TPS5113 **Poster Session**

Mevrometostat in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with abiraterone acetate: The phase 3, randomized MEVPRO-1 study.

Neeraj Agarwal, Michael Thomas Schweizer, Elena Castro, Arun Azad, Daniel J. George, Jayeta Chakrabarti, Sujata Narayanan, Yiyun Tang, Karim Fizazi; Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT; Division of Medical Oncology, University of Washington, and Clinical Research Division, Fred Hutchinson Cancer Cancer, Seattle, WA; Medical Oncology, Hospital 12 de Octubre, Madrid, Spain; Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Duke Cancer Institute, Duke University School of Medicine, Durham, NC; Oncology, Pfizer Inc., New York, NY; Pfizer Inc., South San Francisco, CA; Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Saclay, Villejuif, France

Background: Resistance to androgen receptor (AR) pathway inhibitors (ARPI; e.g., abiraterone, enzalutamide) in mCRPC may be driven by preservation of AR signaling through various mechanisms. Enhancer of zeste homolog 2 (EZH2) is implicated in the pathogenesis of prostate cancer and ARPI resistance. Combining ARPI with therapies that modulate alternative signaling pathways, including epigenetic modifiers such as EZH2, could be a promising treatment approach to overcome resistance. Mevrometostat is a potent and selective small molecule EZH2 inhibitor. The optimal treatment sequence for patients with mCRPC who progress after first-line treatment with ARPI is not defined; a second ARPI or docetaxel are options used in real-world settings. Results from the dose-escalation period of a phase 1 study (NCT03460977) showed promising activity for mevrometostat combined with enzalutamide, with a manageable adverse-event profile in abiraterone-exposed patients with mCRPC (Schweizer MT, et al. *J Clin Oncol*. 2024;42(16_suppl):5061). Diarrhea, dysgeusia, and anemia were the most common adverse events considered to be related to mevrometostat. The current trial aims to evaluate radiographic progression-free survival (rPFS), overall survival (OS), and safety of mevrometostat plus enzalutamide compared with standard of care in patients with mCRPC previously treated with abiraterone. **Methods:** MEVPRO-1 (NCT06551324) is a global, open-label, phase 3 trial in patients with mCRPC aged ≥18 years with progression on ≥12 weeks of abiraterone, castration testosterone levels ≤50 ng/dL, ECOG performance status 0–2, and life expectancy ≥6 months. Approximately 600 patients will be randomized 1:1 to receive mevrometostat (875mg twice daily with food) with enzalutamide (160 mg once daily [QD]), or physician's choice of enzalutamide (160 mg QD) or docetaxel (75 mg/m^2 intravenously every 21 days). Randomization will be stratified by previous docetaxel in the metastatic castration-sensitive setting, physician's choice of comparator (enzalutamide/docetaxel) prior to randomization, and presence of hepatic metastases. The primary endpoint is blinded independent central review-assessed rPFS per RECIST 1.1 (soft tissue) and PCWG3 (bone) assessed by blinded central radiology review. Key secondary endpoint is OS. Secondary endpoints include antitumor activity by objective response rate and duration of response, safety, pharmacokinetics, ctDNA, and patient-reported outcomes. Time to event endpoints will be compared between treatment arms using a stratified log-test. HRs and 95% CIs will be estimated using a stratified Cox proportional hazard model, and Kaplan–Meier analysis will summarize time-to-event endpoints. Clinical trial information: NCT06551324. Research Sponsor: This study is sponsored by Pfizer Inc. Enzalutamide for the study is provided by Astellas Pharma Inc. Medical writing support was provided by Michelle Mancher, Allison TerBush, and Rosie Henderson of Onyx (a division of Prime), funded by Pfizer Inc.