Phase 1 trial of mevrometostat (PF-06821497), a potent and selective inhibitor of enhancer of zeste homolog 2 (EZH2), in castration-resistant prostate cancer (CRPC)

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Background: Mevrometostat (PF-06821497) is a potent and selective small molecule inhibitor of EZH2. Dose exploration of mevrometostat with enzalutamide plus androgen deprivation therapy showed a manageable safety profile and evidence of objective response (OR), a decline in prostate-specific antigen of ≥50% from baseline (PSA_{50}), and pharmacodynamic (PD) modulation in patients with CRPC in part 2A of a phase 1 study (NCT03460977). Here, we report longer term follow-up from the dose-escalation cohort.

Methods: This open-label, phase 1 study evaluated mevrometostat (orally, 150–1250 mg BID) plus enzalutamide (orally, 160 mg QD) in adults with CRPC who had evidence of cancer progression per Prostate Cancer Working Group 3 criteria and had received prior abiraterone and/or enzalutamide. Primary endpoint was safety. Pharmacokinetics, radiographic progression-free survival (rPFS), PSA_{50}, and OR were also assessed. Dose/response relationship of mevrometostat on-target H3K27Me3 PD modulation and circulating tumor DNA mutational profiling were exploratory endpoints.

Results: As of November 2, 2023, 47 patients received ≥1 dose of study treatment. Median (interquartile range [IQR]) follow-up was 9.7 (2.0–22.8) months. Median (range) age was 70 (53–87) years. Overall, 27 (57.4%) patients had received prior abiraterone, 35 (74.5%) had received prior enzalutamide, and 23 (48.9%) had received prior taxane therapy. At data cut-off, 18 events were observed (14 progressions and 4 deaths). Median (95% CI) rPFS was 17.0 (6.3, not estimable [NE]) months in all patients (n=47); 17.1 (6.2, NE) months for patients with prior abiraterone (without enzalutamide; n=12), and 11.7 (4.2, NE) months for patients with prior enzalutamide (± abiraterone; n=35). Confirmed PSA_{50} (95% CI) was observed in 14.9% (7.0, 31.4) of patients. In 22 patients with baseline measurable disease, OR rate (95% CI) was 27.3% (10.7, 50.2; 1 complete response, 5 partial responses). Geometric mean (95% CI) H3K27Me3 reduction was −75% (−93, −11) for mevrometostat plus enzalutamide (at mevrometostat 1250 mg BID) in tumor-paired biopsies (n=6). Durable antitumor activity was observed in both post-abiraterone (without enzalutamide) and post-enzalutamide (± abiraterone) patients with and without androgen receptor and/or TP53 mutations. Safety is reported in the **Table**.

Conclusions: Mevrometostat plus enzalutamide shows activity in both post-abiraterone without enzalutamide and post-enzalutamide (± abiraterone) patients with CRPC, with evidence of tumor PD modulation and a manageable safety profile. Further investigation is warranted.

Table. Summary of AEs

n (%)	All patients (N=47)
AEs leading to treatment discontinuation	9 (19.1)
Most common TEAEs related to mevrometostat	
Diarrhea	20 (42.6)
Dysgeusia	20 (42.6)
Anemia	17 (36.2)
Grade ≥3 TEAEs related to mevrometostat	8 (17.0)
Serious TEAEs related to mevrometostat	3 (6.4)
Treatment-related deaths	0 (0)

AE, adverse event; TEAE, treatment-emergent AE.

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Conflicts of Interest:

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