Please note, these are the actual video-recorded proceedings from the live CME event and may include the use of trade names and other raw, unedited content.

PARP inhibitors: Other than Olaparib

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Disclosures

Contracted Research	Amgen Inc, Eisai Inc, Genentech BioOncology, GlaxoSmithKline, Lilly, MacroGenics Inc, Merck, Novartis, OBI Pharma Inc, Pfizer Inc, Roche Laboratories Inc

Case presentation: Dr Rugo

44-year-old woman with BRCA2 germline mutation

- 2010: Biopsy: LN-positive, ER/PR-positive, HER2-negative IDC, 70-gene signature high risk, treated on ISPY2 with weekly paclitaxel/neratinib x 12 weeks followed by dose-dense AC x 4 and bilateral MRMs with 1.7-cm residual disease and 1/4 LN+
- 2010-2015: Hormonal therapy (tamoxifen; letrozole)
- 2015: Metastatic breast cancer treated with fulvestrant and palbociclib with denosumab
- 2015-2016: Talazoparib on the EMBRACA Phase III trial
- 2016: Cerebellar metastases: Gamma knife, capecitabine

Case presentation: Dr Robson

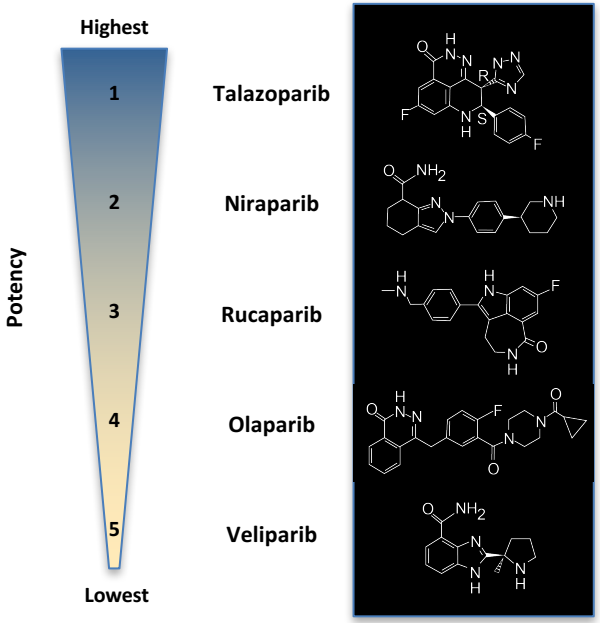
55-year-old woman with BRCA2 germline mutation

- Metastatic TNBC to bone, liver and lung: Capecitabine, weekly paclitaxel, vinorellbine → PD
- Talazoparib - developed significant (Grade 4) elevations of AST and ALT within 1 month, requiring discontinuation of study drug with slow resolution of LFTs thereafter

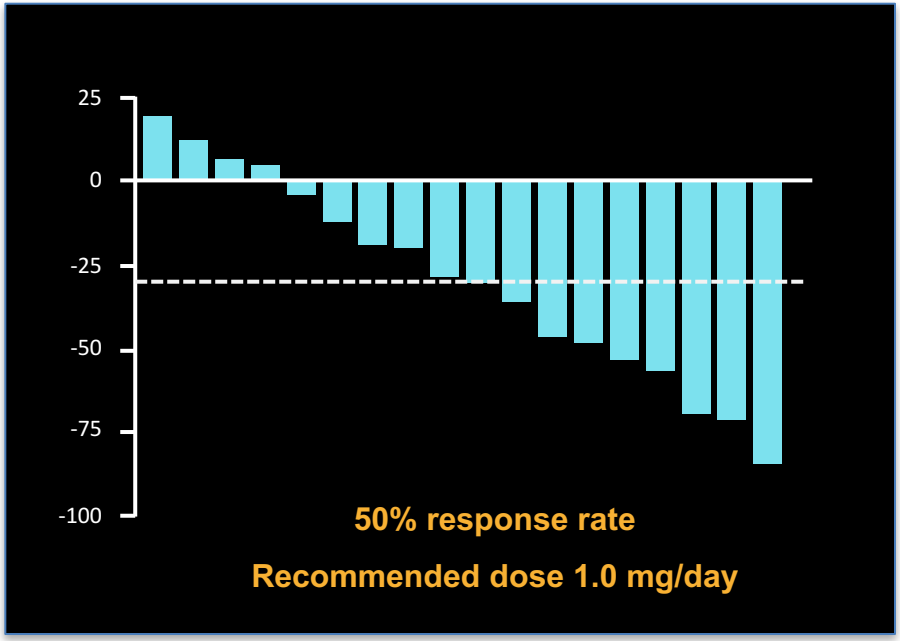
PARP Inhibitors Under Development

Compound	AKA	Phase
Olaparib	KU0059436, AZD2281	Approved (OC)
Talazoparib	MDV3800, BMN-673	III
Veliparib	ABT888	III
Niraparib	MK4827	Approved (OC)
Rucaparib	PF01367338, AG014699	Approved (OC)

Talazoparib: Highly Potent Inhibitor of PARP



Phase 1 trial – 18 breast cancer patients with *BRCA1/2* germline mutations[2]



1. Lord CJ, Ashworth A. *Science.* 2017;355:1152-1158; 2. de Bono J et al. *Cancer Discov.* 2017 Feb 27.

Talazoparib Following Platinum or Multiple Cytotoxic Regimens in MBC Patients with gBRCA Mutations: ABRAZO

Eligibility

- Patients with advanced breast cancer with a deleterious or suspected deleterious germline BRCA1/2 mutation (by central laboratory or a local report approved by the sponsor)
  - **Cohort 1:** PR or CR to last platinum-containing regimen for metastatic disease with disease progression > 8 weeks following the last dose of platinum
  - **Cohort 2:** 3 or more prior cytotoxic regimens for metastatic disease; no prior platinum for metastatic disease
- Measurable disease by RECIST v1.1
- CNS metastases permitted, provided stable following local therapy
- HER2+ breast cancer permitted, provided the patient's disease was refractory to HER2-targeted therapy

Turner et al, ASCO 2017

Select Baseline Characteristics

ITT Population

	Cohort 1 Prior Platinum (n = 49)	Cohort 2 3L+, No Prior Platinum (n = 35)	Total (N = 84)
Age, median (range), years	50 (31-74)	52 (33-75)	50 (31-75)
ECOG PS = 0, % (No.)	69 (34)	43 (15)	58 (49)
History of CNS metastasis, % (No.)	16 (8)	3 (1)	11 (9)
Visceral disease, % (No.)	78 (38)	66 (23)	73 (61)
Receptor status, % (No.)			
HER2+	2 (1)	14 (5)	7 (6)
Triple-negative	59 (29)	17 (6)	42 (35)
ER+ or PR+	41 (20)	83 (29)	58 (49)
BRCA status, % (No.)			
BRCA1+	53 (26)	43 (15)	49 (41)
BRCA2+	45 (22)	57 (20)	50 (42)
Unknown	2 (1)	0	1 (1)

Abbreviations: ITT, intent-to-treat. All HER2+ were also ER+

Primary and Secondary Efficacy Endpoints

	Cohort 1 Prior Platinum (n = 48)	Cohort 2 3L+, No Prior Platinum (n = 35)	Total (N = 83)
Objective response rate, % (95% CI)	**21 (10-35)**	**37 (22-55)**	**28 (18-39)**
Best overall response, % (No.)			
Complete response	4 (2)	0	2 (2)
Partial response	17 (8)	37 (13)	25 (21)
Stable disease	38 (18)	51 (18)	43 (36)
Progressive disease	38 (18)	11 (4)	27 (22)
Not evaluable	4 (2)	0	2 (2)

	Cohort 1 Prior Platinum (n = 48)	Cohort 2 3L+, No Prior Platinum (n = 35)	Total (N = 83)
Duration of response by IRF (months)			
No.	10	13	23
Events, % (No.)	50 (5)	77 (10)	65 (15)
Median (95% CI)	**5.8 (2.8-NE)**	**3.8 (2.8-10.1)**	**4.9 (2.9-9.7)**
Clinical benefit rate by investigator (CR, PR or SD ≥ 24 weeks), % (No.)	38 (18)	66 (23)	49 (41)
95% CI	24-53	48-81	38-61

To be Presented Friday, December 8th at 4:45 PM

Abstract GS6-07

EMBRACA: A Phase 3 Trial Comparing Talazoparib, an Oral PARP Inhibitor, to Physician's Choice of Therapy in Patients with Advanced Germline BRCA-Mutation Breast Cancer

Litton J, Rugo HS, Ettl J, Hurvitz S, Goncalves A, Lee K-H, Fehrenbacher L, Yerushalmi R, Mina LA, Martin M, Roche H, Im Y-H, Quek RGW, Tudor C, Hannah A, Eiermann W, Blum JL.

I-SPY2: Sporadic TNBC Veliparib/Carboplatin GRADUATES in the Triple Negative Signature

SIGNATURE	Estimated pCR Rate (95% probability interval)		Probability Veliparib + Carbo is Superior to Control	Predictive Probability of Success in Phase 3
	Veliparib/ Carbo	Concurrent Control		
All HER2-	33% (22-43%)	22% (10-35%)	92%	55%
HR+/HER2-	14% (4-27%)	19% (6-35%)	28%	9%
HR-/HER2-	**52%** (35-69%)	**26%** (11-40%)	**99%**	**90%**

Rugo et al, NEJM 2016

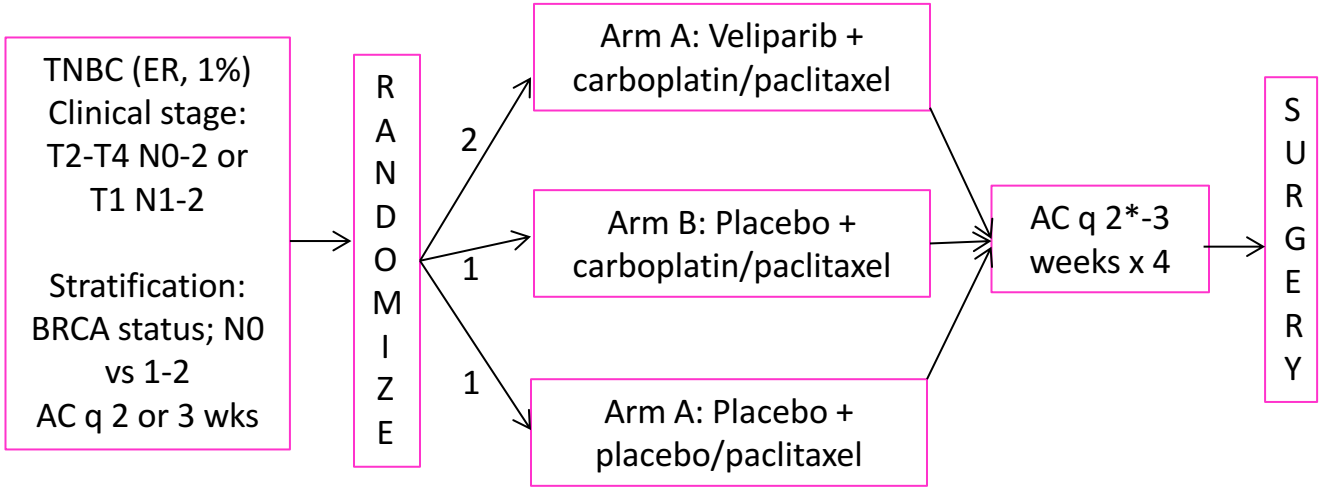
BROCADE:
Platinum in MBC with BRCA1/2 mutations

- 280 patients randomized to carboplatin/paclitaxel with placebo or veliparib
- Up to 2 prior lines of chemotherapy for MBC
  - 42% TNBC
- Results
  - Not much difference in hematologic toxicity with addition of veliparib
  - **No difference in PFS regardless of receptor status**
    - **12.3 vs 14.1 months (HR 0.789, p=.231)**
  - Response rates higher with veliparib
    - 61.3% (49/80) vs 77.8% (56/72), p=0.027
- BROCADE3 ongoing:
  - Maybe the addition of platinum is good enough (TNT trial)?
  - Differential efficacy between PARP inhibitors?
  - BRCA mutations confer chemotherapy sensitivity (GeparSixto)

Hahnen et al, JAMA Onc 2017

BrighTNess: A Randomized Phase III Neoadjuvant Trial in TNBC

N = 624; primary endpoint pCR breast/axilla



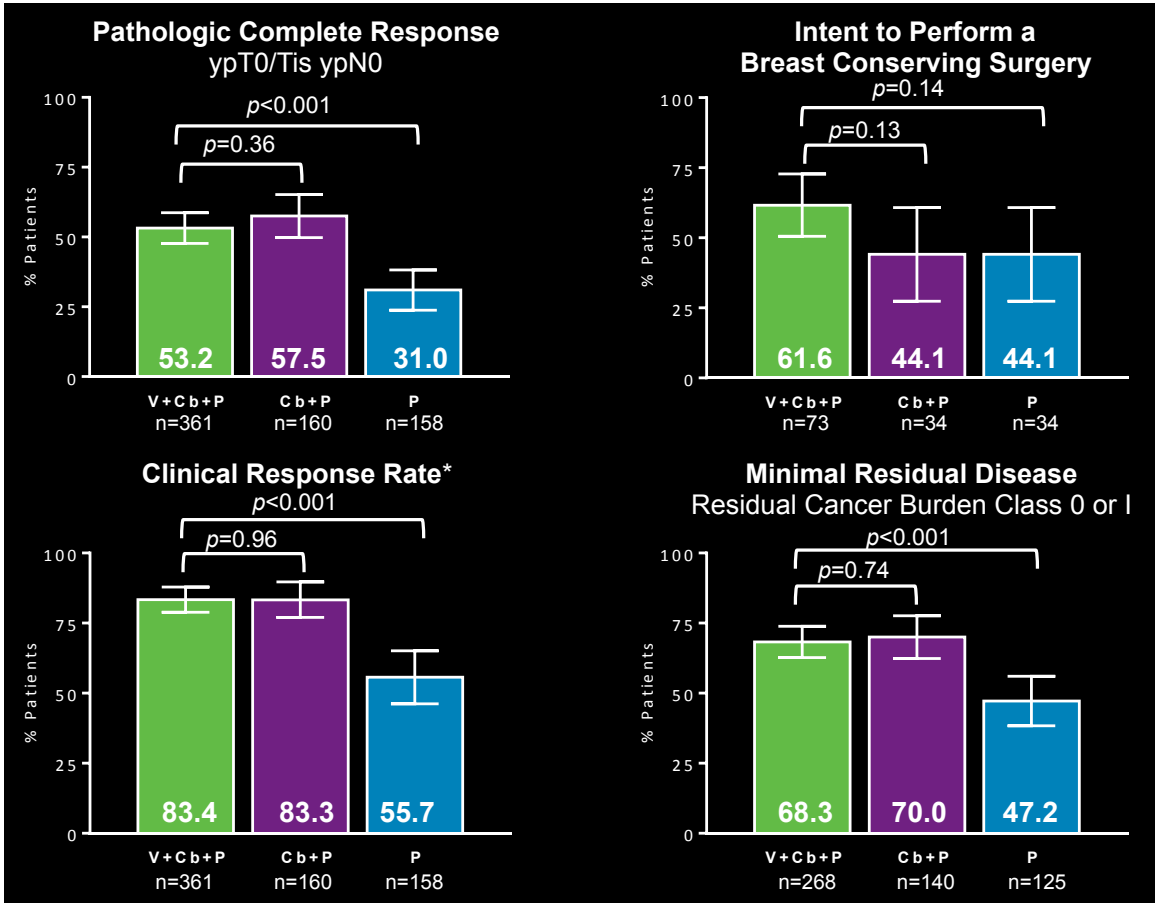
Veliparib: 50 mg PO BID x 12 weeks; carboplatin: AUC 6 IV q 3 weeks x 4; paclitaxel 80 mg/m^2 IV weekly x 12, AC: doxorubicin 60 mg/m^2/cyclosphosphamide 600 mg/m^2

*with G-CSF support

14-15% with gBRCA mutations (45/25/23)

Geyer et al, ASCO 2017

Efficacy

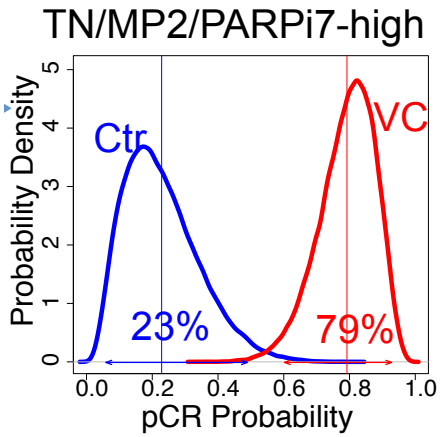

Pathologic Complete Response
ypT0/Tis ypN0
p<0.001
p=0.36
% Patients
100
75
50
25
0
53.2
57.5
31.0
V+Cb+P
n=361
Cb+P
n=160
P
n=158
Intent to Perform a
Breast Conserving Surgery
p=0.14
p=0.13
61.6
44.1
44.1
V+Cb+P
n=73
Cb+P
n=34
P
n=34
Clinical Response Rate*
p<0.001
p=0.96
83.4
83.3
55.7
V+Cb+P
n=361
Cb+P
n=160
P
n=158
Minimal Residual Disease
Residual Cancer Burden Class 0 or I
p<0.001
p=0.74
68.3
70.0
47.2
V+Cb+P
n=268
Cb+P
n=140
P
n=125

Conclusions

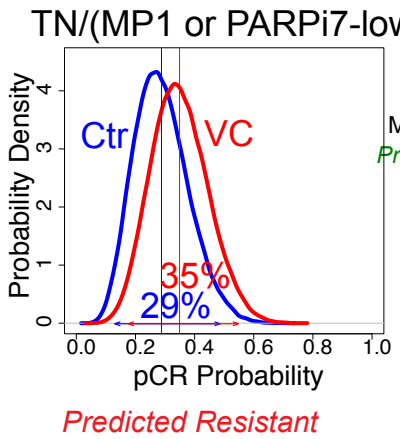
The bottom line:

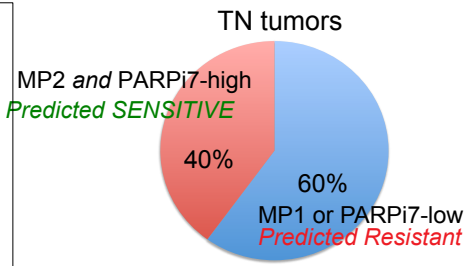
- Carboplatin improves pCR in sporadic TNBC
- Veliparib doesn’t add anything here
  - Minimal additional toxicity
  - Lower potency or dose is too low?
- Similar results in the phase II BROCADE trial in MBC
- No evidence that any known marker identifies a group that will benefit
- Role of platinum?

Biomarker Proposals for Specific Predictors of Veliparib/Carboplatin Response



Vs.



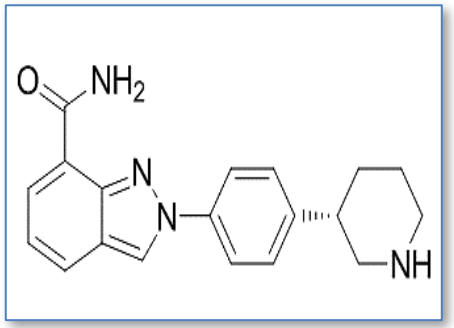


Combining Biomarkers Improves Predictive Performance in TNBC

Wolf et al, SABCS 2016

Niraparib

- Orally active inhibitor of PARP
  - High selectivity for PARP1 (IC_{50}=3.8 nM) and PARP2 (IC_{50}=2.1 nM)



Steffen JD et al. *Front Oncol*. 2013.

NOVA STUDY Summary:

Phase III study; n=553 pt with recurrent ovarian cancer with response to platinum-based therapy

Randomized to niraparib 300mg po daily vs. placebo

Primary endpoint = PFS:

BRCA mutant: 21 vs. 5.5 mos (HR 0.27, $p < 0.0001$)
BRCA WT: 9.3 vs. 3.9 mos (HR 0.45, $p < 0.0001$)
BRCA WT/HRD+: 12.9 vs. 3.8 mos (HR 0.38, $p < 0.0001$)

Mizra et al. NEJM. October 2016

FDA approval as maintenance therapy for pts with recurrent ovarian, fallopian tube or primary peritoneal cancer following CR or PR after platinum therapy: **March 27, 2017**

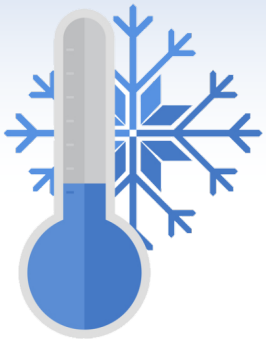
IC_{50}=median inhibition concentration.
Jones P et al. *J Med Chem*. 2009;52:7170-7185.

Hypotheses: PARP inhibition May Enhance Immune-surveillance Through Multiple Mechanisms

Key Pre-clinical Findings in the Literature

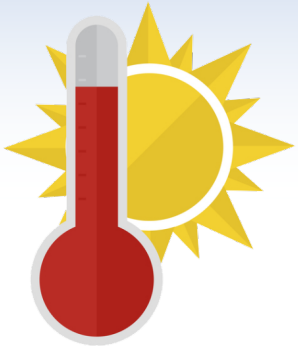
- PARP inhibitor increases peritoneal CD8+ T, NK cell levels as well as their production of IFN-γ and TNF-α in mouse tumor model[1]
- PARP inhibitor increases PD-L1 expression in mouse tumor model[2]
- PARP inhibitor increases PBMC regulatory T cell suppression function[3]

Immunologically 'COLD' Tumor → **PARP Inhibition** → **Immunologically 'HOT' Tumor**



Absence or limited tumor infiltrating lymphocytes

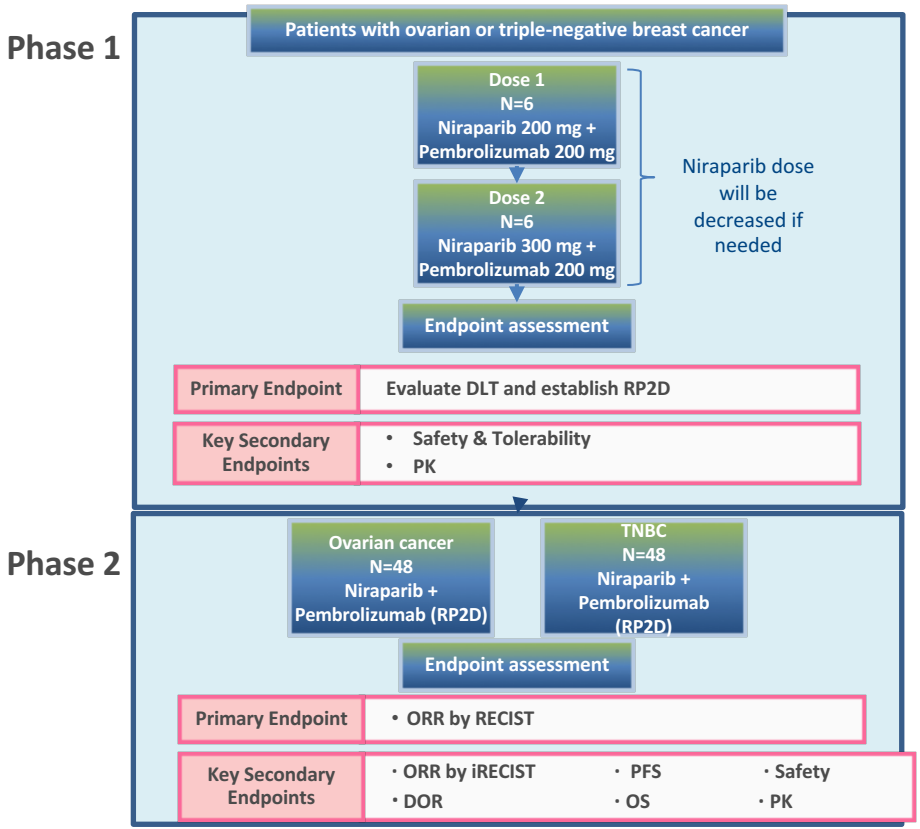
- Type-I IFN activation via STING
- Cell-death mediated inflammation
- Increased neoantigen load



Presence of tumor infiltrating lymphocytes

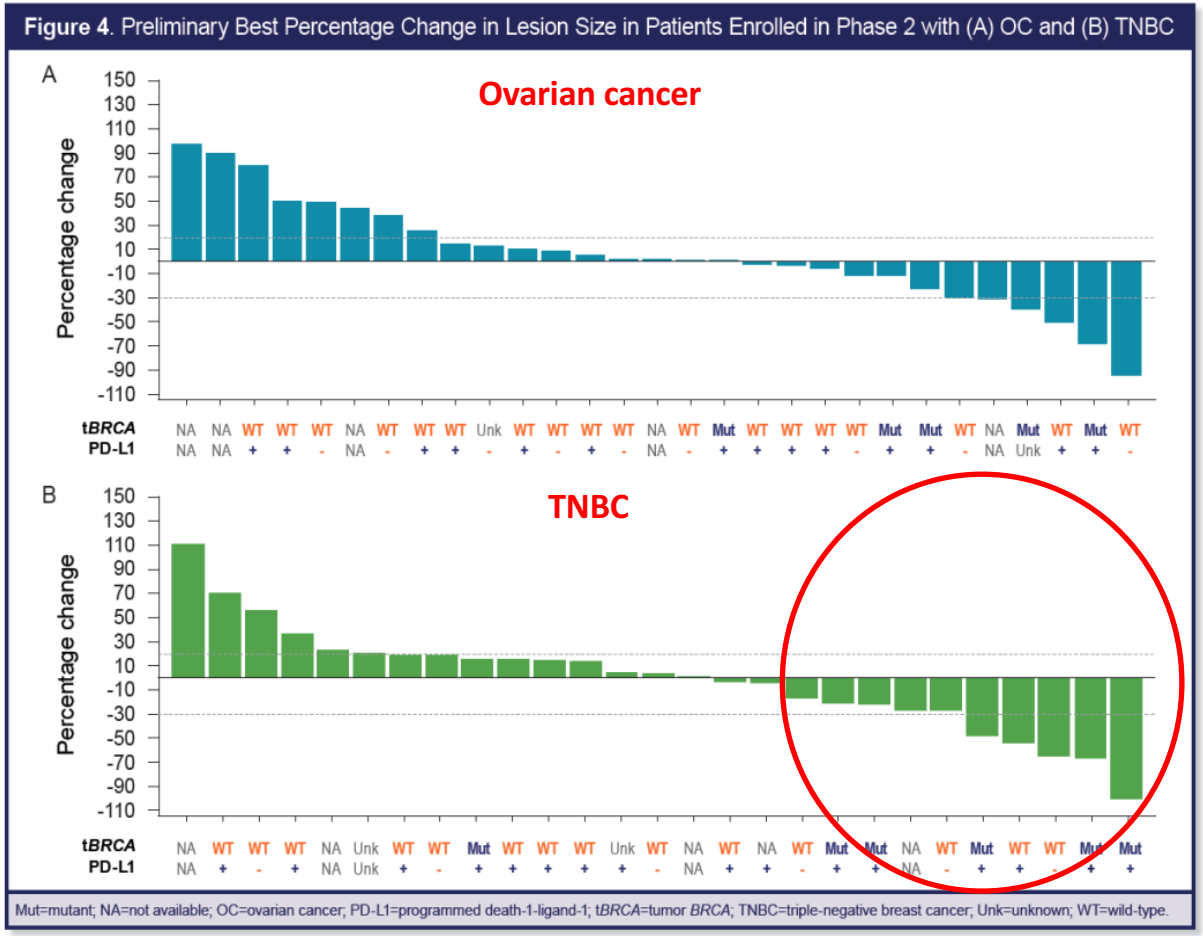
1. Huang J.,et al. *Biochem and Biophy Res Comm*. 2015; 463:551-6.; 2. Jiao S.p., et al. *Clin Cancer Res.* 2017; 3. Luo X., et al. *J of Biol Chem.* 2015; 290(48):28675-82.
http://www.jbc.org/lookup/doi/10.1074/jbc.M115.661611

Niraparib-Pembrolizumab Schema



DLT=dose-limiting toxicity; RP2D=recommended phase 2 dose; PK=pharmacokinetics; TNBC=triple-negative breast cancer; ORR=overall response rate; DOR=duration of response; PFS=progression free survival; OS=overall survival

Preliminary Best % Change In Lesion Size in Patients Enrolled in Phase 2 with (A) OC and (B) TNBC



Konstantinopoulos et al., ESMO 2017

Phase II/III Ongoing Trials of PARPi in Advanced Breast Cancer

Name	Phase	Arms	Eligibility	Clinicaltrials.gov
BROCADE	III	paclitaxel/carbo +/- veliparib	gBRCA1/2	NCT02163694
BRAVO*	III	niraparib vs TPC (2:1)	gBRCA1/2	NCT01905592
S1416	II	cisplatin +/- veliparib	gBRCA1/2 TNBC	NCT02595905
TBB	II	talazoparib	HRD high gHR/sHR mutation**	NCT02401347
Ruby	II	rucaparib	BRCAness sBRCA1/2 mutation	NCT02505048
TOPACIO	II	niraparib + pembrolizumab	TNBC OvCa	NCT02657889
(LoRusso)	II	Veliparib vs atezolizumab vs the combination	gBRCA1/2	NCT02849496

*Interim analysis by IDMC felt data uninterpretable due to a large number of patients in the chemotherapy control arm discontinuing the trial early before scans (very high censoring rate). Trial closed to accrual in 3/2017 after 106 out of 185 enrolled. Tesaro is working with the FDA to determine how to proceed in terms of registration.

**PTEN, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, FANC genes

Select Ongoing Neoadjuvant/Adjuvant Trials of PARPi in Breast Cancer

Name	Phase	Arms	Clinicaltrials.gov
ISPY2	II	paclitaxel → AC irinotecan + talazoparib → AC (closed for futility)	NCT01042379
MDACC	II	talazoparib x 6 mos	NCT02282345
NSABP B-55 (OlympiA)	III	olaparib vs placebo x 1 year	NCT02032823

PARP inhibitors: Other than Olaparib

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