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

- Androgen receptor signaling inhibitors (ARSI) such as abiraterone (ABI) and enzalutamide (ENZ) demonstrate frequent cross-resistance, limiting efficacy of sequential AR targeting in CRPC
- Bromodomain and Extra-Terminal domain (BET) inhibitors (BETi) inhibit several hallmark drivers of CRPC, including AR and MYC signaling, and the E26 transformation-specific (ETS) family
- ZEN-3694 is an orally bioavailable, potent, and selective BET bromodomain inhibitor with pre-clinical activity in ENZ-resistant CRPC models
- The combination of ZEN-3694 + ENZ in ABI/ENZ-resistant mCRPC was evaluated in a Phase 1b/2a multi-center study (NCT02711956) through the Prostate Cancer Clinical Trials Consortium

Clinical Trial Design

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

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

→ ZEN-3694 + ENZ

Key Eligibility Criteria

- mCRPC with progression by PCWG2 criteria prior to study entry
- Prior progression on ABI and/or ENZ
- No prior chemotherapy for mCRPC
- ECOG performance status of 0 or 1

Baseline Characteristics

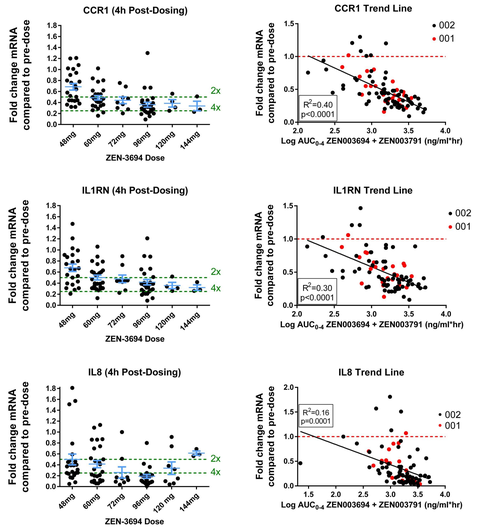
	Study Cohort (N = 71)
Median Age (range)	70 (47 – 89)
Race/Ethnicity (%) *White/Black/Asian*	60 (84)/ 3 (4)/ 4 (6)
Median PSA, ng/mL (range)	26.7 (0.1 – 1701.8)
Median LDH, U/L (range)	190 (98 – 352)
Median alkaline phosphatase, U/L (range)	81 (33 - 487)
Visceral metastases (%)	12 (18)
Bone pain requiring opioid analgesic use (%)	15 (24)
Low PSA secretors and high risk CRPC* (%)	11 (17)
Prior Therapy (%) *ABI/ENZ/Both*	30 (40)/ 37 (49)/ 8 (11)
Reason for prior ABI/ENZ discontinuation	
• Radiographic progression	13 (21)
• Radiographic and PSA progression	20 (32)
• Clinical and PSA progression	3 (5)
• PSA progression	27 (42)

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

Dose Escalation/Expansion Summary

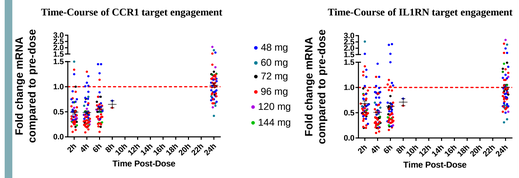
- ZEN-3694 dosed from 36 mg to 144 mg with 160 mg ENZ daily without reaching a MTD
- 35 patients were treated in the Dose Escalation
- 40 patients were treated in the Dose Expansion (26 at 96mg, 14 at 48mg)
- The combination of ZEN-3694 and enzalutamide was well tolerated[1]

ZEN-3694 Exposure-Dependent Target Engagement in Whole Blood



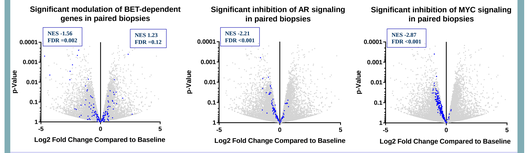
Exposure-dependent target engagement of ZEN-3694 in patient's whole blood. Fold changes in mRNA expression were compared to the Pre-Dose sample on Day 1 for each patient. Data from the -001 single agent trail (NCT02705469) is also depicted in the trend lines (red dots).

Sustained Target Engagement by ZEN-3694



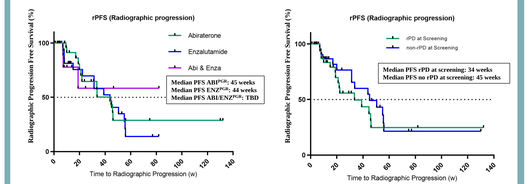
ZEN-3694 elicits target mRNA engagement for >8 hours in patient's whole blood and for 24 hours in several patients.

In-Tumor BETi Target Engagement by ZEN-3694: Inhibition of AR and MYC Signaling



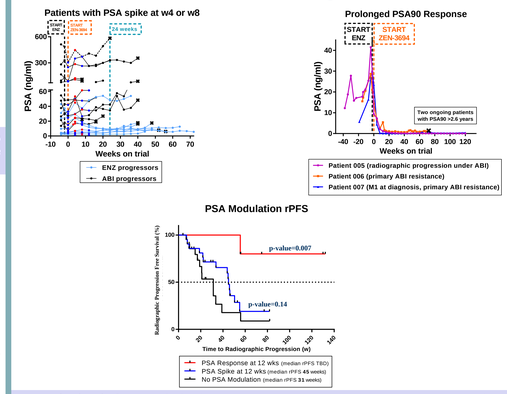
Volcano plots showing changes in gene expression between Pre- and On-Treatment (8 weeks) biopsies from 4 patients showing modulation (in blue) of BET-dependent genes[2], (left), significant inhibition of the Hallmark of androgen response (MSigDB, Center), and Hallmark MYC V1 Response (MSigDB, Right).

Prolonged Time to Radiographic Progression (TTP)



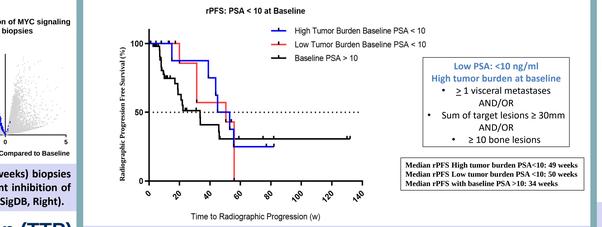
LEFT: Significantly longer time to radiographic progression (TTP) for some patients that previously progressed on ABI or ENZ compared to standard second line therapy with ARSI. RIGHT: Several patients with radiographic progression (rPD) with a previous ARSI also showed longer TTP.

Early PSA Spikes and PSA Responses are Associated with Longer TTP



LEFT: 26/75 (35%) of patients had either a PSA response or a transient increase in PSA at week 4 or week 8 (PSA spike). RIGHT: Prolonged PSA90 response seen in three patients. BOTTOM: Patients with either a PSA response or spike showed longer TTP. P-values are shown compared to no PSA modulation.

Low PSA Secretors and High Disease Burden Patients Have Prolonged rPFS



Low PSA: <10 ng/ml
High tumor burden at baseline
- ≥ 1 visceral metastases AND/OR
- Sum of target lesions ≥ 30mm AND/OR
- ≥ 10 bone lesions

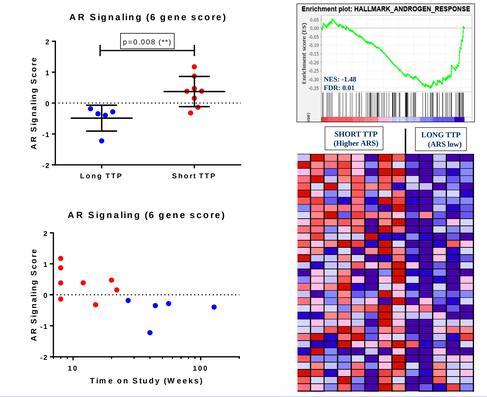
Median rPFS High tumor burden PSA<10: 49 weeks
Median rPFS Low tumor burden PSA <10: 50 weeks
Median rPFS with baseline PSA >10: 34 weeks

Patients with low PSA and high disease burden, a group with generally poor prognosis, showed improved time to progression (TTP).

Baseline Biopsies Show Several Hallmarks of Resistance to ARSI and AR-Independence

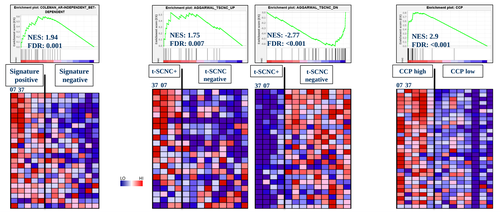
	Patient ID	Mutations in genes of interest: AR AMP or mutations	TP53	PTEN	RB1	Mechanisms of ARSI resistance: AR SIGNALING	AR-INDEPENDENT	t-SCNC	BASAL MARKERS	CCP SIGNATURE	UPREGULATION alt. STEROID RECEPTORS	UPREGULATION MYC SIGNALING
Long TTP (>24 weeks)	101007		WT	WT	WT	LOW	YES	YES	YES	YES		YES
	101037		WT	LOSS	WT	LOW	YES	YES		YES		
	101029	AMP	MUT	LOSS	WT	LOW					YES	
	102036		MUT	MUT	WT	LOW			YES		YES	
	101047	AMP	WT	WT	WT	LOW			YES			
Short TTP (<24 weeks)	101076	AMP	MUT	LOSS	WT	LOW	YES	YES	YES		YES	
	101069	AMP	MUT	WT	WT	LOW	YES	YES	YES			YES
	104034		MUT	LOSS	WT	HIGH				YES		YES
	102059		WT	WT	WT	HIGH						YES
	103066		MUT	LOSS	WT	HIGH					YES	YES
	102068	AMP	MUT	MUT	WT	HIGH				YES		YES
	107027		WT	LOSS	WT	HIGH			YES			YES
	101078	AMP, Q876X, F877L,M895I	MUT	WT	WT	HIGH						YES

Longer TTP Associated with Lower AR Signaling



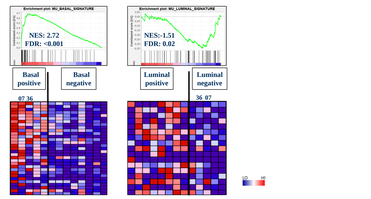
Baseline biopsies from patients with longer TTP had lower AR signaling using either a 6 gene signature score (AR, KLK2/3/4, FKBP5, and TMPRSS2, Left) or the Hallmark of genes involved in androgen response (MSigDB, Right).

Two Patients with Longer TTP Had Signatures of AR-independence, t-SCNC, and High Cell Cycle Progression (CCP) Scores



Baseline biopsies from patients 007 and 037 with longer TTP had increased expression of AR-independent, BET-dependent master regulators[3] (LEFT), t-SCNC signatures[4] (CENTER) and high cell cycle progression[5] (CCP) scores (RIGHT). 3 out of 4 t-SCNC mRNA signature positive biopsies were also t-SCNC positive by histopathology (not shown).

Loss of Luminal Identity in Two Patients with Longer TTP



Loss of luminal identity signature in 2 patients with longer TTP (007 and 036) through upregulation of basal cell markers[6].

Conclusions

- ZEN-3694 + ENZ patients showed longer TTP, comparing favorably with historical control of sequential AR targeting
- Analysis of paired biopsies shows inhibition of AR and MYC signaling and modulation of BET-dependent genes by ZEN-3694
- Baseline biopsies harbored several hallmarks of resistance to ARSI suggesting limited clinical activity of enzalutamide alone in these patients
- Initial results suggest that ZEN-3694 + ENZ can target tumors that developed ARSI resistance through loss of AR-dependency and restore sensitivity to ARSI
- Further clinical development of this combination is warranted

References

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