Next Generation in Targeting DNA Repair

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Jennifer Keating Litton, M.D., MHCM
Vice President Clinical Research
Professor and Chair *ad interim*, Breast Medical Oncology

Objectives

- Metastatic
- Early Stage: Neoadjuvant and Adjuvant

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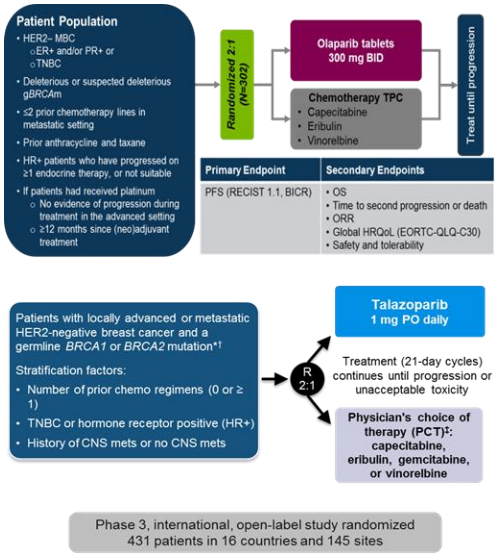
- Metastatic
- Early Stage: Neoadjuvant and Adjuvant

Current FDA-approved PARP Inhibitors

- **OlympiAD**



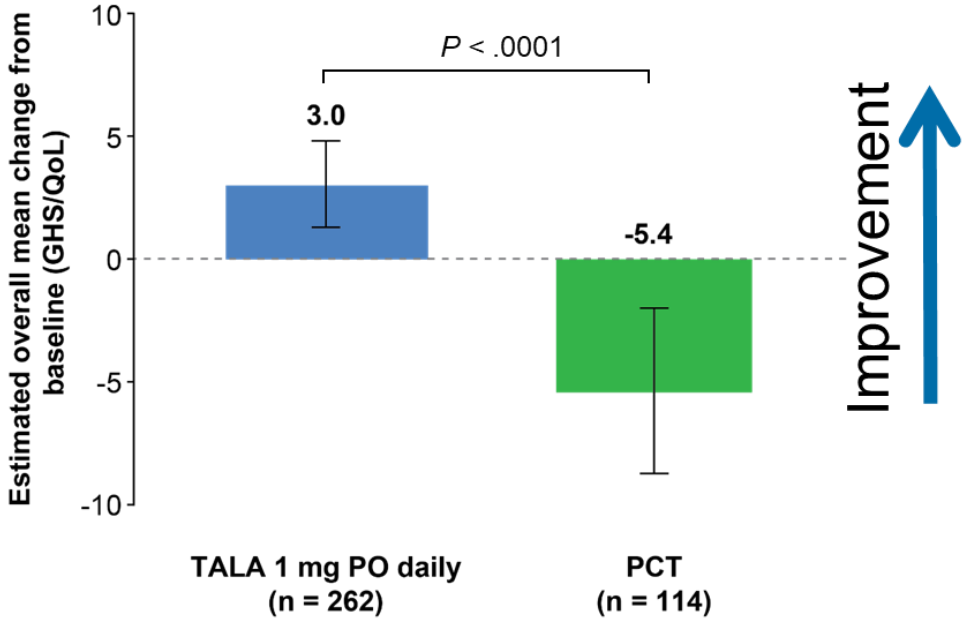
Drug	ORR PARPi vs. control	mPFS (months) PARPi vs. control	Median DoR (months) PARPi vs. control
Olaparib	59.9% vs. 28.8%	7.0 vs. 4.2	6.4 vs. 7.1
Talazoparib	62.6% vs. 27.2%	8.6 vs. 5.6	5.4 vs. 3.1

- **EMBRACA**

Litton JK et al. *N Engl J Med.* 2018;379(8):753-763.
Robson M et al. *N Engl J Med.* 2017;377(6):523-533.

EMBRACA: EORTC QLQ-C30
Patient-Reported Global Health Status (GHS)/QoL

Statistically significant improvement in estimated overall mean change from baseline in GHS/QoL for TALA-treated patients [3.0 (95% CI, 1.2, 4.8)] compared to PCT-treated patients [-5.4 (-8.8, -2.0)]

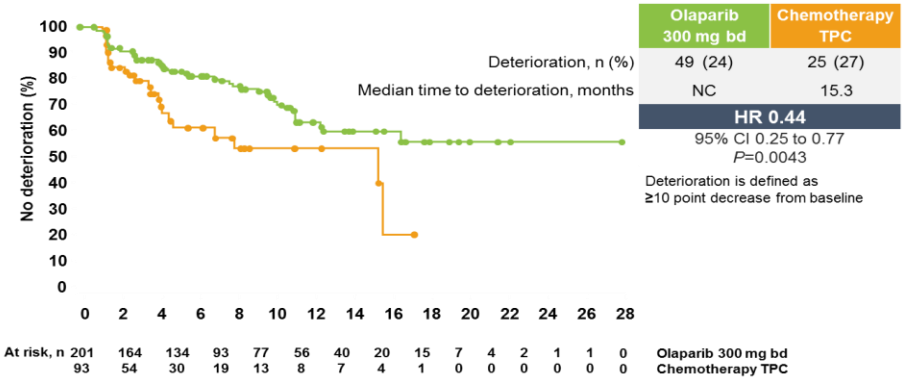


Note: Results from longitudinal repeated measures mixed effects model.

Litton JK et al. *N Engl J Med*. 2018;379(8):753-763.

Time to Deterioration of Global HRQoL

- **OlympiAD**



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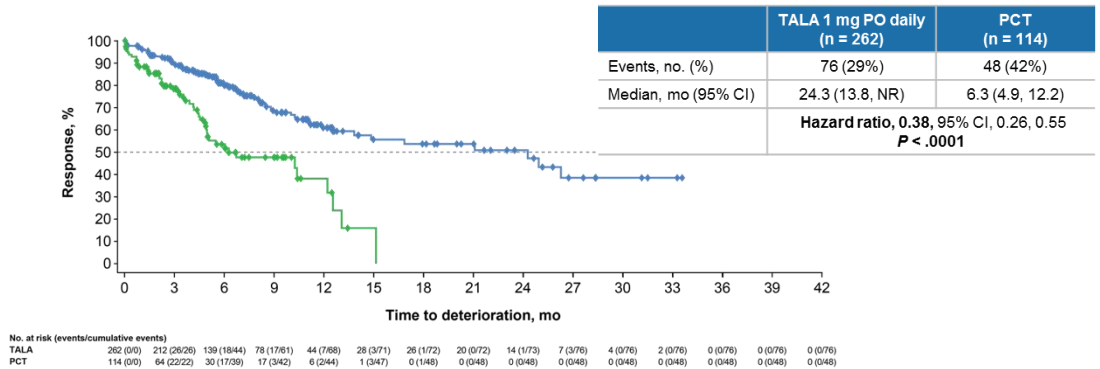

Litton JK et al. *N Engl J Med.* 2018;379(8):753-763.
Robson M et al. *N Engl J Med.* 2017;377(6):523-533.

AACR American Association for Cancer Research®
ANNUAL MEETING
2024 • SAN DIEGO
APRIL 5-10
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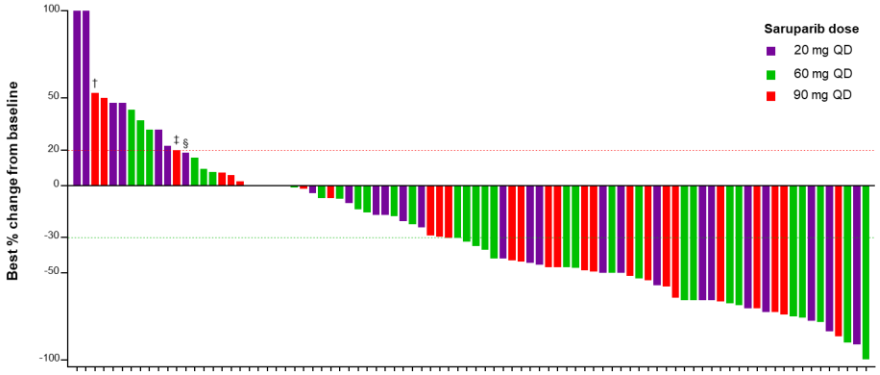
PETRA: First-in-human Phase 1/2a trial of the first-in-class new generation poly(ADP-ribose) polymerase-1 selective inhibitor (PARP1i) saruparib (AZD5305) in patients with advanced solid tumors with *BRCA1/2*, *PALB2* or *RAD51C/D* mutations

Timothy A. Yap,[1] Alison M. Schram,[2] Judith Balmaña,[3] Alejandro Falcón,[4] Javier García-Corbacho,[5] Seock-Ah Im,[6] Richard D. Baird,[7] Jiong Wu,[8] Donglin Zou,[9] Kan Yonemori,[10] Min Hwan Kim,[11] Gabor Rubovszky,[12] Ganesh Moorthy,[13] Spiros Linardopoulos,[14] Suman Nanda,[15] Ko Sugibayashi,[14] Caroline Kennedy,[14] Jessica S. Brown,[14] Mark Albertella,[14] Sabina Cosulich,[14] Victor Amezcua,[14] Edit Lukacs,[14] Stephen J. Luen[16]

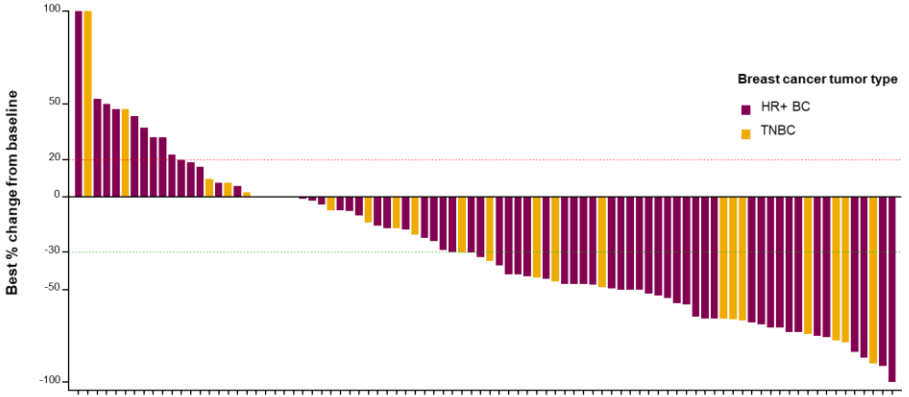
[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]Virgen del Rocío University Hospital, Seville, Spain; [5]Hospital Virgen de la Victoria, Málaga, Spain; [6]Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [7]Addenbrooke's Hospital, Cambridge, England, UK; [8]Shanghai Cancer Center, Fudan University, Shanghai, China; [9]Chongqing University Cancer Hospital, Chongqing, China; [10]National Cancer Center Hospital, Tokyo, Japan; [11]Severance Hospital, Seoul, Republic of Korea; [12]National Institute of Oncology, Budapest, Hungary; [13]AstraZeneca, Waltham, MA, USA; [14]AstraZeneca, Cambridge, England, UK; [15]AstraZeneca, Gaithersburg, MD, USA; [16]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Saruparib



Key eligibility criteria:

- No limit on prior chemotherapy lines
- *BRCA1/2*m, *PALB2*m, or *RADC51C/D*m



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Yap T et al. AACR Annual Meeting 2024

Saruparib

	Saruparib dose											
	10 mg QD Part A (n=8)		20 mg QD Part A + B (n=66)		40 mg QD Part A (n=17)		60 mg QD Part A + B (n=141)		90 mg QD Part A + B (n=41)		140 mg QD Part A (n=9)	
Saruparib-related TRAEs[†]	6 (75.0)		45 (68.2)		9 (52.9)		108 (76.6)		33 (80.5)		7 (77.8)	
Grade ≥3 TRAEs	4 (50.0)		15 (22.7)		1 (5.9)		39 (27.7)		22 (53.7)		3 (33.3)	
Serious TRAEs	0		2 (3.0)		0		3 (2.1)		6 (14.6)		1 (11.1)	
Discontinuations	0		2 (3.0)		0		5 (3.5)		2 (4.9)		1 (11.1)	
Dose reductions	2 (25.0)		4 (6.1)		1 (5.9)		20 (14.2)		10 (24.4)		1 (11.1)	
Dose interruptions	3 (37.5)		13 (19.7)		1 (5.9)		41 (29.1)		22 (53.7)		4 (44.4)	
TRAE by preferred term ≥20% any Grade overall, n (%)[†‡]												
Grade	**≥3**	**All**	**≥3**	**All**	**≥3**	**All**	**≥3**	**All**	**≥3**	**All**	**≥3**	**All**
Anemia[§]	3 (37.5)	3 (37.5)	10 (15.2)	16 (24.2)	1 (5.9)	2 (11.8)	16 (11.3)	38 (27.0)	16 (39.0)	20 (48.8)	2 (22.2)	5 (55.6)
Nausea	0	3 (37.5)	0	20 (30.3)	0	2 (11.8)	0	35 (24.8)	0	16 (39.0)	0	0
Fatigue and asthenia[§]	0	2 (25.0)	0	6 (9.1)	0	3 (17.6)	5 (3.5)	41 (29.1)	0	5 (12.2)	0	1 (11.1)
Neutropenia[§]	1 (12.5)	3 (37.5)	5 (7.6)	13 (19.7)	0	2 (11.8)	15 (10.6)	31 (22.0)	11 (26.8)	15 (36.6)	2 (22.2)	3 (33.3)
Thrombocytopenia[§]	1 (12.5)	1 (12.5)	4 (6.1)	15 (22.7)	0	4 (23.5)	8 (5.7)	27 (19.1)	3 (7.3)	8 (19.5)	0	3 (33.3)

Dose reductions in this study were numerically less than in other PARP trials in the metastatic setting

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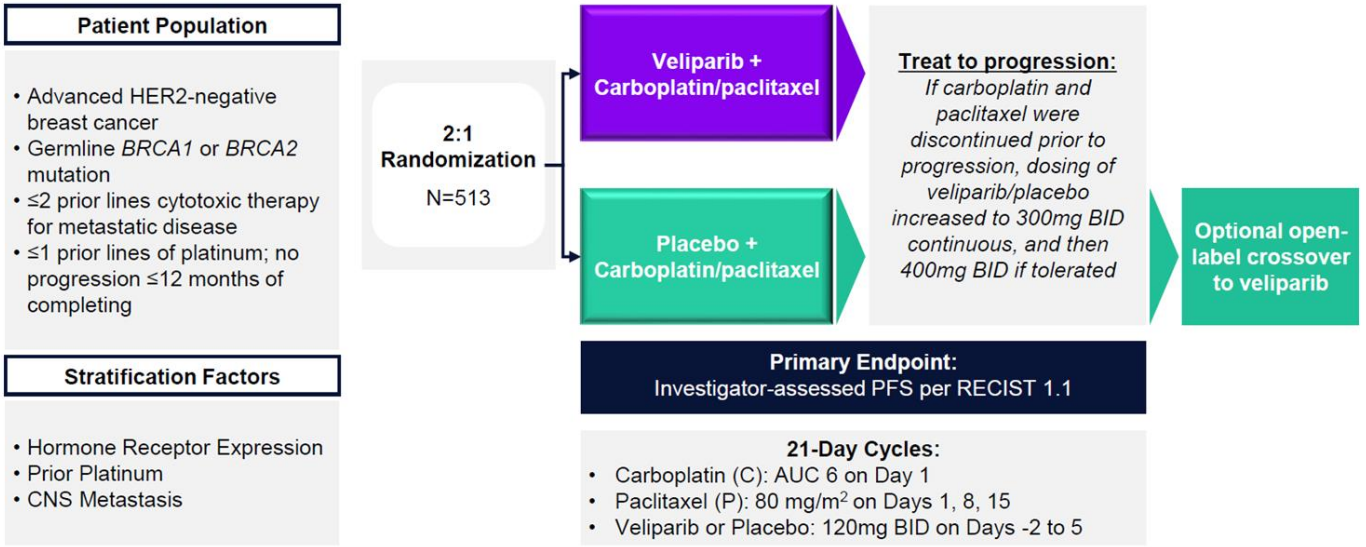
BROCADE 3: Study Design



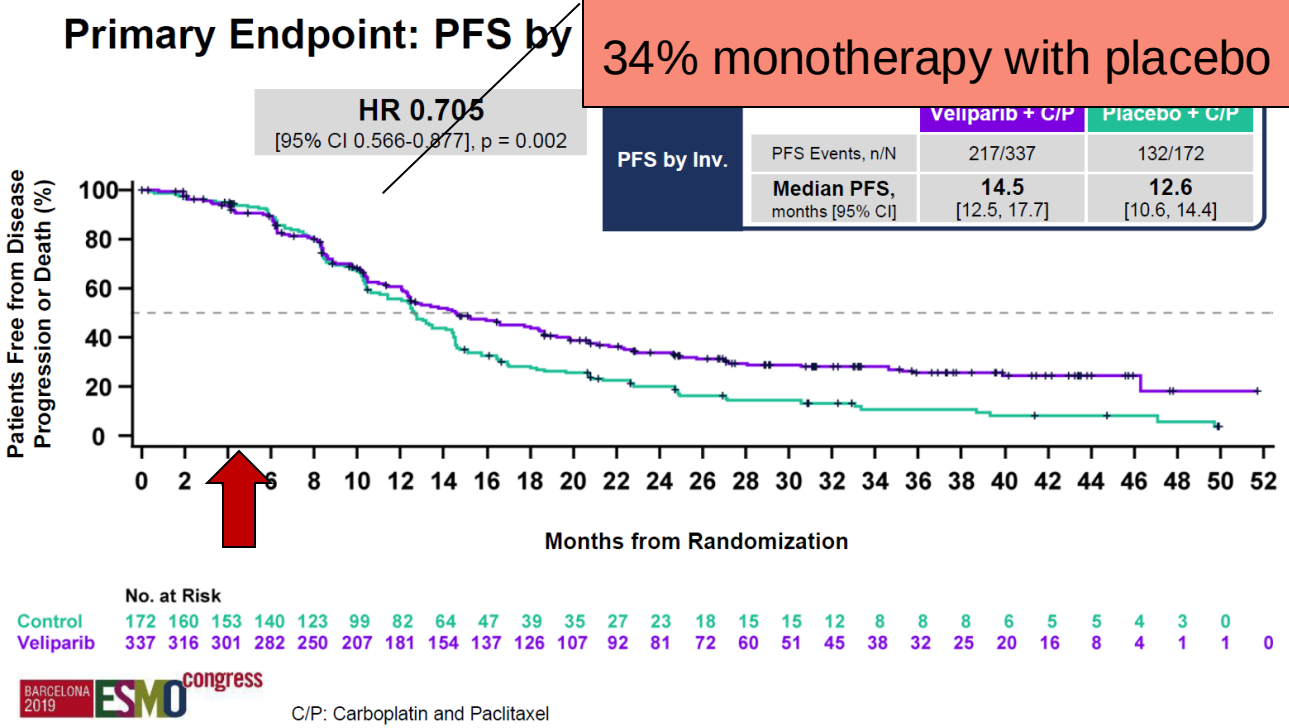
BARCELONA 2019 ESMO congress

Dieras V et al. ESMO 2019. Abstract LBA9.

BROCADE 3: PFS by Investigator Assessment

40% monotherapy veliparib

34% monotherapy with placebo



C/P: Carboplatin and Paclitaxel

Dieras V et al. ESMO 2019. Abstract LBA9.

Study Schema: SWOG 1416

Metastatic and/or loco-regionally recurrent TNBC[a]
or
***BRCA1* or *BRCA2* germline mutation-associated HER2-negative MBC**

0/1 prior cytotoxic chemotherapy for metastatic disease

R[b]

1

Cisplatin 75 mg/m² Day 1 every 21 days
Veliparib 300 mg PO BID (D1-14) every 21 days

1

Cisplatin 75 mg/m² Day 1 every 21 days
Placebo PO BID (D1-14) every 21 days

Tumor Blood

Post-randomization germline and BRCA-like biomarker testing assigned patients into pre-specified groups

Germline *BRCA* testing

Deleterious germline *BRCA1/2* mutation detected

Deleterious germline *BRCA1/2* mutation not detected

BRCA-like Biomarker Analysis
1. HRD genomic instability score ≥42
2. Somatic *BRCA1/2* mutation
3. *BRCA1* promoter methylation (PM)
4. Germline HR repair genes mutation (excluding *BRCA1/2*)

Primary tumor

Positivity on any one of the above four marker/s placed patient in BRCA-like group

g*BRCA* group

BRCA-like group

Non-BRCA-like group

Primary end point:
Progression- free survival in three pre-specified groups:
- g*BRCA*
- BRCA-like
- non-BRCA-like

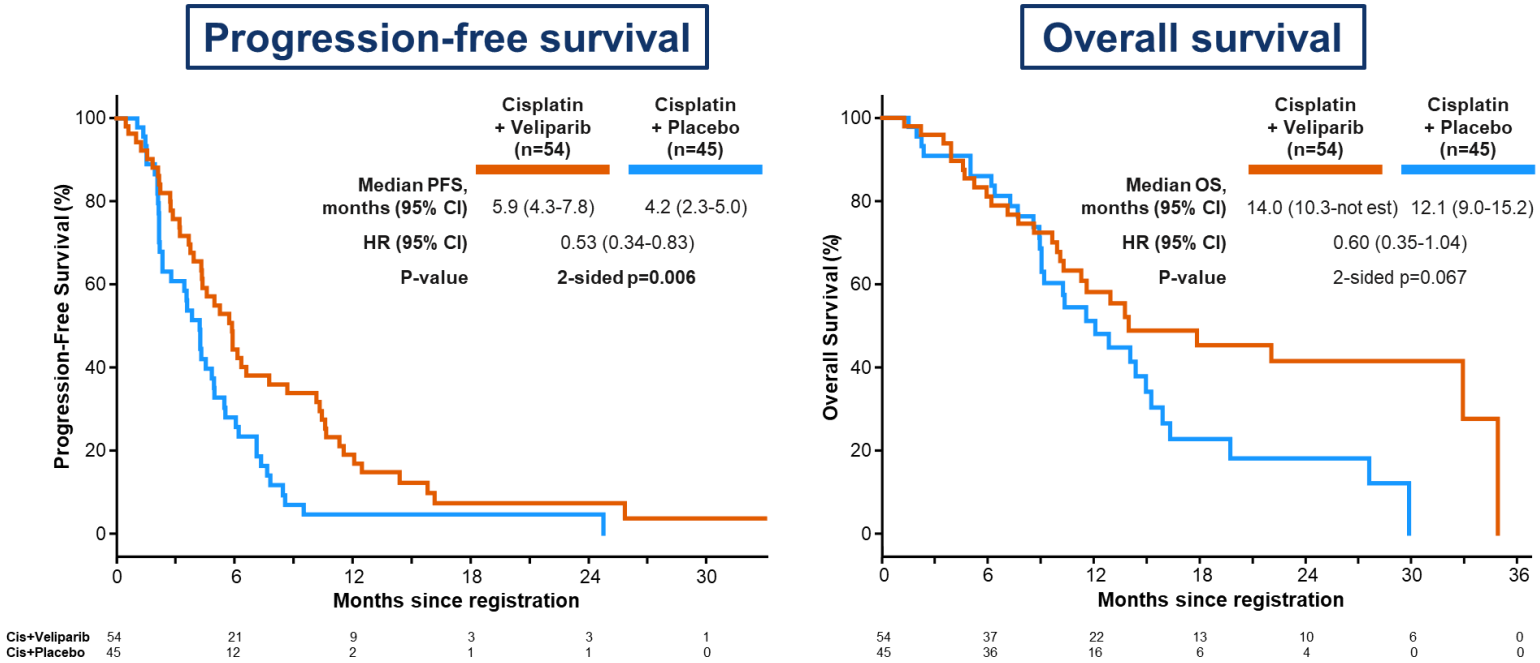
Secondary end points:
- Overall survival
- Objective response rate
- Clinical benefit rate

[a]TNBC defined as estrogen receptor (ER) and progesterone receptor (PgR) immunohistochemical (IHC) nuclear staining of ≤1% and HER2 negative per ASCO/CAP guidelines
[b]Randomization stratified by number of prior cytotoxic regimens for metastatic disease (0 vs. 1)

Rodler E. et al. Lancet Oncol. 2023 Feb;24(2):162-174.

SWOG CANCER RESEARCH NETWORK

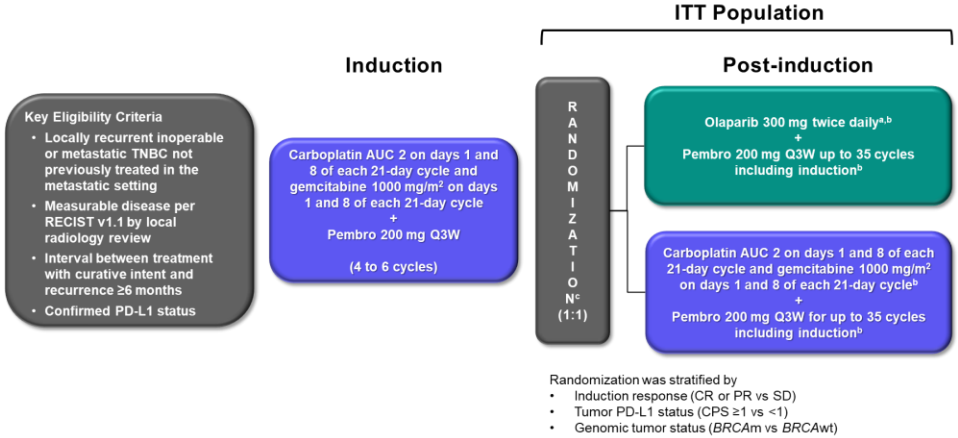
SWOG 1418: BRCA-like Group



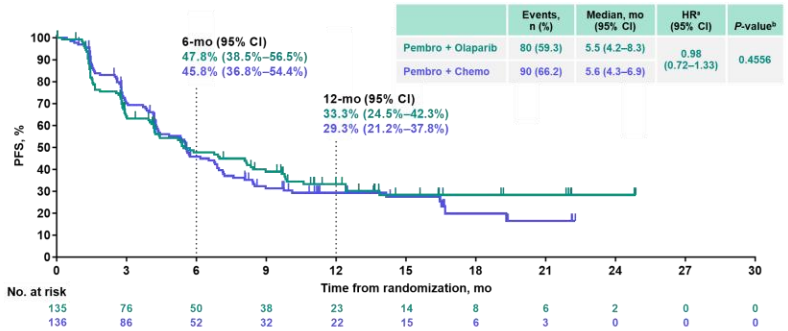
ORR (n=83): 45% vs 33%

Rodler E. et al. Lancet Oncol. 2023 Feb;24(2):162-174.

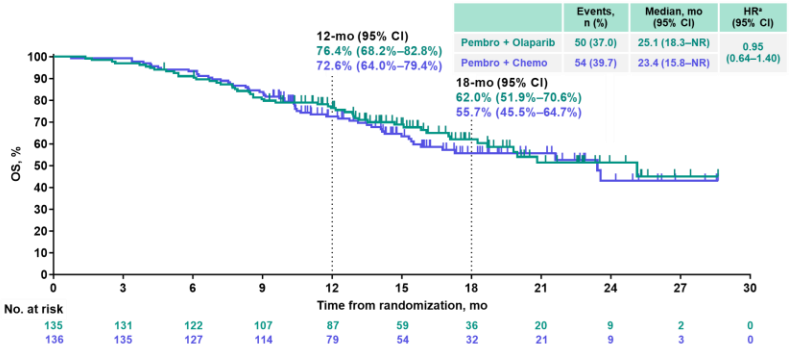
KEYLYNK-009 (NCT04191135) (TNBC)



PFS



OS

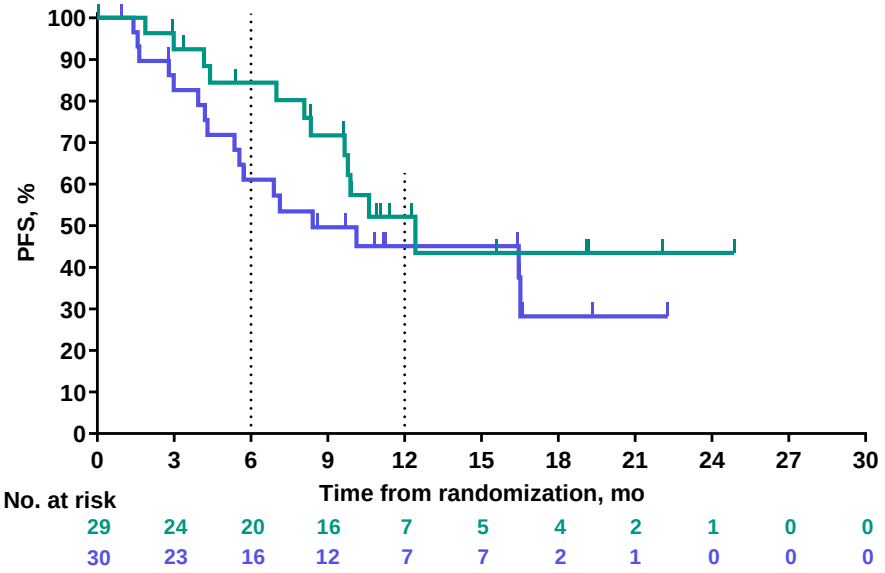


Rugo H. et al AACR 2024

KEYLYNK-009 (NCT04191135)

t*BRCA*m Population

	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	12 (41.4)	12.4 (8.3–NR)	0.70 (0.33–1.48)
Pembro + Chemo	17 (56.7)	8.4 (5.4–NR)	



Rugo H. et al AACR 2024

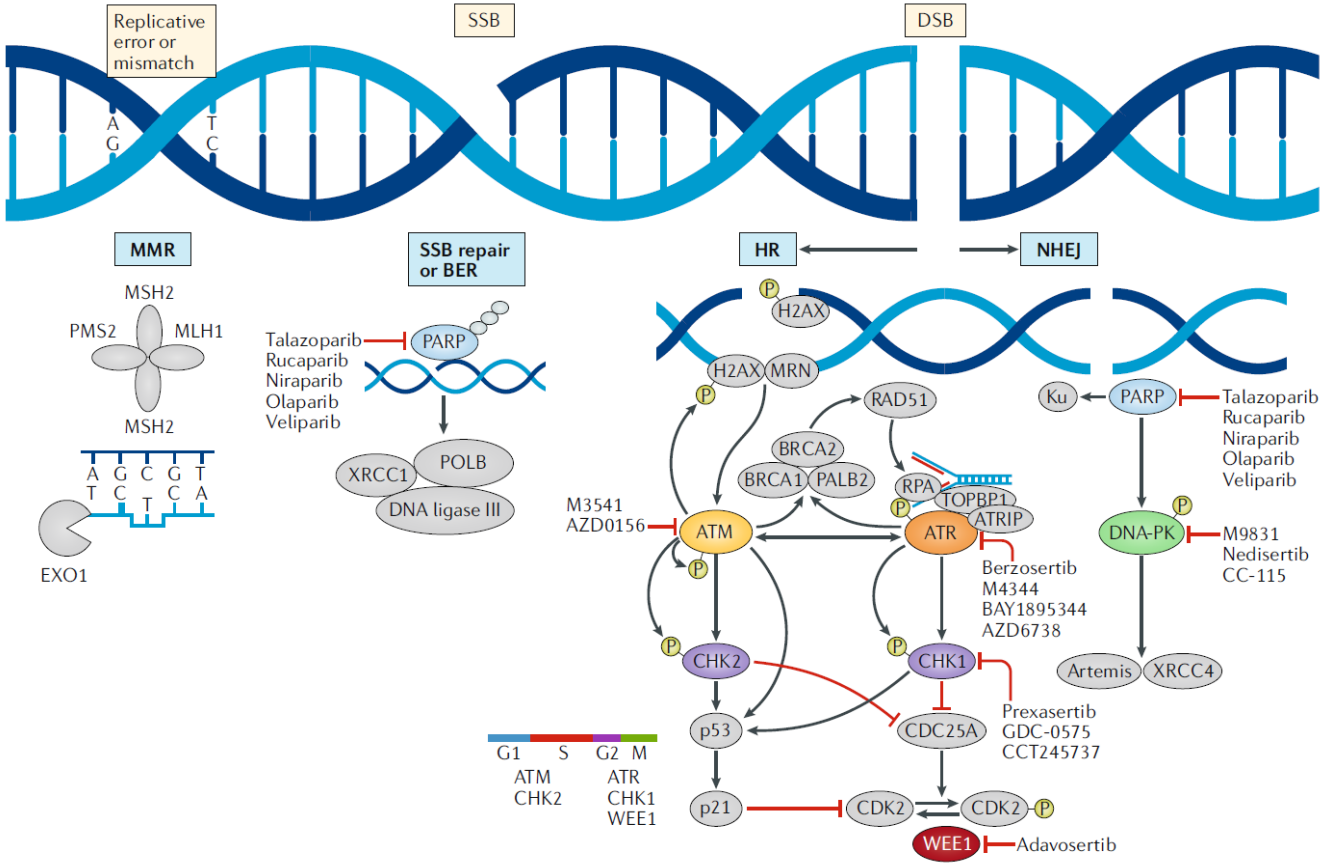
So, What to Choose? Key Takeaways.

Drug	ORR PARPi vs. control	mPFS (months) PARPi vs. control	Median Duration of Response (months) PARPi vs. control
Olaparib	59.9% vs. 28.8%	7.0 vs. 4.2	6.4 vs. 7.1
Talazoparib	62.6% vs. 27.2%	8.6 vs. 5.6	5.4 vs. 3.1
CbT + Veliparib	75.8% vs. 74.1%	14.5 vs. 12.6	14.7 vs. 11.0

- None of the trials were able to demonstrate OS benefit
- The addition of lower dose veliparib to chemo did not move the needle clinically, in my opinion over chemotherapy alone or 2 sequential therapies
- Still consider single agent PARP inhibitor or a clinical trial
- Combinations with next generation PARP inhibitors should also be considered in future trials

* based on month length of 30 days

Litton JK et al. *N Engl J Med.* 2018;379(8):753-763. Robson M et al. *N Engl J Med.* 2017;377(6):523-533 Dieras V et al. Lancet Oncol. 2020 Oct;21(10):1269-1282.



Pilie, Tang, Mills and Yap. Nat Rev Clin Oncol 2018 Oct 24

Objectives

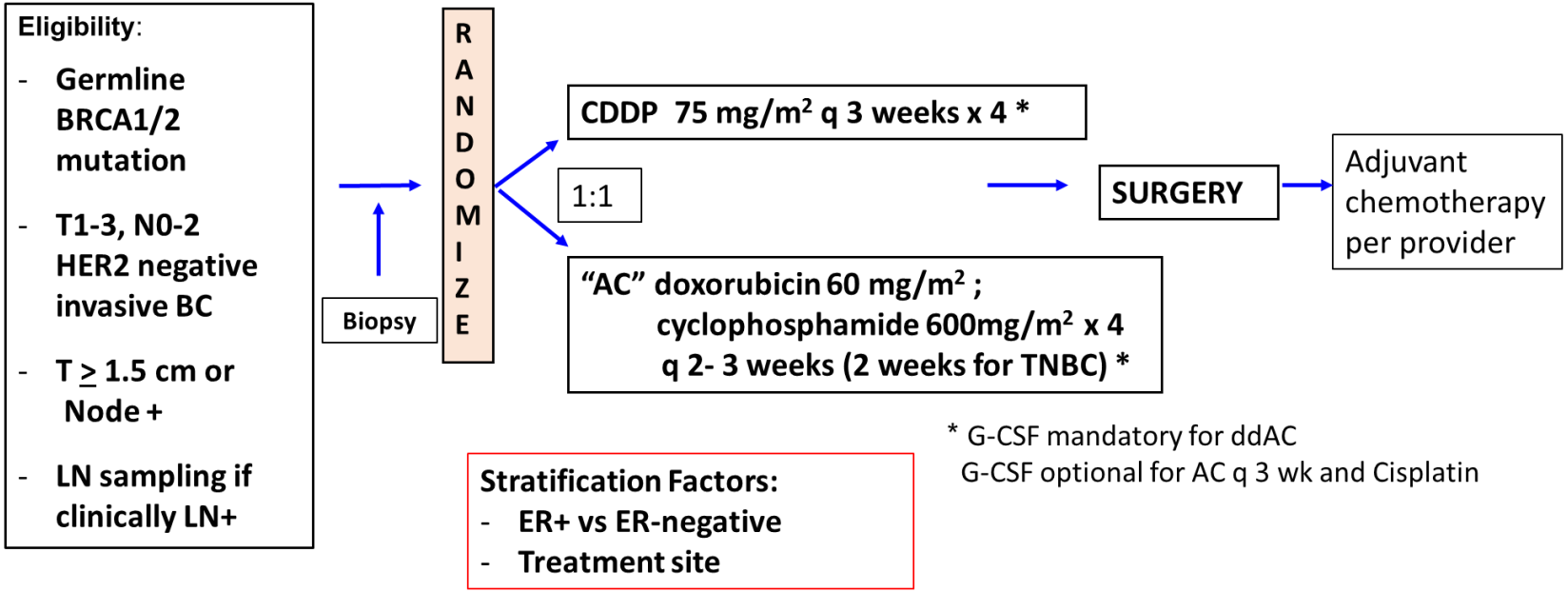
- Metastatic TNBC
- **Neoadjuvant TNBC**
- Adjuvant TNBC

Neoadjuvant PARP/Chemo Combination Trials

PARP inhibitor (dose)	Phase/Name	Treatment Arms	Patient Population	Response Rate
veliparib (50 mg BID)	II / I-SPY 2	veliparib-carboplatin (AUC=6, q3 weeks) vs. standard NAC	stage II-III (n=39 in exp arm, n=21 in control) 100% TNBC	**estimated pCR:** 51% vs 26% in control
veliparib (50 mg BID)	III / BrighTNess	3 arms: paclitaxel/carboplatin/veliparib vs. paclitaxel/carboplatin vs. paclitaxel (all pts received AC x 4 prior to surgery)	stage II-III (n=634, assigned 2:1:1) 100% TNBC (15% w/ *gBRCA)*	**pCR:** Pac/Cb/Veliparib = 53% Pac/Cb arm = 58% Pac arm = 31%
olaparib (100 mg BID)	II / GeparOla NCT02789332	standard neoadjuvant chemotherapy with either olaparib or carboplatin (AUC=2, weekly)	High-risk Stage I (either TNBC or HRD+) or stage II-III Pac+Olaparib vs. Pac/Cb All followed by EC	**pCR (overall):** Pac/Olaparib: 55.1% Pac/Cb: 48.6% ***tBRCA 1/2m:*** Pac/Olaparib: 60% Pac/Cb: 60%
olaparib (150 mg BID day -2 to 10 or 150 mg BID day 3 to day 14)	II/III/ PARTNER NCT03150576	olaparib with weekly paclitaxel and carboplatin (AUC=5, q3 weeks) vs paclitaxel and carboplatin (all get anthracycline-based regimen prior to surgery)	TNBC or *gBRCA*	AACR 2024

Rugo HS et al. N Engl J Med. 2016; 375 (1): 23-34; Loibl S et al. Lancet Oncol. 2018; 19 (4): 497-509; Fasching P. et al. Ann Oncol. 2021 Jan;32(1):49-57; Abraham JE.et al. Nature. 2024 Apr 8 epub

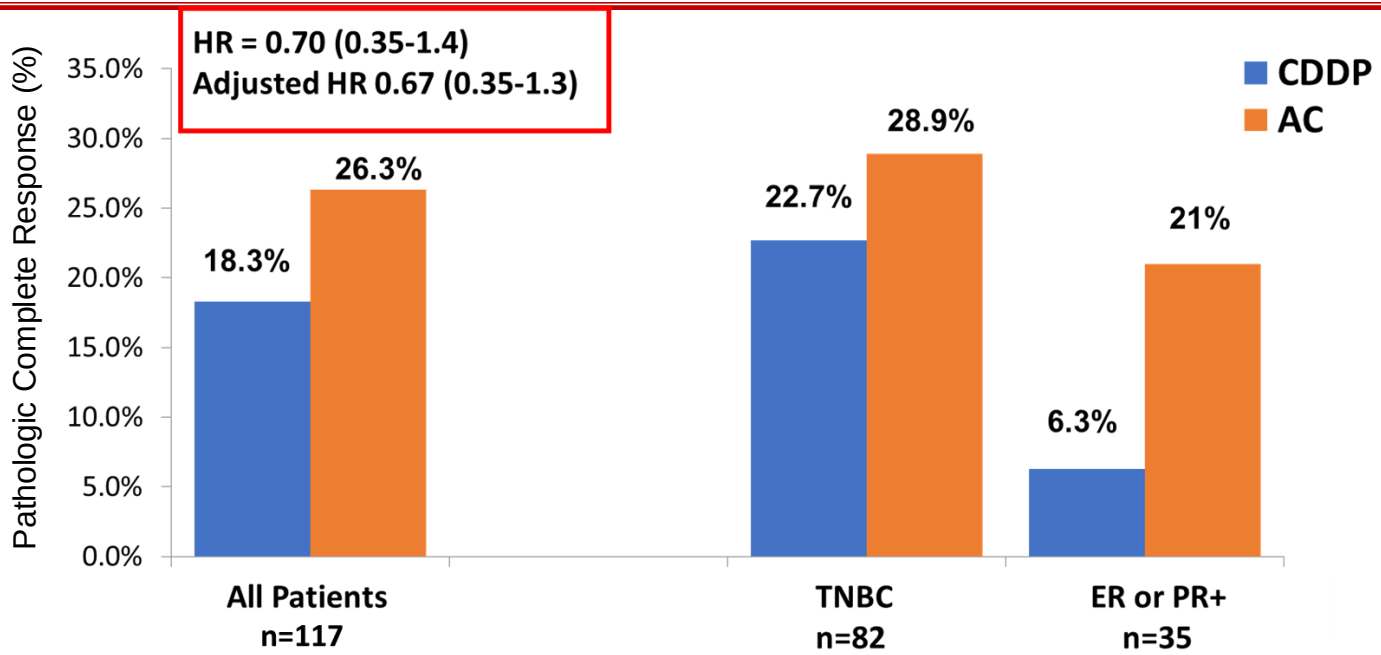
INFORM (TBCRC 031): Study Design



Original target accrual was 170, ↓ to 118 after slow accrual

Tung N et al. SABCS 2019. Abstract GS6-03.
Tung N et al. *J Clin Oncol.* 2020;38(14):1539-1548.

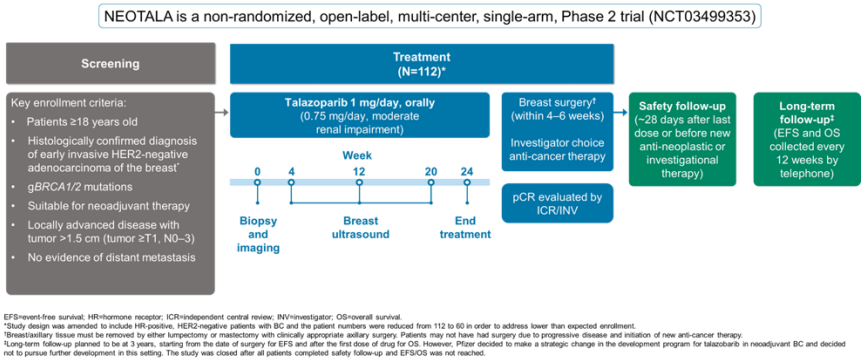
INFORM (TBCRC 031): pCR



Tung N et al. SABCS 2019. Abstract GS6-03.
Tung N et al. *J Clin Oncol.* 2020;38(14):1539-1548.

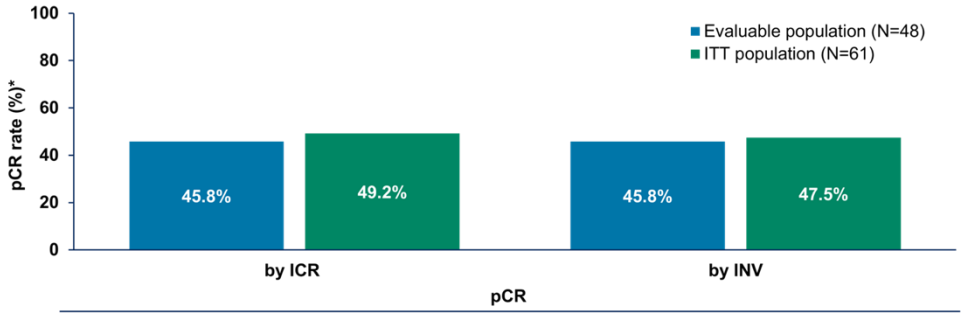
NeoTALA

Schema



EFS=event-free survival; HR=hormone receptor; ICR=independent central review; INV=investigator; OS=overall survival.
*Study design was amended to include HR-positive, HER2-negative patients with BC and the patient numbers were reduced from 112 to 60 in order to address lower than expected enrollment.
†Breast/axillary tissue must be removed by either lumpectomy or mastectomy with clinically appropriate axillary surgery. Patients may not have had surgery due to progressive disease and initiation of new anti-cancer therapy.
‡Long-term follow-up planned to be at 3 years, starting from the date of surgery for EFS and after the first dose of drug for OS. However, Pfizer decided to make a strategic change in the development program for talazoparib in neoadjuvant BC and decided not to pursue further development in this setting. The study was closed after all patients completed safety follow-up and EFS/OS was not reached.

Results



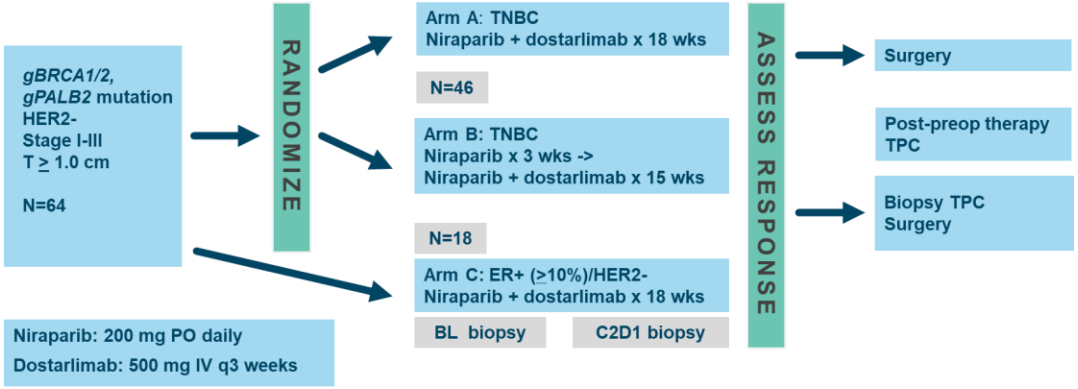
95% CI†	(32.0–60.6)	(36.7–61.6)	(32.0–60.6)	(35.0–60.1)
80% CI†	(36.4–55.2)	(41.0–57.4)		
Posterior probability that true pCR rate exceeds 45%	0.55	0.75		

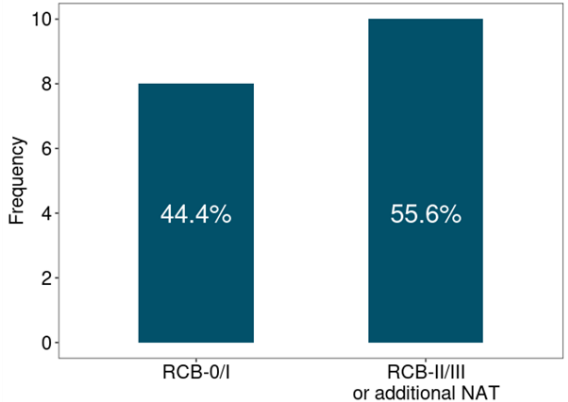
*The denominator is N, the number of patients in the evaluable/ITT analysis set as per ICR/INV.
†The exact CI was calculated using the Blaker's method.

Trial stopped early by sponsor for business reasons (N=61).
pCR rates similar to previous pilot study, but did not meet prespecified significance

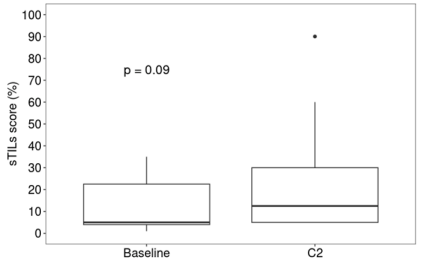
Litton J et al. Oncologist. 2023 Oct 3;28(10):845-855

TBCRC-056





- **12 patients** with evaluable paired BL and C2 sTILs
- Exposure to therapy led to an **11.9% increase** in sTILs at 3 weeks (mean increase 11.9% to 23.8%, p=0.09)



Mayer EL et al. SABCS 2025

Neoadjuvant PARP/Chemo Combination Trials

PARP inhibitor (dose)	Phase/Name	Treatment Arms	Patient Population	Response Rate
veliparib (50 mg BID)	II / I-SPY 2	veliparib-carboplatin (AUC=6, q3 weeks) vs. standard NAC	stage II-III (n=39 in exp arm, n=21 in control) 100% TNBC	**estimated pCR:** 51% vs 26% in control
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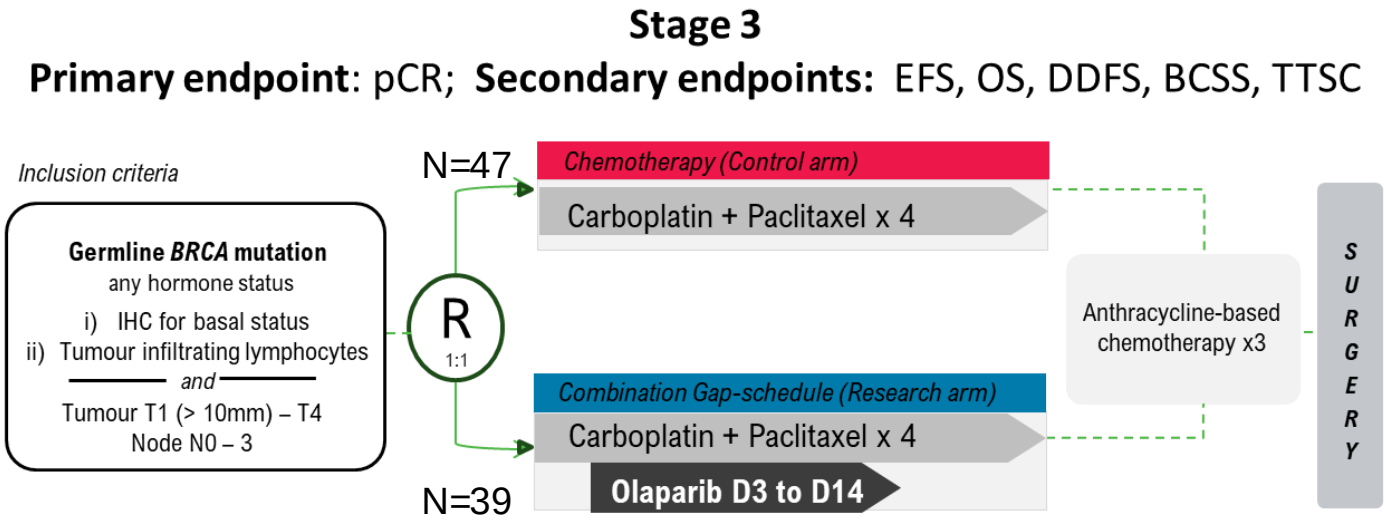
olaparib (100 mg BID)	II / GeparOla NCT02789332	standard neoadjuvant chemotherapy with either olaparib or carboplatin (AUC=2, weekly)	High-risk Stage I (either TNBC or HRD+) or stage II-III Pac+Olaparib vs. Pac/Cb All followed by EC	**pCR (overall):** Pac/Olaparib: 55.1% Pac/Cb: 48.6% ***tBRCA 1/2m:*** Pac/Olaparib: 60% Pac/Cb: 60%
olaparib (150 mg BID day -2 to 10 or 150 mg BID day 3 to day 14)	II/III/ PARTNER NCT03150576	olaparib with weekly paclitaxel and carboplatin (AUC=5, q3 weeks) vs paclitaxel and carboplatin (all get anthracycline-based regimen prior to surgery)	TNBC or *gBRCA*	AACR 2024

Rugo HS et al. N Engl J Med. 2016; 375 (1): 23-34; Loibl S et al. Lancet Oncol. 2018; 19 (4): 497-509; Fasching P. et al. Ann Oncol. 2021 Jan;32(1):49-57; Abraham JE.et al. Nature. 2024 Apr 8 epub

PARTNER trial

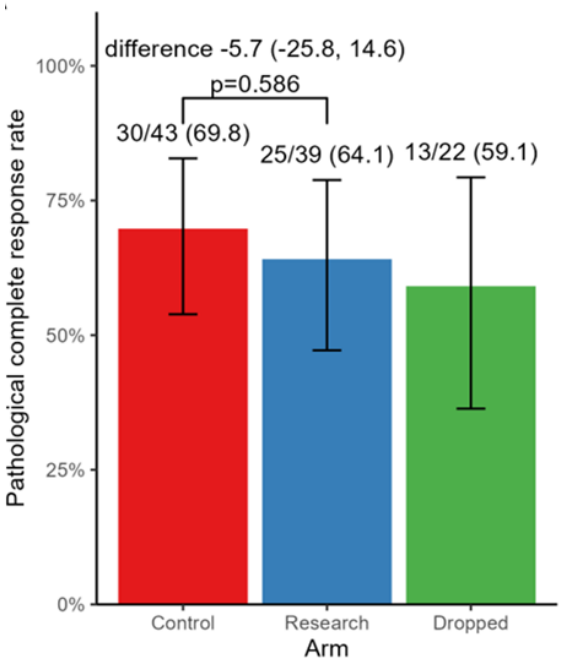


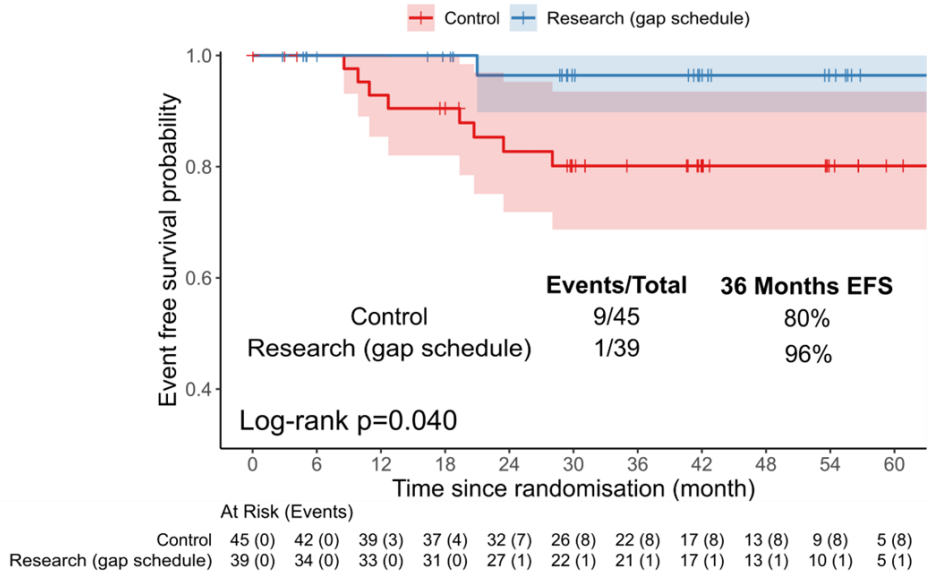
Stratification factors: Histopathological involvement of axillary nodes, Tumour size <=50mm, >50mm, TILs <=60, >60%
Paclitaxel 80mg/m2 Day 1,8,15 every 3 weeks, Carboplatin AUC5 Day 1 every 3 weeks, Olaparib 150mg twice daily Day-2 to Day 10 or Day 3 to Day 14 every three weeks

Stopped early because OlympiA trial reported out (188 randomized patients originally planned)

Abraham JE.et al. Nature. 2024 Apr 8 epub and Abraham JE et al AACR Annual meeting 2024

PARTNER Trial Results





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Objectives

- Metastatic TNBC
- Neoadjuvant TNBC
- **Adjuvant TNBC**

OlympiA: Study Design

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → Surgery → +/- Radiotherapy

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → **≥ 6 cycles** Adjuvant Chemotherapy → +/- Radiotherapy

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

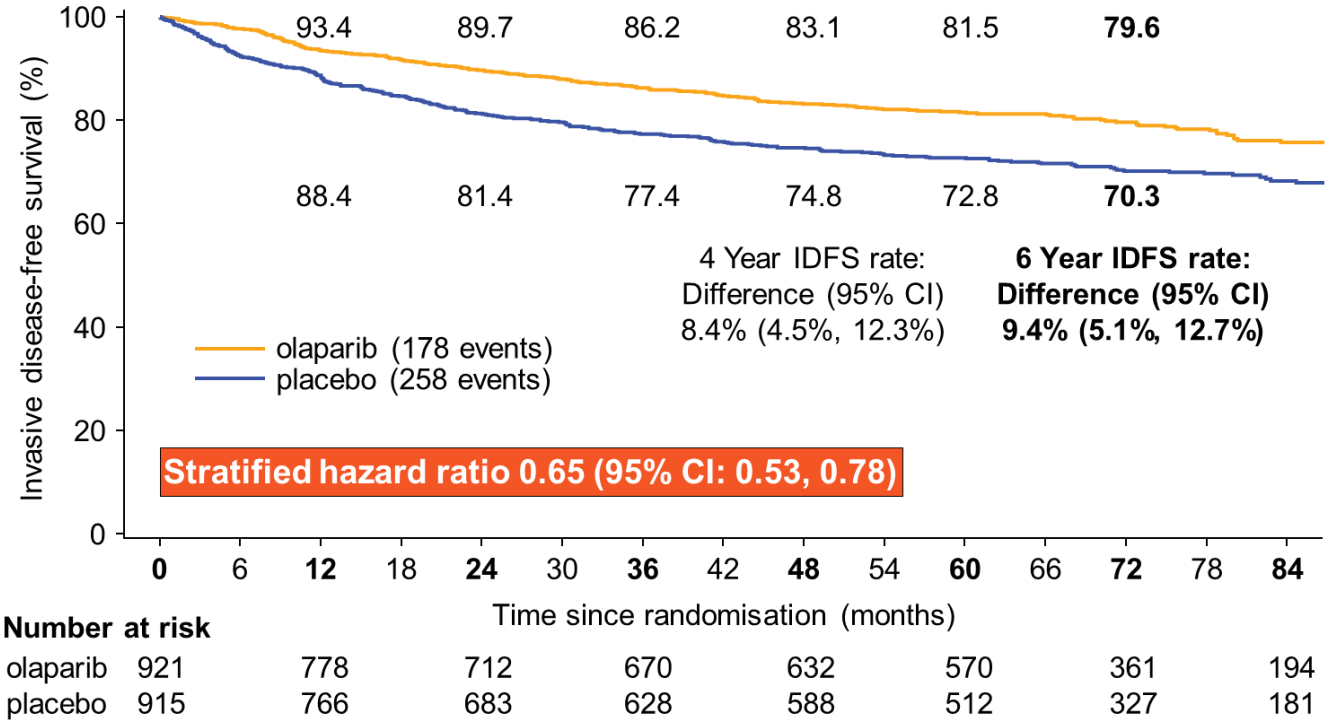
Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

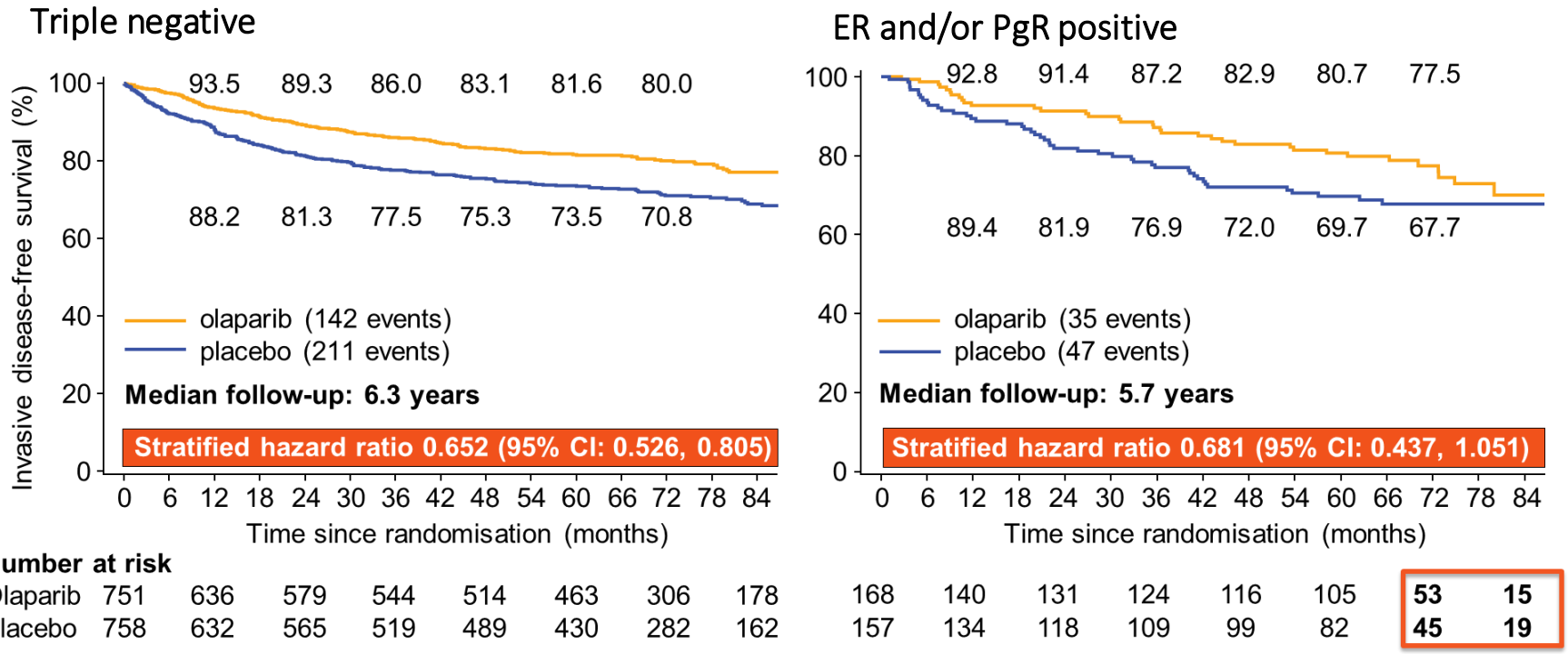
Tutt A et al. ASCO 2021. Abstract LBA1.

2025 Updated Survival Analysis-OlympiA



Garber JE et al. SABCS 2025.

2025 Updated Survival Analysis-OlympiA



Number at risk

Olaparib	751	636	579	544	514	463	306	178	168	140	131	124	116	105	**53**	**15**
Placebo	758	632	565	519	489	430	282	162	157	134	118	109	99	82	**45**	**19**

Garber JE et al. SABCS 2025.

What should I give in adjuvant setting for high-risk early breast cancer now?

In my opinion only, because we do not have all the data needed:

g*BRCA*wt HR+

- Tamoxifen or AI ± ovarian suppression and abemaciclib

g*BRCA*m HR+

- Olaparib ± tamoxifen or AI ± ovarian suppression
- ***Consider*** starting ET + abemaciclib after olaparib completed

g*BRCA*wt TNBC

- Capecitabine
  - Continue the adjuvant immunotherapy

g*BRCA*m TNBC

- Olaparib ± continued immunotherapy

Waiting on SWOG 1418 to give more information on the benefit of adjuvant immunotherapy

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