Percorso del paziente al alto rischio di mutazione BRCA: carcinoma mammario e carcinoma ovarico

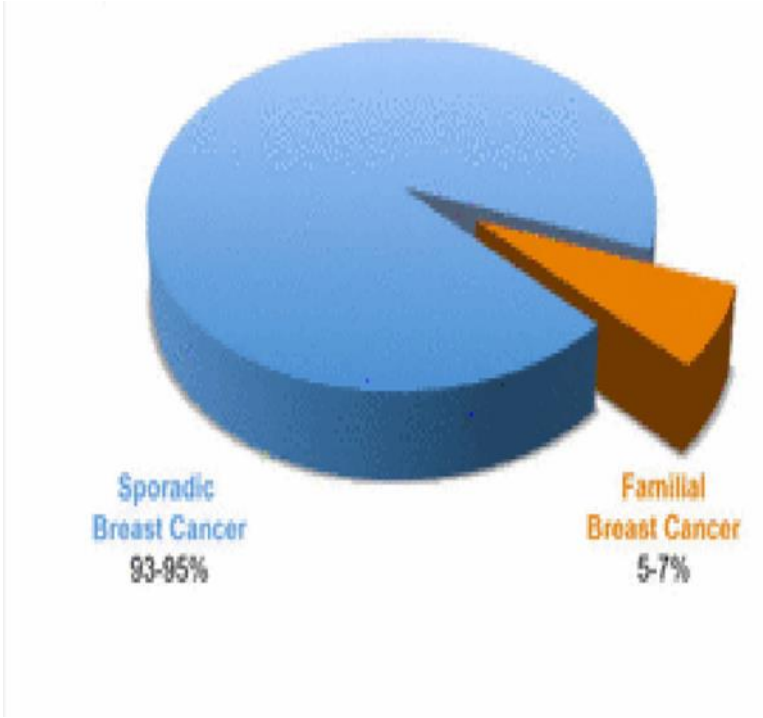
Carcinoma mammario BRCA-correlato Quale terapia sistemica antitumorale?

Dr. Monica Turazza

Negrar, 8 giugno 2017

Sacro Cuore Don Calabria
Negrar - Verona
Ospedale Sacro Cuore Don Calabria
PRESIDIO OSPEDALIERO ACCREDITATO - REGIONE VENETO
Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona
Cancer Care Center
Numero Verde
800 143 143
Numero per la Cura del Tumore

Distribution of breast cancer patients between sporadic forms and germ line mutation forms
(Melchor et al, Human genetics 2013; 132)



CARCINOMI MAMMMARI BRCA1 e 2-mutati

TERAPIA SISTEMICA
Terapia endocrina
Chemioterapia
Terapia a bersaglio molecolare

TERAPIA LOCO-REGIONALE
Chirurgia
Radioterapia

PREVENZIONE/ FOLLOW UP

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

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

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	+	+	+	–	–	+	–

Tend to occur in younger women

Often grow rapidly-DCSI often absent

May or not be associated with a family history of breast and/or ovarian carcinoma

Risultato Test genetico

Negativo o “non informativo”

Positivo o “informativo”

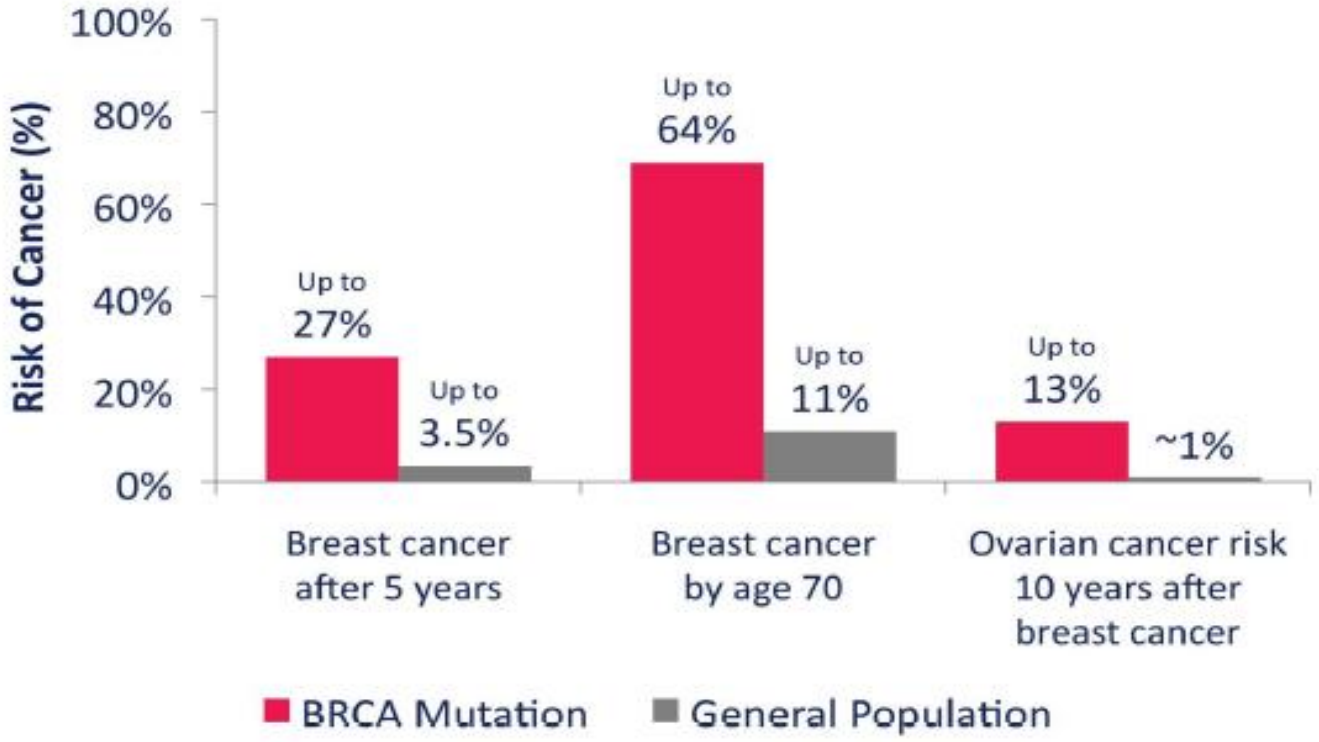
***Informazione**→aumentato rischio di sviluppare:
un tumore mammario controlaterale (**12% a 5 aa in BRCA2-, 20% a 5 aa in BRCA1-)**
un carcinoma ovarico **(63% in BRCA1-, 9-27% in BRCA2-)**

- **Prevenzione SECONDARIA** (DIAGNOSI PRECOCE)
RMN mammaria alternata a eco-mammoRX
Dosaggio Ca125 e Eco transvaginale aternata a visita ginecologica
- **Prevenzione PRIMARIA**→ CHIRURGIA PROFILATTICA
Asportazione di tessuto mammario e/o ovarico
- **Chemioprevenzione**
Utilizzo di farmaci potenzialmente preventivi (in fase sperimentale)

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

LIBERO ARBITRIO DELLA PAZIENTE

BRCA MUTATIONS INCREASE RISK OF A SECOND CANCER



Ca Epi Biomarkers Prev. 1999;8(10):855-61
JNCI 1999;15:1310-6
JCO 1998;16:2417-25
Lancet 1998;351:1316-21
JCO 2004;22:2328-35
Lancet 1994;3343:692-5
Gynecol Oncol 2005 Jan;96(1):222-6
JCO 2010;28(14):2404-10

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

Table

Clinical Factors Which Modulate the Risk of Future Ipsilateral and Contralateral Breast Cancer in *BRCA1/2* Mutation Carriers with Breast Cancer

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

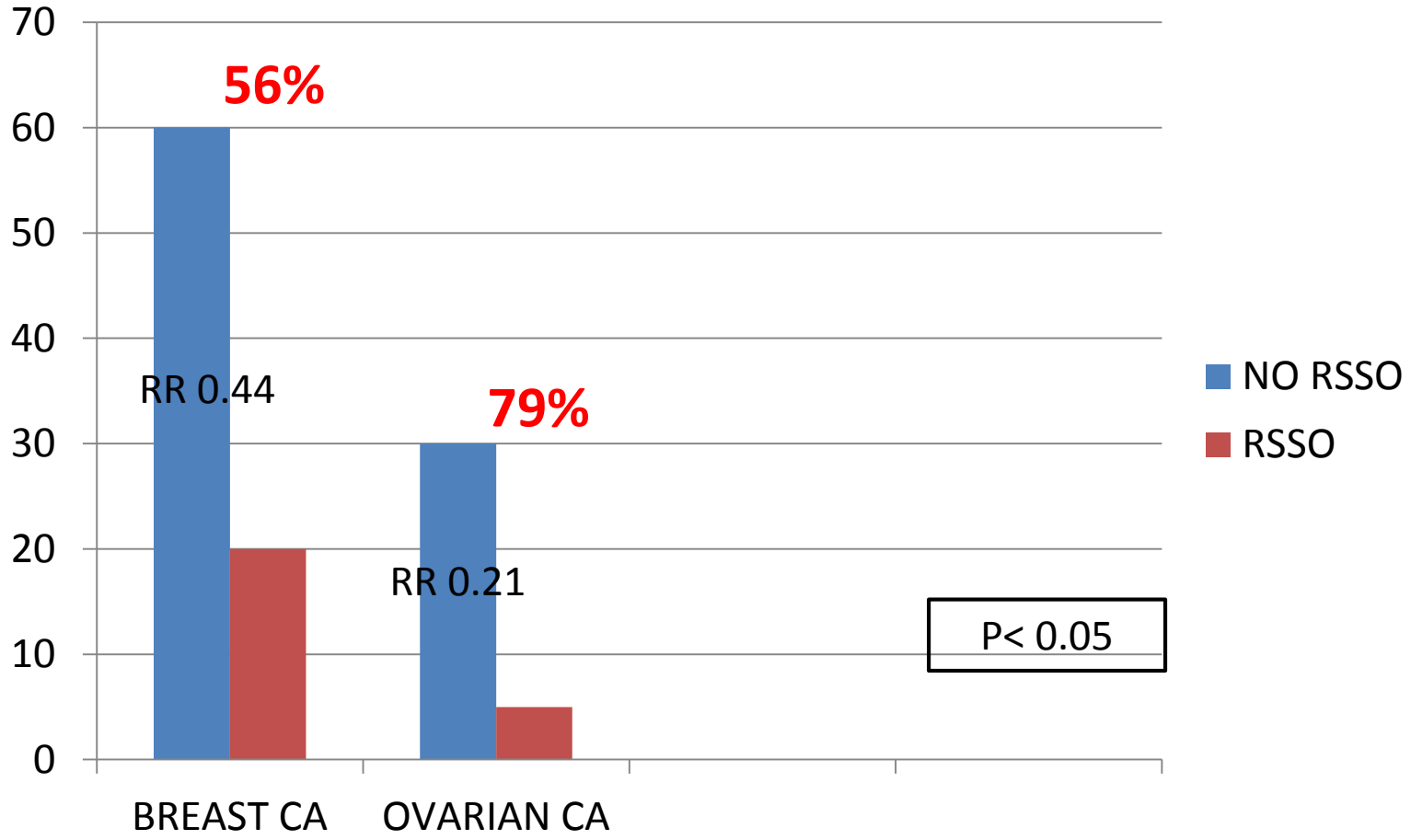
* Reduction in risk demonstrated in some studies, but not confirmed in all studies. Uncertain if this clinical factor independently modulates risk of future ipsilateral and/or contralateral breast cancer in *BRCA1/2* mutation carriers with breast cancer.

Cancer J 2011 November

Published in final edited form as:
JAMA. 2010 September 1; 304(9): 967–975. doi:10.1001/jama.2010.1237.

Association of Risk-Reducing Surgery in *BRCA1* or *BRCA2* Mutation Carriers with Cancer Risk and Mortality

Susan M. Domchek[1,2], Tara M. Friebel[3], Christian F. Singer[4], D. Gareth Evans[5], Henry T. Lynch[6], Claudine Isaacs[7], Judy E. Garber[8], Susan L. Neuhausen[9], Ellen Matloff[10], Rosalind Eeles[11], Gabriella Pichert[12], Laura Van t'veer[13], Nadine Tung[14], Jeffrey N. Weitzel[15], Fergus J. Couch[16], Wendy S. Rubinstein[17], Patricia A. Ganz[18], Mary B. Daly[19], Olufunmilayo I. Olopade[20], Gail Tomlinson[21], Joellen Schildkraut[22], Joanne L. Blum[23], and Timothy R. Rebbeck[1,3]



Risk Reducing Mortality with Salpingo-Oophorectomy in BRCA Carriers

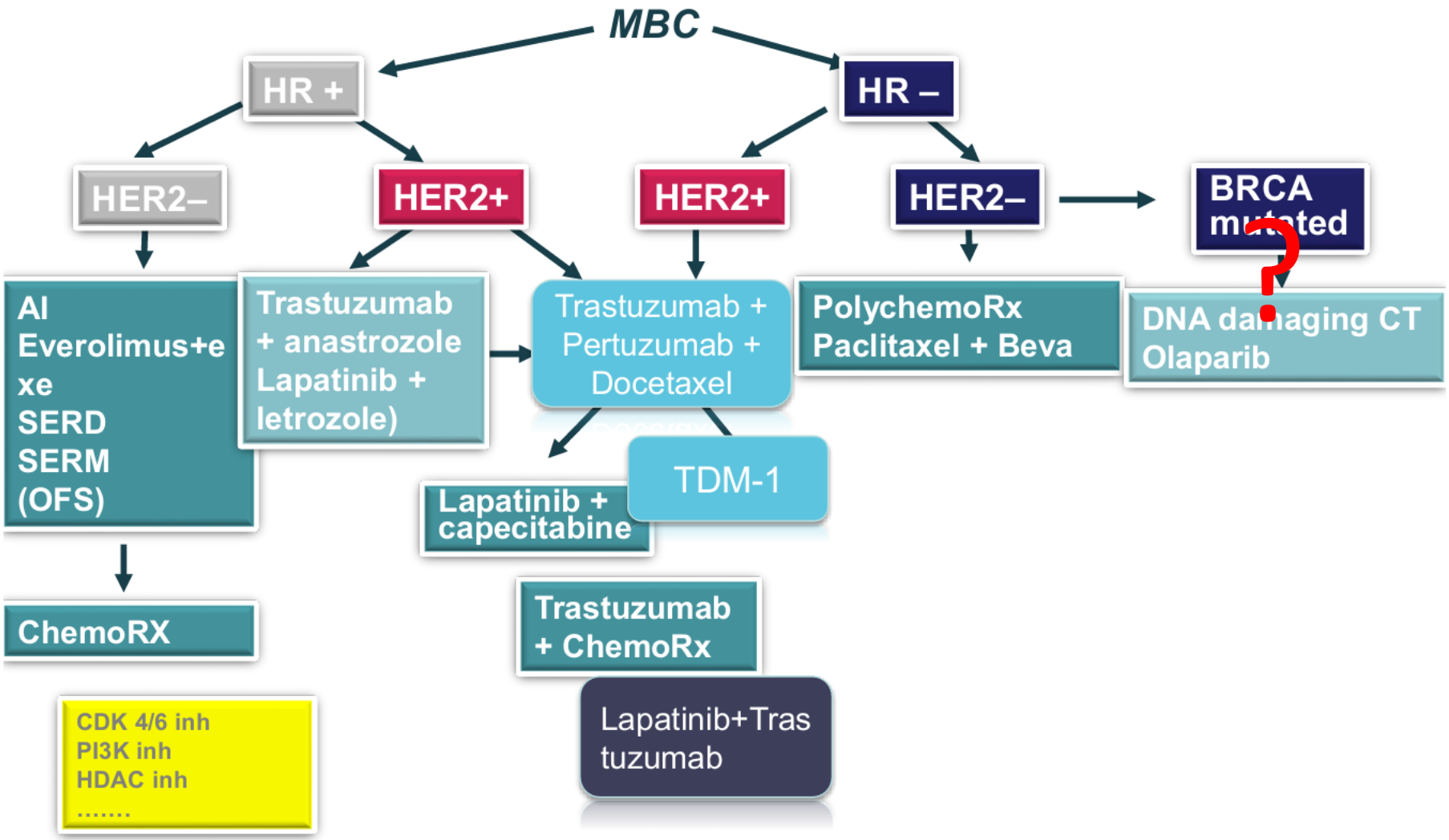
Molecolar and immuno-phenotypic classification

Subtype	These tumors tend to be*	Prevalence (approximate)
Luminal A	ER+ and/or PR+, HER2-, low Ki67	40%
Luminal B	ER+ and/or PR+, HER2+ (or HER2- with high Ki67)	20%
Triple negative/basal-like	ER-, PR-, HER2-	15-20%
HER2 type	ER-, PR-, HER2+	10-15%

Subtype-specific general systemic strategies in adjuvant setting

- HR+/HER2- and "low risk":
  - Endocrine therapy without chemotherapy
- HR+/HER2- and "high risk"
  - Conventionally dosed AT-based chemotherapy
  - Dose dense & escalated in case of high tumor burden
  - Followed by endocrine therapy
- HER2+
  - Trastuzumab plus
    - Sequential A/T-based regimen with concurrent T + H
    - Anthracycline-free, carboplatin-cont. regimen

TREATMENT OPTIONS in METASTATIC BREAST CANCER



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

Identification of articles:

(BRCA* mutation) AND (*survival* or *prognosis* or outcome or mortality or relapse or recurrence) AND (*breast neoplasms* or breast neoplasm or breast cancer or breast tumor)

no limits set; until 08-2013

+ references cited in review papers were hand searched

N = 1067 articles retrieved and summaries reviewed for subject appropriateness

Data extraction and quality assessment of selected articles: N=66 contained 73 studies

Overall survival
breast cancer specific-survival
metastasis-free survival
recurrence-free survival

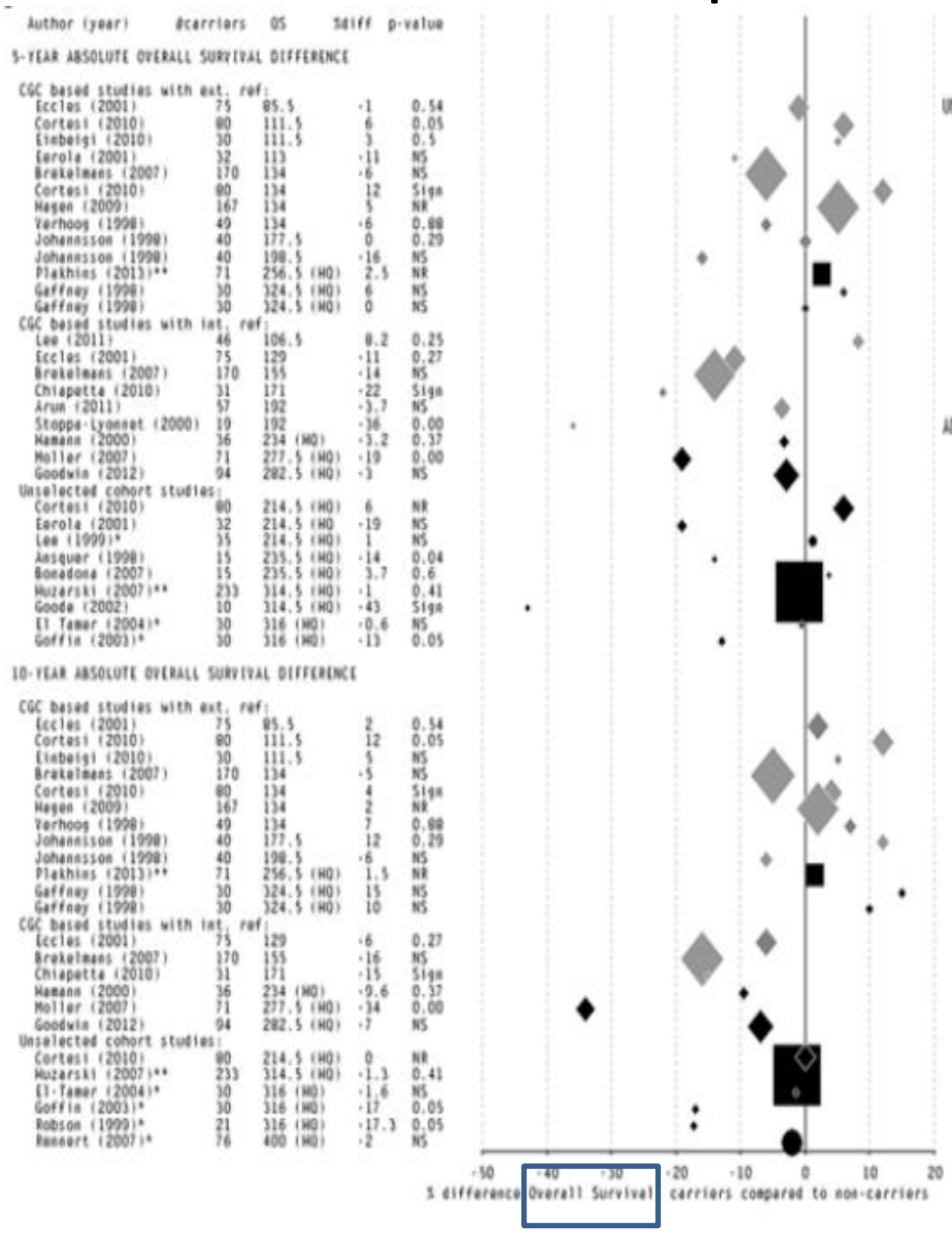
BRCA1
BRCA2
BRCA1 e 2

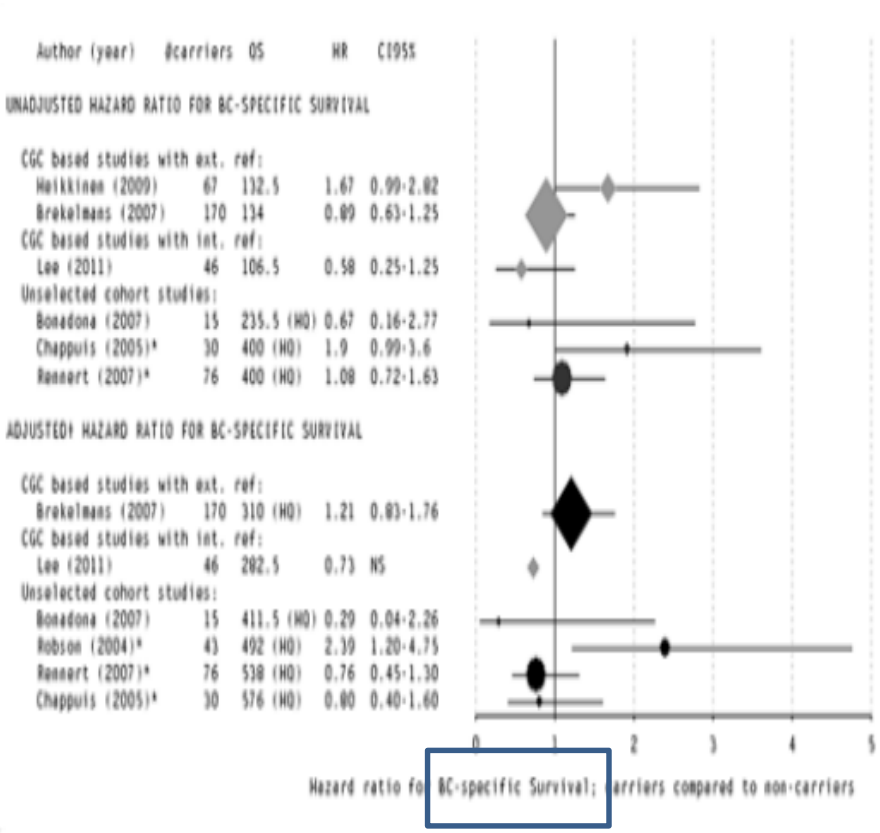
vs

Non-carriers

Cut-offs arbitrarily chosen for carriers vs no-carriers to have a clinical rilevance was:
Better survival as an absolute survival difference ≥10% or a risk estimate ≤0.88;
Worse survival as an absolute survival difference ≥ 10% or a risk estimates ≥ 1.14
No association as an absolute survival difference < 10% and risk estimate between 0.88 and 1.14

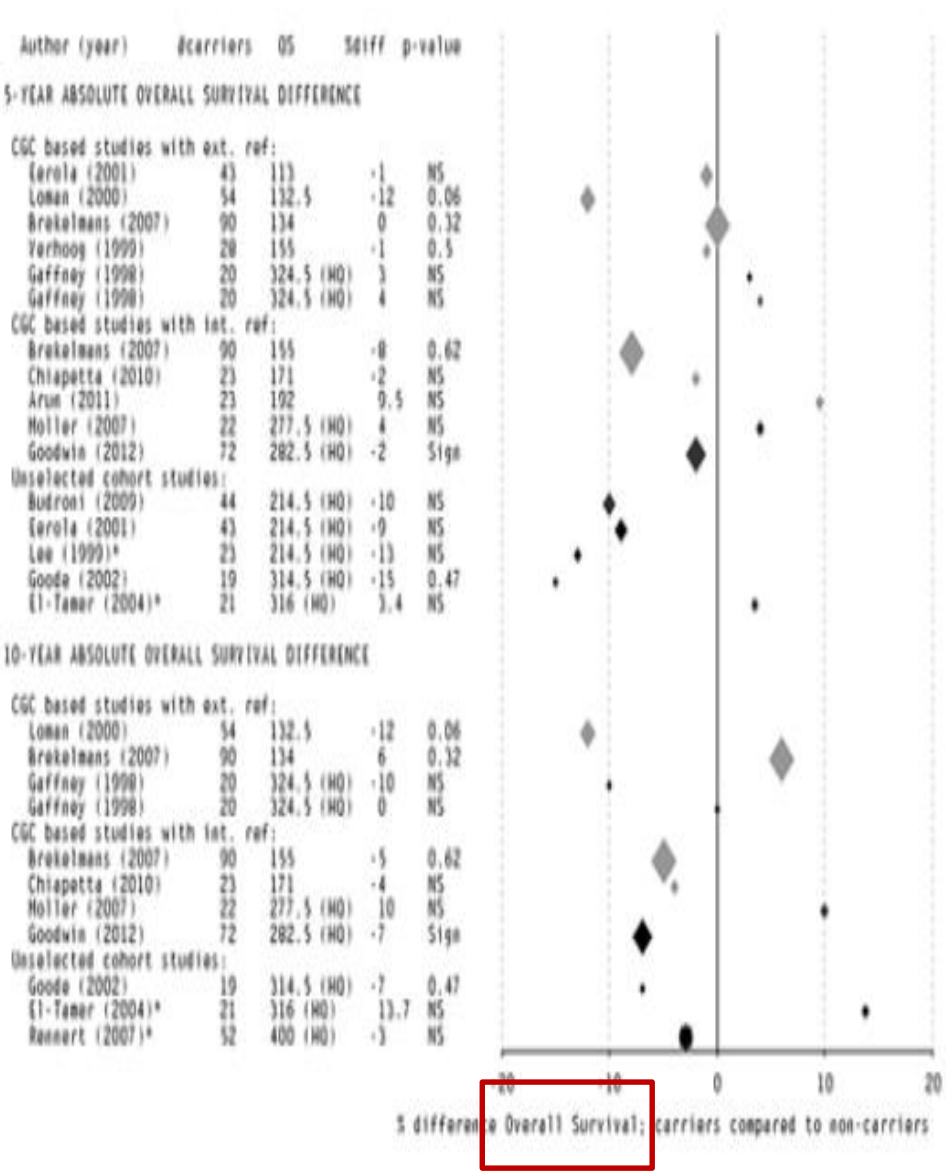
Forest plot of studies reporting survival estimates for «BRCA1-carriers» compared to «non-carrriers»

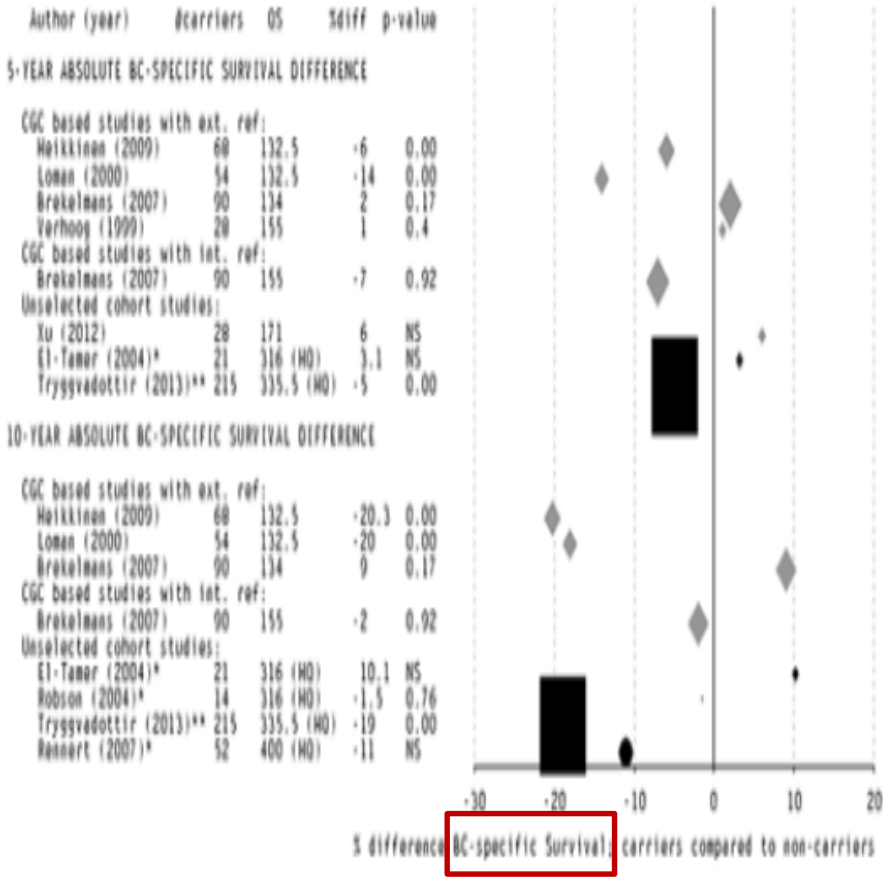




- difference show «inconsistent results»
- none of the pooled estimates were statistically significant

Forest plot of studies reporting survival estimates for «BRCA2-carriers» compared to «non-carriers»





- tendency to worse overall survival for BCRA2 carriers vs non-carriers
- Absolute survival difference below 10% and the results inconsistent

Effects of confounders/mediating factors on the association between BRCA1 and BRCA2 mutation carriership and prognosis

- BRCA1 mutation exhibit different pathological characteristics compared to tumors in «non-carriers» leading to treatment differences
- Only 32 studies reported HRs adjusted for tumor characteristics/treatment

↓

Compared pairs of an HR unadjusted and HR adjusted

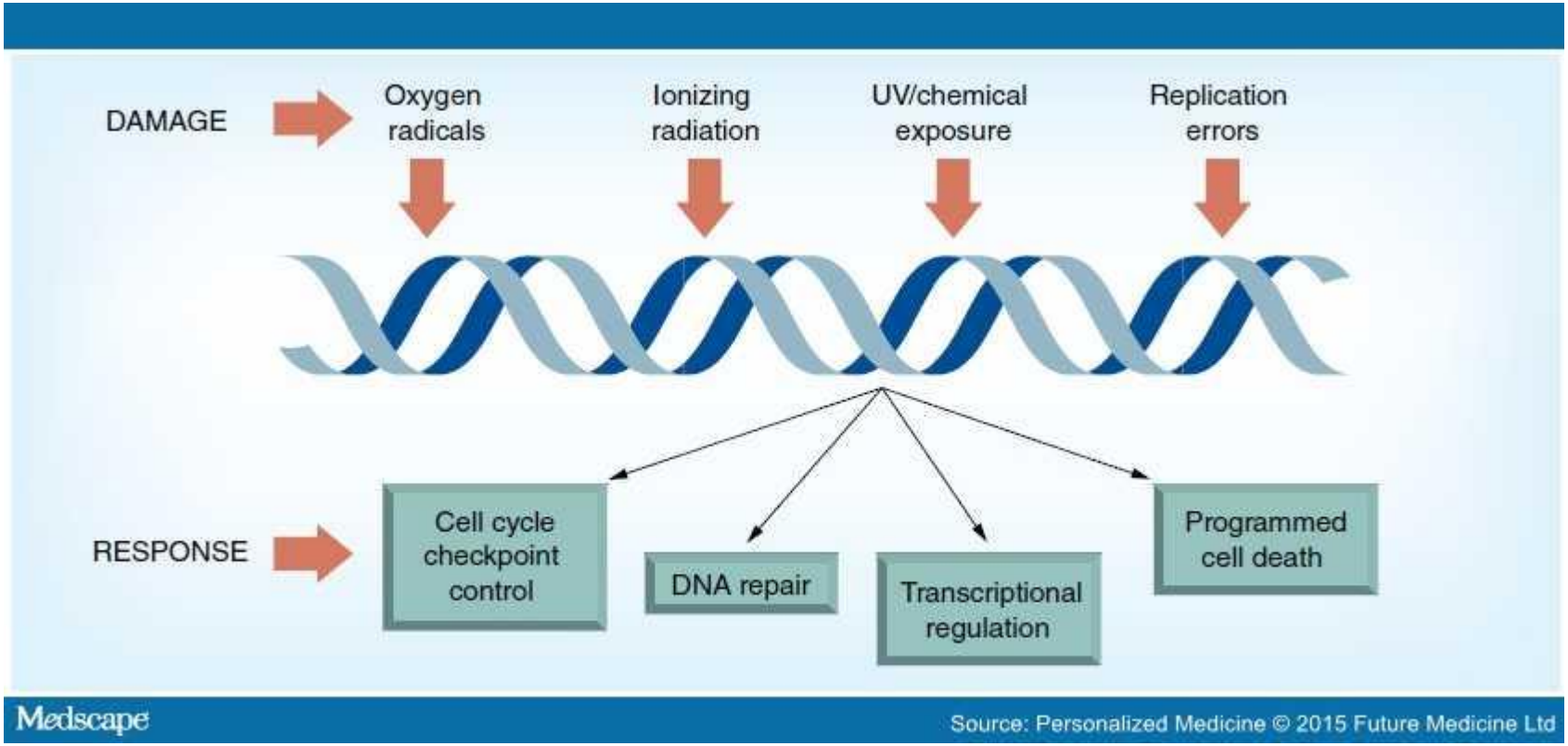
↓

Systemic treatments (ADJUVANT CHEMOTHERAPY) makes difference

BRCA1-carriers vs «non-carriers» :no difference in survival if treated with «chemo»

BRCA2-carriers vs «non-carriers» :worse outcome for BRCA2-carriers «no- chemo» treated

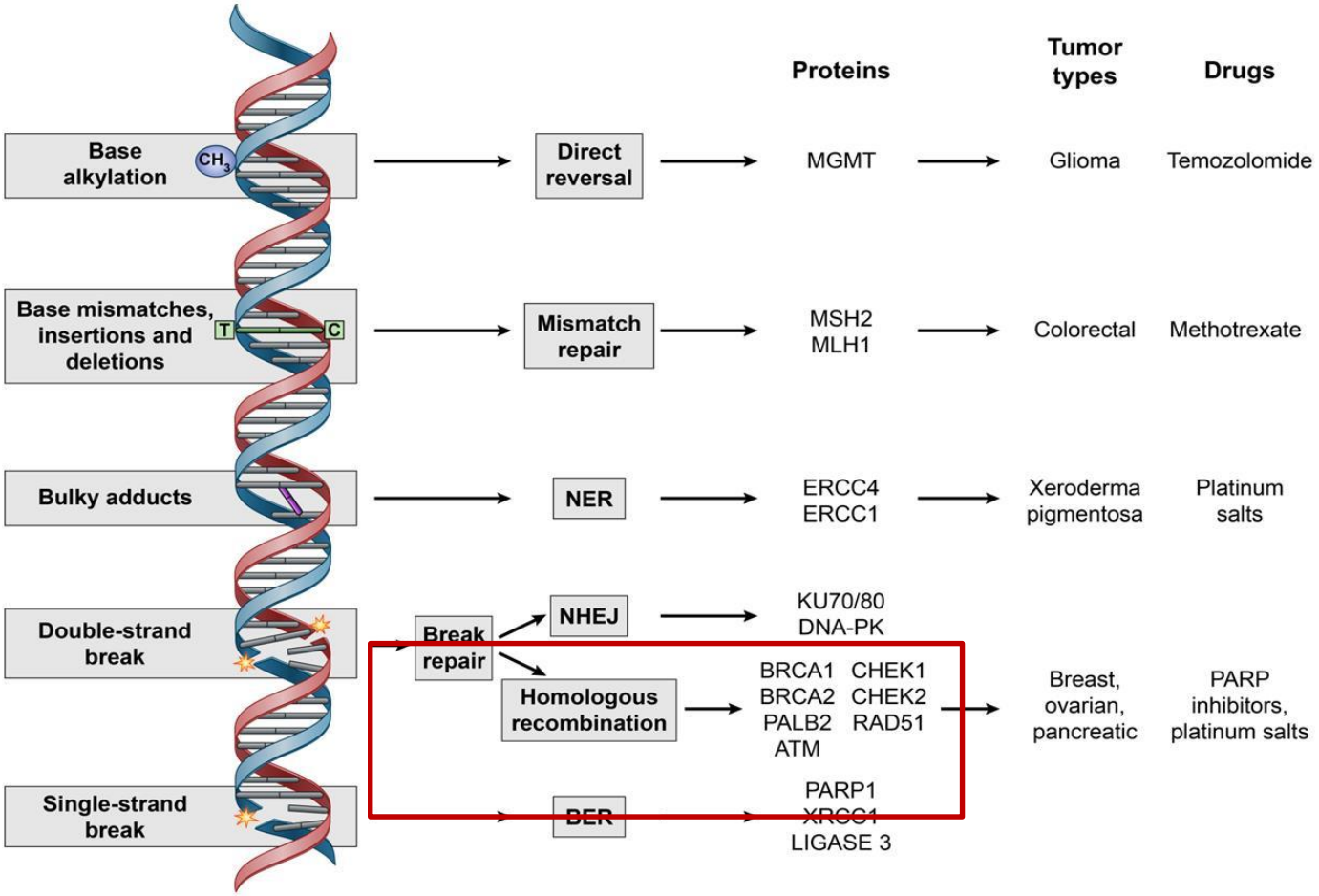
AJ van den Broek et al, Plos ONE, March 2015



Medscape

Source: Personalized Medicine © 2015 Future Medicine Ltd

DNA Repair Mechanisms Maintain Genomic Stability



Lord CJ, et al. *Nature*. 2012;481:287-294.[2]

Original Article

The Efficacy of Taxane Chemotherapy for Metastatic Breast Cancer in BRCA1 and BRCA2 Mutation Carriers

Mieke Kriege, PhD[1]; Agnes Jager, MD, PhD[1]; Maartje J. Hooning, MD, PhD[1]; Elisabeth Huijskens[1]; Jannet Blom[1]; Carolien H. M. van Deurzen, MD, PhD[2]; Marijke Bontenbal, MD, PhD[1]; J. Margriet Collee, MD[3]; Marian B. E. Menke-Pluijmers, MD, PhD[4]; John W. M. Martens, PhD[1]; and Caroline Seynaeve, MD, PhD[1]

Background

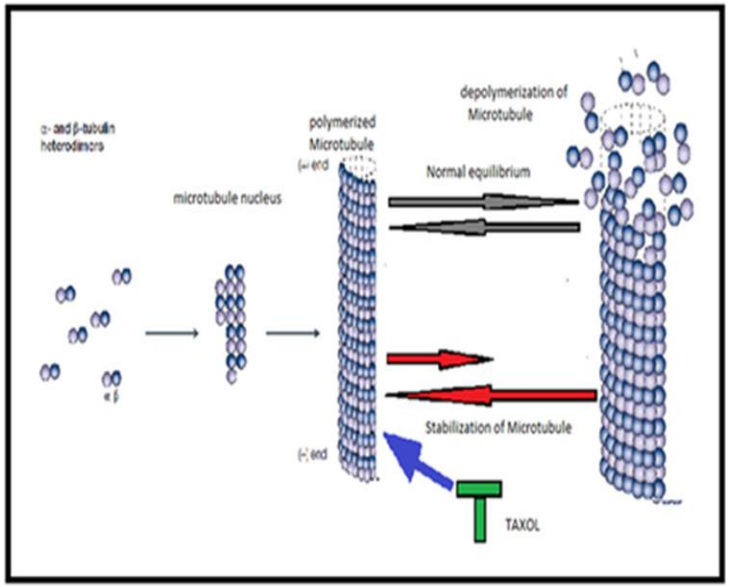
To assess the efficacy of taxane chemotherapy in BRCA1 and BRCA2-associated patients compared with sporadic metastatic breast cancer patients

Method:

To compare response rate and progression free survival after taxane chemotherapy of 35 BRCA1-associated metastatic breast cancer, 13 BRCA2-associated metastatic breast cancer and 95 matched (1:2) sporadic patients.

Matching was performed for age and year of diagnosis of primary breast cancer, year of metastatic disease and line of therapy (first vs second vs third)

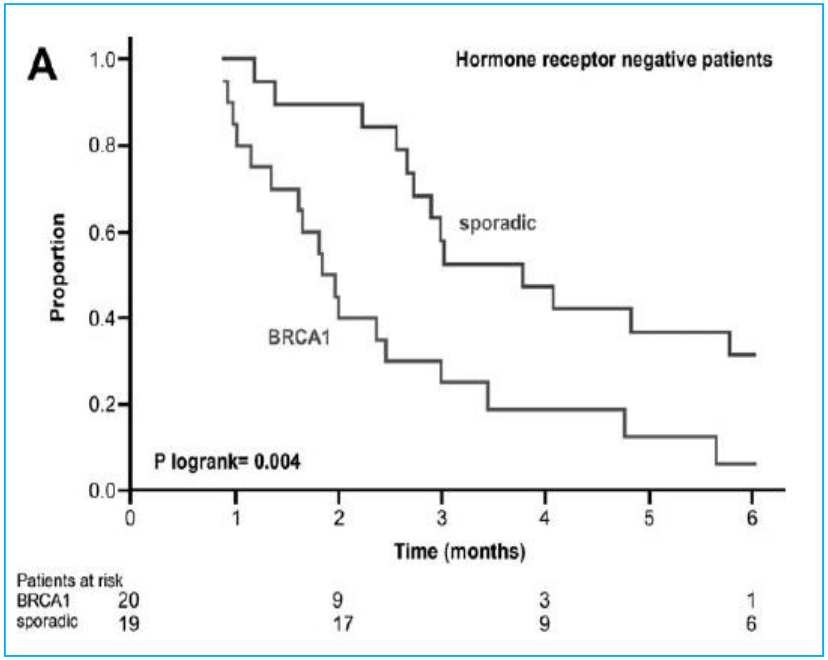
Cancer, feb 15 2012

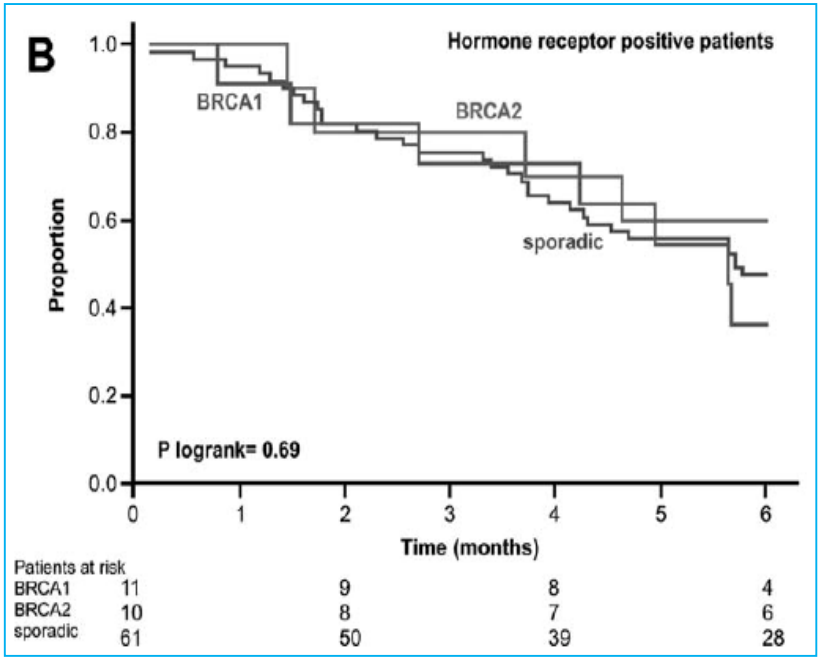


Mechanism of action of «Taxol»

RESULTS

Progression free survival





CONCLUSION

BRCA1-associated, HR-negative metastatic breast cancer were less sensitive to «taxanes» chemotherapy than sporadic HR-negative patients

CONCLUSION

BRCA1 and BRCA2 and HR-positive associated patients had a sensiivit to taxane chemotherapy similar to sporadic patients.

Cancer, feb 15 2012

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

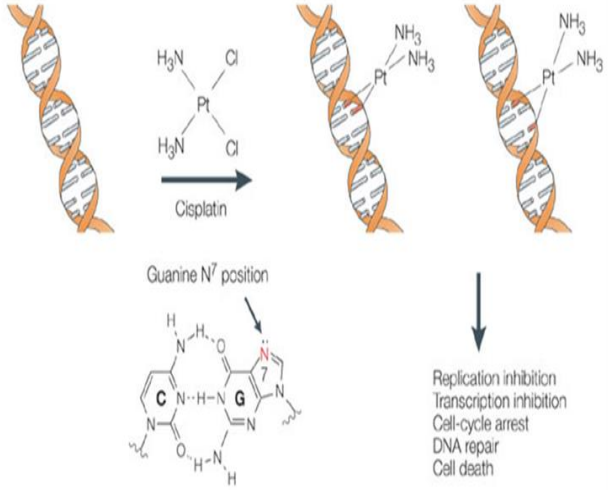
Patients and Methods

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.



Mechanism of action of «Platinum»

Genomic alteration in TNBC unselected age and family history in litterature:
BRCA1 mutations 9-28%
BRCA2 mutations 4-17%

Recomended BRCA1/2 testing in diagnosis of TNBC< 60 years of age

TRIPLE NEGATIVE BREAST CANCER

No target therapy

(lack of Estrogen and progesterone receptors)
(lack of overespression/amplification of the HER2)

Deficency to DNA repair process

(Homologous recombinant deficiency or **HRD**)

Increased sensitivity to platinum salts

BRCA 1/2 MUTATED-BREAST CANCER

Basal-like gene expression profile

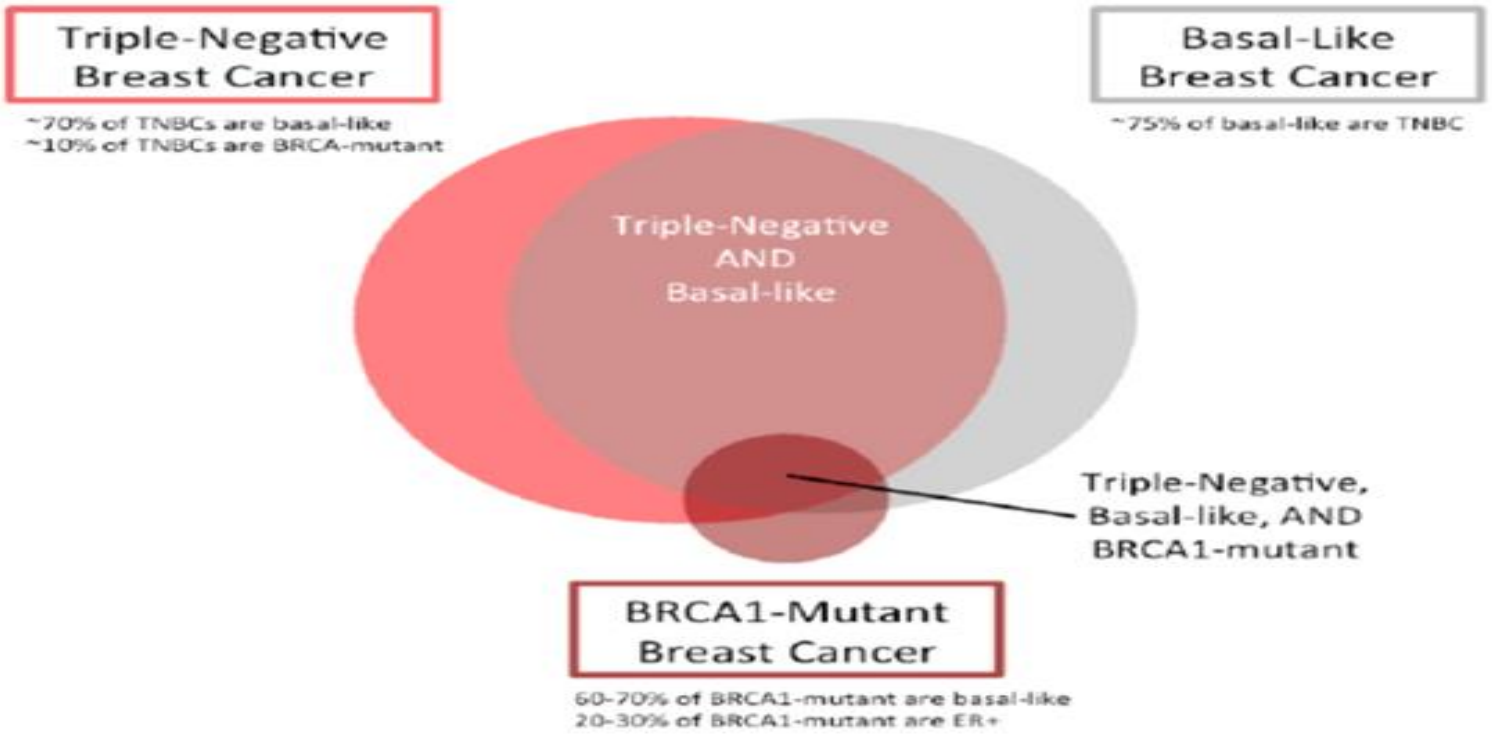
High burden of genomic aberrations

Deficency to DNA repair process

(including homologous recombinant deficiency or **HRD**)

Increased sensitivity to platinum salts

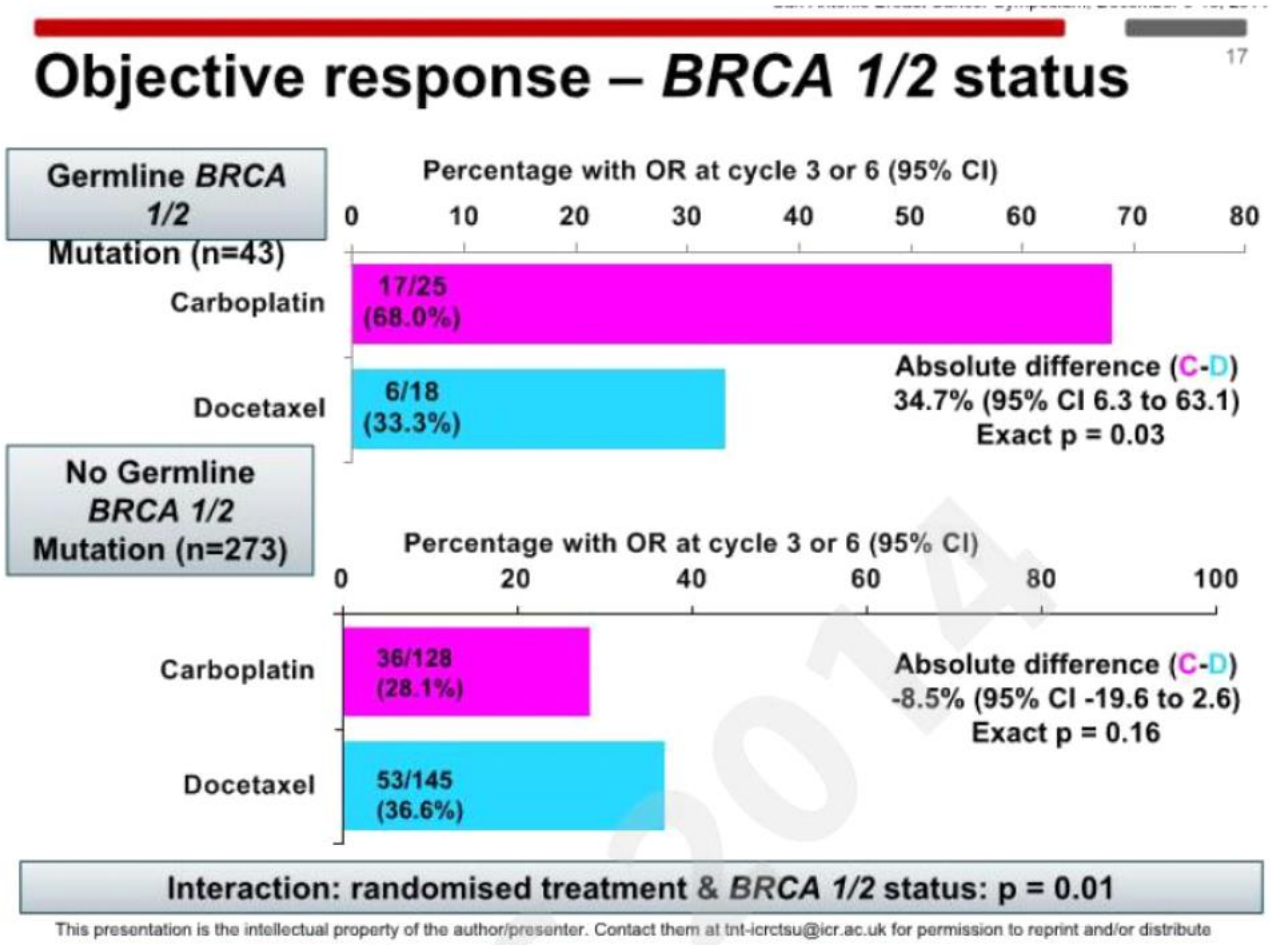
FIGURE 1. Overlap of Triple-Negative, Basal-like, and *BRCA1*-Mutant Breast Cancers.



Proportional representation of the overlap among triple-negative, basal-like, and *BRCA1*-mutant breast cancers. Most TNBC are basal-like (BLBC) and vice versa. While most *BRCA1*-mutant breast cancers are both TNBC and BLBC, only a small proportion of total TNBCs or BLBCs are *BRCA1*-mutant. Venn diagram created with BioVenn.[53]

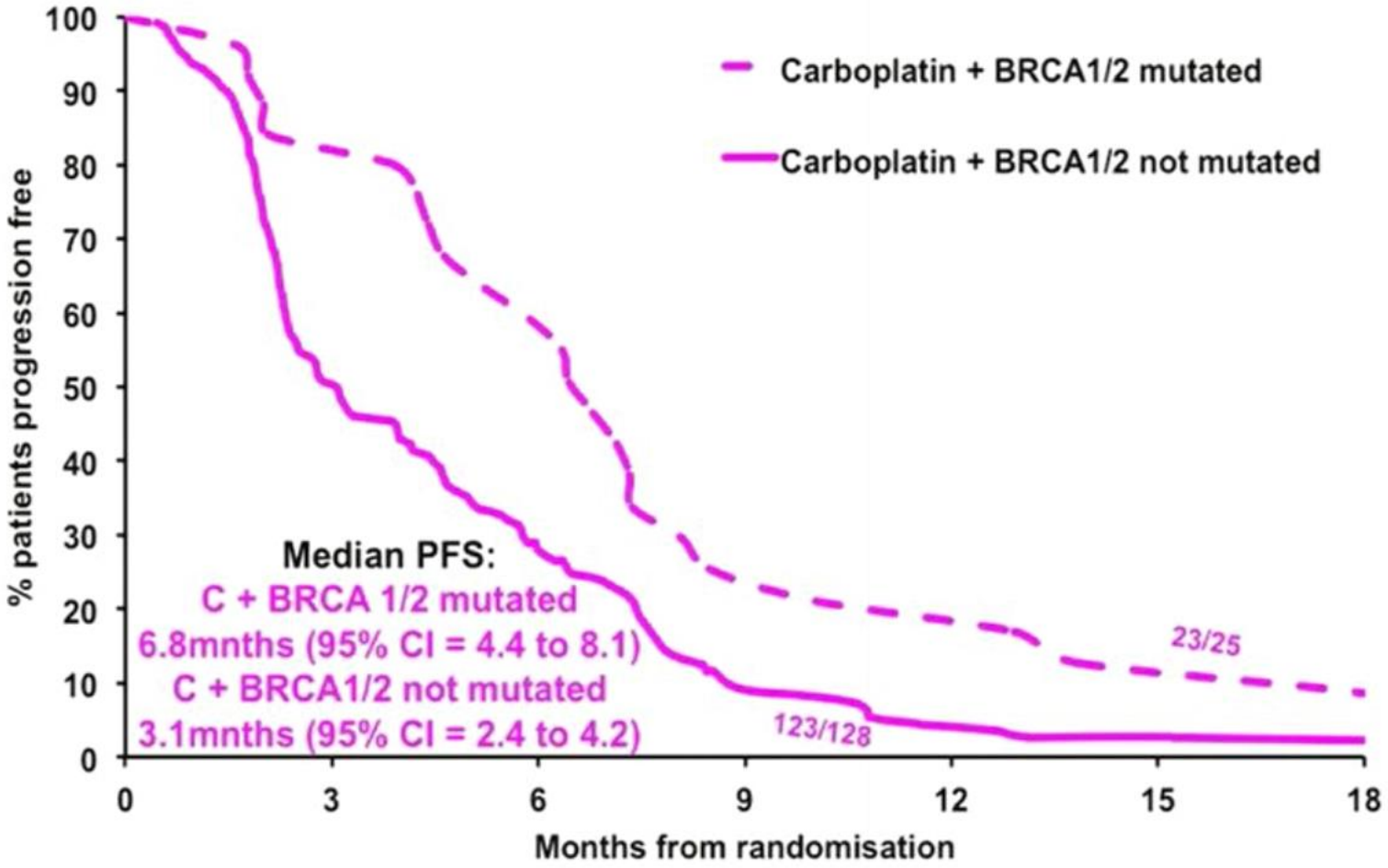
The American Journal of Hematology/Oncology 12 (3), 2016

TNT: Carboplatin vs Docetaxel as 1st line for TNBC



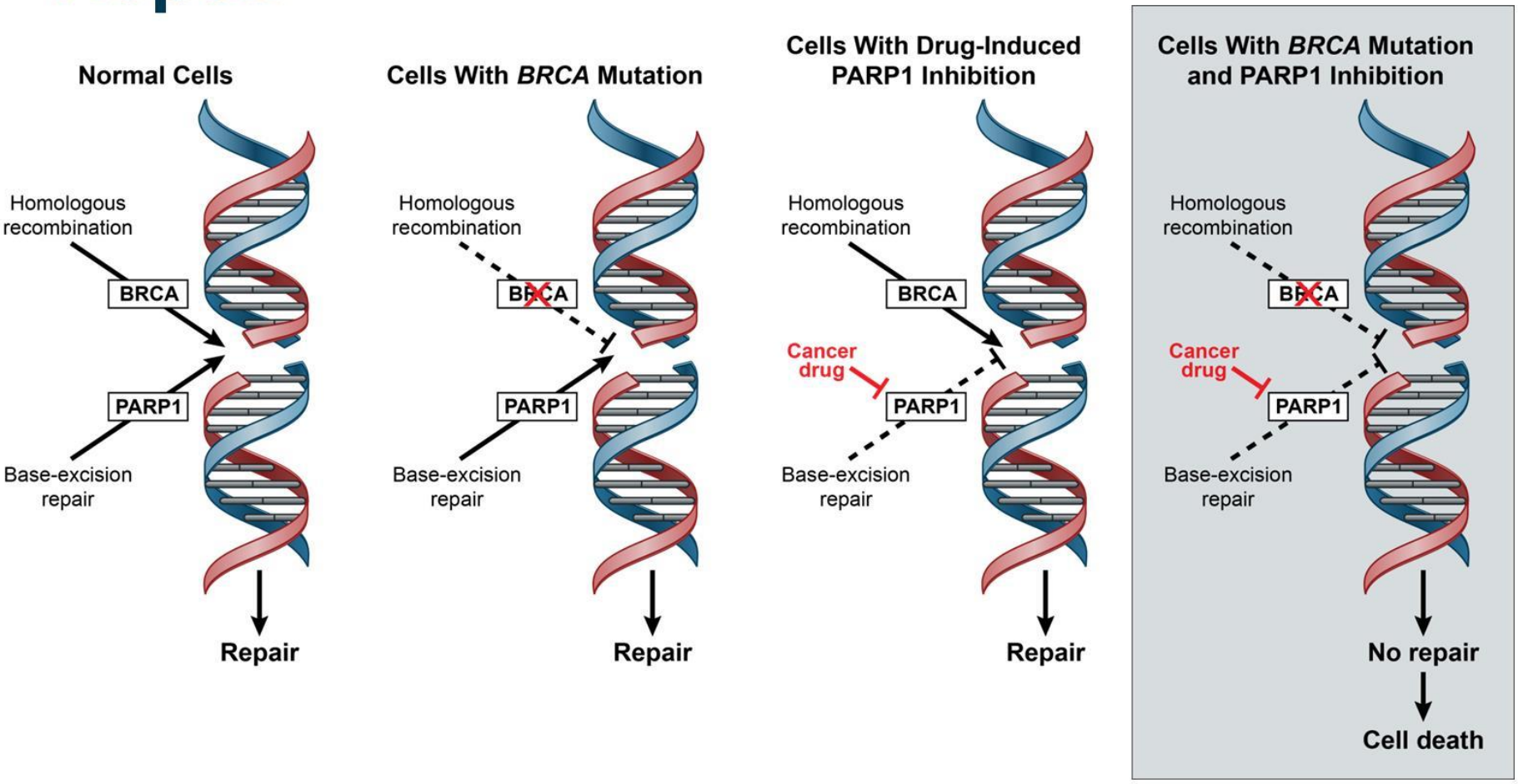
Tutt A, SABCS 2014

PFS – *BRCA 1/2* status



Tutt A, SABSC 2014

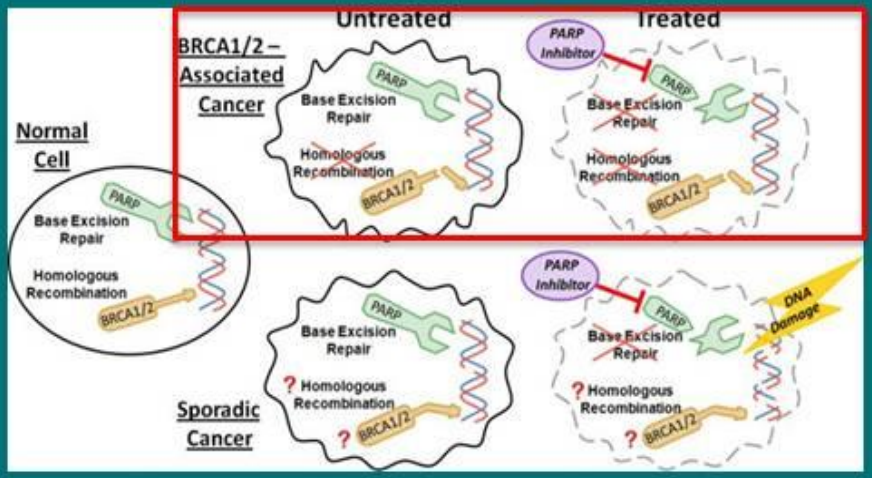
DNA Repair: Role of Homologous Recombination and Base-Excision Repair

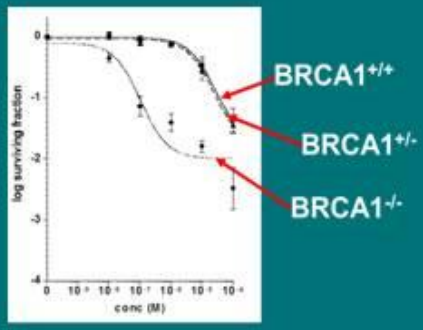


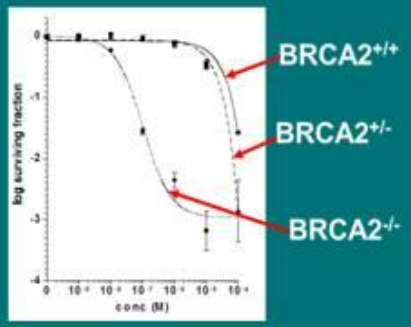
Iglehart JD, et al. *N Engl J Med.* 2009;361:189-191.[3]

PARP Inhibitor Treatment of BRCA1/2-Associated Cancer

- PARP plays important role in repair of DNA single-strand breaks via BER.
- BRCA1/2 is required for efficient repair of DNA damage i.e. homologous recombination.
- Cells with BRCA mutations are deficient in homologous recombination and lack the ability to efficiently repair double-strand breaks.







BRCA1- and BRCA2-deficient cells are extremely sensitive to PARP inhibitors, compared to wild-type cells.

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

Ellisen LW et al. Cancer Cell 2011; 19:165-167
Farmer H et al. Nature 2005; 434:917-921

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Antoinette Tan at 2015 ASCO Annual Meeting

PARP Inhibitors in Clinical Development

	Company	Route	Dose	Phase
Olaparib* AZD2881	AstraZeneca	Oral	400 mg po BID	I, II, III
Rucaparib** AG014699 PF-01367338	Clovis Oncology	PO	600 mg po BID	I, II, III
Veliparib ABT-888	Abbott	Oral	400 mg po BID	I, II, III
Niraparib MK-4827	Tesaro	Oral	300 mg po BID	I, II, III
Talazoparib BMN 673	Biomarin	Oral	1 mg po QD	I, II, III

*Approved in BRCA-mutated advanced ovarian cancer treated with 3 or more lines of chemotherapy
**Granted Breakthrough Therapy Designation in BRCA-mutated pretreated ovarian cancer

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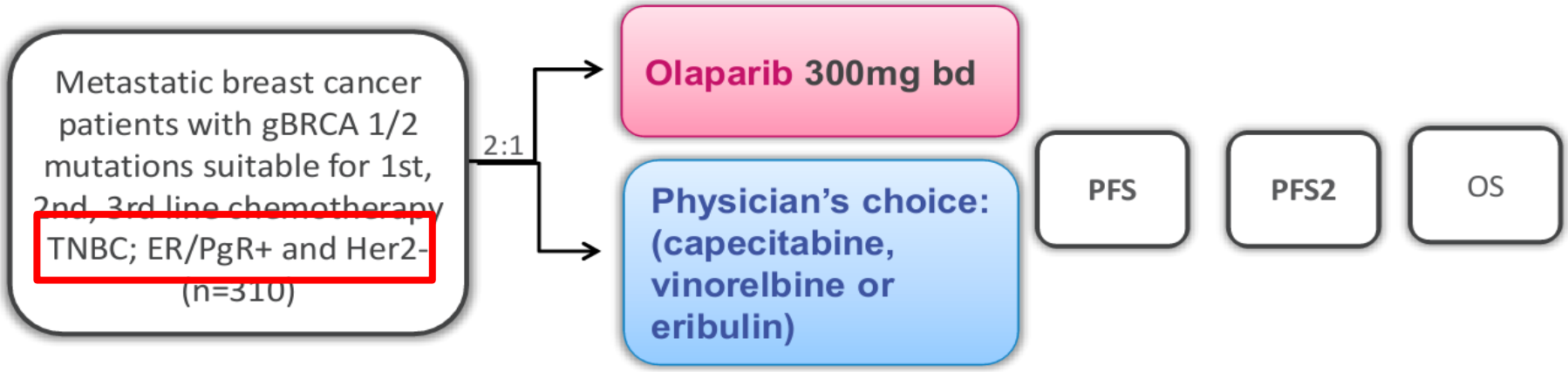
PRESENTED AT: ASCO Annual '15 Meeting

Presented By Antoinette Tan at 2015 ASCO Annual Meeting

Olympiad

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



Primary Objective: efficacy of single agent olaparib vs chemotherapy by PFS
Safety Objective: safety and tollerability of olaparib vs chemotherapy
Secondary Objective: OS, ORR

ESTIMATION COMPLETATION DATE: december 2018
Worldwide sites recruitment: 121 (4 in Italy)

OLYMPIAD - Primary Analysis (From ASCO Meeting, June 2017)	Olaparib	Pysician's choice chemotherapy	
Number of patients	205	92	
dead	45.9%	47.4%	
Median time to death	19.3 months	19.6 months	p= NS
AT 77% DATA MATURITY			
Progression free survival	7 months	4.5 months	HR 0.58 p=0.009
Objective Response Rate	59.9%	28.8%	
Median time from randomization to a 2°progression event or death after a 1° progression	13.2 months	9.3 months	HR 0.57 P=0.03
Rate treatment discontinuation due to toxicity	4.9%	7.7%	
Rate of Grade 3 of adverse events	36.6% Anemia, nausea, fatigue, Cough, headhache	50.5% Neutropenia, Palmar-plantar erythrodysestesia, increase of liver function enzymes	

AstraZeneca

BIG

NSABP

Revised Clinical Study Protocol

Drug Substance	Olaparib (AZD2281)
Study Code	D081CC00006
Study Number	BIG 6-13, NSABP B-55
Edition Number	1
Date	14 March 2014

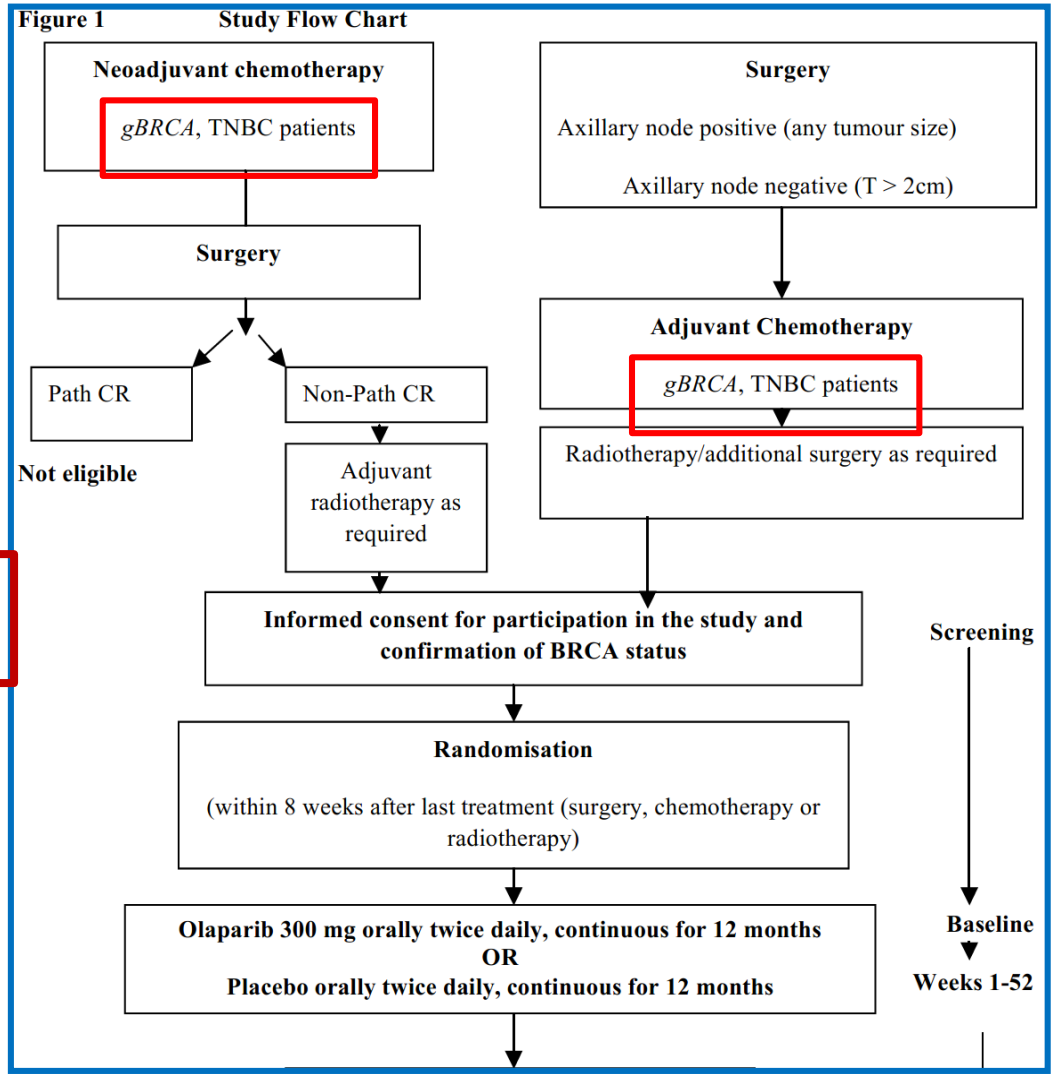
(OLYMPIA study)

Olaparib in Adjuvant BRCAm Breast Cancer

A randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA1/2* mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy

PROTOCOLLO DI RICERCA ATTIVO c/o Oncologia di Negrar

Figure 1 Study Flow Chart

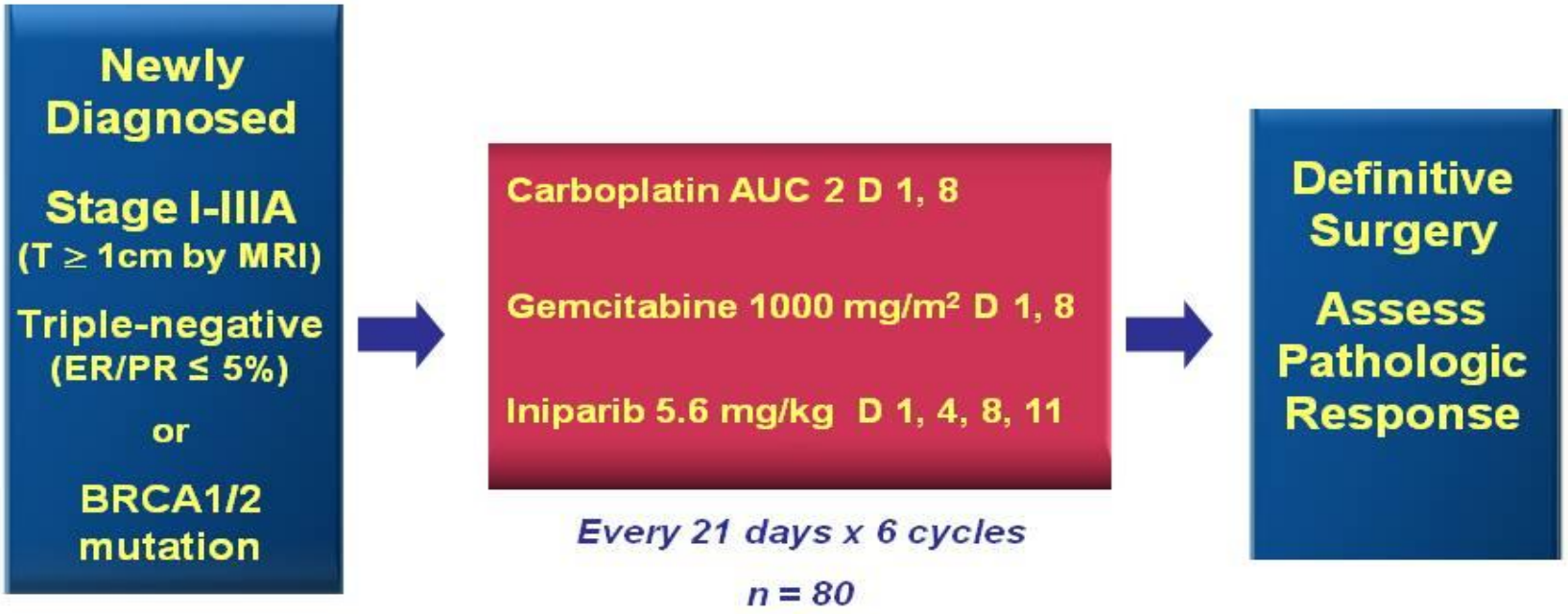


2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to assess the effect of adjuvant treatment with olaparib on Invasive Disease Free Survival (IDFS).

PrECOG 0105 Schema



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

PRESENTED AT: ASCO Annual '13 Meeting

Presented By Judy Ellen Garber, MD, MPH at 2013 ASCO Annual Meeting

Results

Intent-to-treat population

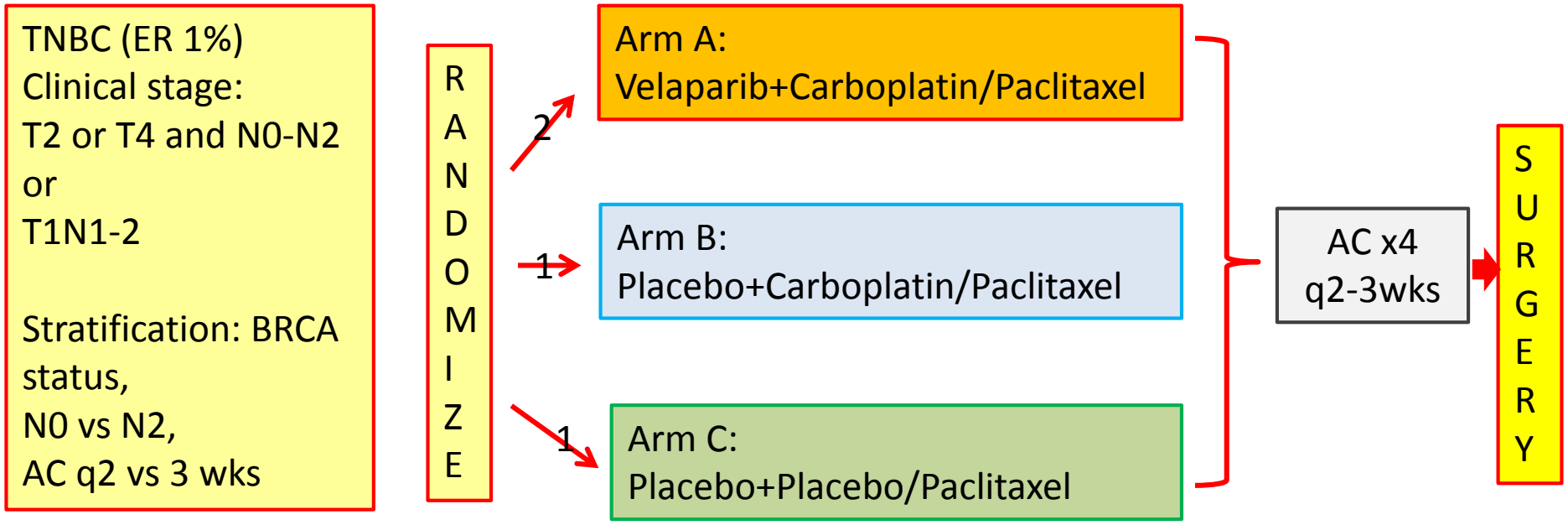
Pathologic Response (n=80)	All patients n = 80	BRCA 1/2 wild-type n = 61	BRCA 1/2 mutant n = 19	TN & BRCA 1/2 mutant n = 16
pCR [RCB 0]; n (%)	29 (36%)	20 (33%)	9* (47%)	9* (56%)
90% CI	27–46	23–44	27-68	33-77
RCB 0/1; n (%)	45 (56%)	31 (51%)	14 (74%)	12 (75%)
90% CI	46-66	40-62	52-89	52-91

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

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of the author.

Presented By Judy Ellen Garber, MD, MPH at 2013 ASCO Annual Meeting

PARP INHIBITOR IN THE NEOADJUVANT SETTING: THE BrighTNess randomized phase III Trial.



Primary end point: pCR breast/axilla

Velaparib 50mg PO BID x12 wks; Carboplatin AUC 6 IV q3 wks, Paclitaxel 80mg/m2 IV weekly x12; AC: doxorubicin 60 mg/m2 and cyclophosphamide 600mg/m2

Published OnlineFirst March 8, 2016; DOI: 10.1158/1078-0432.CCR-15-2477

Cancer Therapy: Clinical

Clinical Cancer Research

Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer

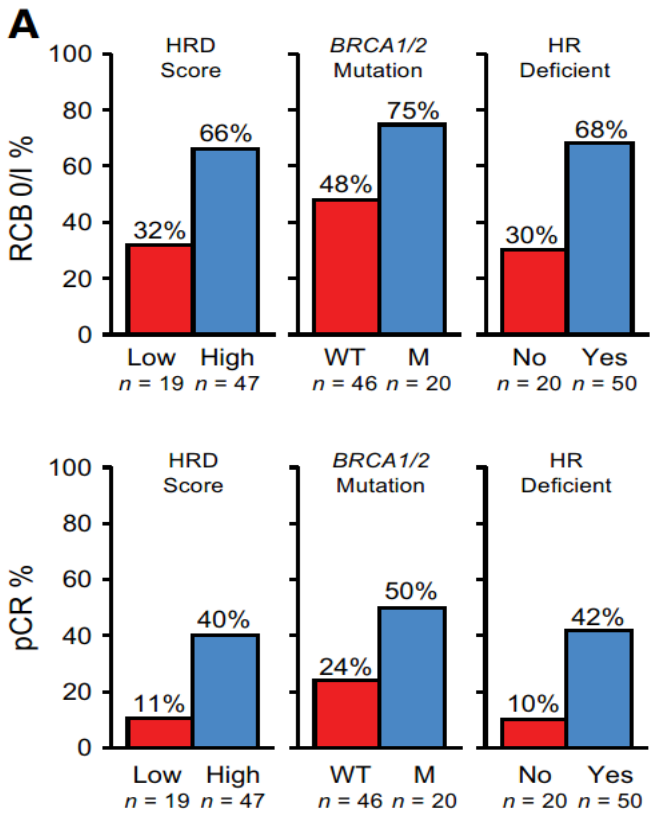
Melinda L. Telli[1], Kirsten M. Timms[2], Julia Reid[2], Bryan Hennessy[3], Gordon B. Mills[3], Kristin C. Jensen[1], Zoltan Szallasi[4,5,6], William T. Barry[6,7], Eric P. Winer[6,7], Nadine M. Tung[6,8], Steven J. Isakoff[6,9], Paula D. Ryan[9], April Greene-Colozzi[7], Alexander Gutin[2], Zaina Sangale[2], Diana Iliev[2], Chris Neff[2], Victor Abkevich[2], Joshua T. Jones[2], Jerry S. Lanchbury[2], Anne-Renee Hartman[2], Judy E. Garber[6,7], James M. Ford[1], Daniel P. Silver[6,7], and Andrea L. Richardson[6,7,10]

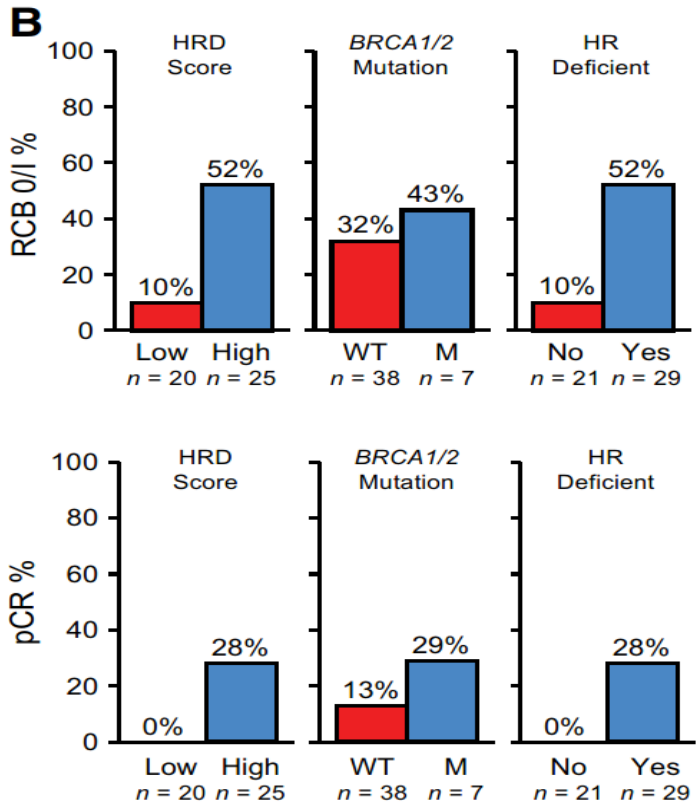
HRD Assay is a next-generation sequency assay to label a tumor homologous recombination (deficency or not) by combining the HRD score generated and the BRCA 1/2 mutation status of the tumor.

HRD as PREDICTIVE MARKER FOR PLATINUM SENSITIVITY

personalize the use of platinum agents

avoid unnecessary toxicity if no benefit





PrECOG 0105 trial

single arm phase II study

I-IIIA, TNBC or BRCA 1-2 germline-associated breast cancer

Gemcitabine1000mg/m2/iv/d1,8 +

Carboplatin AUC2/iv/d1,8 and

Iniparib 5,6mg/Kg/iv/d1,4,11 q21

Neoadjuvant cisplatin trial

II or III TNBC or BRCA 1-2 germiline associated breast cancer

1) Cisplatin75mg/m2 q21x 4 cycles 2) Cisplatin 75mg/m2+Bevacizumab 15mg/Kg d1 for the first 3 cycles

HRD: score $\geq$ 42; **BRCA1/2 mutation**: mutated tumors; **HR deficent**: defined as HRD $\geq$ 42 or BRCA1/2 mutation

RCB (residual cancer burden) 0=pCR;I=minimal res disease;II=moderate res disease;III=extensive res disease

Cancer Cell (2011)
Article

BRCA1 RING Function Is Essential for Tumor Suppression but Dispensable for Therapy Resistance

Rinske Drost,[1,2] Peter Bouwman,[1,2] Sven Rottenberg,[1,2] Ute Boon,[1,2] Eva Schut,[1,2] Sjoerd Klarenbeek,[1,2] Christiaan Klijn,[1,2] Ingrid van der Heijden,[1,2] Hanneke van der Gulden,[1,2] Ellen Wientjens,[1,2] Mark Pieterse,[1,2] Aurelie Catteau,[3] Pete Green,[3] Ellen Solomon,[3] Joanna R. Morris,[3,4,*] and Jos Jonkers[1,2,*]
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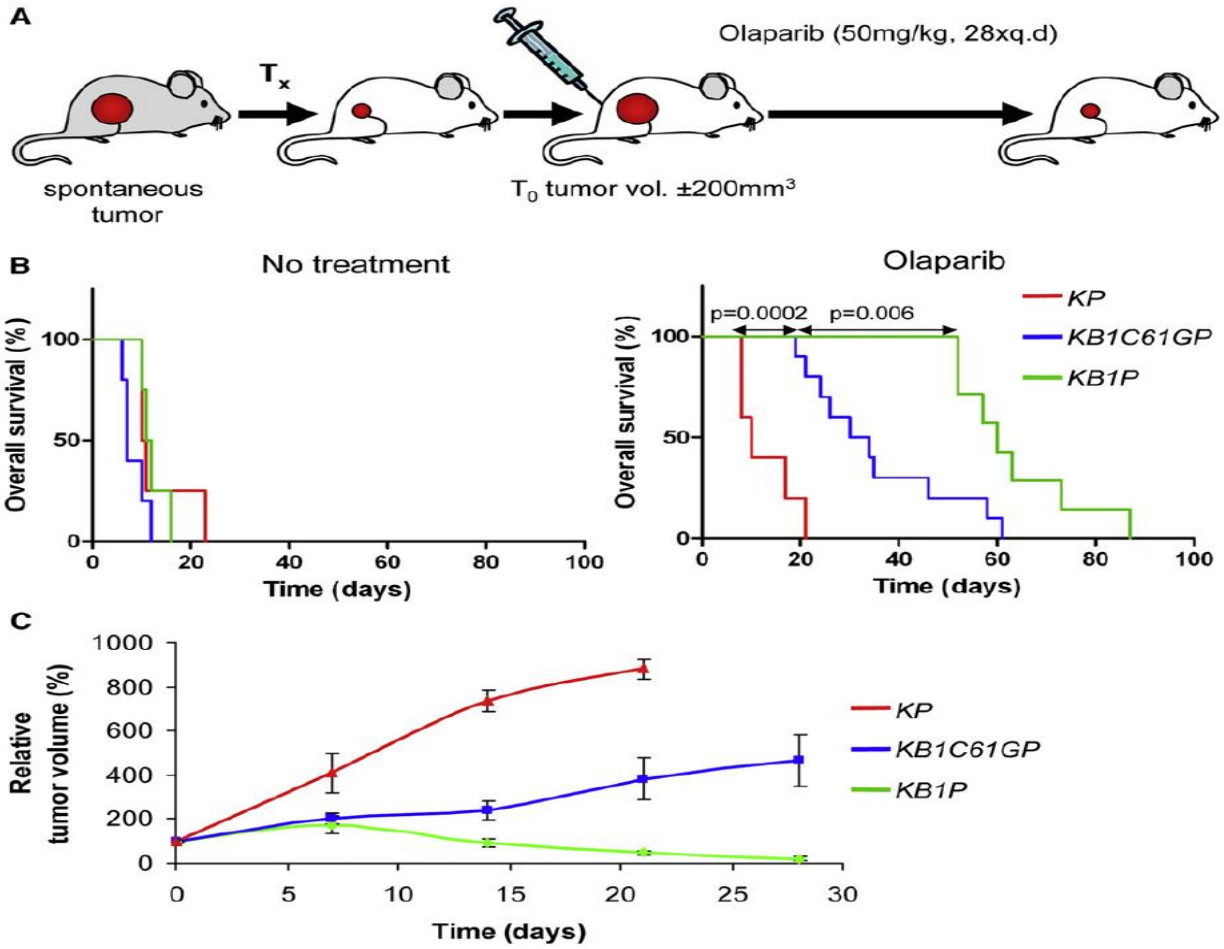
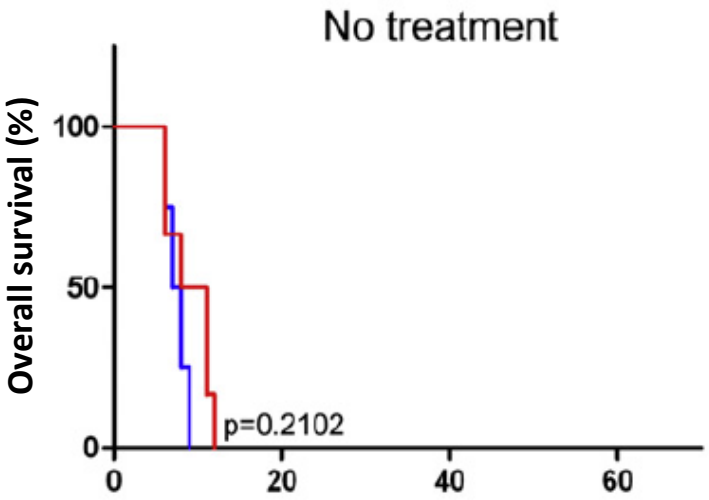
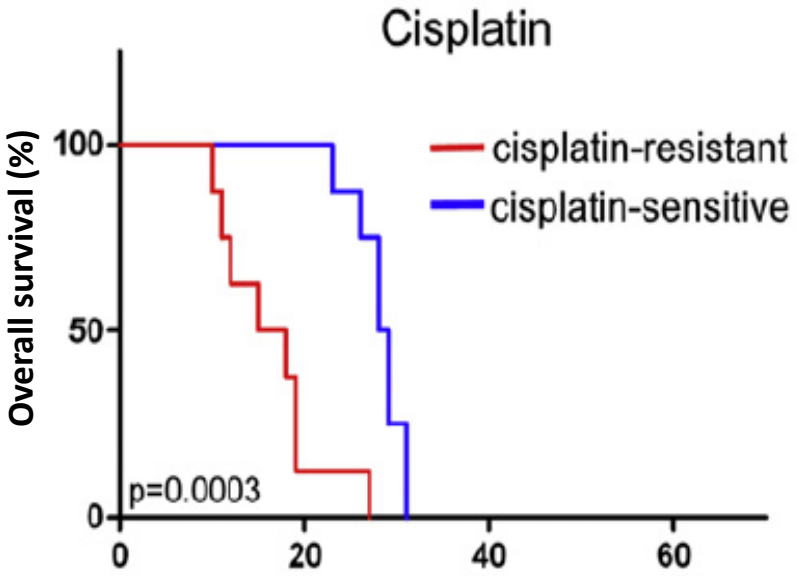
Significance

Whereas BRCA1-related cancers respond well to therapies targeting homologous recombination deficiency (HRD), resistance is a serious clinical problem. Although reversion of *BRCA1* germline mutations has been observed in resistant tumors, it is unclear which functions of BRCA1 are required for therapy resistance. Here we show that residual activity of mutant BRCA1 proteins with a dysfunctional RING domain triggers acquired resistance to PARP inhibitors and platinum drugs. Genomic instability is viewed as a potential HRD biomarker. However, we show that although mammary tumors with different *Brca1* mutations have identical genomic profiles, they respond differently to HRD-targeting therapeutics. It may therefore be useful to stratify patients according to the underlying *BRCA1* mutation and functional biomarkers such as loss of RAD51 foci formation.

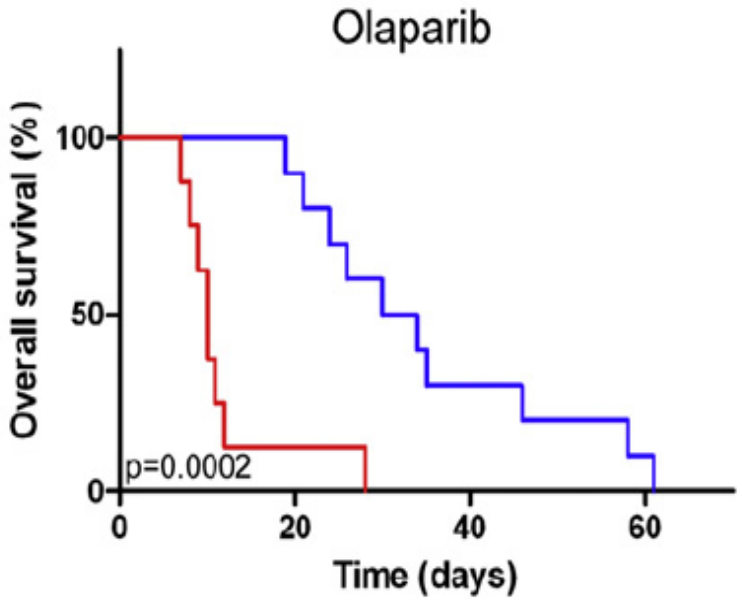


platinum-resistant *KB1C61GP* tumors display cross-resistance to olaparib.





Effects of cisplatinum, olaparib on **OS** of mice transplanted with cisplatin-sensitive (blue) and cisplatin-resistant (red) KB1C61GP tumors



Percorso del paziente al alto rischio di mutazione BRCA: carcinoma mammario e carcinoma ovarico

Carcinoma mammario BRCA-correlato
Quale terapia sistemica antitumorale?

Grazie dell'attenzione

Dr. Monica Turazza

Negrar, 8 giugno 2017

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