PS11-10: A Phase 1b/2 Study of the BET inhibitor ZEN003694 in combination with talazoparib for treatment of patients with TNBC without gBRCA1/2 mutations

Plain language summary
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Background

- **Locally advanced/metastatic triple-negative breast cancer (TNBC) is an aggressive and heterogeneous cancer with limited therapeutic options.**
- **Poly (ADP-ribose) polymerase inhibitors (PARPi) are approved to treat metastatic breast cancer harboring germline BRCA1/2 (gBRCA1/2) mutations and have not shown efficacy in homologous recombination DNA repair (HRR) proficient tumors.**
- **In pre-clinical models, the BET inhibitor (BETi) ZEN003694 (ZEN-3694) sensitizes wild-type BRCA1/2 tumors to PARPi through downregulation of HRR gene expression, providing a rationale for combination therapy.**
- **We report initial results from a Ph 1b/2 trial evaluating the combination of ZEN-3694 and the PARPi, talazoparib (TALA), in patients with TNBC without gBRCA1/2 mutations (NCT03901469). The data cut-off date is October 6, 2020.**

Study Design and Patient Population

Objective	Show safety and activity of ZEN-3694 + TALA in patients with TNBC
Patient Population	Locally advanced/metastatic TNBC, without gBRCA1/2 mutations
Study Design	Phase 1b: Dose escalation (3 + 3 design) Phase 2: Simon 2 stage (17 patients in Stage 1, 20 patients in Stage 2) CBR = CR+PR+SD (≥ 4 mo) Ho = 20%, Ha = 40%
Dose	Dose Escalation: TALA: 0.75-1.0 mg daily ZEN-3694: 36-48 mg daily Simon 2-Stage: TALA: 0.75 mg daily ZEN-3694: 48 mg daily
Endpoints	Phase 1b: Safety, PK/PD, DLT, MTD, RP2D Phase 2: CBR, ORR, DOR, PFS • Tumor assessment every 2 cycles (1 cycle = 28 days)
Major Inclusion Criteria	• Locally advanced/metastatic TNBC • No germline pathogenic mutations in BRCA1/2 Dose Escalation: • At least 1 prior cytotoxic chemotherapy Simon 2-Stage: • No more than 2 prior chemotherapy regimens for locally advanced or metastatic disease
Major Exclusion Criteria	• Disease progression during platinum treatment (neoadjuvant or metastatic setting) • Prior exposure to PARPi or BETi
Translational Medicine Endpoints	• ZEN-3694 target engagement in whole blood and tumor biopsies • Evaluate somatic mutations in HR genes, and HRD markers • Identify predictors of response

ABBREVIATIONS: AE= Adverse Event, CBR=Clinical Benefit Rate, CR=Complete Response, DLT=Dose Limiting Toxicity, DOR=Duration of Response, Ha=Alternative Hypothesis, Ho=Null Hypothesis, HR=Homologous Recombination, HRD=Homologous Recombination Deficiency, MTD=Maximum Tolerated Dose, ORR=Overall Response Rate, PD=Pharmacodynamic, PFS=Progression-free Survival, PK=Pharmacodynamic, PR=Partial Response, RP2D=Recommended Phase 2 Dose, SD=Stable Disease, TCP=Thrombocytopenia

Patient Baseline Characteristics

	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)**
TNBC at diagnosis [n = 18 (56%)]	30.5 (5.0 – 130.0)
HR+ →TNBC [n = 14 (44%)]	95.5 (16.0 – 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 Tx with a checkpoint inhibitor	**8 (25%)**

Dose Escalation Results and Selection of RP2D

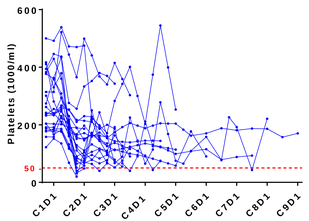
	ZEN-3694 48 mg QD	ZEN-3694 36 mg QD
TALA 1 mg QD	Dose Escalation Cohort 1 2/6 patients with DLT (TCP)	Dose Escalation Cohort 3 0/3 patient with DLT
TALA 0.75 mg QD	**Dose Escalation Cohort 2** **1/6 patient with DLT (TCP)** **Dose selected for Simon 2-stage**	

Common Treatment-related Adverse Events (AEs)

AEs in > 1 patient across all cohorts)	DE Cohort 1 48mg ZEN + 1.0mg Tala (n = 6)		DE Cohort 2 48mg ZEN + 0.75mg Tala (n = 6)		DE Cohort 3 36mg ZEN + 1.0mg Tala (n = 3)		Simon Stage 1 48mg ZEN + 0.75mg 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
Abdominal Pain	2								2 (6.3%)	
Alopecia	2		1				1		4 (12.5%)	
Anemia	1		1		2		1		5 (15.6%)	
Anorexia	3		2		1		1		7 (21.9%)	
ALT increase[A]			1				4	2 (G3)	5 (15.6%)	2 (G3)
AST increase[A]	1		1				3	1 (G3)	5 (15.6%)	1 (G3)
Constipation	1		3				1		5 (15.6%)	
Creatinine increase	2								2 (6.3%)	
Dehydration	1						1		2 (6.3%)	
Diarrhea	2	1 (G3)			1		1		4 (12.5%)	1 (G3)
Dry Mouth	2								2 (6.3%)	
Dysgeusia	2		1		1		2		6 (18.8%)	
Fatigue	4		3		1				8 (25.0%)	
Hyperglycemia	1						1	1 (G3)	2 (6.3%)	1 (G3)
Hyponatremia	2						1		3 (9.4%)	
Lymphopenia	1				1				2 (6.3%)	
Mucositis, oral			1				1		2 (6.3%)	
Nausea	3		4	1(G3)			6	1 (G3)	13 (40.6%)	2 (G3)
Neutropenia	1		2	2(G3)			2		5 (15.6%)	2 (G3)
Rash	2						2		4 (12.5%)	
Thrombocytopenia	6	3 (G3), 2 (G4)	5	3 (G3), 1 (G4)	1	1 (G3)	5	4 (G3), 1 (G4)	17 (53.1%)	12 (G3), 4 (G4)[B]
Vomiting	2		1				2		5 (15.6%)	
Visual Symptoms	3		2		2		9		17 (53.1%)	
Weight loss	2		1		1				4 (12.5%)	

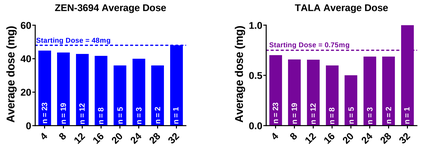
[A]ALT/AST self resolved
[B]DLTs = Four patients with Grade 4 TCP, one patient in Cohort 1 required platelet transfusion. One patient with Grade 4 TCP in Stage 1 required transfusion but was not a DLT

Manageable Thrombocytopenia (TCP)



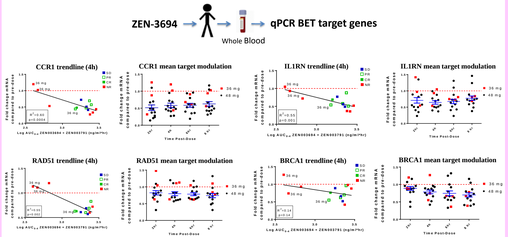
Platelet counts could be maintained above 50,000/ml (red line) with appropriate dose holds and modifications (see next panel). C1D1 = Cycle 1 Day 1.

Dose Intensity for ZEN-3694 and TALA Through First Eight Cycles



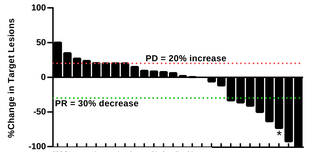
High dose intensities of ZEN-3694 and TALA were maintained through the first 8 cycles (32 weeks). Data shows only patients that started at 48 mg ZEN-3694 and 0.75 mg TALA. Number of patients at each cycle is also shown.

Target Engagement in Whole Blood vs. Clinical Response



Whole blood qPCR demonstrates exposure-dependent decrease in CCR1, IL1RN, and RAD51 mRNAs (trendline graphs). Clinical responses of each patient is also shown: CR= complete response, NR= non responder, PR = partial response, SD = stable disease. Mean target modulation of each pharmacodynamic marker show sustained inhibition up to 8 hours Post-Dosing. Reduction of BRCA1 and RAD51 mRNAs by ZEN-3694 demonstrates its capacity to inhibit the expression of HR genes and sensitize tumors to PARP inhibitors.

Evidence of Anti-Tumor Activity of ZEN-3694 + TALA in TNBC Patients without gBRCA1/2m

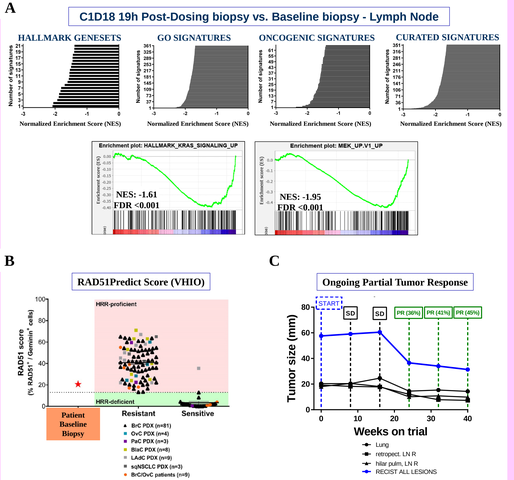


*BRCA1 somatic mutation detected in Baseline biopsy

Overall response rate (ORR): CR + PR = 29% (8/28 patients, 5 confirmed, 2 pending)
Clinical benefit rate (CBR): ORR + SD (≥ 4mo) = 44% (11/25 patients, 8 confirmed, 2 pending)

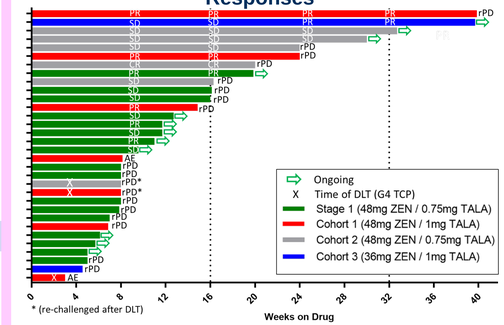
Best overall tumor responses in patients with TNBC. Data cut-off: October 6, 2020. CR=Complete Response, PD=Progressive Disease, PR=Partial Response, SD=Stable Disease

Sustained Target Engagement in a Paired Biopsy From a Patient with Ongoing Partial Response



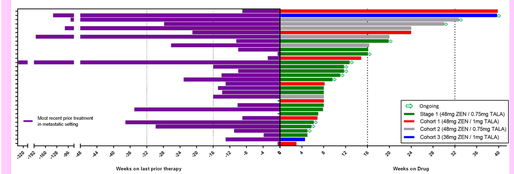
A) RNA-Seq geneset enrichment analysis (GSEA) of a paired biopsy from a patient with an ongoing partial response > 40 weeks in the ZEN-3694 36 mg + TALA 1 mg cohort. On-Treatment biopsy was taken 18 days after the start of dosing (C1D18), 19 hours after the last dose of ZEN-3694 + TALA from the same site as the Baseline biopsy. TOP: overview of gene signatures significantly inhibited On-Treatment vs. Baseline (FDR <0.05). BOTTOM: Significant down-regulation of KRAS and MEK signaling gene signatures On-Treatment. B) RAD51Predict tumor score of Baseline biopsy predicts HRR-proficiency and resistance to single agent PARP inhibitors. Furthermore, no mutations were found in the >30 HR genes surveyed, and no mutational signature #3 associated with HR deficiency was detected (results not shown). C) The patient had a stable disease (SD) for 2 cycles, followed by a partial response (PR) for the subsequent six cycles and is ongoing for > 40 weeks.

TNBC Study Weeks on Treatment: Durable Responses



Time on study of patients with TNBC enrolled in the different cohorts. AE = adverse event, CR = complete response, DLT = dose limiting toxicity, PR = partial response, rPD = radiographic progressive disease, SD= stable disease

Weeks on Previous and Current Therapy



Duration of prior therapy vs. ZEN-3694 + TALA treatment. Some patients with poor response to prior therapy achieved a response to ZEN-3694 + TALA. Previous most recent therapy shown was given in the metastatic setting.

Conclusions

- **Combination of ZEN-3694 + TALA demonstrated 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.**
- **The Phase 2 portion of the trial is ongoing.**