Poster #D20

Modulation of enhancer of zeste homolog 2 (EZH2) pharmacodynamic markers and tumor gene expression by mevrometostat (PF-06821497) in combination with enzalutamide in patients with castration-resistant prostate cancer (CRPC)

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Objective

- To assess the modulation of EZH2 pharmacodynamic markers and tumor gene expression following administration of mevrometostat (mevro) in combination with enzalutamide (enza) in patients with CRPC

Key Findings and Conclusions

- Mevro twice daily (BID), administered on an empty stomach in combination with enza 160 mg daily (QD), effectively inhibited EZH2 in a dose-dependent manner, as demonstrated by reduction of the pharmacodynamic biomarker H3K27Me3 and tumor gene expression changes.
- This treatment approach may overcome drug resistance and/or enhance androgen-targeting drug activity by restoring the function of tumor suppressor genes and blocking tumor cell proliferation and cell cycle progression.
- Pivotal phase 3 studies of mevro with enza in patients with metastatic CRPC are ongoing.

Additional findings from this study will be presented by Dr. Schweizer during the Rapid Oral Abstract Session A: Prostate Cancer on Thursday, February 13, from 5:00–5:45 PM (LBA138).

ePoster

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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: Disclosures for the authors can be viewed as a supplementary material using the poster QR code.

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This presentation is intended for a healthcare provider audience.

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Introduction

- Despite initial response to androgen deprivation therapy, many patients with prostate cancer develop resistance and progress to CRPC.[1]
- EZH2 is overexpressed in CRPC,[2] and is associated with more advanced disease and poor prognosis. EZH2 has histone methyltransferase activity and catalyzes H3K27 trimethylation (H3K27Me3), leading to chromatin condensation and the epigenetic silencing of target genes, including tumor-suppressor genes, leading to prostate cancer cell growth.[3] EZH2 is a coactivator for critical transcription factors, including the androgen receptor (AR),[4] and also induces neuroendocrine differentiation.[5]
- Mevro is a potent and selective small molecule inhibitor of EZH2.[6]
- Mevro in combination with the AR pathway inhibitor, enza, may restore gene functions repressed by EZH2 and the AR, which results in robust inhibition of tumor cell proliferation, survival, and cell cycle progression.
- Dose exploration of mevro in combination with enza showed a manageable safety profile and promising activity in patients with CRPC in a phase 1 study (NCT03460977),[7] where mevro has exhibited dose-dependent pharmacokinetic exposure increases up to 1250 mg BID in combination with enza (160 mg QD).
- We report the pharmacodynamic effects of EZH2 inhibition and tumor gene expression changes by mevro with enza in patients with CRPC.

Methods

- Serial whole blood and paired tumor biopsy samples were collected during dose escalation of mevro from 150 to 1250 mg BID in combination with enza (160 mg QD) given on an empty stomach in patients with CRPC.
- Paired tumor biopsy samples were collected before the study and after 21 days of mevro + enza or enza alone.
- The H3K27Me3 pharmacodynamic marker was evaluated in peripheral granulocytes by flow cytometry and in paired tumor biopsy samples by an immunohistochemistry assay.
- Tumor gene expression was profiled by whole transcriptomic RNA sequencing; 22,954 genes were reported,19,903 genes were included for data processing (value=0 in >50% samples were excluded).
- Pre- and post-treatment sample gene expression levels and gene signature gene set variation analysis (GSVA) enrichment scores were analyzed by a simple linear model with transformation, if appropriate.
  - Simple linear model: Log2(C2D1/C1D1)=$\beta 0+\beta 1*$dose groups+ϵ; the variance was estimated from overall samples for *P*-value calculation for each dose group, including the ones with only one pair observation.

Results

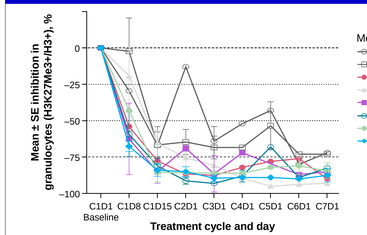
Reduction of H3K27Me3 in blood and tumor

- Dosing with mevro + enza resulted in a dose-dependent reduction of H3K27Me3 in peripheral granulocytes and paired tumor biopsies from patients with CRPC.
  - Strong H3K27Me3 reduction (≥75%) in granulocytes was achieved at ≥375 mg of mevro + enza (**Figure 1**).
  - Tumor H3K27Me3 reduction was also dose dependent within the range of 500–1250 mg; 1250 mg provided maximum reduction (**Table 1**).
  - Tumor H3K27Me3 levels were effectively reduced from baseline in six patients who received mevro at 1250 mg + enza with a geometric mean change (95% confidence interval) of –67% (–86%, –23%) determined by H score (**Table 1A**), and –75% (–93%, –11%) determined by H3K27Me3-positive cells with high and medium intensity staining in tumor area (**Table 1B**).
  - No significant change in H3K27Me3 levels was observed in the four patients receiving mevro at 500 mg + enza (**Table 1**).

Tumor gene expression changes

- In paired tumor samples with RNA sequencing data, based on fold of gene expression level change cutoff value ≥2 (*P*≤0.05, model based), 168 and 128 genes were up- and downregulated, respectively, by mevro 1250 mg + enza (n=3). A similar trend was observed for mevro 875 mg + enza (n=1), but not for mevro 500 mg + enza (n=3) (**Figure 2**).
- GSVA was performed using 56 published pathway signatures[8,9] (**Table 2**).
- A subset of genes upregulated by mevro 1250 mg + enza are those reported to be repressed by the PRC2/EZH2 complex (e.g., *BMP7*, *CPAMD8*, *EYA4*, *FHL1*, *IGFBP3*, and *NOV*), consistent with the strong EZH2 target inhibition measured by tumor H3K27Me3 reduction.
- Furthermore, mevro 1250 mg + enza decreased EZH2 expression by ~50% and decreased expression of genes involved in the E2F pathway, the G2-M checkpoint, Myc responsive genes, and/or cell cycle progression (e.g., *AURKA*, *CDK1*, *FOXM1*, *RAD54L*, *TOP2A*, and *TYMS*; **Table 3**).

Figure 1. Peripheral H3K27Me3 reduction by mevro + enza combination in CRPC



†Plus enza.
BID, twice daily; C, cycle; CRPC, castration-resistant prostate cancer; D, day; enza, enzalutamide; mevro, mevrometostat; SE, standard error.

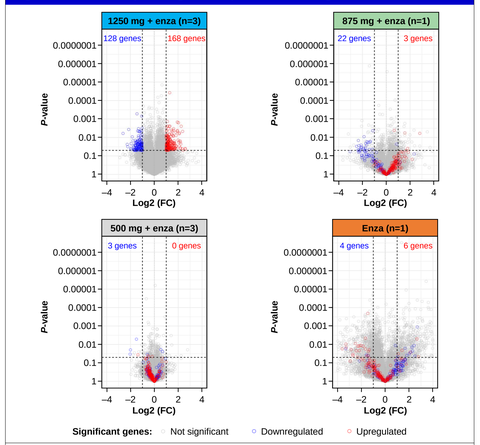
Table 1. Tumor H3K27Me3 levels in patients who received mevro BID administered on an empty stomach + enza

A	H3K27Me3+ cells in tumor areas by H score				
Patient	**Mevro dose (BID)**	**Screening**	**Cycle 2, day 1**	**Change from baseline (%)**	**Geometric mean (95% CI), %†**
A	1250 mg + enza	73.0	6.1	–92	–67 (–86, –23), *P*=0.020
B‡		156.1	38.4	–75	
C		9.8	2.8	–72	
D		177.6	74.4	–58	
E		45.0	30.1	–33	
F‡		86.9	67.5	–22	
G	875 mg + enza	96.1	52.7	–45	N/A
H	500 mg + enza	12.6	8.4	–33	+84 (–58, +712), *P*=0.282
I		51.1	57.9	+13	
J		6.4	17.6	+177	
K		4.9	26.7	+447	

B	H3K27Me3+ cells in tumor areas by staining (% positive cells with high and medium intensity)				
Patient	**Mevro dose (BID)**	**Screening**	**Cycle 2, day 1**	**Change from baseline (%)**	**Geometric mean (95% CI), %†**
A	1250 mg + enza	21.4	0.5	–98	–75 (–93, –11), *P*=0.038
B‡		55.1	12.7	–77	
C		0.7	0.2	–71	
D		64.1	23.7	–63	
E		11.4	6.3	–45	
F‡		28.2	20.2	–28	
G	875 mg + enza	25.4	10.8	–57	N/A
H	500 mg + enza	3.3	1.6	–52	+80 (–70, +989), *P*=0.373
I		15.6	17.0	+9	
J		1.4	4.6	+229	
K		0.9	5.5	+511	

†Paired t-test, unadjusted. ‡Archival tumor sample used as baseline.
BID, twice daily; CI, confidence interval; enza, enzalutamide; mevro, mevrometostat; N/A, not applicable.

Figure 2. Volcano plot of gene expression changes in tumors



Red and blue dots are the genes up- and downregulated based on fold of changes ≥2, *P*≤0.05 (model based), respectively, by mevro 1250 mg + enza combination treatment.
Enza, enzalutamide; FC, fold of gene expression level change from baseline; mevro, mevrometostat.

Table 2. Dose-dependent gene pathway/signature changes in tumors following treatment with mevro + enza

Patient	Mevro dose (BID)	PRC2 repression in CRPC (87)	Myogenesis	Mesenchymal stem cell differentiation	Tumor stemness genes	Hedgehog signalling	Wnt beta-catenin signalling	Apical surface	Notch signalling	G2M checkpoint	E2F targets	MYC targets v1	MTORC1 signaling	Reactive oxygen species pathway	DNA repair	MYC targets v2	Androgen response	Spermatogenesis
F†	1250 mg + enza	0.54	0.40	0.60	0.46	0.21	0.20	0.31	0.38	–0.62	–0.69	–0.33	–0.10	0.05	–0.15	–0.26	–0.23	–0.09
E	1250 mg + enza	0.12	–0.02	0.39	0.29	0.26	0.23	0.15	0.05	–0.64	–0.50	–0.50	–0.49	–0.60	–0.30	–0.33	–0.23	–0.12
A	1250 mg + enza	0.15	0.45	0.12	0.58	0.22	0.24	0.12	0.13	–0.07	–0.11	0.00	0.00	–0.02	–0.09	0.09	0.01	–0.16
G	875 mg + enza	0.05	0.05	0.13	–0.02	0.15	0.11	0.05	0.10	–0.57	–0.71	–0.25	–0.13	–0.08	–0.15	–0.31	0.06	–0.05
I	500 mg + enza	–0.05	–0.26	0.11	0.13	0.12	–0.36	–0.26	0.01	–0.63	–0.69	–0.01	–0.15	–0.01	–0.08	–0.13	–0.08	0.06
K	500 mg + enza	–0.04	–0.10	0.10	0.03	–0.21	–0.02	–0.02	0.03	0.02	0.05	–0.01	–0.03	–0.02	–0.02	–0.04	–0.02	–0.05
H	500 mg + enza	–0.14	–0.31	–0.29	–0.27	–0.14	–0.10	–0.21	–0.10	0.12	0.09	0.39	0.40	0.46	0.06	0.64	0.38	0.04
L†	Enza alone	0.19	0.13	–0.18	–0.19	0.07	0.10	0.19	–0.02	0.38	0.31	–0.05	0.26	0.54	0.03	–0.06	0.11	0.19

The table shows the top signatures with most difference from baseline in GSVA score.
†Archival tumor sample used as baseline.
BID, twice daily; CRPC, castration-resistant prostate cancer; enza, enzalutamide; GSVA, gene set variation analysis; mevro, mevrometostat; MTORC1, mammalian target of rapamycin complex 1; PRC2, polycomb repressive complex 2.

Table 3. Summary of changes in tumor gene expression for mevro + enza in CRPC

	Patient treatment history and clinical activity (November 2, 2023)				Changes of PRC2/EZH2 repressed genes						Changes of E2F/G2M/Mitotic/DDR/Myc pathway genes																Changes of AR genes			
Patient	**Mevro dose (BID)**	**Prior treatment**	**Best response**	**Treatment duration, days**	***BMP7*†**	***CPAMD8*†**	***ITGB8*†**	***FHL1*†**	***EYA4*†**	***IGFBP3*†**	***NOV*†**	***EZH2*†**	***AURKA*†**	***RAD54L*†**	***TOP2A*†**	***E2F1*†**	***CCNE1*†**	***FOXM1*†**	***TYMS*†**	***CDK1*†**	***BIRC5*†**	**E2F sign.‡**	**G2M sign.‡**	**DDR sign.‡**	**MYC v1‡**	**MYC v2‡**	***TMPRSS2*†**	**Androgen response‡**	***APOBEC3B*†**	***AR*†**
F§	1250 mg + enza	Enza/ sipuleucel-T	NE	723	1029	421	198	255	1104	75	829	–76	–70	–85	–86	–71	–64	–79	–75	–82	–85	–0.69	–0.62	–0.15	–0.33	–0.26	–72	–0.23	–54	11
E	1250 mg + enza	Abi	PR	339‖	189	37	115	169	303	97	126	–39	–66	–88	–87	–37	–43	–81	–86	–87	–81	–0.50	–0.64	–0.30	–0.50	–0.33	–30	–0.23	–79	56
A	1250 mg + enza	Abi/ chemo	Non-CR/ PD	221	527	282	78	252	171	341	162	–38	–49	–77	–24	–25	–43	–34	–42	–6	–37	–0.11	–0.07	–0.09	0.00	0.09	–52	0.01	–44	–19
G	875 mg + enza	Abi/enza	SD	210	38	–7	130	134	1293	53	243	–15	–67	–84	–89	–78	–26	–84	–82	–80	–87	–0.71	–0.57	–0.15	–0.25	–0.31	–21	0.06	–77	–3
I	500 mg + enza	Abi/ chemo	SD	321	–17	–19	–33	–24	–13	–36	34	–58	–53	–67	–65	–64	–48	–63	–67	–70	–68	–0.69	–0.63	–0.08	–0.01	–0.13	–17	–0.08	–24	52
K	500 mg + enza	Enza/ chemo/ PARPi	Non-CR/ PD	281	–17	–19	–33	–24	–13	–35	41	29	–53	–67	–27	–14	17	11	1	–70	–68	0.05	0.02	–0.02	–0.01	–0.04	5	–0.02	–24	13
H	500 mg + enza	Enza/ chemo	Non-CR/ PD	119	–11	2	–47	–62	–40	–57	15	14	10	1	29	–19	31	9	–1	18	51	0.09	0.12	0.06	0.39	0.64	43	0.38	–6	52
L§	Enza alone	Abi	PD	63	58	–31	–97	14	–81	–62	34	16	56	163	112	167	455	212	119	169	201	0.31	0.38	0.03	–0.05	–0.06	1	0.11	184	732

†For single genes, changes are % change from baseline expression. ‡For gene signatures, enrichment GSVA score difference from baseline is shown. §Archival tissue used as baseline. ‖Treatment ongoing.
Abi, abiraterone; AR, androgen receptor; BID, twice daily; chemo, chemotherapy; CR, complete response; CRPC, castration-resistant prostate cancer; DDR, DNA damage response; enza, enzalutamide; EZH2, enhancer of zeste homolog 2; GSVA, gene set variation analysis; mevro, mevrometostat; NE, non-evaluable; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PD, progressive disease; PR, partial response; PRC2, polycomb repressive complex 2; SD, stable disease.