Clinical Development of the BET bromodomain inhibitor ZEN-3694 in multiple oncology indications
Sarah Attwell, May 2021
ZEN-3694 is a pan BET bromodomain inhibitor

- BET proteins (BRD 2, 3, 4) bind to histone acetylated lysines
- BRD4 is involved in ‘superenhancer’ formation, which drives oncogene expression (such as MYC, JUN, CDK6, Cyclins), as evidenced by the BRD4-NUT fusion in Nut-midline carcinoma
- Unlike writers and erasers, targeting the reader class of epigenetic modifiers is immediate and quickly reversible
- ZEN-3694 is a dual bromodomain pan-BET inhibitor currently in a phase 2 clinical trials in metastatic castration resistant prostate cancer (mCRPC) and triple negative breast cancer (TNBC), and soon to enter in ovarian cancer
10 years of BET inhibitor development in oncology indications

<table>
<thead>
<tr>
<th>2010</th>
<th>2012</th>
<th>2015</th>
<th>2021</th>
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<tbody>
<tr>
<td><strong>First BETi published</strong></td>
<td><strong>BETi enter the clinic</strong></td>
<td><strong>20 BETi in clinical trials</strong></td>
<td><strong>5 BETi in clinical trials</strong></td>
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<tr>
<td>• First BETi (benzodiazepines)</td>
<td>• Potent, long half life molecules (kinase inhibitor approach)</td>
<td>• CYP liabilities</td>
<td>Combinations-based approach</td>
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<td>• Broad activity in cell lines and animal models</td>
<td>• Early clinical trials targeted cancers most sensitive in pre-clinical models</td>
<td>• Off-target toxicities</td>
<td>• Hematological cancers, myelofibrosis, and solid tumors (Ph. 2/3)</td>
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<td>• Dosing near DLT requiring dose holds and intermittent schedules</td>
<td>• Combinations target BET-dependent resistance mechanisms (lower BETi dosing)</td>
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<td>• Limited efficacy due to epigenetics biology</td>
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We are here:

**Early excitement**
- First BETi show broad anti-tumor activity in pre-clinical models

**Early attempts**
- Toxicity
- All comer trials
- Limited single agent activity

**Improvements**
- Better drug properties
- Novel Targeted combinations (IO/PARPi/Kinase/ARSi)
- Selected patient populations
- Optimal dosing
Epigenetic mechanisms involved in resistance to anti-cancer therapies

- Tumor initially responds to treatment
- Acquisition of drug resistance almost invariably occurs
- Epigenetic mechanisms often involved in drug resistance
- ZEN-3694 can prevent and/or reverse resistance

Synergistic combinations approach allows for lower BETi dosing
ZEN-3694 is a leading best-in-class & clinically differentiated bromodomain inhibitor (BETi)

**ZEN-3694 Differentiation Advantages**

- Well tolerated
- Optimal PK profile
- Good pharmacological properties
- Minimal CYP Liabilities
- Focused combinations driven clinical strategy
- Advancing to registration enabling studies
- Being clinically tested in multiple indications and combinations
- Has attracted multiple collaborations (Big Pharma, NCI)
- Chronic dosing
- Combinable with various targeted drugs
- Only BETi to have shown clinical Proof of concept in 2 solid tumor types
Zenith advancing pipeline with strong collaborators

**ZEN-3694 BETi Programs**

- **AR Independent mCRPC (+ enzalutamide, ARSi)**
- **TNBC (+ talazoparib, PARPi)**
- **AR Independent mCRPC IO Combo (+ Keytruda + enzalutamide)**
- **Checkpoint Inhibitor Combination Ovarian Cancer**
- **Other Combinations (multiple indications)**

**Phase 1**

**Phase 2**

**Registration Studies**
Prostate cancer (mCRPC) program overview
Phase 2a completed; Phase 2b randomized study in implementation stage

- Prolonged rPFS of 39 wks with ZEN-3694 + enzalutamide compared to expected rPFS of 12-24 wks with single agent enzalutamide
- Significant benefit in patients with poor response to abiraterone
- Target engagement in blood and in tumor
- Well tolerated, chronic daily dosing
- Study results published in Clinical Cancer Research (Aggarwal et al. 2020)
- Randomized Phase 2b study in poor responders to abiraterone in implementation stage – 2 year study
Detection of target engagement in 4 paired biopsies (Baseline, C3D1)
Inhibition of androgen and MYC signaling, modulation of BET-dependent genes

- Inhibition of androgen signaling
- Inhibition of MYC signaling
- Inhibition of BET-dependent genes
- Inhibition of prostate cancer signature

- 3/4 patients already receiving enzalutamide at time of Baseline biopsy
- Inhibition of several hallmarks of prostate cancer by ZEN-3694

Aggarwal et al. CCR 2020
Evidence of ZEN-3694 + ENZA activity in low AR signaling tumors: Not expected to respond to single agent enzalutamide

- Low AR activity in CRPC tumors associated with shorter time on ABI
- Low AR activity in CRPC tumors associated with shorter time on ENZA
- Low AR activity in CRPC tumors associated with longer time on ZEN-3694 + ENZA

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 ABI data calculated from Abida et al. 2020, ENZA data from Alumkal et al. 2020
A BRD4-dependent axis drives AR-independence and resistance to enzalutamide (results in press)
Combining talazoparib with ZEN003694 in people with triple-negative breast cancer without inherited faulty BRCA1/2 genes

Date of summary: December 2020
Study number: NCT03901469 | Study start date: June 2019 | Estimated study end date: January 2022

The full title of this abstract is: A phase 1b/2 study of the BET inhibitor ZEN003694 in combination with talazoparib for treatment of patients with TNBC without gBRCA1/2 mutations
ZEN-3694 + TALA is active in tumors that do not respond to single agent PARPi

- In breast cancer, only ~20% of patients receive a PARPi (BRCA1/2 mutant)
- PARPi single agent does not shrink TNBC tumors without mutations in BRCA1/2 or PALB2
- ZEN-3694 sensitizes tumors with functional BRCA1/2 (or PALB2), thus expanding the use of PARPi in TNBC
- ZEN-3694 reduces the mRNA levels of several DNA repair genes as a potential mechanism of sensitization to PARPi
Activity of ZEN-3694 + talazoparib in HRRwt TNBC tumors
Dose escalation + Stage 1 (December 2020)

Best overall tumor response

Overall response rate (ORR): CR + PR = 29%
Clinical benefit rate (CBR): ORR + SD (> 4mo) = 44%

- Patients screened for absence of gBRCA1/2m for enrollment on trial
- CLIA sequencing of biopsies from patients rule out tumor mutations in BRCA1/2 or PALB2
  ⇒ Combination activity unlikely due to single agent talazoparib

HRR= homologous recombination repair
Mechanisms of resistance to Checkpoint therapy

**Response**

- APC
- MHC
- TCR
- Tumor associated antigen
- Co-stimulator

**Generation**

- APC
- MHC
- TCR
- T-cell
- Tumor cell
- Tumor associated antigen

**Response**

- APC
- MHC
- TCR
- T-cell
- Tumor killing
- PD-L1
- PD-1

**Memory**

- APC
- MHC
- TCR
- T-cell
- T-effector memory
Mechanisms of resistance to Checkpoint therapy

**Response**
- Impaired immune infiltration
- Lack of neoantigens
- Impaired antigen processing/presentation

**Generation**
- Co-stimulator
- T-cell
- Tumor associated antigen

**Response**
- Tumor killing
- PD-L1
- CD8 T-cell
- TCR
- MHC

**Memory**
- T-effector memory

**Resistance**
- Immune suppressive cells
- Alternate checkpoints
- Impaired IFNγ signaling
- T-cell epigenetic changes
- T-cell exhaustion

Adapted from Jenkins et al, 2018
mCRPC clinical trial: immune modulation in patient blood and tumors

Fold change at 4h in patient blood (analysis of 37 patients)

- Inhibition of checkpoints and Immune Suppressve factors at safe doses
- Doesn’t seem to be an advantage at higher doses
- Combination with a checkpoint inhibitor at lower dose ZEN-3694?
- Two ZEN-3694 Checkpoint inhibitor combination trials have just entered the clinic
Summary and conclusions

• ZEN-3694 is a leading BET inhibitor, with proof of concept clinical activity now shown in two indications

• BET protein target engagement has been demonstrated both in patient blood and tumor

• ZEN-3694 is safe and well tolerated, with good drug-like properties

• We are pursuing several promising combination strategies in the clinic, in multiple solid tumor indications

Zenith translational team

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