A Randomized Phase 2b Study of the BET Bromodomain Inhibitor (BETi) ZEN-3694 and Enzalutamide vs. Enzalutamide Monotherapy in Metastatic Castration Resistant Prostate Cancer

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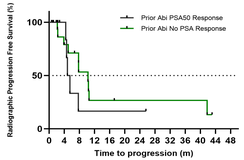
Background

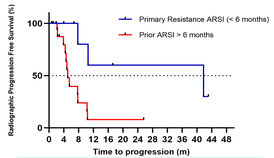
- **Androgen receptor signaling inhibitors (ARSI), such as enzalutamide (Enza), and abiraterone (Abi), are standard therapies for metastatic hormone-sensitive and metastatic castration-resistant prostate cancer (mHSPC, mCRPC)**
- **Patients who respond to the initial ARSI are frequently prescribed a 2nd ARSI upon progression. However, tumors with a suboptimal response to first line ARSI are not likely to respond to a second ARSI as they may have AR-independent mechanisms of resistance, including treatment-emergent neuroendocrine prostate cancer (t-NEPC).**
- **BETi have been shown pre-clinically to block the neuroendocrine prostate cancer lineage plasticity program through modulating AR-independent survival factors, including E2F1, a transcription factor involved in stemness and cell differentiation.**
- **Prior results from a mCRPC Ph. 1b/2a trial of ZEN-3694+ Enza support this notion, as higher expression of BRD4, E2F1, and lower AR activity measured in baseline biopsies was associated with longer rPFS.**
- **Furthermore, patients who were primary refractory to 1st line Abi or whose tumors had lower AR activity had prolonged radiographic free progression (rPFS) with ZEN-3694 + Enza, suggesting that the patients with primary resistance may benefit from the combination.**
- **To test this hypothesis, we initiated a Ph. 2b randomized trial, enriching for mCRPC with suboptimal response to 1st line ARSI.**

Rationale

Poor response to Abi is associated with a longer rPFS with ZEN-3694+ Enzalutamide (phase 1b/2a study)



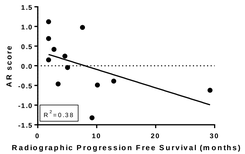
	Prior Abi PSA50	Prior Abi No PSA50
Number reporting	14	16
rPFS (months) ZEN-3694 + Enza	5.16	10.26

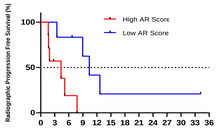


	Abi < 6 mos	Abi > 6 mos
Number reporting	7	23
rPFS (months) ZEN-3694 + Enza	41.8	5.03

Aggarwal et al., Clinical Cancer Research 2020

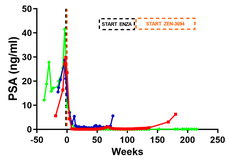
Low AR activity is associated with longer time on ZEN-3694 + Enzalutamide



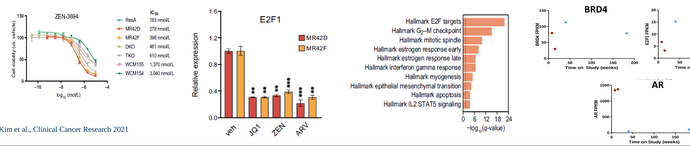


	Low AR score	High AR score
Number reporting	6	7
rPFS (months) ZEN-3694 + Enza	10.4	4.4

Durable PSA90 responses with ZEN-3694 + Enzalutamide in patients with poor prior response to Abi



ZEN-3694 blocks an AR-repressed, E2F1-driven t-NEPC lineage plasticity program



Kim et al., Clinical Cancer Research 2021

Trial Design

NCT04986423

Cohort A: Poor Abi responders/AR independent (n=150)

Abi-HSPC: < 12 months duration on Abi or failure to achieve a PSA nadir of 0.2 ng/ml
Abi-CRPC: < 6 months duration on Abi or failure to achieve PSA 50 response

→ ZEN-3694 (72 mg QD) + Enza (160 mg QD)
→ Enza (160 mg QD)
Cross-over at progression

Cohort B: Abi responders (n=50)

Abi-HSPC: ≥ 12 months duration on Abi and nadir PSA < 0.2 ng/mL
Abi CRPC: ≥ 6 months duration on Abi and PSA50 response

→ ZEN-3694 (72 mg QD) + Enza (160 mg QD)
→ Enza (160 mg QD)
Cross-over at progression

Primary Endpoint
- rPFS Cohort A (PCGW3)-BICR (Blinded Independent Central Review)

Key Secondary Endpoints
- rPFS Cohort A+B (PCGW3-BICR)
- PFS Cohorts A, A+B
- OS: Cohort A
- PSA50 Cohorts A, A+B

Stratification factors
- HSPC vs CRPC
- China vs US

Statistics
- Ho (rPFS Cohort A) = 6 months, HR = 0.6
- Alpha = 0.10, Power = 80%

Key Inclusion Criteria

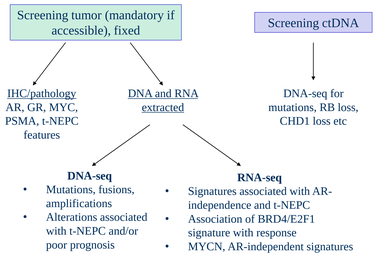
1. Males age ≥ 18 years, Metastatic, castration-resistant, histologically confirmed prostate cancer
2. Surgical castration or continuous medical castration for ≥ 8 weeks prior to screening; serum testosterone < 50 ng/dL confirmed within 4 weeks of first administration of study drug
3. Have progressed on prior abiraterone treatment by PCWG3 criteria
4. Patients who are not candidates for chemotherapy in the opinion of the investigator or patients who decline chemotherapy
5. Cohort A only - Patient must meet definition of poor responder to abiraterone by one of the following:
   1. Abiraterone started in hormone-sensitive prostate cancer (HSPC) disease setting: < 12 months duration on abiraterone or failure to achieve PSA nadir of 0.2 ng/mL while taking abiraterone
   2. Abiraterone started in castrate-resistant prostate cancer (CRPC) disease setting: < 6 months duration on abiraterone or failure to achieve a PSA50 response
6. Cohort B only - Patient must meet definition of responder to abiraterone by one of the following:
   1. Abiraterone started in hormone-sensitive prostate cancer (HSPC) disease setting: ≥ 12 months duration on abiraterone and nadir PSA < 0.2 ng/mL
   2. Abiraterone started in castrate-resistant prostate cancer (CRPC) disease setting: ≥ 6 months duration on abiraterone and PSA50 response
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key Exclusion Criteria

1. Receipt of prior second-generation androgen receptor inhibitors (enzalutamide, darolutamide, apalutamide)
2. Prior investigational BET inhibitor treatment
3. Prior chemotherapy in the metastatic castration-resistant setting (prior chemotherapy in the hormone-sensitive setting is allowed provided last dose was at least 6 months prior to first dose of study drug)
4. Prior systemic anti-cancer therapy within 2 weeks or five half-lives, whichever is shorter, prior to the first administration of study drug
5. Prior testosterone therapy since discontinuation of abiraterone.
6. Any history of brain metastases, prior seizure, conditions predisposing to seizure activity

Translational Plan

Objective: to support the mechanistic rationale for a ZEN-3694 + ENZA combo in AR-independent tumors



Summary

- Data from a completed Phase 1b/2a mCRPC trial has shown that the combination of ZEN-3694 + Enza may be effective in tumors that are primary refractory to abiraterone and are less dependent on AR signaling.
- To confirm this hypothesis, a mCRPC Phase 2b randomized trial has been initiated which will measure the efficacy of ZEN-3694 + Enza vs single agent Enza in patients whose tumors had a suboptimal response to Abi.
- The combination of ZEN-3694+Enza has the potential to provide a non-chemotherapy option for patients whose tumors are not expected to respond to a second AR signaling inhibitor.
- The translational plan is expected to support mechanistic rationale for a ZEN-3694 plus Enza combination in AR-independent mCRPC, through modulation of a BRD4/E2F1 driven lineage plasticity program.
- NCT04986423 is a collaboration with Newsoara and Astellas, and is currently accruing patients from 7 clinical sites in the US and 15 clinical sites in China.

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