Poster #5046

Safety and pharmacokinetics of mevrometostat in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC)

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Objective

- To characterize mevrometostat safety and pharmacokinetics in patients with mCRPC who received mevrometostat 875 mg twice daily (BID) with food, plus enzalutamide, in the phase 1 mevrometostat clinical study (NCT03460977).

Conclusions

- In patients with mCRPC treated with mevrometostat in combination with enzalutamide, mevrometostat 875 mg BID and enzalutamide with food had an improved safety profile, including better gastrointestinal tolerability, compared with mevrometostat 1250 mg BID and enzalutamide on an empty stomach.
- Mevrometostat 875 mg BID and enzalutamide with food resulted in similar plasma exposures to mevrometostat 1250 mg BID and enzalutamide on an empty stomach.
- Based on these safety and pharmacokinetic observations from this phase 1 clinical study, mevrometostat 875 mg BID with food was selected as the recommended dose in the phase 3 program in combination with enzalutamide.
- Pivotal phase 3 studies using this dose regimen are currently ongoing in patients with mCRPC previously treated with abiraterone (MEVPRO-1, NCT06551324), or naïve to androgen receptor pathway inhibitors (ARPIs) (MEVPRO-2; NCT06629779), and in patients with mCSPC who are ARPI-naïve (MEVPRO-3).

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Supplementary materials

The aPLS and mechanism of action of mevrometostat can be viewed as supplementary materials using the poster QR code.

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Introduction

- Enhancer of zeste homolog 2 (EZH2) is overexpressed in castration-resistant prostate cancer (CRPC), and contributes to disease progression through transcriptional repression of tumor suppressor genes and androgen receptor (AR) activation, co-regulation of AR-mediated transcriptional programs, and cell cycle deregulation.[1-4]
- Mevrometostat (PF-06821497) is an oral, potent, and selective small molecule inhibitor of EZH2.
- It is hypothesized that the addition of an EZH2 inhibitor to an ARPI may improve ARPI clinical response and delay or prevent antiandrogen resistance.
- In the randomized dose-expansion part of a phase 1 study (NCT03460977), mevrometostat (1250 mg BID on an empty stomach) plus enzalutamide (160 mg once daily [QD]) improved outcomes versus enzalutamide alone, with a manageable safety profile.[5]
- Efficacy and safety of doses of mevrometostat ranging from 150 mg BID to 1250 mg BID in combination with enzalutamide, and the effects of food were also investigated within the study.

Methods

- This is an open-label dose-escalation and dose-expansion study.
- Patients ≥18 years with mCRPC who had received prior treatment with abiraterone and/or enzalutamide with evidence of progression per modified Prostate Cancer Working Group 3 criteria were included.
- In the dose-expansion part of the study, patients were randomized 1:1 (unblinded) to receive either mevrometostat 1250 mg BID on an empty stomach, in combination with enzalutamide 160 mg QD, or enzalutamide only, from day 1 to day 21 in each cycle.
- Observations from the non-randomized part of the study, which tested a range of mevrometostat doses, including a food cohort, indicated that mevrometostat 875 mg BID given with food resulted in improved safety outcomes versus mevrometostat 1250 mg BID on an empty stomach.
- The current analysis included patients who received mevrometostat 875 mg BID with food in combination with enzalutamide 160 mg QD plus androgen deprivation therapy.
- The primary endpoint of this analysis was safety of mevrometostat in patients receiving mevrometostat 875 mg BID with food.
  - Assessment of the food effect on pharmacokinetics was a secondary endpoint.
- Data were compared with those of patients included in the dose-expansion cohort with CRPC who had received mevrometostat 1250 mg BID on an empty stomach plus enzalutamide 160 mg QD.

Results

Patients

- As of February 28, 2025, 29 patients had received mevrometostat at 875 mg BID with food plus enzalutamide.
- Median (interquartile range [IQR]) duration of treatment in patients who received mevrometostat 875 mg BID with food was 8.0 (4.5–10.4) months.
  - Median (IQR) duration of treatment in patients who received mevrometostat 1250 mg BID on an empty stomach was 7.6 (3.7–12.8) months.
- Baseline demographics and disease characteristics are shown in **Table 1**.
  - Median (range) age was 73 (55–86) years in patients who received mevrometostat 875 mg BID and enzalutamide with food.
  - Demographics and characteristics of patients who received mevrometostat 875mg BID and enzalutamide with food were generally similar to those in the dose-expansion cohort who had received 1250 mg BID and enzalutamide on an empty stomach (**Table 1**).[5]

Table 1. Baseline demographics and disease characteristics

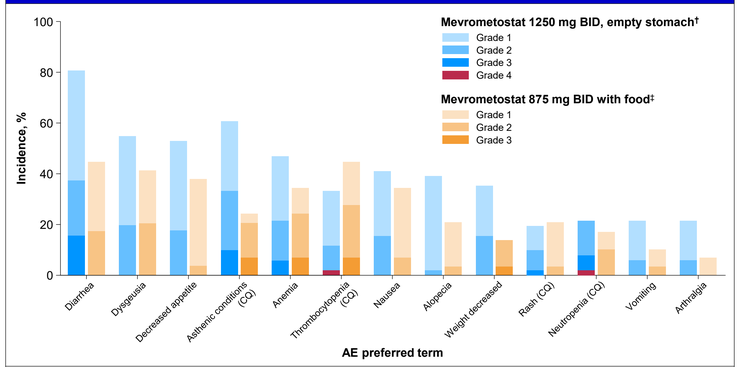
Characteristic	Mevrometostat (875 mg BID with food) + enzalutamide (n=29)†	Mevrometostat (1250 mg BID on an empty stomach) + enzalutamide (n=41)‡§
Age, median (range), years	73.0 (55–86)	70.0 (48–86)
Race, n (%)		
White	24 (82.8)	31 (75.6)
Asian	5 (17.2)	6 (14.6)
Black or African American	0	2 (4.9)
Prior treatment at baseline, n (%)		
Taxane	15 (51.7)	18 (43.9)
Abiraterone	23 (79.3)	41 (100)
Enzalutamide	9 (31.0)	0 (0)
Baseline PSA, median (range), µg/L	21.0 (0–1000)	15.5 (0–259)
Gleason score, n (%)		
<8	2 (6.9)	11 (26.8)
≥8	17 (58.6)	26 (63.4)
ECOG Performance Status, n (%)		
0	14 (48.3)	26 (63.4)
1	15 (51.7)	15 (36.6)
Lesions at baseline, n (%)		
Bone	21 (72.4)	36 (87.8)
Lymph nodes	9 (31.0)	12 (29.3)
Liver	2 (6.9)	3 (7.3)

†Data cut-off February 28, 2025. ‡Data presented at ASCO-GU 2025, with a data cut-off of September 2, 2024.
BID, twice daily; ECOG, Eastern Cooperative Oncology Group; PSA, prostate specific antigen.

Safety

- All 29 patients (100%) who received mevrometostat 875 mg BID and enzalutamide with food experienced a treatment-emergent adverse event (TEAE; **Table 2**).
- The most common all-cause TEAEs were diarrhea (n=13 [44. 8%]), thrombocytopenia (n=13 [44.8%]), and dysgeusia (n=12 [41.4%]) (**Table 2**).
- Rates of gastrointestinal TEAEs were numerically considerably lower in the 875 mg BID with food cohort versus the 1250 mg on an empty stomach cohort (**Figure 1**).
- There were no occurrences of grade ≥3 diarrhea in the 875mg BID with food cohort (**Table 2**).
- One patient in the mevrometostat 875 mg BID and enzalutamide with food cohort had a fatal (grade 5) event of osteonecrosis of the jaw (present at baseline) that was not considered related to mevrometostat.
  - This was the only occurrence of a TEAE leading to withdrawal of mevrometostat treatment.
- AEs leading to mevrometostat dose reduction in the with food cohort occurred in 5 (17.2%) of patients (**Table 2**).
  - These were two cases of dysgeusia and one case each of asthenic conditions, diarrhea, dyspepsia, prolonged electrocardiogram QT, fall, and thrombocytopenia.

Figure 1. Most common TEAEs that occurred in ≥20% of patients in either treatment arm, according to maximum AE grade



†Data cut-off September 2, 2024. ‡Data cut-off February 28, 2025.
AE, adverse event; BID, twice daily; CQ, coding qualifier; TEAE, treatment-emergent adverse event.

Table 2. Summary of AEs and most common (all-causality) AEs

n (%)	Mevrometostat (875 mg BID with food) + enzalutamide (n=29)†		Mevrometostat (1250 mg BID on an empty stomach) + enzalutamide (n=41)‡§	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	29 (100)	12 (41.4)	40 (97.6)	22 (53.7)
Treatment-related TEAE	28 (96.6)	8 (27.6)	39 (95.1)	20 (48.8)
Serious AE	7 (24.1)	5 (17.2)	14 (34.1)	13 (31.7)
Serious treatment-related TEAE§	3 (10.3)	30 (10.3)	10 (24.4)	10 (24.4)
TEAE leading to dose reduction	5 (17.2)	1 (3.4)	15 (36.6)	7 (17.1)
TEAE leading to study treatment discontinuation	1 (3.4)	1 (3.4)	1 (2.4)	0
Most common all-cause TEAEs that occurred in ≥30% of patients¶				
Diarrhea	13 (44.8)	0	32 (78.0)	7 (17.1)
Thrombocytopenia	13 (44.8)	2 (6.9)	12 (29.3)	1 (2.4)
Dysgeusia	12 (41.4)	0	24 (58.5)	0
Decreased appetite	11 (37.9)	0	24 (58.5)	0
Anemia	10 (34.5)	2 (6.9)	20 (48.8)	2 (4.9)
Nausea	10 (34.5)	0	17 (41.5)	0
Asthenic conditions	7 (24.1)	2 (6.9)	23 (56.1)	2 (4.9)
Alopecia	6 (20.7)	0	16 (39.0)	0

†Data cut-off February 28, 2025.‡Data cut-off September 2, 2024. §Related to mevrometostat and/or enzalutamide. ¶For patients in either treatment arm.
AE, adverse event; BID, twice daily; IQR, interquartile range; TEAE, treatment-emergent adverse event.

- The most common treatment-related TEAEs of any grade in the mevrometostat 875 mg BID and enzalutamide with food cohort were diarrhea (n=12 [41.4%]), thrombocytopenia (n=12 [41.4%]), dysgeusia (n=11 [37.9%]), and decreased appetite and nausea (both n=9 [31.0%].
- Serious drug-related TEAEs were reported in three (10.3%) patients (one case each of grade 3 anemia, prolonged electrocardiogram QT, and hemorrhagic enterocolitis).

Pharmacokinetics

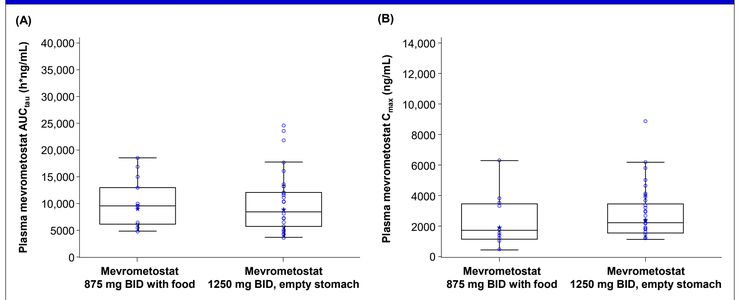
- Plasma exposures of mevrometostat after multiple doses were comparable between mevrometostat 875 mg BID with food (n=12) and mevrometostat 1250 mg on an empty stomach (n=51) (**Table 3**, **Figure 2**).

Table 3. Key pharmacokinetic parameters of mevrometostat after multiple doses (pharmacokinetic analysis set)†

Pharmacokinetic characteristic, geometric mean (coefficient of variation)	Mevrometostat (875 mg BID with food) + enzalutamide (n=12)	Mevrometostat (1250 mg BID on an empty stomach) + enzalutamide (n=51)
AUC_{tau}, h*ng/mL	8984 (48)	8690 (54)
C_{max}, ng/mL	1868 (85)	2371 (54)

†Data cut-off November 15, 2024.
AUC, area under the curve; BID, twice daily; C_{max}, maximum concentration.

Figure 2. Plasma mevrometostat AUC_{tau} (A) and C_{max} (B) after multiple doses (pharmacokinetic analysis set)†



†Data cut-off November 15, 2024.
AUC, area under the curve; BID, twice daily; C_{max}, maximum concentration.