

Results from a Phase 1b/2a study of the BET bromodomain inhibitor ZEN-3694 in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC)

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Background: Abiraterone (ABI) and enzalutamide (ENZ) have significant activity in mCRPC yet demonstrate frequent cross-resistance limiting efficacy of sequential androgen receptor (AR) targeting. Bromodomain extra terminal (BET) inhibitors (BETi) modulate various putative drivers of ABI/ENZ resistance. ZEN-3694 is an orally bioavailable BETi with anti-tumor activity in ENZ resistant pre-clinical models. The safety and efficacy of ZEN-3694 in combination with ENZ was evaluated in a phase 1b/2a mCRPC study (NCT02711956), and translational analyses were conducted to identify molecular characteristics of patients with longer time to radiographic progression (TTP).

Methods: Patients were required to have progressive mCRPC, prior resistance to ABI and/or ENZ, and no prior chemotherapy for mCRPC. A 3 + 3 dose escalation schema was utilized followed by dose expansion in parallel cohorts at low and high-dose ZEN-3694 (48 and 96 mg daily, respectively). The primary objective was determination of maximally tolerated dose (MTD). Key secondary endpoints included TTP and pharmacokinetic parameters. Pharmacodynamic (PD) markers included whole blood RNA expression of BET targets including MYC, IL-8, CCR1, and IL1RN. Differential gene expression analysis was conducted on biopsies from patients with the longest TTP (N=6) and shortest TTP (N=7), including paired biopsies before and on-treatment from the same patients (N=4).

Results: 75 patients were enrolled. At study entry, 30 (40.0%) of patients were resistant to ABI, 34 (45.3%) were resistant to ENZ, and 11 (14.7%) to both. ZEN-3694 dose levels ranged from 36 mg to 144 mg daily without reaching a MTD. The combination of ZEN-3694 and enzalutamide was well tolerated. PD analyses demonstrated that ZEN-3694 is associated with an exposure-dependent decrease in expression of BET targets in whole blood (up to 4-fold mean difference). RNA-Seq of paired tumor biopsies demonstrated modulation of BET-dependent genes, and suppression of AR and MYC signaling. The overall median TTP was 44.4 weeks, and was similar in patients with prior ABI vs. ENZ resistance. Pre-treatment biopsies from patients with longer TTP harbored several hallmarks of resistance to ABI/ENZ, including lower AR signaling, upregulation of a basal cell signature and markers of treatment-emergent small cell neuroendocrine prostate cancer (t-SCNC). Consistent with these findings, patients with low baseline PSA levels relative to tumor burden had a median TTP of 48 weeks. Transitory serum PSA increases or PSA responses were associated with better TTP of 50.4 weeks.

Conclusion: Clinical activity of ZEN-3694 appears enhanced in patients demonstrating gene expression changes compatible with loss of AR-dependency and luminal identity. Based on these clinical observations and supporting pre-clinical data, it is hypothesized that ZEN-3694 exerts its effects through inducing differentiation of AR inhibitor resistant CRPC cells to a phenotype that is more sensitive to AR inhibition. Further studies testing ZEN-3694 in combination with AR signaling inhibitors are warranted.

Conflicts of Interest:

Sanjay Lakhota, Lisa Bauman, Margo Snyder, Emily Gesner, Sarah Attwell, and Eric Campeau are employees of Zenith Epigenetics

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