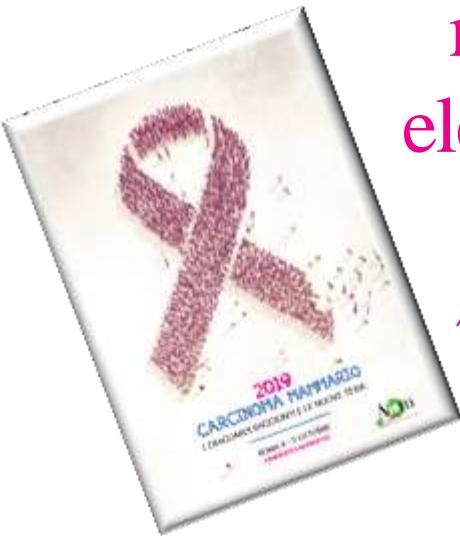


Raccomandazioni 2019 per l'implementazione del test BRCA nelle pazienti con carcinoma mammario e nei familiari a rischio elevato di neoplasia e ruolo dei PARP inhibitors nel setting metastatico

A cura del Gruppo di Lavoro AIOM-ANISC- SICO- SIGU - SIBIOC - SIAPEC-IAP- Fondazione AIOM



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Oncogenetic Counselling

BRCA1 BRCA2

Risk Factor

Predictive Factor

EBC

ABC



Criteri per l'invio alla consulenza genetica oncologica del/della paziente con carcinoma mammario

Storia personale di:

- 1.Maschio con carcinoma mammario**
- 2.Donna con carcinoma mammario e carcinoma ovarico;**
- 3.Donna con carcinoma mammario < 36 anni**
- 4.Donna con carcinoma mammario triplo negativo < 60 anni;**
- 5.Donna con carcinoma mammario bilaterale < 50 anni;**

Storia personale di carcinoma mammario < 50 anni
e familiarità di primo grado per:

- Carcinoma mammario < 50 anni;
- Carcinoma ovarico non mucinoso o borderline a qualsiasi età ;
- Carcinoma mammario bilaterale;
- Carcinoma mammario maschile;

Storia personale di carcinoma mammario > 50 anni
e familiarità per carcinoma mammario, ovarico,
in 2 o più parenti in primo grado tra loro

Storia familiare di:

Variante patogenetica nota in un gene predisponente in un familiare



EBC: CHIRURGIA E RADIOTERAPIA

REVIEW ARTICLE

Prophylactic mastectomy for the prevention of breast cancer: Review of the literature

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Tabuk University College of Medicine, Medina, Departments of ¹Surgery and ²Medicine, King Abdulaziz University, Jeddah, Saudi Arabia



ABSTRACT

The high incidence and recurrence rate of breast cancer has influenced multiple strategies such as early detection with imaging, chemoprevention and surgical interventions that serve as preventive measures for women at high risk. Prophylactic mastectomy is one of the growing strategies of breast cancer risk reduction that is of a special importance for breast cancer gene mutation carriers. Women with personal history of cancerous breast lesions may consider ipsilateral or contralateral mastectomy as well. Existing data showed that mastectomy effectively reduces breast cancer risk. However, careful risk estimation is necessary to wisely select individuals who will benefit from preventing breast cancer.

Key words: BRCA, breast neoplasms, ductal carcinoma *in situ*, prophylactic mastectomy, risk reduction

AVICENNA
—JOURNAL OF MEDICINE—

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Table 6: Studies reporting the impact of contralateral mastectomy

Study (author, year)	Population	Main findings
Metcalfe, 2004 ^[7]	BRCA1/2	Decreased occurrence of CBC after PM (HR=0.03; P=0.0005)
van Sprundel, 2005 ^[8]	BRCA1/2	Decreased occurrence of CBC after PM (P<0.001)
Manning, 2015 ^[9]	BRCA1/2	No newly diagnosed breast cancers
Peralta, 2000 ^[10]	Unilateral BC	Decreased occurrence of CBC after PM (P=0.005)
Herrinton, 2005 ^[11]	Unilateral BC	Decreased occurrence of CBC after CPM (HR=0.03; 95% CI=0.006-0.13)
Boughery, 2010 ^[12]	Stage I or II BC and family history	95% decreased risk of CBC (HR=0.05; 95% CI=0.01-0.22; P<0.0001)
Babiera, 1997 ^[13]	IFLC	No significant difference in DFS between mastectomy and conservation (P=0.98)

BRCA1: Breast cancer 1, BRCA2: Breast cancer 2, CBC: Contralateral breast cancer, PM: Prophylactic mastectomy, HR: Hazard ratio, BC: Breast cancer, CPM: Contralateral prophylactic mastectomy, CI: Confidence interval, IFLC: Infiltrating lobular carcinoma, DFS: Disease free survival



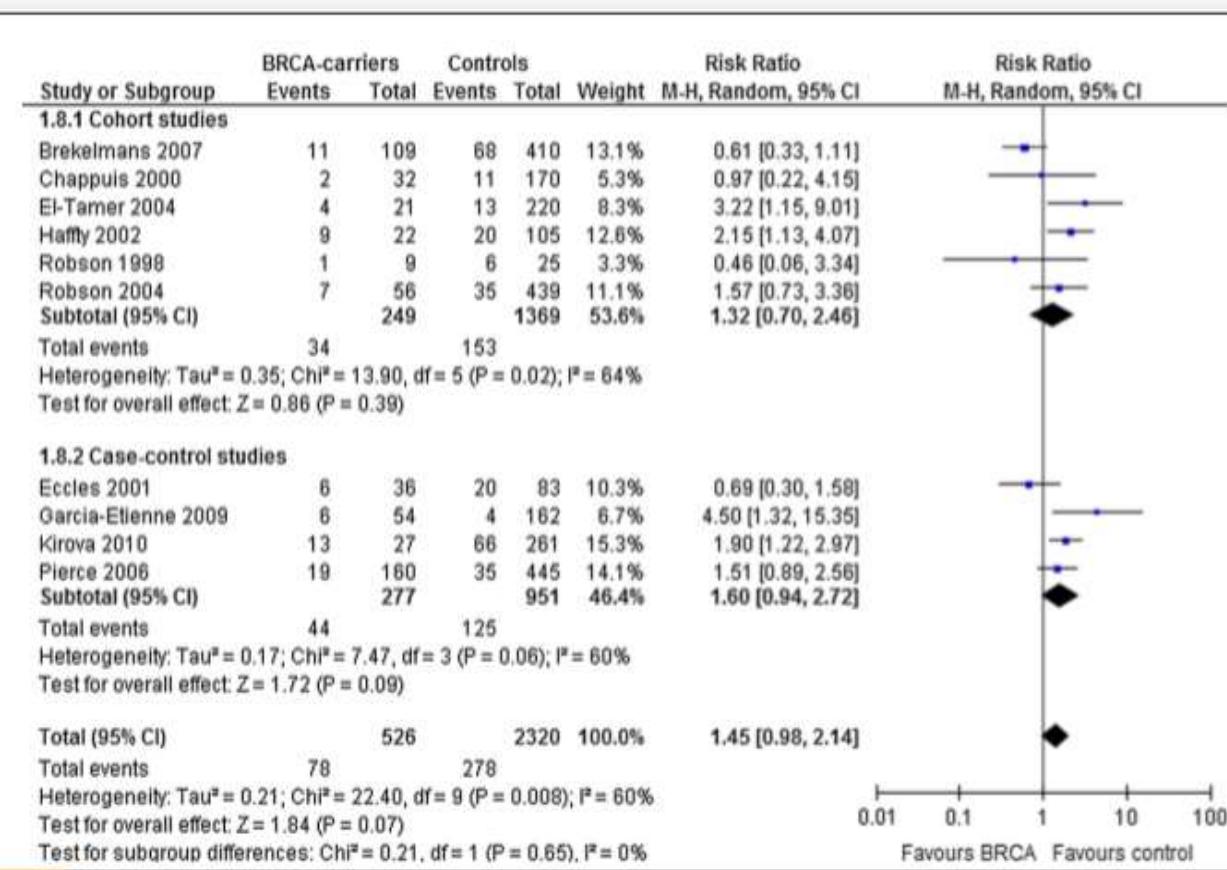
Mastectomy contra



INDICATION	NO. OF PROCEDURES†	BREASTS OPERATED ON		WOMEN OPERATED ON	
		NO.‡	% OF TOTAL (1454)	NO.§	% OF TOTAL (749)
Clinical					
Capsular contracture	272	212	14.6	131	17.5
Rupture	60	56	3.9	43	5.7
Hematoma	55	51	3.5	43	5.7
Wound infection	23	21	1.4	19	2.5
Wound seroma	17	16	1.1	16	2.1
Extrusion of implant	15	14	1.0	14	1.9
Leakage, sweating of implant	14	14	1.0	9	1.2
Chronic pain	13	13	0.9	8	1.1
Necrosis of nipple, areola, or flap	12	12	0.8	11	1.5
Filler-port malfunction	5	5	0.3	5	0.7
Wound dehiscence	5	5	0.3	4	0.5
Other¶	4	4	0.3	4	0.5
Total	359	274	18.8	178	23.8



Forest plot of risk for ipsilateral breast recurrence: BRCA mutation carriers versus non-carriers



Valachis A, BCRT 2014



EBC: CHIRURGIA E RADIOTERAPIA

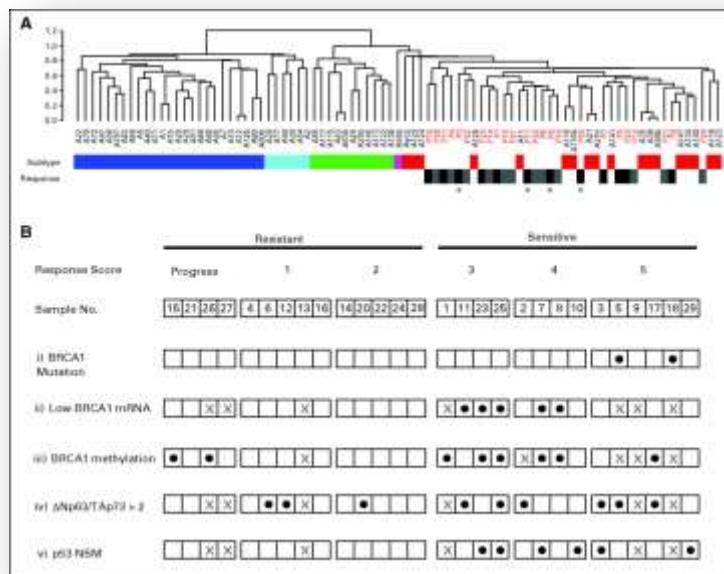
L'intervento di **mastectomia bilaterale** è in grado di ridurre il rischio di un nuovo tumore mammario del **90%**, rendendo minima anche se non nulla la possibilità di dover affrontare una nuova diagnosi di carcinoma mammario e i successivi trattamenti antitumorali. Tuttavia, i benefici di una chirurgia estesa in termini di riduzione del rischio oncologico vanno ponderati con i rischi e le possibili conseguenze post-operatorie e discussi in relazione alle opzioni alternative di riduzione del rischio.

..... pur considerati i limiti dei dati disponibili, **entrambe le opzioni chirurgiche rimangono valide anche tenendo conto che la radioterapia mammaria non sembra comportare un effetto nocivo**



EBC: Terapia antitumorale sistemica neoadiuvante

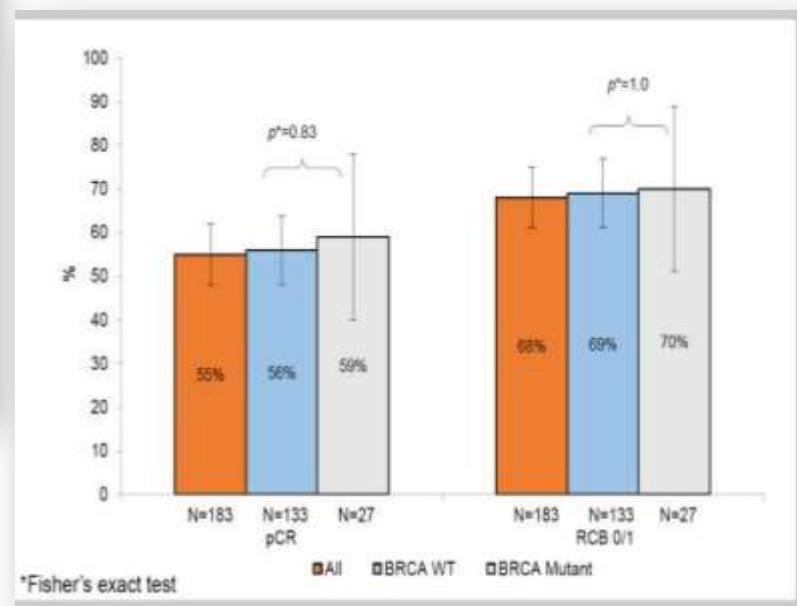
PREDICTORS OF RESPONSE TO CISPLATIN THERAPY IN TRIPLE-NEGATIVE BASAL-LIKE TUMORS



JOURNAL OF CLINICAL ONCOLOGY

Silver D P et al. JCO 2010;28:1145-1153

EFFICACY OF RESPONSE TO CARBOPLATIN AND DOCETAXEL IN TRIPLE-NEGATIVE BASAL-LIKE TUMORS



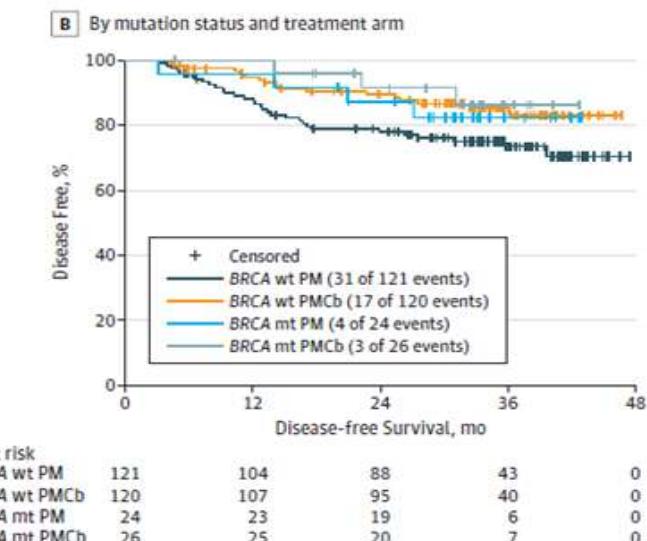
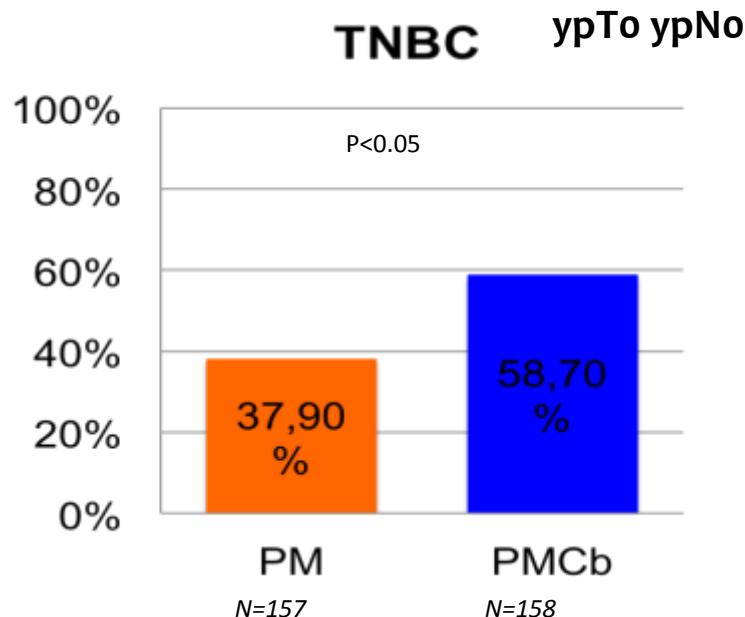
Clinical Cancer Research

Sharma P et al., Clin Cancer Res 2017;23:649-657



Paclitaxel/non-pegylated liposomal doxorubicin (PM) PM plus weekly carboplatin (AUC2) (PMCb)

GEPAR Sixto



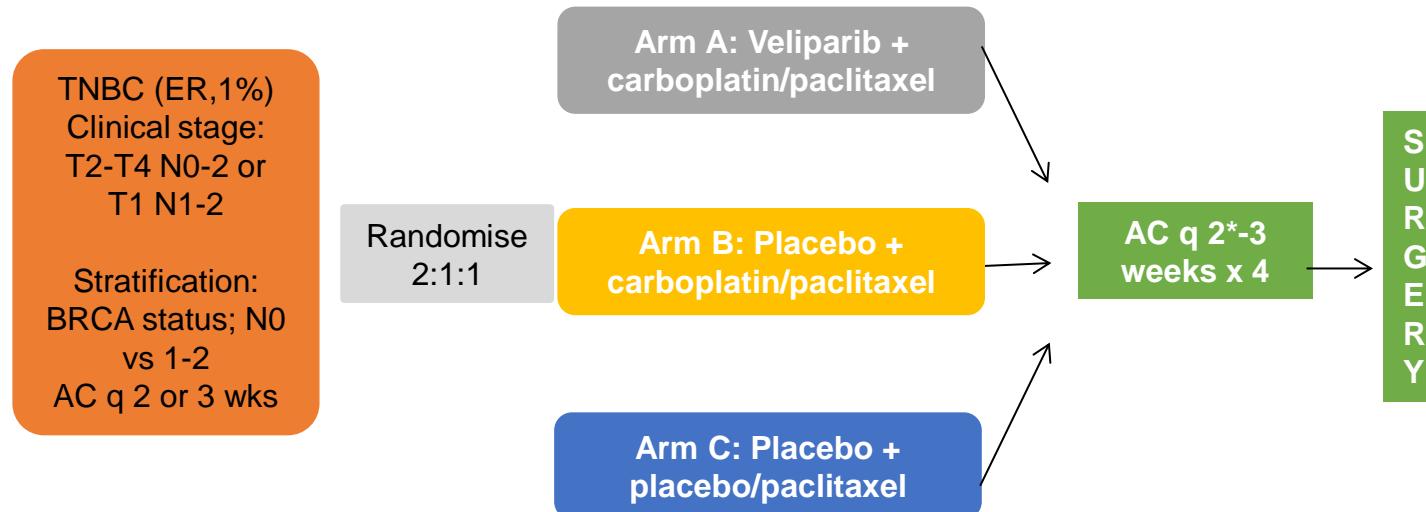
Von Minckwitz G. Lancet Oncol 2014; 15:747-56

Hehnen E. JAMA Oncol 2017; 3:1378-1385.



BrightNess: A randomised Phase III neoadjuvant trial in TNBC

N=624; primary endpoint pCR breast/axilla



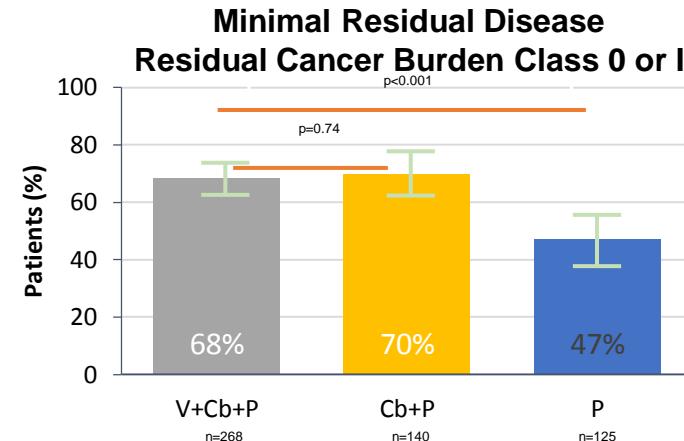
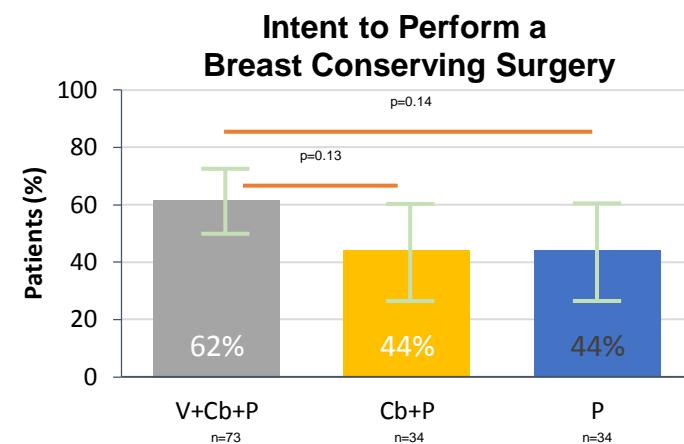
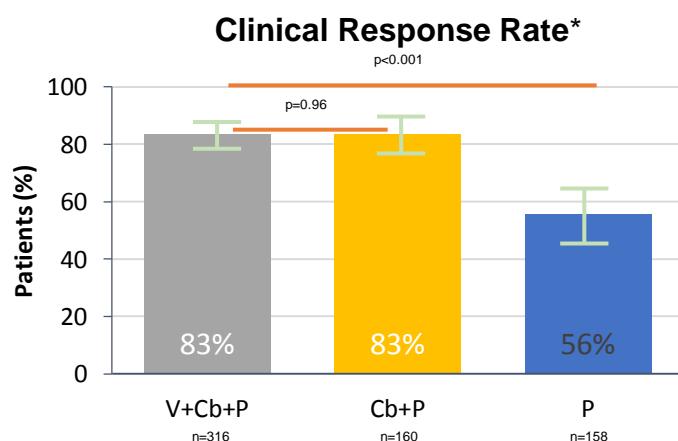
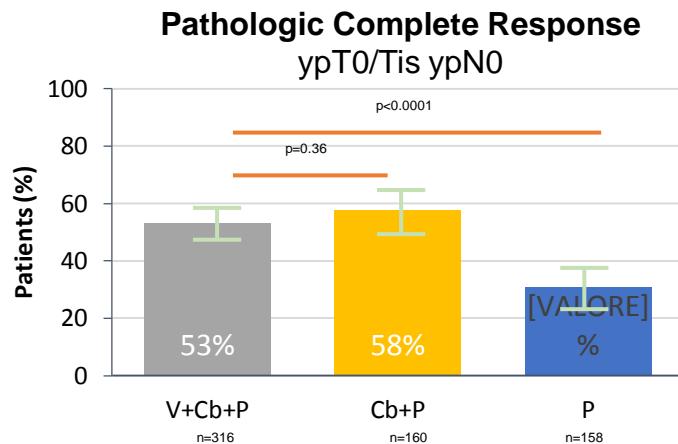
15% with gBRCA mutations (45/25/23)

Veliparib: 50 mg PO BID x 12 weeks;
carboplatin: AUC 6 IV q 3 weeks x 4; *paclitaxel:* 80 mg/m² IV weekly x 12; *AC:* *doxorubicin:* 60 mg/m²/cyclophosphamide 600 mg/m²

- *With G-CSF support
- Loibl S et al. Lancet Oncol. 2018 Apr;19(4):497-509



Efficacy



*with G-CSF support

• Loibl S et al. Lancet Oncol. 2018 Apr;19(4):497-509



Differential benefit in gBRCA carriers?

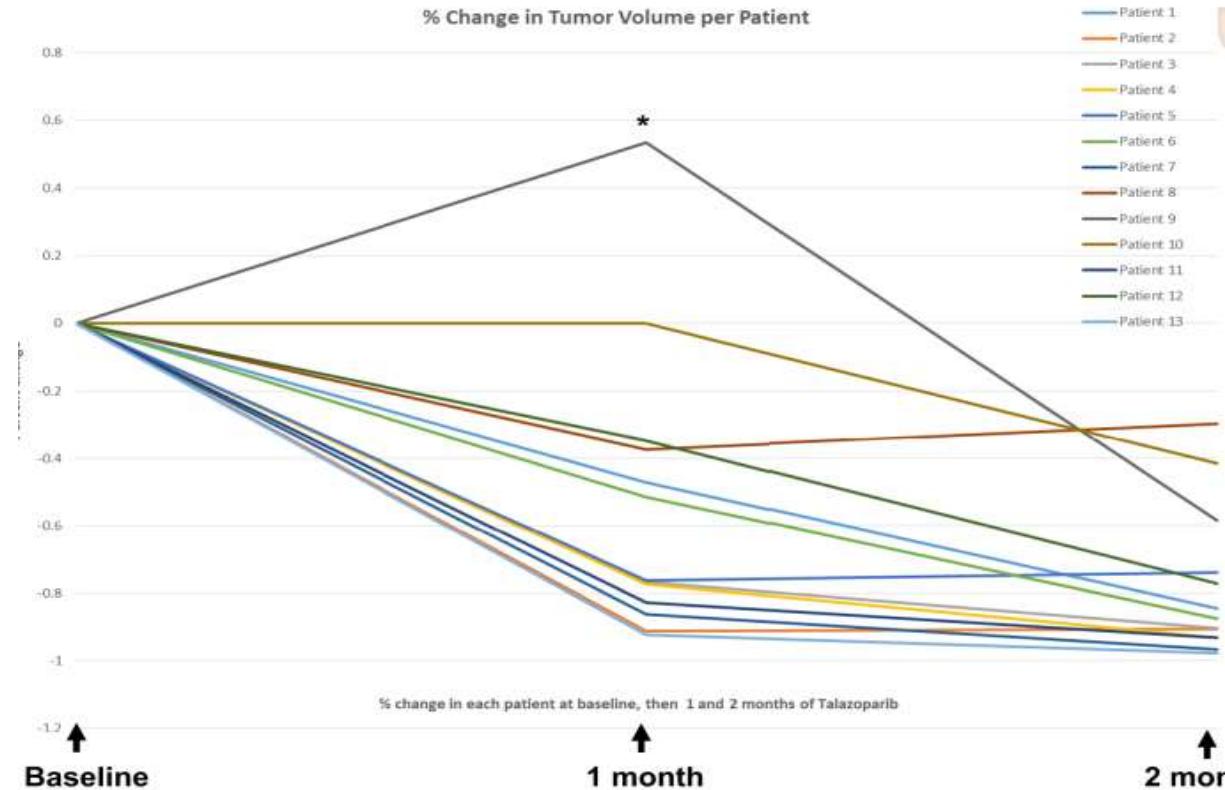
pCR rates by germline mutation and treatment arm

pCR	gBRCAm	gBRCAwt
Placebo + placebo/paclitaxel	41% (9/22)	29% (40/136)
Veliparib + carboplatin/paclitaxel	57% (26/46)	53% (142/270)
Placebo + carboplatin/paclitaxel	50% (12/24)	59% (80/136)

- Loibl S et al. Lancet Oncol. 2018 Apr;19(4):497-509



NEOADJUVANT TALAZOPARIB



EBC: Terapia antitumorale sistemica neoadiuvante

Ad oggi i dati disponibili sul **beneficio dell'aggiunta dei derivati del platino nel trattamento neoadiuvante delle pazienti con tumore mammario BRCA-correlato sono ancora controversi** e non permettono di definire un potenziale trattamento personalizzato.

Attualmente le **linee guida raccomandano di basare la decisione del tipo di chemioterapia o terapia ormonale sui fattori prognostici e predittivi consolidati per le forme sporadiche.**

Nel setting neo-adiuvante, l'**aggiunta dei sali di platino a una chemioterapia standard (contenente antracicline e taxani)** può essere considerata nelle pazienti con **neoplasia mammaria triplo negativa**. L'uso degli inibitori di PARP in fase neo-adiuvante è ancora oggi valutato in studi clinici.

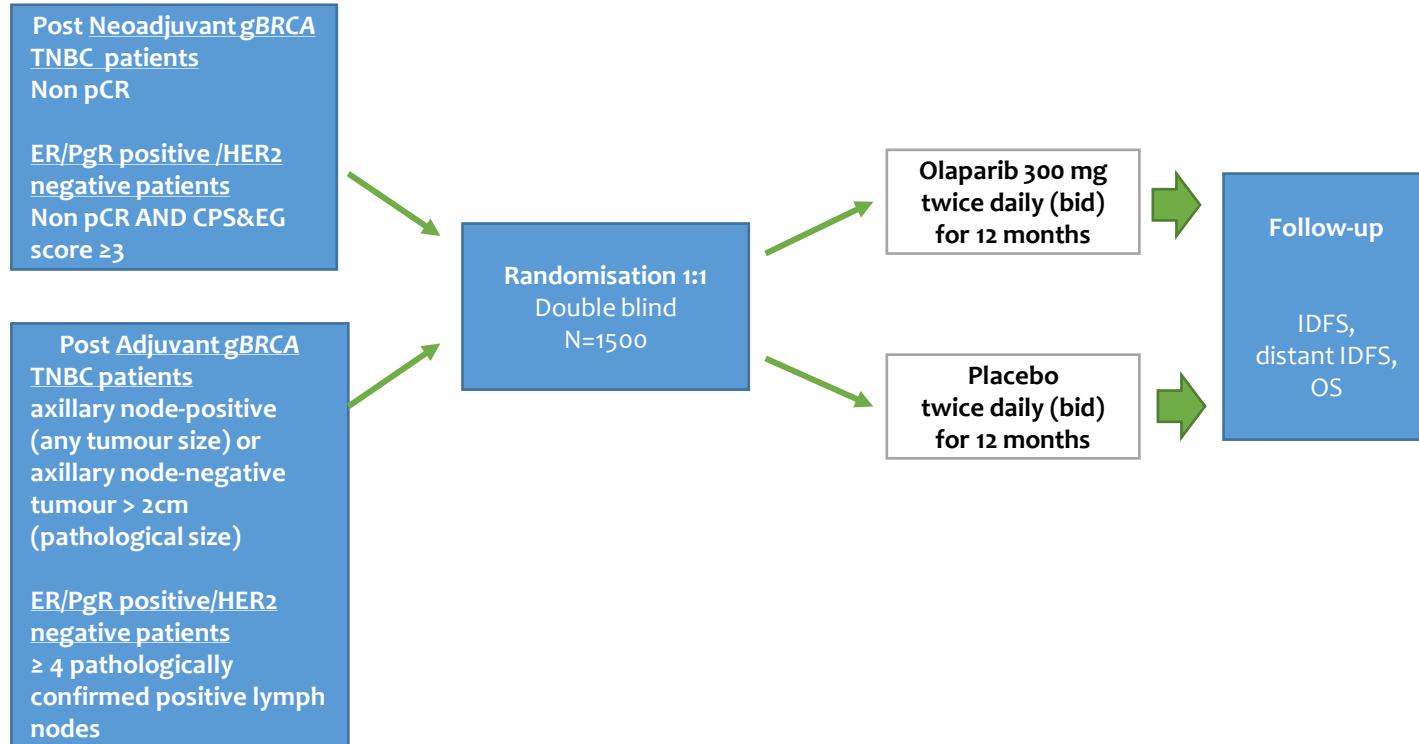
Dieci MV et al., Cancers (Basel). 2019, 8;11(8)



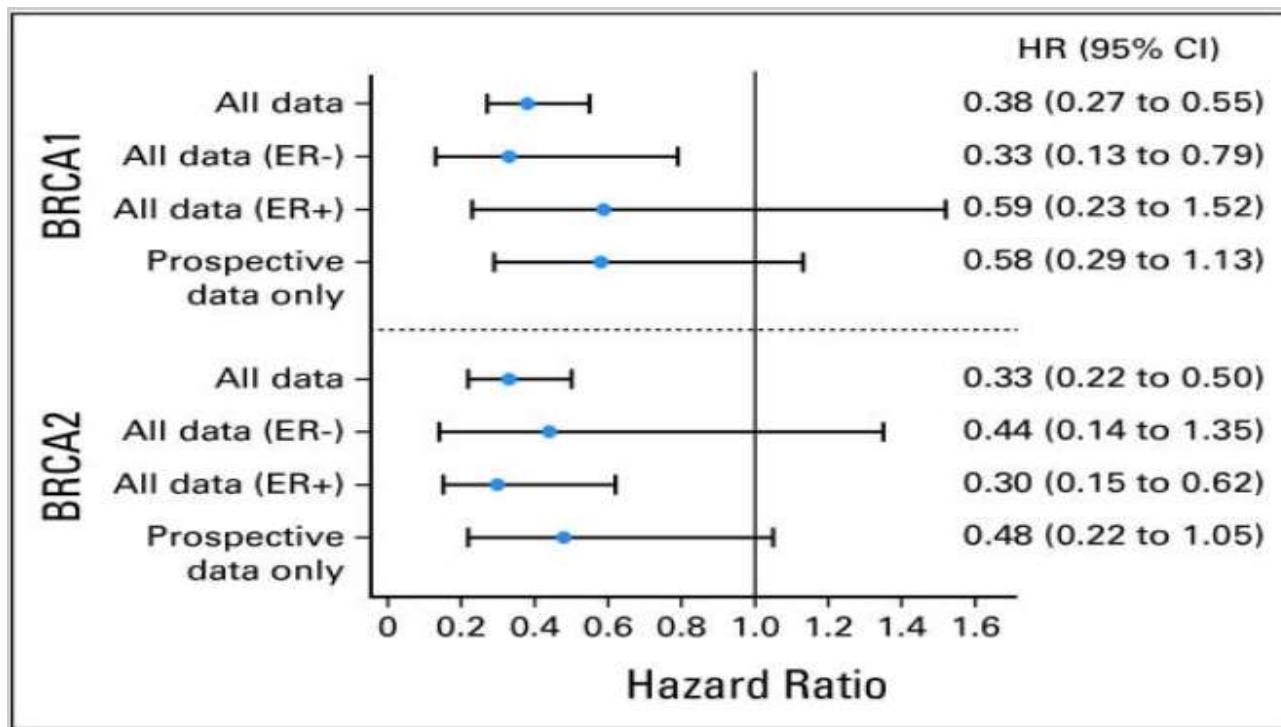
EBC: Terapia antitumorale sistemica adiuvante



OlympiA: Updated Design Chart



Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers



Philips KA, JCO 2013; 31(25):3091-9



Terapia adiuvante in gBRCAm

- Nel setting **adiuvante non esistono solidi dati prospettici** sull'uso dei **derivati del platino** nelle pazienti con carcinoma mammario **BRCA-correlato**.
- Il possibile ruolo dei **PARP-inibitori** dovrà essere stabilito dagli **studi in corso**.
- Il trattamento **endocrino adiuvante** segue le **stesse raccomandazioni** date per le pazienti con **carcinoma mammario senza VP BRCA**.



ABC:Trattamento della malattia metastatica

- *OlympiAD*¹

*EMBRACA*²

gBRCAm HER2- mBC

≤2 prior chemotherapy lines for mBC

Previous treatment with anthracycline and taxane
in either the (neo)adjuvant or metastatic setting

Randomise
2:1

Olaparib
300mg po bid

Treatment of
Physician's Choice
(TPC)

Primary endpoint
PFS (BICR)

gBRCAm HER2- locally advanced or metastatic
BC

≤3 prior lines of chemotherapy for locally
advanced/metastatic disease

Previous treatment with a taxane, an anthracycline,
or both, unless this treatment was contraindicated

Randomise
2:1

Talazoparib
1mg po qd

Treatment of
Physician's Choice
(TPC)

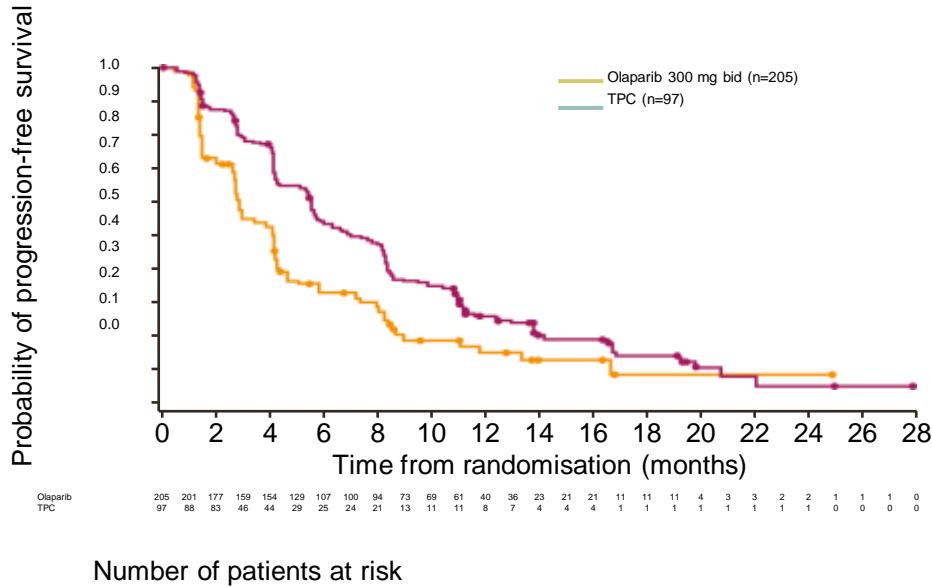
Primary endpoint
PFS (BICR)

1. Robson et al. N Engl J Med. 2017; 377:523-533;

2. Litton J et al. N Engl J Med 2018; 379:753-763



Primary endpoint: Olaparib treatment significantly improved PFS assessed by BICR compared to TPC



	Olaparib	TPC
n	205	97
Events (%)	163 (79.5%)	71 (73.2%)
Median (m)	7.0	4.2

HR=0.58
95 % CI (0.43, 0.80)
p=0.0009

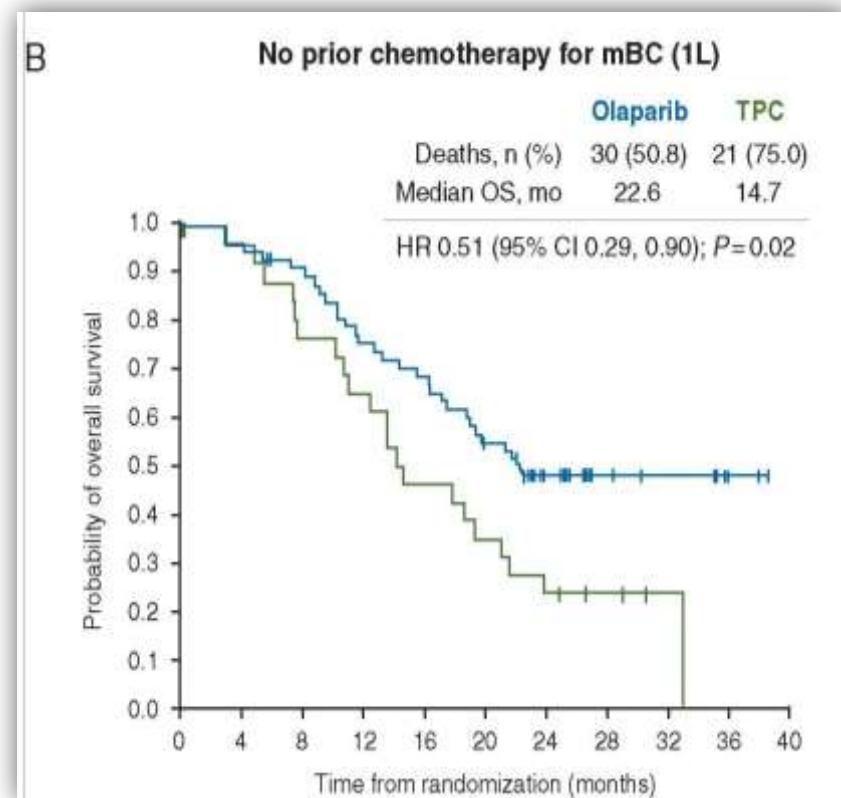
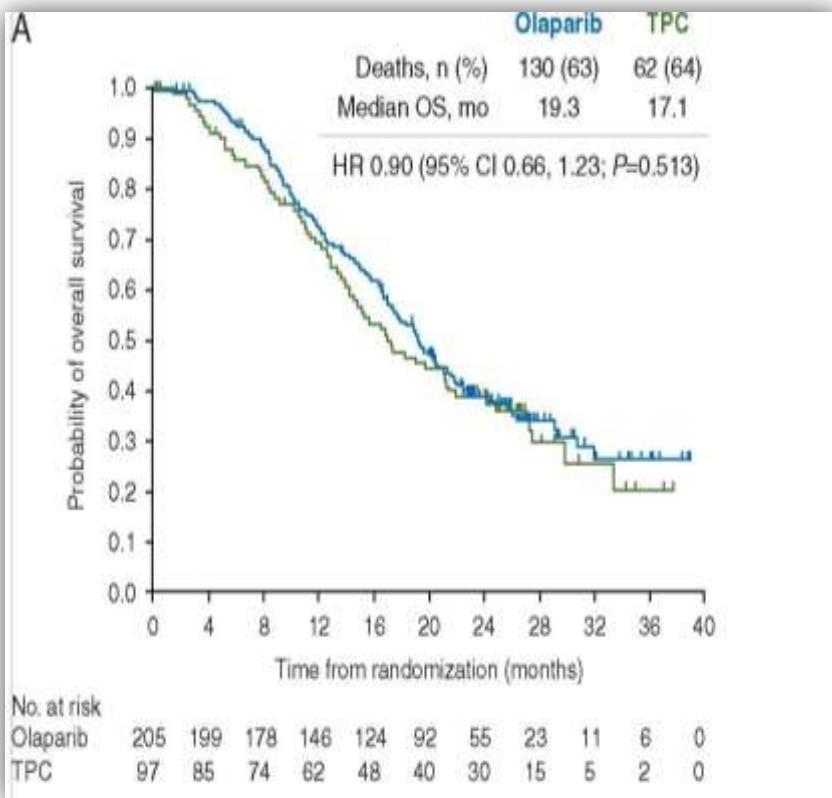
PFS free at 6m (%)	54.1	32.9
PFS free at 12m (%)	25.9	15.0

Median PFS was improved by 69% with olaparib treatment compared to standard of care chemotherapy

Robson et al. N Engl J Med. 2017; 377:523-533;



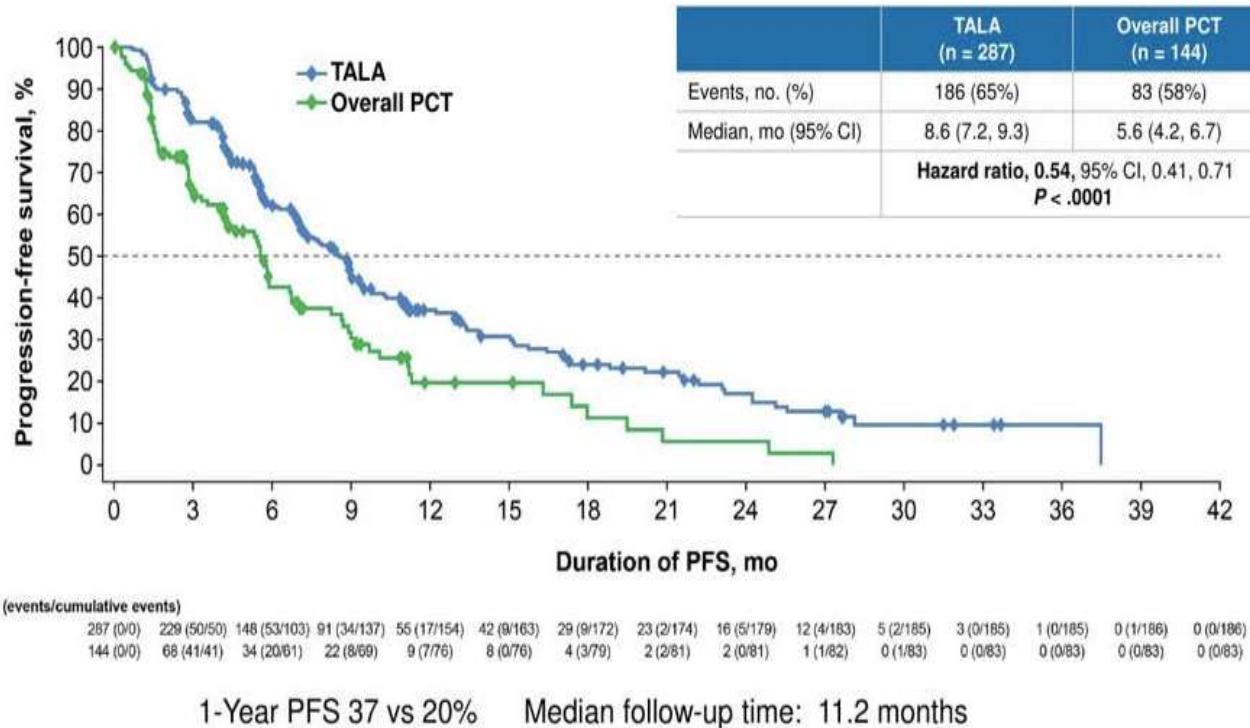
Overall Survival



Robson ME, Ann Oncol. 2019; 30(4): 558–566.



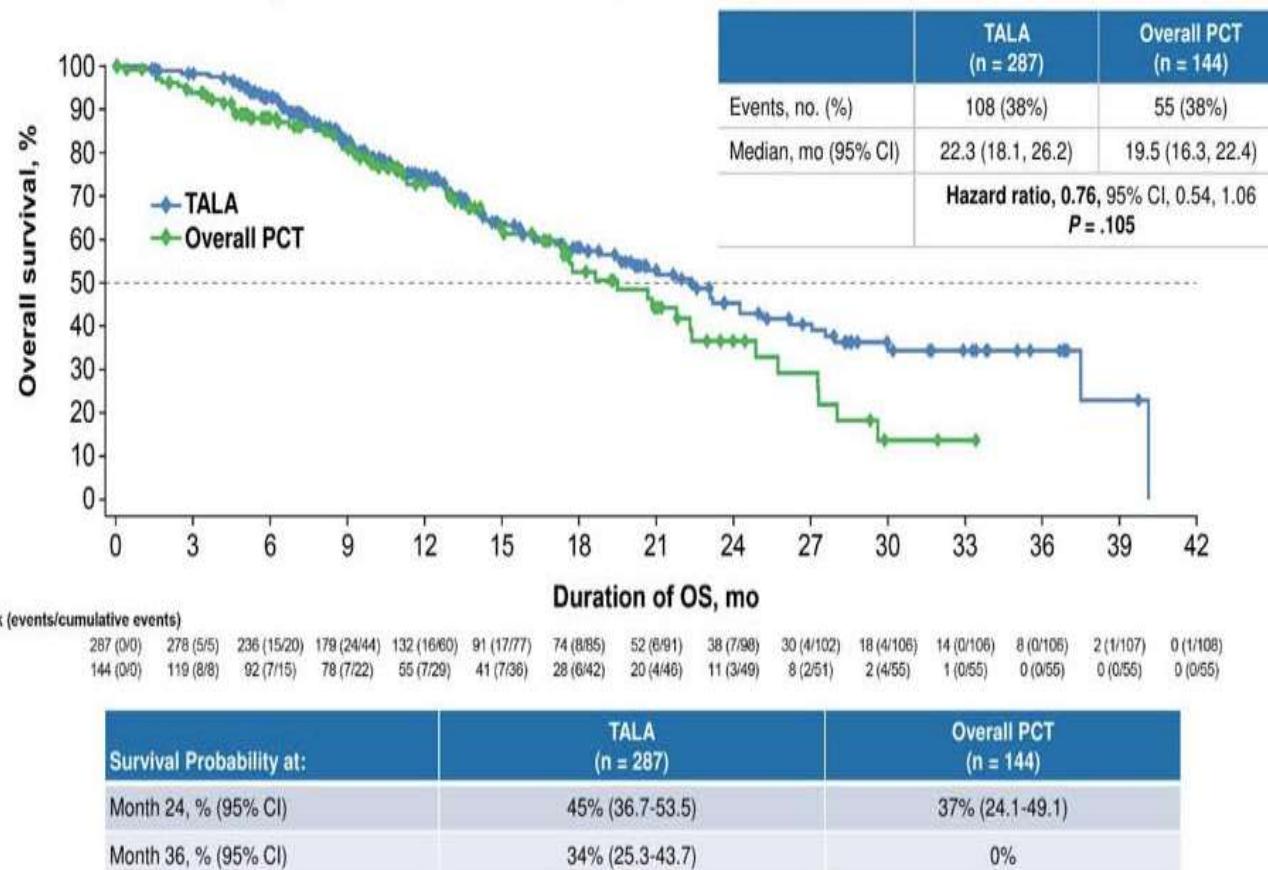
Primary Endpoint: PFS by Blinded Central Review



Litton JK NEJM 2018 379:753-763



Interim OS Analysis: Secondary Endpoint



Litton JK NEJM 2018;379:753-763

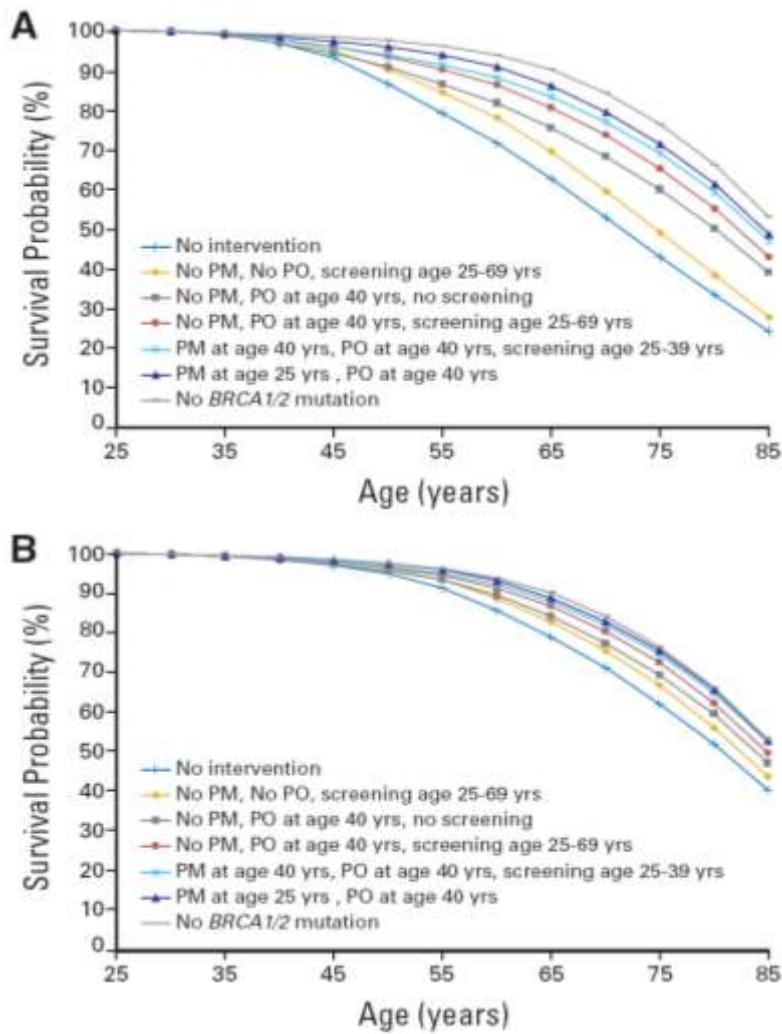


TERAPIA METASTATICA gBRCAm

La presenza di una variante patogenetica BRCA in donne con diagnosi di carcinoma mammario in fase metastatica può avere un impatto sulla scelta del trattamento antiblastico sistematico.

Attualmente in **Italia** un inibitore di PARP, **Olaparib**, è infatti utilizzabile nell'ambito di un **programma compassionevole** dal 28-2-2019 per le pazienti con **carcinoma mammario metastatico con mutazione (VP) BRCA germline**, sia nei tumori **Triplo-negativo** che **recettori ormonali positivi, HER2-negativi**.





Survival Analisys of Cancer Risk Reduction Strategies for BRCA 1/2 Mutation Carriers

Survival probability after different risk-reducing strategies performed at various ages in 25-year-old women with mutations in (A) BRCA1 and (B) BRCA2, compared with women without BRCA1/2 mutations.

Kurian AW et al, JCO; 28:222-231; 2010



Mastectomia Bilaterale Profilattica

Al momento la chirurgia rappresenta ancora la modalità più efficace di prevenzione primaria. L'intervento di **mastectomia bilaterale** è infatti in grado di ridurre di circa il 90% il rischio di sviluppare in futuro un tumore mammario, sebbene non sia possibile azzerarlo completamente, poiché permane un **rischio residuo** pari a circa l'1-2% .

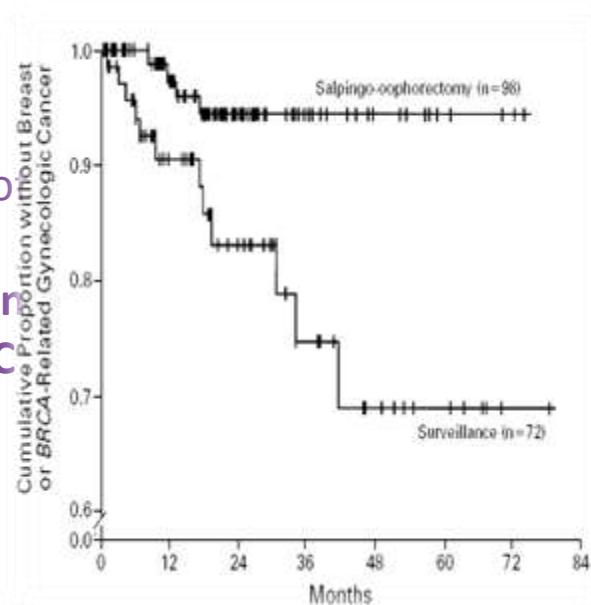
Ad oggi, **non** è stato dimostrato che la mastectomia profilattica bilaterale determini un **beneficio in termini di sopravvivenza globale**.



Ovariectomia Profilattica

BILATERAL PROPHYLACTIC OOPHORECTOMY

The Prevention and Observation of Surgical Endpoints (PROSE) study group reported a **96% reduction in OC risk** and a **53% reduction in BC risk** after PO.



Rebbek TR et al, NEJM; 346: 1616-1622; 2002



THE NEW ENGLAND
JOURNAL of MEDICINE

Kauff N.D. et al.; 2002; 346(21): 1609-1615



Vantaggio della RM annuale associata alla mammografia nelle donne portatrici di VP BRCA

BRCA risk management: a systematic review of effectiveness and cost-effectiveness | PETELIN et al.

SYSTEMATIC REVIEW

Table 2. Continued

Study, country	Intervention ^a	Comparator	Gene	Incremental effectiveness			Total cost ^b	ICER ^c		
				LYG	QALY	Other ^d		LYG	QALY	Other ^d
HQQA, Ireland ⁴⁰	Mammography/MRI from age 30	MRI	BRCA1	—	-0.011	—	\$14,074	—	Dominated ^e	—
			BRCA2	—	-0.009	—	\$12,027	—	Dominated ^e	—
MSAC, Australia ⁴¹	Mammography/MRI age 30-49	Mammography	BRCA1/2	+0.344	+0.264	—	\$12,798	\$19,837	\$25,848	—
NICE, UK ⁴²	MRI age 30-39	Mammography	BRCA1	—	+0.137	—	\$13,422	—	\$24,437	—
	Mammography/MRI age 30-39	MRI	BRCA1	—	+0.03	—	\$14,270	—	\$28,273	—
NICE, UK ⁴³	MRI age 40-49	Mammography	BRCA1	—	+0.153	—	\$7,486	—	\$10,494	—
			BRCA2	—	+0.143	—	\$7,085	—	\$11,005	—
	Mammography/MRI age 40-49	MRI	BRCA1	—	+0.005	—	\$8,462	—	\$195,340	—
			BRCA2	—	+0.004	—	\$8,114	—	\$257,468	—
Obdeijn, Netherlands ²²	MRI age 25-60 mammography age 40-60	MRI age 25-60 mammography age 30-60	BRCA1	+0.002	—	—	\$14,053	\$342,105	—	—
Pataky, Canada ⁴⁴	Mammography/MRI age 30-64 ^f	Mammography	BRCA1/2	—	+0.09	—	\$8,954	—	\$47,189	—
Plevritis, USA ³²	Mammography/MRI age 30-59	Mammography	BRCA1	+0.389	+0.284	—	\$97,360	\$61,275	\$83,929	—
	Mammography/MRI age 35-59	Mammography	BRCA2	+0.164	+0.117	—	\$58,532	\$117,187	\$164,262	—
Rijnsburger, Netherlands ⁵³	Mammography/MRI age 30-50	Mammography	BRCA1/2	+0.018	—	—	\$2,737	\$95,648	—	—
Taneja, USA ³⁷	Mammography/MRI age 40 (one exam only)	MRI	BRCA1/2	+0.0017	+0.002	—	\$3,293	\$39,041	\$30,168	—

Petelin L, Genet Med. 2018 Oct;20(10):1145-1156.



Surveillance for risk categories

RISK PROFILE	START	US	MX	MRI
Profile 1	45 yrs	If suspected mammogram image	45 -50 yrs A 51 -74 yrs B (Population Screening)	
Profile 2	25 yrs (if familiar with EOBC) 36 yrs	\geq 41yrs if high breast density or suspected mammogram image	40 -50 yrs A 51 -74 yrs B (Population Screening)	According to FONCAM guidelines
Profile 3 (without detected mutations)	25 yrs	25 – 60 yrs S	35-69 yrs A 70-74 yrs B	According to FONCAM guidelines
Profile 3 (with detected mutations)	From the mutation detection	From the mutation detection-69 yrs S	35-69 yrs A 70-74 yrs B	\geq 25 yrs A

A = annual; B = biennial; S = six-monthly; EOBC = Early Onset Breast Cancer

DGR 220/2011



CHEMIOPREVENZIONE

Un trattamento di **chemioprevenzione con tamoxifene 20 mg/die per 5 anni non** ha dimostrato un beneficio reale nella prevenzione dell'insorgenza di neoplasia mammaria nelle donne sane portatrici di VP BRCA.

Il **tamoxifene è consigliato nelle pazienti** con carcinoma mammario portarici di VP di BRCA per ridurre l'incidenza di tumore controlaterale.

Nelle donne sane portatrici di VP BRCA, non è indicato l'utilizzo di **inibitori di aromatasi** in chemioprevenzione.



Dieta e attività fisica in BRCA1/2

Table 3 Anthropometric measures and risk of postmenopausal breast cancer

	Person-years	Cases	Multivariate HR (95% CI) unweighted ^a
Height (m)			
<1.67 ^b	1,589	35	1.00
≥1.67	1,333	28	1.67 (1.01–2.74)
Body weight at age 18 (kg)			
<58 ^b	1,146	20	1.00
≥58	1,776	43	1.18 (0.62–2.23)
BMI at age 18 (kg/m ²)			
<22.50 ^b	2,157	42	1.00
≥22.50	765	21	0.94 (0.37–2.39)
Current body weight (kg)			
<72 ^b	1,764	29	1.00
≥72	1,158	34	2.10 (1.23–3.59)
Current BMI (kg/m ²)			
<25.00 ^b	1,608	27	1.00
≥25.00	1,314	36	1.46 (0.86–2.51)
Adult weight change (kg)			
<5 kg weight gain ^b	695	14	1.00
≥5 kg weight gain	2,227	49	1.56 (0.85–2.87)
Relative adult weight change			
<20% ^b	1,520	31	1.00
≥20%	1,402	32	1.60 (0.97–2.63)

^a A time-varying Cox proportional hazards model, stratified for genes (BRCA1 and BRCA2) and birth cohort (<1945, 1946–1955, 1956–1964, ≥1965), clustered on family (185 clusters), and adjusted for parity (nulliparous, 1–2 children, >2 children), type of menopause and HRT use [natural menopause and never HRT use, natural menopause and ever HRT use, BPSO and never HRT use, BPSO and ever HRT use, surgical (ovarian cancer) and never HRT use] and lifetime sports activity (mean MET-h/week in active period; time-varying)

^b Reference category



Gravidanza e Allattamento

	HR	CI95	p-value
Pregnancy, yes			
BRCA	0.27	0.12-0.58	0.001
HR	0.94	0.43-2.02	0.869
IR	1.00	0.31-3.29	0.999
N° of pregnancies, 1			
BRCA	0.31	0.12-0.85	0.022
HR	0.84	0.37-1.87	0.662
IR	0.75	0.22-2.63	0.650
N° of pregnancies, 2			
BRCA	0.29	0.12-0.66	0.003
HR	0.99	0.45-2.18	0.975
IR	1.09	0.32-3.69	0.885
N° of pregnancies, 3			
BRCA	0.08	0.01-0.67	0.019
HR	1.17	0.46-2.99	0.740
IR	1.80	0.45-7.20	0.407
Age at first full term pregnancy, ≤ 30 years			
BRCA	0.49	0.19-1.26	0.138
HR	0.62	0.38-0.99	0.048
IR	0.61	0.29-1.32	0.213
Breastfeeding, 1-12 months			
BRCA	0.24	0.09-0.66	0.005
HR	1.12	0.49-2.58	0.784
IR	1.49	0.42-5.22	0.536
Breastfeeding, > 12 months			
BRCA	0.25	0.08-0.82	0.022
HR	1.91	0.79-4.61	0.151
IR	1.86	0.49-7.03	0.357

Toss A. et al.. Oncotarget 2017 :8:9144-9154



Combined hormonal contraceptives use does not increase the risk of breast cancer in a population of women with a family history

Variable	Group	HR	CI 95 %	p
CHCs use <10 years	Intermediate	0.80	0.36-1.79	0.583
CHCs use >10 years	Intermediate	0.52	0.11-2.33	0.390
CHCs use <10 years	High	0.95	0.59-1.54	0.849
CHCs use >10 years	High	1.18	0.62-2.26	0.613
CHCs use <10 years	Very high (BRCA)	1.60	0.70-3.65	0.267
CHCs use >10 years	Very high (BRCA)	1.00	0.22-4.60	0.995

Grandi G. et al., Clinical Breast Cancer 2018;18:e15-e24.



Pillola e rischio di carcinoma mammario in BRCA1 mutate

Table 3 Relationship between duration of oral contraceptive use prior to age 20 and breast cancer risk among *BRCA1* mutation carriers

Variable	Controls (n)	Cases (n)	OR (95 % CI) ^a	P
Duration of use <20 years old				
Never	1,084	1,018	1.00	
<5 years	154	164	1.39 (1.06–1.83)	0.02
5–<10 years	180	208	1.39 (1.07–1.80)	0.01
10–<15 years	118	152	1.49 (1.12–1.99)	0.007
≥15 years	74	95	1.63 (1.14–2.35)	0.007
Trend ^b				0.0003

^a All ORs and 95 % CIs were calculated using a multivariate con-

Kotsopoulos J, Breast Cancer Res Treat. 2014;143:579–86.



HRT and BPO in BRCA1/2 carriers

Table 3. Breast Cancer Risk Reduction After BPO Stratified by Postsurgical HRT Use

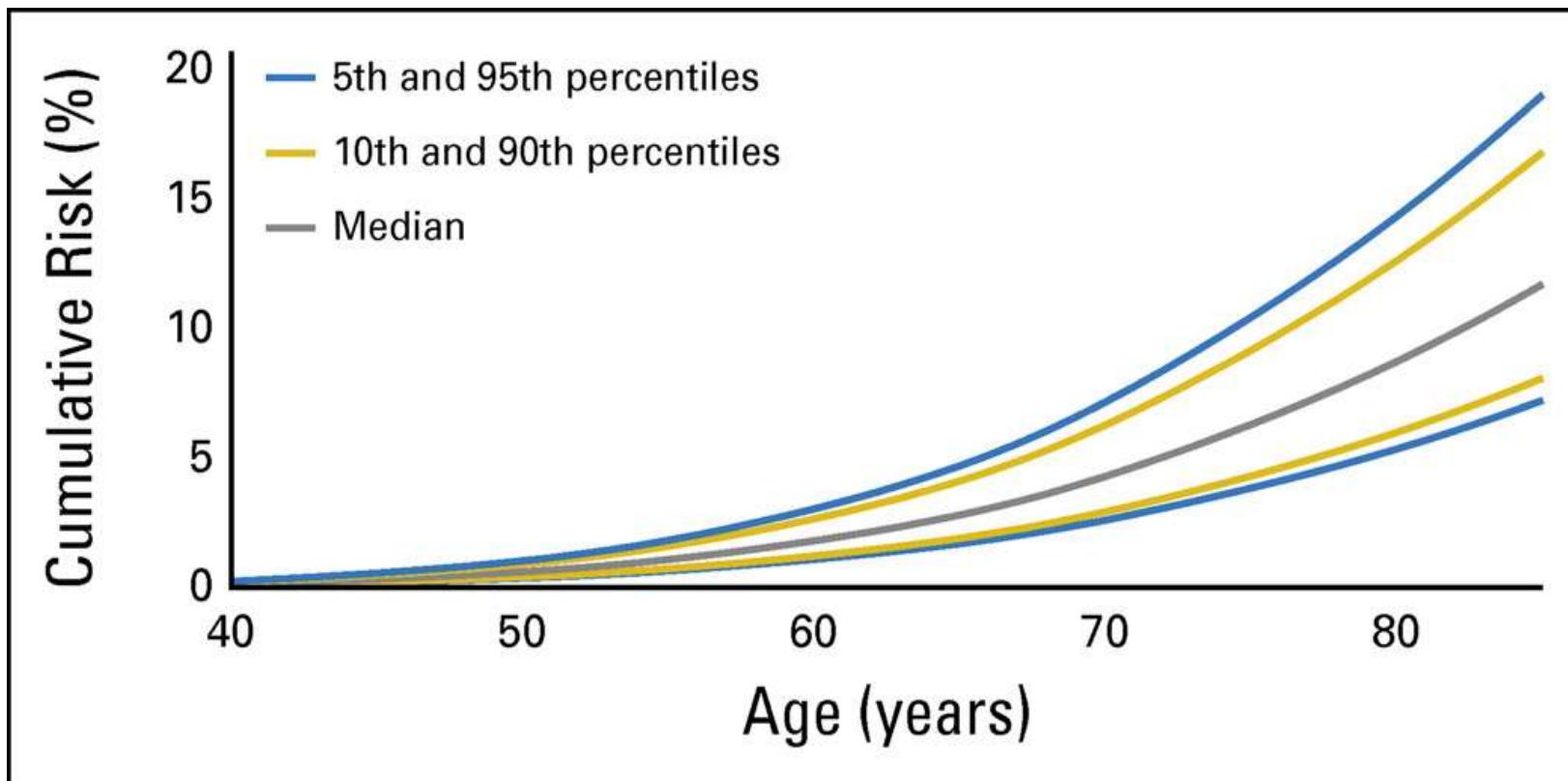
Variable	Total Sample			BPO Before Age 50			
	No.	HR	95% CI*	No.	HR	95% CI*	
No surgery	No HRT	286	1.0	—	286	1.0	—
BPO	No HRT	62	0.38	0.09 to 1.59	50	0.59	0.14 to 2.52
BPO	Any HRT	93	0.37	0.14 to 0.96	89	0.30	0.11 to 0.85
BPO	E2 only	50	0.44	0.12 to 1.61	50	0.44	0.12 to 1.61
BPO	PROG ± E2	34	0.43	0.07 to 2.68	34	0.43	0.07 to 2.68

Abbreviations: BPO, bilateral prophylactic oophorectomy; HRT, hormone replacement therapy; HR, hazard ratio; E2, estrogen; PROG, progesterone.

*Adjusted for birth year, *BRCA1* versus *BRCA2*, center of ascertainment, and parity.



Carcinoma mammario maschile in BRCA1 e BRCA2 mutati



: Julie Lecarpentier; *Journal of Clinical Oncology* 2017 35:2240-2250.



Sorveglianza soggetti maschili BRCA2 mutati

Prevention and screening of other *BRCA*-associated cancers and approach to male carriers

- BRCA2 carriers may consider annual skin and eye examination as screening for melanoma V,C
- BRCA2 carriers may consider annual screening for pancreatic cancer with EUS or MRI/MRCP while being informed that data supporting this approach is very limited. There is no consensus when screening should commence—however, age 50 or 10 years before the earliest diagnosed case in the family would be reasonable V,C
- Carriers should be strongly encouraged to participate in clinical trials evaluating the efficacy of screening techniques for pancreatic cancer V,C
- Male carriers should be advised to undergo annual clinical breast examination by a physician, starting from the age of 30. No evidence exists to justify or support routine annual breast imaging among male carriers V,C
- Annual screening for prostate cancer may be considered from the age of 40, particularly for *BRCA2* carriers V,C
- Screening recommendations for *BRCA*-associated malignancies should be tailored to an individual's family history of malignancy V,C

Paluch-Shimon S et al., Ann Oncol. 2016 Sep;27(suppl 5):v103-v110.



Test BRCA

- 1) Test BRCA su sangue periferico (test costituzionale o germinale)**
- 2) Next Generation Sequencing-NGS e sequenziamento Sanger**
- 3) VP BRCA di tipo costituzionale ereditate dalla madre o dal padre e trasmissibili ai figli (50% di probabilità per ogni figlio/a)**
- 4) Non test BRCA su tessuto tumorale**
- 5) Se chemioterapia o chirurgia profilattica il test entro 30-40 giorni**
- 6) Refertazione secondo criteri ENIGMA**



ENIGMA BRCA Classification Scheme

Class 5 Pathogenic:	Class 4 Likely pathogenic:	Class 3 Uncertain:	Class 2 Likely not pathogenic:	Class 1 Not pathogenic:
<p>Probability of pathogenicity >0.99 by multifactorial model</p> <p>OR</p> <p>Copy number deletion confirmed to disrupt clinically important functional domain</p> <p>OR</p> <p>Copy number duplication confirmed to encode a frameshift disrupting a clinically important functional domain</p> <p>OR</p> <p>Allele-specific patient mRNA splicing assay producing only transcripts with PTC or disrupting a known clinically important function domain</p> <p>OR</p> <p>Nonsense or frameshift variant leading to premature termination codon</p>	<p>Probability of Pathogenicity 0.95-0.99 by multifactorial model</p> <p>OR</p> <p>Canonical splice site, untested for splicing, not predicted to lead to naturally occurring isoform(s)</p> <p>OR</p> <p>All of the following:</p> <ul style="list-style-type: none"> Encodes same amino acid change as pathogenic missense No evidence of splicing aberration Absent from outbred control reference groups <p>OR</p> <p>All of the following:</p> <ul style="list-style-type: none"> Deletes in-frame a codon for which a pathogenic missense variant has been described Absent from outbred control reference groups 	<p>Probability of pathogenicity 0.05-0.949 by multifactorial model</p> <p>OR</p> <p>Insufficient evidence to classify</p> <p>OR</p> <p>Predicted splice variants at exon borders with known interpretation issues</p> <p>OR</p> <p>Potential intermediate risk variant as indicated by conflicting evidence for pathogenicity</p>	<p>Probability of pathogenicity 0.001-0.049 by multifactorial model</p> <p>OR</p> <p>Encodes same amino acid change as non-pathogenic AND no evidence of mRNA aberration</p>	<p>Probability of pathogenicity <0.001 by multifactorial model</p> <p>OR</p> <p>AF ≥1% in control reference groups</p> <p>OR</p> <p>All of the following:</p> <ul style="list-style-type: none"> In Trans with pathogenic and no clinical phenotype other than breast cancer Predicted low likelihood to disrupt splicing OR predicted high likelihood to disrupt splicing with no evidence of mRNA splicing aberration



Open Questions: Mini-Counseling

Poiché nei prossimi anni è atteso un notevole incremento della richiesta di test genetici, può essere auspicabile istituire un “mini-counseling”, per ridurre i tempi di attesa e il carico di lavoro per le figure professionali impegnate nel processo di counseling oncogenetico.

Il mini-counseling dovrebbe essere effettuato entro **1 settimana dalla diagnosi istologica**.

Si ribadisce che una conoscenza esperta è richiesta anche nel caso del cosiddetto “mini-counseling” perché durante un breve colloquio occorre riuscire a veicolare in un breve tempo i contenuti fondamentali della consulenza genetica pre-test adattandoli alla situazione oncologica e familiare della paziente.



Il test genetico dovrebbe includere altri geni oltre allo studio di BRCA1/2? Quando è raccomandabile eseguire un'analisi di un pannello di geni? Quali geni andrebbero inseriti nel pannello?

Utilizzare pannelli comprendenti esclusivamente geni “**clisticamente utili**”, corrispondenti ai geni ad alta penetranza per il carcinoma mammario, per i quali le raccomandazioni sono abbastanza uniformi. Anche in questo caso va comunque considerato che alterazioni di questi geni sono generalmente associate a caratteristiche specifiche e di conseguenza il sospetto di un loro coinvolgimento dovrebbe essere già posto su base clinica (associazione con altre neoplasie, caratteristiche istologiche, manifestazioni non tumorali associate).

L’uso dei pannelli deve comunque consentire di mantenere **livelli accettabili di sensibilità per i geni BRCA**.



Sindromi ereditarie associate ad un alto rischio di tumore della mammella

SINDROME	SPETTRO TUMORALE	GENI
TUMORI EREDITARI MAMMELLA/OVAIO	Mammella, ovaio, utero, prostata, pancreas, melanoma	<i>BRCA 1</i> <i>BRCA2</i>
LI-FRAUMENI	Sarcomi, mammella, leucemia, SNC, carcinoma surrenalico, encefalo, altri	<i>TP53</i>
COWDEN/PHTS ¹	Mammella, tiroide, endometrio	<i>PTEN</i>
PEUTZ-JEGHERS	Colon-retto, stomaco, ovaio, testicolo, cervice uterina, pancreas, mammella	<i>STK11</i>
<i>PALB2</i> ^{2, 3}	Mammella, ovaio, pancreas	<i>PALB2</i>
<i>ATM</i> ^{2, 3, 4}	Mammella, stomaco	<i>ATM</i>
<i>CHEK2</i> ^{2, 3}	Mammella	<i>CHK2</i>





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