Mevrometostat, an enhancer of zeste homolog 2 inhibitor (EZH2), in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC): A randomized dose-expansion study

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Key findings

- Mevrometostat in combination with enzalutamide showed promising antitumor activity/ oncological outcomes compared with enzalutamide alone in patients with metastatic castration-resistant prostate cancer (mCRPC; radiographic progression-free survival [rPFS]: hazard ratio 0.51; 90% confidence intervals: 0.28, 0.95).
- Mevrometostat 1250 mg twice daily (BID) on an empty stomach in combination with enzalutamide has a manageable safety profile.
- Plasma exposure with mevrometostat 875 mg BID with food was similar to 1250 mg BID on an empty stomach, with an improved safety profile.
  - Mevrometostat 875 mg BID with food is the recommended phase 3 dose.
- Pivotal phase 3 studies are in progress in patients with mCRPC previously treated with abiraterone (MEVPRO-1; NCT06551324) or who are androgen receptor pathway inhibitor-naïve (MEVPRO-2; NCT06629779)

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Mechanism of action

The mechanism of action of mevrometostat can be viewed as a supplementary material using the poster QR code.

Disclosures: The presenter of this poster is an employee of Pfizer Inc. who has been authorized to present on behalf of the authors. Disclosures for the authors can be viewed as supplementary material using the poster QR code.

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Background

- Enhancer of zeste homology 2 (EZH2) is overexpressed in CRPC[1] and is associated with poor prognosis.
- Mevrometostat is a selective EZH2 inhibitor.[2]
- Dose exploration of mevrometostat + enzalutamide + androgen deprivation therapy in patients with mCRPC showed[3]:
  - a manageable safety profile,
  - on-target pharmacodynamic inhibition of EZH2,
  - preliminary evidence of clinical activity
- We report clinical outcomes and impact of administration with food on pharmacokinetics and safety from the open-label, randomized, dose-expansion part of this study (NCT03460977).

Methods

Patient population:
- mCRPC
- Prior abiraterone
- ≤1 regimen of prior chemotherapy in any setting
- Evidence of progression per modified PCWG3 criteria
- Ongoing ADT

R 1:1

N=81

Stratification factor:
- Prior chemotherapy

Mevrometostat 1250 mg orally BID, empty stomach + enzalutamide 160 mg orally QD n=41

Enzalutamide160 mg orally QD n=40

Primary endpoints:
- rPFS per investigator assessment
- Safety

Secondary endpoints:
- OR†
- PSA_{50}
- Pharmacokinetics‡

†Measured by RECIST 1.1 in patients with measurable disease at baseline.
‡Including evaluation of the effect of food on the pharmacokinetics and safety profile of mevrometostat.
ADT, androgen deprivation therapy; BID, twice daily; mCRPC, metastatic castration-resistant prostate cancer; OR, objective response; PCWG, Prostate Cancer Working Group; PSA_{50}, decline in prostate-specific antigen of ≥50% from baseline; QD, once daily; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiographic progression-free survival

Results

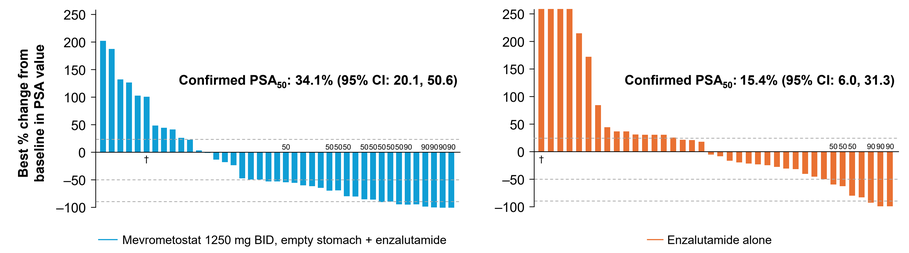
Baseline characteristics

Characteristic	Mevrometostat 1250 mg BID, empty stomach + enzalutamide (n=41)	Enzalutamide alone (n=40)
Age, median (range), years	70.0 (48–86)	71.5 (50–86)
Race, n (%)†		
White	31 (75.6)	30 (75.0)
Asian	6 (14.6)	8 (20.0)
Black or African American	2 (4.9)	0
Prior taxane, n (%)	18 (43.9)	18 (45.0)
Gleason score, n (%)		
<8	11 (26.8)	8 (20.0)
≥8	26 (63.4)	30 (75.0)
ECOG Performance Status, n (%)		
0	26 (63.4)	15 (37.5)
1	15 (36.6)	25 (62.5)
Lesions at baseline, n (%)		
Bone	36 (87.8)	38 (95.0)
Lymph nodes	12 (29.3)	16 (40.0)
Liver	3 (7.3)	2 (5.0)
Lung	3 (7.3)	2 (5.0)

Data cutoff: September 2, 2024.
†Race was not reported for two patients (4.9%) in the mevrometostat + enzalutamide group and two patients (5.0%) in the enzalutamide alone group.
BID, twice daily; ECOG, Eastern Cooperative Oncology Group.

PSA_{50} response

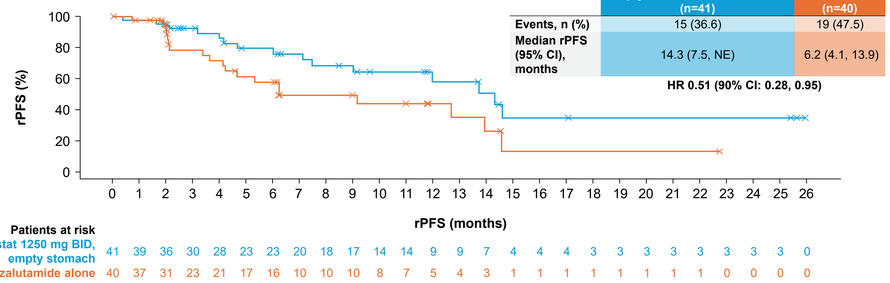
Mevrometostat 1250 mg BID on an empty stomach + enzalutamide improved PSA_{50} vs enzalutamide.



Data cutoff: September 2, 2024. †Baseline PSA ≤0.2 µg/L.
50, PSA response of ≥50% confirmed; 90,PSA response of ≥90% confirmed; BID, twice daily; CI, confidence interval; PSA, prostate-specific antigen; PSA_{50}, decline in prostate-specific antigen of ≥50% from baseline.

Primary endpoint: rPFS by investigator

49% reduction in the risk of progression or death and ~8-month improvement in median rPFS.



	Mevrometostat 1250 mg BID, empty stomach + enzalutamide (n=41)	Enzalutamide alone (n=40)
Events, n (%)	15 (36.6)	19 (47.5)
Median rPFS (95% CI), months	14.3 (7.5, NE)	6.2 (4.1, 13.9)

HR 0.51 (90% CI: 0.28, 0.95)

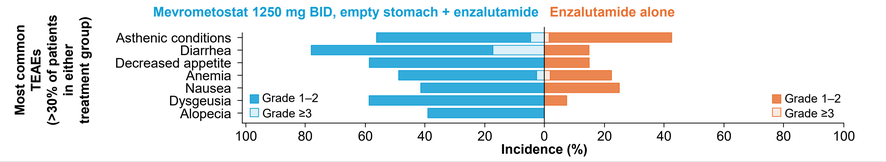
Patients at risk																										
Mevrometostat 1250 mg BID, empty stomach	41	39	36	30	28	23	23	20	18	17	14	14	9	9	7	4	4	4	3	3	3	3	3	3	3	0
Enzalutamide alone	40	37	31	23	21	17	16	10	10	10	8	7	5	4	3	1	1	1	1	1	1	1	0	0	0	0

Median (IQR) duration of follow-up for rPFS was 9.6 (3.1–14.5) months. Data cutoff: September 2, 2024.
BID, twice daily; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NE, not estimable; rPFS, radiographic progression-free survival.

Safety summary

Mevrometostat 1250 mg BID on an empty stomach + enzalutamide has a manageable safety profile.

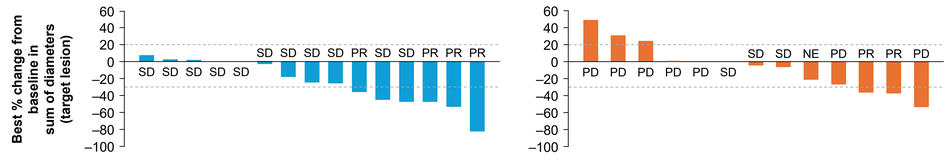
Event, n (%)	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41) All grades	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41) Grade ≥3	Enzalutamide alone (n=40) All grades	Enzalutamide alone (n=40) Grade ≥3
Any TEAE	40 (97.6)	22 (53.7)	37 (92.5)	17 (42.5)
Treatment-related TEAE	39 (95.1)	20 (48.8)	33 (82.5)	9 (22.5)
Serious AE	14 (34.1)	13 (31.7)	11 (27.5)	10 (25.0)
Treatment-related serious TEAE†	10 (24.4)	10 (24.4)	1 (2.5)	1 (2.5)
TEAE leading to dose reduction	15 (36.6)	7 (17.1)	3 (7.5)	0
TEAE leading to study discontinuation	1 (2.4)	0	2 (5.0)	1 (2.5)



Data cutoff: September 2, 2024.
†No treatment-related serious TEAEs led to death.
AE, adverse event; BID, twice daily; TEAE, treatment-emergent adverse event.

Objective response rate

Mevrometostat 1250 mg BID on an empty stomach + enzalutamide improved ORR vs enzalutamide.



	Mevrometostat 1250 mg BID, empty stomach + enzalutamide (n=15)	Enzalutamide alone (n=14)†
Confirmed BOR, n (%)		
PR	4 (26.7)	2 (14.3)
SD	11 (73.3)	3 (21.4)
PD	0	7 (50.0)
ORR (CR + PR), % (95% CI)	26.7 (7.8, 55.1)	14.3 (1.8, 42.8)

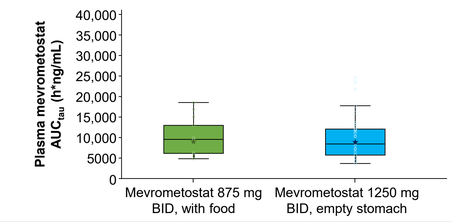
Data cutoff: September 2, 2024.
†One patient did not have any evaluable post-baseline target lesion measurements and was therefore not included in the waterfall plot.
BOR, best overall response; BID, twice daily; CI, confidence interval; CR, complete response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

Pharmacokinetics exposure comparison

Plasma exposure with mevrometostat 875 mg BID with food was similar to mevrometostat 1250 mg BID on an empty stomach.

Geometric mean (geometric % coefficient of variation)	Mevrometostat 875 mg BID, with food (n=12)†	Mevrometostat 1250 mg BID, empty stomach (n=51)‡
AUC_{tau} (h*ng/mL)	8984 (48)	8690 (54)
C_{max} (ng/mL)	1868 (85)	2371 (54)

- Patients treated with mevrometostat 875 mg (BID, with food) had an improved safety profile, including better gastrointestinal tolerability, compared with mevrometostat 1250 mg (BID, on an empty stomach).



Data cutoff: November 15, 2024.
Box plot provides the median and 25% and 75% quartiles, with whiskers to the last data points within 1.5 times the interquartile range. Stars represent geometric means and circles represent individual values.
†Patients from the dose escalation cohort that received mevrometostat 875 mg with food and had pharmacokinetic data available.
‡Patients in the dose-escalation and dose-expansion cohorts that received mevrometostat 1250 mg on an empty stomach and had pharmacokinetic data available.
AUC, area under the curve; BID, twice daily; C_{max}, maximum concentration.