11ª EDIZIONE

Progetto CANOA

CARCINOMA MAMMARIO: QUALI NOVITA' PER IL 2021?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Il carcinoma mammario metastatico nella paziente portatrice di VP germline BRCA: dalle evidenze scientifiche alle opzioni terapeutiche

I tumori HR-positivi

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Conflict of interest

Research funding:
none

Lectures:
Lilly

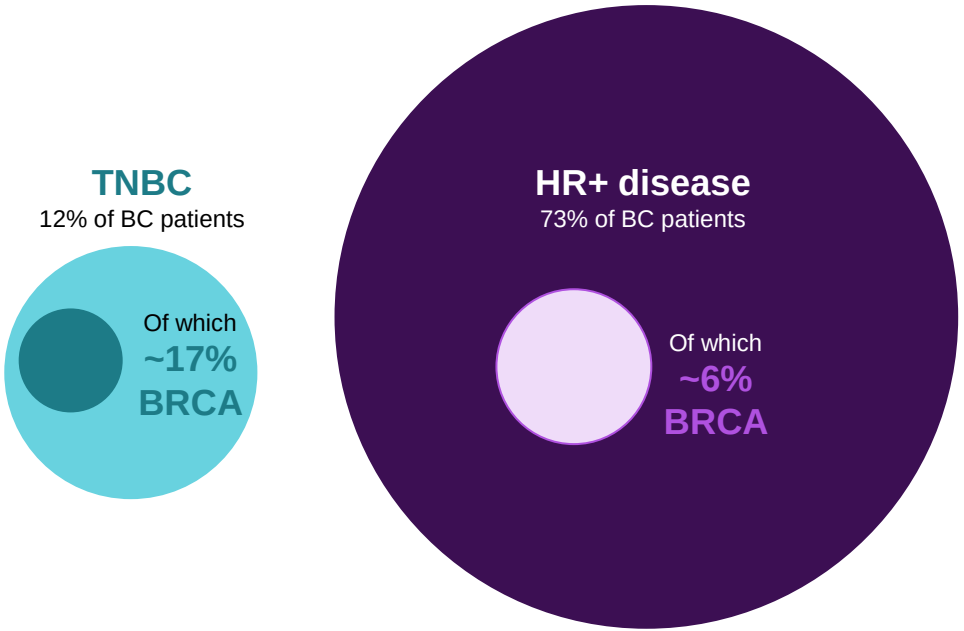
Advisor:
Lilly, Novartis, Roche

Stock options, ownership:
None

OUTLINE

- The prevalence of these patients in the population
- Characteristics and outcomes of gBRCA HR+ breast cancer patients
- Treatment strategies in BRCA mutation carriers
- Data in neoadjuvant setting
- Data in metastatic setting
- Suggestions on how to bring this together into a treatment pathway for this population

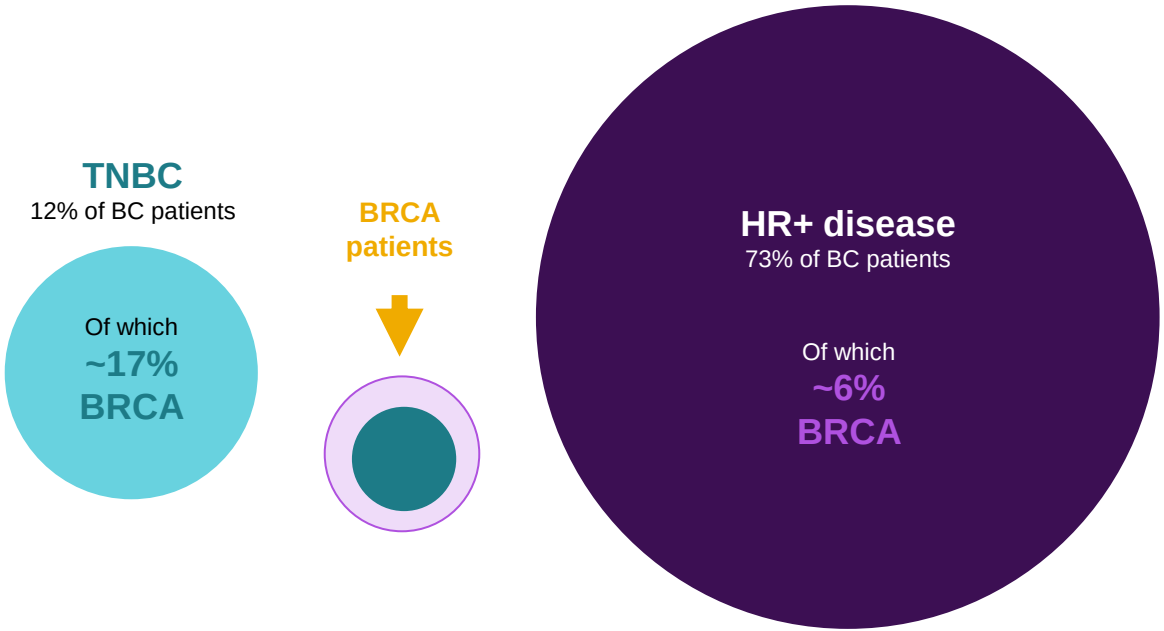
A higher proportion of patients with TNBC have a BRCAm than those with HR+ disease



Note that these calculations are based on very small patient populations; images are representative only
Detailed analysis of BRCAm prevalence, age of onset and survival outcomes are currently lacking for breast cancer subtypes.

Winter et al. Ann Oncol. 2016 Aug; 27(8): 1532–1538[4]

However, due to the relative prevalence, the majority of BRCA are found in patients with HR+ disease vs. TNBC



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Winter et al. Ann Oncol. 2016 Aug; 27(8): 1532–1538

BRCA HR+ tumours have distinct characteristics

Young age	Aggressive disease	High probability of recurrence
Often younger at diagnosis than sporadic HR+ patients Average age of diagnosis is under 45 years*[1–5]	Often have aggressive disease vs. non-BRCA breast cancers • Higher levels of nodal involvement* • Higher Ki67 proliferation marker expression[1,6,7]	Higher recurrence scores compared to sporadic HR+ patients >80% being classed as intermediate or high risk patients**[8–10]

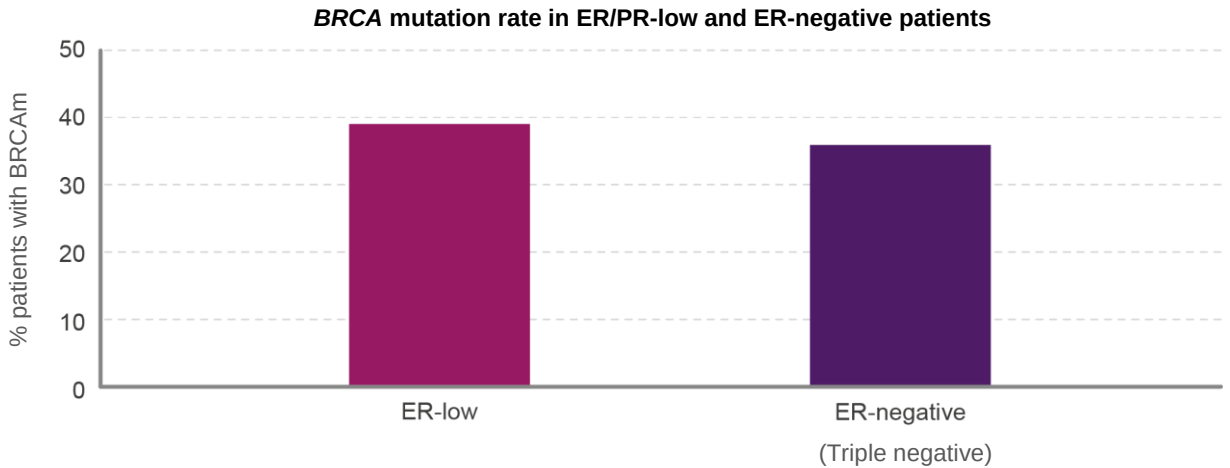
*Based on patients with *BRCA2*m breast cancer. At least 85% of *BRCA2* are HR+

**Intermediate and high risk disease are classified as having recurrence scores of 18-30 or >30 respectively

1. Mavaddat N et al. Cancer Epidemiol Biomarkers Prev. 2012; 21(1):134–47; 2. Krammer J, et al. Breast Cancer Res Treat. 2017;163:565-571; 3. Fostira F, et al. Poster 105P, presented at ESMO 2016; 4. Peretz TY et al. Poster P3-03-02, presented at SABCS 2017; 5. Pellegrino B, et al. Acta Biomed. 2016;87:54-63; 6. Aleskandarany M, et al. Breast Cancer Res Treat. 2015;150:81-90; 7. Tredan O et al. Poster P3-03-05, presented at SABCS 2017; 8. Halpern N, et al. Int J Cancer. 2017;140:2145-2149; 9 Lewin R, et al. Breast Cancer Res Treat. 2016;157:511-516; 10.Shah PD, et al. Cancer. 2016;122:1178-1184

BRCA prevalence in ER/PR low breast tumours may also be as high as TNBC

Both HR positive low (ER and/or PR 1–9%) tumours and triple negative tumours have a higher BRCAm rate than ER high tumours[1]

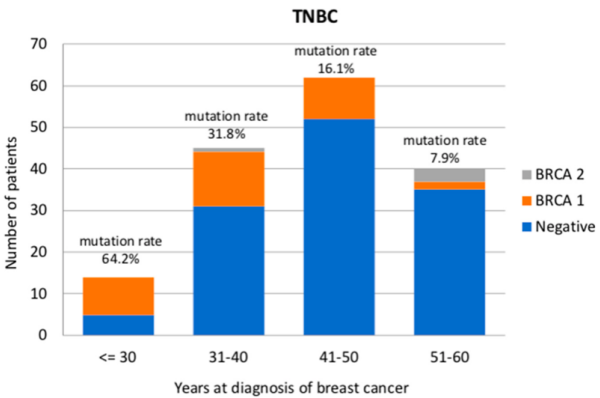


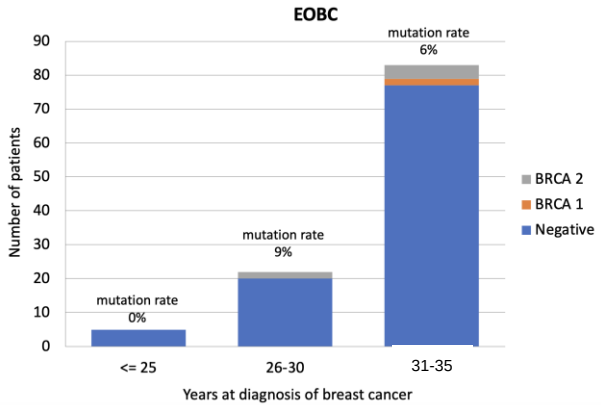
Sanford RA, et al., Cancer. 2015 Oct 1;121(19):3422-7

Article

BRCA Detection Rate in an Italian Cohort of Luminal Early-Onset and Triple-Negative Breast Cancer Patients without Family History: When Biology Overcomes Genealogy

Angela Toss [1,2,*], Eleonora Molinaro [1], Marta Venturelli [1], Federica Domati [1], Luigi Marcheselli [1], Simonetta Piana [3], Elena Barbieri [1], Giovanni Grandi [4], Claudia Piombino [1], Isabella Marchi [1], Elena Tenedini [5], Enrico Tagliafico [5,6,7], Giovanni Tazzioli [7,8] and Laura Cortesi [1]





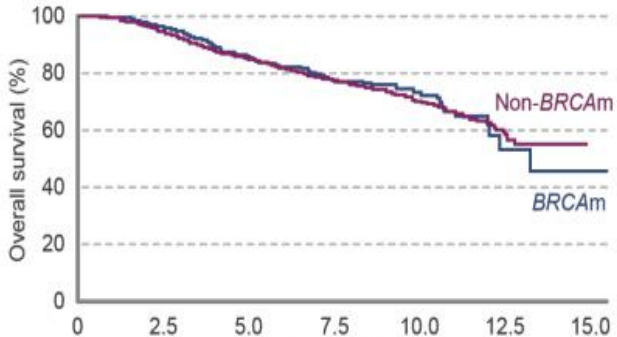
A total of 40% of patients with estrogen receptors (ER) 1–9% were BRCA1 carriers.

Whether presence of a BRCAm impacts breast cancer survival outcomes remains unclear[1-3]

Whilst a large number of studies have investigated outcomes of BRCAm breast cancer patients, these studies have had conflicting outcomes[1-3]

Study	Result
Copson ER et al. Lancet Oncol 2018[1]	• The UK based POSH study (n=2,733) found **no significant difference in OS between BRCAm and non-BRCAm patients** in a cohort of early onset BC patients (see figure)
Baretta et al., 2016 Oct; 95(40): e4975[2]	• A large meta-analysis by Baretta et al. (n=105,220) found that **BRCAm patients were associated with worse OS** compared to non-BRCAm patients • However there was some variability in these results by BRCA mutation type
Zhu et al. Oncotarget. 2016 Oct 25;7: 70113-70127[3]	• Another meta-analysis by Zhu et al. (overall meta-analysis n=297,402) found **worse OS for *BRCA1*m patients vs non-BRCAm patients and also for *BRCA2*m patients vs. non-BRCAm patients** • However, studies which only analysed *BRCA1* and *BRCA2* mutations together found **no significant difference in OS between BRCAm and non-BRCAm patients**

OS KM curve for early-onset breast cancer patients by BRCAm status[1]



Number at risk (number censored)							
Non-*BRCAm*	2395 (125)	2217 (217)	1805 (141)	1160 (78)	452 (30)	48 (3)	0 (0)
BRCAm	338 (13)	313 (38)	245 (18)	163 (5)	71 (9)	10 (1)	2 (0)

Reactive Oxygen Species (ROS)

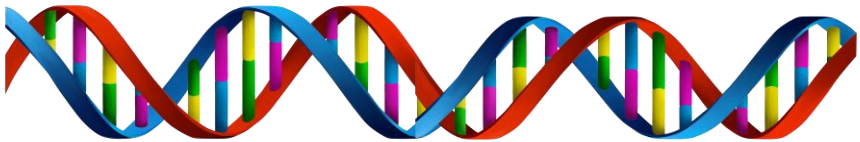
Replication Errors

X Rays

UV Light

Alkylating Agents

Spontaneous Reactions



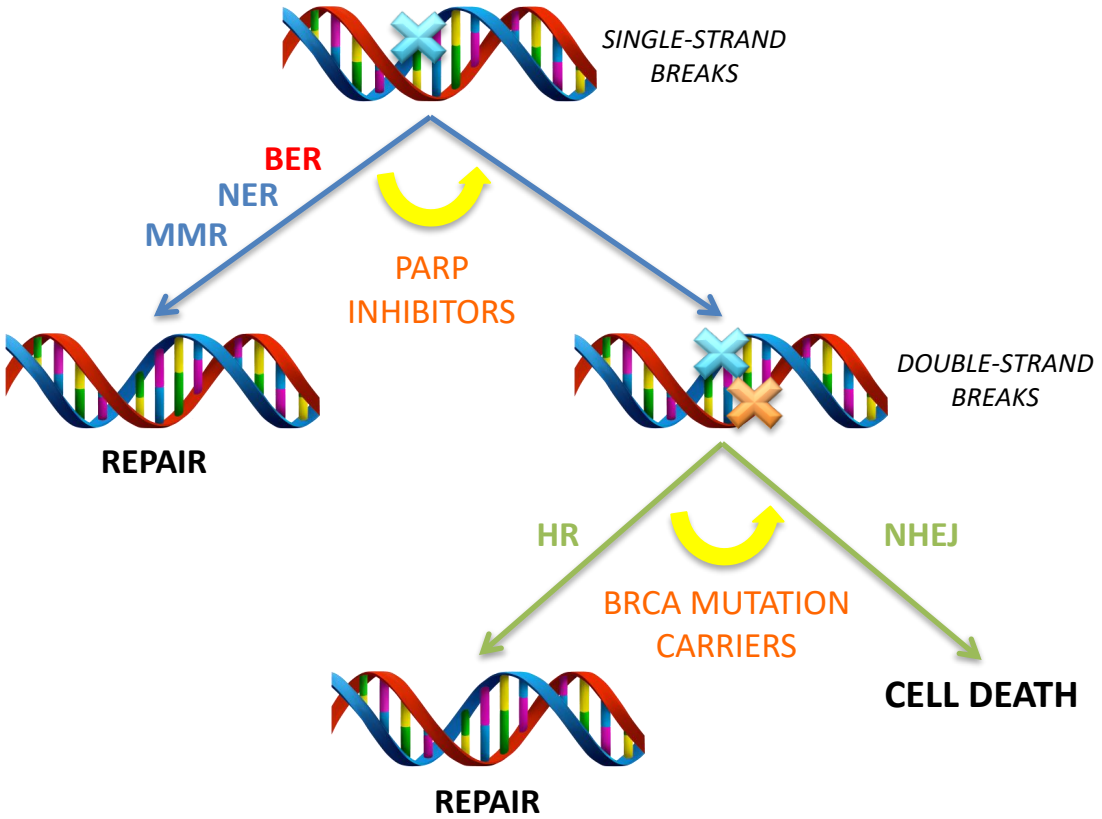
SINGLE-STRAND BREAKS (SSBs) DELETIONS and INSERTIONS

DOUBLE-STRAND BREAKS (DSBs)

BASE EXCISION REPAIR (BER)	NUCLEOTIDE EXCISION REPAIR (NER)	MISMATCH REPAIR (MMR)	HOMOLOGOUS RECOMBINATION (HR)	NON HOMOLOGOUS END JOINING (NHEJ)
PARP	XP, POLYMERASES	MLH1, MSH2, MSH6, MLH3, PMS2	ATM/ATR, BRCA1/2, CHEK2, RAD51, BRIP1, PALB2	DNA-PXcs, Mre11, RAD50, NBS1

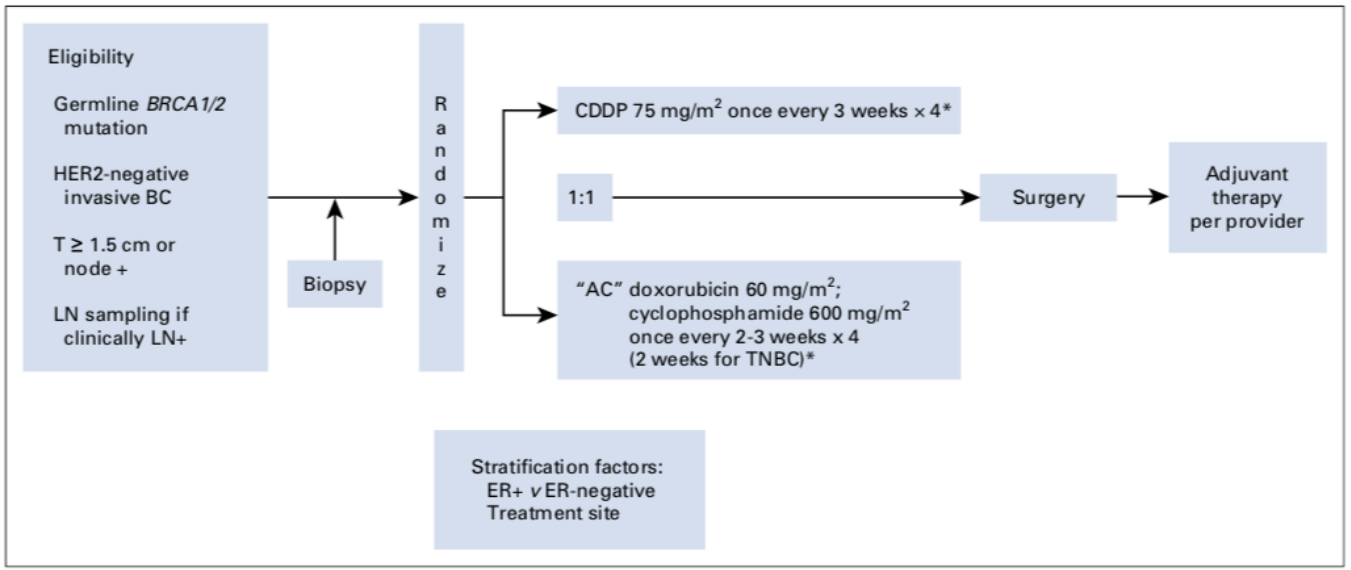
Toss and Cortesi. J Canc Sci Therapy 2013
Cortesi L et al. Curr Cancer Drug Targets 2018

SYNTHETIC LETALITY



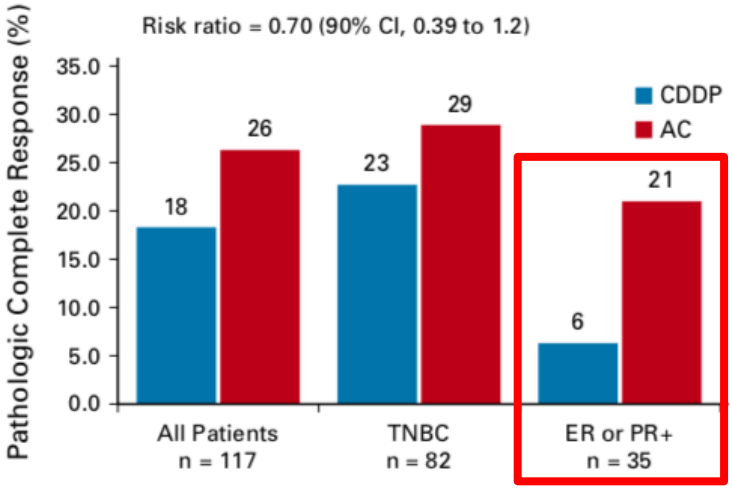
Toss and Cortesi. J Canc Sci Therapy 2013
Cortesi L et al. Curr Cancer Drug Targets 2018

TBCRC 031: Randomized Phase II Study of Neoadjuvant Cisplatin Versus Doxorubicin-Cyclophosphamide in Germline *BRCA* Carriers With HER2-Negative Breast Cancer (the INFORM trial)



Pathologic response was documented using the Residual Cancer Burden (RCB) Calculator (www.mdanderson.org/breastcancer_RCB).

Tung N et al. J Clin Oncol 2020



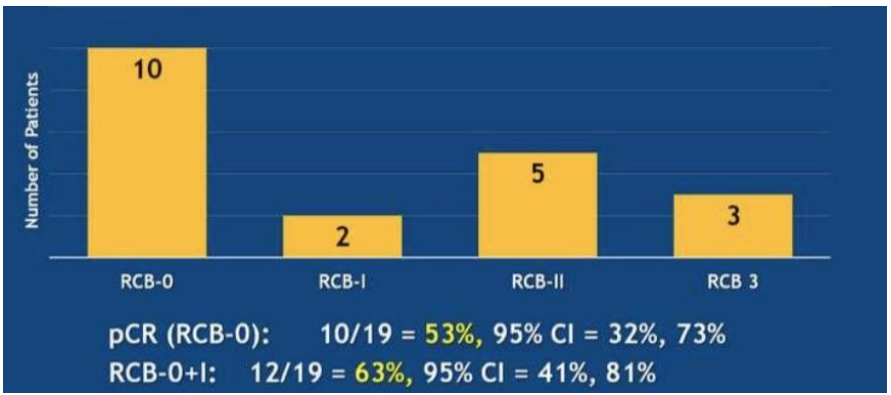
117 pts were included in outcome analyses:

- Mean age was 42 years (range, 24-73 years).
- 69% BRCA1+, 30% BRCA2+, and 2% had both mutations.
- Clinical stage was I for 19%, II for 63%, and III for 18%; 45% had nodal involvement at baseline.
- 70% had TNBC.

The **pCR rate** was **18% with CDDP and 26% with AC**
(RR, 0.70; 90% CI, 0.39 to 1.2).
The risk of **RCB 0/1** was **33% with CDDP and 46% with AC**
(RR, 0.73; 90% CI, 0.50 to 1.1).

Tung N et al. J Clin Oncol 2020

Neoadjuvant Talazoparib for Patients With Operable Breast Cancer With a Germline *BRCA* Pathogenic Variant



Pathologic response was documented using the Residual Cancer Burden (RCB) Calculator (www.mdanderson.org/breastcancer_RCB).

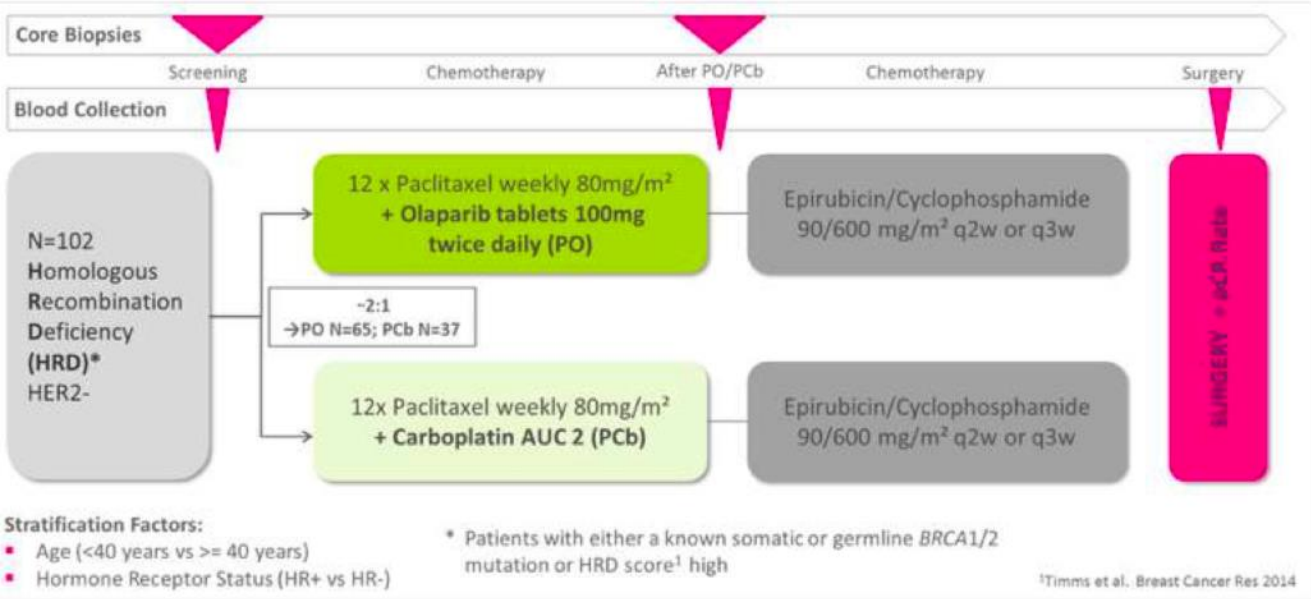
Neoadjuvant single-agent oral talazoparib once per day for 6 months without chemotherapy produced substantial RCB-0 rate with manageable toxicity. The substantive pathologic response to single-agent talazoparib supports the larger, ongoing neoadjuvant trial.

Litton JK et al. JCO 2019

BRCA 1 or *BRCA 2*	Tissue Receptor	Clinical Stage	Surgery	RCB	Systemic Therapy After Surgery	Dose of Talazoparib at End of Study, mg	Highest-Grade Toxicity
1	TNBC	T2N3a	N/A	Did not go to surgery	N/A	1	2
1	TNBC	T2N1	SM	III	AC+PTX	0.75	3
1	TNBC	T2N0	BM	I	AC+PTX	0.5	3
1	HR positive	T1cN0	SM	0	TC	0.5	3
1	TNBC	T3N1c	UM	III	AC+PTX	1	2
1	TNBC	T2N0	BM	0	Declined chemotherapy	1	2
1	TNBC	T2N1	BM	0	AC+PTX	1	1
2	TNBC	T1cN0	BM	0	Declined chemotherapy	1	1
1	TNBC	T2N0	BM	II	AC+PTX	0.5	3
1	TNBC	T2N1	BM	0	AC+PTX	0.5	4
1	HR positive	T1cN0	BM	II	Endocrine only	1	3
1	TNBC	T4dN2	UM	0	AC+PTX	0.5	3
1	TNBC	T2N1	BM	II	AC+PTX	1	1
1	TNBC	T1cN0	BM	0	Declined chemotherapy	0.75	3
2	Invasive lobular HR positive	T1cN0	SM	0	Endocrine only	0.25	3
1	TNBC	T2N0	UM	II	AC+PTX	0.5	3
2	TNBC/metaplastic (chondrosarcomatous)	T2N0	BM	0	TC	1	1
1	TNBC	T2N0	BM	II	AC+PTX	1	2
1	HR positive	T1cN1	UM	0	Endocrine only	1	1
2	HR positive	T2N1	BM	I	Endocrine only	1	2

Litton JK et al. JCO 2019

GeparOla



Stratification Factors:

- Age (<40 years vs >= 40 years)
- Hormone Receptor Status (HR+ vs HR-)

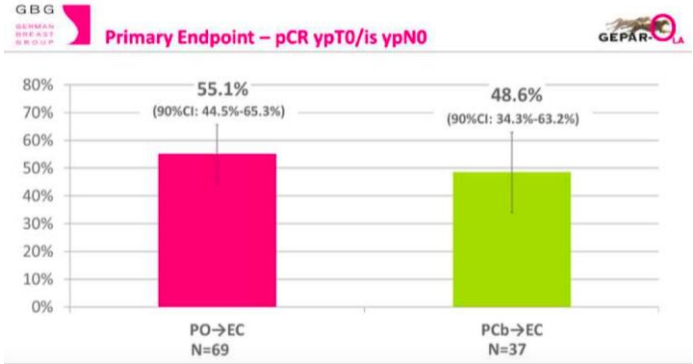
* Patients with either a known somatic or germline *BRCA*1/2 mutation or HRD score[1] high

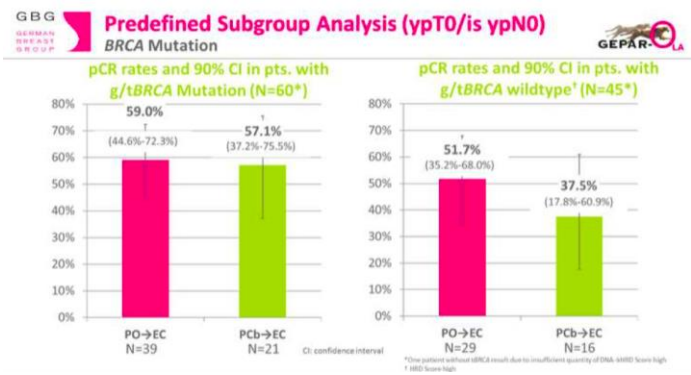
[1]Timms et al. Breast Cancer Res 2014

Primary Objective and Endpoint:

- To assess the pathological complete response **(ypT0/is ypN0)** rate of neoadjuvant treatment of olaparib and paclitaxel followed by epirubicin and cyclophosphamide (PO→EC) in patients with early BC and HR deficient tumors (defined as either t*BRCA1/2* mutation and/or HRD score high and/or known g*BRCA* mutation).

Fasching AP et al. J Clin Oncol 2019





	Olaparib+Paclitaxel pCR rate (90%CI)	Carboplatin+Paclitaxel pCR rate (90%CI)
HR+ patients (n = 29)	52.6% (32.0%, 72.6%)	20.0% (3.7%, 50.7%)
HR- patients (n = 77)	56.0% (43.4%, 68.0%)	59.3% (41.7%, 75.2%)
Patients age < 40 (n = 32)	76.2% (56.3%, 90.1%)	45.5% (20.0%, 72.9%)
Patients age ≥ 40 (n = 74)	45.8% (33.4%, 58.6%)	50.0% (32.7%, 67.3%)

Fasching AP et al. J Clin Oncol 2019

OlympiAD: Phase III study of olaparib vs. TPC in gBRCAm HER2- mBC[1]

Study design

- **gBRCAm mBC**
- **TNBC or HER2-negative, ER/PR positive**
- **≤2 prior chemotherapy lines for mBC**
- **Previous treatment with anthracycline and taxane in either the (neo)adjuvant or metastatic setting**
- **Hormone receptor positive (HR+) disease progressed on ≥1 endocrine therapy, or not suitable**
- If patients have received platinum therapy there should be:
  - No evidence of progression during treatment in the advanced setting
  - At least 12 months since (neo)adjuvant treatment and randomisation
- ECOG PS 0-1
- At least one lesion that can be assessed by RECIST v1.1

FSI May 2014:[3]

Global Study in 19 countries and approximately 141 sites[1]

Randomise 2:1
n=302[4]

Stratification by:[2]

- *Prior chemotherapy regimens for metastatic breast cancer*
- *Hormonal receptor (HR) status*
- *Prior platinum therapy*

Olaparib
300mg**po* bid

Treatment of Physician's Choice (TPC)

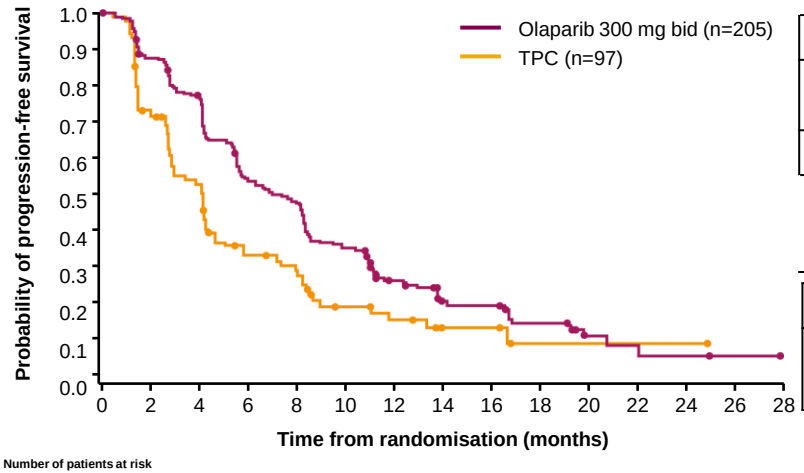
Primary endpoint
- PFS (RECIST 1.1, Independent Review)

Secondary endpoints
- OS
- PFS2
- ORR
- PFS, PFS2 and OS based on Myriad gBRCAm status
- HRQoL (EORTC-QLQ-C30)
- Safety and tolerability

* Tablet formulation (2 tablets twice daily)

1. https://clinicaltrials.gov/ct2/show/NCT02000622 [Accessed February 2019]; 2. Robson et al. Poster OT1-1-04, presented at SABCS 2014; 3. AZ data on file (2017); 4. Robson et al. N Engl J Med. 2017; 377:523-533

Primary endpoint: Olaparib treatment significantly improved PFS assessed by BICR compared to TPC[1]



	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[2]

Stratified log rank test, stratified by previous chemotherapy for mBC (yes/no) and HR+ versus TNBC
FAS; Maturity rate: 234/302=77%; 2 sided p value; figure adapted with permission[1]
Data cutoff: 9 December 2016

1. Robson et al. N Engl J Med. 2017; 377:523-533; 2. AZ data on file (2017)

50% of patients in OlympiAD were HR+

	Olaparib n=103 n (%)	TPC n=49 n(%)
Number of prior chemotherapy lines		
0	28 (27.2)	13 (26.5)
1	43 (41.7)	17 (34.7)
2	32 (31.1)	19 (38.8)
Received previous chemotherapy for mBC	80 (77.7)	37 (75.5)
Received prior endocrine therapy*		
Adjuvant/neoadjuvant	71 (68.9)	36 (73.5)
Metastatic	66 (64.1)	28 (57.1)
Total	97 (94.2)	45 (91.8)
Received prior platinum therapy for breast cancer	24 (23.3)	11 (22.4)

- Among patients with ER/PgR+ breast cancer, two olaparib patients (1.9%) and three TPC patients (6.1%) reported prior use of CDK4/6 inhibitors

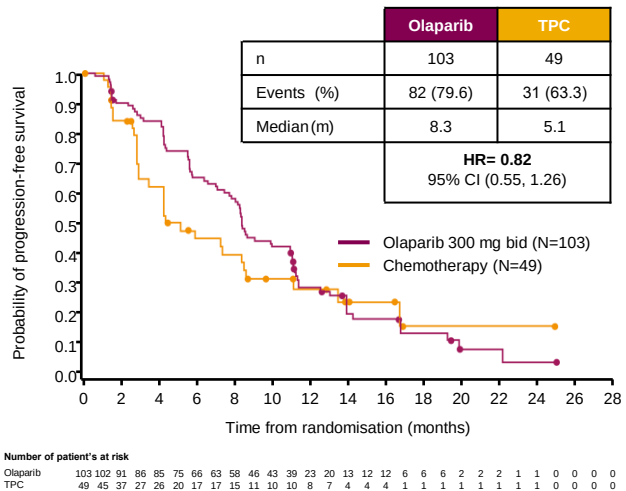
*Patients may appear under more than one previous treatment modality

Data cutoff: 9 December 2016

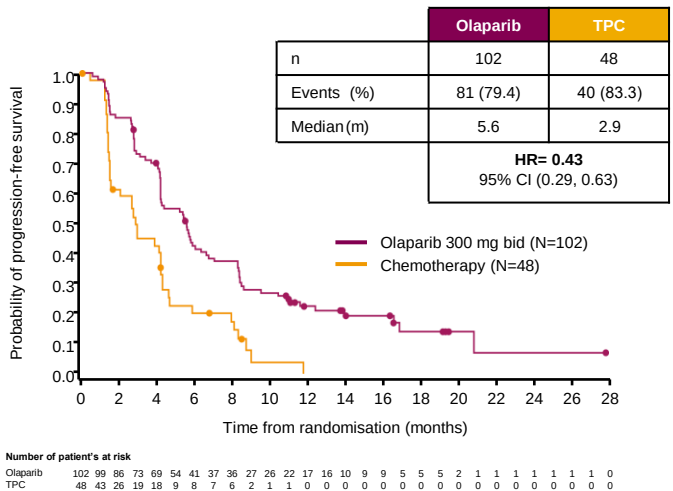
1. Robson et al. N Engl J Med. 2017; 377:523-533

Risk of progression was reduced in olaparib-treated patients with HR+ disease and TNBC compared to TPC[1]

Patients with HR+ mBC[2]



Patients with TNBC[2]

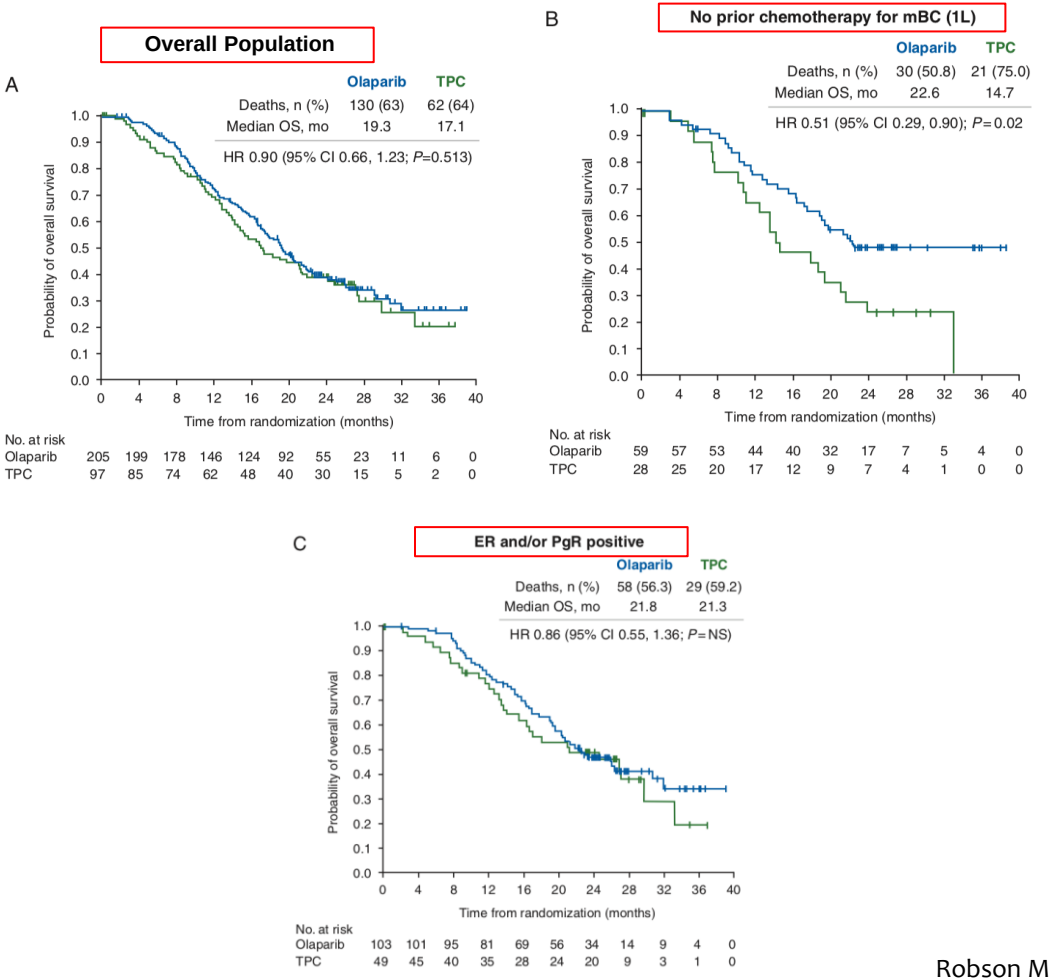


The OlympiAD study was not powered to identify differences in treatment effect between subgroups, and any differences observed here are hypothesis-generating

Data Cutoff : 9 December 2016

1. Robson et al. N Engl J Med. 2017; 377:523-533, 2. Robson et al. J Clin Oncol 35, 2017 (presentation associated with abstr LBA4)

OVERALL SURVIVAL



Robson ME, Ann Oncol. 2019

EMBRACA: Phase III study of talazoparib vs. TPC in patients with locally advanced or metastatic breast cancer

Study design

- Locally advanced breast cancer and/or metastatic disease appropriate for systemic single cytotoxic chemotherapy
- **gBRCAm**
- ECOG 0-2
- **≤3 prior lines of chemotherapy for locally advanced/metastatic disease**
- **HER2-negative**
- Prior platinum permitted if:
  - In (neo-)adjuvant setting: disease-free interval of ≥6 months after the last dose
  - In advanced setting: no objective disease progression while receiving platinum
- **Previous treatment with a taxane, an anthracycline, or both**, unless this treatment was contraindicated

Randomise 2:1

Patients stratified according to:

- *Number of prior chemotherapy regimens (0 vs. 1,2,3)*
- *Triple negative status (HR+ vs. TNBC)*
- *History of CNS metastasis (y/n)*

Talazoparib (n=287)
1 mg/day 21 day cycles *po*

Therapy of physician's choice (TPC) (n=144)
(capecitabine, eribulin, gemcitabine or vinorelbine)

Primary endpoint:
- PFS (BICR)

Secondary endpoints include:
- ORR
- OS
- Safety and tolerability
- PK

Exploratory endpoint:
- HRQoL

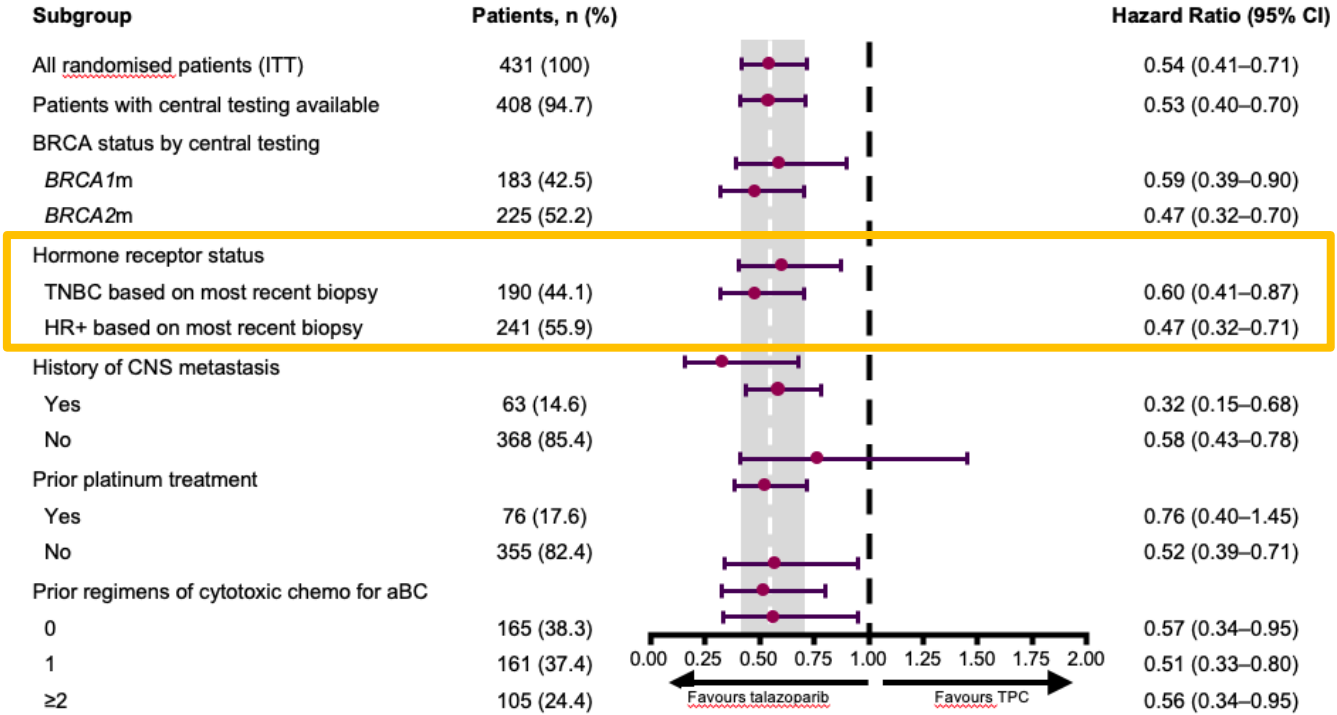
Litton J et al. N Engl J Med 2018; 379:753–763

56% of patients in EMBRACA were HR+

	Talazoparib (n=157)	Overall TPC (n=84)
Number of prior chemotherapy lines		
0	59 (37.6)	28 (33.3)
1	57 (36.3)	33 (39.3)
2	36 (22.9)	19 (22.6)
3	5 (3.2)	4 (4.8)
≥4	0 (0.0)	0 (0.0)
Number of prior cytotoxic chemotherapy for ABC, median (min, max)	1 (0,3)	1 (0,3)
Prior endocrine therapy	142 (90.4)	70 (80.3)
CDK4/6 inhibitors	16 (10.2)	6 (7.1)
mTOR inhibitor	20 (12.7)	13 (15.5)
Received prior platinum therapy for breast cancer	15 (9.6)	11 (13.1)

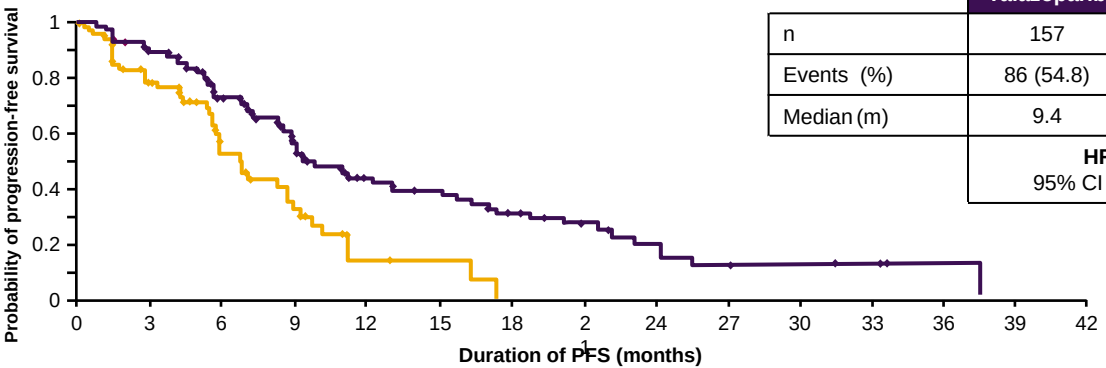
Eiermann W et al. Abstract 1070, presented at ASCO 2018

EMBRACA: PFS: Subgroup analysis



Litton J, et al. N Engl J Med 2018;379:753-63

HR+ HER2- mBC: Subgroup analysis of PFS shows benefit of PARPi



	Talazoparib	TPC
n	157	84
Events (%)	86 (54.8)	43 (51.2)
Median (m)	9.4	6.7
	HR=0.47 95% CI (0.32, 0.71)	

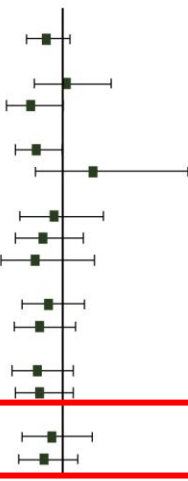
Number at risk (events/cumulative events)

Talazoparib	157 (0/0)	135 (16/16)	93 (24/40)	53 (19/59)	29 (10/69)	24 (3/72)	17 (5/77)	12 (2/79)	8 (3/82)	5 (3/85)	4 (0/85)	3 (0/85)	1 (0/85)	0 (1/86)	0 (0/86)
Overall PCT	84 (0/0)	47 (15/15)	24 (13/28)	12 (8/36)	3 (5/41)	2 (0/41)	0 (2/43)	0 (0/43)	0 (0/43)	0 (0/43)	0 (0/43)	0 (0/43)	0 (0/43)	0 (0/43)	0 (0/43)

Eiermann W et al. Abstract 1070, presented at ASCO 2018

Talazoparib versus chemotherapy in patients with germline *BRCA1/2*-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial

Subgroup	Talazoparib *n* (events)	Chemotherapy *n* (events)	Hazard ratio and 95% CI
All randomized patients (ITT)	287 (216)	144 (108)	0.848 (0.670-1.073)
Age			
<50 years	182 (148)	67 (49)	1.036 (0.742-1.447)
≥50 years	105 (68)	77 (59)	0.705 (0.492-1.012)
Race			
White	190 (143)	108 (85)	0.755 (0.571-0.998)
Other	97 (73)	36 (23)	1.278 (0.758-2.155)
Geographic region			
North America	99 (79)	57 (39)	0.921 (0.615-1.380)
Europe	134 (96)	56 (44)	0.825 (0.570-1.192)
Rest of the world	54 (41)	31 (25)	0.750 (0.432-1.300)
ECOG PS			
ECOG 0	153 (106)	84 (60)	0.870 (0.629-1.203)
ECOG >0	133 (109)	59 (47)	0.788 (0.555-1.121)
***BRCA* status by central testing**			
BRCA1	123 (97)	60 (47)	0.772 (0.539-1.104)
BRCA2	147 (103)	78 (60)	0.794 (0.571-1.106)
HR status			
TNBC based on most recent biopsy	130 (102)	60 (47)	0.899 (0.634-1.276)
HR+ based on most recent biopsy	157 (114)	84 (61)	0.827 (0.597-1.143)



Litton JK et al. Annals of Oncology 2020

BROCADE 3: Phase III study in gBRCAm HER2- mBC

Patient Population

- Advanced HER2-negative breast cancer
- Germline *BRCA1* or *BRCA2* mutation
- ≤2 prior lines cytotoxic therapy for metastatic disease
- ≤1 prior lines of platinum; no progression ≤12 months of completing

Stratification Factors

- Hormone Receptor Expression
- Prior Platinum
- CNS Metastasis

2:1 Randomization
N=513

Veliparib + Carboplatin/paclitaxel

Placebo + Carboplatin/paclitaxel

Treat to progression:
If carboplatin and paclitaxel were discontinued prior to progression, dosing of veliparib/placebo increased to 300mg BID continuous, and then 400mg BID if tolerated

Optional open-label crossover to veliparib

Primary Endpoint:
Investigator-assessed PFS per RECIST 1.1

21-Day Cycles:
- Carboplatin (C): AUC 6 on Day 1
- Paclitaxel (P): 80 mg/m^2 on Days 1, 8, 15
- Veliparib or Placebo: 120mg BID on Days -2 to 5

BARCELONA 2019 ESMO congress

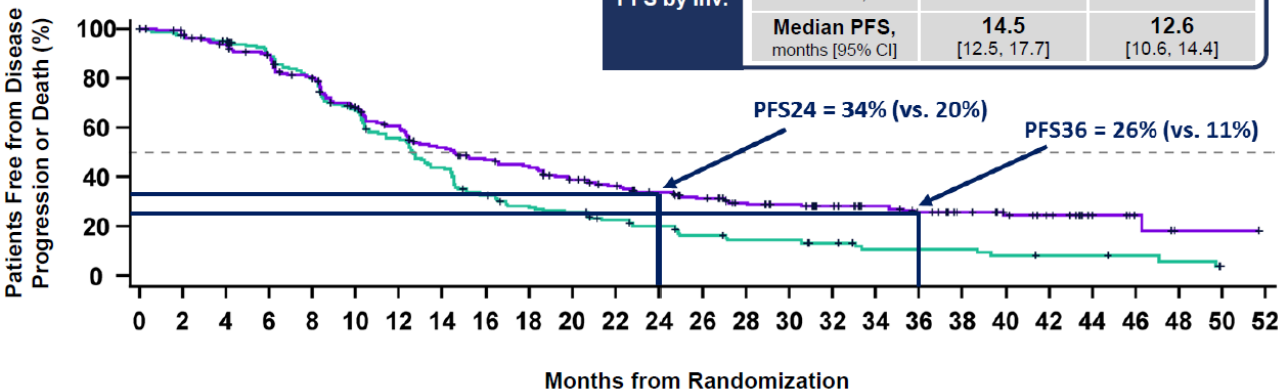
Dieras V et al, ESMO 2019

Primary Endpoint: PFS by Investigator Assessment

HR 0.705
[95% CI 0.566-0.877], p = 0.002

PFS by Inv.

	Veliparib + C/P	Placebo + C/P
PFS Events, n/N	217/337	132/172
Median PFS, months [95% CI]	**14.5** [12.5, 17.7]	**12.6** [10.6, 14.4]



No. at Risk

Control	172	160	153	140	123	99	82	64	47	39	35	27	23	18	15	15	12	8	8	8	6	5	5	4	3	0
Veliparib	337	316	301	282	250	207	181	154	137	126	107	92	81	72	60	51	45	38	32	25	20	16	8	4	1	1	0

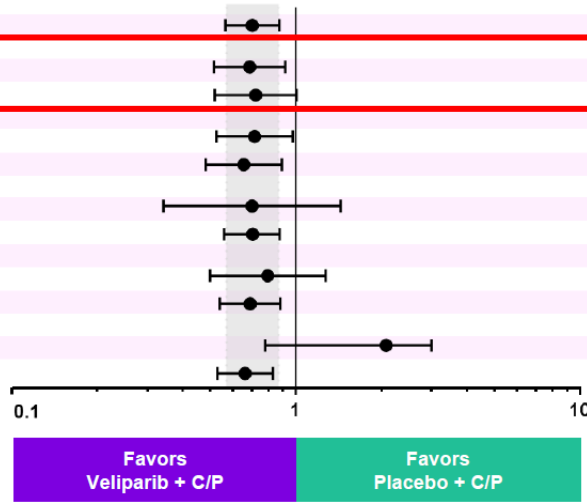
BARCELONA 2019 ESMO congress

C/P: Carboplatin and Paclitaxel

Dieras V et al, ESMO 2019

PFS Subgroup Analysis (Investigator-Assessed)

Subgroup	Veliparib+C/P	Placebo+C/P	Hazard Ratio for Disease Progression or Death (95% CI)
	No. of patients with events/total		
All patients	217/337	132/172	0.70 (0.57, 0.87)
Hormone receptor status			
ER positive and/or PgR positive	124/174	74/92	0.69 (0.52, 0.92)
ER negative and PgR negative (TNBC)	93/163	58/80	0.72 (0.52, 1.01)
***BRCA* status**			
BRCA1 mutation	113/177	68/89	0.72 (0.53, 0.97)
BRCA2 mutation	106/167	67/86	0.66 (0.48, 0.89)
Prior platinum therapy			
Prior platinum therapy	19/27	14/16	0.70 (0.34, 1.44)
No prior platinum therapy	198/310	118/156	0.71 (0.56, 0.89)
Prior cytotoxic therapy for metastatic disease			
Prior chemotherapy in metastatic setting	46/63	29/33	0.80 (0.50, 1.27)
No prior chemotherapy in metastatic setting	171/274	103/139	0.69 (0.54, 0.88)
History of CNS metastases			
Yes	14/16	8/10	2.08 (0.78, 5.52)
No	203/320	124/161	0.66 (0.53, 0.83)

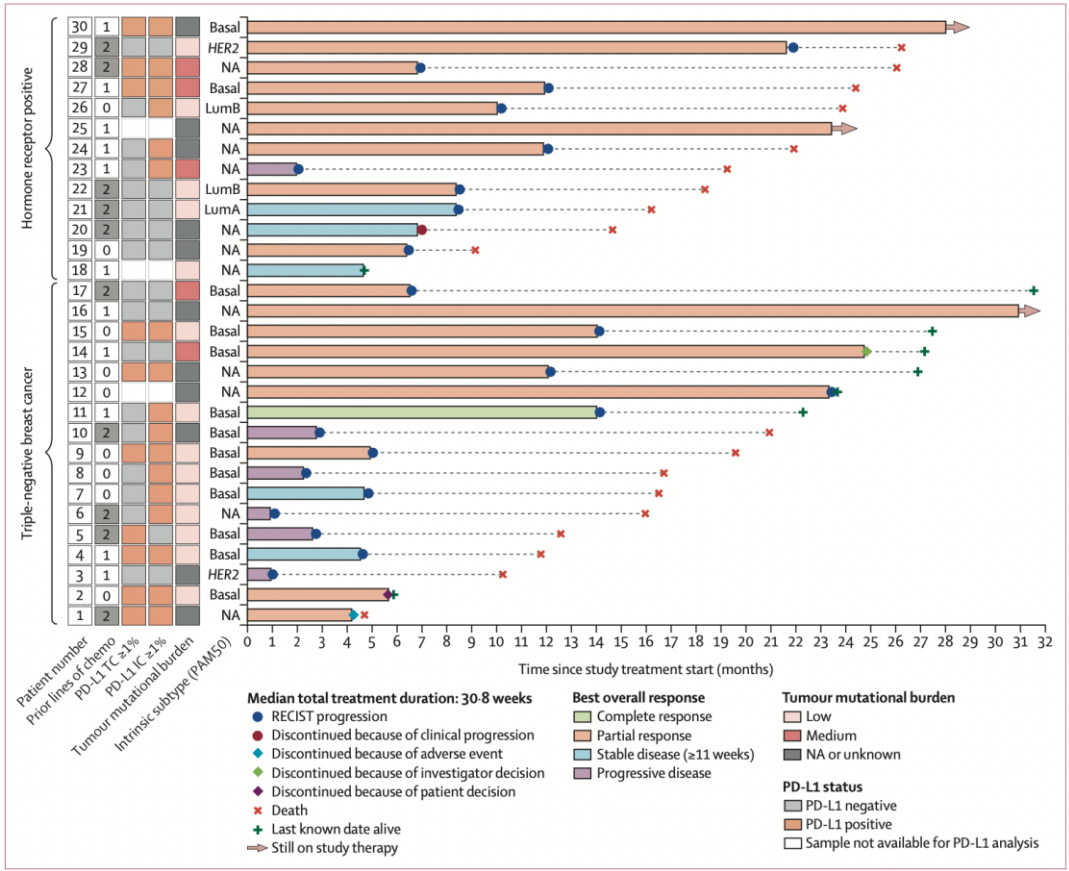


BARCELONA 2019 ESMO congress

C/P: Carboplatin and Paclitaxel

Dieras V et al, ESMO 2019

Olaparib and durvalumab in patients with germline *BRCA*-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study



HR+
1/13 PD 7.7%
3/13 SD 23%
9/13 PR 69%

TNBC
5/17 PD 29.4%
2/17 SD 11.7%
9/17 PR 53%
1/17 CR 6%

Domchek SM et al. Lancet Oncology 2020

Questions for the treatment of gBRCAm HR+ mBC patients

When should we be testing our HR+ patients?

How does gBRCAm status impact standard of care?

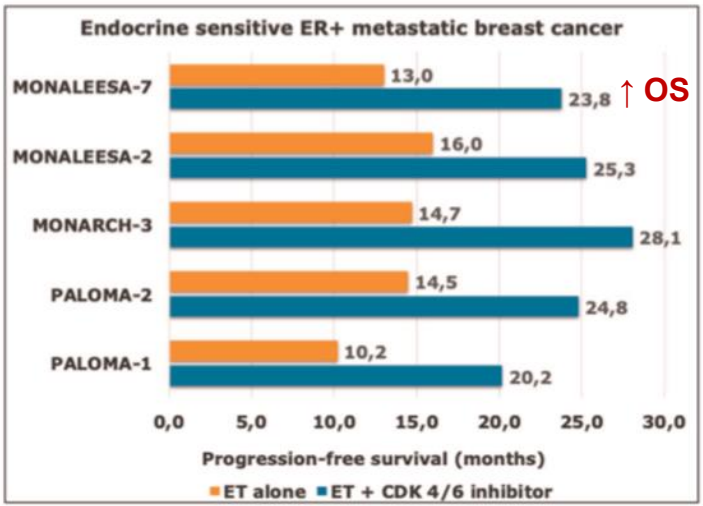
How should we sequence PARP inhibitors with other drug classes?

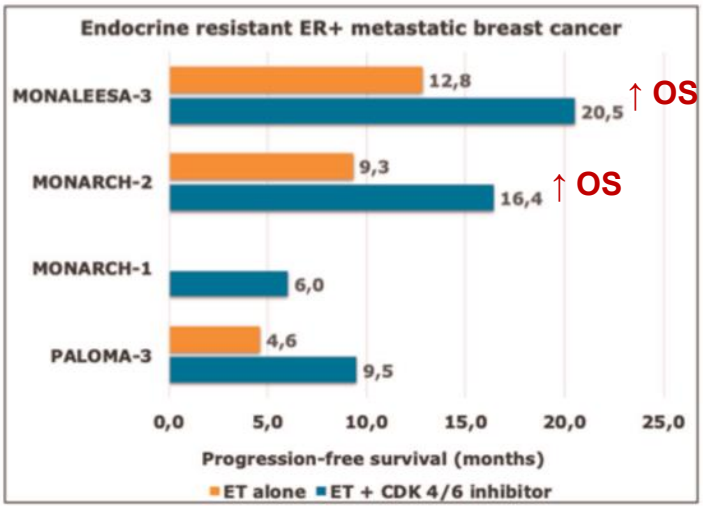
With regards to CDK4/6i use?

Before or after chemotherapy?

At first opportunity or save for later?

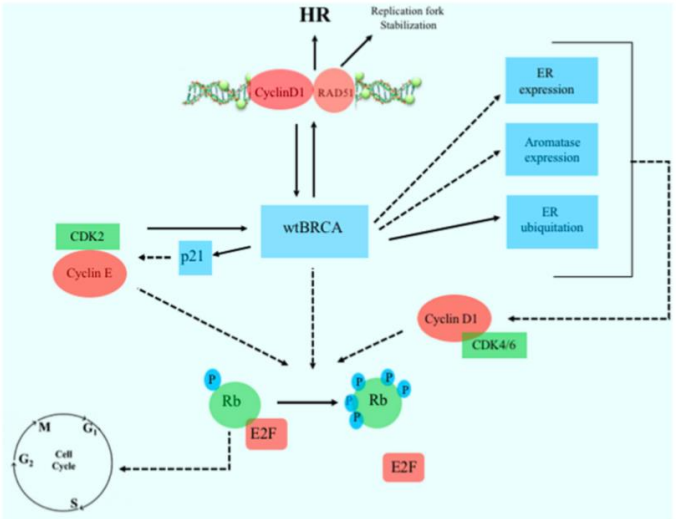
Progression-free survival (PFS) of CDK4/6 inhibitors in clinical trials

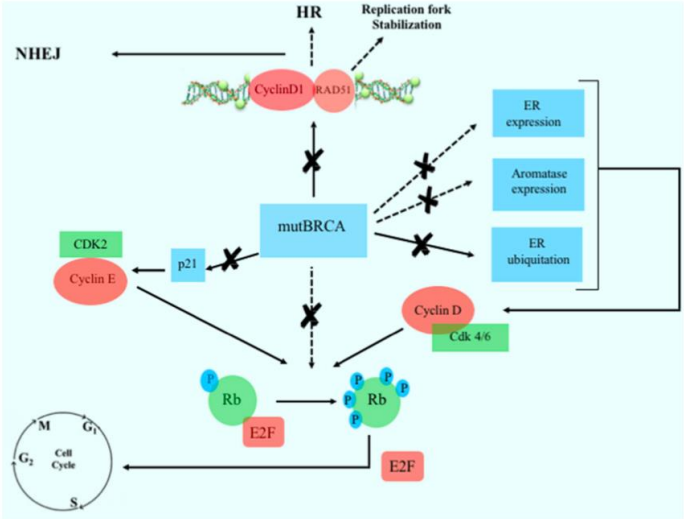




Marra A and Curigliano G. npj Breast Cancer (2019)

Mechanism of Action and Clinical Efficacy of CDK4/6 Inhibitors in BRCA-Mutated, Estrogen Receptor-Positive Breast Cancers: Case Report and Literature Review





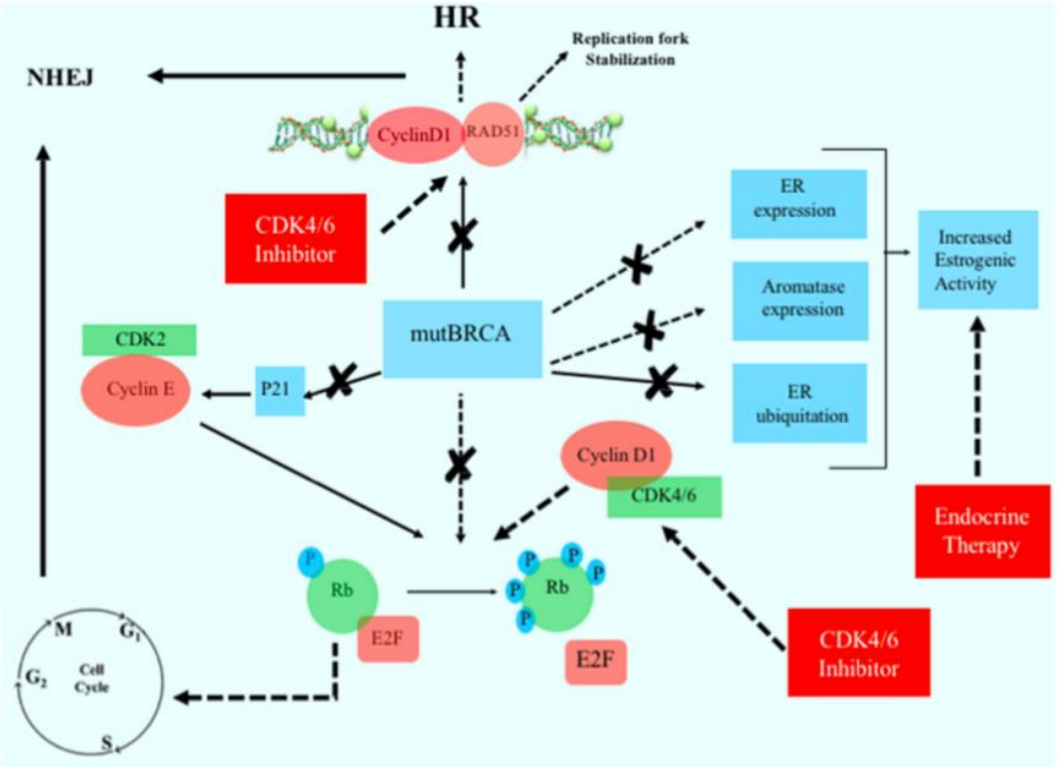
wtBRCA

1. decreased ER activity
2. G1 cell cycle arrest

mutBRCA

1. increased ER activity
2. cell cycle arrest fails

Militello AM et al. Frontiers in Oncology 2019



mutBRCA + ET + CDKi

1. ET inhibits the ER activity
2. CDKi restore G1 cell cycle arrest -> major activity of NHEJ -> genomic instability and cell death

Militello AM et al. Frontiers in Oncology 2019

CANCER PREVENTION, HEREDITARY GENETICS, AND EPIDEMIOLOGY

A real-world evidence study of CDK4/6 inhibitor treatment patterns and outcomes in metastatic breast cancer by g*BRCA* mutation status.

Patients received letrozole plus palbociclib (42.4 and 39.8%, respectively), fulvestrant plus palbociclib (32.9 and 30.7%), or other CDK4/6 regimens (24.7 and 29.5%) across all lines.

The gBRCAm group had a non-significant, shorter Time to first subsequent therapy or death (TFST) than gBRCAwt (stratified HR 1.24; 95% CI 0.96–1.59). OS was significantly shorter in gBRCAm than gBRCAwt patients (stratified HR 1.50; 95% CI 1.06–2.14).

The results of this real-world study suggest that treatment outcomes with CDK4/6 inhibitors may be poorer in patients with gBRCAm compared with gBRCAwt disease.

Characteristic or Outcome	g*BRCA*m (N = 85; 9.9%)	g*BRCA*wt (N = 774; 90.1%)
Mean (SD) age, years	53 (13.4)	58 (12.0)
Line of earliest CDK4/6 use		
First, %	42.4	37.9
TFST, months*	11 (6–18)	14 (12–15)
Second, %	31.8	32.7
TFST, months*	10 (6–11)	10 (8–12)
Third and higher, %	25.9	29.5
TFST, months*	6 (3–11)	7 (5–9)

*Data are KM median (95% confidence interval [CI])

McLaurin K, et al. *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 1563-1563 (ASCO Annual Meeting 2019)

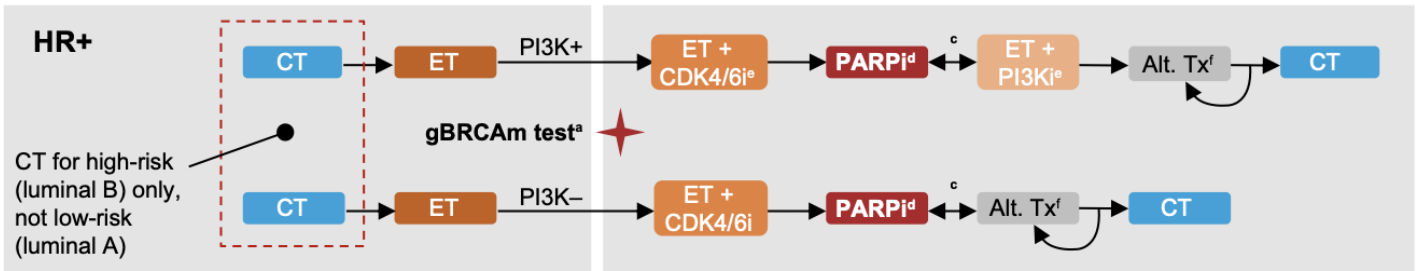
Pooled ctDNA analysis of the MONALEESA (ML) phase III advanced breast cancer (ABC) trials.

Gene	WT RIB Median PFS, mo	WT PBO median PFS, mo	HR (95% CI)	Altered RIB Median PFS, mo	Altered PBO Median PFS, mo	HR (95% CI)	*P* Value for Gene-Treatment Interaction[a]
FRS2	n = 829 22.21	n = 629 13.24	0.60 (0.52-0.69)	n = 23 12.52	n = 22 1.87	0.26 (0.11-0.58)	.03
PRKCA	n = 830 22.14	n = 632 13.04	0.60 (0.52-0.70)	n = 22 17.18	n = 19 7.23	0.23 (0.09-0.60)	.04
BRCA1/2	n = 817 22.14	n = 631 12.98	0.60 (0.52-0.70)	n = 35 NA	n = 20 7.06	0.30 (0.15-0.61)	.06
MDM2	n = 835 22.21	n = 633 13.11	0.60 (0.52-0.69)	n = 17 11.27	n = 18 1.87	0.29 (0.12-0.70)	.06
ERBB2	n = 818 22.34	n = 632 13.24	0.59 (0.51-0.69)	n = 34 12.75	n = 19 1.99	0.33 (0.16-0.69)	.13
AKT1	n = 812 22.14	n = 630 13.04	0.60 (0.52-0.69)	n = 40 18.63	n = 21 7.56	0.39 (0.18-0.84)	.33

WT, wildtype. [a] Not corrected for multiple testing; results are exploratory.

Andrè F et al. ASCO 2020

Possible treatment options in BRCAm HR+ HER2- mBC



Cortesi L et al. Targeted Oncology 2021

CONCLUSIONS

- The majority of BRCA are found in patients with HR+ disease vs. TNBC.
- About 40% of patients with ER low positive tumors are BRCA carriers.
- BRCA HR+ tumours have acknowledged distinct characteristics but conflicting results on outcomes with traditional therapies.
- Olaparib and Talazoparib improve PFS compared to TPC in the overall population of gBRCAm.
- There is a biological rationale for CDKi + ET in gBRCAm tumors but, at present, real-world data suggest that treatment outcomes with CDKi may be poorer in patients with gBRCAm.
- BRCA genetic testing should be introduced in MBC regardless family history and tumor biology.

11ª EDIZIONE

Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2021?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

GRAZIE PER L'ATTENZIONE!