AG-270 Data at 2019 AACR-NCI-EORTC International Conference 2019

October 27, 2019

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 AG-270; the potential benefits of Agios' product candidates; its key milestones for 2019; its plans regarding future data presentations; and the potential benefit of its strategic plans and focus. The words "anticipate," "expect," "hope," "milestone," "plan," "potential," "possible," "strategy," "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 collaborators 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, the EMA or 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; 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 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

- Opening Remarks – **Jackie Fouse, Ph.D.,** Chief Executive Officer
- Preclinical AG-270 Data – **Kevin Marks, Ph.D.,** Vice President, Head of Biology
- AG-270 Phase 1 Results – **Chris Bowden, M.D.,** Chief Medical Officer
- Q&A – **Keith T. Flaherty, M.D.,** Director of Clinical Research MGH Cancer Center

2019 Key Milestones & Data Presentations Position Agios for Long-term Value Creation

Key 2019 Milestones

- ✓ FDA approval and commercialization of monotherapy TIBSOVO® in untreated AML
- ✓ Initiate AG-636 Phase 1 dose-escalation trial in lymphoma in 1H 2019
- ✓ Complete AG-270 Phase 1 dose-escalation and select go forward dose
- ✓ Initiate expansion arms in the AG-270 Phase 1 study in Q3 2019
- Achieve proof-of-concept for mitapivat in thalassemia in 2H 2019
- Submit sNDA for TIBSOVO® in second line or later cholangiocarcinoma by YE
- Initiate Phase 3 INDIGO study of vorasidenib in low grade glioma by YE
- Complete enrollment in PK deficiency pivotal trials ACTIVATE-T and ACTIVATE by YE

Key Upcoming Data Presentations

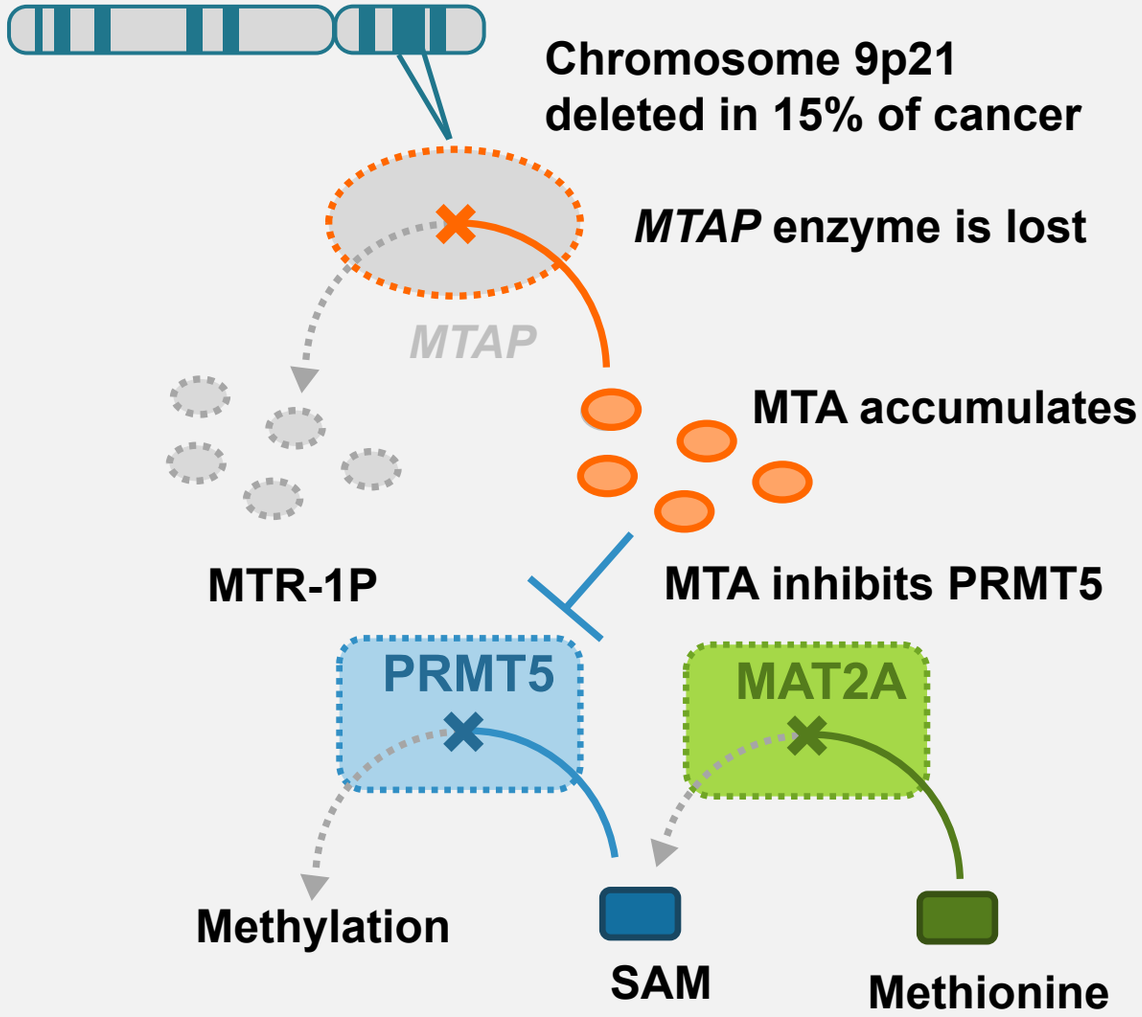
- Updated data from the perioperative study of ivosidenib and vorasidenib accepted for presentation at the SNO Annual Meeting
- Data from IDH and PKR programs have been accepted for presentation at ASH, including:
  - New data from the extension phase of the Phase 2 DRIVE PK study of mitapivat in adults with PK deficiency
  - Important translational data from the Phase 1 study of TIBSOVO® and azacitidine in frontline AML

Targeting MAT2A in *CDKN2A*/*MTAP*-deleted Cancers

Kevin Marks, Vice President and Head of Biology

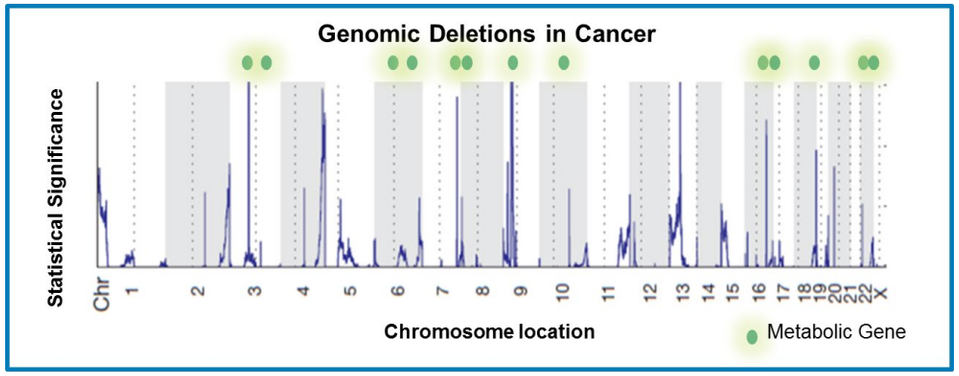
A Key Insight: Deletion of *MTAP* Makes Cancers Vulnerable to Targeting of MAT2A

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**

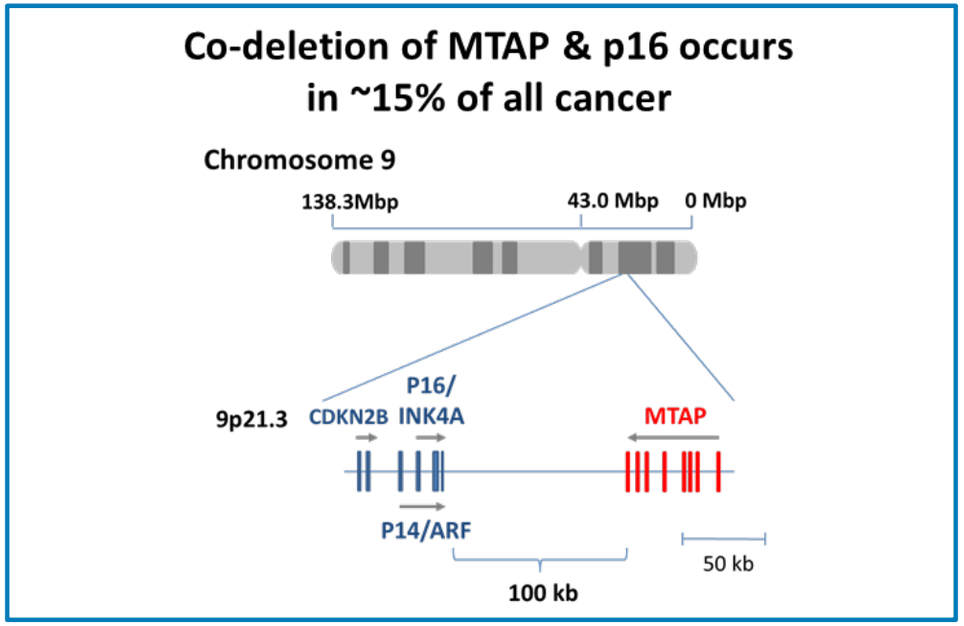


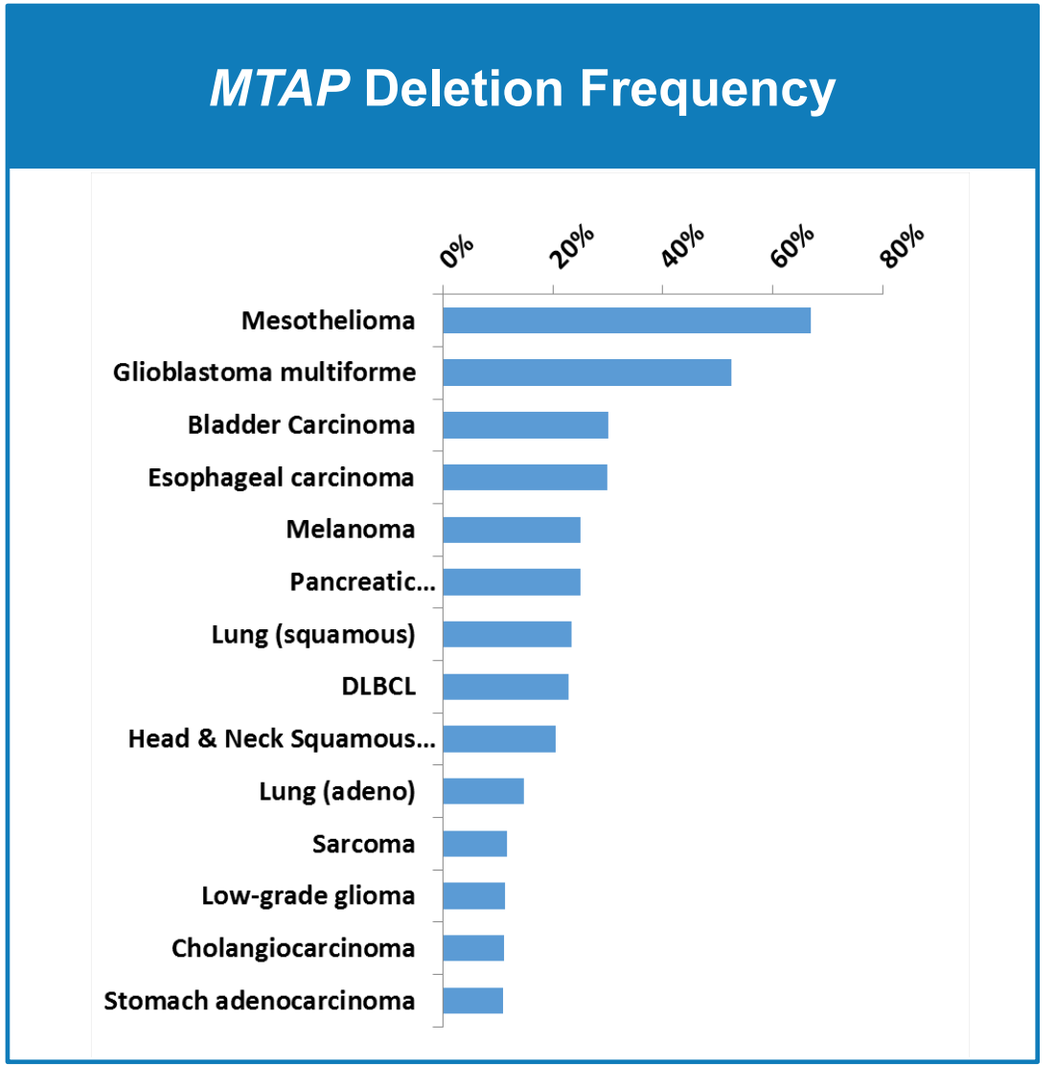
Sources: Marjon et al Cell Reports. 2016 Apr 19;15(3):574-587 and MTAP deletion frequency from Agios analysis of data from The Cancer Genome Atlas

MTAP Deletions Occur in ~15% of All Cancers



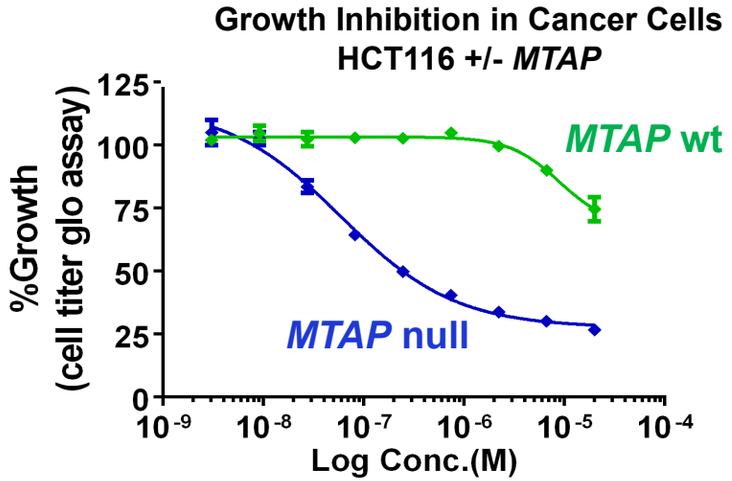
Source: Adapted from Beroukhim et al Nature 2010

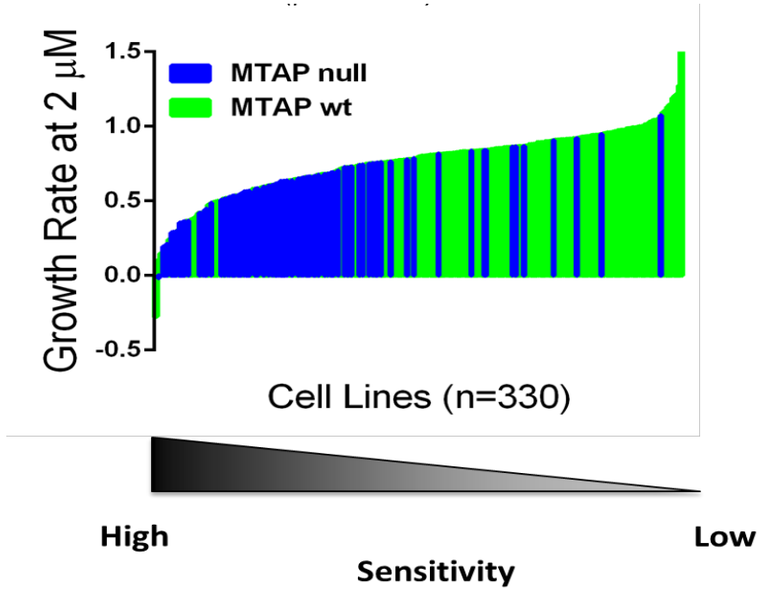


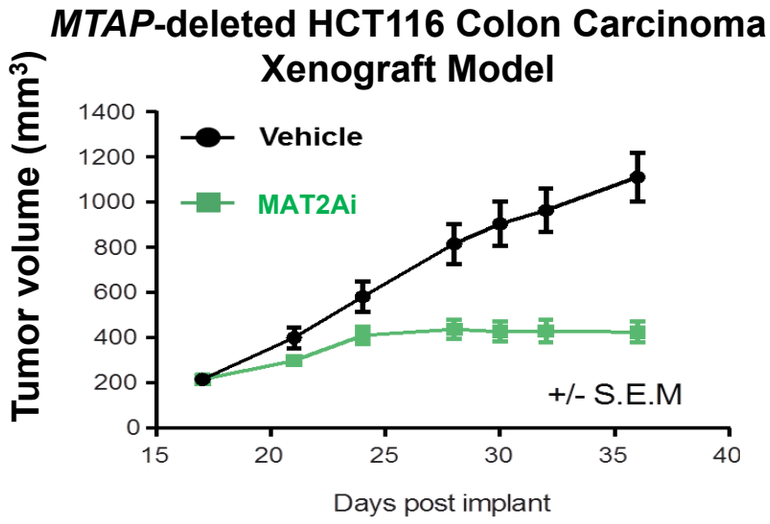


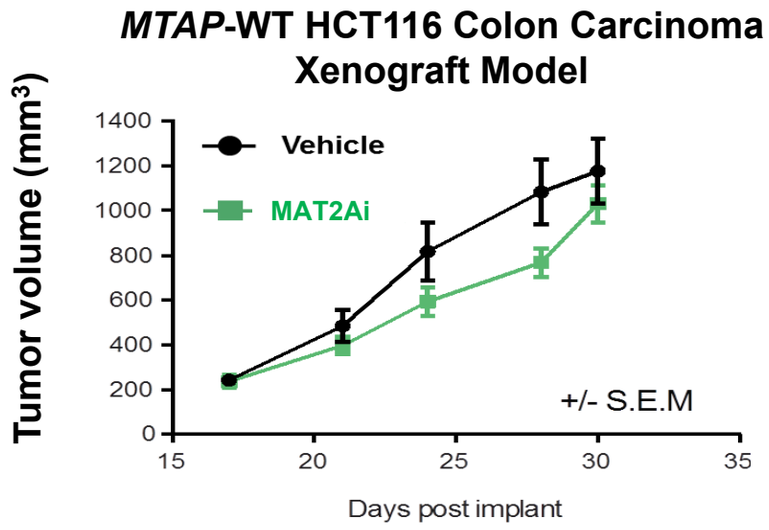
Sources: Marjon et al Cell Reports. 2016 Apr 19;15(3):574-587; Agios data on file; Illei et al Clinical Cancer Research. 2003 Jun; 9(6):2108-13;
MTAP deletion frequencies are from Agios analysis of data from The Cancer Genome Atlas

Agios MAT2A Inhibitors Selectively Impact Proliferation of *MTAP*-null Cancers

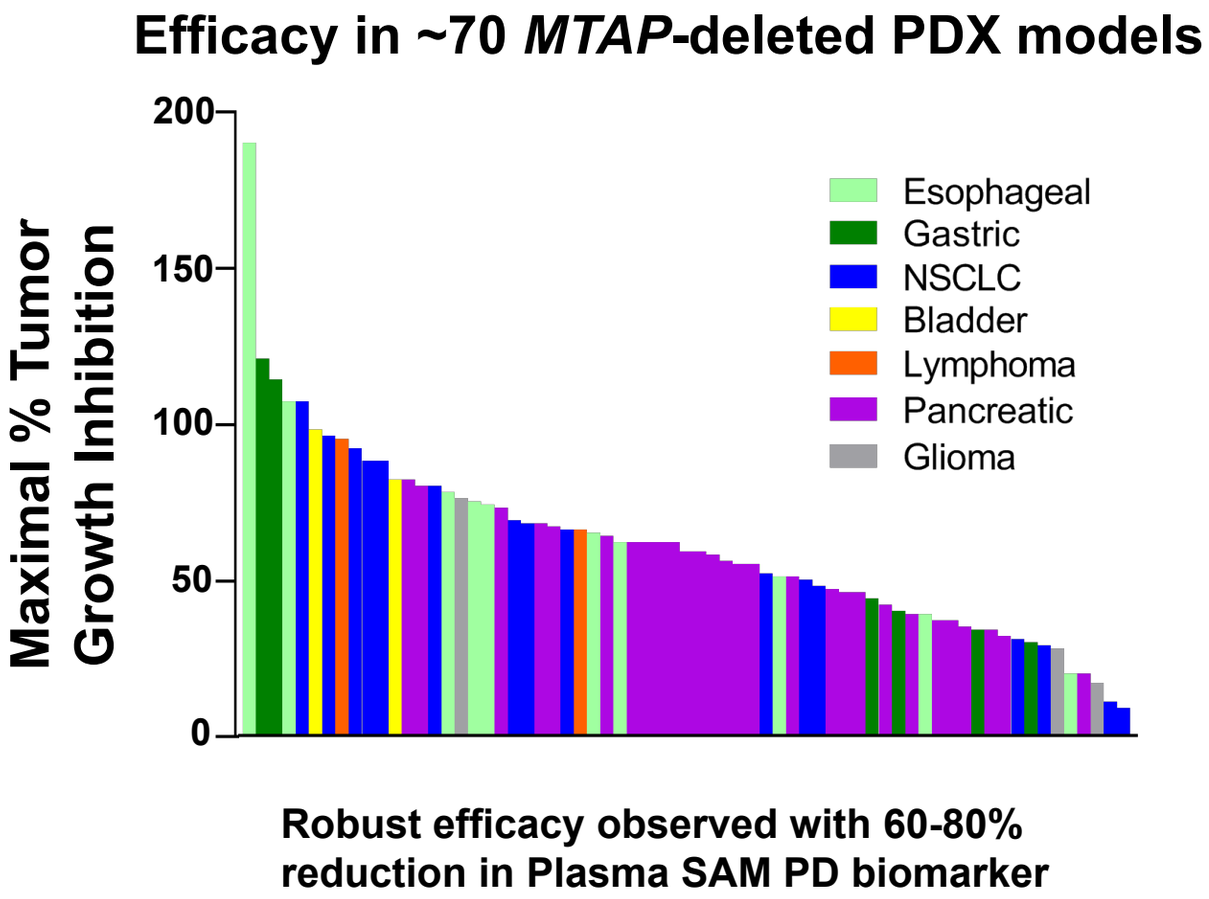


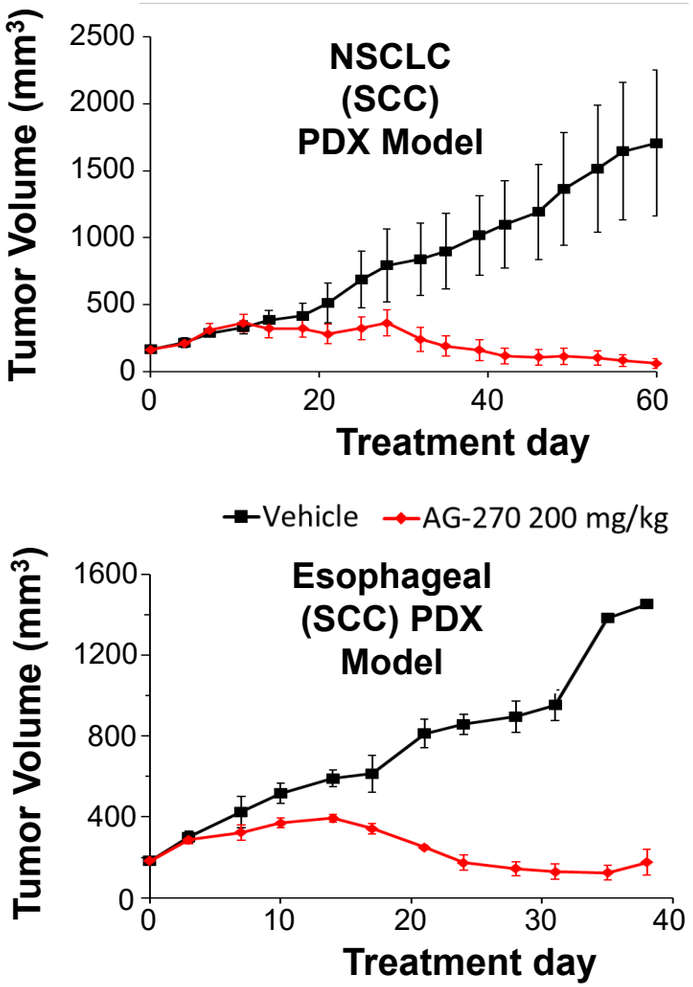






MAT2A Inhibitor AG-270 Possesses Broad Activity in 'Mouse Clinical Trial' Using Patient Derived Xenograft Models



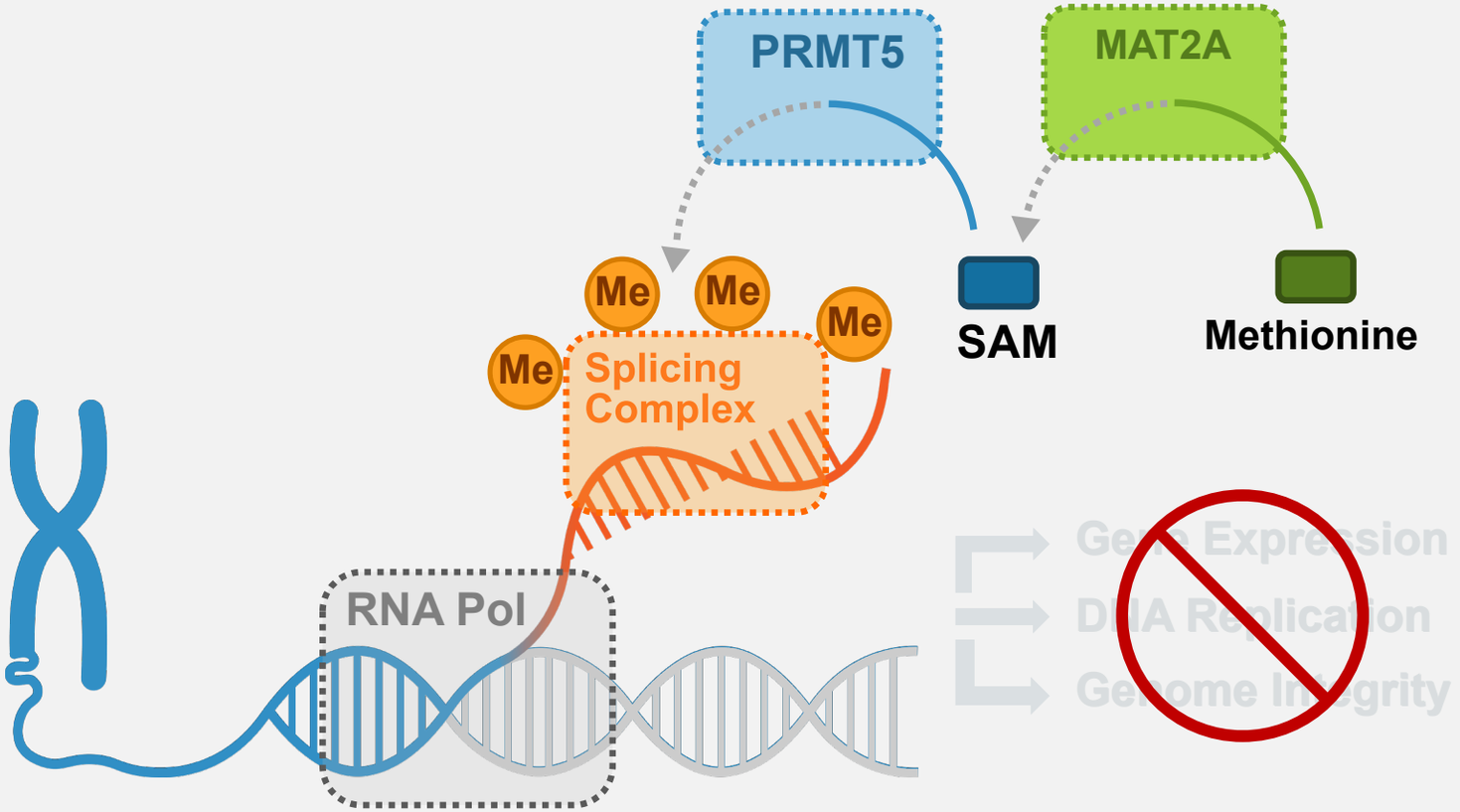


N=3 per model; established tumors treated at 200 mpk AG-270 QD

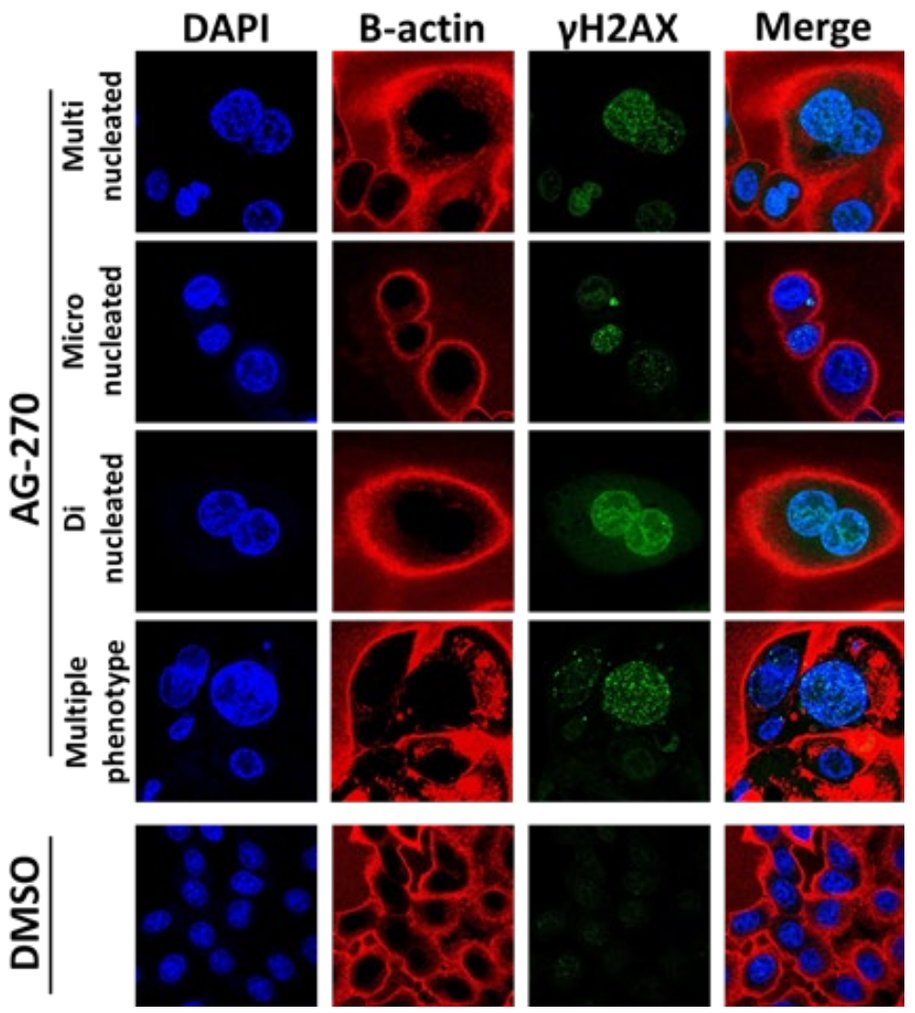
Anti-tumor activity observed in a variety of models, with examples of regressions / tumor stasis

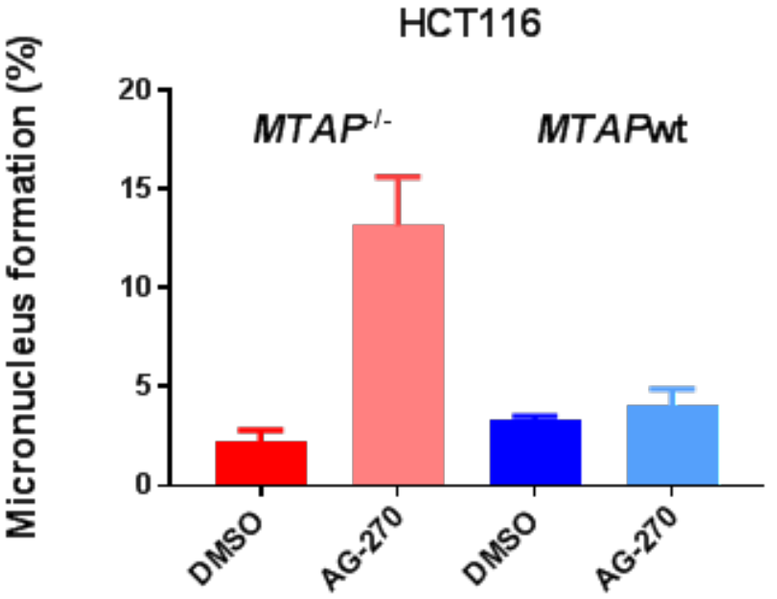
Mechanistic Understanding of the Pathway Downstream of MAT2A

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
5. DNA repair and cell cycle defects, leading to actionable combination partners including taxanes



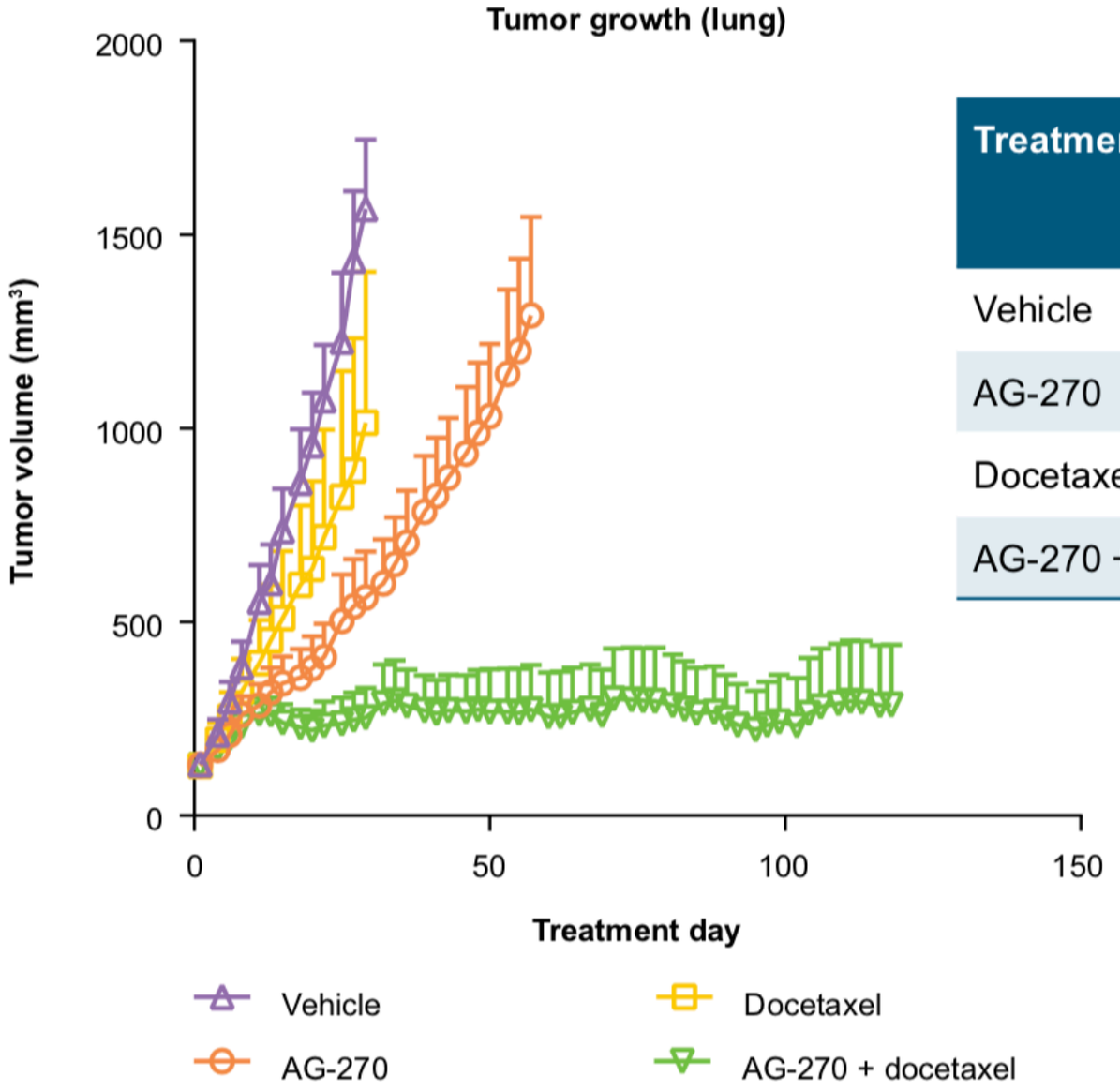
AG-270 Treatment Induces Substantial Mitotic Defects in HCT116 *MTAP*-/- cells





- Single Agent AG-270 treatment leads to DNA damage (γH2AX) and micronuclei formation
- Effects are selectively observed in *MTAP*-/- cells and not in *MTAP*-wt cells

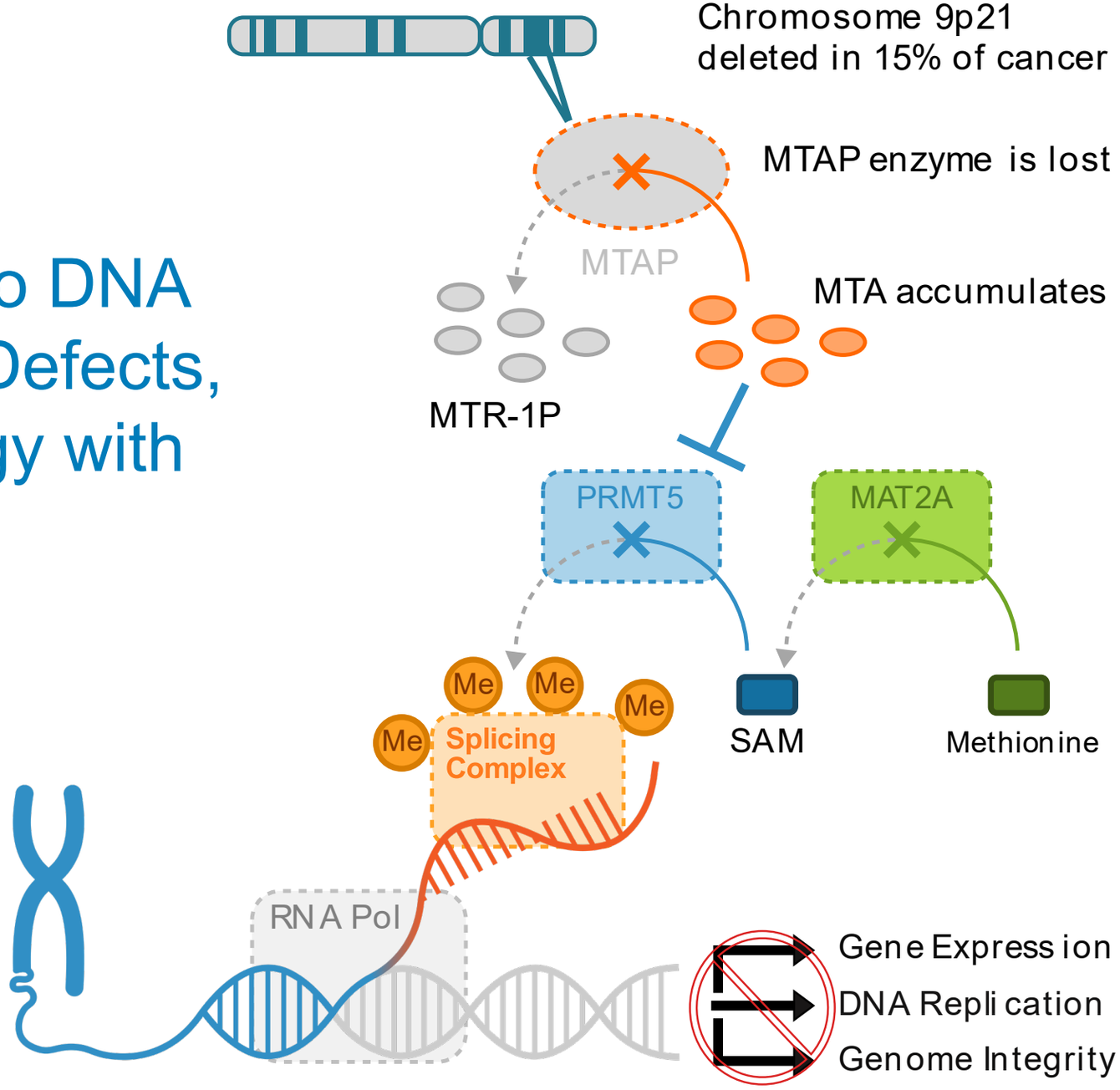
AG-270 Enhanced Docetaxel Treatment in an NSCLC (SCC) *MTAP*-null Mouse Model



Treatment group	Days to ~1000 mm³	Tumor growth inhibition, %
Vehicle	21	–
AG-270	48	70
Docetaxel	28	38
AG-270 + docetaxel	–	91

4 of 8 animals were tumor free at last dose and remained tumor free until the arm was terminated on Day 141

MAT2A Inhibition Leads to DNA Damage and Cell Cycle Defects, Leading to Strong Synergy with Anti-mitotic Taxanes



A phase 1 trial of AG-270 in patients with advanced solid tumors or lymphoma with homozygous *MTAP* deletion

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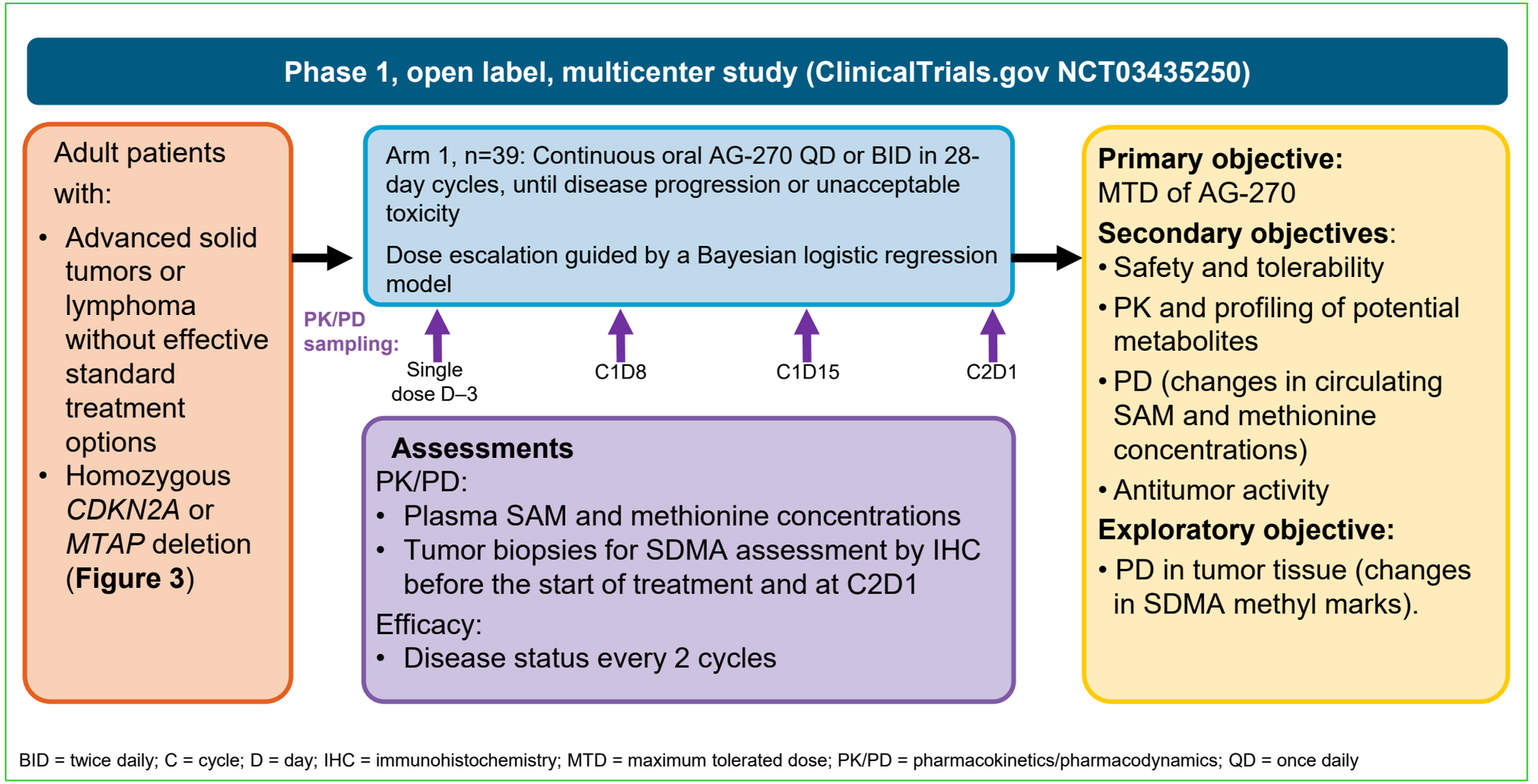
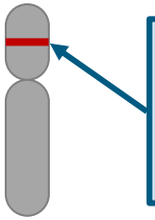
Study design



BID = twice daily; C = cycle; D = day; IHC = immunohistochemistry; MTD = maximum tolerated dose; PK/PD = pharmacokinetics/pharmacodynamics; QD = once daily

MTAP and *CDKN2A* deletion for patient selection



MTAP and *CDKN2A* within 100 kbp of each other on chromosome 9p21

- Chr9p21 deleted in ~15% of cancers[1]
- *MTAP* loss commonly coincides with *CDKN2A* loss[2]

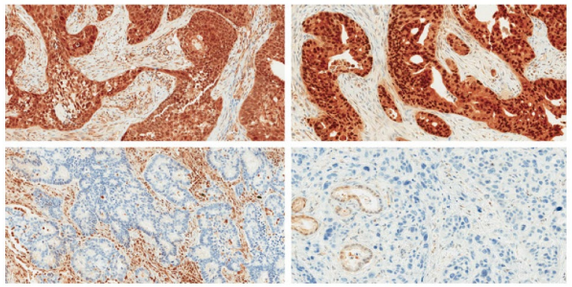
Analysis of Cancer Genome Atlas data

Cancer type	*CDKN2A* deletion, %	*MTAP* deletion, %	Tumors with *CDKN2A/MTAP* co-deletion, %
Pancreatic	28	25	88
DLBCL	31	23	73
Esophageal and gastric	25	19	76
Lung (all)	23	19	82

Required for patient enrollment: evidence of homozygous *CDKN2A* deletion by local testing (e.g. next-generation sequencing) or of homozygous MTAP deletion by a central IHC assay

IHC assay optimized for MTAP protein expression in FFPE tumor tissue, with <20% MTAP-positive cells as the cutoff value for MTAP deletion

NSCLC (SCC)
MTAP-positive tumor cells = 100%



Pancreatic (adenocarcinoma)
MTAP-positive tumor cells = 100%

NSCLC (adenocarcinoma)
MTAP-positive tumor cells = 0%

Pancreatic (adenocarcinoma)
MTAP-positive tumor cells = 0%

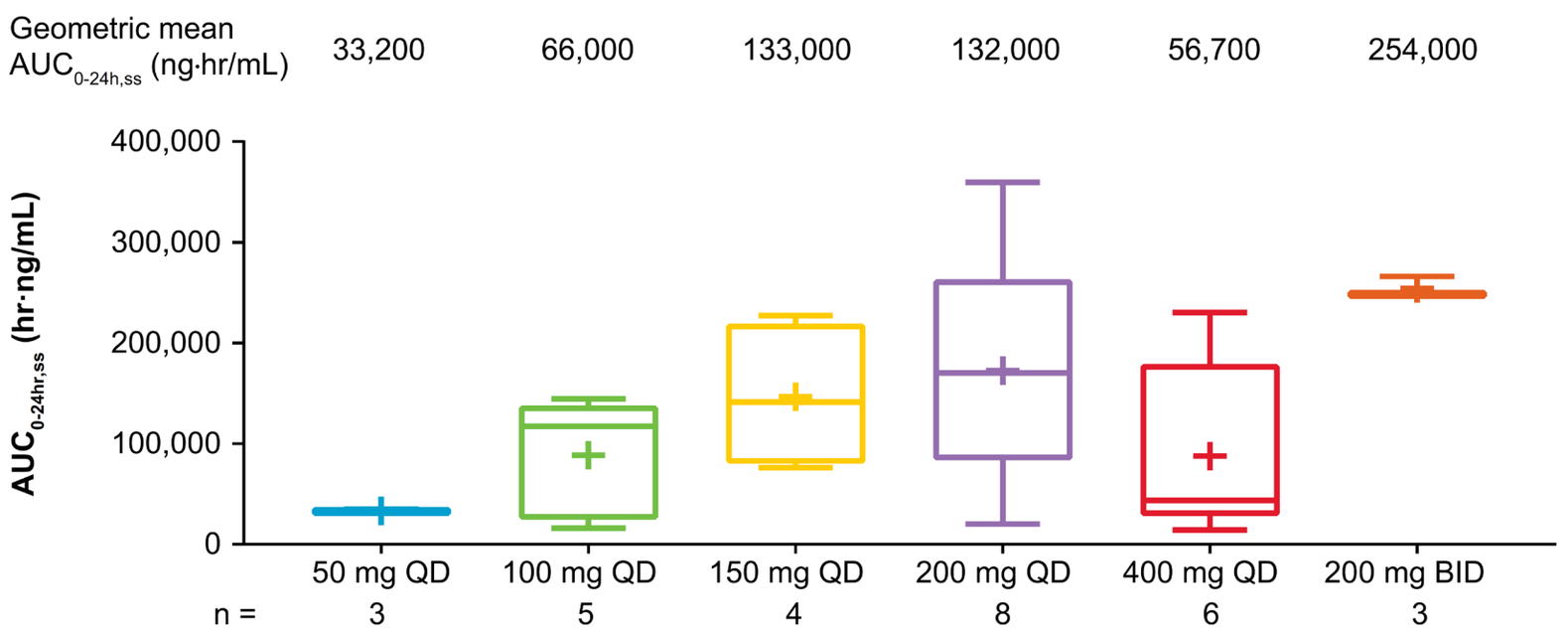
DLBCL = diffuse large B-cell lymphoma; FFPE = formalin-fxed paraffn-embedded; NSCLC = non–small-cell lung cancer; SCC = squamous cell carcinoma

Patient Characteristics

Dose	50 mg QD	100 mg QD	150 mg QD	200 mg QD	400 mg QD	200 mg BID
Patients, n	3	7	6	11	6	6
Baseline characteristic	**N=39**					
Age, median (range), years <60, n (%) ≥60, n (%)	65 (32–87) 17 (44) 22 (56)					
Male sex, n (%)	21 (54)					
Enrollment on the basis of:[a] *CDKN2A* deletion, n (%) *MTAP* deletion, n (%)	 34 (87) 5 (13)					
Patients with both *CDKN2A* deletion and tumor tissue evaluable for *MTAP* deletion by IHC, n (%) Patients with both *CDKN2A* deletion and MTAP deletion by IHC, n (%)	22 (56) 15 (68)					
Primary tumor type, n (%) Bile duct cancer Pancreatic cancer Mesothelioma NSCLC Other cancer type	 7 (18) 7 (18) 4 (10) 4 (10) 17 (44)					
Number of lines of prior therapy, n (%) One Two Three or more	 12 (31) 9 (23) 18 (46)					

[a]*CDKN2A* status based on local testing, MTAP status by IHC performed centrally

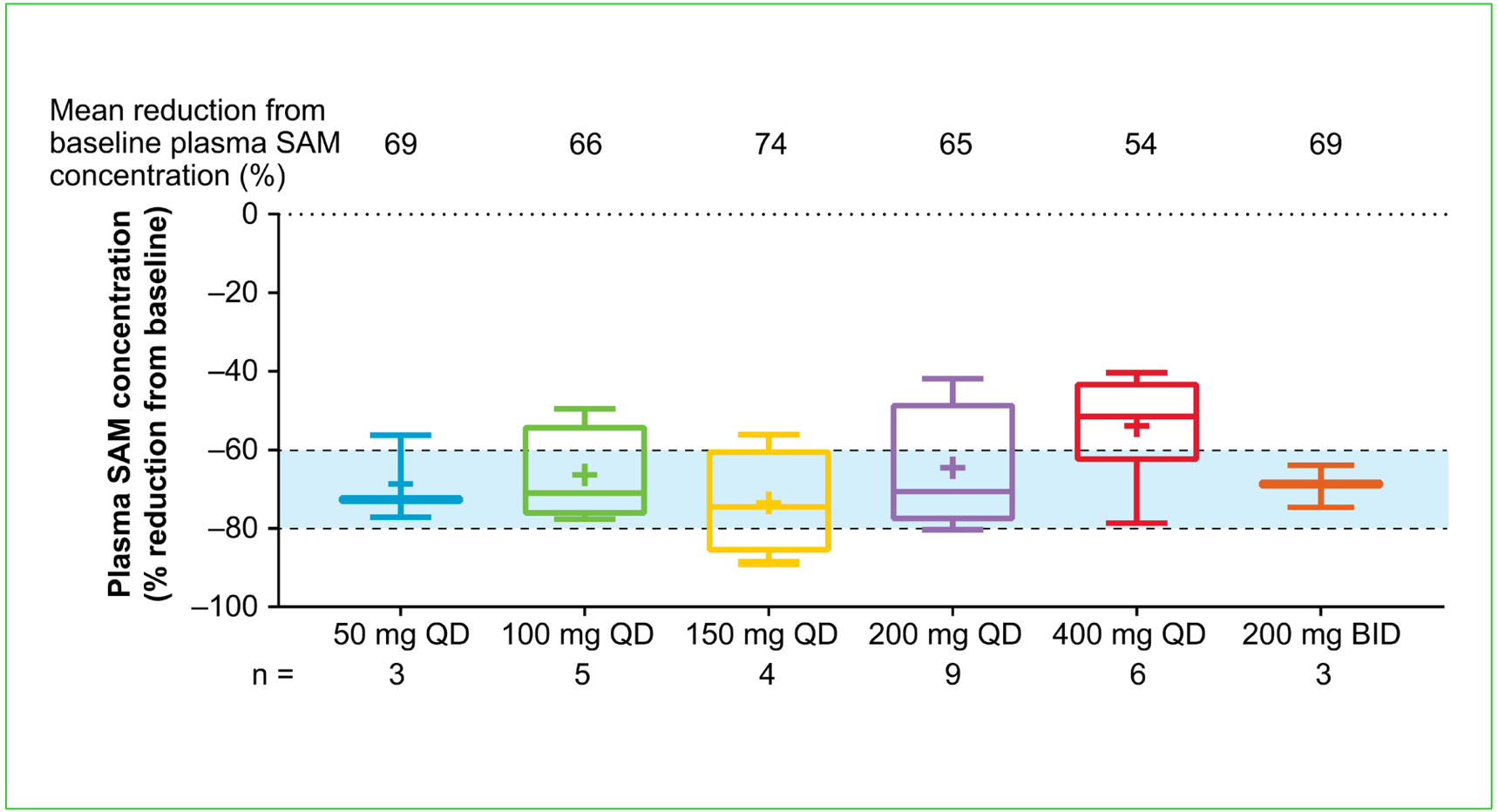
Pharmacokinetics



Box denotes 25th to 75th percentiles, horizontal bar the median, and + the mean, with whiskers extending to the minimum and maximum values
$AUC_{0\text{-}24hr}$ = AUC from 0 to 24 hr; ss = steady state

- Mean exposure increased in an approximately dose-proportional manner between 50 mg QD and 200 mg QD
- Mean exposure was lower at 400 mg QD than 200 mg QD, possibly secondary to a reduction in oral bioavailability
- Due to this observation, a dose of 200 mg BID was evaluated, which increased steady-state area under the plasma concentration-time curve (AUC) by 1.9-fold relative to a dose of 200 mg QD.

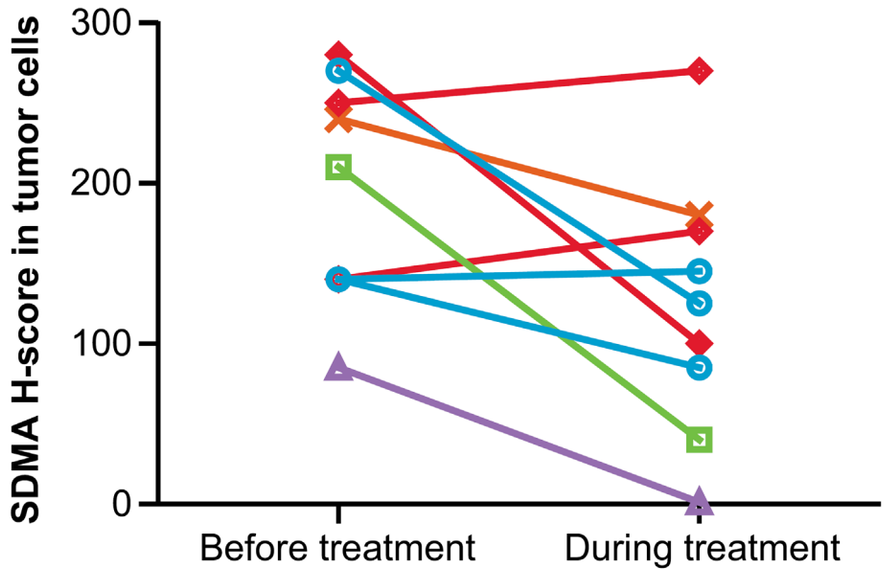
Reductions in plasma SAM concentration at steady state (C1D15)



Box denotes 25th to 75th percentiles, horizontal bar the median, and + the mean, with whiskers extending to the minimum and maximum values

- Plasma SAM concentration at C1D15 decreased by 65–74% across doses of 50–200 mg QD and 200 mg BID
  - The lower reduction in plasma SAM concentration (~54%) observed at 400 mg QD is consistent with the lower AG-270 exposure observed at this dose
- Average reductions in plasma SAM concentration are within the range associated with maximum tumor growth inhibition in preclinical models (60–80%)

SDMA expression by IHC in paired pre- and post-dose tumor biopsies



Cohort	SDMA relative % change (H-score)
	Mean ± SEM
50 mg QD (n=3)	–29.8 ± 17.2
100 mg QD (n=1)	–80.9
200 mg QD (n=1)	–98.8
400 mg QD (n=3)	–11.6 ± 26.6
200 mg BID (n=1)	–25
Total (n=9)	**–36.5 ± 14.0**

SEM = standard error of the mean

- Analysis of nine paired tumor biopsies by IHC showed decreases in levels of SDMA residues, consistent with MAT2A inhibition
- The average (min, max) H-score reduction compared with baseline was 36.5% (–98.8%, +21.4%).

Summary of AEs and dose-limiting toxicities by dose cohort

	50 mg QD n=3	100 mg QD n=7	150 mg QD n=6	200 mg QD n=11	400 mg QD n=6	200 mg BID n=6	Total N=39
Patients with any AG-270–related AE, n (%)	3 (100)	4 (57)	4 (67)	6 (55)	4 (67)	5 (83)	26 (67)
Most common (>10%) AG-270–related AE, n (%)							
Increased blood bilirubin	0	1 (14)	2 (33)	4 (36)	0	3 (50)	10 (26)
Fatigue	2 (67)	3 (43)	1 (17)	1 (9)	1 (17)	1 (17)	9 (23)
Decreased platelet count	0	1 (14)	1 (17)	1 (9)	0	3 (50)	6 (15)
Rash	2 (67)	0	2 (33)	1 (9)	0	1 (17)	6 (15)
Patients with grade 3 or higher AG-270–related AE, n (%)	0	0	1 (17)	2 (18)	0	4 (67)	7 (18)
Increased blood bilirubin	0	0	1 (17)	1 (9)	0	2 (33)	4 (10)
Decreased neutrophil count	0	0	1 (17)	1 (9)	0	0	2 (5)
Decreased platelet count	0	0	1 (17)	0	0	2 (33)	3 (8)
Decreased white blood cell count	0	0	1 (17)	0	0	0	1 (3)
Lymphopenia	0	0	1 (17)	0	0	0	1 (3)
Anemia	0	0	1 (17)	0	0	0	1 (3)
Rash	0	0	1 (17)	0	0	1 (17)	2 (5)
Liver injury	0	0	0	0	0	2 (33)	2 (5)
Dose-limiting toxicities, n (%)							
Increased blood bilirubin	0	0	1 (17)	0	0	0	1 (3)
Decreased neutrophil count	0	0	0	1 (9)	0	0	1 (3)
Decreased platelet count	0	0	0	0	0	1 (17)	1 (3)
Rash	0	1 (14)	1 (17)	0	0	1 (17)	3 (8)
Acute liver injury	0	0	0	0	0	2 (33)	2 (5)

Summary of AEs and dose-limiting toxicities

- Generalized erythematous rash in three patients, treated at 100 mg QD, 150 mg QD and 200 mg BID:
  - Onset during second week of treatment, resolved <1 week after AG-270 interruption
  - Successful rechallenge at a lower dose in two patients.

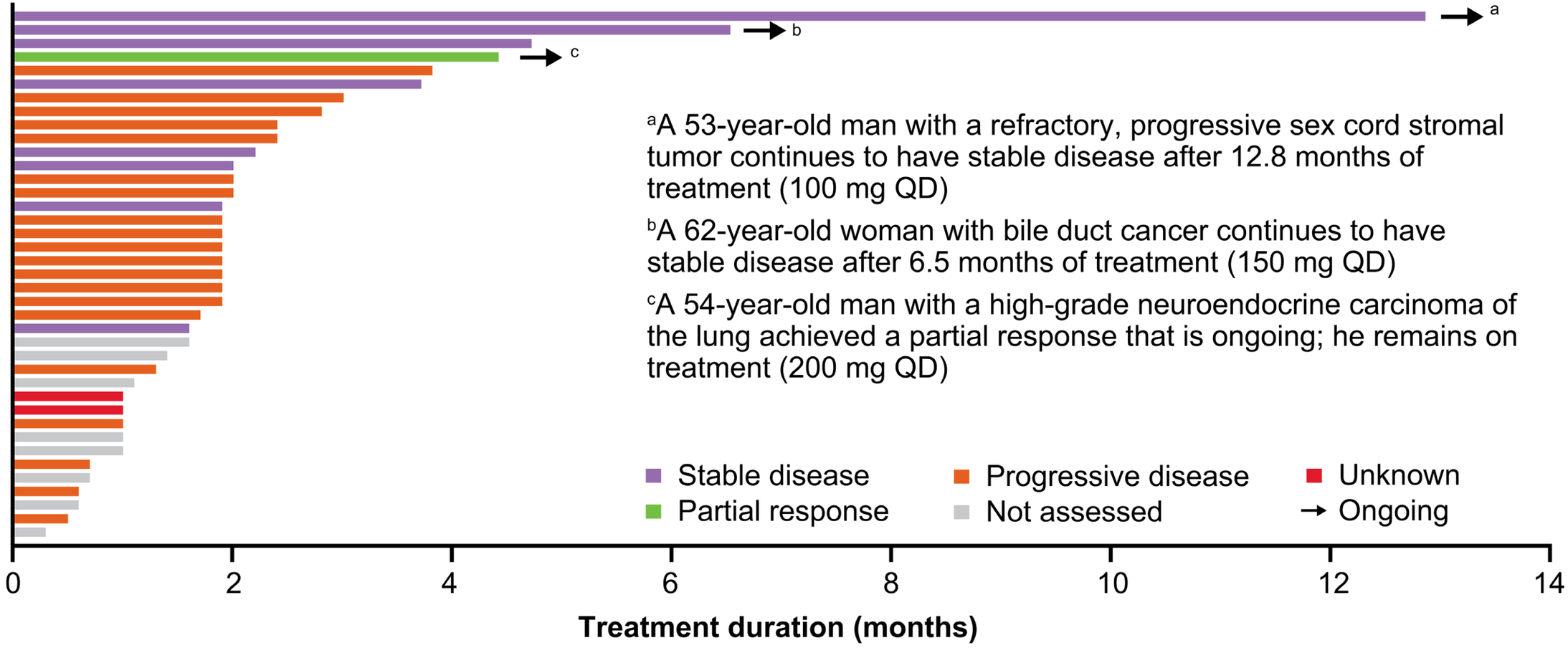
QD cohorts

- Increases in unconjugated bilirubin, starting at 100 mg QD:
  - Consistent with UGT1A1 inhibition, exposure-dependent, reversible.
- Mild myelosuppression, starting at 200 mg QD:
  - Most consistently manifested as reversible thrombocytopenia (with or without leukopenia/anemia).

200 mg BID cohort

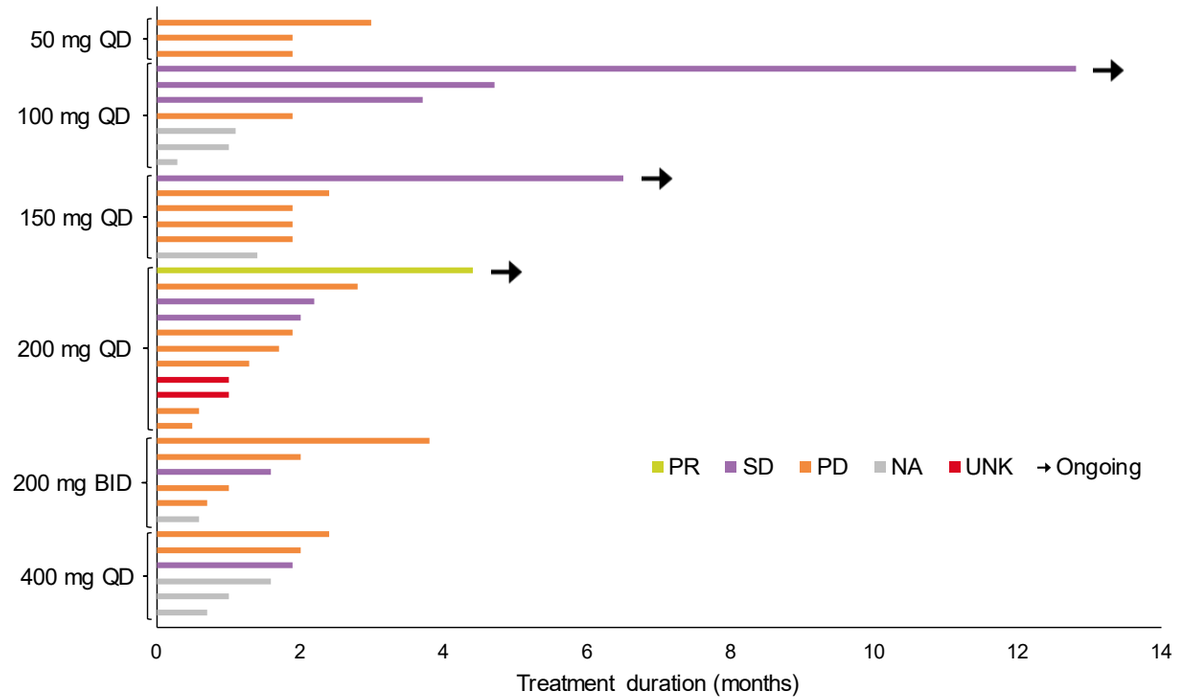
- Reversible acute liver injury in two of six patients:
  - Asymptomatic grade 3 and 4 increases in alanine aminotransferase, aspartate aminotransferase, and total bilirubin
  - Outpatient treatment with oral steroids, leading to complete resolution
  - Not clearly related to higher AG-270 systemic exposure.
- Grade 3 and 4 thrombocytopenia in two of six patients.
- **MTD was determined to be 200 mg QD.**

Duration of treatment and best overall response in patients receiving AG-270

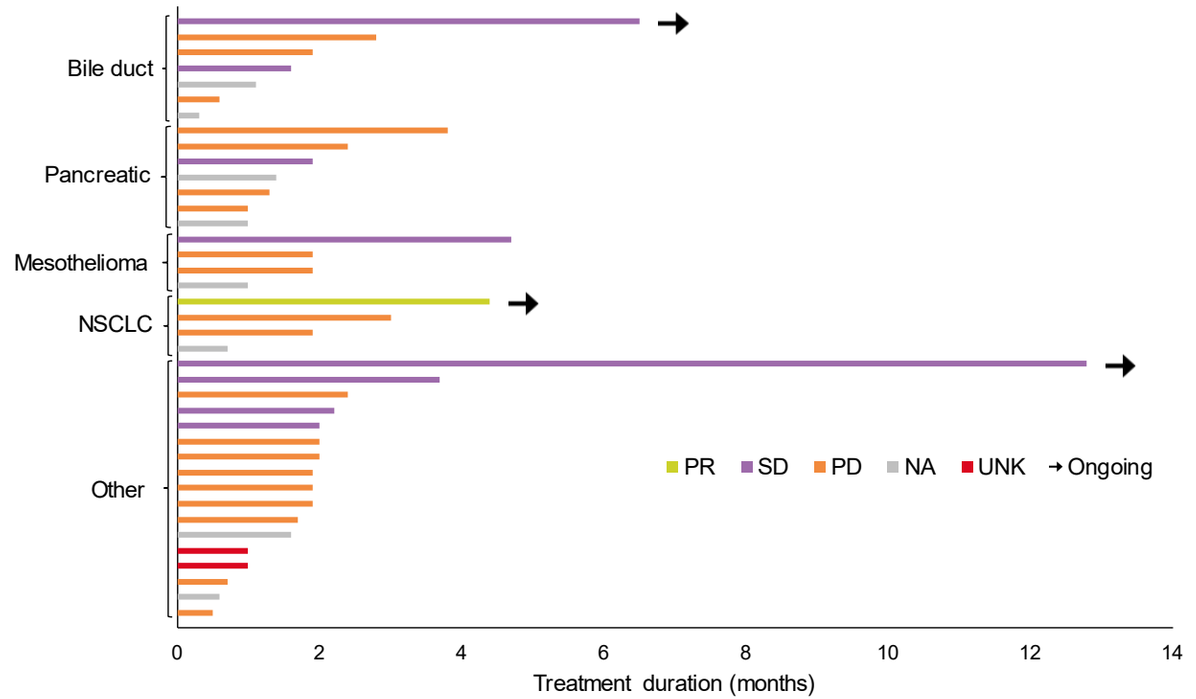


Duration of treatment and best overall response in patients receiving AG-270

Response by dose



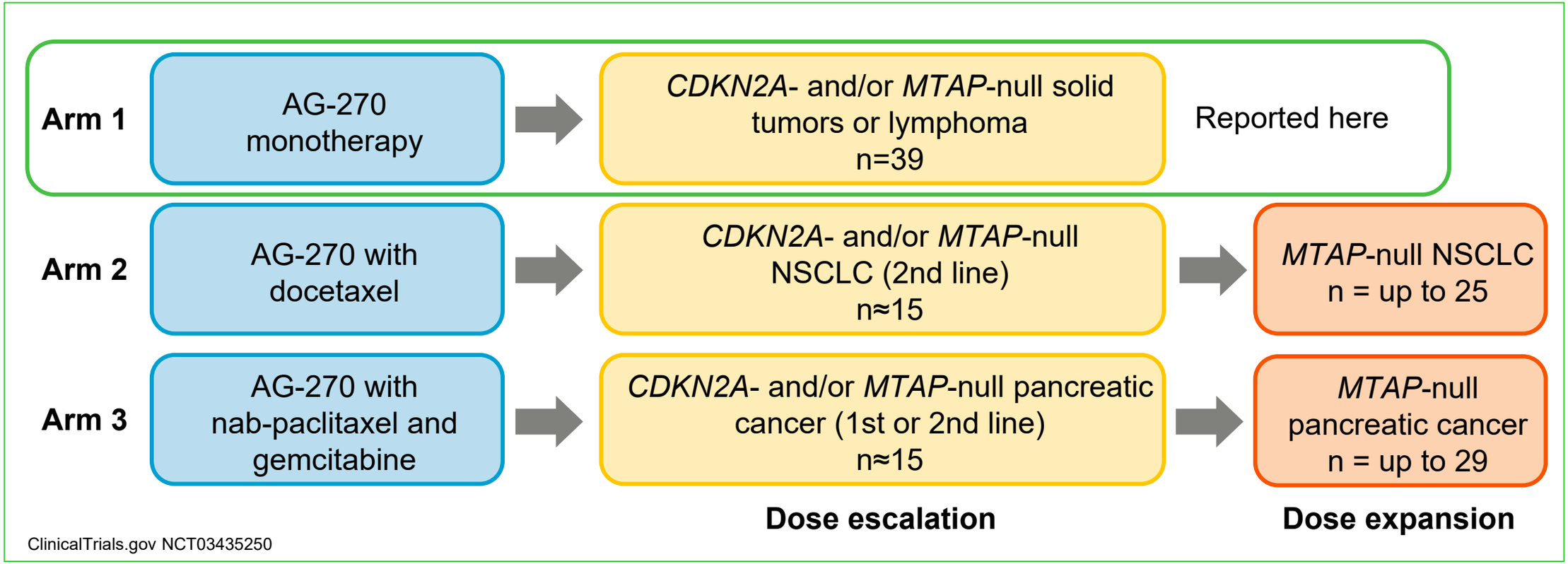
Response by tumor type



Conclusions

- AG-270 is the first MAT2A inhibitor to be evaluated in humans.
- The MTD was determined to be 200 mg QD.
  - DLTs included transient diffuse rashes, neutropenia and thrombocytopenia, and reversible acute liver injury.
- AG-270 generates reductions in plasma SAM concentration and in levels of tumor SDMA at well-tolerated doses.
- Average reductions in plasma SAM concentration were similar between 50 and 200 mg QD, and within the range associated with maximum tumor growth inhibition in preclinical models (60–80%).
- Objective tumor response was uncommon in this group of patients with treatment-refractory malignancies.
  - However, a confirmed partial response was observed in a patient with a high-grade neuroendocrine carcinoma of the lung and two patients experienced prolonged stable disease of more than 6 months.

Two arms of the Phase 1 trial combining AG-270 with taxanes currently enrolling patients



- Dosing with AG-270 in the combination arms will start at 100 mg QD and can be increased to 200 mg QD

Q&A