QUESITO CLINICO: Nelle pazienti BRCA mutate con carcinoma mammario metastatico pretrattate con chemioterapia, è opportuno considerare un trattamento con olaparib rispetto a chemioterapia

Le evidenze derivanti dalla letteratura

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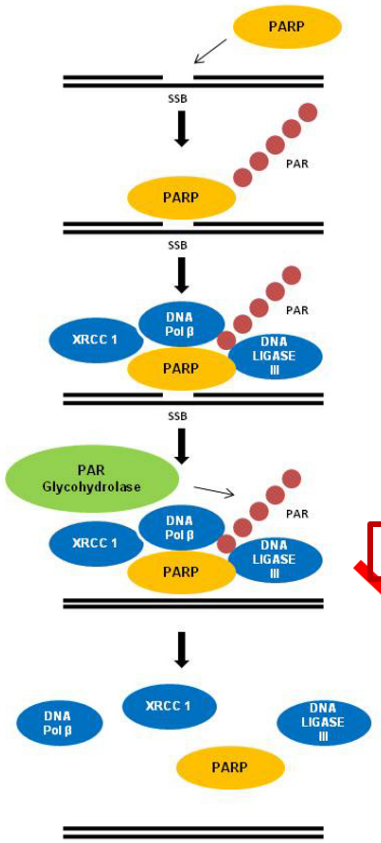
PARP

PARP Inhibitors Mechanism of Action



1. Single Strand Breaks in DNA Recognized by PARP

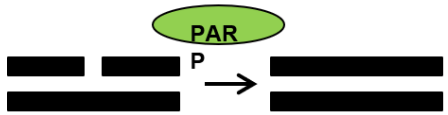
Inhibit Catalytic Activity

2. PARP flags DNA for repair and recruits help, and adds PAR to itself

PARP trapping

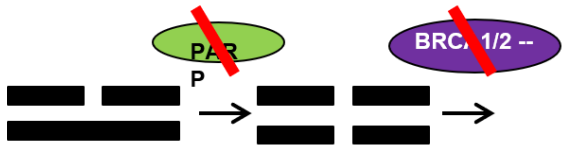
3. After DNA is fixed, the help is released

Cancer Cell able to repair single strand break



Cancer Cell treated with PARP inhibitor

BRCA Cancer Cell treated with PARP inhibitor



Cancer Cell dies

PALB2 and other mutations may have similar sensitivity

OlympiAD

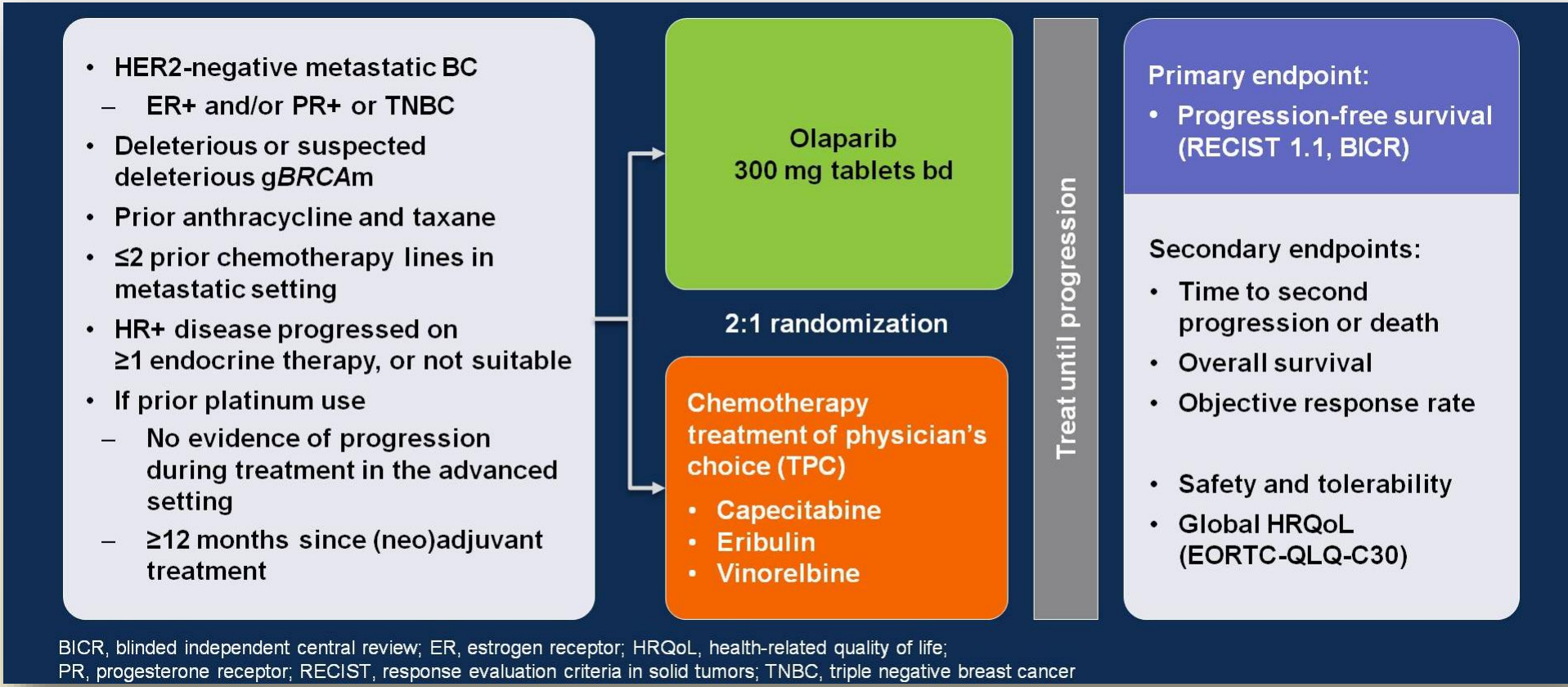
ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

Robson m, NEJM 2017

OlympiAD: study design



BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

Robson M, ASCO 2017

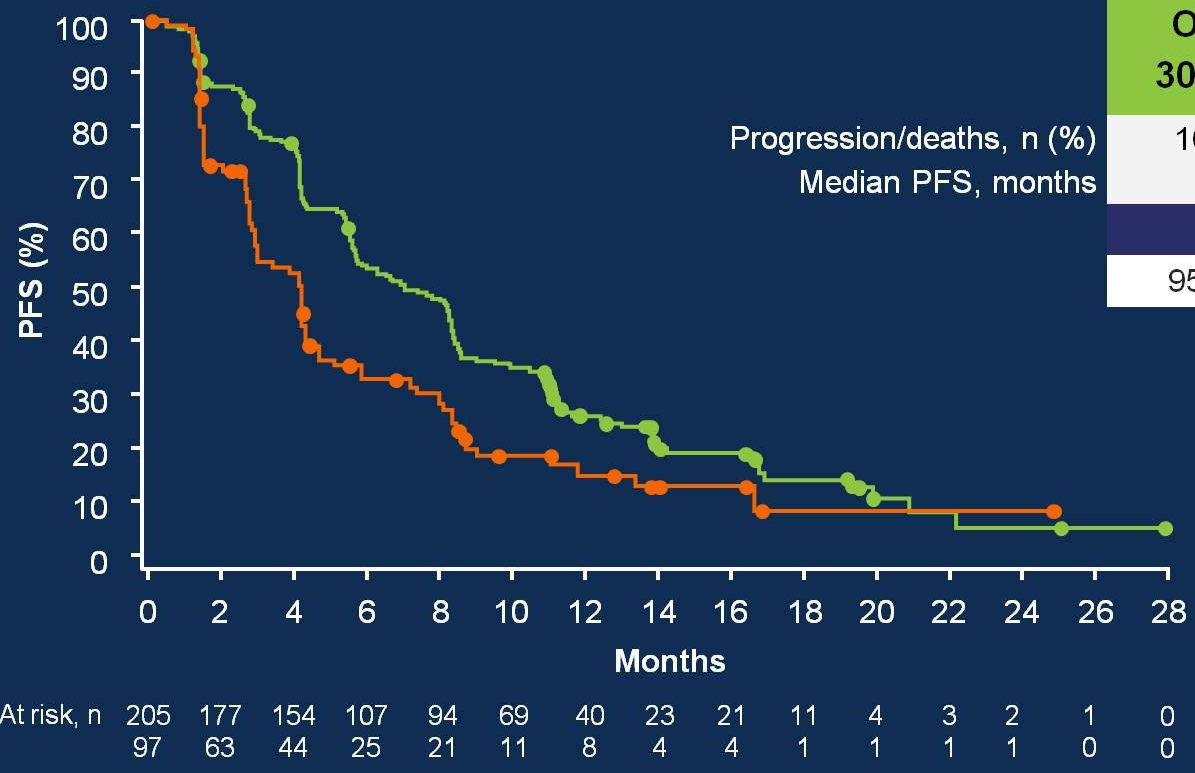
OlympiAD: Patients Characteristics

	Olaparib 300 mg bd (N=205)	Chemotherapy TPC (N=97)
Age, years (median, range)	44 (22–76)	45 (24–68)
Male, n (%)	5 (2)	2 (2)
White race, n (%)	134 (65)	63 (65)
BRCA mutation status, n (%)		
BRCA1	117 (57)	51 (53)
BRCA2	84 (41)	46 (47)
Both	4 (2)	0
Hormonal receptor status, n (%)		
ER+ and/or PR+	103 (50)	49 (51)
TNBC	102 (50)	48 (49)
Prior chemotherapy for metastasis, n (%)	146 (71)	69 (71)
Prior platinum treatment, n (%)	60 (29)	26 (27)

Robson M, ASCO 2017

OlympiAD: PFS

Primary endpoint: progression-free survival by BICR

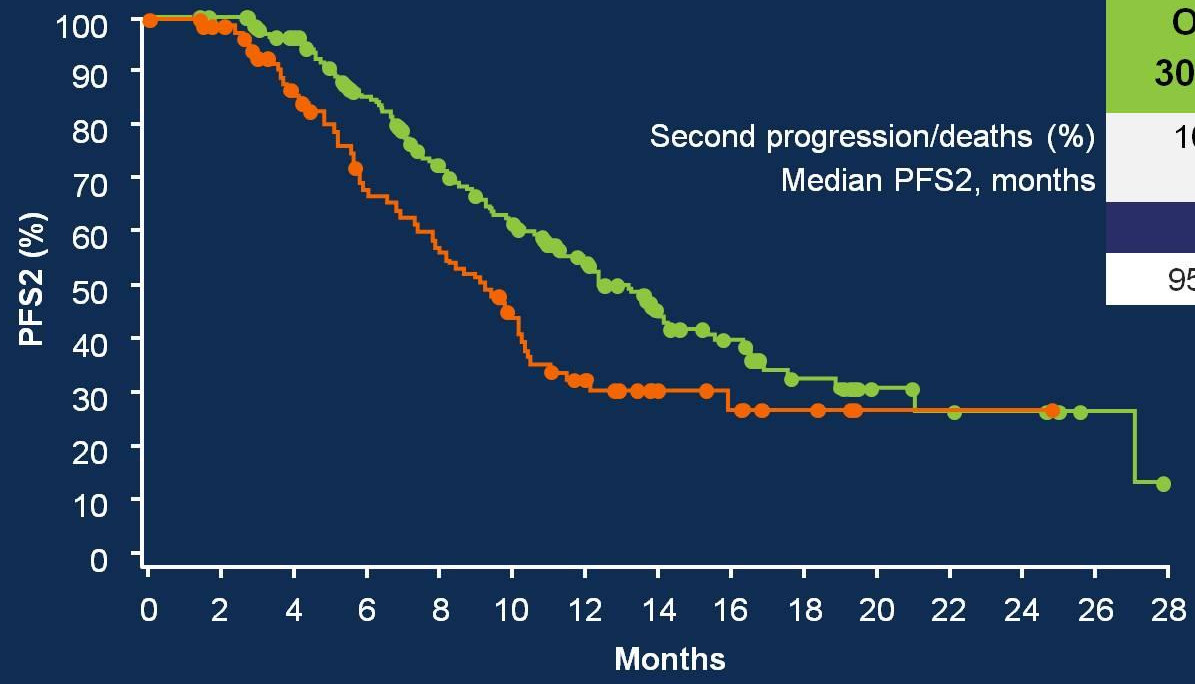


	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

Robson M, ASCO 2017

OlympiAD: PFS by investigators

Time to second progression or death (PFS2) by investigator assessment

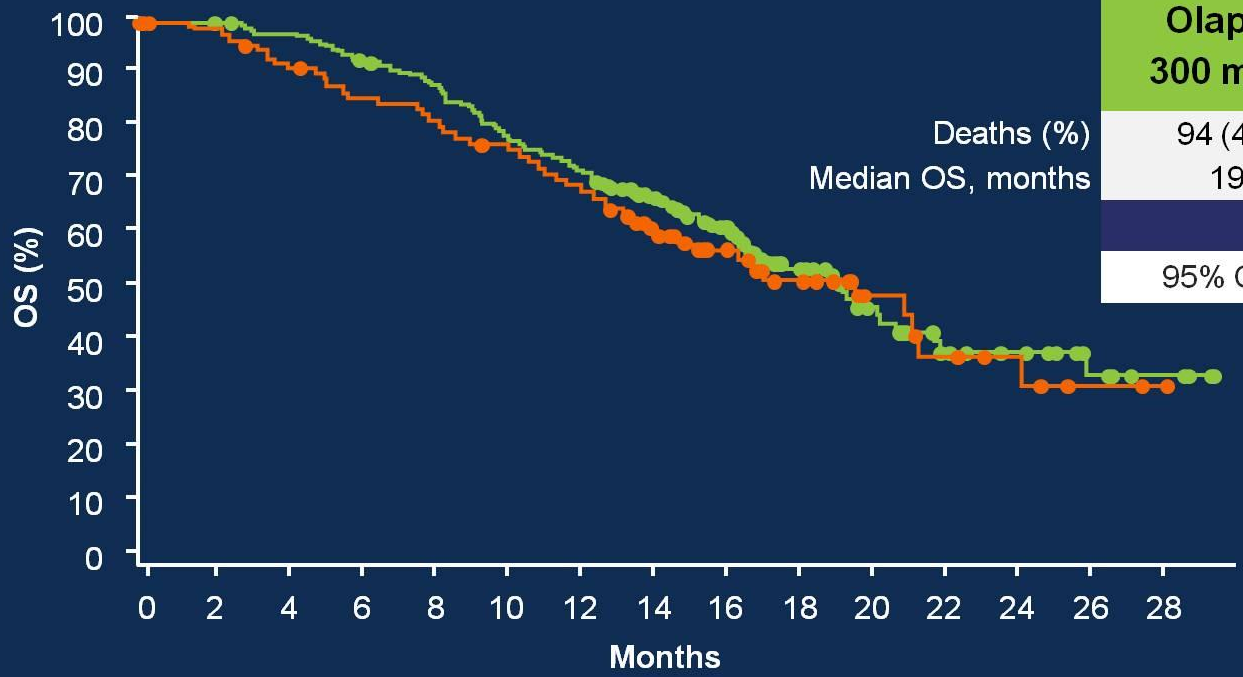


	Olaparib 300 mg bd	Chemotherapy TPC
Second progression/deaths (%)	104 (50.7)	53 (54.6)
Median PFS2, months	13.2	9.3
HR 0.57		
95% CI 0.40 to 0.83; *P*=0.0033		

Robson M, ASCO 2017

OlympiAD: Overall Survival

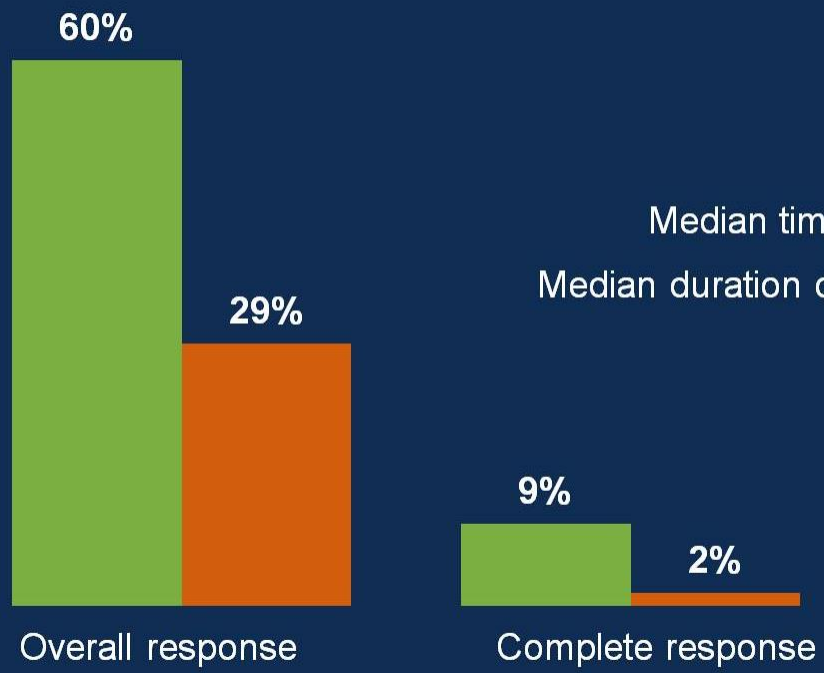
Overall survival (interim analysis; 46% data maturity)



	Olaparib 300 mg bd	Chemotherapy TPC
Deaths (%)	94 (45.9)	46 (47.4)
Median OS, months	19.3	19.6
HR 0.90		
95% CI 0.63 to 1.29; *P*=0.5665		

Robson M, ASCO 2017

OlympiAD: Objective response (ICR)

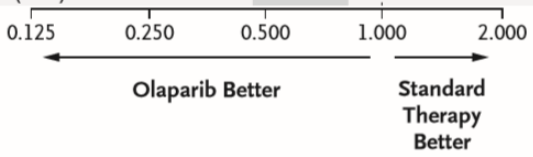


	Olaparib 300 mg bd	Chemotherapy TPC
n	167	66
Median time to response, days	47	45
Median duration of response, months	6.2 (4.6–7.2)	7.1 (2.8–12.2)

Robson M, ASCO 2017

OlympiAD: Subgroup Analysis

Subgroup	Olaparib	Standard Therapy	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	163/205 (79.5)	71/97 (73.2)	0.58 (0.43–0.80)
Previous chemotherapy for metastatic breast cancer			
Yes	119/146 (81.5)	51/69 (73.9)	0.65 (0.47–0.91)
No	44/59 (74.6)	20/28 (71.4)	0.56 (0.34–0.98)
Hormone-receptor status			
Hormone-receptor positive	82/103 (79.6)	31/49 (63.3)	0.82 (0.55–1.26)
Triple negative	81/102 (79.4)	40/48 (83.3)	0.43 (0.29–0.63)
Previous platinum-based therapy for breast cancer			
Yes	50/60 (83.3)	21/26 (80.8)	0.67 (0.41–1.14)
No	113/145 (77.9)	50/71 (70.4)	0.60 (0.43–0.84)
Measurable disease			
Yes	139/165 (84.2)	56/72 (77.8)	0.58 (0.43–0.80)
No	24/40 (60.0)	15/25 (60.0)	0.57 (0.30–1.12)
Progressive disease at the time of randomization			
Yes	127/159 (79.9)	53/73 (72.6)	0.60 (0.43–0.83)
No	36/46 (78.3)	18/24 (75.0)	0.72 (0.41–1.30)
BRCA mutation type			
BRCA1	94/114 (82.5)	41/50 (82.0)	0.54 (0.37–0.79)
BRCA2	64/84 (76.2)	30/45 (66.7)	0.68 (0.45–1.07)
Age			
<65 yr	154/194 (79.4)	67/93 (72.0)	0.66 (0.49–0.88)
≥65 yr	9/11 (81.8)	4/4 (100.0)	Not calculated
Region			
Asia	46/59 (78.0)	21/28 (75.0)	0.57 (0.34–0.97)
Europe	77/97 (79.4)	34/35 (75.6)	0.71 (0.48–1.08)
North America and South America	40/49 (81.6)	16/24 (66.7)	0.39 (0.22–0.73)
Race			
White	109/134 (81.3)	47/63 (74.6)	0.67 (0.48–0.95)
Other	54/71 (76.1)	24/34 (70.6)	0.51 (0.32–0.85)



Robson, NEJM 2017

OlympiAD: Adverse events

Table 2. Summary of Adverse Events.*

Variable	Olaparib Group (N=205)		Standard-Therapy Group (N=91)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event				
Any	199 (97.1)	75 (36.6)	88 (96.7)	46 (50.5)
Anemia†	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia‡	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Decreased white-cell count	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Fatigue	59 (28.8)	6 (2.9)	21 (23.1)	1 (1.1)
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Cough	35 (17.1)	0	6 (6.6)	0
Increased alanine aminotransferase level	23 (11.2)	3 (1.5)	16 (17.6)	1 (1.1)
Increased aspartate aminotransferase level	19 (9.3)	5 (2.4)	15 (16.5)	0
Palmar–plantar erythrodysesthesia	1 (0.5)	0	19 (20.9)	2 (2.2)
Dose reduction owing to adverse event	52 (25.4)	NA	28 (30.8)	NA
Treatment interruption or delay owing to adverse event	72 (35.1)	NA	25 (27.5)	NA
Treatment discontinuation owing to adverse event	10 (4.9)	NA	7 (7.7)	NA

Robson, NEJM 2017

Quality of life

The mean (±SD) score on the QLQ-C30 at baseline was **63.2±21.0 in the olaparib group** and **63.3±21.2 in the standard-therapy group**.

The adjusted mean (±SE) change from baseline across all time points was **3.9±1.2 in the olaparib group** and **–3.6±2.2 in the standard-therapy group**, with a corresponding **estimated difference of 7.5 points (95% CI, 2.5 to 12.4; p = 0.004).**

Author's comment

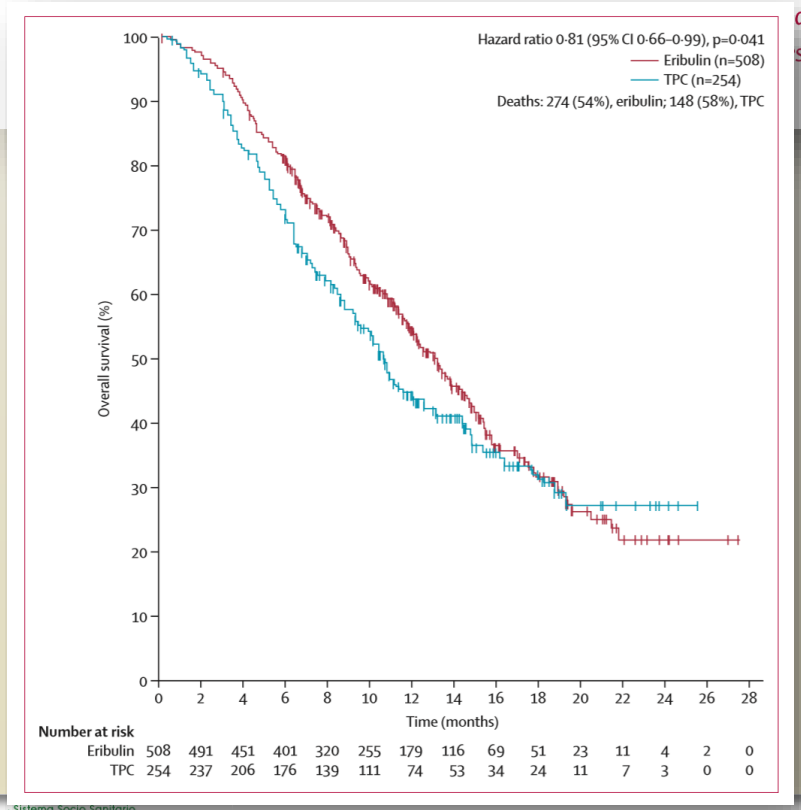
"Olaparib will probably be best used early in the course of metastatic breast cancer. It helps preserve patient quality of life, offers the chance to postpone the need for [intravenous] chemotherapy, and avoids side effects like hair loss and low white blood cell counts"

Robson, The ASCO Post, 4.6.2017

EMBRACE

Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study

Javier Cortes, Joyce O'Shaughnessy, David Loesch, Joanne L Blum, Linda T Vahdat, Katarina Petrakova, Philippe Chollet, Alexey Manikas, dimirov, Fatima Cardoso, Han Koh, Philippe Bougnoux, Corina E Dutcus, Seth Seegobin, Denis Mir, s, on behalf of the EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice



Median overall survival was 13·1 months (95% CI 11·8–14·3) in patients receiving eribulin and 10·6 months (9·3–12·5)

Cortes, Lancet 2011

TNT study

TNT: A randomized phase III trial of carboplatin compared with docetaxel for patients with metastatic or recurrent locally advanced triple negative or *BRCA1/2* breast cancer

Andrew Tutt, *Paul Ellis, Lucy Kilburn, Cheryl Gillett, Sarah Pinder, Jacinta Abraham, Sophie Barrett, Peter Barrett-Lee, Stephen Chan, Maggie Cheang, Mitch Dowsett, Lisa Fox, Patrycja Gazinska, Anita Grigoriadis, Alexander Gutin, Catherine Harper-Wynne, Matthew Hatton, Sarah Kernaghan, Jerry Lanchbury, James Morden, Julie Owen, Jyoti Parikh, Peter Parker, Nazneen Rahman, Rebecca Roylance, Adam Shaw, Ian Smith, Rose Thompson, Kirsten Timms, Holly Tovey, Andrew Wardley, Gregory Wilson, Mark Harries, Judith Bliss*

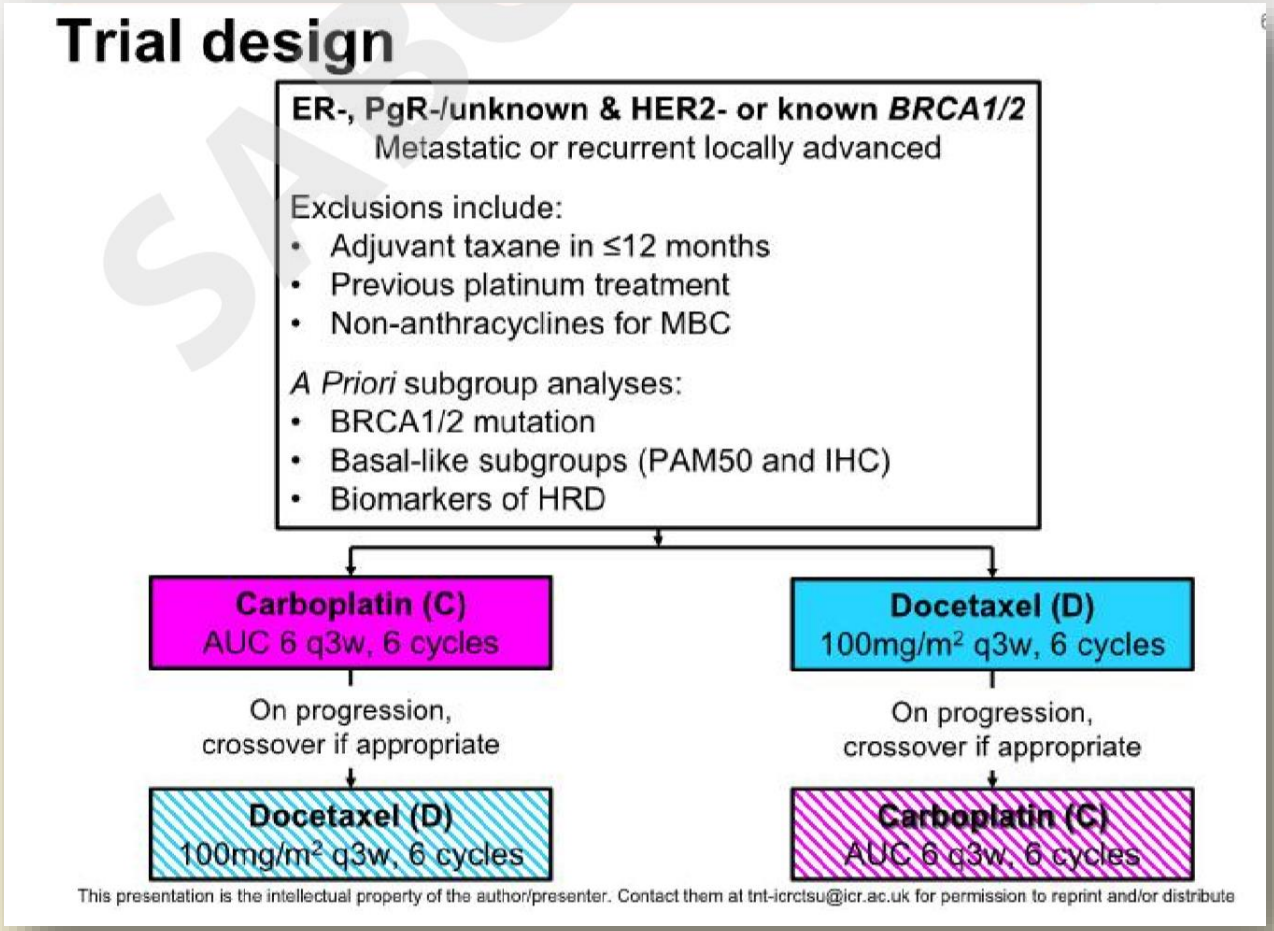
on behalf of the TNT trial management group and investigators

CRUK/07/012

Making the discoveries that defeat cancer

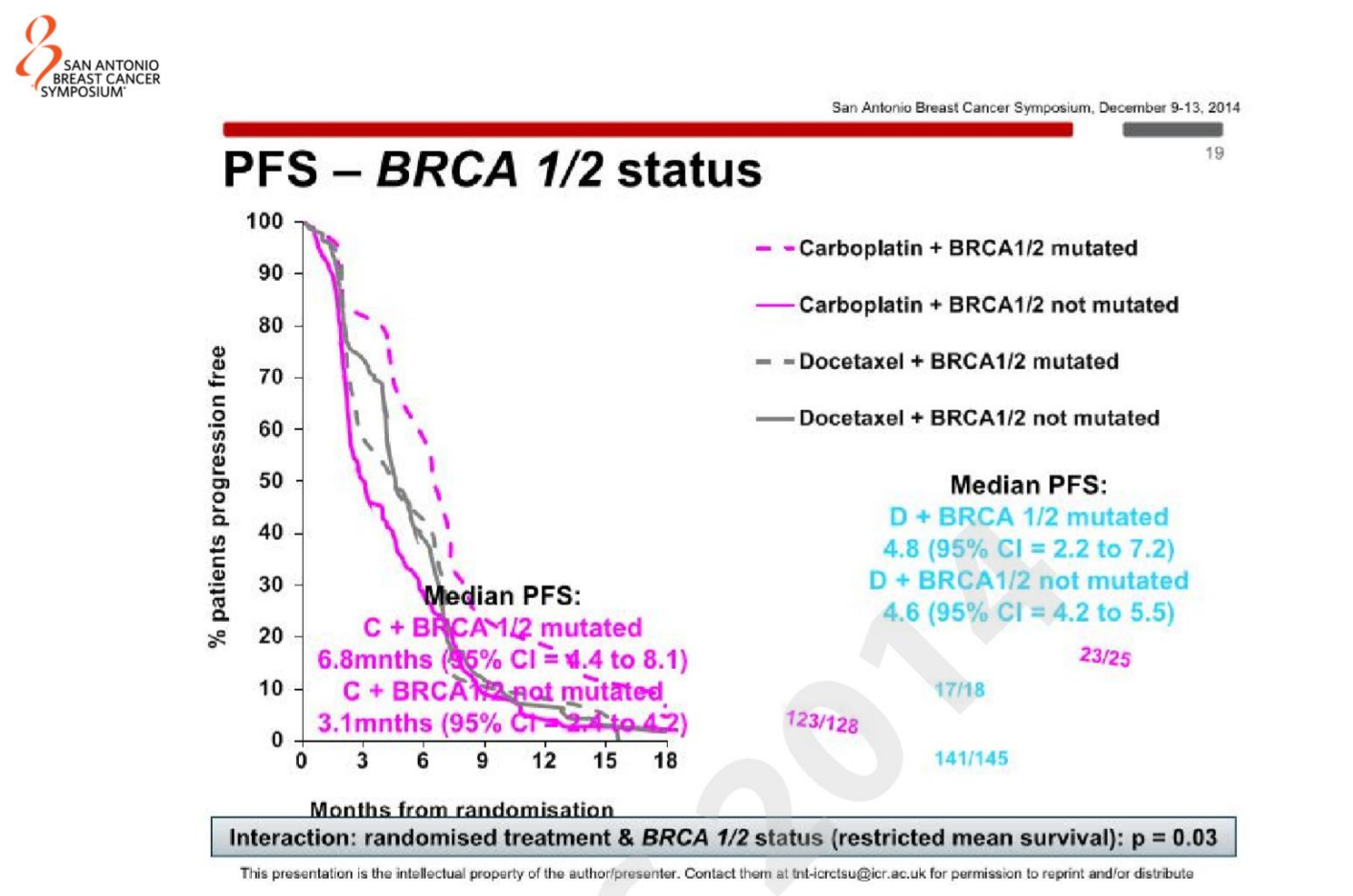
Tutt, SABCS 2014

TNT study



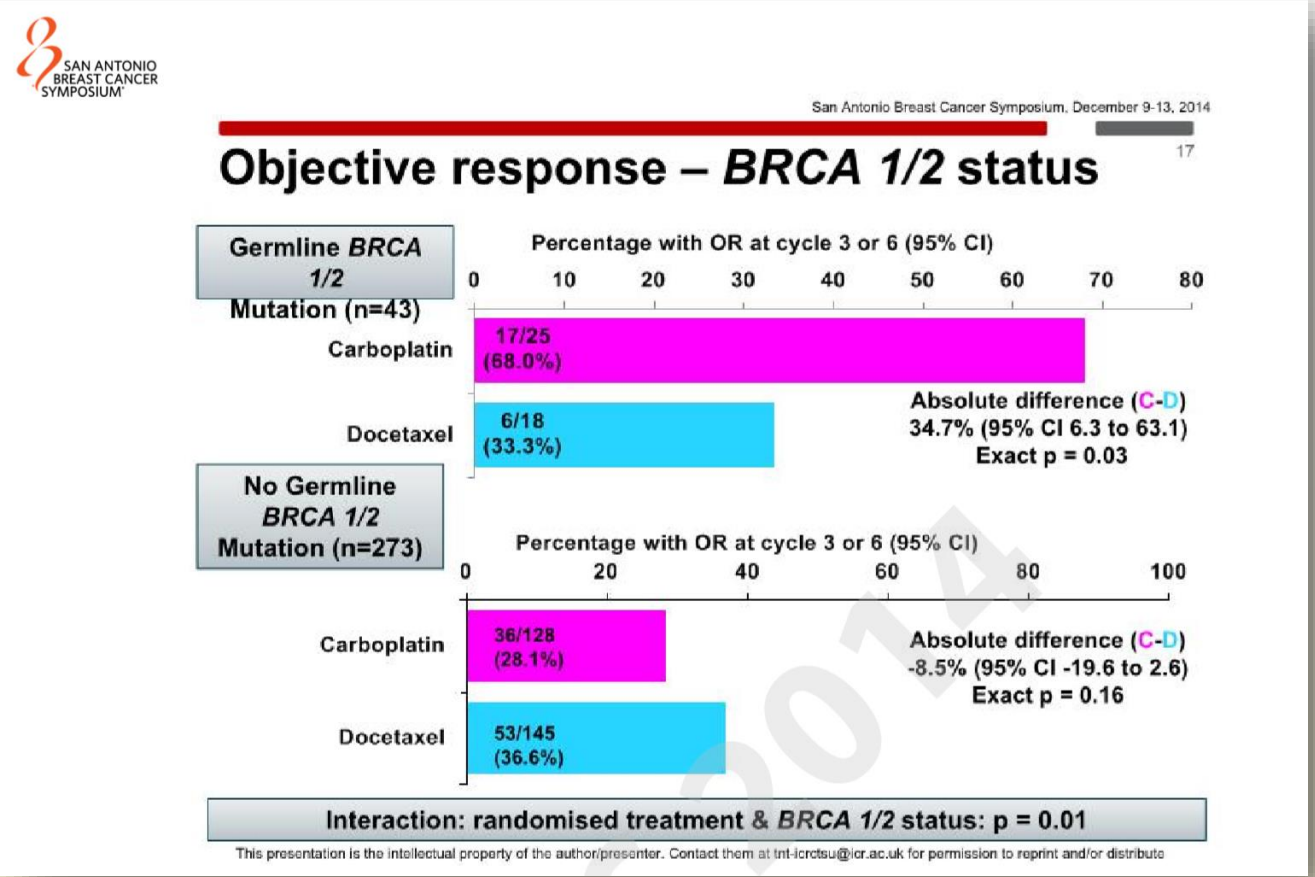
Tutt, SABCS 2014

TNT study



Tutt, SABCS 2014

TNT study



Tutt, SABCS 2014

Strength points

- ↑ PFS by 2.8 m (7.0 v 4.2 m); HR 0.58 (95% CI 0.43 to 0.80)
- Tumors shrinkage in about 60% pts in O vs 29% in CT pts
- Toxicity: anemia
- Gain in QoL

Weak points

- No OS advantage (19.3 vs 19.6 m – 95% CI 0.63-1.29); it wasn't the primary objective of the study
- Pretreatment with Carboplatin: 27-29% (only?)
- Control arm: Carboplatin
- Toxicity: not well evaluable because of the 3 drugs in the treatment arm

CONCLUSIONS

- Olaparib has a role as a proper alternative to CT in BRCA 1/2 carriers pts
- TNBC subgroup is the one who better benefits from this treatment