MountainTAP-29: a randomized phase 2/3 study of first-line navlimetostat (BMS-986504) + pembrolizumab + chemotherapy in patients with metastatic NSCLC with homozygous *MTAP* deletion

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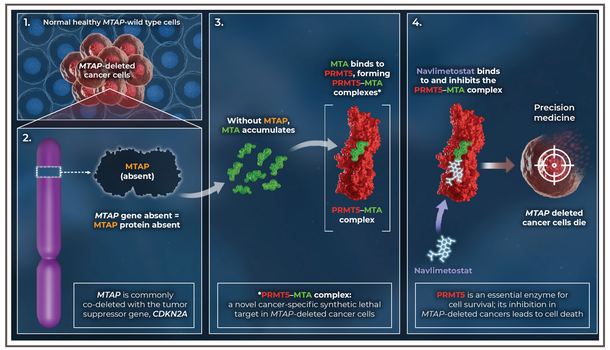
Background

- Immune checkpoint inhibitor–based regimens with or without platinum chemotherapy (chemo) are the standard of care (SOC) for first-line (1L) treatment for metastatic non-small cell lung cancer (NSCLC), demonstrating meaningful survival improvements over chemo alone[1,2]
  - Despite these advances, long-term survival remains limited, with 5-year overall survival (OS) rates of approximately 19% observed with 1L SOC immunotherapy-chemo regimens[3]
- Methylthioadenosine phosphorylase deletion (*MTAP*-del) is present in approximately 13% of NSCLC tumors and across 10%-15% of solid malignancies overall and has been linked to poor prognosis and substantial unmet clinical need [4-7]
  - Notably, homozygous *MTAP*-del has been associated with inferior survival with SOC therapy in NSCLC, with median OS of 11.2 months vs 16.3 months in *MTAP*-wild-type (WT) NSCLC[8]
- Navlimetostat (Navli; BMS-986504/MRTX1719) is a first-in-class methylthioadenosine (MTA)-cooperative protein arginine methyltransferase 5 (PRMT5) inhibitor designed to selectively target the PRMT5-MTA complex (**Figure 1**)[9]
  - The PRMT5-MTA complex represents a synthetic lethal vulnerability in *MTAP*-del cancer cells, while sparing *MTAP*-WT cells

Figure 1. Navlimetostat (Navli; BMS-986504) mechanism of action

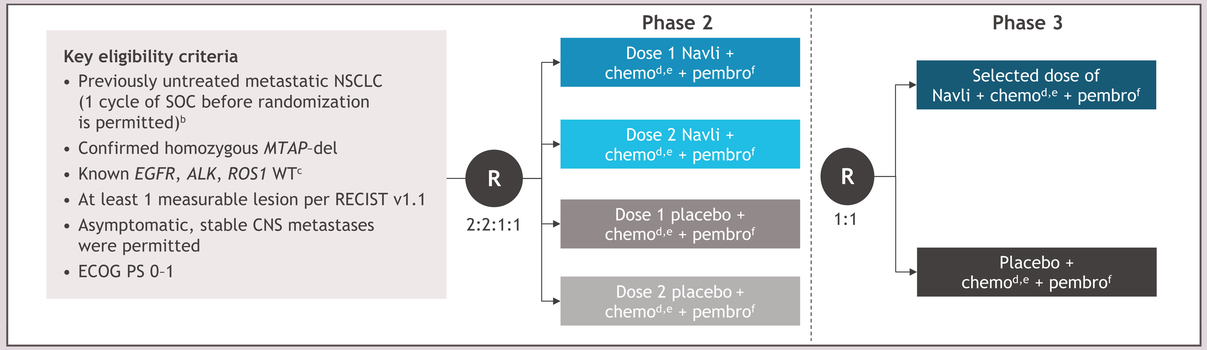


Rationale

- Results of preclinical studies demonstrated that MTA-cooperative PRMT5 inhibition enhances tumor immunogenicity, increases programmed death-ligand 1 (PD-L1) expression, and sensitizes *MTAP*-del tumors to anti-programmed death 1 (PD-1) therapy and platinum-based chemo[10,11]
- In the first-in-human phase 1 trial CA240-0007 (NCT05245500), Navli was well tolerated across all evaluated doses up to 600 mg once daily and demonstrated antitumor activity in heavily pretreated patients with homozygous *MTAP*-del advanced, unresectable, or metastatic solid tumors, including NSCLC[12]
  - With a median follow-up of 11.7 months[a] in patients with NSCLC treated with Navli (n = 35), the objective response rate (ORR) was 34%,[b] the disease control rate was 80%, and the median duration of response (DOR) was 10.5 months
  - Treatment-related adverse events with Navli led to discontinuation in 5% of patients with NSCLC, and no patient discontinued due to treatment-related hematologic toxicities
- MountainTAP-29 is designed to evaluate the efficacy and safety of Navli + chemo + pembrolizumab (pembro) vs placebo + chemo + pembro in patients with previously untreated, metastatic NSCLC with *MTAP*-del

[a]Data cutoff date: May 7, 2025. [b]Including 2 unconfirmed responses that were confirmed after data cutoff.

Figure 2. MountainTAP-29[a] phase 2/3 study design



[a]NCT07063745. [b]Phase 2: SOC is defined as chemo with or without anti-PD-(L)1 therapy (Q3W regimens preferred). Phase 3: SOC is defined as pembro + chemo. [c]Patients with NSQ histology with documented targetable oncogenic mutations or AGAs (eg, *EGFR*, *ALK*, *ROS1*) eligible for an approved targeted therapy in 1L, as deemed appropriate by the investigator will be excluded. Patients with NSQ histology with unknown actionable AGA status of *EGFR*, *ALK*, and *ROS1* will be excluded. [d]NSQ = carboplatin AUC 5 or cisplatin 75 mg/m^2 IV Q3W for up to 4 cycles and pemetrexed 500 mg/m^2 IV Q3W for up to 4 cycles + optimal maintenance. SQ = carboplatin AUC 5 or 6 IV Q3W for up to 4 cycles and paclitaxel 175 or 200 mg/m^2 IV Q3W or nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 of each 21-day cycle for up to 4 cycles. [e]Treatment will continue until disease progression (per RECIST v1.1), up to 2 years, unacceptable toxicity, start of subsequent anticancer therapy, death, patient withdrawal of consent, or conclusion of the study, whichever occurs first. Patients with radiographic disease progression assessed by investigator may be permitted to continue treatment beyond progression at the discretion of the investigator. [f]Pembro 200 mg IV Q3W for up to 2 years. AGA, actionable genomic alteration; AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; NSQ, nonsquamous; Q3W, every 3 weeks; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SQ, squamous.

Study design

- MountainTAP-29 (NCT07063745) is a global, operationally seamless phase 2/3 study comparing Navli + chemo + pembro with placebo + chemo + pembro in patients with untreated metastatic NSCLC with homozygous *MTAP*-del (**Figure 2**)
  - After all patients have completed approximately 6 months of follow-up, the safety and efficacy data from phase 2 will be reviewed and utilized to select the dose of Navli to be used in phase 3
- Key inclusion and exclusion criteria are listed in **Table 1**
- Study endpoints are listed in **Table 2**

Table 1. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Histologically confirmed diagnosis of metastatic NSCLC • Evidence of *MTAP*-del or MTAP loss detected in tumor tissue using a sponsor-provided central test or a sponsor preapproved local test • Metastatic disease with ≥ 1 measurable lesion as per RECIST v1.1 • No prior systemic anticancer treatments in the metastatic setting – For patients who receive 1 cycle of SOC[a] before randomization, TRAEs associated with this first cycle of SOC must resolve to grade ≤ 1 or baseline before randomization, except those with alopecia, fatigue,[b] or endocrine-related AEs requiring treatment or hormone replacement • Adequate organ function • ECOG PS 0-1 • Aged ≥ 18 years	• NSQ histology with documented targetable oncogenic mutations or AGAs (eg, *EGFR*, *ALK*, *ROS1*) eligible for an approved therapy in 1L, as deemed appropriate by the investigator – Patients with unknown AGA status of *NTRK*, *BRAF*, *MET* exon 14 skipping, *RET*, or those without access to the approved targeted inhibitor therapies of these AGAs as 1L therapy may be enrolled • Concurrent malignancy requiring treatment or history of prior malignancy active within 2 years before screening • Known or suspected impairment of gastrointestinal function that may prohibit the ability to absorb or swallow an oral medication without chewing or crushing • Symptomatic brain metastases or spinal cord compression

[a]Phase 2: SOC is defined as chemo with or without anti-PD-(L)1 therapy (Q3W regimens preferred). Phase 3: SOC is defined as pembro + chemo. [b]Grade 2.
AE, adverse event; TRAE, treatment-related adverse event.

Table 2. Study endpoints

Endpoints	Phase 2	Phase 3
Primary[a]	• PFS by RECIST v1.1	• PFS by RECIST v.1.1 • OS
Secondary	• ORR, DCR, DOR, and TTOR by RECIST v1.1 • Safety	• ORR, DCR, and DOR by RECIST v.1.1 • PFS by RECIST v.1.1 • PFS2 by RECIST v.1.1
Exploratory	• OS	• Safety • ORR, DCR, and DOR by RECIST v.1.1 • CBR and TTOR by RECIST v.1.1 • HRQOL

[a]In phase 3, PFS and OS are dual primary endpoints.
CBR, clinical benefit rate; DCR, disease control rate; HRQOL, health-related quality of life; PFS, progression-free survival; PFS2, progression-free survival 2; TTOR, time to objective response.

Study treatments

- In the phase 2 portion of the study, there are 2 doses of Navli or placebo given in combination with pembro and chemo
  - Dose 1: Navli or placebo in 21-day cycles
  - Dose 2: Navli or placebo in 21-day cycles
  - Chemo regimen for NSQ NSCLC includes:
    - Carboplatin AUC 5 or cisplatin 75 mg/m^2 IV Q3W for up to 4 cycles
    - Pemetrexed 500 mg/m^2 IV Q3W for up to 4 cycles + optional maintenance
  - Chemo regimen for SQ NSCLC includes:
    - Carboplatin AUC 5 or 6 IV Q3W for up to 4 cycles
    - Paclitaxel 175 mg/m^2 or 200 mg/m^2 IV Q3W[c] or nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 of each 21-day cycle for up to 4 cycles
  - Pembro 200 mg IV Q3W for up to 2 years
- In the phase 3 portion of the study, the dose determined in phase 2 will be used for Navli given in combination with chemo and pembro 200 mg IV Q3W, compared with placebo in combination with chemo and pembro 200 mg IV Q3W

[c]Paclitaxel dosing reflects a US-approved protocol update, with approval pending in other jurisdictions.

Study sites and dates

- MountainTAP-29 is enrolling patients in 261 study sites globally (**Figure 3**)
- Study start date: January 2026
- Estimated primary and study completion date: August 2031
- Navli is currently being investigated in multiple studies, including in patients with advanced solid tumors (CA240-0007), in NSCLC (MountainTAP-9), and in pancreatic ductal adenocarcinoma (MountainTAP-30)

Figure 3. MountainTAP-29 study sites (actively enrolling)

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Disclosures

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