Breast Cancer in Patients with BRCA1/2 mutations

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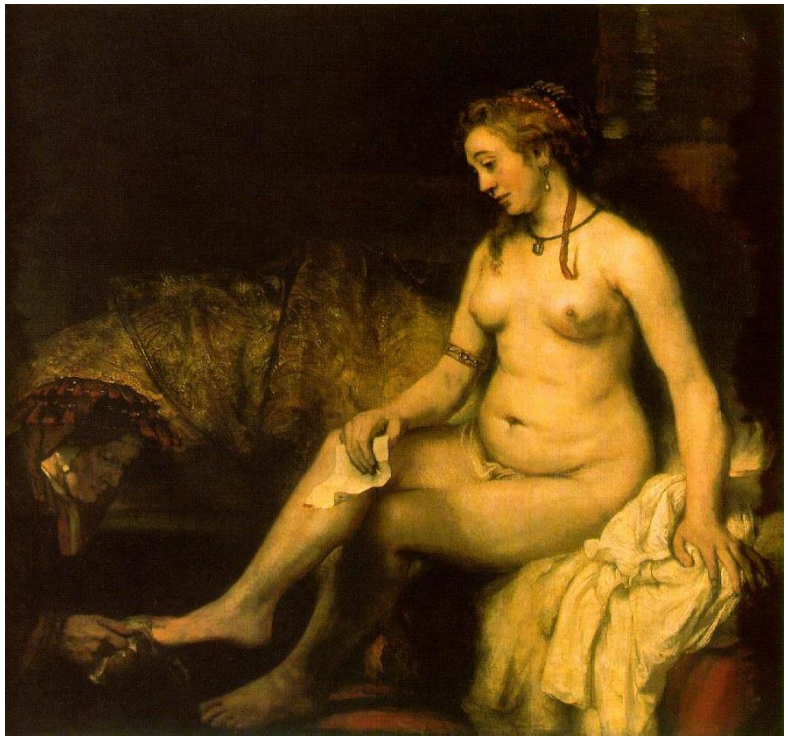


What distinguishes BRCA1/2 associated breast cancer?

- Younger age at diagnosis
- Imaging – better visualized on MRI
- Amongst women being screened– often interval cancers
- Distinct histo-pathological features
- Bilaterality

BRCA 1\2 incidence by age at BC diagnosis

Age at BC diagnosis	N	carriers	%
dx 20-29	11	3	27%
dx 30-39	74	18	24%
dx 40-49	245	29	11.8%
dx 50-59	345	33	9.5%
dx >60	368	27	7.3%

Ashkenazi Jewish cohort

IMAGING FOR SCREENING AND DIAGNOSIS IN BRCA1/2

Screening & Diagnosis:
MRI in women with high risk of breast cancer

TABLE 2 Published Breast MRI Screening Study Results

	The Netherlands	Canada	United Kingdom	Germany	United States	Italy
No. of centers	6	1	22	1	13	9
No. of women	1,909	236	649	529	390	105
Age range	25–70	25–65	35–49	≥30	≥25	≥25
No. of cancers	50	22	35	43	4	8
Sensitivity (%)						
MRI	80	77	77	91	100	100
Mammogram	33	36	40	33	25	16
Ultrasound	n/a	33	n/a	40	n/a	16
Specificity (%)						
MRI	90	95	81	97	95	99
Mammogram	95	>99	93	97	98	0
Ultrasound	n/a	96	n/a	91	n/a	0

n/a = not applicable.

Exclusively BRCA+ cohort

$$\text{sensitivity} = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false negatives}}$$

$$= \frac{\text{number of true positives}}{\text{total number of sick individuals in population}}$$

= probability of a positive test given that the patient has the disease

$$\text{specificity} = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}}$$

$$= \frac{\text{number of true negatives}}{\text{total number of well individuals in population}}$$

= probability of a negative test given that the patient is well

American Cancer Society Guidelines, 2007

Screening & Diagnosis:
MRI in women with high risk of breast cancer

TABLE 3 Rates of Detection and Follow-up Tests for Screening MRI Compared with Mammography

	MRI		Mammography	
	The Netherlands	United Kingdom	The Netherlands	United Kingdom
Positives	13.7%	19.7%	6.0%	7.2%
Recalls	10.84%	10.7%	5.4%	3.9%
Biopsies	2.93%	3.08%	1.3%	1.33%
Cancers	1.04%	1.44%	0.46%	0.69%
False negatives	0.23%	0.43%	0.81%	1.52%

American Cancer Society Guidelines, 2007

Why is MRI superior to mammography in BRCA+?

- BRCA+ breast tumors are:
- often in younger women with dense breasts – sensitivity of mammography inversely related to breast density
- with “pushing margins” rather then scirrhous, irregular margins, giving a more “benign” appearance on mammography
- Less-often associated with DCIS (which often have micro-calcifications that are detected on mammography) – especially true for BRCA1

Distinct features in BRCA1/2 associated breast cancer

BRCA-Related Breast Cancer – distinct features

BRCA1

* Breast cancer arises at early age
* Risk of ovarian cancer
* Most (60-70%) are triple negative and basal-like
* Breast cancer reported in very limited number of men

BRCA2

* Breast cancer arises at slightly older age
* Risk of ovarian cancer
* Most cancers are ER+ and luminal
* Breast cancer arises in 5-10% of men

Many similarities, but they are distinct entities and BRCA1 and BRCA2 cancers may not respond Identically to treatment

Predicting BRCA by pathological features

Table 7. Predicted Probabilities of Carrying a *BRCA1* Mutation, by Age, ER Status, and Grade

	All Histologies (%)	ER-Positive			ER-Negative		
		Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Age group							
< 30 years	8	1.1	1.6	2.7	14.4	21.0	35.0
30-34 years	5	0.8	1.2	2.0	10.9	15.9	26.5
35-39 years	2	0.2	0.3	0.5	2.7	4.0	6.6
40-44 years	1.5	0.1	0.2	0.3	1.5	2.2	3.7
45-49 years	1	0.1	0.1	0.2	1.0	1.5	2.5
50-59 years	0.3	0.03	0.04	0.07	0.4	0.6	0.9

From Lakhani SR, Van De Vijver MJ, Jacquamier J, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor,HER-2, and p53 in patients with mutations in BRCA1and BRCA2. J Clin Oncol2002;20:2310–2318,

BRCA-Related Breast Cancer – distinct features

- Other features:

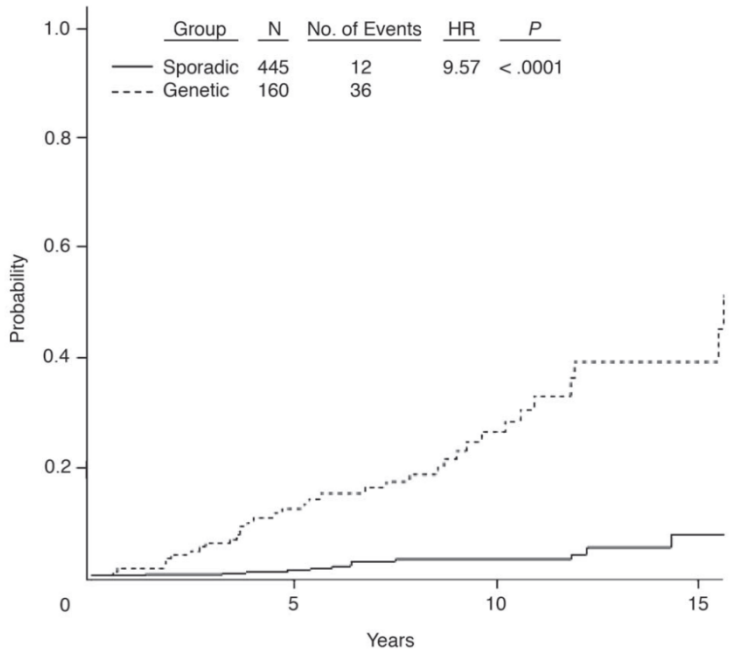
High grade	Lymphocytic infiltrate
Mostly invasive ductal carcinoma	TP53 mutations
Medullary carcinoma	Basal phenotype
Pushing margins	EGFR expression
DCIS less common	C-myc amplified

- Bilaterality

Prognosis in BRCA1/2+ Breast Cancer

Is Prognosis different in BRCA1/2 Breast Cancer?

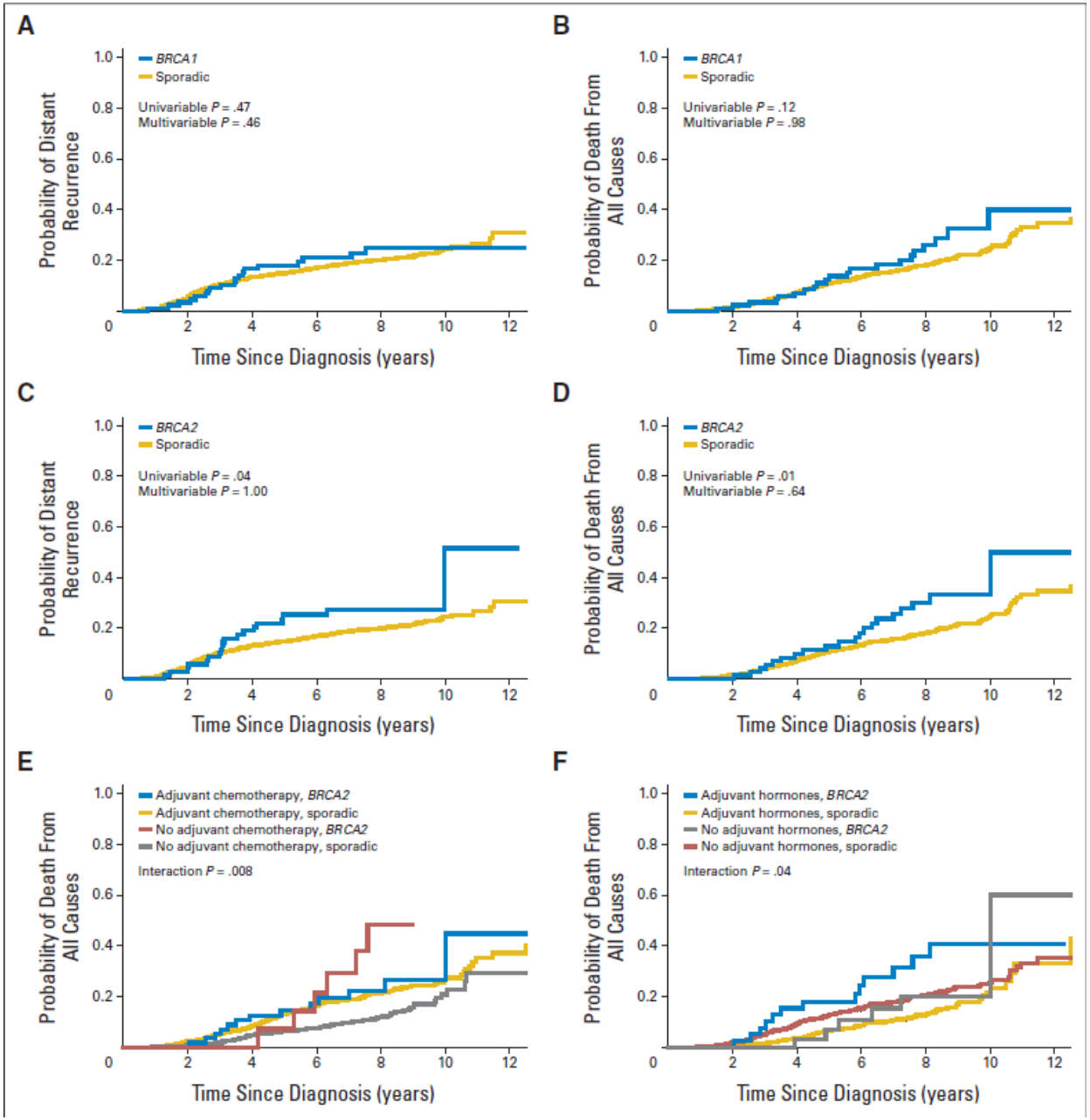
- Local disease
- Greater incidence of ipsilateral disease
- Greater incidence of contra-lateral breast cancer – 10yr rate of 26% vs 3% in non-carriers (Pierce et al JCO 2006)



Pierce et al, JCO, 2006

Is Prognosis different in BRCA1/2 Breast Cancer?

- Systemic relapse
- Most studies report no difference in OS or breast cancer specific survival compared to non-carriers, especially if standard systemic therapy received
- Rennert et al, NEJM, 2007
- Goodwin et al, JCO 2012
- Huzarski et el, JCO, 2013



Goodwin et al, JCO 2012

IMPACT OF A BRCA1/2 MUTATION ON TREATMENT DECISIONS

Impact of a BRCA1/2 mutation on treatment decisions

- **Local management**
- Lumpectomy vs mastectomy
- Bilateral mastectomy?
- **Systemic therapy**
- No EBM to change adjuvant chemotherapy
- Evidence to support use of DNA cross-linking agents & alkylating agents:
- Platinum agents, Mitomycin
- CMF (Cyclophosphamide/MTX/5FU)
- **Reproductive considerations**
- **Ongoing follow-up**

LOCAL THERAPY CONSIDERATIONS

BCS vs Mastectomy

- BCS is a legitimate and safe choice
- Therapeutic radiation is safe:
- Reduces local ipsilateral recurrence
- Does not increase contra-lateral disease
- Contralateral mastectomy – some studies suggest that there may be a long term survival benefit
- **Decision must be tailored to individual's needs**

Does CRRM improve survival?

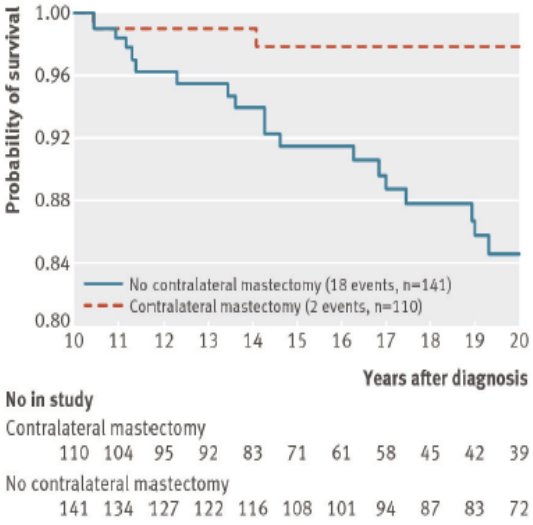


Fig 2 Survival from 10 to 20 years after breast cancer, by contralateral mastectomy

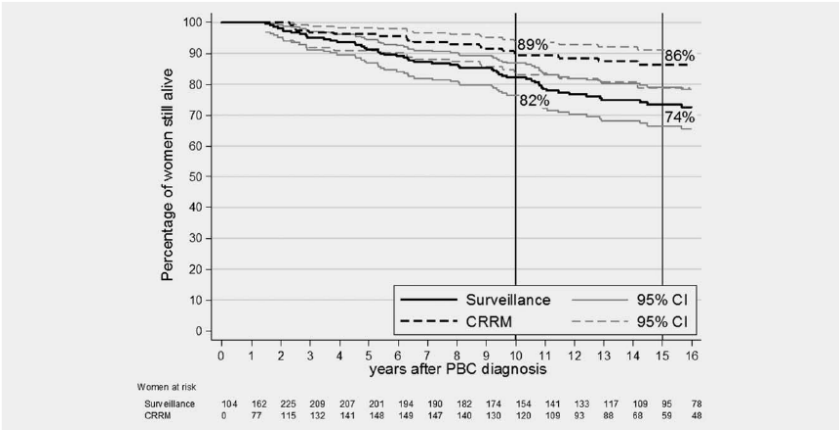


Figure 2. Unadjusted overall survival curves for BRCA1/2-associated breast cancer patients (including patients who deceased or had distant metastases within 2 years after primary breast cancer (PBC) diagnosis) opting for contralateral risk-reducing mastectomy (CRRM) versus not opting for risk-reducing mastectomy (Surveillance), using the Simon and Makuch method—which takes into account the change in an individual's covariate status over time—with years after PBC diagnosis as the time variable.

Stage 1 & 2 at Dx
Most were <50 at Dx

Metcalfe, BMJ, 2014

Greatest benefit in <40 & low risk/favorable features

Heemskerk-Gerritsen, Int J Cancer, 2015

SYSTEMIC THERAPIES IN BRCA1/2+ BREAST CANCER

Types of DNA damage and repair

Type of damage:

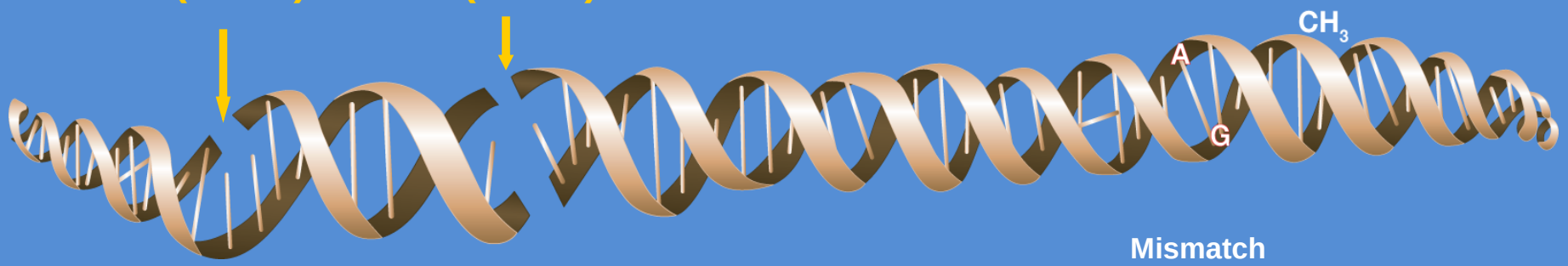
Single-strand breaks (SSBs)

Double-strand breaks (DSBs)

Bulky adducts

O6-alkylguanine

Insertions & deletions



Repair pathway:

Base excision repair

Recombinational repair

HR

NHEJ

Mismatch repair

Nucleotide-excision repair

Direct reversal

Repair enzymes:

PARPs

ATM
BRCA1\2
RAD51

DNA-PK

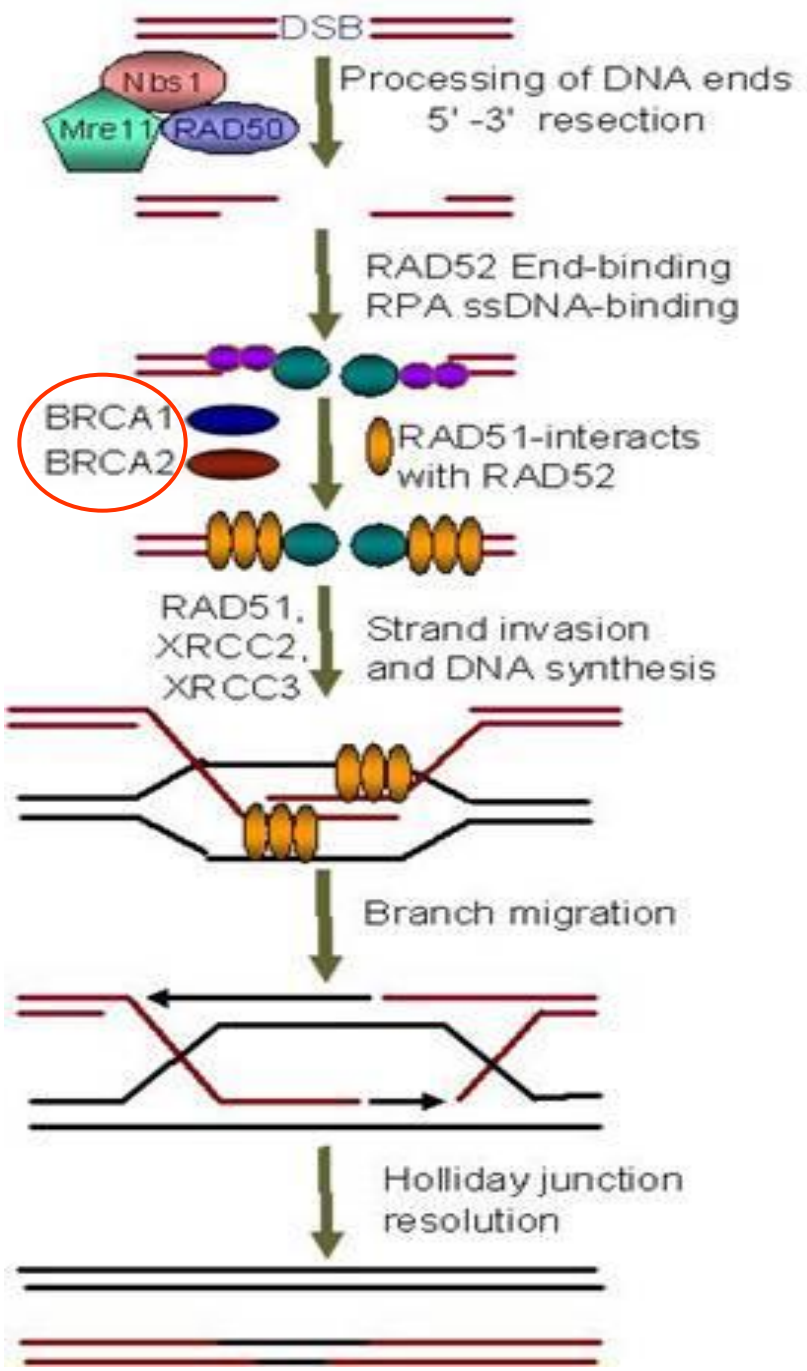
XP, poly-merases

MSH2, MLH1

AGT

Homologous recombination repair pathway:

- important for repairing replication lesions
- depends on the RAD51-family of proteins
- makes use of a homologous DNA sequence.
- BRCA1/2 play a key role in this repair pathway



Chemotherapy

Chemotherapy in BRCA1/2+ Breast Cancer

- Pre-clinical studies suggest increased sensitivity to agents that damage DNA in a way that interferes with DNA replication forks & which subsequently require DNA repair by HR:
- DNA cross-linking agents (carboplatin, cisplatin, mitomycin)
- Growing body of clinical evidence to support this

Chemotherapy – platinum agents

- Growing number of prospective clinical trials supporting:
- Incorporation of platinum agents in neo-adjuvant triple-negative BRCA+ breast cancer
- Phase III study (TNT study) in the metastatic setting favoring caboplatin over docetaxel in triple negative BRCA+ MBC

PARP Inhibitors

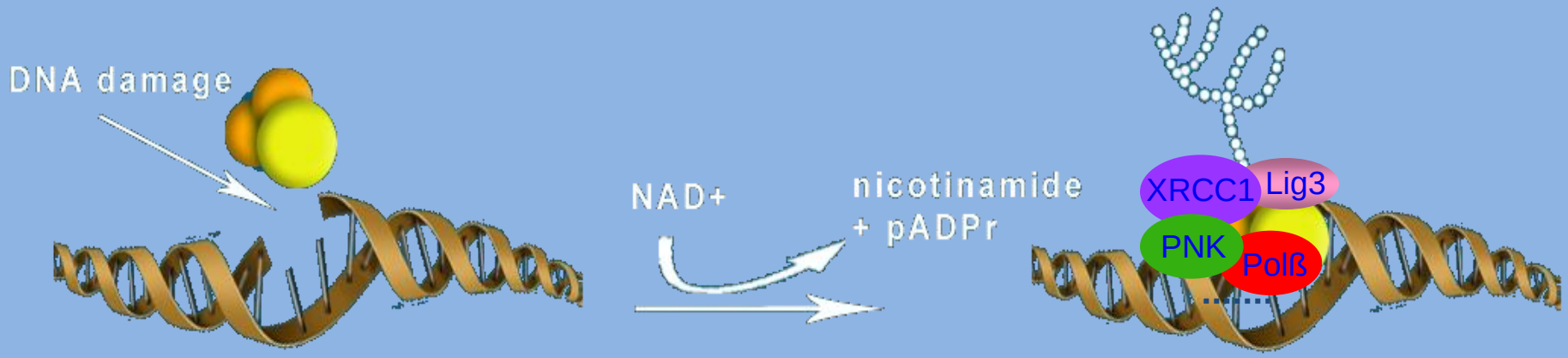
The PARP Superfamily

PARP consists of a family of proteins which has multiple members (18) involved in diverse functions including:

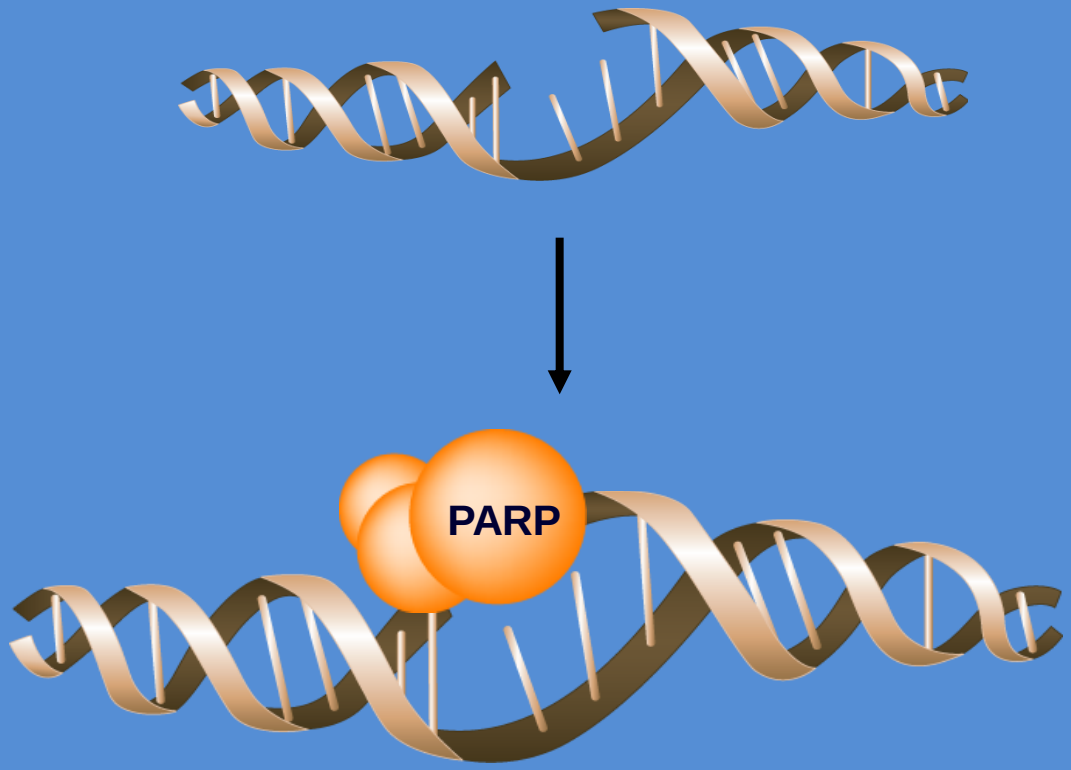
- DNA repair
- telomere maintenance
- epigenetic regulation
- centrosomer function

PARP-1 is a key enzyme involved in the repair of single-strand DNA breaks

- A key role in the repair of DNA single-strand breaks
- Uses the base excision repair pathway
- Binds directly to sites of DNA damage
- Once activated, it uses NAD as a substrate and generates large, branched chains of poly(ADP-ribose) polymers on multiple target proteins
- Recruits other DNA repair enzymes

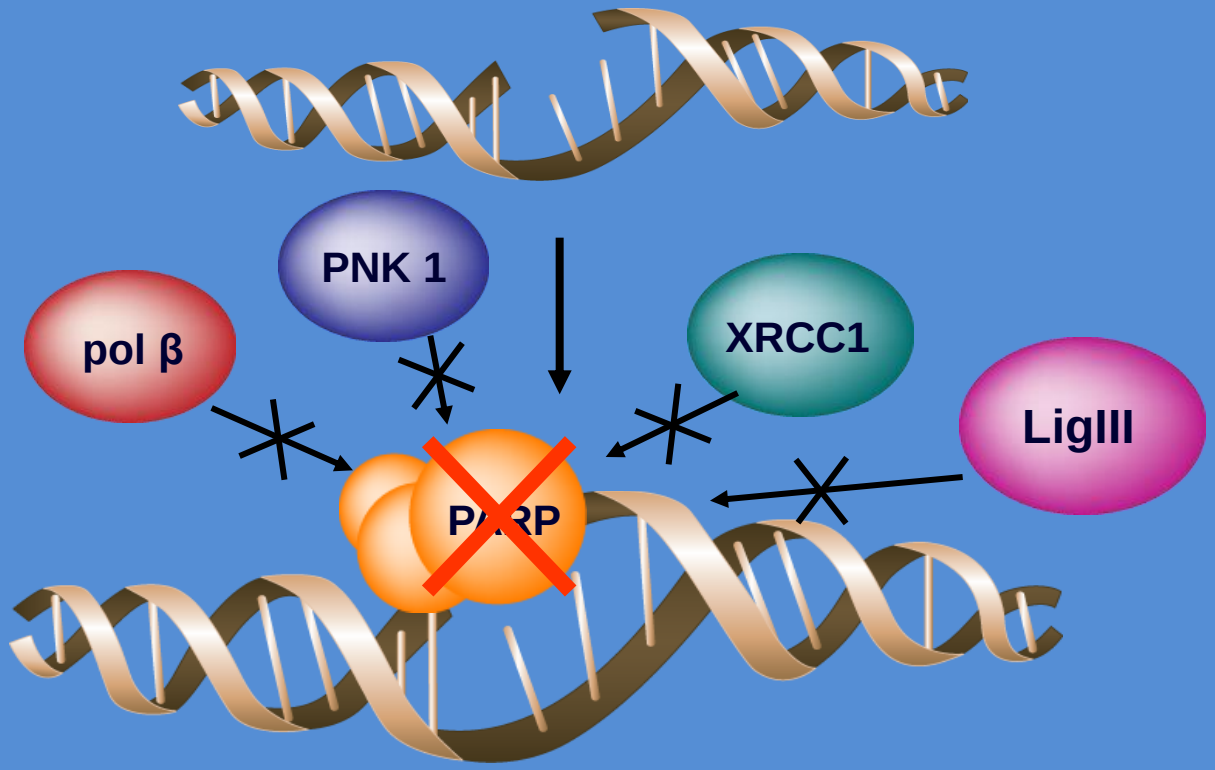


Inhibiting PARP-1 increases double-strand DNA damage



DNA SSB

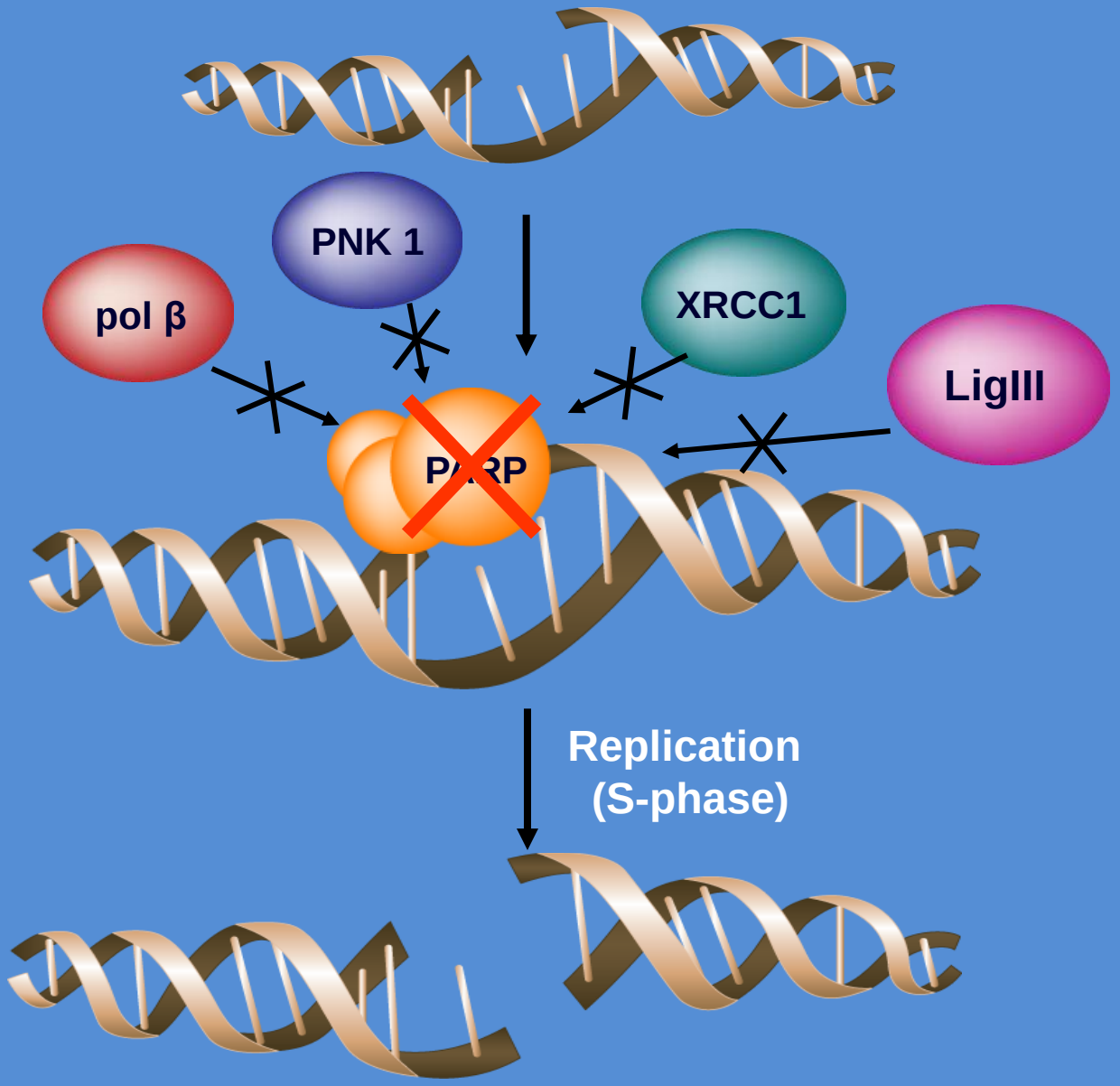
Inhibiting PARP-1 increases double-strand DNA damage



DNA SSB

Inhibition of PARP-1 prevents recruitment of repair factors to repair SSB

Inhibiting PARP-1 increases double-strand DNA damage

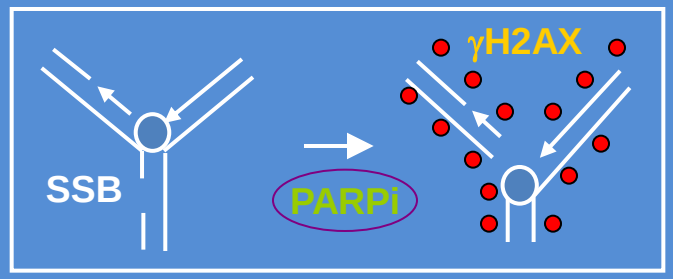


DNA SSB

Inhibition of PARP-1 prevents recruitment of repair factors to repair SSB

DNA DSB

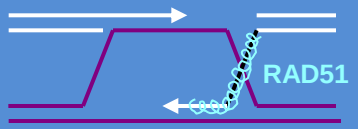
PARP inhibition and tumor-selective synthetic lethality



DNA replication fork arrest and collapse

Normal BRCA1/BRCA2

BRCA1/BRCA2 failure



HR-based repair

Impaired HR repair

Alternative error prone repair

Chromosome Stability

Cell Survival

Chromosomal Instability

Cell Death

Farmer H *et al. Nature* 2005;434:917–921; Bryant HE *et al. Nature* 2005;434:913–917

Main parachute

Reserve Parachute

PARP inhibitor

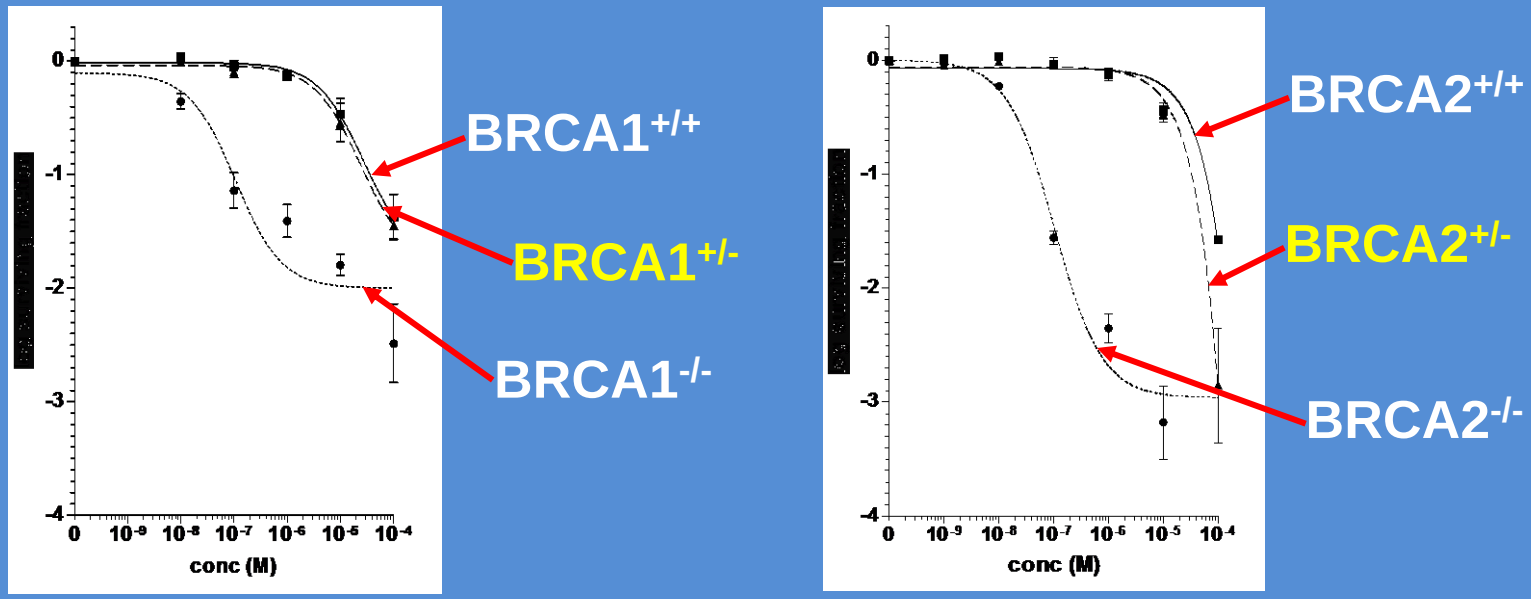
Main parachute

BRCA mutation

Reserve Parachute

Death of the cancer cell

Increased sensitivity of BRCA1$^{-/-}$ and BRCA2$^{-/-}$ cells to PARP inhibition



No difference in sensitivity between heterozygous and wild-type BRCA cells

Targeted inhibition → selective and less toxic therapy

Farmer et al. Nature 2005; 434:917-21

Phase II, proof-of-concept - Olaparib study, refractory BRCA1/2+ MBC

ITT cohort	Olaparib 400 mg bid (n=27)	Olaparib 100 mg bid (n=27)
Overall Response Rate, n (%)	11 (41)*	6 (22)*
Complete Response, n (%)	1 (4)	0
Partial Response, n (%)	10 (37)	6 (22)

***An additional 1 patient in the 400 mg cohort and 3 patients in the 100 mg cohort had unconfirmed responses**

Tutt et al, Lancet, 2010

Olaparib Monotherapy in Patients With Advanced Cancer and Germline *BRCA1/2* Mutation

- open-label non-comparative trial
- assessing efficacy of olaparib monotherapy (400 mg bid) against *BRCA1/2* mutant tumors - ‘’**basket study**”
- Tumor types included ovarian, breast cancer, prostate cancer and pancreatic cancer
- All patients were heavily pretreated
- 298 patients, responses across all tumor type, ORR was 26.2%

Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-250.

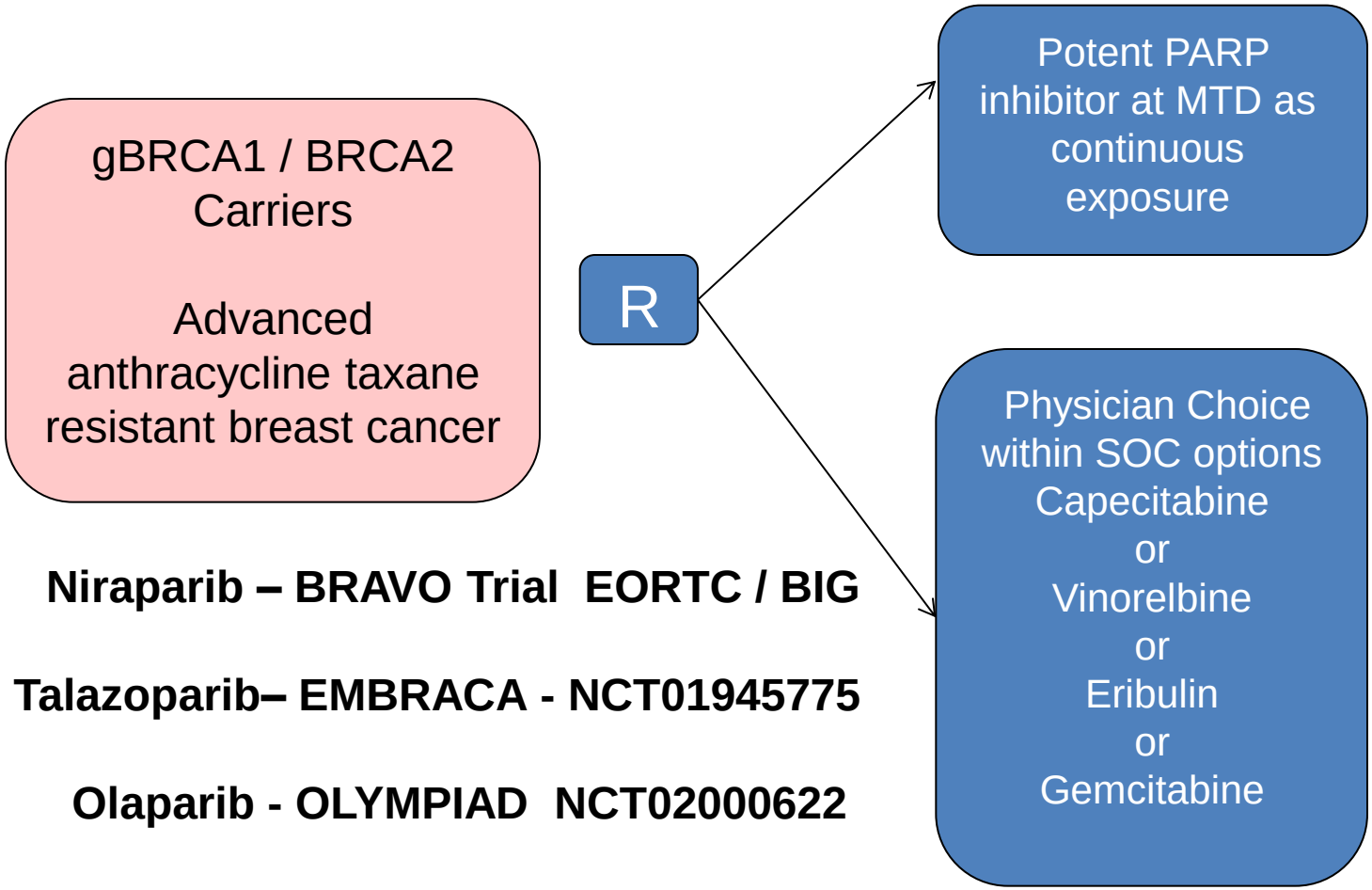
Olaparib for advanced cancer – study 42

Response status, n (%)	Tumour type					
	Ovarian (n=193)	Breast (n=62)	Pancreas (n=23)	Prostate (n=8)	Other (n=12)	Total (n=298)
Tumour response rate	60 (31.1)	8 (12.9)	5 (21.7)	4 (50.0)	1 (8.3)	78 (26.2)
CR*	6 (3.1)	0	1 (4.3)	0	0	7 (2.3)
PR*	54 (28)	8 (13)	4 (17)	4 (50)	1 (8.3)	71 (23.8)
SD ≥8 weeks	78 (40)	29 (47)	8 (35)	2 (25)	7 (58)	124 (42)
SD	64 (33)	22 (36)	5 (22)	2 (25)	6 (50)	99 (33)
Unconfirmed PR†	12 (6)	7 (11)	3 (13)	0	1 (8.3)	23 (8)
PD‡	41 (21)	23 (37)	9 (39)	2 (25)	3 (25)	78 (26)
RECIST progression	33 (17)	16 (26)	6 (26)	1 (13)	3 (25)	59 (20)
Early death§	8 (4)	7 (11)	3 (13)	1 (13)	0	19 (6)
Not evaluable	14 (7)	2 (3)	1 (4)	0	1 (8.3)	18 (6)
No follow-up assessments	12 (6)	2 (3)	1 (4)	0	0	15 (5)
SD <8 weeks	2 (1)	0	0	0	1 (8.3)	3 (1)

80% of ovarian cancer patients – 3+ lines of chemotherapy

Kaufman et al , JCO 2015

PARP inhibition vs chemotherapy



Primary endpoint PFS

Niraparib – BRAVO Trial EORTC / BIG

Talazoparib– EMBRACA - NCT01945775

Olaparib - OLYMPIAD NCT02000622

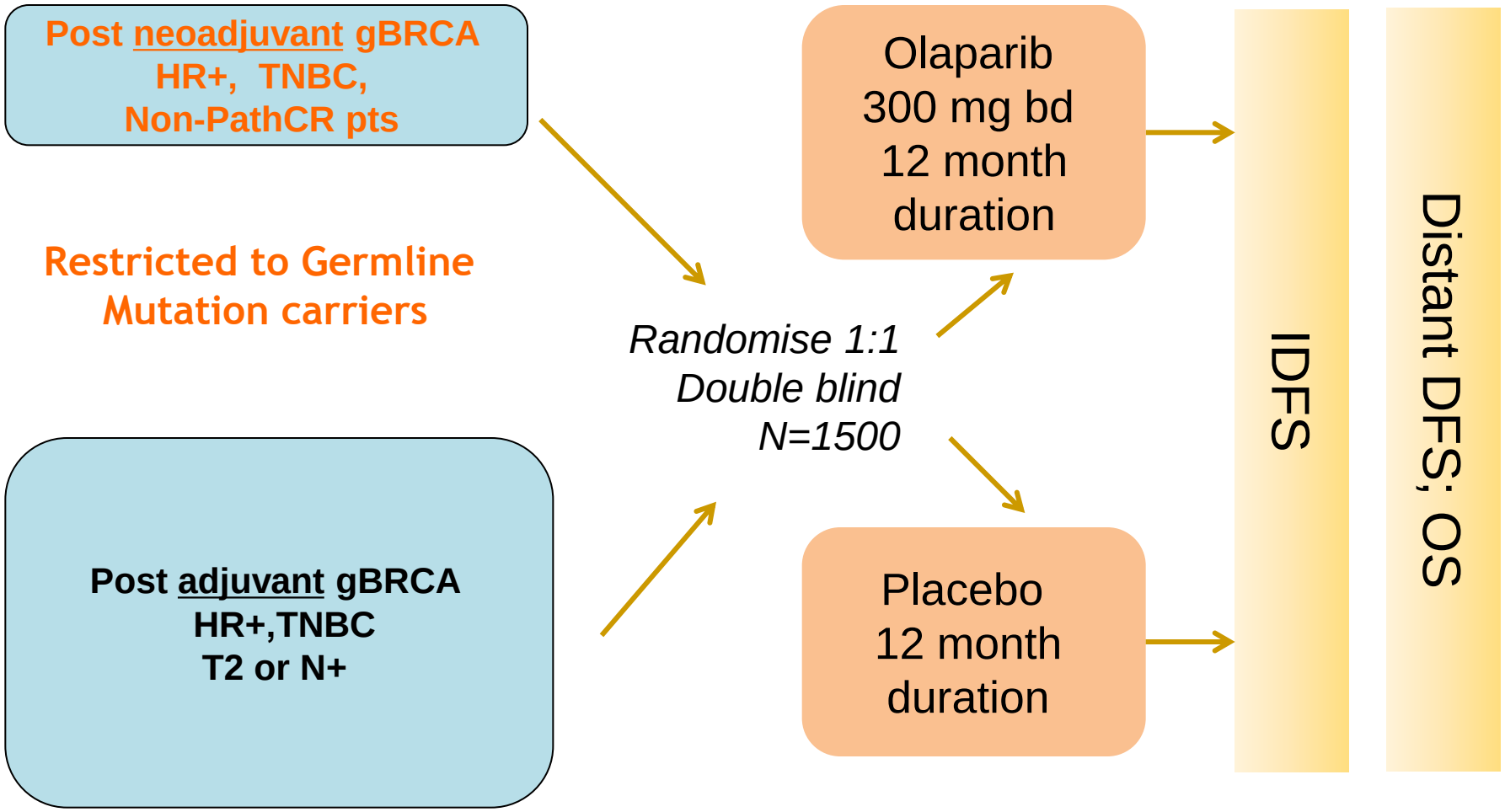
National Institutes of Health, Available at: https://clinicaltrials.gov/ct2/results?term=NCT01945775 and https://clinicaltrials.gov/ct2/results?term=NCT02000622 . Accessed: September 27, 2015.

BIG
Breast International Group

OlympiA
OLaparib in Adjuvant
BRCAm breast cancer

frontier science

NRG ONCOLOGY
Advancing Research. Improving Lives.



REPRODUCTIVE ISSUES

Reproductive issues

- Timing of RRSO (risk reducing oophorectomy)
- For BRCA1 – between 35-40
- For BRCA2 – by 40
- Fertility preservation
- PGD – pre-implantation genetic diagnosis
- Premature menopause – impact on sexual health, bone health, quality of life

Unique challenges in BRCA1/2 associated Breast Cancer

- Multitude of therapeutic decisions and reproductive decisions
- Knowledge of BRCA1/2 status may arrive at a time of great distress
- Risk reducing measures are often an assault on self-image, “womanhood”
- Far reaching implications for family planning and for the extended family
- Multiple psychosocial issues - support is imperative
- **Multi-disciplinary care – is a MUST**

Thank you

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