A Phase 1b/2 study of the BET inhibitor ZEN-3694 in combination with talazoparib for treatment of patients with TNBC without gBRCA1/2 mutations

Philippe Aftimos[1], Mafalda Oliveira[2], Kevin Punie[3], Valentina Boni[4], Erika Hamilton[5], Ayca Gucalp[6], Payal Shah[7], Lida Mina[8], Maria de Miguel[4], Priyanka Sharma[9], Lisa Bauman[10], Eric Campeau[11], Sarah Attwell[11], Margo Snyder[10], Karen Norek[11], Emily Johnson[11], Akos Czibere[12], Yanke Yu[13], Michael H Silverman[10], Sanjay Lakhotia[10], Susan Domchek[7], Jennifer Litton[14] and Mark Robson[6].

[1]Institut Jules Bordet - Université Libre de Bruxelles, Brussels, Belgium; [2]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [3]UZ Leuven, Leuven, Belgium; [4]START, Madrid, Spain; [5]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [6]Memorial Sloan Kettering Cancer Center, New York City, NY; [7]Abramson Cancer Center University of Pennsylvania, Philadelphia, PA; [8]Banner MD Anderson Cancer Center, Gilbert, AZ; [9]University of Kansas Medical Center, Westwood, KS; [10]Zenith Epigenetics, San Francisco, CA; [11]Zenith Epigenetics, Calgary, AB, Canada; [12]Pfizer, Cambridge, MA; [13]Pfizer, La Jolla, CA; [14]The University of Texas MD Anderson Cancer Center, Houston, TX

Background and Trial Design

- Metastatic triple negative breast cancer (mTNBC) is an aggressive and heterogeneous cancer.
- PARP inhibitors (PARPi), approved to treat patients with HER2- breast cancer with a germline BRCA1/2 (gBRCA1/2) mutation, have not shown efficacy in homologous recombination repair (HRR) proficient tumors.
- In pre-clinical models, the BET inhibitor (BETi) ZEN-3694 sensitizes wild-type (WT) BRCA1/2 tumors to PARPi through downregulation of HRR gene expression, providing a rationale for combination therapy.
- We previously reported results from the Phase 1b portion of the trial evaluating the combination of ZEN-3694 plus talazoparib, in TNBC patients without gBRCA1/2 mutations; here we present results from the completed Phase 1b/2 study (NCT03901469).

Objective	Demonstrate safety and activity of ZEN-3694 + Talazoparib in patients with TNBC
Patient Population	Locally advanced, metastatic TNBC, without germline BRCA1/2 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) - *confirmed* Ho = 20%, Ha=40%, Power=90%, Type I error rate=0.1
Dose	Dose Escalation: Talazoparib: 0.75-1.0 mg PO daily ZEN-3694: 36-48 mg PO daily Simon 2-Stage: Talazoparib: 0.75 mg PO daily ZEN-3694: 48 mg PO daily
Endpoints	Phase 1b: Safety, MTD, RP2D 2°: PK/PD Phase 2: Clinical benefit rate (CBR) 2°: ORR, DOR, PFS (Tumor assessment every 2 cycles, 1 cycle =28d)
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

Baseline Characteristics

	Total (N=52)	DE (N=15)	Simon Two-Stage (N=37)
Median age (range)	56 (28-80)	57 (31-74)	53 (28-80)
ECOG 0	36 (69%)	11 (70%)	25 (68%)
ECOG 1	16 (31%)	4 (30%)	12 (32%)
Metastatic location:			
Visceral (liver, lung, pleura, ovary, kidney, brain)	38 (73%)	12 (80%)	26 (70%)
Non-visceral only (lymph, bone, breast, chest)	14 (27%)	3 (20%)	11 (30%)
# All prior tx regimens (regardless of setting) - median (range)	3 (1-8)	4 (2-8)	3 (1-6)
# All prior tx regimens (in metastatic setting) - median (range)	1.5 (0-5)	2 (0-4)	1 (0-3)
# Prior chemo tx regimens (in metastatic setting) - median (range)	1 (0-4)	1 (0-4)	1 (0-3)
Prior taxane/anthracycline regimens - median (range)	1 (0-3)	2 (0-3)	1 (1-2)
Prior platinum	18 (35%)	6 (40%)	12 (32%)
Prior checkpoint inhibitor	23 (44%)	7 (47%)	16 (43%)
Duration of last prior metastatic tx regimen - median wks (range)	18.3 (2-384)	17 (3-187)	19 (2-384)
Time from metastasis to C1D1 - median months (range)	11 (1-71)	26 (2-48)	9 (1-57)
History of HR+ disease (primary)	18 (35%)	5 (33%)	13 (35%)
History of HR+ disease (metastatic)	3 (6%)	2 (13%)	1 (3%)
Known PIK3CA mutation	12/41 (29%)	4/12 (33%)	8/29 (28%)
Adjuvant therapy	33 (63%)	9 (60%)	24 (65%)
Disease free interval < 1yr (DFI = time from surgery to diagnosis of metastases)	13/44 (30%)	4/13 (31%)	9/31 (29%)
Metastatic at diagnosis	8 (15%)	2 (13%)	6 (16%)

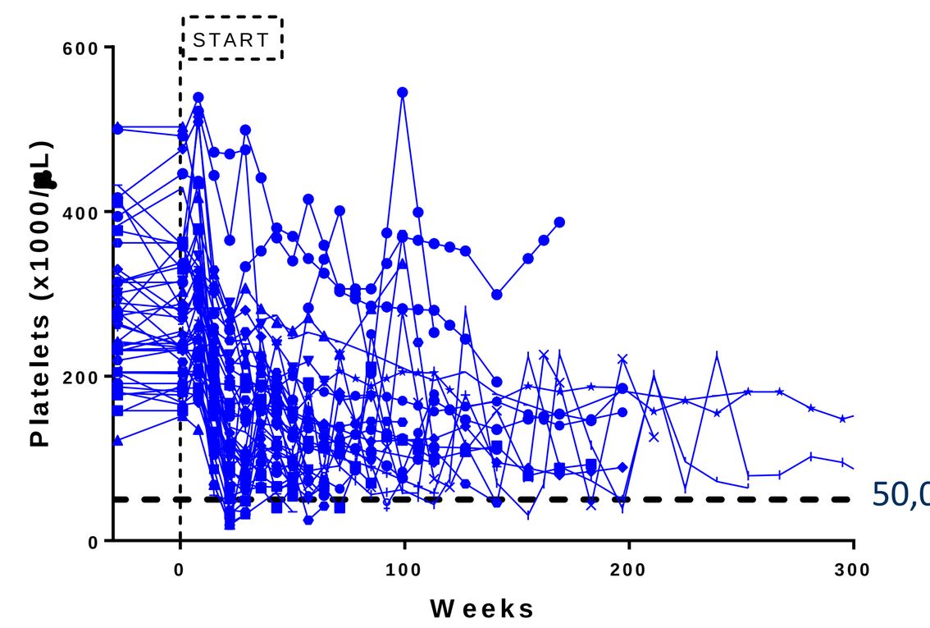
Safety

ZEN-3694 and Talazoparib combination was generally well tolerated with thrombocytopenia being the dose limiting toxicity

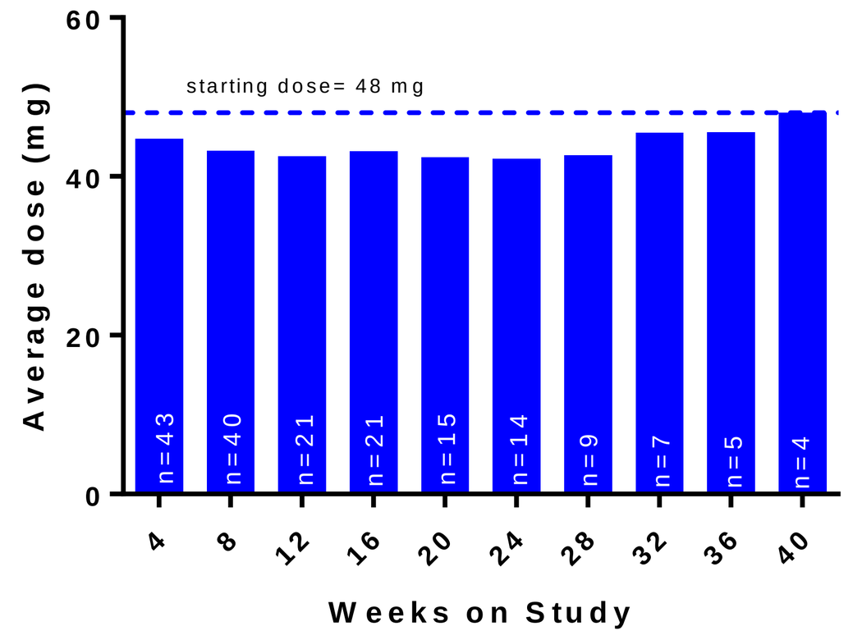
TRAEs (in ≥ 15% of total subjects)[1]	36 mg ZEN-3694 1 mg Talazoparib (n=3)			48 mg ZEN-3694 + 1 mg Talazoparib (n=6)			48 mg ZEN-3694 0.75 mg Talazoparib (n=43) RP2D			Total (n=52)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Thrombocytopenia[2]	1 (33%)	1 (33%)		6 (100%)	3 (50%)	2 DLT (33%)	25 (58%)	10 (23%)	4 (9%); 1 DLT (2%)	32 (61%)	14 (27%)	6 (11%); 3 DLT (6%)
Visual Symptoms[3]	2 (66%)			2 (33%)			23 (53%)			27 (52%)		
Nausea				3 (50%)			21 (49%)	1 (2%)		24 (46%)	1 (2%)	
Fatigue	1 (33%)			4 (67%)			12 (28%)			17 (33%)		
Vomiting				2 (33%)			11 (26%)			13 (25%)		
Dysgeusia	1 (33%)			2 (33%)			10 (23%)			13 (25%)		
Decreased appetite	1 (33%)			2 (33%)			9 (21%)			12 (23%)		
Neutropenia				1 (17%)			8 (19%)	3 (7%)		9 (17%)	3 (6%)	
AST increased							9 (21%)			9 (17%)		
ALT increased							8 (19%)	1 (2%)		8 (15%)	1 (2%)	

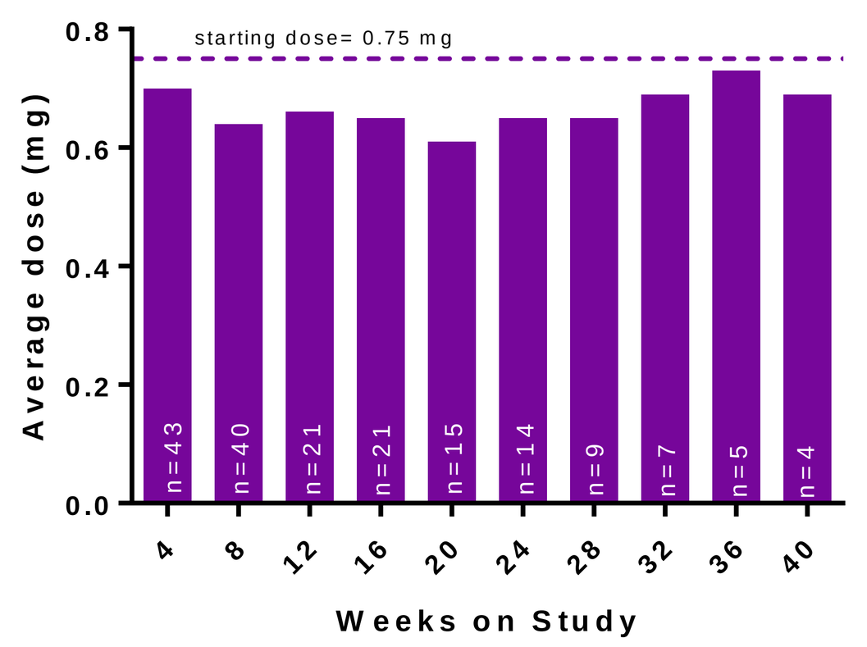
[1] No Grade 5 AEs, no deaths
[2] Thrombocytopenia resolved spontaneously or with a dose interruption of ZEN-3694 and talazoparib and/or dose reduction of talazoparib with no bleeding.
[3] Visual symptoms characterized by perception of brighter lights and/or light flashes, with or without visual color tinges were mild (Grade 1), transitory, and reversible with no anatomic or functional consequences. These symptoms are due to the modulation of PDE-6 by ZEN-3694.

Platelets maintained above 50,000/µL with appropriate dose holds and modifications



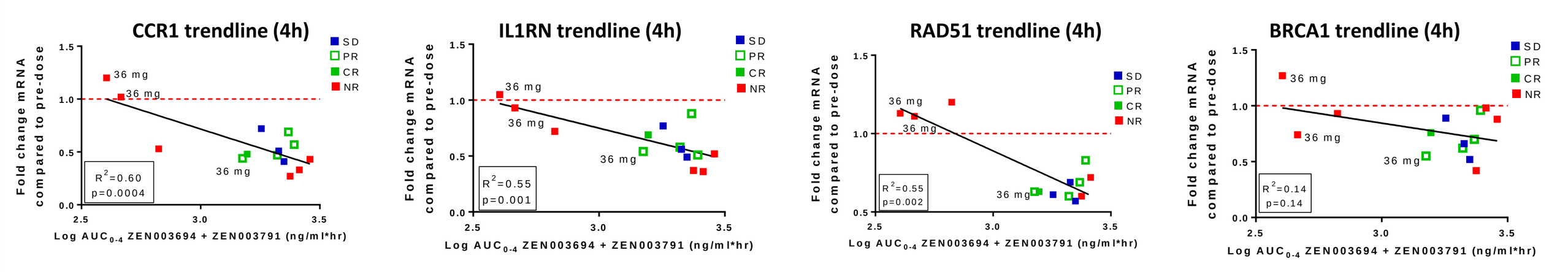
Dose Intensity for ZEN-3694 and Talazoparib Maintained Through First 10 Cycles



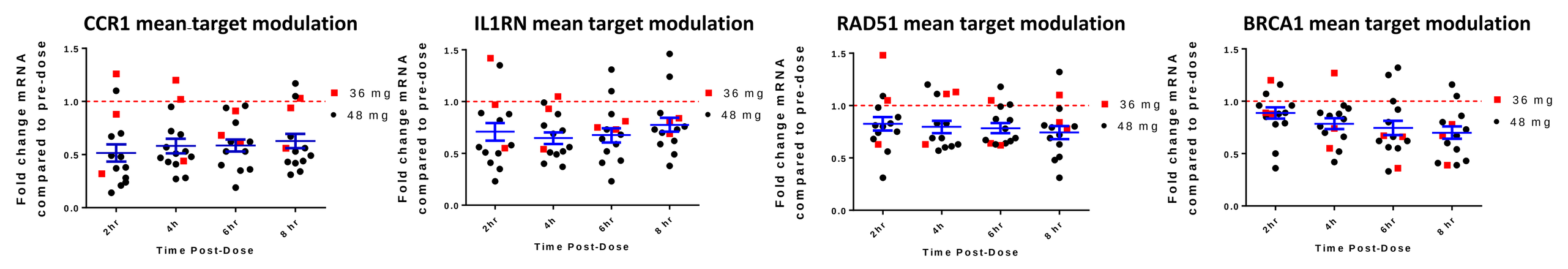


PK and target engagement in blood

Target modulation is associated with exposure



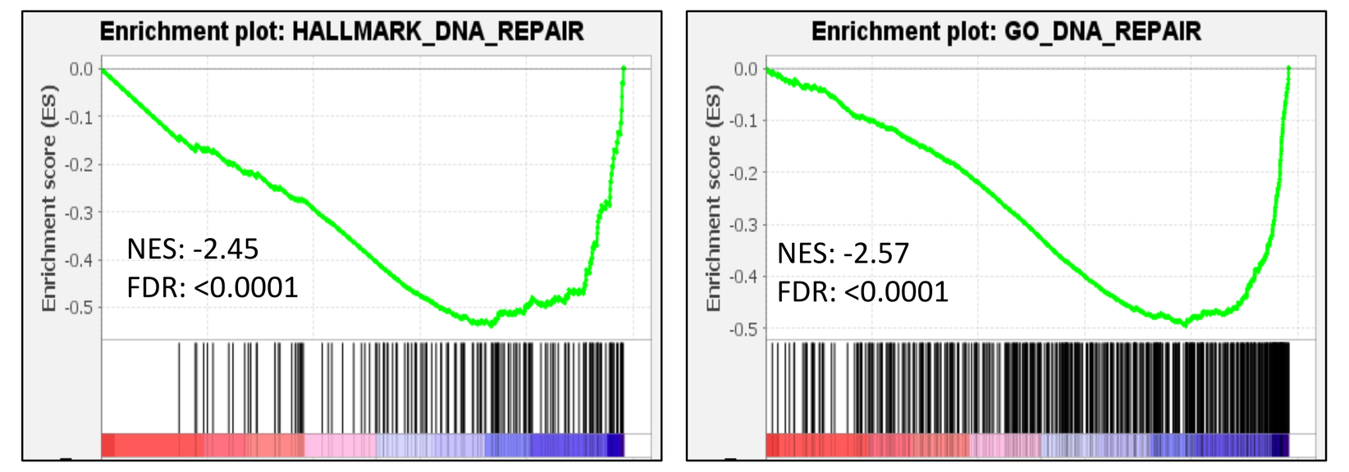
Durable target modulation over 8 hours



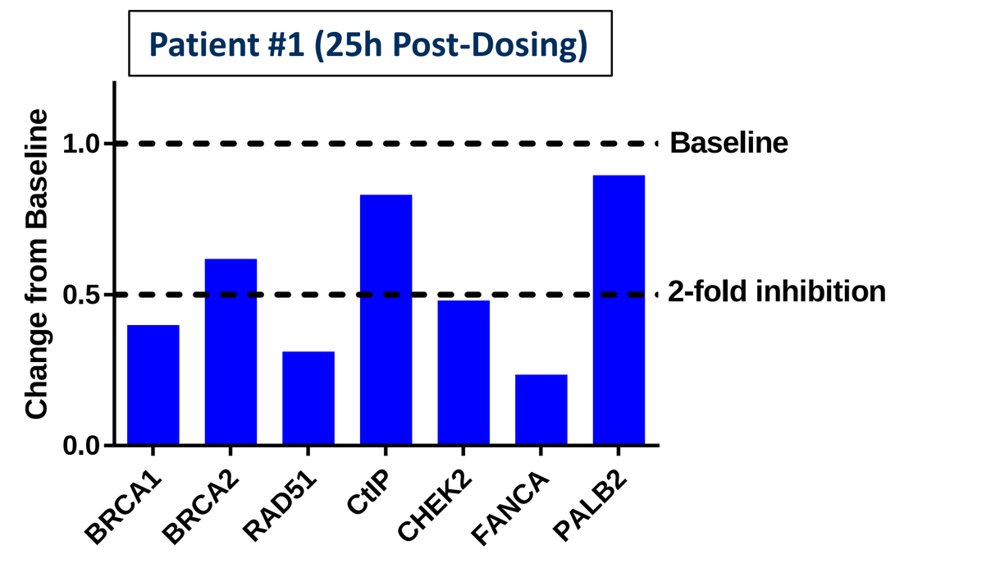
Whole blood qPCR demonstrates exposure-dependent decrease in CCR1, IL1RN, and RAD51 mRNAs (trendline graphs). Mean target modulation of each pharmacodynamic marker shows sustained inhibition up to 8 hours Post-Dosing. Reduction of BRCA1 and RAD51 mRNAs by ZEN-3694 demonstrates its capacity to inhibit the expression of DNA repair genes

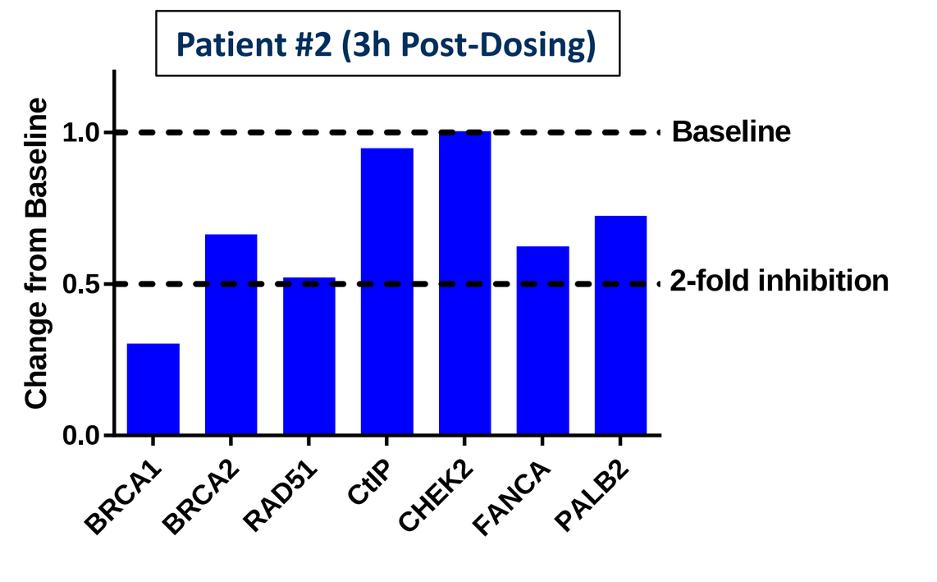
Target engagement in tumors

Significant inhibition of DNA repair Gene expression in tumors from two paired patient biopsies



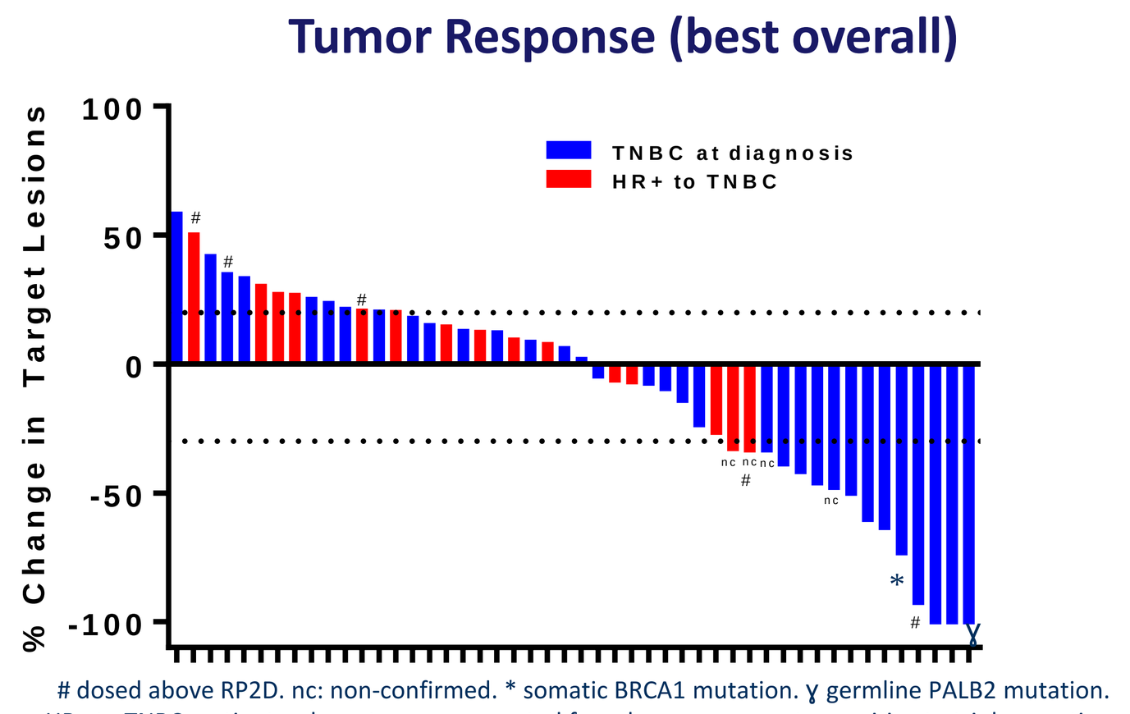
Inhibition of HRR gene expression in tumors



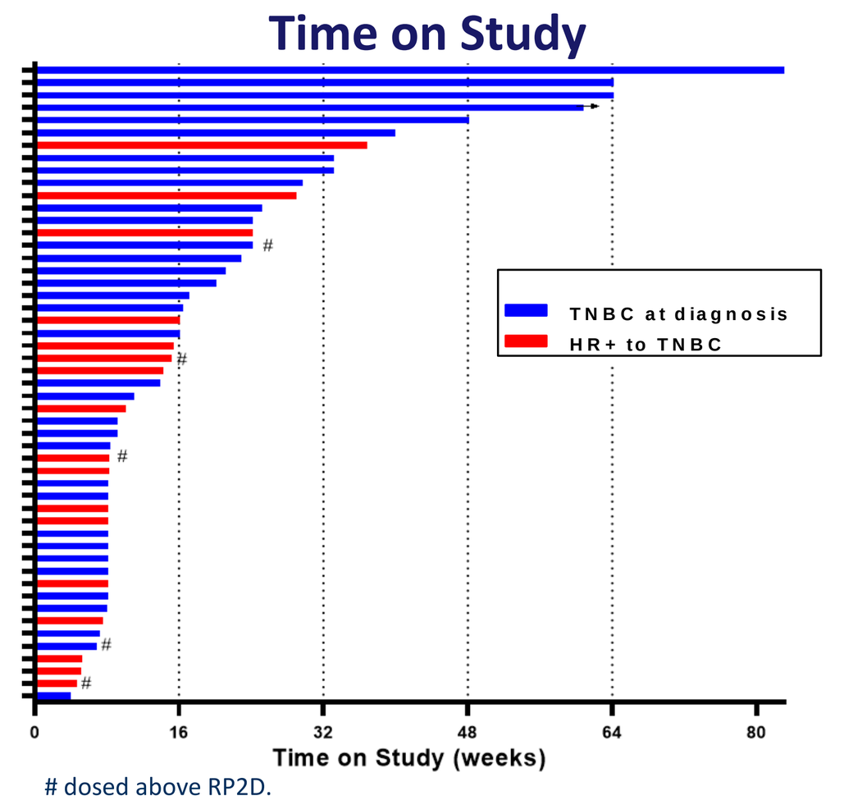


RNA-Seq analysis of paired biopsies from 2 patients. TOP: significant inhibition of DNA repair by Gene Set Enrichment Analysis (GSEA) BOTTOM: Inhibition of individual DNA repair genes in each patient

Efficacy



dosed above RP2D. nc: non-confirmed. * somatic BRCA1 mutation. ɣ germline PALB2 mutation.
HR+ to TNBC: patients whose tumors converted from hormone receptor positive to triple negative.



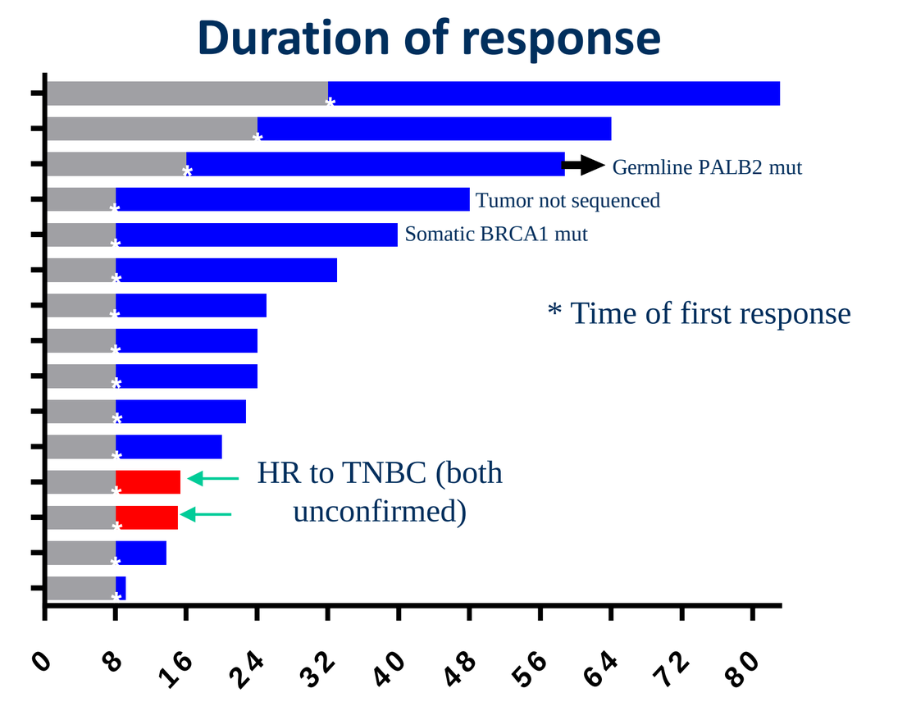
dosed above RP2D.

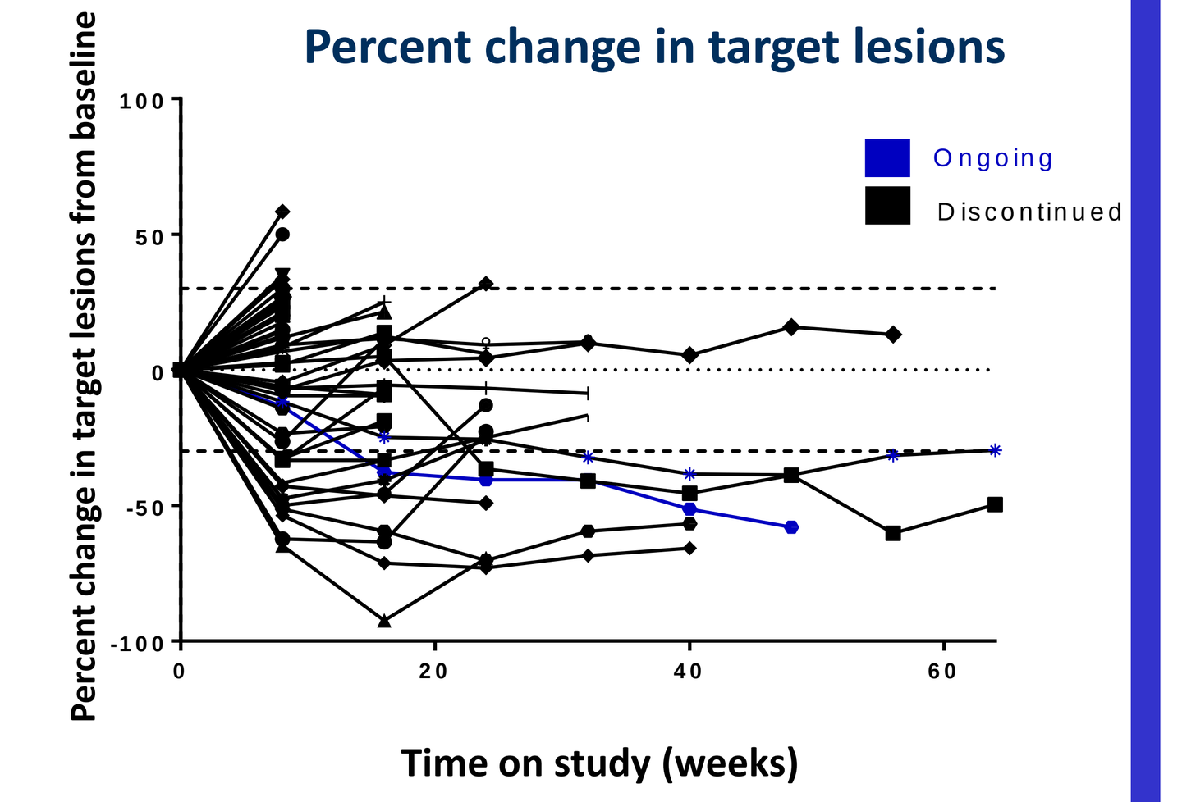
	All Population (n=51)	TNBC at Diagnosis (n=34)	HR+ to TNBC (n=17)
ORR % (confirmed)	22 (n=11, 9 PRs, 2 CRs)	**32** (n=11)	0
ORR % (conf. + unconfirmed)	30 (n=15)	**38** (n=13)	12.5 (n=2)
CBR at 4 mo % (confirmed)	35	**44**	18
Median duration of confirmed response (DOR) (wks)	24 (1 response ongoing)	**24**	0
Median PFS (wks)	15.3	**17**	10

* 1 patient with non-measurable lesions not included in ORR, 1 patient with DLT not included

Response by lines of prior metastatic therapy

	≥2 lines therapy (n=25)	<2 lines therapy (n=26)
ORR % (confirmed)	29	15
ORR % (confirmed and unconfirmed)	37.5	23
CBR % (confirmed)	56	30
DFI< 1yr %	25	33
visc met %	85	61
met at diag %	23	8
Duration previous therapy (wks)	18.3	19.3



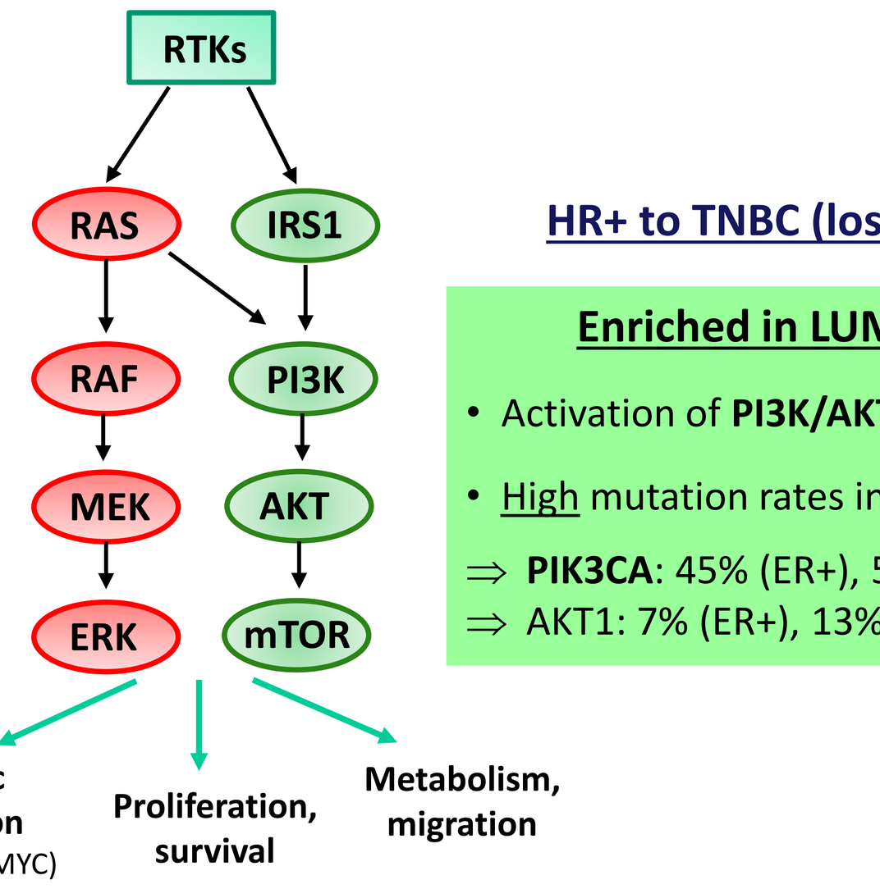


Increased response rate in patients without history of HR+ disease

TNBC at Diagnosis

Enriched in BASAL subtype
- Activation of **RAS/MAPK (~50%) (synergistic activity of BETi + PARPi)**
- Low mutation rates in pathway

⇒ **KRAS**: 5% (basal TNBC)
⇒ NF1: 7% (basal TNBC)



HR+ to TNBC (lose ER/PR receptors)

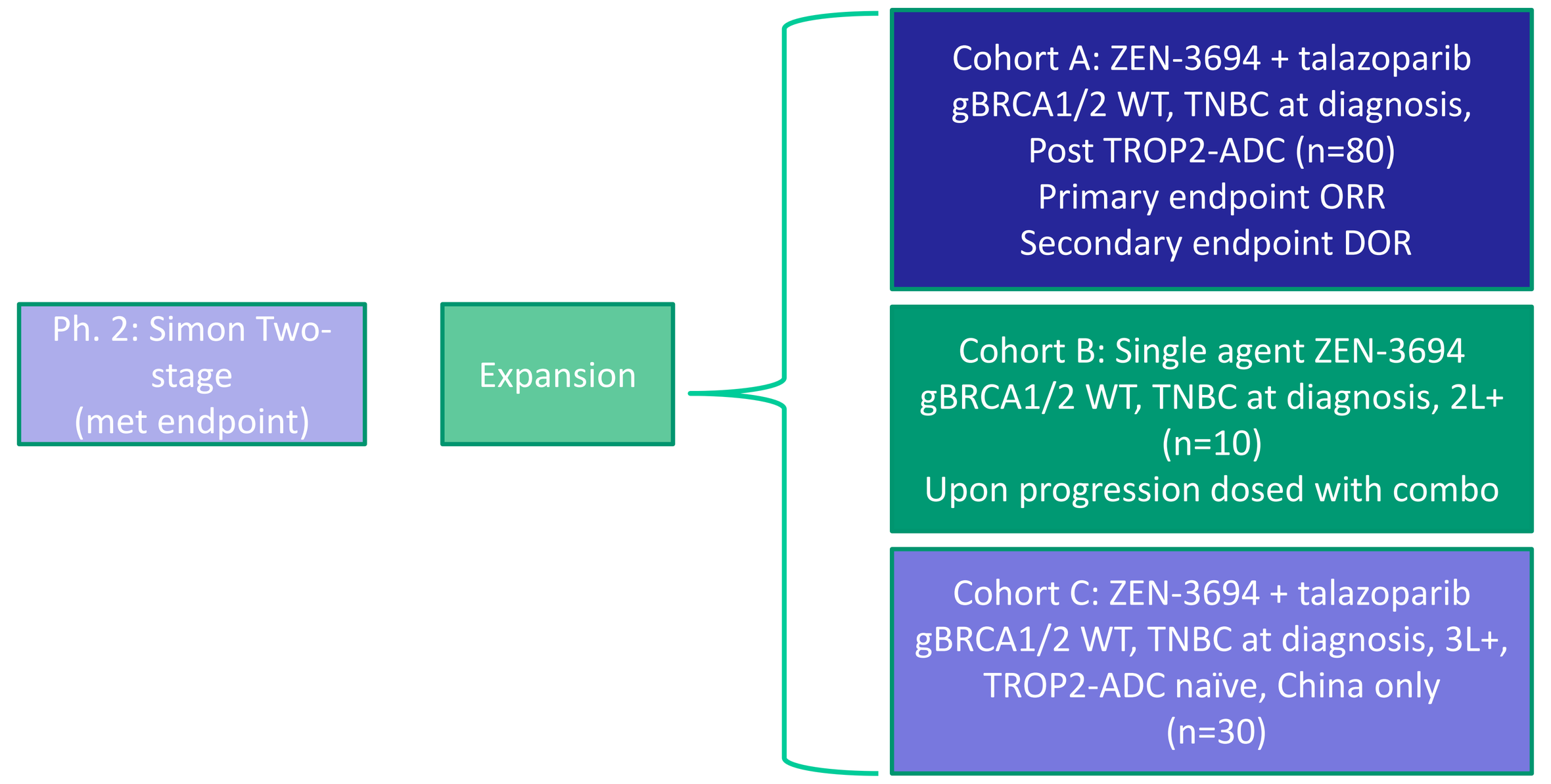
Enriched in LUMINAL subtype
- Activation of **PI3K/AKT (resistant to BETi)**
- High mutation rates in pathway

⇒ **PIK3CA**: 45% (ER+), 55% (luminal AR TNBC)
⇒ AKT1: 7% (ER+), 13% (luminal AR TNBC)

Hypothesis:
- RAS/MAPK activation associated with synergistic PARP and BET inhibitor activity
- PIK3CA activating mutations associated with resistance to PARP and BET inhibitors
- Selecting for TNBC at diagnosis would enrich for basal, RAS/MAPK pathway activated tumors that are more responsive to combination PARP and BET inhibitor therapy

Expansion Plan

Objectives:
- Further evaluate efficacy and safety by expanding current trial with an additional 80 patients in the gBRCA1/2 WT, TNBC at diagnosis, post TROP2-ADC, population: powered to show lower limit of the 95% confidence interval above 20% ORR.
- Evaluate potential single agent ZEN-3694 activity per regulatory feedback
- Evaluate activity of combination in 3L+ mTNBC Chinese population



Summary

- RP2D was determined to be 48mg qd ZEN-3694 plus 0.75mg qd talazoparib.
- The most common AE for the Ph 1b/2 study was thrombocytopenia (TCP) (61% any grade, 38% G3/4), which was managed with dose holds and reductions.
- Dose intensity analysis showed average daily doses of ZEN-3694 and talazoparib could be maintained above 40mg and 0.5mg, respectively, over 8 cycles.
- Robust target engagement was demonstrated using BET-dependent and HRR transcripts assessed in paired tumor biopsies.
- Ph 2 portion of the trial met its primary endpoint with a CBR of 30% (11/37). For the Ph 1b/2 trial, investigator assessed ORR was 22% (30% including unconfirmed), including 2 CR, CBR was 35% and the median confirmed DOR was 24 weeks.
- For the subset of TNBC at diagnosis patients (no history of HR+ disease), ORR was 32% (38% including unconfirmed), and CBR was 44% (15/34).
- The response rate increased with higher number of prior metastatic therapies, independent of other prognostic factors.
- Of the 15 responses, only 2 had a homologous repair mutation (1 patient was unknown, the remaining 12 were wild-type).
- These data confirm that ZEN-3694 can sensitize BRCA wild-type tumors to talazoparib.
- An 80 pt expansion has been planned to further examine the efficacy of this combination in the TNBC at diagnosis, post-TROP2-ADC population.

Trial Contact: Philippe Aftimos philippe.Aftimos@bordet.be