Design of combination strategies and identification of biomarkers associated with clinical response to ZEN-3694 in combination with enzalutamide in mCRPC

Eric Campeau, Epigenetic Therapeutic Targets Summit, July 28, 2020
Changes in epigenetic landscape in response to anti-cancer treatments

“Mountain” Transcriptional Program

“Plain” Transcriptional Program

Epigenetic regulation

- Epigenetic regulation allows rapid adaptation to changes in (tumor) environment
  ⇒ No required changes in DNA
  ⇒ Dynamic, reversible

- Use of combination strategies for optimal therapeutic efficacy
  ⇒ Combination of epigenetic inhibitors with optimal agents
Our Approach: Making Great Drugs Work Better & Longer

Combinations with ZEN-3694 to **prevent** and **reverse** resistance to standard of care therapies

Current possibilities include:
- Androgen receptor signaling inhibitors (ARSIs)
- PARP inhibitors
- PD-1/PD-L1 monoclonal antibodies (checkpoint inhibitors)
- CDK4/6 inhibitors
Selection of the BET inhibitor ZEN-3694 with ideal combinatorial properties

> 1800 synthesized compounds  
(incl. different chemical scaffolds)

23 lead compounds  
Preclinical off-target/PK/TOX: in vitro and in vivo

6 DC compounds  
Rat 5 day tox + xenografts

ZEN-3694 selected

<table>
<thead>
<tr>
<th>Compound</th>
<th>BRD4 (BD1)</th>
<th>PK (Rat 10 mg/kg)</th>
<th>Efficacy (21 days, 60 mg/kg QD)</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Half-life</td>
<td>C_max</td>
<td>AUC</td>
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<tr>
<td>ZEN-3694</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ZEN-3803</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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</tbody>
</table>
| ZEN-3717 | ++         | +        | +++   | +++ | +++              | • Severe PLT reduction  
|          |            |          |       |     |                  | • Decreased in body weight |

PLT= platelet

ZEN-3694 with a moderate half-life showed better or similar efficacy in xenografts without tolerability issues
**Other Clinical BETi**

- Suboptimal benzodiazepine scaffold with poor pharmacological properties
- Off target toxicities
- CYP liabilities
- Thrombocytopenia DLT, require 1-2 weeks off, difficult to combine

**Zenith’s BETi (ZEN-3694)**

- Orthogonal scaffold with very good pharmacological properties
- On target toxicity profile
- Minimal CYP liabilities
- Minimal thrombocytopenia liability, safety profile allows continuous dosing and combinations
Prioritization of combinatorial strategies with ZEN-3694

Selection of optimal combination agents and patient populations with unmet medical needs

1) Metastatic castration-resistant prostate cancer (mCRPC)
   ⇒ Combination ZEN-3694 + enzalutamide
   ⇒ Combination ZEN-3694 + enzalutamide + pembrolizumab (Q4 2020)

2) Metastatic triple negative breast cancer (TNBC) patients without germline BRCA1/2 mutations (gBRCA1/2wt)
   ⇒ Combination ZEN-3694 + talazoparib (in collaboration with Pfizer)
A Phase 1b/2a Study of the Pan-BET Bromodomain Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration Resistant Prostate Cancer

Castration-resistant prostate cancer (CRPC):

Disease progression and treatment algorithm

- **1<sup>st</sup> line AR signaling inhibitor (ARSI)**
  - Enzalutamide, apalutamide, darolutamide, abiraterone
  - Clinical benefits in several patients

- **2<sup>nd</sup> line ARSI post 1<sup>st</sup> line ARSI associated with lower activity**
  - Most patients progress between 3-6 mo

- **ARSI now prescribed in castration sensitive setting**
  - Unmet need to prolong ARSI activity in castration sensitive and resistant settings

**ZEN-3694 + enzalutamide can address multiple resistance mechanisms**

- **Inhibits AR signaling**
- **Inhibits GR signaling**
- **Resensitizes cells to AR signaling**

**Castration therapy + ADT**

**New AR targeted agents (enzalutamide, abiraterone)**

**Chemotherapy**

**Death**

**Disease Burden**

**Time**

**Castration-sensitive**

**Castration-resistant**

**Non-metastatic**

**Metastatic**

**Restore AR signaling**

- (AR mutations and amplification, splice variants, androgen biosynthesis)

**Bypass AR signaling**

- (GR up-regulation)

**Alternate pathway (AR-)**

- (Transdifferentiation, AR-independent)
**Phase 1b/2a: ZEN-3694 in combination with enzalutamide in mCRPC**

(NCT02711956)

- **Inclusion criteria:**
  - Progression on prior ABI and/or ENZA (radiographic, clinical, PSA)
  - No prior chemotherapy in castration-resistant setting
  - On trial until radiographic or clinical progression (PCWG2)

- **ESCALATION**
  - **ZEN-3694 + ENZA dose escalation**
    - Doses 36-144mg daily

- **EXPANSION**
  - **ZEN-3694 + ENZA expansion #1**
    - Patients progressing on prior ABI
    - Doses 48 mg OR 96 mg daily
  - **ZEN-3694 + ENZA expansion #2**
    - Patients progressing on prior ENZA
    - Doses 48 mg OR 96 mg daily

- **75 patients dosed (35 pts in dose escalation, 14 in dose expansion #1, 26 in dose expansion #2)**
- **MTD not reached (36mg – 144mg daily dose range) → RP2D 96mg**
- **Clinical activity at well tolerated doses, prolonged dosing without dose interruptions/reductions**
ZEN-3694 related Grade 3 or 4 adverse events

On target tox profile and good tolerance of daily dosing

<table>
<thead>
<tr>
<th></th>
<th>36mg QD</th>
<th>48mg QD</th>
<th>60mg QD</th>
<th>72mg QD</th>
<th>96mg QD</th>
<th>120mg QD</th>
<th>144mg QD</th>
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<td>n</td>
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<tr>
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<td>Fatigue</td>
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<td>GFR Decreased*</td>
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<tr>
<td>Hypokalemia**</td>
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<td>Hypophosphatemia**</td>
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<td>Nausea</td>
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<tr>
<td>Thrombocytopenia</td>
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<td></td>
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<td></td>
<td></td>
<td>2</td>
<td>1</td>
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<tr>
<td>QT prolongation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1***</td>
</tr>
</tbody>
</table>

*Patient previously had kidney resected due to RCC
**Hypokalemia and hypophosphatemia resolved with oral potassium and phosphorus
*** Patients had QT prolongation prior to treatment, QT prolongation resolved and patient continued treatment

Grade 1-2 AE mainly GI related toxicities
Grade 3-4 thrombocytopenia in 3/75 (4%) patients
75 patients enrolled
- 30 patients with prior ABI progression (19 with rPD on ABI)
- 34 patients with prior ENZA progression (18 with rPD or cPD on ENZA)
- 11 patients with prior ABI + ENZA progression (5 with rPD on ABI/ENZA)
- 5 ongoing patients (July 2020) (from 1.7 to 3.3 years On-Treatment)

rPD = radiographic progressive disease
cPD = clinical progressive disease
Prolonged time to radiographic progression vs. historical 2\textsuperscript{nd} line ARSI

Similar mPFS between ABI and ENZA progressors

Median rPFS\textsubscript{ALL patients} = 9.0 mo
Median rPFS\textsubscript{ABI progressors} = 7.8 mo
Median rPFS\textsubscript{ENZA progressors} = 10.1 mo

Historical median rPFS* = 3 to 6mo
*2\textsuperscript{nd} line single agent ARSI

Evidence of ZEN-3694 activity in both Post-ABI and Post-ENZA settings
Patients with clinical factors associated with aggressive disease benefited from combination therapy

Evidence of clinical activity of ZEN-3694 in populations with clinical factors associated with poor responses to ARSI

*Non-rPD = PSA and or clinical progression
Examples of best responders #1
Sustained PSA90 or partial tumor response

Four patients with prolonged PSA90 responses
(3/4 patients ongoing)

Sustained tumor partial response of 1.8 years in patient with radiographic progression of visceral lesions on prior ENZA

Pantuck et al. 2018, Aggarwal et al. CCR 2020 + unpublished results
Examples of best responders #2

Clinical and radiographic progression on prior ENZA - Stabilization of disease with PSA85 > 2 years

Stabilization of metastatic disease for >2 years
(rPD on prior ENZA)

Unconfirmed growth of visceral lesions (ENZA stopped)

Stabilization of disease for > 2 years + PSA85

Stabilization of metastatic tumors >2 years

Omental nodule #1
Central mesenteric module
Omental nodule #2

Estimated time of previous scan
Progressive Disease (Stopped enza)
Detection of ZEN-3694 target engagement in whole blood and tumor biopsies
Detection of target engagement in whole blood

Significant exposure-dependent target engagement for 5 PD markers

Target engagement detected at all doses (48-144mg ZEN-3694)

Aggarwal et al. CCR 2020, Aggarwal et al. AACR2019, Tsujikawa et al. AACR2017 + unpublished results
Detection of target engagement in 4 paired biopsies (Baseline, C3D1)
Inhibition of androgen and MYC signaling, modulation of BET-dependent genes

- 3/4 patients already receiving enzalutamide at time of Baseline biopsy
- Inhibition of several hallmarks of prostate cancer by ZEN-3694
Evidence of an adaptive immune response On-Treatment in 2/4 paired biopsies

GSEA of paired biopsies

<table>
<thead>
<tr>
<th>Immune Cell type</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T and B lymphocytes</strong> (Antigen presentation/T cell migration)</td>
<td>CD8a</td>
<td>CD4</td>
</tr>
<tr>
<td></td>
<td>CD27</td>
<td>LY9</td>
</tr>
<tr>
<td></td>
<td>MYO1G</td>
<td>IRF4</td>
</tr>
<tr>
<td><strong>NK cells</strong></td>
<td>KLRK1</td>
<td>FCGR3A</td>
</tr>
<tr>
<td><strong>B cells</strong></td>
<td>LILR1A</td>
<td></td>
</tr>
<tr>
<td><strong>Leukocyte</strong></td>
<td>LAIR1</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor NK receptor</strong></td>
<td>HLA-E</td>
<td></td>
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<tr>
<td><strong>Class II MHC</strong></td>
<td>HLA-DRB5, HLA-DQA2, HLA-DOA, HLA-DOB, HLA-DMA</td>
<td></td>
</tr>
<tr>
<td><strong>Antigen processing presentation</strong></td>
<td>TAP1, TAP2, PSMB8, PSMB9, IFNg</td>
<td></td>
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</tbody>
</table>

Unpublished results
Evidence of an adaptive immune response On-Treatment in 2/4 paired biopsies

<table>
<thead>
<tr>
<th>GSEA of paired biopsies</th>
<th>Induction of genes involved in immune response On-Treatment</th>
<th>Overlap of induced genes between patients A and B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient B</td>
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</tbody>
</table>

ZEN-3694, Enzalutamide, and Pembrolizumab for the Treatment of Metastatic Castration-Resistant Prostate Cancer

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

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Rahul Aggarwal

Collaborators:
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U.S. Army Medical Research and Development Command

Information provided by (Responsible Party):
Rahul Aggarwal, University of California, San Francisco

Unpublished results

<table>
<thead>
<tr>
<th>Enrichment plot</th>
<th>Fold change mRNA</th>
<th>NES</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION</strong></td>
<td>Treatment vs. Baseline biopsy</td>
<td>1.85</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Class II MHC
- HLA-DRB5, HLA-DQA2, HLA-DOA, HLA-DOB, HLA-DMA

Antigen processing presentation
- TAP1, TAP2, PSMB8, PSMB9, IFNγ
Detection of gene signatures of poor response to ARSI in patients with longer time on the trial
Signatures of enzalutamide resistance detected in two patients with longer time to progression (TTP > 24 weeks)

- Treatment-induced small cell neuroendocrine prostate cancer (t-SCNC) is associated with poor prognosis on ARSI
- Cell cycle progression score (CCP) has been associated with poor responses to 1st line ARSI

Tumor biopsies from 4 evaluable patients had t-SCNC signature

High CCP score associated with 2 t-SCNC tumors with long TTP

Two patients with long TTP had signatures of t-SCNC and high CCP associated with poor response to ARSI

ARSI = AR signaling inhibitor (enzalutamide, apalutamide, darolutamide, abiraterone)

Analysis of CRPC patient biopsies shows loss of AR signaling and dependence associated with longer time to progression

AR-independence/BET-dependence signature associated with t-SCNC tumors with long TTP

Association of lower AR signaling in baseline biopsies with longer rPFS

Aggarwal et al. PCF2019, CCR 2020, Coleman et al. 2019, unpublished results
Identification of PSA spikes as a candidate biomarker of response to ZEN-3694 + enzalutamide
PSA spikes at either 4 or 8 weeks in several patients with longer TTP

21/75 (28%) of patients with PSA spike

Median rPFS_{PSA SPIKE} = 10.1 mo
Conclusions

• Combination of ZEN-3694 with ENZA was well tolerated with daily dosing
  ⇒ Combination → right targeted agent
  ⇒ Patient population → chemo-naïve
  ⇒ BET inhibitor → moderate half-life

• Evidence of clinical activity in AR-low and AR-independent patients with candidate predictive biomarkers
  ⇒ PSA spikes at 4 or 8 weeks
  ⇒ t-SCNC, AR-independent/BET-dependent, CCP gene signatures

Future clinical development of ZEN-3694:
• Phase 2 ZEN-3694 + enzalutamide + pembrolizumab in mCRPC patients (initiation Q4 2020)
• Phase 2 ZEN-3694 + PARPi talazoparib in TNBC patients without germline BRCA1/2 mutations (gBRCA1/2wt)
  ⇒ Manageable combination, RP2D determined
  ⇒ Early results show promising activity (SABCS 2020)
• Randomized study of ZEN-3694 + enzalutamide in prostate cancer patients (early 2021)
Acknowledgements

• Patients and their family

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