CT095: A Phase Ib/IIa 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: 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) down-regulate the expression of putative drivers of ABI/ENZ resistance. ZEN-3694 is an orally bioavailable, potent, and selective BETi with significant 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 study in mCRPC (NCT02711956).

Methods: Patients (pts) 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, with a starting daily oral dose of ZEN-3694 36 mg plus ENZ 160 mg. Dose expansion was conducted 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 time to radiographic progression (TTP) and pharmacokinetic (PK) parameters. Pharmacodynamic (PD) markers included whole blood RNA expression of BETi targets including MYC, IL-8, CCR1, and IL1RN.

Results: 74 pts were enrolled. The median age and PSA at study entry was 70 (range 47 – 89) and 26.7 (range 0.1 – 1701.8), respectively. At study entry, 27 (38%) of pts were resistant to ABI, 44 (62%) were resistant to ENZ, and 11 (15%) to both. ZEN-3694 dose levels ranged from 36 mg to 144 mg daily without reaching a MTD. The most common treatment-related adverse events (AEs) (any grade) included transient photophobia (66%), nausea (40%), fatigue (31%), decreased appetite (22%), and dysgeusia (16%). Grade ≥ 3 related AEs (N = 8) and dose-limiting toxicities (N = 1 at 96 mg dose level) were uncommon. No Grade ≥ 3 thrombocytopenia was observed. Exposure to ZEN-3694 increased with dose without significant drug-drug interaction with ENZ. PD analyses demonstrated exposure-dependent, up to 4-fold decrease in expression of BETi targets. RNA-Seq of paired tumor biopsies demonstrated suppression of BET-dependent genes. The overall median TTP was 44.4 weeks, and was similar in subgroups with prior ABI vs. ENZ resistance. Durable responses were observed, including 3 pts with disease primarily refractory to ABI on study treatment for 23.8 +, 23.3 +, and 17.3 months, respectively, with > 90% decline in serum PSA. Early transitory serum PSA increases were associated with longer TTP.

Conclusions: ZEN-3694 demonstrates an acceptable safety and PK profile, robust target modulation, and encouraging disease stabilization in combination with ENZ in ABI/ENZ-refractory mCRPC. Analysis of paired metastatic tumor biopsies, circulating tumor cells and ctDNA is ongoing. Further investigation of the combination is warranted.

Background

- **Abiraterone (ABI) and enzalutamide (ENZ) demonstrate frequent cross-resistance limiting efficacy of sequential AR targeting in CRPC**
- **ZEN-3694 is an orally bioavailable, potent, and selective BET bromodomain inhibitor with pre-clinical activity in ENZ-resistant CRPC models**
- **In pre-clinical models ZEN-3694 down-regulates the expression of putative drivers of ABI/ENZ resistance including AR splice variants, glucocorticoid receptor (GR) and MYC and demonstrates synergy with ENZ**
- **We evaluated the combination of ZEN-3694 + ENZ in ABI/ENZ-resistant mCRPC in a Phase 1b/2a multi-center study through the Prostate Cancer Clinical Trials Consortium**

Clinical Trial Design

Progression on 1st line abiraterone (PSA and/or radiographic)

Progression on 1st line enzalutamide (PSA and/or radiographic)

→ **ZEN-3694 + enzalutamide**

Key Eligibility Criteria

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

Dose Escalation/Expansion Schema

ZEN-3694 36 mg/d + ENZ 160 mg/day (N = 4)	0 DLTs
ZEN-3694 48 mg/d + ENZ 160 mg/day (N = 6)	0 DLTs
ZEN-3694 60 mg/d + ENZ 160 mg/day (N = 6)	0 DLTs
ZEN-3694 72 mg/d + ENZ 160 mg/day **(N = 6)**	0 DLTs
ZEN-3694 96 mg/d + ENZ 160 mg/day **(N = 6)**	1 DLT
ZEN-3694 120 mg/d + ENZ 160 mg/day **(N = 4)**	0 DLTs
ZEN-3694 144 mg/d + ENZ 160 mg/day **(N = 3)**	0 DLTs

Expansion Cohort A: Low Dose ZEN-3694 48 mg/d + ENZ 160 mg/d N = 15

Expansion Cohort B: High Dose ZEN-3694 96 mg/d + ENZ 160 mg/d N = 24

Baseline Characteristics

	Study Cohort (N = 74)
Median Age (range)	70 (47 – 89)
Race/Ethnicity (%) *White/Black/Asian*	60 (84)/ 3 (4)/ 4 (6)
Median PSA, ng/mL (range)	26.7 (0.1 – 1701.8)
Median LDH, U/L (range)	190 (98 – 352)
Median alkaline phosphatase, U/L (range)	78.5 (33 - 487)
Visceral metastases (%)	12 (18)
Bone pain requiring opioid analgesic use (%)	15 (24)
Disease out of proportion to PSA* (%)	11 (17)
Prior Therapy (%) *Abiraterone/Enzalutamide/Both*	27 (38)/ 44 (62)/ 11 (15)

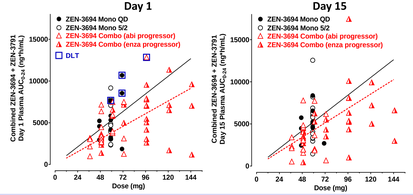
* PSA < 10 ng/mL with concomitant presence of visceral metastases and/or ≥ 10 bone metastases

Grade ≥ 3 Toxicities Related to ZEN-3694

	36mg		48mg		60mg		72mg		96mg		120mg		144mg	
	N = 4		N = 21		N = 6		N = 6		N = 30		N = 4		N = 3	
Grade	3	4	3	4	3	4	3	4	3	4	3	4	3	4
Decreased appetite									1					
Dehydration									1					
Fatigue			1											
GFR Decreased									1					
Hypokalemia							1							
Low phosphorous					1		1							
Nausea									2					
QT prolongation													1	

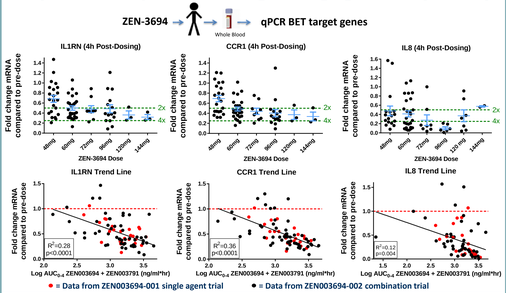
No Grade ≥ 3 thrombocytopenia and minimal toxicity observed

AUC_{0-24} vs. ZEN-3694 Dose



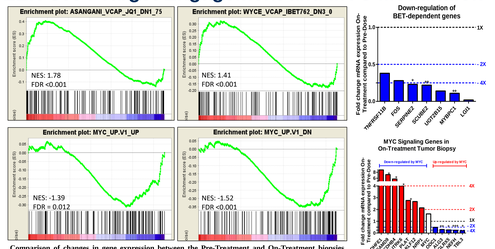
- **ZEN-3694 metabolized to active metabolite ZEN-3791**
- **Exposure to ZEN-3694 + ZEN-3791 indicates moderate inter-patient variability**

Exposure-Dependent Target Engagement (Blood)



Whole blood qPCR demonstrates exposure-dependent decrease in BET inhibitor target genes including IL1RN, CCR1, and IL8.

Evaluable Paired Tumor Biopsy Shows Evidence of ZEN-3694 Target Engagement and MYC Modulation

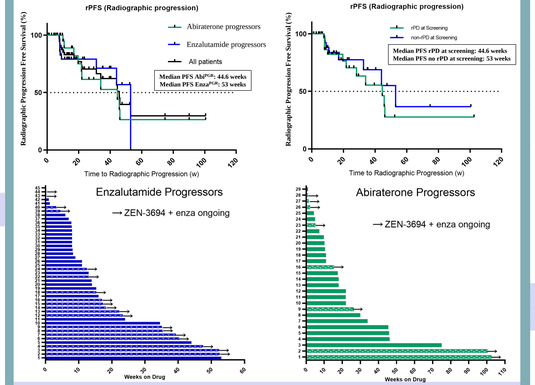


Comparison of changes in gene expression between the Pre-Treatment and On-Treatment biopsies from the same patient. Geneset enrichment analysis (GSEA) shows significant correlation with genes down-regulated by JQ1 (Asangani et al. 2014) and I-BET762 (Wyce et al. 2013) in prostate cancer cell lines as well as inhibition of MYC activity (Bild et al. 2006) during treatment.

*** P<0.001 ** P<0.01 * P<0.05

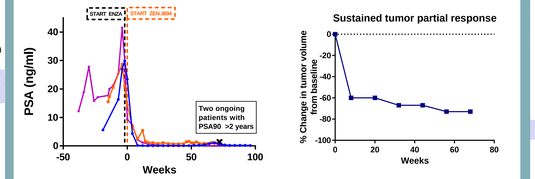
Evaluable paired tumor biopsy obtained on treatment demonstrates down-regulation of MYC signaling and BET-dependent gene expression.

Prolonged Time to Radiographic Progression



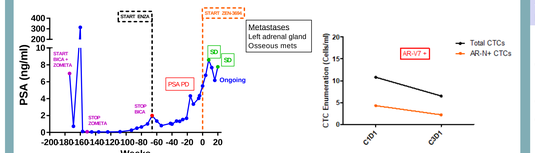
Significant longer time to radiographic progression for some patients that previously progressed on abiraterone or enzalutamide compared to standard second line therapy with ARSi.

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



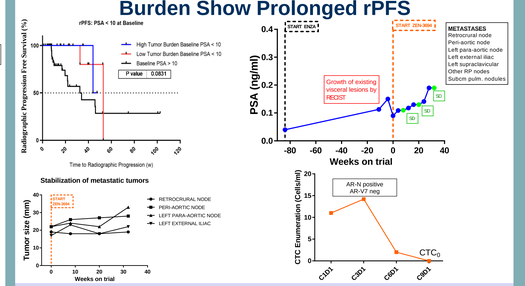
Durable PSA90 response in 3 patients that had primary resistance to abiraterone. Two patients are still on trial with a PSA90 response > 2 years. One patient had a sustained partial response for >1.5 years.

Disease Stabilization of AR-V7+ $Enza^{PGR}$ Patient



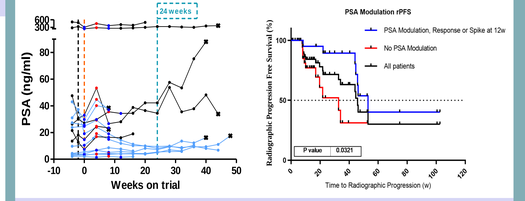
Patients with AR-V7+ CTCs have normally a poor response to enzalutamide. A patient with a previous PSA progression with enzalutamide showed a decrease in AR-V7+ CTCs (using Epic Sciences' CTC platform) and stabilization of visceral metastases.

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



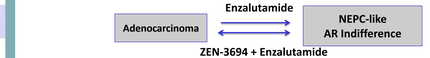
Several patients with low PSA and high disease burden had longer median rPFS. Example of a patient with growth of visceral lesions while on enzalutamide, with disease stabilization as well as concomitant decrease in CTCs with ZEN-3694 and enzalutamide combination.

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



Several patients with a transient increase in PSA at either week 4 or week 8 have longer median rPFS.

Proposed Transdifferentiation Model



ZEN-3694 may promote differentiation of transdifferentiated tumor cells towards an adenocarcinoma phenotype that is sensitive to enzalutamide.

Conclusions

- **ZEN-3694 administered once daily in combination with enzalutamide is well tolerated and the MTD was not reached**
- **Robust target modulation was observed in a dose-dependent fashion**
- **Prolonged rPFS and longer duration of treatment were observed, comparing favorably with historical control of sequential AR targeting**
- **Analysis of additional paired biopsies is ongoing to evaluate potential of ZEN-3694 to restore dependence on AR**
- **Further clinical development of this combination is warranted**