Acquired resistance to anti-cancer therapies through epigenetic mechanisms

- Tumors initially respond to treatment
- Acquisition of drug resistance almost invariably occurs
- Epigenetic mechanisms often involved
- Epigenetic inhibitor to prevent and/or reverse resistance
Targeting epigenetic mechanisms of resistance to anti-cancer therapies: examples with the BET bromodomain inhibitor ZEN-3694

Two examples from recent clinical trials with ZEN-3694:
• Reversion of ARSI resistance → AR-independent resistance in prostate cancer
• Induction of synthetic lethality → PARP inhibitor in BRCA1/2 wild-type triple-negative breast cancer
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

Phase 1b/2a: ZEN-3694 in combination with enzalutamide in mCRPC
(NCT02711956, NCT04145375)

**Summary of findings:**
- 75 patients dosed, MTD not reached → RP2D 96mg
- ZEN-3694 target engagement seen in whole blood and tumor biopsies
- Clinical activity at well tolerated doses, prolonged daily dosing without dose interruptions/reductions
- Clinical activity seen at LO and HI doses
  - One ongoing patient at LO dose (> 4.3 years with PSA90 response, prior progression on ABI)
  - One ongoing patient at HI dose (> 2.7 years, prior progression on bicalutamide, ABI, and ENZA)
- Median radiographic progression-free survival of 9.0 mo vs. 3 mo (historical value for second line ARSI)
- Evidence for activity in tumors from patients with low androgen receptor (AR) signaling

---

ABI = abiraterone; ARSI = AR Signaling Inhibitor; ENZA = enzalutamide; mCRPC = metastatic castration-resistant prostate cancer, RP2D = recommended Phase 2 dose
HI Dose = 96 mg ZEN-3694, LO Dose = 48 mg ZEN-3694

Aggarwal et al. CCR 2020
Loss of AR signaling is associated with gain of neuroendocrine characteristics (NEPC): lineage plasticity

- Shift from adenocarcinoma (AR-dependent) towards neuroendocrine (AR-independent) → lineage plasticity
  ⇒ Involvement of several epigenetic processes
- Occurs in ~20% of patients treated with ARSI → associated with poor prognosis
- Treatment-induced NEPC (t-NEPC): limited treatment options (unmet treatment need)

**AR signaling score**: 21 gene signature upregulated upon incubation of prostate cancer cell line with androgen

**Integrated NEPC score**: 70 gene signature upregulated in NEPC

ZEN-3694 blocks a BRD4/E2F1 lineage plasticity program associated with ARSI resistance in prostate cancer

- Identification of a BRD4/E2F1 axis responsible for lineage plasticity in prostate cancer
- Two t-NEPC patients on ZEN-3694 + ENZA trial with BRD4\textsuperscript{HI}, E2F1\textsuperscript{HI}, AR\textsuperscript{LO}, (+ AR repressed signature) had longer time on study

Baseline tumor biopsies from four evaluable patients had t-NEPC signature

Higher expression of BRD4, E2F1, and lower AR activity was associated with longer time on study

ARSI = AR signaling inhibitor, t-NEPC = treatment-induced neuroendocrine prostate cancer

Mechanisms of resistance to ADT and ARSI in prostate cancer

Prostate Cancer (HSPC, CRPC)

ADT/ARSI THERAPY

Maintenance of AR signaling (80%)
- AR amplification (enhancer) + mutations
- AR splice variant (AR-V7)
- Upregulation of alternative steroid receptor (GR)

AR repression (20%)
- AR-independence (low AR, AR null)
- Transdifferentiation + neuroendocrine markers (t-SCNC, t-NEPC)
- Activation of alternate proliferation pathways (BRD4/E2F1-dependent)

- Recent approval of ARSIs in earlier disease setting (HSPC) is associated with increased cases of AR-repressed CRPC
- Patients with loss of AR activity have a worse prognosis on ARSI and fewer treatment options

ARSI = Androgen Receptor Signaling Inhibitor; CRPC = castration-resistant prostate cancer; GR = Glucocorticoid Receptor; HSPC = hormone sensitive prostate cancer
Mechanisms of resistance to ADT and ARSI

Prostate Cancer (HSPC, CRPC)

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- AR amplification (enhancer) + mutations
- AR splice variant (AR-V7)
- Upregulation of alternative steroid receptor (GR)

**AR repression (20%)**
- AR-independence (low AR, AR null)
- Transdifferentiation + neuroendocrine markers (t-SCNC, t-NEPC)
- Activation of alternate proliferation pathways (BRD4/E2F1-dependent)

Increased ZEN-3694 + ENZA activity

- Recent approval of ARSIs in earlier disease setting (HSPC) is associated with increased cases of AR-repressed CRPC
- Patients with loss of AR activity have a worse prognosis on ARSI and fewer treatment options

ARSI = Androgen Receptor Signaling Inhibitor; CRPC = castration-resistant prostate cancer; GR = Glucocorticoid Receptor, HSPC = hormone sensitive prostate cancer
Mechanisms of resistance to ADT and ARSI

Prostate Cancer (HSPC, CRPC)

How to enrich for patients with AR-independent prostate cancer (HSPC, CRPC)?

**Biopsies:**
- Hard to get (bone)
- Archival biopsies might not be reliable (esp. before prior ARSI)
- What is the best signature(s)/score cut-off?
- How to implement in the real world?

→ Clinical history readout to enrich for AR-independence

ARSI = Androgen Receptor Signaling Inhibitor; CRPC = castration-resistant prostate cancer; GR = Glucocorticoid Receptor, HSPC = hormone sensitive prostate cancer
Low AR signaling associated with **shorter time** (primary resistance) on ARSI in patients with mCRPC

---

**Low AR activity in CRPC tumors associated with shorter time on ENZA**

**Low AR activity in CRPC tumors associated with shorter time on ABI**

---

Low AR activity associated with **rapid progression** (primary resistance) on ARSI

---

ABI data calculated from Abida et al. 2020, ENZA data from Alumkal et al. 2020
Low AR signaling and primary ABI resistance associated with longer time on ZEN-3694 + ENZA in patients with mCRPC

Low AR activity in baseline biopsies associated with longer time on ZEN-3694 + ENZA

Patients with prior primary resistance to ABI associated with longer time on ZEN-3694 + ENZA

<table>
<thead>
<tr>
<th>Time on prior ABI &lt; 6 months</th>
<th>Time on prior ABI &gt; 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>4</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>11</td>
</tr>
</tbody>
</table>

Low AR activity and rapid progression on prior ABI associated with longer time on ZEN-3694 + ENZA study
Poor PSA responses associated with lower survival in mHSPC and mCRPC

Latitude Phase 3 trial (mHSPC), Sequencing ABI and ENZA trial (mCRPC)

Lack of PSA50 response with ABI is associated with lower survival of patients with mHSPC

Failure to reach PSA ≤ 0.1 ng/ml nadir with ABI is associated with more rapid progression and lower survival

mCRPC patients with poor response to 1st ARSi have a worse response to a 2nd ARSi

<table>
<thead>
<tr>
<th>Time to confirmed PSA progression on 1st ARSi</th>
<th>HR (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 mo</td>
<td>&lt; 3 mo</td>
</tr>
<tr>
<td>% of patients with PSA30 response on 2nd ARSi</td>
<td>40% (21/53)</td>
</tr>
</tbody>
</table>

2.92 (1.5-5.9), p=0.003

Poor PSA response to ARSi is associated with:
- Rapid progression in both mHSPC and mCRPC
- Poor response to 2nd ARSi

Matsubara et al. 2020, Khalaf et al. 2019
Poor PSA50 response on prior ABI associated with longer time on ZEN-3694 + ENZA study

Lack of PSA50 response with prior ABI is associated with longer time on ZEN + ENZA

Radiographic PFS

- PSA50 response on prior ABI
- No PSA50 response on prior ABI

<table>
<thead>
<tr>
<th>PSA50 response on prior ABI (n=14)</th>
<th>No PSA50 response on prior ABI (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>5</td>
</tr>
<tr>
<td>Median rPFS (months)</td>
<td>5.2</td>
</tr>
</tbody>
</table>

3/14 patients with PSA50 to prior ABI had rPFS > 6 mo
9/15 patients without PSA50 to prior ABI had rPFS > 6 mo

Prior poor PSA response on prior ABI associated with longer time on ZEN-3694 + ENZA study
~20% of mHSPC patients progress in less than 12 mo. on ABI (primary resistance) (LATITUDE trial)

- Primary resistance to ABI in either HSPC or CRPC is predicted to enrich for AR-independence
  ⇒ Enrichment for patients with predicted poor response to 2nd ARSI with fewer therapy options

Fizazi et al. 2017
Phase 2b mCRPC study design: Pre-select patients with poor response to prior ABI (AR-independent/BET-dependent) Scheduled start in August 2021

Objectives:
- Test ZEN-3694 + ENZA in mCRPC patients that have progressed on ABI
- Evaluate efficacy in both poor ABI responders/AR-independent and ABI responders
- Open label, randomized, Blinded Independent Central Review (BICR)

Key Eligibility Criterion
- mCRPC progressed on ABI
- Not candidates for chemotherapy (Physician judgment)
- Patients with prior enzalutamide/apalutamide/darolutamide excluded

Cohort A: Poor ABI responders/AR-independent*
- ZEN-3694 + ENZA
- ENZA

Cohort B: ABI responders
- ZEN-3694 + ENZA
- ENZA

Primary Endpoint
- rPFS Cohort A

Key Secondary Endpoints
- rPFS Cohort A+B
- PFS Cohort A
- PFS Cohort A+B
- OS: Cohort A

Collaboration with Astellas and Newsoara

*HSPC: < 12 months duration on prior ABI, or failure to achieve a PSA nadir of 0.2 ng/ml
CRPC: < 6 months duration on ABI, or failure to achieve PSA50 response
Epigenetic modulation by ZEN-3694 restores sensitivity to enzalutamide

- ARSI induces loss of AR signaling
- Gain of AR-independent features
- BET-dependent transcriptional reprogramming

ARSI

Epigenetic remodeling

AR-dependent CRPC

AR-independent CRPC
Epigenetic modulation by ZEN-3694 restores sensitivity to enzalutamide

- ZEN-3694 inhibits maintenance of AR-independence
- Restoration of ARSI sensitivity
Epigenetic modulation by ZEN-3694 restores sensitivity to enzalutamide

- ZEN-3694 inhibits maintenance of AR-independence
- Restoration of ARSI sensitivity

**Single Agent ZEN-3694**

START (48 mg ZEN-3694)

Time on Study (weeks)

PSA (ng/ml)

0 100 200 300 400

0 5 10 15

Dose hold

Dose hold
Epigenetic modulation by ZEN-3694 restores sensitivity to enzalutamide

- ZEN-3694 inhibits maintenance of AR-independence
- Restoration of ARSI sensitivity

Single Agent ZEN-3694

Combination ZEN-3694 + ENZA

Patients with PSA spike at w4 or w8
A Phase 1b/2 Study of ZEN003694 and Talazoparib in Patients With Triple Negative Breast Cancer (TNBC) and Without Germline BRCA1/2 Mutations

Aftimos et al. SABCS 2020 (PS11-10)
Induction of homologous recombination deficiency by ZEN-3694 and sensitization to PARP inhibitors in BRCAwt cells

- In breast cancer, only ~20% of patients are eligible to receive a PARPi (germline BRCA1/2 mutant)
- Additional clinical activity in advanced breast cancer is currently limited to somatic BRCA1/2 or germline PALB2 mutations, not in other DNA repair genes
- Acquired resistance limits the clinical activity of PARPi (recovery of DNA repair capacity)
- ZEN-3694 reduces the mRNA levels of several DNA repair genes as a potential mechanism of sensitization to PARPi
  - BRCAwt tumors
  - BRCA1/2 mutant tumors PARPi-resistant

Adapted from Sun et al. 2018
ZEN-3694 + talazoparib trial design (Phase 2, Pfizer/Zenith collaboration)

Patients with advanced TNBC and no germline BRCA1/2 mutations

**Objectives:**
- Show safety and activity of ZEN-3694 + talazoparib
- Identify potential biomarkers of response

**Design:**
- Dose escalation followed by Simon 2-stage, n= 17 1st stage, n=20 2nd stage

**Patient population:**
- TNBC: locally advanced or metastatic

**Endpoints:**
- Part 1: Safety, pharmacokinetics/pharmacodynamics, maximum tolerated dose, Phase 2 dose (RP2D)
- Part 2: Objective response rate (ORR), clinical benefit rate (CBR), duration of response (DOR), progression free survival (PFS)

**Locally advanced/metastatic TNBC**
- No germline mutations in BRCA1 and BRCA2 (gBRCA1/2m) (CLIA test)
- No prior progression during platinum treatment
- No prior exposure to BETi or PARPi

**Dose Escalation**
- Patients with at least one prior cytotoxic chemotherapy

**Simon 2-Stage Dose Expansion**
- < 2 prior chemotherapy regimens for mTNBC

NCT03901469
# Common treatment-related adverse events (AEs)

<table>
<thead>
<tr>
<th>Grade 3/4 AEs across all cohorts</th>
<th>DE Cohort 1</th>
<th>DE Cohort 2</th>
<th>DE Cohort 3</th>
<th>Simon Stage 1</th>
<th>Total n = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
<td>Any Grade</td>
<td>Grade 3/4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>ALT increase^</td>
<td>1</td>
<td>4</td>
<td>2 (G3)</td>
<td>5 (15.6%)</td>
<td>2 (G3)</td>
</tr>
<tr>
<td>AST increase^</td>
<td>1</td>
<td>3</td>
<td>1 (G3)</td>
<td>5 (15.6%)</td>
<td>1 (G3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (G3)</td>
<td>1 (G3)</td>
<td>1</td>
<td>4 (12.5%)</td>
<td>1 (G3)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1</td>
<td>1 (G3)</td>
<td>2 (6.3%)</td>
<td>1 (G3)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>4 (G3)</td>
<td>1 (G3)</td>
<td>13 (40.6%)</td>
<td>2 (G3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>2 (G3)</td>
<td>2</td>
<td>5 (15.6%)</td>
<td>2 (G3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (G3), 2 (G4) #</td>
<td>5 (G3), 1 (G4) #</td>
<td>1 (G3)</td>
<td>5 (G3), 1 (G4)</td>
<td>17 (53.1%), 2 (G3), 4 (G4) #</td>
</tr>
</tbody>
</table>

^ALT/AST self resolved

#DLTs (thrombocytopenia) = two patients in Cohort 1, one patient in Cohort 2

- 48 mg QD ZEN-3694 + 0.75 mg QD talazoparib selected as RP2D
- Thrombocytopenia reversible with dose hold and reduction in sensitive patients

List of Grade 1/2 AEs presented at SABCS2020 and available at [https://www.zenithepigenetics.com/Science-Epigenetics/publications-posters](https://www.zenithepigenetics.com/Science-Epigenetics/publications-posters)
Sustained whole blood target engagement for > 8 hours
Similar exposure-dependent target engagement as prior trials in prostate cancer

**CCR1**

- 36 mg ZEN003694
- 48 mg ZEN003694

**IL1RN**

- 36 mg ZEN003694
- 48 mg ZEN003694

**CCR1 Trend Line (4h)**

- 002 mCRPC
- 001 mCRPC
- 004 mTNBC (48 mg)
- 004 mTNBC (36 mg)

**IL1RN Trend Line (4h)**

- 002 mCRPC
- 001 mCRPC
- 004 mTNBC (48 mg)
- 004 mTNBC (36 mg)
Inhibition of DNA repair and HRR gene expression in tumors from two TNBC patients On-Treatment

Significant inhibition of DNA repair (GSEA) in tumors

Inhibition of HRR gene expression in tumors

Patient #1 (25h Post-Dosing)

Patient #2 (3h Post-Dosing)

HRR= homologous recombination repair
Significant inhibition of oncogenic hallmarks in tumor biopsies On-Treatment (GSEA)

Volcano plot (Hallmark MYC V1)

Hallmark MYC V1

Inhibition of oncogenic hallmarks and perturbation of cell cycle regulation On-Treatment

Hallmark MYC V2

Hallmark E2F targets

Hallmark G2/M checkpoint

Hallmark mitotic spindle
Activity of ZEN-3694 + talazoparib in HRRwt TNBC tumors
Dose escalation + Stage 1 (December 2020)

Best overall tumor response

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

HRR= homologous recombination repair
Clinical activity of PARP inhibitors in advanced breast cancer

Limited activity in BRCA1/2 wild-type breast cancer patients

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Agent(s)</th>
<th>BRCA1/2 and PALB2 status</th>
<th>MUTANT</th>
<th>“WT”</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEN + TALA vs. single agents</td>
<td>ZEN-3694 + TALA</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BETi</td>
<td>✓</td>
<td></td>
<td>×</td>
</tr>
<tr>
<td></td>
<td>PARPi</td>
<td>✓</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATRi</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>DNA damage response</td>
<td>ATRi + PARPi</td>
<td>✓</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATRi + carboplatin</td>
<td>✓ (×)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WEE1</td>
<td>✓ (×)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WEE1 + PARPi</td>
<td>✓ (toxic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI3K/AKT/mTOR</td>
<td>AKT† + PARPi</td>
<td>✓</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AKT† + paclitaxel</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td></td>
<td>panPI3Ki</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PIK3CAi + PARPi</td>
<td>✓ (×)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mTORi + PARPi</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>MAPK</td>
<td>EGFRi + PARPi</td>
<td>✓ (×)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>αPD-1 + PARPi</td>
<td>✓ (×)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial clinical results (advanced breast cancer):

- Limited activity of PARPi outside BRCA1/2m or PALB2m
  ⇒ ~ 5-10% tumor response rates in unselected populations
  ⇒ Need to identify additional biomarkers of response

- Potential to increase and extend current PARPi activity
  ⇒ Increase response rates and/or duration of response?
  ⇒ Promising strategy

- Most agents currently tested did not sensitize to PARPi
  ⇒ Limited evidence of creation of “BRCAAness” phenotype in the clinic

✓ = evidence of clinical activity
× = limited clinical activity in unselected patient population or compared to single agent
✓ (✓) or (×) = initial clinical evidence (currently low number of TNBC cases)

Preliminary retrospective results suggest patient enrichment strategy

<table>
<thead>
<tr>
<th></th>
<th>All patients (N=31)</th>
<th>Biomarker unselected (N=8)</th>
<th>Biomarker selected (N=19)</th>
<th>Trodelvy (FDA approved)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>27%</td>
<td>13%</td>
<td><strong>33%</strong></td>
<td>35%</td>
</tr>
<tr>
<td><strong>CBR (≥ 6 mo)</strong></td>
<td>32%</td>
<td>13%</td>
<td><strong>47%</strong></td>
<td>45%</td>
</tr>
</tbody>
</table>

ORR = overall response rate (complete + partial tumor responses, confirmed and unconfirmed)

CBR = clinical benefit rate (ORR + stable disease for ≥ 6 months)
Summary and conclusions: TNBC study

- Combination of ZEN-3694 + TALA demonstrated evidence of anti-tumor activity in previously treated patients with metastatic TNBC without gBRCA1/2 mutations.

- The combination is generally well-tolerated. Thrombocytopenia is the most common adverse event and dose-limiting toxicity, but it is manageable with dose adjustments. High dose intensity was maintained.

- PK is predictable, and PD data show meaningful and durable target engagement.

- Evidence that ZEN-3694 can induce synthetic lethality in combination with PARP inhibitors

- ZEN-3694 + talazoparib Simon Stage 2 is fully enrolled

- Translational Program to prospectively test identified biomarkers involved in response to combination regimen ongoing

**ZEN-3694 can sensitize BRCA1/2 wild-type TNBC tumors to PARP inhibitors**
Use of ZEN-3694 to prevent and reverse drug resistance
Tackling epigenetic-based drug resistance using epigenetic inhibitors

- Additional BETi-based combinations with immunotherapies in clinical development
- Optimal length of target engagement (hours vs. days)? Epigenotype specific?
- Post-BETi? EZH2, LSD1, HDAC, CBP/P300, PRMT inhibitors?

Common themes

- Requirement of the combination agent
  - Induce DNA damage (PARPi)
  - Kill re-sensitized tumor cells (ARSI)

- Early identification of biomarkers of response
### Zenith advancing pipeline with strong collaborators

<table>
<thead>
<tr>
<th>ZEN-3694 BETi Programs</th>
<th>Pre-Clin.</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Registration Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR Independent mCRPC (+ enzalutamide, ARSi)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNBC (+ talazoparib, PARPi)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR Independent mCRPC IO Combo (+ Keytruda + enzalutamide)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer IO Combo (+ Nivolumab + Ipilimumab)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Combinations (multiple indications)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Collaboration with the National Cancer Institute Cancer Therapy Evaluation Program (NCI-CTEP)
- Leverage knowledge gained from prostate and breast cancer trials
10 years of BET inhibitor development in oncology indications

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
</table>
| 2010 | First BETi published | - First BETi (benzodiazepines)
- Broad activity in cell lines and animal models |
| 2012 | BETi enter the clinic | - Potent, long half life molecules ("kinase inhibitor approach")
- Biology of epigenetic readers
- Single agent approach |
| 2015 | 20 BETi in clinical trials | - CYP liabilities, off-target toxicities
- Dosing near DLT, requiring dose holds and intermittent schedules
- Limited efficacy due to epigenetics biology |
| 2021 | 5 BETi in clinical trials | Combination-based approach
- Hematological cancers, myelofibrosis, and solid tumors (Ph. 2/3)
- Combinations target BET-dependent mechanisms |

**Visibility**

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

**Knowledge**

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

**We are here**

**Improvements**
- Better drug properties
- Optimal dosing
- Targeted combinations (IO/PARPi/Kinase/ARSi)
- Selected patient populations
Acknowledgements

- **Patients and their family**

**Principal Investigators CRPC Trial**
- Rahul Aggarwal (UCSF)
- Joshi Alumkal (OHSU-U. Michigan)
- Wassim Abida (MSKCC)
- Michael Schweizer (U.Washington)
- David Nanus (Cornell)
- Allan Pantuck (UCLA)
- Elisabeth Heath (Karmanos)

**East/West Coast Dream Teams**
- Felix Feng (UCSF)
- Adam Foye (UCSF)
- Jiaoti Huang (Duke U.)
- Eva Corey (U. Washington)
- Moon Chung (U. Washington)
- Colin Pritchard (U. Washington)
- Eric Small (UCSF)
- Howard Scher (MSKCC)

**Principal Investigators TNBC Trial**
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- Susan Domchek (UPenn)
- Ayca Gucalp (MSKCC)
- Erika Hamilton (Sarah Cannon)
- Jennifer Litton (MD Anderson)
- Lida Mina (MD Anderson)
- Mafalda Oliveira (VHIO)
- Kevin Punie (UZ Leuven)
- Mark Robson (MSKCC)
- Payal D. Shah (UPenn)
- Priyanka Sharma (UKansas)

**Zenith Team**
- Sarah Attwell
- Lisa Bauman
- Emily Gesner
- Sanjay Lakhotaia
- Karen Norek
- Michael H Silverman
- Margo Snyder
- Philip Wegge