Incontri di aggiornamento del Dipartimento Oncologico

Le mutazioni BRCA 1-2: da fattore di rischio a target terapeutico

IL CANCRO DELLA MAMMELLA BRCA-CORRELATO: CARATTERISTICHE E TRATTAMENTO MEDICO

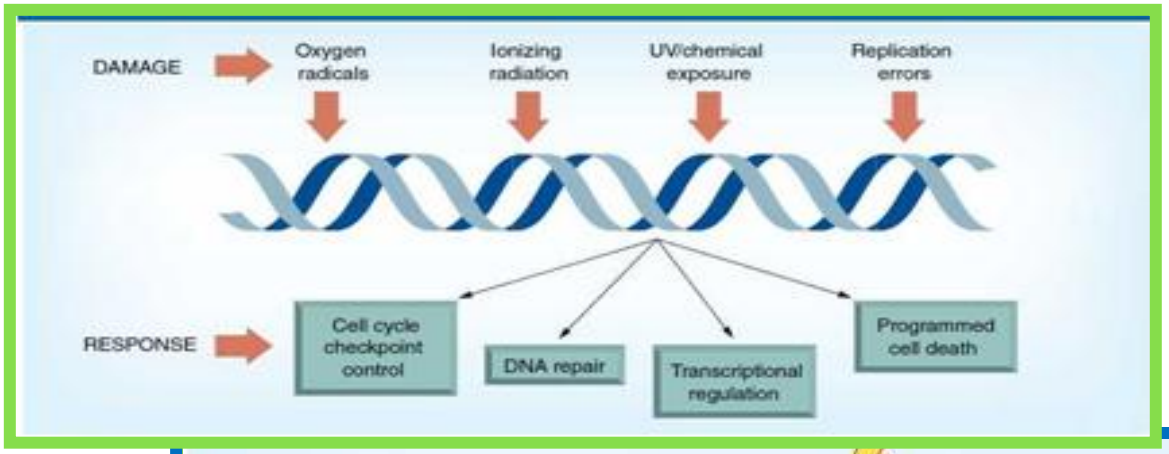
Monica Turazza

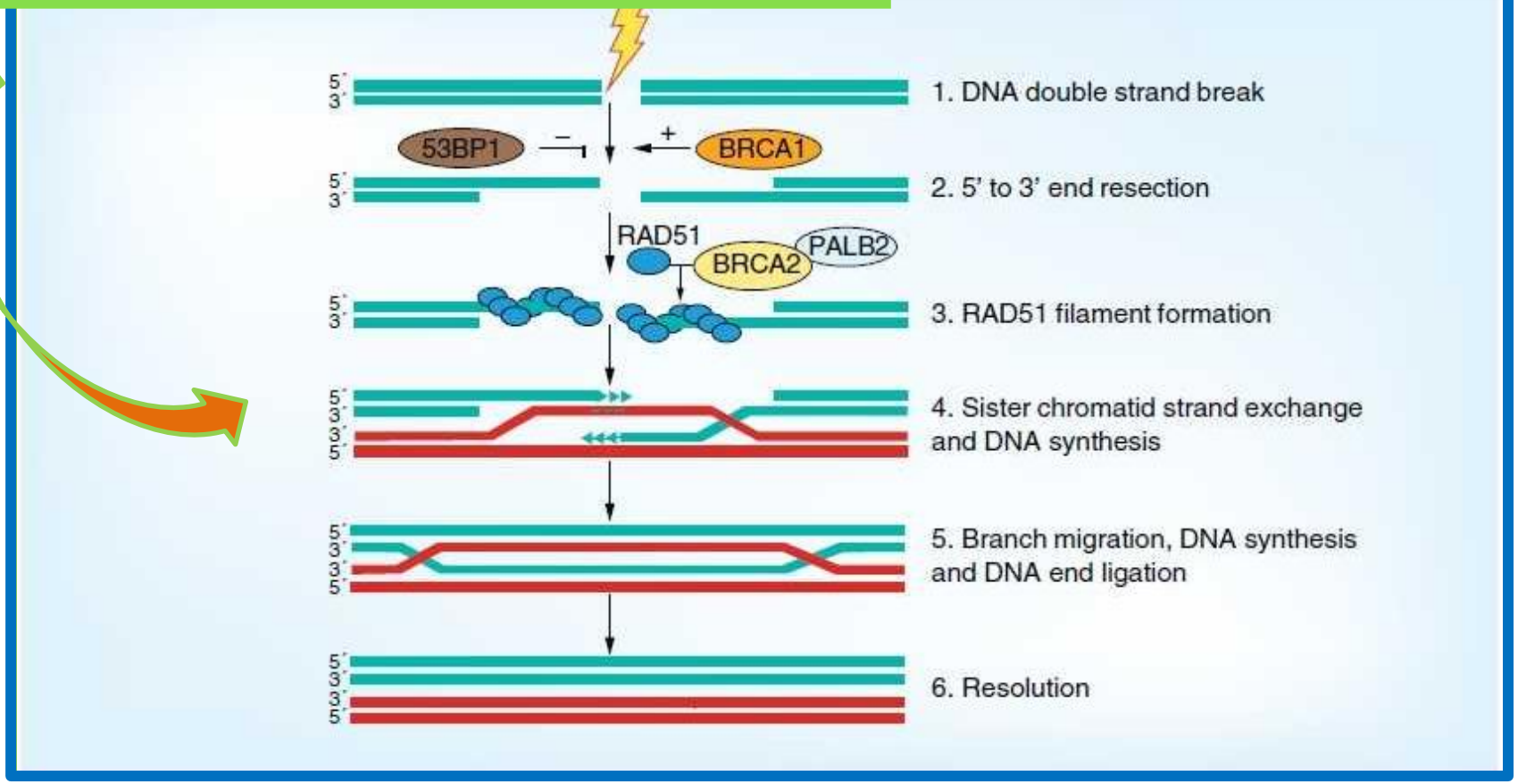
Ospedale "Sacro Cuore- Don Calabria" – Negrar (Verona)

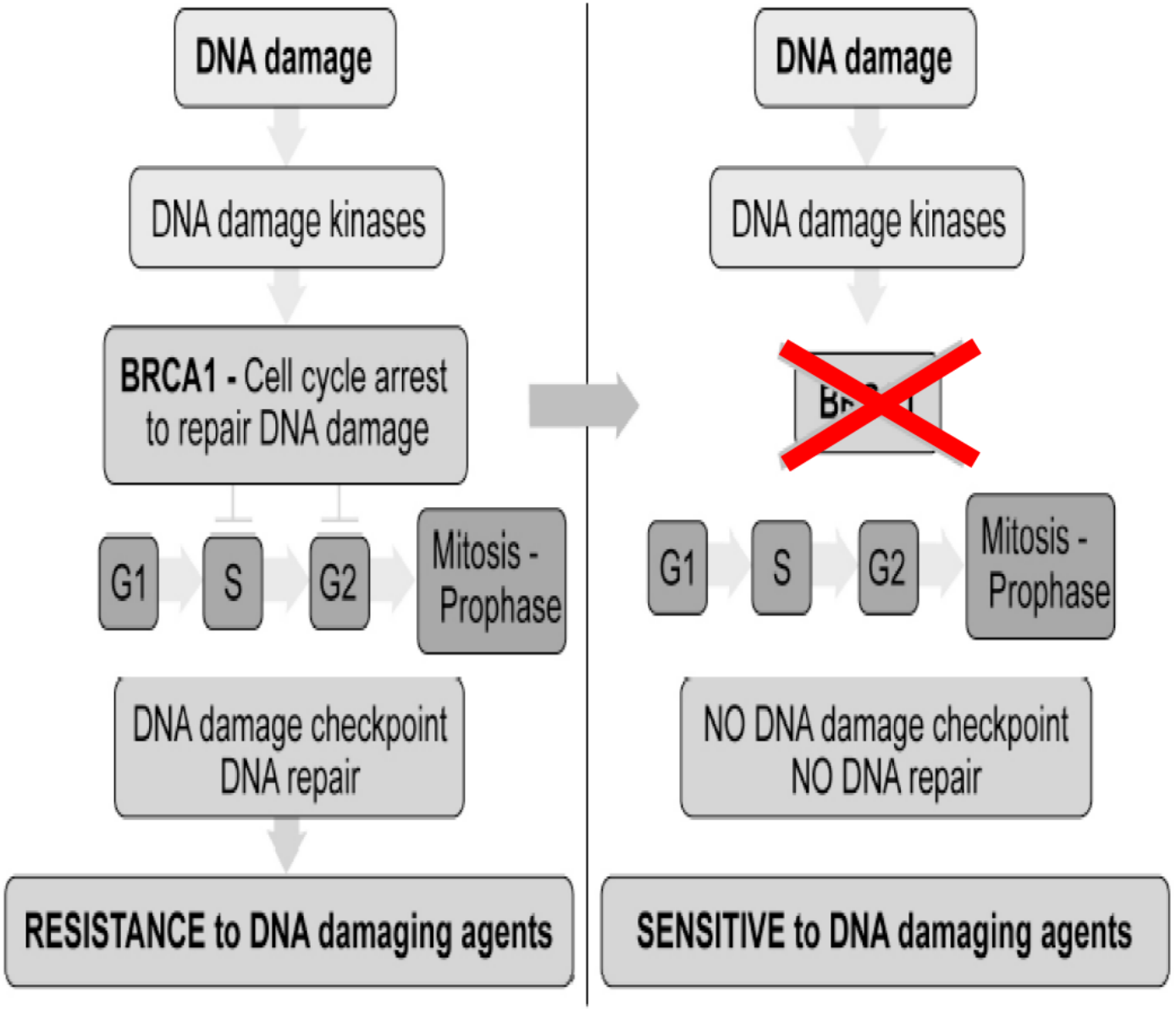
13 ottobre 2015

BRCA FUNCTIONS

- DNA repair
- chromatin remodelling
- transcriptional regulation
- G2-M cell cycle checkpoint control
- ubiquitylation
- SUMOlyation

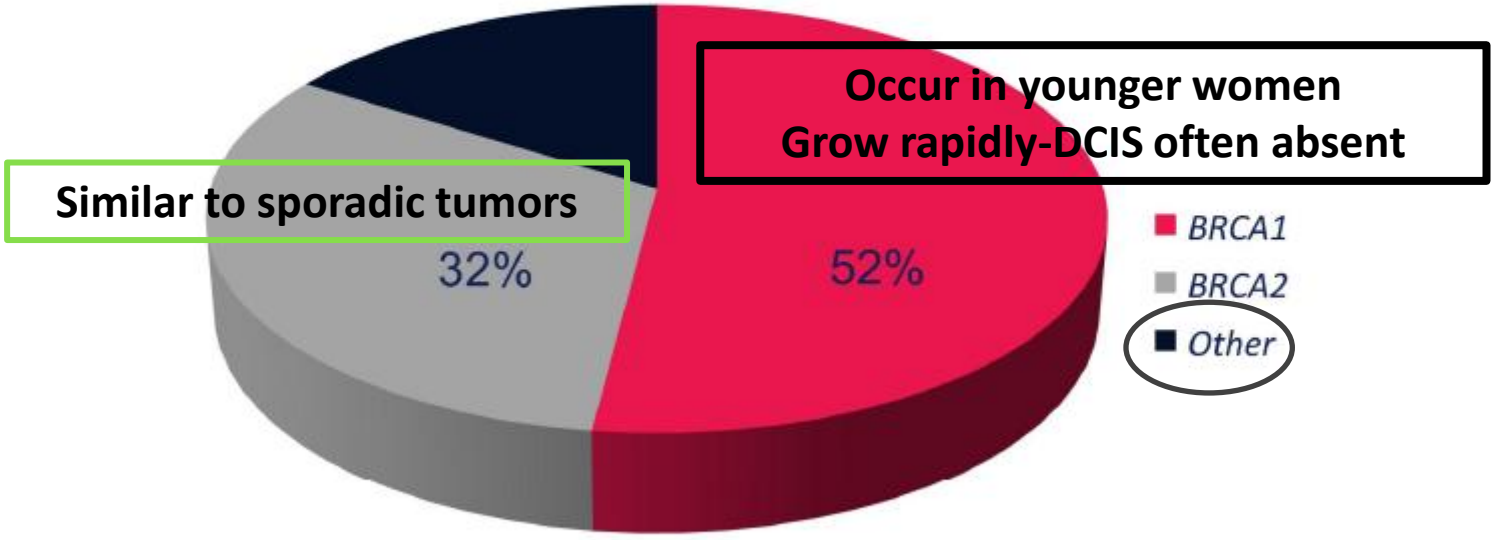





DNA damage
DNA damage kinases
BRCA1 - Cell cycle arrest to repair DNA damage
G1
S
G2
Mitosis - Prophase
DNA damage checkpoint
DNA repair
RESISTANCE to DNA damaging agents
DNA damage
DNA damage kinases
G1
S
G2
Mitosis - Prophase
NO DNA damage checkpoint
NO DNA repair
SENSITIVE to DNA damaging agents

BRCA MUTATIONS AND HEREDITARY BREAST AND OVARIAN CANCER

BEHAVIOUR

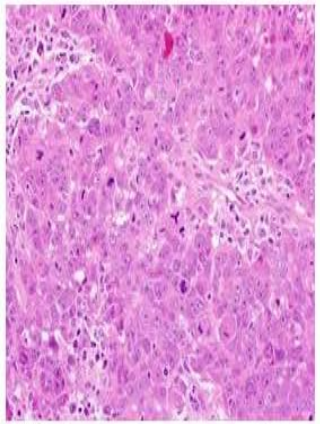


5-10% of breast cancer are hereditary and attributable to mutations in several highly penetrant susceptibility genes, of which only two have been identified: BRCA 1 and BRCA2

BRCA1 downregulation

IDC

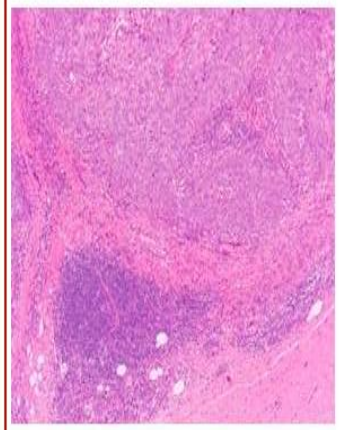
TN/ Basal-like



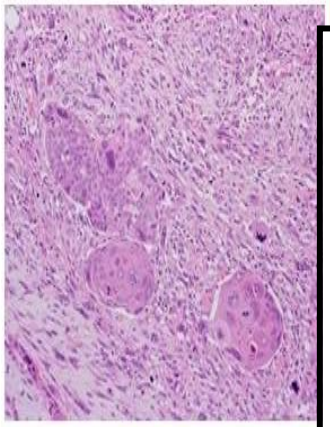
ID4 overexpression

***BRCA1* methylation**

Medullary

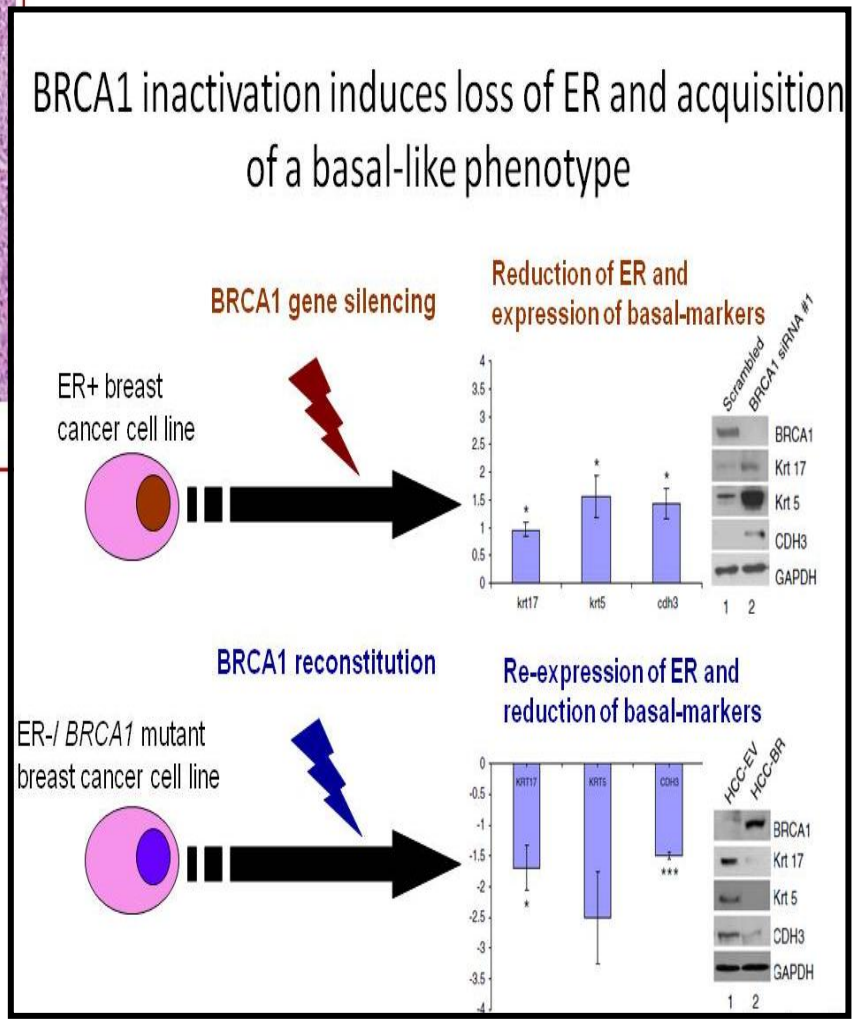


Metaplastic



Turner et al, Oncogene 2007; Rakha, Reis-Filho, Ellis. J Clin Oncol, 2008

BRCA1 inactivation induces loss of ER and acquisition of a basal-like phenotype



Hosey et al. JNCI 2007; Gorski et al. Breast Cancer Res Treat 2009

Clinical-pathological features in breast cancers BRCA-carriers

Hereditary Cancer in Clinical Practice 2004; 2(3) pp. 131-138

The Pathology of Hereditary Breast Cancer

Emiliano Honrado[1], Javier Benítez[1], José Palacios[2]

[1]Human Genetics Department; [2]Group of Breast and Gynecological Cancer, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

Cell Oncol. (2011) 34:71–88
DOI 10.1007/s13402-011-0010-3

ORIGINAL PAPER

Pathology of hereditary breast cancer

Petra van der Groep · Elsken van der Wall · Paul J. van Diest

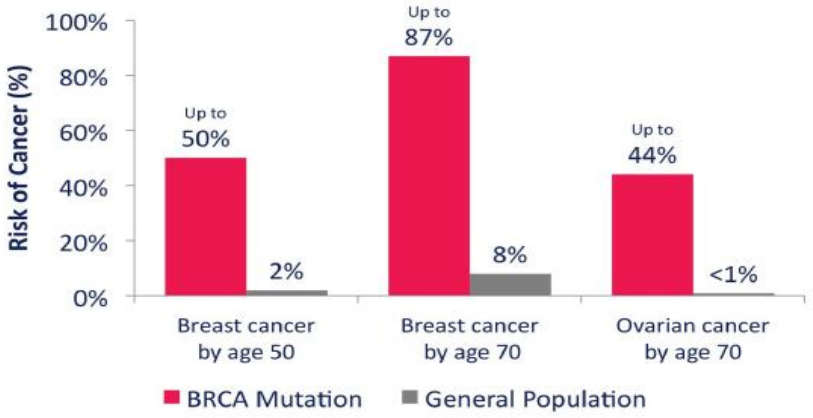
Table 1. Morphological and immunohistochemical profiles associated with hereditary breast cancer tumours

	GRADE	RE	RP	BCL2	P53	Ki-67	Cyclin D1	CK5/6
BRCA1	3	–	–	–	++	++	–	+
BRCA2	2/3	+	+	+	+	+	±	–
non-BRCA1/2	1/2	+	+	+	–	–	+	–

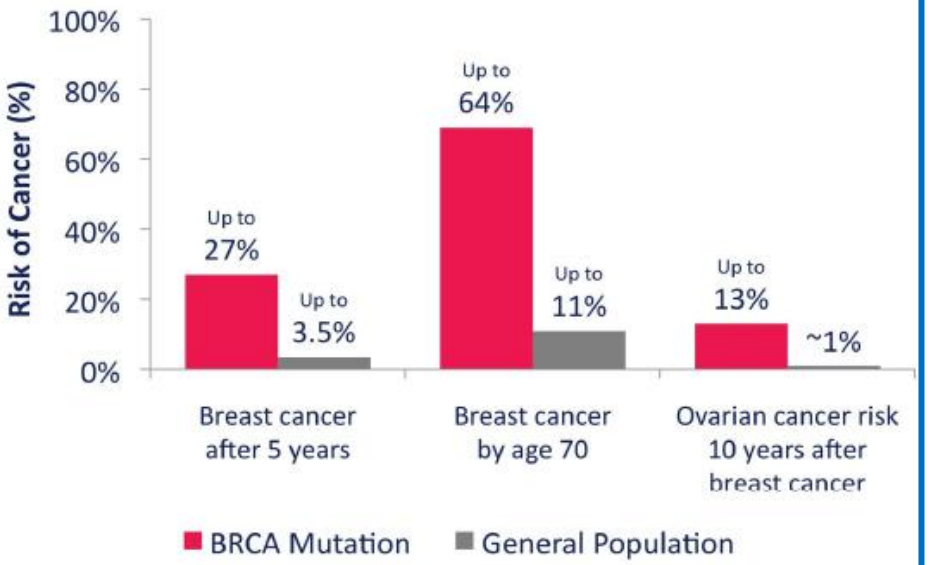
HISTOLOGICAL TYPE

	BRCA 1-carriers	BRCA2-carriers	Non-carriers
Invasive ductal carcinoma NOS	74%		70-80%
Medullary carcinoma	13%	3%	2%
Invasive ductal carcinoma with lymhocitic infiltrate (otherwise “medullary carcinoma)	++		
Invasive lobular carcinoma		++	

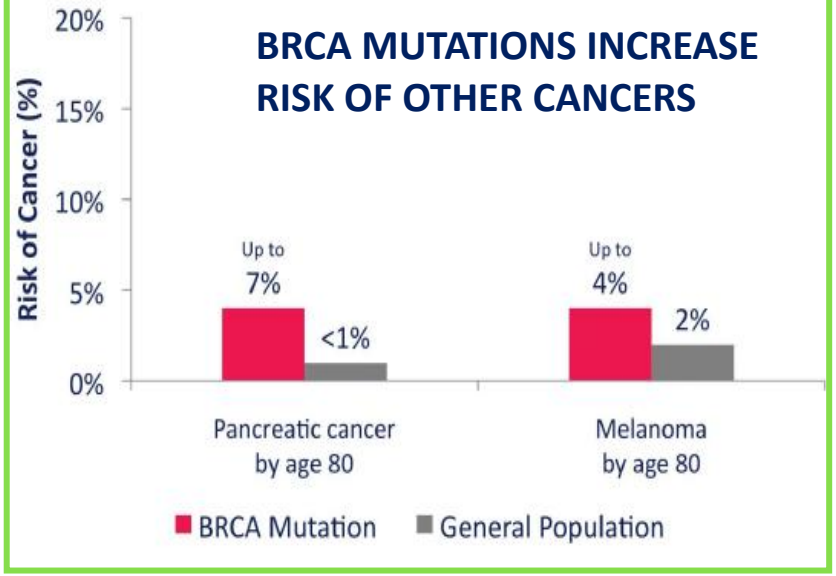
BRCA MUTATIONS INCREASE BREAST AND OVARIAN CANCER RISKS



BRCA MUTATIONS INCREASE RISK OF A SECOND CANCER



BRCA MUTATIONS INCREASE RISK OF OTHER CANCERS



Cancer J. 2011 November ; 17(6)

BRCA Mutation Testing in Determining Breast Cancer Therapy

Karen Lisa Smith, MD MPH[Assistant Professor of Medicine] and
Georgetown University, Attending Physician, Washington Cancer Institute, Washington Hospital Center

Claudine Isaacs, MD[Professor of Medicine and Oncology]
Co-Director Fisher Center for Familial Cancer Research, Lombardi Comprehensive Cancer Center, Georgetown University

BRCA mutation testing at the time of breast cancer diagnosis and the incorporation of test results into the complex treatment and prevention decisions required for *BRCA* mutation carriers with breast cancer.

-SURVEILLANCE (follow up)
-SURGICAL MANAGEMENT
-TARGET THERAPIES? (platinum-based therapy, PARP inhibitors)

SURVEILLANCE FOR FEMALE BRCA CARRIERS

	PROCEDURE	AGE TO BEGIN	FREQUENCY
Breast cancer surveillance	Breast self-exam training	18 yrs	
	Clinical breast exam	25 yrs	Every 6-12 months
	Mammography	25 yrs	Yearly
	MRI	25 yrs	Yearly
Ovarian cancer surveillance	Pelvic exam	35 yrs in patients not electing RRBSO	Every 6 months
	TVUS and CA-125*	35 yrs in patients not electing RRBSO	Every 6 months

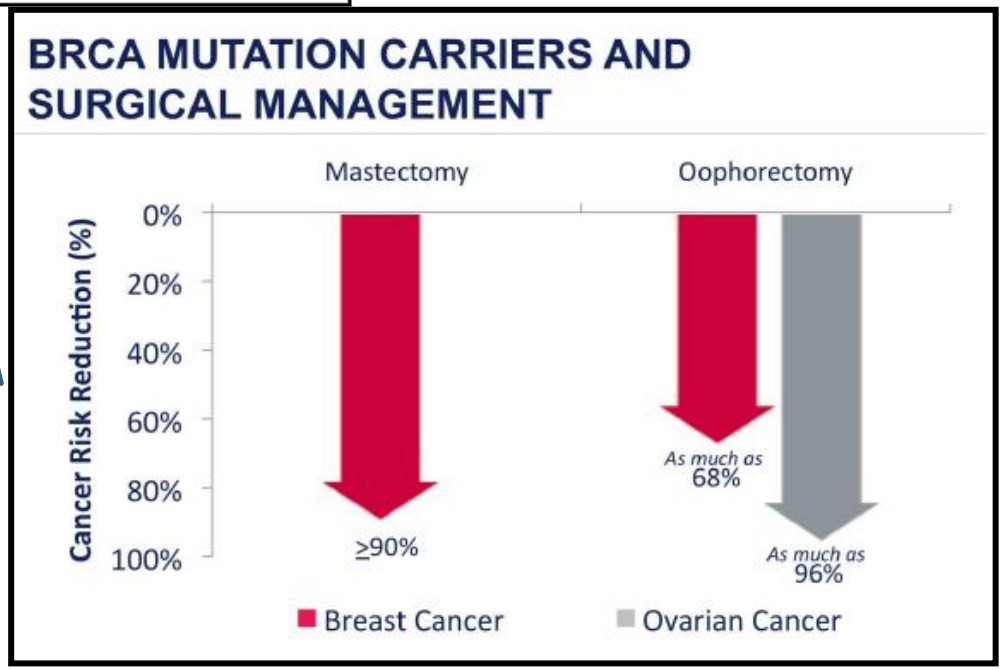
*limited efficacy, limited data

www.nccn.org
CA Cancer J Clin 2007;57(2):75-89

Clinical factors which modulate the risk of future ipsilateral and controlateral breast cancer in BRCA1/2 mutations carriers with breast cancer. Cancer J, 2011; 17(6)

Clinical Factor	Effect on Risk of Future Ipsilateral Breast Cancer	Effect on Risk of Future Contralateral Breast Cancer
Young Age at Diagnosis	↑	↑
Gene Mutated (*BRCA1* or *BRCA2*)	No Effect	*BRCA1* > *BRCA2*
Adjuvant Tamoxifen	↓ / No Effect *	↓ / No Effect *
Adjuvant Chemotherapy	↓	↓ / No Effect *
Oophorectomy	↓ / No Effect *	↓
Contralateral Prophylactic Mastectomy	No effect	↓
Radiation to the Affected Breast	↓	No effect

Cancer J. 2011 November ; 17(6)



Breast Cancer Research Vol 6 No 1 Robson *et al.*

Published 24 october 2003

Research article

Open Access

A combined analysis of outcome following breast cancer: differences in survival based on *BRCA1/BRCA2* mutation status and administration of adjuvant treatment

Mark E Robson[1†], Pierre O Chappuis[2*†], Jaya Satagopan[3], Nora Wong[4], Jeff Boyd[5], John R Goffin[6*], Clifford Hudis[1], David Roberge[6], Larry Norton[1], Louis R Bégin[7*], Kenneth Offit[1] and William D Foulkes[2,4,8]

Methods: Two retrospective cohorts of Ashkenazi Jewish women undergoing breast-conserving treatment for invasive cancer between 1980 and 1995 (n=584) were established. Archived tissue blocks were used as the source of DNA for Ashkenazi Jewish *BRCA1/BRCA2* founder mutation analysis. Paraffin-embedded tissue and follow-up information was available for 505 women.

Conclusion: *BRCA1* mutations, but not *BRCA2* mutations, are associated with reduced survival in Ashkenazi women undergoing breast-conserving treatment for invasive breast cancer, but the poor prognosis associated with germline *BRCA1* mutations is mitigated by adjuvant chemotherapy. The risk for metachronous ipsilateral disease does not appear to be increased for either *BRCA1* or *BRCA2* mutation carriers, at least up to 10 years of follow up.

original article

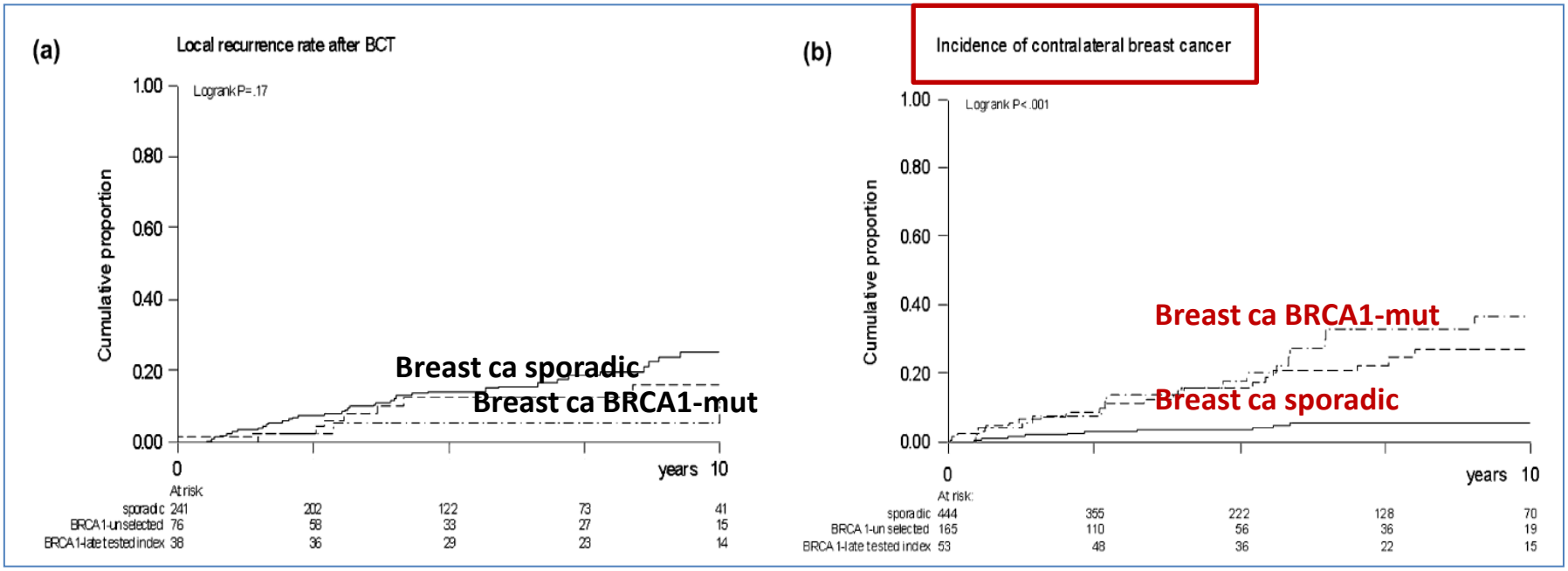
Annals of Oncology 17: 391–400, 2006
doi:10.1093/annonc/mdj095
Published online 1 December 2005

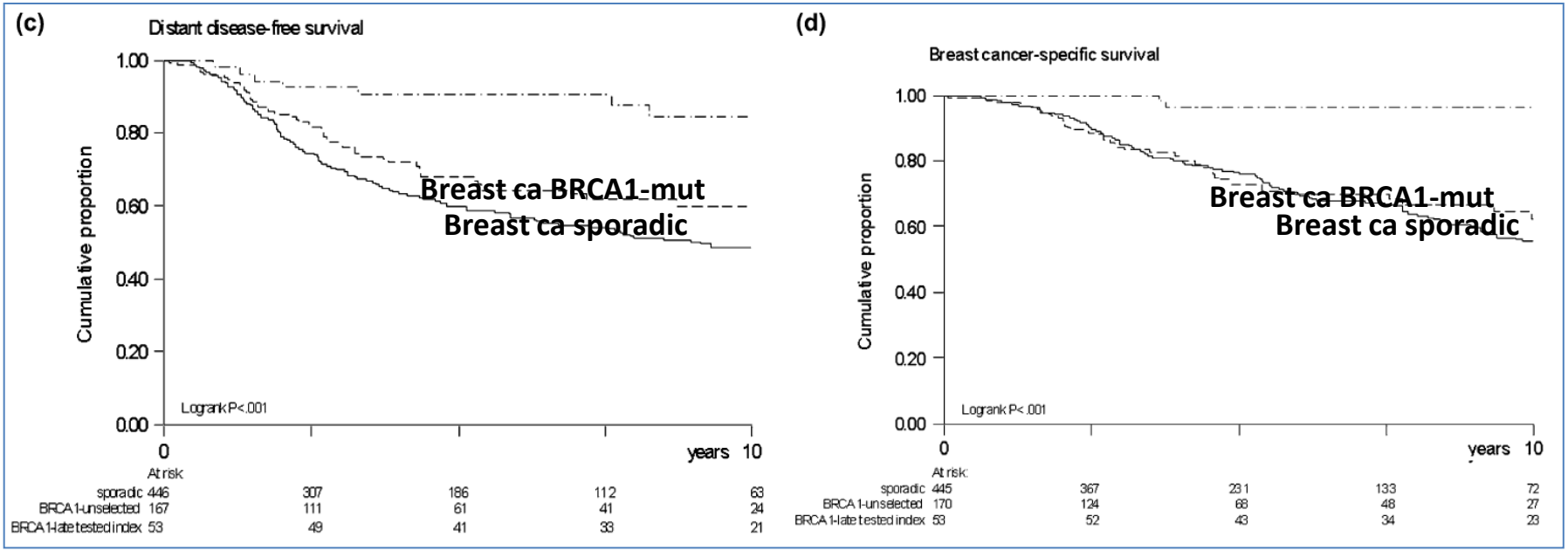
Survival and prognostic factors in BRCA1-associated breast cancer

C. T. M. Brekelmans[1]*, C. Seynaeve[1], M. Menke-Pluymers[2], H. T. Brüggenwirth[3], M. M. A. Tilanus-Linthorst[2], C. C. M. Bartels[2], M. Kriege[1], A. N. van Geel[2], C. M. G. Crepin[1], J. C. Blom[1], H. Meijers-Heijboer[3] & J. G. M. Klijn[1]

[1]Department of Medical Oncology, [2]Department of Surgical Oncology and [3]Department of Clinical Genetics, Family Cancer Clinic, Erasmus MC – Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

Patients and methods: We selected 223 BC patients diagnosed between 1980 and 2001 within families with a deleterious germline BRCA1-mutation ascertained at the Rotterdam Family Cancer Clinic. To correct for ascertainment bias, the group of index patients undergoing DNA testing more than 2 years after BC diagnosis (n = 53) was separated from the other BRCA1-patients (n = 170). All BRCA1-associated patients were matched in a 1:2 ratio for age and year of diagnosis to sporadic BC patients. We compared the occurrence of ipsi- and contralateral BC (CBC) as well as distant disease-free (DDFS), BC-specific (BCSS) and overall survival (OS). By multivariate modelling, the prognostic impact of tumour and treatment factors was investigated separately in BRCA1-associated and sporadic breast cancers.





Ann Oncol 2006

Conclusions: BRCA1-associated BC is characterised by specific tumour characteristics, a high incidence of CBC and a trend towards a worse survival for the ductal tumour type. Our observation that tumour size and nodal status are also prognostic factors for BRCA1-associated BC implies that the strategy to use these factors as a proxy for ultimate mortality, for instance in BC screening programmes or the consideration of (contralateral) preventive mastectomy, appears to be valid in this specific group of patients.

Ann Oncol 2006

PLOS | ONE

March 27, 2015

RESEARCH ARTICLE

Worse Breast Cancer Prognosis of *BRCA1/BRCA2* Mutation Carriers: What's the Evidence? A Systematic Review with Meta-Analysis

Alexandra J. van den Broek[1], Marjanka K. Schmidt[1,2]*, Laura J. van 't Veer[2], Rob A. E. M. Tollenaar[3], Flora E. van Leeuwen[1]

1 Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, Netherlands, **2** Division of Molecular Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands, **3** Department of Surgery, Leiden University Medical Centre, Leiden, Netherlands

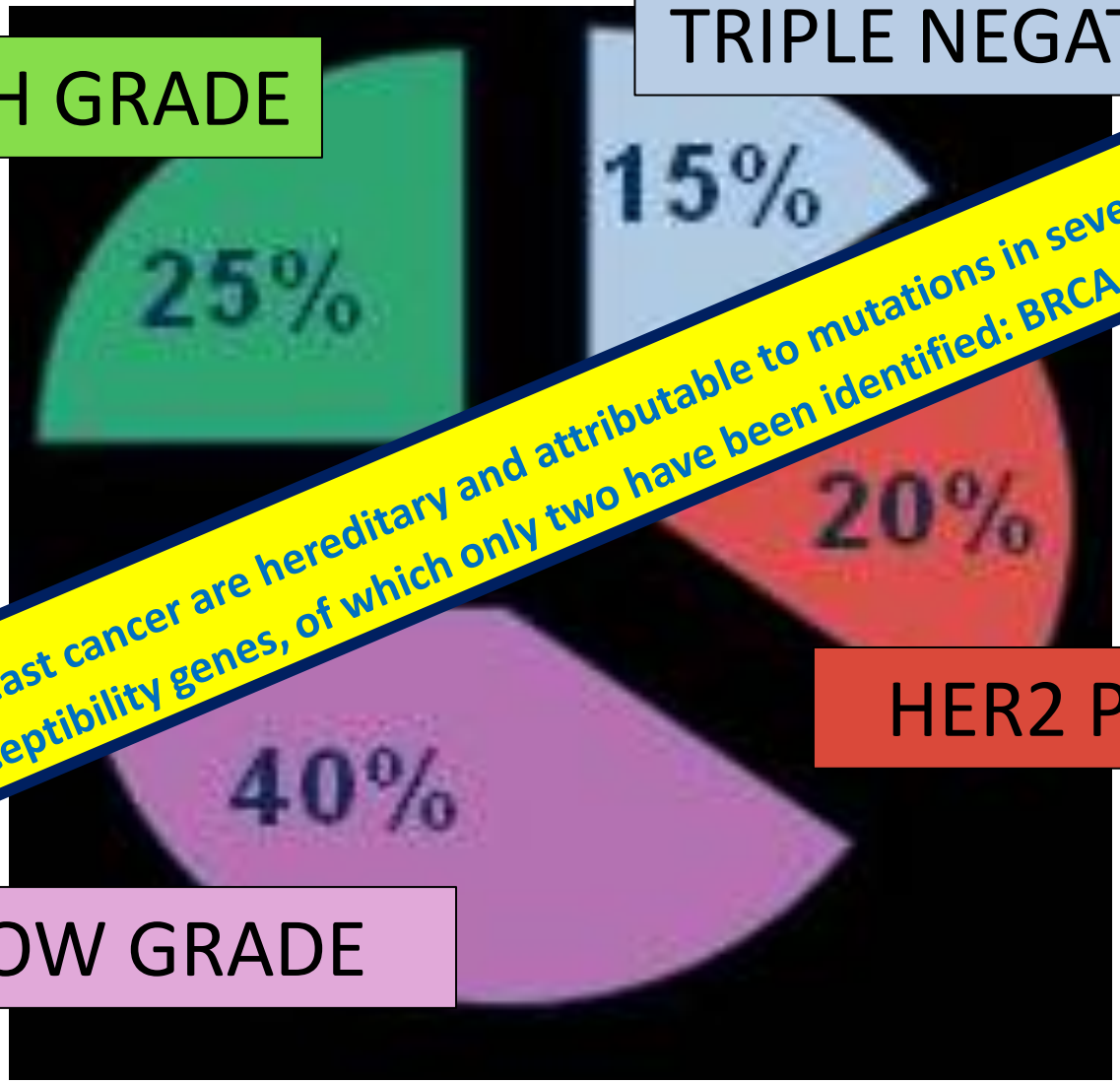
Methods

Eligible publications were observational studies assessing the survival of breast cancer patients carrying a *BRCA1/2* mutation compared to non-carriers or the general breast cancer population. We performed meta-analyses and best-evidence syntheses for survival outcomes taking into account study quality assessed by selection bias, misclassification bias and confounding.

Conclusions

In contrast to currently held beliefs of some oncologists, current evidence does not support worse breast cancer survival of *BRCA1/2* mutation carriers in the adjuvant setting; differences if any are likely to be small. More well-designed studies are awaited.

BREAST CANCER PHENOTYPES



5-10% of breast cancer are hereditary and attributable to mutations in several highly penetrant susceptibility genes, of which only two have been identified: BRCA 1 and BRCA2

TERAPIA SISTEMICA PER IL CARCINOMA MAMMARIO

CHEMOTHERAPY

- Anthracycline-containing
  - Doxorubicin or epirubicin monotherapy (weekly or tri-weekly)
  - Doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide
  - Liposomal doxorubicin ± cyclophosphamide
  - Fluorouracil/doxorubicin/cyclophosphamide or fluorouracil/epirubicin/cyclophosphamide
- Taxane-containing
  - Paclitaxel monotherapy weekly
  - Docetaxel monotherapy tri-weekly or weekly
  - Abraxane (nab-paclitaxel)
  - Anthracycline (doxorubicin or epirubicin)/taxane (paclitaxel or docetaxel)
  - Docetaxel/capecitabine
  - Paclitaxel/gemcitabine
  - Paclitaxel/vinorelbine
  - Paclitaxel/carboplatin
- New cytotoxic agents
  - Eribulin
  - Ixabepilone (not approved by EMA)
- Non-anthracycline-containing
  - Cyclophosphamide/methotrexate/fluorouracil (CMF)
  - Platinum-based combinations (e.g. cisplatinum + 5-fluorouracil; carboplatin + gemcitabine)
  - Capecitabine
  - Vinorelbine
  - Capecitabine + vinorelbine
  - Vinorelbine ± gemcitabine
  - Oral cyclophosphamide with or without methotrexate (metronomic chemotherapy)

ENDOCRINE THERAPY

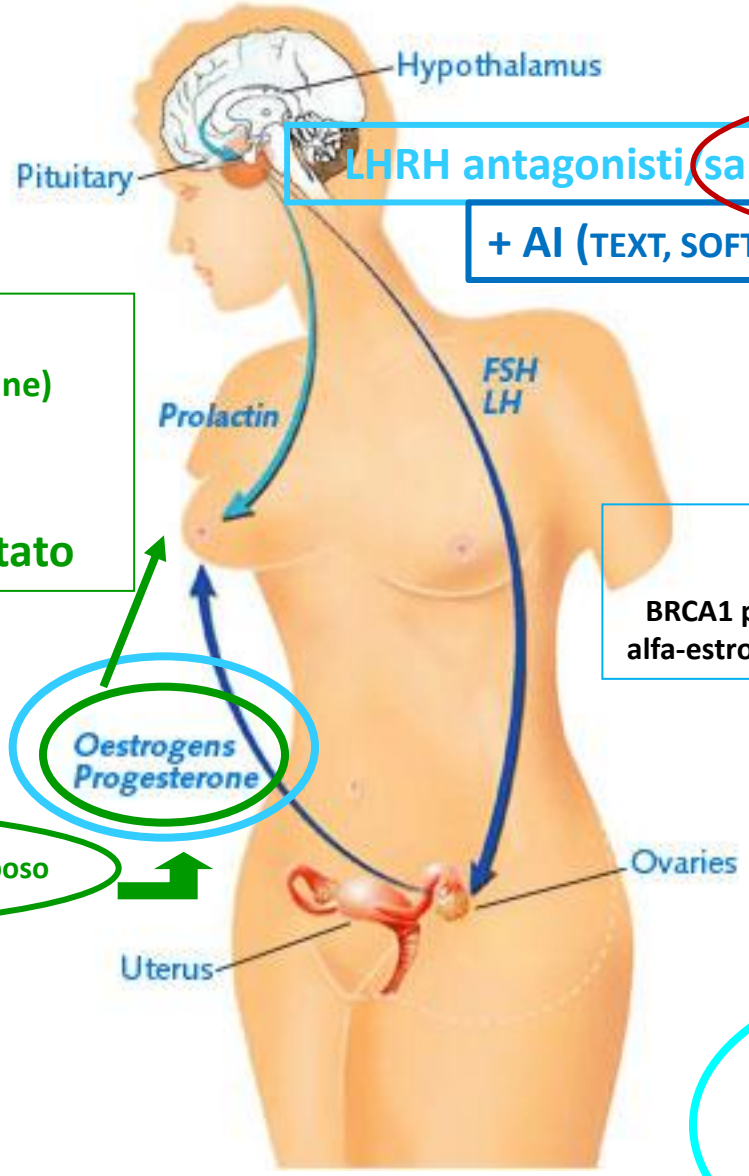
Selective estrogen receptor modulators	Tamoxifen; toremifene
Estrogen receptor down-regulator	Fulvestrant
Luteinizing hormone-releasing hormone analogues	Goserelin, leuprorelin, triptorelin
Third-generation aromatase inhibitors	
Non-steroidal	Anastrozole, letrozole
Steroidal	Exemestane
Progestins	Medroxyprogesterone acetate; megestrol acetate
Anabolic steroids	Nandrolone decanoat
Estrogens	Estrogens

«TARGET MOLECULAR THERAPY»

Anti Her2 (trastuzumab, pertuzumab, TDM-1, lapatinib, neratinib)
Anti mTor (everolimus)
Anti CD4/CD6 (palbociclib)
Anti VEGF (bevacizumab)

ORMONOTERAPIA

POST-MENOPAUSA



LHRH antagonisti, salpingo-annessiectomia

+ AI (TEXT, SOFT trials)

Inibitori dell'aromatasi
(letrozolo, anastrozolo, exemestane)

Fulvestrant

Medrossiprogesterone acetato

Tamoxifene

BRCA1 protein producted interacts with alfa-estrogen receptor to which TAM binds

Fegato, ghiandole surrenaliche, tess. adiposo

PRE-MENOPAUSA

TRIPLE NEGATIVE BREAST CANCER

(80% of TNBCs are basal-like BUT 18-40% of basal like do not have a TN phenotype)

- **80% of tumors in women with BRCA1-mutation are «triple-negative» phenotype, basal-like phenotype, or both**
- **10% of early-onset TNBC have BRCA1-mutation**

(Breast Cancer Res Treat, July, 2012)

NO TARGET THERAPY

POOR PROGNOSIS

PLATINUM in METASTATIC TNBC

Regimen	n	ORR (%)	PFS (months)	Prior Chemo (%)	Disease-free interval (median)
Gemcitabine / Carboplatin[1]	**258**	**30%**	**4.1**	**90%**	**15 mos**
1st line	*148*		*4.6*		*15.9 mos*
2nd/3rd line	*110*		*2.9*		*13.8 mos*
Carboplatin or cisplatin[2]	**86**	**30%**	**3.2**	**86%**	**NA**
1st line		*32%*			
2nd line		*20%*			
Cisplatin – 1st & 2nd line[3]	**58**	**10%**	**1.5**	**83%**	**15.4 mos**

1. O'Shaughnessy J, et al. ASCO 2011 (abstract)
2. Isakoff S, et al. ASCO 2011 (abstract)
3. Baselga J, et al. JCO 2013

VOLUME 28 · NUMBER 3 · JANUARY 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pathologic Complete Response Rates in Young Women With *BRCA1*-Positive Breast Cancers After Neoadjuvant Chemotherapy

Tomasz Byrski, Jacek Gronwald, Tomasz Huzarski, Ewa Grzybowska, Magdalena Budryk, Malgorzata Stawicka, Tomasz Mierzwa, Marek Szwiec, Rafal Wiśniowski, Monika Siolek, Rebecca Dent, Jan Lubinski, and Steven Narod

Patients and Methods

From a registry of 6,903 patients, we identified 102 women who carried a *BRCA1* founder mutation and who had been treated for breast cancer with neoadjuvant chemotherapy. Pathologic complete response was evaluated using standard criteria.

Table 2. Treatment and Response to Different Chemotherapy Regimens

Regimen	No. of Patients Treated	No. of pCRs	% pCRs
CMF	14	1	7
AC	23	5	22
FAC	28	6	21
AT	25	2	8
Cisplatin	12	10	83

NOTE. The CMF category includes four patients treated with cyclophosphamide, methotrexate, fluorouracil, and prednisone and two patients with cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone.

Abbreviations: pCR, pathologic complete response; CMF, cyclophosphamide, methotrexate, and fluorouracil; AC, doxorubicin and cyclophosphamide; FAC, fluorouracil, doxorubicin, and cyclophosphamide; AT, doxorubicin and docetaxel.

Table 1. Characteristics of Patients in the Study by Treatment Regimen

Characteristic	All Regimens (N = 102)		CMF (n = 14)		AC (n = 23)		FAC (n = 28)		AT (n = 25)		Cisplatin (n = 12)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years												
Mean	42.1		43.9		41		43.1		40.2		43.3	
Range	26-50		31-50		26-49		33-50		26-49		37-50	
Type of *BRCA1* mutation												
5382insC	79	78	11	79	17	74	22	78	18	72	11	92
C61G	19	19	3	21	5	21	5	18	5	20	1	8
4153delA	4	4	—		1	5	2	8	2	8	0	0
Tumor stage												
T1 (< 2 cm)	8	8	1	7	1	4	1	4	2	8	4	33
T2 (≥ 2-5 cm)	66	65	9	64	18	78	18	64	18	72	4	33
T3/T4 (> 5 cm)	28	27	4	29	4	18	9	32	5	20	4	33
Nodal status												
N0	33	33	2	15	7	30	13	46	5	20	6	50
N1-N3	69	67	12	85	16	70	15	54	20	80	6	50
Estrogen receptor status												
Positive	15	15										
Negative	87	85	1	7	3	13	6	21	4	16	1	8
Missing	0	0	13	93	20	87	22	79	21	84	11	92
Progesterone receptor status												
Positive	14	14	0	0	2	9	6	21	6	24	0	0
Negative	77	75	11	79	18	78	20	71	17	68	11	92
Missing	11	11	3	21	3	13	2	8	2	8	1	8
HER-2 status												
Positive	6	6	0	0	3	13	2	8	1	4	0	0
Negative	60	59	7	50	15	65	14	50	15	60	11	92
Ambiguous	7	7	1	7	1	4	3	10	2	8	0	0
Missing	29	28	6	43	4	18	9	32	7	28	1	8

***«Cisplatinum-group» close to «basal like» definition subgroup**

JCO, 28, 2010

Comment of authors:

A high proportion of women with *BRCA1*-associated breast cancer in our study responded to platinum-based chemotherapy. The homogeneity in response to treatment in the *BRCA1*-positive subgroup may be a reflection of the underlying homogeneity in etiology. It is important that these results be confirmed in more patients and by other groups, preferably using a wide range of end points, before making clinical recommendations.

JCO, 28, 2010

CARBOPLATIN IN NEOADJUVANT TNBC SETTING

Study	Population	n	Design	Treatment	pCR	p
GEICAM/2006-03[1]	operable IHC-defined basal-like BC (ER-/PR-/HER2- and cytokeratin 5/6+ or EGFR+)	94	Phase II	EC→Doc	**35%**	
				EC→Doc+Carbo	**30%**	0.6
GeparSixto[2]	Stage II-III HER2neg BC	315 (TNBC)	Phase II	PM+Beva	**37%**	
				PM+Beva+Carbo	**53%**	0.005
CALGB 40603[3]	Stage II-III TNBC	433	Phase II	P→ddAC (+/-Beva)	**41%**	
				P+Carbo→ddAC (+/-Beva)	**54%**	0.003
I-SPY2[4]	T≥2.5 cm, HER2neg	60 (TNBC)	Phase II	P→AC (n=21)	**26%***	
				Valiparib+Carbo+P→AC (n=39)	**52%***	-------
Ca.Pa.Be.[5]	Stage II-III TNBC	44	Phase II	Carbo+P+Beva	**50%**	

*Estimated pCR rates; actual pCR rates biased by adaptive randomization

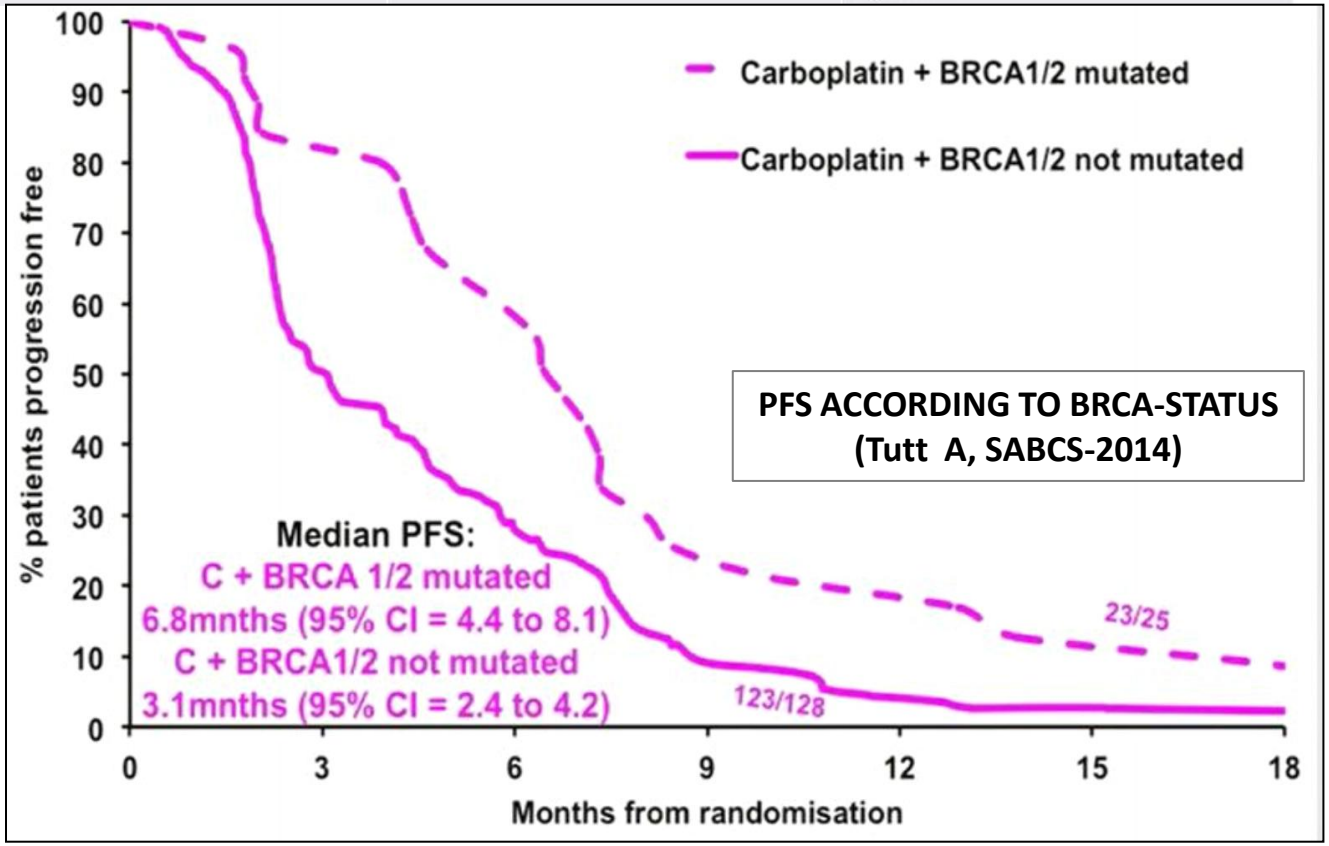
[1]Alba et al., Breast Cancer Res Treat 2012; [2]von Minckwitz et al., Lancet Oncol 2014; [3]Sikov et al., SABCS 2013; [4]Rugo et al., SABCS 2013; [5]Guarneri et al., SABCS 2013

CHEMOTHERAPY IN BRCA-mutated BREAST CANCER

a) TNT trial, Tutt et al, San Antonio 2014 Breast meeting

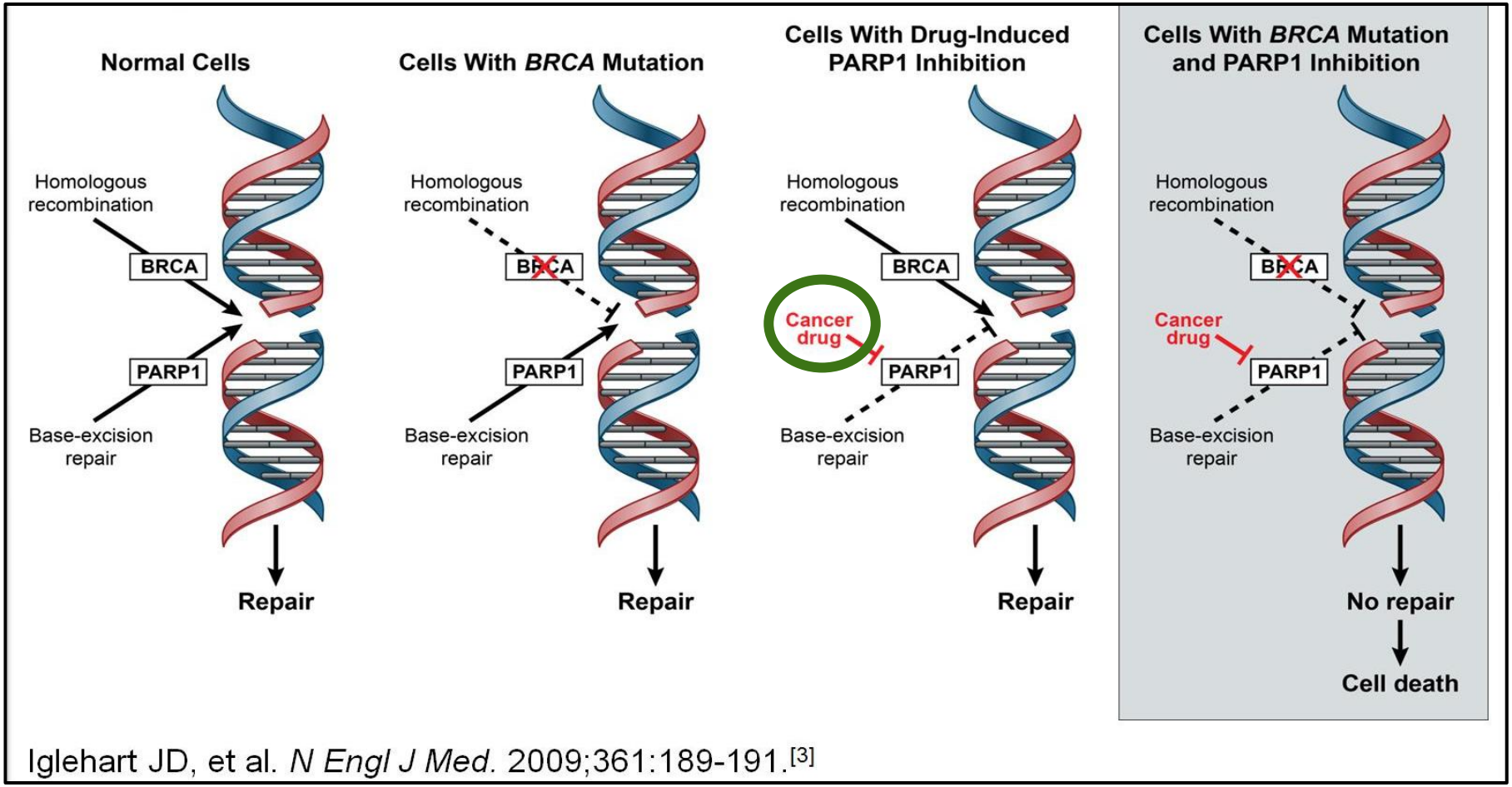
- Patients with metastatic TNBC randomised to either docetaxel or carboplatin (first-line)

	Total (n= 376)	BRCAm (n=43)
Docetaxel	35% resp	33% resp; med PFS 4.5m
Carboplatin resp	31% resp	68% resp; med PFS 6.8m



PFS ACCORDING TO BRCA-STATUS (Tutt A, SABCS-2014)

BRCA-mutated: PREDICTIVE MARKER for a TARGET THERAPY with PARP INHIBITORS?



Iglehart JD, et al. *N Engl J Med.* 2009;361:189-191.[3]

PARP Inhibitors as Targeted Therapy

- Selectively inhibit the growth of cells with defects in either *BRCA1* or *BRCA2* genes
- In vitro models: Cells with *BRCA* mutations > 1000 times more sensitive to PARP inhibitors than wild-type cells
- Led to development of clinical trials in patients with metastatic breast, ovarian, and other cancers (particularly in those with g*BRCA* mutations)

Farmer H, et al. *Nature*. 2005;434:917-921[6]; Bryant HE, et al. *Nature*. 2005;434:913-917.[7]

Differential mechanisms defines two classes of PARPi

	Catalytic inhibition (IC50 nM)	Cytotoxicity (IC_{90} µM)	PARP-trapping potency (relative to olaparib)	Class
Veliparib	30	>50	<0.2	Class 1
Olaparib	6	4.5	1	Class 2
Rucaparib	21	3	1	Class 2
Niraparib	60	2.3	~2	Class 2
Talazoparib	4	0.04	~100	Class 2

Class 1: catalytic inhibition >> PARP trapping

Class 2: PARP trapping (stabilization of toxic PARP1/2-DNA complexes) correlates with cytotoxicity:

Talazoparib >> Niraparib, Olaparib >> Veliparib

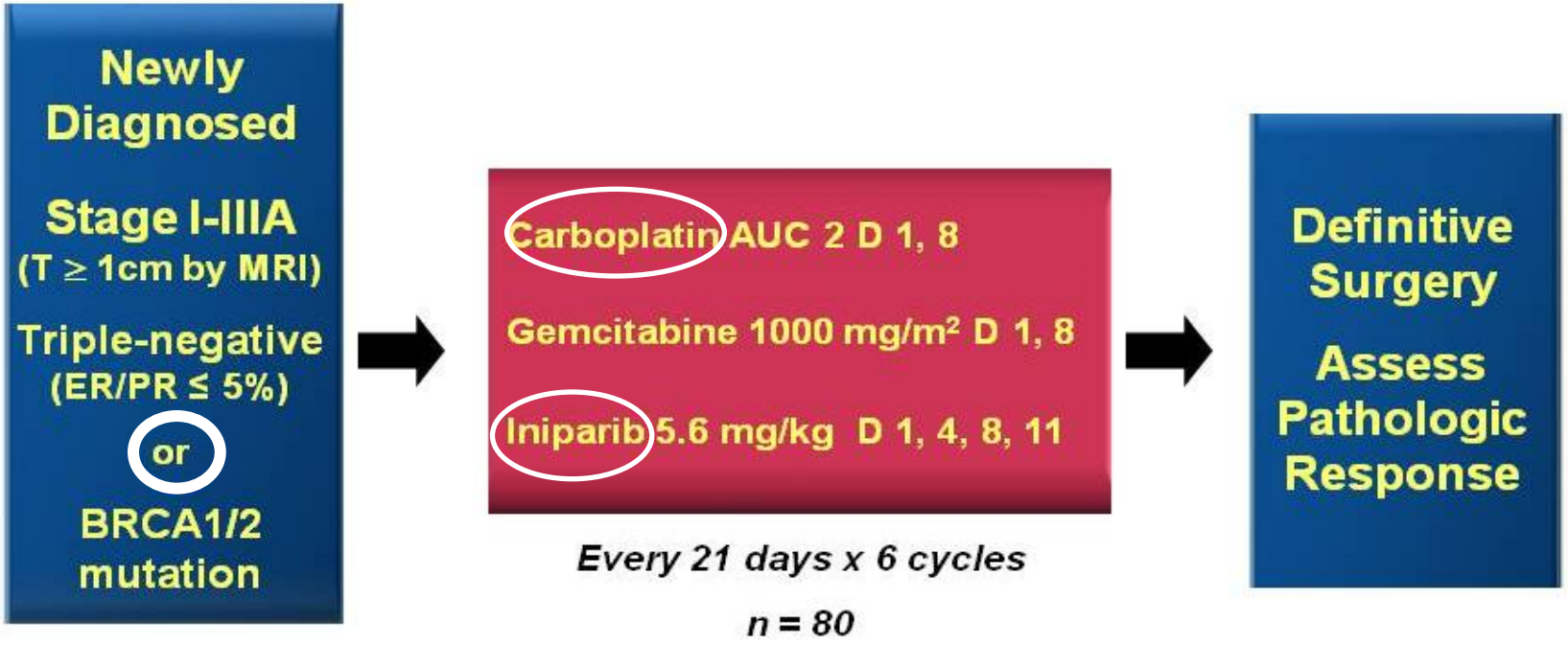
Yves Pommier, with thanks

Murai et al, Ca Res 2012& JPET, 2014

PARP INHIBITORS: PHASE II TRIALS IN METASTATIC BREAST CANCER

Trial	Agent	Author	BRCA1/BRCA2	TNBC	Response rate
Phase II (Lancet 2010, 376)	Olaparib 400 mg po BID	Tutt	27 patients BRCA1: 67% BRCA2: 33%	50%	54% 0 CR, 7 PRs
	Olaparib 100 mg po BID		27 patients BRCA1: 59% BRCA2: 41%	64%	25% 0 CR, 4 PRs
Phase II (JCO 2015, 33)	Olaparib 400 mg po BID	Kaufman	62 patients BRCA1:60% BRCA2: 40%	48% ER-negative	13.3% 0 CR, 8 PRs
Phase II (Lancet Oncol 2011,12)	Olaparib 400 mg po BID	Gelmon	15 patients non-BRCA	100%	0%
Phase II (JCO, 2010, 28)	Veliparib 30 mg po BID D 1-7 + TMZ 100 mg/m^2 PO QD D 1-5 q 28 days	Isakoff	41 patients BRCA1: 7% BRCA2: 12%	56%	BRCA1/2: 37.5% 1 CR, 2 PRs No responses in non-BRCA

PrECOG 0105: Final efficacy results from a phase II study of gemcitabine & carboplatin plus iniparib (BSI-201) as neoadjuvant therapy for triple-negative and BRCA1/2 mutation-associated breast cancer



Primary Endpoint:	Pathologic complete response (pCR) [no invasive disease in breast + axilla]
Secondary Endpoints:	Radiographic response by MRI Breast conservation eligibility Safety Correlation of gene expression profiles & gene copy number with response

ASCO Meeting 2013

Results

Intent-to-treat population

Pathologic Response (n=80)				
	All patients n = 80	BRCA 1/2 wild-type n = 61	BRCA 1/2 mutant n = 19	TN & BRCA 1/2 mutant n = 16
pCR [RCB 0]; n (%)	29 (36%)	20 (33%)	9* (47%)	9* (56%)
90% CI	27–46	23–44	27-68	33-77
RCB 0/1; n (%)	45 (56%)	31 (51%)	14 (74%)	12 (75%)
90% CI	46-66	40-62	52-89	52-91

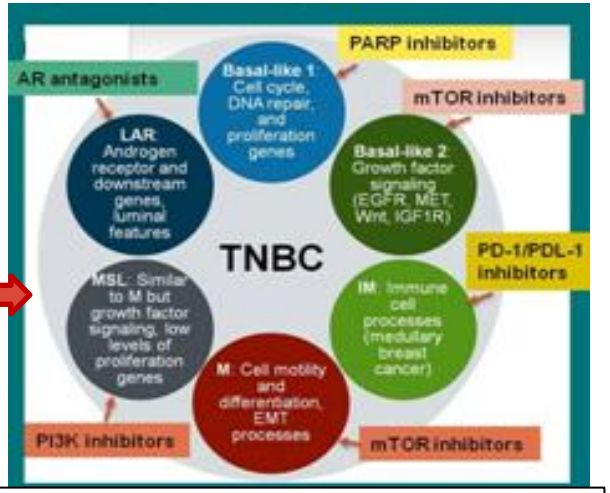
* One BRCA1 carrier had bilateral TNBC & achieved pCR in both breasts

Grade 3/4 Events

	Grade 3 n (%)	Grade 4 n (%)
Neutropenia* Febrile neutropenia	33 (41%) 0	6 (8%) 0
ALT elevation	12 (15%)	0
Anemia	8 (10%)	0
AST elevation	7 (9%)	0
Thrombocytopenia	4 (5%)	2 (3%)
Fatigue	2 (3%)	0

Conclusions

- Germline BRCA1/2 mutation carriers had a higher rate of response compared to non-carriers
- Pathologic response varied among TNBC subtypes
  - 11/14 (79%) of immunomodulatory (IM) subtype pts responded
  - No luminal androgen receptor (LAR) subtype pts responded



Emerging target therapy in TNBC

ASCO meeting, 2015

Breast Cancer Res Treat
DOI 10.1007/s10549-012-2158-6

July 2012

REVIEW

Systemic therapy options in BRCA mutation-associated breast cancer

Soley Bayraktar · Stefan Glück

This article will review our current understanding of the functions of the BRCA1 and BRCA2 genes, their roles as a determinant of differential chemosensitivity in clinical settings, the relationship between BRCA1 and the triple-negative breast cancers (TNBCs), and the concept that BRCA1 may be a potential novel predictive biomarker in future studies.

	BRCA1-carriers	BRCA2-carriers	Non-carriers
Platinums			
Byrski et al. [9] ($n = 102$, of 12 were treated with neoadj. cisplatin)	12 BRCA1-carriers: pCR: 83 %	–	–
Moiseyenko et al.[29] (case-report, failed 1st line neoadj. epirubicin–docetaxel therapy)	1 BRCA1-carrier: major response to 2nd line single-agent cisplatin	–	–
Silver et al. [28] ($n = 28$, TNBC patients were treated with neoadj. cisplatin)	2 BRCA1-carriers: pCR: 100 %	–	–
Rhiem et al. [30] (case-report, treated with cisplatin-gemcitabine doublet, metastatic setting)	1 BRCA1-carrier: major response in this heavily pretreated patient, with the duration >6 months	–	–
Taxanes			
Kriege et al. [36] ($n = 140$, treated with taxane-monotherapy, metastatic setting)	32 BRCA1-carriers: OR: 23 %, PD: 60 %, median PFS:2.2 months	13 BRCA2-carriers: OR: 89 %, PD: NR, median PFS: 7.1 months	95 non-carriers: OR: 38 %, PD: 19 %, median PFS: 5.7 months
Wysocki et al. [37] ($n = 175$, treated with docetaxel-based therapy, metastatic setting)	BRCA1-mutation was detected 26 % (5/19) of non-responders to docetaxel	–	–
Kurebayashi et al. [75] ($n = 50$, treated with taxane-based therapy, metastatic setting)	29 BRCA1-carriers: mean TTP ± SD: 6.5 ± 4.9 months	–	21 non-carriers: mean TTP ± SD: 14.7 ± 5.9 months
Anthracyclines			
Delaloge et al.[38] (n = 77, treated with neoadj. anthracycline-based therapy)	15 BRCA1-carriers: OR: 100 %, pCR: 53 %	5 BRCA2-carriers: OR: 80 %, pCR: 0 %	57 non-carriers: OR: 63 %, pCR: 14 %
Chappuis et al.[39] (n = 38, treated with neoadj. anthracycline-based therapy)	7 BRCA1 and 4 BRCA2-carriers: overall cCR: 91 %, overall pCR: 44 %. After a median follow-up of 7 years, among complete clinical responders, 17 % (1/6) of BRCA1-carriers and 75 % (3/4) BRCA2-carriers) died of breast cancer		27 non-carriers: cCR: 30 %, pCR: 4 %
Petit et al. [40] (n = 55, TNBC patients treated with neoadj. FEC)	12 BRCA1-carriers: pCR: 17 %	–	43 non-carriers: pCR: 53 %
Byrski et al. [9] ($n = 102$, of 51 were treated with neoadj. AC or FAC)	51 BRCA1-carriers: pCR: 22 %	–	–
Kriege et al. [42] ($n = 242$, of 239 treated with anthracycline-based therapy, metastatic setting)	93 BRCA1-carriers: OR: 66 %, median PFS: 7.6 months, median OS: 15 months	28 BRCA2-carriers: OR: 89 %, median PFS: 11.4 months, median OS: 19.3 months	121 non-carriers: OR: 50 %, median PFS: 6.7 months, median OS: 13.6 months
Warner et al. [76] (case-report, treated with neoadj. FEC)	1 BRCA-carrier: pCR: 100 %	–	–
Hubert et al. [77] ($n = 22$, treated with neoadj. anthracycline-based therapy)	15 BRCA1-carriers: pCR: 13 %, cCR: 40 %	7 BRCA2-carriers: pCR: 0 %, cCR: 14 %	–

	BRCA1-carriers	BRCA2-carriers	Non-carriers
Fourquet et al. [78] (*n* = 74, treated with neoadj. anthracycline-based therapy)	33 BRCA1 and BRCA2-carriers: cCR: 46 %		41 non-carriers: cCR: 17 %
Anthracycline–taxane-containing regimens			
Raphael et al. [43] (*n* = 658, treated with anthracyclin/taxane-containing neoadj. therapy)	–	155 BRCA2-carriers: pCR: 18 %	503 non-carriers: pCR: 39 %
Arun et al. [10] (n = 317, of 261 were treated with neoadj. FEC followed by weekly taxol)	57 BRCA1-carriers: pCR: 46 %, 5-yr RFS: 72 %, 5-yr OS: 87 %	23 BRCA2-carriers: pCR: 13 %, 5-yr RFS: 93 %, 5-yr OS: 100 %	237 non-carriers: pCR: 22 %, 5-yr RFS: 73 %, 5-yr OS: 90 %
Byrski et al.[9] (n = 102, of 25 were treated with doxorubicin-docetaxel-containing neoadj. therapy)	25 BRCA1-carriers: pCR: 8 %	–	–
Melichar et al.[79] (n = 2, treated with neoadj. dose-dense AC followed by weekly taxol)	2 BRCA1-carriers: pCR: 100 %	–	–
Alkylating agents			
Byrski et al.[9] (n = 102, of 14 were treated with neoadj. CMF)	14 BRCA1-carriers: pCR: 7 %	–	–

N total number of patients included in the study; *TNBC* triple-negative breast cancer; *NR* not-reported; *neoadj* neoadjuvant; *cCR* complete clinical response; *pCR* pathologic complete response; *OR* objective response; *CMF* cyclophosphamide, methotrexate, fluorouracil; *FEC* fluorouracil, epirubicin, cyclophosphamide; *AC* doxorubicin, cyclophosphamide

Table 2 Clinical trials of various PARP inhibitors as a single-agent or in combination with chemotherapy

PARPI	Combination agent	Study	Population	Outcomes
Phase I trials				
Olaparib	Carboplatin	Lee et al. [80][a]	$N = 30$, of 4 were BRCA1/2-carriers	PR: 3/4, clinical benefit: 4/4
Olaparib	Cedinarib (anti-angiogenic agent)	Liu et al. [81][a]	$N = 18$, of 5 were TNBC (BRCA status unknown)	cSD: 1/5, uSD: 2/5, PD:2/5
Iniparib	Irinotecan	Moulder et al. [82][a]	$N = 34$, MBC	PR: 5/26, SD: 10/26 for >4 cycles
Veliparib	Doxorubicin and cyclophosphamide	Tan et al. [72][a]	$N = 18$, of 14 BC, and 5/14 were BRCA1/2-mutation carriers	PR:3/5 (all BRCA1/2-carriers), SD: 8/18 (all breast cancer patients)
Veliparib	Metronomic cyclophosphamide	Kummar et al. [83][a]	$N = 18$, of 3 were TNBC	cPR: 1/3
Veliparib	Carboplatin	Somlo et al. [84][a]	$N = 22$, BRCA1/2-carriers	ORR: 67 %, clinical benefit 75 %
Phase II trials				
Olaparib	–	Tutt et al. [58][a]	$N = 54$, BRCA1/2-carriers	ORR in 400 mg cohort: 11/27; 100 mg cohort: 6/27
Olaparib	–	Gelmon et al. [85][a]	$N = 91$, of 11 were BRCA1/2-carriers	ORR: 0 %
Olaparib	Paclitaxel	Dent et al.[a]	$N = 19$, TNBC (BRCA status unknwn)	cPR: 7/19, uPR: 10/19 data on PFS yet to be published
Veliparib	Temozolamide	Isakoff et al. [71][a]	$N = 41$, MBC, 8 were BRCA1/2-carriers	Activity limited to BRCA1/2-carriers only uCR: 1/35, uPR: 2/35, uSD: 7/35
Iniparib	Gemcitabine and Carboplatin	O'Shaughnessy et al. [59]	$N = 519$, TNBC (BRCA1/2-status yet to be published)	PFS: GC: 4.1 mo, GCI: 5.1 mo; OS: GC: 11.1 mo, GCI: 11.8 mo

PARPI poly9adenosine diphospahe[ADP]-ribose) polymerase inhibitor, *TNBC* triple-negative breast cancer, *MBC* metastatic breast cancer, *PR* partial response, *ORR* overall response rate, *cSD* confirmed stable disease, *uSD* unconfirmed stable disease, *uCR* unconfirmed complete response, *PD* progressive disease, *cPR* confirmed partial response, *GC* gemcitabine and carboplatin arm, *GCI* gemcitabine–carboplatin–iniparib arm, *PFS* progression-free-survival, *OS* overall survival

[a] Clinical trials published in abstract format only

Conclusions

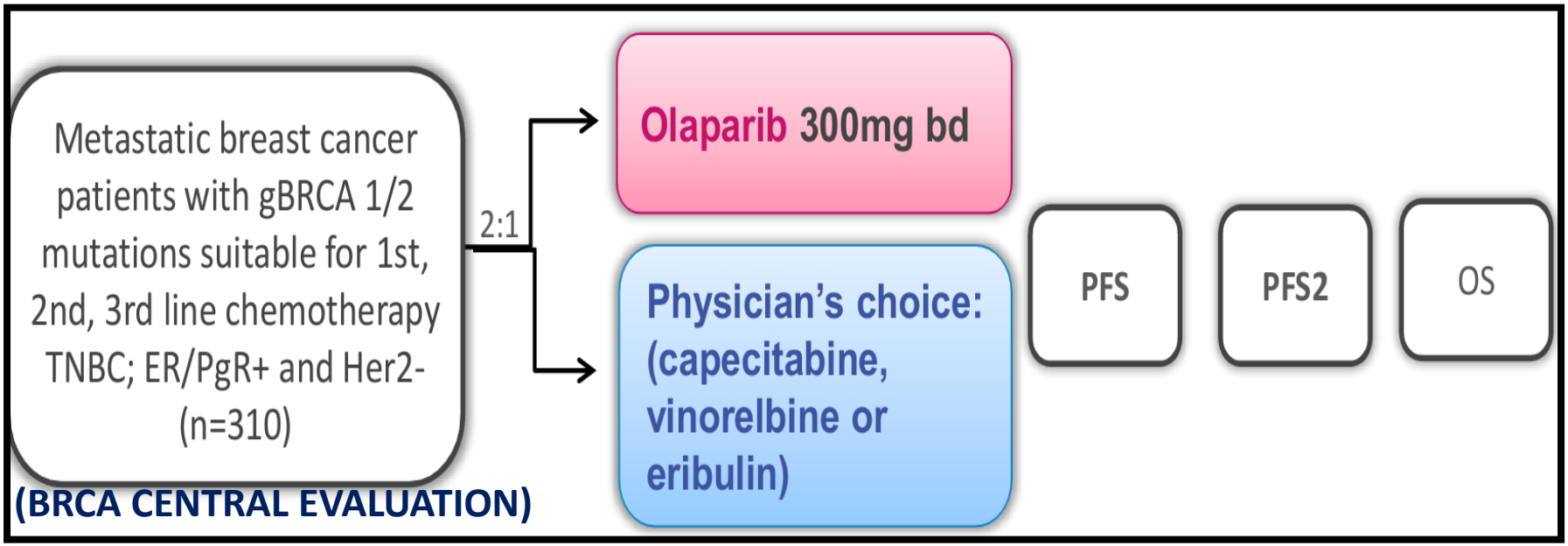
There is no definitive conclusion on the best chemotherapy regimen for BRCA mutation carriers, and standard prognostic features are used to decide the treatment. In particular, neoadjuvant studies support the continued use of anthracycline-taxane-containing regimens in the treatment of early-stage breast cancer in BRCA1 carriers. Similarly, clinical studies suggest that taxanes can be effective in ER-positive BRCA1 mutation-associated breast cancer patients compared with sporadic patients. At the moment, the evidence is insufficient to recommend routine use of platinum treatment over other standard regimens and also to change practice from the standard drugs to targeted agents; however, there is compelling evidence enough to suggest that prospective trials are needed. In addition, widespread genetic testing may accelerate the identification of the comparatively small number of carriers who would be candidates for prospective biomarker-driven studies are critically needed.

Bayraktar S, Gluck S. Breast Cancer Res Treat; July 2012

ON GOING TRIALS

1) OLYMPIAD in METASTATIC BRCA-mutated BREAST CANCER

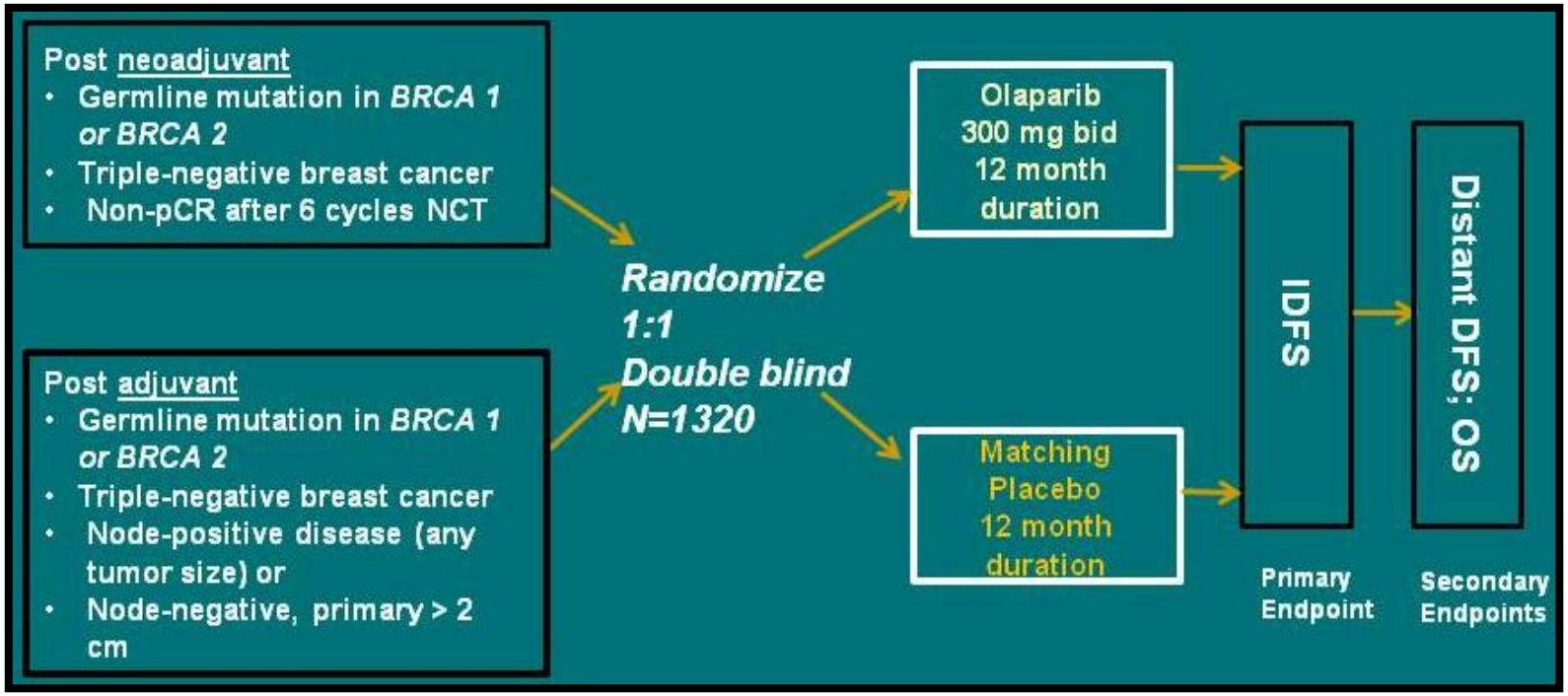
A Phase III, Open Label, Randomized, Multi-centre Study to assess the efficacy and safety of Olaparib Monotherapy versus Physician's Choice Chemotherapy in the Treatment of Metastatic Breast Cancer patients with BRCA1/2 Mutations



2) OLYMPIA (Olaparib)

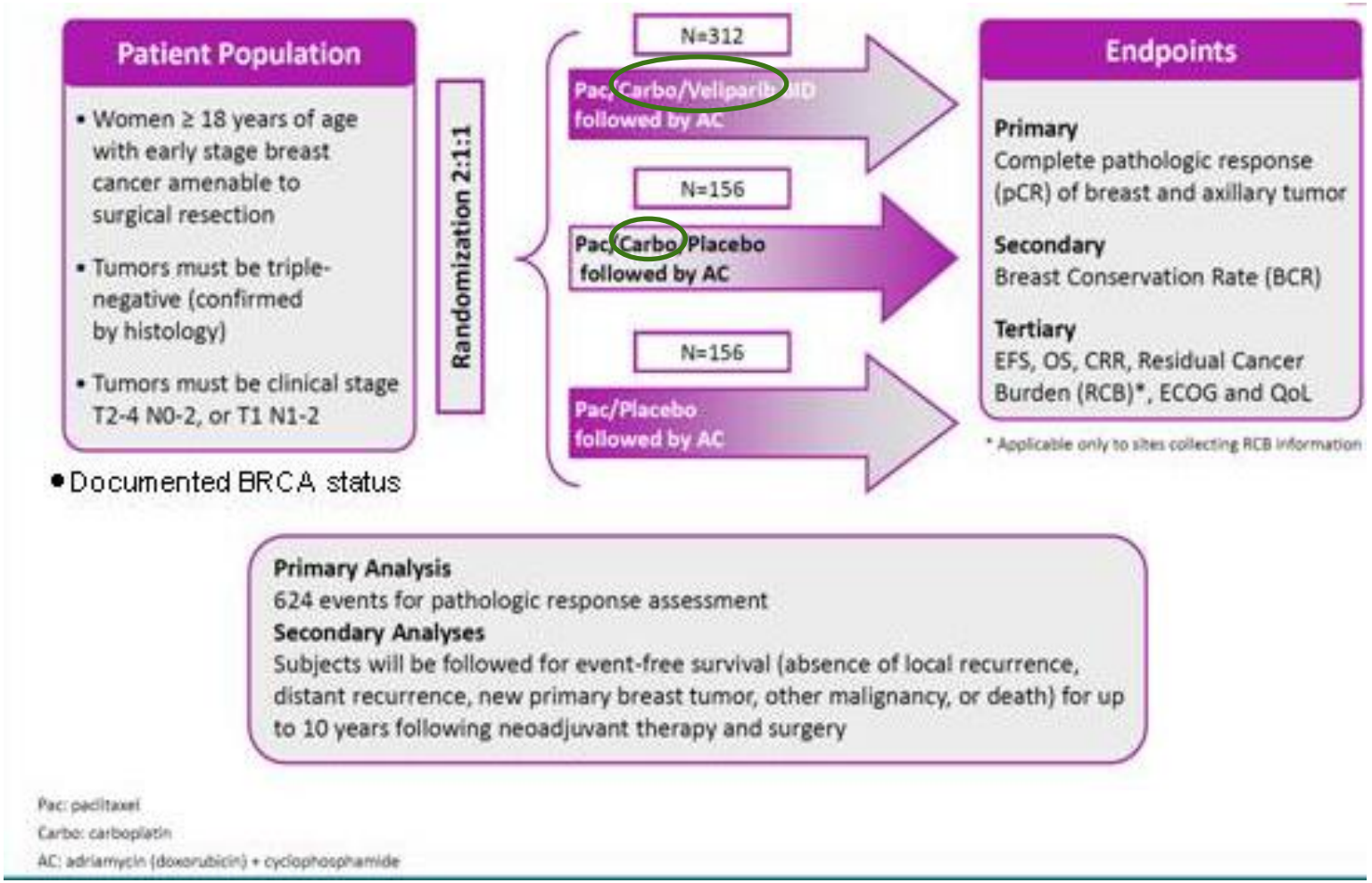
PARP INHIBITOR IN ADJUVANT BRCA-mutated BREAST CANCER

(NSABP B-55/BIG 6-13 trial)



Completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or both

PARP INHIBITORS IN NEOADJUVANT BRCA-mutated BREAST CANCER



CHI?

I principali criteri che inducono il sospetto di un rischio ereditario, e che vengono attualmente valutati per l'accesso alla consulenza oncogenetica di soggetti con storia personale e/o familiare di tumore della mammella e/o ovaio, sono i seguenti:

a) carcinoma mammario e ovarico nella stessa persona
b) carcinoma della mammella prima dei 36 anni
c) carcinoma dell'ovaio prima dei 45 anni
d) carcinoma della mammella maschile
e) carcinoma della mammella bilaterale prima dei 50 anni

o in presenza di altri familiari affetti:

f) tre o più casi di carcinoma della mammella e/o ovaio nello stesso ramo parentale
g) almeno due casi di tumore della mammella insorto prima dei 50 anni e/o bilaterale
h) almeno due casi di carcinoma ovarico
i) un caso di carcinoma della mammella insorto prima dei 50 anni ed uno di carcinoma ovarico

Carcinomi mammari "triple negative":
≤ 50 anni di età (ESMO guidelines)
≤ 60 anni (NCCN guidelines version 2.2015)

QUESTIONARIO

CONSULENZA GENETICA

Score di rischio >10%

Prelievo per test

Risultato Test genetico

→ Negativo o “non informativo”

↓

Positivo o “informativo”

***Informazione** → aumentato rischio di sviluppare:
un tumore mammario controlaterale **(12% a 5 aa in BRCA2-, 20% a 5 aa in BRCA1-)**
un carcinoma ovarico **(63% in BRCA1-, 9-27% in BRCA2-)**

***Estensione ai membri adulti della famiglia** della ricerca della specifica alterazione

- **Sorveglianza** → FAVORISCE UNA DIAGNOSI PRECOCE
  clinico-strumentale delle mammelle
  Eco transvaginale+dosaggio marker sierico Ca125
- **Prevenzione** → CHIRURGIA PROFILATTICA
  Asportazione di tessuto mammario e/o ovarico
- **Trials clinici** → TARGET THERAPY

LIBERTA’ DI SCELTA DELLA PAZIENTE