Medikamentöse Prävention und zielgerichtete Therapie im Hochrisikokollektiv

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Risiko

Lebenszeitrisiko (non-BRCA pos):

Brustkrebs: 12% **Ovarial-CA: 1,4%**

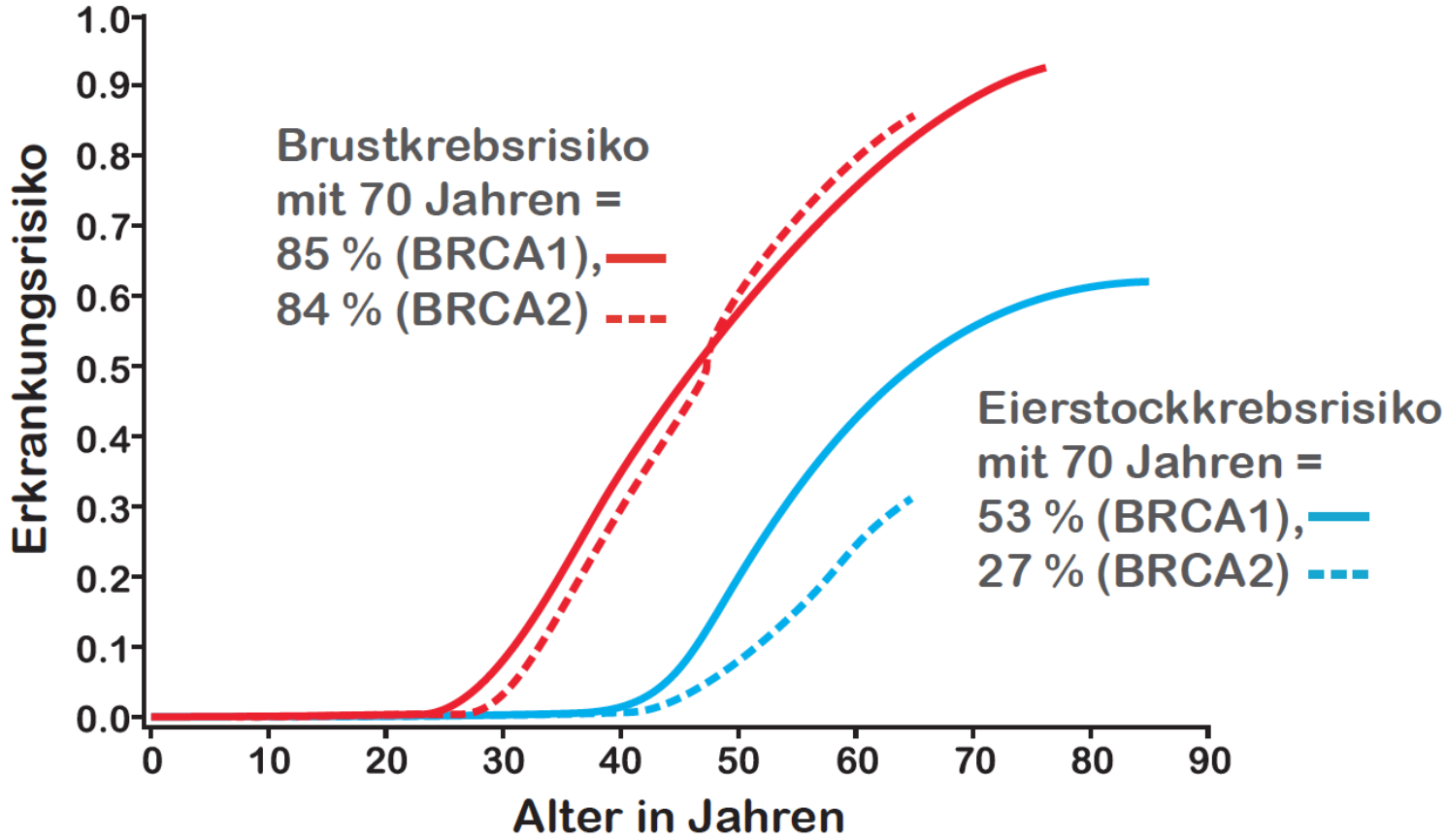
Lebenszeitrisiko BRCA 1:

Brustkrebs: 65% (47-85) **Ovarial-CA: 39%** (39-46)

Lebenszeitrisiko BRCA 2:

Brustkrebs: 45% (40-85) **Ovarial-CA: 11%** (11-27)

BRCA Erkrankungsrisiko



Erblicher Brust- und Eierstockkrebs

Mögliche persönliche Konsequenzen für Gesunde

Früherkennung

Brustkrebs:

Eierstockkrebs: X

Vorbeugung

Medikamentöse Behandlung: ?

Brustgewebeentfernung: ✓

Eierstockentfernung: ✓

„Nichts tun“

Brustkrebs: X

Eierstockkrebs X

Hat Schutzwirkung ✓
Hat wahrscheinlich Schutzwirkung ?
Hat keine Schutzwirkung X

Vorsorge

Medikamentös

Lifestyle

Operativ

Lifestyle

Alcohol: every 10g increases BC risk by 10%

Exercise: 4-10 hours of exercise reduces BC risk by 25-45%

Diet: no impact

Weight/ BMI: Weight loss reduces BC risk by -30%
Weight gain increases BC risk by -40%

PILLE

Minimale Erhöhung des Brustkrebsrisikos (RR 1.13)

Halbierung (!!!) des Risikos für Eierstockkrebs (RR 0.5)

Tamoxifen

- Data regarding tamoxifen risk reduction are limited to pre and postmenopausal women 35 y of age or older with a Gail model 5-year breast cancer risk of ≥1.7% or a history of LCIS.
- Tamoxifen: 20 mg per day for 5 years was shown to reduce risk of breast cancer by 49%. Among women with a history of atypical hyperplasia, this dose and duration of tamoxifen was associated with an 86% reduction in breast cancer risk.[3]

Raloxifen

- Data regarding raloxifene risk reduction are limited to postmenopausal women 35 y of age or older with a Gail model 5-year breast cancer risk ≥1.7% or a history of LCIS.
- Raloxifene: 60 mg per day was found to be equivalent to tamoxifen for breast cancer risk reduction in the initial comparison. While raloxifene in long-term follow-up appears to be less efficacious in risk reduction than tamoxifen consideration of toxicity may still lead to the choice of raloxifene over tamoxifen in women with an intact uterus.

Exemestane

- Data regarding exemestane are from a single large randomized study limited to postmenopausal women 35 years of age or older with a Gail model 5-year breast cancer risk ≥1.7% or a history of LCIS.
- Exemestane: 25 mg per day was found to reduce the relative incidence of invasive breast cancers by 65% from 0.55% to 0.19% with a median follow-up of 3 years. There are ongoing trails evaluating prolonged aromatase inhibitor therapy in postmenopausal healthy women at risk for breast cancer.

Tamoxifen and BC in BRCA1/2 Mutation Carriers: Primary and Secondary Prevention

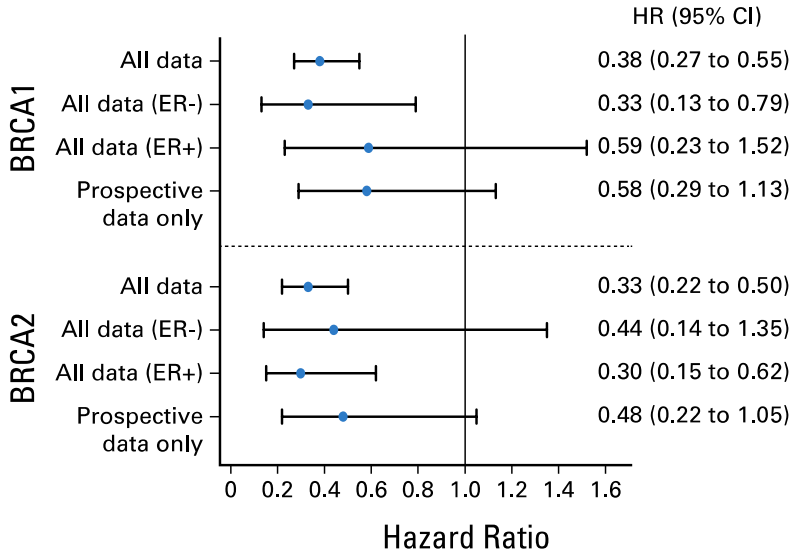
Table 3. Study Participants Who Developed Breast Cancer

	Placebo	Tamoxifen	Risk Ratio (95% Confidence Interval)
BRCA1 mutation	3	5	1.67 (0.32-10.70)
BRCA2 mutation	8	3	0.38 (0.06-1.56)
Wild type	182	87	0.48 (0.37-0.61)
All participants*	211	109	0.52 (0.41-0.65)

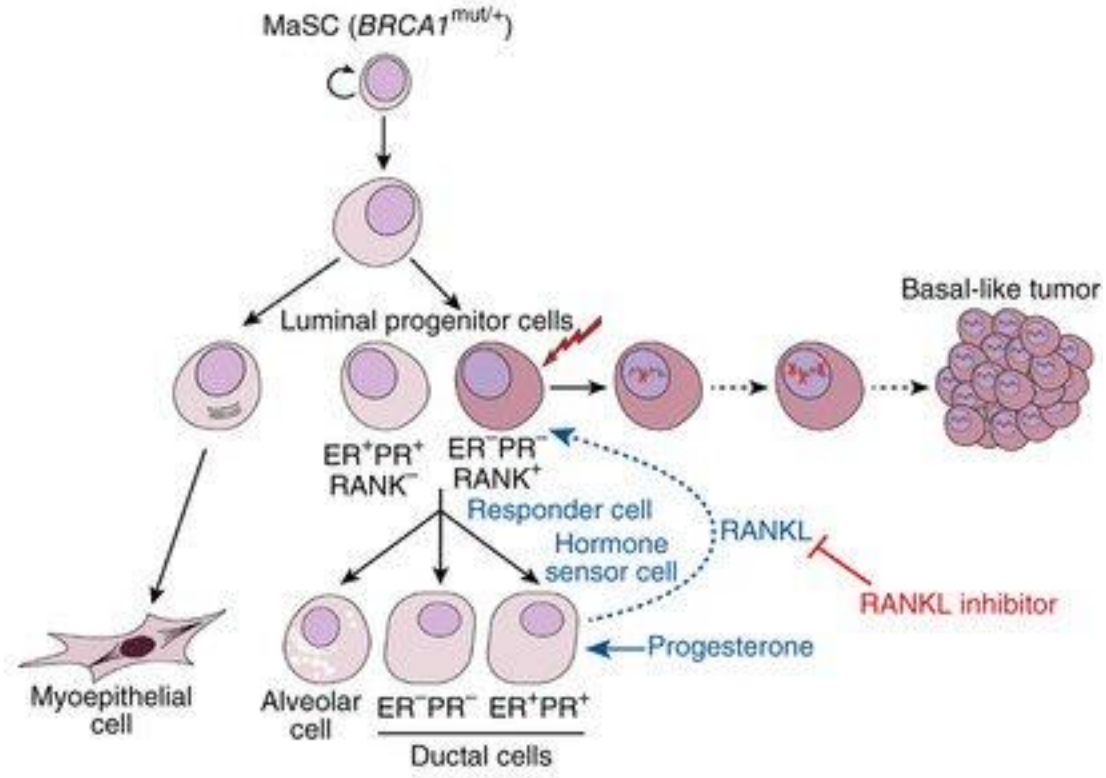
*Includes 288 genotyped cases and 32 cases without DNA available.

Tamoxifen and incident BC;
NSABP-P1 subpopulation

Tamoxifen and contralateral BC
In BRCA1/2 mutation carriers

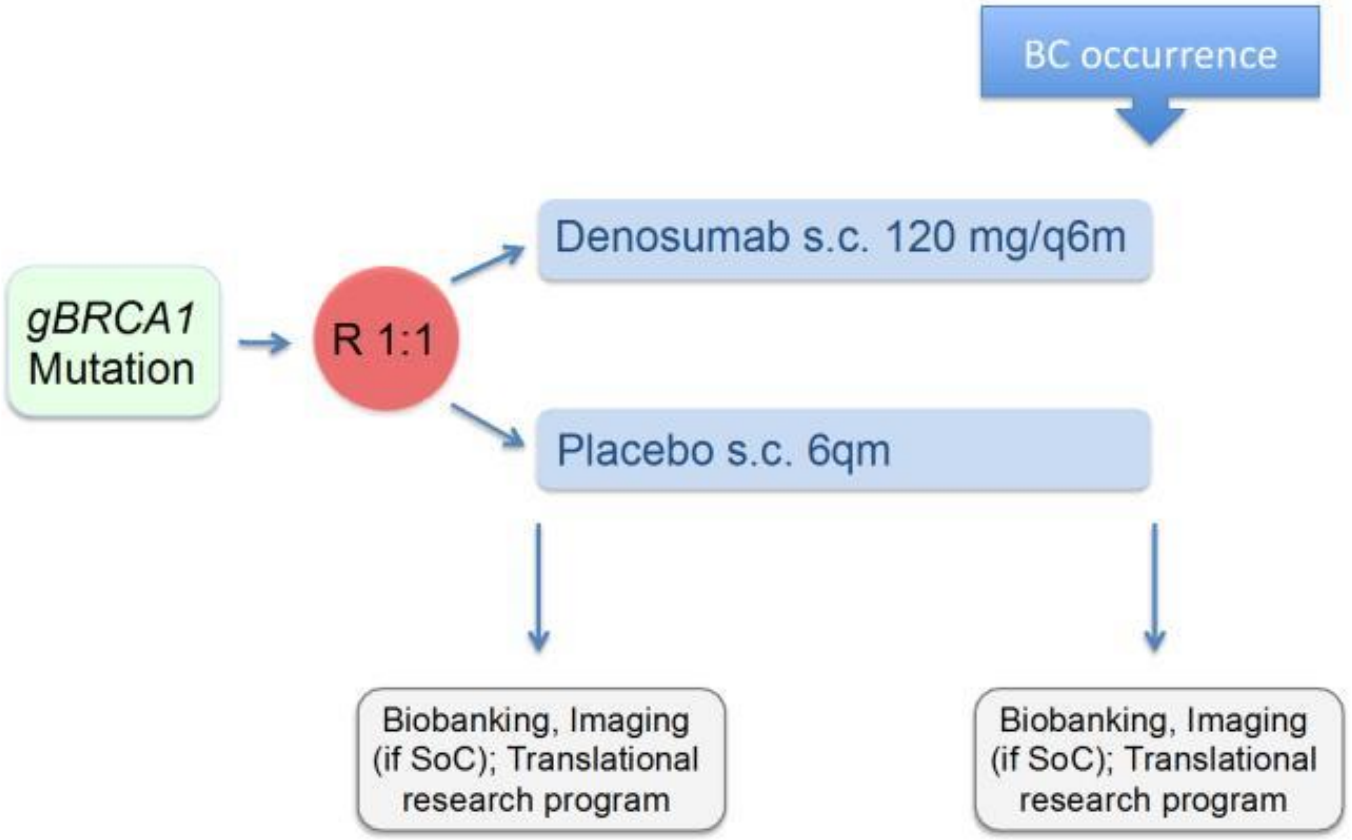


RANKL-Inhibition in *mBRCA1* Carriers



Nolan et al, Nature Medicine 2017

BRCA-P: Studiendesign

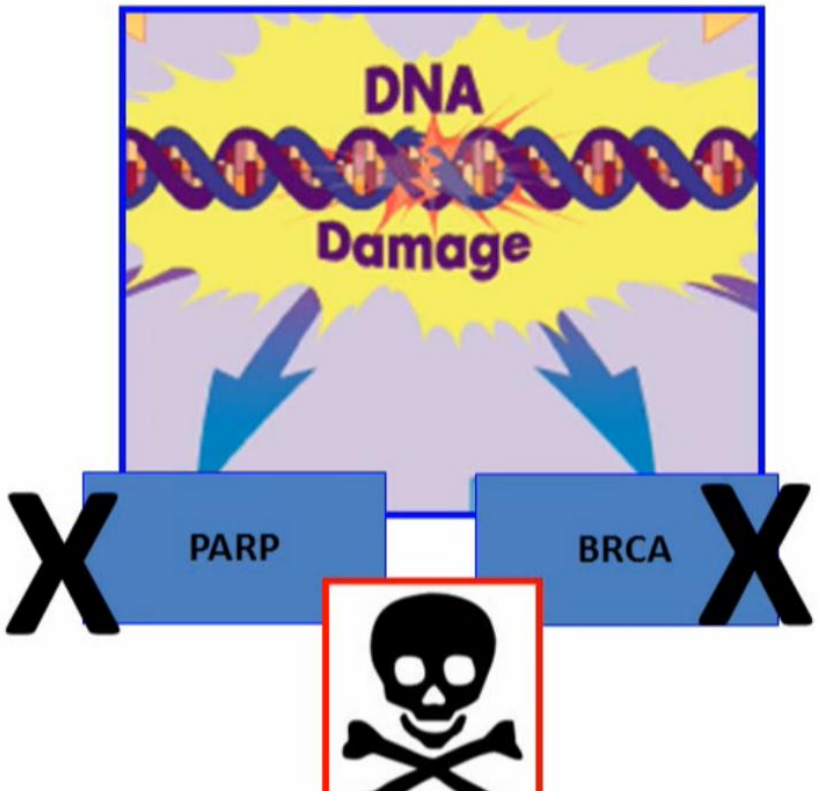


Blocking PARP affects BRCA mutant cancers:

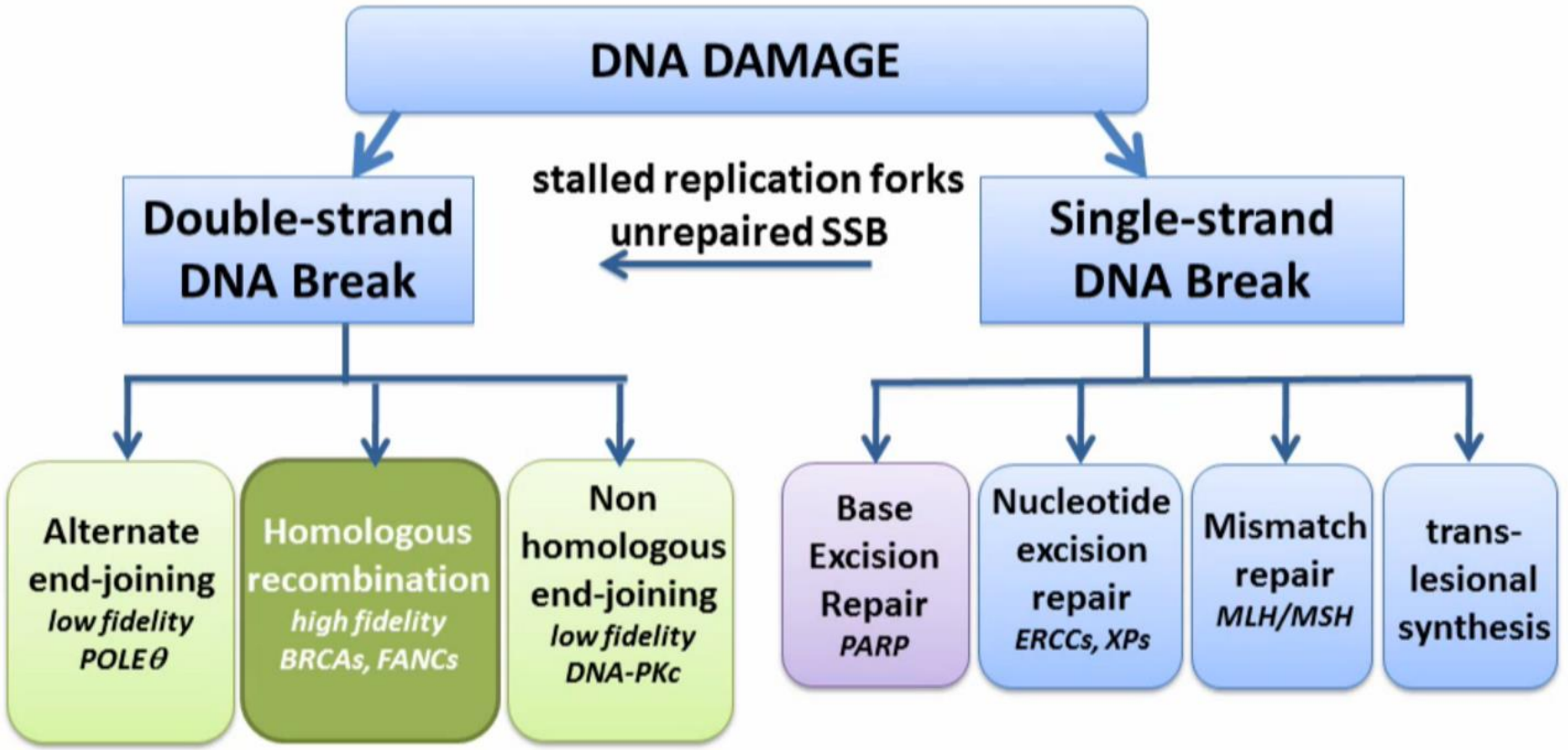
The synthetic lethality hypothesis

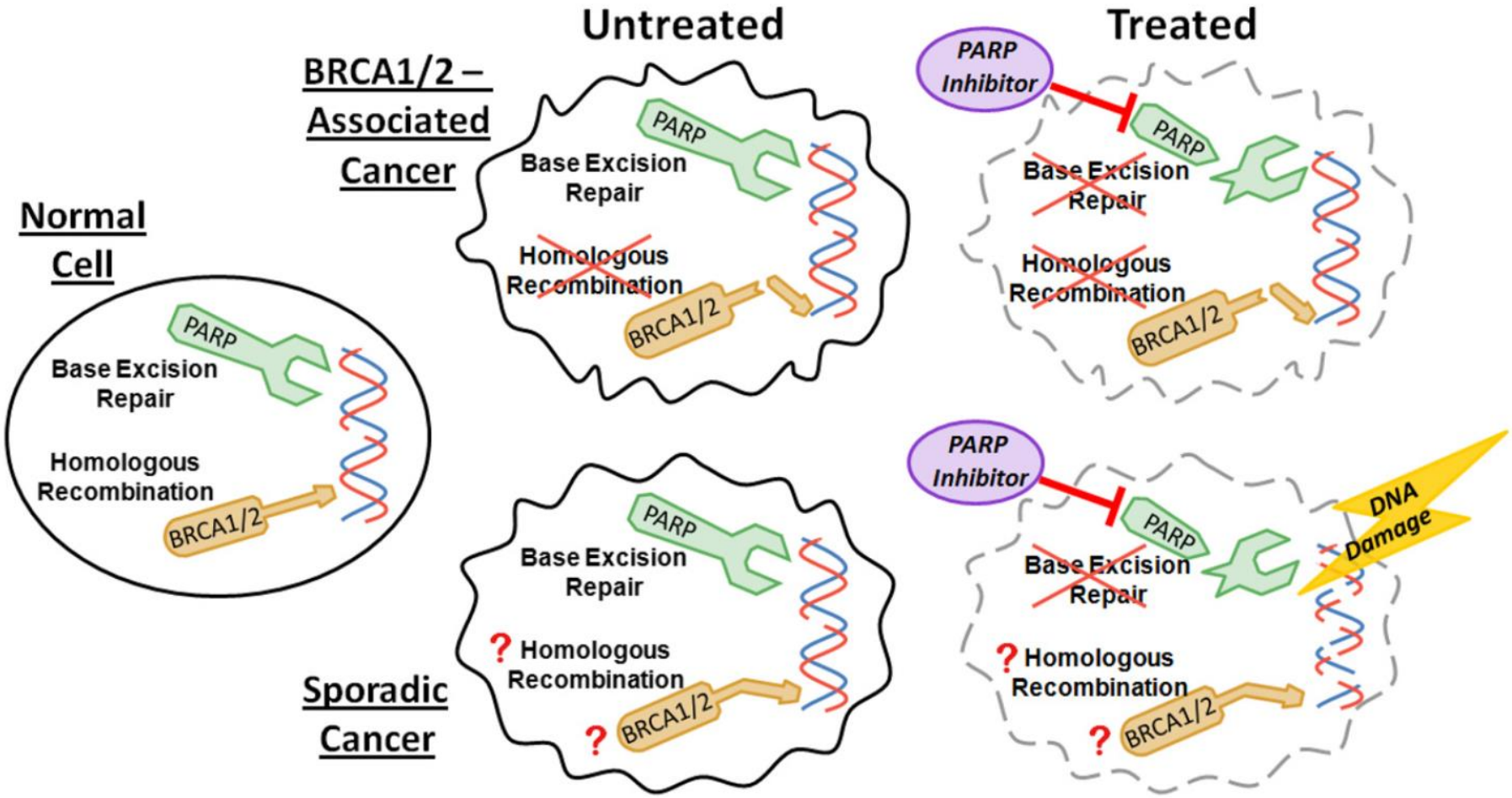
(looking back, it seemed very simple)

- DNA in the BRCA mutant cancer cell is not properly repaired
- It is worse with addition of DNA repair inhibitors
- Trigger cancer cell death



DNA repair: complex, interconnected



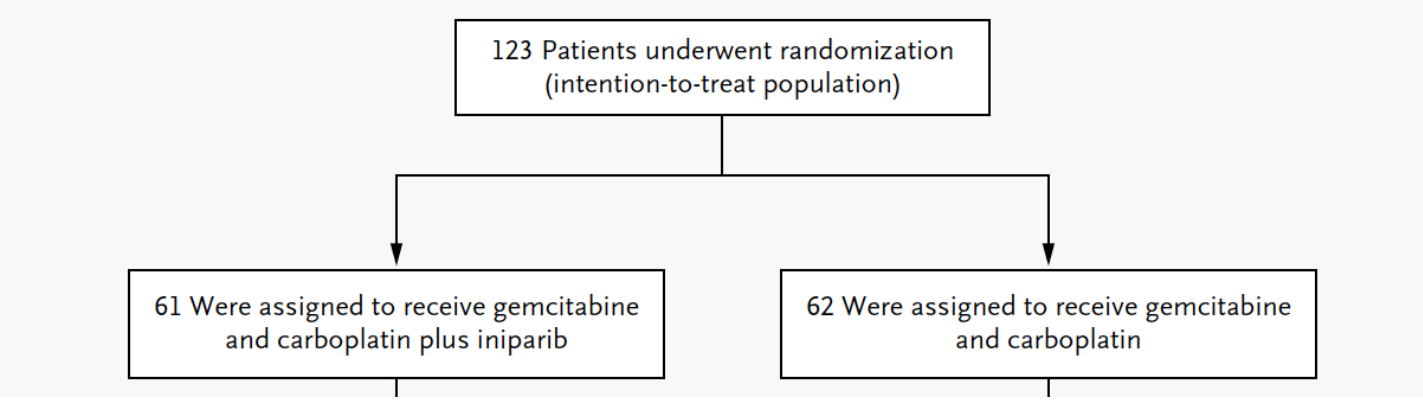

Untreated
Treated
BRCA1/2 – Associated Cancer
Normal Cell
Sporadic Cancer
PARP
Inhibitor
PARP
Base Excision Repair
Homologous Recombination
BRCA1/2
DNA Damage
?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 20, 2011 VOL. 364 NO. 3

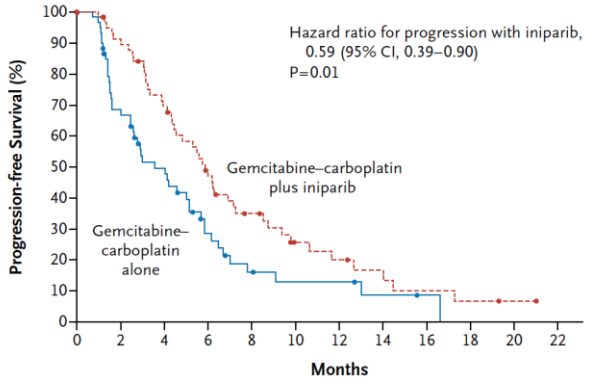
Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer

Joyce O'Shaughnessy, M.D., Cynthia Osborne, M.D., John E. Pippen, M.D., Mark Yoffe, M.D., Debra Patt, M.D., Christine Rocha, M.Sc., Ingrid Chou Koo, Ph.D., Barry M. Sherman, M.D., and Charles Bradley, Ph.D.*



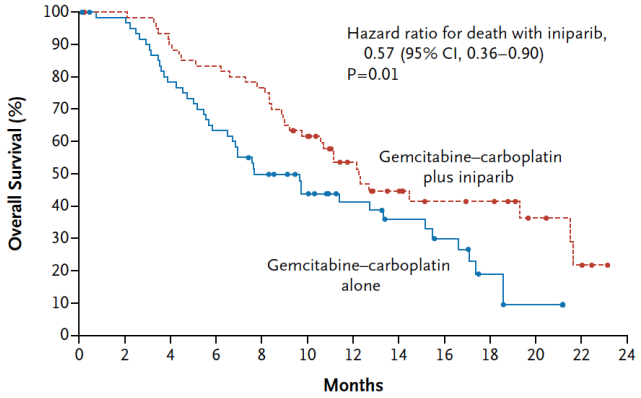
TNBC

A Progression-free Survival



No. at Risk												
Gemcitabine–carboplatin plus iniparib	61	51	38	25	16	9	7	5	3	2	1	0
Gemcitabine–carboplatin alone	62	38	25	12	6	4	4	2	1	0	0	0

B Overall Survival



No. at Risk													
Gemcitabine–carboplatin plus iniparib	61	60	54	50	46	35	24	17	12	11	6	3	0
Gemcitabine–carboplatin alone	62	59	47	38	29	22	16	12	9	4	1	0	0

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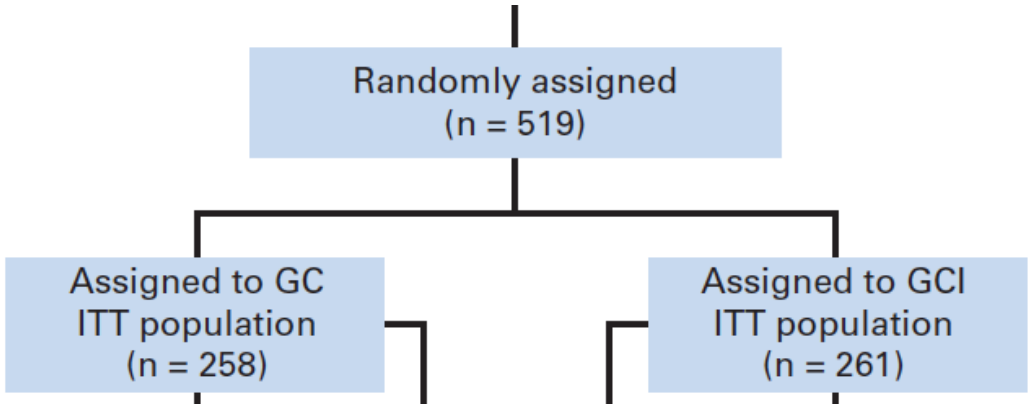
JOURNAL OF CLINICAL ONCOLOGY

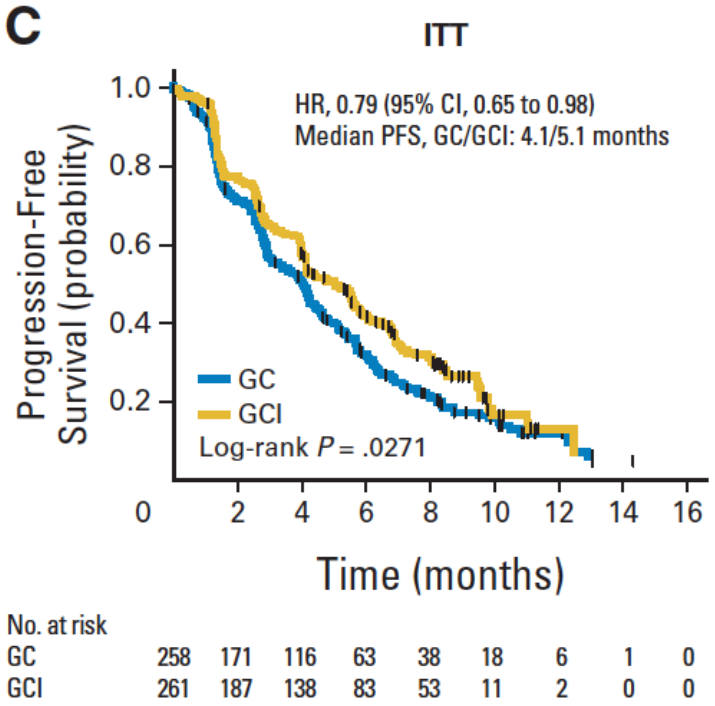
ORIGINAL REPORT

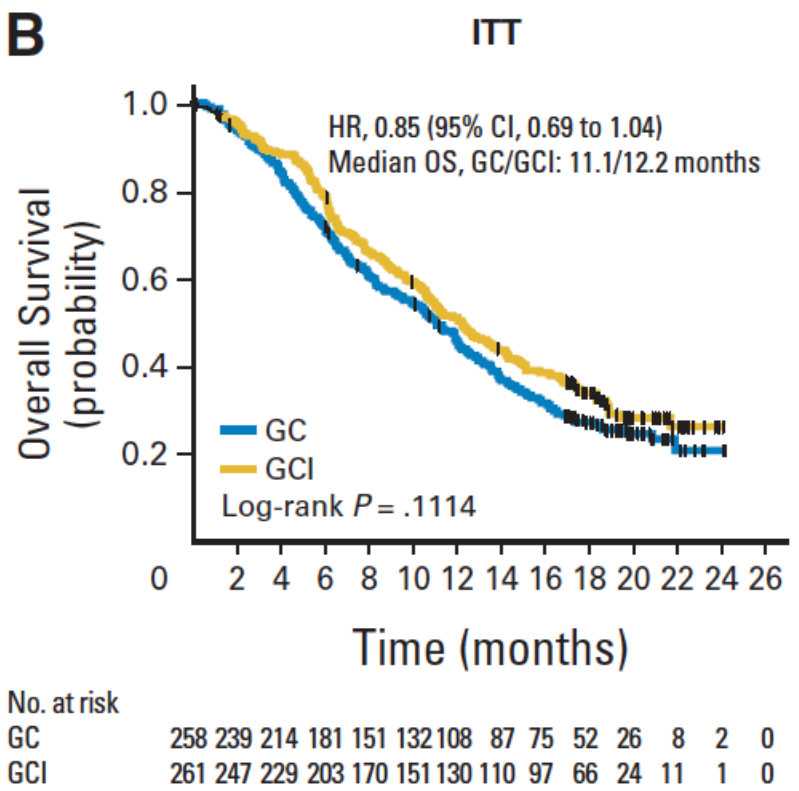
Phase III Study of Iniparib Plus Gemcitabine and Carboplatin Versus Gemcitabine and Carboplatin in Patients With Metastatic Triple-Negative Breast Cancer

Joyce O'Shaughnessy, Lee Schwartzberg, Michael A. Danso, Kathy D. Miller, Hope S. Rugo, Marcus Neubauer, Nicholas Robert, Beth Hellerstedt, Mansoor Saleh, Paul Richards, Jennifer M. Specht, Denise A. Yardley, Robert W. Carlson, Richard S. Finn, Eric Charpentier, Ignacio Garcia-Ribas, and Eric P. Winer



TNBC


C
ITT
HR, 0.79 (95% CI, 0.65 to 0.98)
Median PFS, GC/GCI: 4.1/5.1 months
Progression-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
GC
GCI
Log-rank P = .0271
2 4 6 8 10 12 14 16
Time (months)
No. at risk
GC 258 171 116 63 38 18 6 1 0
GCI 261 187 138 83 53 11 2 0 0


B
ITT
HR, 0.85 (95% CI, 0.69 to 1.04)
Median OS, GC/GCI: 11.1/12.2 months
Overall Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
GC
GCI
Log-rank P = .1114
2 4 6 8 10 12 14 16 18 20 22 24 26
Time (months)
No. at risk
GC 258 239 214 181 151 132 108 87 75 52 26 8 2 0
GCI 261 247 229 203 170 151 130 110 97 66 24 11 1 0

Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial

Andrew Tutt, Mark Robson, Judy E Garber, Susan M Domchek, M William Audeh, Jeffrey N Weitzel, Michael Friedlander, Banu Arun, Niklas Loman, Rita K Schmutzler, Andrew Wardley, Gillian Mitchell, Helena Earl, Mark Wickens, James Carmichael

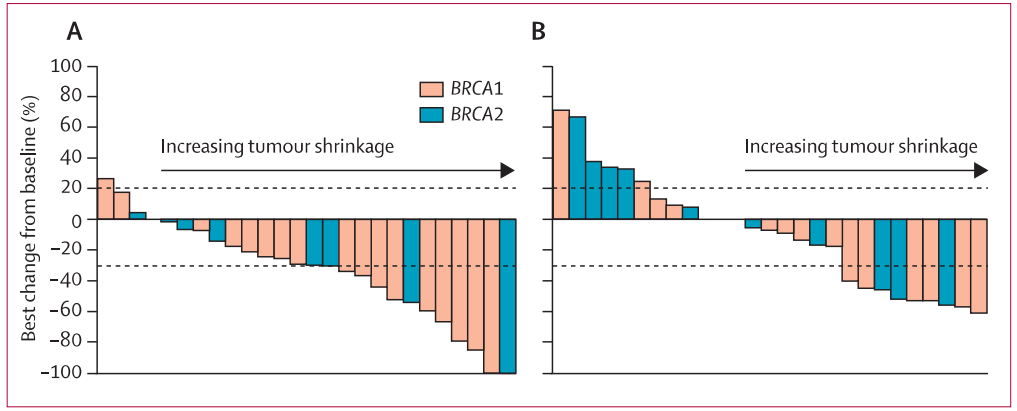
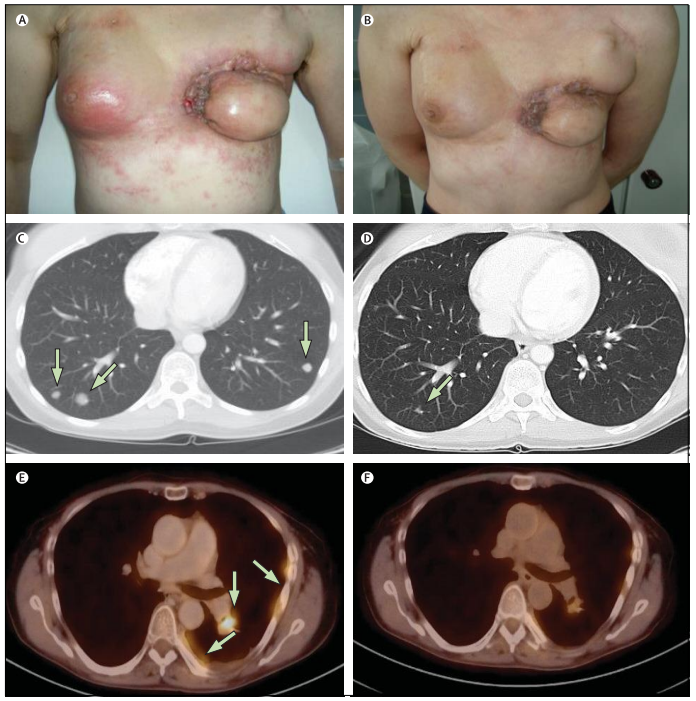


Figure 2: **Best percentage change from baseline in target lesion size by *BRCA* mutation genotype in the intention-to-treat population**
(A) Olaparib 400 mg twice daily. (B) Olaparib 100 mg twice daily. Reference lines indicate boundaries for progressive disease (20%) and partial response (−30%).



Tutt et al. Lancet 2010

OlympiAD: Phase III trial of olaparib monotherapy versus chemotherapy for patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation

Mark Robson,[1] Seock-Ah Im,[2] Elżbieta Senkus,[3] Binghe Xu,[4] Susan M Domchek,[5] Norikazu Masuda,[6] Suzette Delaloge,[7] Wei Li,[8] Nadine Tung,[9] Anne Armstrong,[10] Wenting Wu,[11] Carsten Goessl,[11] Sarah Runswick,[12] Pierfranco Conte[13]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Seoul National University Hospital, Seoul, Korea; [3]Medical University of Gdańsk, Gdańsk, Poland; [4]Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [5]Basser Center, University of Pennsylvania, Philadelphia, USA; [6]National Hospital Organization, Osaka National Hospital, Osaka, Japan; [7]Institut Gustave Roussy, Villejuif, France; [8]The First Hospital of Jilin University, Changchun, China; [9]Beth Israel Deaconess Medical Center, Dana-Farber Harvard Cancer Center, Boston, USA; [10]Christie Hospital NHS Foundation Trust, Manchester, UK; [11]AstraZeneca, Gaithersburg, USA; [12]AstraZeneca, Macclesfield, UK; [13]University of Padova and Istituto Oncologico Veneto IRCCS, Padova, Italy

ClinicalTrials.gov identifier: NCT02000622. This study was sponsored by AstraZeneca

OlympiAD study design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious g*BRCA*m
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥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

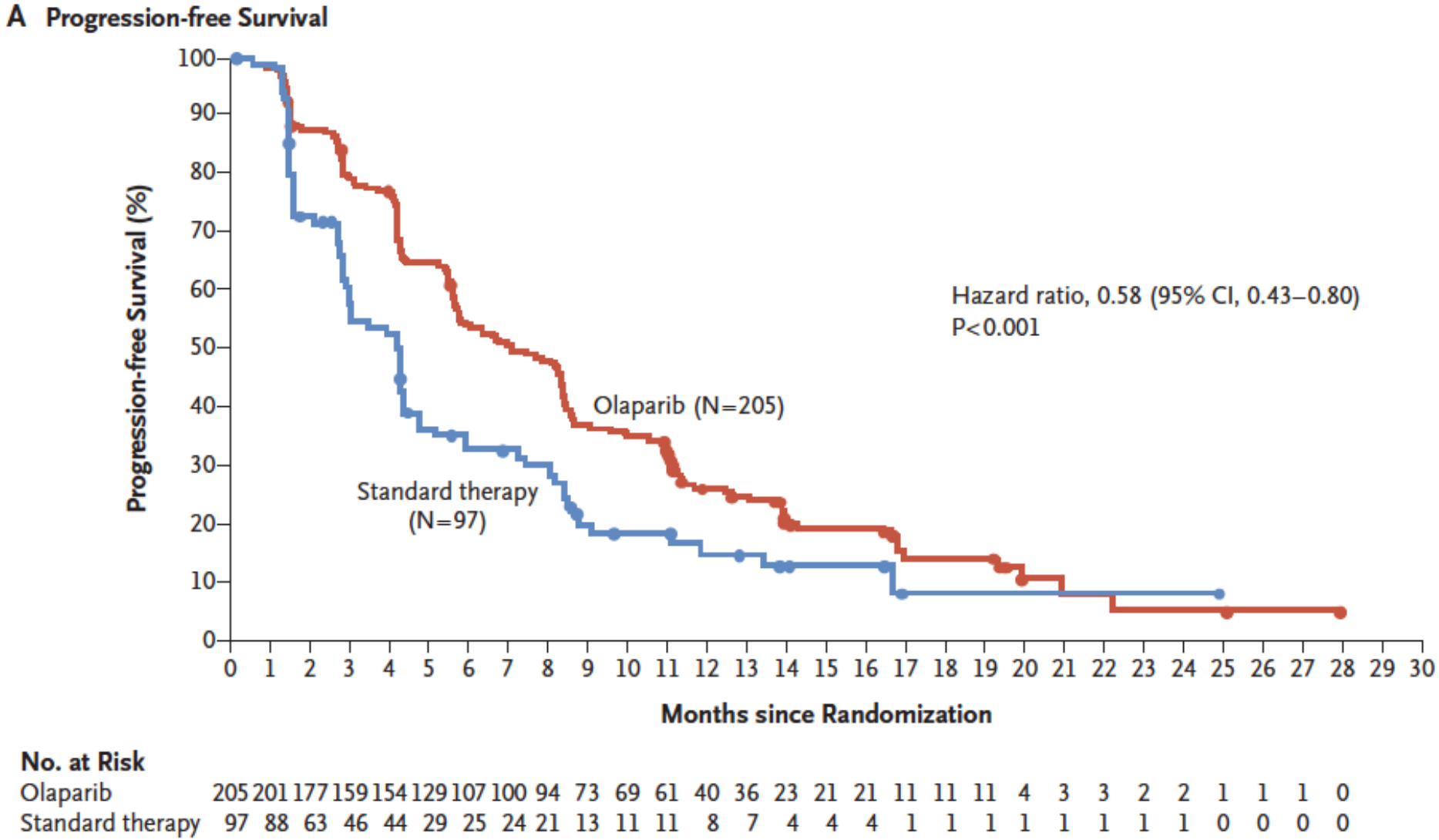
Primary endpoint:
- Progression-free survival (RECIST 1.1, BICR)

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

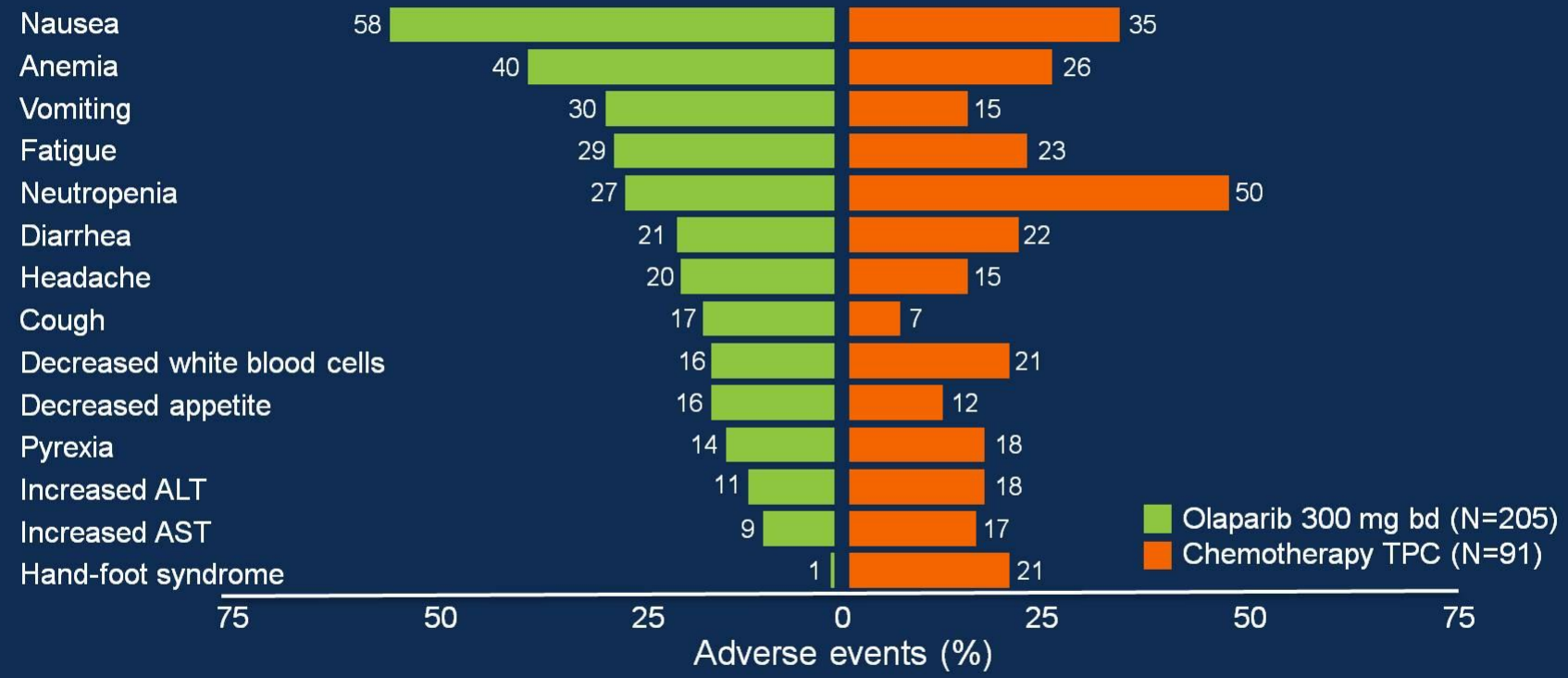
BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

Characteristic	Olaparib Group (N=205)	Standard-Therapy Group (N=97)
Age — yr		
Median	44	45
Range	22–76	24–68
Male sex — no. (%)	5 (2.4)	2 (2.1)
Race or ethnic group — no. (%)†		
White	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Other	5 (2.4)	6 (6.2)
ECOG performance status — no. (%)‡		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
BRCA mutation type — no. (%)§		
BRCA1	117 (57.1)	51 (52.6)
BRCA2	84 (41.0)	46 (47.4)
BRCA1 and *BRCA2*	4 (2.0)	0
Hormone-receptor status — no. (%)¶		
Hormone-receptor positive	103 (50.2)	49 (50.5)
Triple negative	102 (49.8)	48 (49.5)
New metastatic breast cancer — no. (%)	26 (12.7)	12 (12.4)
Previous chemotherapy for metastatic breast cancer — no. (%)	146 (71.2)	69 (71.1)
Previous platinum-based therapy for breast cancer — no. (%)	60 (29.3)	26 (26.8)
≥2 Metastatic sites — no. (%)	159 (77.6)	72 (74.2)
Location of the metastasis — no. (%)		
Bone only	16 (7.8)	6 (6.2)
Other‖	189 (92.2)	91 (93.8)
Measurable disease — no. (%)	167 (81.5)	66 (68.0)

N Engl J Med 2017;377:523-33.


A Progression-free Survival
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Hazard ratio, 0.58 (95% CI, 0.43–0.80)
P<0.001
Olaparib (N=205)
Standard therapy
(N=97)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Months since Randomization
No. at Risk
Olaparib 205 201 177 159 154 129 107 100 94 73 69 61 40 36 23 21 21 11 11 11 4 3 3 2 2 1 1 1 0
Standard therapy 97 88 63 46 44 29 25 24 21 13 11 11 8 7 4 4 4 1 1 1 1 1 1 1 1 0 0 0 0

Adverse events (any grade) in ≥15% of patients



Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia
ALT, alanine aminotransferase; AST, aspartate aminotransferase


San Antonio Breast Cancer Symposium, December 5-9, 2017
EMBRACA
A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline *BRCA*-mutation
Jennifer K. Litton, Hope S. Rugo, Johannes Ettl, Sara Hurvitz,
Anthony Gonçalves, Kyung-Hun Lee, Louis Fehrenbacher, Rinat Yerushalmi,
Lida A. Mina, Miguel Martin, Henri Roché, Young-Hyuck Im, Ruben G. W. Quek,
Iulia Cristina Tudor, Alison L. Hannah, Wolfgang Eiermann, Joanne L. Blum
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Background

- Talazoparib (TALA) is a highly potent dual-mechanism PARP inhibitor[1-3]
  - Inhibits the PARP enzyme
  - Traps PARP on single-stranded DNA breaks[4]
  - Prevents repair of DNA damage, resulting in cell death
- Phase 1 trial established a tolerable dose of 1 mg/day for continuous dosing (fed or fasting)[5]
  - Single-agent activity in other tumor types (prostate, ovarian, SCLC)
- The phase 2 ABRAZO trial showed encouraging efficacy and safety in patients with germline *BRCA1/2* mutations and prior platinum therapy or at least 3 prior cytotoxic regimens[6]

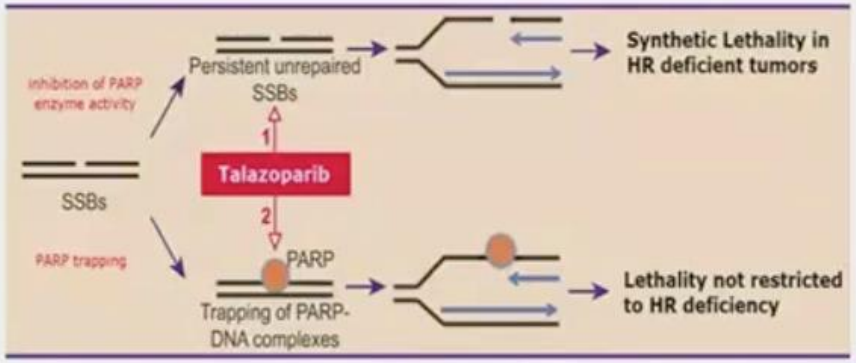


Figure adapted from Murai J et al. *Cancer Res*. 2012;72:5588-5599, with permission from AACR.

		ABRAZO	
	Phase 1 (n = 14)[a]	Prior Platinum (n = 48)	≥ 3 Lines, No Platinum (n = 35)
Confirmed ORR, % (95% CI)	50%	21% (10, 35)	37% (22, 55)
PFS, mo (95% CI)	7.5	4.0 (2.8, 5.4)	5.6 (5.5, 7.8)
CBR24, % (95% CI)	86%	38% (24, 53)	66% (48, 81)

[a]Data shown for the phase 1 study is only in breast cancer patients.

Abbreviations: CI, confidence interval; CBR24, clinical benefit rate at 24 weeks; HR, homologous recombination; PARP, poly(ADP-ribose) polymerase; ORR, objective response rate; PFS, progression-free survival; SCLC, small cell lung cancer; SSB, single-strand break.

1. Ashworth A. *J Clin Oncol*. 2008;26:3785-3790. 2. Jalve M, Curtin NJ. *Ther Adv Med Oncol*. 20113:257-267. 3. Helleday T. *Mol Oncol*. 2011;5:387-393. 4. Lord CJ, Ashworth A. *Science*. 2017;355:1152-1158. 5. de Bono J et al. *Cancer Discov*. 2017;7:620-629. 6. Turner NC et al. Presented at ASCO; June 3, 2017; Chicago, IL. Abstract 1007.

Study Design: EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:

- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

R 2:1

Talazoparib 1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

Physician's choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine

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)

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

Abbreviations: CNS, central nervous system; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; mets, metastases; PO, orally (per os); QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; TNBC, triple-negative breast cancer.
*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated.
†HER2-positive disease is excluded. ‡Physician's choice of therapy must be determined prior to randomization.
www.clinicaltrials.gov (NCT01945775)

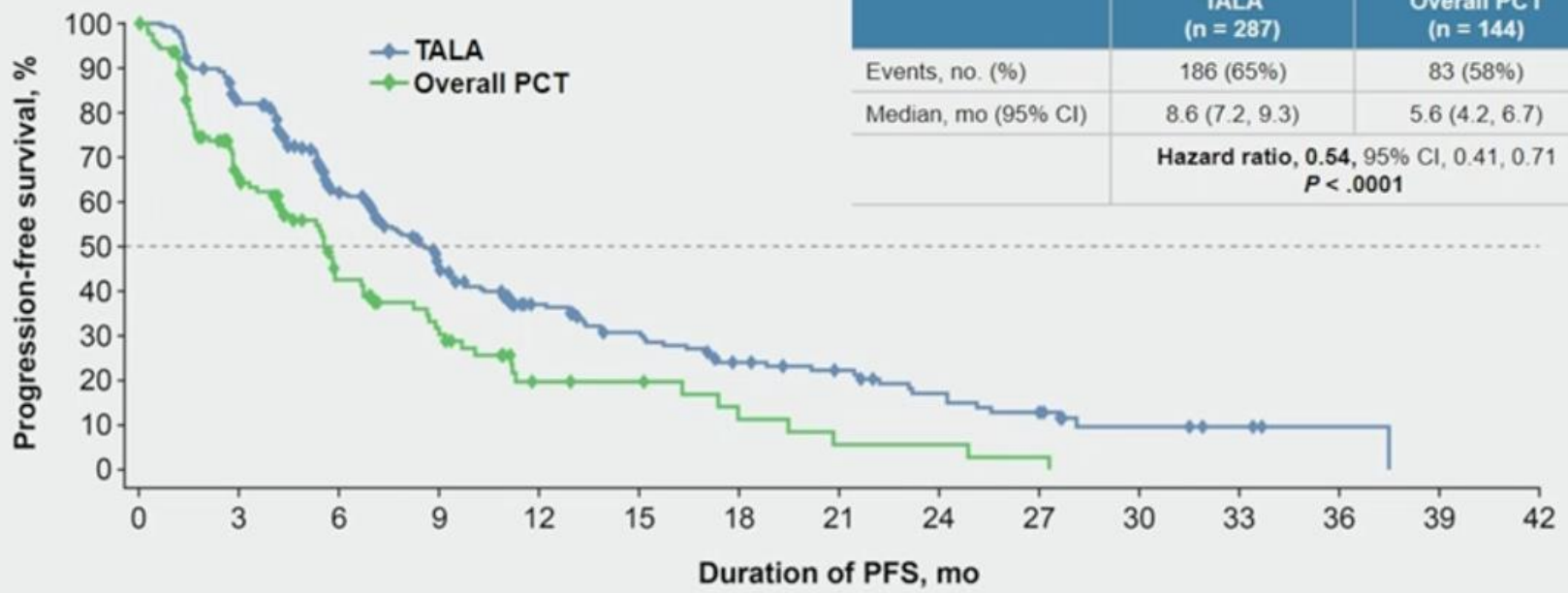
Baseline Characteristics (ITT Population)

	TALA (n = 287)	Overall PCT (n = 144)
Age, median (range), y	45 (27.0-84.0)	50 (24.0-88.0)
<50 y, no. %	182 (63.4%)	67 (46.5%)
Gender, % female	98.6%	97.9%
ECOG = 0 / 1 / 2, %	53.0% / 44.0% / 2.0%	58.0% / 40.0% / 1.0%
Measurable disease by investigator, no. (%)	219 (76.3%)	114 (79.2%)
History of CNS metastasis, no. (%)	43 (15.0%)	20 (13.9%)
Visceral disease, no. (%)	200 (69.7%)	103 (71.5%)
Hormone receptor status, no. (%)		
TNBC	130 (45.3%)	60 (41.7%)
HR+	157 (54.7%)	84 (58.3%)
BRCA status, no. (%)		
BRCA1+	133 (46.3%)	63 (43.8%)
BRCA2+	154 (53.7%)	81 (56.3%)
Disease free interval (initial diagnosis to aBC) <12 months	108 (37.6%)	42 (29.2%)

Abbreviations: aBC, advanced breast cancer; ITT, intent to treat.

San Antonio Breast Cancer Symposium, December 5-9, 2017

Primary Endpoint: PFS by Blinded Central Review



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

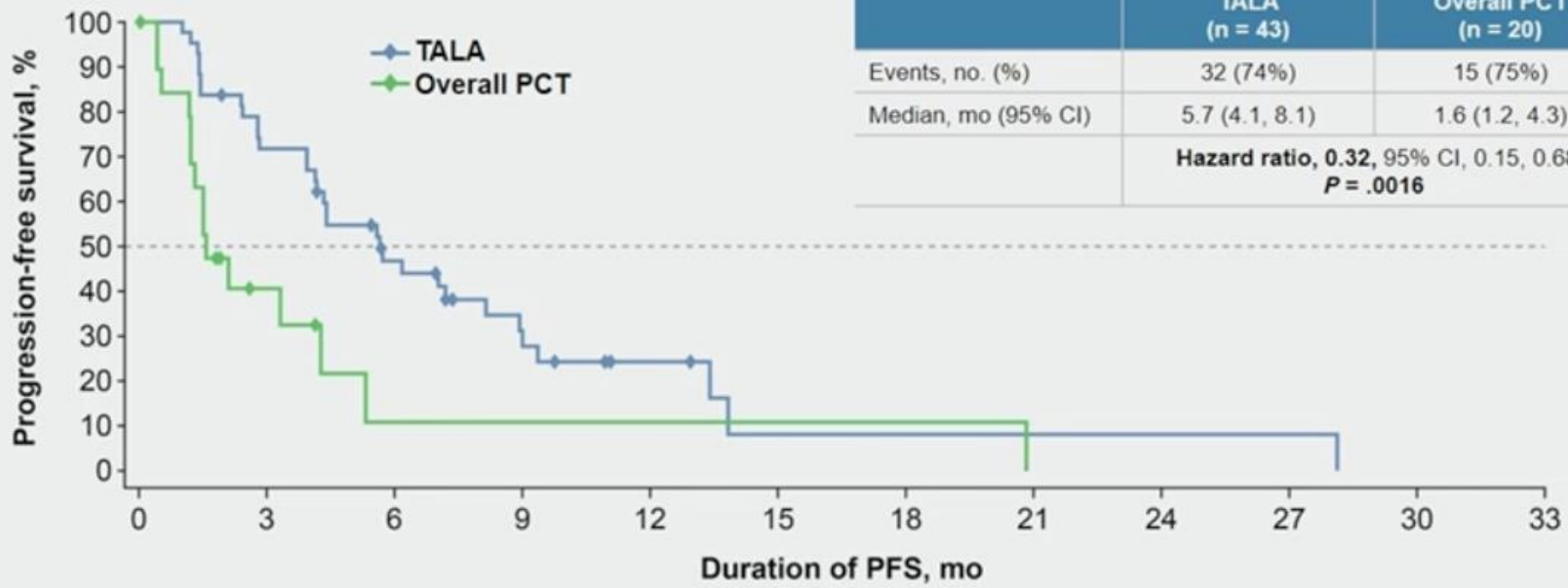
No. at risk (events/cumulative events)														
TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

1-Year PFS 37 vs 20% Median follow-up time: 11.2 months

12

San Antonio Breast Cancer Symposium, December 5-9, 2017

PFS: CNS Metastases Subgroup



	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**	

No. at risk (events/cumulative events)												
TALA	43 (0/0)	30 (12/12)	17 (10/22)	9 (5/27)	4 (2/29)	1 (2/31)	1 (0/31)	1 (0/31)	1 (0/31)	1 (0/31)	0 (1/32)	0 (0/32)
PCT	20 (0/0)	5 (11/11)	1 (3/14)	1 (0/14)	1 (0/14)	1 (0/14)	1 (0/14)	0 (1/15)	0 (0/15)	0 (0/15)	0 (0/15)	0 (0/15)

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Adverse Events: Hematologic

	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
No. of patients with ≥ 1 AE, no. (%)	194 (67.8%)	140 (49.0%)	17 (5.9%)	63 (50.0%)	29 (23.0%)	19 (15.1%)
Anemia	151 (52.8%)	110 (38.5%)	2 (0.7%)	23 (18.3%)	5 (4.0%)	1 (0.8%)
Neutropenia	99 (34.6%)	51 (17.8%)	9 (3.1%)	54 (42.9%)	25 (19.8%)	19 (15.1%)
Thrombocytopenia	77 (26.9%)	32 (11.2%)	10 (3.5%)	9 (7.1%)	2 (1.6%)	0
Lymphopenia	21 (7.3%)	9 (3.1%)	0	4 (3.2%)	0	1 (0.8%)
Febrile neutropenia	1 (0.3%)	0	1 (0.3%)	1 (0.8%)	0	1 (0.8%)

MDS / AML: none reported in the TALA arm; 1 patient on capecitabine

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

Adverse Events: Nonhematologic

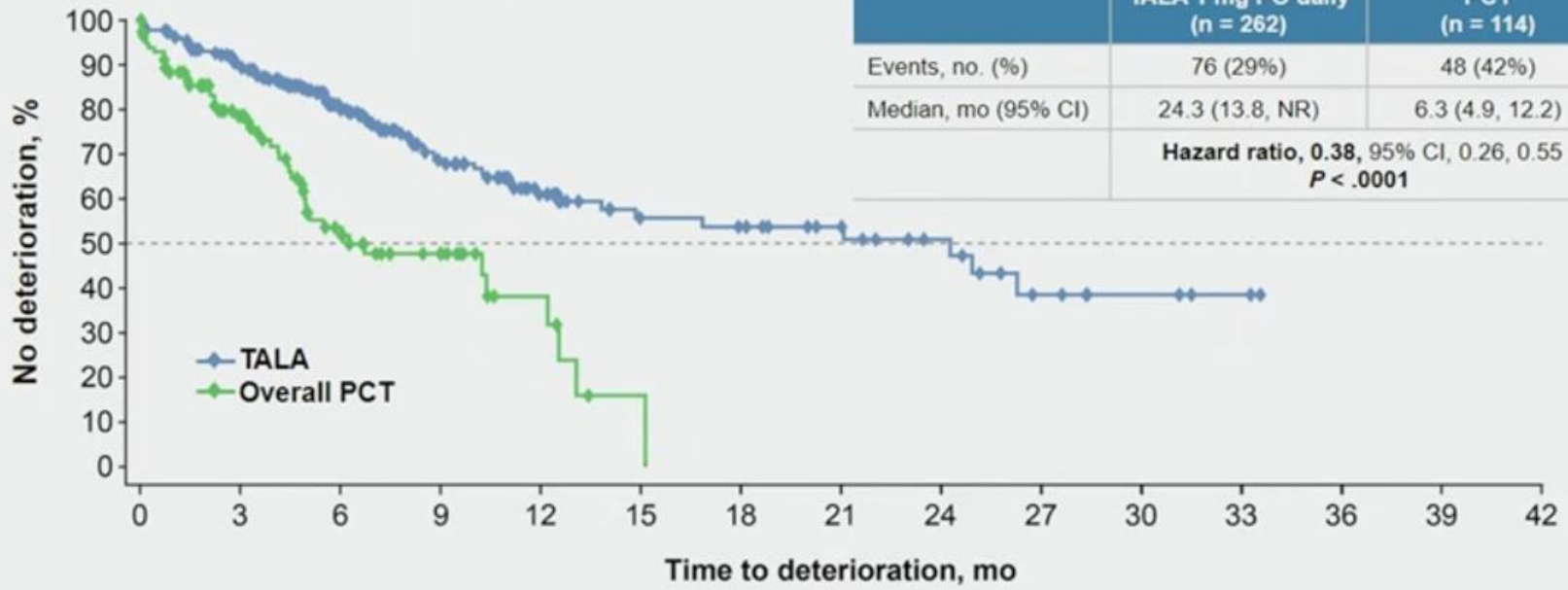
	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
No. of patients with ≥ 1 nonhematologic AE, no. (%)	282 (98.6%)	91 (31.8%)		123 (97.6%)	48 (38.1%)	
Fatigue	144 (50.3%)	5 (1.7%)	0	54 (42.9%)	4 (3.2%)	0
Nausea	139 (48.6%)	1 (0.3%)	0	59 (46.8%)	2 (1.6%)	0
Headache	93 (32.5%)	5 (1.7%)	0	28 (22.2%)	1 (0.8%)	0
Alopecia	72 (25.2%)	-	-	35 (27.8%)	-	-
Vomiting	71 (24.8%)	7 (2.4%)	0	29 (23.0%)	2 (1.6%)	0
Diarrhea	63 (22.0%)	2 (0.7%)	0	33 (26.2%)	7 (5.6%)	0
Constipation	63 (22.0%)	1 (0.3%)	0	27 (21.4%)	0	0
Decreased appetite	61 (21.3%)	1 (0.3%)	0	28 (22.2%)	1 (0.8%)	0
Back pain	60 (21.0%)	7 (2.4%)	0	20 (15.9%)	2 (1.6%)	0
Dyspnea	50 (17.5%)	7 (2.4%)	0	19 (15.1%)	3 (2.4%)	0
Palmar-plantar erythrodysesthesia syndrome	4 (1.4%)	1 (0.3%)	0	28 (22.2%)	3 (2.4%)	0
Pleural effusion	6 (2.1%)	5 (1.7%)	0	11 (8.7%)	5 (4.0%)	0

- All adverse events (AEs) in ≥ 20% of patients and grade 3-4 AEs in ≥ 2.4% of patients
- No clinically relevant cardiac or vascular toxicity observed in the TALA arm
- Alopecia: all grade 1 except 2.4% grade 2 in TALA; 7.9% grade 2 in PCT

Time to Deterioration in EORTC QLQ-C30: GHS/QoL

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.

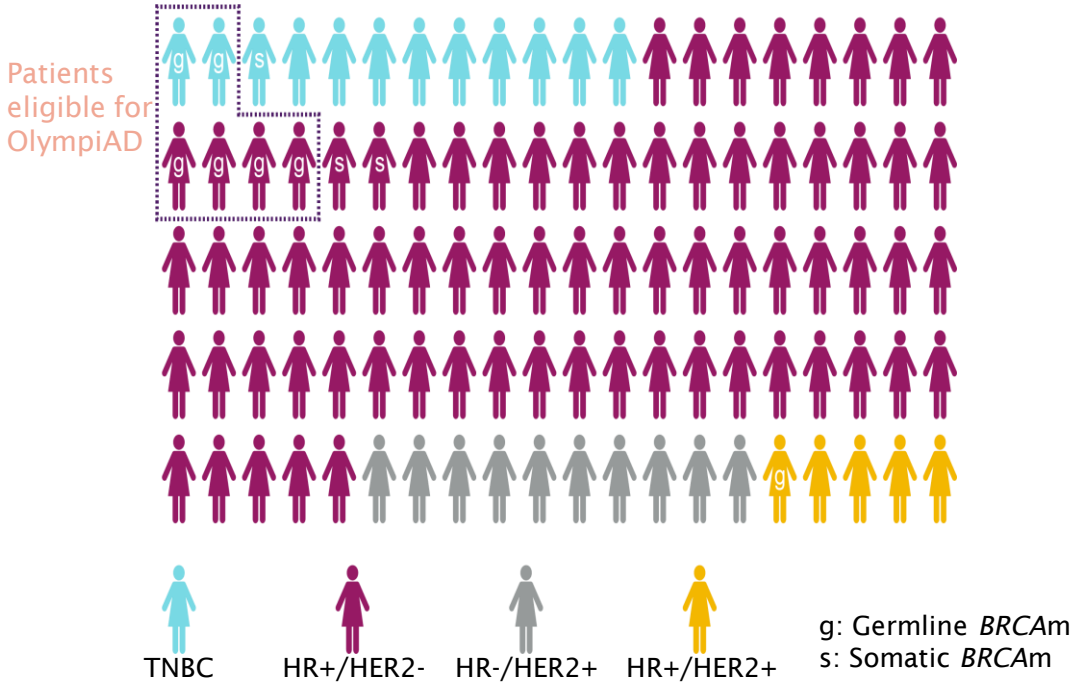
Wir müssen unterscheiden...

Prädiktive Testung vs. Therapeutische Testung

Prevalence of *BRCA*m in breast cancer

It has been estimated that approximately 7% of breast cancers are associated with gBRCAm and additional 3% have sBRCAm.[1] However, founder mutations in certain geographical locations do skew these data

Estimated prevalence of *BRCA*m within mBC segments
Based on Winter et al. 2016[1]



*BRCA*m and HR+ BC

While *BRCA*m are widely associated with TNBC, the clinical community are less likely to associate *BRCA*m with HR+ disease

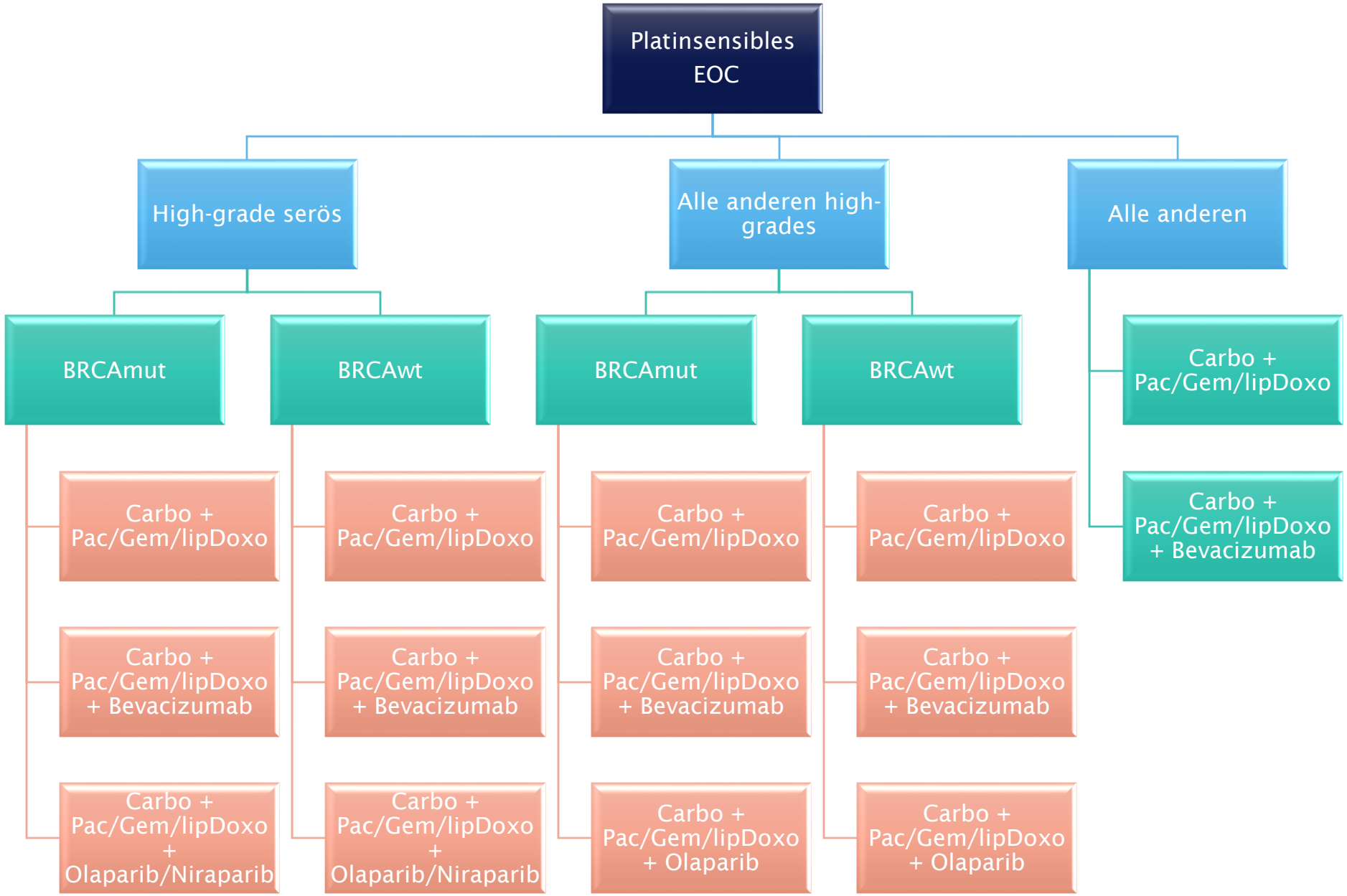
However, evidence suggest that HR+ patients account for at least half all *BRCA*m carriers:

- ~1 in 17 HR+ patients are g*BRCA*m (~65% of BC g*BRCA*m population)[1] – the majority of these will be *BRCA2* mutations[2,3]
- ~1 in 6 TNBC patients are g*BRCA*m (30% of BC g*BRCA*m population)[1] – the majority of these will be *BRCA1* mutations[4]

Calculations based on Winter et al. 2016

TNBC=triple negative breast cancer, HER=human epidermal growth factor, mBC=metastatic breast cancer

1. Winter et al. Ann Oncol. 2016 Aug; 27(8): 1532–1538; 2. Atchley DP et al. J Clin Oncol 2008; 26:4282-4288; 3.Mavaddat N et al. Cancer Epidemiol Biomarkers Prev 2012;21:134-147; 4. Couch FJ et al J Clin Oncol 33:304-311; 3.


Platinsensibles EOC
High-grade serös
Alle anderen high-grades
Alle anderen
BRCAmut
BRCAwt
BRCAmut
BRCAwt
Carbo + Pac/Gem/lipDoxo
Carbo + Pac/Gem/lipDoxo + Bevacizumab
Carbo + Pac/Gem/lipDoxo + Olaparib/Niraparib
Carbo + Pac/Gem/lipDoxo
Carbo + Pac/Gem/lipDoxo + Bevacizumab
Carbo + Pac/Gem/lipDoxo + Olaparib/Niraparib
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Carbo + Pac/Gem/lipDoxo + Bevacizumab
Carbo + Pac/Gem/lipDoxo + Olaparib
Carbo + Pac/Gem/lipDoxo
Carbo + Pac/Gem/lipDoxo + Bevacizumab

Neoadjuvant / Adjuvant Setting

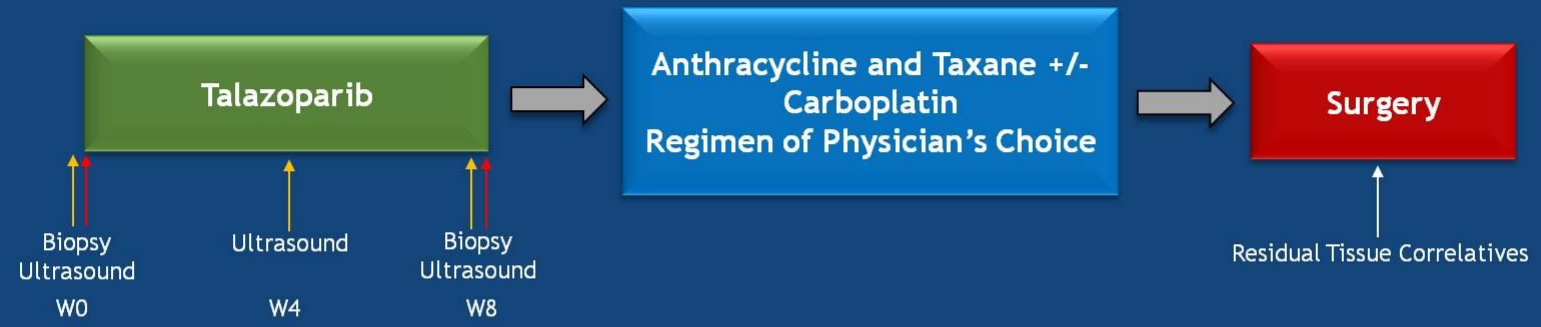
Previous Neoadjuvant Studies with Chemotherapy in BRCA+ Patients

Study	Patient Number	Chemotherapy Regimens	pCR (ypT0/is ypN0)	Rate of Grade 3 and 4 Toxicities
MDACC[1]	80	Multiple, retrospective review	**46% BRCA1** **13% BRCA2**	NR
BrighTNess[2]	92	AC Randomization: P +/- Cb, +/-veliparib	**57% P/Cb/veliparib** **50% P/Cb** **41% P**	**71% P/Cb/veliparib** **68% P/Cb** **15% P**
Byrski et al.[3]	107 BRCA1	Cisplatin	**61%**	NR
GeparSixto[4]	50	Non-pegylated liposomal doxorubicin + P+ weekly Cb	**65.4% Cb** **66.7% no Cb**	***70%-82% hematologic** **59%-78% nonhematologic** In entire study, not BRCA subset[5]

P=paclitaxel; Cb= carboplatin; NR= not reported

1. Arun et al. J Clin Oncol. 2011 Oct 1;29(28):3739-46. 2. Loibl et al. Lancet Oncol 2018 Apr;19(4):497-509. 3.Byrski et al. Breast Cancer res Treat 2014 Sep;147(2):401-5. 4.Hahnen et al. JAMA Oncol. 2017 Oct 1;3(10):1378-1385. 5. von Minckwitz et al. Lancet Oncol. 2014 Jun;15(7):747-756

Background – Initial Feasibility Trial



Eligibility:

- Tumors > 1 cm
- Clinical Stage I-III
- Germline BRCA+
- No previous therapy for invasive breast cancer

Exclusion:

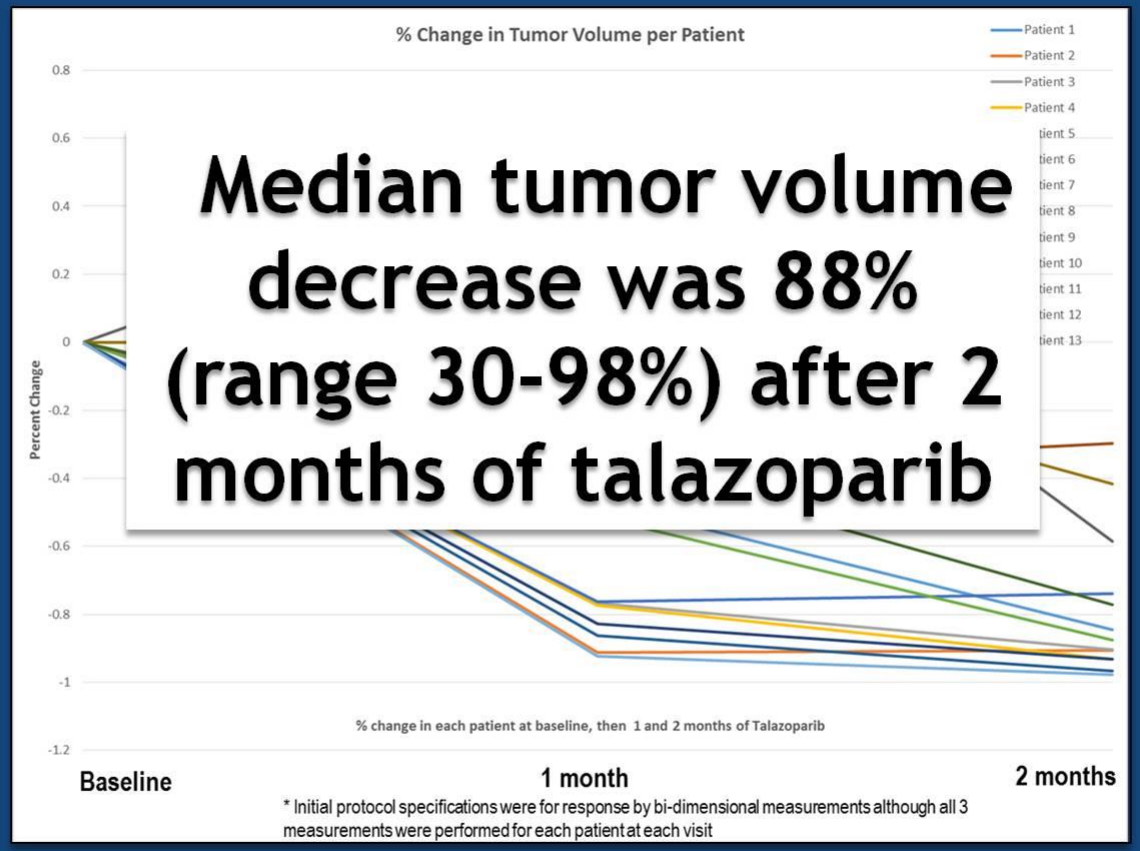
- HER2-positive

Primary Objective:

- Accrual of 20 patients within 2 years
- < 33% with Grade 4 toxicity

Litton et al. NPJ Breast Cancer. 2017 Dec 6;3:49

Response



Median tumor volume decrease was 88% (range 30-98%) after 2 months of talazoparib

Litton et al. NPJ Breast Cancer. 2017 Dec 6;3:49

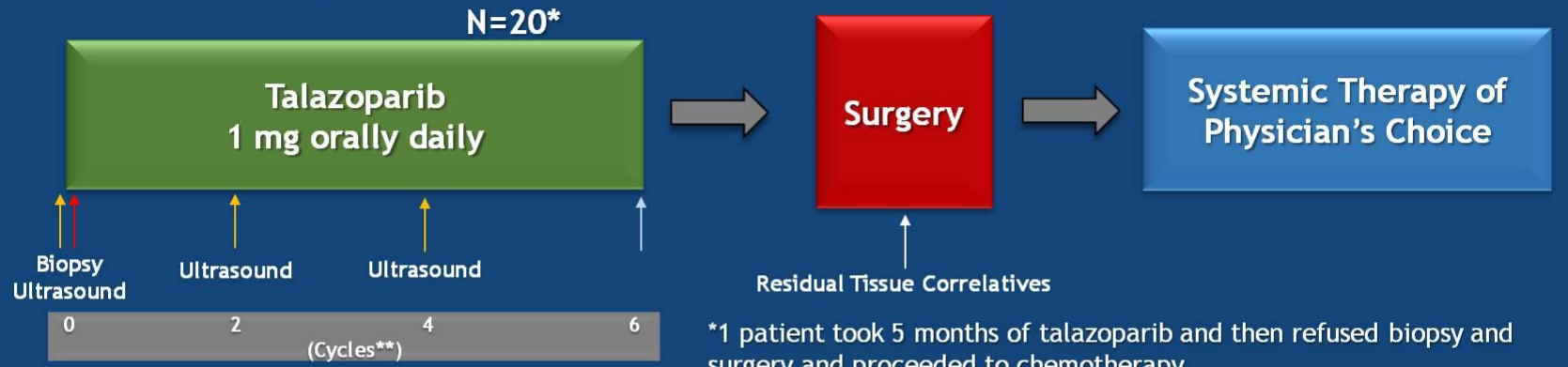
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: JENNIFER K. LITTON, M.D.

Background – Pilot Window Trial: Toxicity

Adverse Events	Grade-1	Grade-2	Grade-3	Grade-4
Hematologic				
Anemia	5	1	2	
Leukopenia	3	4	1	
Neutropenia (decreased ANC)	2	2	3	
Thrombocytopenia	3		1	
Non-Hematologic				
Mucositis	3	1		
Dizziness	8			
Fatigue	7			
Nausea	7			
Dyspnea	3			
GI Disorder (stomach cramps/pain)	3			
Headache	3			
Memory Impairment	2			

Study Design



*1 patient took 5 months of talazoparib and then refused biopsy and surgery and proceeded to chemotherapy
** 1 cycle=28 days

Eligibility

- Tumors > 1 cm
- Clinical Stage I-III
- Germline BRCA mutation
- No previous therapy for invasive breast cancer

Exclusion

- HER2 positive

Primary Objectives

- pCR (ypT0/is ypN0)
- RCB-0 + RCB-I

Secondary Objective

- Evaluate toxicity

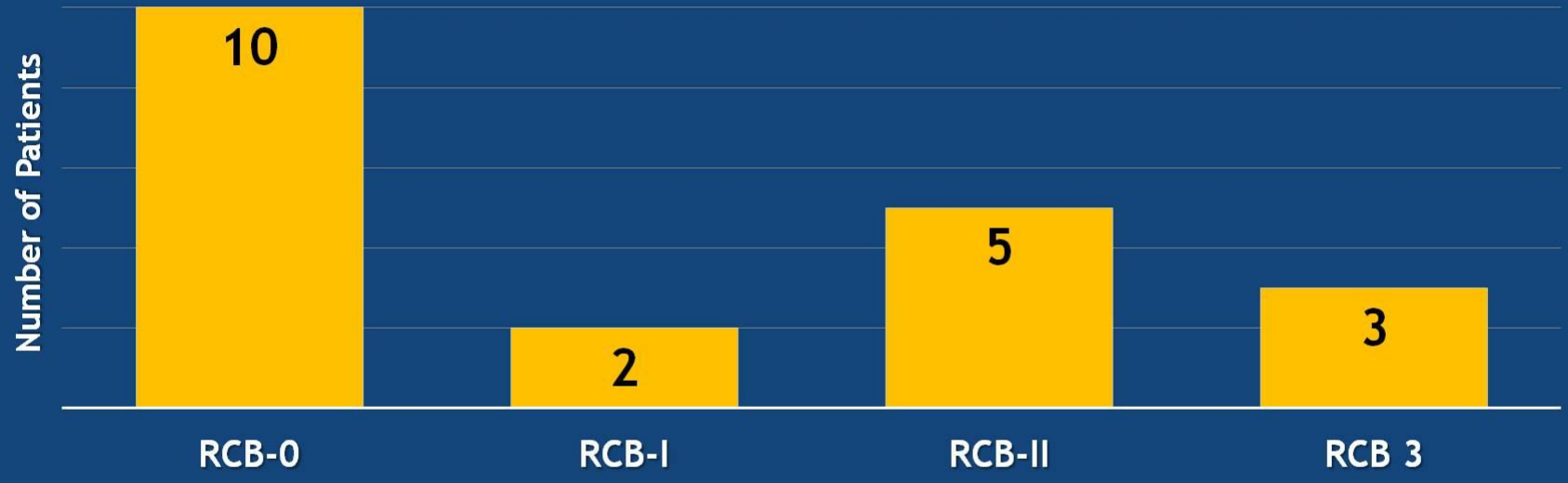
Baseline Characteristics N = 20

Characteristics		Number of Patients
Age	Median=38 (Range 23-58)	20
Race	White	7
	Black	5
	Hispanic	5
	Asian	3
Clinical Stage	I	5
	II	12
	III	3
Histology	Ductal	18
	Lobular	1
	Metaplastic-chondrosarcomatous	1

Baseline Characteristics N = 20

Characteristics		Number of Patients
BRCA mutation	1	17
	2	3
Tissue Receptor Subtype	TNBC (<10% ER or PR)	15
	Hormone Receptor positive (≥10%)	5

Pathologic Results



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

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

PRESENTED BY: JENNIFER K. LITTON, M.D.

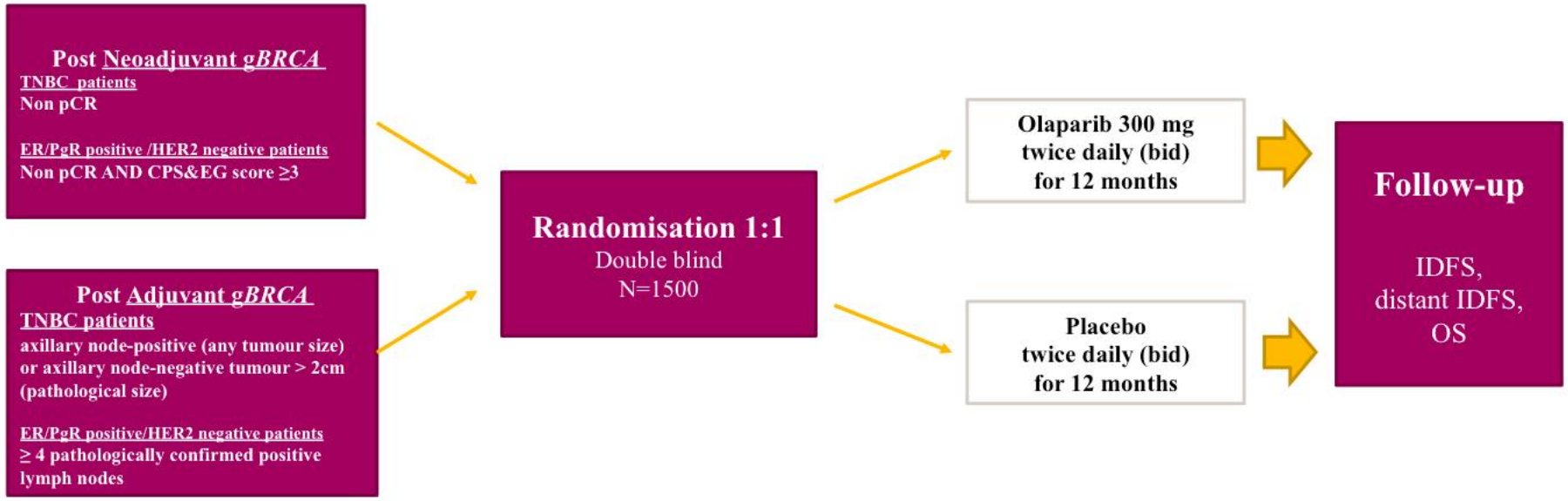
Toxicities – Hematologic

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	4	3	8	-
WBC Decreased	8	4	-	-
Thrombocytopenia	-	-	-	1
Neutropenia	-	4	3	-

ABCSG 41

OlympiA: Updated Design Chart

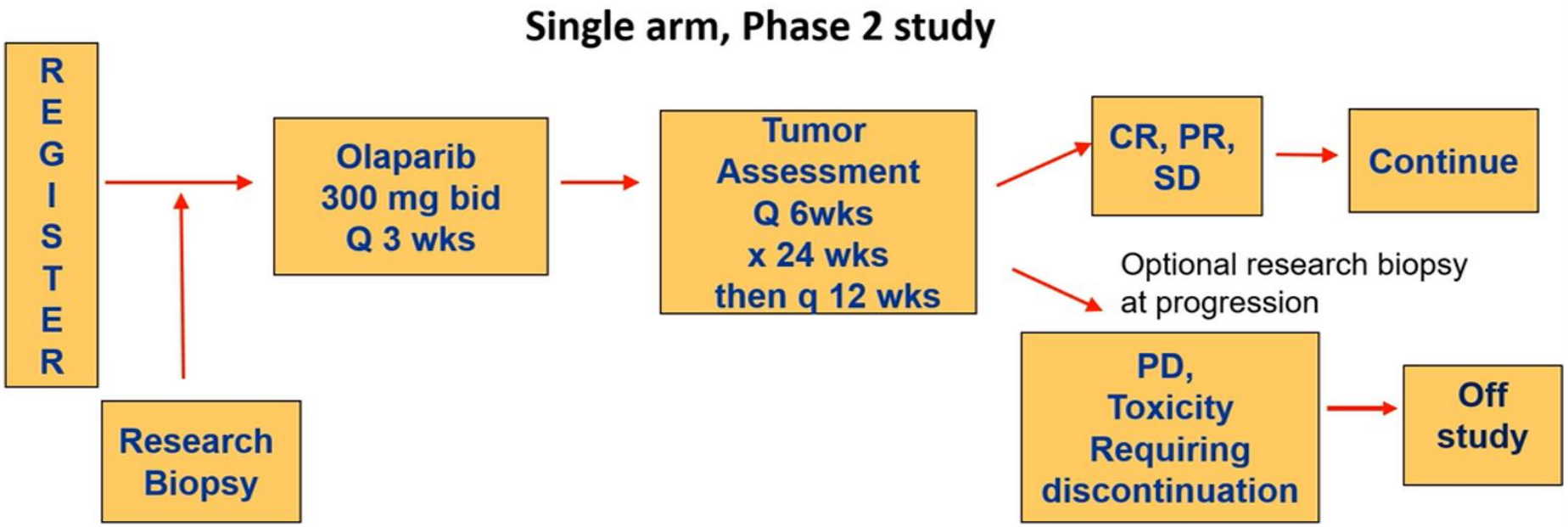
OlympiA
Olaparib in adjuvant BRCAm breast cancer



BIG Breast International Group | frontier science | NRG ONCOLOGY | AstraZeneca

BIG 6-13/ D081CC00006/ NSABP B-55 | Investigators training

Schema: Olaparib Expanded



Cohort 1: Germline Mutation
Cohort 2: Somatic Mutation

s*BRCA1/2* allowed if g*BRCA* negative

ATM, ATR, BAP1, BARD1, BLM, BRIP1 (FANCJ), CHK1 (CHEK1), CHEK2 , CDK12, FANCA, FANCC, FANCD2, FANCF, MRE11A, NBN (NBS1), PALB2, RAD50, RAD51C, RAD51D, WRN

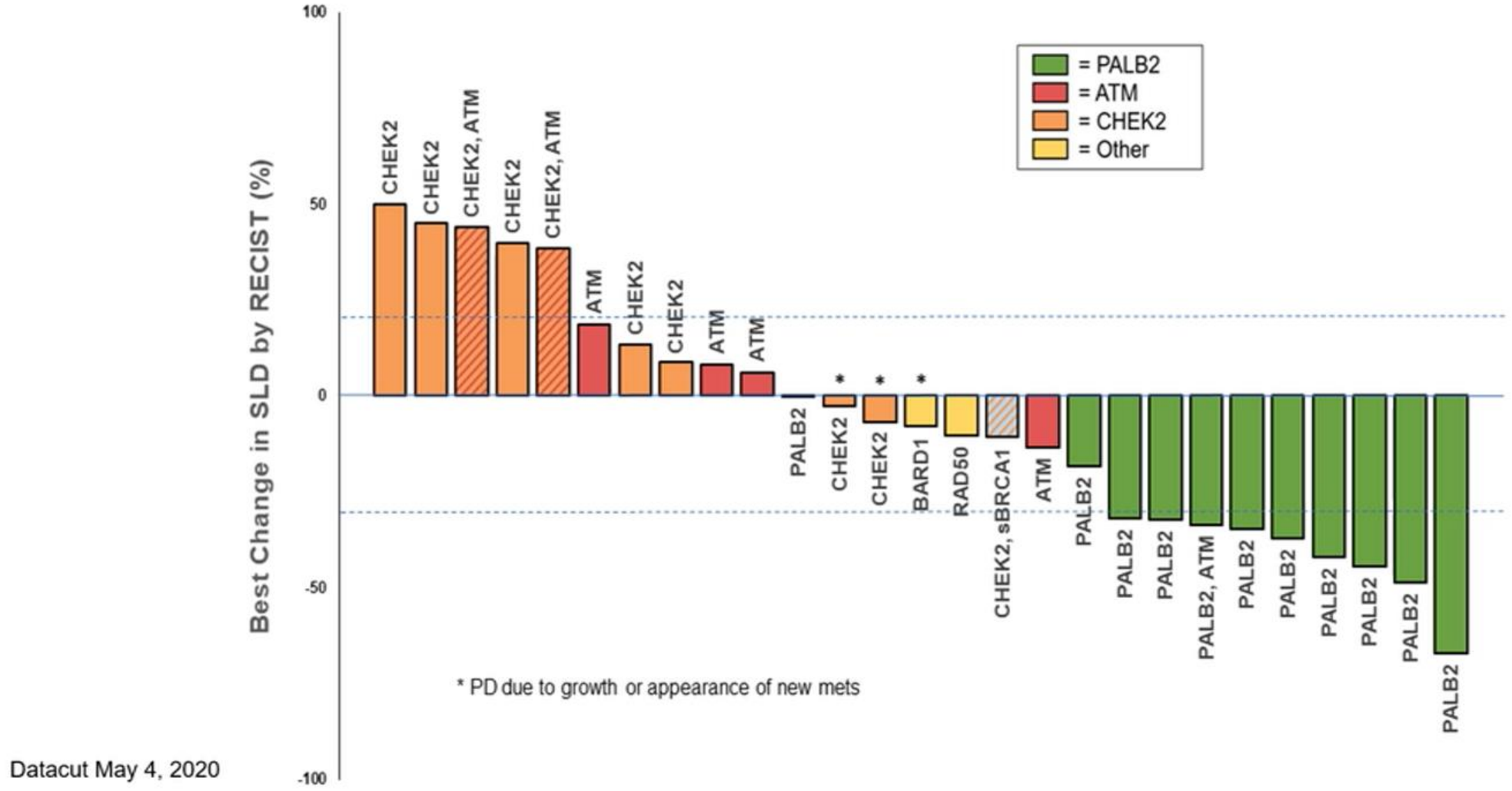
Genetic Mutations

Germline (Cohort 1)			Somatic (Cohort 2)[4]		
• *CHEK2*[1,2]	n=8	14 *ATM CHEK2*	• *sBRCA1*[5]	n=6	15 *sBRCA1/2*
• *ATM*	n=4		• *sBRCA2*	n=9	
• *ATM & CHEK2*[1]	n=2		• *ATM*[6]	n=4	
• *PALB2*[3]	n=11		• *PALB2*	n=2	
• *BARD1*	n=1		• *CDK12*	n=2	
• *RAD50*	n=1		• *BRIP1*	n=1	
			• *BLM*	n=1	
			• *FANCA*	n=1	

[1] CHEK2: 5 missense, 5 frameshift/truncating
[2] 1 pt with missense CHEK2 found to also have sBRCA1 mutation (not listed with Cohort 2)
[3] 1 gPALB2 also had gATM mutation (not listed with ATM group)

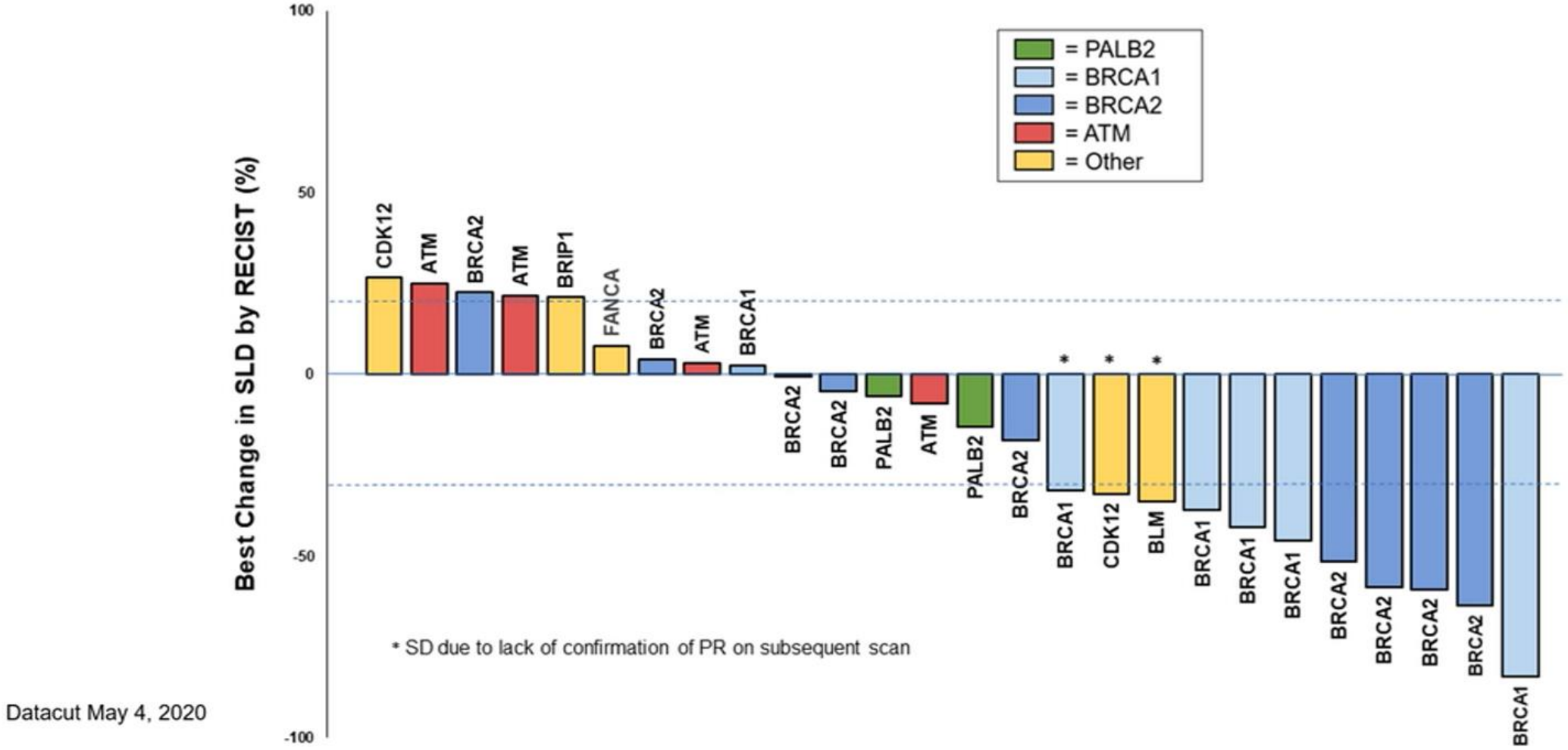
[4] For 8 patients in Cohort 2, germline status is unknown
[5] One sBRCA1 also had sATM (not listed with ATM group)
[6] 1 sATM also had also had a sFANCF mutation

Best Overall Responses: Cohort 1 (Germline)



Datacut May 4, 2020

Best Overall Responses: Cohort 2 (Somatic)



Responses for 5 most common genes (somatic and germline mutations)

PALB2 N=13	*sBRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr **Somatic: 0/2 – both SD*** **(limited assessments)**	**8/16 PR (50%)**	**0/13 germline** **0/4 somatic**

15 patients remain on study

* 1 sPALB2- lost to follow-up after 1st tumor assessment with skin and tumor marker response
^ includes patient from Cohort 1 with sBRCA1 and gCHEK2
** Not included: patient with both gCHEK2 & sBRCA1; patient with gATM and gPALB2

Datacut May 4, 2020

Conclusion

- Prevention possible (Sport, Weight, Tamoxifen, AI, ABCSG 50)
- PARPi is a targeted treament for BRCA patients
- Frist line in OVCA
- In metastatic Breast Cancer
- Perhaps soon in adjuvant Breast Cancer
- PARPi for other Gene Mutations