Poster #M6

Mevrometostat (PF-06821497) in combination with enzalutamide for androgen receptor pathway inhibitor (ARPI)-naïve patients with metastatic castration-resistant prostate cancer (mCRPC): The phase 3, randomized MEVPRO-2 trial

Michael T. Schweizer,[1, 2] Jayeta Chakrabarti,[3] Sujata Narayanan,[3] Stella Lin[3]

[1]*Division of Medical Oncology, University of Washington Seattle, WA, USA;* [2]*Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA, USA;* [3]*Oncology, Pfizer Inc., New York, NY, USA*

Summary

- MEVPRO-2 (NCT06629779) is a global, randomized, double-blind, placebo-controlled, phase 3 trial. It will evaluate radiographic progression-free survival (rPFS), overall survival (OS), time to pain progression, and safety of mevrometostat plus enzalutamide compared with enzalutamide alone in patients who are treatment naïve in the mCRPC setting, and have received no ARPI or abiraterone in any prostate cancer setting.

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.

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Contact: Michael T. Schweizer, schweize@uw.edu

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Introduction

- Mevrometostat (PF-06821497) is a potent, selective inhibitor of the histone methyltransferase enhancer of zeste homolog 2 (EZH2), which is canonically involved in epigenetic repression of target genes.[1]
- In prostate cancer, EZH2 overexpression is associated with poor prognosis, contributing to disease progression through transcriptional repression of tumor suppressor genes and androgen receptor (AR) co-activation, co-regulation of AR-mediated transcriptional programs, and cell cycle deregulation through methylation of nonhistone targets.[2–4]
- Given the associations between EZH2 and the AR, the addition of an EZH2 inhibitor to an ARPI is hypothesized to extend the duration of clinical response, and delay or prevent antiandrogen resistance compared with an ARPI alone.[5]
- Enzalutamide is an ARPI approved for the treatment of patients with CRPC, metastatic castration-sensitive prostate cancer (CSPC), and nonmetastatic CSPC with biochemical recurrence at high risk for metastasis.[6]
- Mevrometostat with enzalutamide showed promising activity and a manageable adverse event profile in a phase 1/2 dose-escalation study (NCT03460977) in patients with CRPC who had received prior treatment with abiraterone or enzalutamide. Diarrhea, dysgeusia, and anemia were the most common adverse events considered to be related to mevrometostat.[7]
- Here, we describe the design of a phase 3 trial that explores whether the addition of mevrometostat to enzalutamide can delay or prevent antiandrogen resistance thereby increasing the duration of clinical benefit of enzalutamide in patients with mCRPC who have not previously received an ARPI.

Methods

- MEVPRO-2 (NCT06629779) is a global, randomized, double-blind, placebo-controlled phase 3 trial in adult patients with mCRPC who are ARPI-naïve.
  – Key inclusion and exclusion criteria are detailed in **Table 1**.

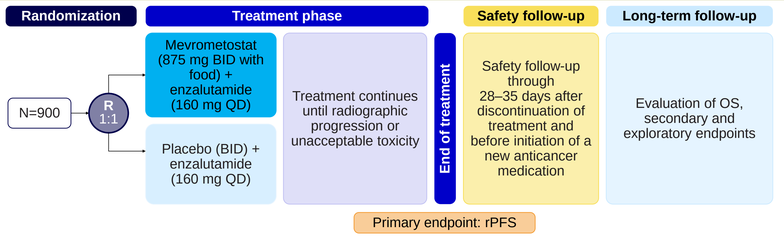
Table 1. Inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
Males aged ≥18 years	Clinically significant cardiovascular disease
Histologically or cytologically confirmed adenocarcinoma of the prostate with no small-cell features	Known or suspected brain metastasis, symptomatic or impending spinal cord compression, or clinically significant history of seizure
Progressive, metastatic disease in bone or soft tissue	Prior treatment for prostate cancer with chemotherapy (except docetaxel in the mCSPC setting), ARPIs (enzalutamide, apalutamide, darolutamide, abiraterone acetate), EZH2 inhibitors, or other systemic treatment
Castrate testosterone levels of ≤50 ng/dL	
ECOG performance status of 0–1	
Life expectancy of ≥12 months as assessed by the investigator	
Treatment-naïve in the mCRPC setting, with the exception of ADT and first-generation antiandrogen agents	

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; ECOG, Eastern Cooperative Oncology Group; EZH2, enhancer of zeste homolog 2; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer.

- Approximately 900 patients will be randomized 1:1 to receive mevrometostat (875 mg twice daily with food) in combination with enzalutamide (160 mg once daily), or placebo (twice daily) with enzalutamide (160 mg once daily; **Figure 1**).
  – The sample size estimation is based on the number of events needed to observe protocol-defined statistical differences between the treatment groups.

Figure 1. Study design



BID, twice daily; OS, overall survival; QD, once daily; R, randomization; rPFS, radiographic progression-free survival.

- Randomization will be stratified by:
  – previous docetaxel in the metastatic CSPC setting and
  – presence of hepatic metastases.
- The primary efficacy endpoint is rPFS per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (soft tissue) and Prostate Cancer Working Group 3 (PCWG3, bone) assessed by blinded central radiology review (**Table 2**).
- The key secondary endpoints are OS and time to pain progression. Other secondary endpoints include measures of antitumor activity by overall response rate and duration of response, patient-reported outcomes, pharmacokinetics, and circulating tumor DNA burden (**Table 2**).
- Safety will be assessed via adverse event monitoring, physical examinations, vital signs, and clinical laboratory tests.

Table 2. Study endpoints

Primary endpoint
- BICR-assessed rPFS per RECIST v1.1 (soft tissue disease) and PCWG3 (bone disease)

Key secondary endpoints
- OS
- Time to pain progression (assessed using BPI-SF item 3 [worst pain])

Other secondary endpoints
- Proportion of patients with measurable soft tissue disease at baseline with an objective response per RECIST v1.1 (assessed by BICR)
- Duration of response in soft tissue disease per RECIST v1.1 (assessed by BICR)
- Proportion of patients with a PSA response of ≥50% in participants with detectable PSA values at baseline
- Time to PSA progression
- Time to initiation of a new antineoplastic therapy
- Time to initiation of cytotoxic chemotherapy
- Time to first symptomatic skeletal event
- PFS on the next line of therapy based on investigator assessment
- Patient-reported outcomes will be assessed by BPI-SF 3 (pain), BPI-SF item 3 (worst pain at week 25), FACT-P (HRQoL, functioning, and symptoms), EQ-5D-5L (health status), and PRO-CTAE and FACT-GP-5 (symptomatic toxicity and overall side-effect burden)
- Pharmacokinetics
- ctDNA burden at baseline and on study

Exploratory endpoints
- Measurements of biomarkers (e.g., DNA, RNA, protein, defined cell types)

Safety
- Adverse events, physical examinations, vital signs, and clinical laboratory tests

BICR, blinded independent central review; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumor DNA; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Levels; FACT-GP-5, Functional Assessment of Cancer Therapy – General Population 5; FACT-P, Functional Assessment of Cancer Therapy – Prostate; HRQoL, health-related quality of life; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PFS, progression-free survival; PRO-CTAE, Patient-Reported Outcome – Common Terminology Criteria for Adverse Events; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiographic progression free survival.

Statistical Analysis

- Time-to-event endpoints will be compared between treatment arms using a stratified log-rank test.
- Hazard ratios and 95% confidence intervals (CIs) will be estimated using a stratified Cox proportional hazard model.
- Kaplan–Meier analysis will summarize time-to-event endpoints, and will include the median and 95% CIs based on the Brookmeyer–Crowley method.

Study Status

- The first patient was enrolled into the study on October 22, 2024.
- The study is currently enrolling in three countries (**Figure 2**) with sites planned in North America, Europe, Asia, and South America.
- The study is estimated to be completed in November 2028.

Figure 2. MEVPRO-2 participating countries