CT095: A Phase Ib/Ila 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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Abstract

Background: BET bromodomains (BET) and enzalutamide (ENA) have significant activity in mCRPC and hold the potential to improve the clinical outcomes of androgen independent prostate cancer (mCRPC). BET bromodomains are crucial for transcriptional regulation, and BET inhibitors (BETi) disrupt the interaction of the protein with chromatin, leading to cell cycle growth arrest, differentiation, and/or apoptosis. In preclinical models, BET inhibitors (BETi) demonstrate anti-cancer activity in mCRPC. To explore the association between BETi and enzalutamide in mCRPC, we report the results of our ongoing, open-label, multicenter, phase Ib/Ila study (NCT02704784).

Methods: Patients with castration-resistant prostate cancer who were refractory to abiraterone and/or enzalutamide were eligible to receive ZEN-3694, a first-in-class BET inhibitor, in combination with enzalutamide. Key study objectives were to assess the safety, tolerability, and preliminary antitumor activity of ZEN-3694 in combination with enzalutamide in patients with mCRPC.

Results: As of May 2023, 90 patients have been enrolled and received ZEN-3694 and enzalutamide at the recommended phase 2 dose. Median patient age was 62 years (range 39-78), 83% were white, and 95% had a baseline PSA > 20 ng/mL. No dose-limiting toxicities were observed, and high-dose enzalutamide was well tolerated. In patients with measurable disease, the objective response rate was 3/90 (3.3%), and 43/90 (47.8%) had disease stabilization. The most common adverse events were fatigue (56%), nausea (14%), and anemia (16%). No patient experienced grade 5 toxicity.

Conclusions: ZEN-3694 demonstrates acceptable safety and PK profile, with potential antitumor activity in the setting of mCRPC. The study is ongoing, and additional data will be presented at a future meeting.

Key Eligibility Criteria

- Metastatic castration-resistant prostate cancer (mCRPC) with progression by PCWG2 criteria prior to study entry
- Prior exposure to abiraterone and/or enzalutamide
- No prior chemotherapy or mCRPC
- Adequate hematologic, renal, and liver function
- ECOG performance status of 0 or 1

Prolonged Time to Radiographic Progression

Patients with Low PSA in Relation to Disease Burden Show Prolonged rPFS

PSA90 Response for >1.5 Years in Patients with Primary Resistance to Abiraterone

Disease Stabilization of AR-V7+ Enza+Patients

Proposed Transdifferentiation Model

CTC Data 002-101037 metastatic in bone to ZEN-3694 and ENZ 160 mg/day (N = 6) with minimal toxicity observed. Further investigation of combination in castrate-resistant prostate cancer (mCRPC) is warranted.

Background

- Abiraterone (ABI) and enzalutamide (ENA) demonstrate frequent resistance limiting efficacy of sequential 4-aromatic targeting in mCRPC
- ZEN-3694 is an orally bioavailable, potent, and selective BET bromodomain inhibitor with preclinical activity in ENA-resistant CRPC models
- In pre-clinical models ZEN-3694 down-regulates the expression of putative drivers of ABI/ENA resistance including AR splice variants, glucocorticoid receptor (GR), and PGR and demonstrates synergy with ENA
- We evaluated the combination of ZEN-3694 + ENA in ABI/ENA-resistant mCRPC in a Phase Ib/la multi-center study through the Prostate Cancer Clinical Trials Consortium

Patients with low PSA and high disease burden had longer median rPFS. Sample of a patient with growth of existing metastatic lesions with disease stabilization, with major clinical benefits despite the development of resistance.

Early PSA Spikes Are Associated with Longer Radiographic Progression-Free Survival

Proposed Transdifferentiation Model

ZEN-3694 may promote differentiation of transformed tumor tissues with increased expression of ZEN-3694 target genes with potential for disease stabilization in enzalutamide-resistant prostate cancer. Further clinical development of this combination is warranted.