TPS5116 Poster Session

Mevrometostat 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 study.

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Background: Mevrometostat is a potent, selective inhibitor of the histone methyltransferase enhancer of zeste 2 (EZH2), which is canonically involved in epigenetic repression of target genes. 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) activation, co-regulation of AR-mediated transcriptional programs, and cell cycle deregulation through methylation of non-histone targets. Given the associations between EZH2 and the AR, the addition of an EZH2 inhibitor to ARPI is hypothesized to extend the duration of clinical response and delay antiandrogen resistance compared with ARPI alone. In a nonrandomized, phase 1 dose-escalation study, objective responses to mevrometostat with enzalutamide were observed in patients with CRPC and prior abiraterone or enzalutamide treatment (NCT03460977; Schweizer MT, et al. *J Clin Oncol.* 2024;42(16_suppl):5061). The most common adverse events considered to be related to mevrometostat were diarrhea, dysgeusia, and anemia. Despite guideline recommendations for treatment intensification with ARPIs or chemotherapy for metastatic castration-sensitive prostate cancer (mCSPC), many patients do not receive ARPIs at the mCSPC stage. MEVPRO-2 (NCT06629779) will evaluate mevrometostat plus enzalutamide compared with enzalutamide alone in ARPI-naïve patients with mCRPC. **Methods:** MEVPRO-2 is a global, double-blind, randomized, phase 3 trial. Key inclusion criteria are males, ≥18 years, with progressive mCRPC, castrate testosterone of ≤50 ng/dL, Eastern Cooperative Oncology Group performance status of 0 or 1, and life expectancy of ≥12 months. Patients with systemic treatments for mCRPC (except androgen deprivation therapy and first-generation antiandrogens) are excluded. Approximately 900 patients will be randomized 1:1 to receive mevrometostat (875 mg, twice daily) with enzalutamide (160 mg, once daily) or placebo with enzalutamide. The primary endpoint is blinded independent central review-assessed radiographic progression-free survival per Response Evaluation Criteria in Solid Tumours 1.1 (soft tissue) or Prostate Cancer Working Group 3 criteria (bone). Key secondary endpoints are overall survival and time to pain progression (Brief Pain Inventory – Short Form question 3 or opioid use). Hazard ratios and 95% confidence intervals will be estimated using a Cox proportional hazard model, stratified by prior docetaxel and presence of hepatic metastases. *P*-values will be provided using a stratified log-rank test. Safety and tolerability will also be assessed. Clinical trial information: NCT06629779. Research Sponsor: This study is sponsored by Pfizer Inc. Enzalutamide for the study will be 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.