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ORIGINAL ARTICLE

First-in-human study of AMG 193, an MTA-cooperative PRMT5 inhibitor, in patients with *MTAP*-deleted solid tumors: results from phase I dose exploration☆

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Background: Homozygous deletion of methylthioadenosine phosphorylase (*MTAP*) occurs in ∼10%-15% of solid tumors. AMG 193, a CNS-penetrant methylthioadenosine-cooperative protein arginine methyltransferase 5 (PRMT5) inhibitor, selectively induces synthetic lethality in *MTAP*-deleted tumor cells. Here, we report results of the completed monotherapy dose exploration evaluating AMG 193 in patients with *MTAP*-deleted solid tumors.

Patients and methods: In this first-in-human, multicenter, open-label, phase I study, patients with advanced *CDKN2A*-deleted and/or *MTAP*-deleted solid tumors received AMG 193 orally [once (o.d.) or twice (b.i.d.) daily] continuously in 28-day cycles. Primary objectives were safety and tolerability assessed by dose-limiting toxicities and determination of the maximum tolerated dose; secondary objectives included pharmacokinetics and preliminary antitumor activity measured by RECIST v1.1.

Results: As of 23 May 2024, 80 patients in dose exploration received AMG 193 at doses 40-1600 mg o.d. or 600 mg b.i.d. The most common treatment-related adverse events were nausea (48.8%), fatigue (31.3%), and vomiting (30.0%). Dose-limiting toxicities were reported in eight patients at doses ≥240 mg, including nausea, vomiting, fatigue, hypersensitivity reaction, and hypokalemia. The maximum tolerated dose was determined to be 1200 mg o.d. Mean exposure of AMG 193 increased in a dose-proportional manner from 40 mg to 1200 mg. Among the efficacy-assessable patients treated at the active and tolerable doses of 800 mg o.d., 1200 mg o.d., or 600 mg b.i.d. ($n = 42$), objective response rate was 21.4% (95% confidence interval 10.3% to 36.8%). Responses were observed across eight different tumor types, including squamous/non-squamous non-small-cell lung cancer, pancreatic adenocarcinoma, and biliary tract cancer. At doses ≥480 mg, complete intratumoral PRMT5 inhibition was confirmed in paired *MTAP*-deleted tumor biopsies, and molecular responses (circulating tumor DNA clearance) were observed.

Conclusions: AMG 193 demonstrated a favorable safety profile without clinically significant myelosuppression. Encouraging antitumor activity across a variety of *MTAP*-deleted solid tumors was observed based on objective response rate and circulating tumor DNA clearance.

Key words: MTAP, methylthioadenosine phosphorylase, non-small-cell lung cancer, pancreas cancer, PRMT5, protein arginine methyltransferase 5, synthetic lethality

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INTRODUCTION

Protein arginine methyltransferase 5 (PRMT5) is an enzyme that plays a crucial role in various cellular processes, including gene expression, RNA processing, DNA damage repair, and immune response.[1] Dysregulation of PRMT5 has

been shown to promote tumor growth and survival by regulating the expression of oncogenes and tumor suppressor genes.[2] Inhibition of PRMT5 has been shown to have antitumor effects in preclinical models by inducing cell cycle arrest and cell death.[3] Furthermore, PRMT5 depletion/inhibition reduced DNA damage repair in response to topoisomerase I inhibitors, poly (adenosine diphosphate-ribose) polymerase inhibitors, and cytarabine[4-7] and PRMT5 depletion/inhibition enhanced the anticancer activity of immune checkpoint blockade *in vivo*.[8] PRMT5 dysregulation has also been associated with poor prognosis in lung cancer, glioblastoma multiforme (GBM), and epithelial ovarian cancer.[2,9-11] These findings have validated PRMT5 as a reasonable therapeutic target; however, the use of first-generation PRMT5 inhibitors was limited by severe dose-limiting hematological toxicities.[12-15]

PRMT5 has been identified as a synthetic lethal target in tumors harboring methylthioadenosine phosphorylase (*MTAP*) homozygous deletion. *MTAP* and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) are co-deleted in ∼10%-15% of human cancers. The role of *CDKN2A* as a tumor suppressor gene and in the tumorigenesis of various malignancies is well documented. The proximity of *MTAP* to *CDKN2A* on C9p21 leads to the co-deletion of both genes in 80% of the cases.[16] MTAP is a key enzyme in the methionine salvage pathway, and its loss leads to the accumulation of methylthioadenosine (MTA),[9] which partially inhibits PRMT5 activity.[17,18] In *MTAP*-deleted cancer cells, PRMT5 expression and activity are preferentially required for cell growth.[17] This makes PRMT5 an attractive synthetic lethal therapeutic target for the treatment of *MTAP*-deleted tumors.[19]

AMG 193 is a first-in-class, novel, MTA-cooperative PRMT5 inhibitor and a highly selective small molecule designed to specifically target *MTAP*-deleted cancer (Amgen Inc.).[3] *In vitro*, AMG 193 preferentially inhibited the MTA-bound PRMT5 enzyme in *MTAP*-null tumor cells. *In vivo*, AMG 193 inhibited the growth of multiple *MTAP*-deleted tumor xenograft models.

Here, we report the results from the completed dose exploration of AMG 193 monotherapy first-in-human (FIH) study. In this phase I trial, we evaluated the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of AMG 193 in patients with selected advanced-stage solid tumors.

METHODS

Study design

This is an FIH, phase I/Ib, multicenter, open-label, dose-escalation/dose-exploration, and dose-expansion study of AMG 193 monotherapy in adult patients with metastatic or locally advanced *MTAP*-deleted solid tumors across 45 sites in Australia, Japan, Hong Kong, Korea, Taiwan, Belgium, France, Switzerland, Germany, Austria, the UK, Canada, and the USA (NCT05094336).[20] Herein, we have summarized the results from the completed dose-exploration phase of the study. The first patient was enrolled on 1 February 2022, and the last was enrolled on 19 February 2024; the data cut-off was 23 May 2024. The design of the dose-escalation/dose-exploration part is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.08.2339.

Study procedures were approved by institutional review boards at each study site (details can be found in Supplementary Appendix 1, available at https://doi.org/10.1016/j.annonc.2024.08.2339), and the study was conducted in accordance with principles originating in the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, and Good Clinical Practice guidelines of the International Conference on Harmonisation (ICH-GCP). Informed consent was obtained from all patients before initiating study screening.

Eligibility criteria

Key inclusion criteria in the phase I monotherapy dose-escalation/dose-exploration part included patients (≥18 years old) with histologically confirmed metastatic or locally advanced solid tumors and locally determined *MTAP* or *CDKN2A* deletion by next-generation sequencing (NGS), or MTAP deficiency of protein expression by immunohistochemistry (IHC) by a central laboratory. Tumor tissue biopsy samples of patients enrolled via local NGS testing were retrospectively assessed by IHC for MTAP deletion if sufficient tissue was available. *CDKN2A* deletion based on local NGS testing as a surrogate for MTAP deletion was acceptable for enrollment during dose exploration only. Patients previously treated with a methionine adenosyltransferase II alpha (MAT2A)/PRMT5 inhibitor were excluded. Other eligibility criteria are mentioned Supplementary Appendix 2.1, available at https://doi.org/10.1016/j.annonc.2024.08.2339.

Treatments

AMG 193 was administered continuously orally once daily (o.d.) at doses ranging from 40 mg to 1600 mg, or twice daily (b.i.d.) at 600 mg in a treatment cycle of 28 days. Treatment with AMG 193 was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Study endpoints

The primary endpoints were dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), serious adverse events (SAEs), clinical laboratory tests, vital signs, and electrocardiogram (ECG). Severity of all AEs was assessed according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Secondary endpoints included objective response (OR) based on RECIST v1.1 by investigator assessment, duration of response (DOR), disease control, duration of disease control (DoDC), time to response (TTR), and PK parameters. Exploratory endpoints included assessment of pharmacodynamic (PD) biomarkers such as symmetric dimethylation of arginine (SDMA) and circulating

tumor DNA (ctDNA). Detailed DLT criteria are described in Supplementary Appendix 2.2, available at https://doi.org/10.1016/j.annonc.2024.08.2339.

Statistical analyses

Descriptive statistics were provided for selected demographics, safety, efficacy, PK, and biomarker data by dose. The determination of maximum tolerated dose was guided by a Bayesian logistic regression model. Patients enrolled based on the *CDKN2A* deletion who did not have *MTAP* deletion by central IHC (*CDKN2A*-deleted/*MTAP*-intact) were excluded from efficacy analyses because of the MTA-cooperative mechanism of action of AMG 193. Further details are described in Supplementary Appendix 2.3, available at https://doi.org/10.1016/j.annonc.2024.08.2339.

RESULTS

Baseline characteristics

At the data cut-off date of 23 May 2024, 80 patients received AMG 193 in dose exploration [cohort 1: 40 mg o.d. ($n = 4$); cohort 2: 120 mg o.d. ($n = 2$); cohort 3: 240 mg o.d. ($n = 7$); cohort 4: 480 mg o.d. ($n = 17$); cohort 5: 800 mg o.d. ($n = 18$); cohort 6: 1200 mg o.d. ($n = 18$); cohort 7: 1600 mg o.d. ($n = 4$); and 600 mg b.i.d. cohort ($n = 10$)]. Baseline patient characteristics are shown in Table 1. Overall, 52.5% of patients were male; the median age was 61.5 years (range: 36-83 years), and 58.8% of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1. Patients received a median of two prior lines of therapy (range: 1-8 lines), and 23 patients (28.8%) received four or more prior lines of therapy. The most common tumor types were pancreatic duct adenocarcinoma (PDAC) (19; 23.8%), non-small-cell lung cancer (NSCLC) (14; 17.5%), biliary tract cancer (BTC) (7; 8.8%), GBM (5; 6.3%), and gastric/esophageal cancer (2; 2.5%). In 6 of the 80 patients (7.5%), tumors were *CDKN2A*-deleted but *MTAP*-intact per central IHC. Therefore, these patients were excluded from the efficacy analysis. All other patients had *MTAP* deletion by local NGS (55.4%) or central IHC (85.1%) or both (41.3%).

Treatment was discontinued in 68 patients (85.0%). The primary reason for discontinuation was progressive disease ($n = 50$; 62.5%) followed by patient request ($n = 9$; 11.3%), AEs ($n = 5$; 6.3%), death, and other ($n = 2$; 2.5% each). Twelve patients continued on treatment at the time of data cut-off.

Table 1. Baseline demographics and disease characteristics

	Dose-exploration ($N = 80$)
Sex, *n* (%)	
Male	42 (52.5)
Female	38 (47.5)
Race, *n* (%)	
White	45 (56.3)
Asian	19 (23.8)
Black or African American	4 (5.0)
Other	4 (5.0)
Missing	8 (10.0)
Median age, years (range)	61.5 (36-83)
ECOG PS, *n* (%)	
0	33 (41.3)
1	47 (58.8)
Tumor type, *n* (%)[a]	
PDAC	19 (23.8)
NSCLC	14 (17.6)
BTC	7 (8.8)
GBM	5 (6.3)
Gastric/esophageal	2 (2.5)
Others[b]	33 (41.3)
Baseline tumor stage, *n* (%)	
Stage IV	69 (86.3)
Stage II/III	4 (5.0)
Unknown	6 (7.5)
Missing	1 (1.3)
Prior lines of therapy received, *n* (%)	
1-3	55 (68.8)
≥4	23 (28.8)
Missing	2 (2.5)
Prior lines of therapy, median (range)	2 (1-8)
Prior radiotherapy, *n* (%)	38 (47.5)
MTAP-deletion status (per central IHC), *n* (%)	
Loss	61 (76.3)
Not evaluable	9 (11.3)
No loss[c]	7 (8.8)
Pending	3 (3.8)

BTC, biliary tract cancer; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; ECOG PS, Eastern Cooperative Oncology Group performance status; GBM, glioblastoma multiforme; IHC, immunohistochemistry; *MTAP*, methylthioadenosine phosphorylase; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PDAC, pancreatic duct adenocarcinoma.

[a]PDAC includes adenocarcinoma pancreas, pancreatic carcinoma metastatic, and pancreatic carcinoma; NSCLC includes non-small cell lung cancer, squamous cell carcinoma of lung and lung neoplasm malignant; BTC includes gallbladder, cholangiocarcinoma, bile duct/biliary tract, ampulla of Vater and duodenal papillary carcinoma; GBM includes glioblastoma and glioblastoma multiforme; esophageal/gastric includes esophageal adenocarcinoma, esophageal carcinoma, and esophageal squamous cell carcinoma.

[b]For more details please refer to Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2024.08.2339.

[c]These patients were enrolled based on local NGS showing *CDKN2A* deletion ($n = 6$) or *MTAP* deletion ($n = 1$) (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2024.08.2339).

Safety

Patients received a median of two cycles of treatment. DLTs were reported in eight patients, all at doses ≥240 mg (Table 2), and were vomiting ($n = 2$), nausea, fatigue, hypersensitivity reaction, hypokalemia, encephalopathy, and palpitations ($n = 1$ each; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.08.2339). The MTD was determined to be 1200 mg o.d. (11.1% of patients experienced DLTs at this dose level). Safety findings are summarized in Table 2 and Figure 1. Any-grade TRAEs were reported in 68 patients (85.0%; Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.08.2339) and grade ≥3 in 11 patients (13.8%; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.08.2339). The most common any-grade TRAEs were nausea (48.8%), fatigue (31.3%), and vomiting (30.0%) occurring mostly at the beginning of treatment and being uncommon past 2 weeks (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.08.2339). Serious TRAEs were reported in eight patients (10.0%).

Table 2. Summary of AEs

n (%)	Cohort 1 40 mg o.d. (*n* = 4)	Cohort 2 120 mg o.d. (*n* = 2)	Cohort 3 240 mg o.d. (*n* = 7)	Cohort 4 480 mg o.d. (*n* = 17)	Cohort 5 800 mg o.d. (*n* = 18)	Cohort 6 1200 mg o.d. (*n* = 18)	Cohort 7 1600 mg o.d. (*n* = 4)	600 mg b.i.d. (*N* = 10)	Dose exploration (*n* = 80)
Patients with DLTs	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	2 (11.1)	2 (11.1)	2 (50.0)	1 (10.0)	8 (10.0)
TEAEs (any grade)	4 (100.0)	2 (100.0)	6 (85.7)	17 (100.0)	18 (100.0)	17 (94.4)	4 (100.0)	10 (100.0)	78 (97.5)
Grade ≥3	2 (50.0)	0 (0.0)	2 (28.6)	10 (58.8)	5 (27.8)	8 (44.4)	4 (100.0)	5 (50.0)	36 (45.0)
Fatal AEs	0 (0.0)	0 (0.0)	0 (0.0)	3 (17.6)	1 (5.6)	2 (11.1)	0 (0.0)	0 (0.0)	6 (7.5)
Serious AEs	2 (50.0)	0 (0.0)	2 (28.6)	8 (47.1)	6 (33.3)	7 (38.9)	1 (25.0)	3 (30.0)	29 (36.3)
Leading to discontinuation	0 (0.0)	0 (0.0)	1 (14.3)	3 (17.6)	3 (16.7)	1 (5.6)	0 (0.0)	0 (0.0)	8 (10.0)
TRAEs (any grade)	3 (75.0)	2 (100.0)	5 (71.4)	10 (58.8)	17 (94.4)	17 (94.4)	4 (100.0)	10 (100.0)	68 (85.0)
Grade ≥3	0 (0.0)	0 (0.0)	2 (28.6)	1 (5.9)	1 (5.6)	4 (22.2)	3 (75.0)	0 (0.0)	11 (13.8)
Fatal AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AEs	0 (0.0)	0 (0.0)	1 (14.3)	1 (5.9)	2 (11.1)	3 (16.7)	1 (25.0)	0 (0.0)	8 (10.0)
Leading to interruption	0 (0.0)	0 (0.0)	1 (14.3)	3 (17.6)	4 (22.2)	8 (44.4)	2 (50.0)	4 (40.0)	22 (27.5)
Leading to dose reduction	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	4 (22.2)	6 (33.3)	2 (50.0)	1 (10.0)	14 (17.5)
Leading to discontinuation	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)

AE, adverse event; b.i.d., twice daily; DLT, dose-limiting toxicity; o.d., once daily; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

There were no fatal TRAEs. TRAEs led to treatment interruption in 22 patients (27.5%), dose reduction in 14 patients (17.5%), and treatment discontinuation in 2 patients (2.5%; Table 2).

Because first-generation non-MTA-cooperative PRMT5 inhibitors were associated with myelosuppression, we evaluated cytopenias as TEAEs of interest. These events (any grade; grade ≥3) were anemia (15.0%; 6.3%), lymphopenia (6.3%; 3.8%), neutropenia (3.8%; 2.5%), and leukopenia (3.8%; 1.3%). Thrombocytopenia was reported in one patient (any grade 1.3%; grade ≥3 none). None of the cytopenia events were dose limiting, and none led to treatment discontinuation.

Efficacy

Nine ORs were observed at 800 mg o.d., 1200 mg o.d., and 600 mg b.i.d. across eight tumor types, namely NSCLC (squamous and non-squamous), PDAC, cholangiocarcinoma, gallbladder cancer, esophageal cancer, melanoma, renal cell carcinoma (RCC), and ovarian Sertoli–Leydig cell tumor (SLCT; Figure 2). The objective response rate in these

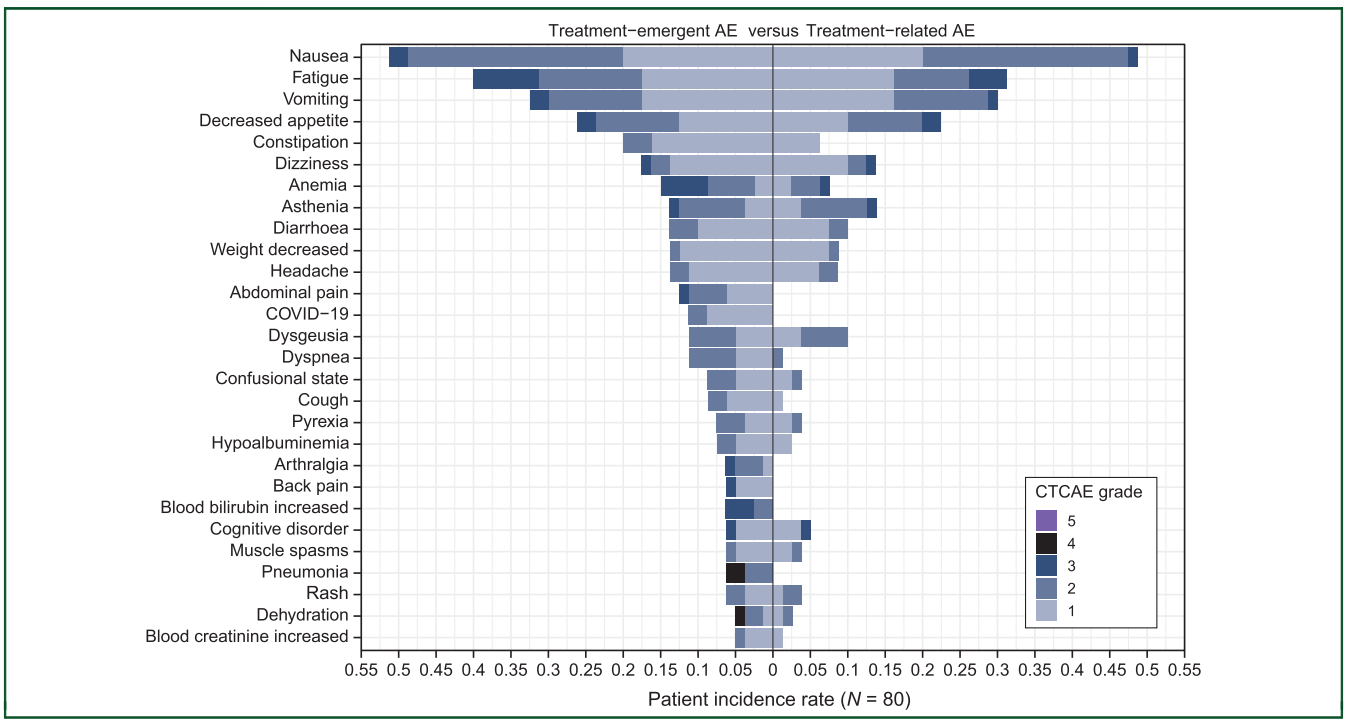

Figure 1. Incidence and severity of AEs (TEAEs occurring in ≥5% of patients).
AE, adverse event; COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

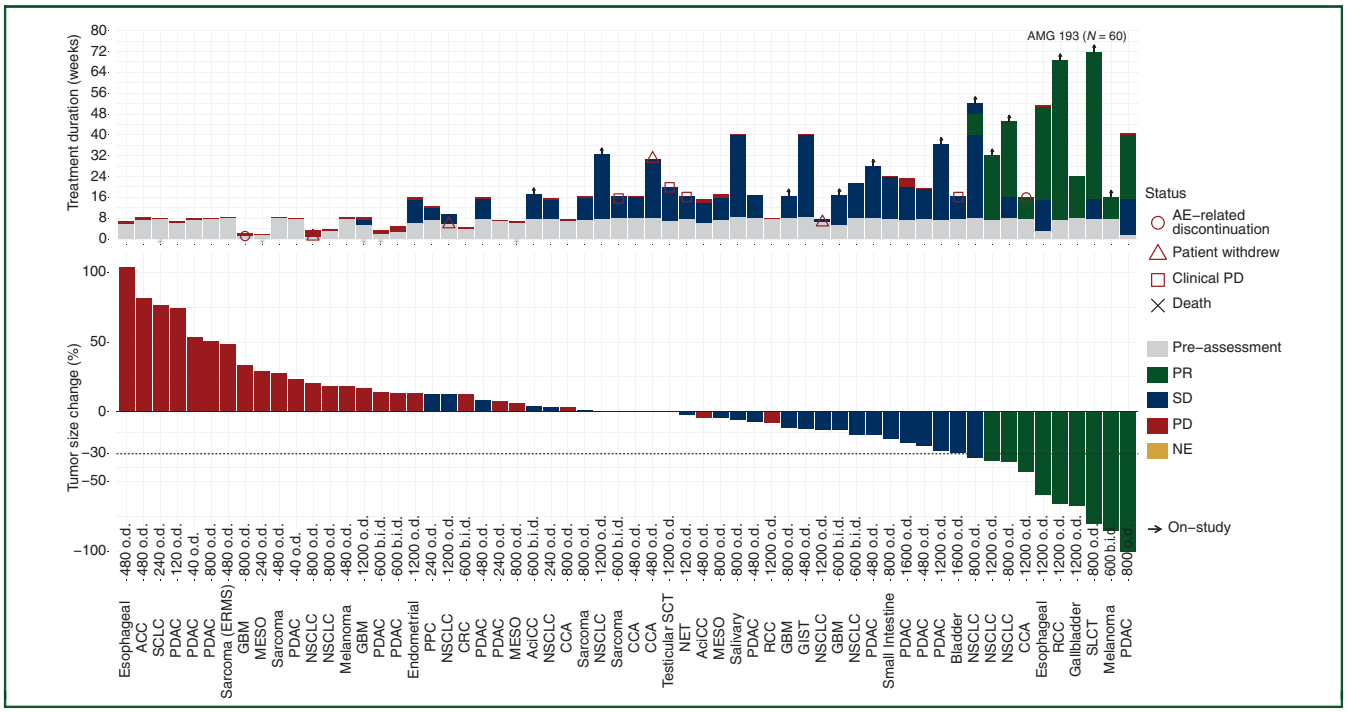

Figure 2. Antitumor activity of AMG 193. Waterfall plot showing response duration and change in tumor burden.
ACC, adenoid cystic carcinoma; AciCC, acinic cell carcinoma; AE, adverse event; b.i.d., twice daily; CCA, cholangiocarcinoma; CRC, colorectal cancer; ERMS, embryonal rhabdomyosarcoma; GBM, glioblastoma multiforme; GIST, gastrointestinal stromal tumor; MESO, mesothelioma; NE, not evaluated; NET, neuroendocrine tumor; NSCLC, non-small cell lung cancer; PD, progressive disease; PDAC, pancreatic duct adenocarcinoma; PPC, primary peritoneal cancer; PR, partial response; o.d., once daily, RCC, renal cell carcinoma; SCLC, small cell lung cancer; SCT, testicular sertoli cell tumor; SD, stable disease; SLCT, Sertoli-Leydig cell tumor.

patients at active dose levels ($n = 42$) was 21.4% [95% confidence interval (CI): 10.3% to 36.8%], and the disease control rate was 54.8% (95% CI: 38.7% to 70.2%) (Table 3). Median TTR was 3.6 months (range: 3.6-3.7 months) and 1.8 months (range: 1.7-3.5 months) at 800 mg o.d. and 1200 mg o.d., respectively, suggesting shorter TTR at higher doses. Median DOR was 8.3 months (95% CI: 2.7 months-NE), and median DoDC was 9.2 months (95% CI: 4.9-11.8 months) across all dose exploration cohorts. The longest DOR reported was 12.9 months for a patient with RCC and 11.0 months for a patient with an ovarian SLCT. At data cut-off, responses were ongoing at data cut-off, and five of the nine responders remained on treatment.

Pharmacokinetics

Preliminary PK data (10 May 2024) for AMG 193 were available for 80 patients on cycle 1 day 1 and 67 patients on cycle 1 day 15. The mean (standard deviation) plasma concentration-time profile of AMG 193 is shown in Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2024.08.2339. AMG 193 demonstrated a dose-proportional increase in plasma exposure within the dose range of 40-1200 mg o.d. The plasma concentration with 1600 mg o.d. was below the mean concentration observed at 1200 mg, possibly due to reduced absorption. Steady-state plasma concentrations were achieved within 2 weeks with o.d. dosing, with minimal accumulation. The PK parameter estimates are provided in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.08.2339.

Biomarkers

SDMA reduction is a PD biomarker of PRMT5 inhibition. While pretreated biopsy samples had high SDMA expression, posttreatment tumor biopsies from eight *MTAP*-deleted patients were observed to have near complete elimination of SDMA levels at dose levels of 480 mg, 800 mg, and 1200 mg (Figure 3A and B), confirming robust intratumoral target engagement. Interestingly, paired tumor biopsies from one patient in the 800 mg o.d. cohort, who was enrolled with local *CDKN2A* loss and later confirmed via IHC to have *MTAP* intact, revealed that intratumoral SDMA levels were not completely inhibited (H-score: 55); consistent with the synthetic lethal inhibition of PRMT5 in tumors with confirmed *MTAP* homozygous deletion.

The dose-response relationship was evaluated measuring serum SDMA levels and by grouping patients into low (40-120 mg o.d.), medium (240-480 mg o.d.), and high ($\geq$800 mg total dose) dose cohorts. PD modeling of SDMA levels across the first five treatment cycles demonstrated a significant dose-response relationship across these three cohorts (Figure 3C).

Molecular responses (-100% ctDNA change from baseline) were observed at doses $\geq$480 mg (Figure 3D). Of the 19 patients with stable disease (SD), 16 patients had $>50\%$ reduction from baseline in ctDNA, and 8 patients with partial response (PR) had $>90\%$ ctDNA reduction

Table 3. Overview of efficacy

	Cohort 1 40 mg o.d. ($n = 4$)	Cohort 2 120 mg o.d. ($n = 2$)	Cohort 3 240 mg o.d. ($n = 6$)	Cohort 4 480 mg o.d. ($n = 16$)	Cohort 5 800 mg o.d. ($n = 16$)	Cohort 6 1200 mg o.d. ($n = 17$)	Cohort 7 1600 mg o.d. ($n = 4$)	600 mg b.i.d. ($n = 9$)	Active dose levels (800/1200 mg daily) ($n = 42$)	Dose exploration ($n = 74$)
BOR, *n* (%)										
Confirmed PR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	5 (29.4)	0 (0.0)	1 (11.1)	9 (21.4)	9 (12.2)
SD	0 (0.0)	1 (50.0)	2 (33.3)	7 (43.8)	5 (31.3)	5 (29.4)	2 (50.0)	4 (44.4)	14 (33.3)	26 (35.1)
Unconfirmed PR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.4)
PD	2 (50.0)	1 (50.0)	2 (33.3)	7 (43.8)	5 (31.3)	2 (11.8)	0 (0.0)	3 (33.3)	10 (23.8)	22 (29.7)
NE	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	1 (11.1)	2 (4.8)	3 (4.1)
Not done	2 (50.0)	0 (0.0)	1 (16.7)	2 (12.5)	3 (18.8)	4 (23.5)	2 (50.0)	0 (0.0)	7 (16.7)	14 (18.9)
ORR, % (95% CI)	0.0 (0.0-60.2)	0.0 (0.0-84.2)	0.0 (0.0-45.9)	0.0 (0.0-20.6)	18.8 (4.0-45.6)	29.4 (10.3-56.0)	0.0 (0.0-60.2)	11.1 (0.3-48.2)	21.4 (10.3-36.8)	12.2 (5.7-21.8)
DCR, % (95% CI)	0.0 (0.0-60.2)	50.0 (1.3-98.7)	33.3 (4.3-77.7)	43.8 (19.8-70.1)	50.0 (24.7-75.3)	58.8 (32.9-81.6)	50.0 (6.8-93.2)	55.6 (21.2-86.3)	54.8 (38.7-70.2)	47.3 (35.6-59.3)
Median DOR, months (95% CI)	– (–)	– (–)	– (–)	– (–)	NE (5.7-NE)	8.3 (2.7-NE)	– (–)	NE (NE-NE)	8.3 (2.7-NE)	8.3 (2.7-NE)
Median DoDC, months (95% CI)	– (–)	NE (NE-NE)	3.2 (2.8-NE)	4.9 (3.6-NE)	9.3 (3.9-NE)	11.8 (4.5-NE)	5.3 (NE-NE)	NE (NE-NE)	11.8 (5.5-NE)	9.2 (4.9-11.8)

Of note, four out of six patients enrolled based on local CDKN2A deletion that were confirmed to have intact MTAP based on central IHC testing, had progressive disease as their best response. These patients were excluded from the efficacy analysis (Figure 2A; Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2024.08.2339).

b.i.d., twice daily; BOR, best overall response; CI, confidence interval; DCR, disease control rate; DoDC, duration of disease control; DOR, duration of response; IHC, immunohistochemistry; MTAP, methylthioadenosine phosphorylase; NE, not estimable; o.d., once daily; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

(Figure 3E). The average reduction in ctDNA levels for patients with progressive disease was significantly less than that observed in patients with SD or PR (Figure 3E), indicating an association between the degree of ctDNA reduction and RECIST response and that disease stabilization was a result of AMG 193 antitumor activity rather than indolent disease.

DISCUSSION

AMG 193 is a novel MTA-cooperative PRMT5 inhibitor designed to induce synthetic lethality in *MTAP*-deleted solid tumors while sparing hematologic toxicity. This phase I study determined the MTD of AMG 193 to be 1200 mg o.d. Nausea, vomiting, and fatigue were the predominant DLTs, while hematological toxicity was rare and not dose-limiting. Overall, the tolerability of AMG 193 was favorable based on the low rate of TRAEs resulting in treatment modification or discontinuation. Consistent with the MTA-cooperative mechanism of action, complete intratumoral inhibition of PRMT5 function in MTAP-deleted tumors was observed across several dose levels ($\geq$480 mg). Finally, the preliminary antitumor activity of AMG 193 in multiple *MTAP*-deleted solid tumors is encouraging and warrants further evaluation. Based on the totality of data including safety, preliminary efficacy, PK, PD, and exposure-response modelling, 1200 mg o.d. is anticipated to achieve maximal antitumor activity with acceptable safety and was therefore selected to be investigated in dose expansion.

These findings contrast with results from studies on first-generation non-cooperative PRMT5 inhibitors (PF-06939999, GSK3326595, JNJ-64619178)[12,13,15] whereby PRMT5 function was inhibited indiscriminately in both tumor and healthy cells irrespective of MTAP status. Myelosuppression, typically thrombocytopenia events[12,15,21] were dose limiting for first-generation PRMT5 inhibitors and likely precluded escalation to dose levels likely necessary for robust PRMT5 inhibition and antitumor activity, as demonstrated by the limited number of clinical responses observed. As a result of the dose-limiting myelosuppression, the clinical development of first-generation PRMT5 inhibitors was limited, and in the absence of a wider therapeutic window, their development was discontinued. In contrast, cytopenia events were infrequent with AMG 193 treatment and not dose limiting. In particular, thrombocytopenia due to AMG 193 was only observed in one patient across all dose-exploration cohorts, confirming a safety profile of AMG 193 that is different from those of first-generation PRMT5 inhibitors.

AMG 193 was well tolerated, and TRAEs more commonly encountered, at a frequency of $\geq$15%, were nausea, fatigue, decreased appetite, and vomiting. These AEs were manageable and typically reversible either with standard antiemetic prophylaxis (e.g. odansetron for nausea and vomiting) or reversed promptly with dose reduction. Tolerability typically improved with time on therapy beyond 2 weeks and was rarely cumulative in nature. While the pathophysiology of nausea and fatigue remains unclear at

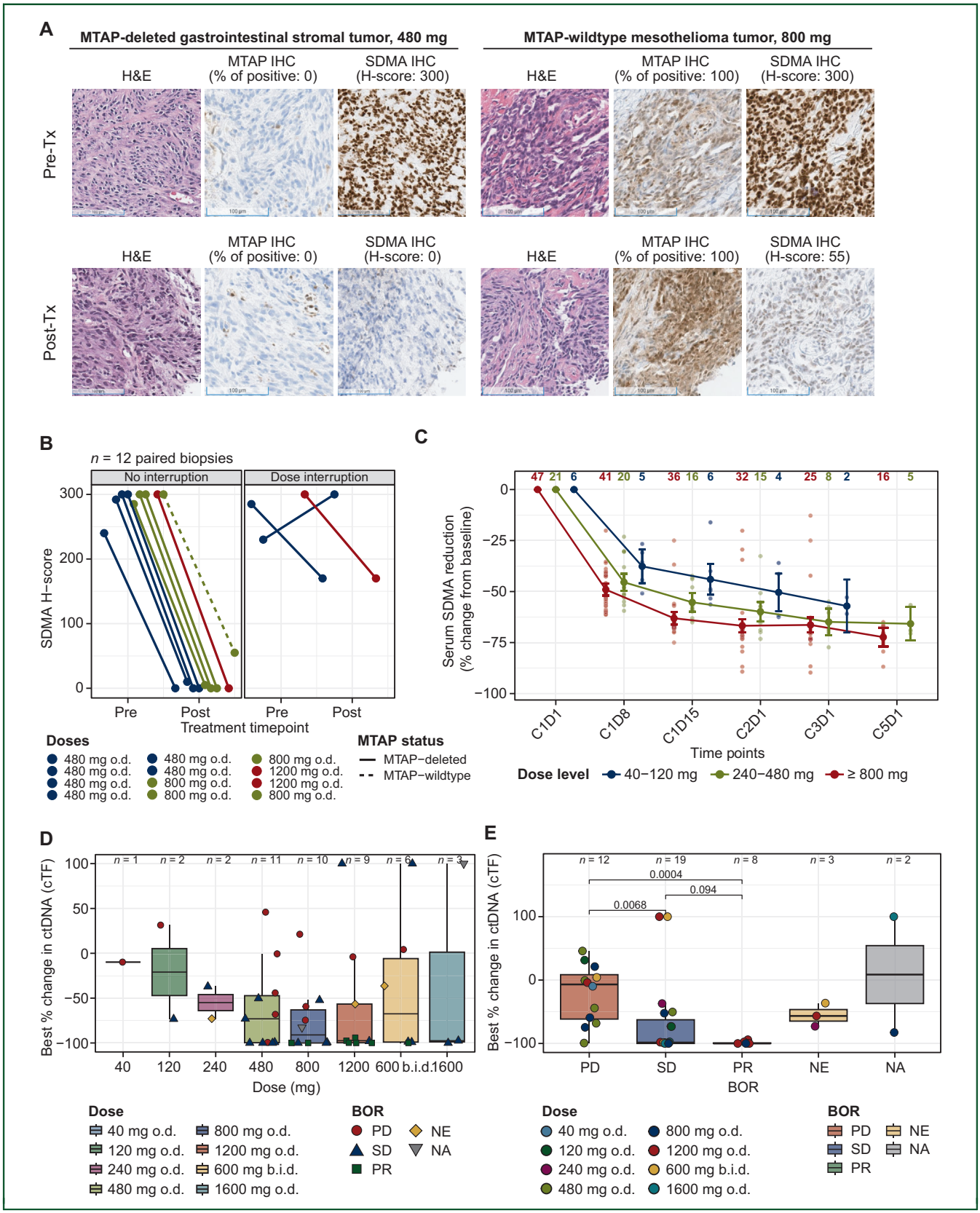

Figure 3. Biomarker analysis of target engagement (SDMA) and antitumor activity (ctDNA). (A) Left: GIST: MTAP IHC showed no MTAP expression in tumor cells, though endothelial cells in capillaries were positive for MTAP; SDMA IHC revealed strong nuclear SDMA staining in the pre-Tx sample, with a notable loss of SDMA expression in the post-Tx sample. Right: metastatic mesothelioma: MTAP IHC reveals nuclear and cytoplasmic MTAP expression in viable tumor cells across both pre- and post-Tx samples. SDMA IHC indicates strong nuclear positivity in the pre-Tx sample, while the post-Tx sample exhibits heterogeneous SDMA staining in tumor cells. (B) Longitudinal view of SDMA H-score in *MTAP*-deleted or *MTAP* wildtype tumor cells. (C) Serum SDMA % reduction from baseline. (D) Best % ctDNA change by dose and (E) Best % ctDNA change by BOR following AMG 193 treatment.

b.i.d., twice daily; BOR, best overall response; CnDn, cycle n day n; ctDNA, circulating tumor DNA; cTF, circulating tumor fraction; GIST, gastrointestinal stromal tumor; H&E, hematoxylin and eosin; H-score, histoscore; IHC, immunohistochemistry; MTAP, methylthioadenosine phosphorylase; NA, not available; NE, not estimable; PD, progressive disease; PR, partial response; o.d., once daily; SD, stable disease; SDMA, symmetric dimethylation of arginine; TMS, tumor methylation score; Tx, treatment.

this time, these adverse events were also observed as a side-effect to treatment with first-generation, non-selective PRMT5 inhibitors, and therefore may be due to inhibition of PRMT5 in the central nervous system. A fractionated dosing schedule was explored to determine whether lowering the peak drug exposure could improve the rate of safety events, however, no appreciable difference was observed in the safety profile between twice daily dosing and once daily dosing. Of note, the first-generation non-selective PRMT5 inhibitors[12-15,21] demonstrated similar non-hematologic adverse events, suggesting these toxicities are on-target and a potential class effect of non-cooperative and cooperative PRMT5 inhibition.

Antitumor activity based on imaging (RECIST) and molecular (ctDNA) responses was observed across a variety of solid tumors, including NSCLC (squamous and non-squamous), PDAC, BTC, and esophageal cancer at total daily doses of $\geq$800 mg. Among patients with SD, the observation of robust ctDNA reductions following treatment supports the likelihood that AMG 193 truly mediated antitumor activity, rather than being confounded by pre-existing indolent disease. Preliminary DOR and DoDC results suggest a sustained treatment effect mediated by AMG 193 on *MTAP*-deleted tumors, and mechanisms of resistance are likely to be intrinsic or acquired with time.

Consistent with the tumor-selective mechanism of action of AMG 193 conferred by MTA cooperativity, near complete intratumoral reduction in SDMA in *MTAP*-deleted tumors was confirmed at well-tolerated doses, while an *MTAP* wildtype tumor showed persistent SDMA as evidence of incomplete intratumoral PRMT5 inhibition. Furthermore, PRMT5 activity was more strongly inhibited within the tumor compared with non-tumor based on the degree of SDMA reduction in paired tumor biopsy tissue samples versus peripheral blood. In tumor tissue, there was near complete SDMA loss in all samples while the highest degree of SDMA reduction in the blood did not exceed 80% from baseline. These results not only support the tumor-selective mechanism of action but also suggest that complete intratumoral PRMT5 inhibition is likely required for antitumor activity. This hypothesis is supported by the early on-treatment disease progression of patients enrolled based on *CDKN2A* loss retrospectively found to have intact *MTAP*, likely resulting in incomplete tumoral PRMT5 inhibition.

MTAP is an emerging biomarker with multiple assays for detecting loss of expression. In this study, patients were allowed to enroll using multiple tests, including local NGS tests to evaluate *MTAP* or *CDKN2A* loss, or a central IHC test for MTAP loss. Although a large majority of patients had concordant assay results, there were six patients enrolled with a local *CDKN2A* copy number loss result which retrospectively were shown to retain MTAP expression via central IHC, none of whom recorded a clinical response. Further one patient who enrolled based on local NGS *MTAP* genomic loss had a discordant central IHC result. Given the importance of MTAP loss for the mechanism of action and efficacy of AMG 193, continued characterization and further development of clinical diagnostics for this emerging biomarker will be critical to support future clinical development.

Evaluation of the AMG 193 monotherapy safety and efficacy profile is ongoing in dose-expansion cohorts in the FIH study (NCT05094336).[20] In addition, AMG 193 is currently being studied in combination with standard-of-care chemoimmunotherapy in NSCLC (NCT06333951)[22] and chemotherapy in PDAC (NCT06360354)[23] as well as in combination with the MAT2A inhibitor IDE397 (NCT05975073).[24]

Conclusions

AMG 193 monotherapy had a manageable safety profile and was tolerable at doses up to 1200 mg o.d., with no dose-limiting cytopenia events reported. Encouraging antitumor activity across multiple *MTAP*-deleted tumors was observed between 800 mg and 1200 mg. This supports further investigation of AMG 193 as monotherapy or in combination with standard-of-care therapies.

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DATA SHARING

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request.

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