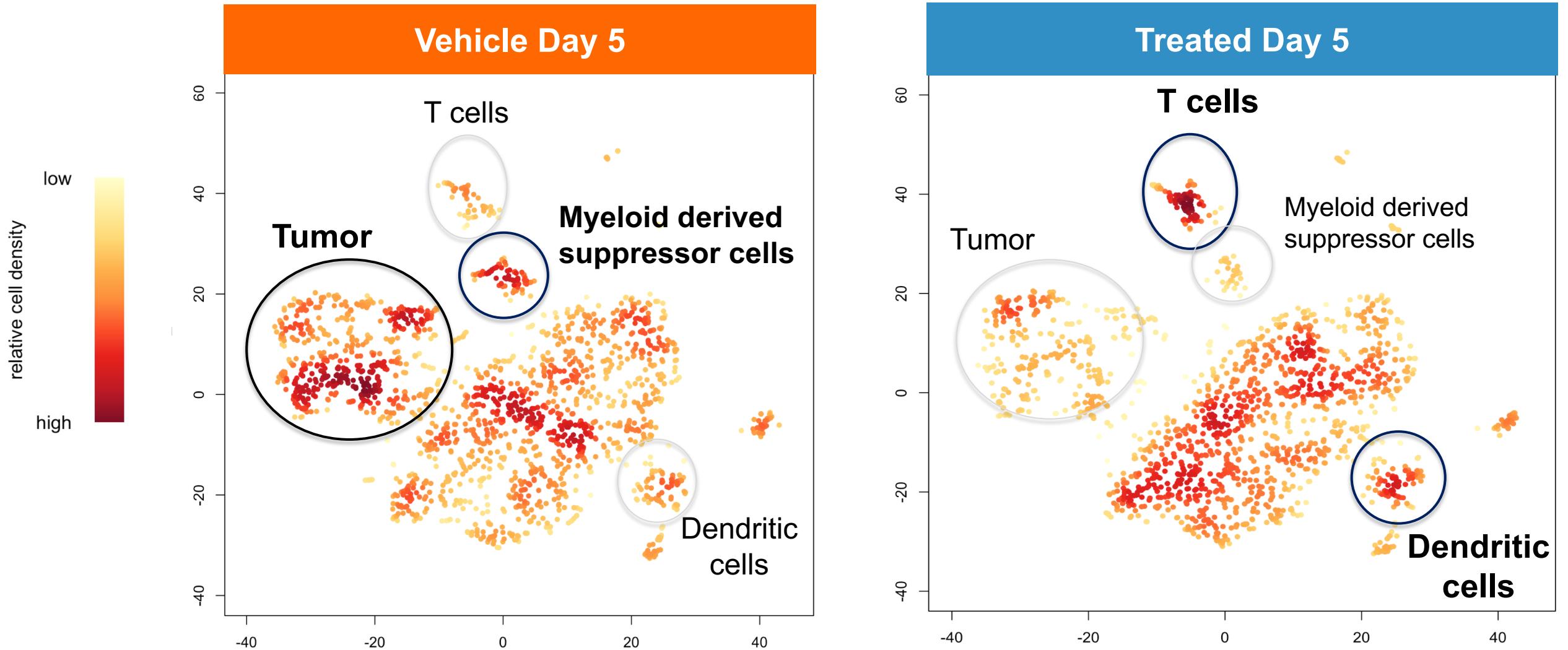
Immunosuppressive Tumor Microenvironment



Activation of Tumor Cell Killing by the Immune System



Inhibitor of Agios Macrophage Target Shows Predicted Immunomodulation and Antitumor Efficacy



Single cell RNA sequencing of tumor, immune cells and stroma



Developing Metabolic Immuno-Oncology Pipeline

Program	Target Discovery	Target Validation	Drug Discovery	Drug Candidate
Metabolic Immuno-Oncology				
T-cell and Tumor Target			●	
Macrophage Target			●	
Macrophage Target		●		
Tumor Target		●		
Other Targets (T-cell, Macrophage, Tumor)	●	●		

● Metabolic Target ■ Celgene Collaboration





Oncology Research Portfolio

Kevin Marks, Ph.D., Senior Director, Head of
Cancer Biology



Multiple Paths to Precision Medicines in Oncology

Clearly Defined Patient Populations



Genetic Target

Target genetically altered

- Gain-of-function mutations
- Fusions
- Amplification

Example: **mutant IDH**



Genetic Context

Synthetic lethal with an oncogene or tumor suppressor

Synthetic lethal with a passenger gene deletion

Example: **MAT2A**



Lineage

Lineage-specific dependency

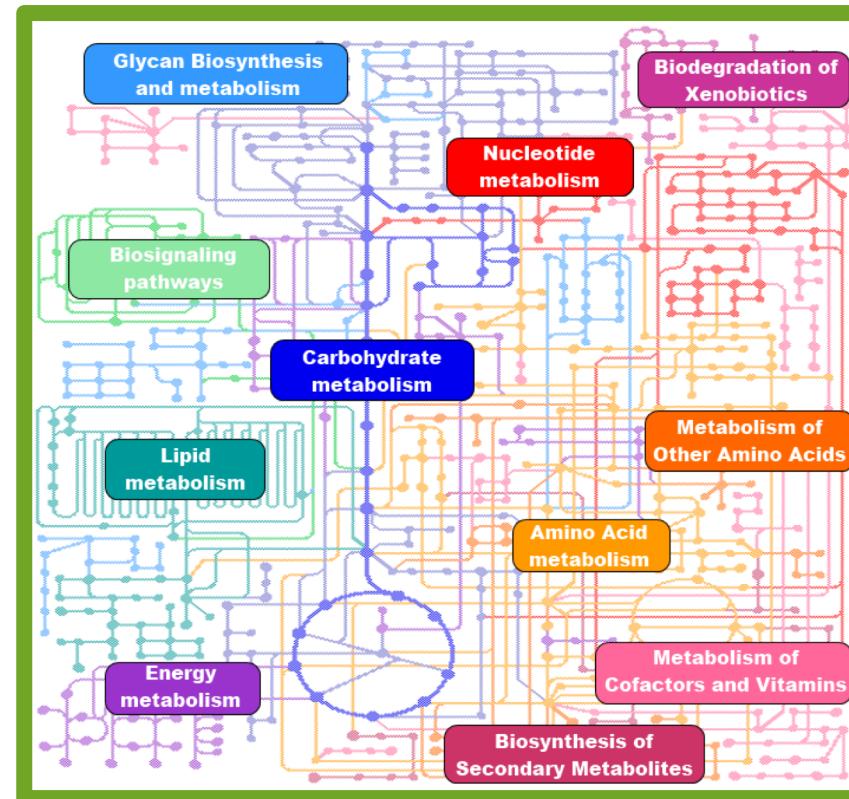
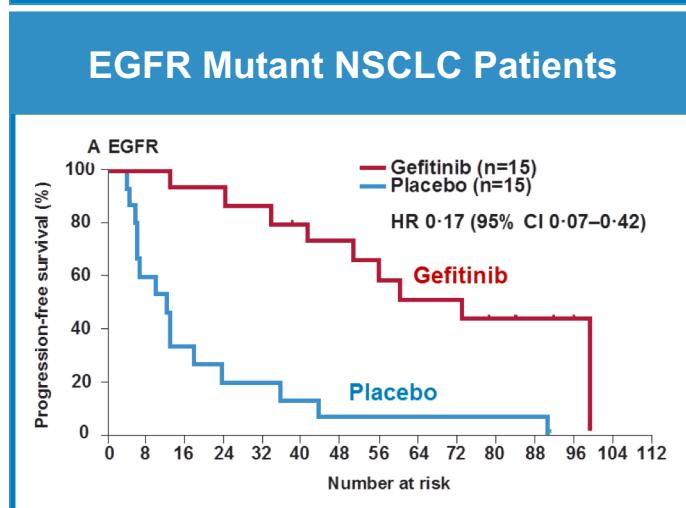
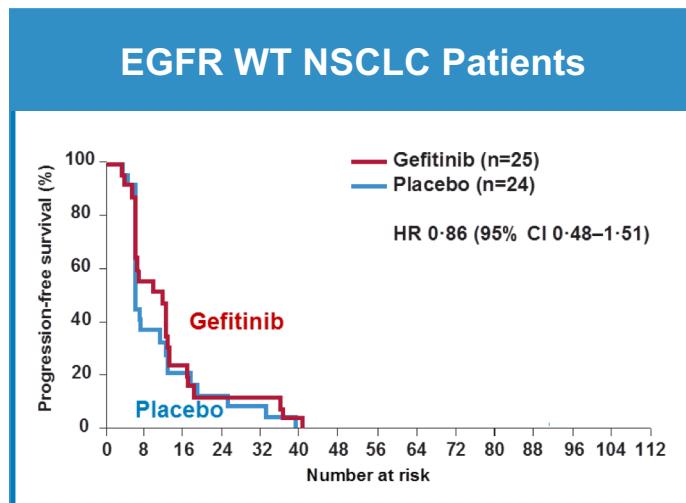
Example: **DHODH**



Precision Medicine in Cancer Metabolism

Directly drugging gain-of-function (GOF) mutants has yielded transformative medicines

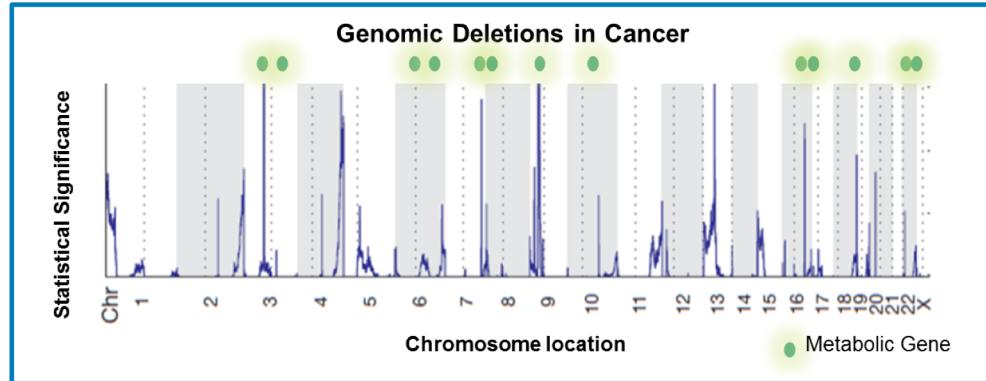
But, despite deep sequencing of many tumor types, IDH1/2 remain the only metabolic GOF mutations



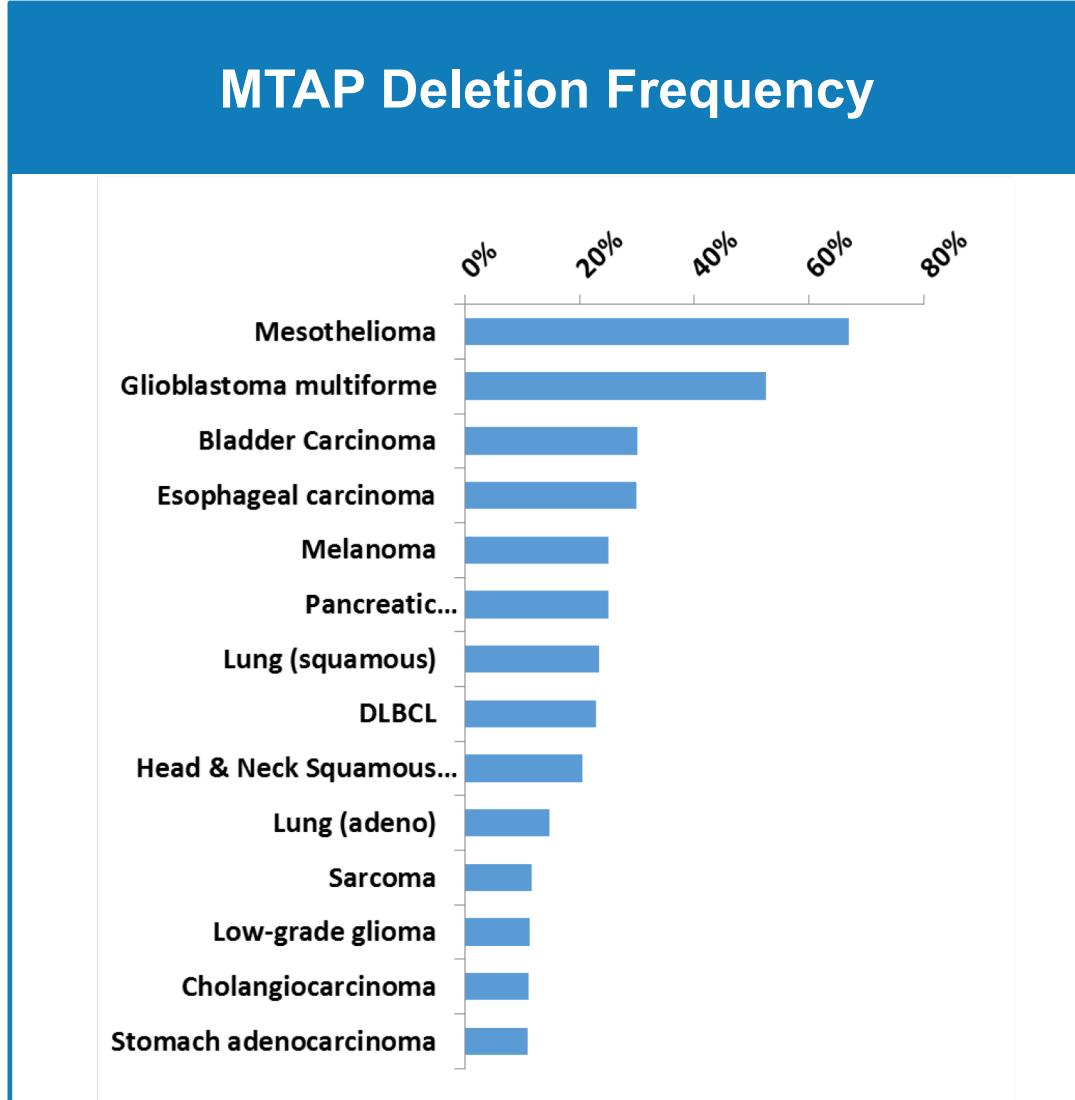
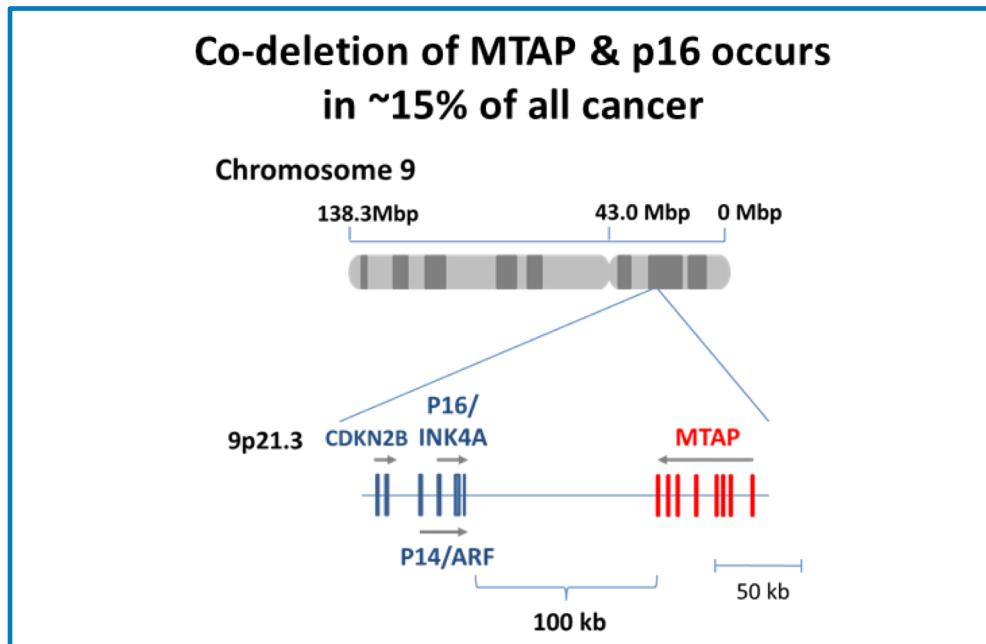
IDH1/2m



While Gain-of-Function Driver Mutations Are Scarce, Loss-of-Function Mutations Are Common

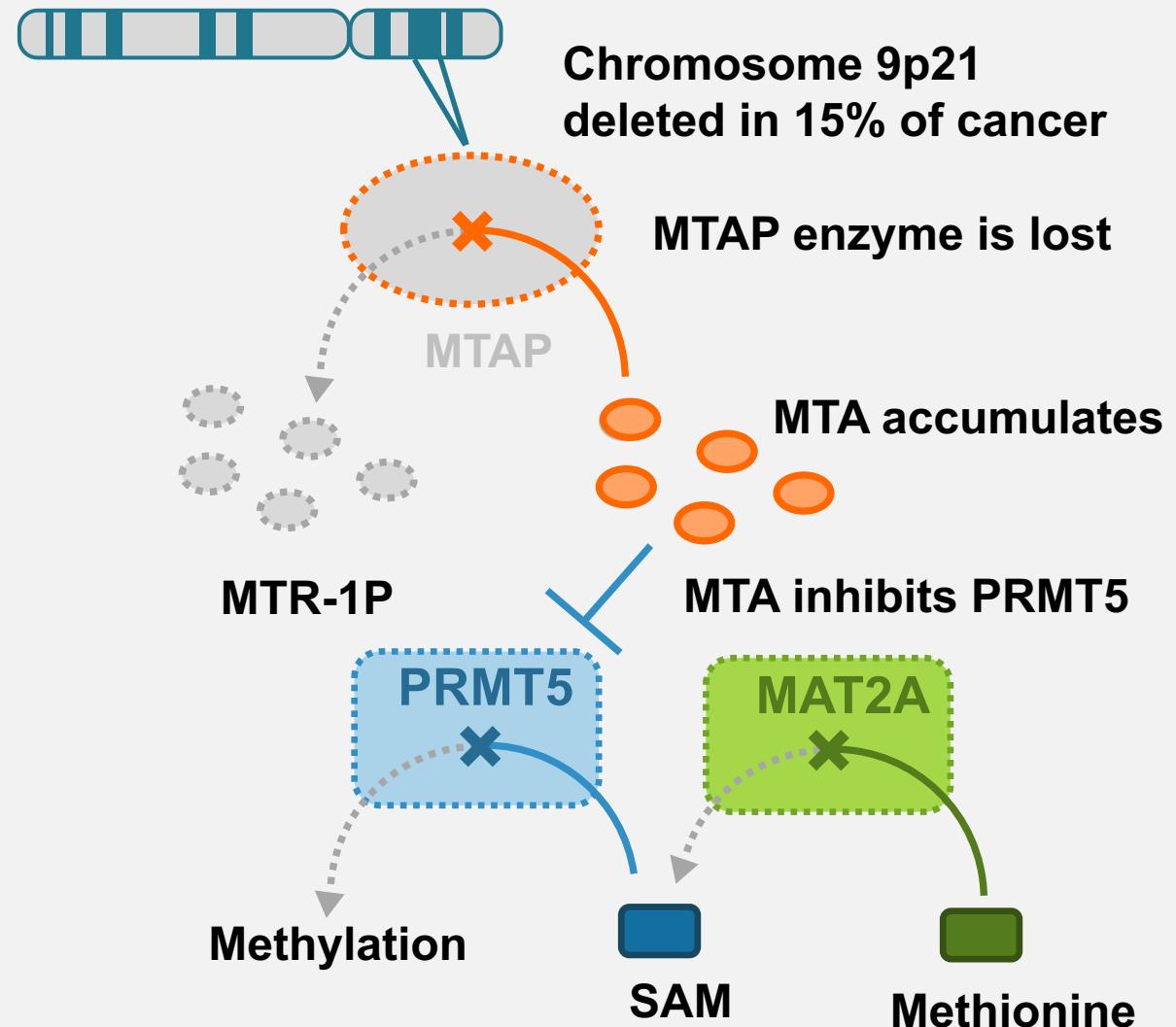


Source: Adapted from Beroukhim et al Nature 2010



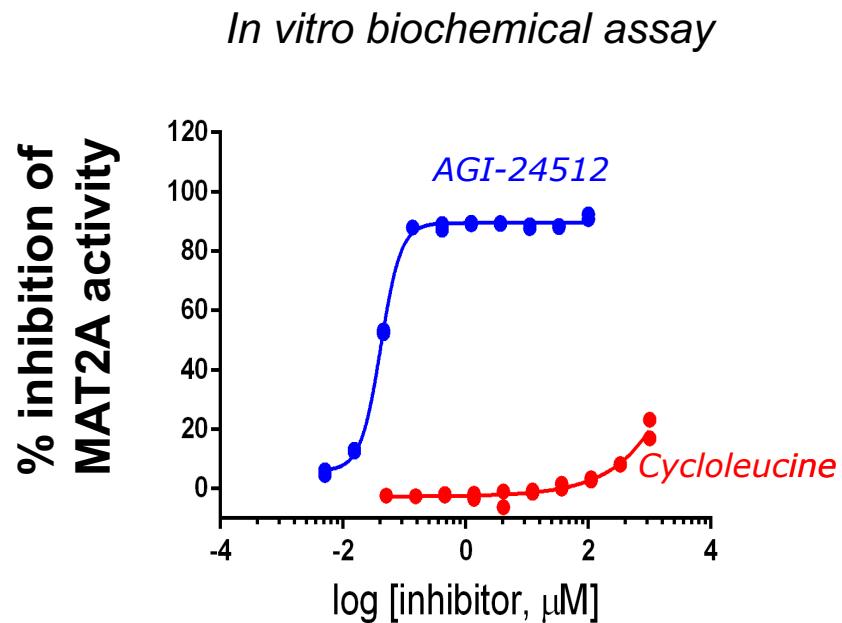
A Key Insight: Deletion of MTAP Makes Cancers Vulnerable to Targeting of MAT2A

1. MTAP deletion
2. Substrate MTA accumulates
3. Partial inhibition of PRMT5
4. Sensitivity to a 'second hit': targeting **MAT2A** starves PRMT5 of its substrate

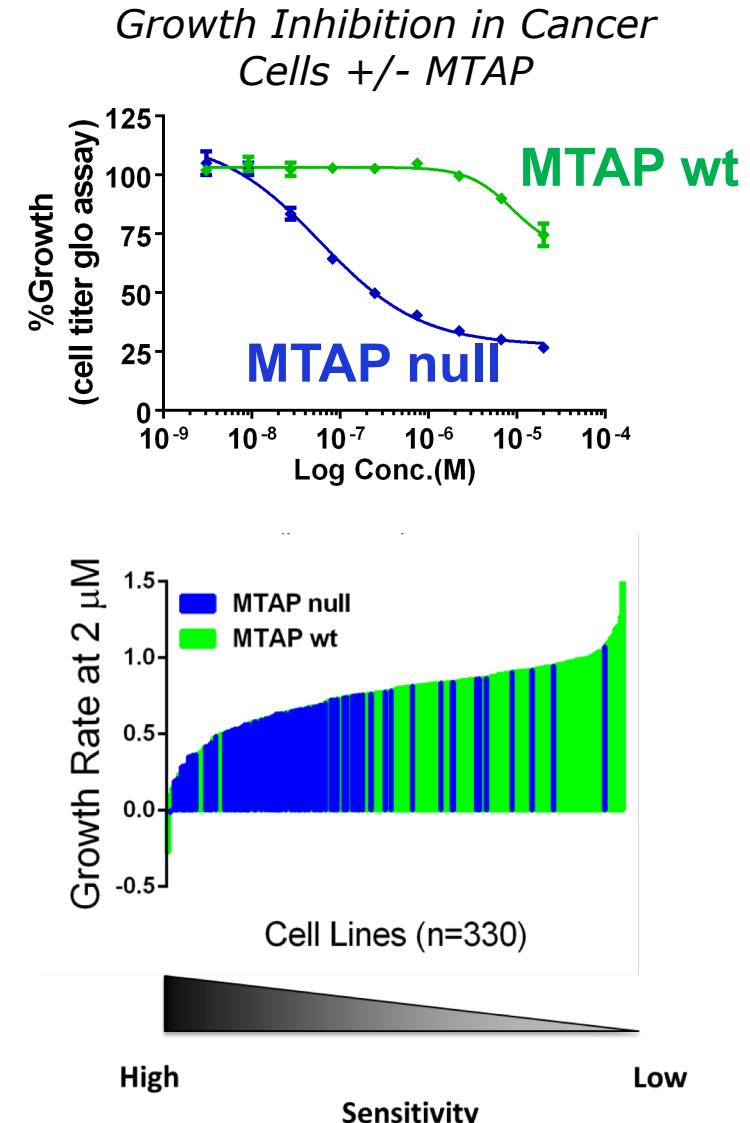


Discovery of First in Class MAT2A Inhibitors and Validation of the MAT2A/MTAP Hypothesis

Identification of MAT2A Inhibitors

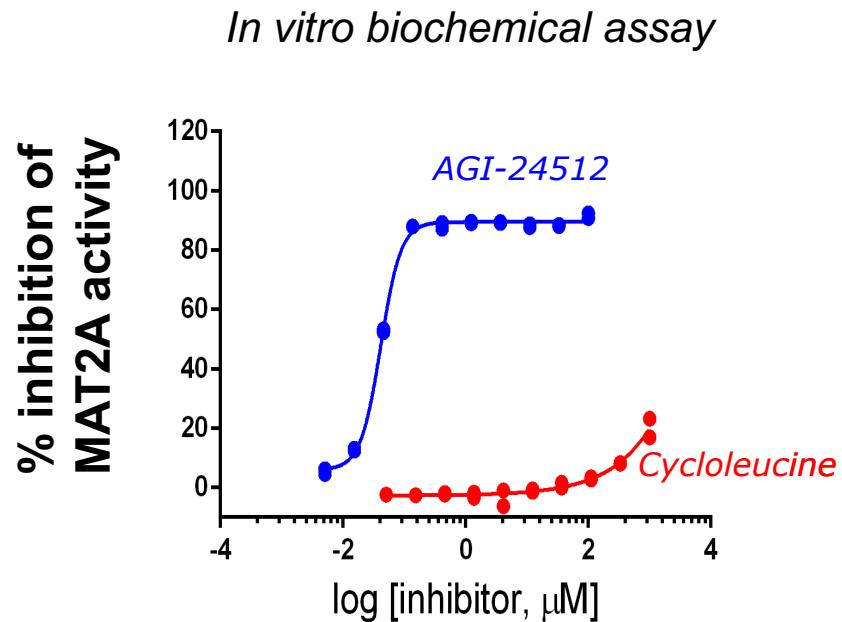


MTAP-selective Growth Inhibition

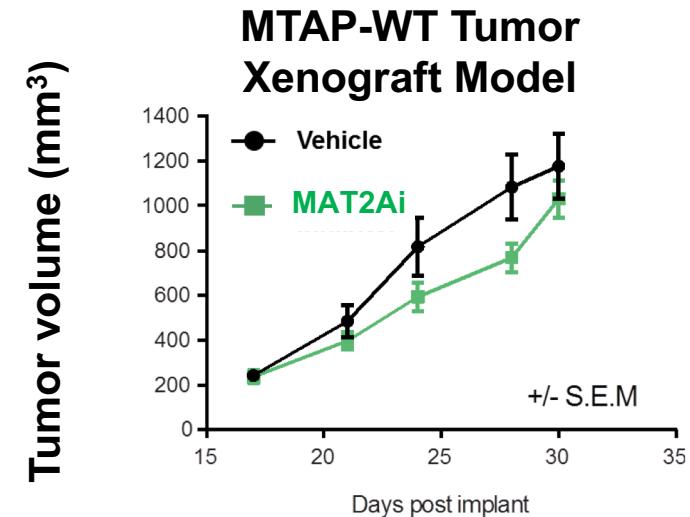
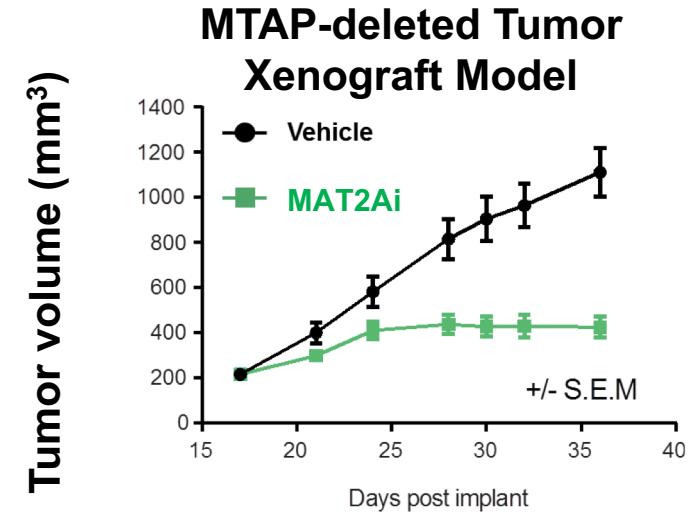


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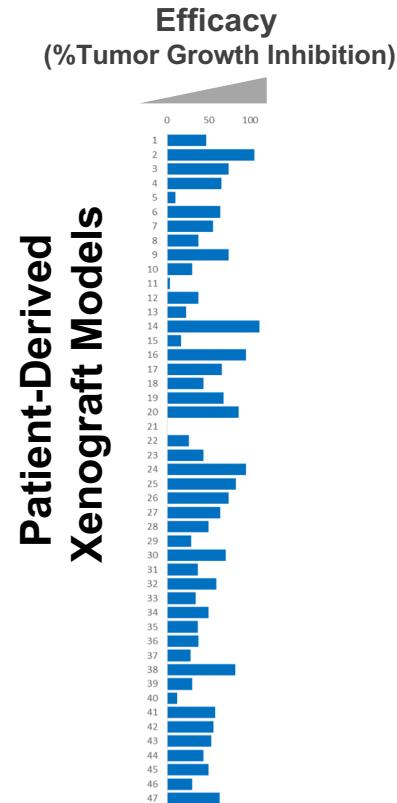
MTAP-selective Growth Inhibition



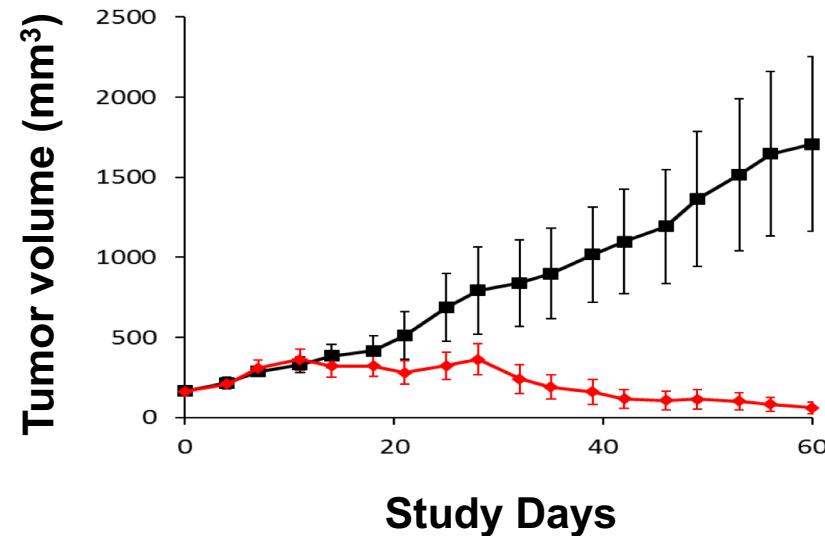
Preclinical Studies Indicate Potential for Use in Variety of MTAP-Deleted Indications

Patient-derived Xenograft (PDX) 'clinical trial'

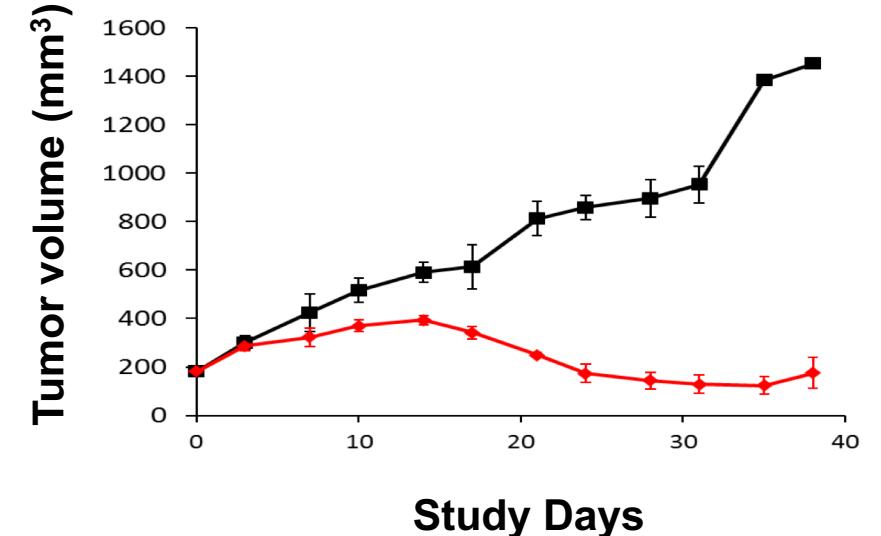
Regressions observed upon single agent AG-270 treatment in some models



NSCLC (SCC) Model



Esophageal (SCC) Model



■ Vehicle ◆ AG-270 200 mg/kg

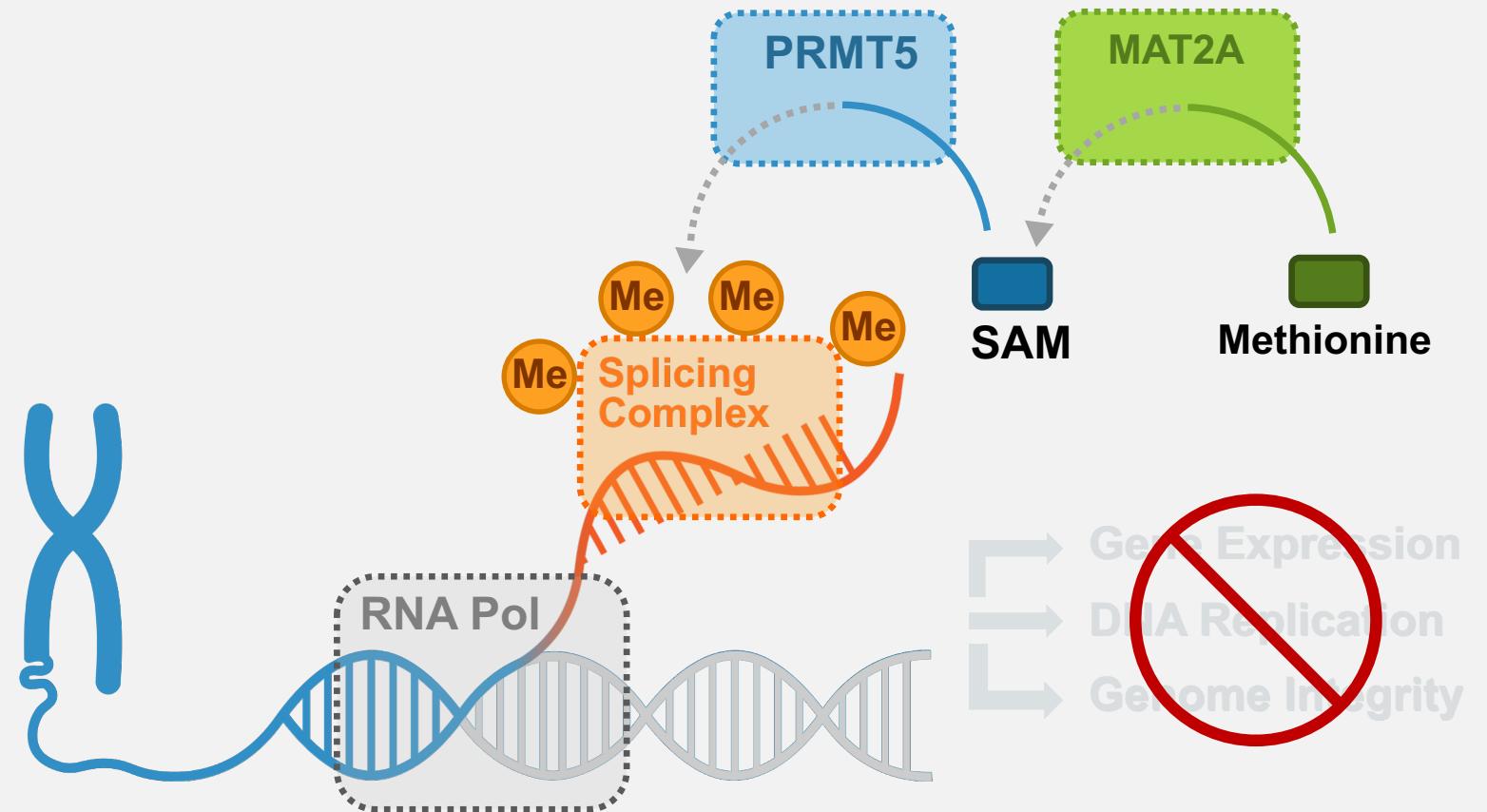
AG-270 is efficacious in MTAP-deleted PDX models from a variety of tissue origins including NSCLC, pancreatic, gastric & esophageal



Emerging Mechanistic Understanding of the Pathway

Downstream of MAT2A

1. RNA splicing concurrent with transcription
2. Splicing complex requires PRMT5
3. MAT2A inhibition blocks splicing
4. Defects in gene expression, DNA replication, genome integrity



AG-270 Program Is Well Poised for Biomarker-driven Clinical Development

Multiple Pharmacodynamic Biomarkers

PATHWAY EFFECTS

MAT2A inhibition



Tumor-selective inhibition of PRMT5



Inhibition of PRMT5 targets including the spliceosome



Antiproliferative & cytotoxic effects

CLINICALLY APPLICABLE BIOMARKERS

Monitor SAM in patient plasma

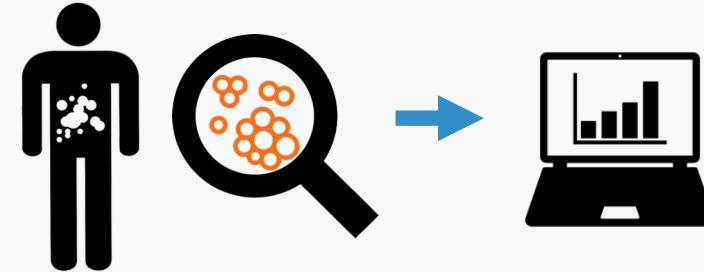
Measure PRMT5 methyl marks in tumor

Assess splicing using RNA seq & other assays

Patient Selection Biomarkers

1.

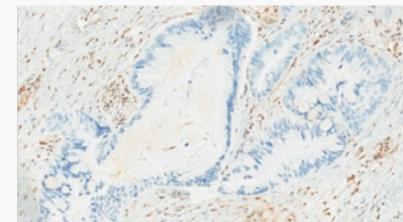
Next-gen sequencing for CDKN2A loss



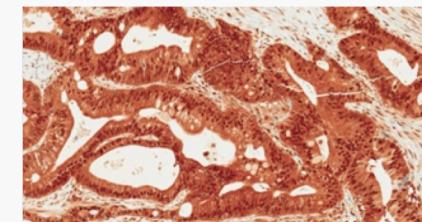
2.

Directly assess MTAP-status by IHC

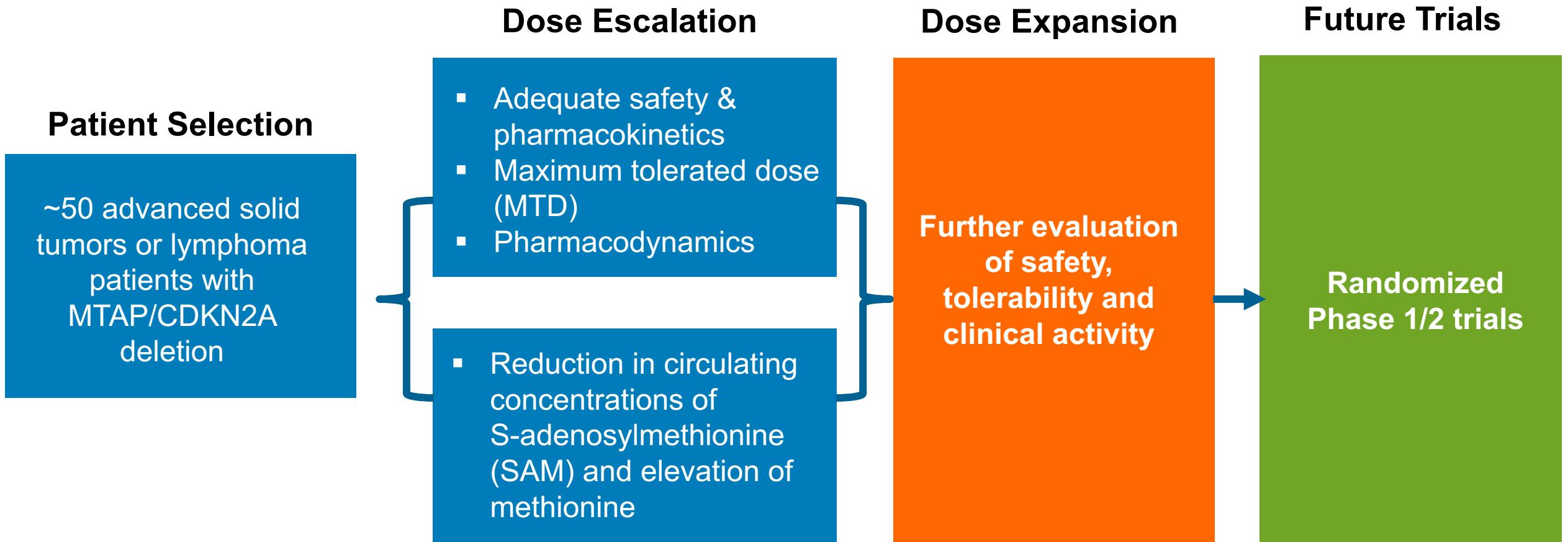
MTAP deficient PDAC



MTAP positive PDAC



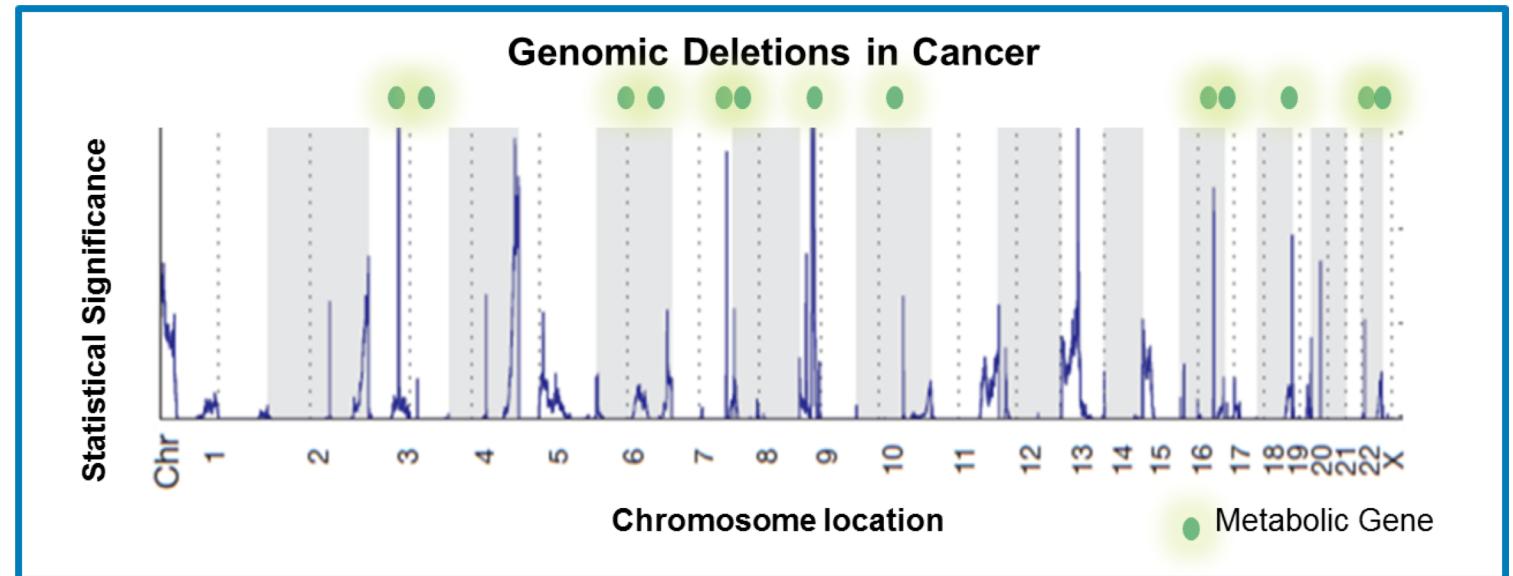
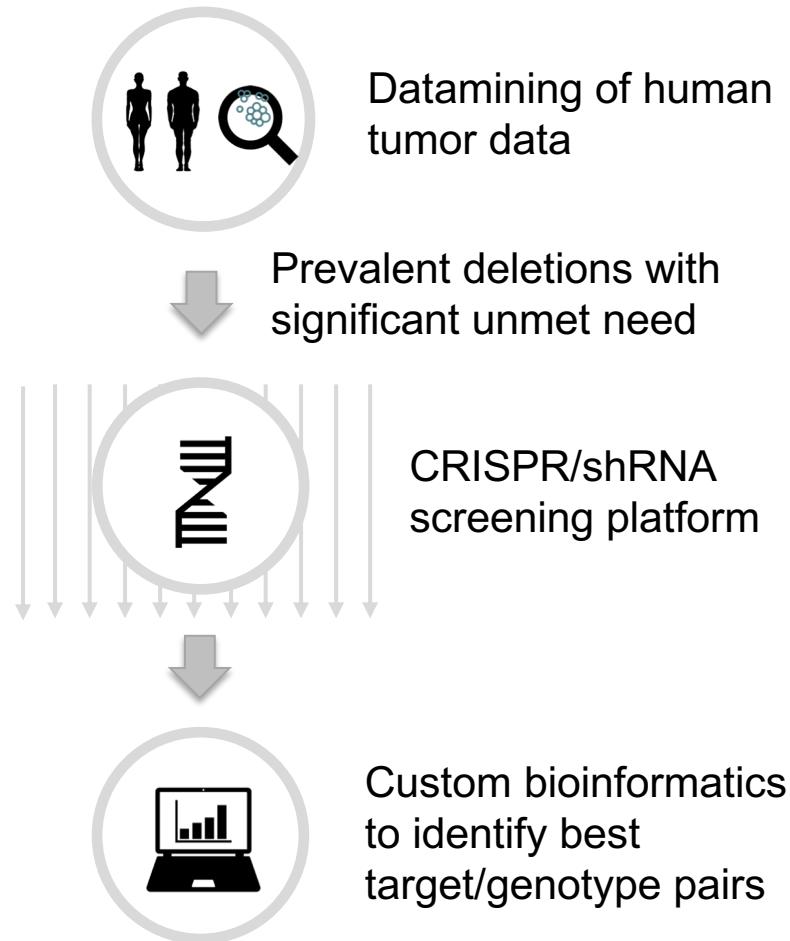
AG-270 First-in-Human Phase 1 Clinical Trial



ClinicalTrials.gov Identifier: NCT03435250



Systematically Searching for Other MAT2A/MTAP-like Programs



Source: Adapted from Beroukhim et al Nature 2010

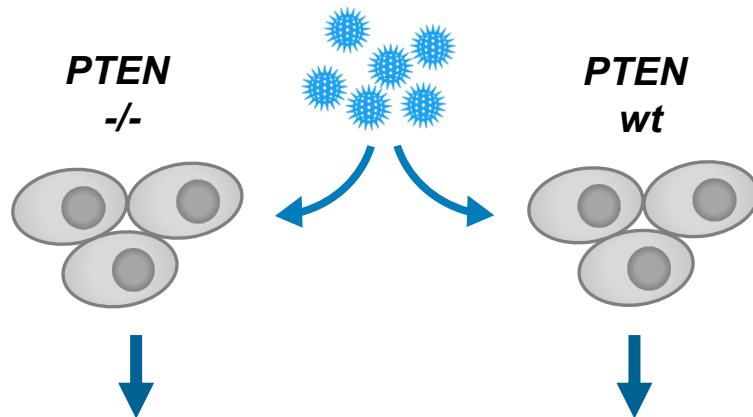
Agios' oncology research team systematically searching for vulnerabilities associated with many other major deletions in cancer



Next Wave Target Example: Novel Selective Vulnerability Target for PTEN-mutant Cancers

Internally identified target with robust target validation in vitro and in vivo

PTEN-selective functional genomics (shRNA) screen

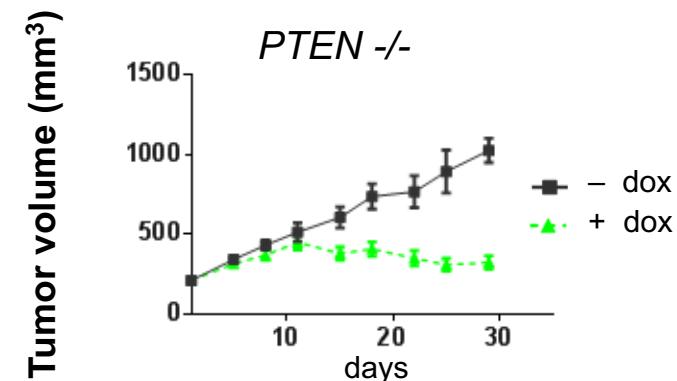
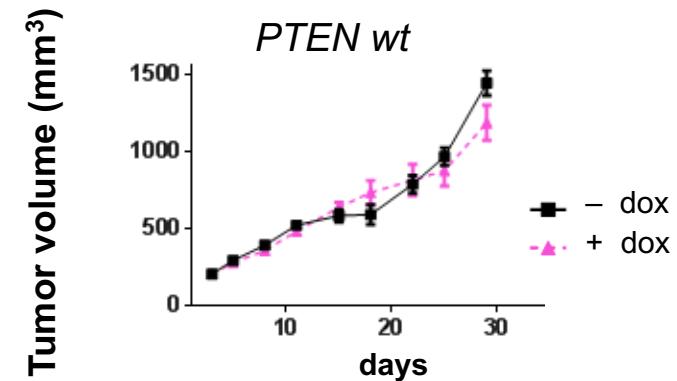


Measure shRNA depletion via RNA-seq of barcodes

$$\frac{PTEN \ -/-}{PTEN \ wt} = \text{Preferential depletion with } PTEN \text{ loss}$$

Successful validation of Target X

* PTEN-selective growth phenotypes upon dox-inducible knockdown of Target X *in vivo*



Multiple Paths to Precision Medicines in Oncology

Clearly Defined Patient Populations



Genetic target

Target genetically altered

- gain-of-function mutations
- fusions
- Amplification

Example: **mutant IDH**



Genetic context

Synthetic lethal with an oncogene or tumor suppressor

Synthetic lethal with a passenger gene deletion

Example: **MAT2A**



Lineage

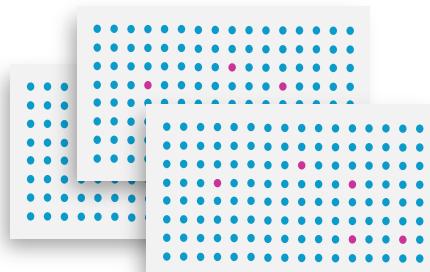
Lineage-specific dependency

Example: **DHODH**

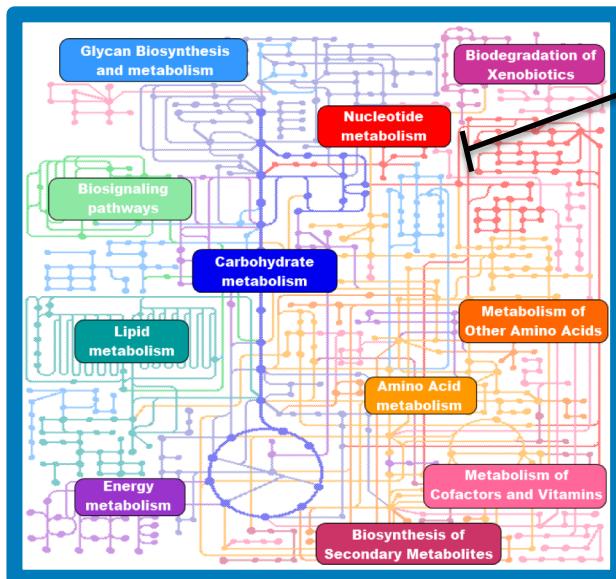


A Chemical Biology Screen Revealed an Unexpected Lineage Dependence on DHODH

Cell line panel screen reveals selective AG-636 sensitivity in heme malignancies

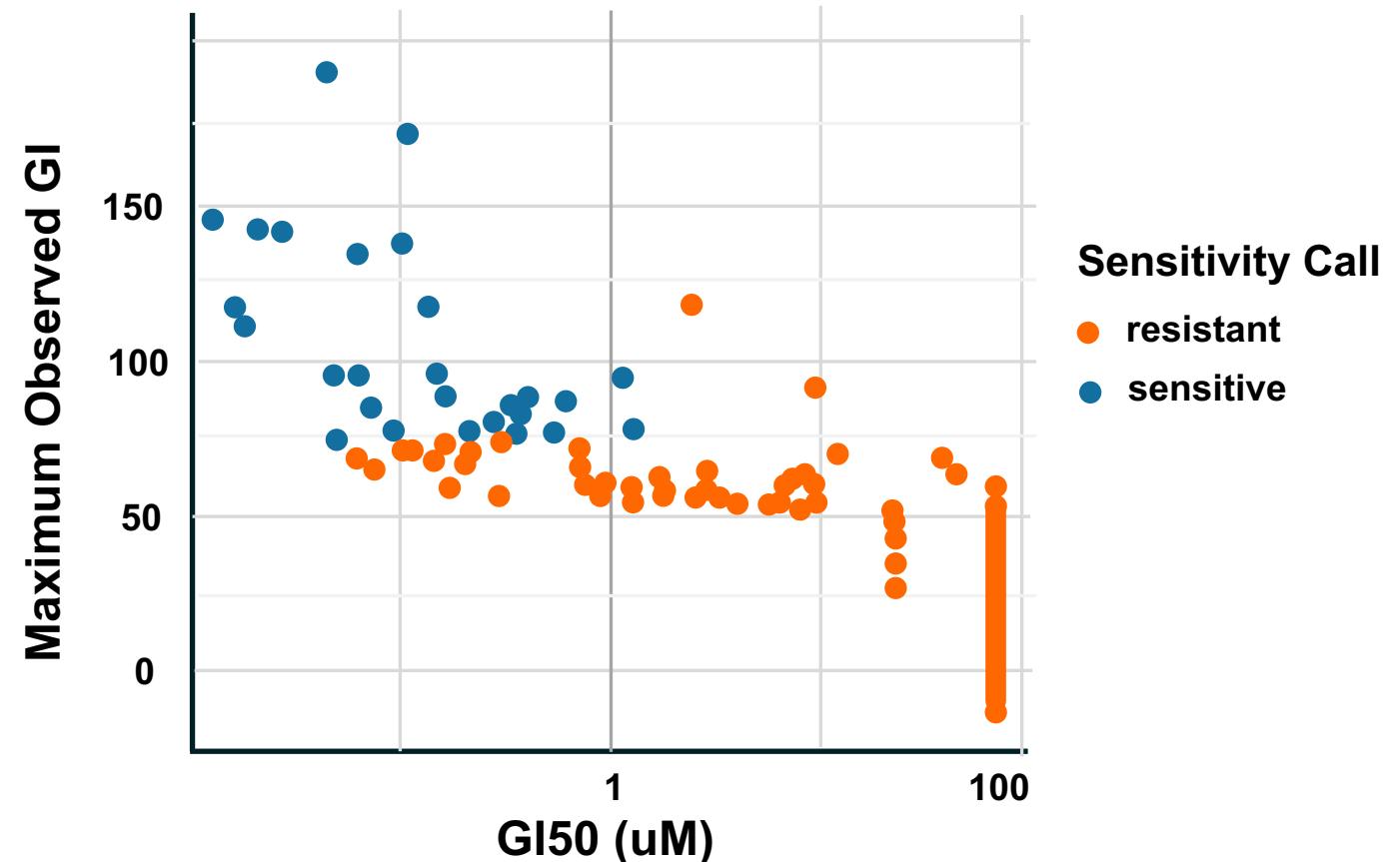


We tested a library of inhibitors of metabolic enzymes vs 100s of cancer cell lines, searching for selective agents



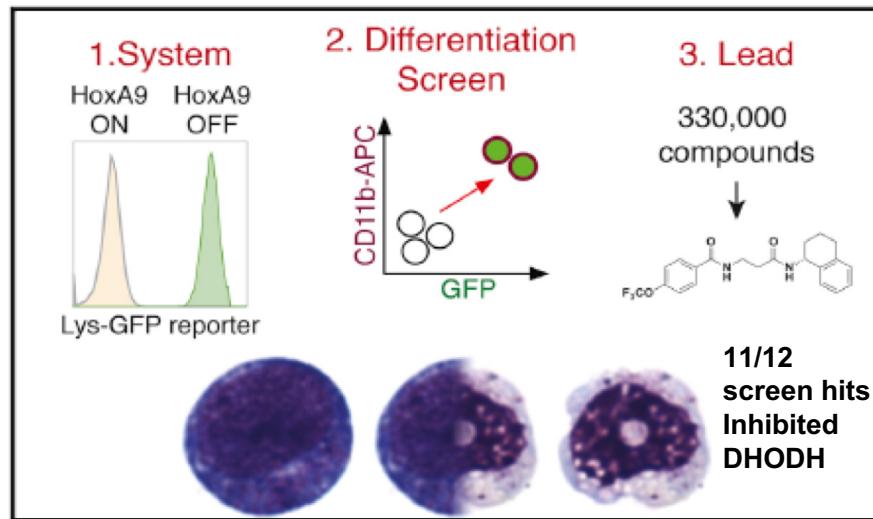
DHODH inhibitor AG-636 blocks production of nucleotides for RNA & DNA

Selective efficacy:
AG-636 active in 8% of cancer cell lines (n=356)



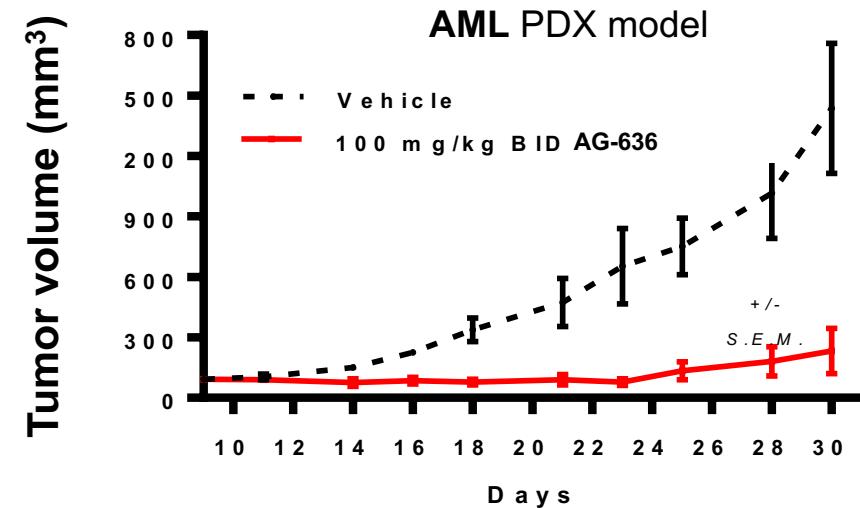
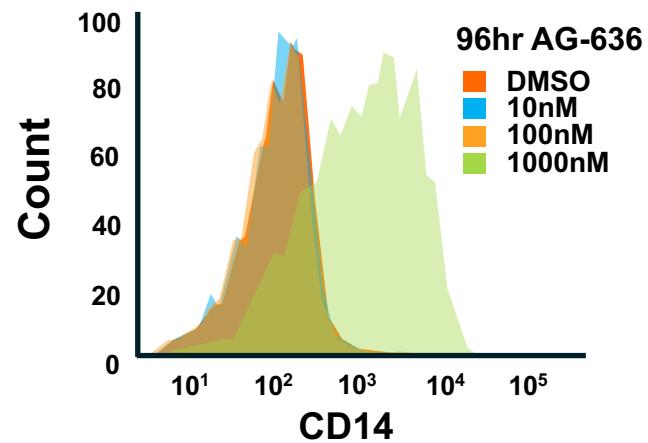
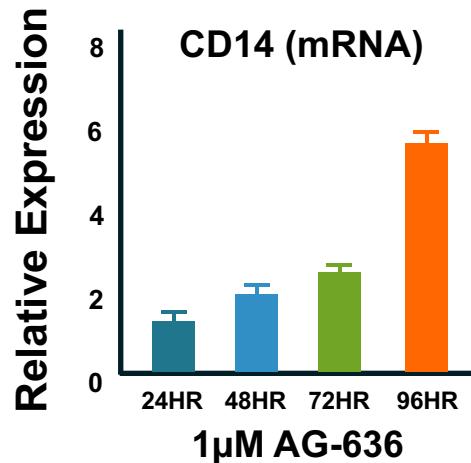
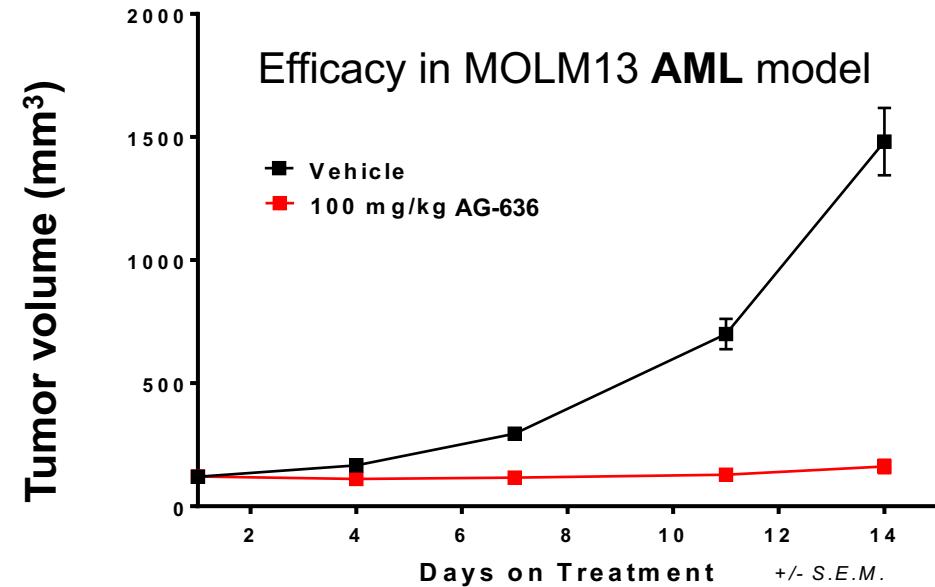
DHODH Inhibitor AG-636 is Efficacious in AML

Inhibition of DHODH overcomes differentiation blockade in AML...



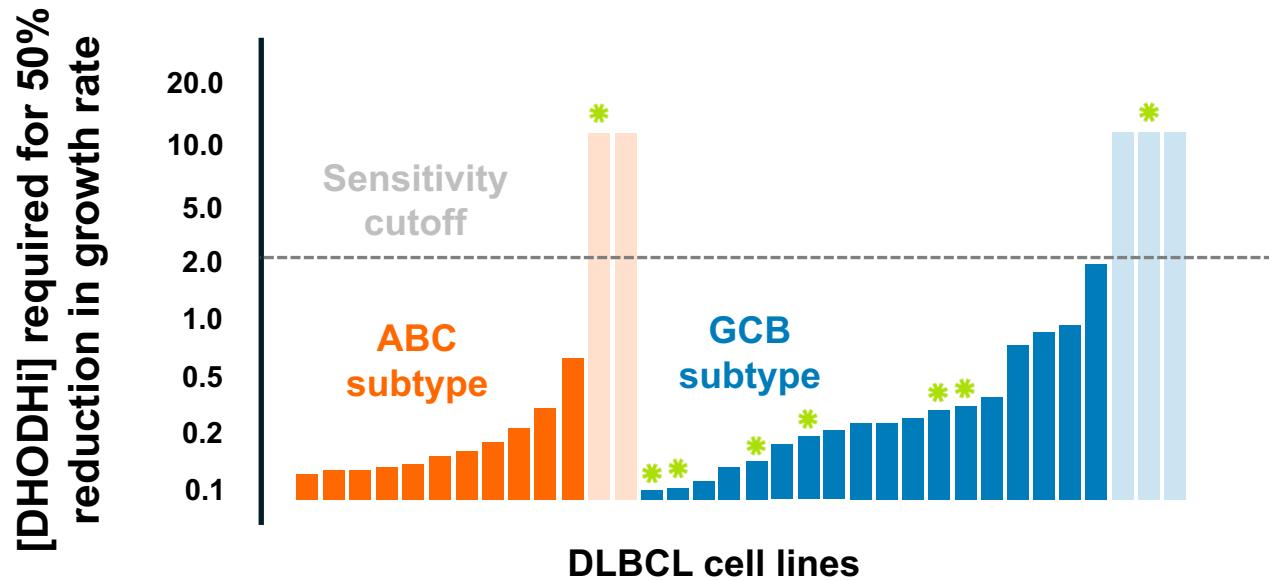
Source: Sykes et al, Cell 2016

...and drives substantial efficacy *in vivo*



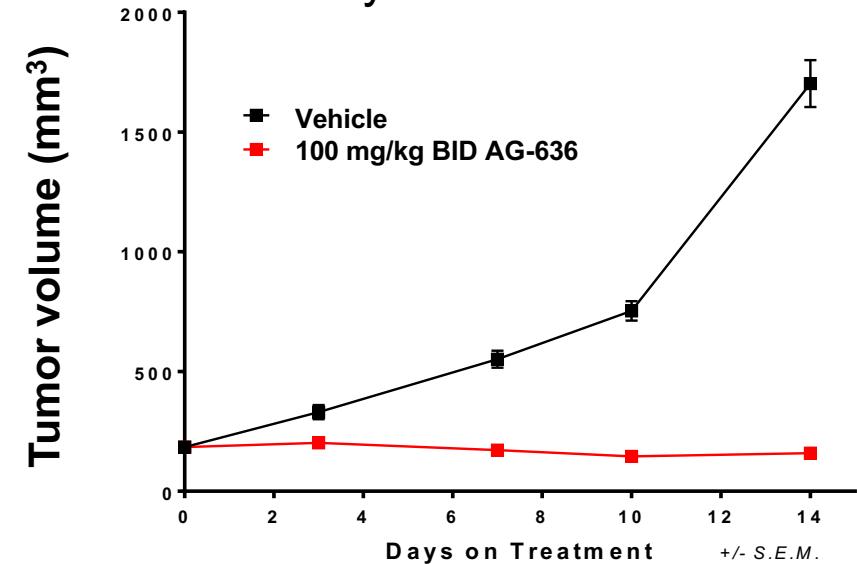
DHODH Inhibitor AG-636 is Efficacious in DLBCL

AG-636 is active in wide range of DLBCL cell lines, including subtypes with poor prognosis

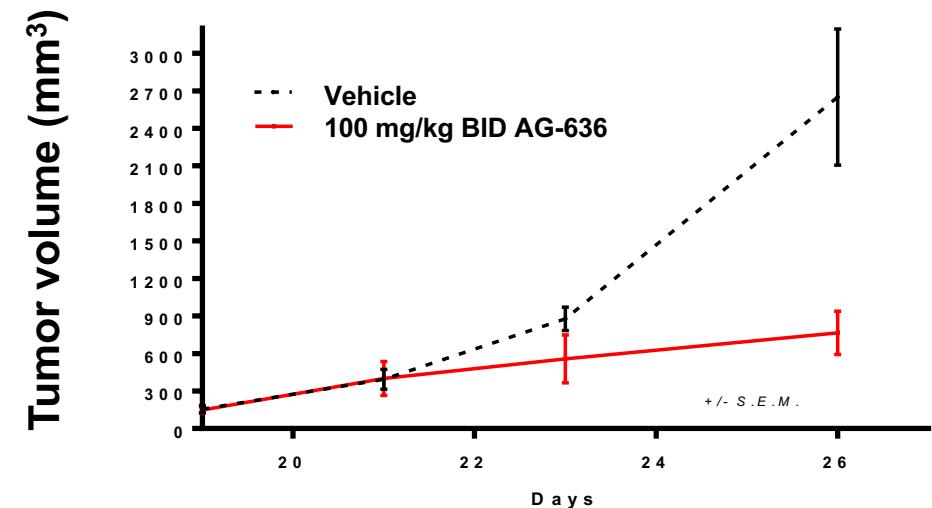


* Reported as double-hit
Source: Drexler et al., *Leukemia Lymphoma* 2016

Efficacy in OCILY19 **DLBCL** model



Aggressive, triple-hit **DLBCL** PDX model



Source: Agios data on file



Agios Preclinical Oncology Pipeline

Program	Target Discovery	Target Validation	Drug Discovery	Drug Candidate
Oncology				
Heme Lineage: AG-636 DHODH				●
MAT2A Follow-Ons			●	
PTEN-mutant Solid Tumors			●	
Genetically Defined Heme Target			●	
Genetically Defined Heme Target		●		
Other Exploratory Programs	●	●		

● Metabolic Target
 ● Non-Metabolic Target
 ● Metabolic and Non-Metabolic Targets
 Celgene Collaboration



Agios Preclinical Pipeline

Program	Target Discovery	Target Validation	Drug Discovery	Drug Candidate
Oncology				
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MAT2A Follow-Ons			●	
PTEN-mutant Solid Tumors			●	
Genetically Defined Heme Target			●	
Genetically Defined Heme Target		●		
Other Exploratory Programs	●	●		
Rare Genetic Diseases				
Pyruvate Kinase Activator Follow-Ons			●	
Phenylketonuria (PKU)			●	
Erythroid Porphyrin			●	
Friedreich's Ataxia			●	
Other Exploratory Programs	●	●		
Metabolic Immuno-Oncology (Celgene Collaboration)				
T-cell and Tumor Target			●	
Macrophage Target			●	
Macrophage Target		●		
Tumor Target		●		
Other Targets (T-cell, Macrophage, Tumor)	●	●		

● Metabolic Target
 ● Non-Metabolic Target
 ● Metabolic and Non-Metabolic Targets
 Celgene Collaboration



Q&A



Ivosidenib Clinical Strategy in Acute Myeloid Leukemia

Darrin Miles, Vice President, IDH Program Management



IDH Mutations Across Many Tumor Types

**ACUTE MYELOID
LEUKEMIA (AML)**

**~20% of Patients Have
IDH1 OR IDH2 Mutation**

~10,000 IDHm Patients

**CHOLANGIO-
CARCINOMA**

**~14 % have IDH1
Mutation**

~3,000 IDH1m Patients

**MYELODYSPLASTIC
SYNDROMES (MDS)**

**~8% have IDH1 or IDH2
Mutation**

~3,000 IDHm Patients

LOW GRADE GLIOMA

**~80% have IDH1
Mutation**

~9,000 IDH1m Patients

CHONDROSARCOMAS

**~50% have IDH1
Mutation**

~900 IDH1m Patients

Sources: SEER. Cancer Stat Facts: AML 2015 and Epiphany EPIC oncology numbers; American Cancer Society. AML 2017.; Visser et. Al. Incidence, survival and prevalence of myeloid malignancies in Europe. Eur J Cancer. 2012 Nov;48(17):3257-66 DiNardo et al. Leukemia 2016;30(4):980-4, Amary MF et al. J Pathol 2011;224:334-43, Epiphany Partners Epic Oncology, DC National Program of Cancer Registries (NPCR); Borger DR et al. Oncologist 2012;17:72-9.; Kipp BR et al. Hum Pathol 2012;43:1552-8.; Goyal L et al. Oncologist 2015;20:1019-27. SEER. Cancer Stat Facts, CBTRUS (Central Brain Tumor Registry in the US); Neurosurg Focus. 2015 Jan; 38(1): E6.

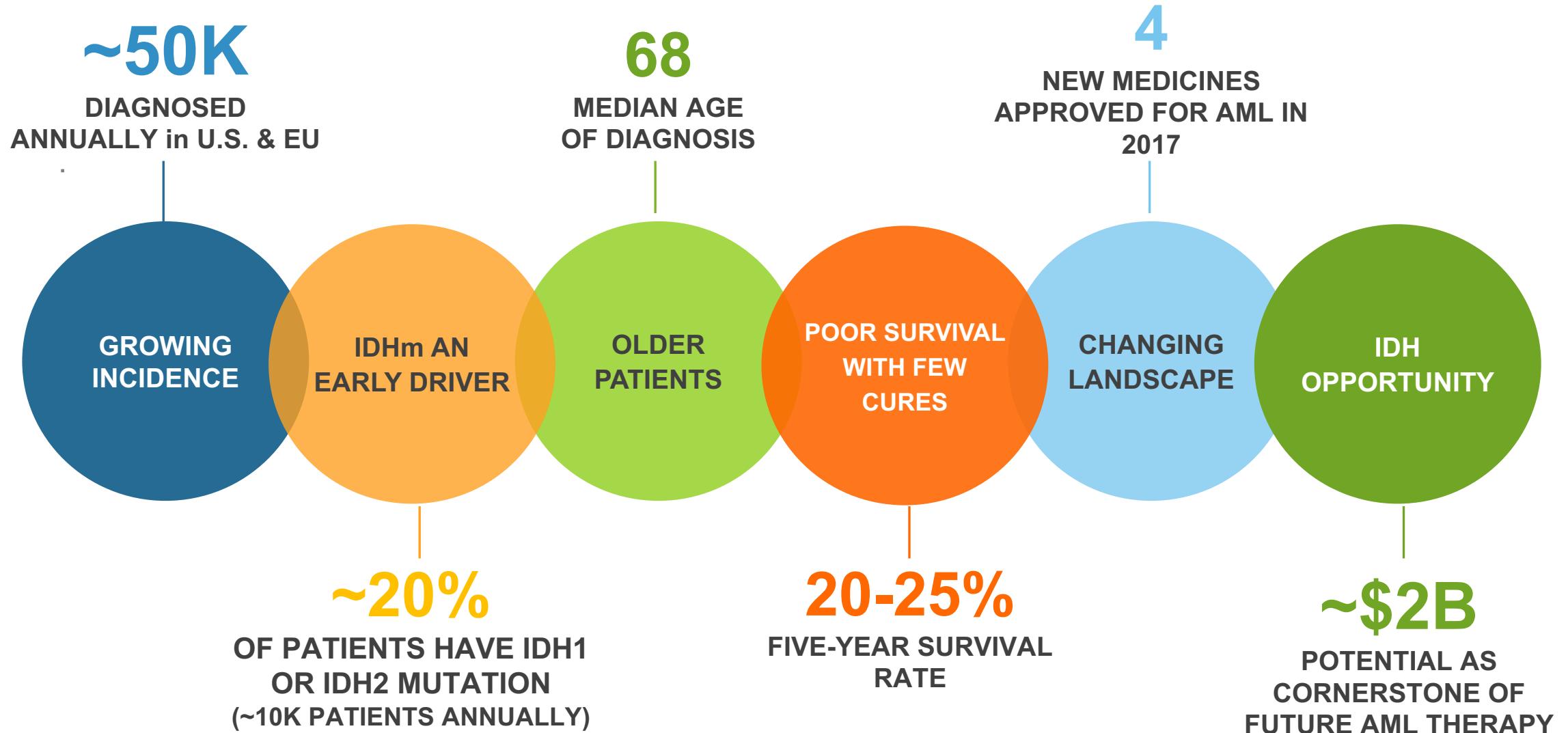


Multiple Opportunities Across IDHm Hematologic and Solid Cancers Originating from Agios Research Platform

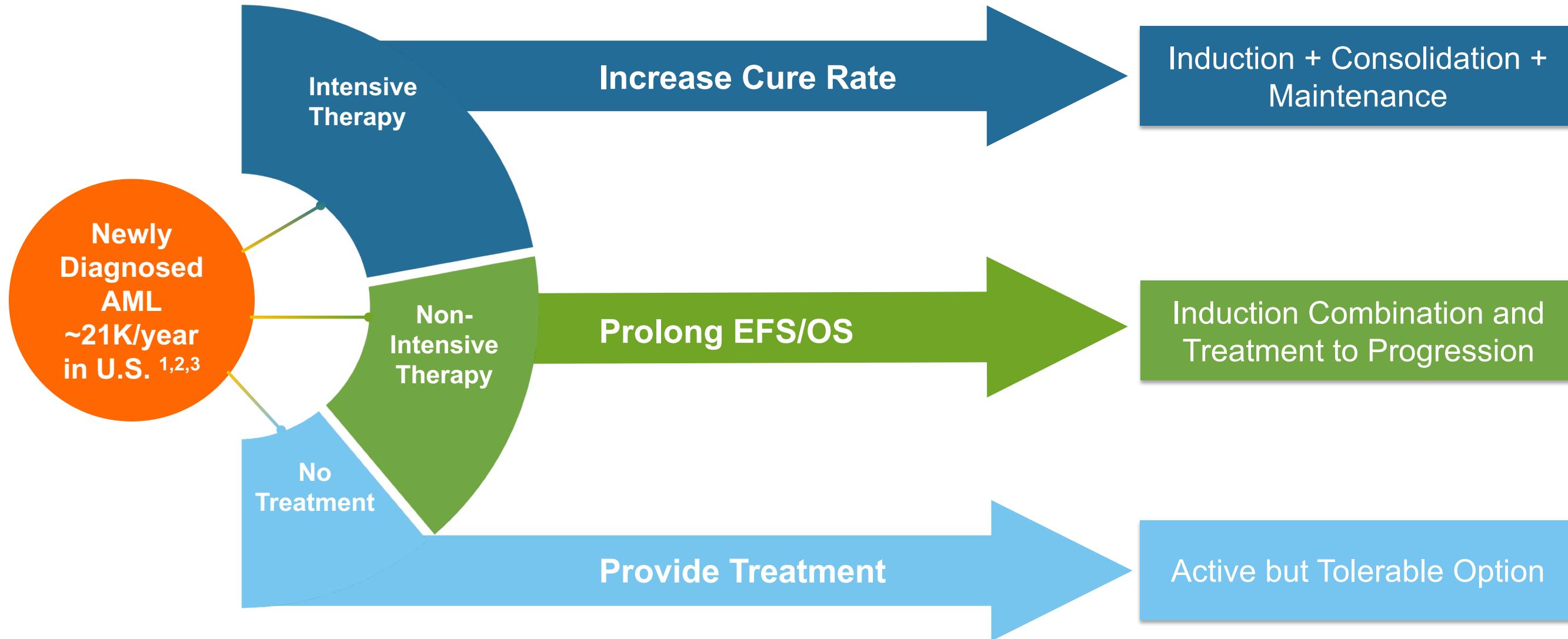
ACUTE MYELOID LEUKEMIA	CHOLANGIOCARCINOMA	LOW GRADE GLIOMA	OTHER INDICATIONS
<p>IDH2m R/R <i>IDHIFA[®] Approved</i></p>	<p>IDH1m R/R <i>Ivosidenib Phase 3 (ClarIDHY) Ongoing</i></p>	<p>IDH1m <i>Ivosidenib & AG-881 Perioperative Study Ongoing</i></p>	<p>MYELODYSPLASTIC SYNDROMES</p>
<p>IDH1m R/R <i>Ivosidenib NDA Accepted</i></p>	<p>IDH1m R/R <i>Ivosidenib Phase 1 Enrollment Complete</i></p>	<p>IDH1m <i>Ivosidenib Phase 1 Enrollment Complete</i></p>	<p>IDHm R/R <i>Ivosidenib Phase 1 Enrollment Complete</i></p>
<p>IDH1m Frontline Non-IC <i>Ivosidenib + Aza Phase 3 (AGILE) Ongoing</i></p>		<p>IDH1m <i>AG-881 Phase 1 Enrollment Complete</i></p>	<p>CHONDROSARCOMAS</p>
<p>IDHm Frontline IC-Eligible <i>Ivo/Ena + 7+3 Phase 3 Q4 2018 Start</i></p>			<p>IDH1m R/R <i>Ivosidenib Phase 1 Enrollment Complete</i></p>
<p>IDHm Frontline Non-IC <i>Ivo/Ena + Aza Phase 1/2 Ongoing</i></p>			
<p>IDHm Frontline IC-Eligible <i>Ivo/Ena + 7+3 Phase 1b Ongoing</i></p>			



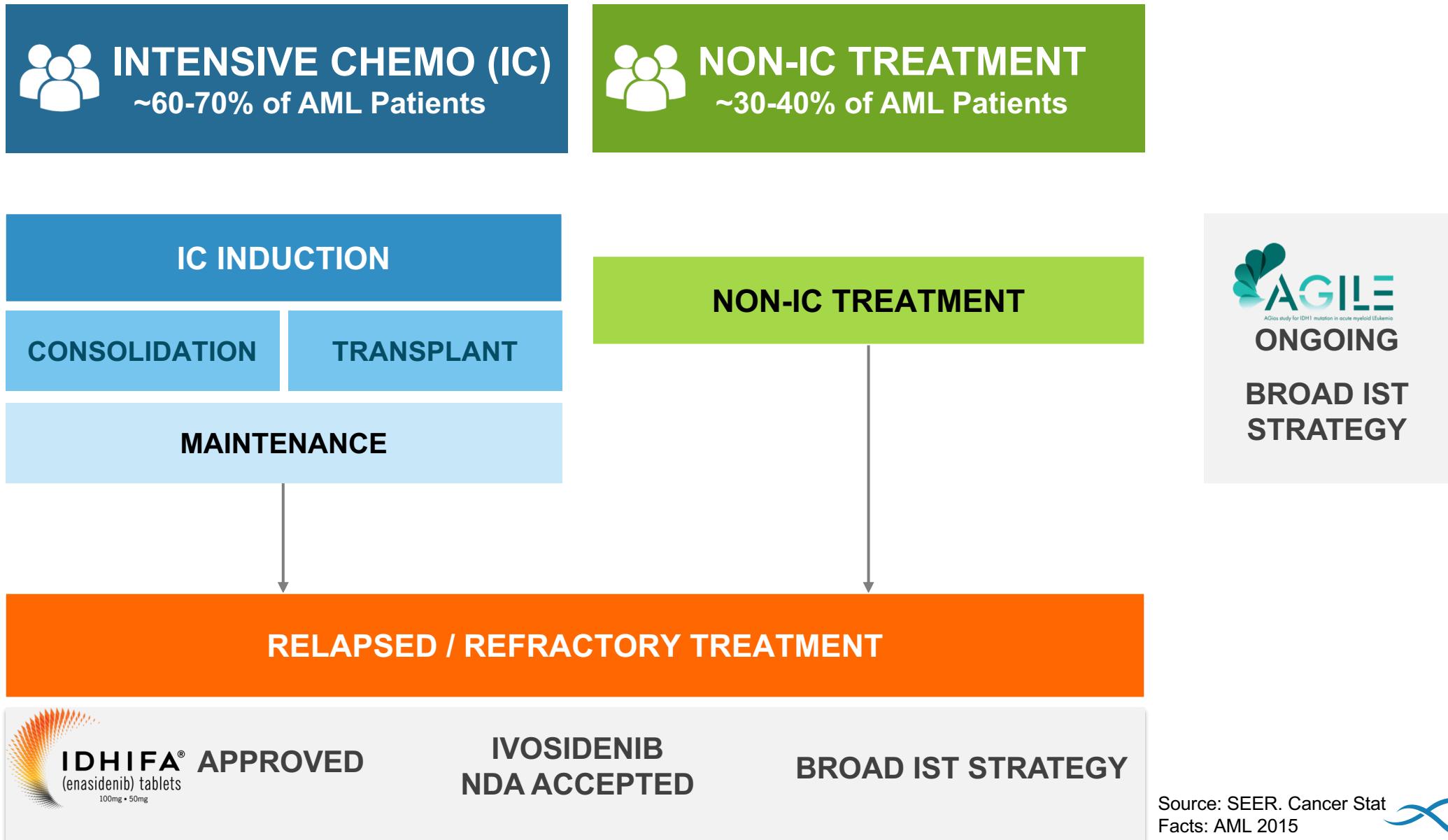
AML Landscape on the Brink of a Therapeutic Tidal Shift



Shifting the Treatment Paradigm for AML with Precision Medicine

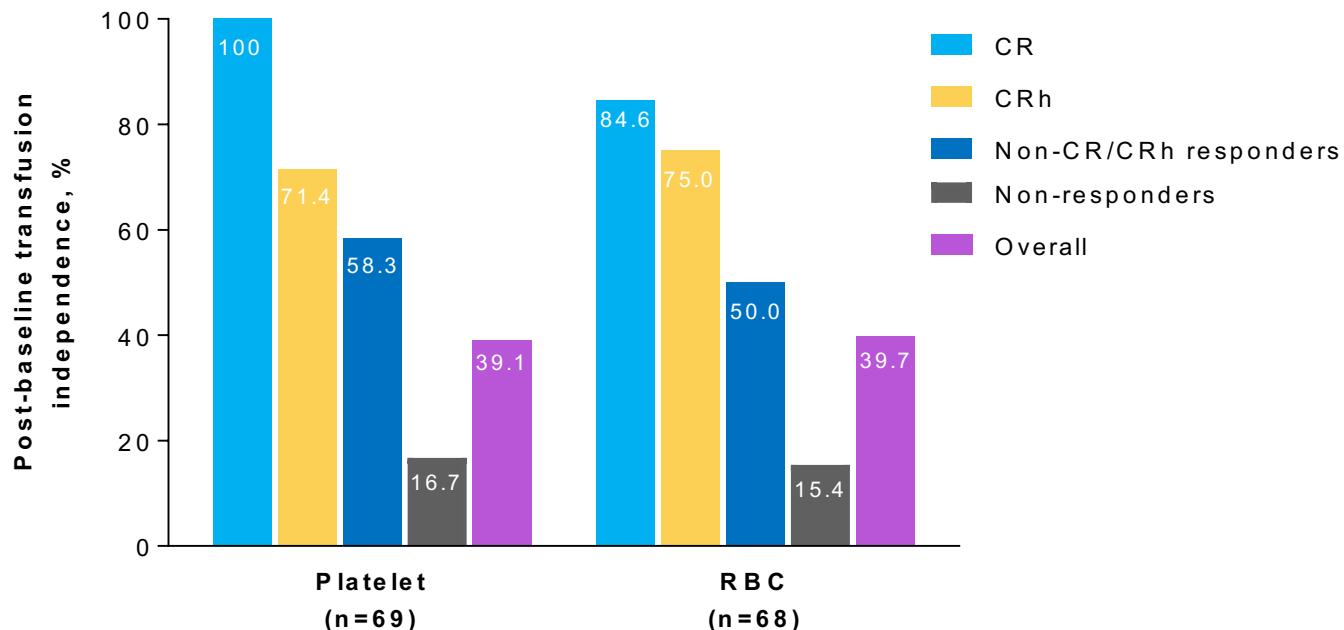


Clinical Development of IDHm Inhibitors Spans All Treatment Lines to Become Cornerstone of Treatment

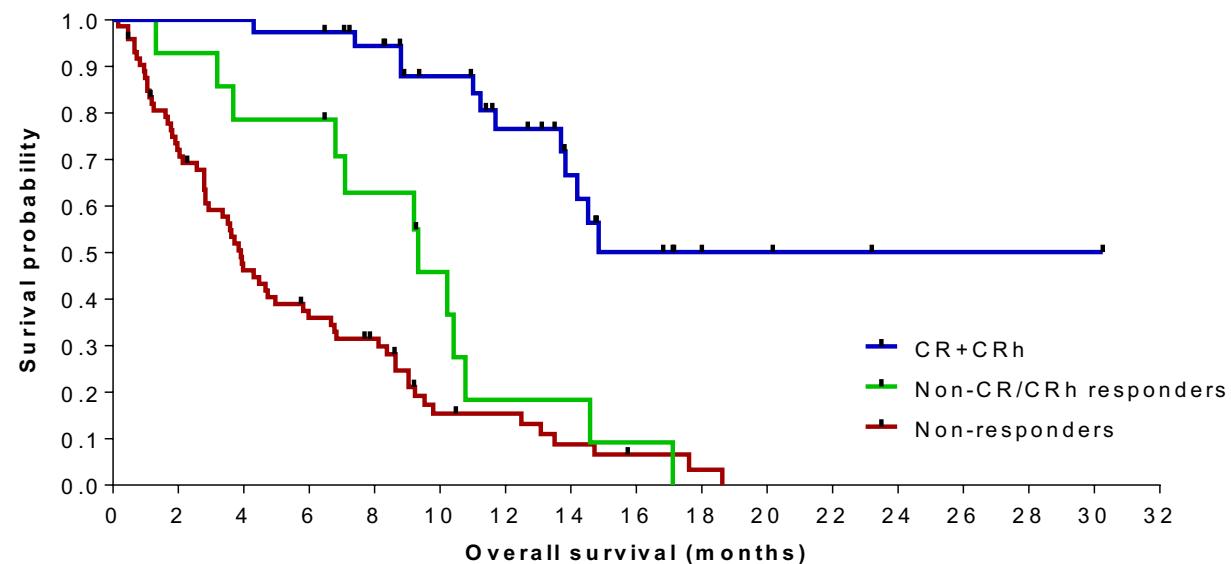


Ivosidenib Phase 1 R/R AML Data

Transfusion Independence Across All Response Categories



Overall Survival by Best Response in R/R AML (n=125)



Number of patients at risk:

38	38	38	37	32	25	19	13	8	5	4	3	1	1	1	1	0	CR
14	13	11	11	8	5	2	2	1	0								No
73	51	32	24	19	8	7	4	2	1	0							No

- Median OS 8.8 months overall
 - mOS for CR+CRh has not been reached
 - 9.3 months for non-CR+CRh responders
 - 3.9 months for non-responders
- Median follow-up, 14.8 months

Source: Data from ASH 2017

Data cutoff: 12May2017. CR, complete remission; CRh, CR with partial hematologic recovery; RBC, red blood cell

**30.4% CR+CRh rate w/ median duration of 8.2 months (125 patient primary analysis set);
Data to be updated at ASCO**



Ivosidenib Phase 1 – Response in Untreated AML and MDS

Characteristics	Response Rates	Untreated AML Arm 2 ^a (n=34)	MDS Arm 3 ^b (n=12)
Untreated AML = patients not eligible for standard of care	Overall Response Rate, n (%) [95% CI]	19 (55.9) [37.9, 72.8]	11 (91.7) [61.5, 99.8]
Median age (years)	Duration of response, median [95% CI] months	9.2 [1.9, NE]	NE [2.3, NE]
<ul style="list-style-type: none"> • Untreated AML – 76.5 • MDS – 72.5 	Duration of CR, median [95% CI] months	NE [5.6, NE]	NE [2.8, NE]
	Best response, n (%)		
	CR	7 (20.6)	5 (41.7)
	CRi/CRp	7 (20.6)	n/a
	PR	1 (2.9)	n/a
	MLFS/mCR	4 (11.8)	6 (50.0)
	SD	10 (29.4)	0
	PD	3 (8.8)	1 (8.3)
	NA	2 (5.9)	0

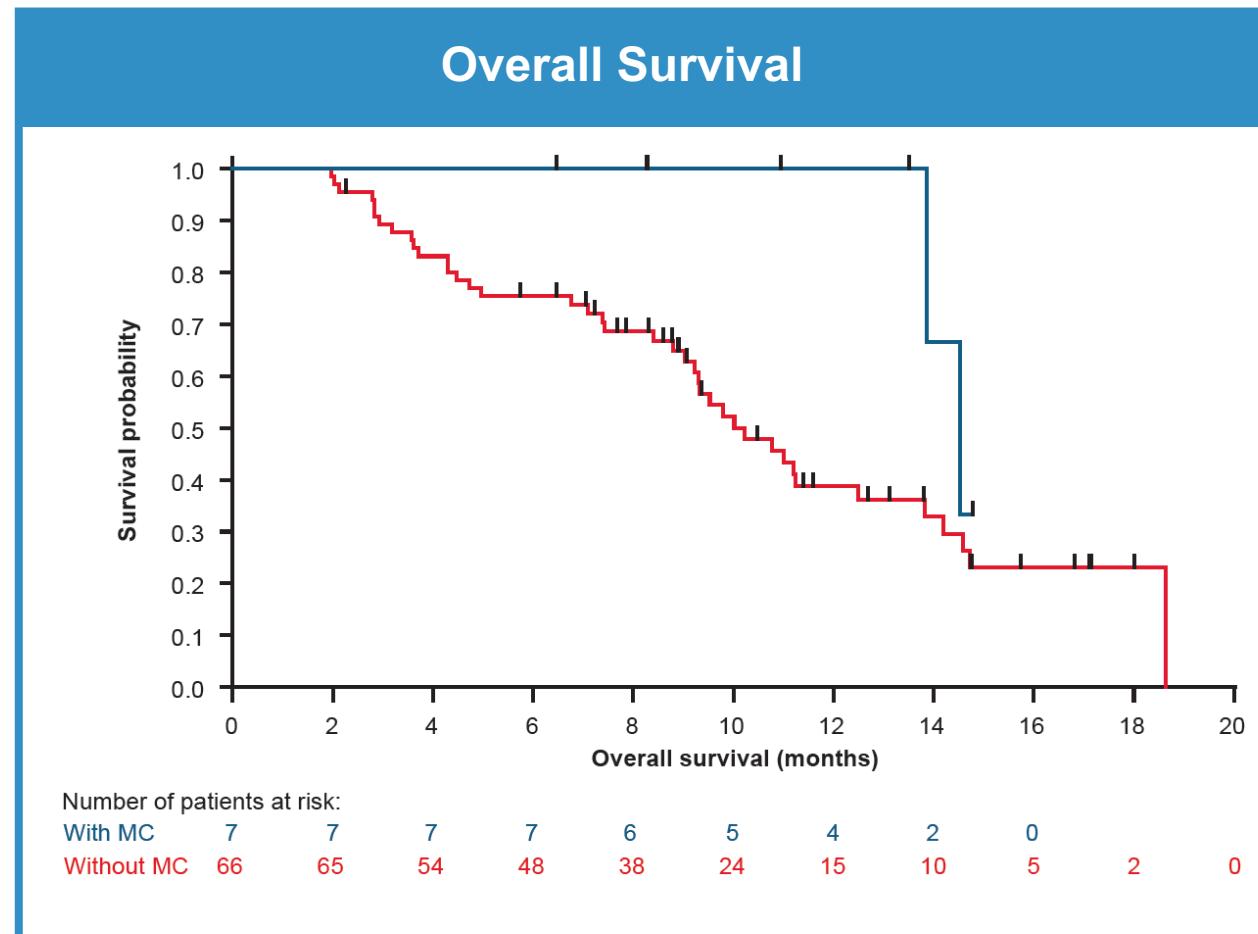
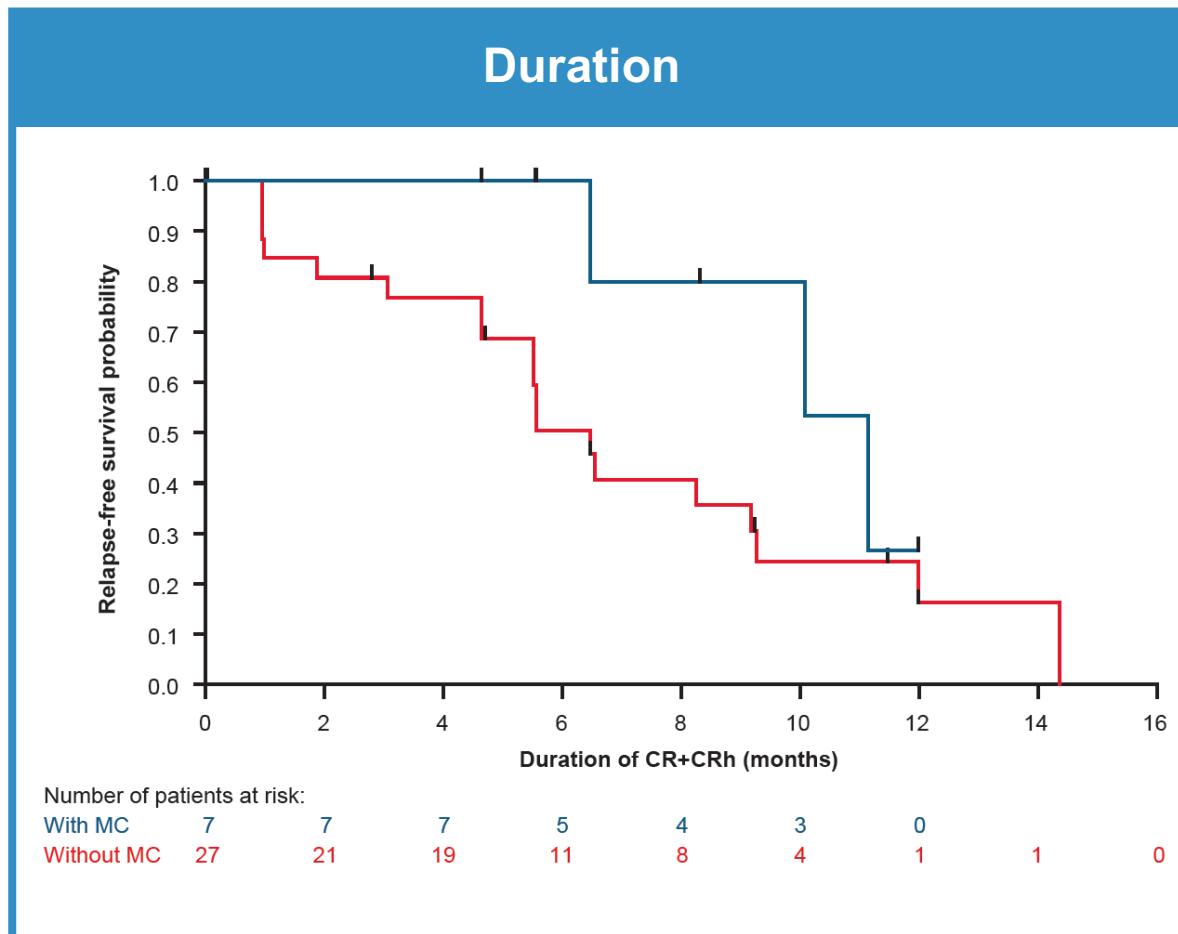
Source: Data from ASH 2017

^aUntreated AML patients not eligible for standard of care therapies in expansion Arm 2 and from dose escalation whose starting dose was 500 mg QD

^bMDS patients in expansion Arm 3 and from dose escalation whose starting dose was 500 mg QD



Molecular MRD-Negative CR Associated with Prolonged Duration of CR+CRh and Improved Overall Survival (R/R AML, BMNCs)



MC = Mutation Clearance, defined as the inability to detect the *MIDH1* variant allele (lower limit of detection for *MIDH1* alleles of 0.02–0.04% ($2-4 \times 10^{-4}$) from ≥ 1 on-study time point in a patient with detectable *MIDH1* at screening.

Duration of CR+CRh = date of first documented CR/CRh to date of first documented confirmed relapse or death

Overall survival = time from first dose to the date of death due to any cause

BMNC = bone marrow mononuclear cells

— With MC — Without MC | Censored



Potential for IDHm inhibitors in AML Frontline Setting: Encouraging Data from Ongoing Phase 1 Combination Trials



Ivosidenib plus 7+3 n=32

- Median age 60.5 years
- 69% (n=22) de novo AML
- Combination safe & well tolerated
- CR+ CRi/CRp rate for all patients = 77% (23 of 30)
- CR+CRi/CRp rate for de novo patients = 91% (19 of 21)

Updated data expected at ASH



Ivosidenib plus Azacitidine n=11

- Median age 76 years
- Combination safe & well tolerated
- ORR rate = 8 of 11
- CR rate = 4 of 11

Updated data at ASCO



Opportunity to Utilize Event-Free Survival (EFS) as Primary Endpoint



**“Improvement in EFS itself represents benefit to patients”
FDA ASH 2017**

- Recent FDA/EMA approval of treatment for newly diagnosed de novo AML based on EFS primary

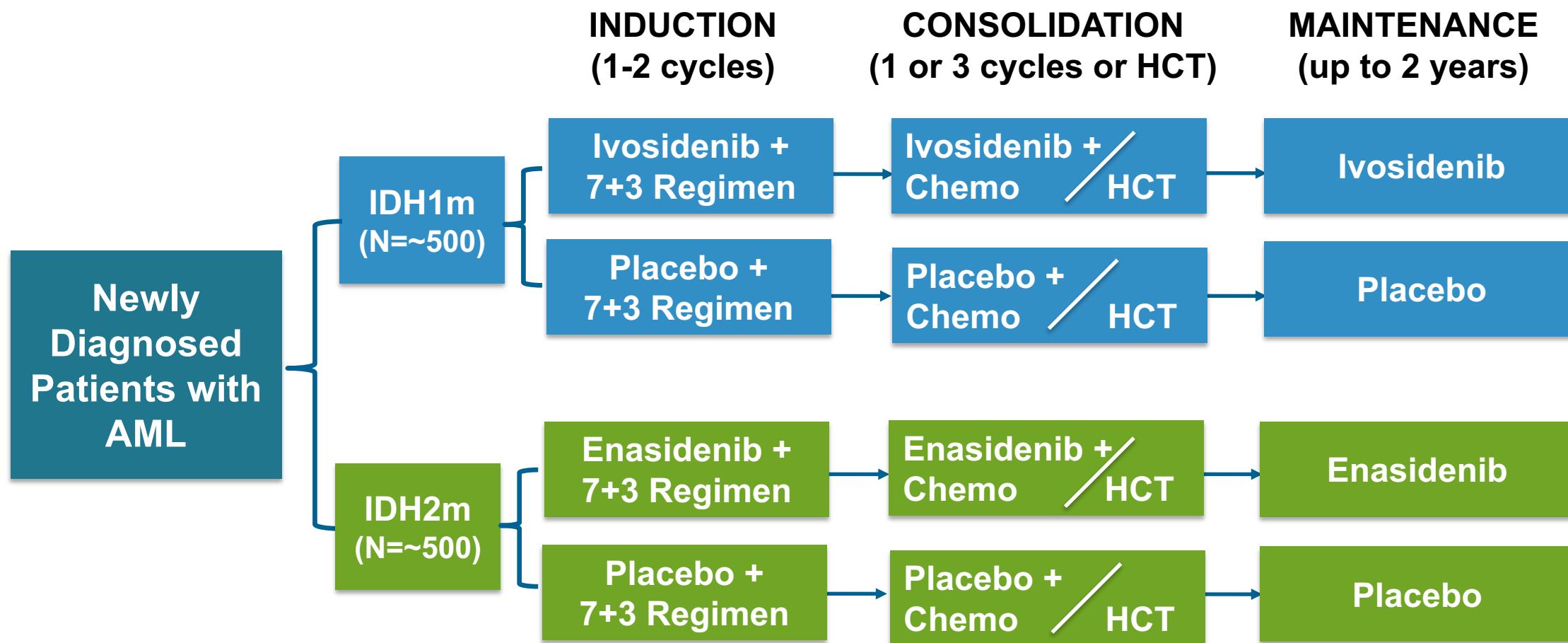


**Evaluating change of Phase 3
AGILE primary endpoint to EFS**

- Like OS, an EFS endpoint will reflect direct clinical benefit of ivosidenib but can be achieved faster than OS
- EFS endpoint enables patient cross-over and is not impacted by subsequent treatments



HO150 Phase 3 Intergroup Frontline AML Trial in Collaboration with Celgene Planned for Q4 2018



EFS = Event Free Survival

HCT = Hematopoietic Cell Transplantation

EFS primary endpoint; sponsored by HOVON and AML-SG

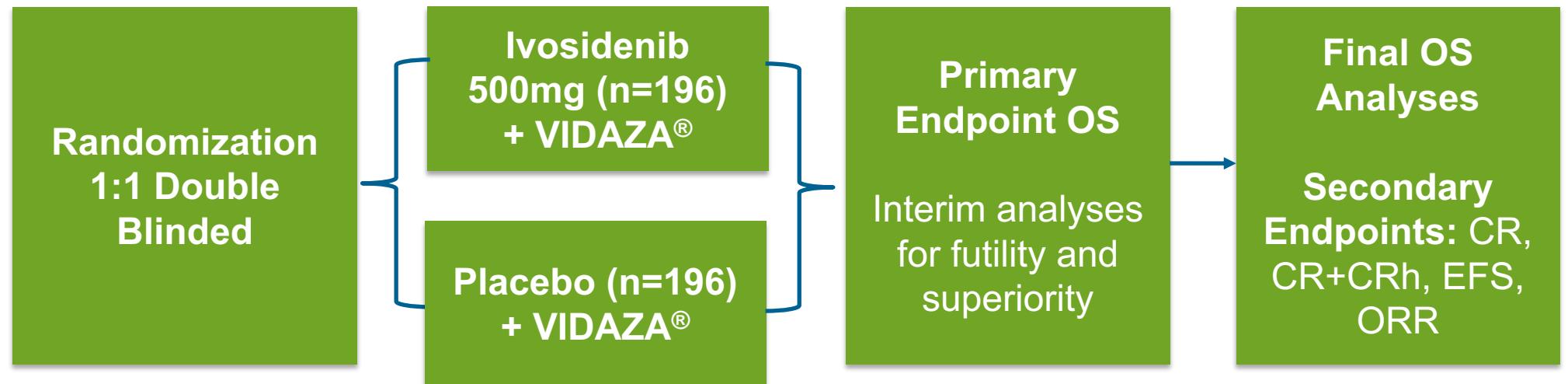


Phase 3 Frontline AGILE Ongoing



**Global Phase 3
Frontline
IC-Ineligible
IDH1m AML**

*Expect to complete
enrollment in 2021*



Executing a Broad IST Strategy

Trial Design	Line
Ongoing	
Venetoclax combination	R/R AML; potential frontline*
Beat AML master trial (+ VIDAZA®)**	Frontline AML
Planned	
Maintenance**	Frontline AML post stem cell transplant
VYXEOS™ combination	R/R AML
VYXEOS™ combination	Secondary AML
Gilteritinib combination**	R/R AML; potential frontline
MDS monotherapy**	Frontline and R/R AML
MEKi combination	R/R AML; potential frontline
ATRA combination	R/R AML; potential frontline

* potential to enroll patients who opt out of standard of care treatment or are otherwise considered ineligible

** Study includes ivosidenib and IDHIFA®

VIDAZA® is a registered trademark of Celgene Corporation

VYXEOS™ is a trademark of Jazz Pharmaceuticals





Updated data from expansion phase of the Phase 1 study of ivosidenib in IDH1m R/R AML accepted to ASCO

Updated data from the Phase 1/2 combo trial of enasidenib or ivosidenib with VIDAZA[®] in newly diagnosed AML accepted to ASCO

First clinical data from the Phase 1 study of AG-881 in advanced IDHm positive solid tumors, including glioma, accepted to ASCO





Ivosidenib Commercial Strategy in Acute Myeloid Leukemia

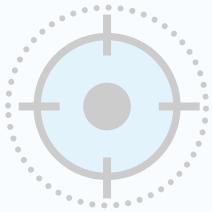
Steve Hoerter, Chief Commercial Officer



Building the Agios IDH Commercial Franchise



IDHIFA[®] commercial performance update

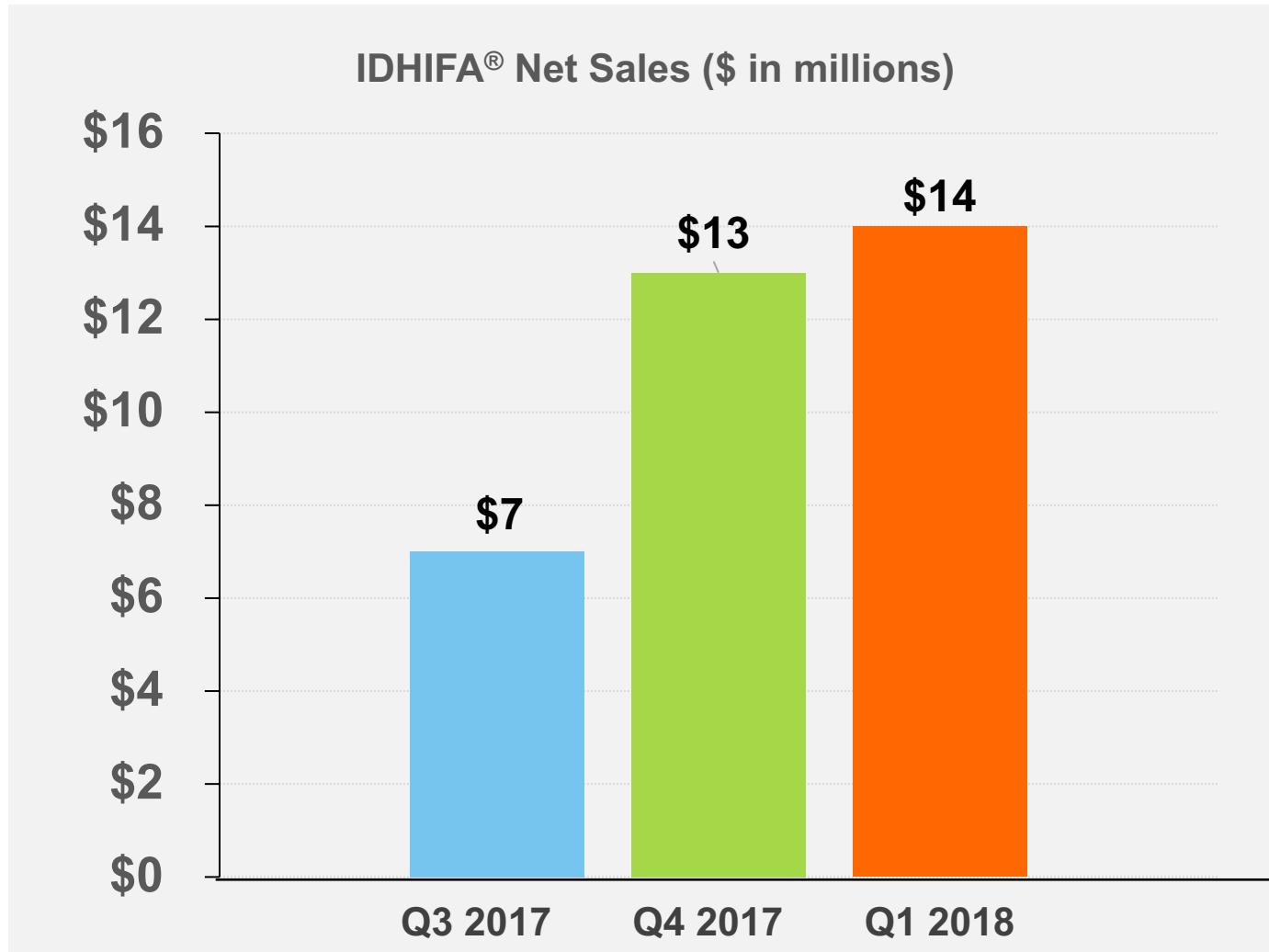


Scoping the IDH1 AML opportunity



Ivosidenib launch preparations

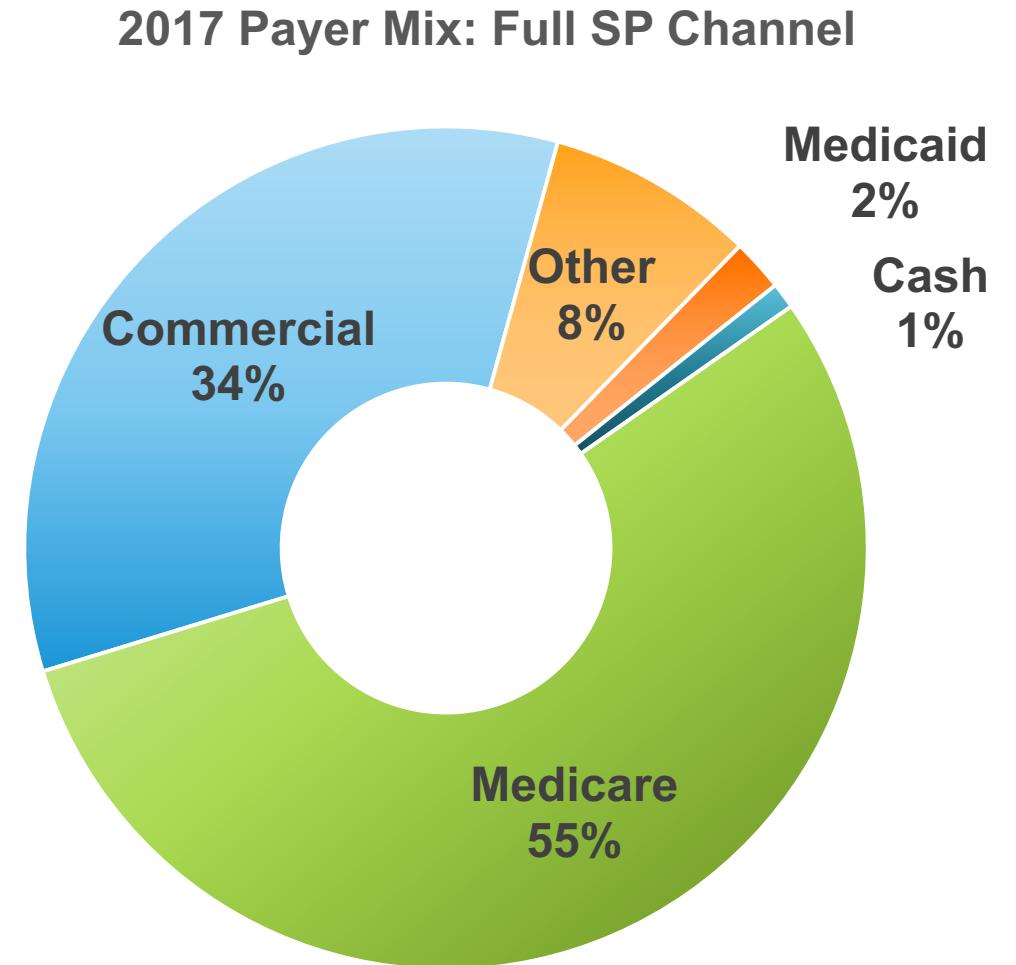
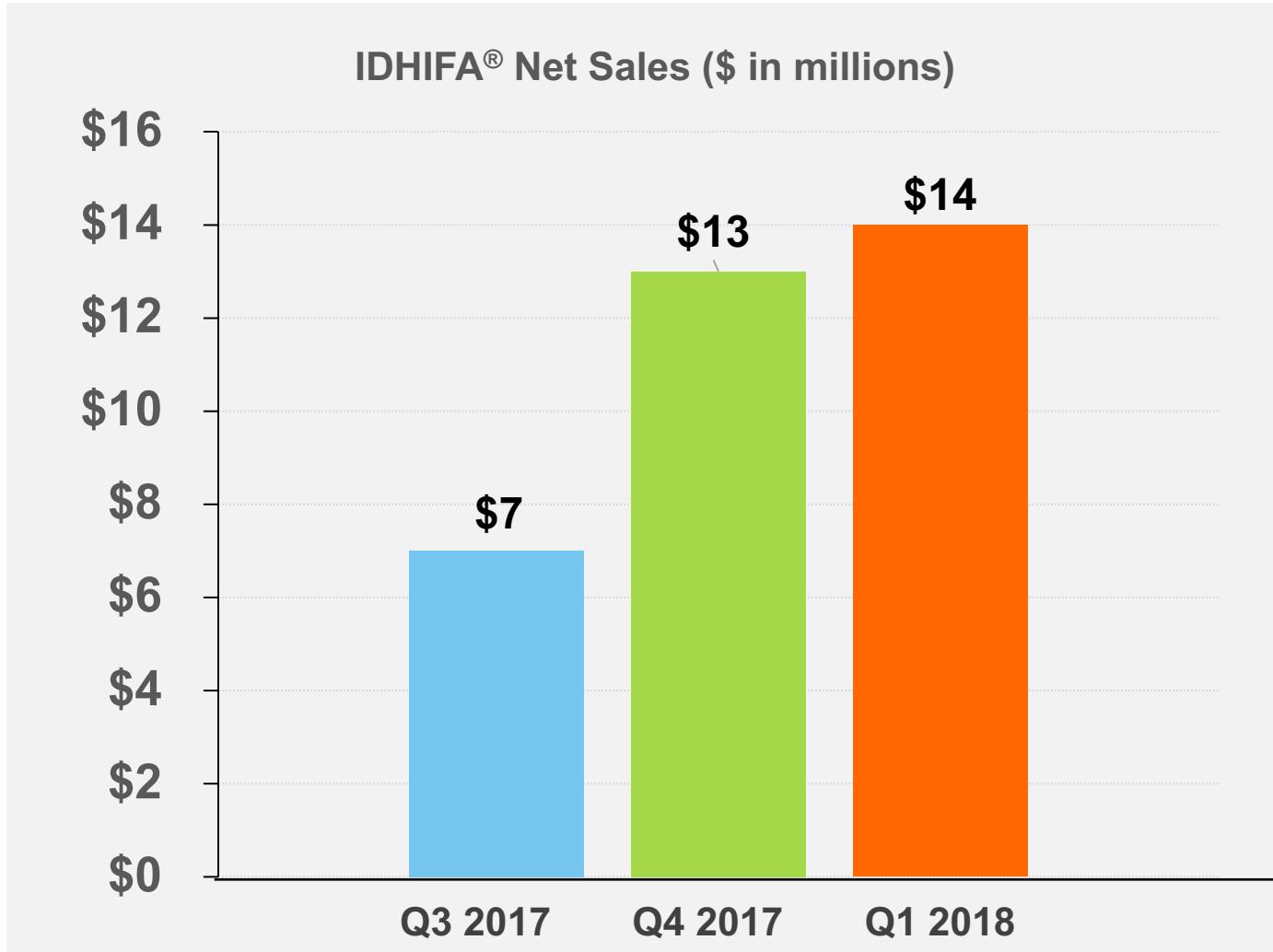
IDHIFA[®] Launch Performance



Revenues reported by Celgene; 2017 Payer Mix, Agios Estimates
IDHIFA[®] is a registered trademark of Celgene Corporation.



IDHIFA[®] Launch Performance



Revenues reported by Celgene; 2017 Payer Mix, Agios Estimates
IDHIFA[®] is a registered trademark of Celgene Corporation.



IDHIFA[®] Launch Metrics Are on Track

Sales

Diagnostic Testing

Prescriber Base

Awareness

Early IDHIFA[®] Success

2017 sales **\$20M**
(Q4 sales **\$13M**)

IDH2m testing at
~50% as of October

>250 unique
prescribers

IDHIFA[®] awareness of
~50% as of October

IDHIFA[®] Launch Metrics Update

2018 Q1 sales **\$14M**

IDH2m testing at
~70% as of January

>300 unique
prescribers

IDHIFA[®] awareness of
~60% as of January

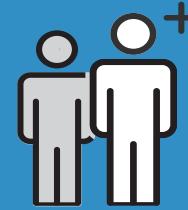


NCCN Treatment Guidelines Address IDHm+ AML



Molecular Testing

IDH1 and IDH2 molecular analyses recommended for workup of all AML cases



IDH2 Mutated AML

Enasidenib is recommended in patients with relapsed/refractory AML and an IDH2 mutation

Enasidenib added as an option in the first-line setting in patients who are not candidates for intensive remission induction therapy, or who decline intensive therapy

For patients who respond to first-line therapy with enasidenib, recommendation is to continue until disease progression

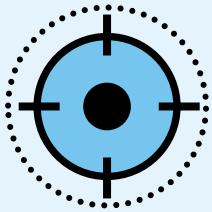
- Footnote added: Response to treatment with enasidenib may take 3-5 months
- Footnote added: Enasidenib increases the risk for differentiation syndrome and hyperleukocytosis that may require treatment with hydroxyurea and steroids



Building the Agios IDH Commercial Franchise



IDHIFA[®] commercial performance update

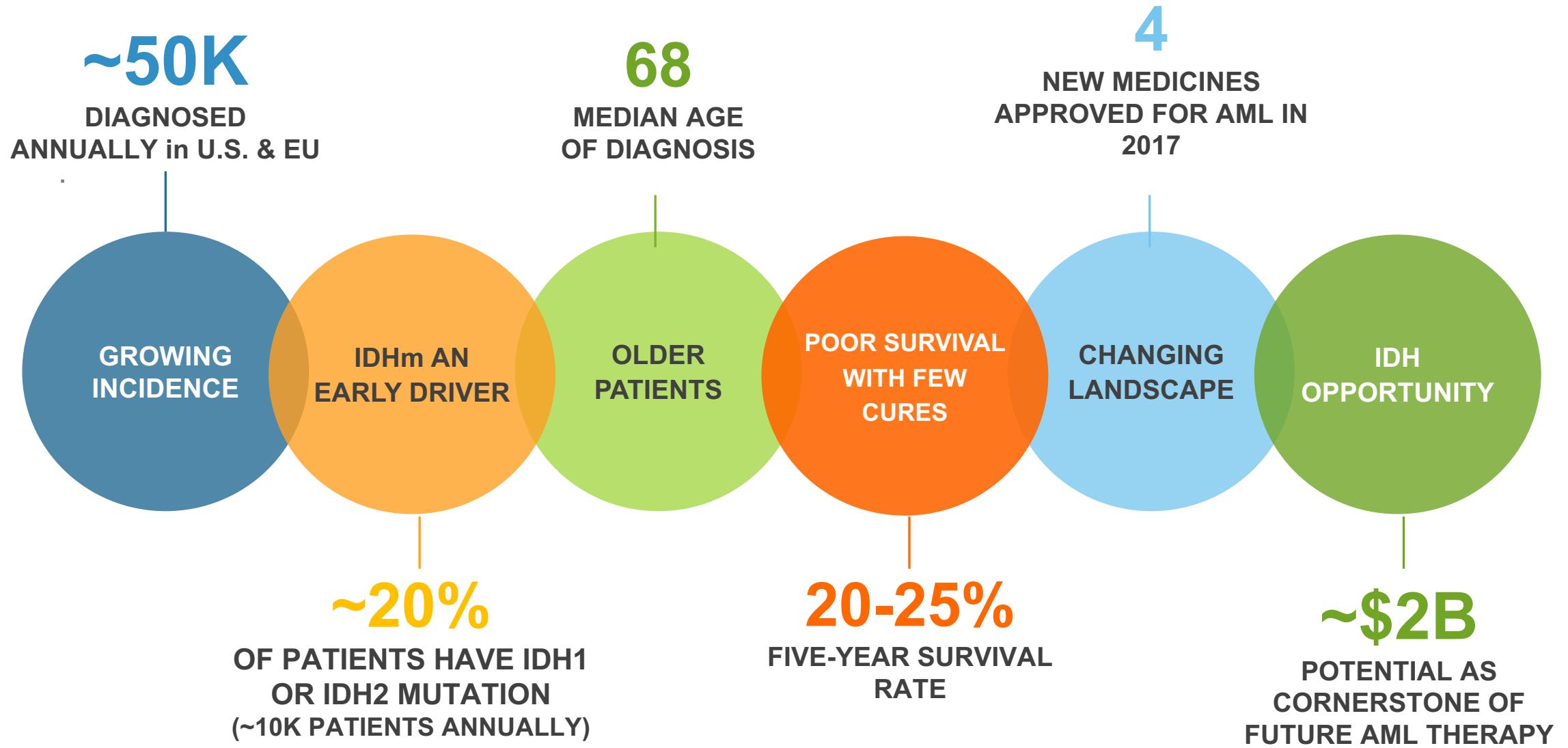


Scoping the IDH1 AML opportunity



Ivosidenib launch preparations

AML Landscape on the Brink of a Therapeutic Tidal Shift



New Medicines to Treat AML: Great News for Patients

Pre-2017

Fit for Intensive
Chemotherapy

Not Fit for Intensive
Chemotherapy

Treatments based on patients
eligibility (or not) for intensive
chemotherapy

Today & The Future



Targeted treatments offering
personalized approach

MYLOTARG™
gemtuzumab ozogamicin INJECTION
FOR IV INFUSION
4.5 mg single-dose vial

Vyxeos™
daunorubicin and cytarabine
liposome for injection

Unselected treatments that offer
improvements over current SoC



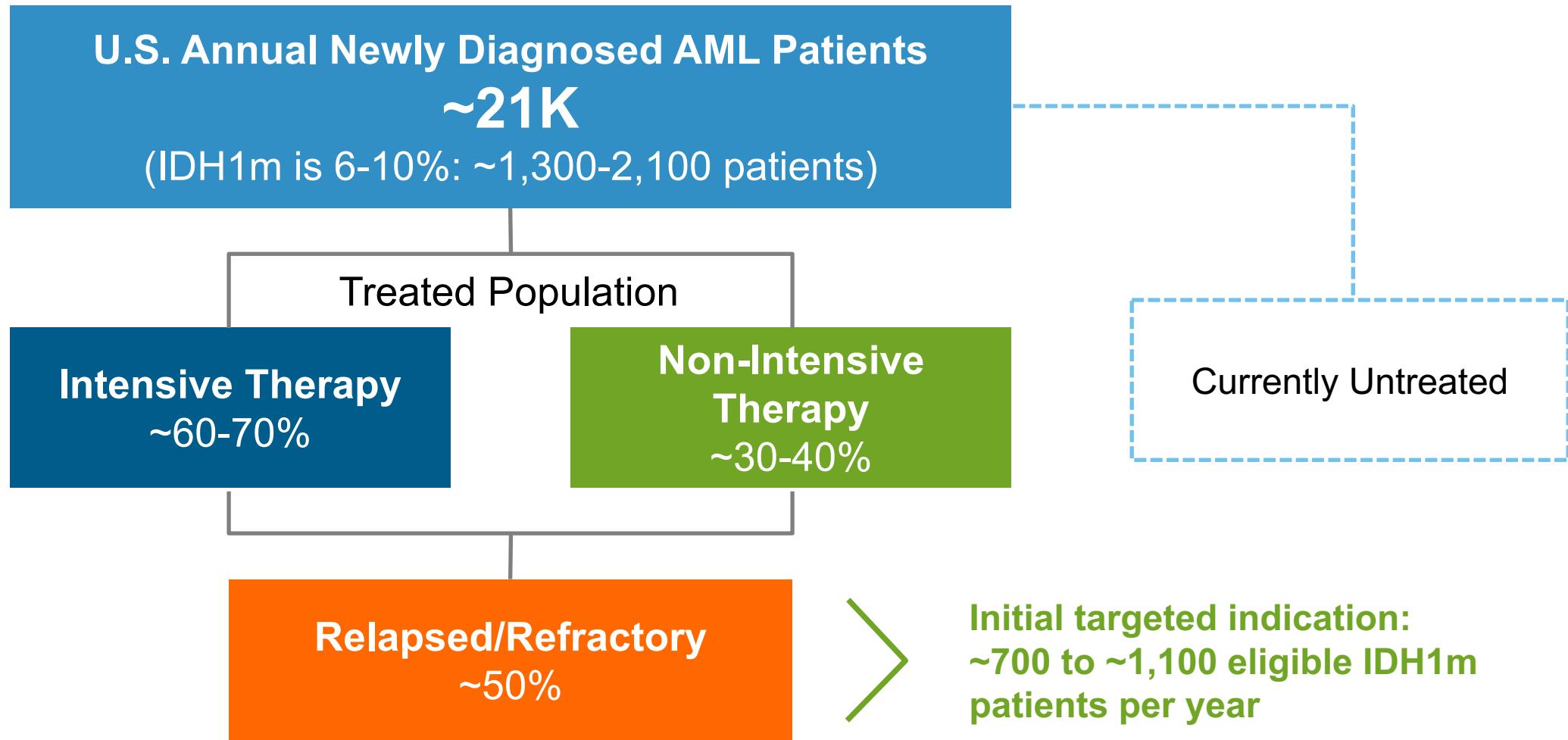
How We Taught Ourselves to Pronounce Ivosidenib

 **vō**  **den' ib**

How We Taught Ourselves to Pronounce Ivosidenib



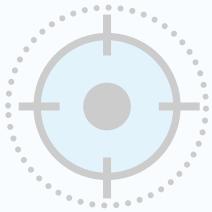
U.S. AML Epidemiology and Treatment Approach – IDH1 Opportunity



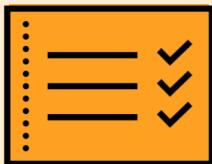
Building the Agios IDH Commercial Franchise



IDHIFA[®] commercial performance update



Scoping the IDH1 AML opportunity

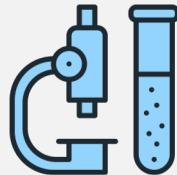


Ivosidenib launch preparations

Strategic Imperatives for the TIBSOVO® Launch



**Physicians test
for IDH1m**



**TIBSOVO® is
recognized as
the best option
for IDH1m+
R/R AML**

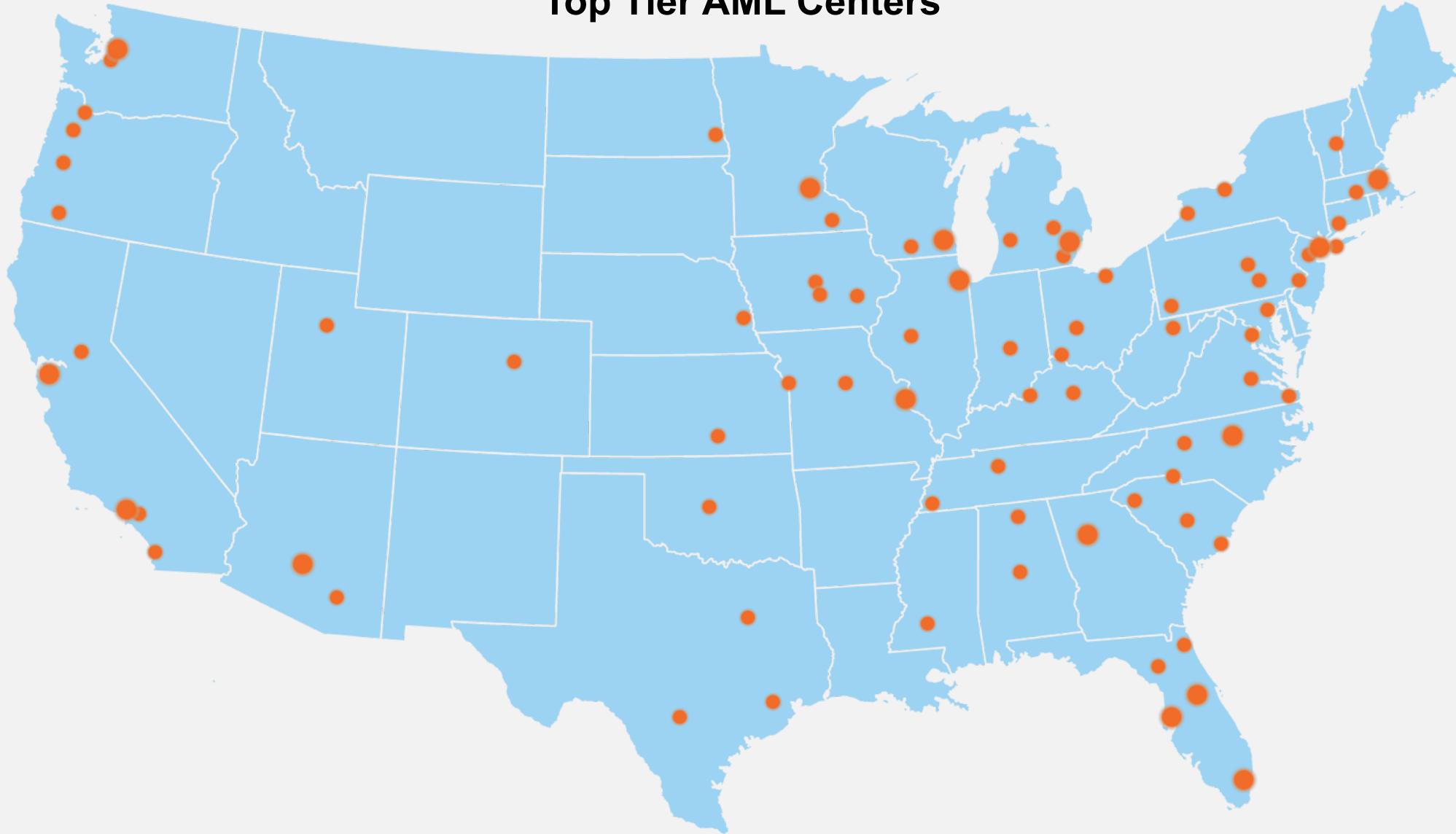


**Patients have
access to
TIBSOVO®**



Sales Team Deployed to Cover Prescriber Base

Top Tier AML Centers



Our Approach to Patient Access is Multifaceted

Patient Access



Distribution Channel

Limited specialty
pharmacy network

Hospital accounts
serviced via specialty
distributors



Patient Services

Copay card for commercial
patients

Patient Assistance Program

Commercial insurance
coverage interruption

Referrals to independent
third-parties for additional
support



Payer Education

Expert field payer team

Focus on education &
payer resources

Educate on disease
burden

Address payer concerns





[Home](#)

[Financial assistance](#)

[Distribution network](#)

[Enroll now](#)

[Resources](#)



Welcome to myAgios™

Patient Support Services



Financial assistance programs



Network of specialty pharmacy and distribution partners



Enroll now

We are Launch Ready, Thanks to a Great Team





IDH1m Inhibition in Solid Tumors

Susan Pandya, M.D., Senior Medical Director



IDH1 Mutation Present in Multiple Solid Tumors

CHOLANGIOCARCINOMA
~14% have IDH1 mutation
~3,000 IDH1m patients

IDH1m R/R
*Ivosidenib Phase 3
(ClarIDHY) Ongoing*

IDH1m R/R
*Ivosidenib Phase 1
Enrollment Complete*

LOW GRADE GLIOMA
~80% have IDH1 mutation
~9,000 IDH1m patients

IDH1m
*Ivosidenib & AG-881 Perioperative Study
Ongoing*

IDH1m
*Ivosidenib
Phase 1 Enrollment Complete*

IDH1m
*AG-881
Phase 1 Enrollment Complete*

IDH1m
Natural History of Tumor Volume

CHONDROSARCOMAS
~50% have IDH1 mutation
~900 IDH1m patients

IDH1m R/R
*Ivosidenib Phase 1
Enrollment Complete*

Sources: Amary MF et al. J Pathol 2011;224:334-43, Epiphany Partners Epic Oncology, DC National Program of Cancer Registries (NPCR); Borger DR et al. Oncologist 2012;17:72-9.; Kipp BR et al. Hum Pathol 2012;43:1552-8.; Goyal L et al. Oncologist 2015;20:1019-27. SEER. Cancer Stat Facts, CBTRUS (Central Brain Tumor Registry in the US); Neurosurg Focus. 2015 Jan; 38(1): E6.



The Story of IDH Inhibition in Solid Tumors is Evolving

2012

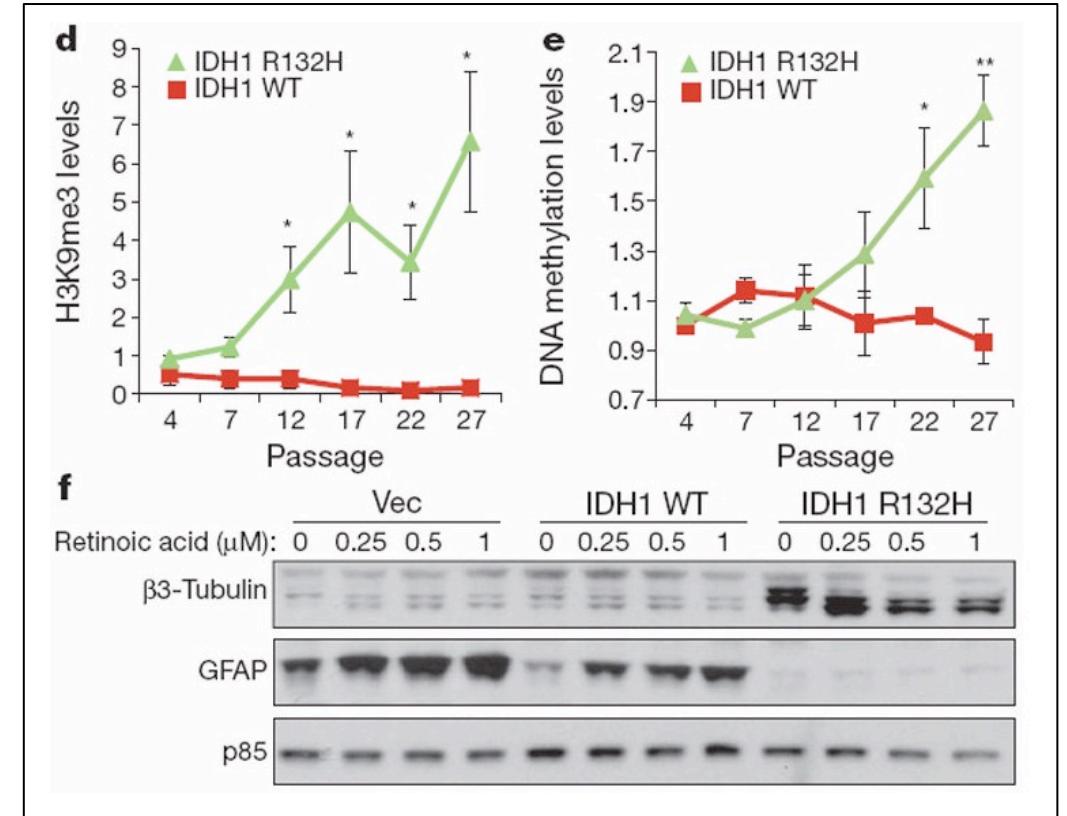
 **NIH Public Access**
Author Manuscript
Nature. Author manuscript; available in PMC 2012 October 23.

Published in final edited form as:
Nature. ; 483(7390): 474–478. doi:10.1038/nature10860.

IDH mutation impairs histone demethylation and results in a block to cell differentiation

Chao Lu^{1,2}, Patrick S. Ward^{1,2}, Gurpreet S. Kapoor³, Dan Rohle^{4,5}, Sevin Turcan⁴, Omar Abdel-Wahab^{4,6}, Christopher R. Edwards⁷, Raya Khanin⁸, Maria E. Figueroa⁹, Ari Melnick⁹, Kathryn E. Weller², Donald M. O'Rourke^{3,10}, Shelley L. Berger⁷, Timothy A. Chan⁴, Ross L. Levine^{4,6}, Ingo K. Mellinghoff^{4,5,11}, and Craig B. Thompson¹

NIH-PA Author Manuscript



The Story of IDH Inhibition in Solid Tumors is Evolving

2012 2013 - 2014

Science

An Inhibitor of Mutant IDH1 Delays Growth and Promotes Differentiation of Glioma Cells

Dan Rohle, Janeta Popovici-Muller, Nicolaos Palaskas, Sevin Turcan, Christian Grommes, Carl Campos, Jennifer Tsoi, Owen Clark, Barbara Oldrini, Evangelia Komisopoulou, Kaiko Kunii, Alicia Pedraza, Stefanie Schalm, Lee Silverman, Alexandra Miller, Fang Wang, Hua Yang, Yue Chen, Andrew Kernytsky, Marc K. Rosenblum, Wei Liu, Scott A. Biller, Shinsan M. Su, Cameron W. Brennan, Timothy A. Chan, Thomas G. Graeber, Katharine E. Yen and Ingo K. Mellinghoff

Science **340** (6132), 626-630.

DOI: 10.1126/science.1236062 originally published online April 4, 2013

LETTER

doi:10.1038/nature13441

Mutant IDH inhibits HNF-4 α to block hepatocyte differentiation and promote biliary cancer

Supriya K. Saha^{1*}, Christine A. Parachoniak^{1*}, Krishna S. Ghanta¹, Julien Fitamant¹, Kenneth N. Ross¹, Mortada S. Najem¹, Sushma Gurumurthy¹, Esra A. Akbay², Daniela Sia^{3,4,5}, Helena Cornella³, Oriana Miltiadous⁴, Chad Walesky⁶, Vikram Deshpande¹, Andrew X. Zhu¹, Aram F. Hezel⁷, Katharine E. Yen⁸, Kimberly S. Straley⁸, Jeremy Travins⁸, Janeta Popovici-Muller⁸, Camelia Gliser⁸, Cristina R. Ferrone¹, Udayan Apte⁶, Josep M. Llovet^{3,4,9,10}, Kwok-Kin Wong², Sridhar Ramaswamy^{1,11} & Nabeel Bardeesy¹



The Story of IDH Inhibition in Solid Tumors is Evolving

2012

2013 - 2014

2014 - Present

OncoImmunology 3:12, e974392; December 2014; © 2014 Taylor & Francis Group, LLC

AUTHOR'S VIEW

Mutant IDH1: An immunotherapeutic target in tumors

Theresa Schumacher^{1,2}, Lukas Bunse^{1,2}, Wolfgang Wick^{1,3}, and Michael Platten^{1,2,*}

Neuro-Oncology

Neuro-Oncology 18(10), 1402–1412, 2016
doi:10.1093/neuonc/now061
Advance Access date 25 April 2016

IDH mutant gliomas escape natural killer cell immune surveillance by downregulation of NKG2D ligand expression

Xiaoran Zhang[†], Aparana Rao[†], Paola Sette, Christopher Deibert, Alexander Pomerantz, Wi Jin Kim, Gary Kohanbash, Yigang Chang, Yongseok Park, Johnathan Engh, Jaehyuk Choi, Timothy Chan, Hideho Okada, Michael Lotze, Paola Grandi, and Nduka Amankulor

CSH PRESS Genes & Development

Mutant IDH1 regulates the tumor-associated immune system in gliomas

Nduka M. Amankulor¹, Youngmi Kim², Sonali Arora², Julia Kargl^{2,3,4}, Frank Szulzewsky², Mark Hanke^{2,3}, Daciana H. Margineantu^{2,3}, Aparna Rao¹, Hamid Bolouri^{2,5}, Jeff Delrow⁶, David Hockenbery^{2,3}, A. McGarry Houghton^{2,3,7} and Eric C. Holland^{2,5}

frontiers in Molecular Neuroscience ORIGINAL RESEARCH published: 28 March 2018 doi: 10.3389/fnmol.2018.00082

The IDH1 Mutation-Induced Oncometabolite, 2-Hydroxyglutarate, May Affect DNA Methylation and Expression of PD-L1 in Gliomas

Luyan Mu^{1,2}, Yu Long^{1,3}, Changlin Yang³, Linchun Jin^{1,3}, Haipeng Tao^{1,3}, Haitao Ge¹, Yifan E. Chang^{3†}, Aida Karachi³, Paul S. Kubilis³, Gabriel De Leon^{3†}, Jiping Qi⁴, Elias J. Sayour³, Duane A. Mitchell³, Zhiguo Lin^{1*} and Jianping Huang^{3*}



Opportunity for an IDH1m Inhibitor in Solid Tumors

- Frequency of IDH1 mutation in a variety of solid tumors + unmet need in these indications = opportunity to make a difference in the treatment paradigm for these patients
- Active clinical development plans in cholangiocarcinoma & glioma
- Understanding the IDH mutation's role in the treatment of solid tumors is evolving
- Opportunity for IO combinations



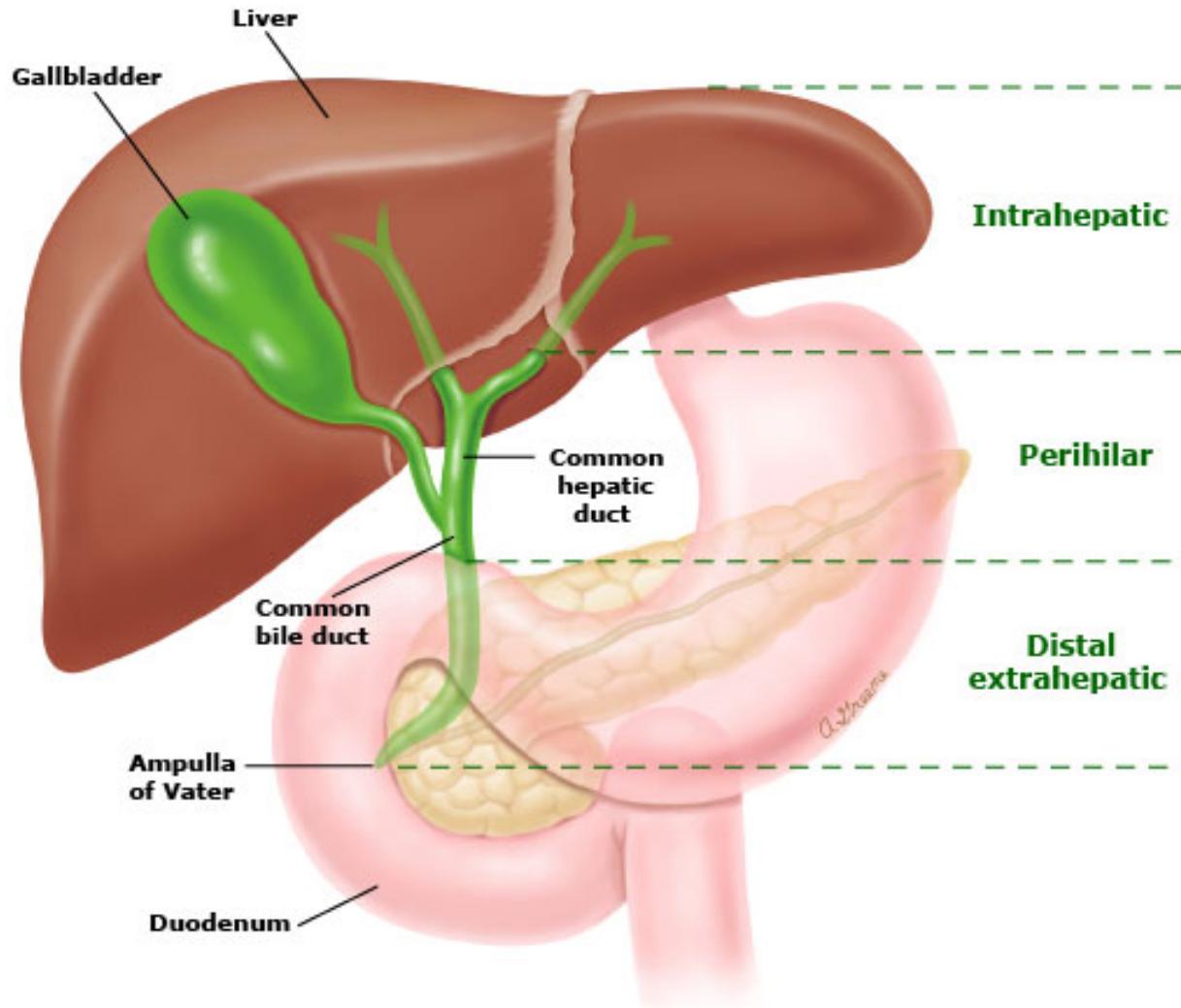


Cholangiocarcinoma

Maeve Lowery, M.B., B.Ch., B.A.O., Trinity
College Dublin



Cholangiocarcinoma a Devastating Disease with No Approved Targeted Therapies



Symptoms:

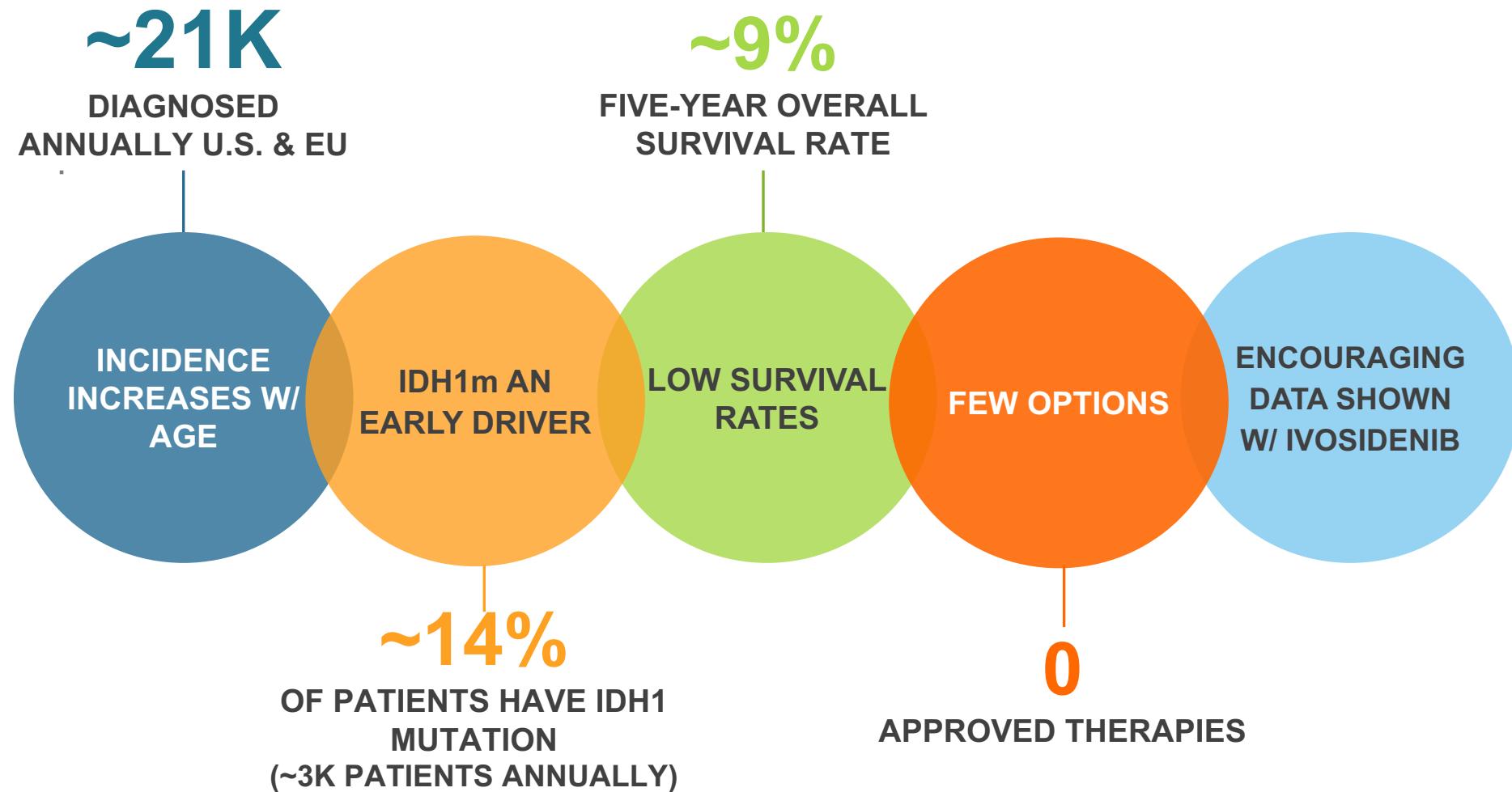
- Abdominal pain (30-50%)
- Weight loss (30-50%)
- Fever (20%)
- Itching
- Jaundice

Increase in laboratory tests:

- Alkaline phosphatase
- GGT
- Total (direct) bilirubin
- AST/ALT
- CA 19-9 (elevated in ~65% cholangiocarcinoma)



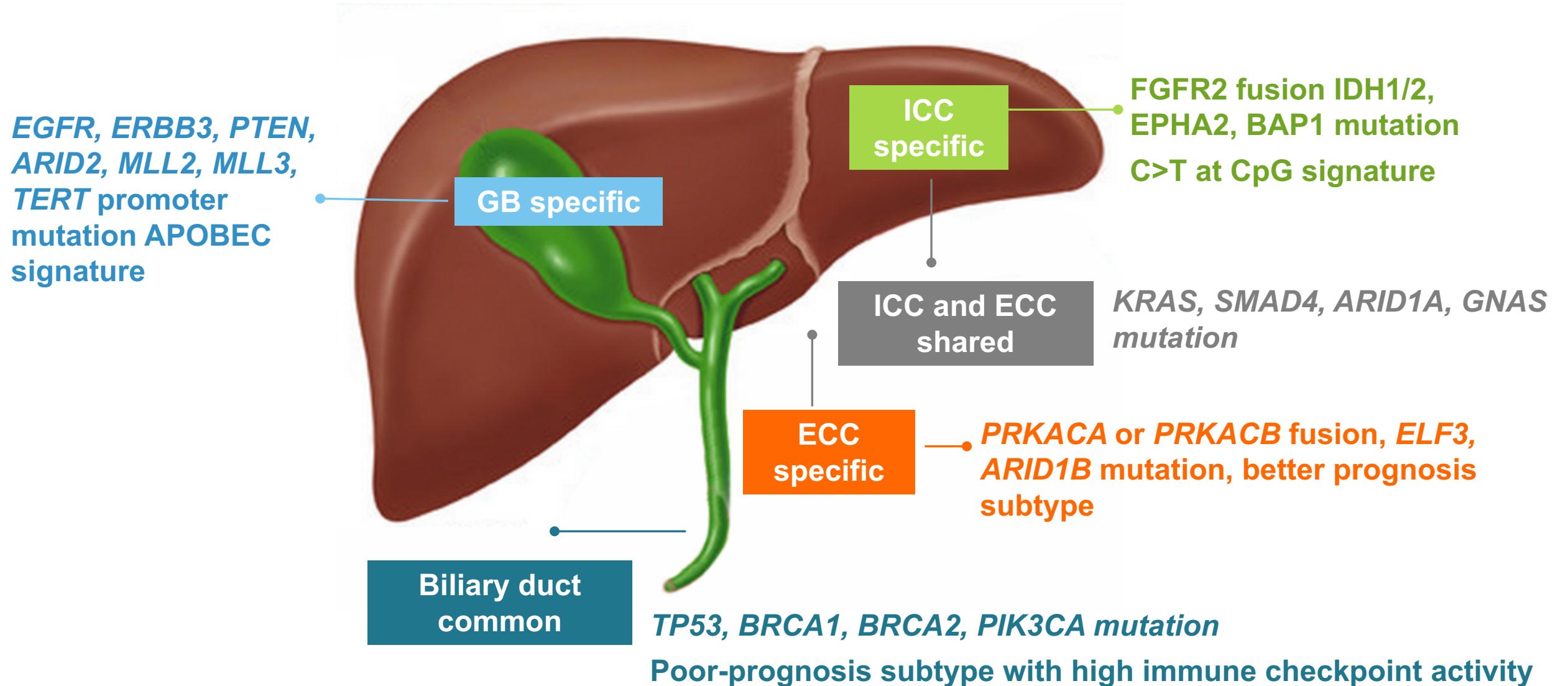
Cholangiocarcinoma a Devastating Disease with No Approved Targeted Therapies



Sources: CDC National Program of Cancer Registries (NPCR); Epiphany Partners Epic Oncology; Decision Resources; Market Research; Borger DR et al. Oncologist 2012;17:72-9.; Kipp BR et al. Hum Pathol 2012;43:1552-8.; Goyal L et al. Oncologist 2015;20:1019-27.



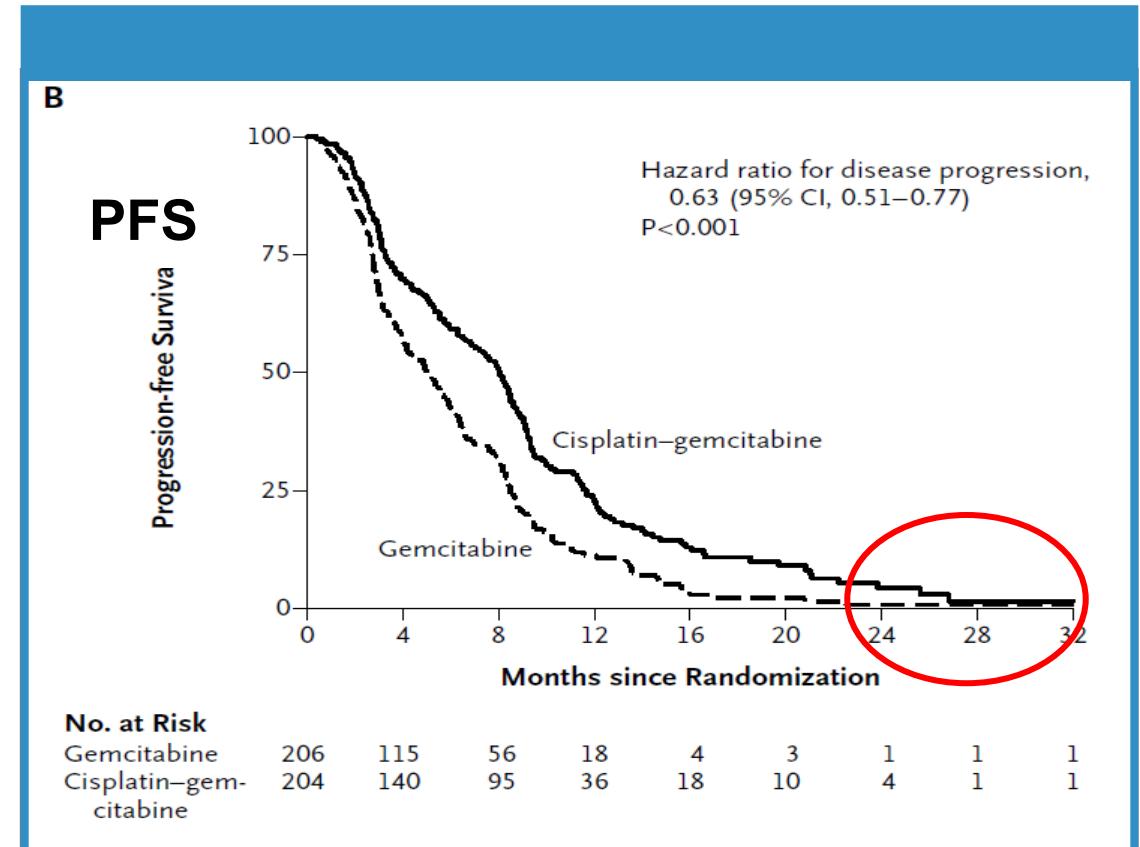
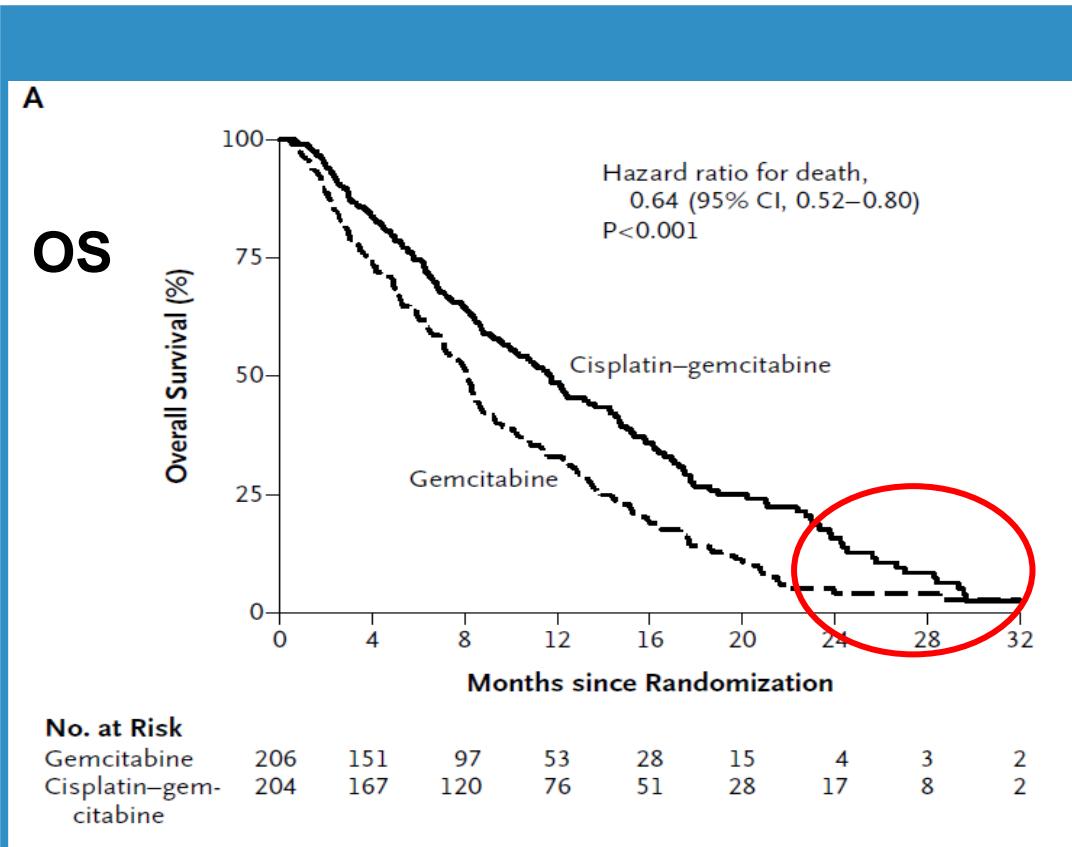
Genetic Alterations in Biliary Tract Cancer



Current Treatments are Limited to Chemotherapy-Based Regimens

Phase 3 ABC-02 Gemcitabine and Cisplatin – standard of care for newly diagnosed metastatic disease

- OS – 11.7 months Gem/Cis vs. 8 months for Gem alone
- PFS – 8 months for Gem/Cis vs. 5 months for Gem alone



Outcomes with Second Line Chemotherapy Remain Poor and Highlight Need for Novel Treatments

- Median PFS range is 2-3 months and PFS6 is 10-25%
- No available historic placebo PFS benchmark

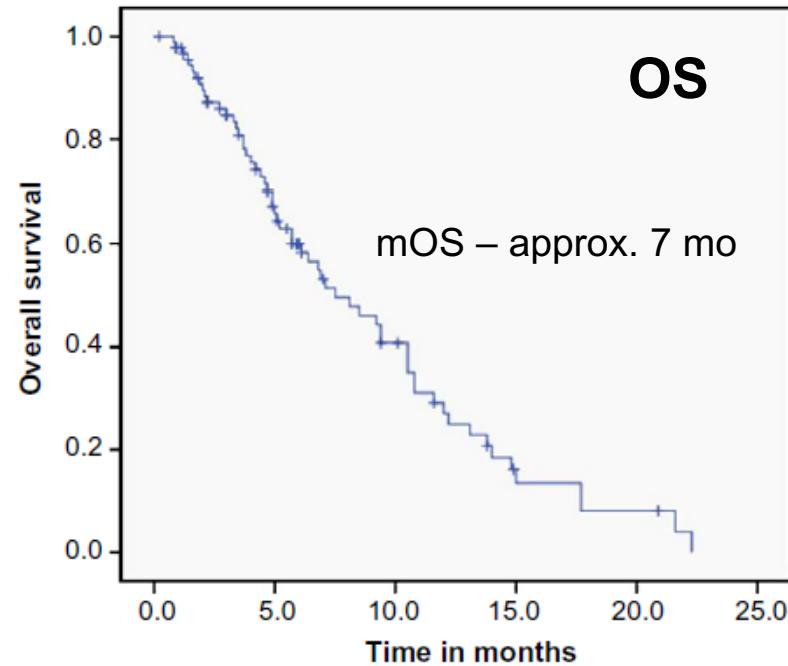


Fig. 2. Overall survival curves from the beginning of second-line chemotherapy in patients with advanced biliary tract cancer.

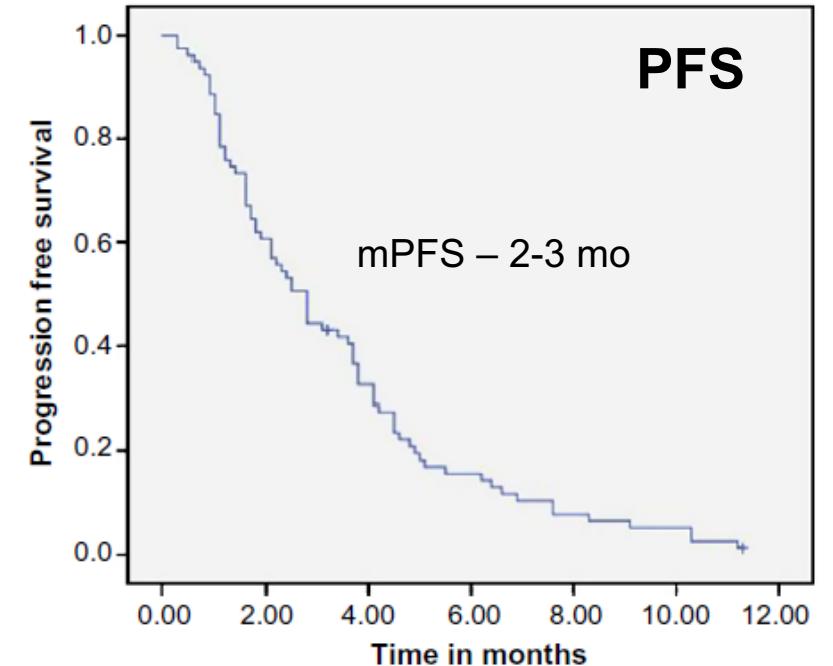
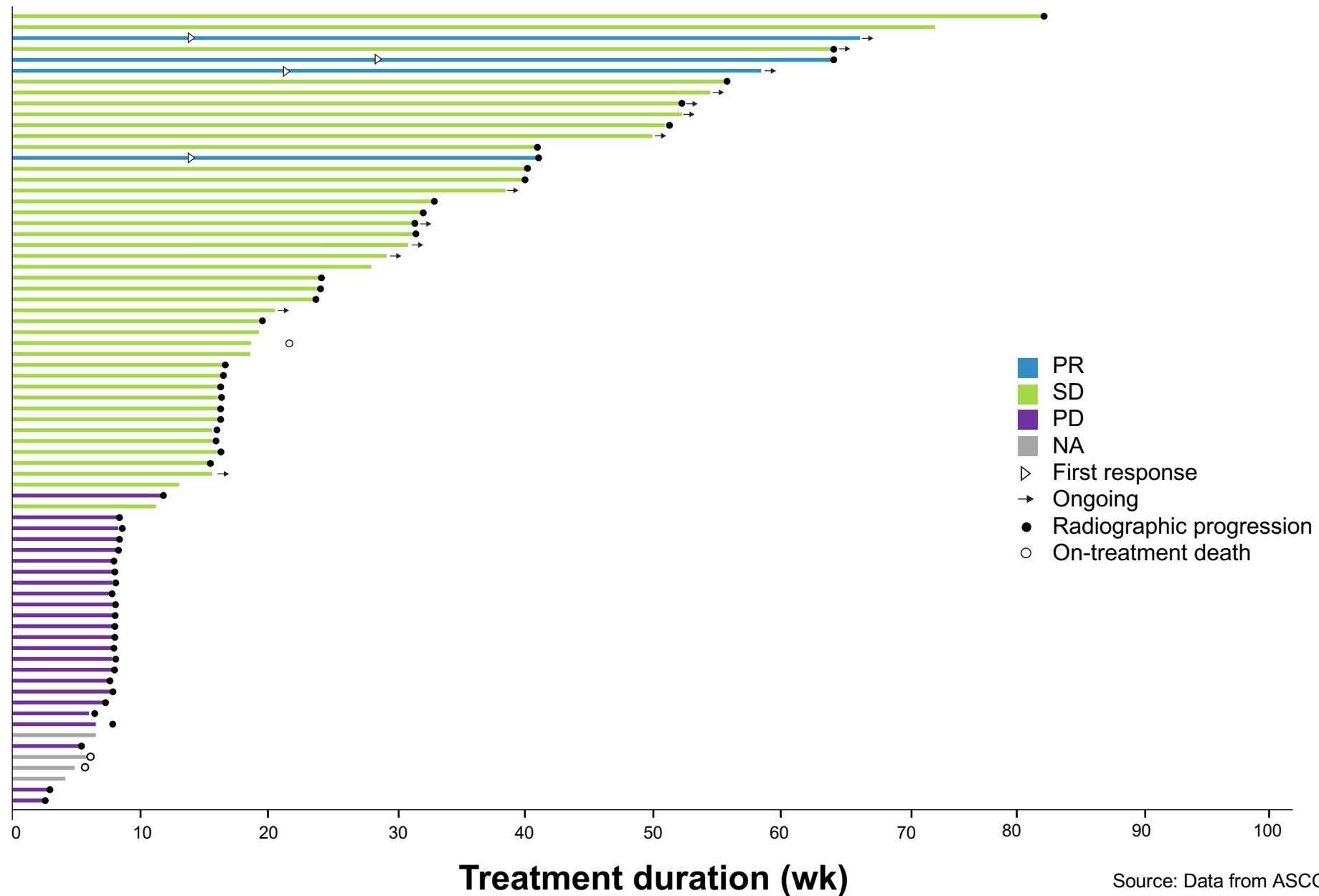


Fig. 1. Progression free survival curve from the beginning of second-line chemotherapy in patients with advanced biliary tract cancer.



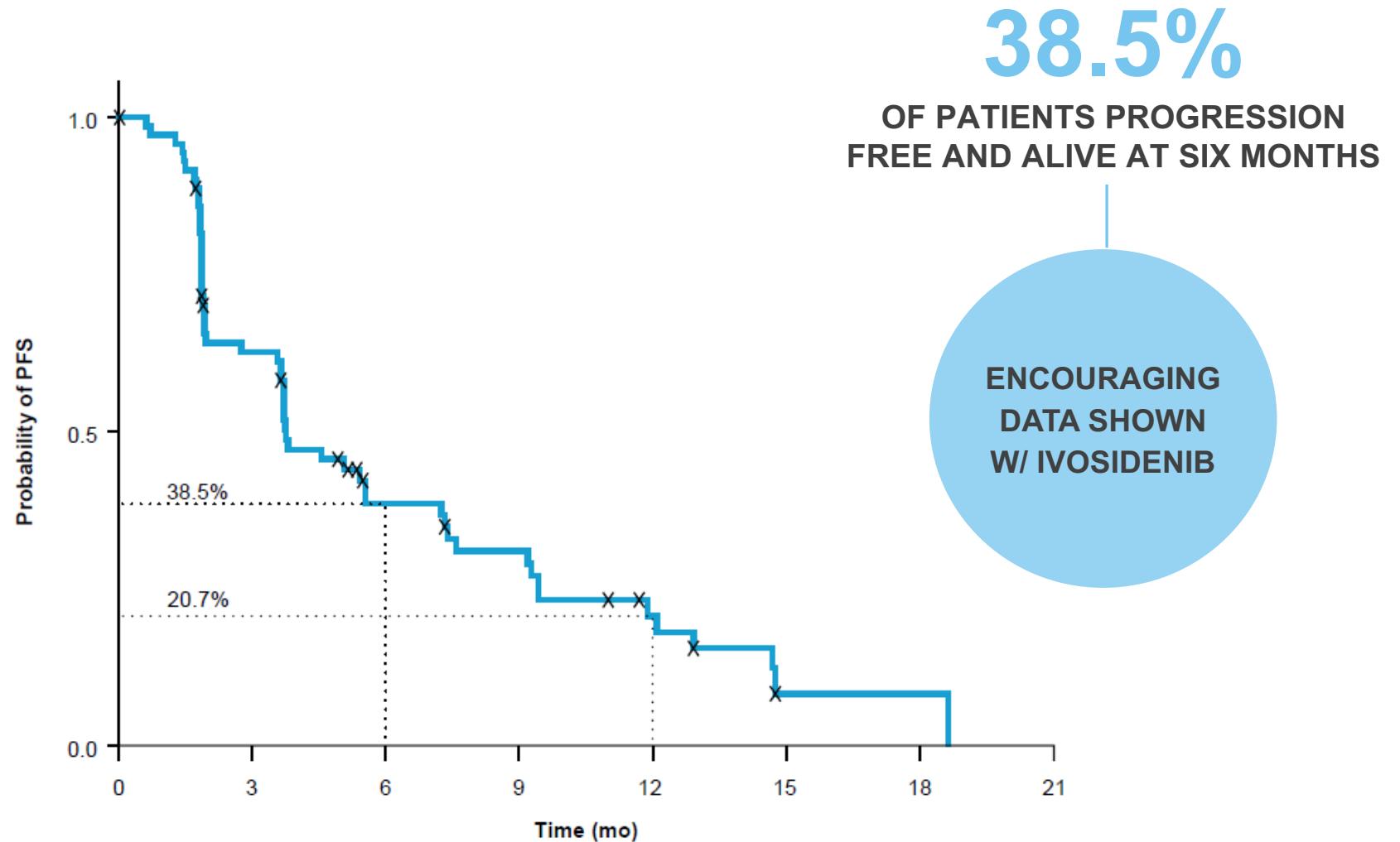
Durable Disease Control with Ivosidenib in a Heavily Pre-treated Population

61%
disease
control
rate
(PR + SD)



Durable Disease Control with Ivosidenib in a Phase 1 Heavily Pre-treated Population

- Ivosidenib well-tolerated in heavily pre-treated population (most common drug-related AEs: fatigue, nausea & vomiting)
- Median of 2 prior systemic therapies (range 1-5)
- Durable disease control with six month PFS rate of 38.5% and 12 month PFS rate of 20.7%; median PFS of 3.8 months



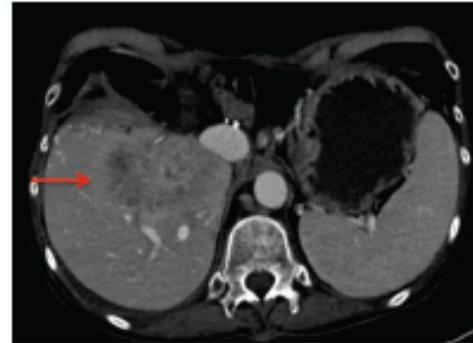
18 of 73 (25%) censored. As of March 10, 2017
Median 2 prior therapies (range 1-5)



Radiographic Changes in a Patient with a PR on Ivosidenib

Computed tomography scans of a 66-year-old woman with intrahepatic CC previously treated with neoadjuvant cisplatin + gemcitabine who then received AG-120

**Screening
Jan 14, 2016**

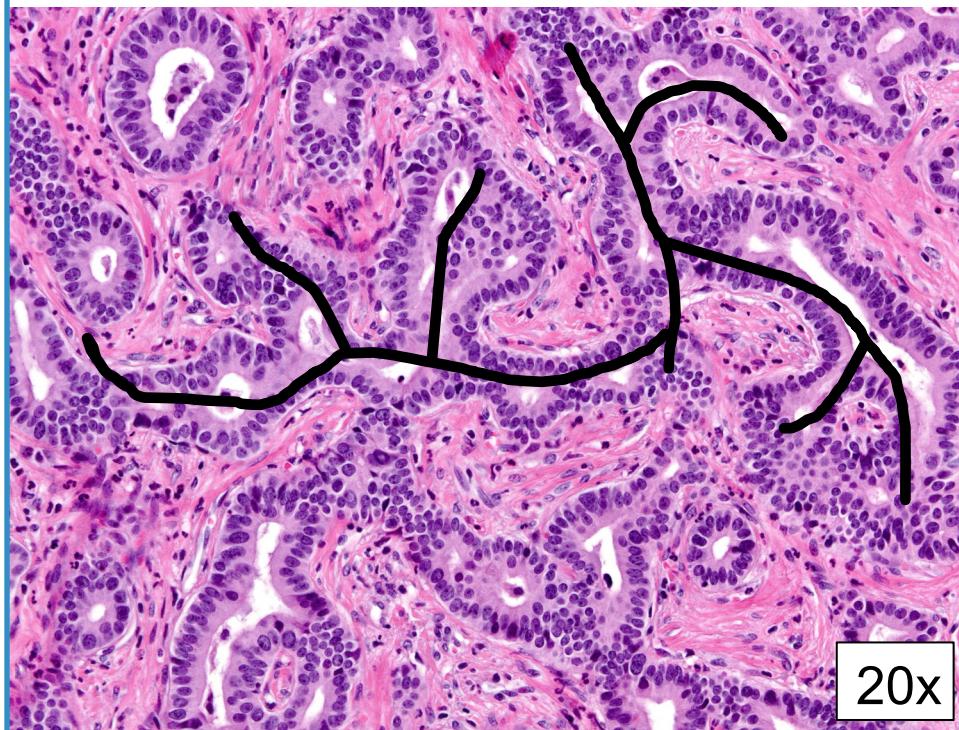


**Cycle 7 (-35%)
Jul 13, 2016**



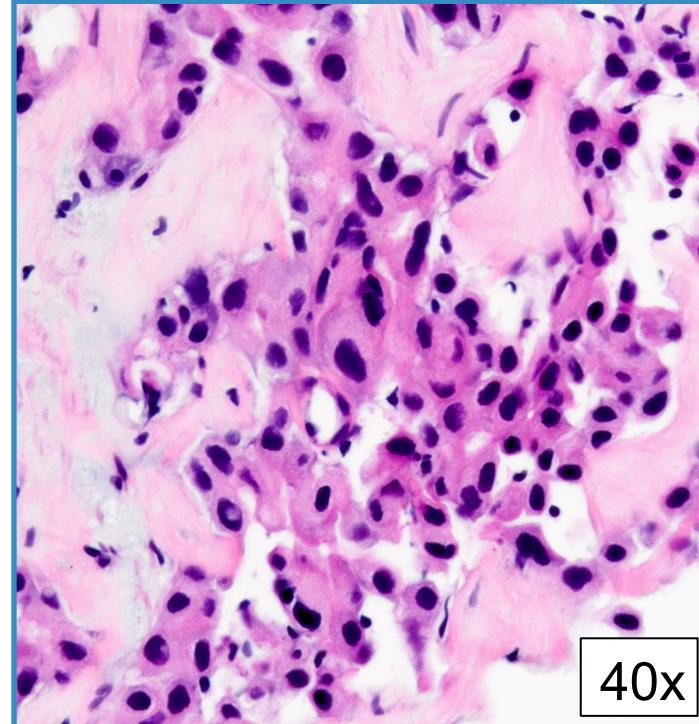
Ivosidenib Promotes Morphologic Changes to Cholangiolar Patterns

Cholangiolar pattern⁴



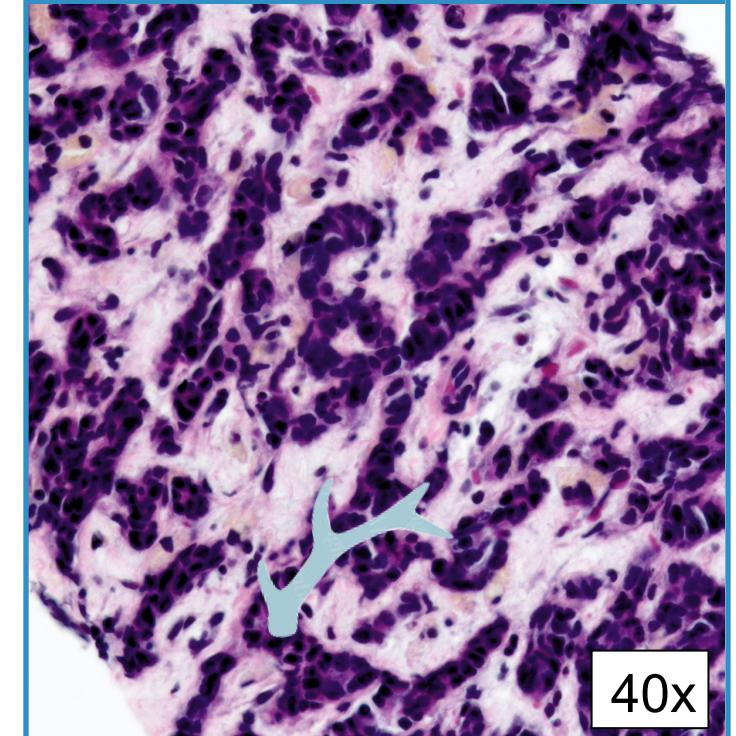
- 'Normal' cholangiolar pattern composed of glands in the shape of antler horns¹⁻³
- Associated w/ better clinical outcomes in patients w/ ICC^{1,4}

Baseline



- Untreated IDH1m+ ICCs often show heterogeneous histoarchitecture

Cycle 7, Day 1 (PR)



- Treatment with ivosidenib shows increased cholangiolar histology and decreased cytoplasm

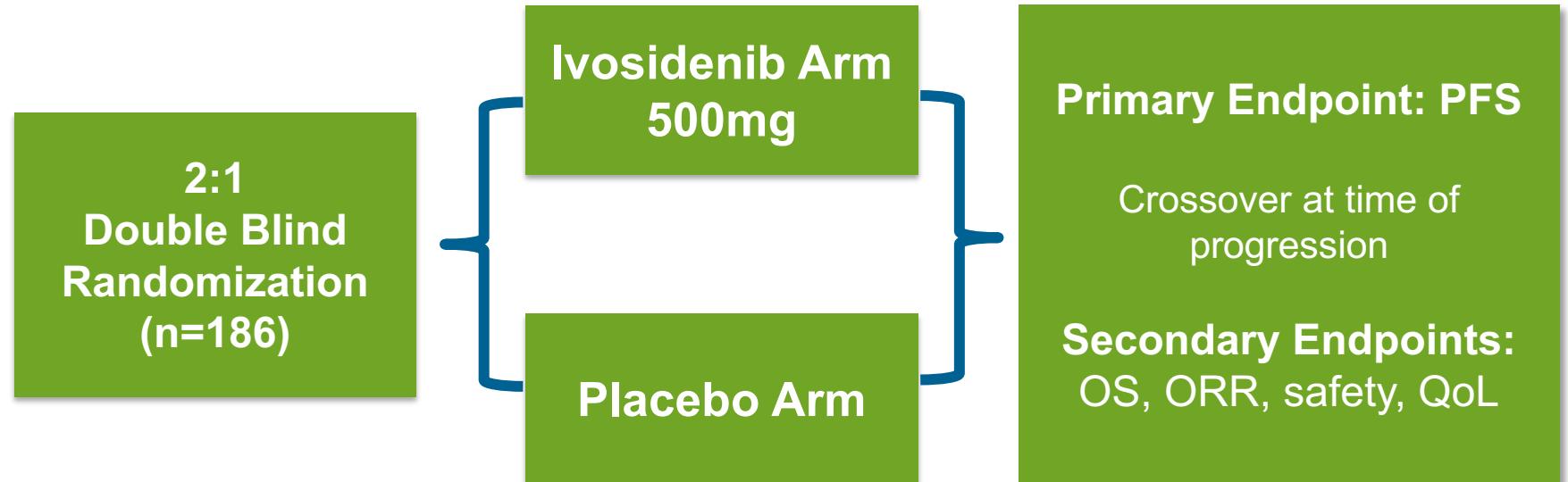


Registration-Enabling Phase 3 Cholangiocarcinoma Study

Ongoing



Global Phase 3 Previously Treated Advanced IDH1m Cholangiocarcinoma (no more than 2 prior therapies)



The study has 96% power to detect a hazard ratio of 0.5 with a one-sided alpha of 0.025

ClinicalTrials.gov Identifier: NCT02989857





Clinical Development in Glioma

Susan Pandya, M.D., Senior Medical Director



Low Grade Glioma (LGG): High Unmet Need Not Adequately Addressed by Chemotherapy or Radiation

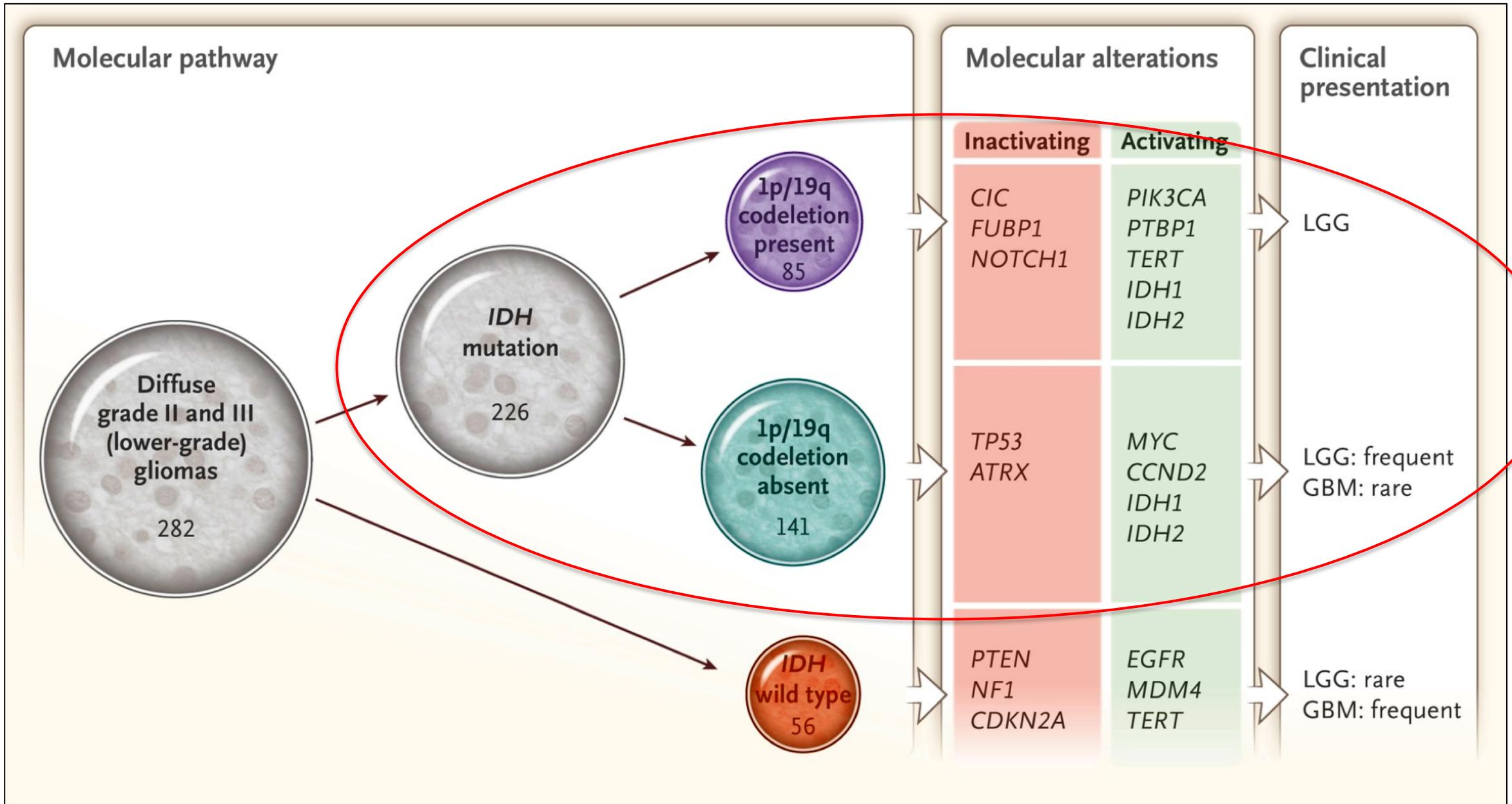
Mean age of diagnosis of 41

~80% of LGG patients present with seizure as initial symptom and up to 90% of patients will have seizures during disease course

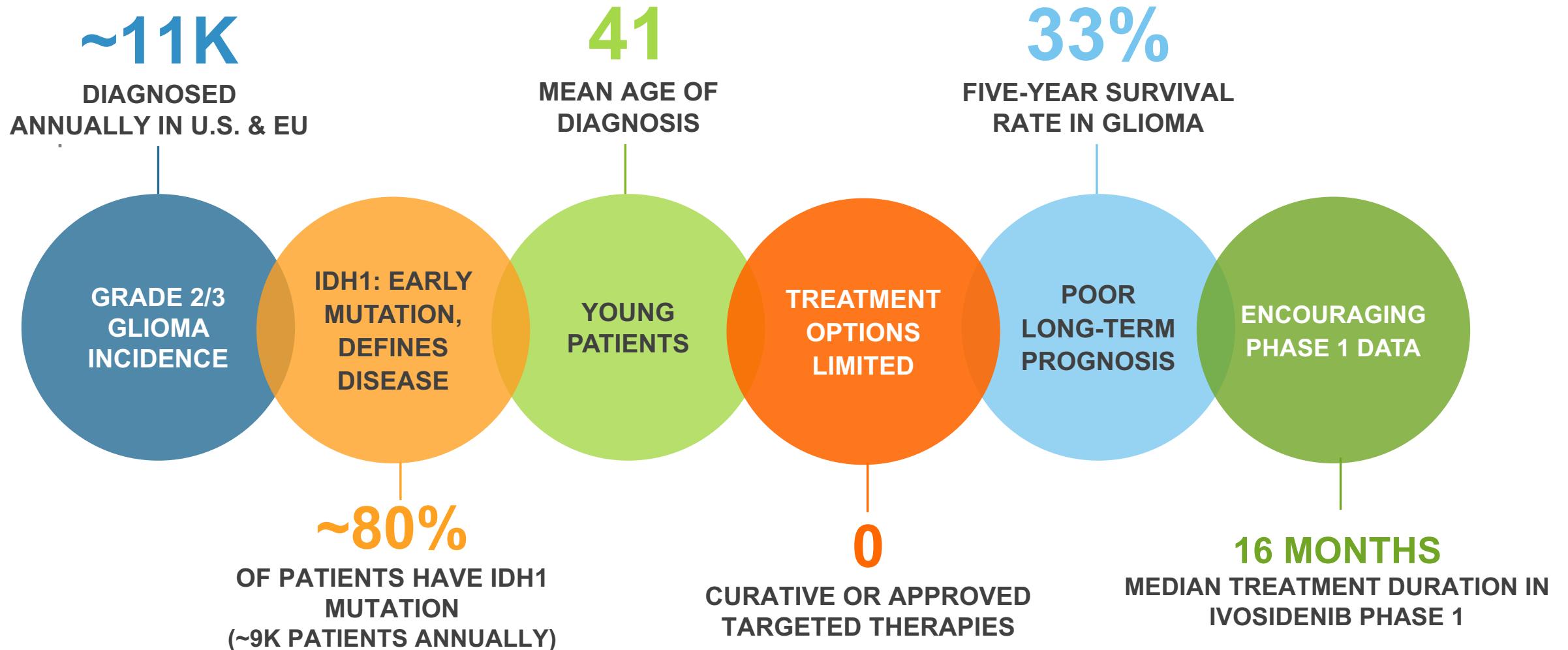
Acute and chronic toxicity associated with chemotherapy and radiation can lead to progressive decline in quality of life (e.g. neurocognitive impairment)



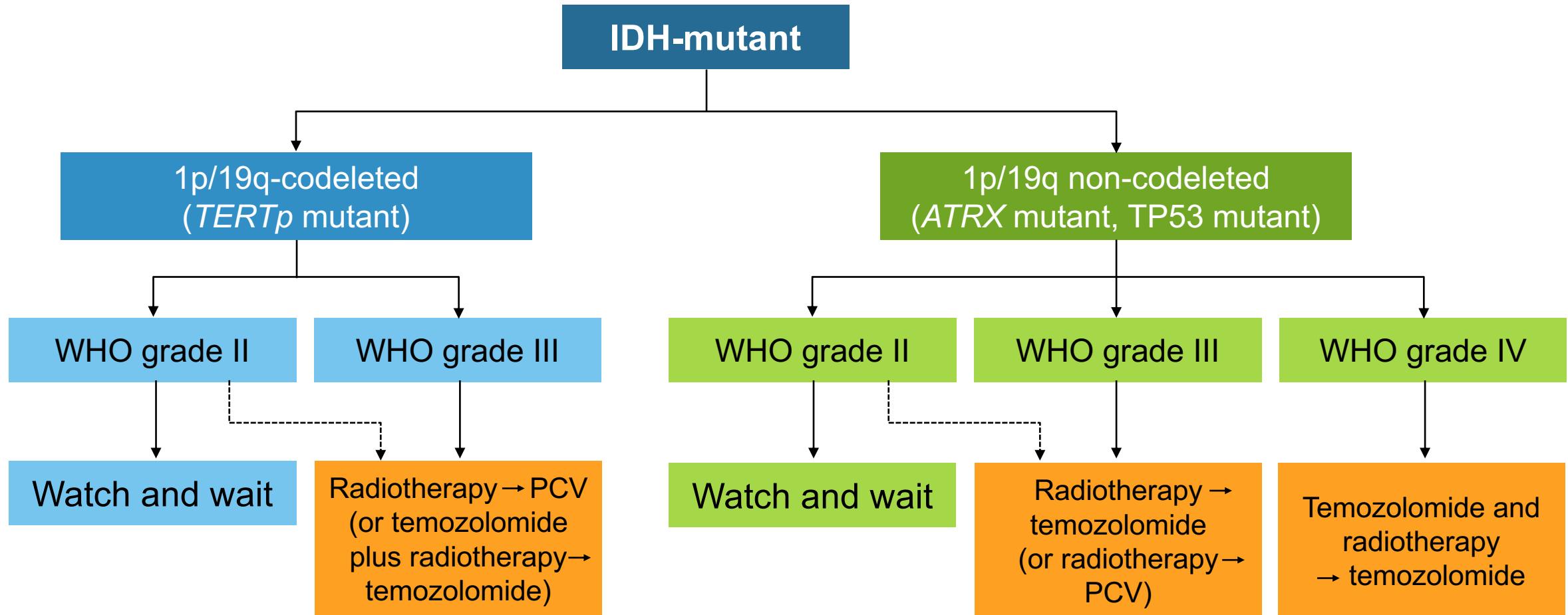
IDHm Glioma Is a Distinct Disease



Low Grade Glioma: High Unmet Need Not Adequately Addressed by Chemotherapy or Radiation

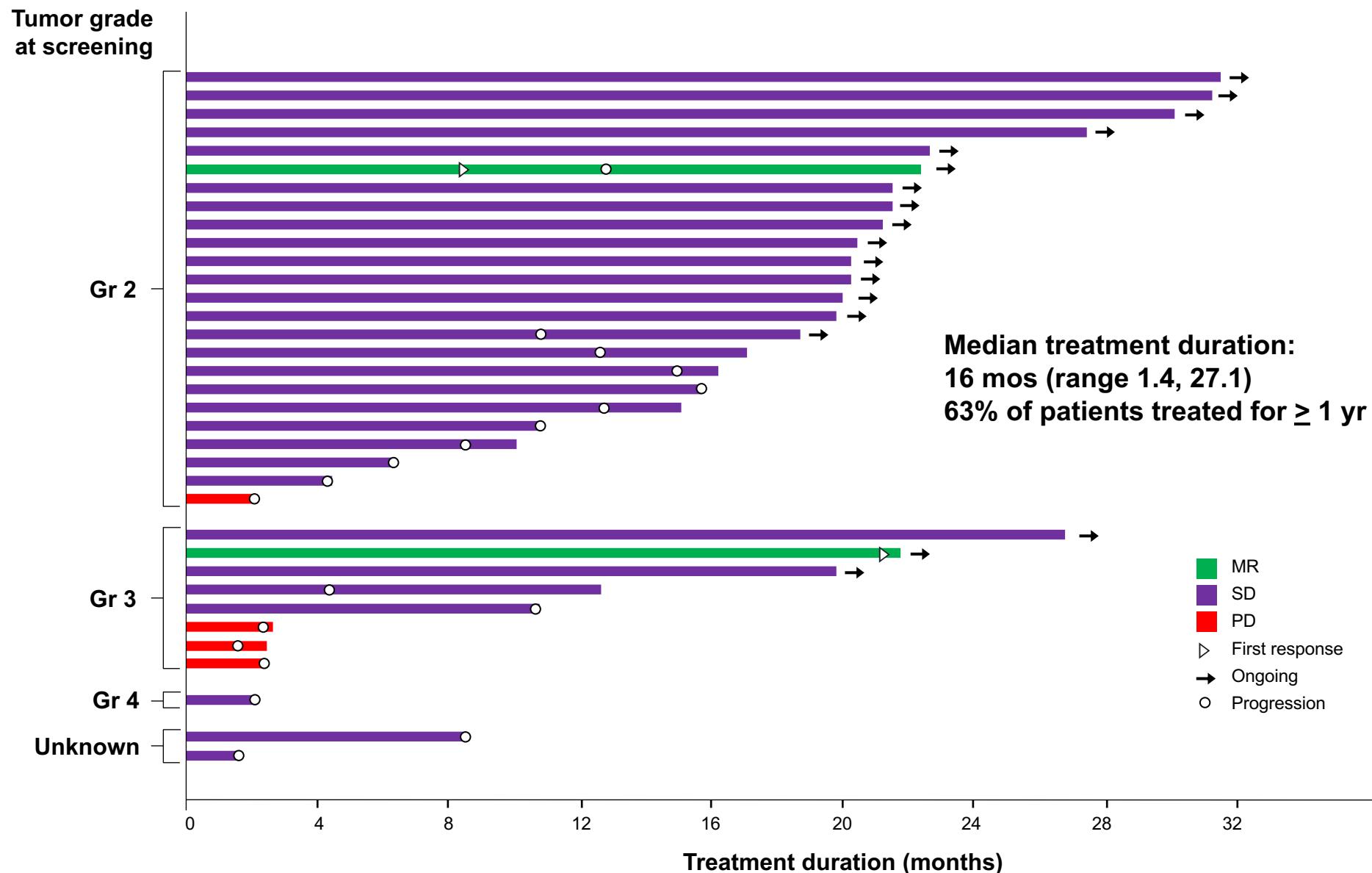


Current Treatment Paradigm for IDHm Gliomas



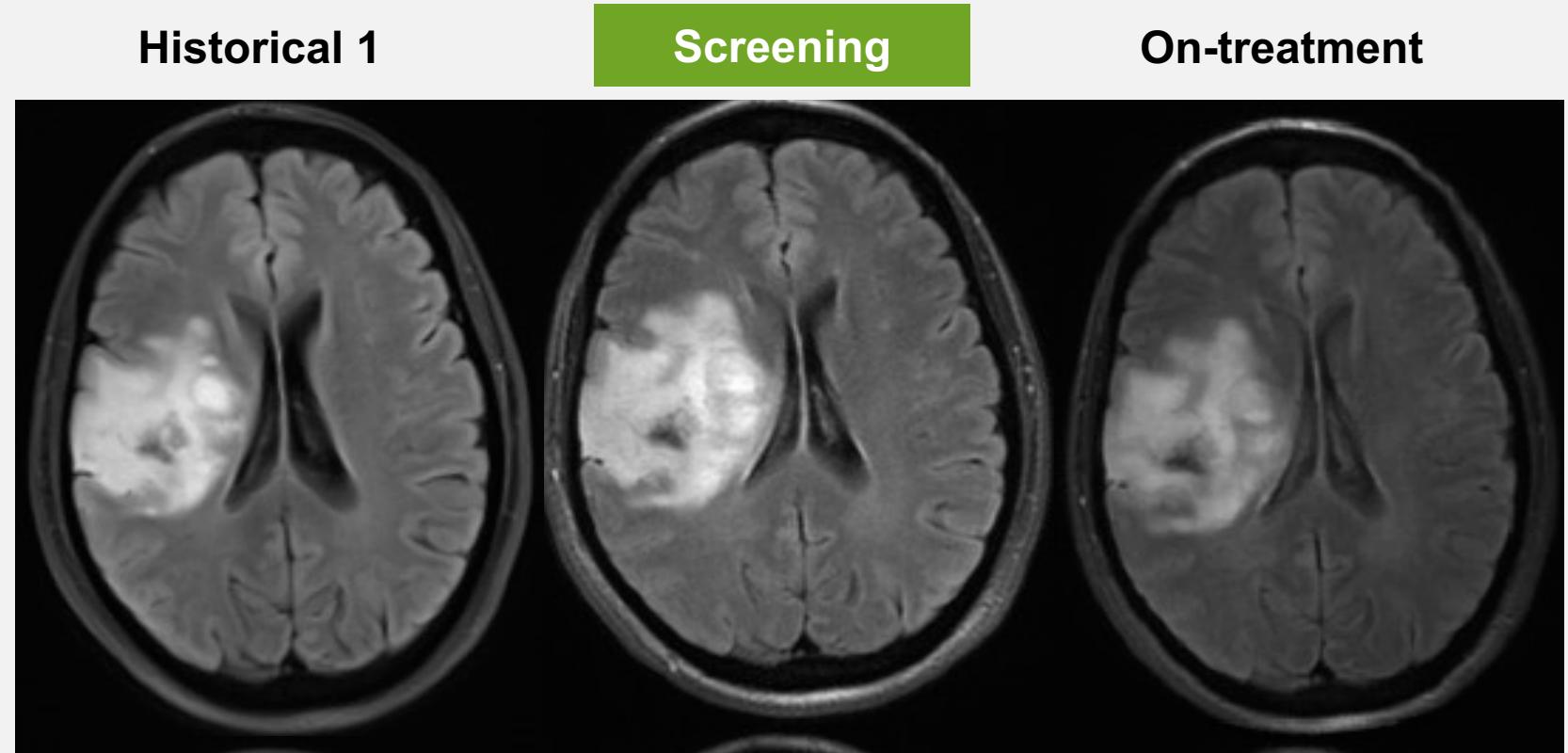
Durable Stable Disease Signal with Ivosidenib Phase 1 Data

- Ivosidenib well tolerated
- Durable stable disease signal encouraging; 51% of patients still on treatment
- Reduction of tumor growth rates also observed



Ivosidenib Phase 1 Data – Reduction in Tumor Growth Rate

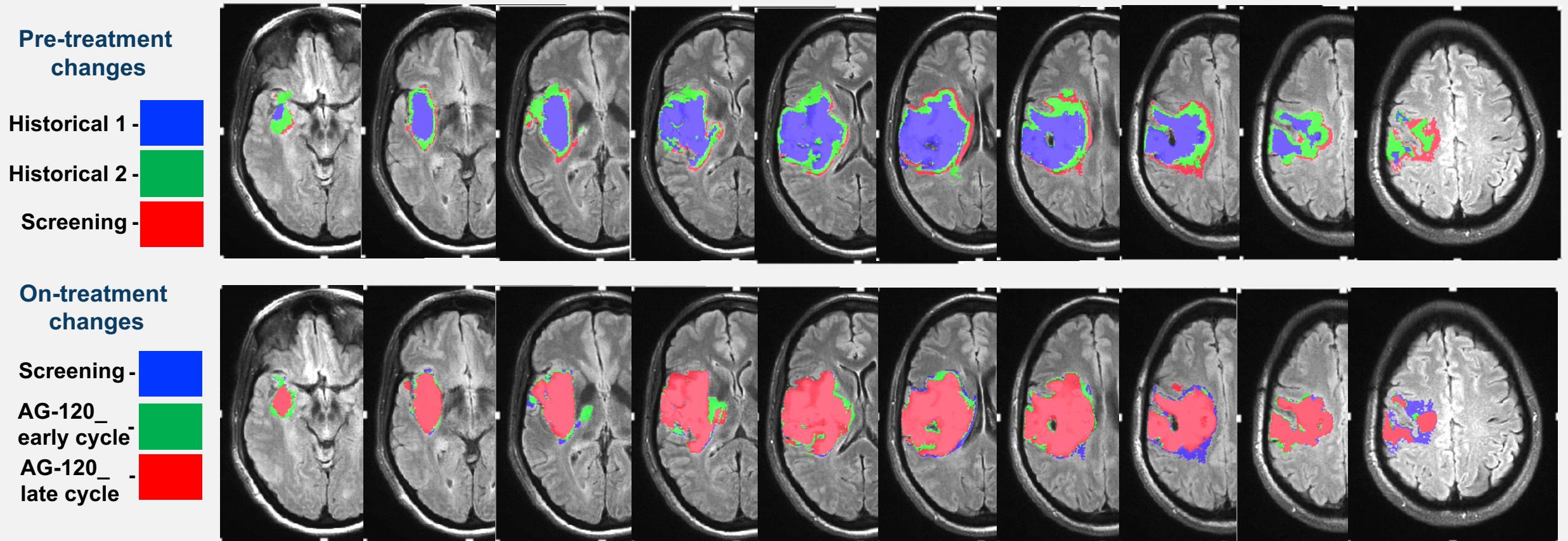
- Oligodendroglioma
1p19q co-del
- Biopsy 2007
- Temozolomide 2007-2008
- No Radiation
- AG-120 Start 10/2015
H1 MRI: 10/2014
- Remains on treatment
(18 mos @ cutoff)
Best RANO response: SD



H1 = historical pre-treatment scans; Screen = screening



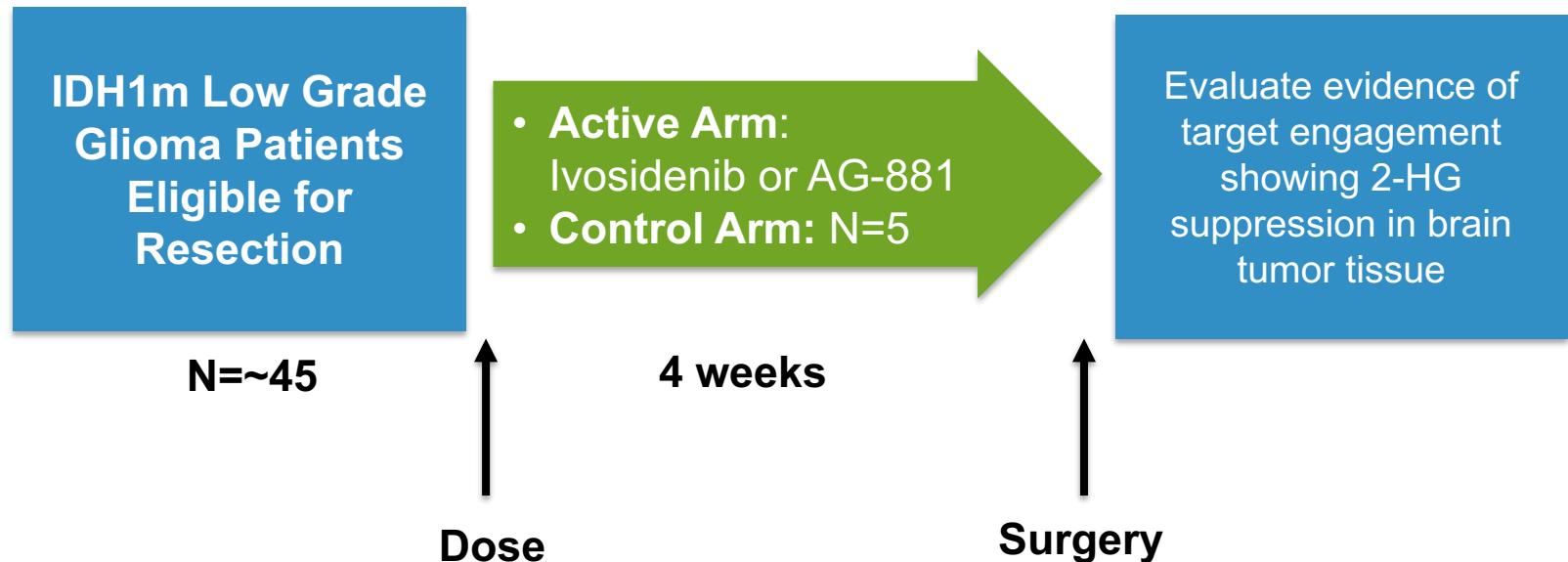
Ivosidenib Phase 1 Data – Reduction in Tumor Growth Rate



Ongoing Phase 1 Perioperative Study with Ivosidenib and AG-881 Evaluating Evidence of Target Engagement

Study Objectives:

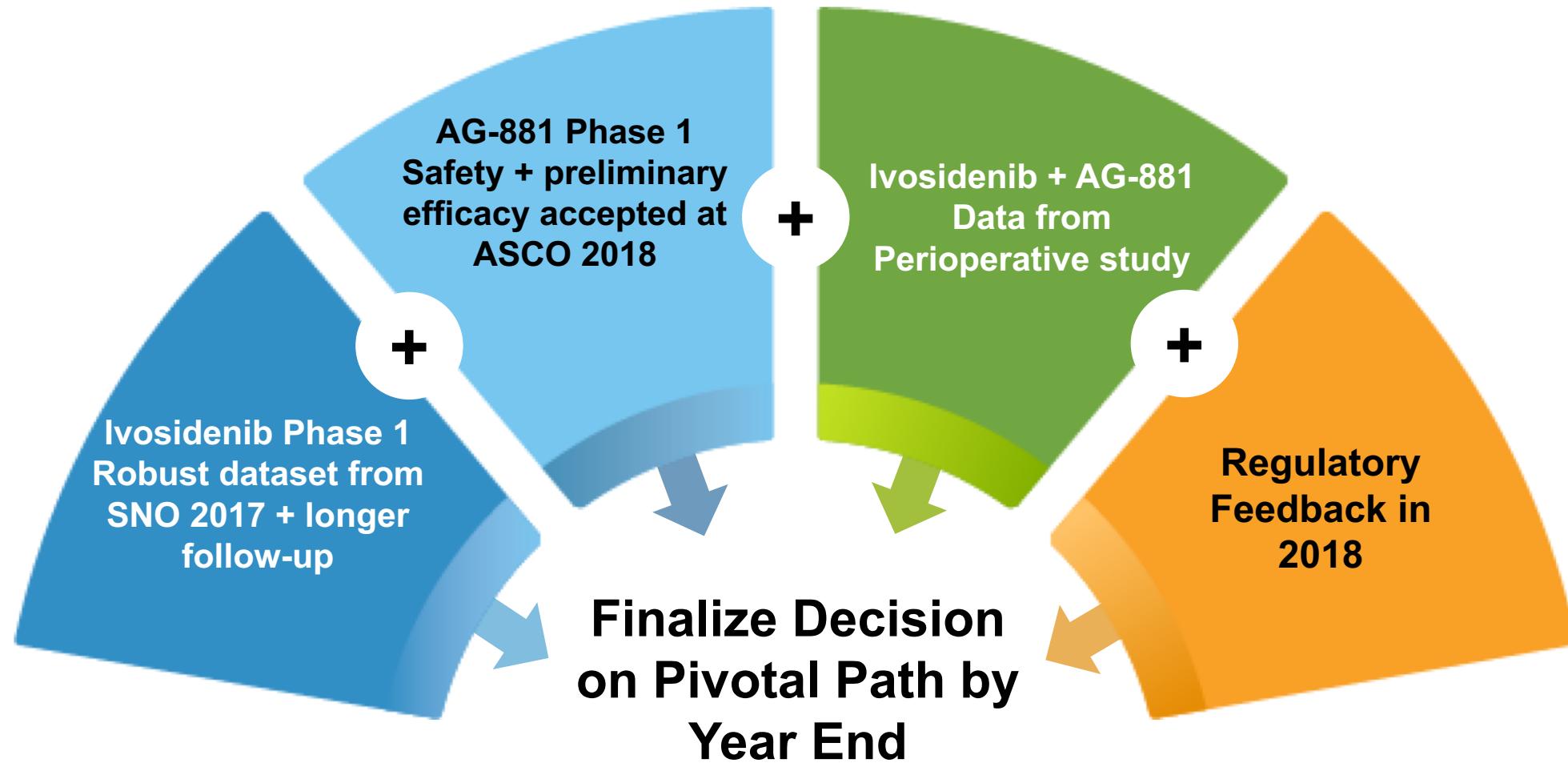
- Determine amount of drug penetration in the brain
- Confirm magnitude of IDHm target engagement as measured by 2HG levels in brain tumor tissue (pre-clincally 85% seen with ivosidenib & 98% with AG-881)
- Assess impact of IDHm inhibition on differentiation and epigenetic profiles in tumor tissue
- Assess the safety of both molecules



ClinicalTrials.gov Identifier: NCT03343197



Next Steps in Glioma





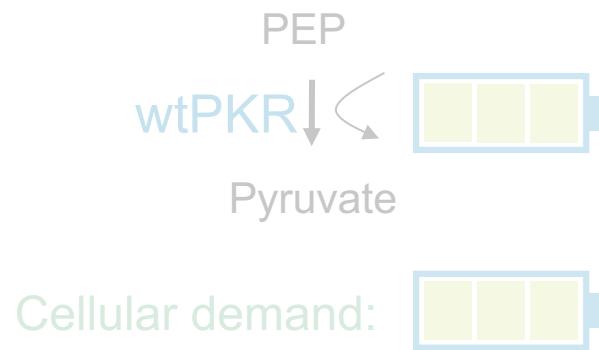
PKR Activation & PK Deficiency

Chris Bowden, M.D., Chief Medical Officer



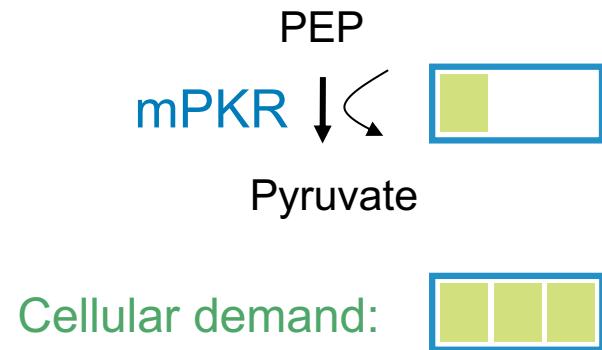
PK Activation Represents Opportunities Across Hemolytic Anemias

Normal Red Cell



ATP production meets demand

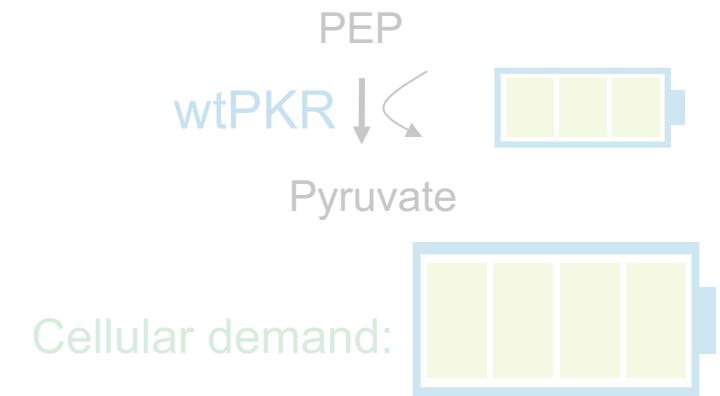
Pyruvate Kinase Deficiency



Inadequate production:
ATP deficiency

✓ **Proof of concept achieved**

Other Hemolytic Anemias



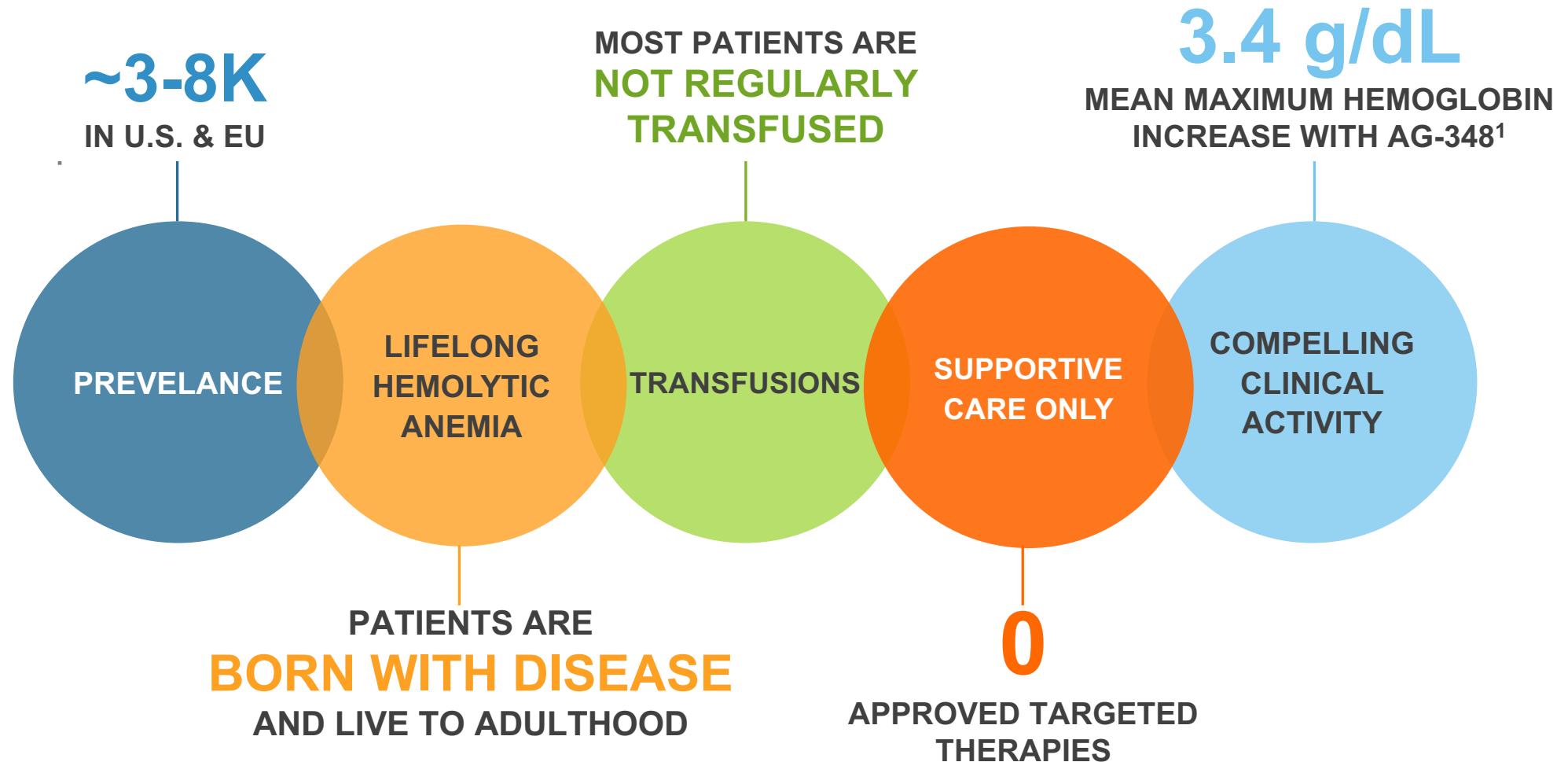
Increased demand:
ATP deficiency

Thalassemia: Expect to initiate Phase 2 proof-of-concept study in Q4 2018

Sickle cell: Planning underway



Opportunity for AG-348 to be the First Disease-Modifying Treatment for PK Deficiency



Sources: Estimated prevalence range from ~1:20K to ~1:485K Grace R et al. *Am J Hematol* 2015;90(9):825-30; ¹Mohrenweiser HW *PNAS* 1981;78(8):5046-50; ²Carey PJ et al. *Blood* 2000;96(12):4005-6; ³Beutler E & Gelbart T *Blood* 2000;95(11):3585-8; ⁴deMedicis et al. *Hum Hered* 1992;42(3):179-83; data presented at ASH 2017
¹Mean maximum hemoglobin increase of 3.4 g/dL in patients to had a >1.0 g/dL increase in haemoglobin on study

ACTIVATE-T initiated and ACTIVATE to begin in Q2 2018



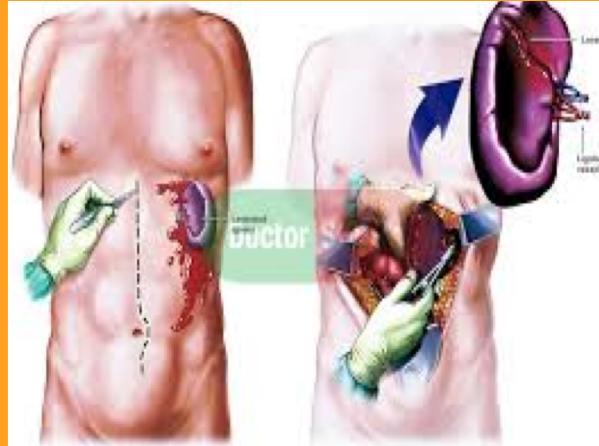
PK Deficiency Carries Lifelong Burden

Infants



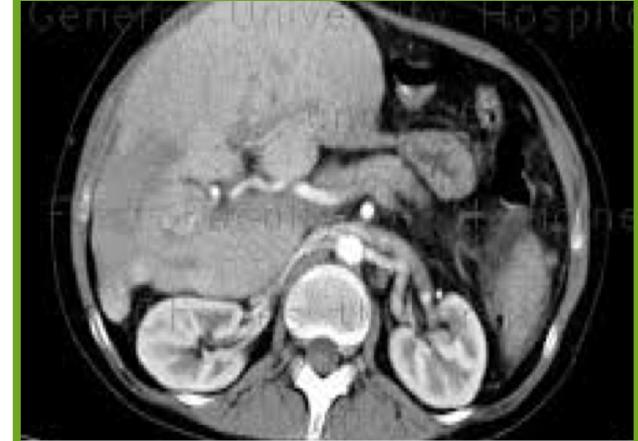
Jaundice, severe anemia,
exchange transfusions

Toddlers, Children



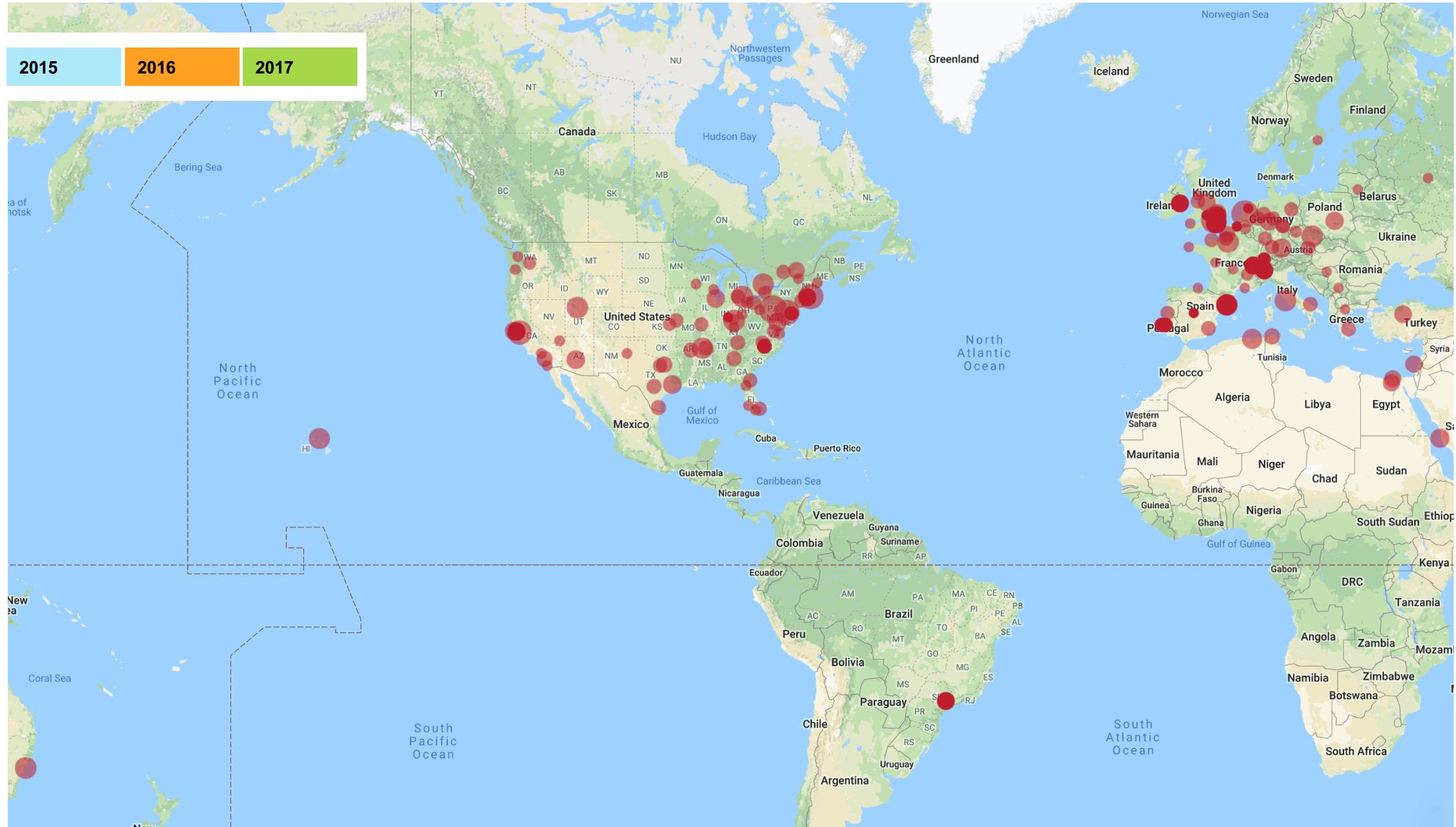
Splenectomy leading to
increased infection risk,
antibiotic prophylaxis

Adults

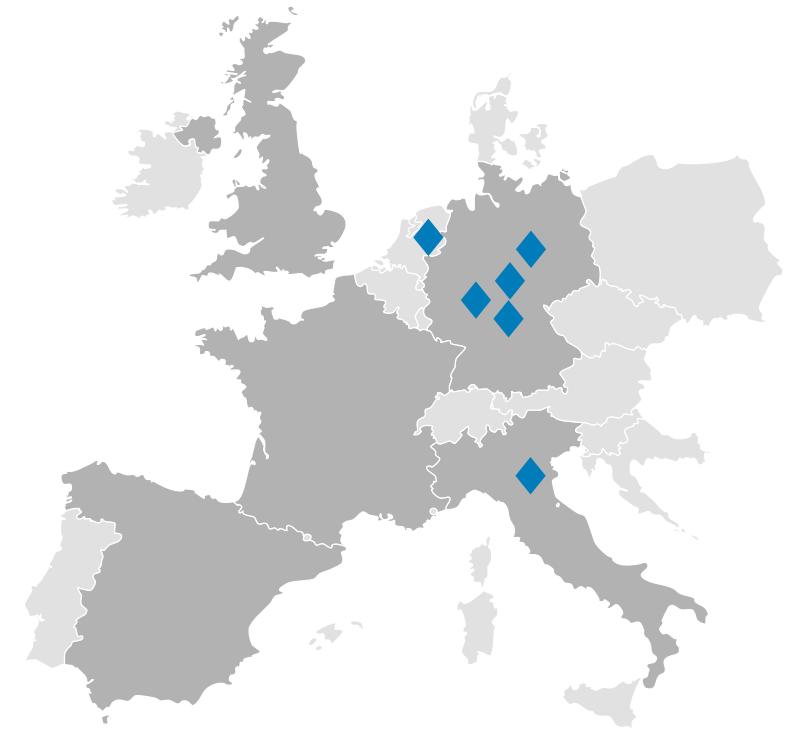
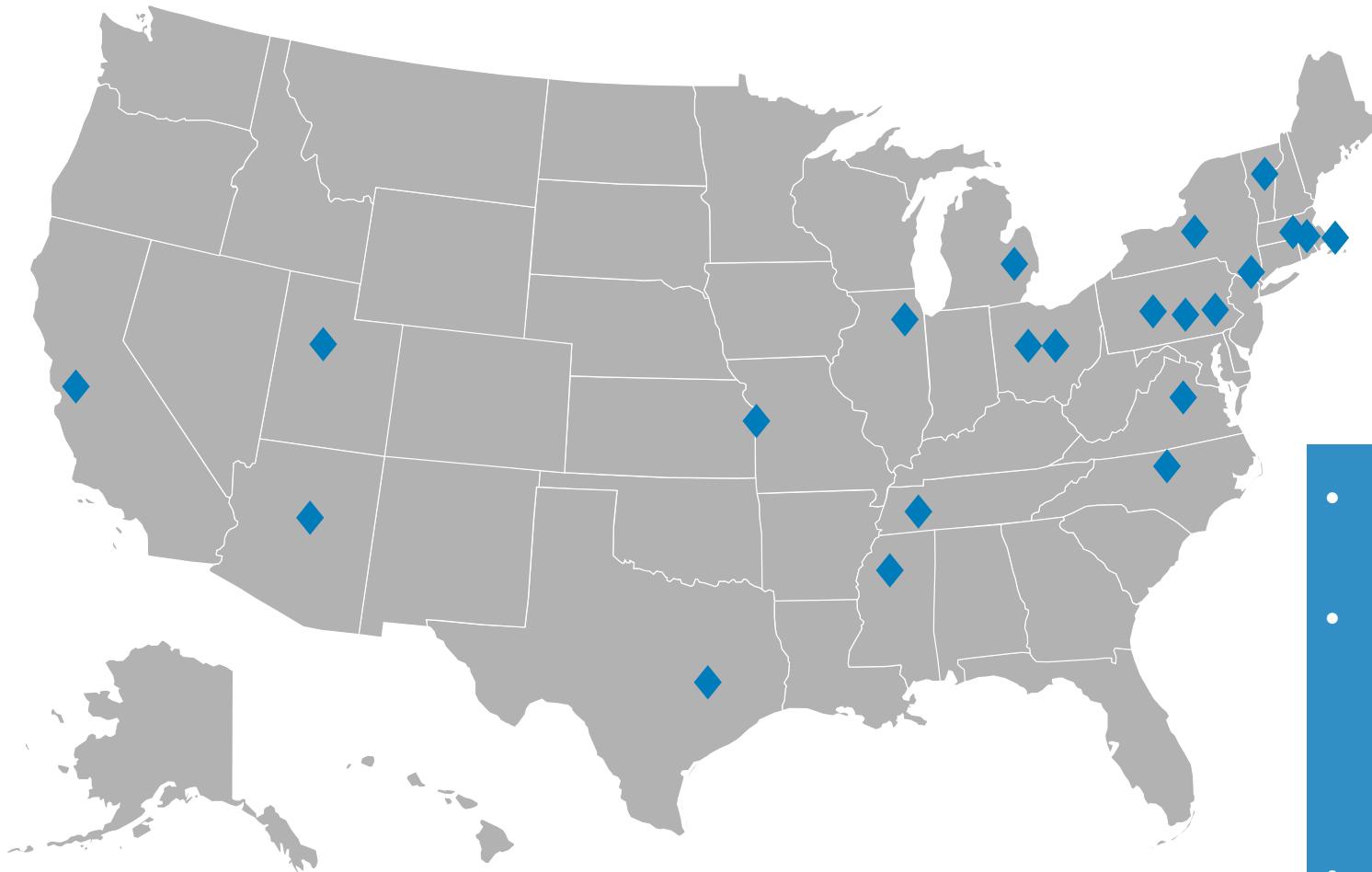


Iron overload leading to
liver cirrhosis, cardiac and
endocrine issues

Global Patient Finding Efforts



Boston Children's Natural History Study

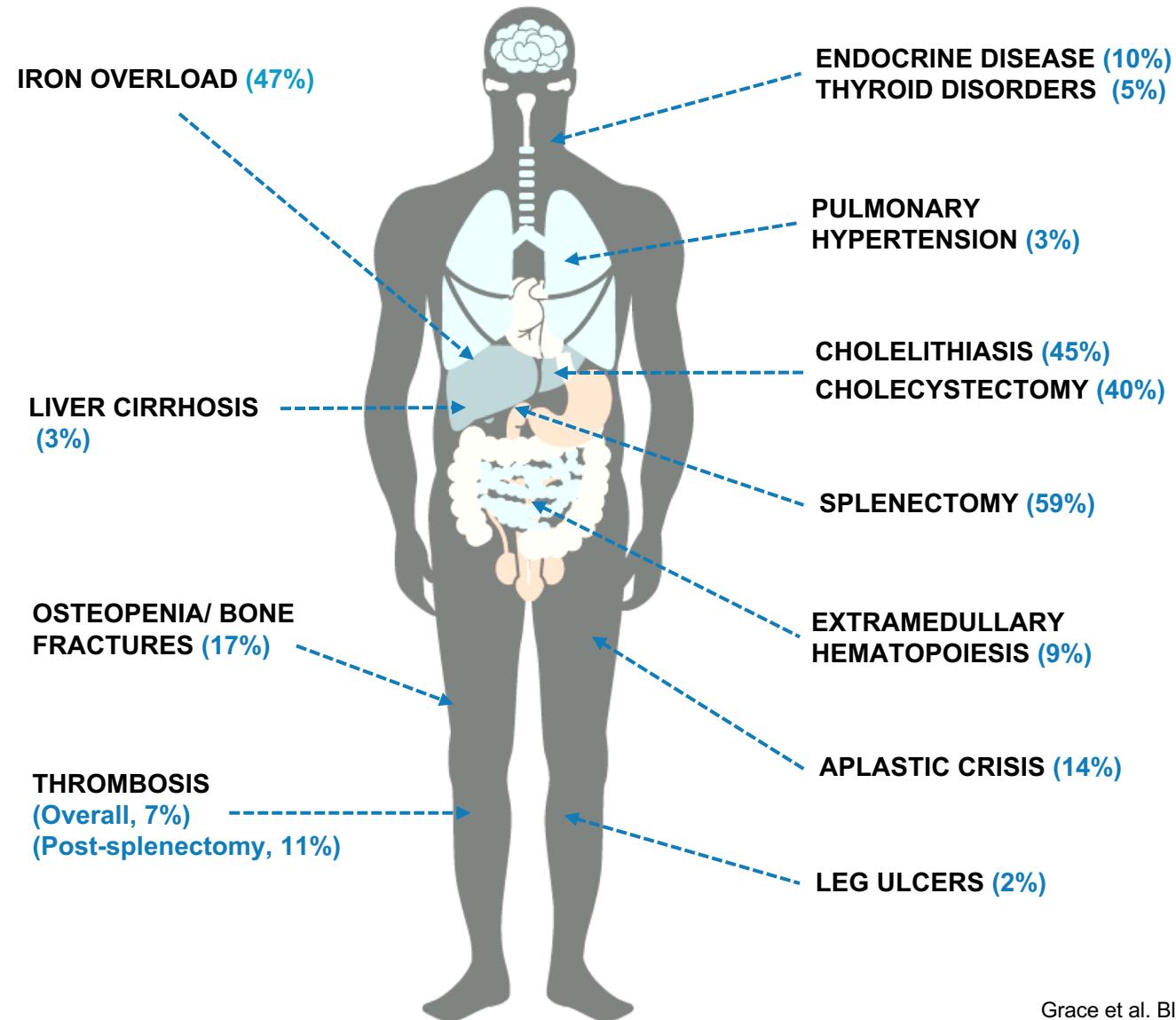


- Initiated in 2014, 278 patients enrolled in 30 sites (North America & EU)
- Understanding symptoms and complications of the disease:
 - Transfusion burden
 - Incidence & timing of splenectomy
 - Prevalence & treatment of iron overload
- Identifying patients & treatment centers
- Identifying molecular characteristics



PK Deficiency: Burden of Disease is Extensive

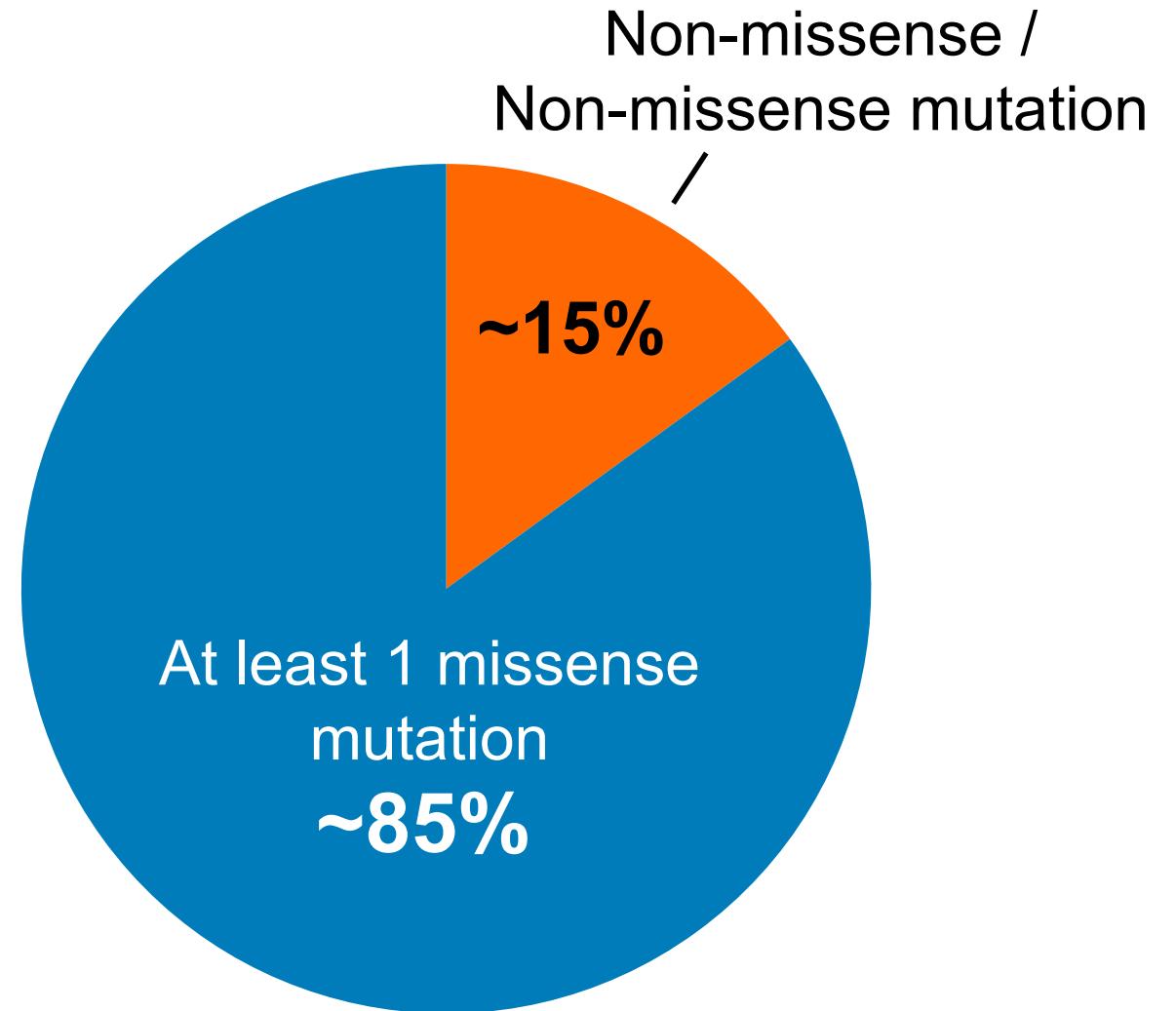
Baseline and Retrospective Data from 254 NHS Patients



Over 300 Mutations Cause a Range of Defective PKR Proteins

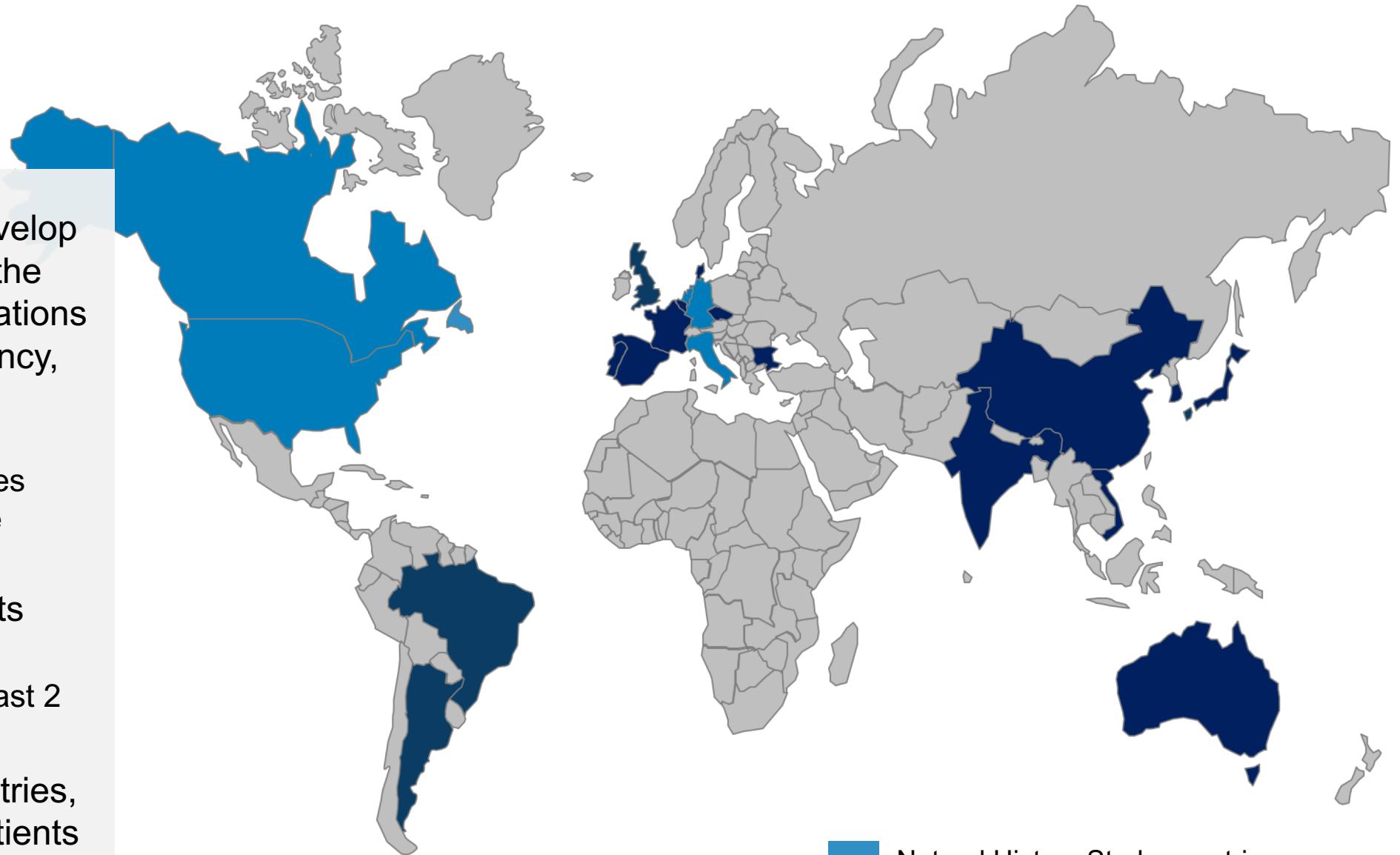
Mutations in PKR have been described in PK deficiency, belonging to one of two categories:

- 1. Missense mutations** cause a single amino acid change in the protein – *generally some functional protein*
- 2. Non-missense mutation** any mutation other than a missense mutation (e.g., stop, frameshift, deletion) – *generally little functional protein*



PEAK Registry Enrolling Patients

- Primary objective is to develop greater understanding of the longitudinal clinical implications of pyruvate kinase deficiency, including:
 - Natural history
 - Treatments and outcomes
 - Variability of clinical care
 - Disease burden
- Adult and pediatric patients eligible
 - Will be followed for at least 2 years
- Will include up to 20 countries, 60 sites and up to 500 patients



■ Natural History Study countries
■ Potential additional countries for registry*

* This list is not exhaustive, and may change



Physician Opinion of Disease Severity is Highly Variable and a Function of Patient Experience

Hematologists specializing in benign heme diseases are most familiar

PK deficiency patients are characterized by the overall disease burden

- Anemia
 - Iron overload, splenectomy, cholelithiasis
- Reduced stress response to viral infections, pregnancy
- Worsening symptoms with age

Significant gaps need to be addressed in the adult PK deficiency patient population

- Age characteristics of common complications, disease course, prognosis
- Risk factors for complications or for overall disease severity



Patients Describe a Constellation of Signs and Symptoms That Challenge Their Efforts to “Be Normal”

“I know more about my disease than my hematologist.”

Living with PK deficiency

Physical burden



- Disease impact increases as patients age



- Adequate health insurance



- Major life decisions (career, marriage, parenting) and everyday choices (travel, social life) affected



- Social QoL impact, not being able to “keep up”



- Bone pain, cognition impact, infections, iron overload, downstream co-morbidities / secondary conditions



- Anxiety about keeping disease private from employers

Caring for PK deficiency



- Relationships with HCPs vary widely



- No published standards of care



- Patients actively keep up with research to compensate for gaps in care & disease education



- Strong desire to participate in advocacy efforts & trials



Agios PRO Tool Integrates Patient Perspective into Disease Burden

Assesses *signs & symptoms* and the *impact on patients reported outcomes*

Signs & Symptoms	Physical limitations	Appearance	Daily life	Social impacts	Emotional impacts
<ul style="list-style-type: none"> • Fatigue / tiredness • Lack of / low energy • Exhaustion • Weakness • Dizziness / lightheadedness • Shortness of breath • Decreased stamina • Jaundice • Pale skin • Cognitive impairment • Bone pain • Joint pain 	<ul style="list-style-type: none"> • Need for additional rest • Difficulty with exercise / sports • Difficulty with stairs / walking uphill • Susceptibility to illness 	<ul style="list-style-type: none"> • Negative impact on appearance 	<ul style="list-style-type: none"> • Difficulty with household activities • Lack of motivation • Less productive 	<ul style="list-style-type: none"> • Negative impact on social activities • Negative impact on relationships with family/friends • Receiving unwanted attention 	<ul style="list-style-type: none"> • Concern about the future

Endpoint in pivotal trials to evaluate treatment benefit



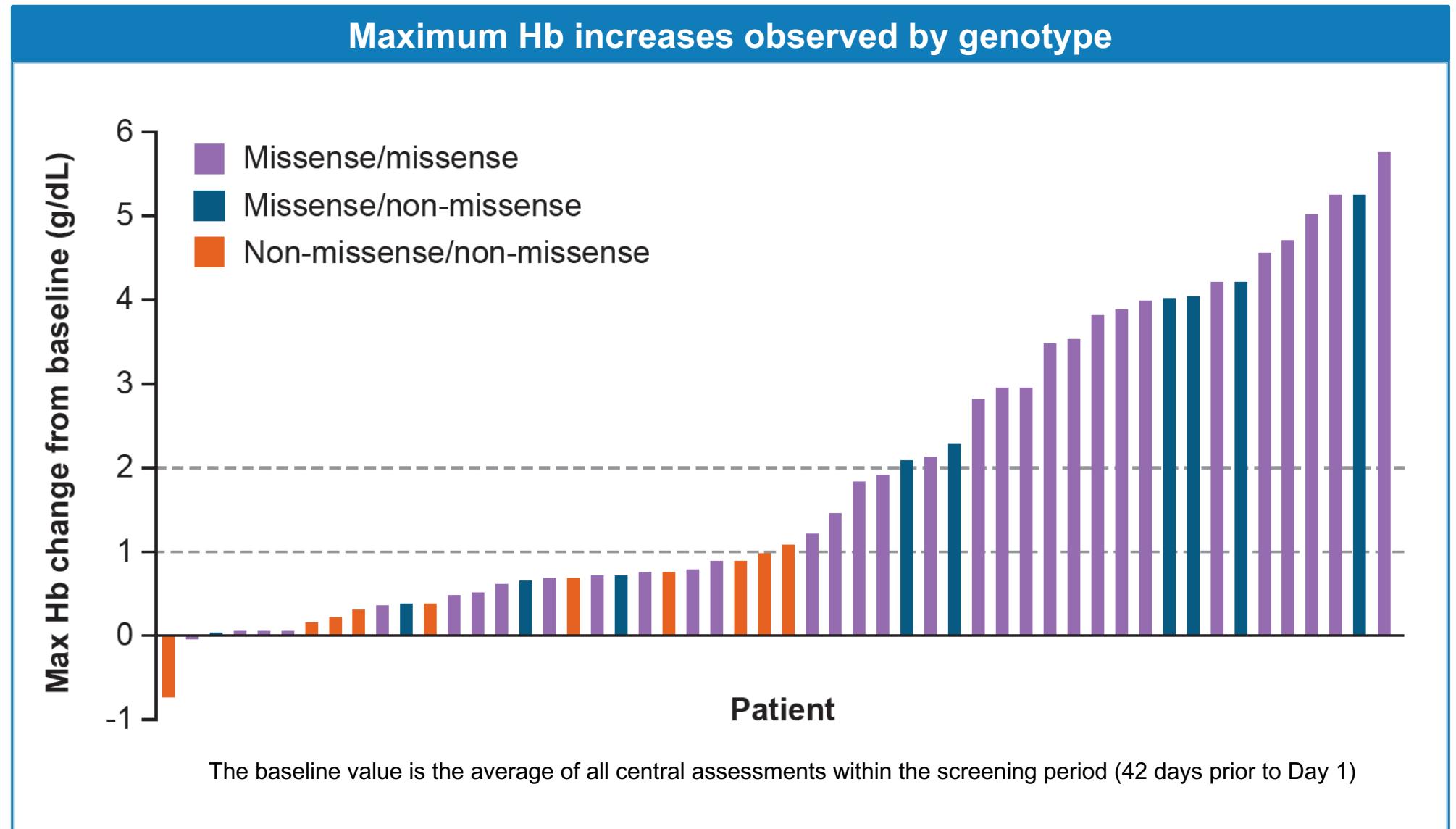


AG-348 Clinical Development Plan

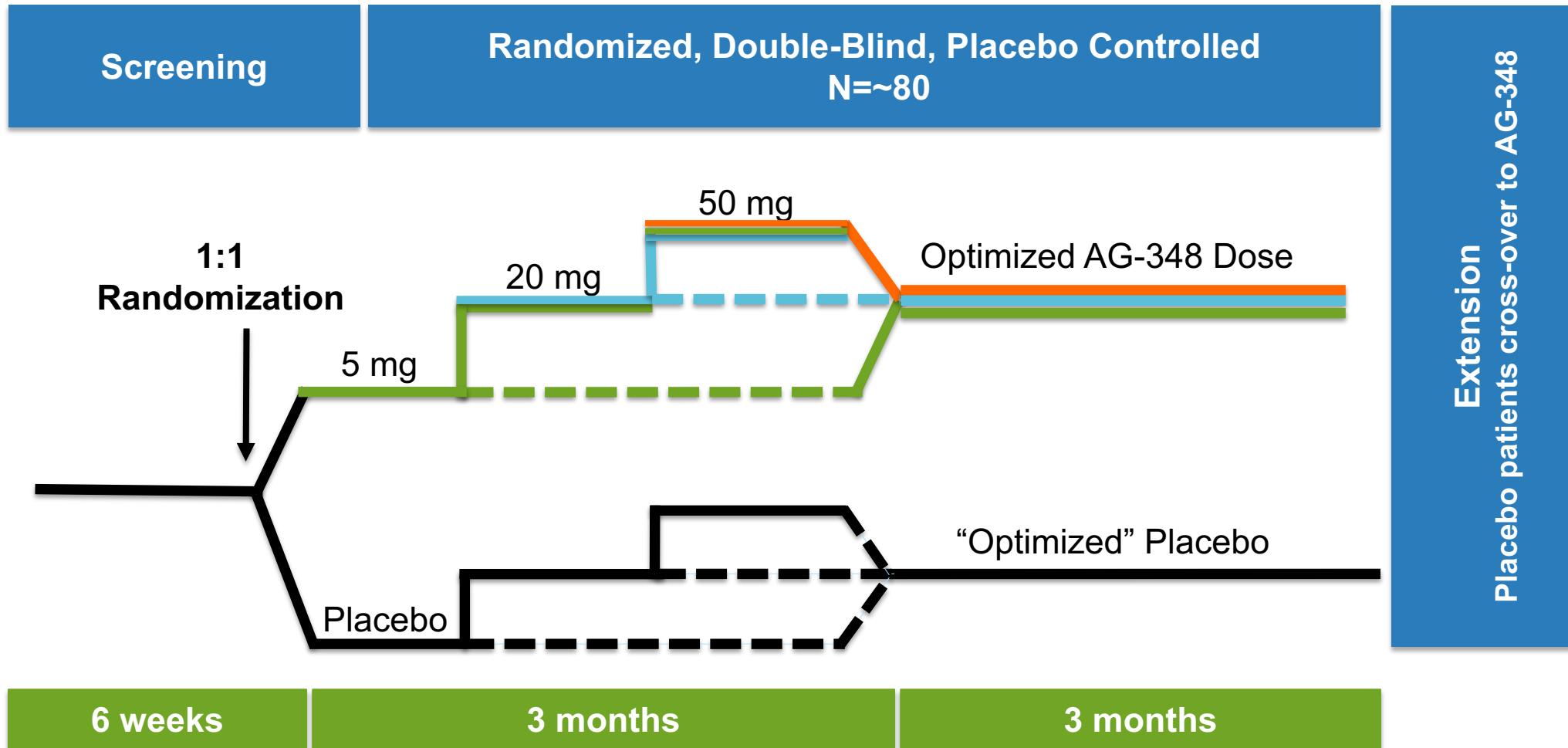


Robust Hemoglobin Increases with AG-348 in DRIVE PK

- AG-348 continues to be well tolerated
- Measurements of hormone levels in men at doses ≤ 50 mg BID suggest mild aromatase inhibition



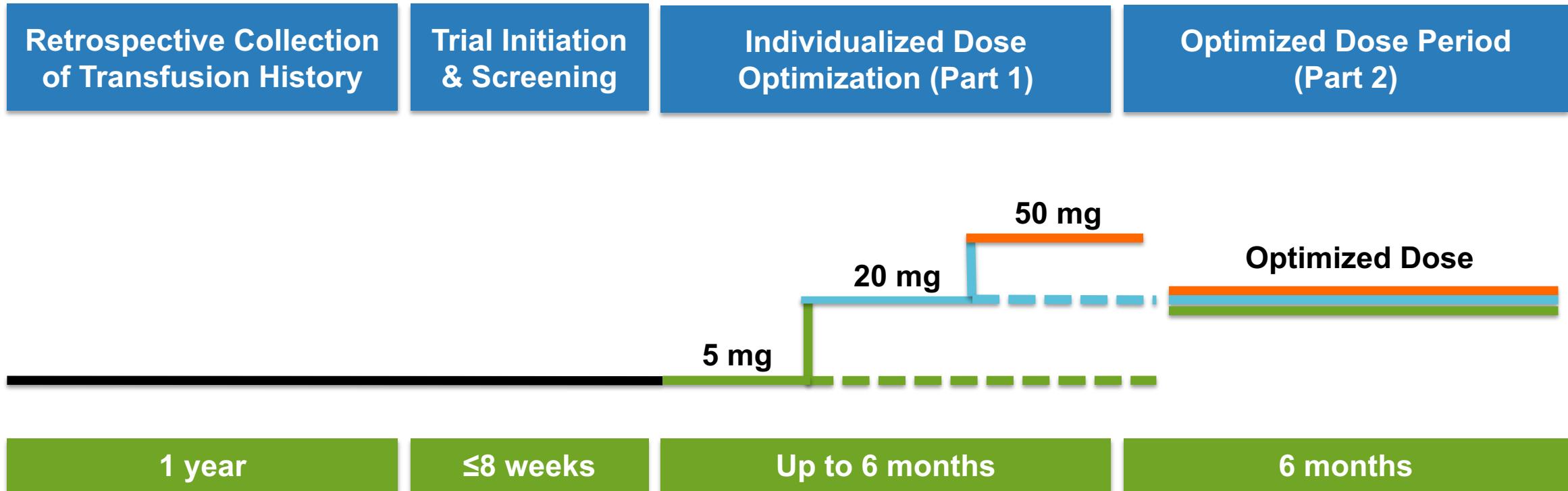
AG-348 ACTIVATE Trial for Non-Regularly Transfused Patients



Primary Efficacy Endpoint: Proportion of patients who achieve at least a 1.5 g/dL increase in hemoglobin sustained over multiple visits



AG-348 ACTIVATE-T Trial for Regularly Transfused Patients



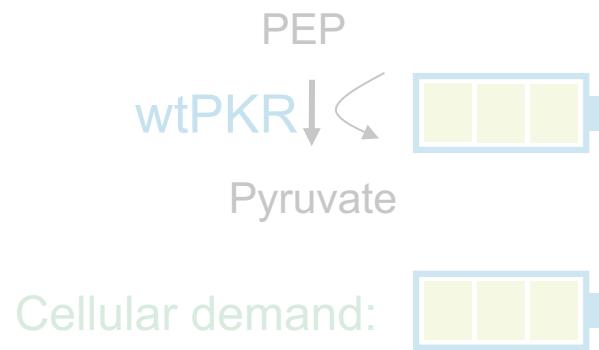
Approximately 20 regularly transfused patients who have required a minimum of 6 transfusions over the year preceding enrollment

Primary Endpoint: Reduction in transfusion burden over a 6 month period compared to the patient's transfusion history



PK Activation Represents Opportunities Across Hemolytic Anemias

Normal Red Cell



ATP production meets demand

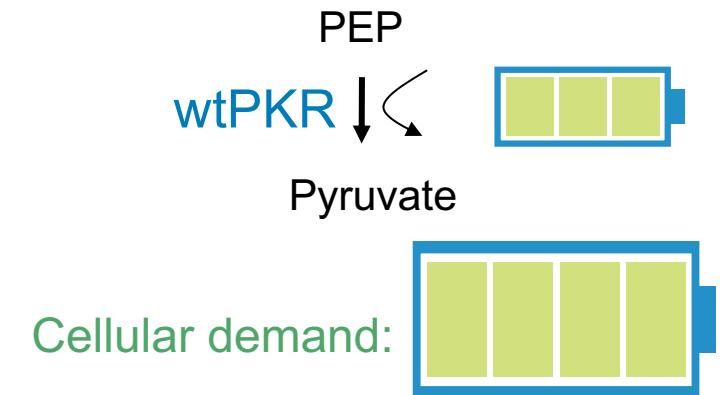
Pyruvate Kinase Deficiency



Inadequate production:
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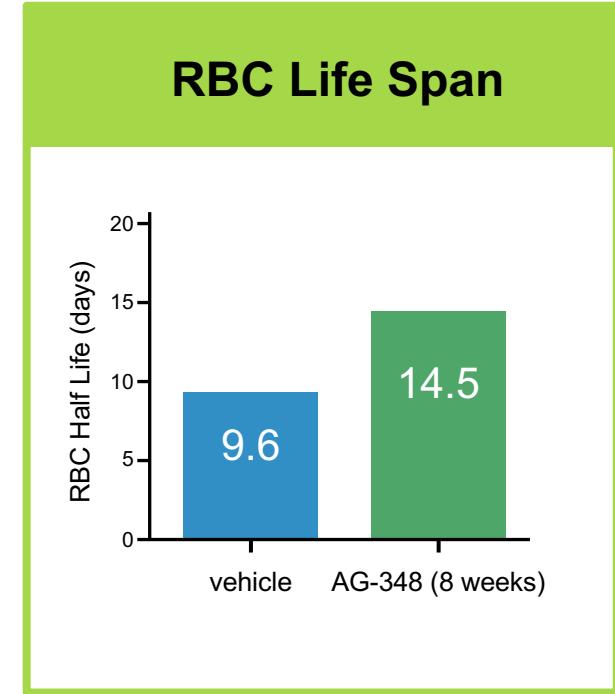
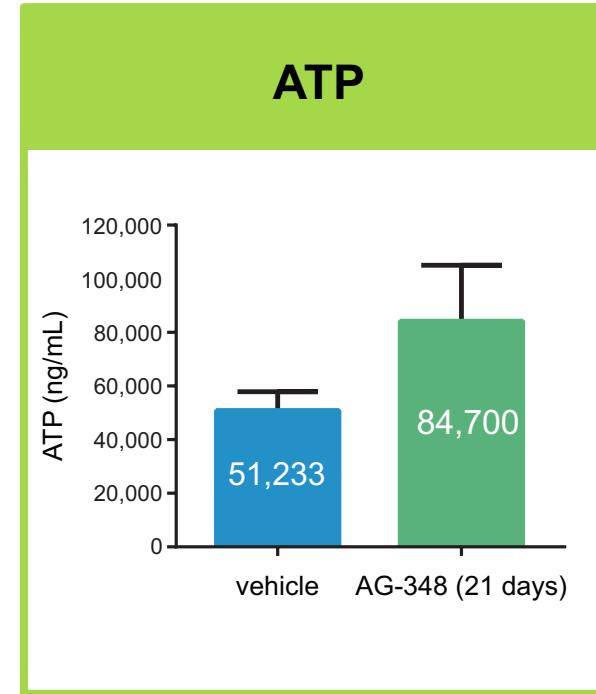
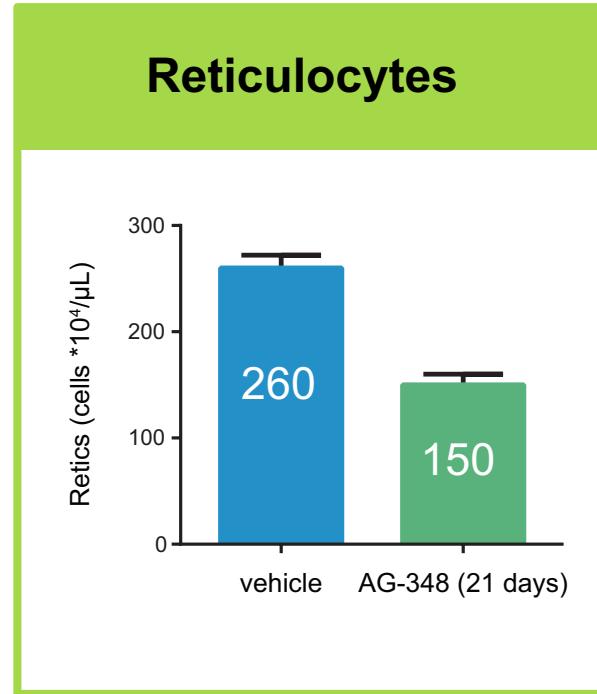
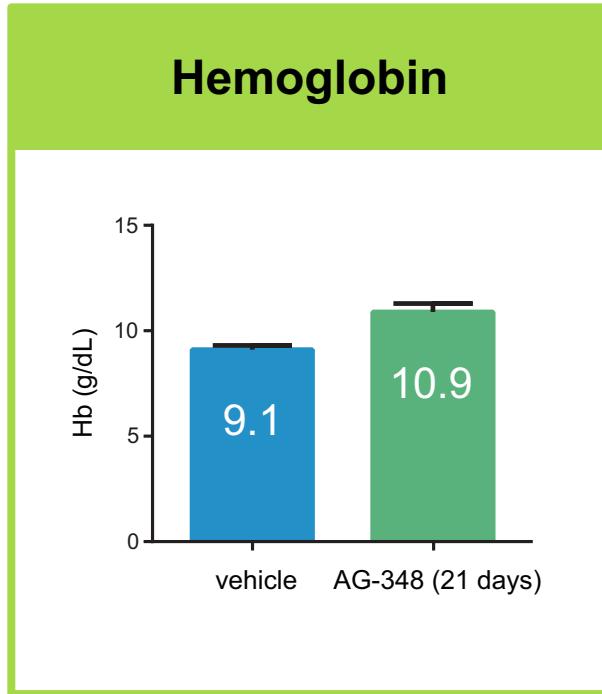
Increased demand:
ATP deficiency

Thalassemia: Expect to initiate Phase 2 proof-of-concept study in Q4 2018

Sickle cell: Planning underway



AG-348 Improves Red Cell Parameters in a Beta-thalassemia Mouse Model



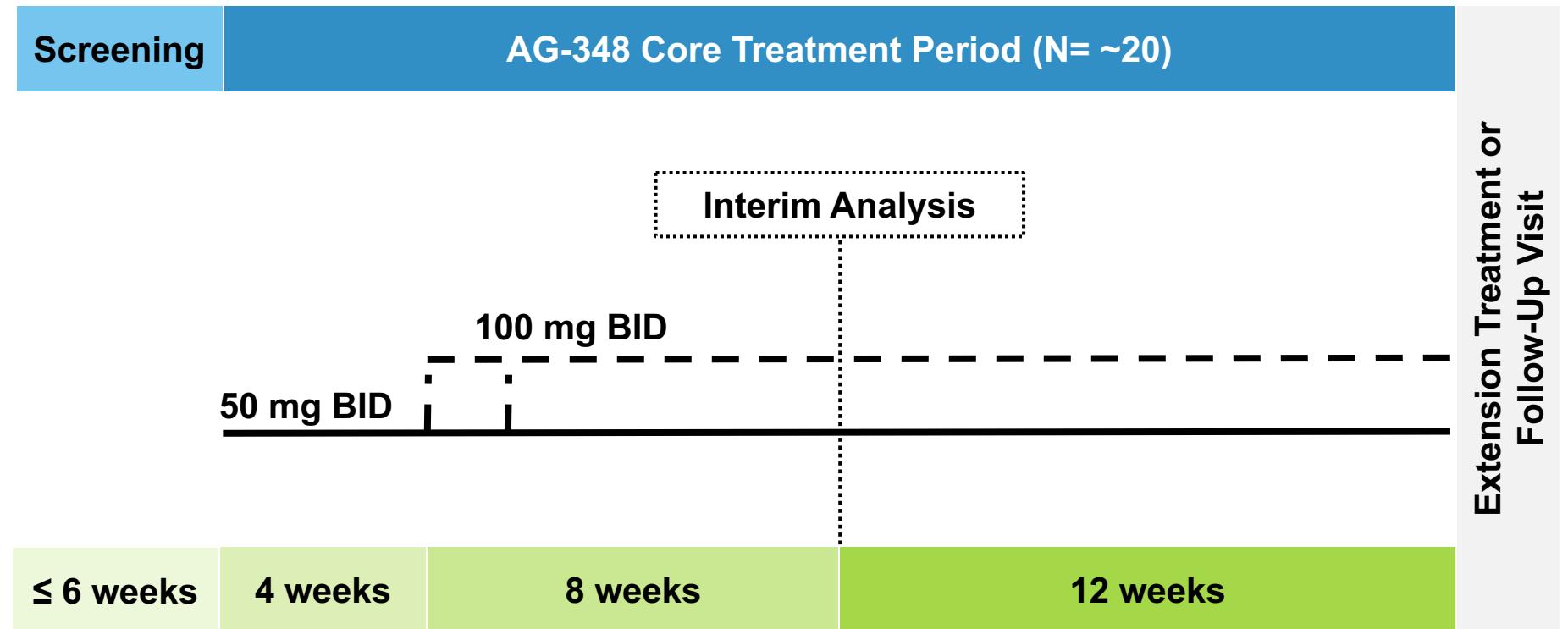
■ Vehicle
■ AG-348
(Hb, reticulocytes & ATP, 21 days RBC half life, 8 weeks)

- Treatment with AG-348 for up to 2 months shows sustained improvement in hematological parameters
- Sharp reduction in circulating immature red cells suggests amelioration of ineffective erythropoiesis
- ~50% increase in lifespan of peripheral RBCs

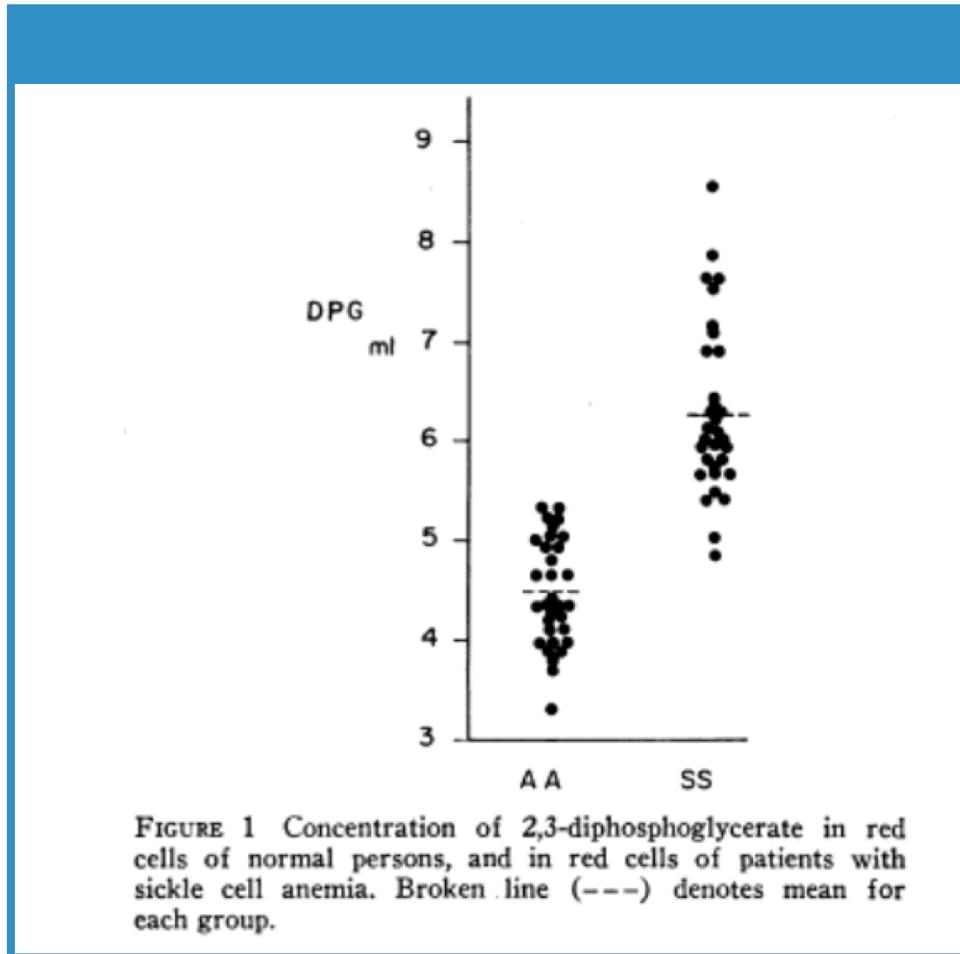


Thalassemia Phase 2 Proof-of-Concept in Non-Transfusion Dependent Adults

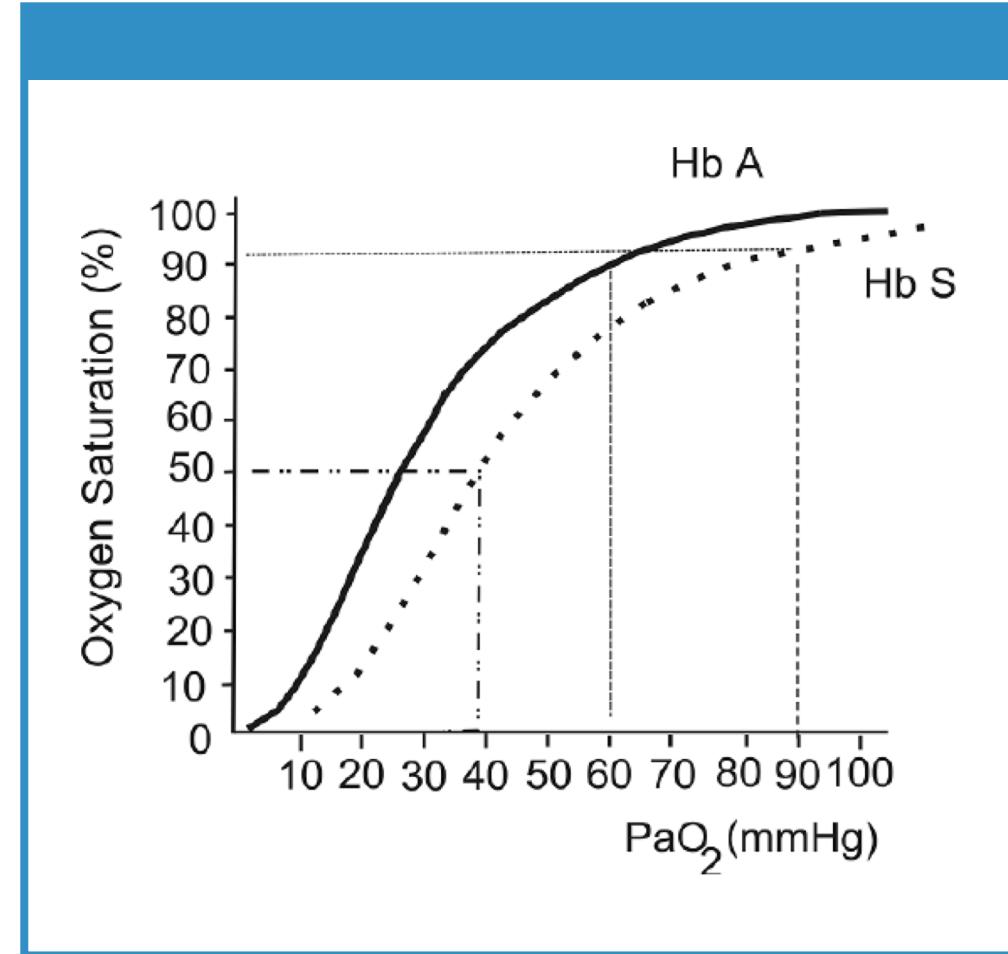
- Open-label trial in ~20 patients with hemoglobin < 9.0.
- Primary endpoint is hemoglobin response, using a definition of 1.0 g/dl over baseline at 12 weeks



2,3-DPG Regulates Hemoglobin Oxygenation in Sickle Cell Disease



Sickle cells (SS) have higher 2,3-DPG compared to normal (AA)



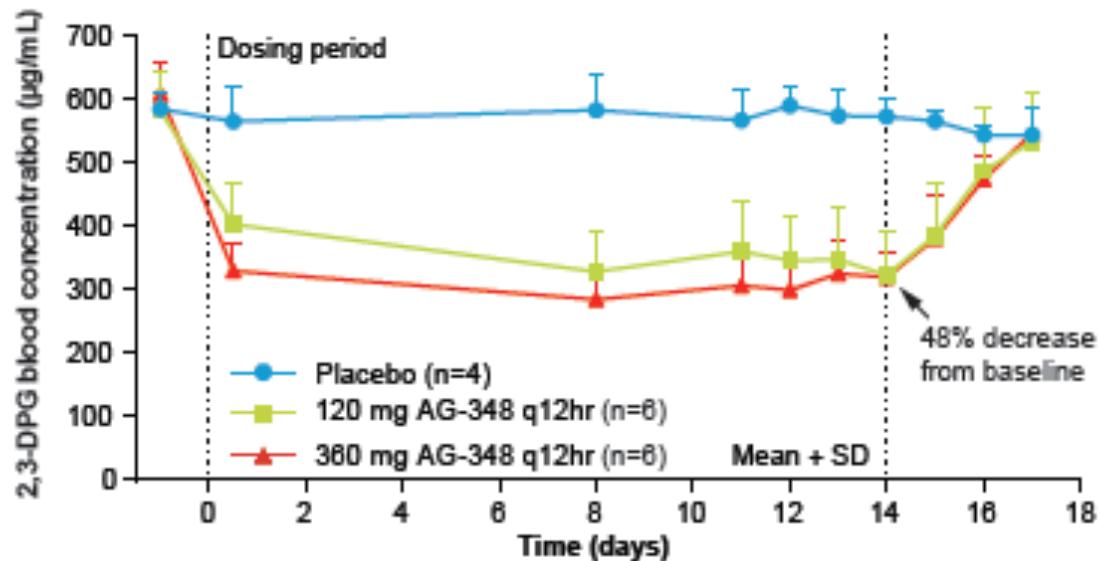
Decreased O₂ affinity can contribute to sickling in SCD
Same affinity for O₂ in Sickle (Hb S) & normal (Hb A)



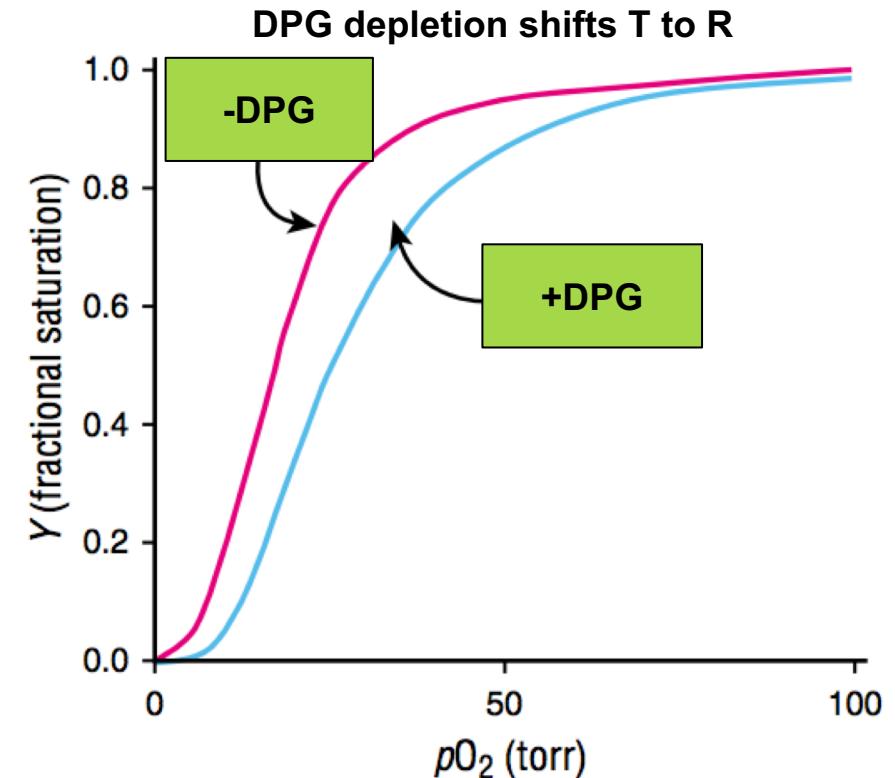
Therapeutic Hypothesis for AG-348: Modulation of 2,3-DPG and ATP Levels Will Reduce HbS Polymerization

Activation of WT PKR in healthy volunteer clinical studies shows ~50% reduction in 2,3-DPG

Mean blood concentration-time profiles of 2,3-DPG following multiple oral doses of AG-348 (cohorts 1 and 2 only)



C



Defining the Potential for PKR Activation in Hemolytic Anemias

- Pyruvate Kinase Deficiency
 - Pivotal program underway for global registration
 - PEAK registry and Natural History Study will further define disease burden
- Life Cycle Expansion
 - Phase 2 proof-of-concept in Thalassemia to start 4Q'18
 - Planning for clinical development in sickle cell underway
 - Assessing biomarker endpoints and study designs for proof-of-mechanism and clinical concept
- Committed to investigating AG-348 in hemolytic anemias where PKR activation can help patients





Financial Overview & Q1 2018 Financial Results

Andrew Hirsch, Chief Financial Officer & Head of Corporate Development



Agios Approach to Drug Discovery and Development Drives Shareholder Value

Discovery Research

6 INDs in 8 years
7th planned for Q4 2018



Discover new cancer or rare genetic disease targets or develop new biological insight to known pathway



Rapidly validate the biology pre-clinically



Develop small molecule chemistry to hit targets

Since 2009

Clinical Development

10+ clinical trials in 6 diseases



Efficiently advance targets into clinic to attain proof-of-concept



Aggressively expand therapeutic opportunity if mechanism warrants

Since 2013

Commercialization

1st medicine approved
2nd NDA under review



Profitably commercialize each approved product



IDHIFA[®]
(enasidenib) tablets
100mg • 50mg



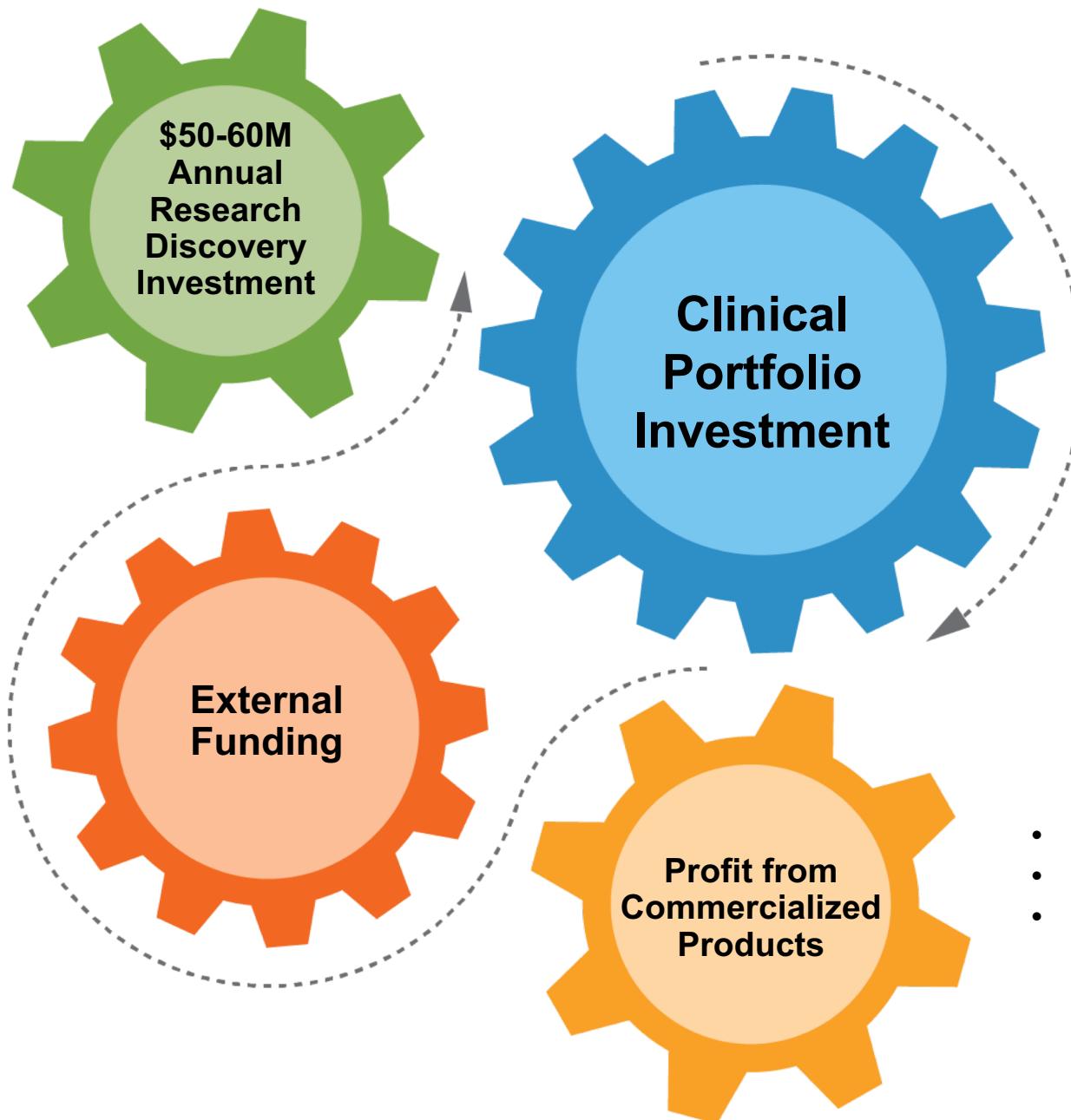
TIBSOVO[®]
(ivosidenib) tablets

Since 2017



Capital Formation and Investment Approach

- 6 INDs in 8 years
- 7th IND planned for Q4 2018
- 9 programs in drug discovery



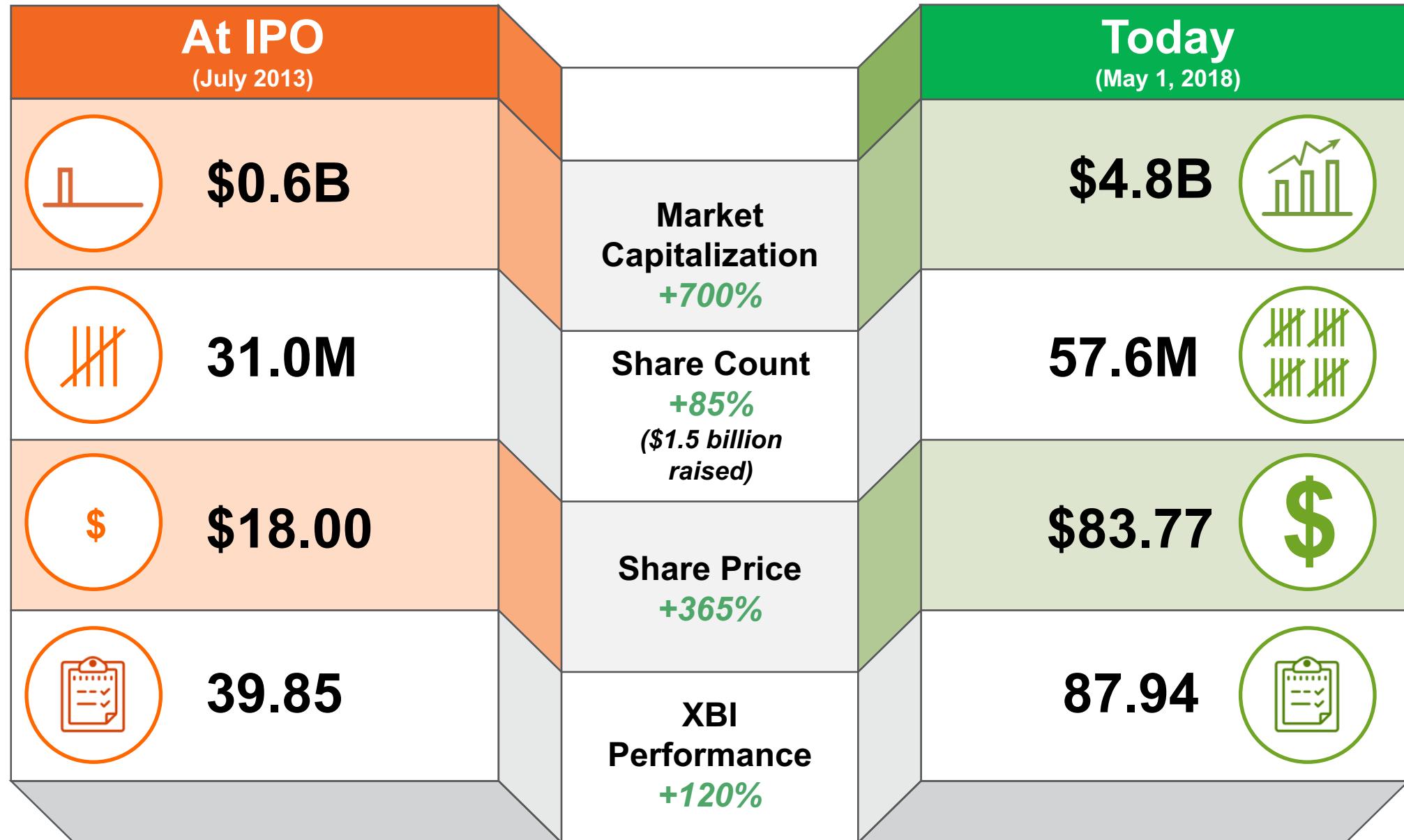
- IDHIFA[®] approval <4 years from 1st patient dosed
- TIBSOVO[®] NDA under priority review
- 10+ clinical trials across 6 disease areas

- ~\$1.5 billion in equity raised from public markets
- ~\$500 million received from Celgene collaborations

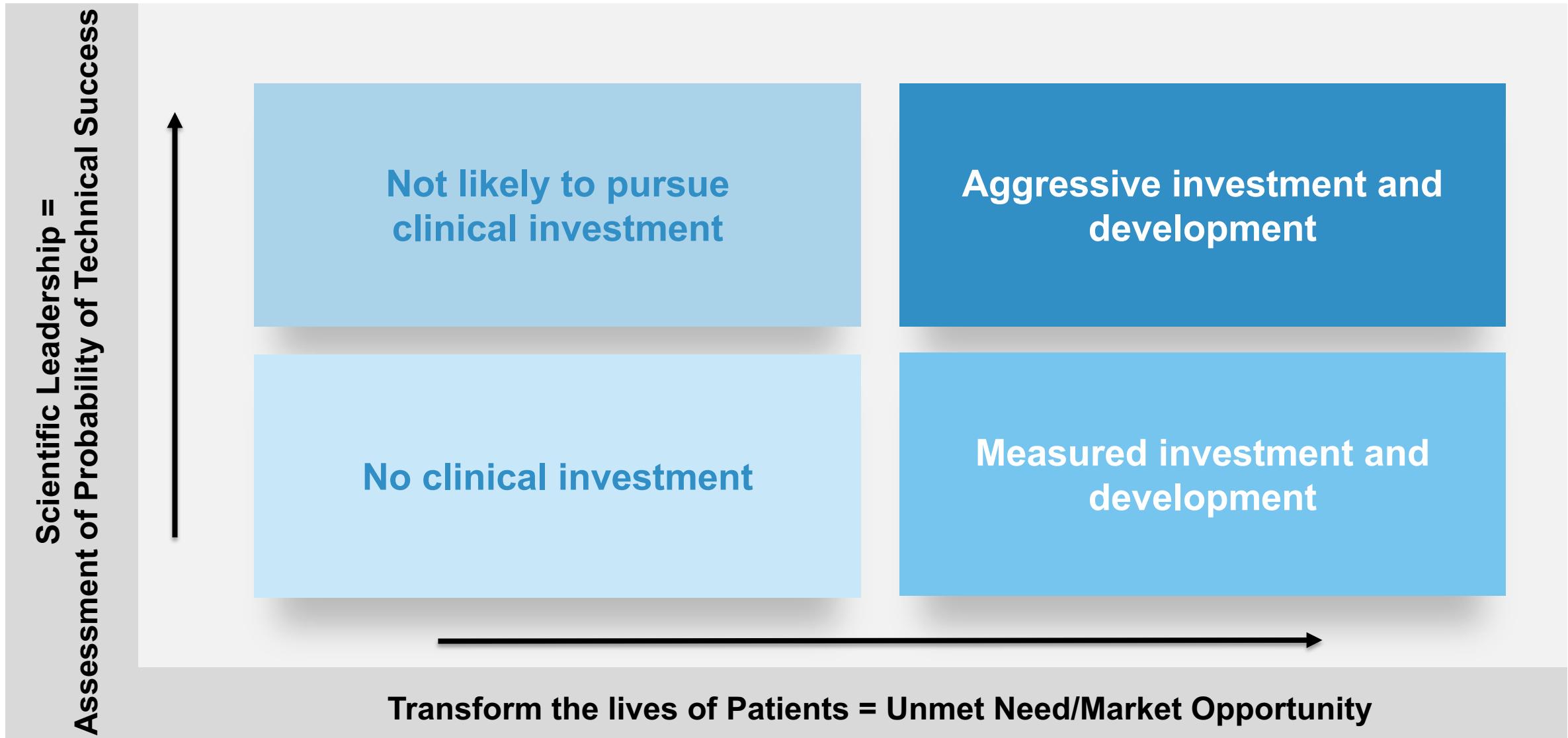
- IDHIFA[®] royalty
- TIBSOVO[®] PDUFA date 8/21/18
- Commercial team in place and “launch ready”



Shareholder Value Creation Since IPO



Clinical Development Decisions Driven By Our Vision and Values



First Quarter Financial Results

Balance Sheet	March 31, 2018	December 31, 2017	Variance
Cash, Cash Equivalents and Marketable Securities	\$995M	\$568M	\$427M
Total Assets	\$1,040M	\$614M	\$426M

Statement of Operations	Three Months Ended March 31, 2018	Three Months Ended March 31, 2017	Variance
Collaboration Revenue	\$7.3M	\$10.5M	(\$3.2M)
Royalty Revenue	\$1.4M	--	\$1.4M
Research & Development Expense (1)	\$78.2M	\$62.7M	\$15.5M
General & Administrative Expense	\$24.6M	\$14.8M	\$9.7M

1) The R&D expenses reported for the three months ended March 31, 2017 are reported net of cost reimbursements of \$2.8 million, for the three months ended March 31, 2018 cost reimbursements are reflected in Collaboration Revenue.

March 31, 2018 cash balance provides runway through at least the end of 2020



Q&A