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

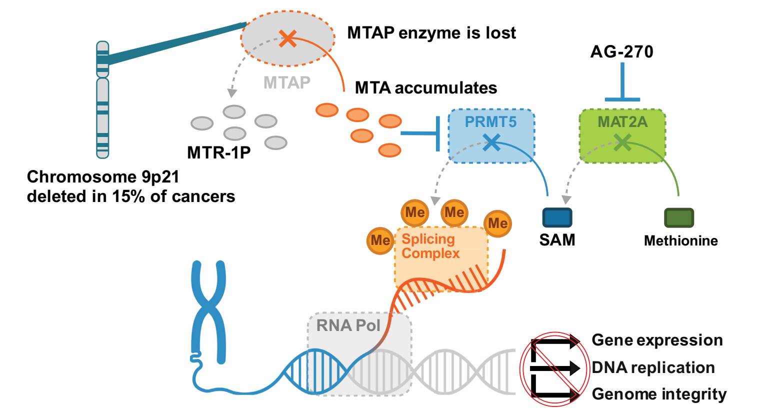
Rebecca S Heist[1], Mrinal M Gounder[2], Sophie Postel-Vinay[3], Frederick Wilson[4], Elena Garralda[5], Khanh Do[6], Geoffrey I Shapiro[6], Patricia Martin-Romano[3], Gerburg Wulf[7], Michael Cooper[8], Caroline Almon[8], Salah Nabhan[8], Varsha Iyer[8], Yanwei Zhang[8], Kevin M Marks[8], Elia Aguado-Fraile[8], Frank Basile[8], Keith Flaherty[1], Howard A Burris[9]

[1]Massachusetts General Hospital, Boston, MA, USA; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [3]Institut Gustave Roussy, Villejuif, France; [4]Yale Cancer Center, New Haven, CT, USA; [5]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]Dana-Farber Cancer Center, Boston, MA, USA; [7]Beth Israel Deaconess Medical Center, Boston, MA, USA; [8]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [9]Sarah Cannon Research Institute, Nashville, TN, USA

BACKGROUND

- Homozygous deletion of *MTAP*, the gene encoding the metabolic enzyme methylthioadenosine phosphorylase, occurs in ~15% of human malignancies.[1,2]
- *MTAP* deletion frequently coincides (~80% of cases) with the loss of cyclin-dependent kinase inhibitor 2A (*CDKN2A*), a well-known negative prognostic factor in cancer.
- Deletion of *MTAP* results in the accumulation of the enzyme's substrate, methylthioadenosine (MTA).
- Increased concentrations of MTA partially inhibit the activity of protein arginine methyltransferase 5 (PRMT5), while other methyltransferases are relatively unaffected.[3]
- Inhibition of PRMT5 activity results in a reduction in symmetrically di-methylated arginine residues (SDMAs) on target proteins, many of which are involved in mRNA splicing.
- Further reduction of PRMT5 activity can be achieved through reductions in the concentration of its normal substrate, the methyl donor S-adenosylmethionine (SAM), via inhibition of the enzyme MAT2A (**Figure 1**).
- AG-270 is a first-in-class, oral, potent, reversible inhibitor of methionine adenosyltransferase 2A (MAT2A), the key enzyme responsible for SAM synthesis.

Figure 1. Targeting MAT2A in cancers with *MTAP* deletion

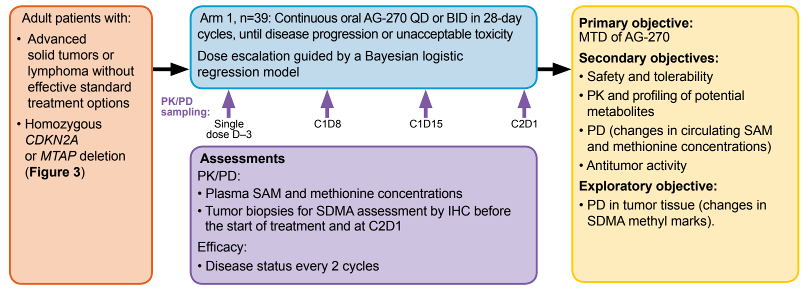


MAT2A = methionine adenosyltransferase 2A; Me = methylation; MTA = methylthioadenosine; MTAP = methylthioadenosine phosphorylase; PRMT5 = protein arginine methyltransferase 5; RNA Pol = RNA polymerase; SAM = S-adenosylmethionine

OBJECTIVE AND METHODS

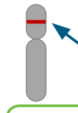
- To report preliminary results from an ongoing, first-in-human, phase 1 trial of AG-270 in patients with advanced solid tumors with homozygous deletion of *MTAP* (**Figure 2**).

Figure 2. Study design



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

Figure 3. Rationale behind *MTAP* and *CDKN2A* deletion for patient selection



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

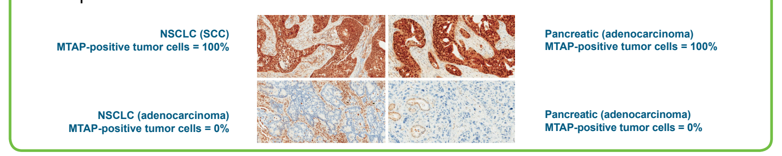
- Chr9p21 deleted in ~15% of cancers[1]
- *MTAP* loss commonly coincides with *CDKN2A* loss[2]

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



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

RESULTS

- As of Aug 16, 2019, 39 patients had been treated with AG-270 (**Table 1**).
  - 36 discontinued AG-270 due to disease progression (22), clinical suspicion of disease progression (6), withdrawal by subject (4), adverse events (AEs) (2), death (1), other (1).
- Baseline characteristics are shown in **Table 1**.

Table 1. Enrollment and demographics

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

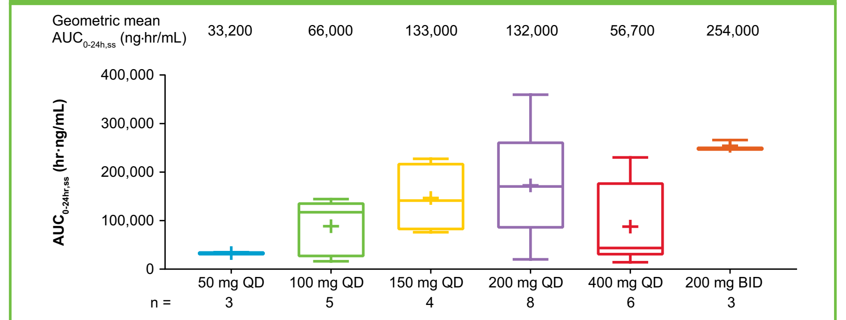
Baseline characteristic	N=39
Age, median (range), years	65 (32–87)
<60, n (%)	17 (44)
≥60, n (%)	22 (56)
Male sex, n (%)	21 (54)
Enrollment on the basis of:[a]	
CDKN2A deletion, n (%)	34 (87)
MTAP deletion, n (%)	5 (13)
Patients with both *CDKN2A* deletion and tumor tissue evaluable for MTAP deletion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

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

Pharmacokinetics

- Median time to maximum plasma concentration (t_{max}) = 3–5 hr.
- Median half-life ($t_{½}$) = 12.5–28.2 hr.
- 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 (**Figure 4**).
  - 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.

Figure 4. AG-270 $AUC_{0\text{-}24h}$ at steady state (C1D15)

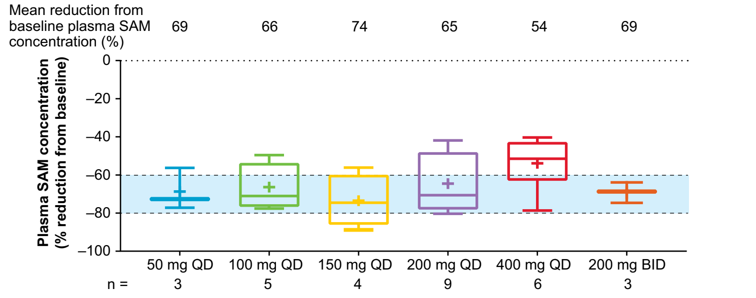


Box denotes 25th to 75th percentiles, horizontal bar the median, and + the mean, with whiskers extending to the minimum and maximum values
$AUC_{0\text{-}24h,ss}$ = AUC from 0 to 24 hr; ss = steady state

Pharmacodynamics

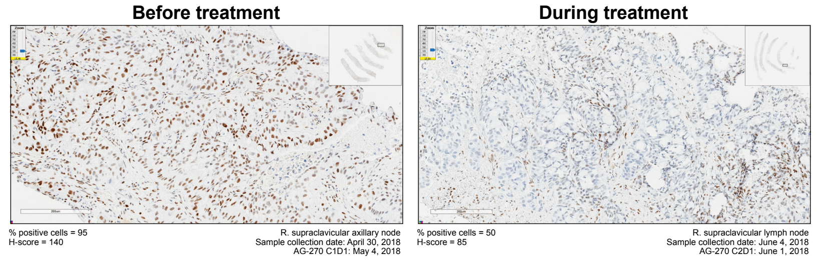
- Plasma SAM concentration at C1D15 decreased by 65–74% across doses of 50–200 mg QD and 200 mg BID (**Figure 5**).
  - The smaller reduction in plasma SAM concentration (~54%) observed at 400 mg QD is consistent with the lower AG-270 exposure observed at this dose.
- An example of a patient with 39% SDMA reduction after 1 month of treatment with AG-270 at 50 mg QD is shown (**Figure 6**).
- Analysis of nine paired tumor biopsies by IHC showed decreases in levels of SDMA residues, consistent with MAT2A inhibition (**Figure 7**).
- The average (min, max) H-score reduction compared with baseline was 36.5% (–98.8%, +21.4%).

Figure 5. Reductions in plasma SAM concentration at steady state (C1D15)



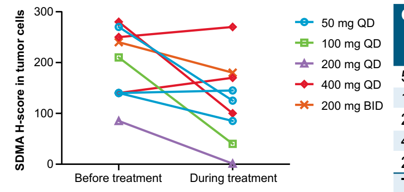
Average reductions in plasma SAM concentration were within the range associated with maximum tumor growth inhibition in preclinical models (60–80%)
Box denotes 25th to 75th percentiles, horizontal bar the median, and + the mean, with whiskers extending to the minimum and maximum values

Figure 6. SDMA staining in paired tumor biopsies



Patient with NSCLC receiving AG-270 50 mg QD
Pretreatment biopsy collected immediately before treatment with AG-270
H-score = semiquantitative IHC measure ranging from 0 to 300

Figure 7. SDMA assessment 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

Safety

- A summary of AEs is shown in **Table 2**.
- 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).

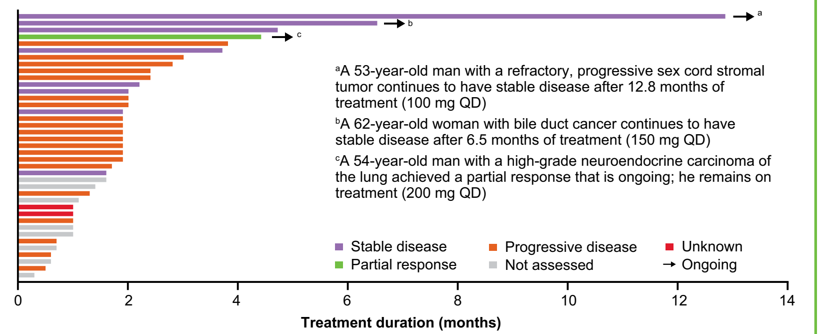
200 mg BID cohort

- 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.**

Table 2. 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)

Figure 8. Duration of treatment and best overall response in patients receiving AG-270



[a]A 53-year-old man with a refractory, progressive sex cord stromal tumor continues to have stable disease after 12.8 months of treatment (100 mg QD)
[b]A 62-year-old woman with bile duct cancer continues to have stable disease after 6.5 months of treatment (150 mg QD)
[c]A 54-year-old man with a high-grade neuroendocrine carcinoma of the lung achieved a partial response that is ongoing; he remains on treatment (200 mg QD)

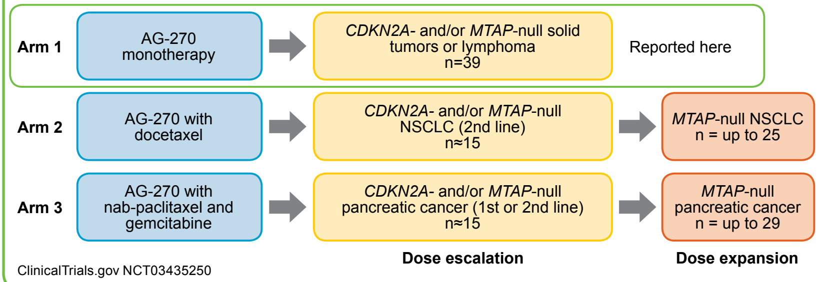
CONCLUSIONS

- 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.

Next steps

- AG-270 demonstrates improved efficacy in combination with taxanes in preclinical tumor models with homozygous *MTAP* deletion, relative to taxanes or AG-270 alone.[4]
- The next step in this phase 1 study will be to evaluate AG-270 in combination with standard taxane-based chemotherapy in patients with *CDKN2A*-null and/or *MTAP*-null cancers starting with an AG-270 dose of 100 mg QD (**Figure 9**).

Figure 9. AG-270 phase 1 trial including combinations with taxanes



ClinicalTrials.gov NCT03435250

Acknowledgments We thank the patients, families, coinvestigators, and all study personnel who participated in this trial.

Disclosures This study was funded by Agios Pharmaceuticals, Inc.

RSH: Apollomics, Boehringer Ingelheim, Tarveda – consultant; Novartis – research funding, consultant; Agios, Celgene, Corvus, Daiichi Sankyo, Genentech, Roche, Mirati – research funding. MMG: Bayer, Daiichi Sankyo, Epizyme, Karyopharm, Springwork Therapeutics – advisor; TRACON – honorarium; Flatiron – consultant. SP-V: Boehringer Ingelheim, Merck KGaA, Roche – research funding, advisor. FW: Agios – research funding; Loxo Oncology – advisor. EG: Novartis – research funding; AstraZeneca/MedImmune, Ellipses Pharma, F. Hoffmann-La Roche, Neomed Therapeutics 1 Inc., Roche-Genentech – consultant; Boehringer Ingelheim, Janssen Global Services, Seattle Genetics, TFS – advisor. KD, GIS, PM-R, GW, and HAB: no conflict of interest to disclose. MC, SN, KMM, and FB: Agios – employment. CA, YZ, and EA-F: Agios – employment and stockholder. VI: Agios – employment and stockholder; Novartis – stockholder. KF: Apricity, Checkmate Pharmaceuticals, Clovis Oncology, Fog Pharma, Fount Therapeutics, Oncoceutics, PIC Therapeutics, Shattuck Labs, Strata Oncology, Tvardi, Vivid Biosciences, xCures, X4 Pharmaceuticals – advisor and stockholder; Adaptimmune, Aeglea, Amgen, Array BioPharma, Asana Biosciences, BMS, Boston Biomedical, Cell Medica, Genentech, Merck, Monopteros, Neon Therapeutics, Pierre Fabre, Takeda, Tolero Pharmaceuticals, Verastem – advisor; Novartis, Sanofi – research funding, advisor.

Editorial assistance was provided by Christine Ingleby, PhD, CMPP, Excel Medical Affairs, Horsham, UK, and supported by Agios.

References

1. Beroukhim R et al. *Nature* 2010;463:899-905. **2.** Zhang H et al. *Cancer Genet Cytogenet* 1996;86:22-8. **3.** Marjon K et al. *Cell Rep* 2016;15:574-87. **4.** Kalev P et al. *2019 AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Conference*: Abstract number B115.

Scan code to receive PDF file of the poster or visit http://bit.ly/2IE4Cke