Navlimetostat (BMS-986504) in patients with advanced solid tumors with homozygous *MTAP* deletion: exploratory pharmacodynamic and biomarker analyses from CA240-0007

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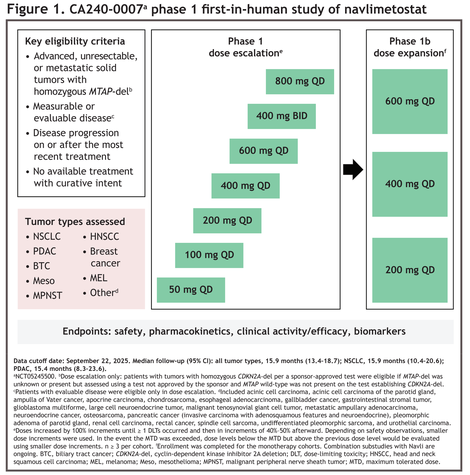
Background

- Homozygous methylthioadenosine phosphorylase deletion (*MTAP*-del), which occurs in 10%–15% of all cancers, is associated with poor prognoses and high unmet need[1-3]
- In the first-in-human phase 1 CA240-0007 study, navlimetostat (Navli; BMS-986504/MRTX1719), a methylthioadenosine (MTA)-cooperative protein arginine methyltransferase 5 (PRMT5) inhibitor, was well tolerated and demonstrated antitumor activity in heavily pretreated patients across multiple solid tumor types, including non-small cell lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDAC)[4-7]
- Consistent with its proposed mechanism of action (MOA), treatment with Navli demonstrated dose-dependent reductions in plasma levels of symmetric dimethylarginine (SDMA), a pharmacodynamic biomarker of PRMT5 inhibition, and downregulation of pathways involved in cell proliferation and DNA damage repair (DDR)[8]
- To further investigate the MOA and pharmacodynamic effects of Navli, we report expanded pharmacodynamic and genomic analyses as well as initial results of plasma proteomic and circulating tumor DNA (ctDNA) analyses from CA240-0007

Methods

- In CA240-0007 (NCT05245500), patients with advanced, unresectable, or metastatic solid tumors with homozygous *MTAP*-del who had disease progression on or after the prior line of therapy received Navli in 3-week cycles (**Figure 1**)
  - Assessed Navli doses included 50 mg once daily (QD), 100 mg QD, 200 mg QD, 400 mg QD, 600 mg QD, 400 mg twice daily (BID), and 800 mg QD
- Clinical response per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) was assessed in clinically evaluable patients
- Pharmacodynamics of PRMT5 inhibition was assessed based on change in SDMA levels from paired plasma samples collected at baseline and cycle 2 day 1 (C2D1) analyzed using mass spectrometry
- Proteomic pathway enrichment was assessed using Gene Set Enrichment Analysis (GSEA) applied to summary statistics derived from a Linear Models for Microarray Data (limma) framework. The limma model evaluated differential protein expression from paired plasma samples collected at baseline and C2D1, as measured by the SomaScan 11K assay
- Tumor genomic information from baseline, including co-alterations in *EGFR*, *KRAS*, and *TP53*, was extracted from local pathology reports that used different next-generation sequencing (NGS) panels
- ctDNA from plasma samples was analyzed using NGS (Guardant Infinity Liquid Core Module; Palo Alto, CA)

Figure 1. CA240-0007[a] phase 1 first-in-human study of navlimetostat



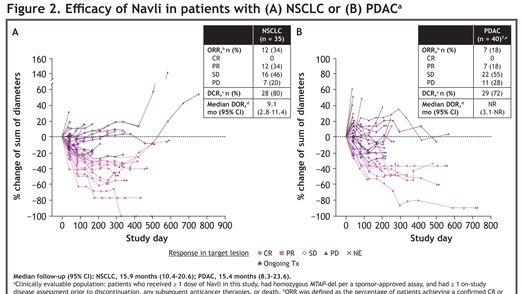
Data cutoff date: September 22, 2025. Median follow-up (95% CI): all tumor types, 15.9 months (13.4-18.7); NSCLC, 15.9 months (10.4-20.6); PDAC, 15.4 months (8.3-23.6).
[a]NCT05245500. [b]Dose escalation only; patients with tumors with homozygous *CDKN2A*-del per a sponsor-approved test were eligible if *MTAP*-del was unknown or present but assessed using a test not approved by the sponsor and *MTAP* wild-type was not present on the test establishing *CDKN2A*-del. [c]Patients with evaluable disease were eligible only in dose escalation. [d]Included acinic cell carcinoma, acinic cell carcinoma of the parotid gland, ampulla of Vater cancer, apocrine carcinoma, chondrosarcoma, esophageal adenocarcinoma, gallbladder cancer, gastrointestinal stromal tumor, glioblastoma multiforme, large cell neuroendocrine tumor, malignant tenosynovial giant cell tumor, metastatic ampullary adenocarcinoma, neuroendocrine cancer, osteosarcoma, pancreatic cancer (invasive carcinoma with adenosquamous features and neuroendocrine), pleomorphic adenoma of parotid gland, renal cell carcinoma, rectal cancer, spindle cell sarcoma, undifferentiated pleomorphic sarcoma, and urothelial carcinoma. [e]Doses increased by 100% increments until ≥ 1 DLTs occurred and then in increments of 40%-50% afterward. Depending on safety observations, smaller dose increments were used. In the event the *MTD* was exceeded, dose levels below the MTD but above the previously tested dose level would be evaluated using smaller dose increments. n ≥ 3 per cohort. [f]Enrollment was completed for the monotherapy cohorts. Combination substudies with Navli are ongoing. BTC, biliary tract cancer; *CDKN2A*-del, cyclin-dependent kinase inhibitor 2A deletion; DLT, dose-limiting toxicity; HNSCC, head and neck squamous cell carcinoma; MEL, melanoma; Meso, mesothelioma; MPNST, malignant peripheral nerve sheath tumor; MTD, maximum tolerated dose.

Results

Efficacy in patients with NSCLC or PDAC

- As of the data cutoff (September 22, 2025), 35 patients with NSCLC and 40 patients with PDAC were evaluable for Navli clinical activity
  - Demographic and clinical characteristics for these patients have been previously reported[6,7]
- In clinically evaluable patients with NSCLC (median follow-up, 15.9 months), objective response rate (ORR) was 34%, disease control rate (DCR) was 80%, and median duration of response (DOR) was 9.1 months (95% CI, 2.8–11.4; **Figure 2A**)
- As reported previously in clinically evaluable patients with PDAC (median follow-up, 15.4 months),[7] ORR was 18%, DCR was 72%, and median DOR was not reached (NR; 95% CI, 3.1–NR; **Figure 2B**)

Figure 2. Efficacy of Navli in patients with (A) NSCLC or (B) PDAC[a]



	NSCLC (n = 35)
ORR,[b] n (%)	12 (34)
CR	0
PR	12 (34)
SD	16 (46)
PD	7 (20)
DCR,[c] n (%)	28 (80)
Median DOR,[d] mo (95% CI)	9.1 (2.8-11.4)

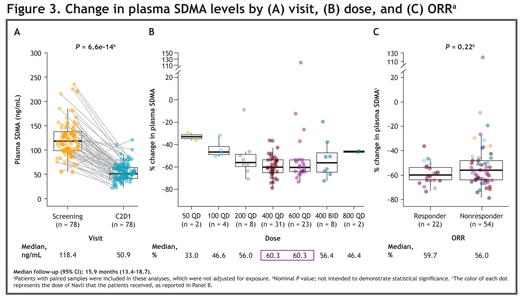
	PDAC (n = 40)[e,f]
ORR,[b] n (%)	7 (18)
CR	0
PR	7 (18)
SD	22 (55)
PD	11 (28)
DCR,[c] n (%)	29 (72)
Median DOR,[d] mo (95% CI)	NR (3.1-NR)

Median follow-up (95% CI): 15.9 months (13.4-18.7).
[a]Clinically evaluable population: patients who received ≥ 1 dose of Navli in this study, had homozygous *MTAP*-del per a sponsor-approved assay, and had ≥ 1 on-study disease assessment prior to discontinuation, any subsequent anticancer therapies, or death. [b]ORR was defined as the percentage of patients achieving a confirmed CR or confirmed PR (based on RECIST v1.1). [c]DCR was defined as the percentage of patients achieving a confirmed CR, confirmed PR, or SD (based on RECIST v1.1). [d]DOR was evaluated in responders only. [e]Reproduced with permission from the authors. CR, complete response, NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; Tx, treatment.

Updated plasma SDMA analysis

- Among 78 patients with paired plasma SDMA samples, median plasma SDMA levels decreased from 118.4 ng/mL at baseline to 50.9 ng/mL at C2D1 (**Figure 3A**)
- Dose-dependent reductions were observed in median plasma SDMA, with the greatest numerical reductions observed in patients treated with Navli 400 mg QD (median, 60.3%; n = 31) or Navli 600 mg QD (median, 60.3%; n = 23; **Figure 3B**)
- There was no notable difference in reductions in plasma SDMA levels between responders (n = 22) vs nonresponders (n = 54) from baseline to C2D1 (median, 59.7% vs 56.0%; **Figure 3C**)

Figure 3. Change in plasma SDMA levels by (A) visit, (B) dose, and (C) ORR[a]



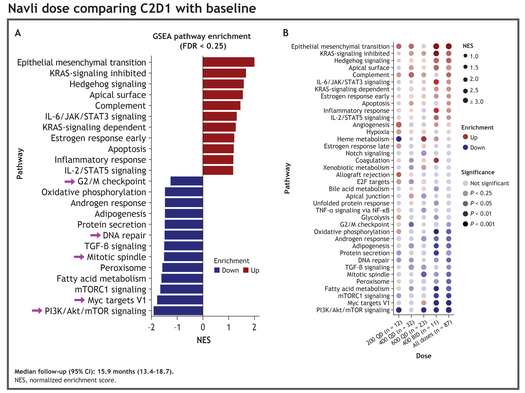
	A	B							C	
Median, ng/mL	118.4	50.9								
Median, %			33.0	46.6	56.0	60.3	60.3	56.4	59.7	56.0

Median follow-up (95% CI): 15.9 months (13.4-18.7).
[a]Patients with paired samples were included in these analyses, which were not adjusted for exposure. [b]Nominal *P* value; not intended to demonstrate statistical significance. [c]The color of each dot represents the dose of Navli that the patients received, as reported in Panel B.

Proteomic profile analysis

- Among 87 patients with paired plasma samples for proteomic analysis, PI3K/Akt/mTOR, Myc target, cell cycle, and DDR pathways were downregulated from baseline to C2D1, consistent with the expected effect of PRMT5 inhibition with Navli (**Figure 4A**)
  - There was a trend of higher doses of Navli resulting in deeper modulation of PRMT5-regulated pathways (**Figure 4B**)
- Among 94 patients with evaluable samples at baseline (responders, n = 20; nonresponders, n = 74), no evaluated proteins had a significant association with ORRs with Navli (false discovery rate [FDR] > 0.05)

Figure 4. Plasma proteomic pathway enrichment analysis (A) overall and (B) by Navli dose comparing C2D1 with baseline

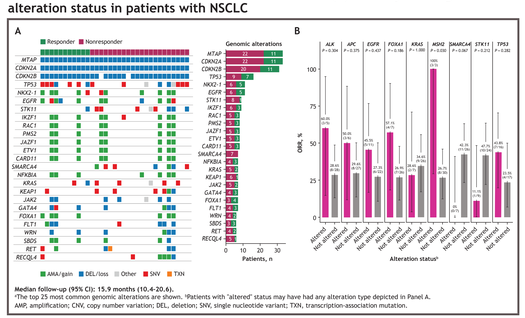


Median follow-up (95% CI): 15.9 months (13.4-18.7).
NES, normalized enrichment score.

Genomic profile analysis

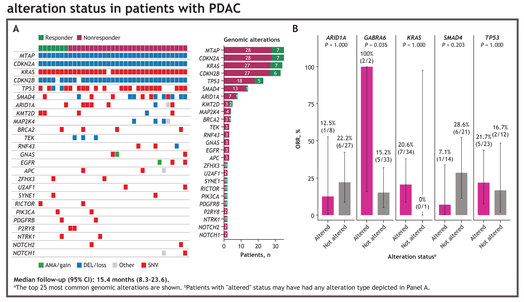
- In clinically evaluable patients with NSCLC with evaluable tumor genomic information from baseline (n = 33), in addition to *CDKN2A* and *CDKN2B*, which are often co-deleted with *MTAP* on the 9p21 locus, the most common co-altered genes were *TP53*, *EGFR*, *NKX-2*, and *STK11* (**Figure 5A**)
  - There was a trend toward enrichment of *STK11* and *SMARCA4* alterations in nonresponders vs responders, and all 3 patients with *MSH2* alterations had objective response (**Figure 5B**)
  - Responses were observed regardless of *ALK*, *EGFR*, or *KRAS* alteration status (**Figure 5B**)
- In clinically evaluable patients with PDAC with evaluable tumor genomic information from baseline (n = 35), in addition to *CDKN2A* and *CDKN2B*, the most common co-altered genes were *KRAS*, *TP53*, *SMAD4*, and *ARIDA1A* (**Figure 6A**)
  - No genomic alterations were associated with response in patients with PDAC except for *GABRA6* alterations, which occurred in 2 patients (both responders), while a trend towards higher ORR was observed in patients with *SMAD4* wild-type vs altered tumors (**Figure 6B**)
  - Among patients with *KRAS* alterations, ORRs were 25.0% (4/16) for *KRAS*^{G12D} alterations, 7.7% (1/13) for *KRAS*^{G12V} alterations, 50.0% (1/2) for *KRAS*^{G12R} alterations, and 33.3% (1/3) for other *KRAS* alterations
  - Responses were observed regardless of *TP53* alteration status (**Figure 6B**)
- Among clinically evaluable patients with alterations in DDR genes at baseline (n = 52), a trend toward higher ORRs was observed among patients with loss of function (LOF) alterations in *CHEK2*, *FANCD2*, *MSH2*, *RAD50*, and/or *XRCC4* vs patients without, consistent with the role of PRMT5 in DDR (**Figure 7**)

Figure 5. (A) Most common[a] genomic alterations and (B) ORRs by select genomic alteration status in patients with NSCLC



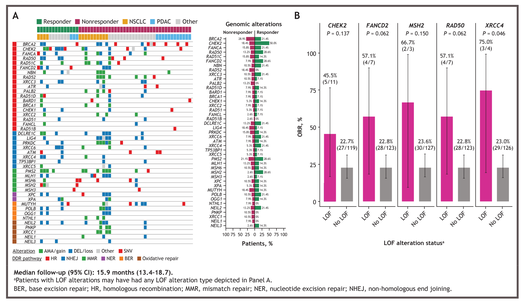
Median follow-up (95% CI): 15.9 months (10.4-20.6).
[a]The top 25 most common genomic alterations are shown. [b]Patients with 'altered' status may have had any alteration type depicted in Panel A.
AMP, amplification; CNV, copy number variation; DEL, deletion; SNV, single nucleotide variant; TXN, transcription-association mutation.

Figure 6. (A) Most common[a] genomic alterations and (B) ORRs by select genomic alteration status in patients with PDAC



Median follow-up (95% CI): 15.4 months (8.3-23.6).
[a]The top 25 most common genomic alterations are shown. [b]Patients with 'altered' status may have had any alteration type depicted in Panel A.

Figure 7. (A) Alterations in DDR genes and (B) ORRs by select DDR gene alteration status

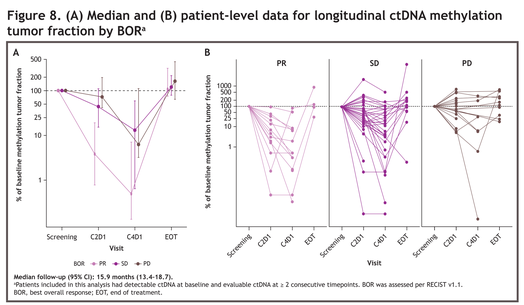


Median follow-up (95% CI): 15.9 months (13.4-18.7).
[a]Patients with LOF alterations may have had any LOF alteration type depicted in Panel A.
BER, base excision repair; HR, homologous recombination; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining.

Molecular response per ctDNA

- In patients with detectable ctDNA at baseline and evaluable ctDNA at ≥ 2 consecutive timepoints (n = 75), reductions from baseline ctDNA methylation tumor fraction were observed as early as C2D1 and continued to deepen on cycle 4 day 1 (C4D1; **Figure 8**)
  - At C2D1, deeper responses were observed in patients with PR: median % reduction in baseline ctDNA methylation tumor fraction was 96.2% (interquartile range [IQR], 81.0-99.2) with PR, 56.2% (IQR, −9.8 to 84.8) with SD, and 27.6% (IQR, −96.0 to 58.6) with PD (Kruskal-Wallis multiple-group test *P* = 0.0002 at C2D1)
  - Responses continued to deepen at C4D1: median % reduction in baseline ctDNA methylation tumor fraction was 99.5% (IQR, 93.0-99.9) in patients with PR, 86.9% (IQR, 41.0-99.4) in patients with SD, and 93.8% (IQR, −10.8 to 96.8) in patients with PD

Figure 8. (A) Median and (B) patient-level data for longitudinal ctDNA methylation tumor fraction by BOR[a]



Median follow-up (95% CI): 15.9 months (13.4-18.7).
[a]Patients included in this analysis had detectable ctDNA at baseline and evaluable ctDNA at ≥ 2 consecutive timepoints. BOR was assessed per RECIST v1.1.
BOR, best overall response; EOT, end of treatment.

Conclusions

- In this first-in-human study, Navli continued to demonstrate robust dose-dependent pharmacodynamic effects in patients with advanced solid tumors and homozygous *MTAP*-del across multiple doses
  - Patients who received Navli 400 mg QD or 600 mg QD had the greatest numerical reductions in plasma SDMA levels from baseline to C2D1
- PRMT5-regulated pathways, including PI3K/Akt/mTOR, Myc target, cell cycle, and DDR pathways, were downregulated at C2D1 in plasma proteomic analyses
  - Trends of greater magnitudes of downregulation for PRMT5-regulated pathways were observed at higher doses of Navli
- Responses to Navli were observed in patients with NSCLC regardless of the presence of key oncogenic driver alterations, including *ALK*, *EGFR*, and *KRAS* gene alterations
- Responses to Navli in patients with PDAC were observed across different types of *KRAS* alterations and regardless of *TP53* alterations
- LOF alterations in DDR genes, including *CHEK2*, *FANCD2*, *MSH2*, *RAD50*, and *XRCC4*, were associated with numerically improved ORRs with Navli
- Molecular response per ctDNA may be an early surrogate for efficacy with Navli
- Together, these results further reinforce the proposed MOA for Navli and support investigations of Navli in the ongoing phase 2/3 MountainTAP-9 (NCT06855771), MountainTAP-29 (NCT07063745), and MountainTAP-30 (NCT07076121) studies as a potential treatment option in patients with advanced solid tumors and homozygous *MTAP*-del

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