ZENITH EPIGENETICS

Phase 1b/2 Combination Study of the BET Inhibitor ZEN-3694 with the PARP Inhibitor Talazoparib for the Treatment of TNBC Patients without germline BRCA1/2 Mutations

Eric Campeau, TNBC Drug Development Summit, April 29, 2021

Outline

- Induction of synthetic lethality with PARP and BET inhibitors in DNA repair-competent cancer cells
- Design of the ZEN003694-004 clinical trial of ZEN-3694 + talazoparib in non gBRCA1/2m TNBC patients
- Results from Dose Escalation and Stage 1 and evidence of clinical activity in non gBRCA1/2m patients
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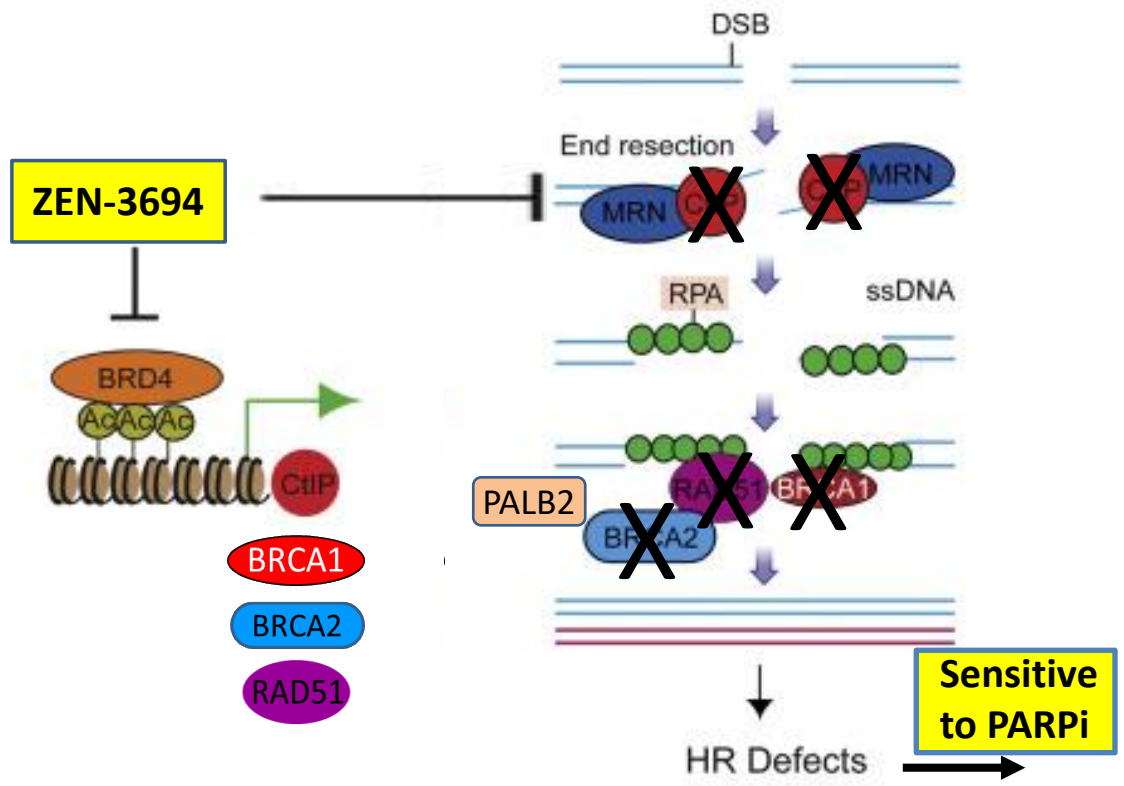
Induction of homologous recombination deficiency by ZEN-3694 and sensitization to PARP inhibitors in BRCAwt cells

- 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

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ZEN-3694 + talazoparib trial design (Phase 2, Pfizer/Zenith collaboration)

Patients with advanced TNBC and no germline BRCA1/2 mutations

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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

Objective: Show safety and activity of ZEN-3694 + talazoparib

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

Patient population: TNBC: **non-germline BRCA1/2 mutations**, 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)

NCT03901469

Patient baseline characteristics (Dose escalation + Stage 1)

December 2020

	Total (n = 32)
Age (median years)	**56 (28 - 74)**
ECOG	
0	**21 (66%)**
1	**11 (34%)**
Time from initial breast cancer diagnosis to ZEN-3694 (median mo.)	**52.0 (5.0 – 342.0)**
Duration of last prior treatment (Tx) regimen in metastatic setting (median weeks)	**14.9 (2.9 – 384.6)**
Primary locations of metastatic disease	
Liver	**12 (38%)**
Lung	**15 (47%)**
Lymph nodes	**16 (50%)**
Number of prior Tx regimens in metastatic setting: median (range)	**2 (0 - 4)**
0	2 (6%)
1	12 (38%)
2	7 (22%)
3	5 (16%)
4	6 (19%)
Prior anthracycline and/or taxane	**30 (94%)**
Prior platinum	**8 (25%)**
Prior checkpoint inhibitor	**8 (25%)**

Dose escalation and selection of the recommended phase 2 dose (RP2D)

		ZEN-3694	
		48 mg (QD)	**36 mg** (QD)
TALAZOPARIB	**1 mg** (QD)	Dose Escalation Cohort 1 2/6 patients with DLT (TCP)	Dose Escalation Cohort 3 0/3 patient with DLT
	0.75 mg (QD)	**Dose Escalation Cohort 2** **1/6 patient with DLT (TCP)** **Dose selected for Simon 2-stage**	

48 mg QD ZEN-3694 + 0.75 mg QD talazoparib selected as RP2D

DLT = dose-limiting toxicity
QD = daily
TCP = thrombocytopenia

Common treatment-related adverse events (AEs)

Grade 3/4 AEs across all cohorts	DE Cohort 1 48 mg ZEN + 1.0 mg Tala (n = 6)		DE Cohort 2 48 mg ZEN + 0.75 mg Tala (n = 6)		DE Cohort 3 36 mg ZEN + 1.0 mg Tala (n = 3)		Simon Stage 1 48 mg ZEN + 0.75 mg Tala (n = 17)		Total n = 32	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
ALT increase^			1				4	2 (G3)	5 (15.6%)	2 (G3)
AST increase^	1		1				3	1 (G3)	5 (15.6%)	1 (G3)
Diarrhea	2	1 (G3)			1		1		4 (12.5%)	1 (G3)
Hyperglycemia	1						1	1 (G3)	2 (6.3%)	1 (G3)
Nausea	3		4	1(G3)			6	1 (G3)	13 (40.6%)	2 (G3)
Neutropenia	1		2	2(G3)			2		5 (15.6%)	2 (G3)
Thrombocytopenia	6	3 (G3), 2 (G4)#	5	3 (G3), 1 (G4)#	1	1 (G3)	5	5 (G3), 1 (G4)	17 (53.1%)	12 (G3), 4 (G4)#

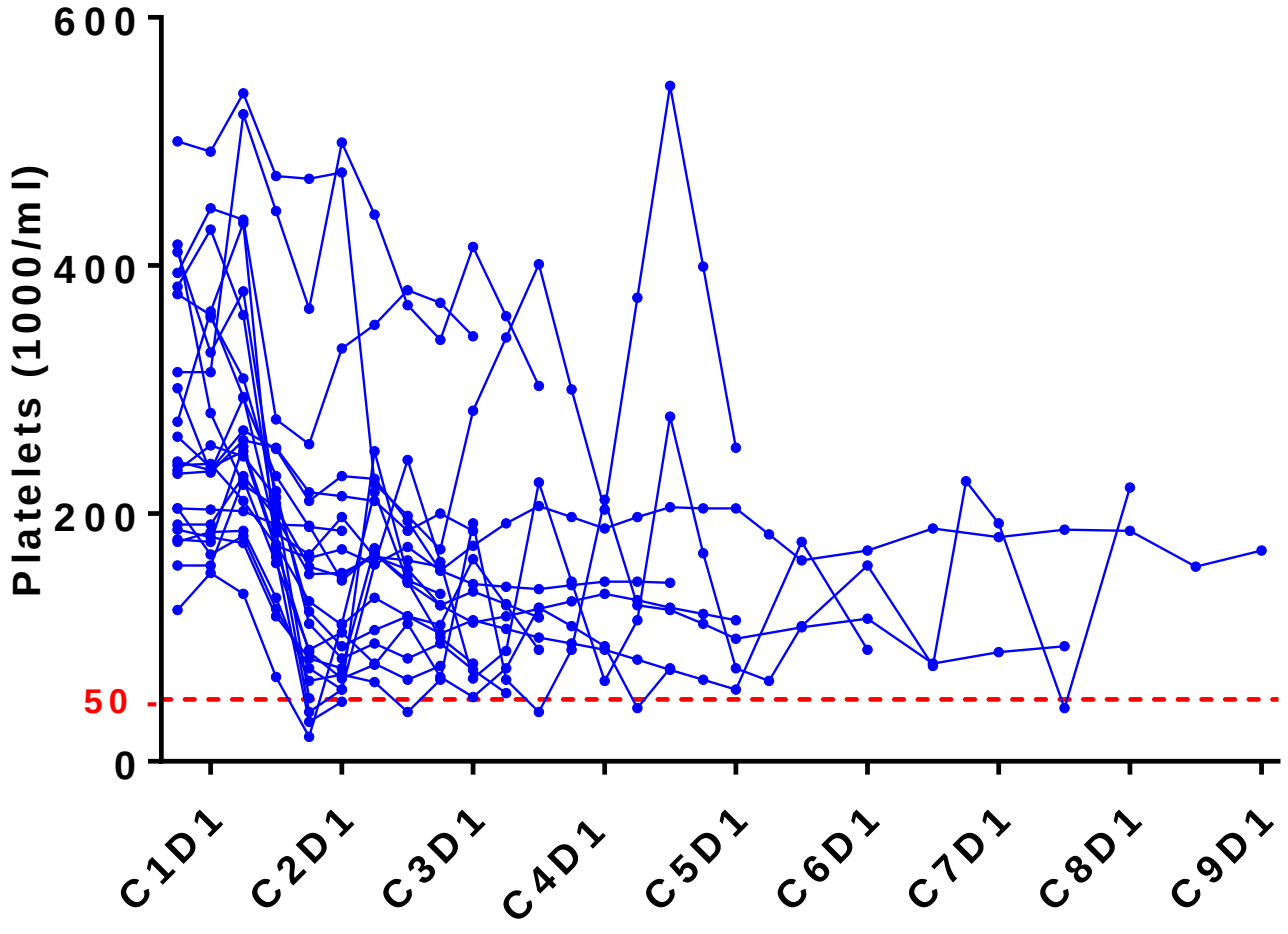
^ALT/AST self resolved

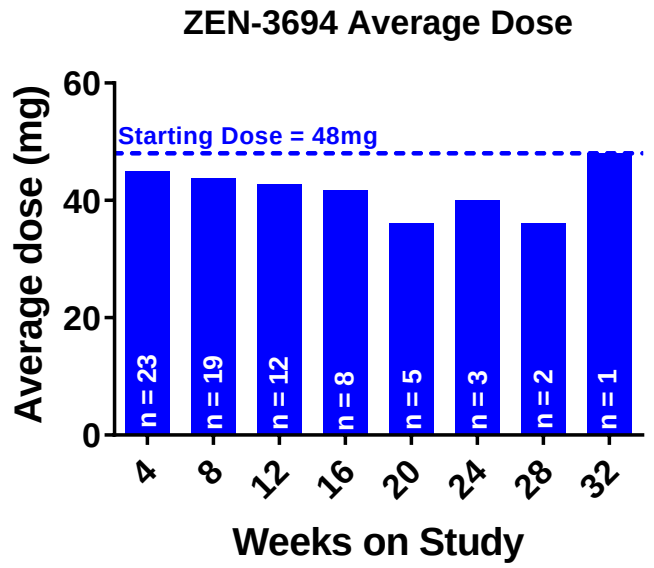
#DLTs (thrombocytopenia) = two patients in Cohort 1, one patient in Cohort 2

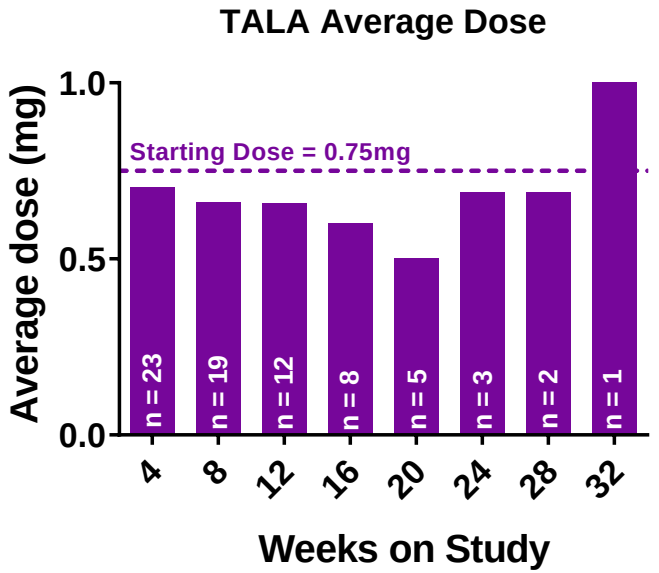
Thrombocytopenia reversible with dose hold and reduction

List of Grade 1/2 AEs presented at SABCS2020 and available at https://www.zenithepigenetics.com/Science-Epigenetics/publications-posters

Manageable thrombocytopenia and maintenance of dose intensity for ZEN-3694 and TALA through first eight cycles







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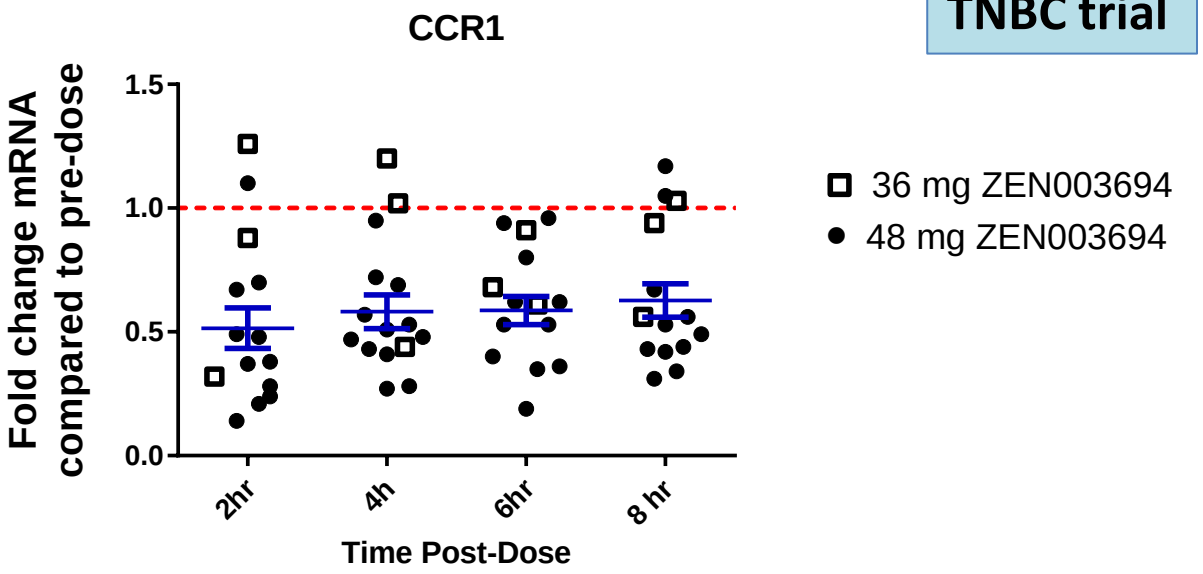
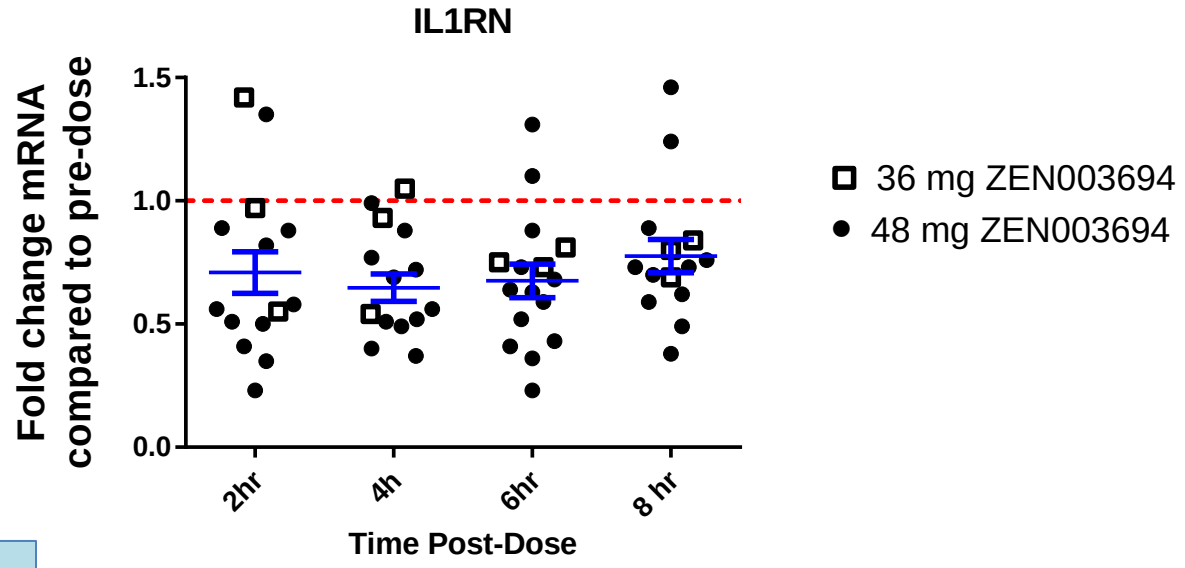
Sustained whole blood target engagement for > 8 hours

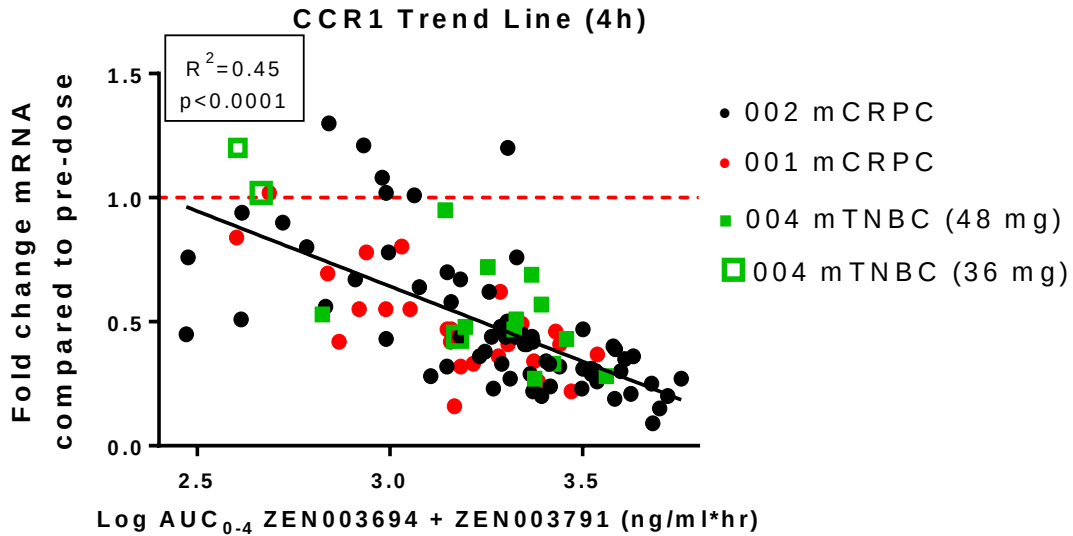
Similar exposure-dependent target engagement as prior trials in prostate cancer

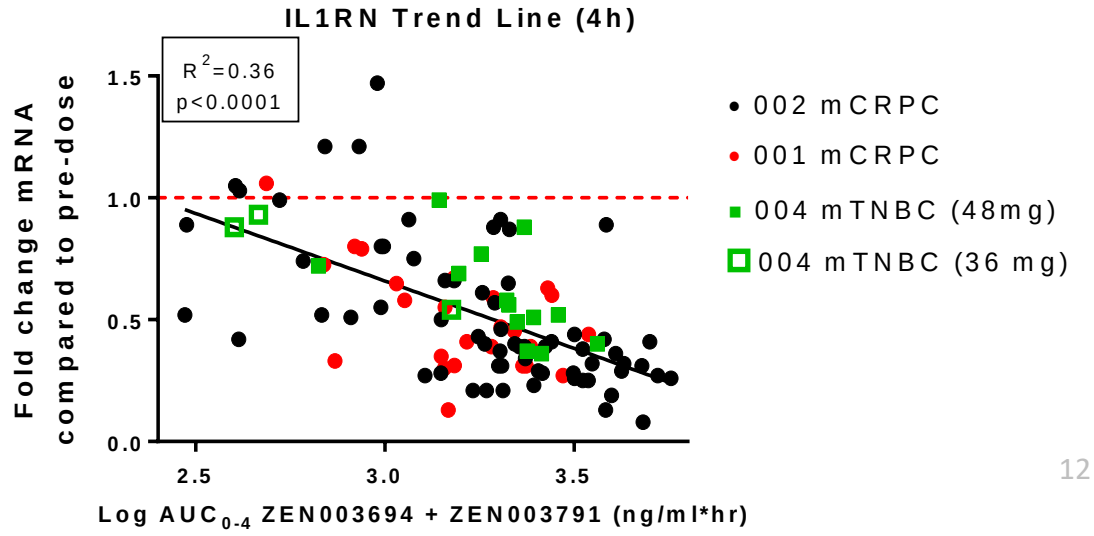
TNBC trial





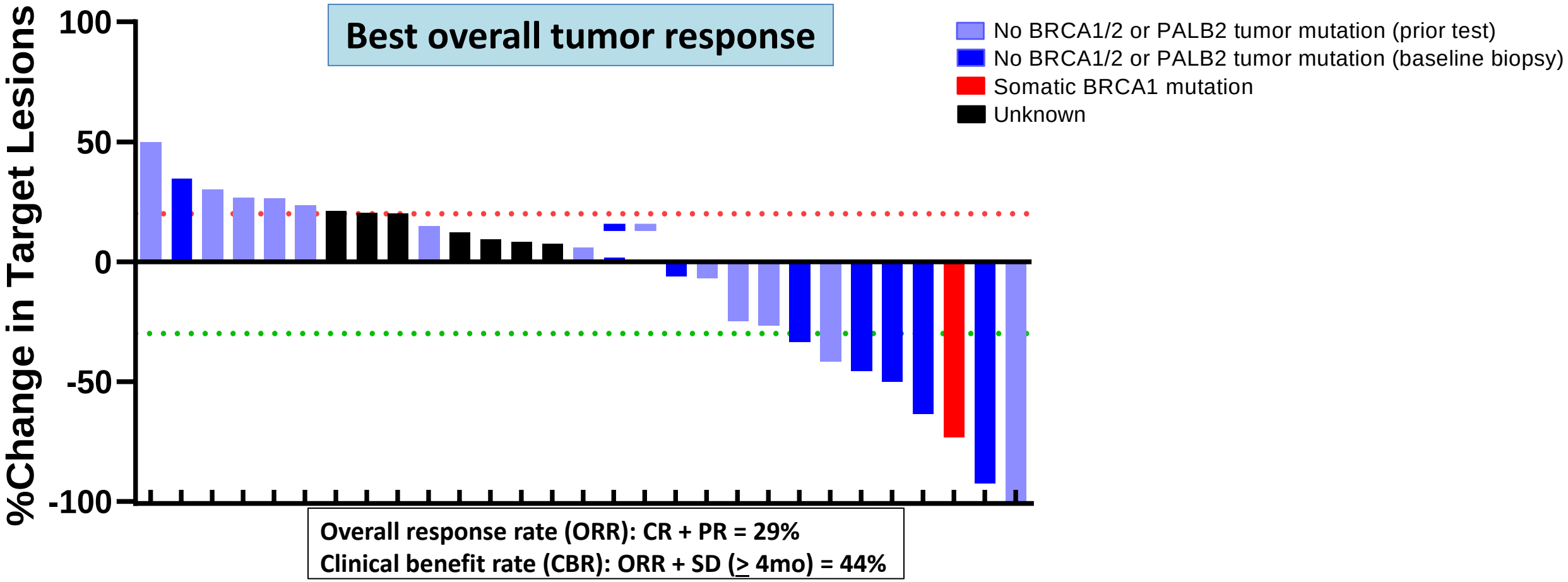
TNBC + CRPC trials





Activity of ZEN-3694 + talazoparib in HRRwt TNBC tumors

Dose escalation + Stage 1 (December 2020)



- **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**

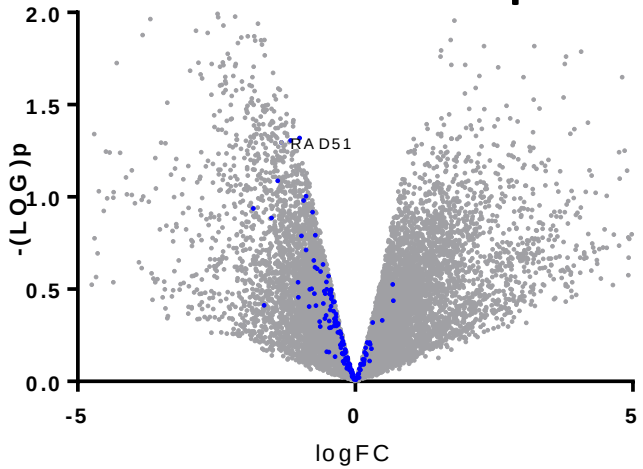
⇒ **Combination activity unlikely due to single agent talazoparib**

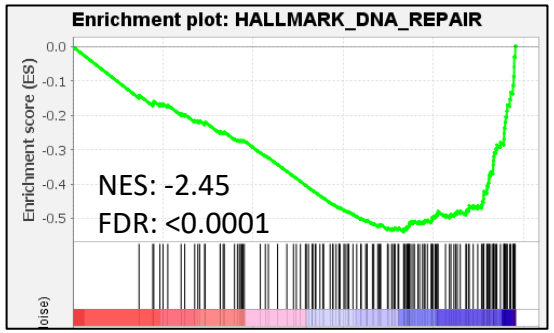
HRR= homologous recombination repair

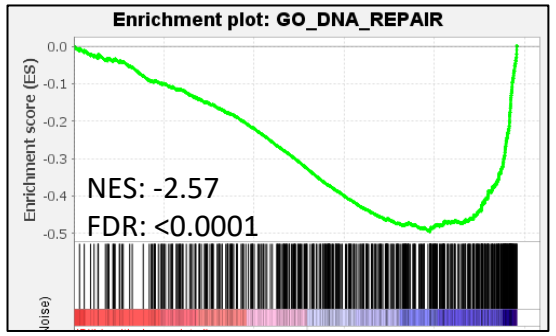
Inhibition of DNA repair and HRR gene expression in tumors from two TNBC patients On-Treatment

Significant inhibition of DNA repair (GSEA) in tumors

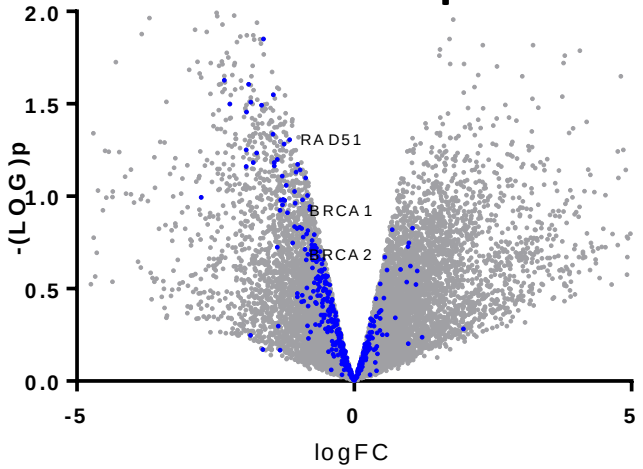
Hallmark DNA repair



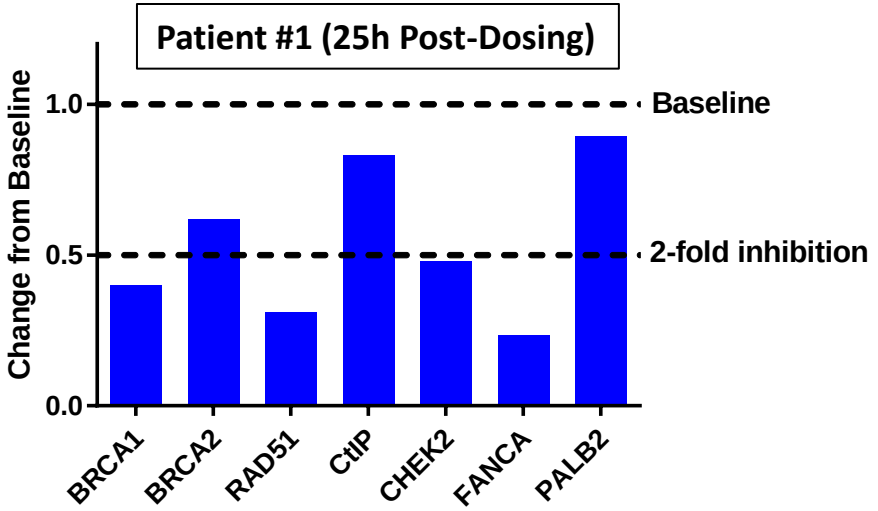


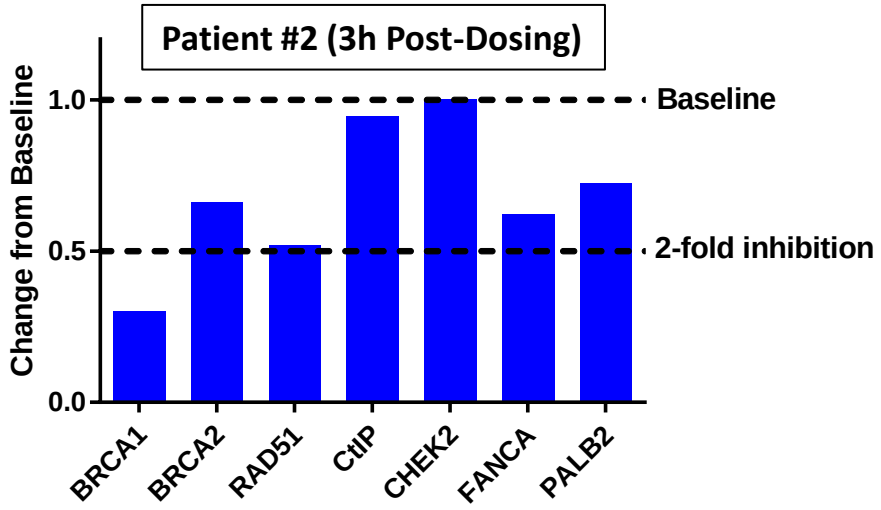


GO DNA repair



Inhibition of HRR gene expression in tumors





HRR= homologous recombination repair

Significant inhibition of oncogenic hallmarks in tumor biopsies On-Treatment (GSEA)

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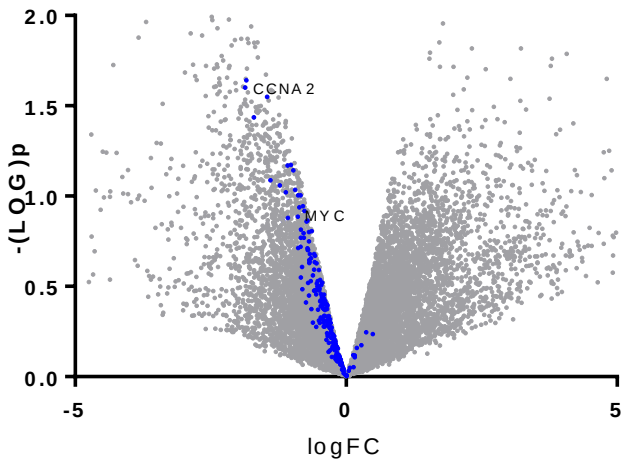
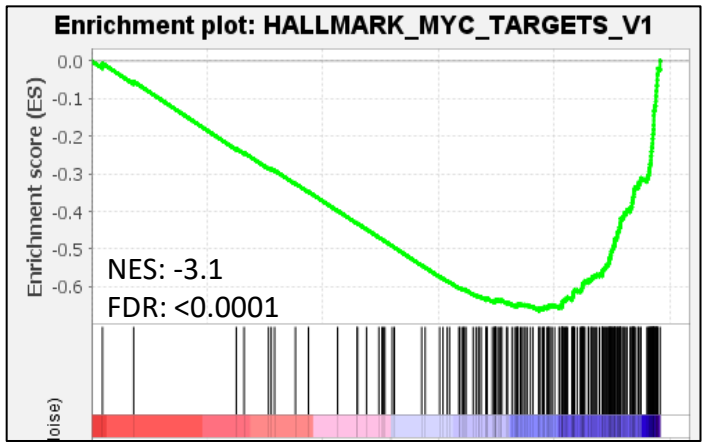
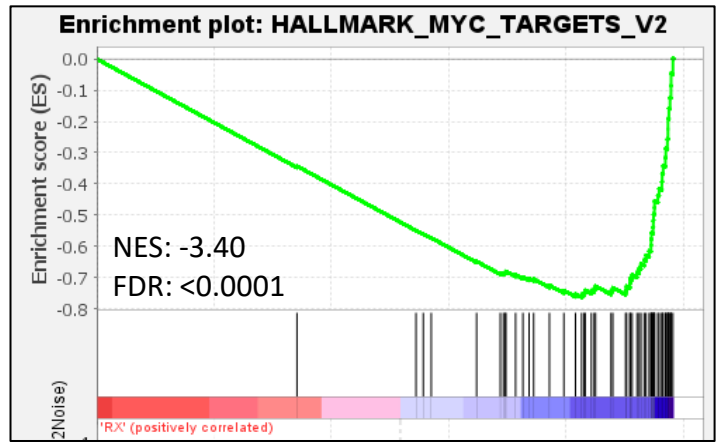
Volcano plot (Hallmark MYC V1)



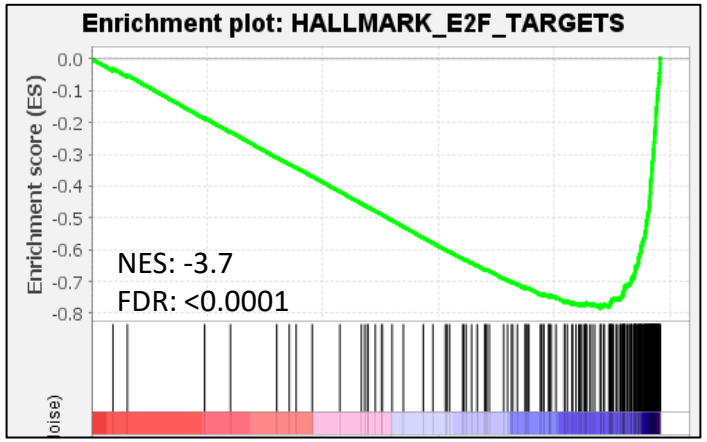
Hallmark MYC V1



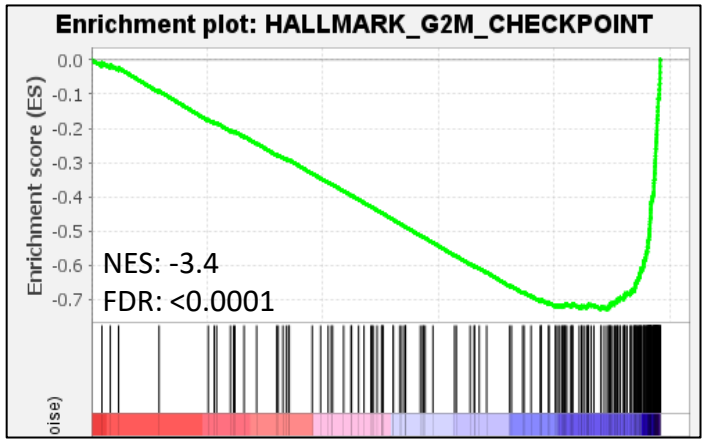
Hallmark MYC V2



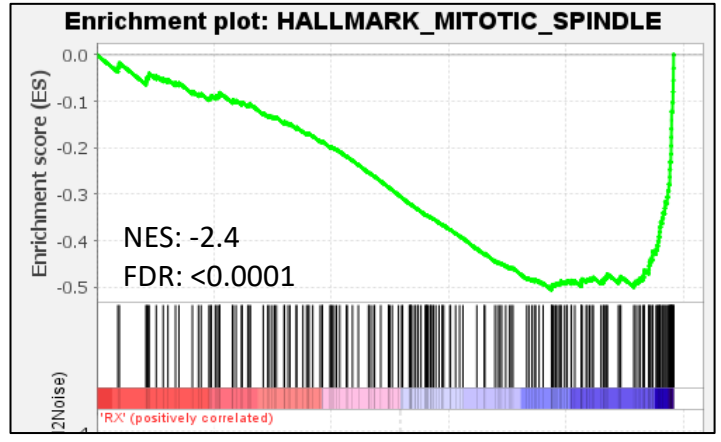
Hallmark E2F targets



Hallmark G2/M checkpoint



Hallmark mitotic spindle



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

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Clinical activity of PARP inhibitors in advanced breast cancer

Limited activity in BRCA1/2 wild-type patients

Pathway	Agent(s)	BRCA1/2 and PALB2 status	
		MUTANT	"WT"
ZEN + TALA vs. single agents	ZEN-3694 + TALA		✓
	BETi		✗
	PARPi	✓	✗
	ATRi	✗	✗
DNA damage response	ATRi + PARPi	✓	✗
	ATRi + carboplatin	(✗)	(✗)
	WEE1	(✗)	(✗)
	WEE1 + PARPi	✓ (toxic)	✗
PI3K/AKT/mTOR	AKTi + PARPi	✓	✗
	AKTi + paclitaxel	✗	✗
	panPI3Ki	✗	✗
	PIK3CAi + PARPi	(✗)	(✗)
	mTORi + PARPi	✗	✗
MAPK	EGFRi + PARPi		(✗)
Immunotherapy	αPD-1 + PARPi	✓	(✗)

✓= 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)

Initial clinical results (advanced breast cancer):

- Limited activity of PARPi outside BRCA1/2m or PALB2m

⇒ ~ 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

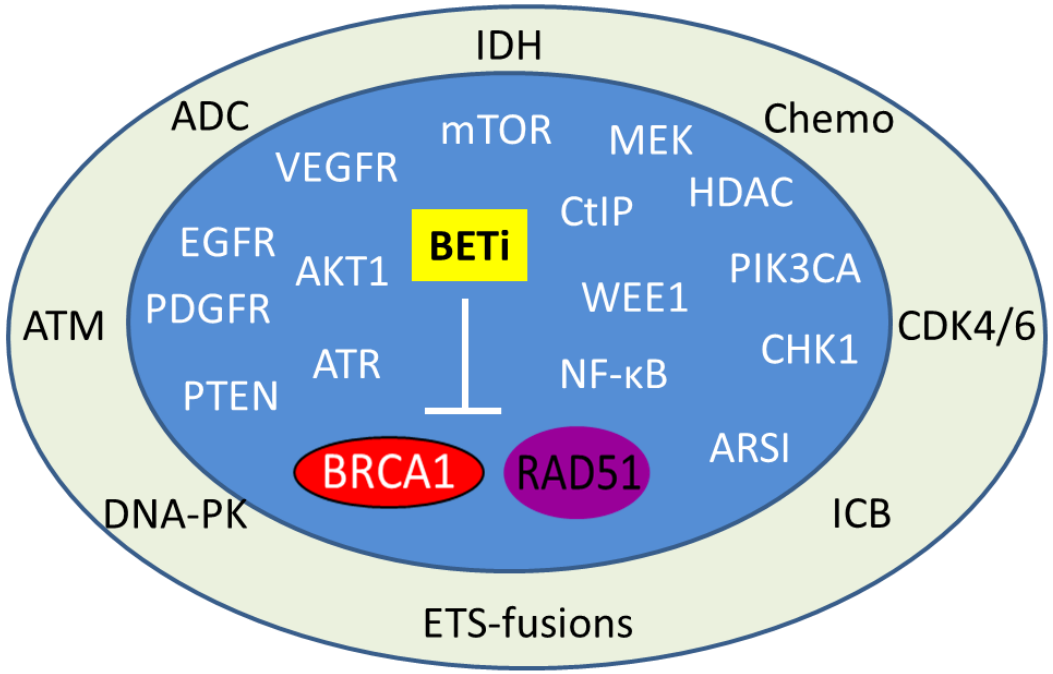
- Most agents currently tested do not sensitize to PARPi

⇒ Limited evidence of creation of "BRCAness" phenotype in the clinic

Tung 2020, Gruber 2019, Patsouris 2020, Stringer-Reasor 2021, Yap 2020, Krebs 2020, Westin 2018, Cousins 2020, Hamilton 2019, Vinayak 2019, Konstantinopoulos 2019, Naqash 2020, Garrido-Castro 2020, Domchek 2020, Domchek 2021

What is the difference from other inhibitors with the same proposed mechanism?

- Inhibition of several pathways have been shown to increase sensitivity to PARPi in preclinical models
- Mitigated success in the clinic at this time



= Inhibition shown to affect RAD51 and/or BRCA1 mRNA or protein levels and increase sensitivity to PARPi

= Inhibition shown to increase sensitivity to PARPi

ADC = Antibody-drug conjugate

ICB = Immune checkpoint blockade (immunotherapy)

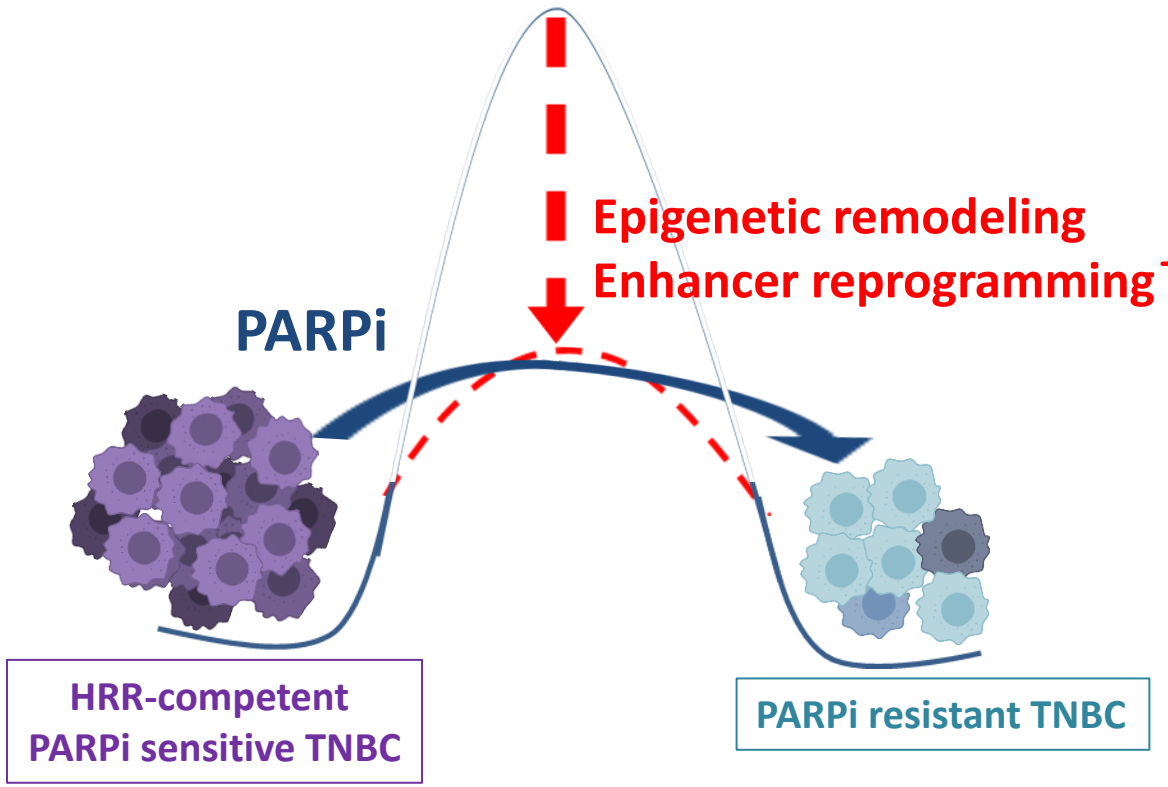
ARSI = Androgen receptor signaling inhibitor (enzalutamide, abiraterone, apalutamide, darolutamide)

Why would ZEN-3694 be different?

Plo 2008, Mendes-Pereira 2009, Weston 2010, Chen 2011, Ibrahim 2012, Juvekar 2012, Nowsheen 2012, Wiegmans 2015, Wang 2016, Li 2017, Yazinski 2017, Vena 2018, Fok 2019, Kaplan 2019, Ha 2020, Li 2020, Smith 2020

BET-dependent mechanism of resistance to PARP inhibitors

Single agent PARPi in BRCA wild-type advanced TNBC

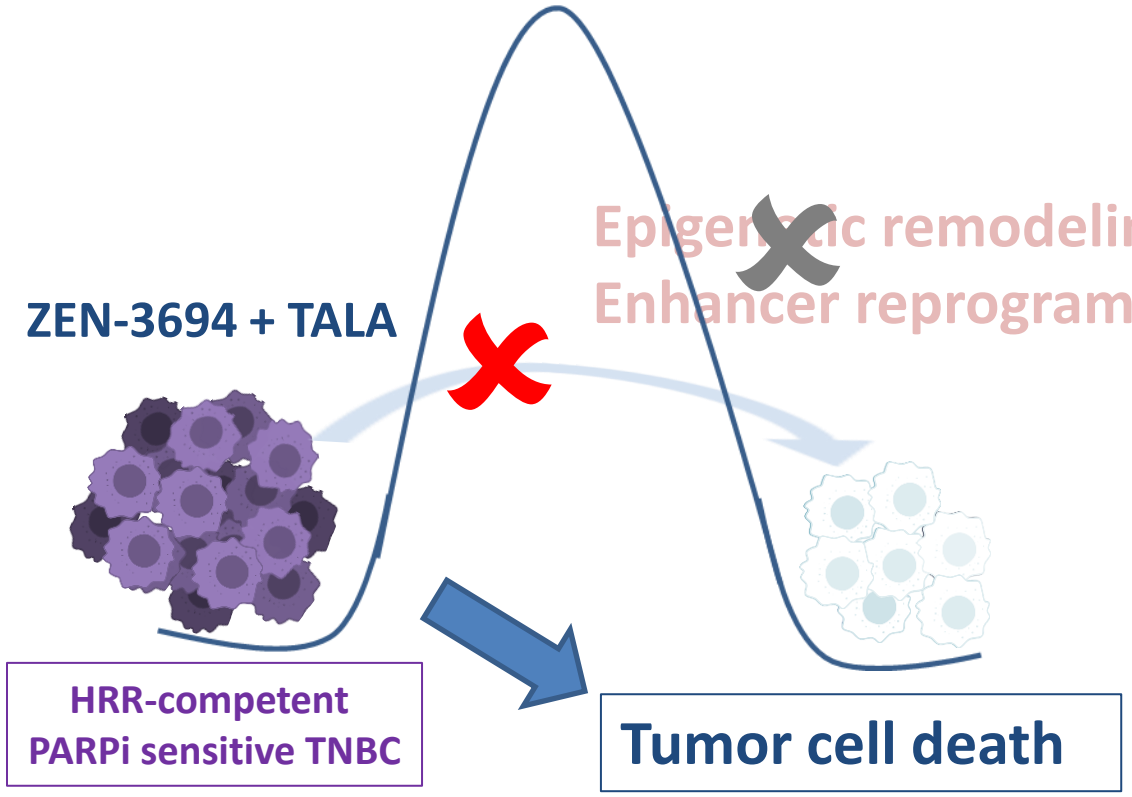


- PARPi induces DNA damage (PARP trapping) and inhibits DNA repair (BER), replication, and transcription
- BET-dependent induction of DNA damage response
- BET-dependent transcriptional reprogramming to maintain genomic integrity
- Induction of alternate DNA repair pathways
- Resistance to PARP inhibitors

BER = base excision repair

BET-dependent mechanism of resistance to PARP inhibitors

Combination of ZEN-3694 + talazoparib in BRCA wild-type advanced TNBC



- ZEN-3694 inhibits adaptation to PARPi
- Loss of genomic integrity
- Tumor cell death

- Combination of PARPi with other agents might be limited by epigenetic plasticity of TNBC tumors
- ZEN-3694 targets epigenetic resistance mechanisms

Summary and conclusions

- 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 target tumor adaptation to PARP inhibitors
- ZEN-3694 + talazoparib Simon Stage 2 is ongoing
- Translational Program to identify factors involved in response to combination regimen ongoing

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