BRCA, HRD and PARPi: Therapies for TNBC

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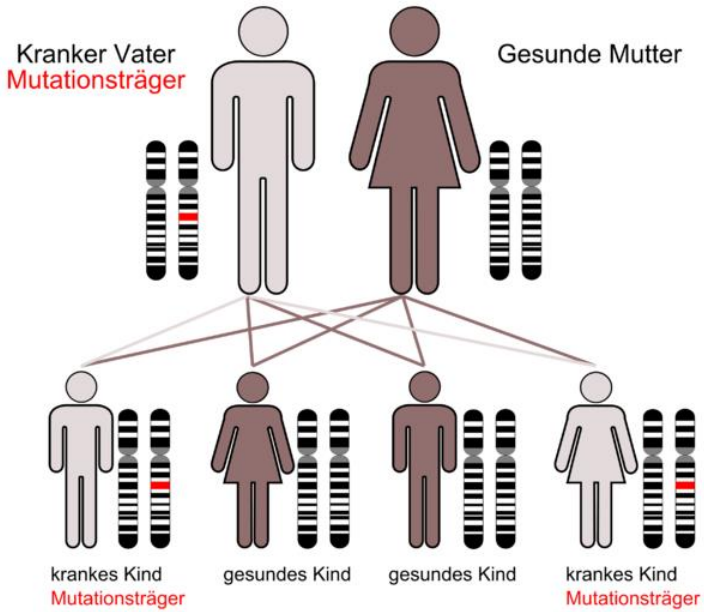
Prevalence of BRCA Germline Mutations

- Prevalence of BRCA 1 or 2 mutations (USA) : 1 in 300
- Males and females can carry and transmit BRCA mutations to offsprings
- BRCA1 and 2 mutations are more common in ethnic subgroups („founder mutations“)
  - Ashkenazi Population: 1 in 40
  - Islandic Population: 1 in 170



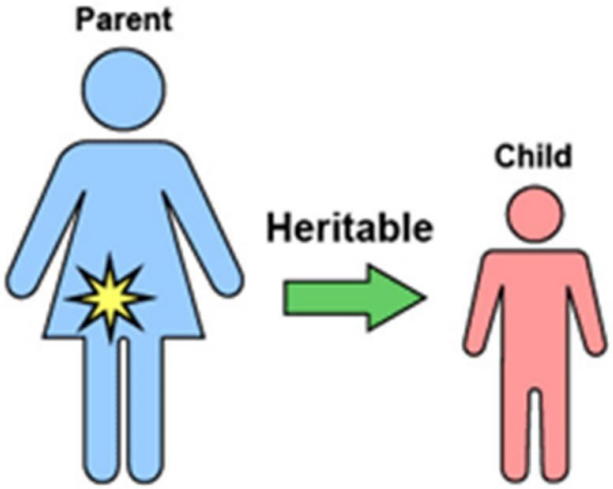
Somatic vs Germline BRCA 1/2 Mutations

Somatic mutations
- Occur in ***nongermline*** tissues
- **Cannot be Inherited if the mutation occurs after the germline differentiates**

Nonheritable

Mutation in tumor only
(for example, breast)

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

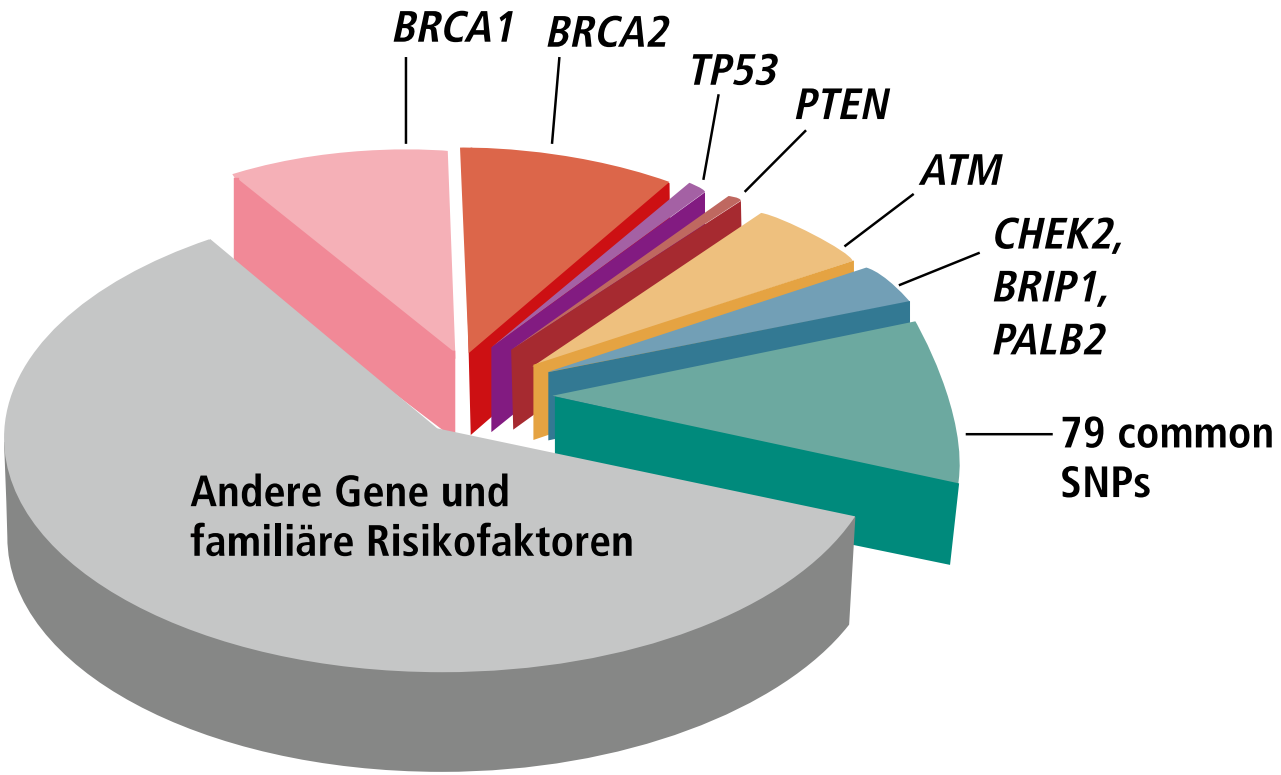


Mutation in
egg or sperm

All cells
affected in
offspring

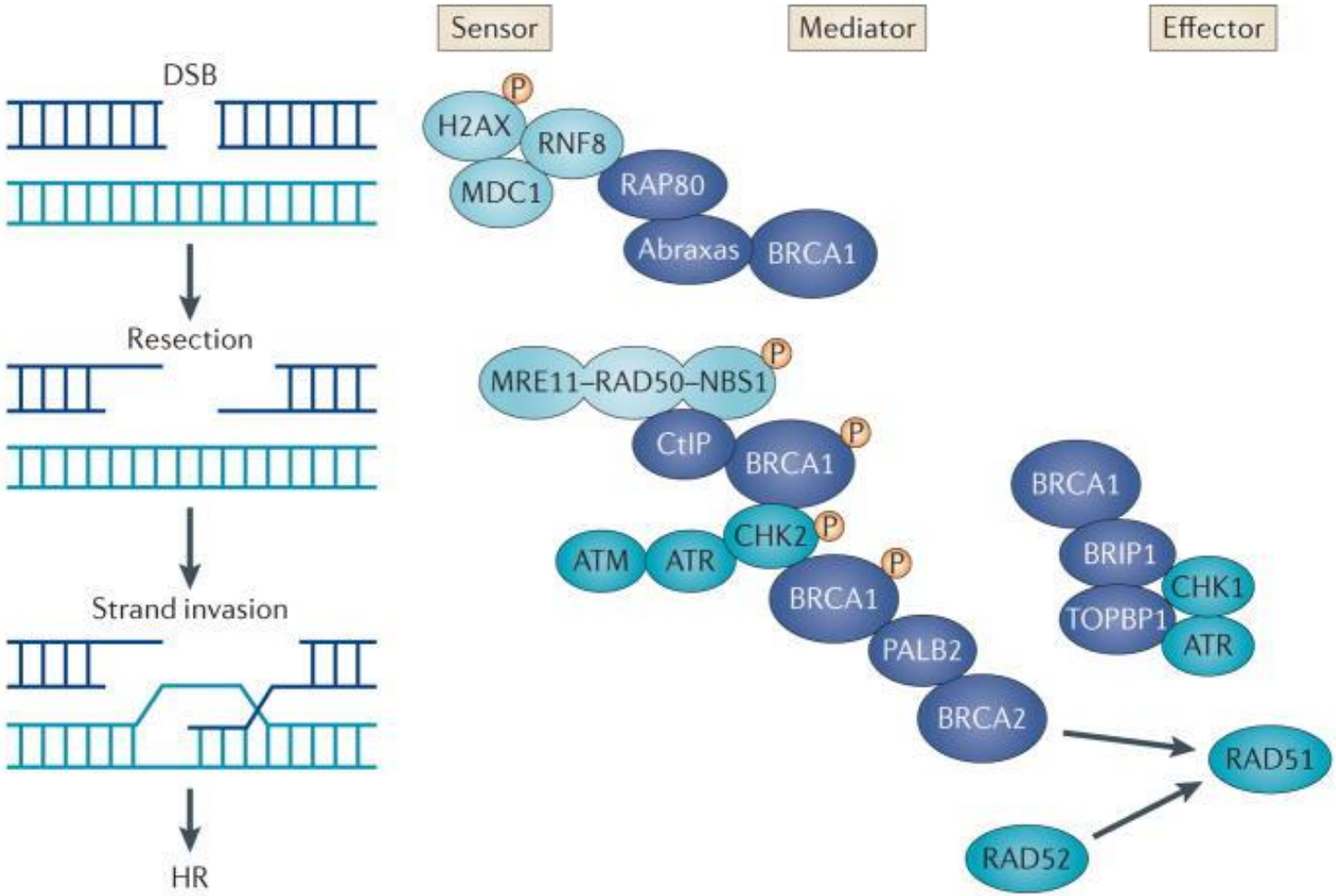
Adapted from the NCI and the Americal Society of Clinical Oncology

Germline Mutations and Breast Cancer



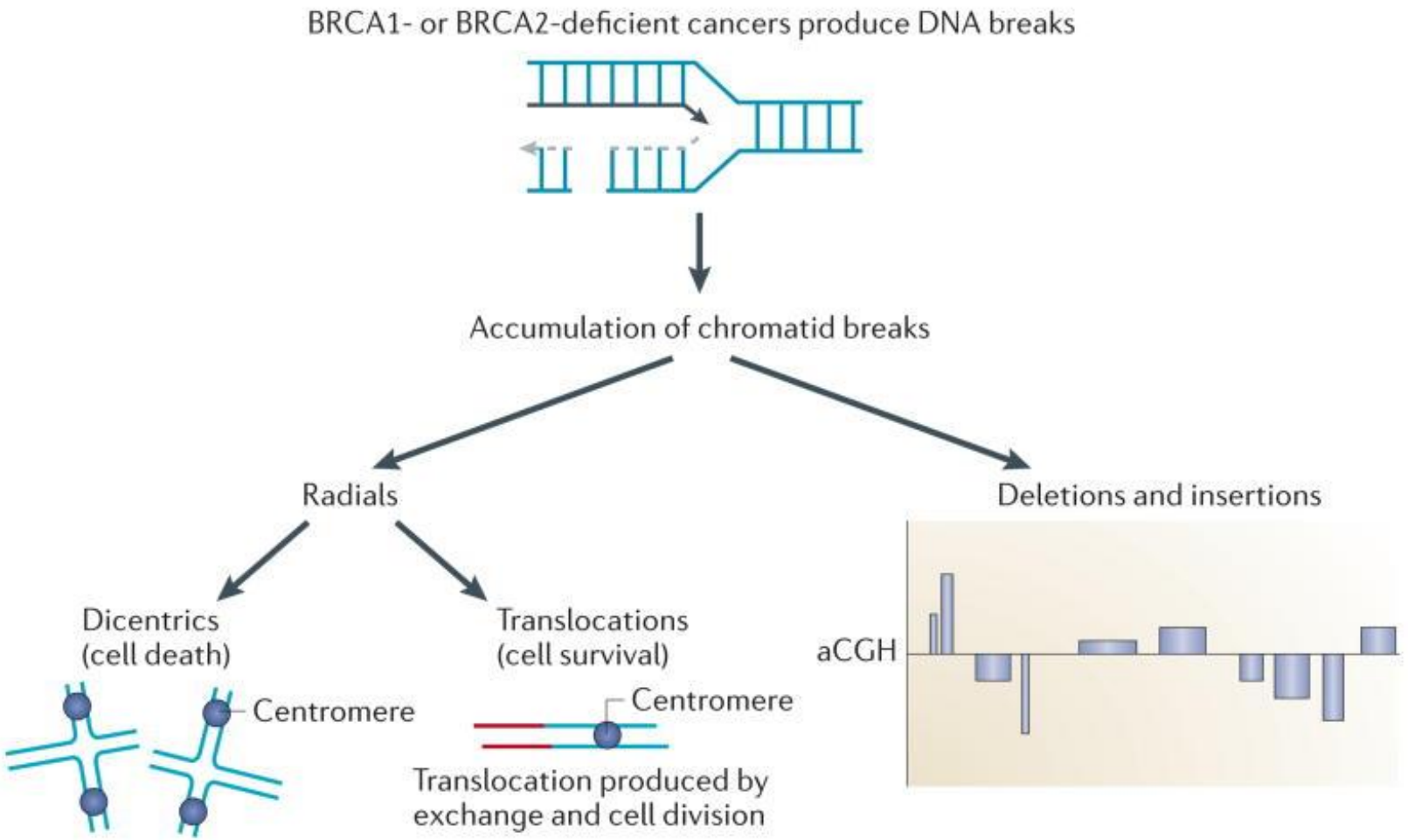
Balmaña J, *et al. Ann Onco*l 2011(Supp 4):iv19–iv20
Venkitaraman AR. *J Cell Sci* 2001;114:3591–3598

Molecular Mechanisms of Cancer Response



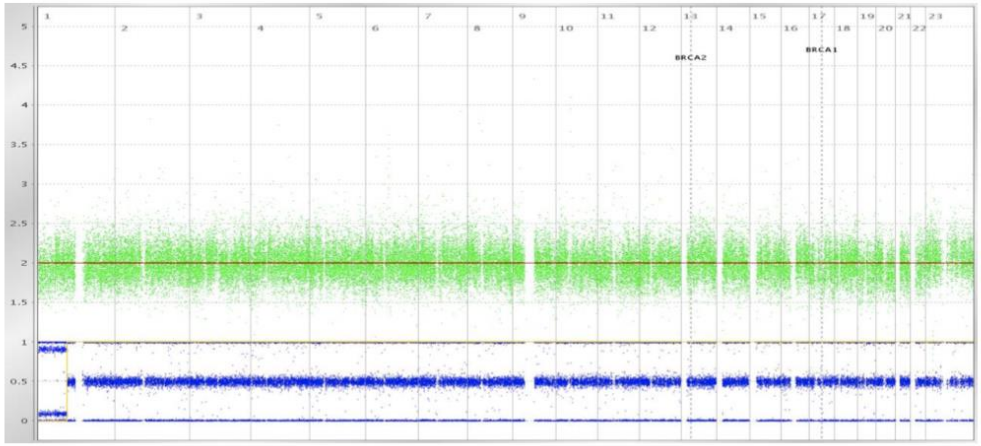
Roy *et al.* Nat Rev Cancer. 2012

BRCA-deficient Cells accumulate Chromatid Breaks and Chromatid Exchanges



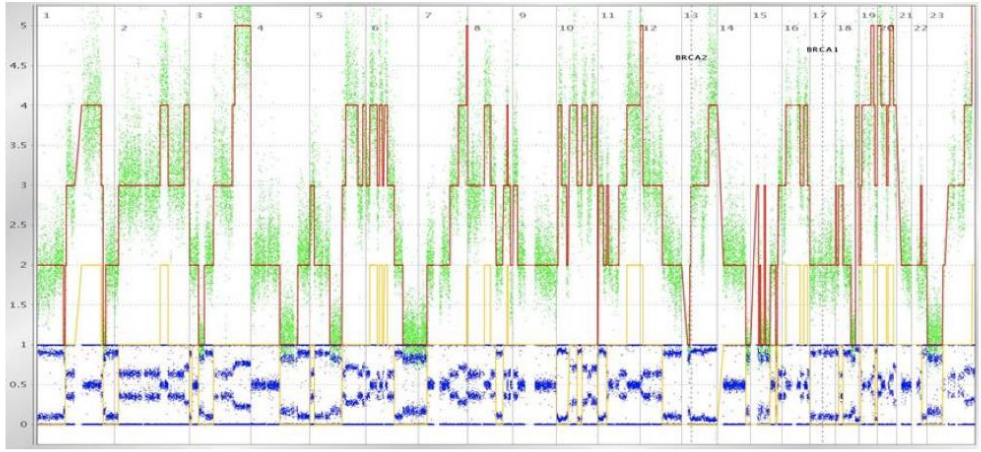
Roy *et al.* Nat Rev Cancer. 2012

Genome Profiles are Pictures of Instability in Tumor DNA



myChoice HRD Negative
(myChoice HRD Score = 3)

Cutoff = 42



myChoice HRD Positive
(myChoice HRD Score = 81)

genomic instability caused by HRD

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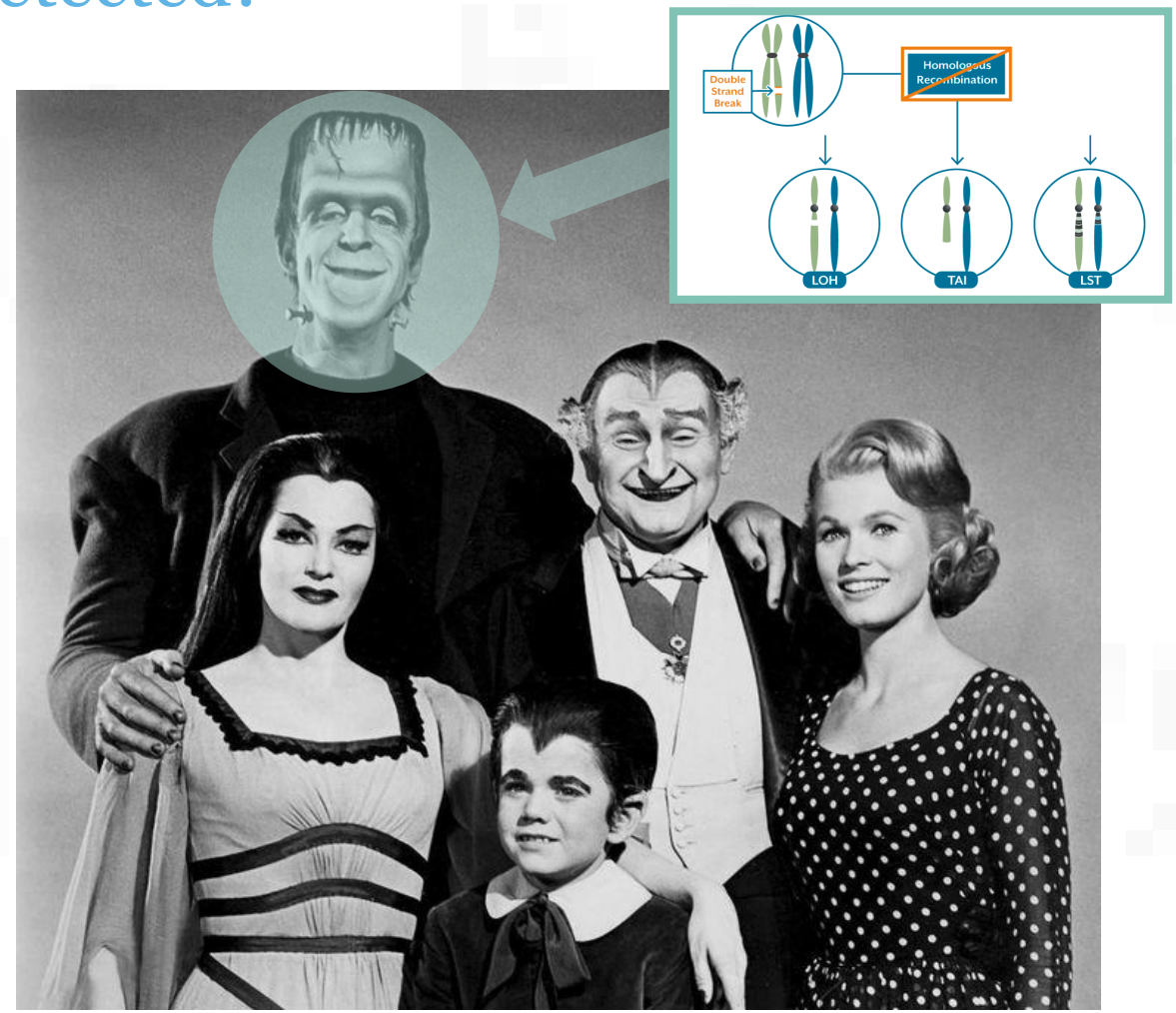
BRCA Inactivation in TNBC

a. Frequency of BRCA mutations in all TNBCs [a]			
	Neoadjuvant (*n* =152)	**Familial (*n* =134)**	**Adjuvant (*n* =91)**
Mutation analysis			
BRCA1 (%)	27 (24)	0 (0)	9
BRCA2 (%)	2 (2)	0 (0)	4
BRCA1 UV (%)	2 (2)	16 (22)	0
BRCA2 UV (%)	1 (1)	7 (9)	0
Wild type (%)	80 (71)	51 (69)	0
ND	40	60	78
b. Frequency of BRCAness in all TNBCs without BRCA1/2 mutations [b]			
	Neoadjuvant (*n* =123)	**Familial (*n* =134)**	**Adjuvant (*n* =78)**
aCGH			
BRCA1 like (%)	70 (66)	92 (69)	53 (68)
Non-BRCA1 like (%)	35 (34)	42 (31)	25 (32)
ND	18	0	0
BRCA1 promoter methylation			
Methylated (%)	31 (29)	47 (37)	21 (27)
Unmethylated (%)	75 (71)	81 (63)	56 (73)
ND	17	6	1

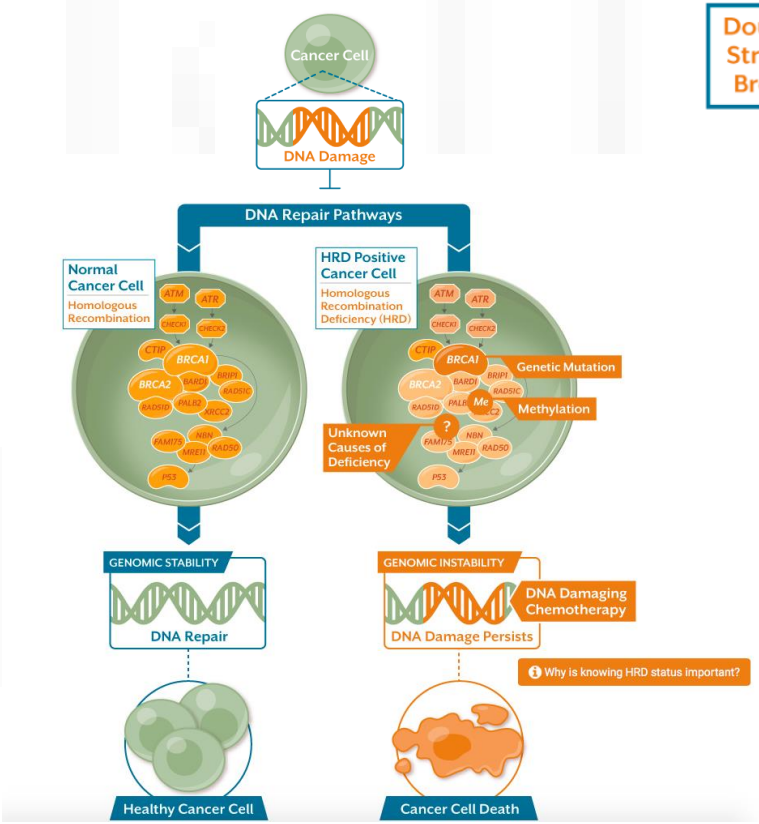
Lips *et al.* Br J Cancer. 2013

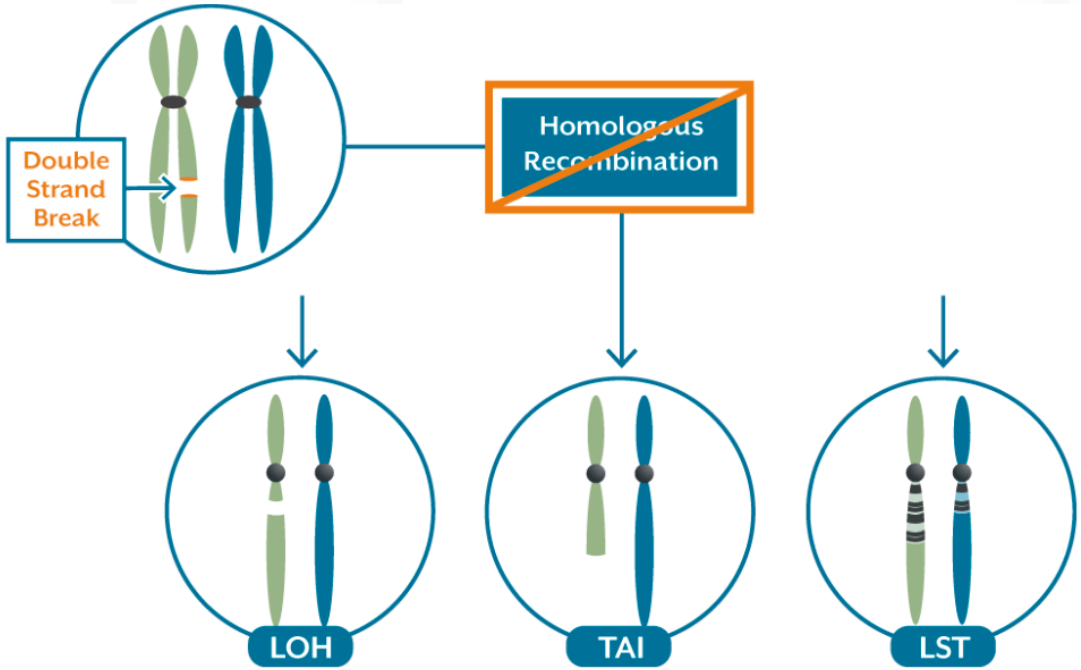
Homologous Recombination Deficience (HRD)

How is it Detected?



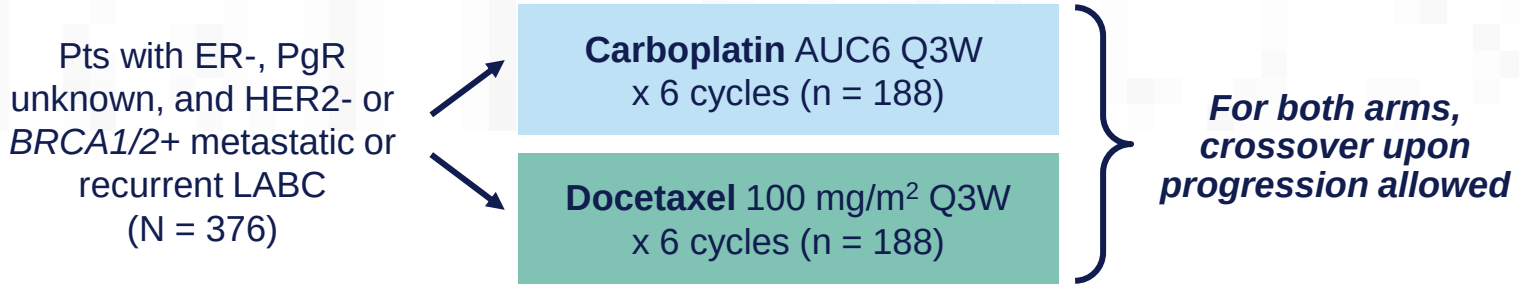
What is Homologous Recombination Deficiency („HRD“)?





LOH: Loss of Heterozygosity
TAI: Telomeric Allelic Imbalance
LST: Large Scale State Transitions

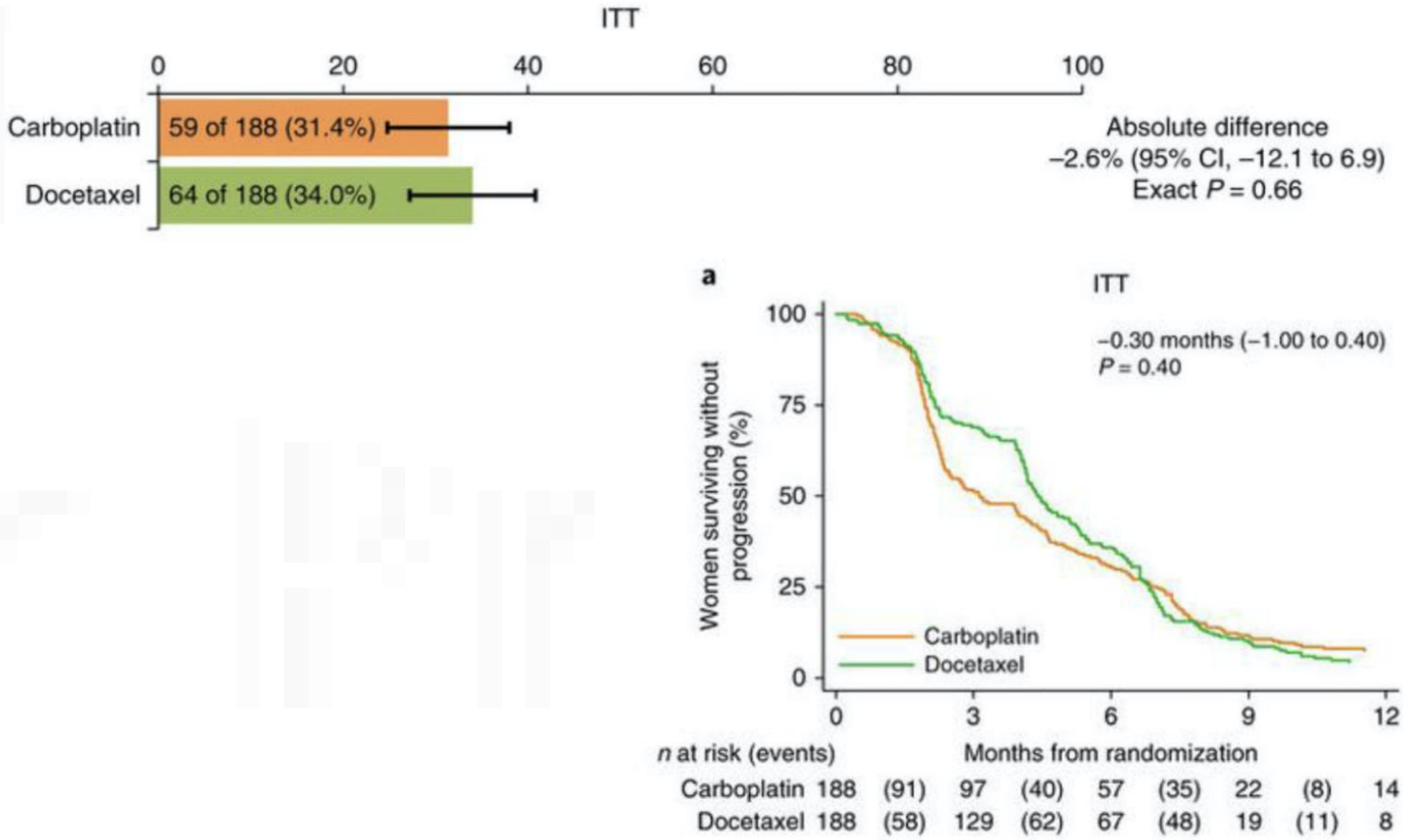
TNT: Carboplatin vs Docetaxel in Advanced TNBC or *BRCA1/2*+ Breast Cancer



- Primary endpoint: ORR in ITT population
- Secondary endpoints: PFS, OS, ORR (crossover), toxicity
- Subgroup analyses: *BRCA*1/2 mutation, basallike subgroups, HRD biomarkers

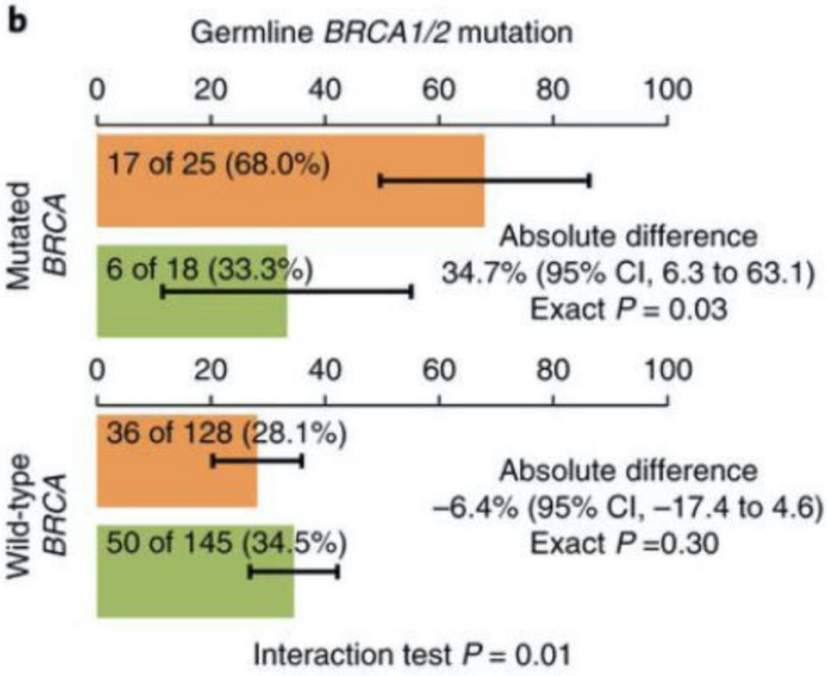
Tutt A, et al. NEJM 2019

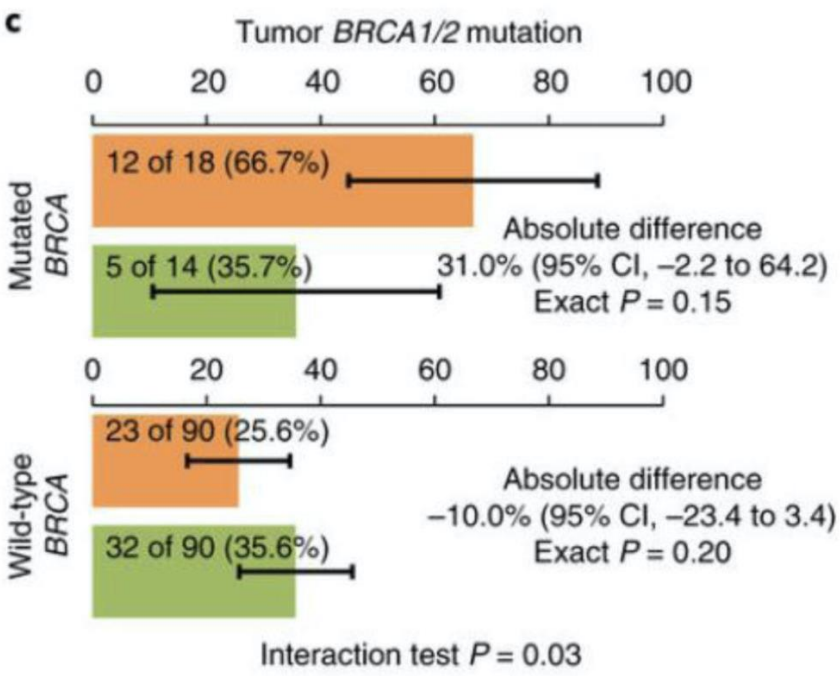
TNT: Overall Response Rate and PFS (ITT Population)



Tutt A, et al. NEJM 2019

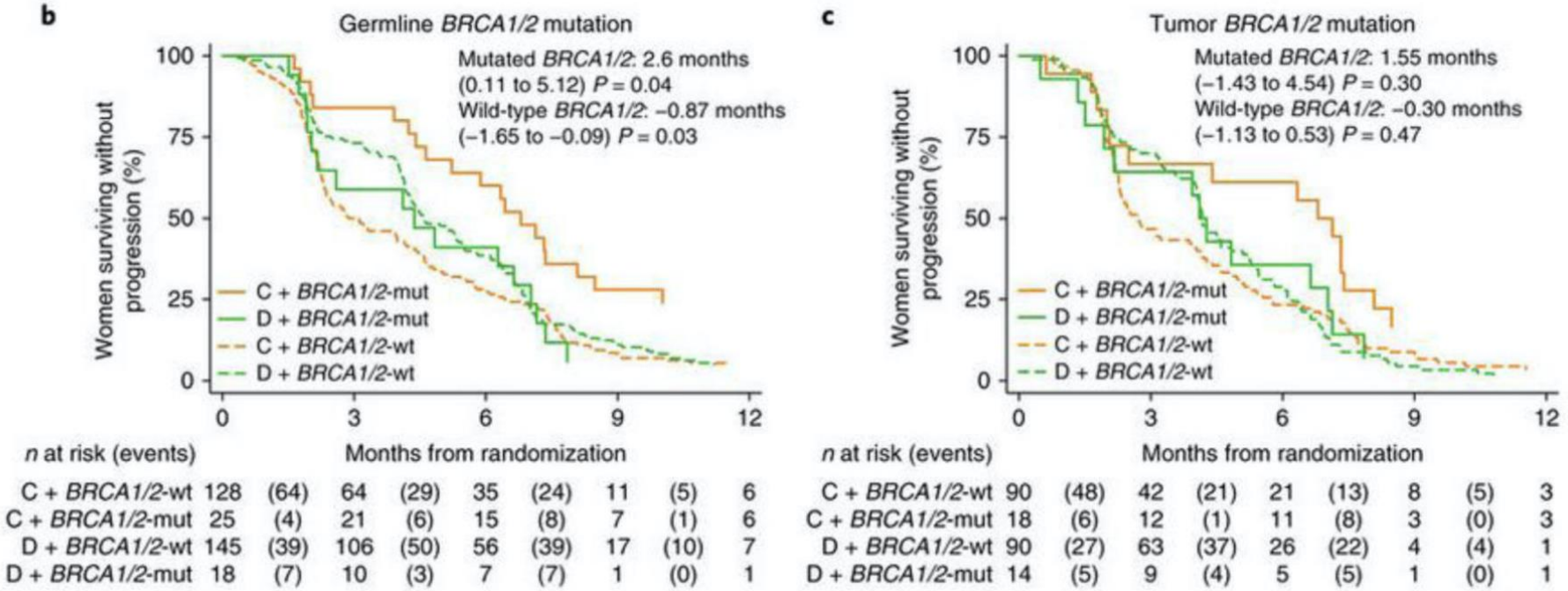
TNT: Overall Response Rate (wt vs mut)





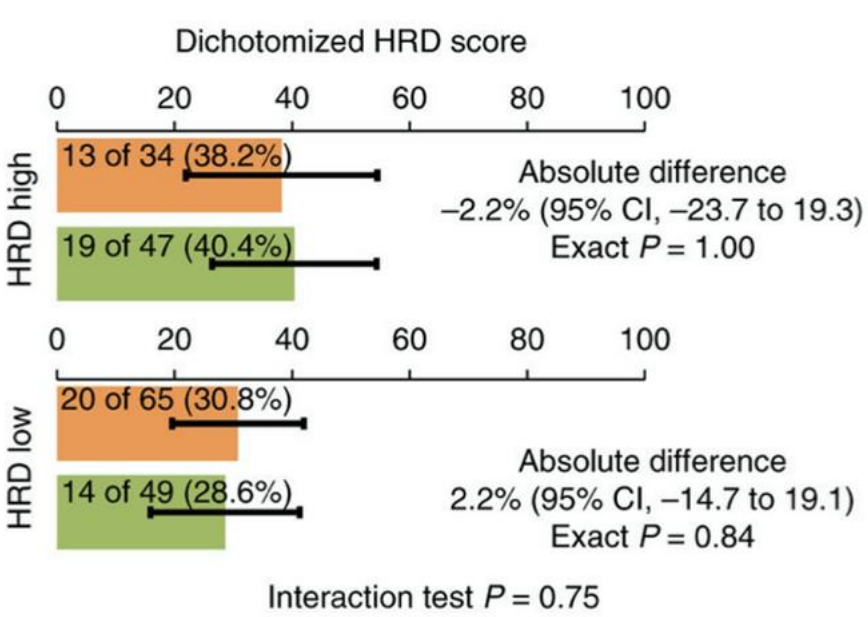
Tutt A, et al. NEJM 2019

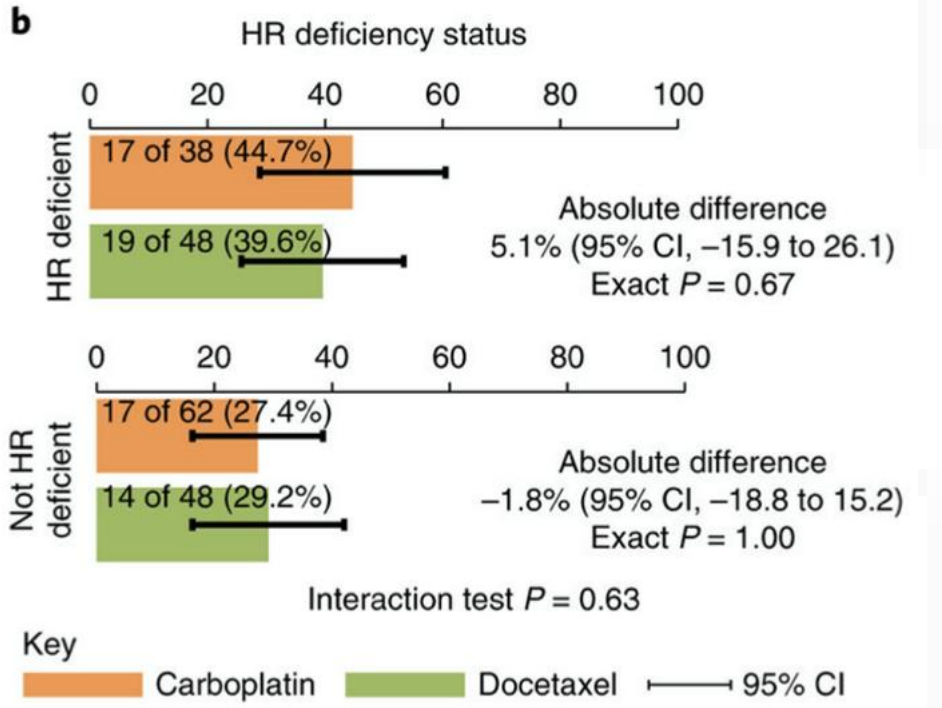
TNT: Progression-free Survival (wt vs mut)



Tutt A, et al. NEJM 2019

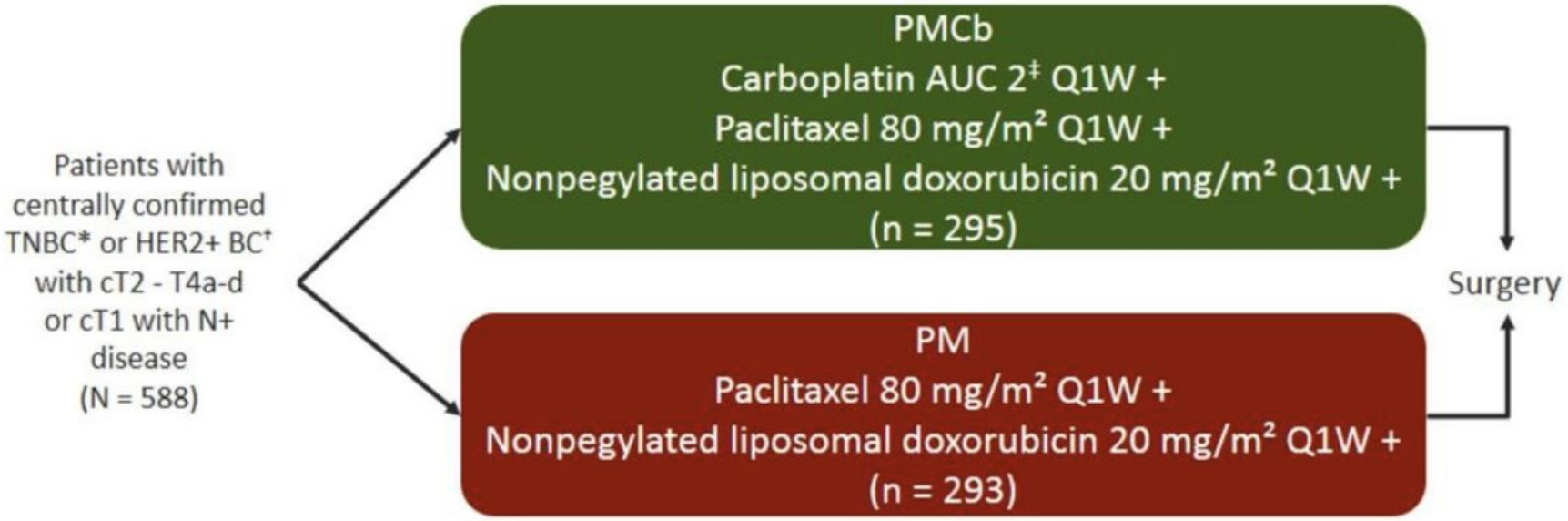
TNT: Overall Response Rate by HRD





Tutt A, et al. NEJM 2019

GeparSixto Trial



- Primary endpoint: pCR
- Secondary endpoints: RFS, DFS, OS

*TNBC pts also received bevacizumab 15 mg/kg IV Q3W.
†HER2+ BC patients also received trastuzumab.
8 mg/kg IV (initial dose), then 6 mg/kg IV Q3d (subsequent doses) and lapatinib 750 mg QD.
‡Dose reduced to AUC 1.5 after 330 patients enrolled.

vonMinckwitz G, et al. Lancet Oncol 2014

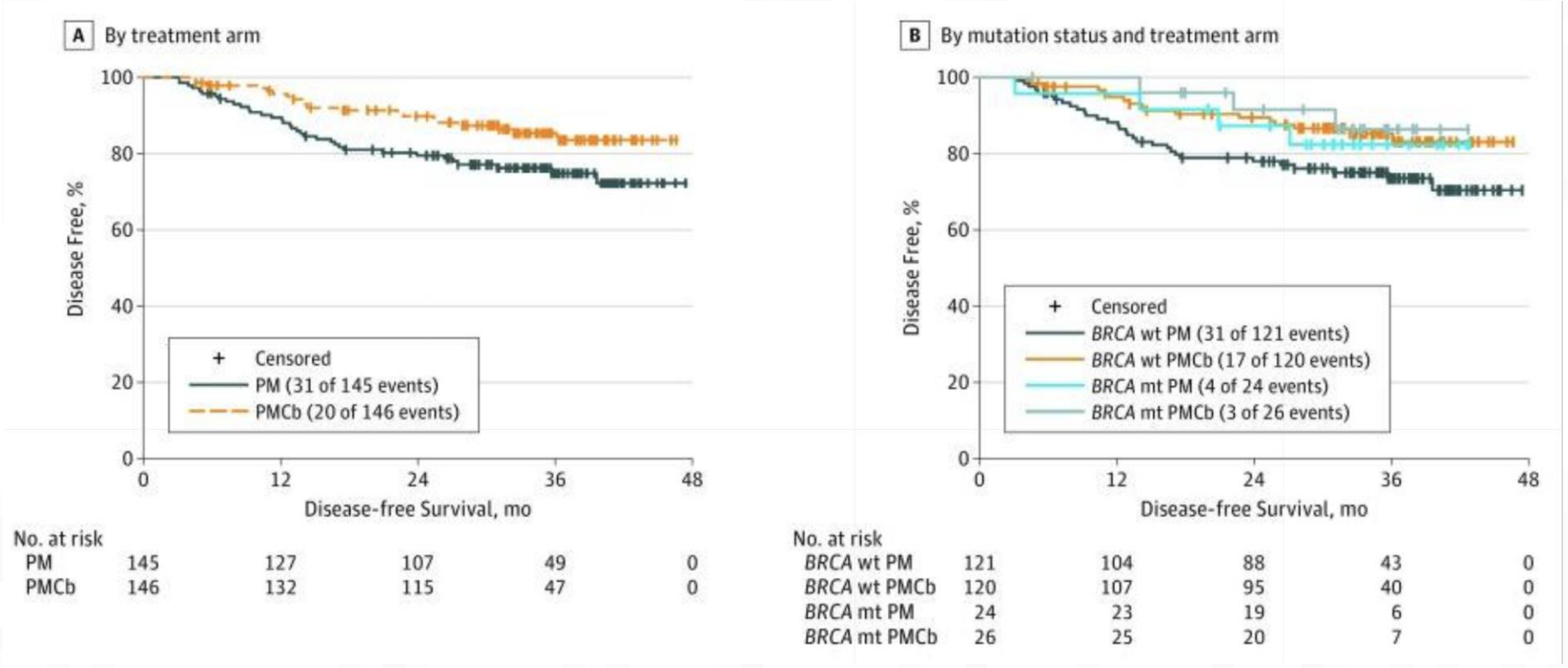
GeparSixto and pCR (wt vs mut)

Type of Treatment	pCR[a]		Mutant vs Wild-type *BRCA*		pCR[b]		Mutant vs Wild-type *BRCA*	
	Yes	No	OR (95% CI)	*P* Value	Yes	No	OR (95% CI)	*P* Value
Noncarboplatin arm, No. (%)								
Overall (n = 145)	60 (41.4)	85 (58.6)			52 (35.9)	93 (64.1)		
Mutant (n = 24)	16 (66.7)	8 (33.3)	3.50 (1.39-8.84)	.008	12 (50.0)	12 (50.0)	2.03 (0.84-4.91)	.12
Wild-type (n = 121)	44 (36.4)	77 (63.6)			40 (33.1)	81 (66.9)		
Carboplatin arm, No. (%)								
Overall (n = 146)	83 (56.8)	63 (43.2)			77 (52.7)	69 (47.3)		
Mutant (n = 26)	17 (65.4)	9 (34.6)	1.55 (0.64-3.74)	.33	16 (61.5)	10 (38.5)	1.55 (0.65-3.68)	.32
Wild-type (n = 120)	66 (55.0)	54 (45.0)			61 (50.8)	59 (49.2)		

- Addition of Cb improves pCR
- Cb benefit restricted to patients without gBRCA mutation
- Patients with gBRCA mutation have superior response rates but no additive effect of Cb

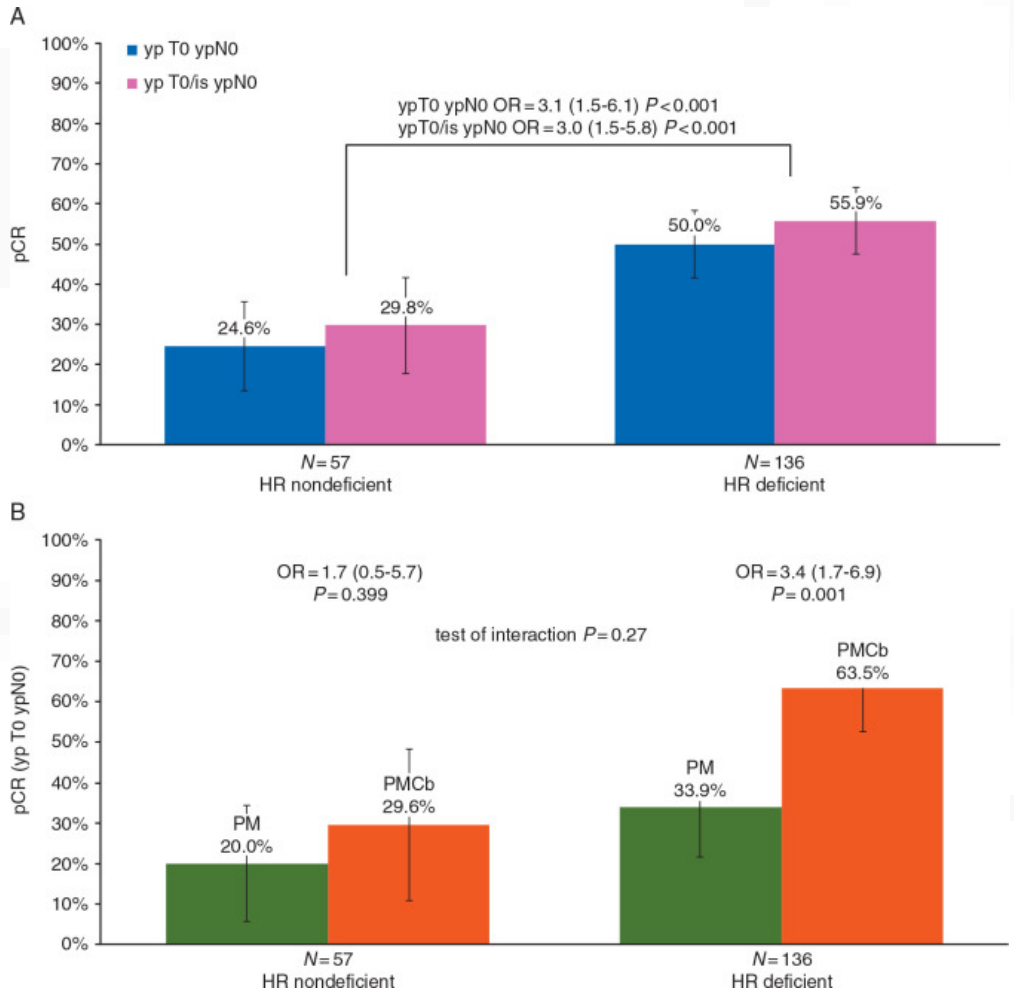
vonMinckwitz, et al. Lancet Oncol 2014
Hahnen, et al. JAMA Oncol 2017

GeparSixto: DFS and gBRCA



Hahnen et al. JAMA Oncol, 2017

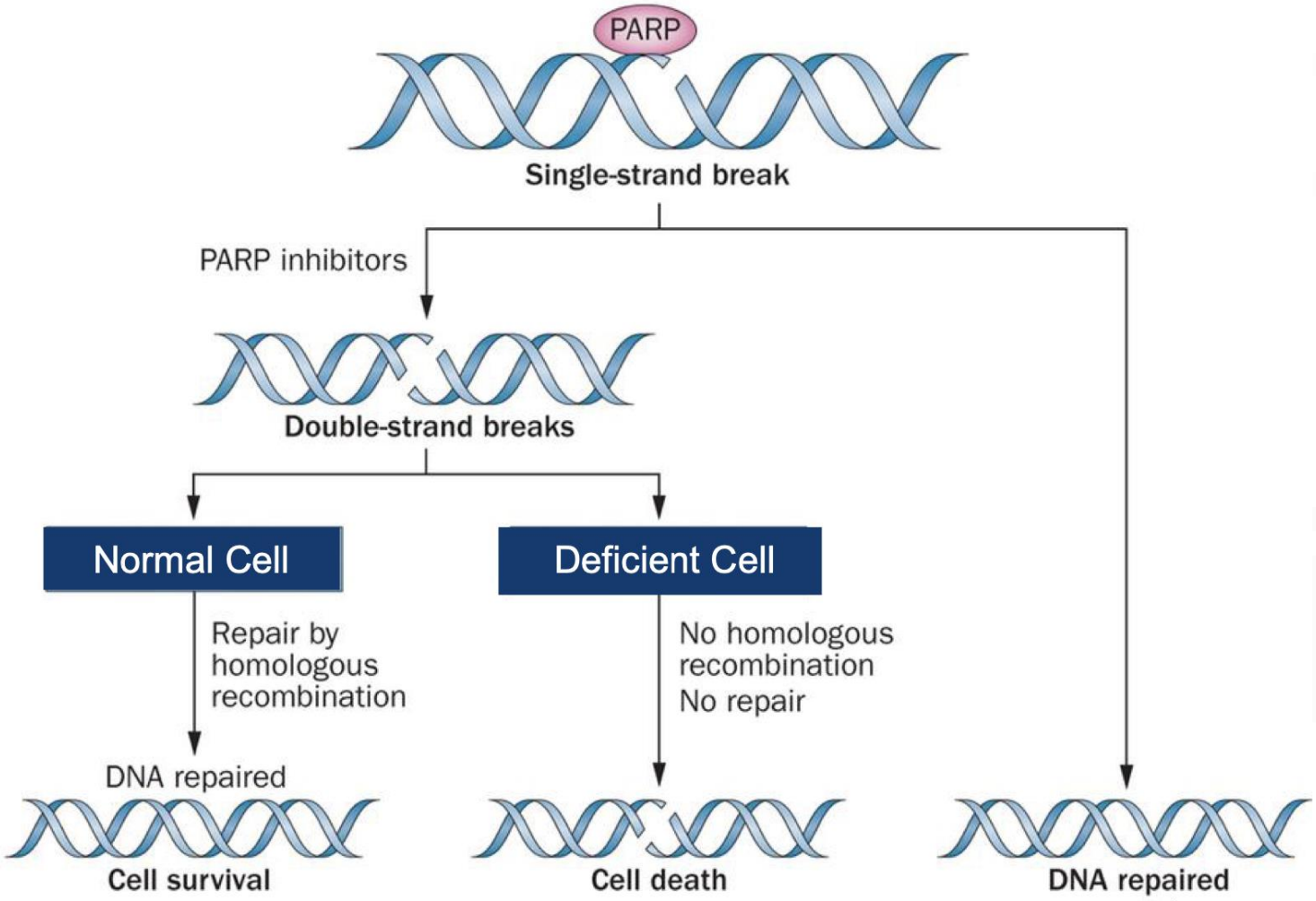
GeparSixto: Prediction of Response by HRD Status



- pCR rate is higher in HR deficient tumors
- Cb improves pCR rate in HR deficient tumors but not in HR non-deficient tumors

Loibl, Annals Oncol 2018

PARP: Mechanism of Action



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PARP Inhibitors for BC and OC

Agent	Company	Clinical Trials[a] (www.ClinicalTrials.gov identifier)
Olaparib (Lynparza)	AstraZeneca	13 active studies, including: 2 phase III trials • OlympiAD—Olaparib monotherapy vs physician's choice chemotherapy in metastatic breast cancer with germline *BRCA1/2* mutations (NCT02000622) • OlympiA—Adjuvant olaparib in germline *BRCA*-mutated high-risk HER2-negative primary breast cancer (NCT02032823)
Veliparib (ABT-888)	AbbVie	22 active studies, including: 2 phase III trials • Carboplatin + paclitaxel with or without veliparib in HER2-negative metastatic or locally advanced unresectable *BRCA*-associated breast cancer (NCT02163694) • 3-arm trial of carboplatin + paclitaxel followed by doxorubicin/cyclophosphamide (AC) with or without veliparib vs placebo + paclitaxel followed by AC in early-stage triple-negative breast cancer (NCT02032277)
Rucaparib	Clovis Oncology	2 ongoing phase I and II studies
Niraparib	Tesaro	1 active phase III study: • BRAVO—Niraparib vs physician's choice in HER2-negative, germline *BRCA* mutation-positive breast cancer (NCT01905592)
Talazoparib (BMN-673)	BioMarin Pharmaceutical	10 studies,[b] including: 1 phase III trial • EMBRACA—Talazoparib vs physician's choice in patients with advanced and/or metastatic germline *BRCA*-mutated breast cancer (NCT01945775)

[a]Some studies listed as active are ongoing but not recruiting participants.
[b]Some studies have not yet started recruiting participants.

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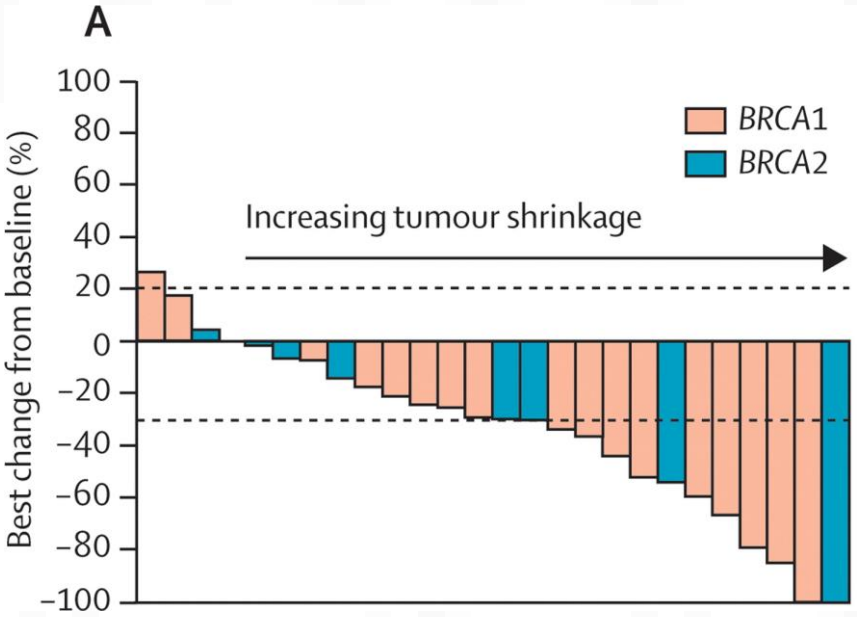
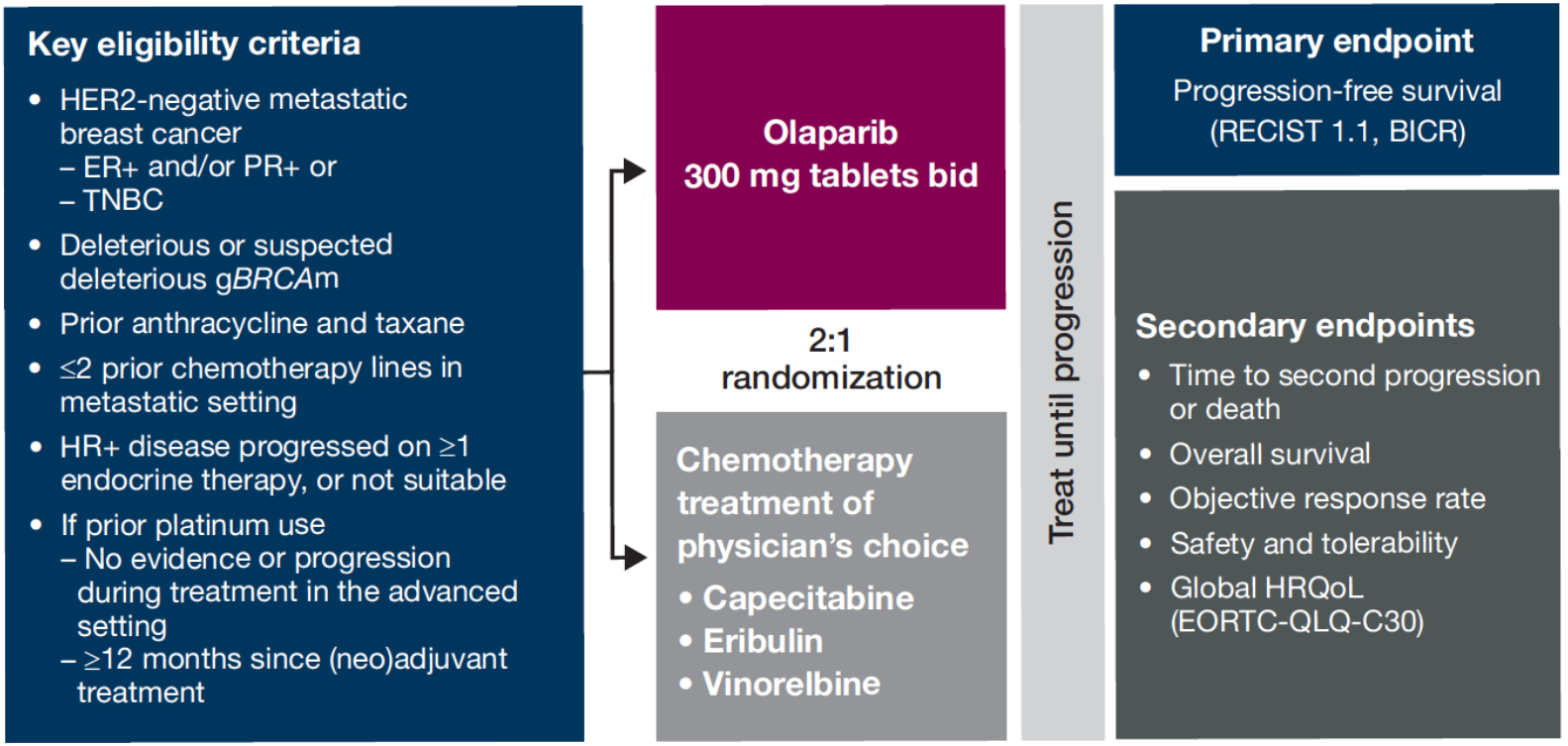
Olaparib Monotherapy in Advanced BRCA1/2 deficient Breast Cancer



Tutt et al, Lancet 2010

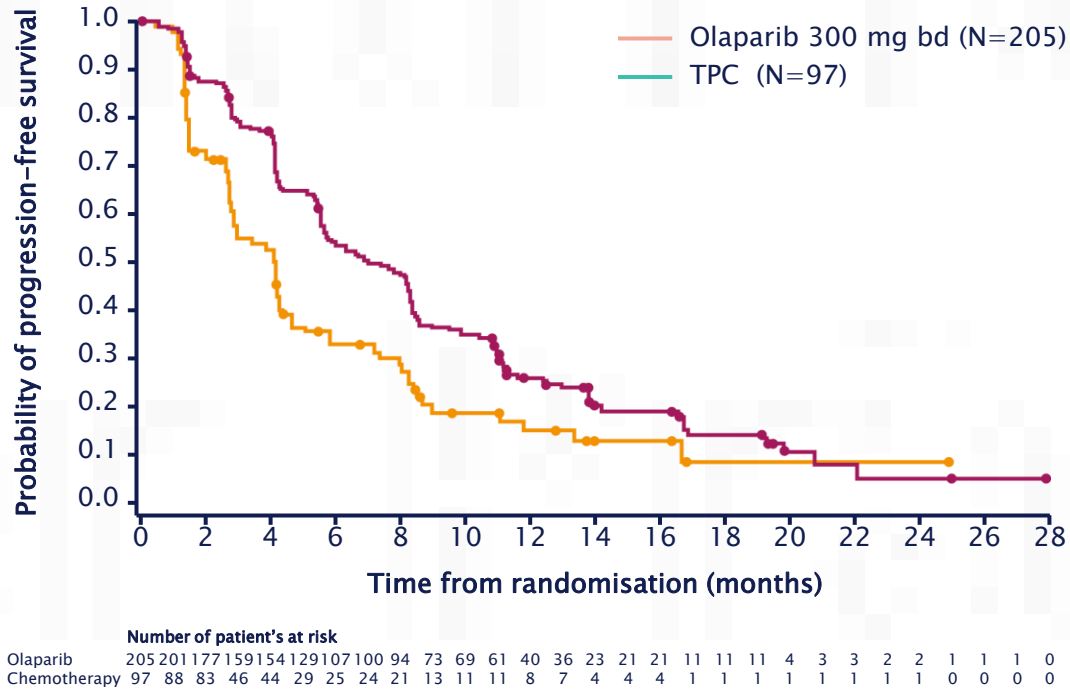
OlympiAD
Studiendesign



Robson et al, NEJM 2017

OlympiAD – Primary Endpoint

Progression-Free Survival (BICR)



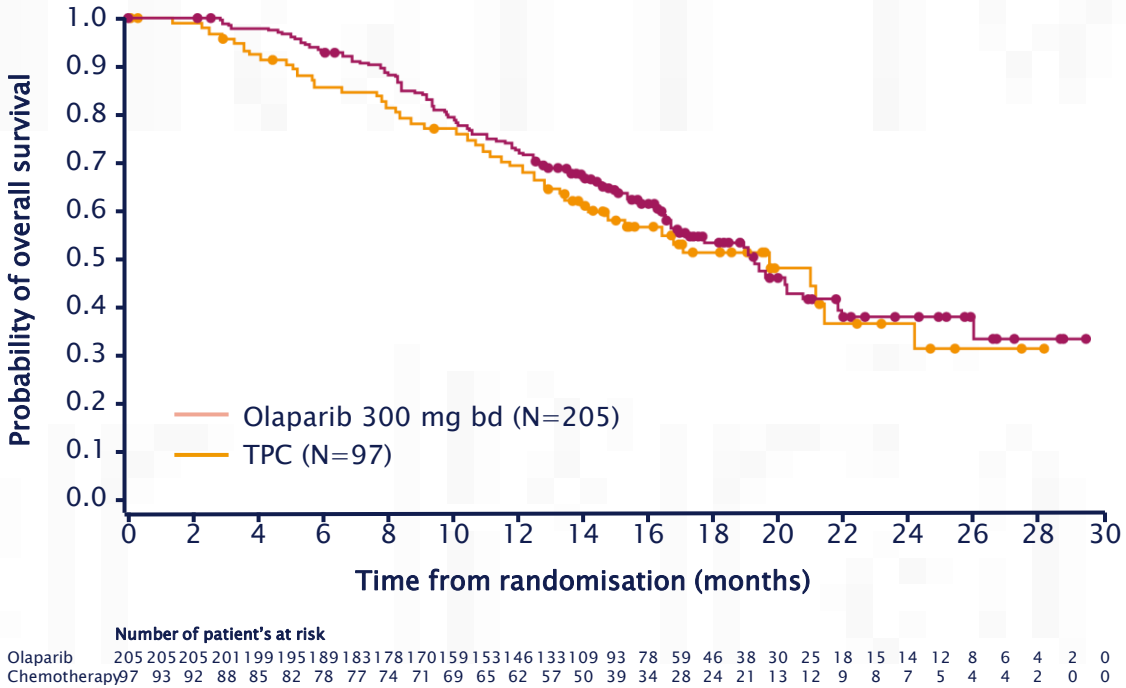
	Olaparib	TPC
n	205	97
Events (%)	163 (79.5%)	71 (73.2%)
Median (m)	7.0	4.2
	HR = 0.58 95 % CI (0.43, 0.80) p=0.0009	
PFS free at 6m (%)	54.1	32.9
PFS free at 12m (%)	25.9	15.0

Median PFS was improved by 69% with olaparib treatment compared to standard of care chemotherapy[2]

- BICR: blind independent centralised review – FAS; Maturity rate: 234/302=77%
- Stratified log rank test, stratified by previous chemotherapy for MBC (yes/no) and HR+ versus TNBC. 2 sided p value
- 1. Robson et al. N Engl J Med. 2017; Epub ahead of print; 2. AZ data on file (2017)

OlympiAD – Secundary Endpoint

Overall Survival (OS)



	Olaparib	TPC
n	205	97
Events (%)	94 (45.9%)	46 (47.4%)
Median (m)	19.3	19.6
	HR = 0.90 95 % CI (0.63, 1.29) p=0.57	

Currently 8 patients in the TPC arm received subsequent treatment with PARP inhibitors[1]

- Maturity rate: 140/302=46% 2 sided p value
- 8 control arm patients have received a subsequent PARPi
- 1. Robson et al. N Engl J Med. 2017; Epub ahead of print

OlympiAD – Secondary Endpoints

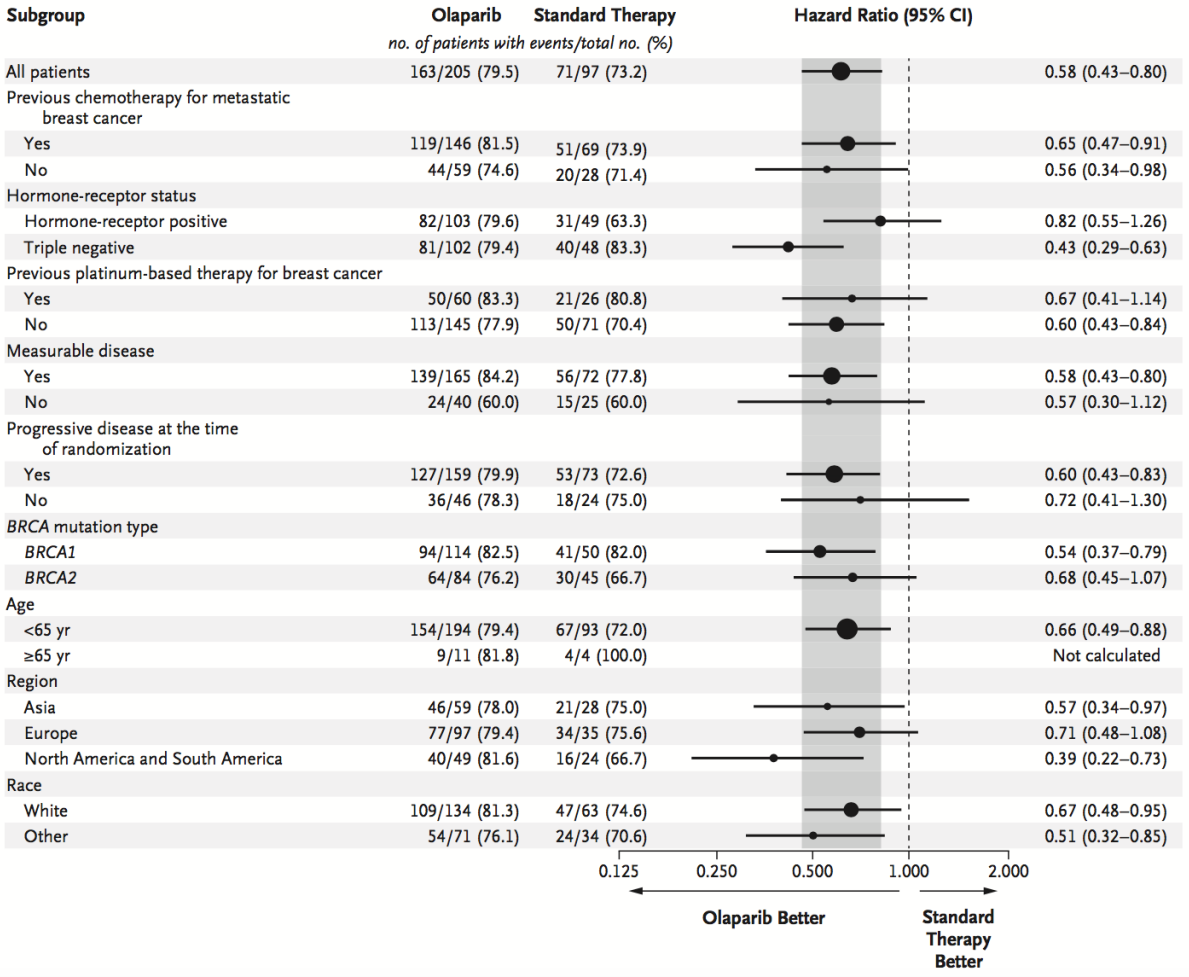
Response Rates and Duration of Response

	Olaparib	TPC
Response Evaluable Population, n	167	66
ORR, n (%)	100 (59.9)	19 (28.8)
Complete Response, n (%)	15 (9.0)	1 (1.5)
Partial Response, n (%)	85 (51.0)	18 (27.3)
Median Duration of Response, months (95%CI)	6.4 (2.9–9.7)	7.1 (3.2–12.2)
Median Time to Onset of Response, days	47	45

Adapted with permission[1]

- BICR Review
- 1. Robson et al. N Engl J Med. 2017; Epub ahead of print

OlympiAD
Subgroup Analysis

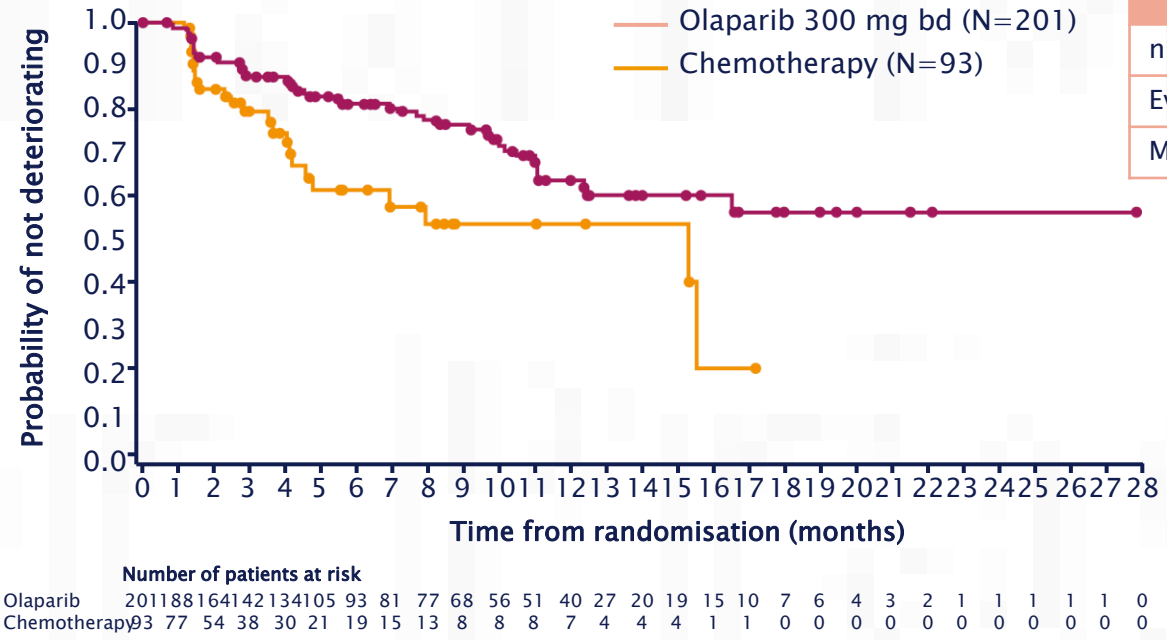


Subgroup	Olaparib	Standard Therapy	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	163/205 (79.5)	71/97 (73.2)	0.58 (0.43–0.80)
Previous chemotherapy for metastatic breast cancer			
Yes	119/146 (81.5)	51/69 (73.9)	0.65 (0.47–0.91)
No	44/59 (74.6)	20/28 (71.4)	0.56 (0.34–0.98)
Hormone-receptor status			
Hormone-receptor positive	82/103 (79.6)	31/49 (63.3)	0.82 (0.55–1.26)
Triple negative	81/102 (79.4)	40/48 (83.3)	0.43 (0.29–0.63)
Previous platinum-based therapy for breast cancer			
Yes	50/60 (83.3)	21/26 (80.8)	0.67 (0.41–1.14)
No	113/145 (77.9)	50/71 (70.4)	0.60 (0.43–0.84)
Measurable disease			
Yes	139/165 (84.2)	56/72 (77.8)	0.58 (0.43–0.80)
No	24/40 (60.0)	15/25 (60.0)	0.57 (0.30–1.12)
Progressive disease at the time of randomization			
Yes	127/159 (79.9)	53/73 (72.6)	0.60 (0.43–0.83)
No	36/46 (78.3)	18/24 (75.0)	0.72 (0.41–1.30)
BRCA mutation type			
BRCA1	94/114 (82.5)	41/50 (82.0)	0.54 (0.37–0.79)
BRCA2	64/84 (76.2)	30/45 (66.7)	0.68 (0.45–1.07)
Age			
<65 yr	154/194 (79.4)	67/93 (72.0)	0.66 (0.49–0.88)
≥65 yr	9/11 (81.8)	4/4 (100.0)	Not calculated
Region			
Asia	46/59 (78.0)	21/28 (75.0)	0.57 (0.34–0.97)
Europe	77/97 (79.4)	34/35 (75.6)	0.71 (0.48–1.08)
North America and South America	40/49 (81.6)	16/24 (66.7)	0.39 (0.22–0.73)
Race			
White	109/134 (81.3)	47/63 (74.6)	0.67 (0.48–0.95)
Other	54/71 (76.1)	24/34 (70.6)	0.51 (0.32–0.85)

Robson et al, NEJM 2017

OlympiAD

Time to Deterioation QoL Score / Health Status



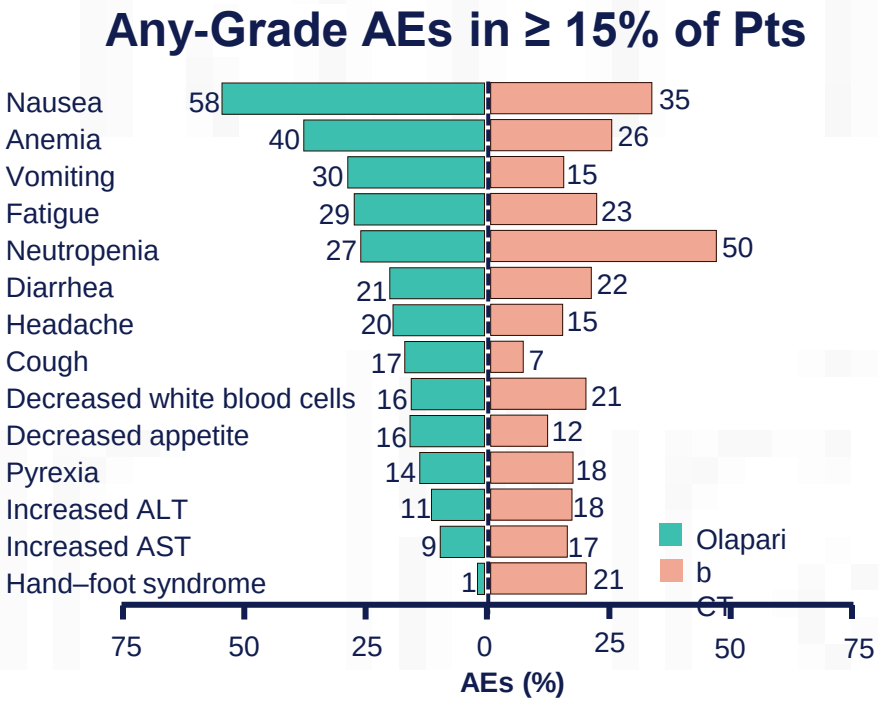
	Olaparib	TPC
n	201	93
Events (%)	49 (24%)	25 (27%)
Median (m)	NC	15.2
	HR = 0.44 95 % CI (0.25, 0.77) p=0.0043	

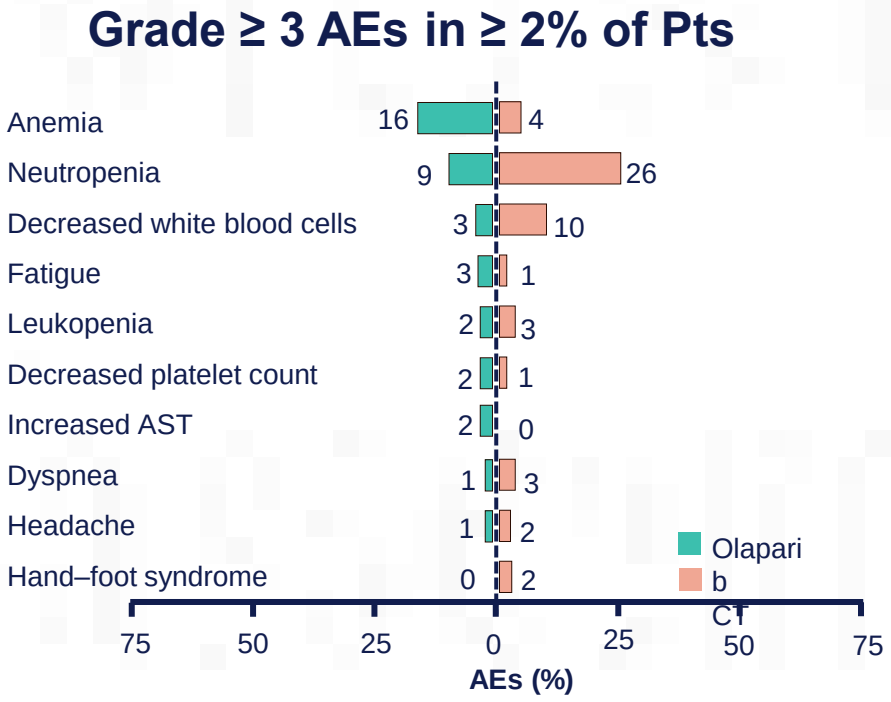
Deterioration is defined as a 10 point or more decrease from baseline

- 2 sided p value

- 1. Robson et al. N Engl J Med. 2017; Epub ahead of print; 2. Robson et al. J Clin Oncol 35, 2017 (presentation associated with abstr LBA4)

OlympiAD: Adverse Events



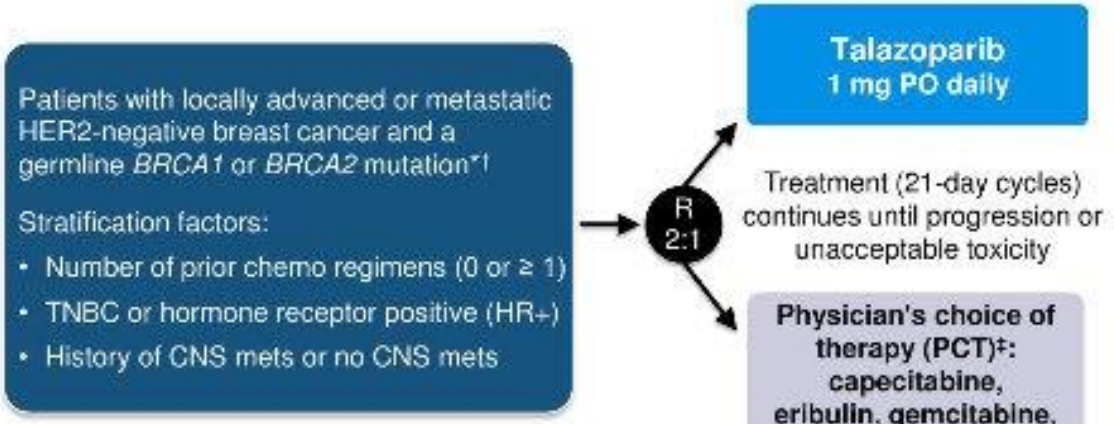


Robson ME, et al. N Engl J Med. 2017;377:523-533. Robson ME, et al. ASCO 2017. Abstract LBA4.

Slide credit: clinicaloptions.com

EMBRACA Talazoparib in BRCA+ mBC

Study Design



Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites

Primary endpoint

- Progression-free survival by RECIST by blinded central review

Key secondary efficacy endpoints

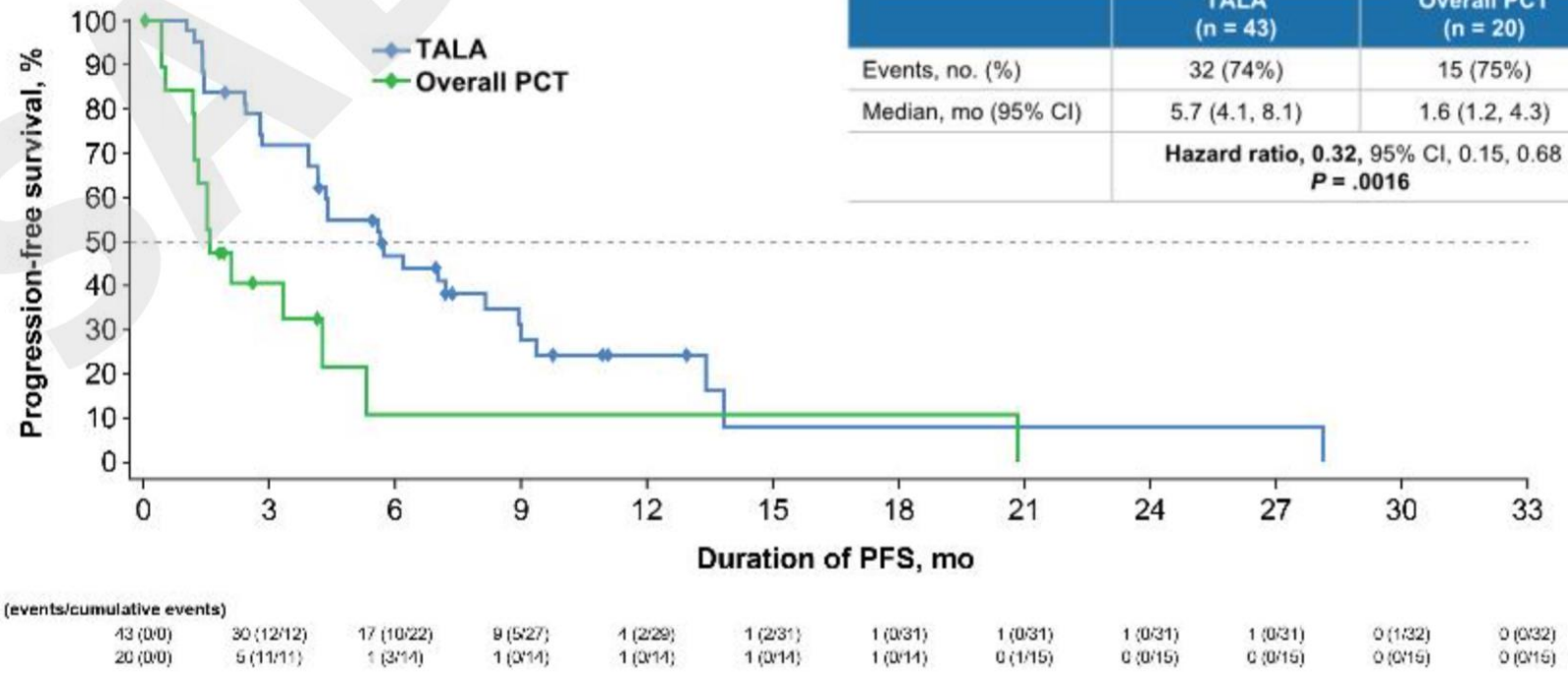
- Overall survival (OS)
- ORR by investigator
- Safety

Exploratory endpoints

- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

EMBRACA – Primary Endpoint

PFS in Patients with Brain Metastasis



	TALA (n = 43)	Overall PCT (n = 20)
Events, no. (%)	32 (74%)	15 (75%)
Median, mo (95% CI)	5.7 (4.1, 8.1)	1.6 (1.2, 4.3)
	Hazard ratio, 0.32, 95% CI, 0.15, 0.68 ***P* = .0016**	

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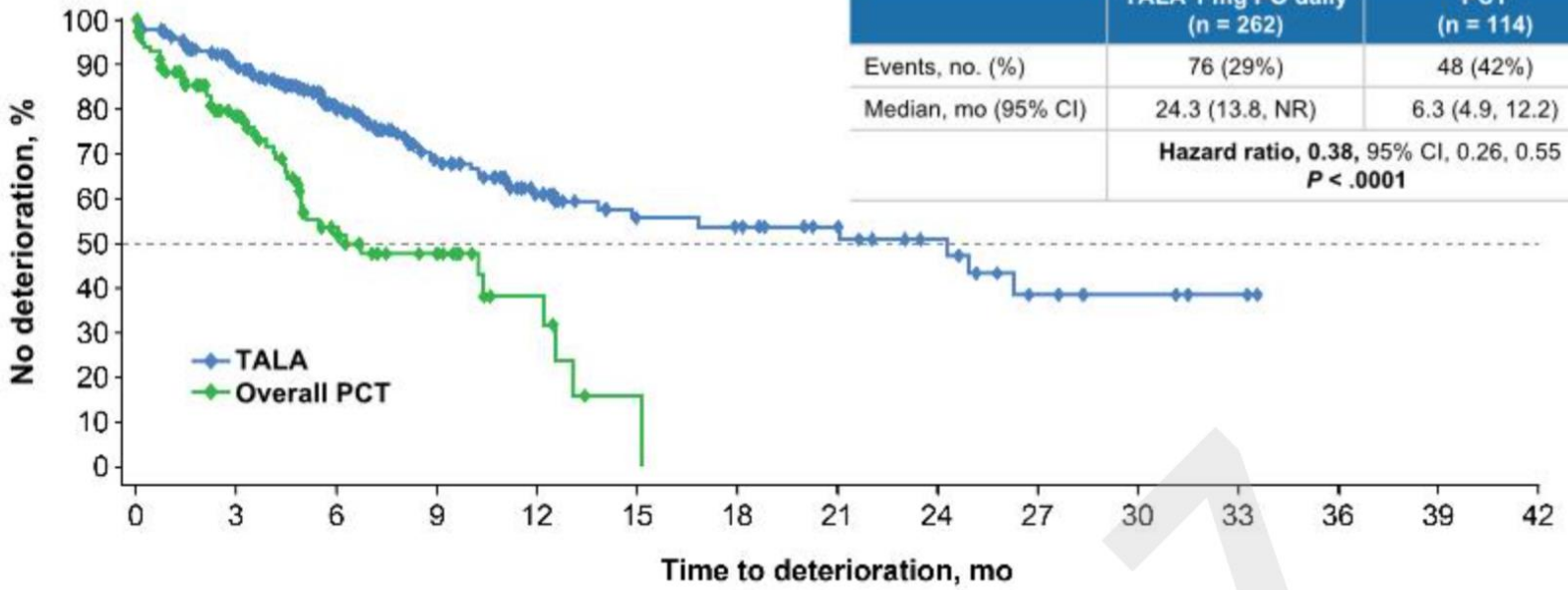
EMBRACA – Quality of Life

Time to Detoriation of QoL (EORTC QLQ-C30)

Statistically significant delay in the time to clinically meaningful deterioration* in GHS/QoL favoring TALA

	TALA 1 mg PO daily (n = 262)	PCT (n = 114)
Events, no. (%)	76 (29%)	48 (42%)
Median, mo (95% CI)	24.3 (13.8, NR)	6.3 (4.9, 12.2)
	Hazard ratio, 0.38, 95% CI, 0.26, 0.55 ***P* < .0001**	



No. at risk (events/cumulative events)														
TALA	262 (0/0)	212 (26/26)	139 (18/44)	78 (17/61)	44 (7/68)	28 (3/71)	26 (1/72)	20 (0/72)	14 (1/73)	7 (3/76)	4 (0/76)	2 (0/76)	0 (0/76)	0 (0/76)	0 (0/76)
PCT	114 (0/0)	64 (22/22)	30 (17/39)	17 (3/42)	6 (2/44)	1 (3/47)	0 (1/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)

Abbreviation: NR, not reached. *≥ 10-point decrease and no subsequent observation with a < 10-point decrease from baseline.

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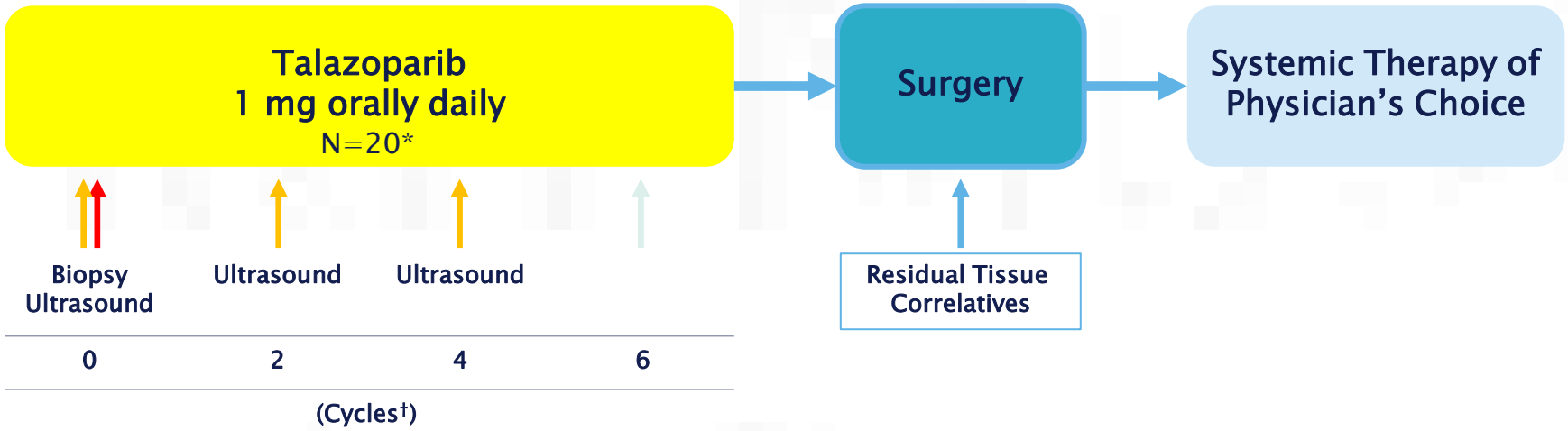
Neoadjuvant Talazoparib for EBC with *mBRCA*



Eligibility

- Tumors > 1 cm
- Clinical Stage I–III
- *BRCA* pathogenic variant
- No previous therapy for invasive breast cancer

Exclusion

- HER2+

Primary Objectives

- pCR (ypTO/is ypNO)
- RCB-0 + RCB-I

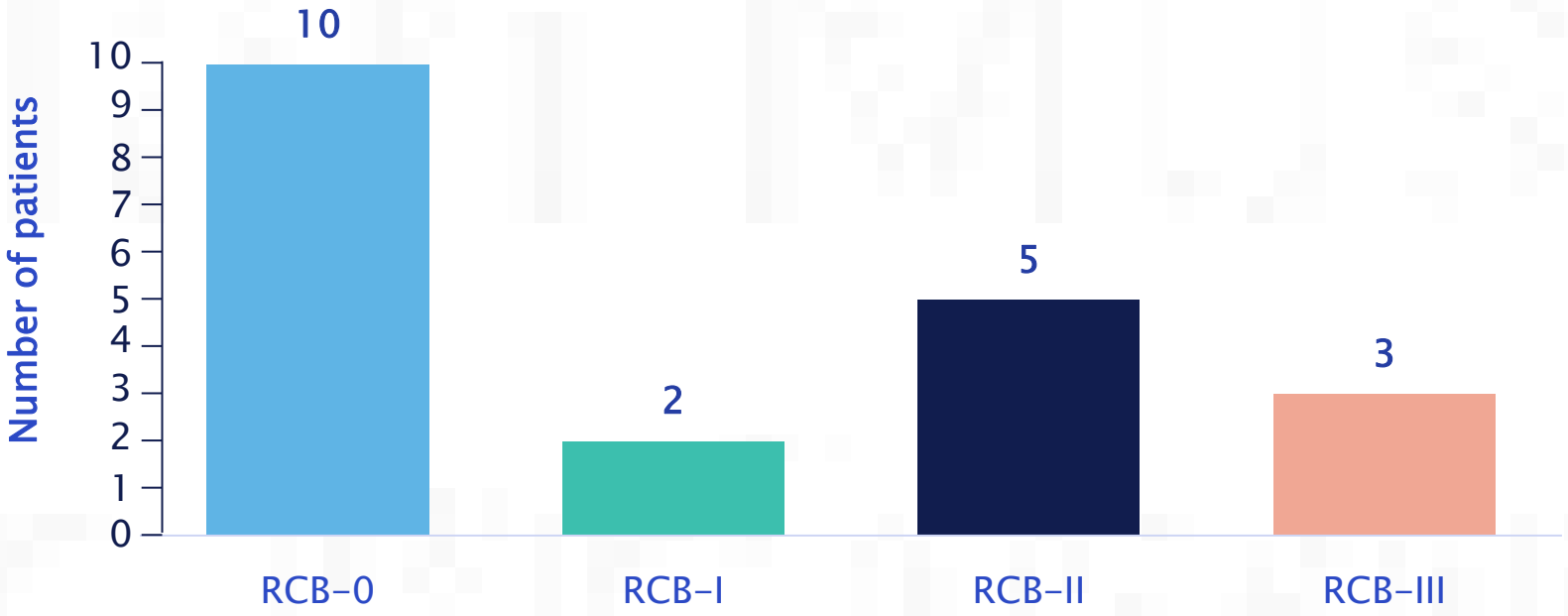
Secondary Objective

- Evaluate toxicity

*1 patient took 5 months of talazoparib and then refused biopsy and surgery and proceeded to chemotherapy.
†1 cycle=28 days.
BRCA=breast cancer susceptibility gene; EBC=early breast cancer; HER2=human epidermal growth factor receptor 2; pCR=pathological complete response; RCB=residual cancer burden.

Litton JK, et al. Abstract 508. ASCO 2018.

Neoadjuvant Talazoparib for EBC With *BRCA* Mutation: Pathologic Results



pCR (RCB-0): 10/19=**53%**; 95% CI=32%-73%

RCB-0+I: 12/19=**63%**; 95% CI=41%-81%

pCR=pathological complete response;

Litton JK, et al. Abstract 508. ASCO 2018.

Neoadjuvant Talazoparib for EBC With *BRCA* Mutation: Hematologic Toxicities and RBC Transfusions

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	4	3	8	–
WBC decreased	8	4	–	–
Thrombocytopenia	–	–	–	1
Neutropenia	–	4	3	–

BRCA=breast cancer susceptibility gene; EBC=early breast cancer; PRBC=packed red blood cell; RBC=red blood cell; WBC=white blood cell.

Litton JK, et al. Abstract 508. ASCO 2018.

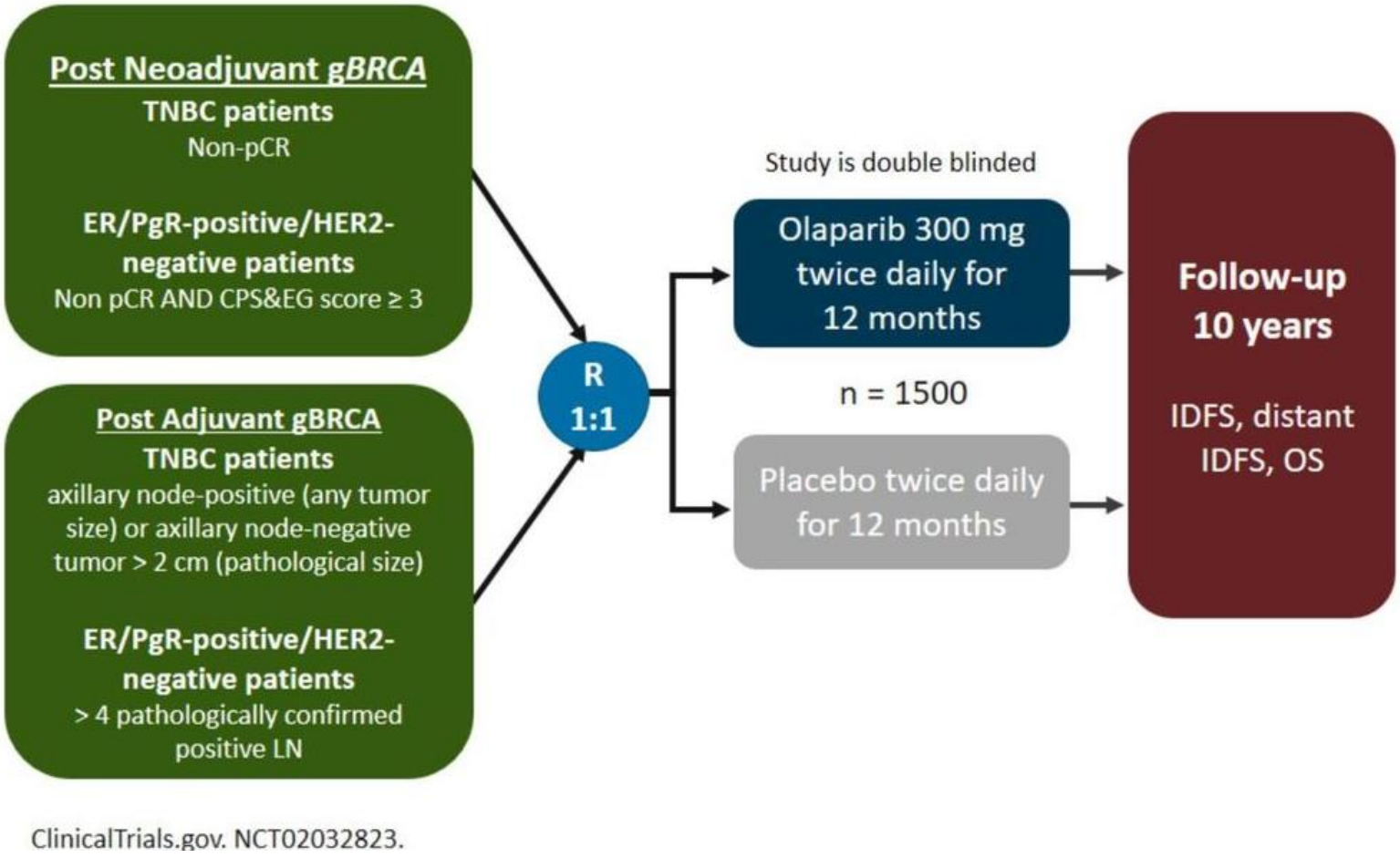
Neoadjuvant Talazoparib for EBC With *BRCA* Mutation: Nonhematologic Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	14	1	–	–
Fatigue	14	–	–	–
Alopecia	11	–		
Dizziness	6	–	–	–
Dyspnea	5	–	–	–
Hyperglycemia	5	–	–	–
Pain (in breast and other)	8	1	–	–
Increased transaminases	4	–	–	–
Mucositis	4	–	–	–
Vomiting	2	1	–	–
UTI		2	1	–
Hypomagnesemia	3	–	–	–

BRCA=breast cancer susceptibility gene; EBC=early breast cancer; UTI=urinary tract infection.

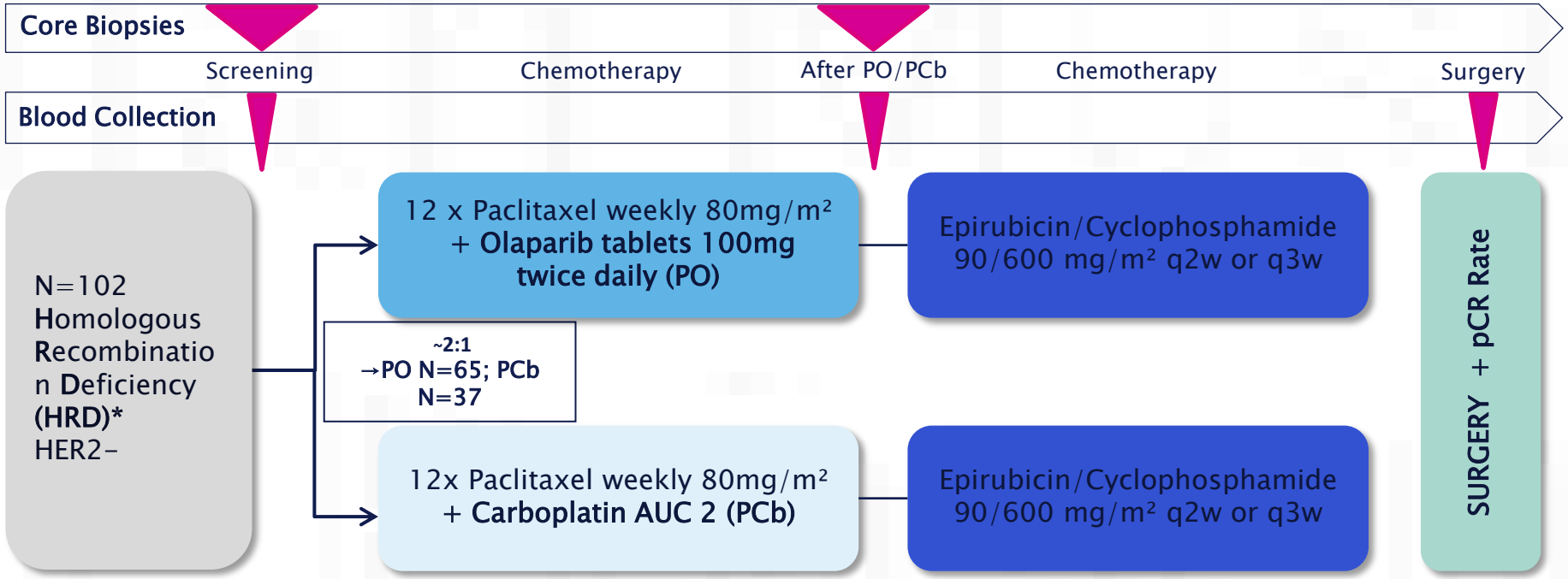
Litton JK, et al. Abstract 508. ASCO 2018.

OlympiA: Phase III Study of Adjuvant Olaparib



ClinicalTrials.gov. NCT02032823.

GeparOla Study Design



Stratification Factors:

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

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

[1]Timms et al. Breast Cancer Res 201

Objectives and Endpoints

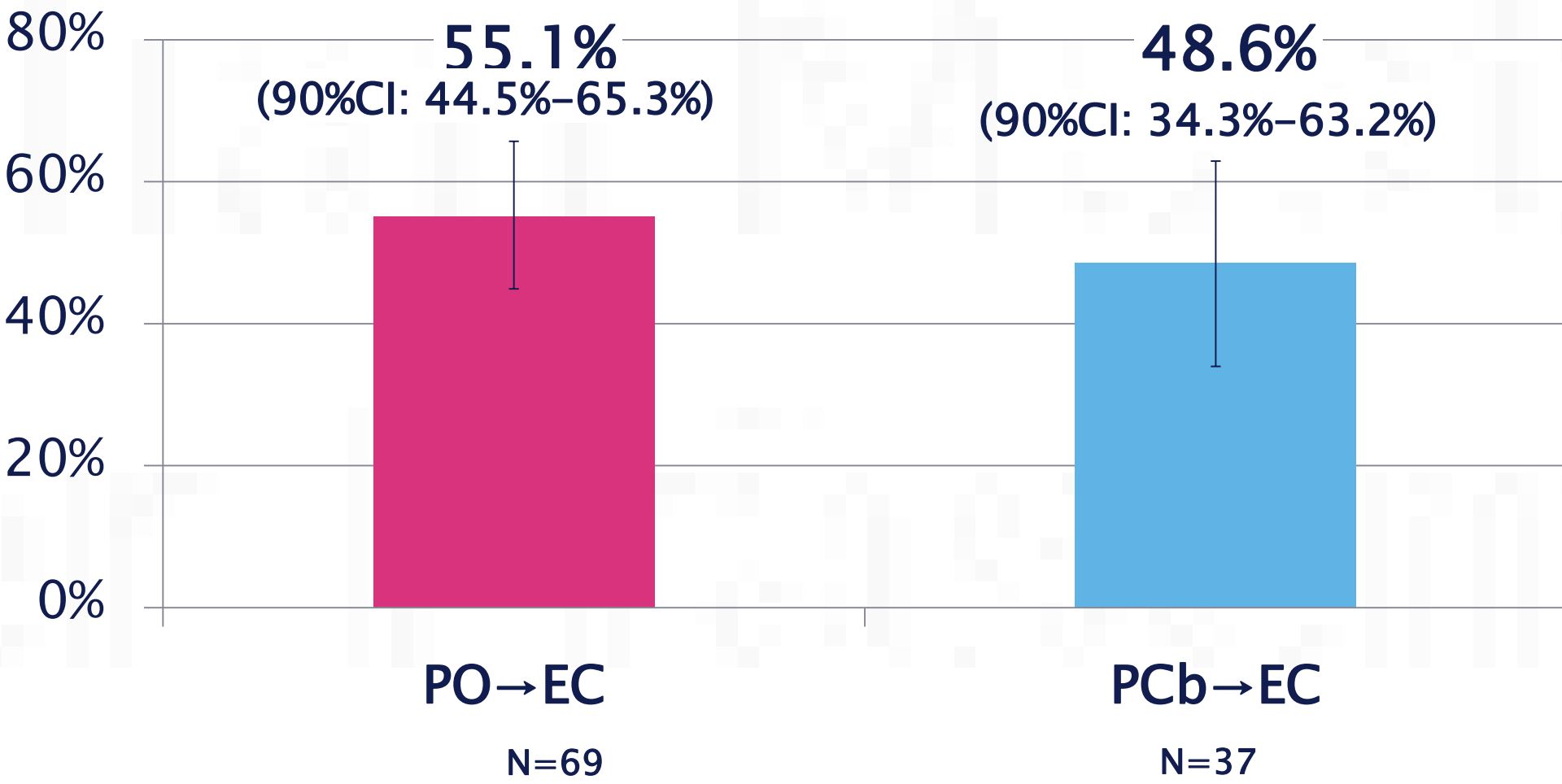
Primary Objective and Endpoint:

- To assess the pathological complete response (ypT0/is ypN0) rate of neoadjuvant treatment of olaparib and paclitaxel followed by EC (PO→EC) in patients with early BC and HR deficient tumors

Main Secondary Objectives and Endpoints:

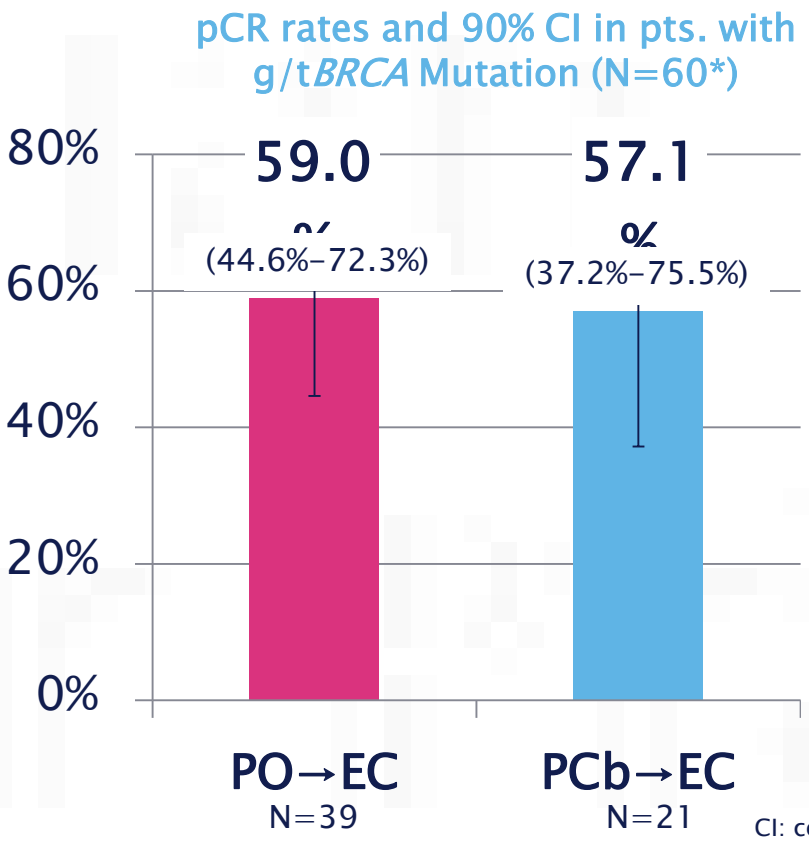
- pCR rate (ypT0/is ypN0) of patients receiving paclitaxel and carboplatin followed by EC (PCb→EC)
- pCR rate (ypT0/is ypN0) in stratified subgroups
- pCR rates according to different pCR definitions: ypT0 ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; $ypT_{(any)}$ ypN0
- pCR rate in HRD Score high with vs without t*BRCA* mutation
- Clinical response rate
- Breast conservation rate
- Toxicity and compliance
- Immune- and biomarker

Primary Endpoint – pCR ypT0/is ypN0

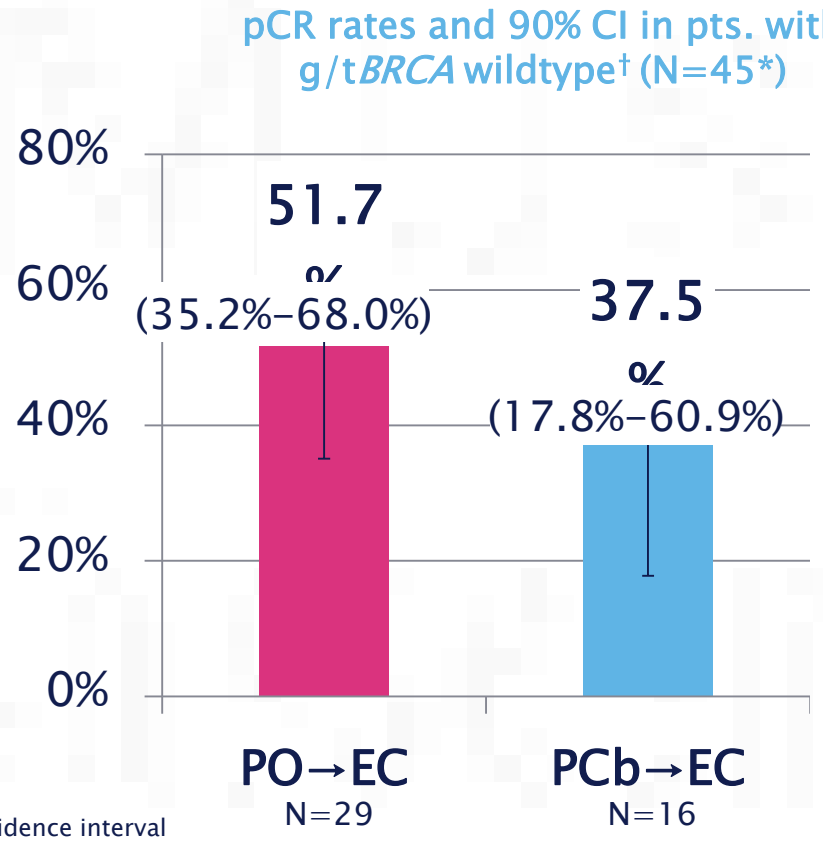


Predefined Subgroup Analysis (ypT0/is ypN0)

BRCA Mutation



CI: confidence interval



*One patient without t*BRCA* result due to insufficient quantity of DNA→HRD Score high
† HRD Score high

Serious Adverse Events

	PO→EC N=69	PCb→EC N=37
Total No of SAEs	11	37
Pts with at least 1 SAE	9 (13.0%)	19 (51.3%)
01. Infections and infestations	4	2
03. Blood and lymphatic system disorders	3	25
04. Immune system disorders	0	1
06. Metabolism and nutrition disorders	0	1
08. Nervous system disorders	0	1
14. Gastrointestinal disorders	2	3
15. Hepatobiliary disorders	1	1
22. General disorders	1	2
24. Injury, poisoning and procedural complications	0	1

- No fatal SAEs or SUSARs occurred

ABRAZO Study: Talazoparib in *gBRCA1/2* Mutation–Positive MBC

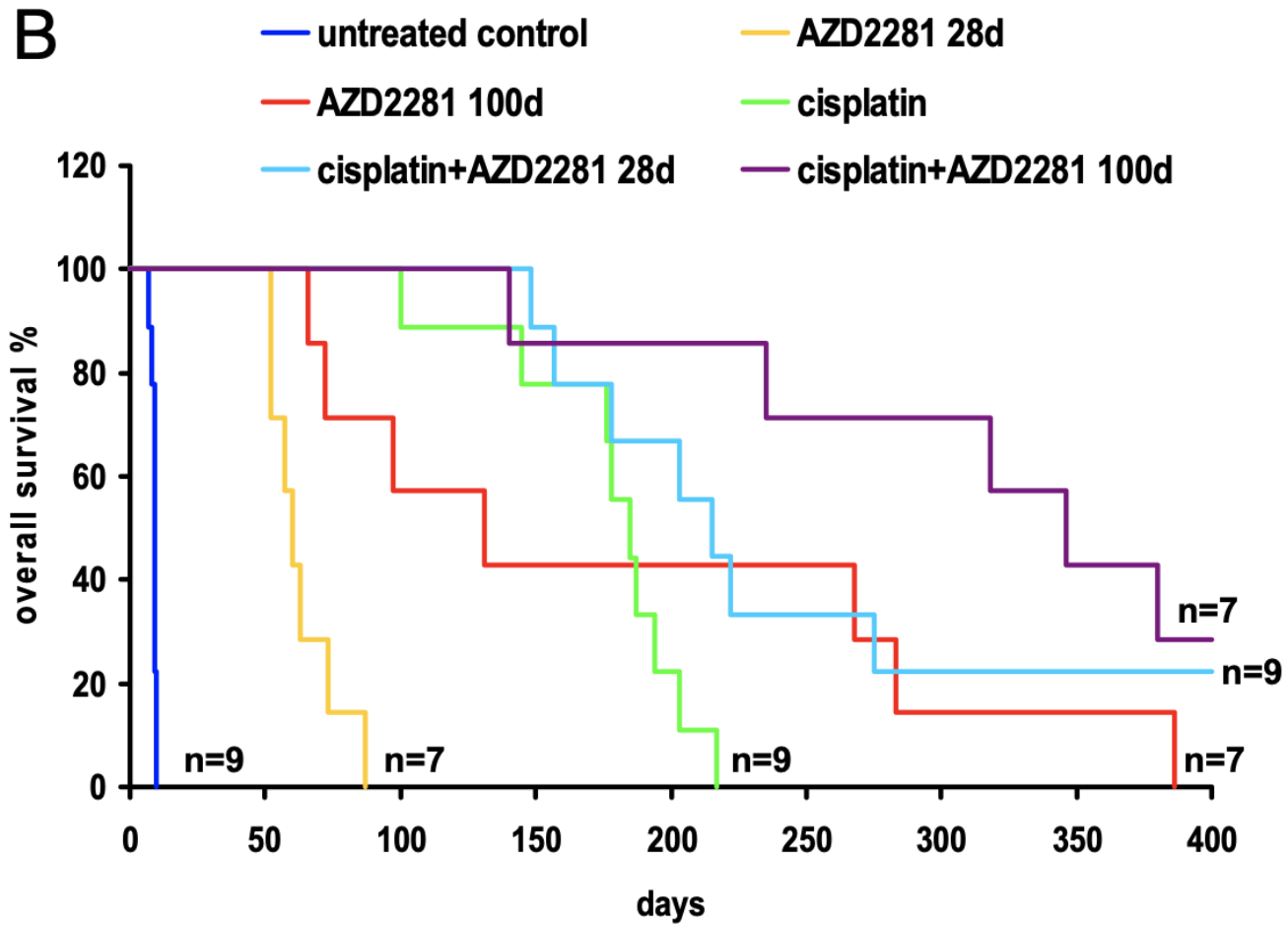
A 2-stage, phase II study of talazoparib (1.0 mg/day) in pts with *gBRCA1/2* mutation–positive MBC and ECOG PS 0-1; primary endpoint: ORR

- Cohort 1: Response to platinum-based therapy, PD > 8 wks after last dose (n = 48)
- Cohort 2: ≥ 3 cytotoxic regimens (n = 35); no prior platinum for metastatic disease

Response, n (%)	**Cohort 1 (n = 48)**	**Cohort 2 (n = 35)**	**Total (N = 83)**
ORR, % (95% CI)	21 (10-35)	37 (22-55)	28 (18-39)
Best response			
▪ CR	2 (4)	0	2 (2)
▪ PR	8 (17)	13 (37)	21 (25)
▪ SD	18 (38)	18 (51)	36 (43)
▪ PD	18 (38)	4 (11)	22 (27)
Not evaluable	2 (4)	0	2 (2)

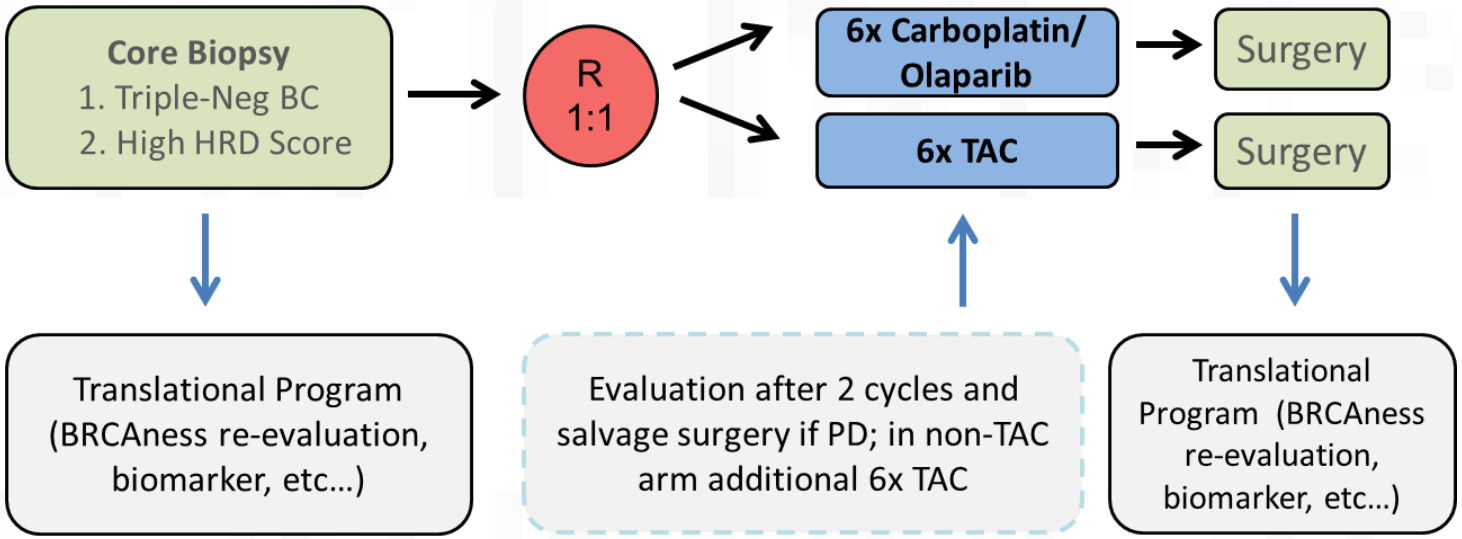
Turner NC, et al. ASCO 2017. Abstract 1007.

Antineoplastic Effect Olaparib +/- Cisplatin in Mammary tumors in BRCA1$^{-/-}$ Mice



Rottenberg et al, PNAS 2007

ABCSG 45 – Study Design



Stratification according to

1. ***BRCA1/2* Mutation status (somatic)**
2. **Menopausal status**

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