CARCINOMA MAMMARIO METASTATICO
I TUMORI BRCA MUTATI

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Aosta

I TUMORI BRCA MUTATI

- CARATTERISTICHE
- TRATTAMENTI
- STRATEGIE FUTURE

NEOPLASIA METASTATICA BRCA MUTATA

- CARATTERISTICHE
- TRATTAMENTI
- STRATEGIE FUTURE

BRCA1/2

odificano per proteine chiave nel processo di riparazione della doppia elica DNA (homologous

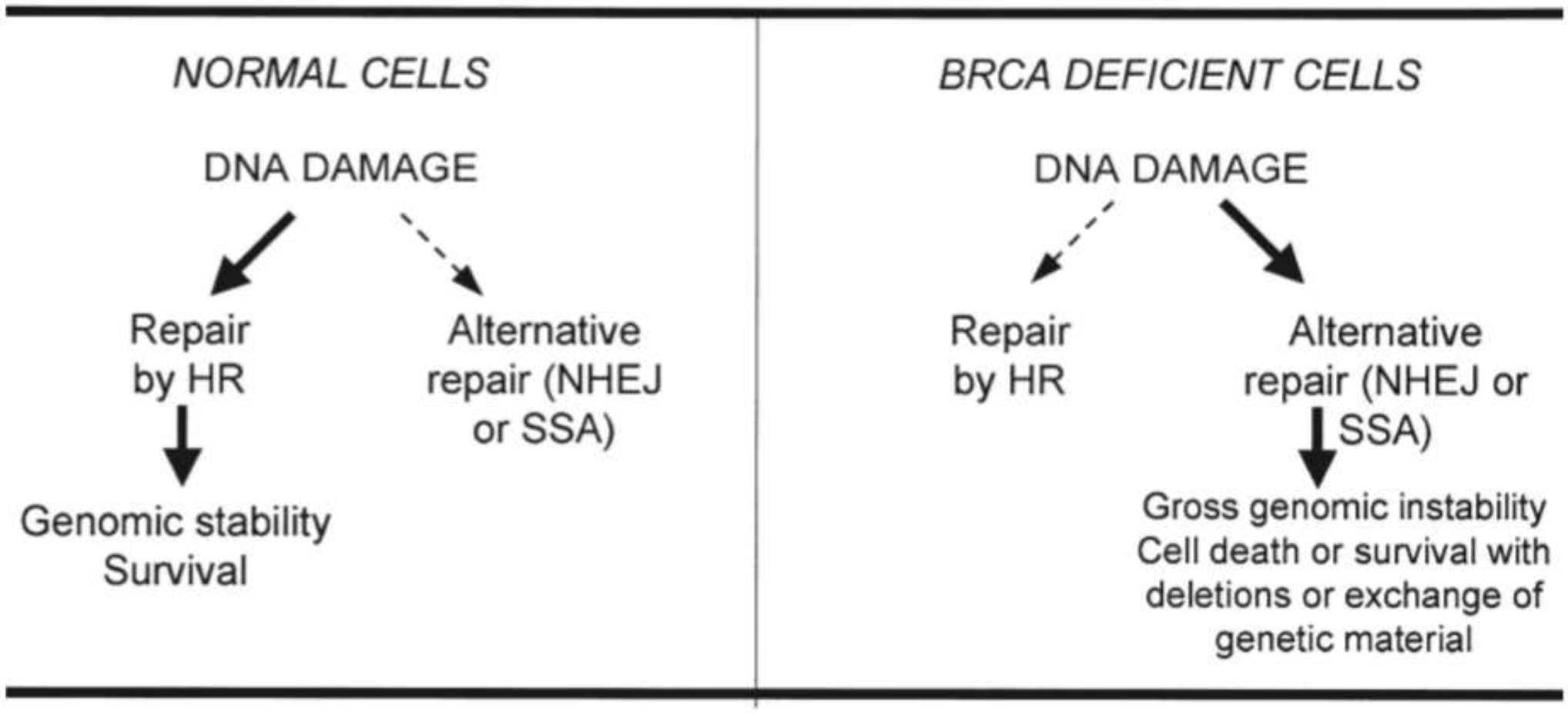


Figure 2. Alternative utilization of DSB DNA pathways in BRCA-deficient cells. DNA DSBs are repaired in normal cells, in part, by HR-based mechanisms. Functional BRCA1 and BRCA2 proteins are required for efficient repair by HR and genomic stability. In the absence of BRCA1 or BRCA2, alternative repair pathways, such as NHEJ and SSA, are utilized leading to cell death or survival with genomic damage.

Tutt et al 2005

I TUMORI BRCA MUTATI:

- Rappresentano 5-10% delle neoplasie mammarie ma circa 20% dei triple negative, neoplasie familiari, generalmente basal like

- BRCA 1 55-65% e BRCA 2 45% di probabilità di ca mammario entro i 70 aa

- BRCAness: alterazione epigenetica, gruppo di tumori che condivide le alterazioni molecolari dei BRCA mutati.

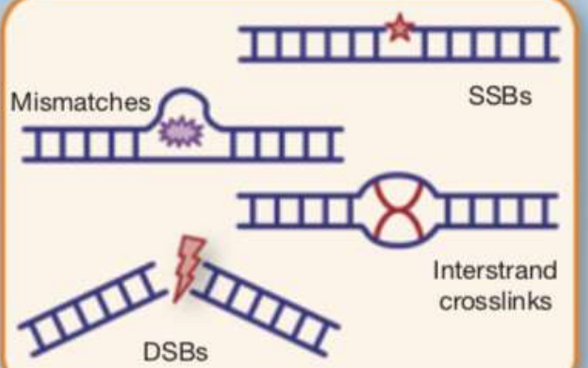
NEOPLASIA METASTATICA BRCA MUTATA

- CARATTERISTICHE
- TRATTAMENTI
- STRATEGIE FUTURE

Mutator phenotype in cancer

Precancerous lesion → Mutation in DNA-repair signaling → Accumulation of somatic mutations → Selection of malignant phenotype

DNA lesions



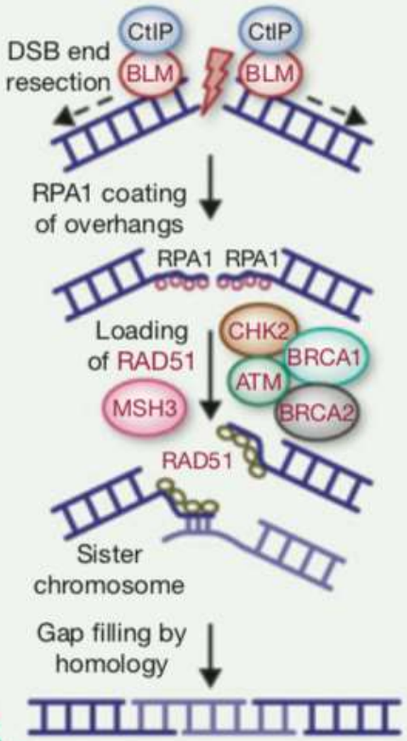
Therapeutic intervention

Compound class	Status of development	Mechanism of action	Representative drugs
PARP inhibitors	Clinical	Blockade of base excision repair	Olaparib, iniparib, rucaparib, and veliparib
DNA-PKcs inhibitors	Preclinical	Blockade of nonhomologous end joining	CC-115 and KU60648
Platinum-based chemotherapies	Clinical	Induction of interstrand crosslinks	Cisplatin, carboplatin, and oxaliplatin

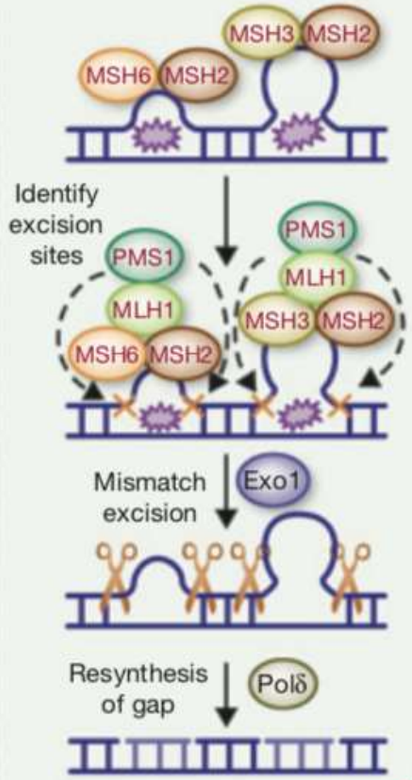
Repair

Repair

Homologous recombination
Repair of DSBs in G_2–S phase

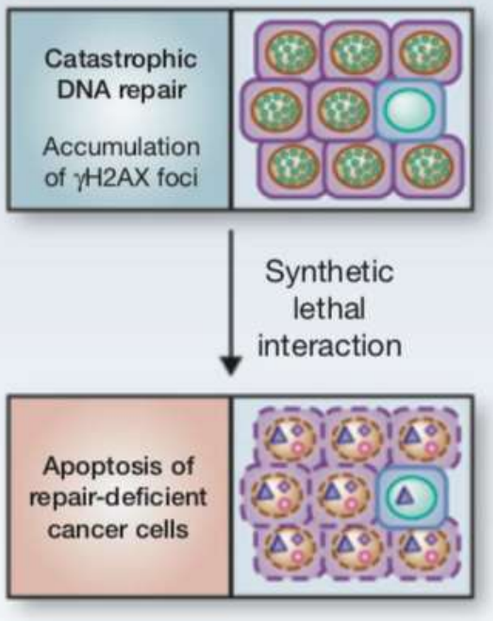


Mismatch repair

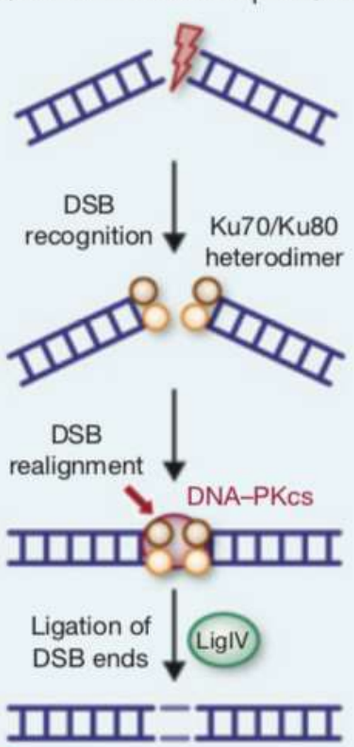


Inactivation by cancer-specific genomic alteration

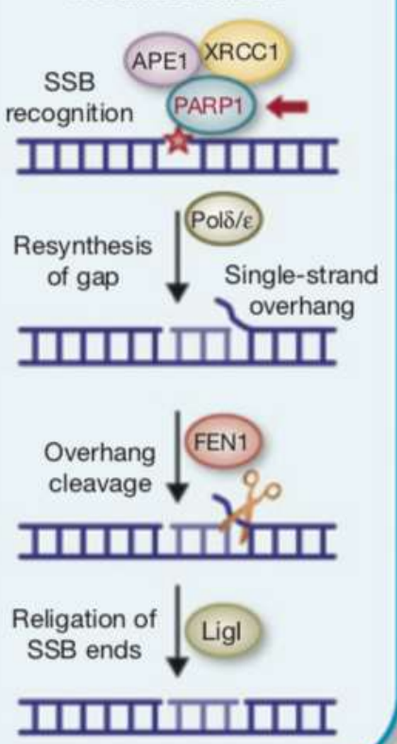
Inactivation by targeted therapeutic intervention



Nonhomologous end joining
Repair of DSBs in G_1–M phase



Base excision repair
Repair of SSBs and modified bases



Gene — Gene recurrently inactivated by genomic alteration in cancer

Gene — Target gene of specific therapeutic intervention

CCR Molecular Pathways

Trial con Platino derivati

Table 1. Selected studies with platinum salts in g*BRCA*1/2m breast cancer

Study	Disease	Phase	Total (*n*)	*BRCA*m (*n*)	TNBC (*n*)	*BRCA*m ER$^+$ (*n*)	Treatment	Response in overall population	Response in patients with wt*BRCA*1/2	Response in patients with g*BRCA*1/2m	Response in patients with *BRCA*1m
Advanced and metastatic breast cancer											
TNT[45]	Metastatic TNBC or *BRCA*1/2 mutation BC	III	376	43	363	12	Carboplatin vs docetaxel	ORR: 31% with carboplatin vs 36% with docetaxel	NR	68% with carboplatin vs 33% with docetaxel	NR
TBCRC009[48]	Metastatic TNBC	II	86	11	86	0	Cisplatin or carboplatin	ORR: 25.6% (22/86)	ORR: 19.7% (13/66)	ORR: 54.5% (6/11)	NR
NCT01611727[47]	Metastatic BC with a *BRCA*1 mutation	II	20	20[a]	14	5	Cisplatin	NR	NR	NR	ORR: 80% CR: 45%
Brocade 2 NCT01506609[82]	Locally recurrent or metastatic BC with a g*BRCA*1/2 mutation	II	99	99	42	56 (ER+ and/or PgR+)	Paclitaxel/ carboplatin/ placebo (PCP)	61%	NR	61%	NR
Early-stage disease											
NCT01630226[85]	Stage I–III BC with a *BRCA*1 mutation	II	107	107[b]	82	16	Cisplatin	NR	NR	NR	pCR: 61%
GeparSixto/ GBG 66 NCT01426880[87,88]	Stage I–III TNBC or HER2+ BC	II/III	588	50	315 291 *BRCA* known	0	Backbone regimen ± carboplatin	With vs without carboplatin: TNBC pCR: 53% vs 37% 291 *BRCA* known status: 57% vs 41%	With vs without carboplatin: TNBC pCR: 55% vs 36%	With vs without carboplatin: TNBC pCR: 65% vs 67%	NR

BC breast cancer, *CR* complete response, *ER+* oestrogen receptor-positive, *gBRCA1/2* germline BRCA1/2, *HER2+* human epidermal growth factor receptor 2-positive, *NR* not reported, *ORR* overall response rate, *pCR* pathologic complete response, *PgR+* progesterone receptor-positive, *TNBC* triple-negative breast cancer, *wtBRCA1/2* wild-type BRCA1/2

[a]All were HER2-negative, 15 were ER-negative, 17 were PgR-negative, and 14 were TNBC

[b]100 were HER2-negative (5 HER2 status unknown), 86 were ER-negative (5 ER status unknown), 91 were PgR-negative (6 PgR status unknown), and 82 were TNBC

BRCA1/2 testing NM Tung and JE Garber Springer Nature on behalf of Cancer Research UK 2018

TNT Trial: CRUK/07/012

ER-, PgR-/unknown & HER2- or known *BRCA1/2*
Metastatic or recurrent locally advanced

Exclusions include:
- Adjuvant taxane in ≤12 months
- Previous platinum treatment
- Non-anthracyclines for MBC

A Priori subgroup analyses:
- BRCA1/2 mutation
- Basal-like subgroups (PAM50 and IHC)
- Biomarkers of HRD

Carboplatin (C)
AUC 6 q3w, 6 cycles

On progression,
crossover if appropriate

Docetaxel (D)
100mg/m² q3w, 6 cycles

n-376

BRCA1/2 =
9%/12%

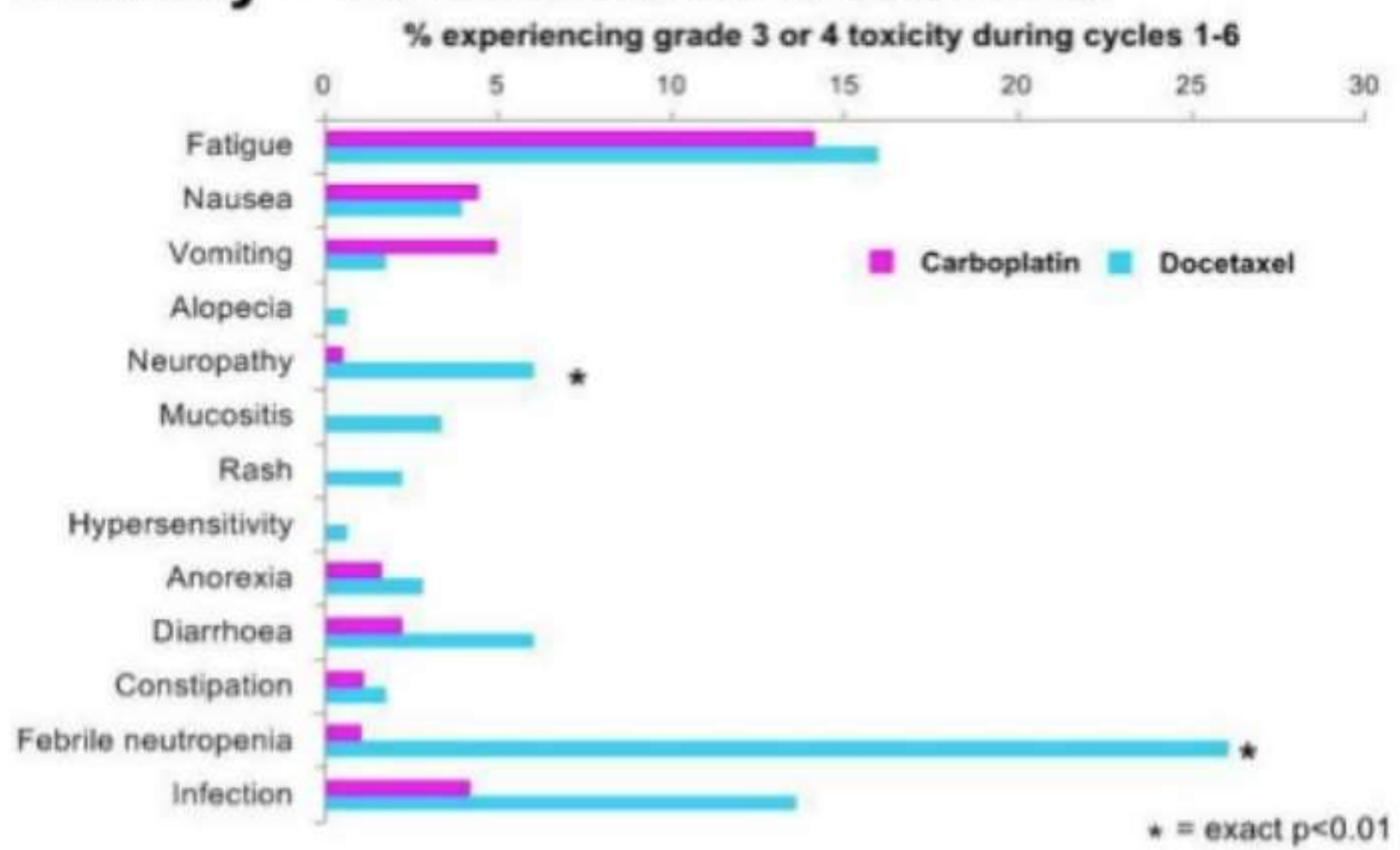
Docetaxel (D)
100mg/m² q3w, 6 cycles

On progression,
crossover if appropriate

Carboplatin (C)
AUC 6 q3w, 6 cycles

Tutt A et al, San Antonio Breast Cancer Symposium 2014

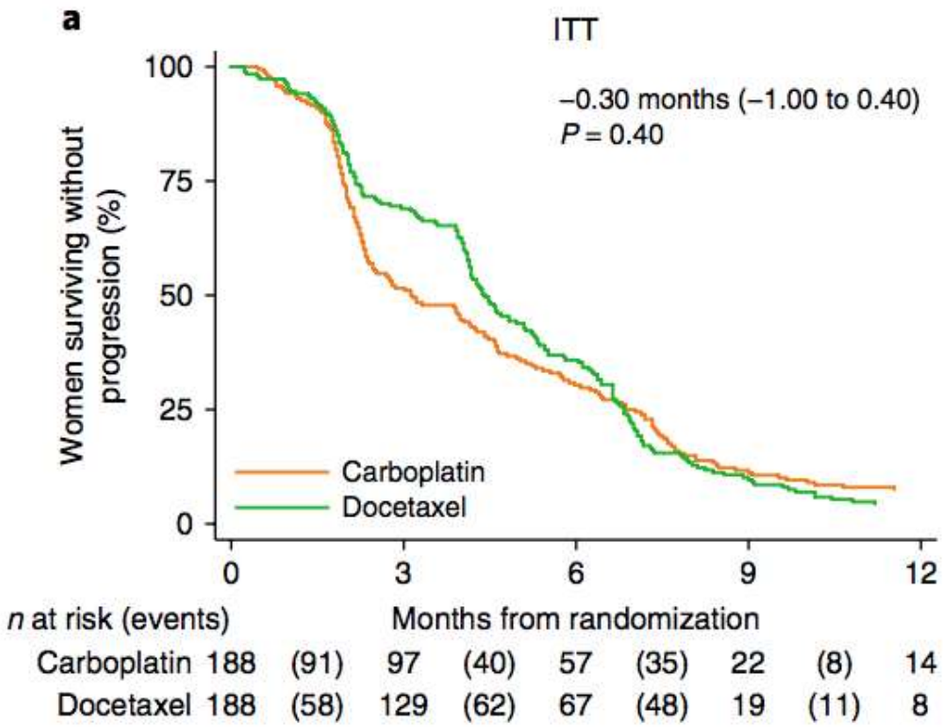
Toxicity – Randomised treatment



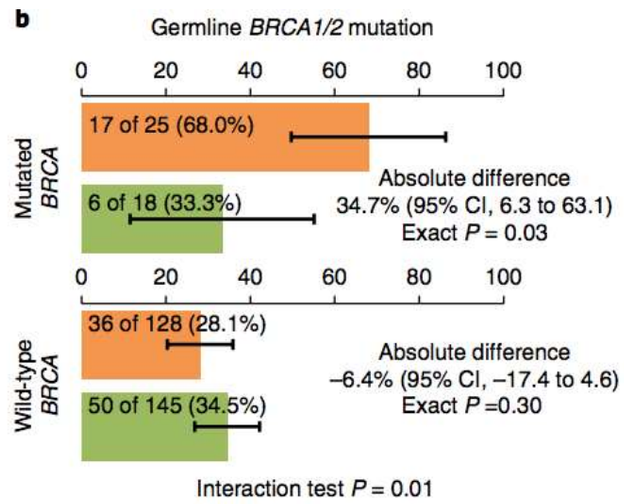
Percentages are calculated out of the number of patients who started randomised treatment.

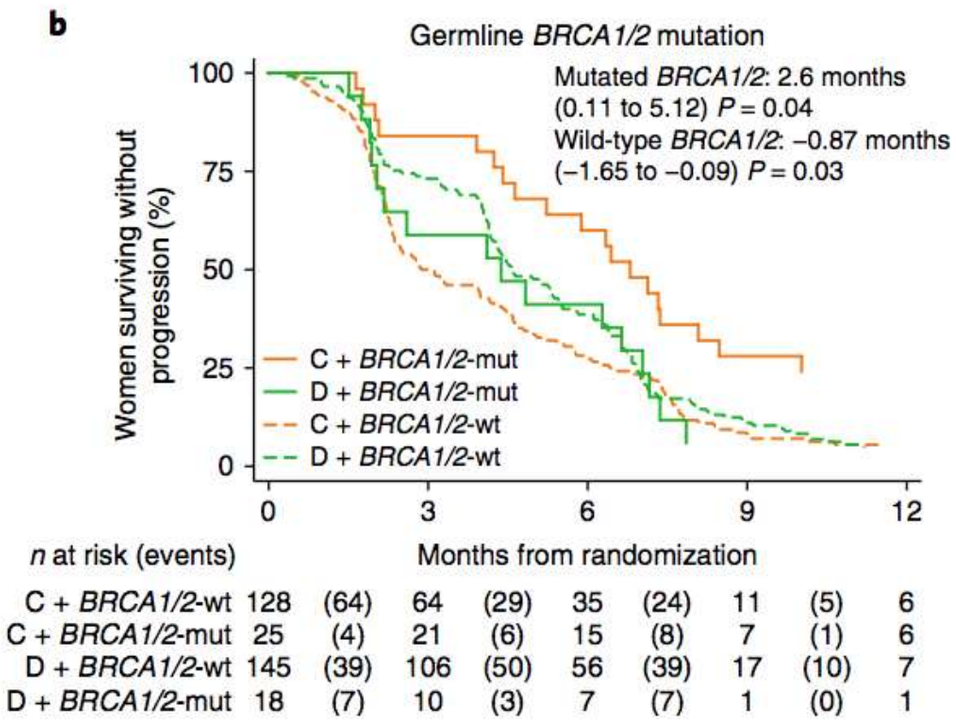
Tutt et al. SABCS 2014

TNT: results



Response Rate



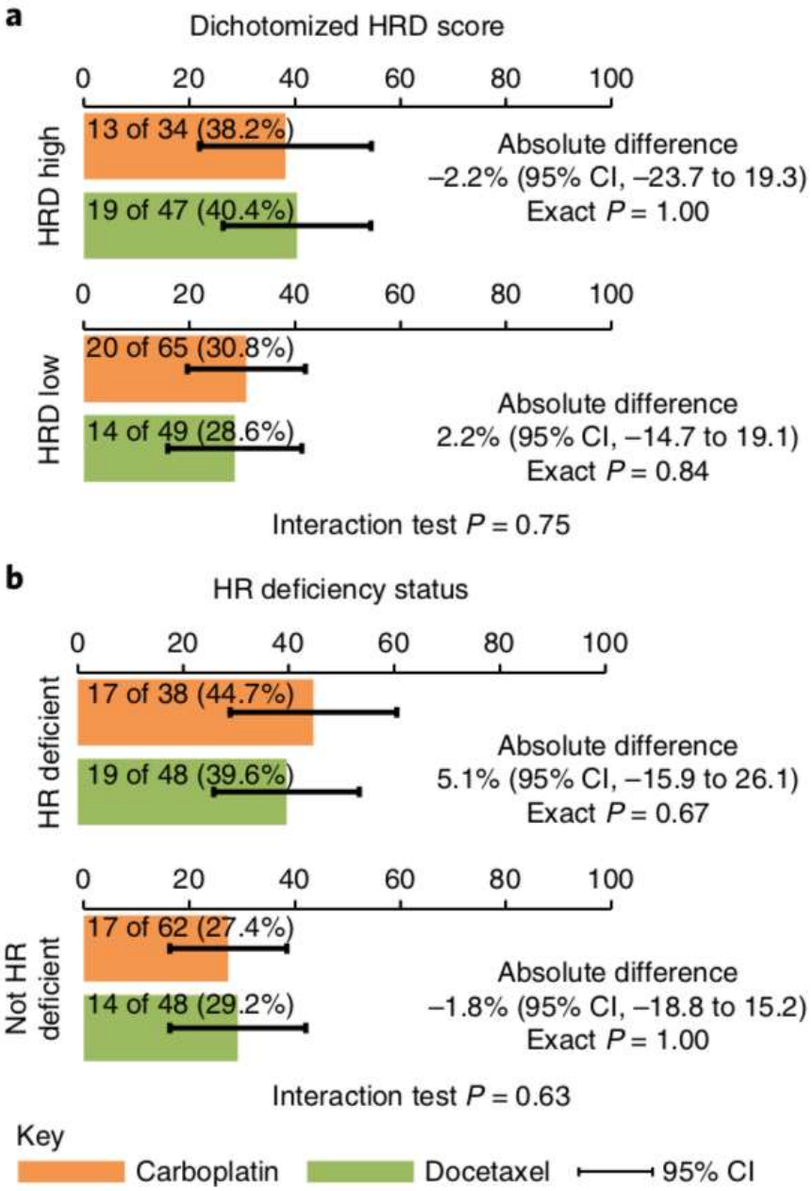


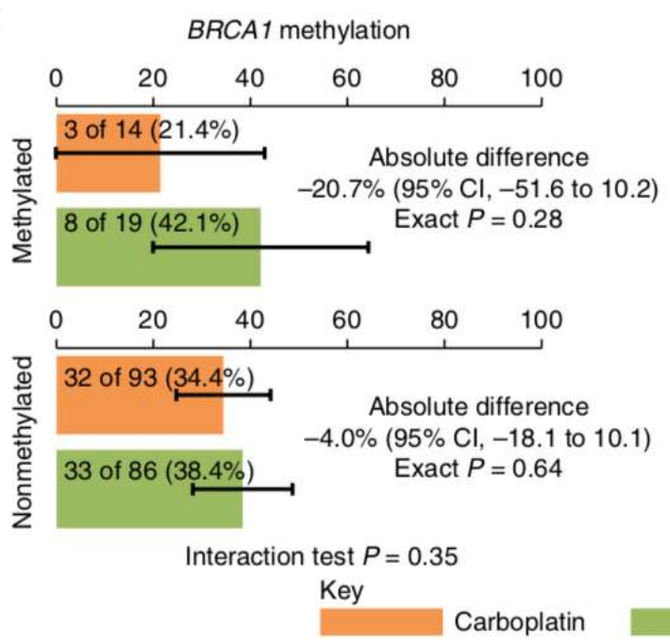
Popolazione generale: nessuna differenza in PFS e OS

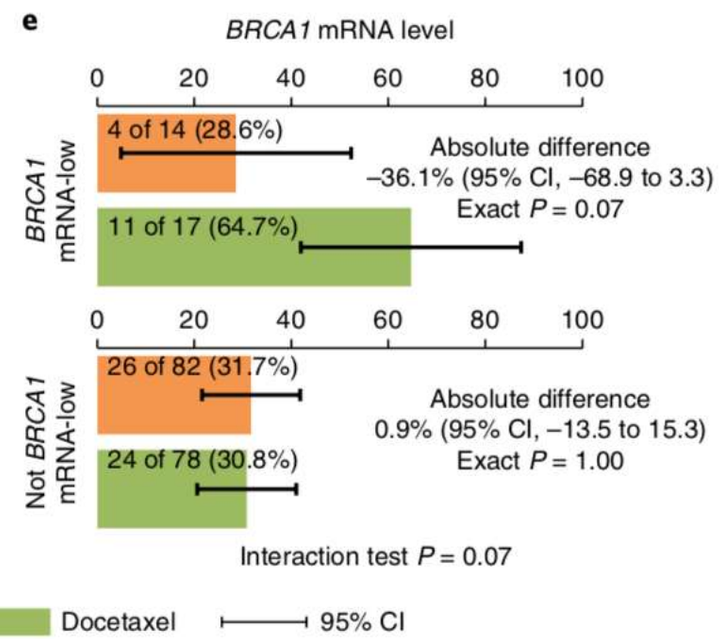
BRCA mutato: vantaggio in PFS per Carboplatino (6,8mo vs 4,4mo)

Tutt et al, Naturemedicine 2018

TNT: BRCAness

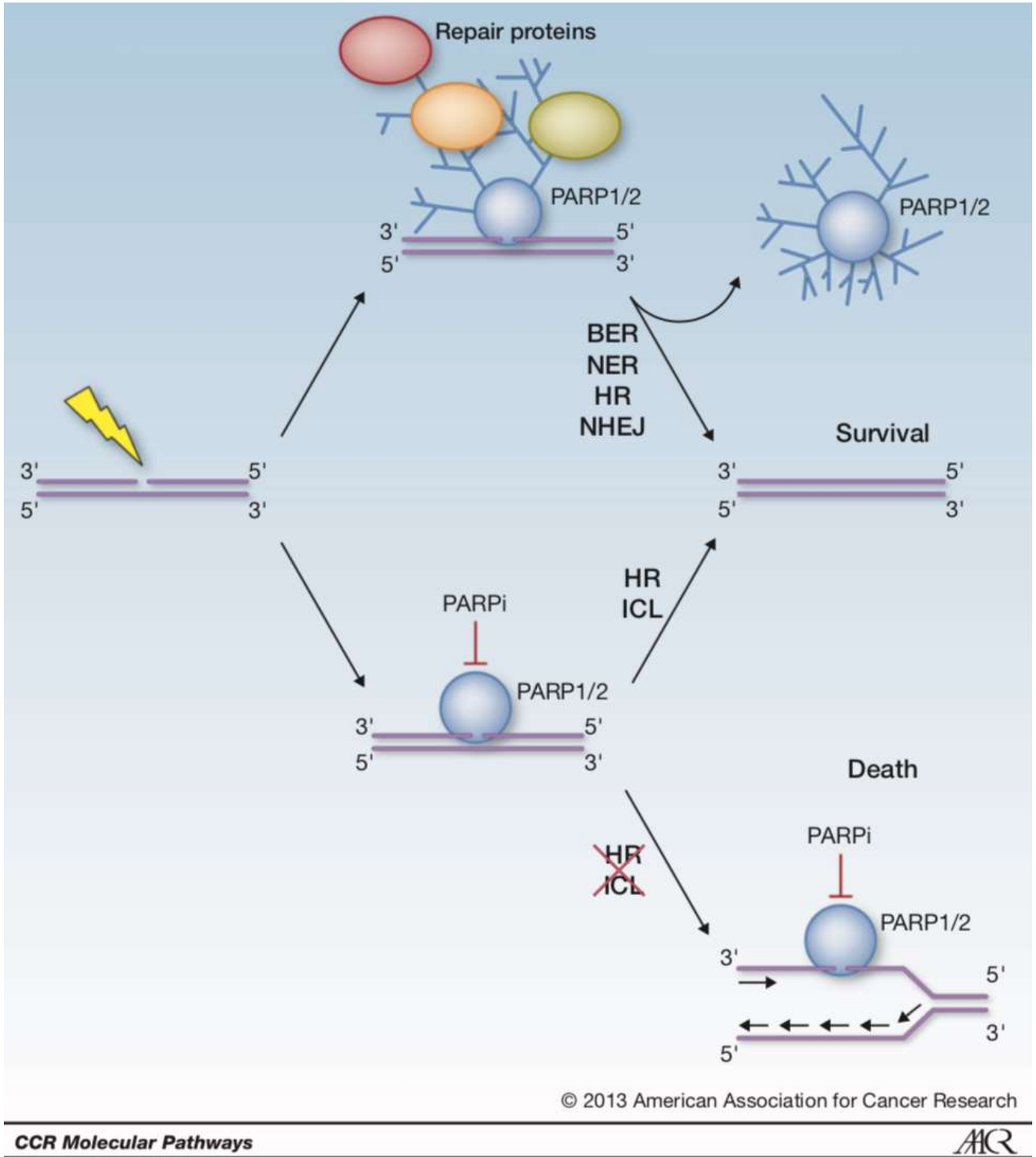






Nessun vantaggio per Carboplatino

PARP inibitori: meccanismo d'azione



OlympiAD: Study Design

- Randomized, open-label phase III study

Stratified by HR status (ER+ and/or PgR+ vs TNBC), prior CT for metastases (yes vs no), prior platinum tx (yes vs no)

Pts with HER2-negative MBC with deleterious or suspected deleterious *gBRCA* mutation; previous anthracycline and taxane, ≤ 2 previous lines of CT* for metastatic disease; if HR+, not suitable for ET or progressed on ≥ 1 ET
(N = 302)

Olaparib 300 mg PO BID
(n = 205)

CT† on 28-d cycles
(n = 97)

Until PD or unacceptable AEs

*If platinum-based therapy, pt could not have experienced progression on tx in advanced setting or ≥ 12 mos since (neo)adjuvant tx.
†Physician's choice of: capecitabine 2500 mg/m² PO Days 1-14; vinorelbine 30 mg/m² IV Days 1, 8; or eribulin 1.4 mg/m² IV Days 1, 8.

- Primary endpoint: PFS per RECIST 1.1 (BICR)
- Secondary endpoints: time to second progression/death, OS, ORR, safety, tolerability, global HRQoL

Robson ME, et al. ASCO 2017. Abstract LBA4. Robson ME, et al. N Engl J Med. 2017;[Epub ahead of print].

OlympiAD: ITT

Table 1. Baseline Characteristics of the Patients.*

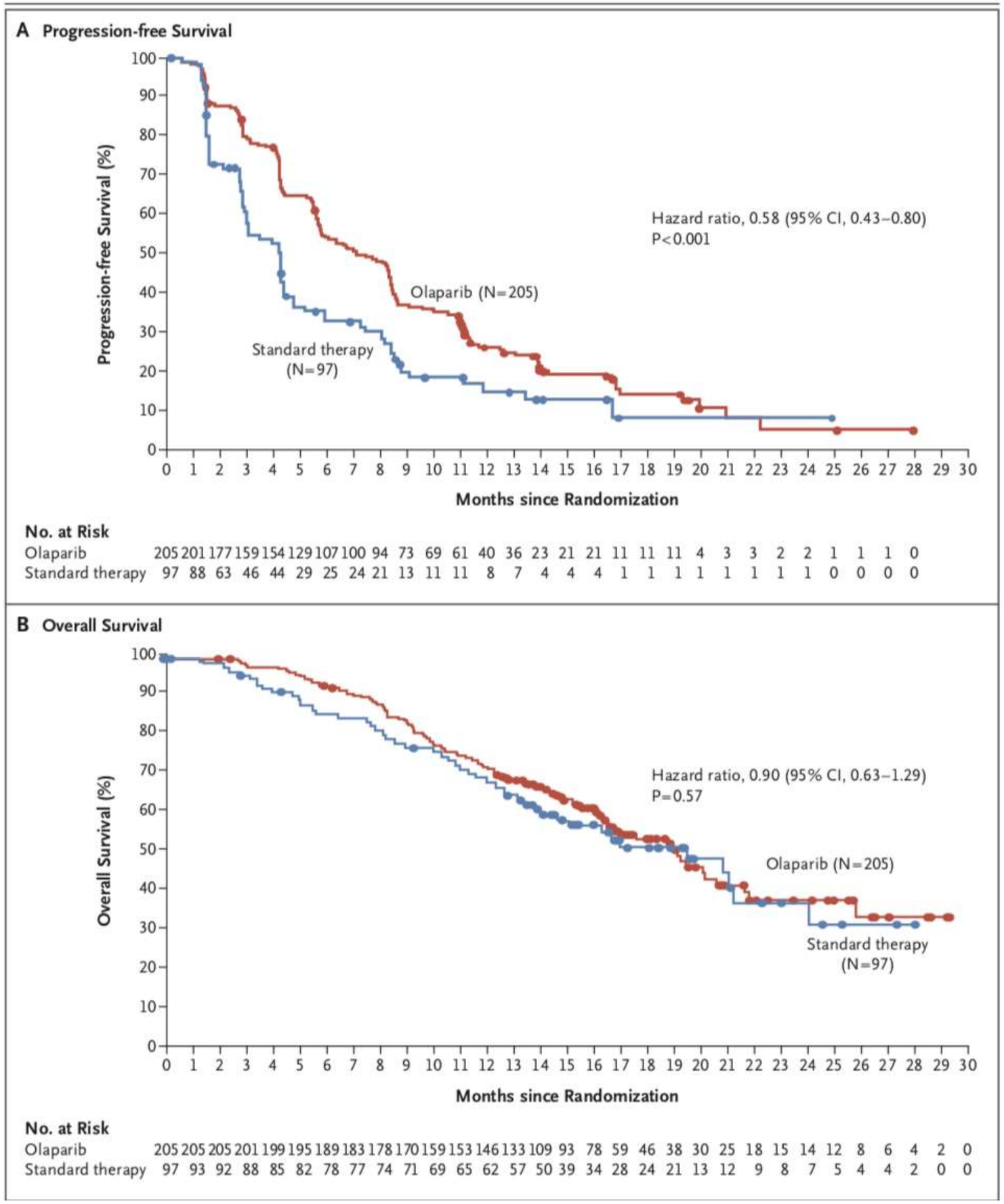
Characteristic	Olaparib Group (N = 205)	Standard-Therapy Group (N = 97)
Age — yr		
Median	44	45
Range	22–76	24–68
Male sex — no. (%)	5 (2.4)	2 (2.1)
Race or ethnic group — no. (%)†		
White	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Other	5 (2.4)	6 (6.2)
ECOG performance status — no. (%)‡		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
BRCA mutation type — no. (%)§		
BRCA1	117 (57.1)	51 (52.6)
BRCA2	84 (41.0)	46 (47.4)
BRCA1 and *BRCA2*	4 (2.0)	0
Hormone-receptor status — no. (%)¶		
Hormone-receptor positive	103 (50.2)	49 (50.5)
Triple negative	102 (49.8)	48 (49.5)
New metastatic breast cancer — no. (%)	26 (12.7)	12 (12.4)
Previous chemotherapy for metastatic breast cancer — no. (%)	146 (71.2)	69 (71.1)
Previous platinum-based therapy for breast cancer — no. (%)	60 (29.3)	26 (26.8)
≥2 Metastatic sites — no. (%)	159 (77.6)	72 (74.2)
Location of the metastasis — no. (%)		
Bone only	16 (7.8)	6 (6.2)
Other‖	189 (92.2)	91 (93.8)
Measurable disease — no. (%)	167 (81.5)	66 (68.0)

OlympiAD AE

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

M.Robson et al, N Engl J Med 2017



Vantaggio PFS

mediana 2,8 mesi in

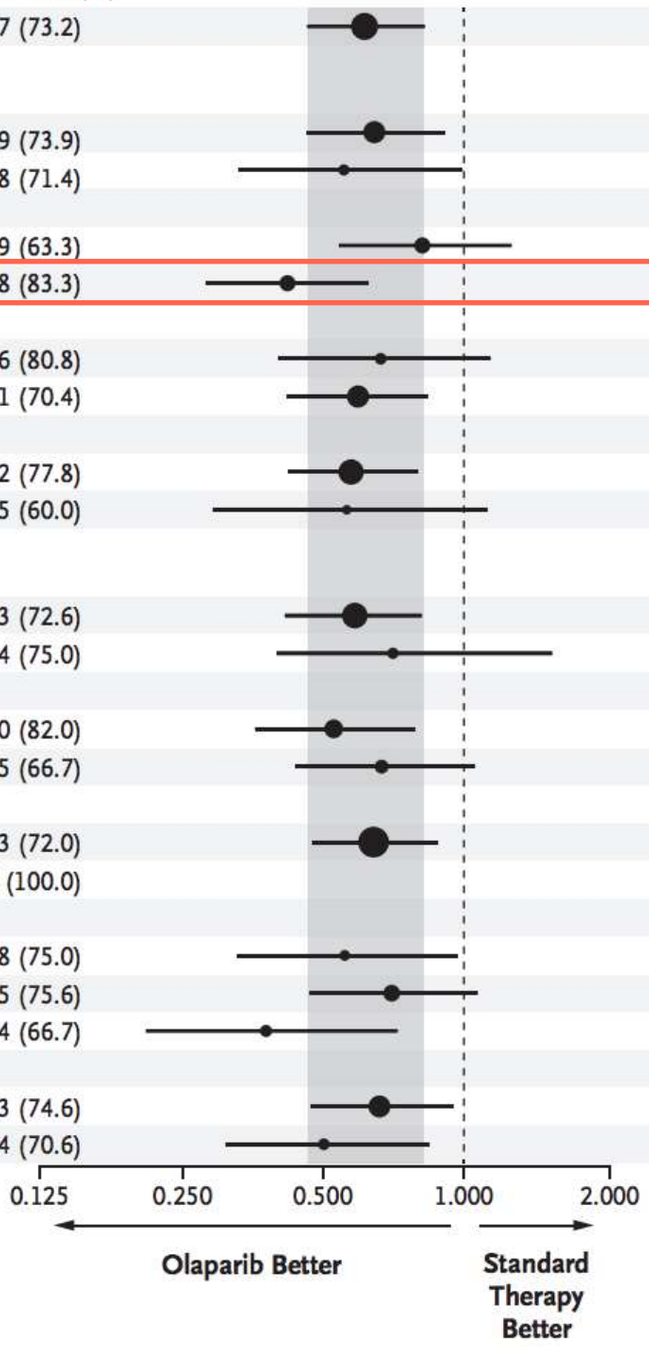
favore Olaparib

(7,0mo vs 4,2mo)

M.Robson et al, N Engl J Med 2017

OlympiAD PFS

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)



M.Robson et al, N Engl J Med 2017

EMBRACA Trial

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:

- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS

R 2:1

Talazoparib 1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

Physician's choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine

Primary endpoint

- **Progression-free survival by RECIST by blinded central review**

Key secondary efficacy endpoints

- **Overall survival (OS)**
- **ORR by investigator**
- **Safety**

Exploratory endpoints

- **Duration of response (DOR) for objective responders**
- **Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)**

Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites

Abbreviations: CNS, central nervous system; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; mets, metastases; PO, orally (per os); QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; TNBC, triple-negative breast cancer.

*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated.

†HER2-positive disease is excluded. ‡Physician's choice of therapy must be determined prior to randomization.

www.clinicaltrials.gov (NCT01945775)

EMBRACA Trial

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Talazoparib Group (N=287)	Standard-Therapy Group (N=144)
Age — yr		
Median	45	50
Range	27.0–84.0	24.0–88.0
Age <50 yr — no. (%)	182 (63.4)	67 (46.5)
Female sex — %	98.6	97.9
ECOG performance status score — %†		
0	53.3	58.3
1	44.3	39.6
2	2.1	1.4
Breast cancer stage — no. (%)‡		
Locally advanced	15 (5.2)	9 (6.2)
Metastatic	271 (94.4)	135 (93.8)
Measurable disease assessed by investigator — no. (%)	219 (76.3)	114 (79.2)
History of CNS metastases — no. (%)	43 (15.0)	20 (13.9)
Visceral disease — no. (%)	200 (69.7)	103 (71.5)
Hormone-receptor status — no. (%)		
Triple-negative	130 (45.3)	60 (41.7)
Hormone-receptor–positive	157 (54.7)	84 (58.3)
BRCA status — no. (%)§		
BRCA1-positive	133 (46.3)	63 (43.8)
BRCA2-positive	154 (53.7)	81 (56.2)
<12-mo disease-free interval from initial diagnosis to advanced breast cancer — no. (%)	108 (37.6)	42 (29.2)
Previous adjuvant or neoadjuvant therapy — no. (%)	238 (82.9)	121 (84.0)
No. of previous hormone-therapy–based regimens for hormone-receptor–positive breast cancer in the talazoparib group (157 patients) and the standard-therapy group (84 patients)		
Median	2.0	2.0
Range	0–6	0–6
Previous platinum therapy — no. (%)	46 (16.0)	30 (20.8)
Previous cytotoxic regimens for advanced breast cancer — no. (%)		
0	111 (38.7)	54 (37.5)
1	107 (37.3)	54 (37.5)
2	57 (19.9)	28 (19.4)
3	12 (4.2)	8 (5.6)

J K Litton et al NEJM 2018

EMBRACA

Table 3. Summary of Adverse Events.*

Adverse Event	Talazoparib Group (N=286)	Standard-Therapy Group (N=126)
	number of patients (percent)	
Any adverse event	282 (98.6)	123 (97.6)
Serious adverse event†	91 (31.8)	37 (29.4)
Serious and drug-related adverse event	26 (9.1)	11 (8.7)
Grade 3 or 4 serious adverse event	73 (25.5)	32 (25.4)
Adverse event resulting in permanent drug discontinuation	17 (5.9)	11 (8.7)

Tox ematologica grado 3 or 4 :

55% Talazoparib vs 38% controllo

Tox non ematologica grado 3 32%

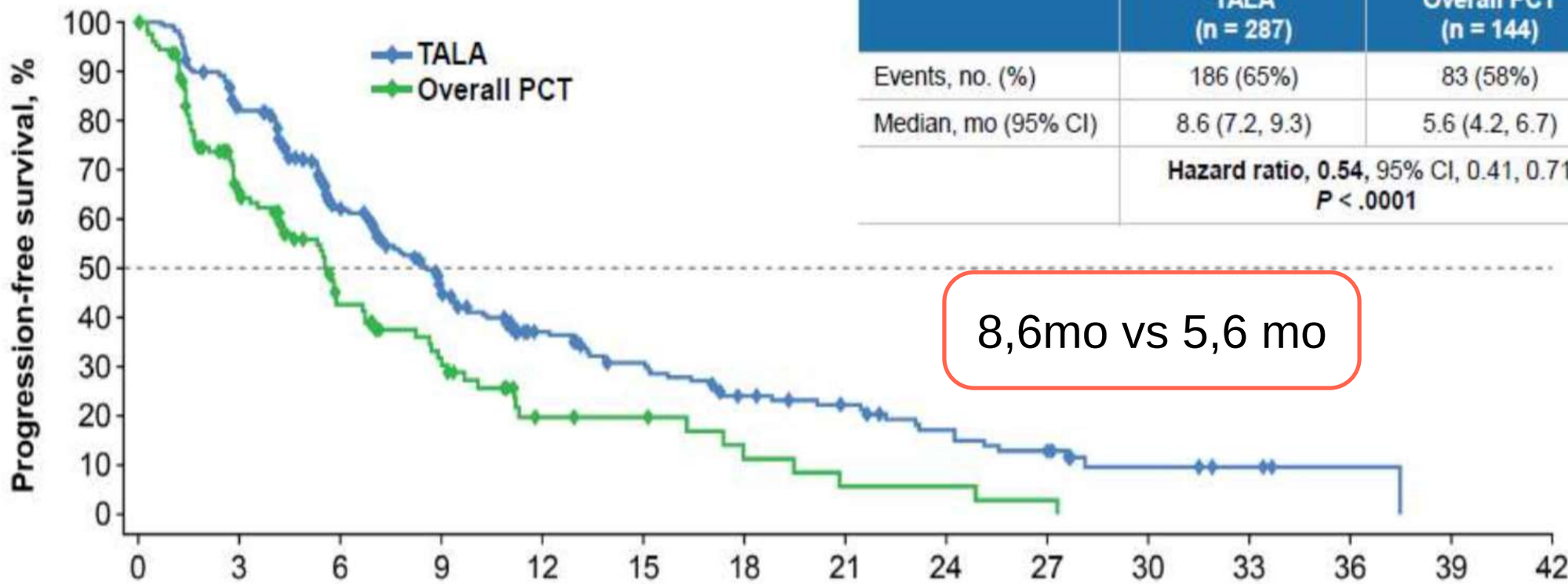
Talazoparib vs 38% controllo

Global Health Status/Quality of Life showed overall improvement from baseline and a delay in the time to clinically meaningful deterioration in patients receiving Talazoparib

J K Litton et al NEJM 2018

EMBRACA: PFS

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	



8,6mo vs 5,6 mo

No. at risk (events/cumulative events)															
TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

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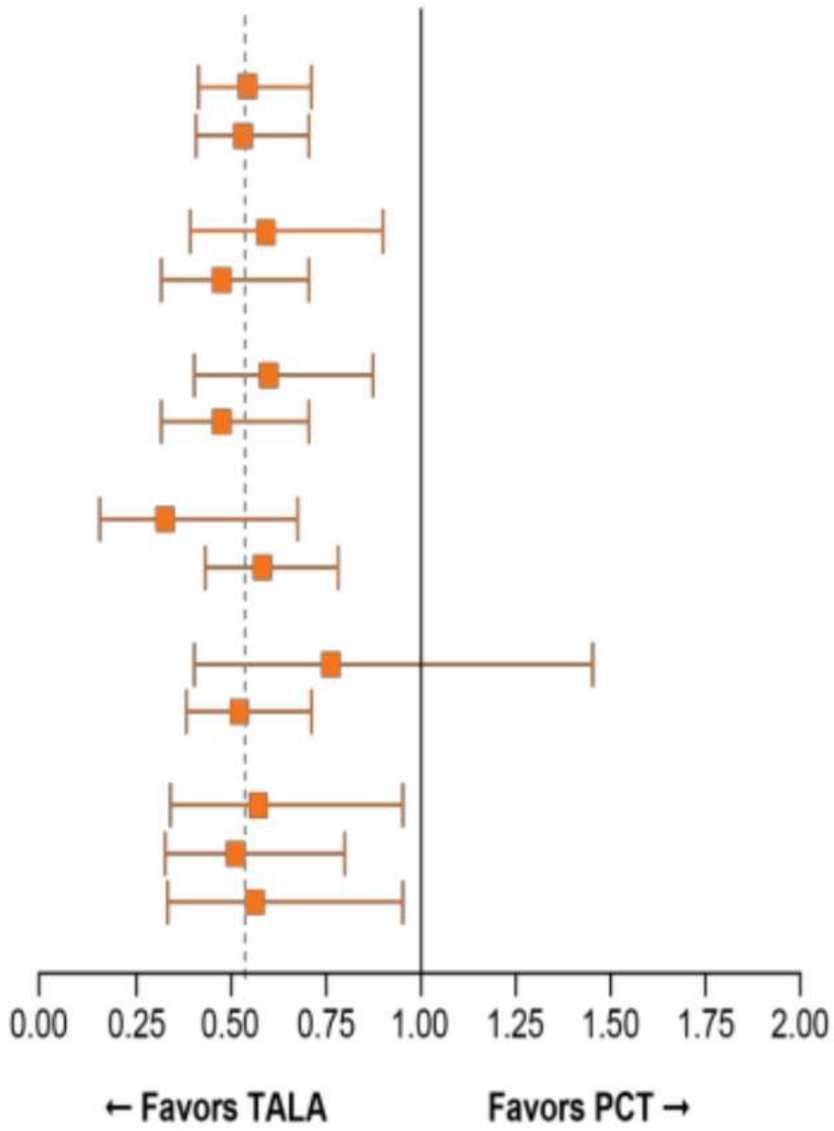
EMBRACA: PFS

Subgroup	Patients, no. (%)	Hazard ratio (95% CI)
All randomized patients (ITT)	431 (100)	0.54 (0.41-0.71)
Patients with central testing available	408 (94.7)	0.53 (0.40-0.70)
BRCA1 status by central testing		
BRCA1	183 (42.5)	0.59 (0.39-0.90)
BRCA2	225 (52.2)	0.47 (0.32-0.70)
Hormone receptor status		
TNBC based on most recent biopsy	190 (44.1)	0.60 (0.41-0.87)
HR+ based on most recent biopsy	241 (55.9)	0.47 (0.32-0.71)
History of CNS metastasis		
Yes	63 (14.6)	0.32 (0.15-0.68)
No	368 (85.4)	0.58 (0.43-0.78)
Prior platinum treatment		
Yes	76 (17.6)	0.76 (0.40-1.45)
No	355 (82.4)	0.52 (0.39-0.71)
Prior regimens of cytotoxic chemo for aBC		
0	165 (38.3)	0.57 (0.34-0.95)
1	161 (37.4)	0.51 (0.33-0.80)
≥ 2	105 (24.4)	0.56 (0.34-0.95)



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MALATTIA METASTATICA

Advanced or metastatic disease		
ESMO	For triple-negative locally advanced BCa, anthracycline–taxane chemotherapy is recommended as initial treatment.	I, A
	In triple-negative advanced BCa patients (regardless of *BRCA* status) previously treated with an anthracycline with or without a taxane in the neoadjuvant or adjuvant setting, carboplatin (compared with docetaxel) demonstrated comparable efficacy and a more favourable toxicity profile. It is therefore an important treatment option.	I, A
	In patients with *BRCA*-associated triple-negative or endocrine-resistant metastatic BCa previously treated with an anthracycline with or without a taxane (in the adjuvant or metastatic setting, or both), a platinum regimen, if not previously administered, is the preferred option when no suitable clinical trial is available.	I, A
ASCO	Tumour type should not be used to dictate the choice of first-line treatment. That choice should be based on efficacy, prior treatment, risk of life-threatening disease, relative toxicities, performance statue, comorbid conditions, and patient choice.	

Lebert et al, Current Oncology, Vol. 25, Supp. 1, June 2018

Metastatic disease—immunotherapy	Anti-programmed death-1 (PD-1)/Programmed death-ligand 1 (PD-L1) antibodies have shown activity as single-agents or in combination with taxane-based chemotherapy in TNBC [72–74].
Metastatic disease—*CDK4/6* inhibitors	Randomized trials have shown that adding *CDK4/6* inhibitors to first- or second line endocrine therapy improves progression free survival [75–77].
Metastatic disease—*HER2* directed therapy	First-line therapy with ado-trastuzumab emtansine and pertuzumab was not superior to chemotherapy and trastuzumab or ado-trastuzumab emtansine, alone [78]. Adding pertuzumab to second-line chemotherapy in patients not previously treated with pertuzumab yielded small clinical benefit [79]. In the PERTAIN trial, adding pertuzumab to first-line trastuzumab and endocrine therapy improved progression free survival [80].
Molecular mechanisms of resistance to therapy	Activating mutations in the estrogen receptor *ESR1* gene arise in 30%–40% of recurrences on AI therapy and likely account for resistance to AI treatment in those cases [81]
BRCA-associated metastatic breast cancer	*BRCA*-mutated tumors show preferential benefit for carboplatin-based chemotherapy in palliation of metastatic disease [82]. The addition of veliparib to carboplatin and paclitaxel chemotherapy did not meaningfully improve outcomes in *BRCA*-associated advanced breast cancer [83]. Preliminary data from the Olympia D trial suggest that olaparib is a more effective treatment of *BRCA*-associated advanced breast cancer than non-platinum chemotherapy options.

G.Curigliano, Annals of Oncology 28: 1700–1712, 2017

NEOPLASIA METASTATICA BRCA MUTATA

- CARATTERISTICHE
- TRATTAMENTI
- STRATEGIE FUTURE

PARP inibitori: resistenza

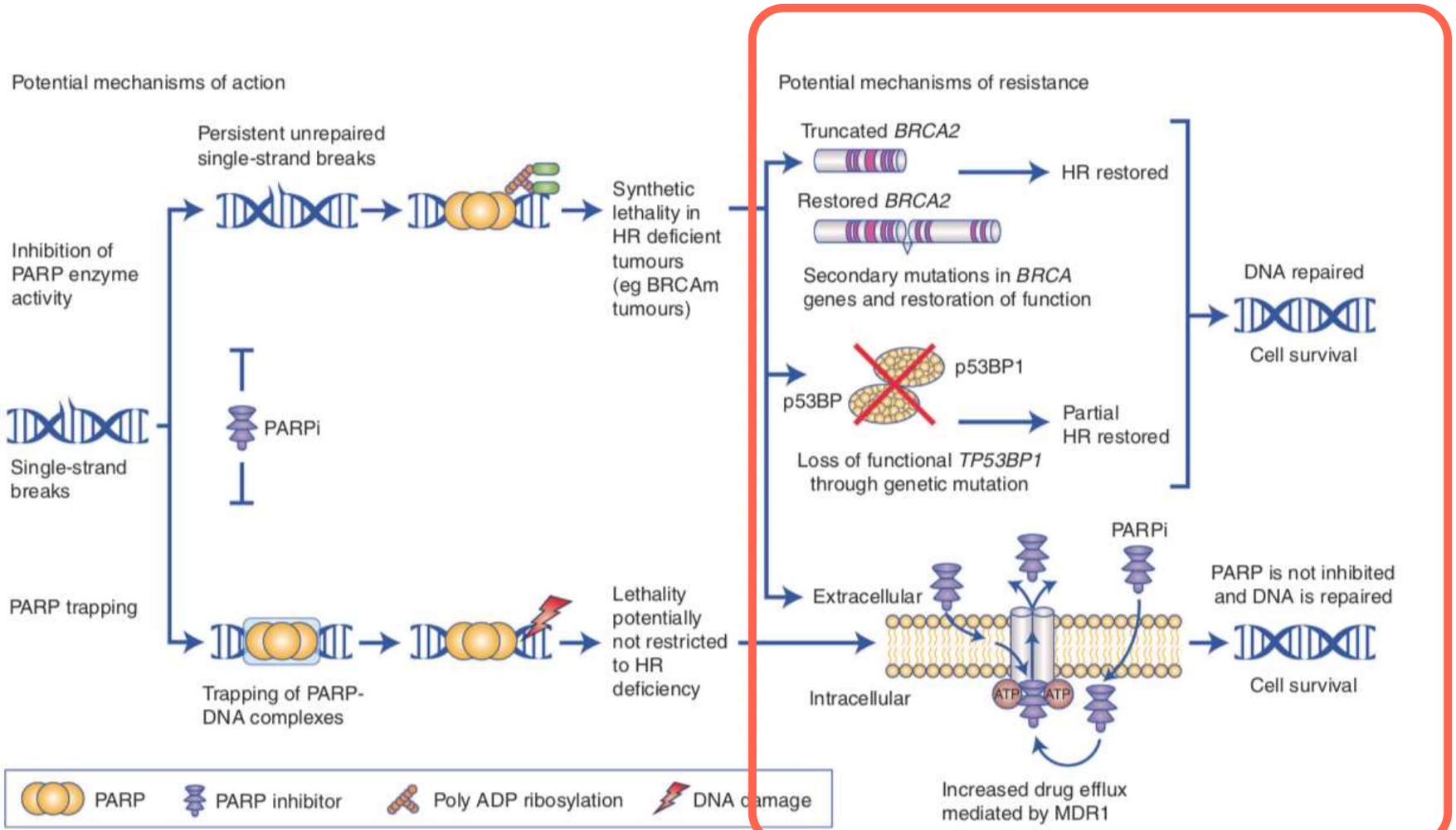

Fig. 1 PARP inhibitors: Some possible mechanisms of action and resistance. The left panel illustrates two possible mechanisms of action of PARPi. Upper pathway: Inhibition of PARP enzyme activity or catalytic inhibition interferes with the repair of single-strand breaks, leading to stalled DNA replication forks that requires HR repair. In HR-deficient tumours, such as those with *BRCA*m, PARP inhibition results in synthetic lethality. Lower pathway: PARP trapping refers to trapping of PARP proteins on DNA, which also leads to replication fork damage, but because this pathway utilises additional repair mechanisms, it is not restricted to tumours with HR deficiency. The right panel illustrates three possible mechanisms of resistance to PARPi. These include: (1) secondary mutations in *BRCA* genes that restore *BRCA* function and HR; (2) somatic mutation of TP53BP1, causing partial restoration of HR; and (3) increased PARPi efflux mediated by MDR1/P-glycoprotein 1, preventing the drugs from acting at the appropriate sites. The first two mechanisms of resistance restore HR and apply to PARP catalytic inhibition in HR-deficient tumours; whereas, the third mechanism applies to both mechanisms of action of PARPi. *BRCA*m *BRCA* mutation; HR homologous recombination; MDR1 multidrug resistance protein 1; p53BP1 tumour suppressor p53-binding protein 1; PARP poly(ADP-ribose) polymerase; PARPi PARP inhibitor

BRCA1/2 testing NM Tung and JE Garber Springer Nature on behalf of Cancer Research UK 2018

TRATTAMENTI DI COMBINAZIONE

- con CT, ma rischio di mielosoppressione dose limitante, necessità di GCSF
  (BROCADE 2 e 3, Paclitaxel e Carboplatino +/- Veliparib)

- con Immunoterapia
  (phase II, Olaparib + Durvalumab; Veliparib e Atezolizumab)

- con Radioterapia, Olaparib, Veliparib

- con antiangiogenetici (antiVEGFR TKI Cediranib)

Table 2. Selected phase II/III studies with PARP inhibitors in g*BRCA*1/2m locally advanced and metastatic breast cancer

Study	Disease	Phase	*N*	Treatment	Efficacy in patients with g*BRCA*1/2m
NCT00494234[57]	Recurrent, advanced BC with median 3 prior regimens and *BRCA*1/2 mutation (*BRCA*1/2m)	II	27	Olaparib 400 mg BID	ORR: 41% (11/27)
OlympiAD NCT02000622[61]	Metastatic BC with g*BRCA*1/2m	III	302	Olaparib 300 mg BID vs treatment of physician's choice (TPC; capecitabine, eribulin, or vinorelbine)	ORR: 60% with olaparib vs 29% with TPC PFS: 7.0 months with olaparib vs 4.2 months with TPC (hazard ratio 0.58; 95% CI: 0.43–0.80; $P < 0.001$) DoR: 6.4 months with olaparib (IQR, 2.8–9.7) vs 7.1 months with TPC (IQR, 3.2–12.2)
ABRAZO NCT02034916[65]	Advanced BC with g*BRCA*1/2m following platinum or multiple cytotoxic regimens	II	84	Talazoparib 1 mg/day following platinum-based therapy (cohort 1) vs ≥3 platinum-free cytotoxic-based regimens (cohort 2)	ORR: 21% (95% CI: 10–35) in cohort 1 vs 37% (95% CI: 21–55) in cohort 2PFS: 4.0 months (95% CI: 2.8–5.4) in cohort 1 vs 5.6 months (95% CI: 5.5–7.8) in cohort 2 DoR: 5.8 months (95% CI: 2.8–NR) in cohort 1 vs 3.8 months (95% CI: 2.8–10.1) in cohort 2 CBR: 38% (95% CI: 24–53) in cohort 1 vs 66% (95% CI: 48–81) in cohort 2
EMBRACA NCT01945775[64]	Advanced BC with g*BRCA*1/2m	III	431	Talazoparib 1 mg/day vs physician's choice of chemotherapy (PCT; capecitabine, eribulin, gemcitabine, or vinorelbine)	ORR: 63% (95% CI: 56–69) with talazoparib vs 27% (95% CI: 19–36) with PCT PFS: 8.6 months (95% CI: 7.2–9.3) with talazoparib vs 5.6 (95% CI: 4.2–6.7) with PCT DoR: 5.4 months (95% CI: 2.8–11.2) with talazoparib vs 3.1 (95% CI: 2.4–6.7) with PCT CBR24: 69% (95% CI: 63–74%) with talazoparib vs 36% (95% CI: 28–45)
BRAVO NCT01905592[66]	Metastatic BC with g*BRCA*1/2m (and HER2-negative)	III	306 (est)	Niraparib vs physician's choice of chemotherapy	ONGOING
Cancer Research UK[67]	Previously treated advanced OC or BC with g*BRCA*1/2m	II	78 $n = 23$ (BC)	Rucaparib	39% of BC patients (9/23) achieved stable disease ≥12 weeks
RUBY NCT02505048[68]	HER2-negative metastatic BC associated with BRCAness phenotype determined by "high-tumour genomic LOH" score and/or a somatic *BRCA*m	II	41 (est)	Rucaparib	ONGOING
Brocade 2 NCT01506609[82]	Locally recurrent or metastatic BC with g*BRCA*1/2m	II	284	Paclitaxel/carboplatin/veliparib (PCV) vs paclitaxel/carboplatin/placebo (PCP)	PFS: 14.1 months with PCV vs 12.3 months with PCP; hazard ratio 0.789 (95% CI: 0.536–1.162); $P = 0.227$ ORR: 78% with PCV vs 61% with PCP; $P = 0.027$
Brocade 3 NCT02163694[83]	Locally advanced or metastatic g*BRCA*1/2m BC (and HER2-negative)	III	500 (est)	Paclitaxel/carboplatin/veliparib vs paclitaxel/carboplatin/placebo	ONGOING

BC breast cancer, *BID* twice daily, *CBR* clinical benefit rate, *CBR24* CBR at 24 weeks, *CI* confidence interval, *DoR* duration of response, *est* estimated, *IQR* interquartile range, *LOH* loss-of-heterozygosity, *gBRCA1/2m* germline *BRCA*1/2 mutation, *OC* ovarian cancer, *ORR* objective response rate, *PARP* poly(ADP-ribose) polymerase, *PCP* paclitaxel/carboplatin/placebo, *PCV* paclitaxel/carboplatin/veliparib, *PCT* physician's choice chemotherapy, *PFS* progression-free survival, *TNBC* triple-negative breast cancer, *TPC* treatment of physician's choice

CONCLUSIONI

- **Mutazione BRCA: fattore predittivo**
- **Consulenza genetic**

Box 1. Characteristics that should trigger testing for germline *BRCA*1/2 mutation in patients already diagnosed with breast cancer

- Family history of breast, ovarian/tubal/peritoneal cancer, pancreatic, or aggressive prostate cancer
- Young age at diagnosis (<50 years)
- Triple-negative breast cancer (ER-negative, PgR-negative, and HER2-negative)
- Breast cancer in a male
- Ashkenazi Jewish heritage
- Personal history of ovarian or pancreatic cancer
- Detection of somatic *BRCA*1/2 mutation
- Patient with metastatic HER2-negative breast cancer who is eligible for treatment with a PARPi[19]

ER-negative oestrogen receptor-negative, *HER2-negative* human epidermal growth factor receptor 2-negative, *PgR-negative* progesterone receptor-negative

BRCA1/2 testing NM Tung and JE Garber Springer Nature on behalf of Cancer Research UK 2018

- **Carboplatino in 1° linea**
- **Olaparib e Talazoparib efficaci in malattia platino sensibile o naive con beneficio in QoL**
- **Olaparib eTalazoparib approvati FDA**
- **Valutare trials clinici**

GRAZIE PER
L'ATTENZIONE