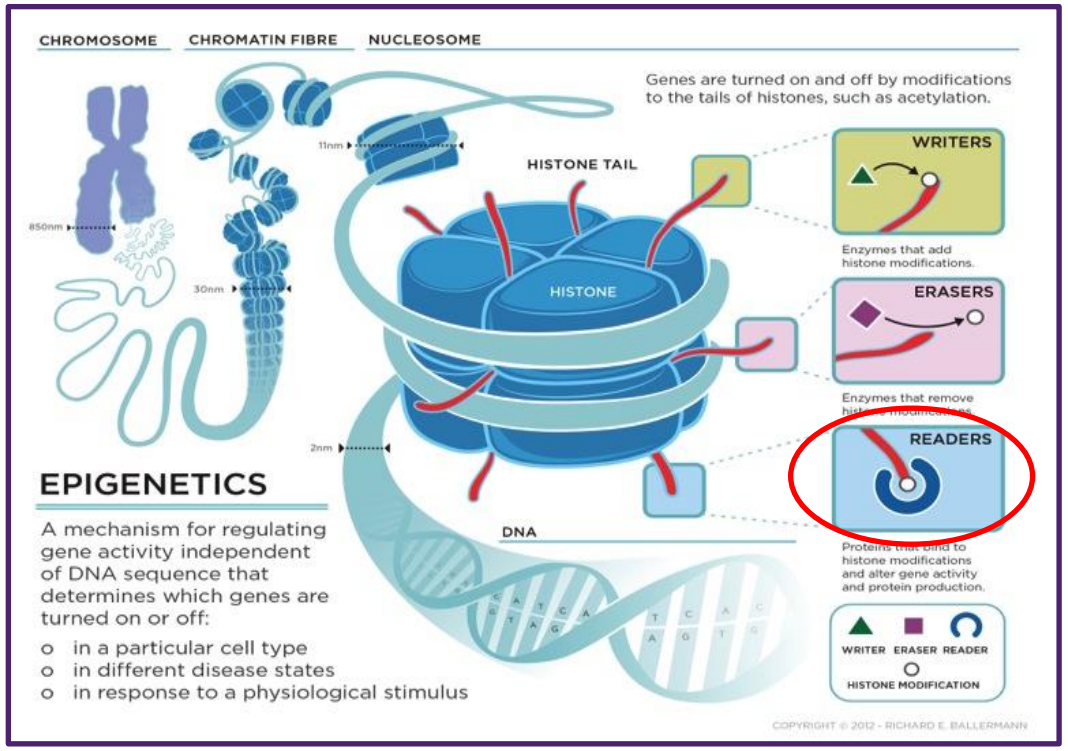
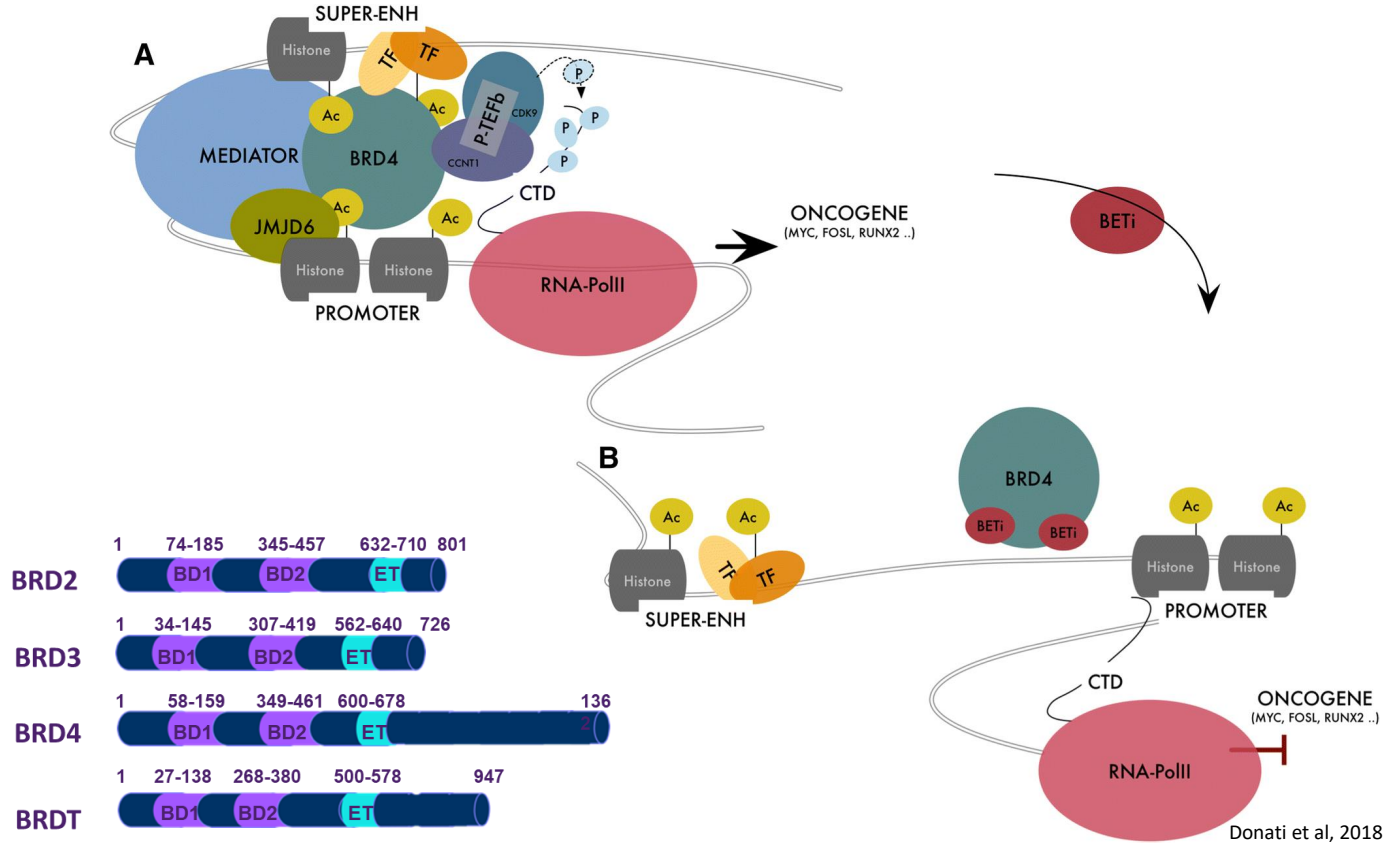
ZENITH EPIGENETICS

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





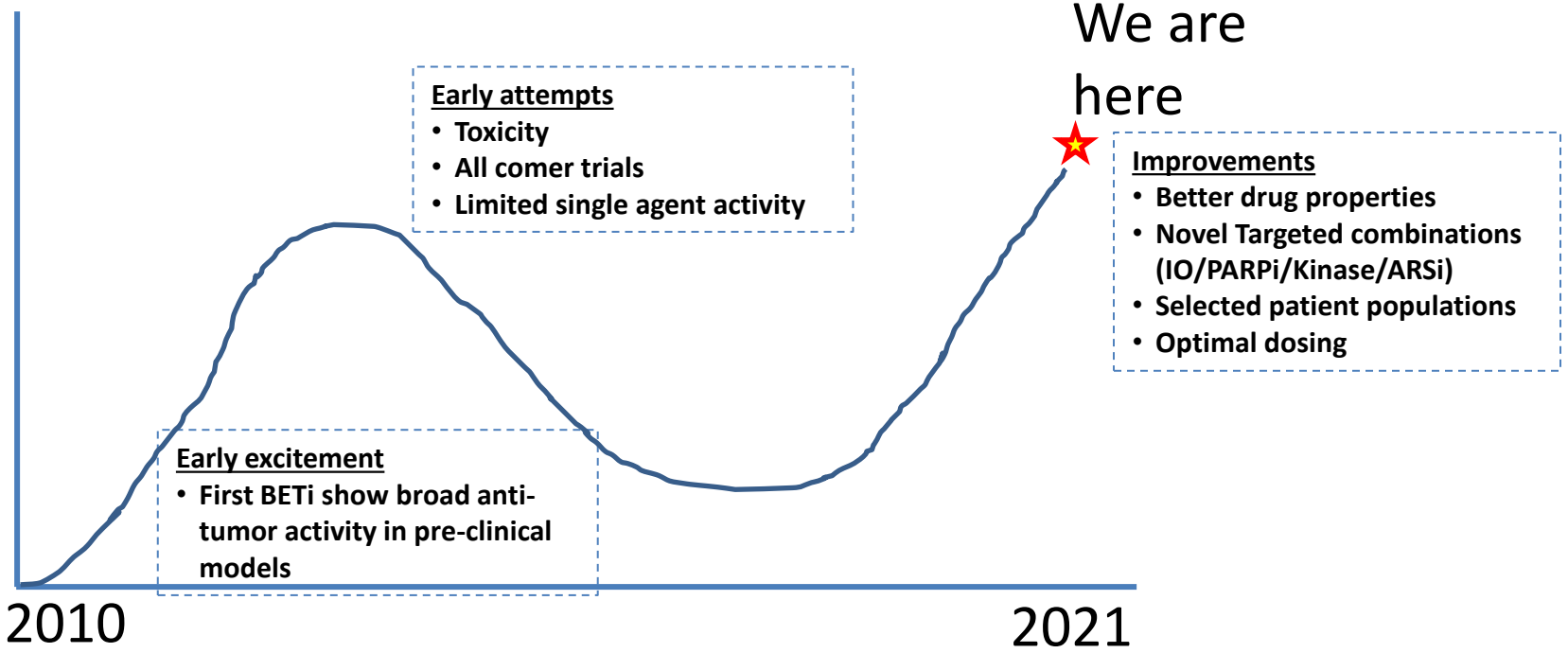
Donati et al, 2018

- 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

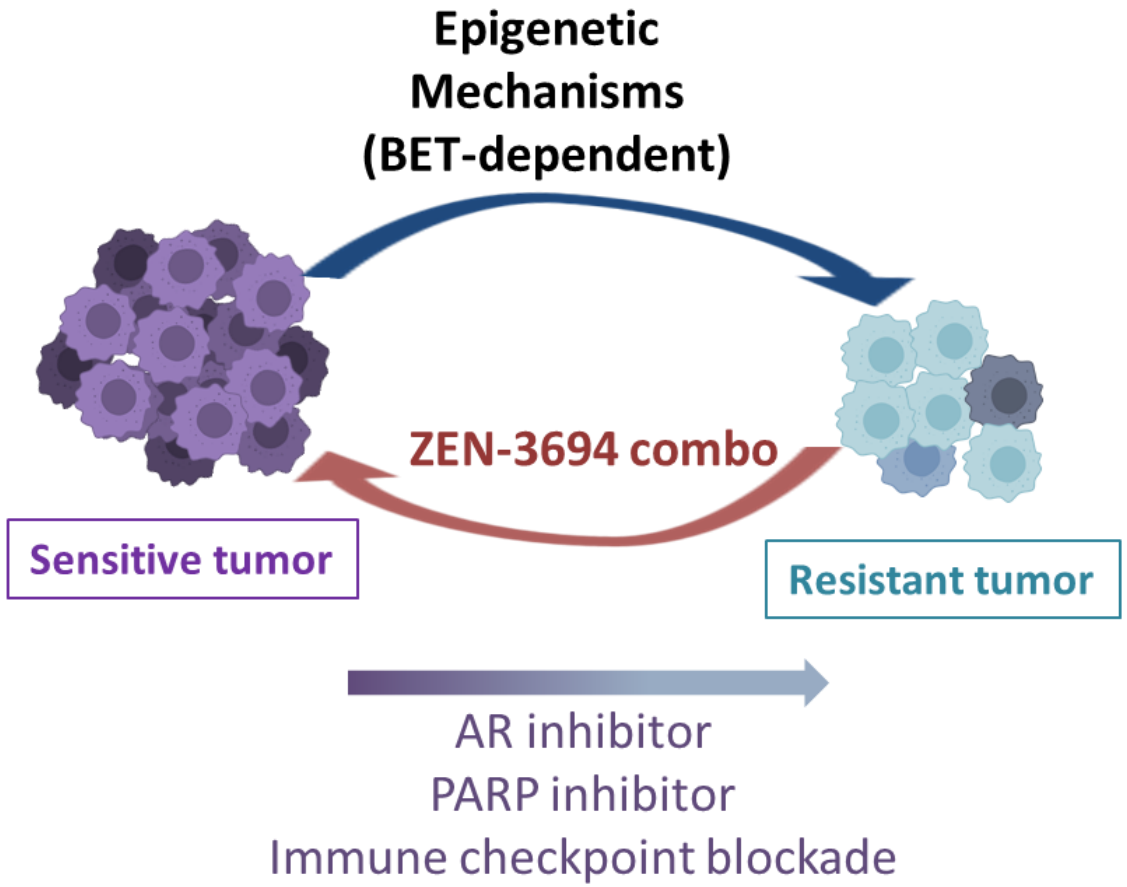
ZENITH EPIGENETICS

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



Epigenetic mechanisms involved in resistance to anti-cancer therapies

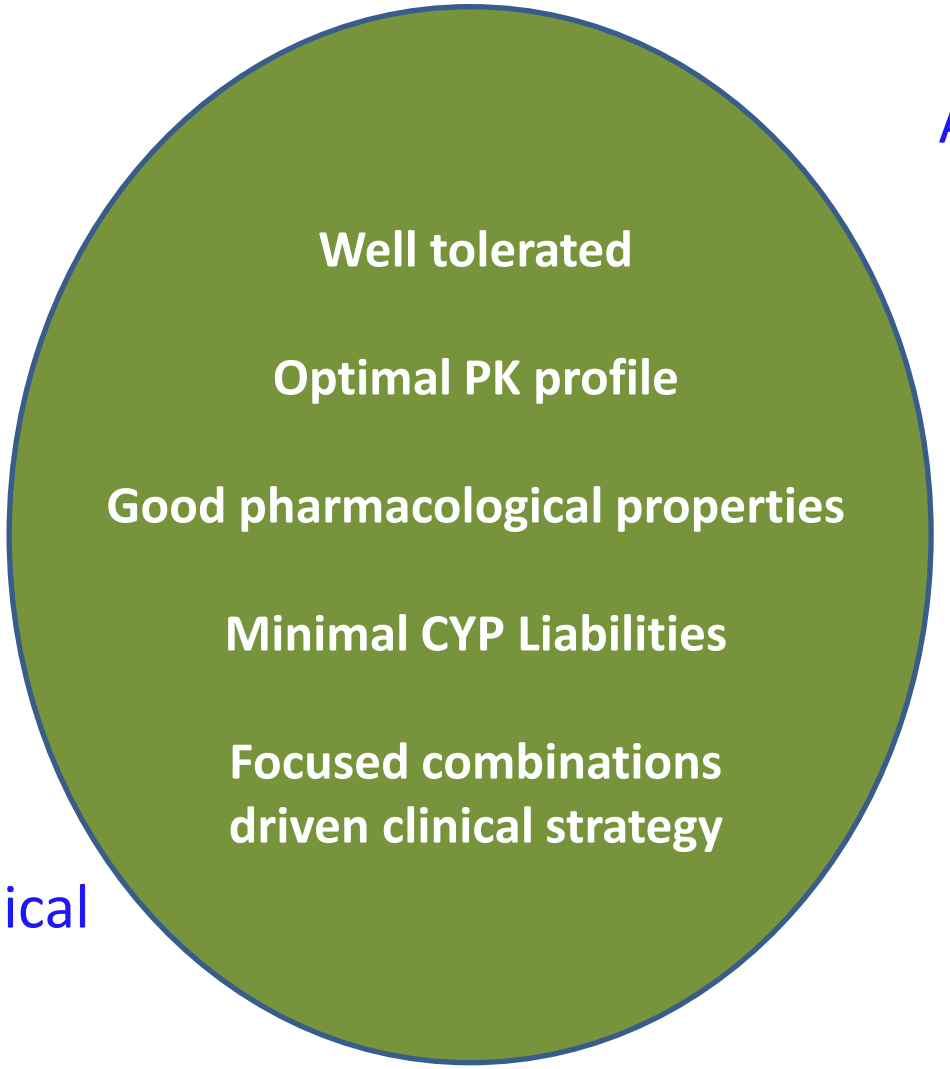
Synergistic combinations approach allows for lower BETi dosing



- **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**

ZEN-3694 is a leading best-in-class & clinically differentiated bromodomain inhibitor (BETi)

ZEN-3694 Differentiation Advantages



Combinable with various targeted drugs

Chronic dosing

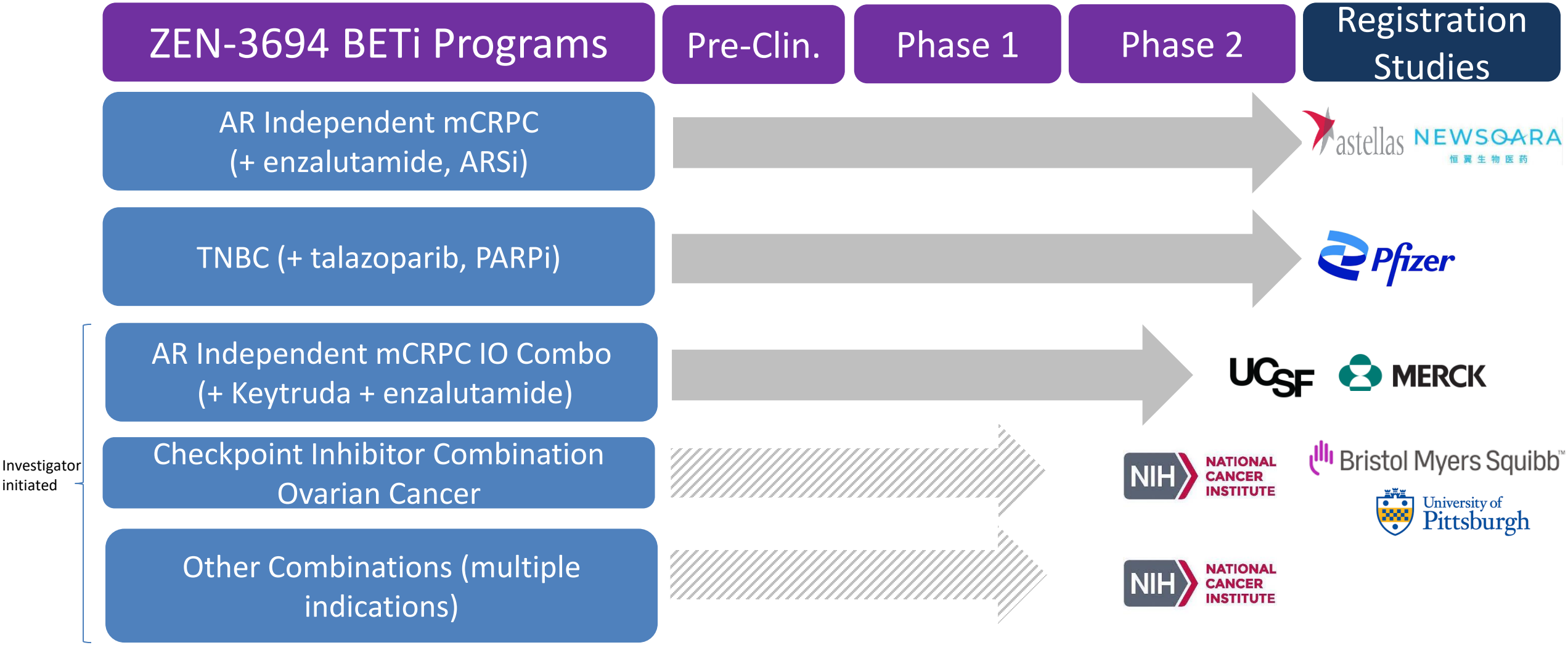
Only BETi to have shown clinical Proof of concept in 2 solid tumor types

Advancing to registration enabling studies

Being clinically tested in multiple indications and combinations

Has attracted multiple collaborations (Big Pharma, NCI)

Zenith advancing pipeline with strong collaborators



Prostate cancer (mCRPC) program overview

Phase 2a completed; Phase 2b randomized study in implementation stage

2018	2019	2020	2021	2022	2023

Ph. 1B/2a: ZEN-3694 + enzalutamide
Patients with prior progression on abiraterone or enzalutamide (n=75)

Ph. 2b randomized trial: ZEN-3694+ enzalutamide vs enza
Patients with poor prior response to Abiraterone (n=200)

- **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

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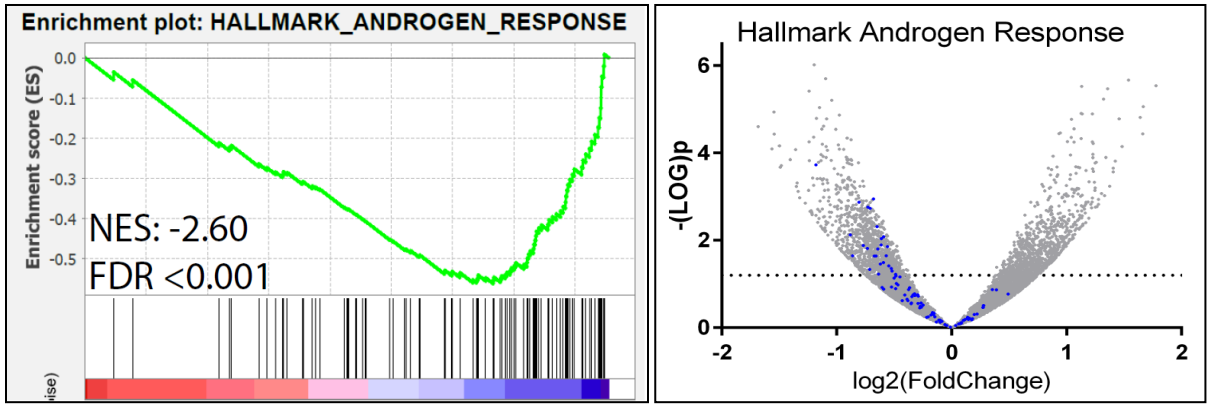
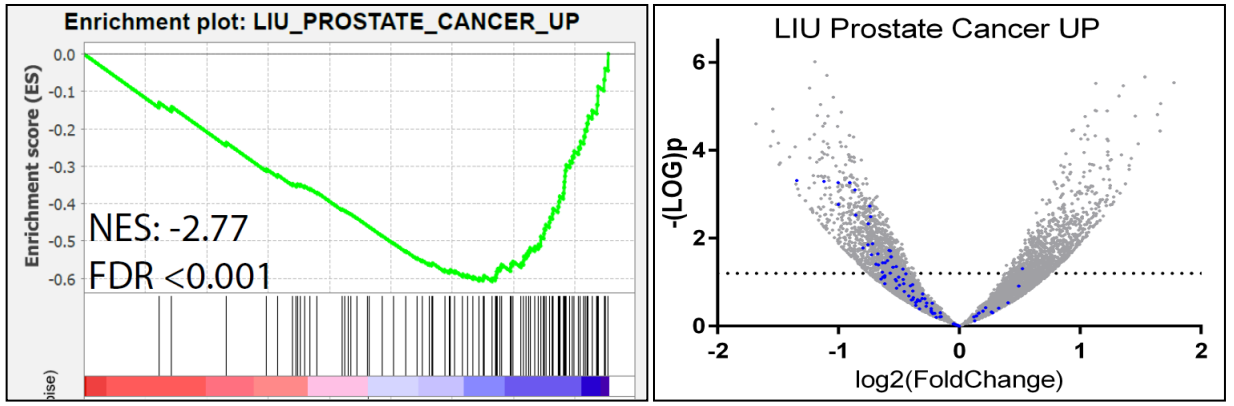
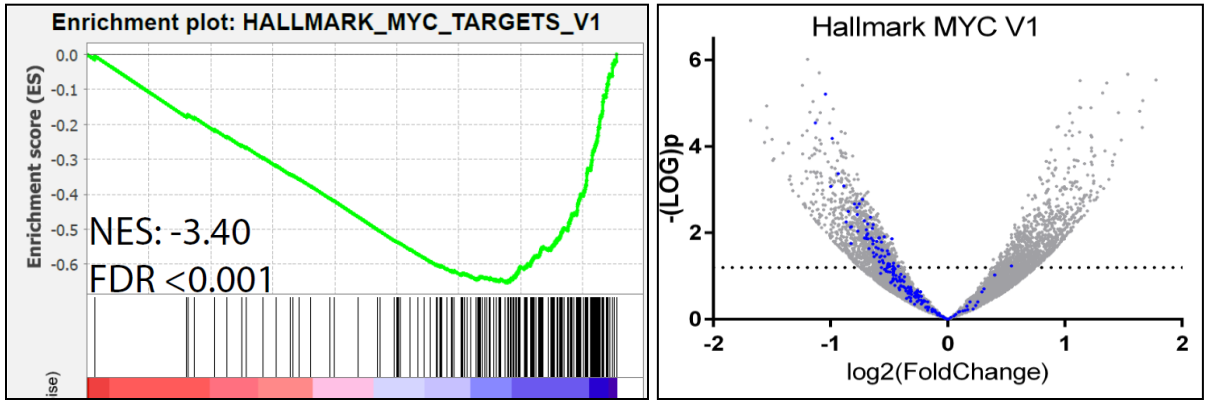
Inhibition of androgen signaling



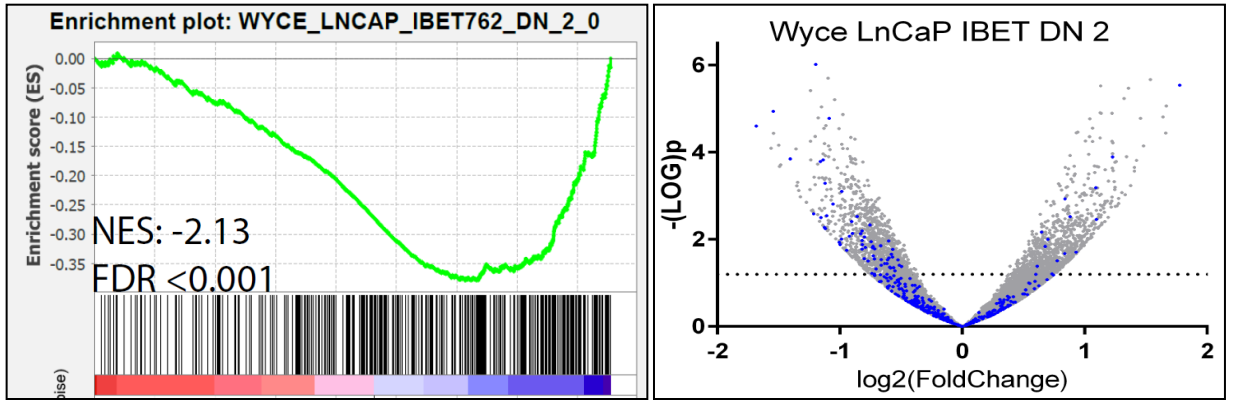
Inhibition of prostate cancer signature



Inhibition of MYC signaling



Inhibition of BET-dependent genes

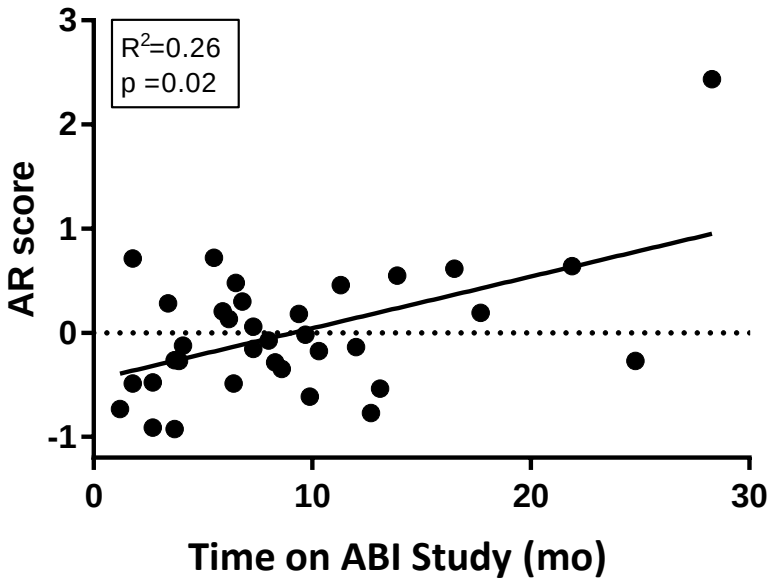


- **3/4 patients already receiving enzalutamide at time of Baseline biopsy**
- **Inhibition of several hallmarks of prostate cancer by ZEN-3694**

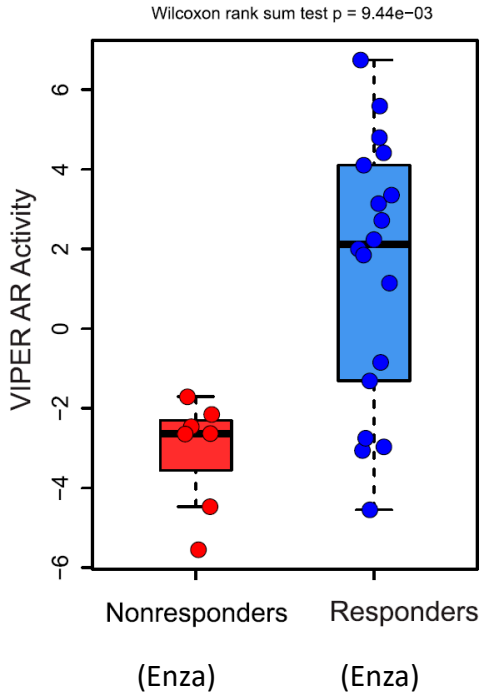
Aggarwal et al. CCR 2020

Evidence of ZEN-3694 + ENZA activity in low AR signaling tumors: Not expected to respond to single agent enzalutamide

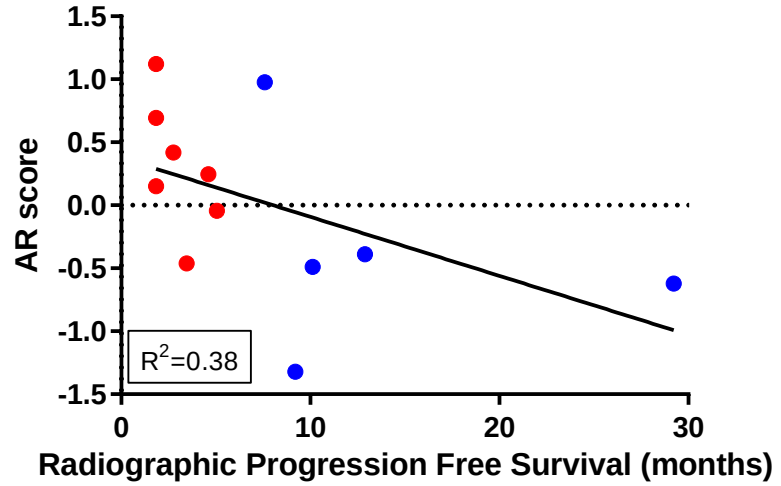
Low AR activity in CRPC tumors associated with shorter time on ABI

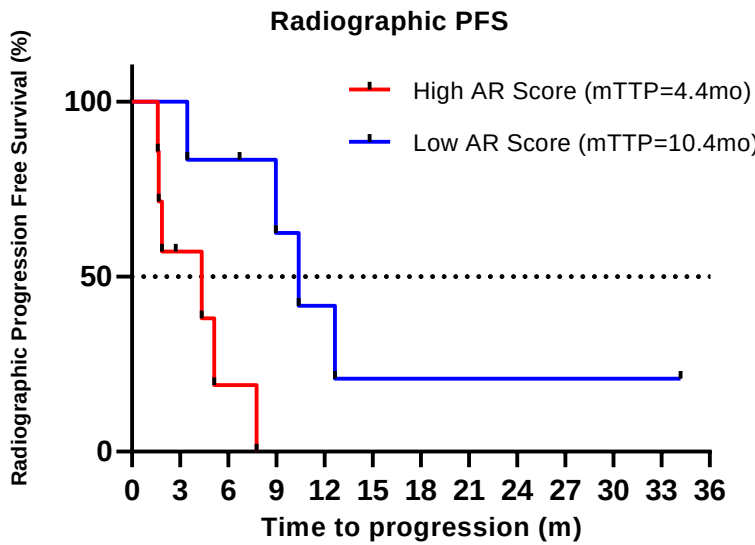


Low AR activity in CRPC tumors associated with shorter time on ENZA



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

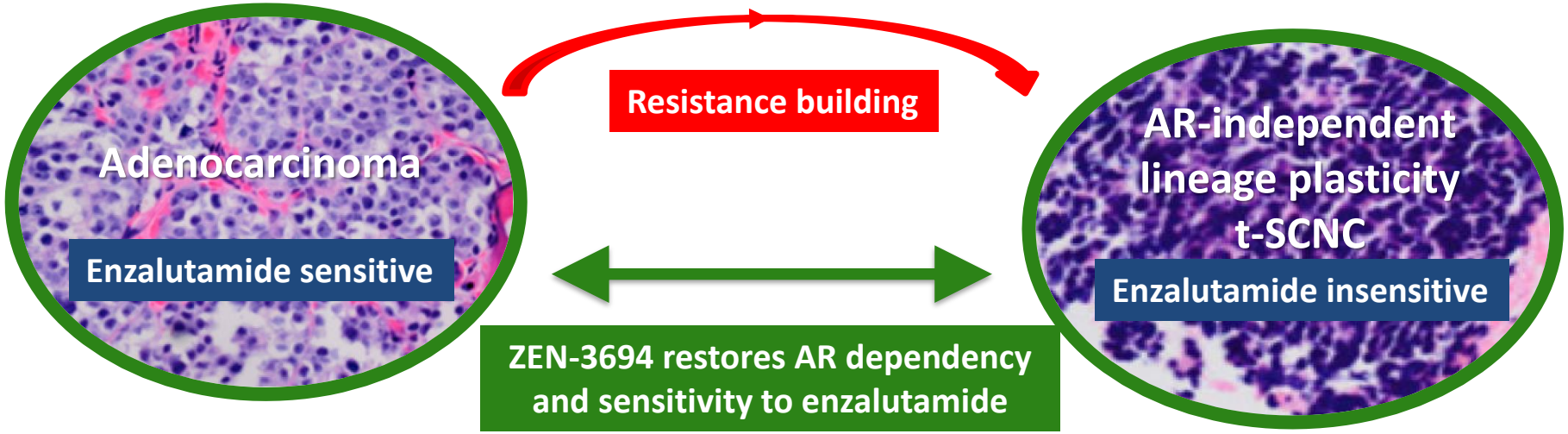




ABI data calculated from Abida et al. 2020, ENZA data from Alumkal et al. 2020

ZEN-3694 Activity in mCRPC Combination Trial

Epigenetic modulation by ZEN-3694 restores sensitivity to enzalutamide



A BRD4-dependent axis drives AR-independence and resistance to enzalutamide (results in press)

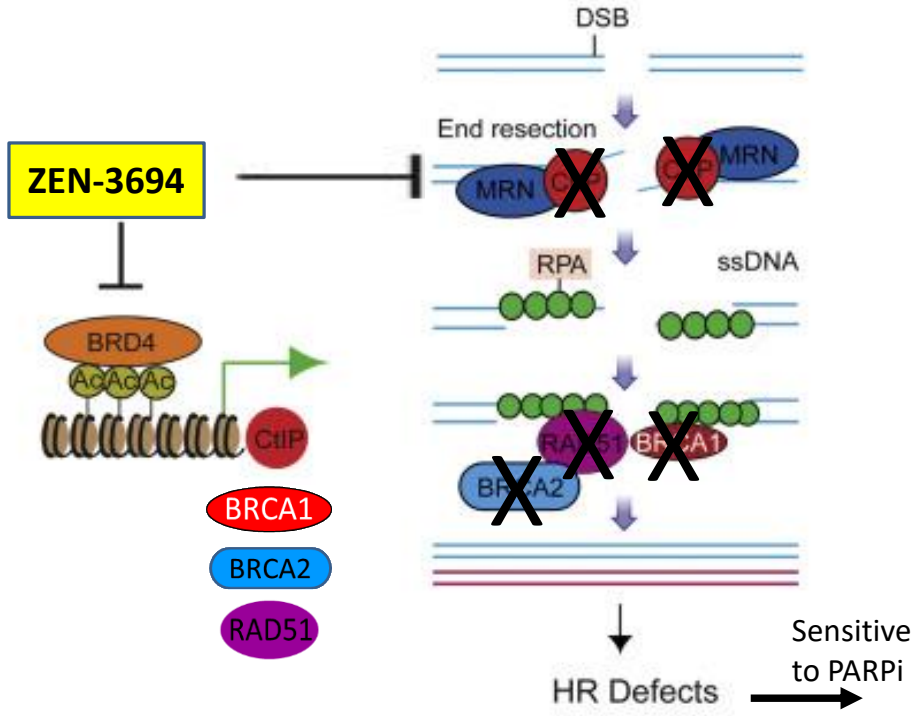
Combining talazoparib with ZEN003694 in people with triple-negative breast cancer without inherited faulty BRCA1/2 genes

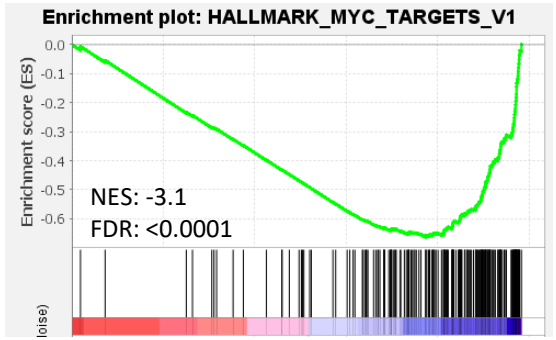
Date of summary: December 2020
Study number: NCT03901469 | **Study start date:** June 2019 | **Estimated study end date:** January 2022

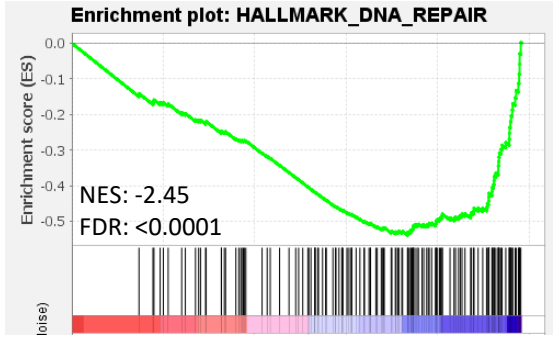
The full title of this abstract is: A phase 1b/2 study of the BET inhibitor ZEN003694 in combination with talazoparib for treatment of patients with TNBC without gBRCA1/2 mutations

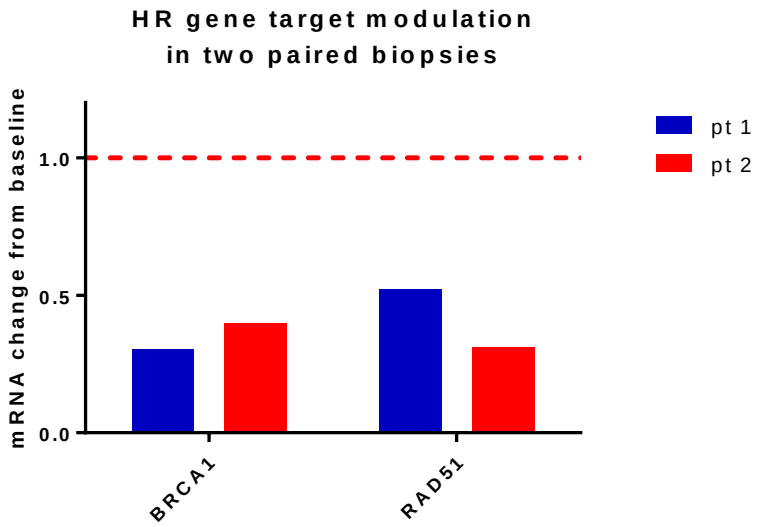
ZEN-3694 + TALA is active in tumors that do not respond to single agent PARPi

- 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



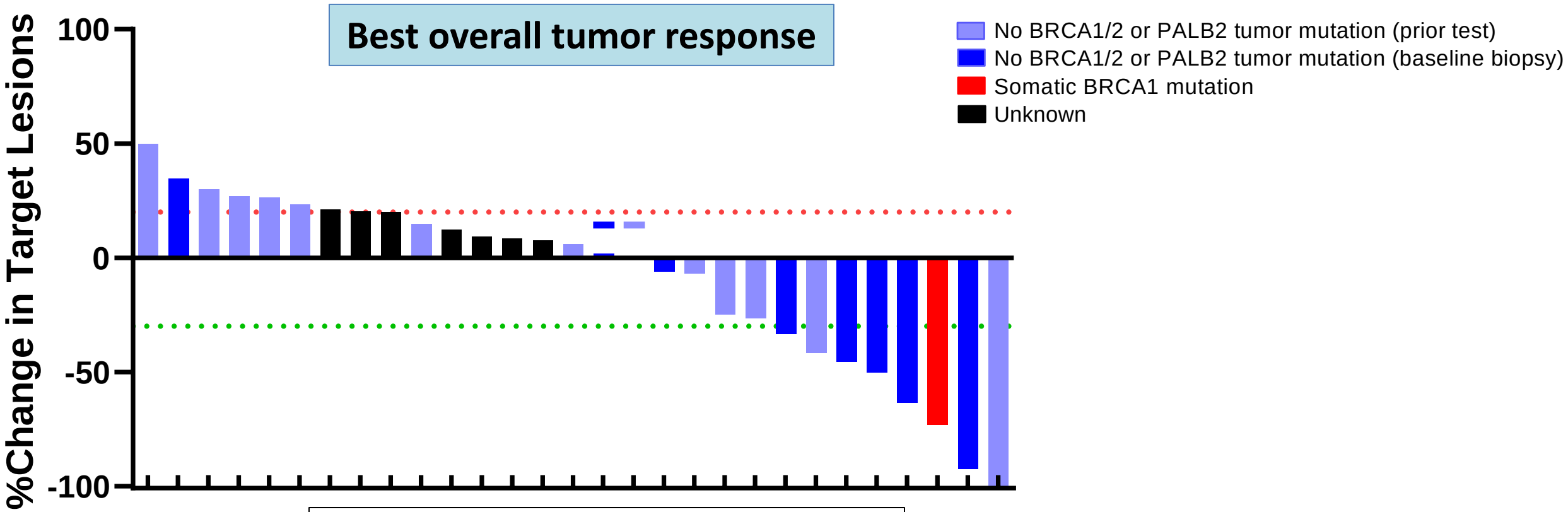






Activity of ZEN-3694 + talazoparib in HRRwt TNBC tumors

Dose escalation + Stage 1 (December 2020)



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**

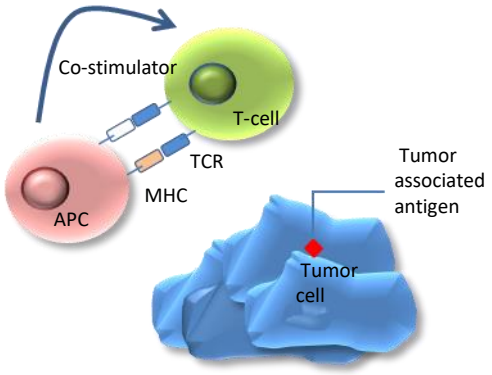
⇒ **Combination activity unlikely due to single agent talazoparib**

HRR= homologous recombination repair

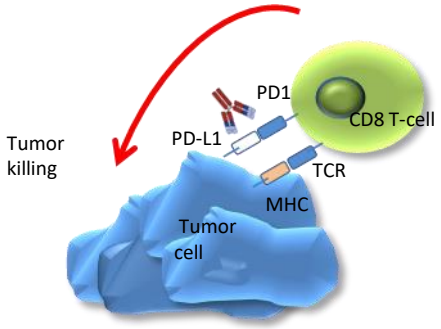
Mechanisms of resistance to Checkpoint therapy

Response

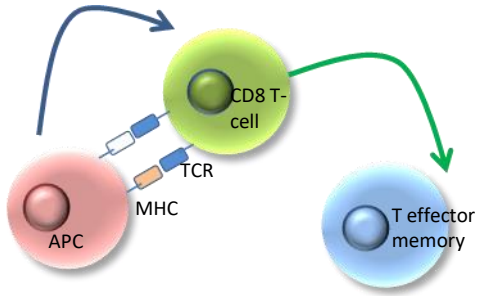
Generation



Response



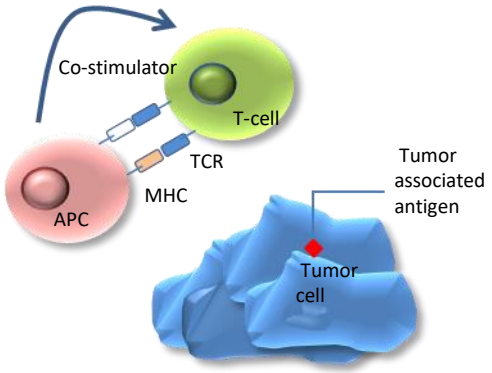
Memory



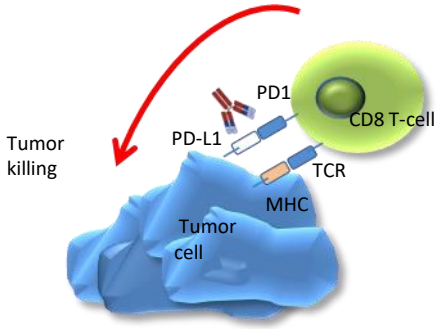
Mechanisms of resistance to Checkpoint therapy

Response

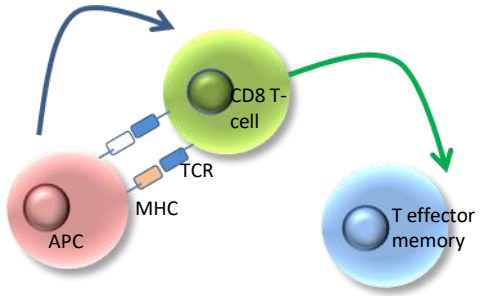
Generation



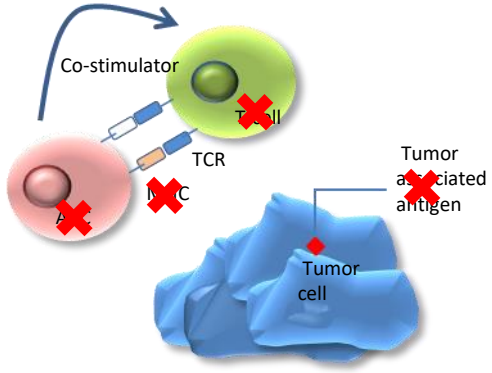
Response

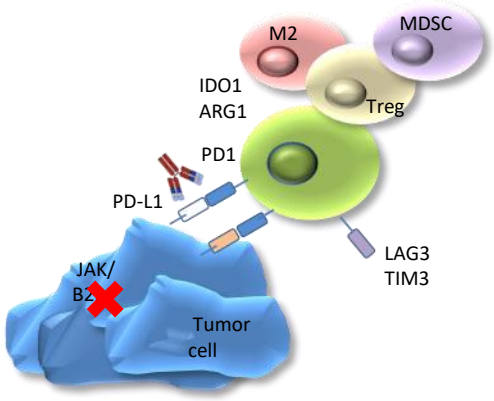


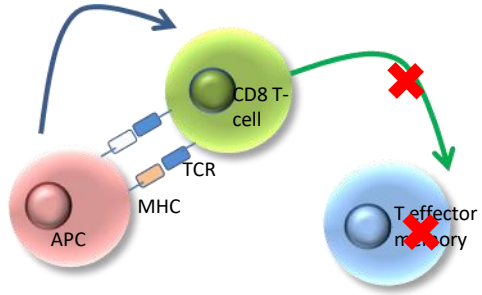
Memory



Resistance







Adapted from Jenkins et al, 2018

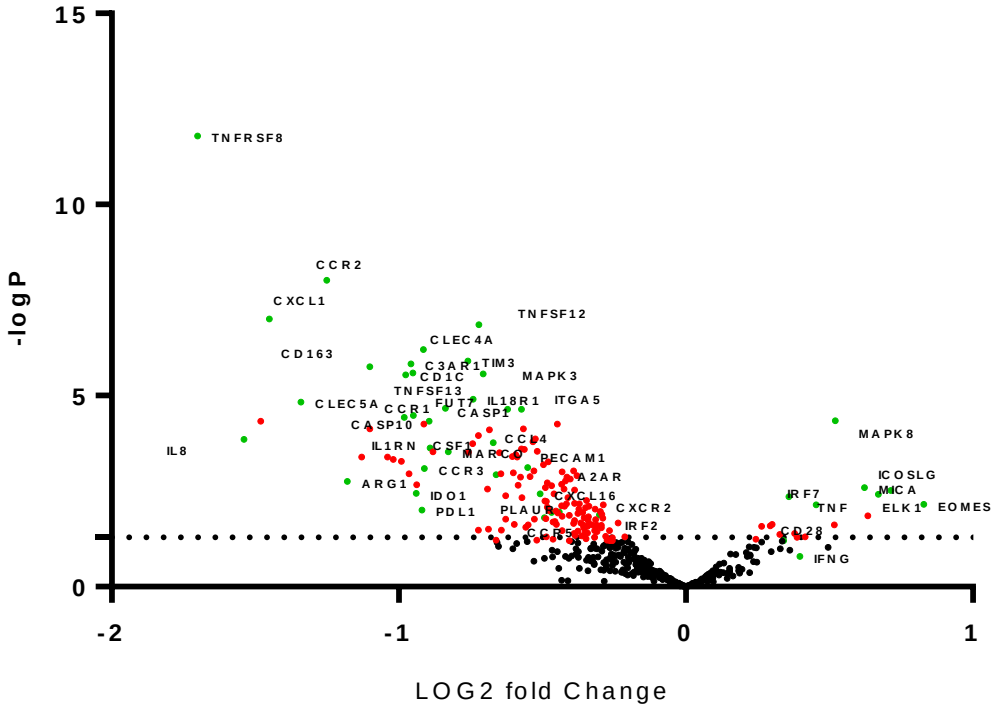
- **Impaired immune infiltration**
- **Lack of neoantigens**
- **Impaired antigen processing/presentation**

- **Immune suppressive cells**
- **Alternate checkpoints**
- **Impaired IFNγ signaling**

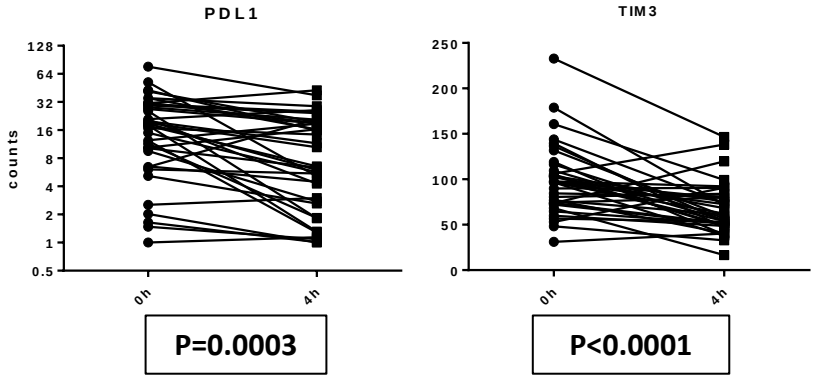
- **T-cell epigenetic changes**
- **T-cell exhaustion**

mCRPC clinical trial: immune modulation in patient blood and tumors

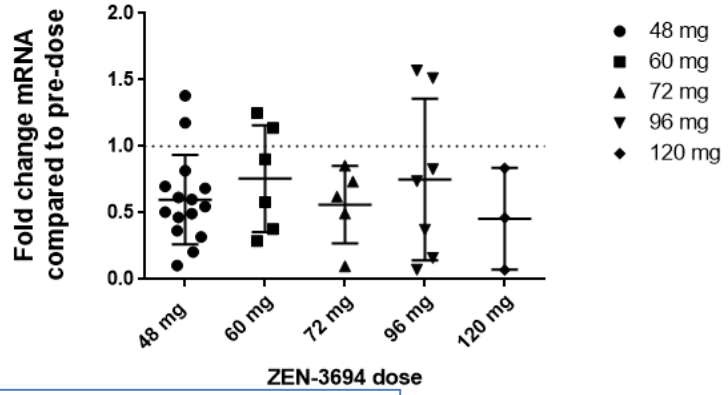
Fold change at 4h in patient blood (analysis of 37 patients)



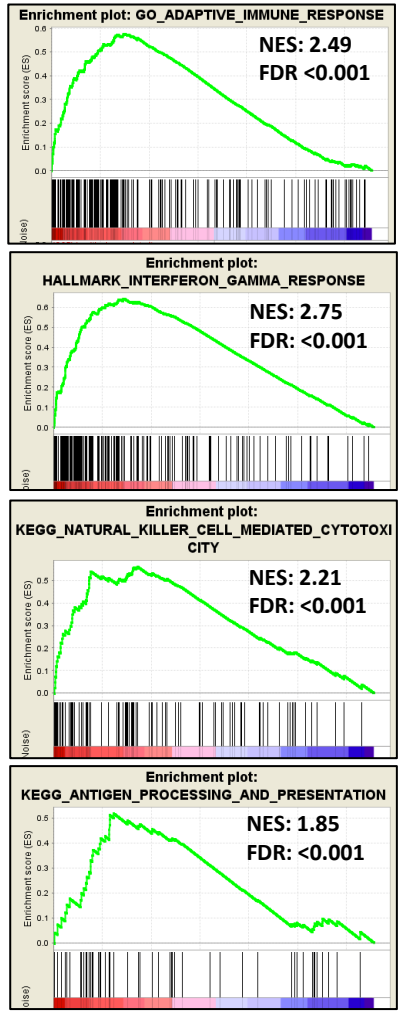
Checkpoint receptors PD-L1 and TIM3 are significantly inhibited



PD-L1 is inhibited at all doses



Evidence of an immune response in patient tumors



- Inhibition of checkpoints and Immune Suppressive 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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- Michael H Silverman
- Margo Snyder
- Philip Wegge