Breast Cancer and Treatment Options in Patients with BRCA1/2 mutations

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On behalf of

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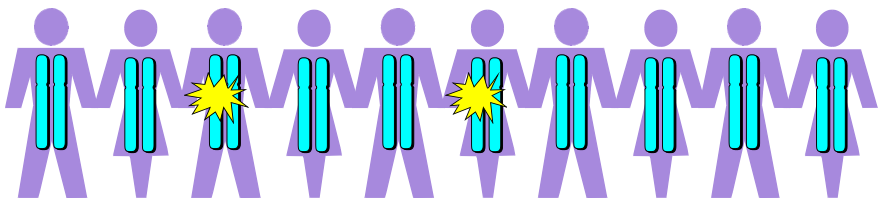
Carrier Frequency

Prevalence of an altered disease gene in a given population



Background

- Over 90% of hereditary breast & ovarian cancer are result of a mutation in BRCA1/2
- Prevalence of a BRCA1/2 mutation is population dependent – 1/300-1/800
- BRCA1/2 mutation more prevalent amongst younger women with breast cancer, TNBC, FHx of BC or OvC and in certain ethnic groups (Ashkenazi Jewish)
- Accounts for ~5-10% of all breast cancer

The prevalence of BRCA1/BRCA2 mutations: Contribution to cancer **in non-selected populations**

- Breast cancer ~ 2.5%-5%
- Ovarian cancer ~ 10-15%
- Pancreatic cancer ?
- Prostate cancer ?

The prevalence of BRCA1/BRCA2 mutations: Contribution to cancer – in an ethnic group (Ashkenazi Jews).

- Breast cancer ~11% of cases are carriers
- Ovarian cancer ~40% of cases are carriers
- Pancreatic cancer ~8% of cases are carriers
- Prostate cancer ~ 5% of cases are carriers

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

Cancer susceptibility genes other than BRCA1/2

Table 1. Cancer Susceptibility Genes Other Than *BRCA1/2*

Cancer Susceptibility Gene	Breast Cancer RR (90% CI when available) or Inclusion Criteria
Breast	
ATM	2.8 (2.2 to 3.7)[35]
BARD1	Breast cancer association reported; RR not yet determined[17,46,47]
BRIP1	2.0 (1.3 to 3.0)[48]; ovarian cancer RR 11.2[9]
CDH1	6.6 (2.2 to 19.9)[49]
CHEK2	3.0 (2.6 to 3.5)[35]; most data for 1100delC
NBN	2.7 (1.9 to 3.7)[35]
PALB2	5.3 (3.0 to 9.4)[35]
PTEN	RR 2.0-5.0[50,51]
STK11	RR 2.0-4.0[52,53]
TP53	105 (62 to 165)[35]

Tung et al JCO 2016

Distinct features in BRCA1/2 associated breast cancer

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-Related Breast Cancer – distinct features

- Other features:

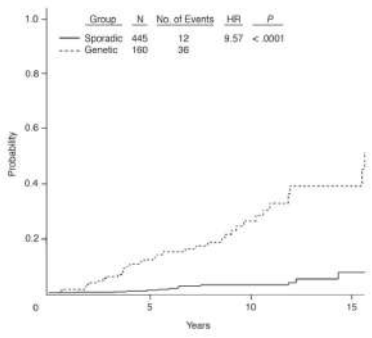
High grade	Lymphocytic infiltrate
Mostly invasive ductal carcinoma	TP53 mutations
Medullary carcinoma	Basal phenotype
Pushing margins	EGFR expression
DCIS less common	C-myc amplified

- Bilaterality

Prognosis in BRCA1/2+ Breast Cancer

Is Prognosis different in BRCA1/2 Breast Cancer?

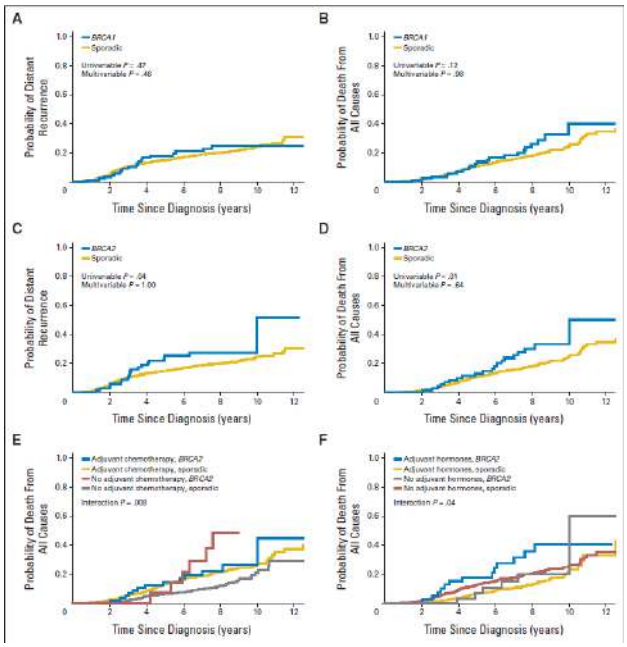
- Local disease
- Greater incidence of ipsilateral disease
- **Greater incidence of contra-lateral breast cancer – 10yr rate of 26% vs 3% in non-carriers** (Pierce et al JCO 2006)



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

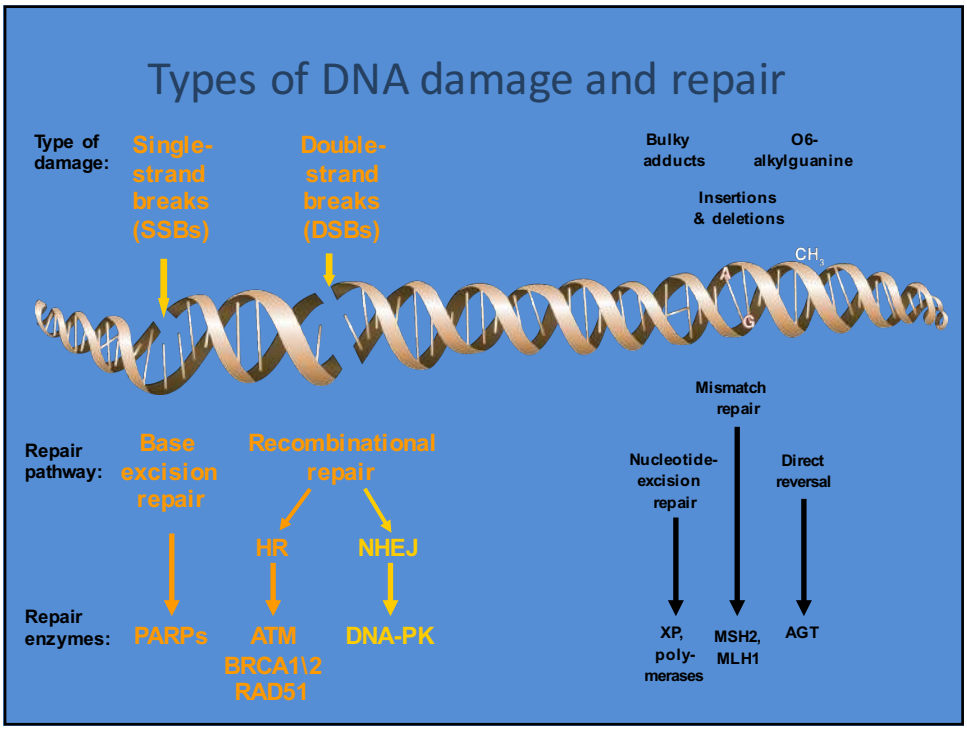
- **Local management**
- Lumpectomy vs mastectomy
- Bilateral mastectomy?
- **Systemic therapy**
- No EBM to change adjuvant chemotherapy
- Evidence to support use of DNA cross-linking agents & alkylating agents:
- Platinum agents, Mitomycin
- CMF (Cyclophosphamide/MTX/5FU)
- PARP inhibitors
- **Reproductive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

WHY DOES PRESENCE OF A BRCA1/2 MUTATION HAVE AN IMPACT ON SYSTEMIC THERAPY?



SYSTEMIC THERAPIES IN BRCA1/2+ BREAST CANCER

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)
- Most NAST studies → increased response to platinum agents

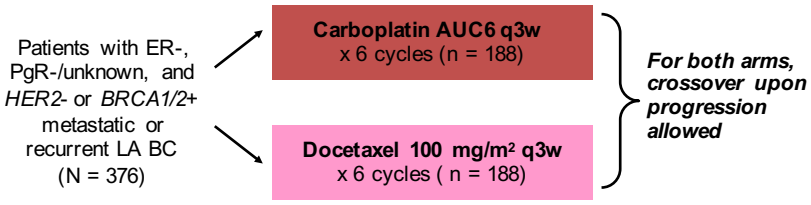
BRCA analysis of GepartSixto

291 specimens for this analysis
50 with BRCA1 and 43 with BRCA2 mutations

	pCR rate With Carboplatin	pCR rate Without Carbo platin
mBRCA	**65.4%**	**66.7%**
Non-BRCA	55%	36.4%

Hahnen et al, JAMA Oncology, 2017

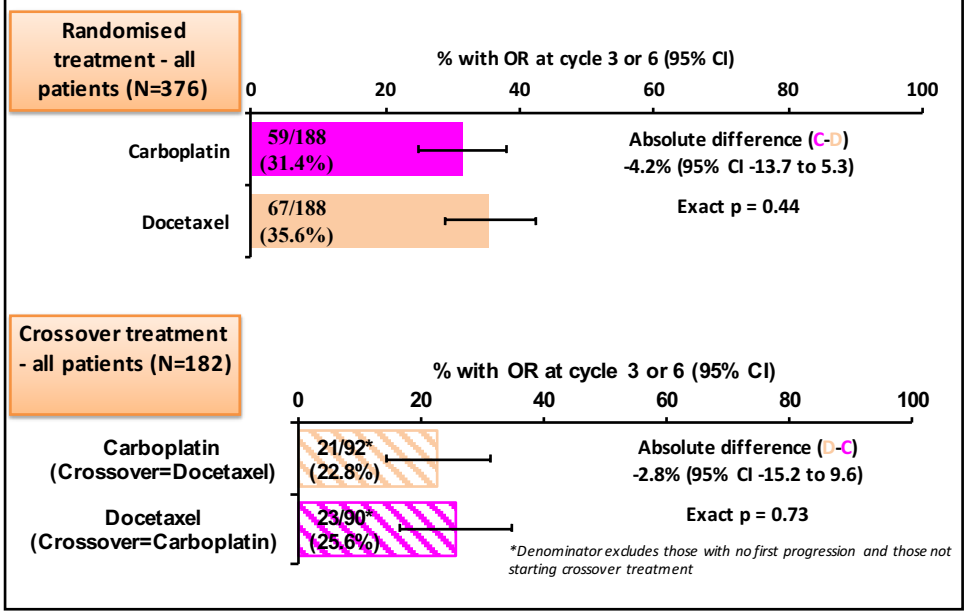
TNT: Carboplatin vs Docetaxel in Advanced TNBC or *BRCA1/2*+ BC



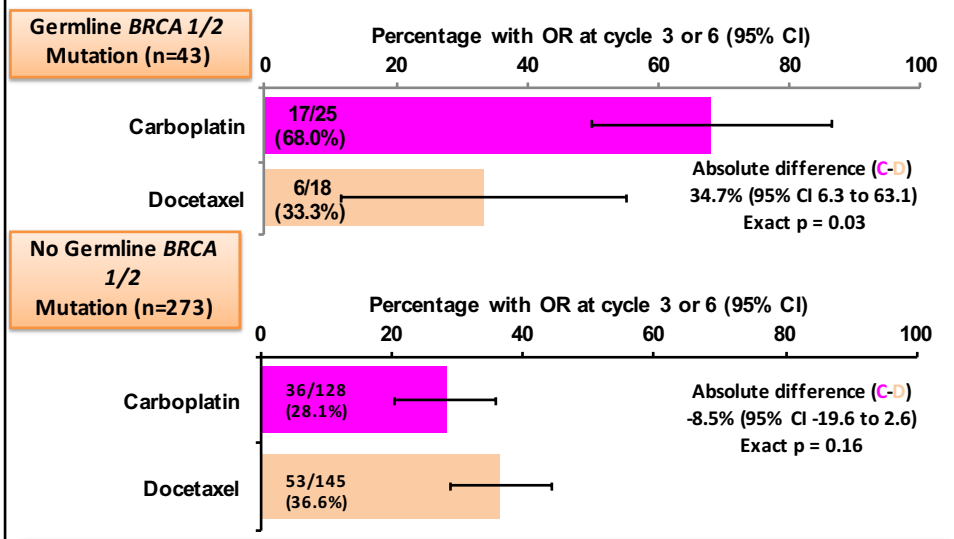
- Primary endpoint: ORR in ITT population
- Secondary endpoints: PFS, OS, ORR (crossover), toxicity
- Subgroup analyses: *BRCA1/2* mutation, basal-like subgroups, HRD biomarkers

Tutt A, et al. SABCS 2014. Abstract S3-01.

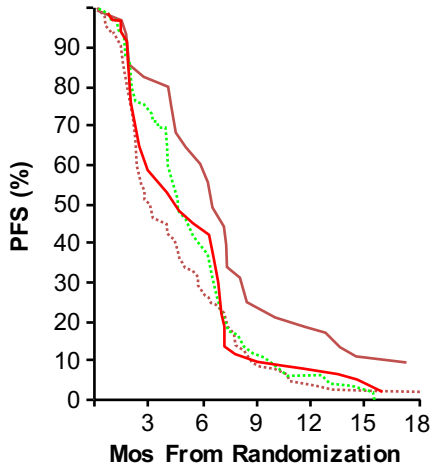
TNT - Objective response



TNT : Objective response – *BRCA 1/2* status



TNT: Carboplatin vs Docetaxel in Adv TNBC or *BRCA1/2*+ BC: PFS by *BRCA1/2*



Carboplatin + *BRCA1/2* mutated
Carboplatin + *BRCA1/2* not mutated
Docetaxel + *BRCA1/2* mutated
Docetaxel + *BRCA1/2* not mutated

Median PFS, Mos	Carbo	Doc
BRCA1/2 mutated	6.8	4.8
BRCA1/2 not mutated	3.1	4.5

BRCA+ N=43
Non-BRCA N=273

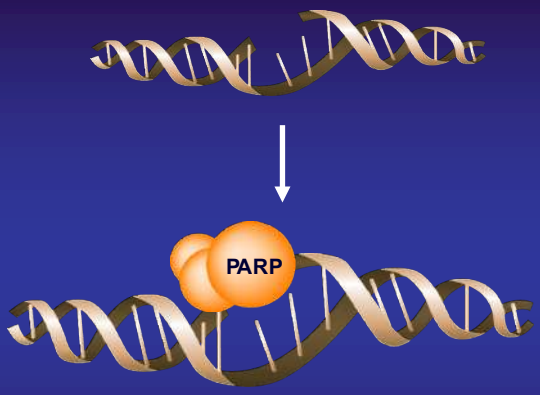
Tutt A, et al. SABCS 2014. Abstract S3-01.

Conclusions from TNT

- BRCA+ triple-negative patients experienced a higher RR and greater PFS with carboplatin compared with docetaxel
- BRCA+ patients had high HRD-scores

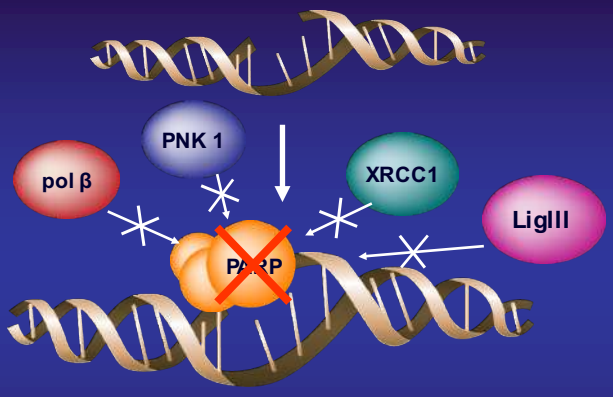
PARP Inhibitors

Inhibiting PARP-1 increases double-strand DNA damage



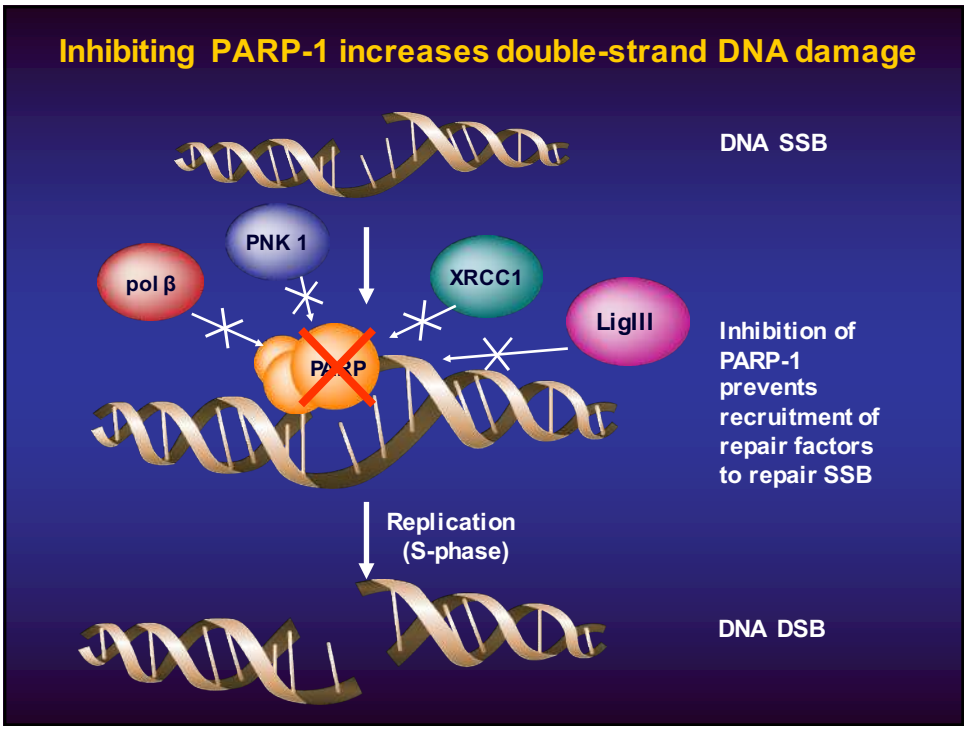
DNA SSB

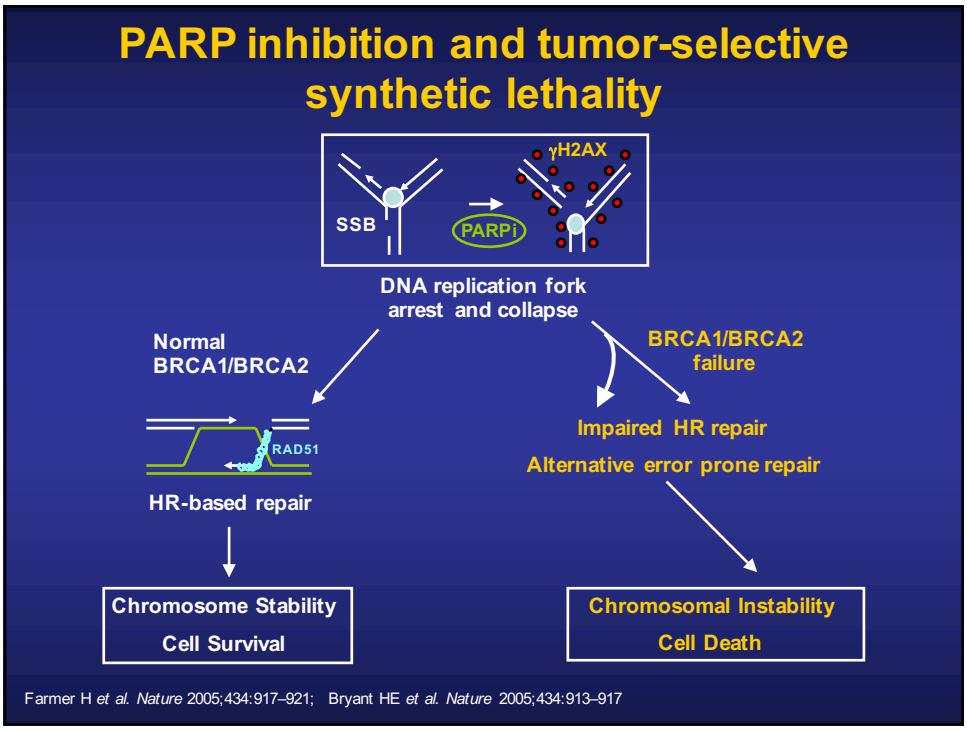
Inhibiting PARP-1 increases double-strand DNA damage



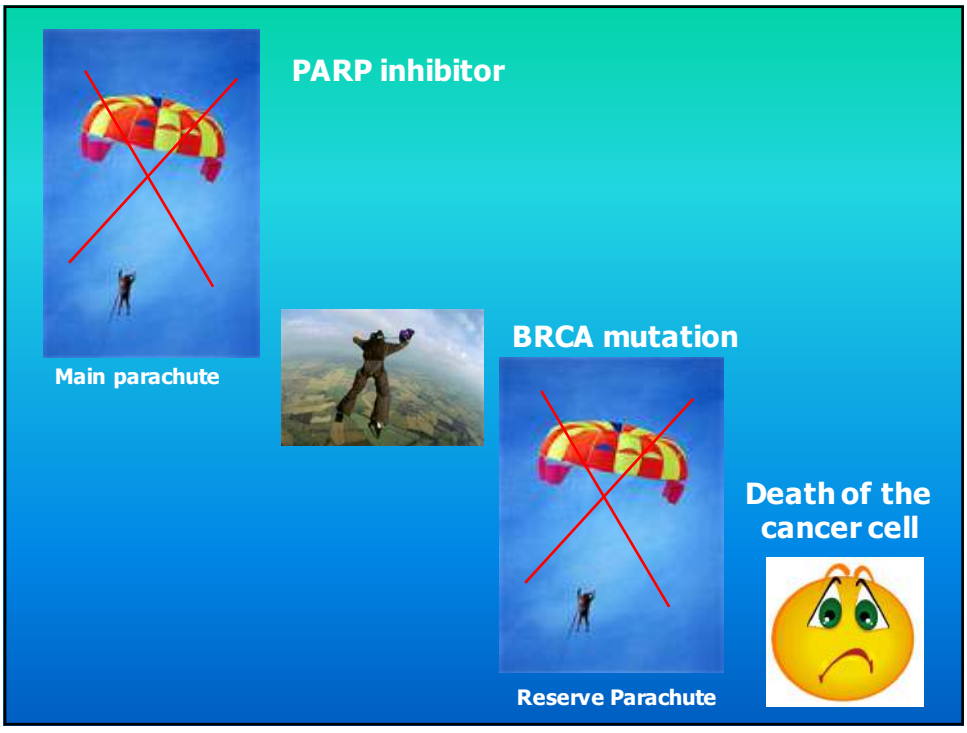
DNA SSB

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


Inhibiting PARP-1 increases double-strand DNA damage
DNA SSB
PNK 1
pol β
XRCC1
LigIII
PARP
Inhibition of PARP-1 prevents recruitment of repair factors to repair SSB
Replication (S-phase)
DNA DSB


PARP inhibition and tumor-selective synthetic lethality
γH2AX
SSB
PARPi
DNA replication fork arrest and collapse
Normal BRCA1/BRCA2
BRCA1/BRCA2 failure
RAD51
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

Olaparib versus physicians' choice: the phase III OLYMPIAD study

- HER2-negative metastatic breast cancer
  - ER and/or PR positive (HR+) or
  - TNBC
- Deleterious or suspected deleterious g*BRCA*m
- ≤2 prior chemotherapy lines in metastatic setting
- Prior anthracycline and taxane
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression adjuvant treatment
  - ≥12 months since (neo)adjuvant treatment

Olaparib 300 mg tablets bd

2:1 randomization

Chemotherapy treatment of physician's choice (TPC)
- **Capecitabine**
- **Eribulin**
- **Vinorelbine**

Treat until progression

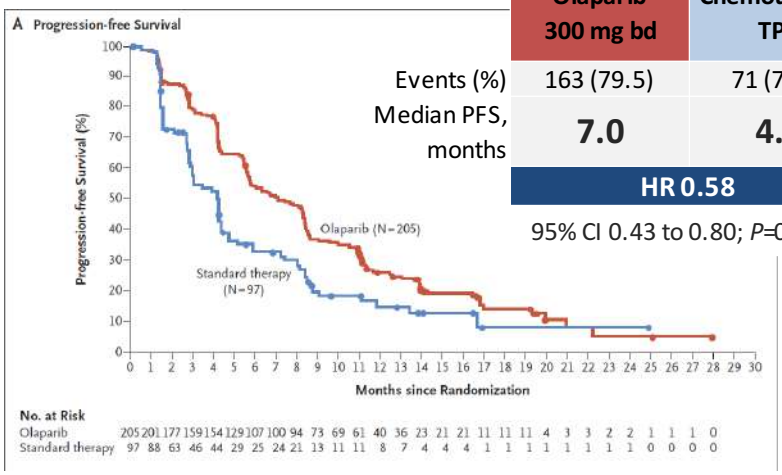
Primary endpoint
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints
- Overall survival
- Time to second progression or death
- Objective response rate
- Global HRQoL (EORTC-QLQ-C30)
- Safety and tolerability

Robson et al, New Engl J Med 2017

Olaparib versus physicians' choice: the phase III OLYMPIAD study

Primary end point: centrally-evaluated PFS



	Olaparib 300 mg bd	Chemotherapy TPC
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	**7.0**	**4.2**
HR 0.58		

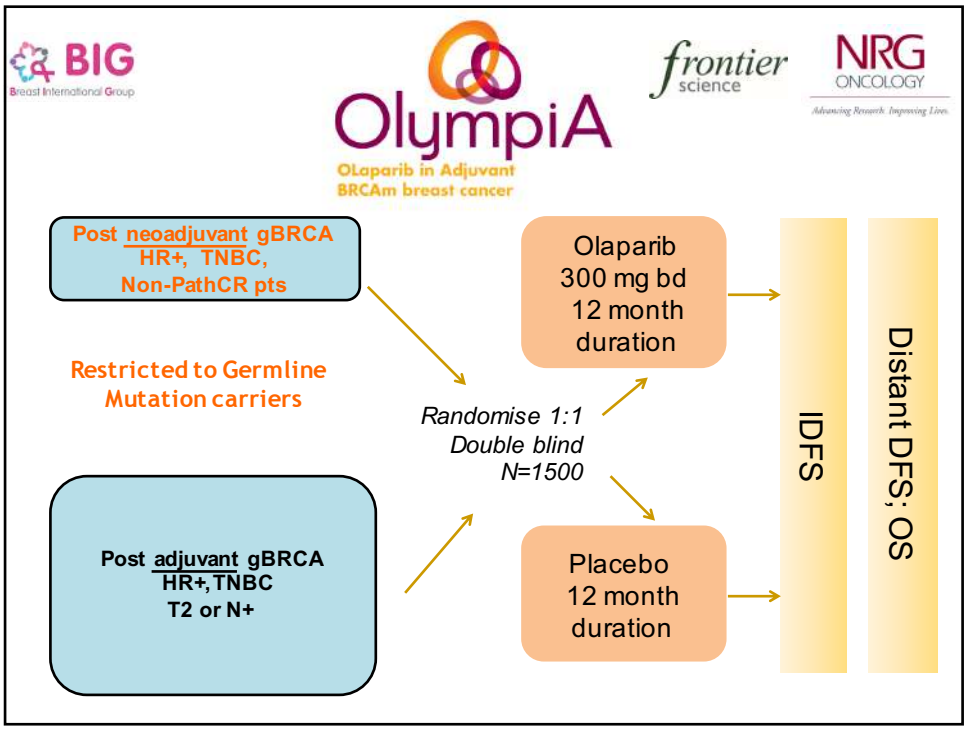
95% CI 0.43 to 0.80; *P*=0.0009

Robson et al, New Engl J Med 2017

OLYMPIAD : Summary of adverse events, all causality

n (%)	Olaparib 300 mg bd (N=205)	Chemotherapy TPC (N=91)
Grade 1–2	124 (60.5)	42 (46.2)
Grade ≥3	**75 (36.6)**	**46 (50.5)**
Death	1 (0.5)	1 (1.1)
Drug discontinuations	**10 (4.9)**	**7 (7.7)**
Dose reductions	**52 (25.4)**	**28 (30.8)**
Dose interruptions/delay	72 (35.1)	25 (27.5)

Robson et al, New Engl J Med 2017



REPRODUCTIVE ISSUES

Reproductive issues

- Timing of RRSO (risk reducing oophorectomy)
- For BRCA1 – between 35-40
- For BRCA2 – by 40 (45?)
- Fertility preservation
- PGD – pre-implantation genetic diagnosis
- Premature menopause – impact on sexual health, bone health, quality of life

Reproductive considerations in carriers

Reproductive considerations in *BRCA* mutation carriers
BRCA1/2 carriers can be reassured that there is no convincing evidence that mutation carriers have reduced ovarian reserve or fertility
All women harbouring a *BRCA1/2* mutation should be encouraged to complete child-bearing prior to planned RRSO
For women who wish to undergo RRSO and have not yet completed child-bearing fertility preservation options should be discussed
BRCA1/2 mutation carriers (male and female) planning to conceive should be made aware of the options of pre-natal diagnosis (via chorio-villous or amniotic fluid sampling in week 11-20 of gestation) and PGD
Women harbouring a BRCA1/2 mutation who have been diagnosed with a malignancy should be counselled about options for fertility preservation prior to the commencement of oncology treatment
Appropriate counselling should be available and vaginal moisturisers and lubricants should be prescribed to all women following RRS
Short term use of HRT to alleviate menopausal symptoms following RRSO is safe amongst healthy *BRCA1/2* mutation carriers
No safety data are available about the use of HRT amongst *BRCA1/2* carriers with a previous diagnosis of breast cancer. The relationship between hormonal influences and the development of different breast cancer subtypes, including triple negative breast cancers, has not been fully elucidated thus HRT in the setting of a past breast cancer diagnosis should be strongly discouraged – irrespective of endocrine status of the initial tumour
Topical oestrogens to alleviate vaginal dryness may be used with caution
As a result of premature menopause, bone health needs to be routinely monitored, preventive measures taken and any reduction in bone density treated as clinically indicated

Paluch-Shimon S, et al, Annals of Oncology, 2016

Multigene testing
Why do this?

- **More cost effective** (for the testing) to do multigene rather than serial testing
- **Patients (and providers!) can get testing fatigue**
- **The same cancer can be seen with different genes mutations**
  - Ovarian cancer in both *BRCA1/2* and Lynch
  - Uterine cancer in Lynch and Cowden
  - Breast in Li-Fraumeni and *BRCA1/2*
- **Isn't more better?**

Management of Mutation Carriers
Consider…

- ***Psychosocial support to assist with:***
  - Adjusting to new information
    - most adjust within 3-6 months
    - subset remain psychologically distressed (16-25% anxiety and/or depression)
  - Making decisions regarding management

    "to inflict surgery is a hard decision to make… when I don't have the disease and feel healthy"
  - Addressing family issues, self concept, body image
  - Dealing with future concerns i.e. child bearing, surgical menopause after oophorectomy
- ***Referral to support groups***

In conclusion – in BRCA+ BC

- Germline testing has therapeutic implications in the setting of ABC
- Platinum agents have been demonstrated to be superior in triple negative BRCA+ MBC
- PARPi – Phase III data that superior to TPC
- Future studies – PARPi in the adjuvant setting immunotherapy, drug combinations to overcome PARPi resistance

In conclusion – in BRCA+ BC (cont.)

- ***All BRCA+ patients should be offered participation in clinical trials!!!***

Genetic testing in BC patients – when is the right time?

The question is not **if** to test, but **when** to test

Thank you