GASCO 2016 San Antonio Breast Cancer Symposium Review

Triple Negative Breast Cancer

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Disclosures: consultant for Novartis, Pfizer

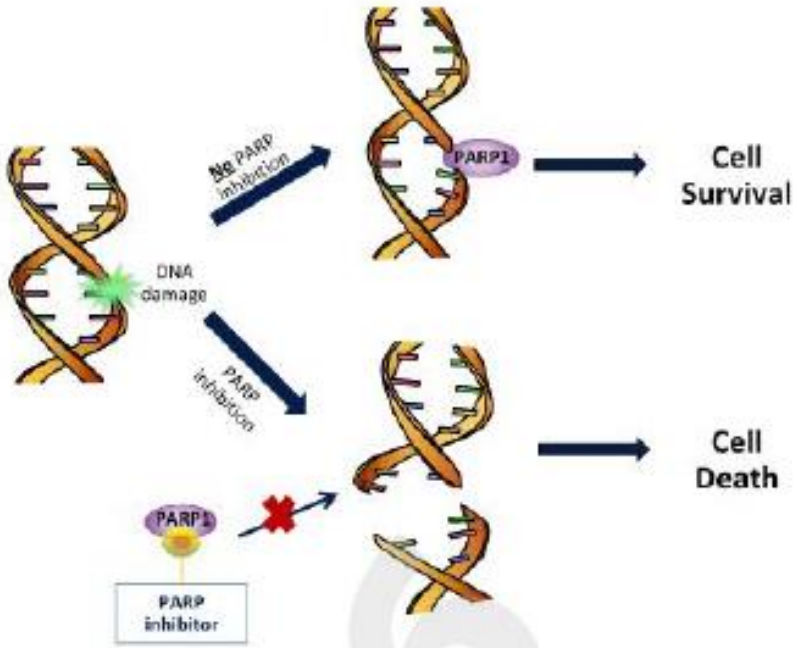
EFFICACY AND TOLERABILITY OF VELIPARIB IN COMBINATION WITH CARBOPLATIN AND PACLITAXEL VS PLACEBO PLUS CARBOPLATIN AND PACLITAXEL IN PATIENTS WITH *BRCA1* OR *BRCA2* MUTATIONS AND LOCALLY RECURRENT OR METASTATIC BREAST CANCER: A RANDOMIZED, PHASE 2 STUDY

Hyo Sook Han, Véronique Diéras, Mark Robson, Markéta Palácová, P. Kelly Marcom, Agnes Jager, Igor Bondarenko, Dennis Citrin, Mario Campone, Melinda L. Telli, Susan M. Domchek, Michael Friedlander, Bella Kaufman,
Christine Ratajczak, Caroline Nickner, Patrick Bonnet, Qin Qin, Jane Qian, Vincent L. Giranda, Stacie P. Shepherd, Steven J. Isakoff, Shannon Puhalla

S2-05 Efficacy and tolerability of veliparib in combination with carboplatin and paclitaxel vs. placebo in patients with BRCA1 or BRCA2 mutations and metastatic breast cancer: a randomized phase 2 study

Background

- Approximately half of women who inherit a *BRCA1/2* mutation will develop breast cancer before the age of 70 years[1]
- Existing homologous recombination DNA damage repair defects in tumors with *BRCA1/2* mutations make them particularly sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors, which interfere with DNA damage repair[2-3]
- Emerging clinical data indicate that patients with *BRCA* mutations may also be particularly sensitive to platinum-containing therapies[4-6]



1. Chen S, et al. *J Clin Oncol*. 2007;25(11):1329-1333; 2. Javle M, et al. *Br J Cancer*. 2011;105(8):1114-1122; 3. Curtin NJ, et al. *Clin Cancer Res*. 2004;10(3):881-889; 4. Byrski T, et al. *Breast Cancer Res*. 2012;14(4):R110; 5. Tutt A, et al. *Cancer Res*. 2015;75(9 suppl): abstract S3-01; 6. Isakoff SJ, et al. *J Clin Oncol*. 2015;33(17):1902-1909.

PARP Inhibitors in Development

Table 1. Poly(ADP-ribose) polymerase inhibitors in clinical development for breast cancer.

PARP inhibitor	Pharmaceutical company	Investigational phase
Veliparib (ABT-888)	AbbVie	Phase III: – Neoadjuvant setting in combination with carboplatin/paclitaxel in triple-negative *BRCA1/2*-mutated metastatic breast cancer Phase II/III: – Combination therapy in germline *BRCA1/2*-mutated metastatic breast cancer
Olaparib (AZD2281)	AstraZeneca	Phase III: – Adjuvant treatment in germline *BRCA1/2*-mutated high-risk, *HER2*- primary breast cancer – Advanced setting monotherapy in germline *BRCA1/2*-mutated breast cancer
Niraparib (formerly MK-4827)	Tesaro	Phase III: – Advanced setting in germline *HER-*, *BRCA1/2*-mutated breast cancer
Talazoparib (BMN 673)	Medivation	Phase III: – Advanced setting monotherapy in germline *BRCA1/2*-mutated breast cancer Phase II: – Advanced setting *BRCA1/2* wild-type, triple-negative breast cancer and homologous recombination deficiency – Advanced setting *BRCA1/2*-mutated breast cancer – Advanced setting in germline *BRCA*-intact breast cancer – Neoadjuvant setting in *BRCA1/2*-mutated breast cancer
Rucaparib (formerly AG 14699)	Clovis Oncology	Phase II: – Advanced setting in patients with known germline *BRCA1/2*-mutated solid tumors – Adjuvant setting in triple-negative breast cancer or germline *BRCA1/2*-mutated breast cancer
CEP-9722	Teva Pharmaceuticals Industries	Phase II: – Advanced setting in solid tumors

PARP: Poly(ADP-ribose) polymerase.
Adapted with permission from Livraghi *et al. BMC Med.* (2015) [12].

Isakoff et al, 2016

PARP inhibitor Breast Trials in Georgia

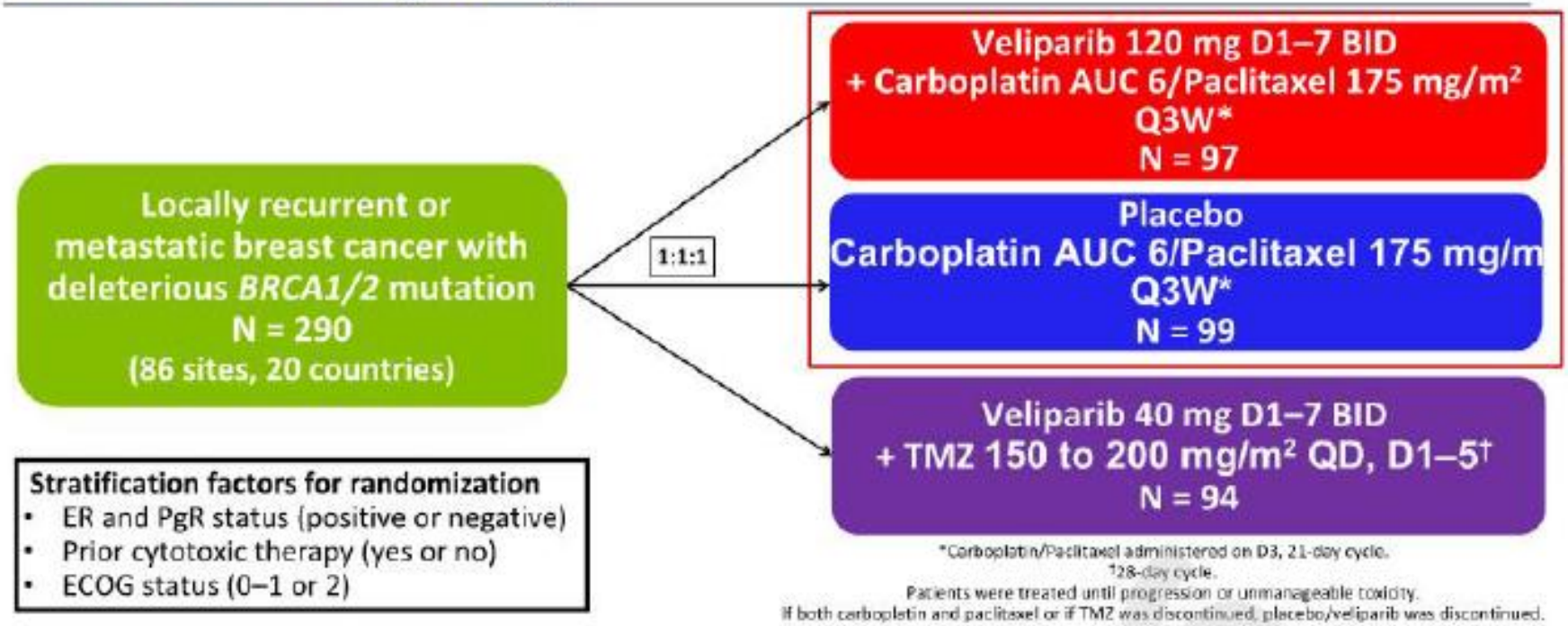
Drug	Study	Georgia Location
Veliparib	A Phase 3 Randomized, Placebo-controlled Trial of Carboplatin and Paclitaxel With or Without Veliparib (ABT-888) in HER2-negative Metastatic or Locally Advanced Unresectable BRCA-associated Breast Cancer	Winship Cancer Institute at Emory University
	Cisplatin With or Without Veliparib in Treating Patients With Stage IV Triple-Negative and/or BRCA Mutation-Associated Breast Cancer	Pearlman Cancer Center in Valdosta
Olaparib	NSABP B55 Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiA)	John B Amos in Columbus, St. Joseph's/Candler in Savannah, Northside Hospital Cancer Institute, Dekalb Medical, Winship Cancer Institute
	Assessment of the Efficacy and Safety of Olaparib Monotherapy Versus Physicians Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients With Germline BRCA1/2 Mutations. (OlympiAD)	NW Georgia Oncology, Marietta (closed to accrual)
Talazoparib	A Study Evaluating Talazoparib (BMN 673), a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation vs. TPC (EMBRACA)	University Cancer and Blood Center in Athens, Navicent Health in Macon

S2-05 BROCADE Veliparib

Background

- Veliparib is a potent orally bioavailable, selective inhibitor of PARP-1 and PARP-2[1]
- Antitumor activity of veliparib monotherapy in patients with *BRCA*-positive breast cancer has been observed in phase 1/2 trials[2,3]
- Phase 1 studies suggest promising antitumor activity and acceptable toxicity of veliparib + carboplatin/paclitaxel (C/P) in breast cancer[4,5]
- Veliparib/carboplatin increased pathologic complete response (CR) rate when added to standard neoadjuvant therapy (51% vs 26%) in the I-SPY 2 phase 2 study of patients with triple-negative breast cancer (TNBC)[6]
- Here, safety and efficacy results for the first randomized phase 2 trial of placebo or veliparib with C/P in patients with locally recurrent/metastatic breast cancer and a *BRCA1/2* mutation are reported

BROCADE: Study Design



Veliparib + TMZ results will be presented separately; December 9, 2016, 7.30 am – 9.30 am
SABCS program number: P4-22-02

- ≤ 2 prior lines of chemotherapy
- No prior platinum or PARP inhibitor
- No CNS metastases

- Primary Endpoint :PFS
- Secondary Endpoints: OS, CBR (week 18 progression-free rate), ORR

BROCADE

Demographics and Baseline Characteristics

Characteristic, n (%)	Placebo + C/P N = 99	Veliparib + C/P N = 97
Median age, years (range)	46 (24–66)	44 (25–65)
ER/PgR status		
ER negative and PgR negative	43 (43.4)	40 (41.2)
ER positive and/or PgR positive	56 (56.6)	57 (58.8)
HER2 overall status*		
Negative	92 (92.9)	94 (96.9)
Positive	7 (7.1)	3 (3.1)
TNBC	42 (42.4)	40 (41.2)
Non-TNBC	57 (57.6)	57 (58.8)
BRCA1 mutation positive	53 (53.5)	51 (52.6)
BRCA2 mutation positive	46 (46.5)	44 (45.4)
ECOG status		
0–1	93 (93.9)	92 (94.8)
2	6 (6.1)	5 (5.2)

Characteristic, n (%)	Placebo + C/P N = 99	Veliparib + C/P N = 97
Number of prior regimens of cytotoxic therapy (any setting)		
0	23 (23.2)	19 (19.6)
1	42 (42.4)	47 (48.5)
2	25 (25.3)	24 (24.7)
>2	9 (9.1)	7 (7.2)
Measurable disease at baseline†		
Yes	81 (83.5)	73 (77.7)
No	16 (16.5)	21 (22.3)
Number of metastatic sites		
No metastases	5 (5.1)	4 (4.1)
1	38 (38.4)	39 (40.2)
2	28 (28.3)	30 (30.9)
3	18 (18.2)	13 (13.4)
≥4	10 (10.1)	11 (11.3)

*Positive in either primary site or metastasis.

†Status missing for 2 patients in the placebo + C/P and 3 patients in the veliparib + C/P arm.

HER2, human epidermal growth factor receptor 2.

BROCADE

Treatment-Emergent Grade 3/4 Adverse Events

	Placebo + C/P N = 96	Veliparib + C/P N = 93
Grade 3/4 AE, n (%)	80 (83.3)	73 (78.5)
Common hematologic grade 3/4 AEs, n (%)		
Anemia	17 (17.7)	16 (17.2)
Febrile neutropenia	3 (3.1)	8 (8.6)
Leukopenia	11 (11.5)	15 (16.1)
Neutropenia	53 (55.2)	52 (55.9)
Thrombocytopenia	25 (26.0)	29 (31.2)
Common non-hematologic grade 3/4 AEs, n (%)		
Diarrhea	7 (7.3)	4 (4.3)
Drug hypersensitivity	0	5 (5.4)*
Fatigue	8 (8.3)	5 (5.4)
Peripheral neuropathy†	5 (5.2)	7 (7.5)

BROCADE

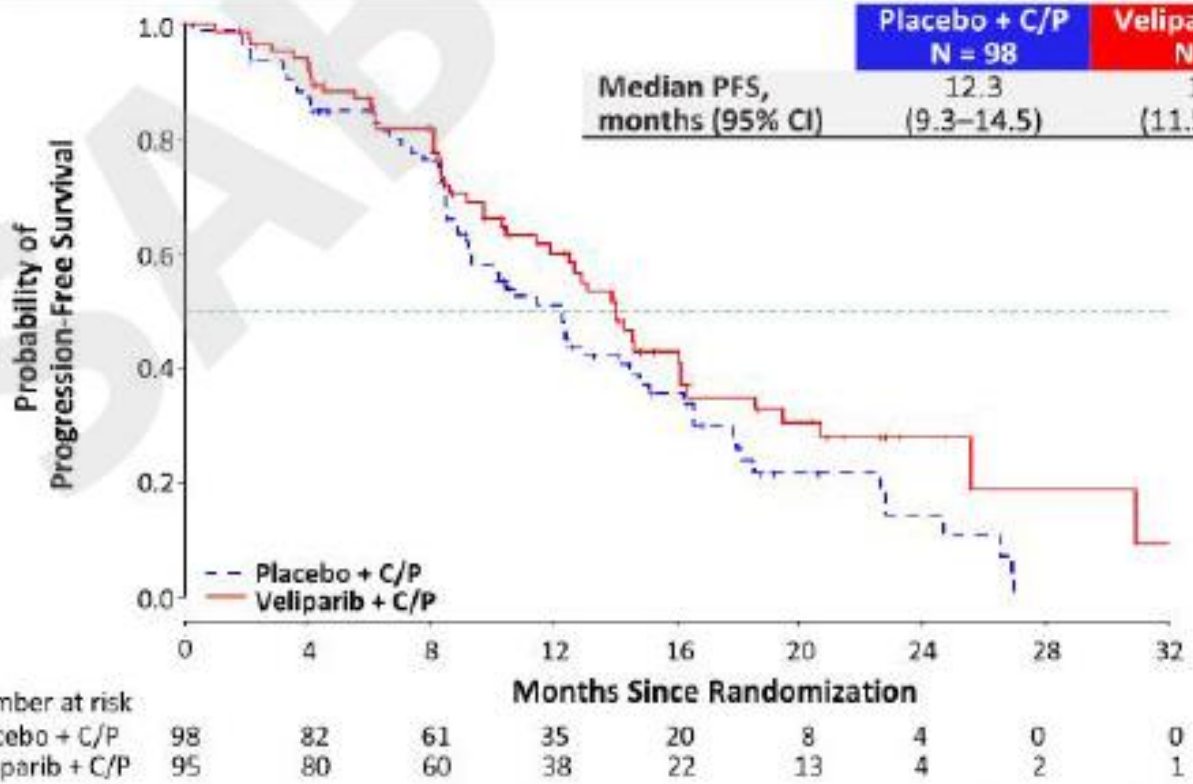
Treatment-Emergent Adverse Events Leading to Study Drug Interruption, Reduction, or Discontinuation

Any adverse event leading to:	Placebo + C/P N = 96	Veliparib + C/P N = 93
Veliparib/Placebo		
Interruption, n (%)	69 (71.9)	70 (75.3)
Reduction, n (%)	10 (10.4)	5 (5.4)
Discontinuation, n (%)	20 (20.8)	26 (28.0)
Carboplatin		
Interruption, n (%)	71 (74.0)	70 (75.3)
Reduction, n (%)	65 (67.7)	56 (60.2)
Discontinuation, n (%)	38 (39.6)	42 (45.2)
Paclitaxel		
Interruption, n (%)	69 (71.9)	72 (77.4)
Reduction, n (%)	51 (53.1)	35 (37.6)*
Discontinuation, n (%)	33 (34.4)	31 (33.3)

BROCADE

Progression-Free Survival

	Placebo + C/P N = 98	Veliparib + C/P N = 95	HR	P value*
Median PFS, months (95% CI)	12.3 (9.3–14.5)	14.1 (11.5–16.2)	0.789 (0.536–1.162)	0.231



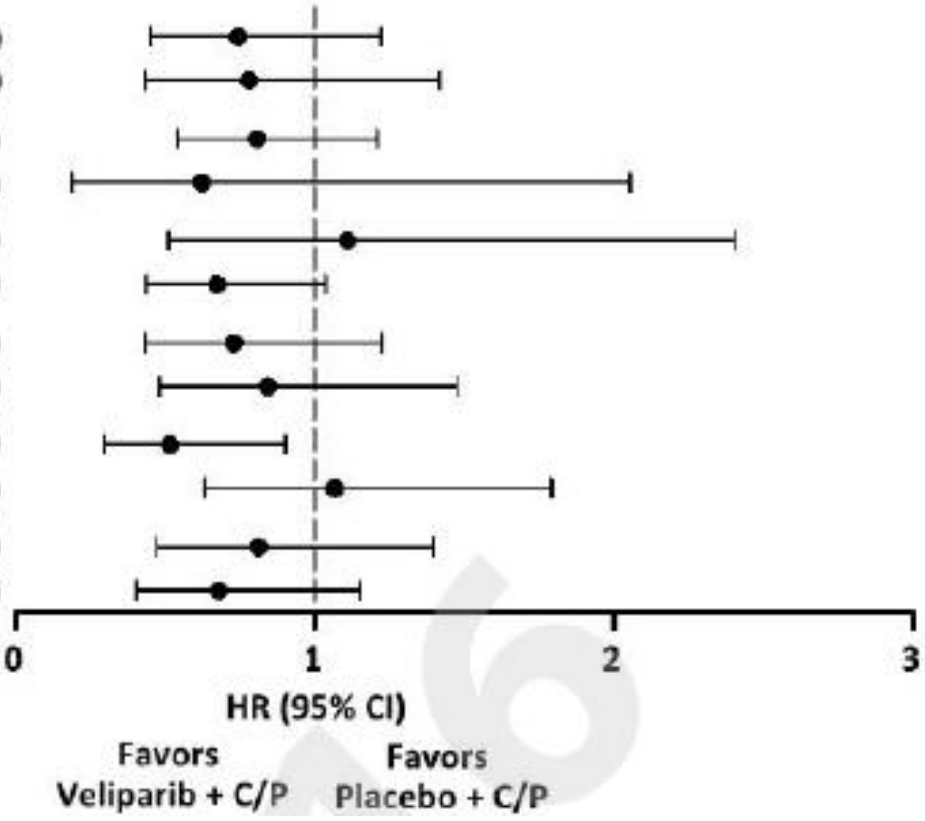
Number at risk									
Placebo + C/P	98	82	61	35	20	8	4	0	0
Veliparib + C/P	95	80	60	38	22	13	4	2	1

Median (95% CI) PFS, Veliparib + TMZ: 7.4 (5.9–8.5) months; HR = 1.858 (1.278–2.702), P = 0.001. (SABCS program number: P4-22-02)

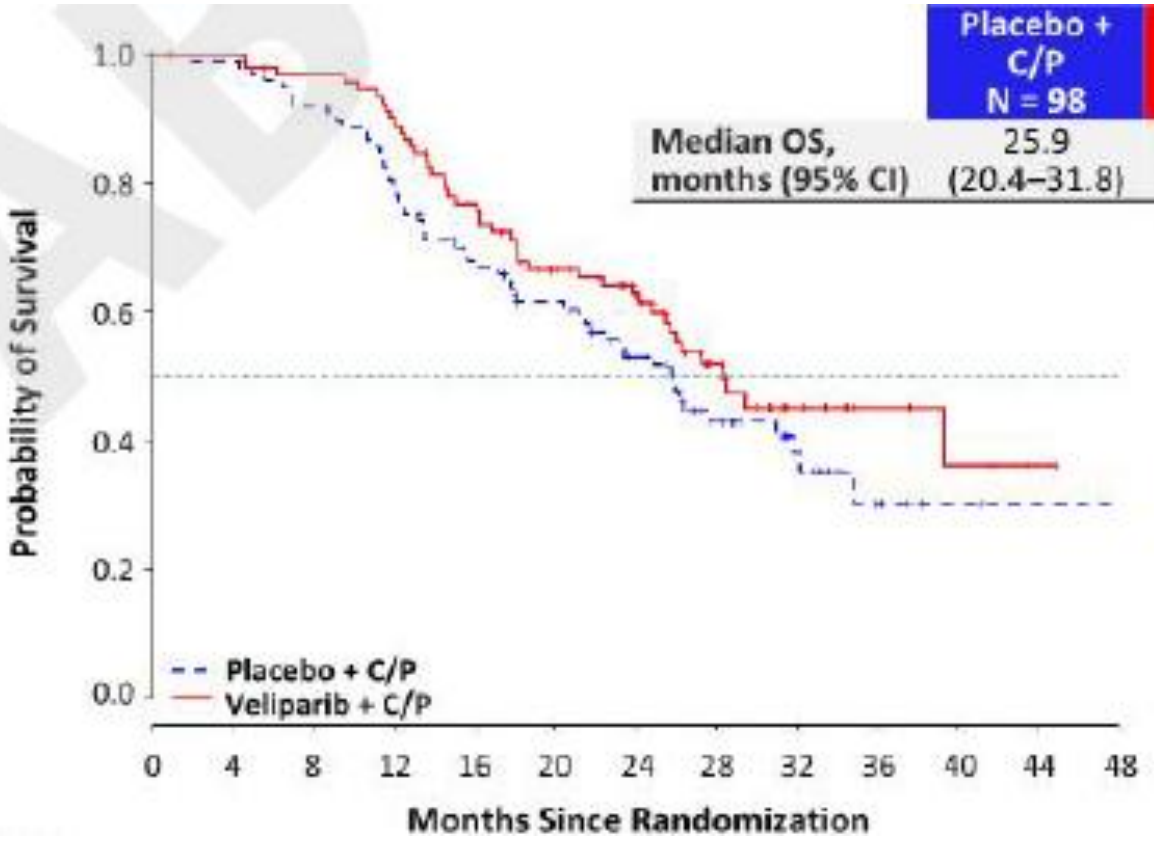
BROCADE

PFS by Subgroups

	Placebo + C/P Event/N	Veliparib + C/P Event/N	HR 95% CI
BRCA1 mutation	36/53	29/51	0.745 (0.454–1.224)
BRCA2 mutation	27/46	20/44	0.783 (0.433–1.417)
Measurable disease	56/80	43/72	0.809 (0.542–1.209)
Non-measurable disease	6/16	6/20	0.624 (0.189–2.056)
No prior cytotoxic therapy	16/23	11/18	1.111 (0.513–2.403)
Prior cytotoxic therapy	47/75	38/77	0.674 (0.437–1.039)
ECOG 0	30/49	29/60	0.730 (0.434–1.227)
ECOG 1–2	33/49	20/35	0.844 (0.482–1.477)
Age <45 yr	29/47	24/48	0.518 (0.297–0.903)
Age ≥45 yr	34/51	25/47	1.067 (0.635–1.792)
TNBC	29/41	24/40	0.815 (0.474–1.401)
Non-TNBC	34/57	25/55	0.681 (0.403–1.152)



BROCADE: Overall Survival

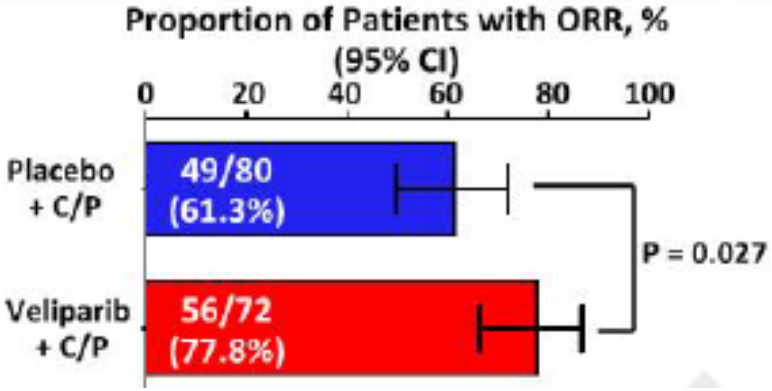


	Placebo + C/P N = 98	Veliparib + C/P N = 95	HR	P value*
Median OS, months (95% CI)	25.9 (20.4–31.8)	28.3 (24.9–NR)	0.750 (0.503–1.117)	0.157

BROCADE

Tumor Response

	Placebo + C/P N = 98	Veliparib + C/P N = 95
ORR (CR + PR), n/N, % (95% CI)	49/80 (61.3%) (49.7–71.9)	56/72 (77.8%)* (66.4–86.7)
CR, n/N, (%)	3/80 (3.8%)	4/72 (5.6%)
PR, n/N, (%)	46/80 (57.5%)	52/72 (72.2%)
CBR (week 18 progression-free rate), % (95% CI)	87.0% (78.3–92.4)	90.7% (82.2–95.2)
DOR, median months, (95% CI)	11.1 (9.5–15.7)	11.7 (8.5–14.1)



BROCADE

Conclusions

- The addition of veliparib to carboplatin/paclitaxel resulted in trends toward improved PFS and OS, and a significant increase in ORR
  - Final OS analysis will occur when the prespecified number of events is reached
- The safety profile of veliparib + carboplatin/paclitaxel was comparable to that of carboplatin/paclitaxel alone
- Addition of veliparib did not increase the frequency of interruption, dose reduction, or discontinuation of veliparib/placebo, carboplatin, or paclitaxel due to adverse events
- Further evaluation of the efficacy and safety of veliparib with weekly paclitaxel and carboplatin in patients with *BRCA*-mutated advanced breast cancer is ongoing in the phase 3 randomized trial BROCADE3 (NCT02163694)

DNA repair deficiency biomarkers and MammaPrint High1/(ultra)High2 risk as predictors of veliparib/carboplatin response: results from the neoadjuvant I-SPY 2 TRIAL for high risk breast cancer

Denise Wolf* & Christina Yau*

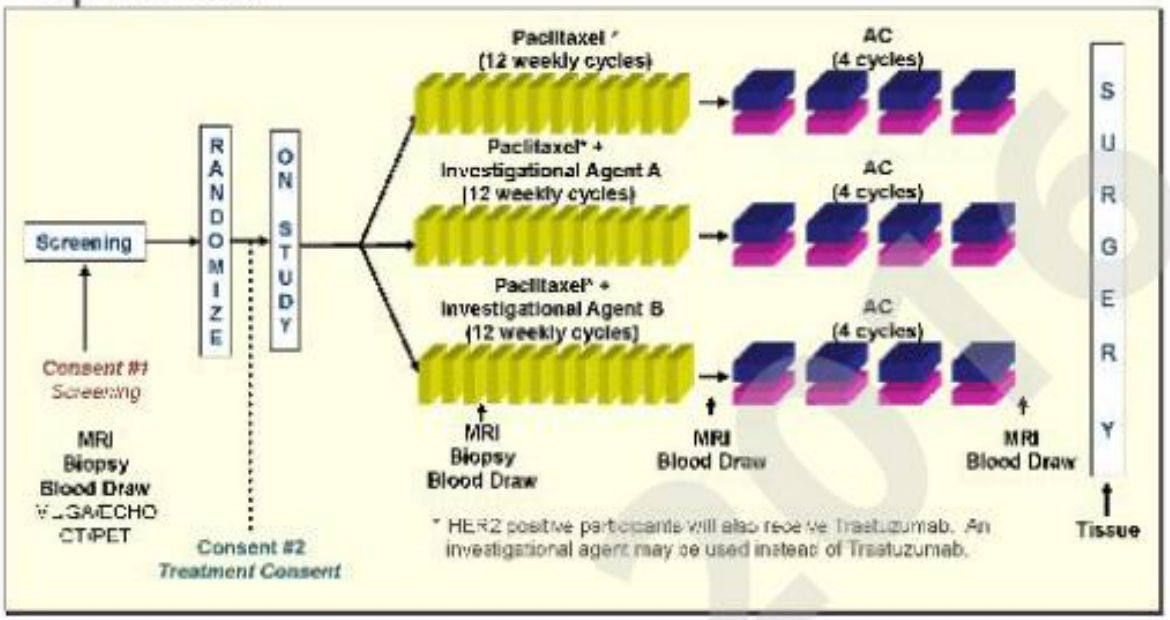
Ashish Sanil, Annuska Glas, Chip Petricoin, Julia Wulkuhle, Lamorna Brown-Swigart, Gillian Hirst, I-SPY 2 TRIAL Investigators, Meredith Buxton, Angela DeMichele, Nola Hylton, Fraser Symmans, Doug Yee, Melissa Paoloni, **Don Berry, Hope Rugo, Olufunmilayo Olopade, Laura Esserman & Laura van 't Veer**

**equal contribution*

S2-06 DNA repair deficiency biomarker and MammaPrint high1/(ultra)high2 risk as predictors of veliparib/carboplatin response: Results from the neoadjuvant I-SPY2 trial for high

The I-SPY2 TRIAL Standing Platform

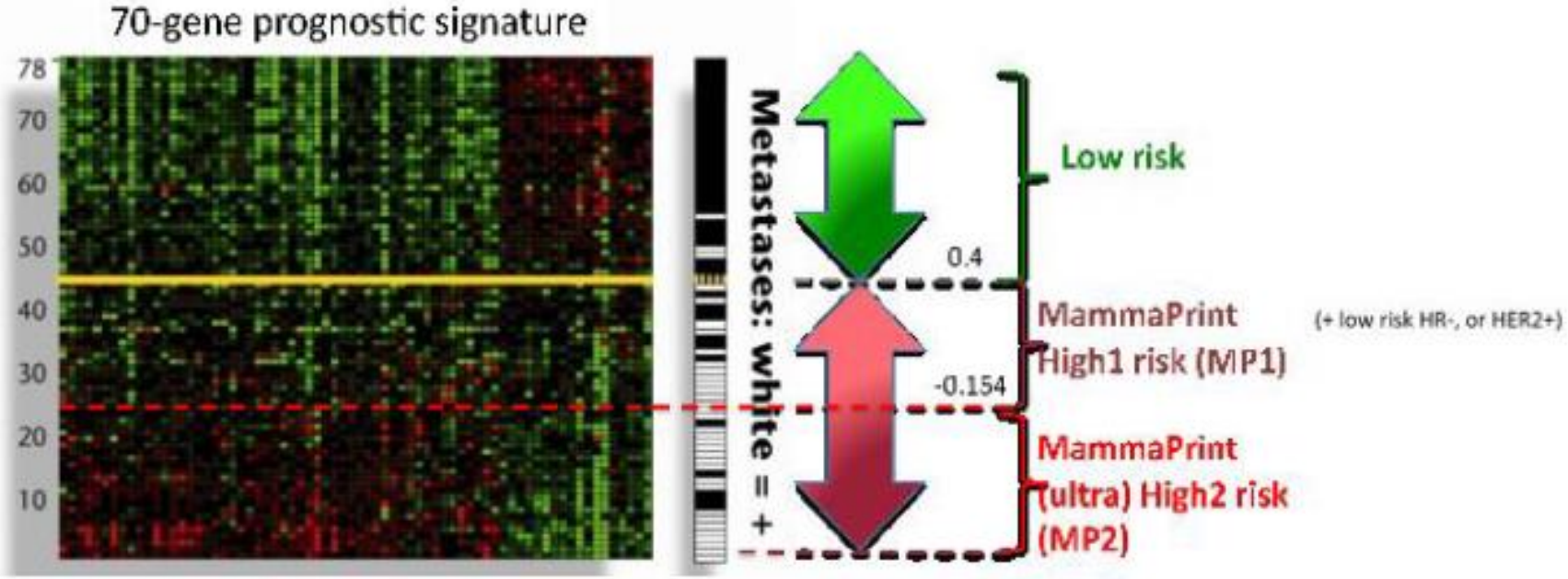
- Phase II, adaptively-randomized neoadjuvant trial
- Shared control arm
  - Standard neoadjuvant chemotherapy
- Simultaneous investigational arms
  - Up to four



The I-SPY2 TRIAL Standing Platform

- **Primary endpoint**: pathologic complete response (pCR)
  - Defined as **no residual invasive cancer in the breast or lymph nodes (ypT0/is and ypN0)**

- **Match therapies with most responsive breast cancer subtypes**
  - Defined by **HR, HER2**, and 70-gene signature (Mammaprint) High1/(ultra)High2 risk (**MP1/2**) status



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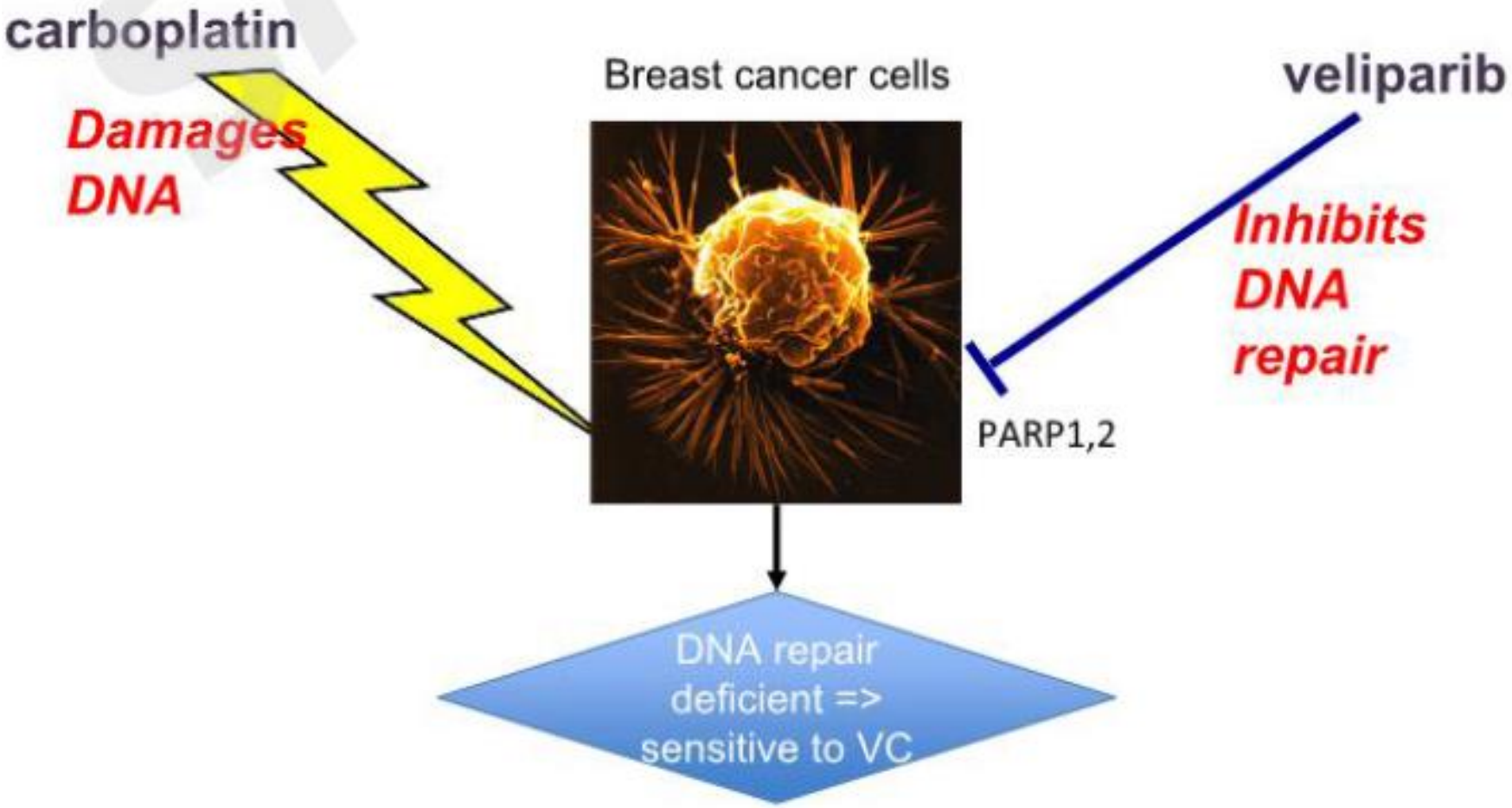
- **Match therapies with most responsive breast cancer subtypes**
  - Defined by **HR, HER2**, and 70-gene signature (Mammaprint) High1/(ultra)High2 risk (**MP1/2**) status
- Agents/combinations **"graduate"** for efficacy = reaching >85% predictive probability of success in a subsequent phase III trial in the most responsive patient subset
- ***Biomarker component:*** evaluate biomarkers associated with mechanism of action of each investigational treatment, along with the pre-defined subsets

veliparib/carboplatin (VC) combination therapy graduated in the triple negative (TN) subset

- *VC was open to Her2- patients*

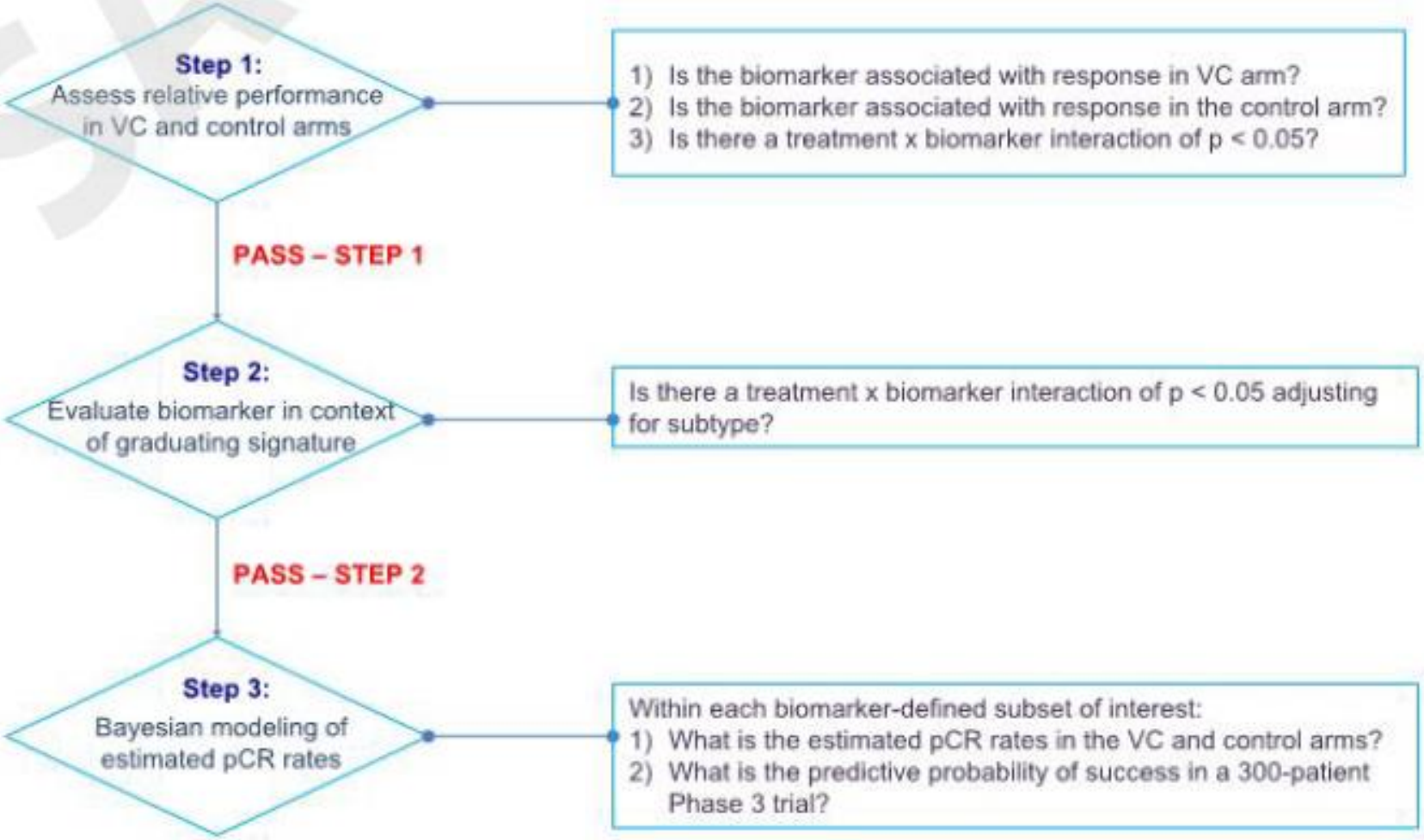


Biomarker proposals for specific predictors of veliparib/carboplatin response

- **BRCA1/2 germline** mutation (Myriad Genetics)
- **PARP1 protein** and cleaved protein levels (RPPA)
- 3 gene expression signatures relating to DNA damage repair deficiency
  - **PARPi-7**
    - 7 gene DNA-repair deficiency signature: BRCA1, CHEK2, MAPKAPK2, MRE11A, NBN, TDG, XPA. Predicts olaparib-sensitivity in cell lines (PMID:22875744)
  - **BRCAness**
    - 77-gene BRCA1/2 deficiency signature. Distinguishes BRCA1 from wildtype (based on PMID:22032731)
  - **CIN70**
    - 70-gene chromosomal instability (PMID:16921376)
- **MP1/2** class

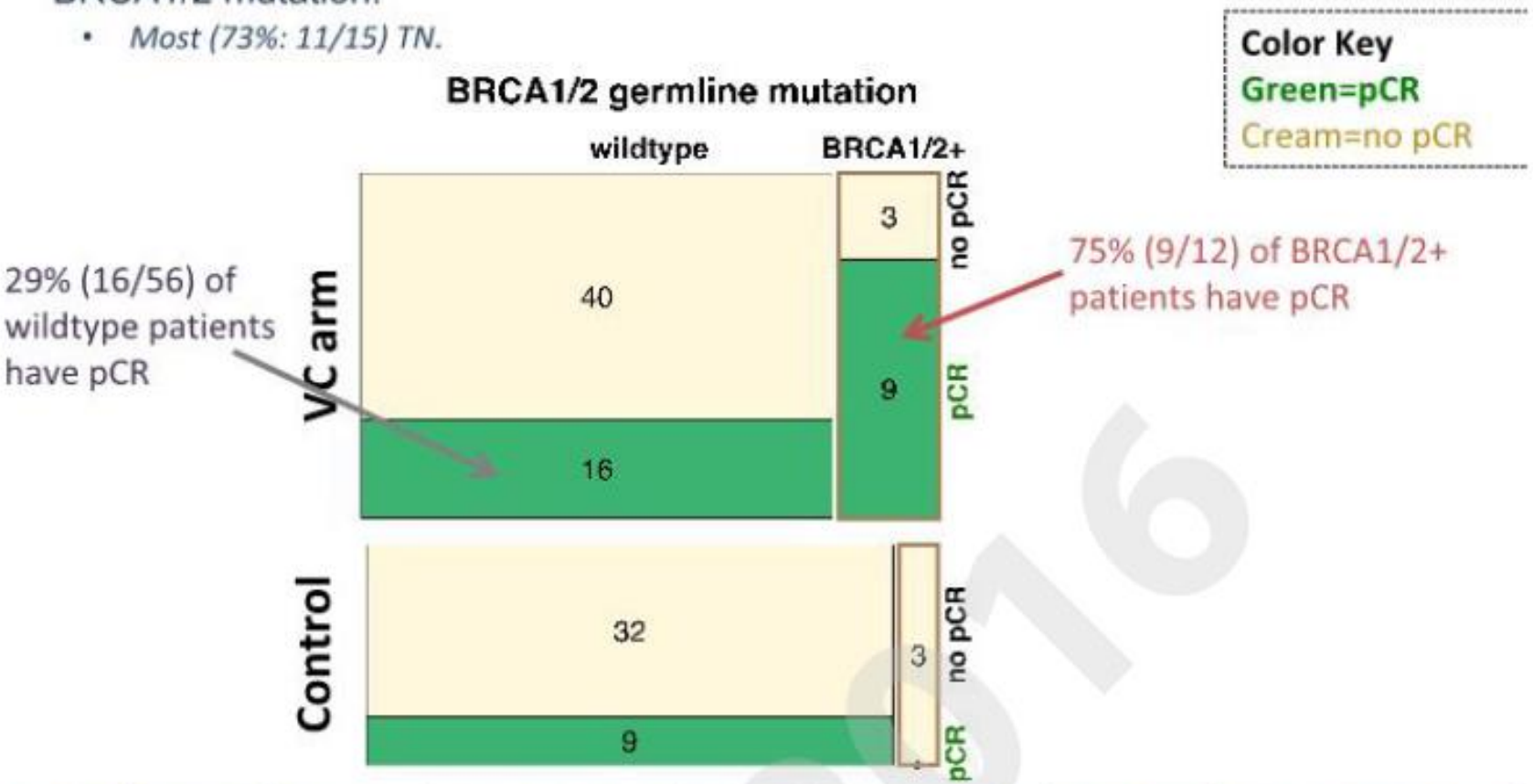
Our Pre-specified Biomarker Evaluation Methodology is a 3-Step Process

116 patients available for analysis in V/C & concurrent control arms; 72 VC + 44 controls.



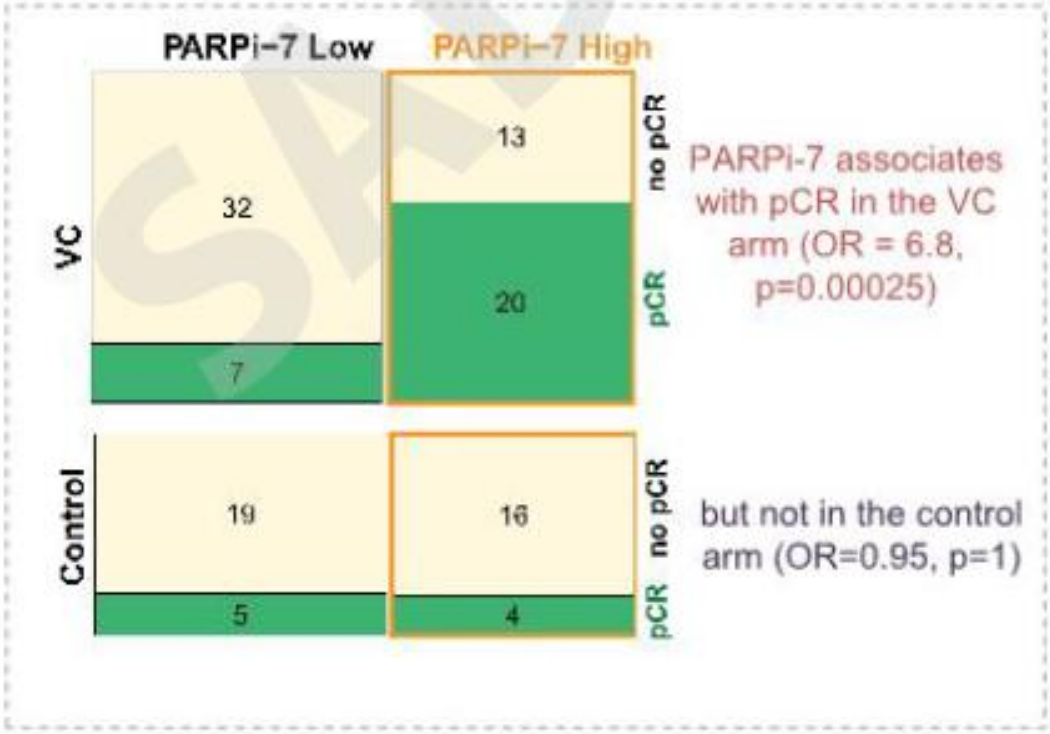
BRCA 1/2 Germline Mutation

- 13% (15/114) of patients were found to carry a deleterious or suspected deleterious BRCA1/2 mutation.
  - *Most (73%: 11/15) TN.*



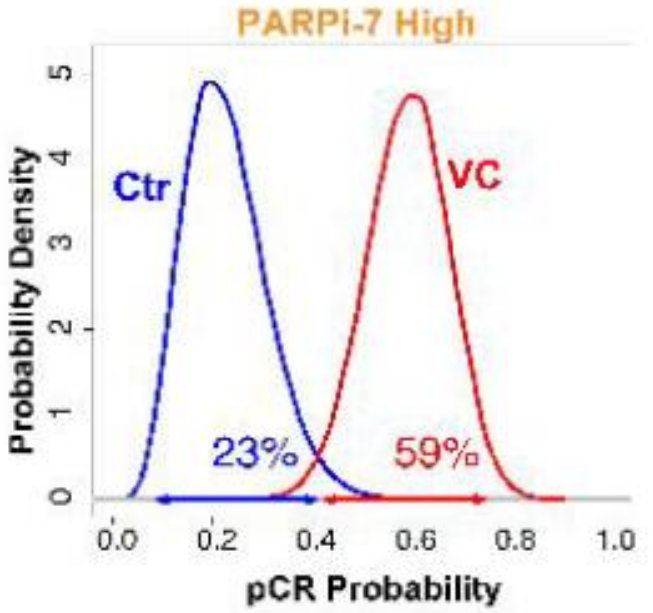
BRCA1/2 germ line mutation status associates with response in the VC arm **(OR=7.25; p=0.006)**
but its low prevalence in the control arm (n=3) precluded further evaluation.

PARPi-7 Signature Example



PARPi-7 associates with pCR in the VC arm (OR = 6.8, p=0.00025)

but not in the control arm (OR=0.95, p=1)



>90% predictive probability of success in phase 3

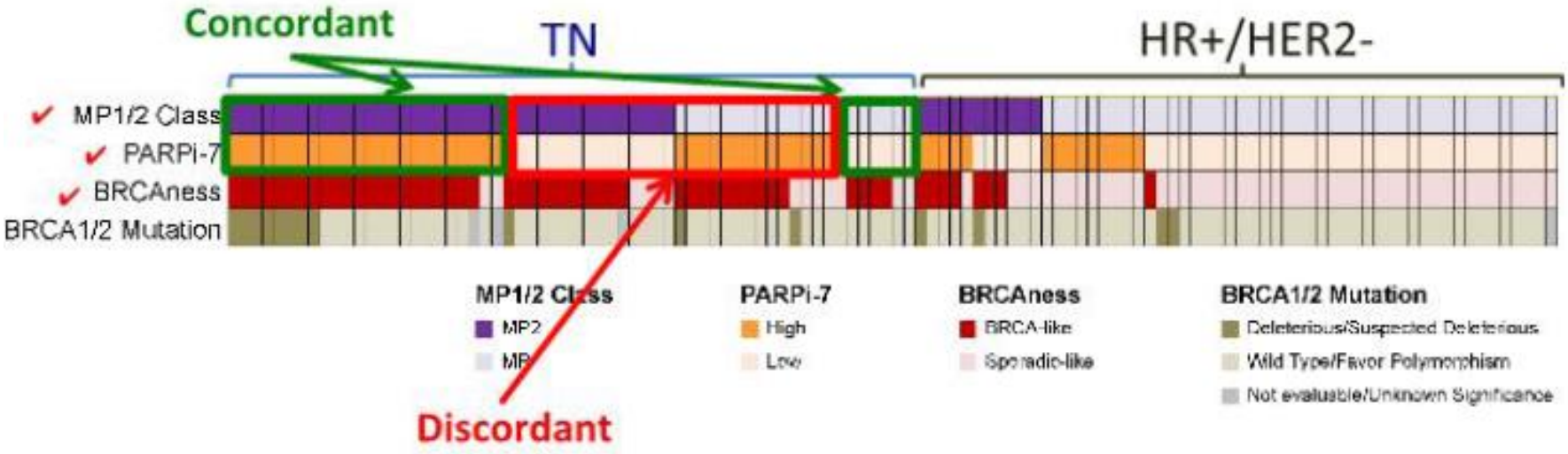
There is a significant biomarker x treatment interaction (p=0.03), which remains upon adjusting for HR status (p= 0.025).

PARPi-7 is a specific predictor of VC response

Specific Predictors of VC Response

- **BRCA1/2 germline** mutation - **not evaluable**
- ~~**PARP1 protein and cleaved protein levels (RPPA) – NO**~~
- 3 gene expression signatures relating to DNA damage repair deficiency
  - **PARPi-7 - YES**
    - 7 gene DNA-repair deficiency signature: BRCA1, CHEK2, MAPKAPK2, MRE11A, NBN, TDG, XPA. Distinguishes between olaparib-sensitive and resistant cell lines (PMID:22875744)
  - **BRCAness – YES**
    - 77-gene BRCA1/2 deficiency signature. Distinguishes between BRCA1 and wildtype within TN (based on PMID:22032731)
  - ~~**CIN70 –**~~ **NO**
    - 70-gene chromosomal instability (PMID:16921376)
- **MP1/2 class - YES**

Concordance between PARP-i7, BRCAness, MP1/2



Concordance between pairs of VC sensitivity biomarkers in TN is just 50-67% (moderate).

(Not identifying exactly the same patients)

Voting Scheme to Combine Biomarkers

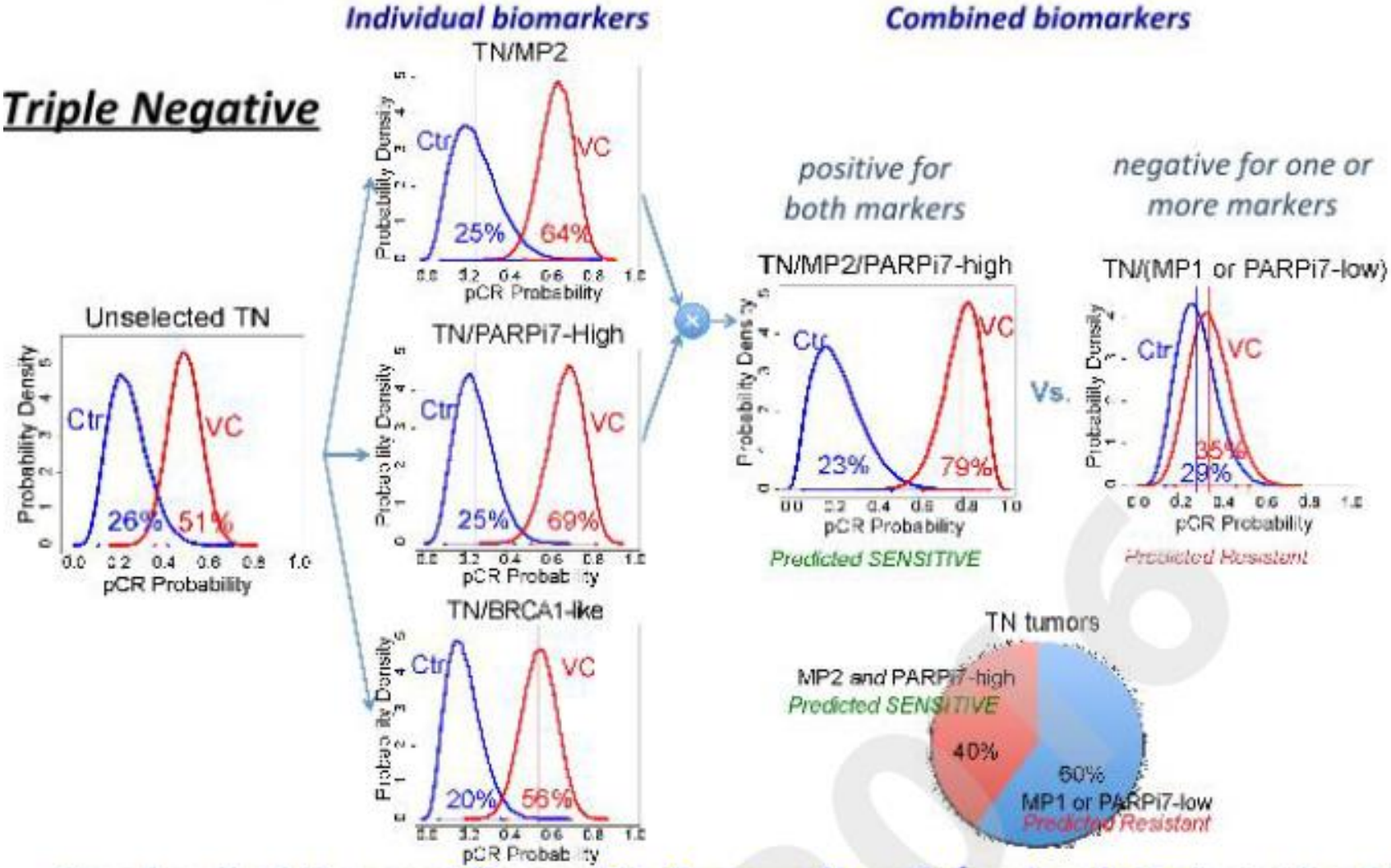
Biomarker 1	Biomarker 2	Combined
Resistant	Resistant	Resistant
Resistant	Sensitive	Resistant
Sensitive	Resistant	Resistant
Sensitive	Sensitive	**SENSITIVE**

Patients positive for both sensitivity markers called 'sensitive'

(need 2 YES votes!)

Combining Biomarkers Improves Predictive Performance

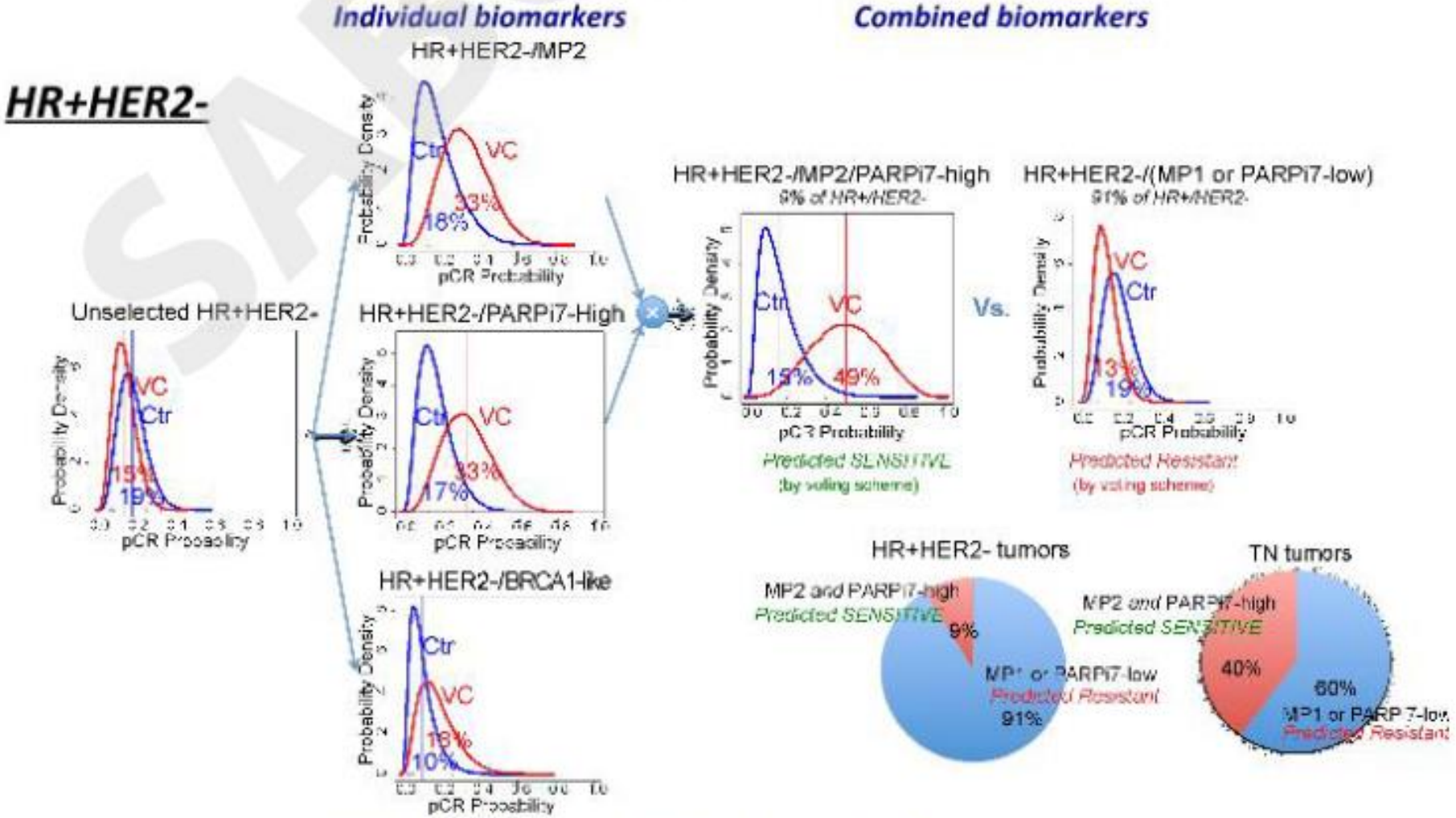
Triple Negative



Nearly all of the specific sensitivity to veliparib/carboplatin is in the 40% of TN patients positive for BOTH sensitivity markers.

(Bayesian models using all data – N=116)

Combining Biomarkers Improves Predictive Performance



Nearly all of the specific sensitivity to veliparib/carboplatin is in the 9% of HR+HER2- patients positive for BOTH sensitivity markers.

(Bayesian models using all data – N=116)

San Antonio Breast Cancer Symposium December 6-10, 2016

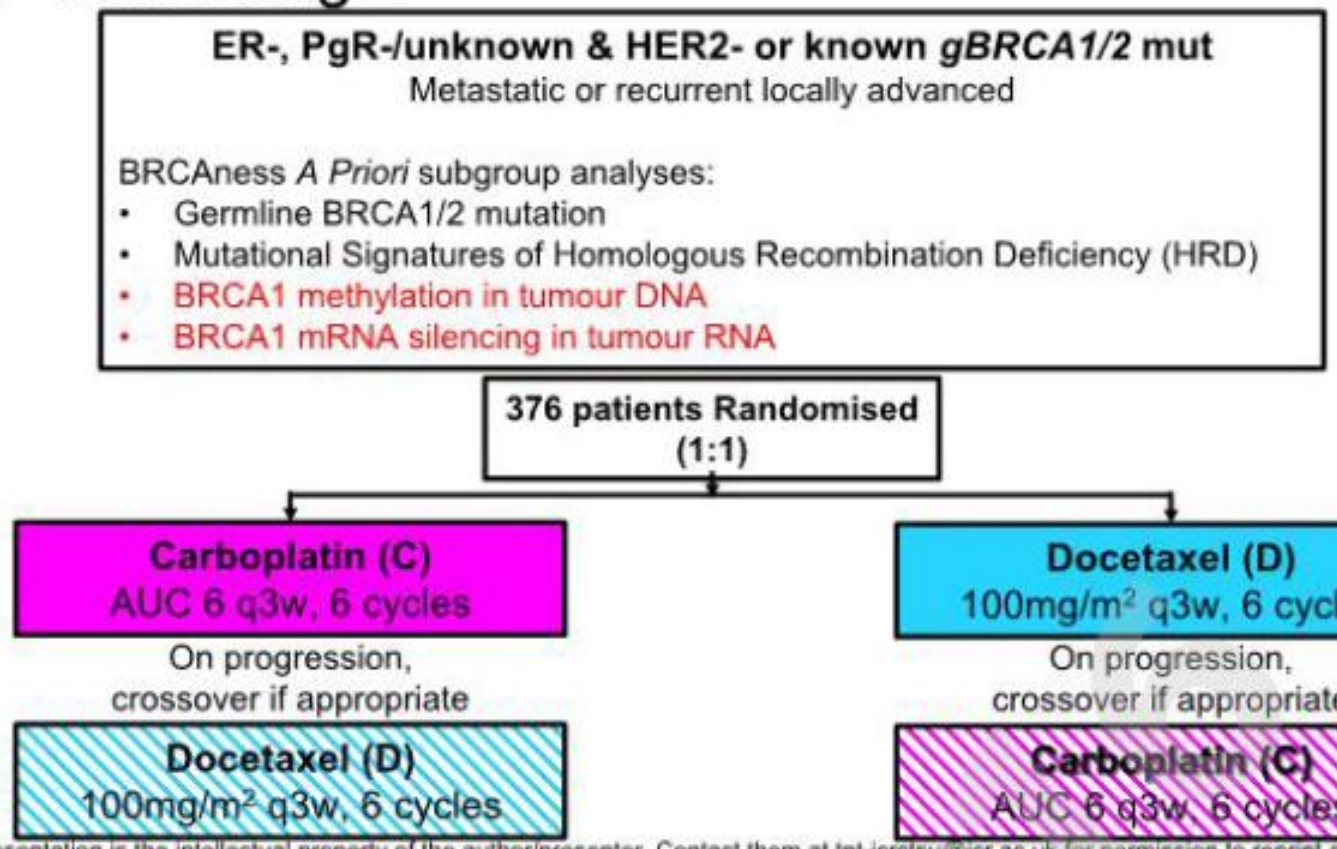
ICR The Institute of Cancer Research in partnership with KING'S College LONDON CANCER RESEARCH UK breast cancer now

BRCA1 methylation status, silencing and treatment effect in the TNT trial: A randomized phase III trial of carboplatin compared with docetaxel for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer

Andrew Tutt, Maggie Chon U Cheang, Lucy Kilburn, Holly Tovey, Cheryl Gillett, Sarah Pinder, Jerry Lanchbury, Jacinta Abraham, Sophie Barrett, Peter Barrett-Lee, Stephen Chan, Patrycja Gazinska, Anita Grigoriadis, Sarah Kernaghan, Katherine Hoadley, Alexander Gutin, Catherine Harper-Wynne, Matthew Hatton, Julie Owen, Peter Parker, Rebecca Roylance, Adam Shaw, Ian Smith, Rose Thompson, Kirsten Timms, Andrew Wardley, Gregory Wilson, Mark Harries, Paul Ellis, Alan Ashworth, James Flanagan, Charles Perou, Judith Bliss, Nazneen Rahman, Robert Brown
on behalf of the TNT Trial Management Group and Investigators

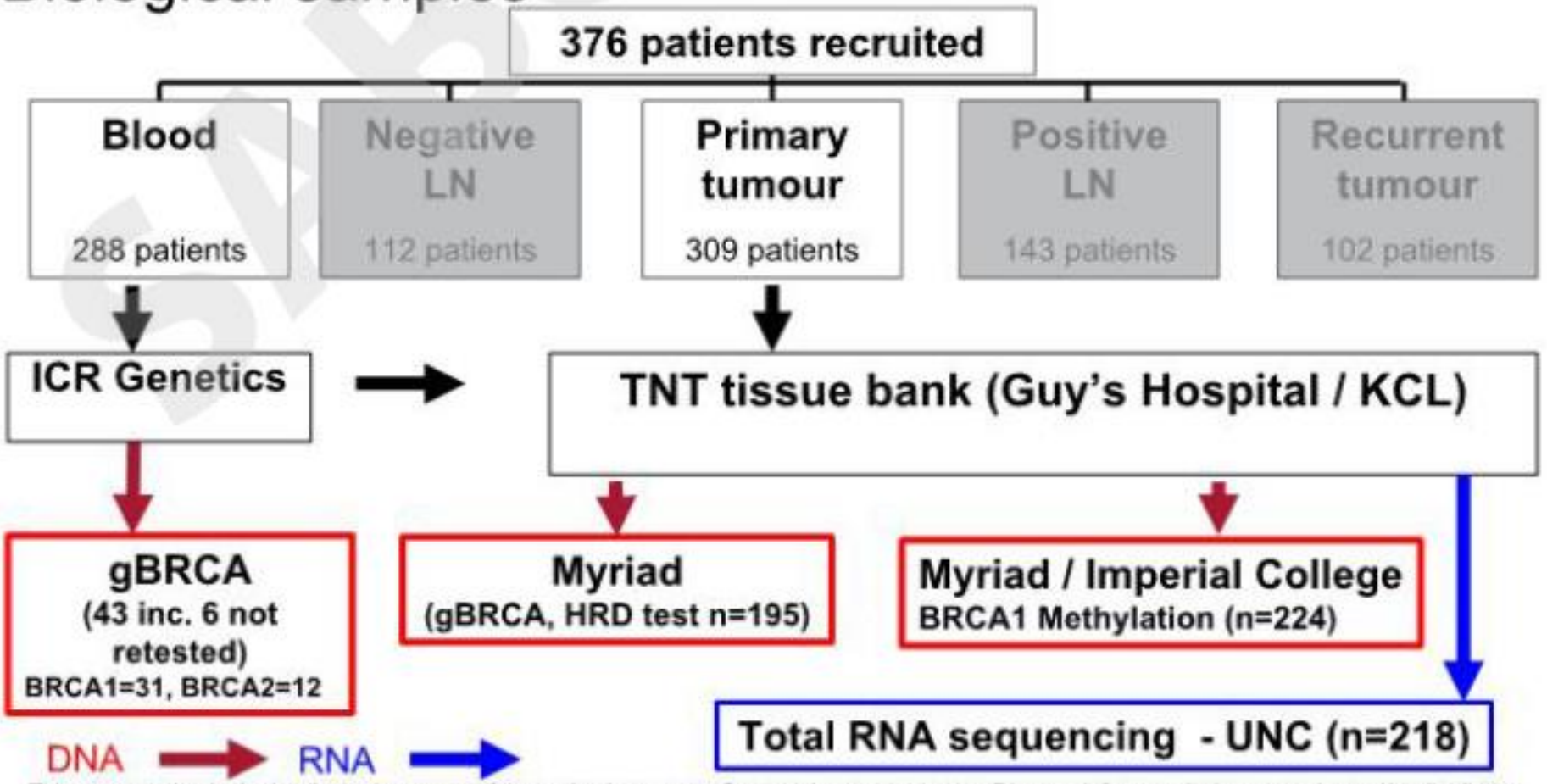
S6-01 BRCA1 methylation status, silencing and treatment effect in the TNT trial

TNT Trial design

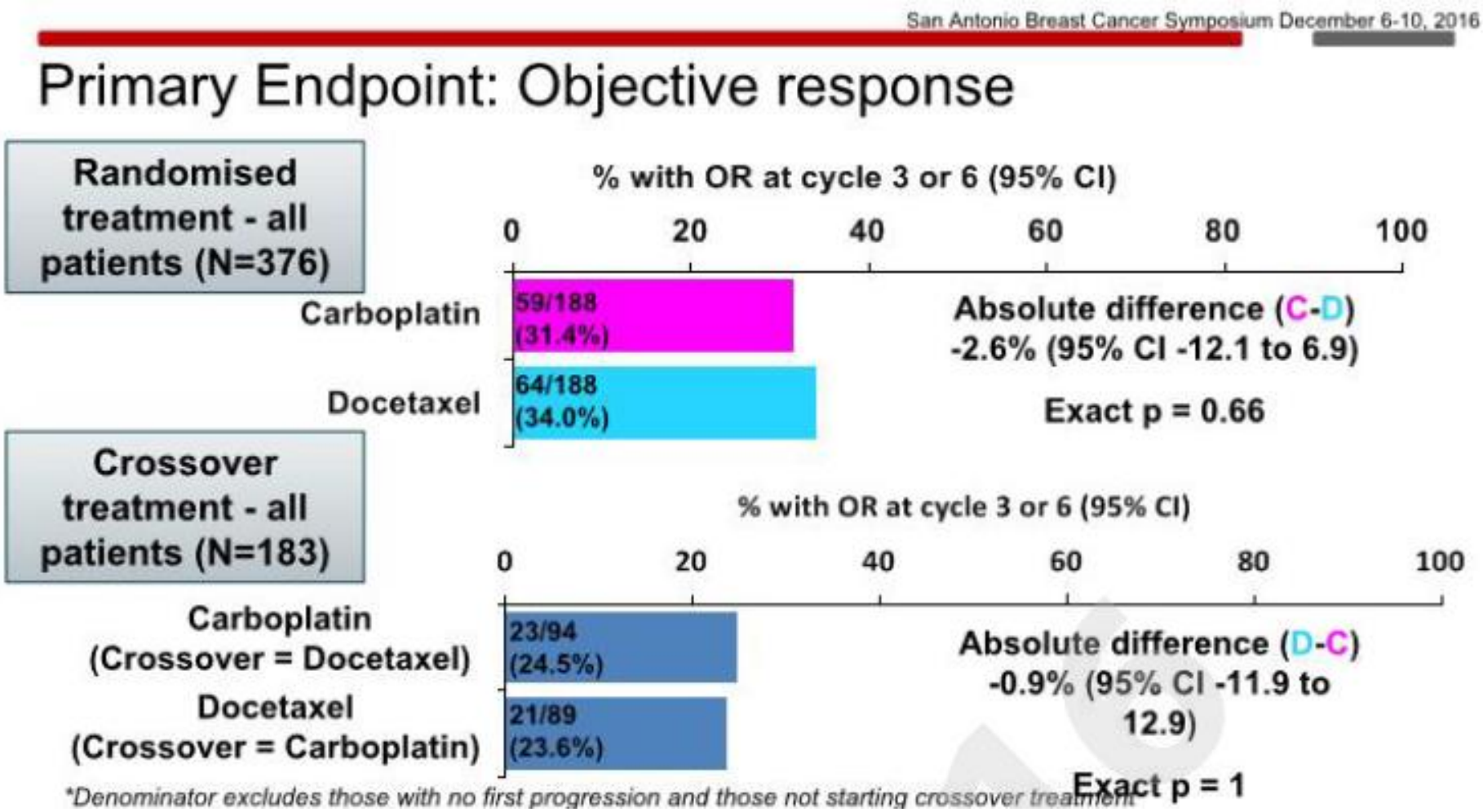


TNT trial

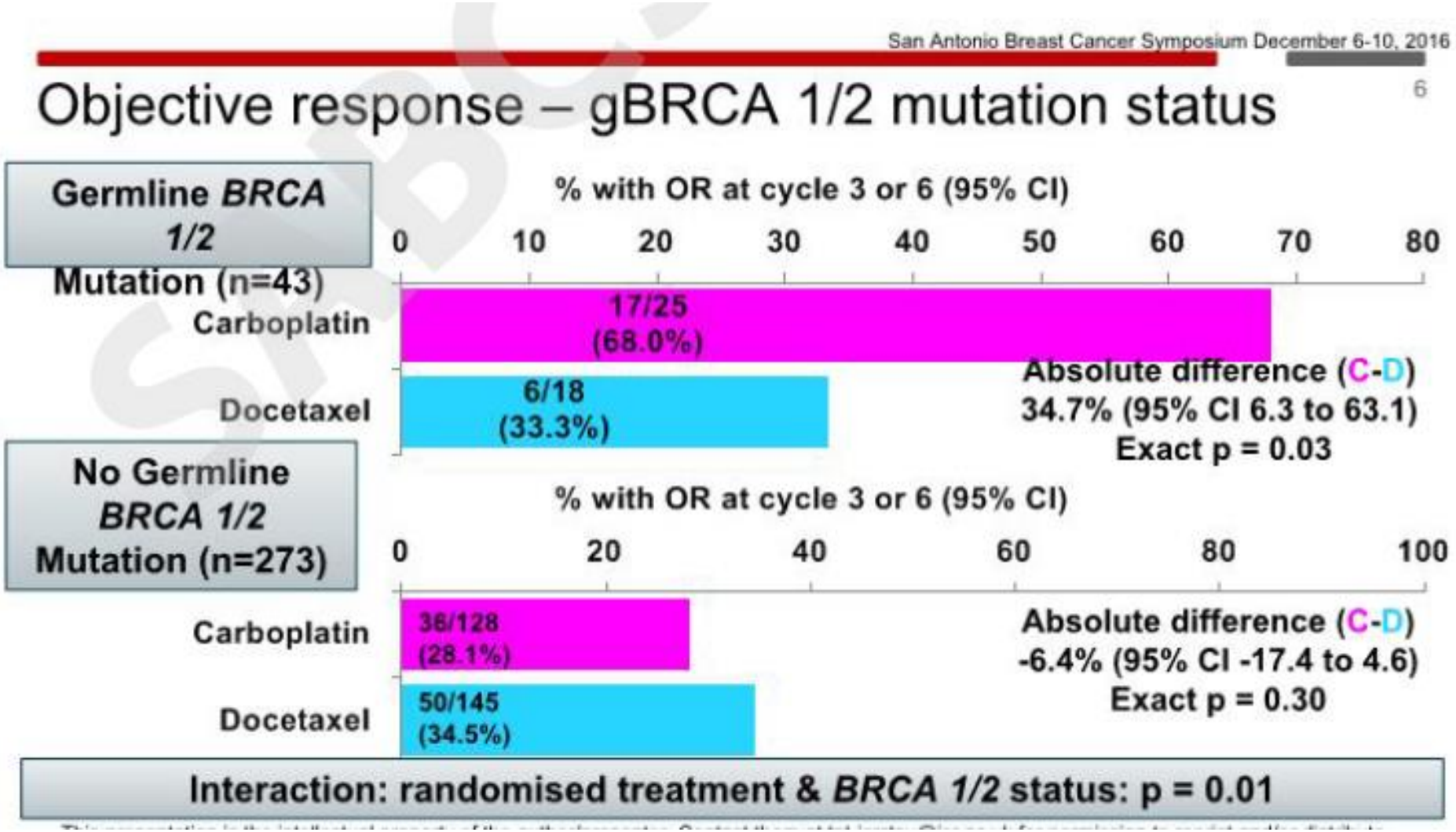
Biological samples



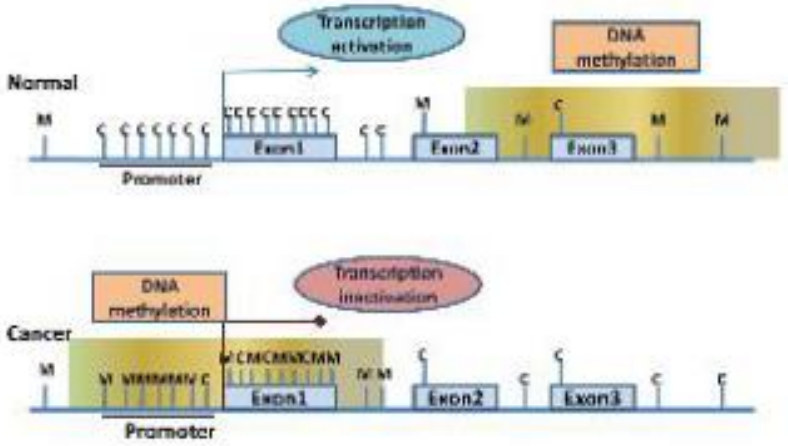
TNT Trial


San Antonio Breast Cancer Symposium December 6-10, 2016
Primary Endpoint: Objective response
Randomised treatment - all patients (N=376)
% with OR at cycle 3 or 6 (95% CI)
0
20
40
60
80
100
Carboplatin
59/188 (31.4%)
Docetaxel
64/188 (34.0%)
Absolute difference (C-D)
-2.6% (95% CI -12.1 to 6.9)
Exact p = 0.66
Crossover treatment - all patients (N=183)
% with OR at cycle 3 or 6 (95% CI)
0
20
40
60
80
100
Carboplatin (Crossover = Docetaxel)
23/94 (24.5%)
Docetaxel (Crossover = Carboplatin)
21/89 (23.6%)
Absolute difference (D-C)
-0.9% (95% CI -11.9 to 12.9)
Exact p = 1
*Denominator excludes those with no first progression and those not starting crossover treatment

TNT Trial


San Antonio Breast Cancer Symposium December 6-10, 2016
6
Objective response – gBRCA 1/2 mutation status
Germline BRCA 1/2 Mutation (n=43)
% with OR at cycle 3 or 6 (95% CI)
0 10 20 30 40 50 60 70 80
Carboplatin
17/25 (68.0%)
Docetaxel
6/18 (33.3%)
Absolute difference (C-D)
34.7% (95% CI 6.3 to 63.1)
Exact p = 0.03
No Germline BRCA 1/2 Mutation (n=273)
% with OR at cycle 3 or 6 (95% CI)
0 20 40 60 80 100
Carboplatin
36/128 (28.1%)
Docetaxel
50/145 (34.5%)
Absolute difference (C-D)
-6.4% (95% CI -17.4 to 4.6)
Exact p = 0.30
Interaction: randomised treatment & BRCA 1/2 status: p = 0.01

Epigenetic BRCAness: CpG methylation of regulatory regions of BRCA gene



In cancer aberrant methylation of cytosines frequently occurs in the context of CpG dinucleotides in the regulatory regions of genes

This is associated with transcriptional epigenetic silencing

The regulatory region of *BRCA1* known to be subject to such epigenetic silencing

Xu et al Annals of Oncology 24: 1498–1505, 2013

The regulatory region of *BRCA1* has multiple CpGs

Methylation of these is found to occur in 10-40% of TNBCs
(Xu et al Annals of Oncology 24: 1498–1505, 2013)

CpG Methylation associated with silencing of *BRCA1* mRNA
(Data from TCGA, 2016)

TNT Trial

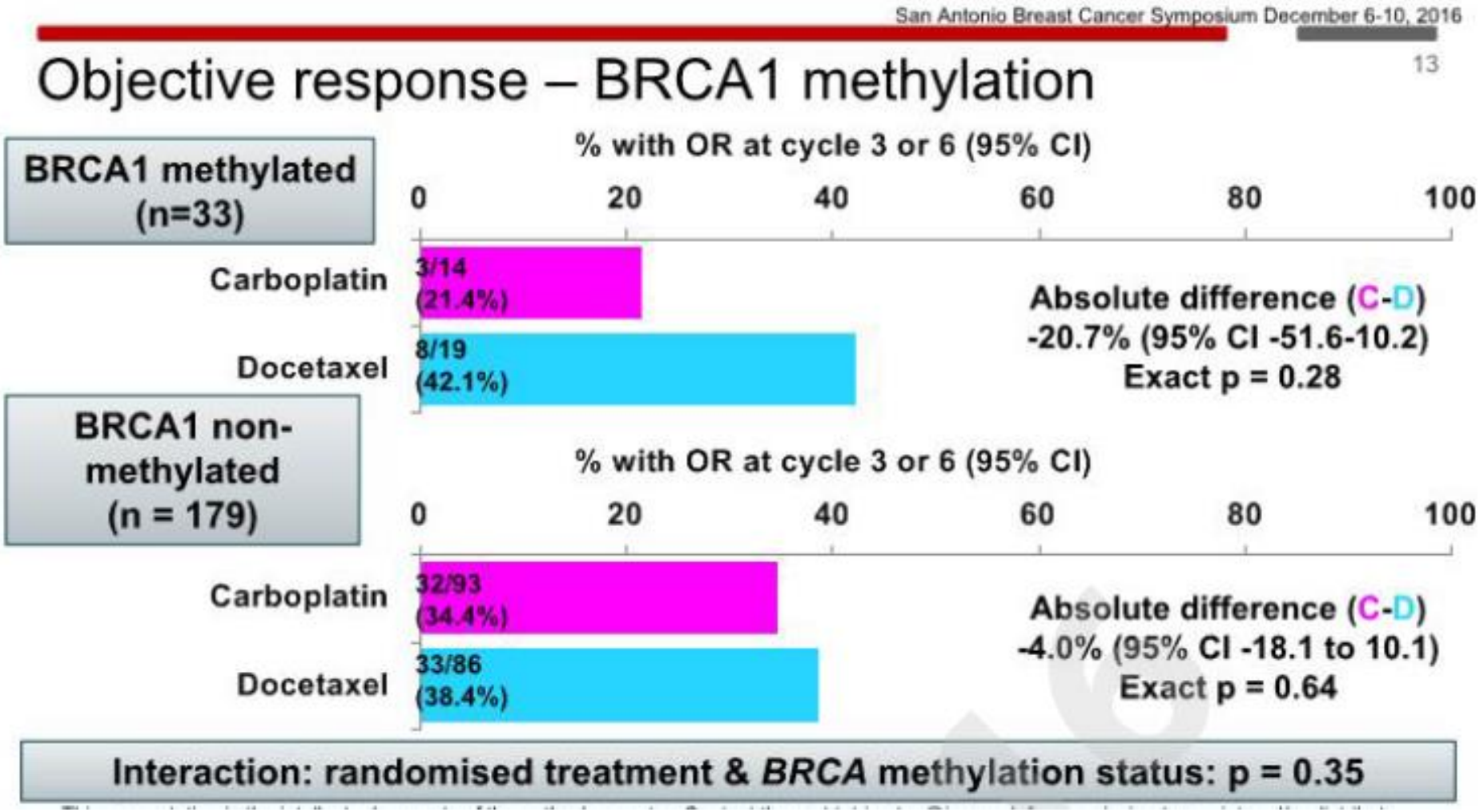
San Antonio Breast Cancer Symposium December 6-10, 2016

BRCA1 methylation status

- 224 primary tumours tested
- **Results met QC for 212 patients**
  - **33 methylated (18%)**
  - **179 non methylated**
- **2 cases had both gBRCA1mut and methylation**

	gBRCA mutated	gBRCA Wildtype	gBRCA Unknown	Total
BRCA Methylated	2	27	4	33
Non BRCA Methylated	20	137	22	179
BRCA Methylation unknown	21	109	34	164
Total	43	273	60	376

TNT Trial

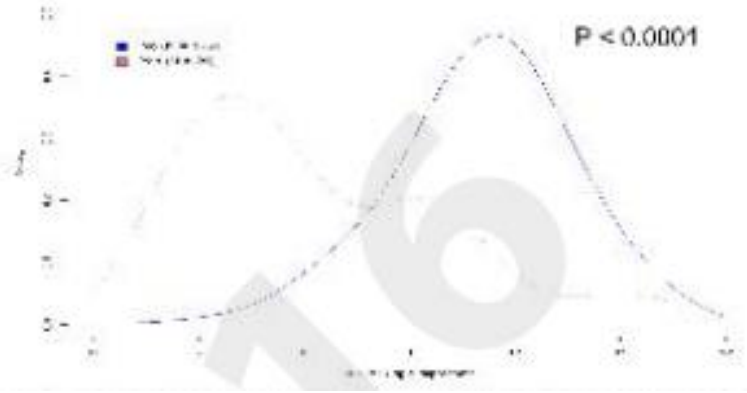

San Antonio Breast Cancer Symposium December 6-10, 2016
13
Objective response – BRCA1 methylation
BRCA1 methylated (n=33)
% with OR at cycle 3 or 6 (95% CI)
0
20
40
60
80
100
Carboplatin
3/14 (21.4%)
Docetaxel
8/19 (42.1%)
Absolute difference (C-D)
-20.7% (95% CI -51.6-10.2)
Exact p = 0.28
BRCA1 non-methylated (n = 179)
% with OR at cycle 3 or 6 (95% CI)
0
20
40
60
80
100
Carboplatin
32/93 (34.4%)
Docetaxel
33/86 (38.4%)
Absolute difference (C-D)
-4.0% (95% CI -18.1 to 10.1)
Exact p = 0.64
Interaction: randomised treatment & BRCA methylation status: p = 0.35

TNT Trial

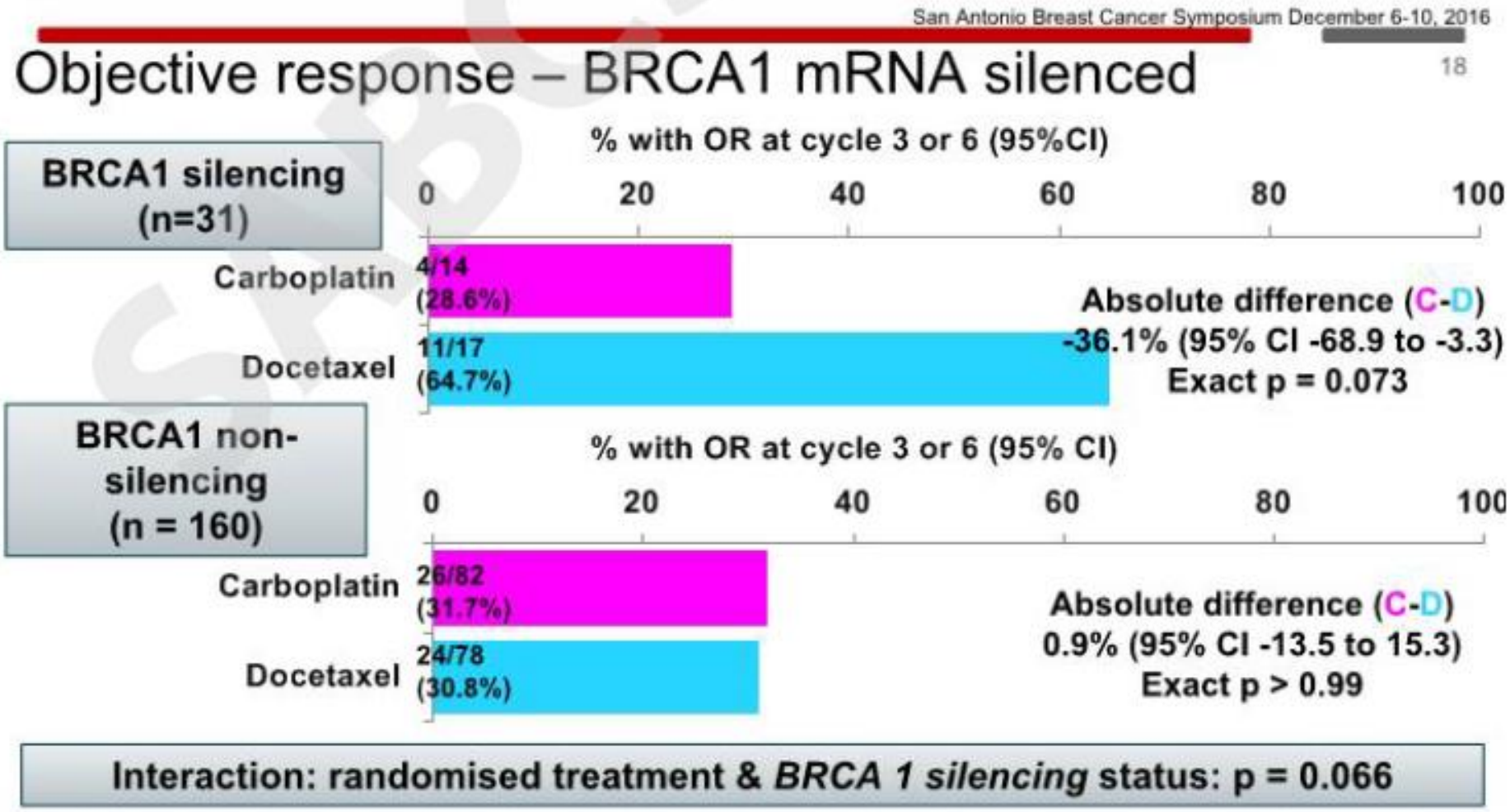
BRCA1 mRNA testing

- 218 primary tumours tested
  - 24 samples failed RNAseq QC
  - 3 duplicates
- Results available for 191 patients
  - **31 silenced (16%)**
  - 160 non-silenced
- 184 patients had both mRNA and methylation status available
- 19/29 (66%) methylated samples were silenced

	Methylated	Non-Methylated	Total
Silenced	19	12	31
Non-Silenced	10	143	153
Total	29	155	184

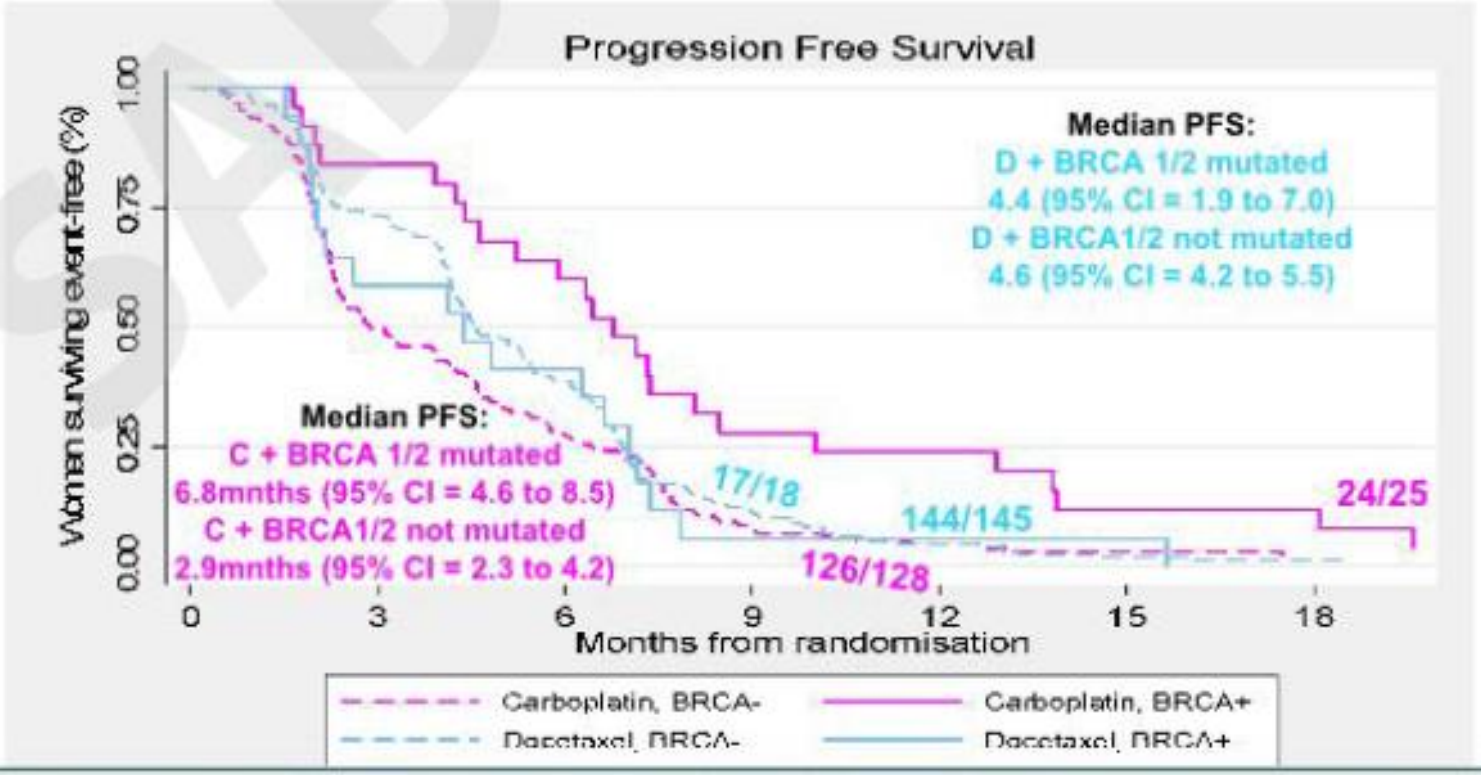


TNT Trial


San Antonio Breast Cancer Symposium December 6-10, 2016
18
Objective response – BRCA1 mRNA silenced
BRCA1 silencing (n=31)
% with OR at cycle 3 or 6 (95%CI)
0
20
40
60
80
100
Carboplatin
4/14 (28.6%)
Docetaxel
11/17 (64.7%)
Absolute difference (C-D)
-36.1% (95% CI -68.9 to -3.3)
Exact p = 0.073
BRCA1 non-silencing (n = 160)
% with OR at cycle 3 or 6 (95% CI)
0
20
40
60
80
100
Carboplatin
26/82 (31.7%)
Docetaxel
24/78 (30.8%)
Absolute difference (C-D)
0.9% (95% CI -13.5 to 15.3)
Exact p > 0.99
Interaction: randomised treatment & BRCA 1 silencing status: p = 0.066

TNT Trial

PFS by germline BRCA1/2 mutation status



Interaction: randomised treatment & *BRCA 1/2* status (restricted mean survival): p = 0.002

TNT Trial Conclusions

- BRCA1/2 mutations associated with response to carboplatin in metastatic setting
  - Consider early testing of metastatic patients
- Epigenetic silencing of BRCA in primary tumor was not associated with response to carboplatin in metastatic setting
  - Unknown if methylation status of primary tumor corresponds to metastatic disease

Can we predict response to Platinum and PARP inhibitors?

- Germline BRCA1/2 status not evaluable in ISPY2 but associated with response to carbo in metastatic setting
  - In GeparSixto trial (Doxil/Taxol ± carbo) higher pCR with carboplatin was independent of BRCA status
- Gene expression signatures in ISPY2 not currently available in clinic but promising
- Epigenetic silencing in primary tumors in TNT not associated with response

San Antonio Breast Cancer Symposium - December 6-10, 2016

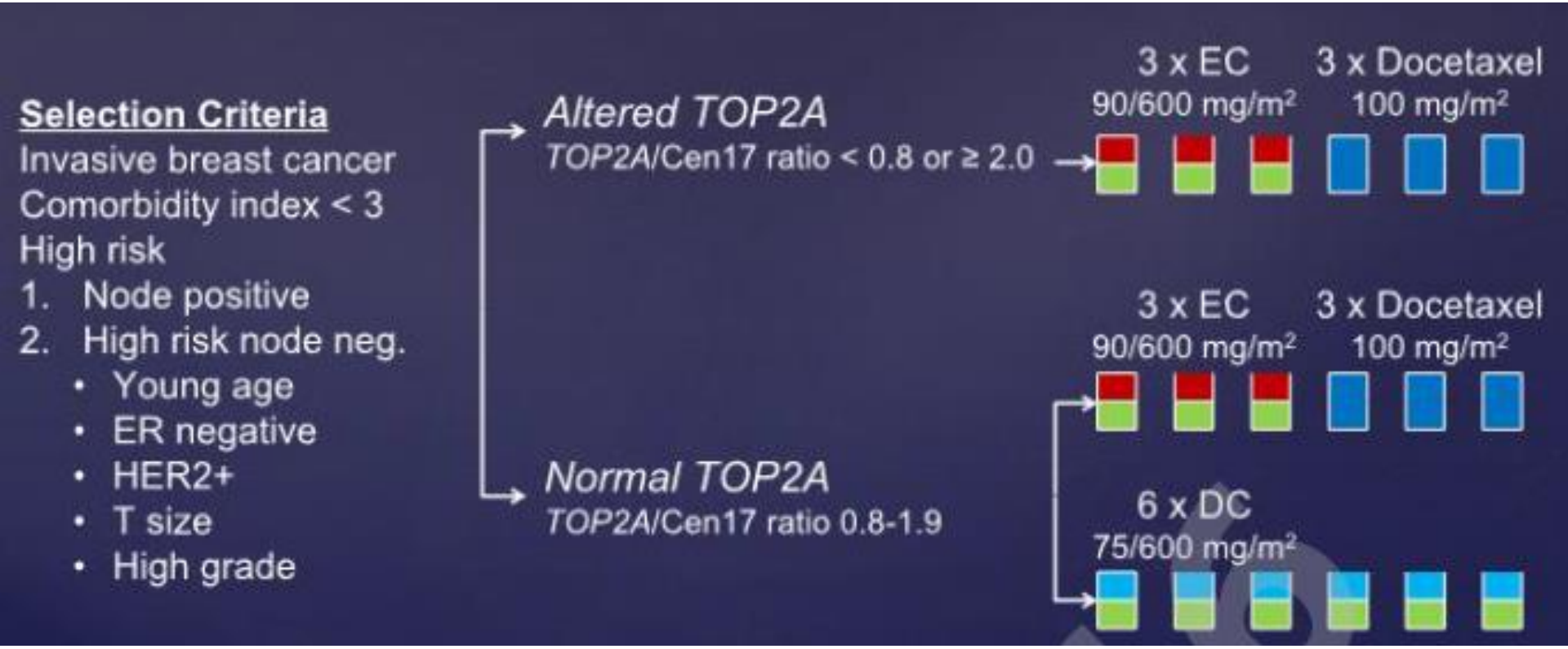
DBCG 07-READ

A randomized phase III trial comparing six cycles of docetaxel and cyclophosphamide (DC) to three cycles of epirubicin and cyclophosphamide followed by three cycles of docetaxel (EC-D) in patients with early breast cancer

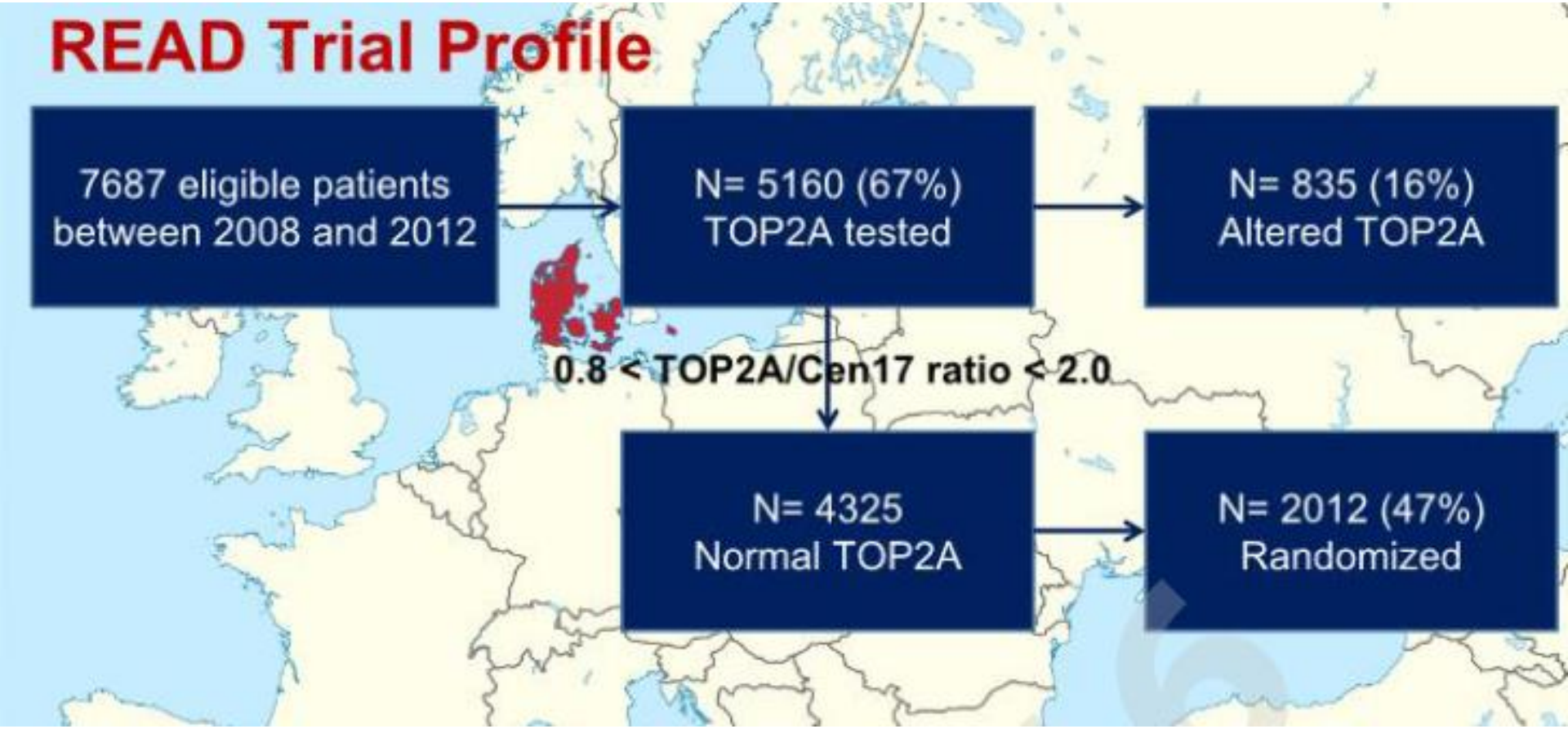
Bent Ejlertsen, Malgorzata K. Tuxen, Erik H. Jakobsen, Maj-Britt Jensen, Ann S. Knoop, Inger Højris, Marianne Ewertz, Eva Balslev, Peter Michael Vestlev, Julia Kenholm, Dorte L. Nielsen, Troels Bechmann, Michael Andersson, Søren Cold, Hanne M. Nielsen, Else Maae, Dorte Carlsen, Henning Mouridsen

for the **Danish Breast Cancer Cooperative Group (DBCG)**

DBCG 07–READ Trial Design



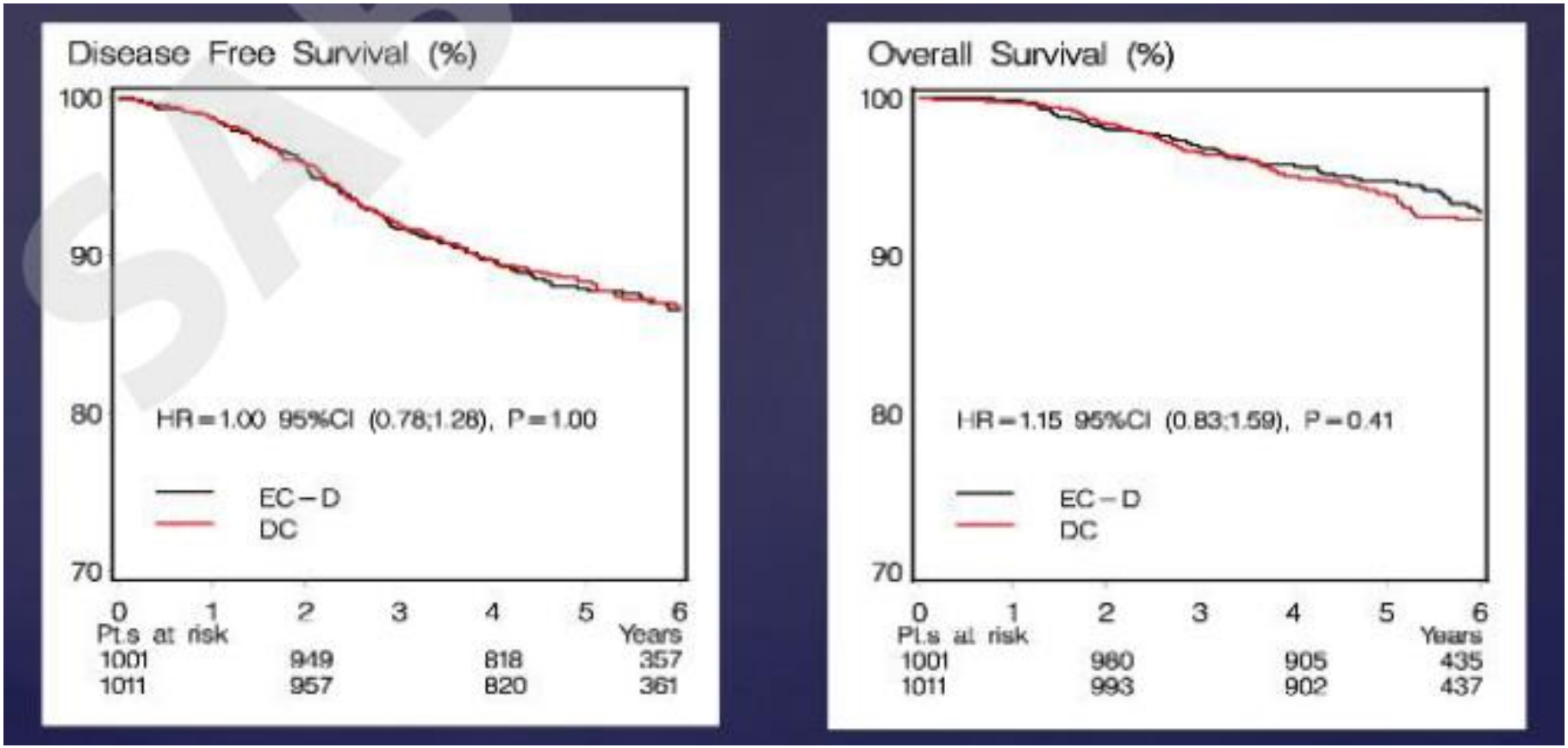
- Anthracycline-based chemotherapy associated with 3% absolute benefit in survival at 10 years compared to CMF (EBCTCG Lancet 2012)
- Could overall benefit be due to small number of patients (HER2+, TOP2 alteration, CEP17 duplication) having larger benefit


READ Trial Profile
7687 eligible patients between 2008 and 2012
N= 5160 (67%) TOP2A tested
N= 835 (16%) Altered TOP2A
0.8 < TOP2A/Cen17 ratio < 2.0
N= 4325 Normal TOP2A
N= 2012 (47%) Randomized

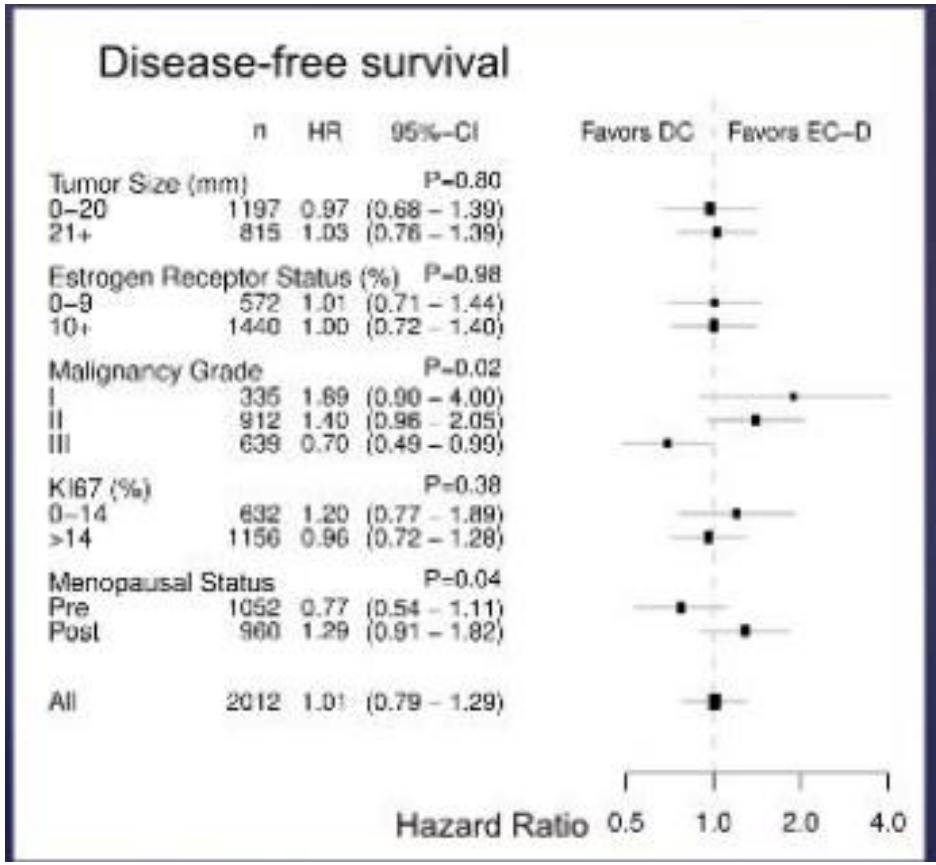
DBCG 07–READ Patient Characteristics

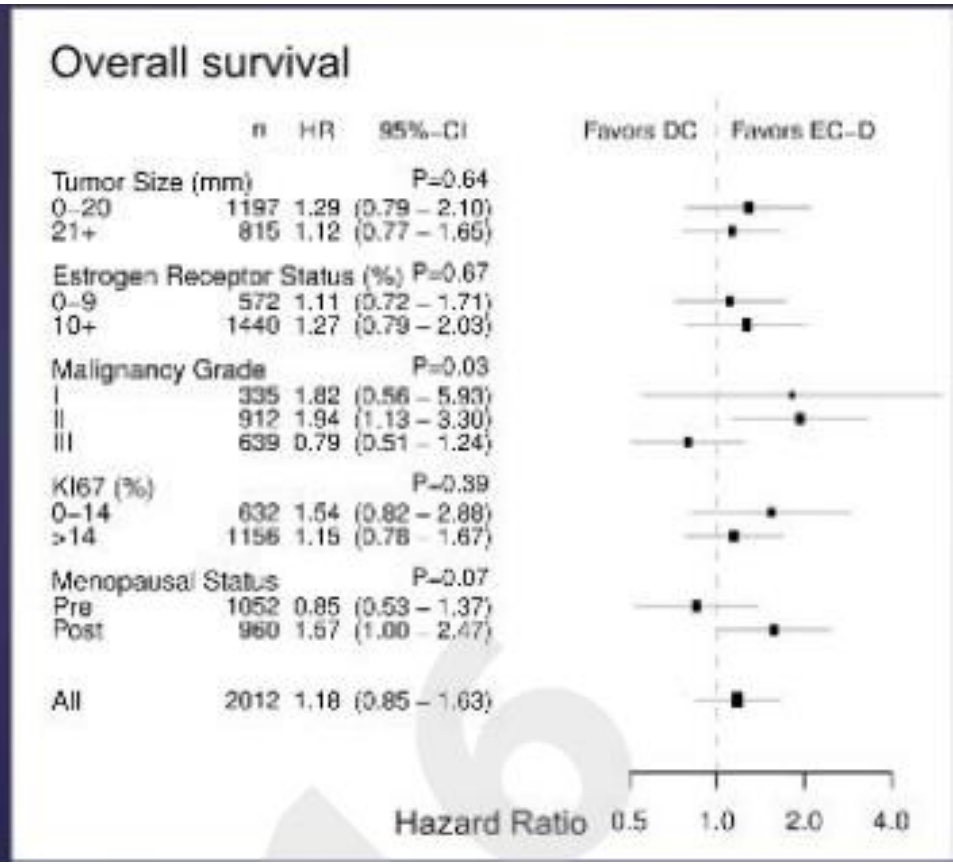
n(%)		EC-D (N=1001)		DC (N=1011)	
Age at diagnosis	< 45	205	(20)	199	(20)
	45 – 49	199	(20)	204	(20)
	50 -54	230	(23)	277	(27)
	55-59	265	(26)	237	(23)
	60-74	102	(10)	94	(9)
Menopausal status	Premenopausal	508	(51)	544	(64)
	Postmenopausal	493	(49)	467	(46)
Co-morbidity	Absent (0)	900	(90)	926	(92)
	Present (1-2)	101	(10)	85	(8)
Tumor size	0 - 10	131	(13)	127	(13)
	11 - 20	487	(49)	452	(45)
	>20	383	(38)	432	(43)
Node negative		448	(45)	467	(46)
Malignancy grade (only ductal/lobular)	Grade 1	159	(16)	176	(17)
	Grade 2	453	(45)	459	(45)
	Grade 3	328	(33)	311	(31)
	Other types	56	(6)	53	(5)
ER positive (≥10%)		702	(70)	738	(73)
HER2 positive (IHC 3+ / FISH ≥ 2.0)		113	(11)	109	(11)
Ki67 high (> 14%, N=1788)		588	(66)	568	(64)

DBCG 07–READ Results



DBCG 07–READ Subgroup Analysis





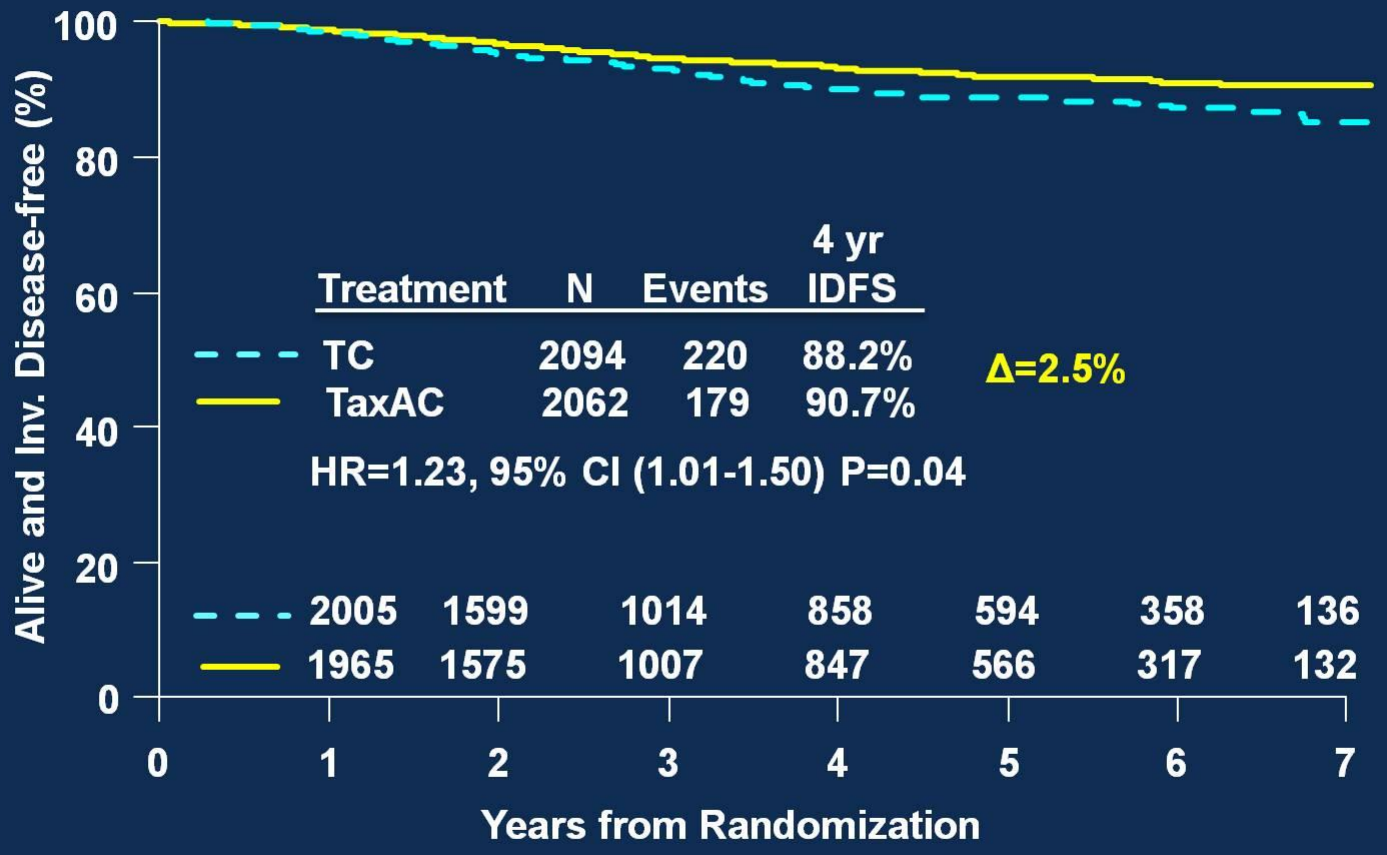
Lymph node status not included in subgroup analysis

Timeline and Accrual of ABC Trials

Trial	Arms	Accrual	Dates of Accrual	Median F/U, yrs	Funding
USOR 06-090	TC TaxAC	1295	MAY 2007 to JUN 2009	6.3	Sanofi
NSABP B-46I USOR 07132	TC TaxAC	1077	MAY 2009 to JAN 2012	4.8	Genentech
	*TC-BV	556			
NSABP B-49	TC TaxAC	1870	APR 2012 to NOV 2013	2.2	CTEP

*not included in ABC Trials analysis

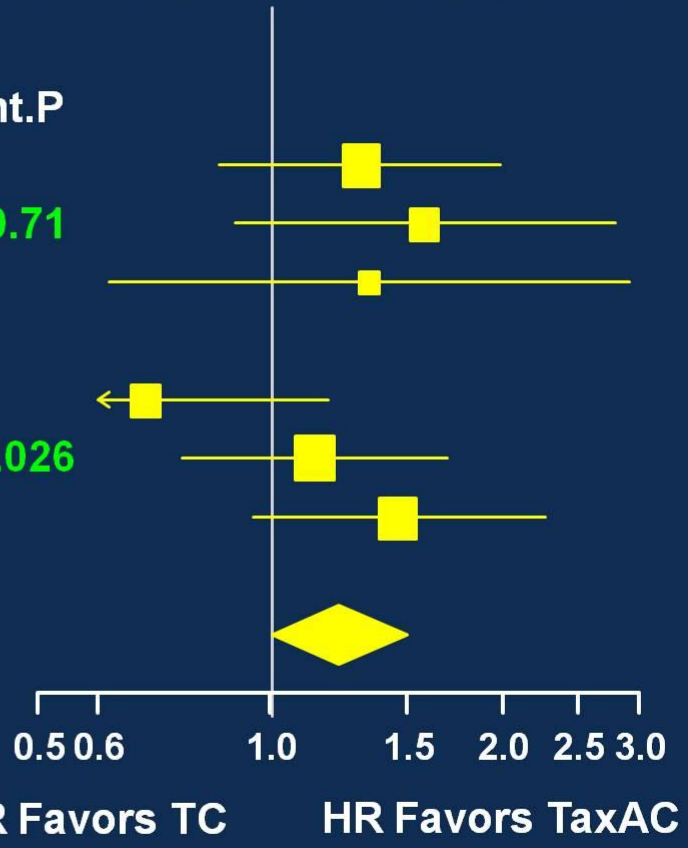
ABC Trials: Invasive Disease Free Survival



Presented By Joanne Blum at 2016 ASCO Annual Meeting

Forest Plot of IDFS By Hormone and Nodal Status

Nodes(+) ER/PgR Neg	HR	95% CI	Int.P
0	1.31	0.86-1.99	
1-3	1.58	0.90-2.79	0.71
4+	1.34	0.62-2.91	
Nodes(+) ER or PgR (+)			
0	0.69	0.39-1.19	
1-3	1.14	0.77-1.69	0.026
4+	1.46	0.95-2.26	
Overall	**1.23**	**1.01-1.50**	



HR = Hazard Ratio

In the Clinic …

- EC→T equivalent to T in READ trial among TOP2A normal patients
- But TOP2A testing is not routinely performed
  - 16% of patients had alterations
- No data presented on nonrandomized cohort with TOP2A alterations with EC→T
- ABC Meta-analysis (ASCO 2016) showed benefit for anthracyclines among HR- and HR+/node+ patients

The PI3K inhibitor, taselisib, has enhanced potency in PIK3CA mutant models through a unique mechanism of action

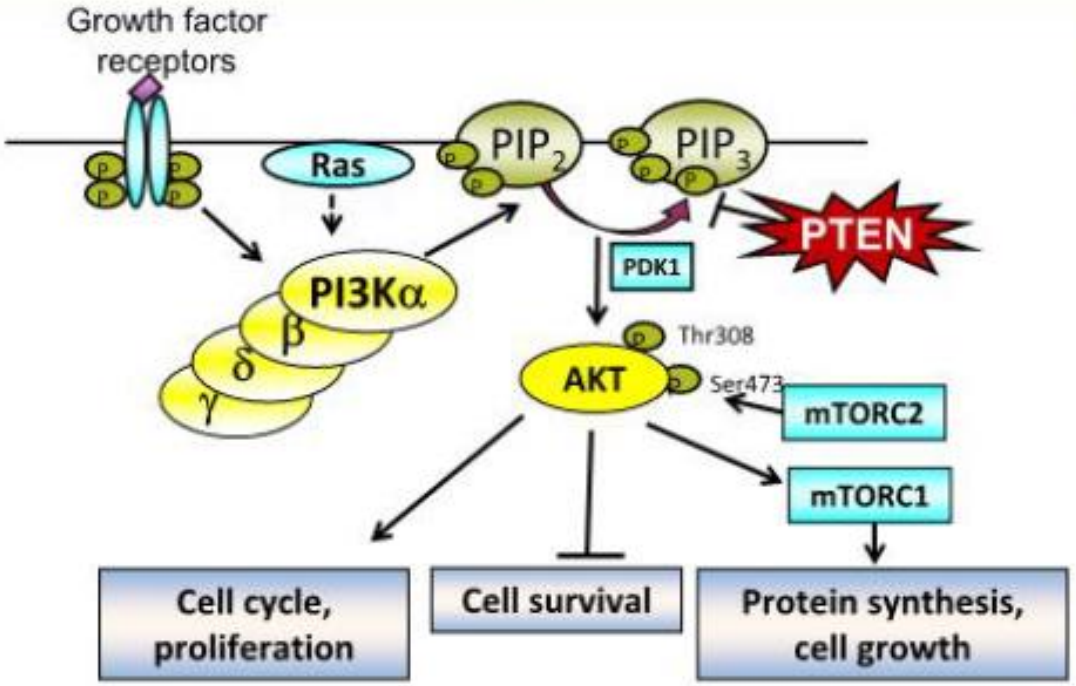
Lori Friedman, Kyle Edgar, Kyung Song, Stephen Schmidt, Donald Kirkpatrick, Lilian Phu, Michelle Nannini, Rebecca Hong, Eric Cheng, Lisa Crocker, Amy Young, Deepak Sampath

Genentech, Inc.

SABCS, December 9, 2016

S6-04 The PI3K inhibitor, taselisib, has enhanced potency in PIK3CA mutant models through a unique mechanism of action

PIK3CA is frequently mutated in cancer



Tumor type	PIK3CA mutation
Breast	
• ER+	40-50%
• Her2+	20-30%
• TNBC	6-12%
Endometrial	20-40%
Colon	13-30%
Bladder	15%
Cervix	14%
HNSCC	7-11%
Gastric	10%
Ovarian	9%

PIK3CA Pathway in Breast Cancer

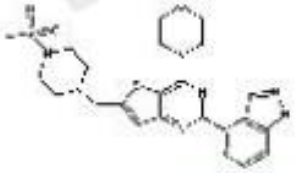
- Prognostic value of PIK3CA mutation status is controversial in HER2-negative patients
- PIK3CA mutations associated with resistance to HER2-directed therapies
  - CLEOPATRA: PIK3CA mutation status associated with shorter PFS in both arms
    - wild-type versus mutated *PIK3CA* in both the control (13.8 *v* 8.6 months) and pertuzumab groups (21.8 *v* 12.5 months).
  - NeoALTTO: PIK3CA single gene and pathway mutations associated with lower pCR rate
    - Adding lapatinib to trastuzumab increased pCR
- PIK3CA mutations may be associated with endocrine resistance
- PI3K inhibitors may be best in combination with other targeted therapies due to activation of compensatory feedback loops

Can a PI3K inhibitor with the right balance of activity and tolerability be created?

Number of PI3K Targets Inhibited → Anticipated Safety Profile

Pan-PI3K

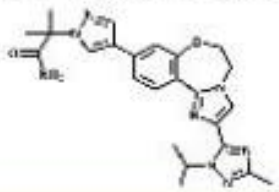
BKM120 buparlisib,
GDC-0941 pictilisib



PI3K β-sparing

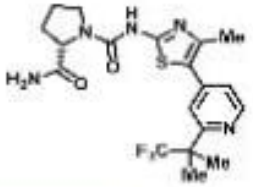
GDC-0032 taselisib

- Increased potency on PI3Kα mutant



PI3K α-specific

G-102, G-326,
BYL-719 alpelisib

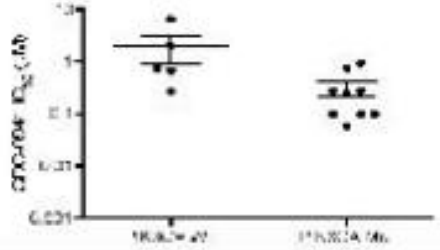


- Therapeutic index is a balance of safety and activity
- PI3K inhibitors have a narrow therapeutic index

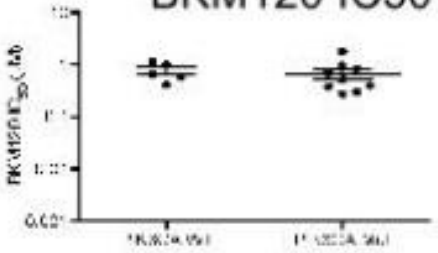
Taselisib shows increased potency against PIK3CA mutant cells – comparison with other PI3K inhibitors

- 4 day Celltiter glo assay; Each dot represents IC50 of a different cancer cell line

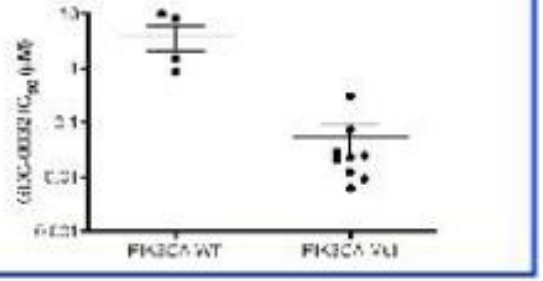
Pictilisib GDC-0941 IC50



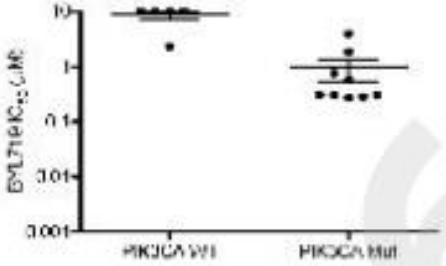
BKM120 IC50



Taselisib GDC-0032 IC50

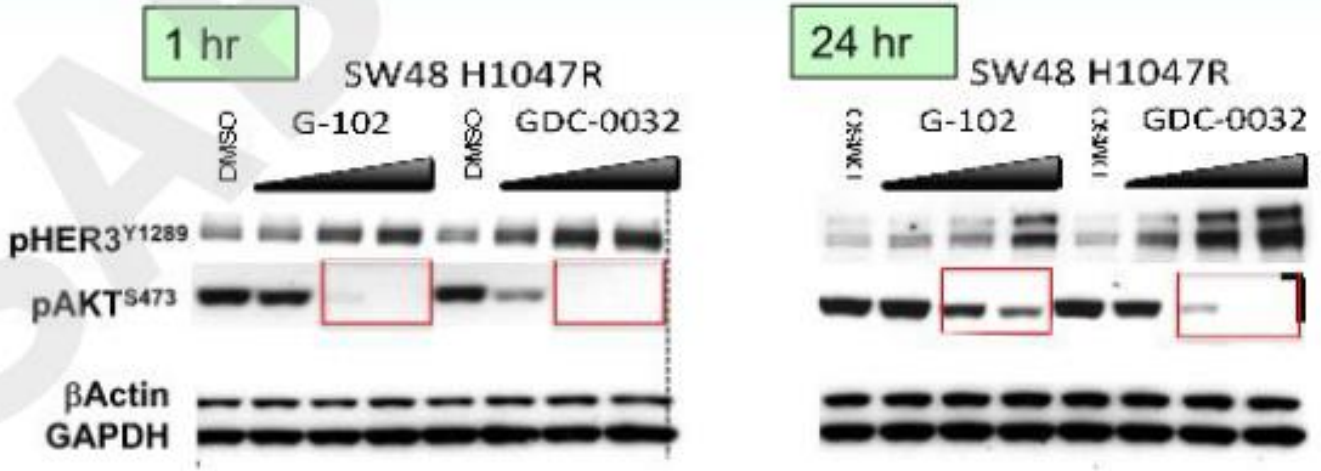


Alpelisib BYL719 IC50



What is the role of feedback? PI3K pathway inhibitors relieve negative feedback, leading to attenuation of anti-tumor activity and priming the pathway for reactivation

Taselisib (GDC-0032) protects against RTK-driven pathway reactivation

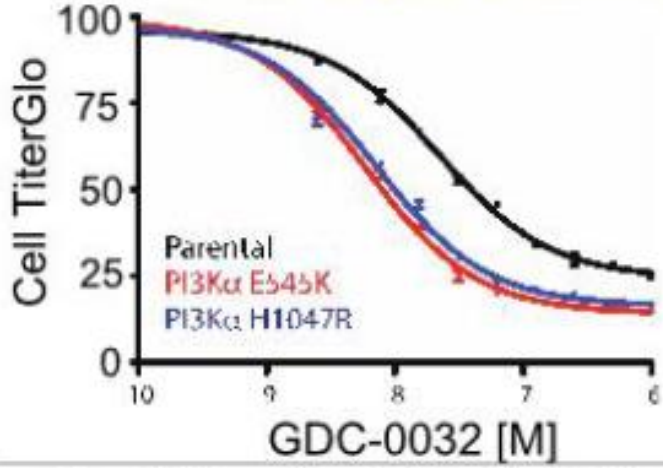


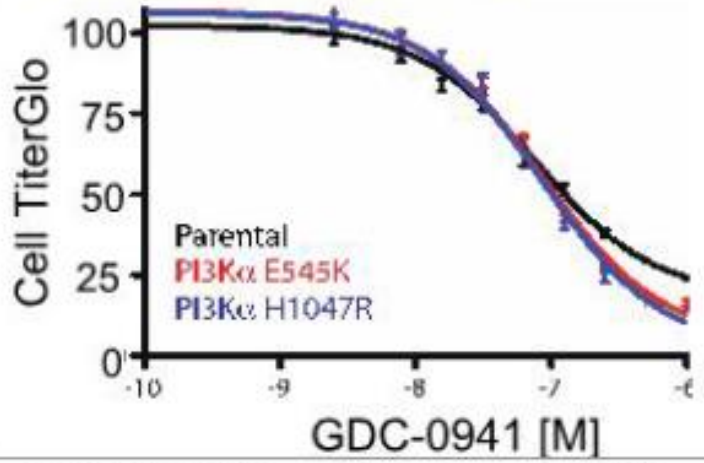
Drugs 0, 1, 10, 100 nM

- Most PI3K inhibitors are effective at 1 hr and lose potency at 24 hrs
- Taselisib (GDC-0032) is better at suppressing signaling at 24 hrs

Knock-in of mutant PI3Kα increases cellular potency for taselisib, but not other PI3K inhibitors

SW48 isogenic cell lines (PI3Ka WT, mutants); 4 day assay



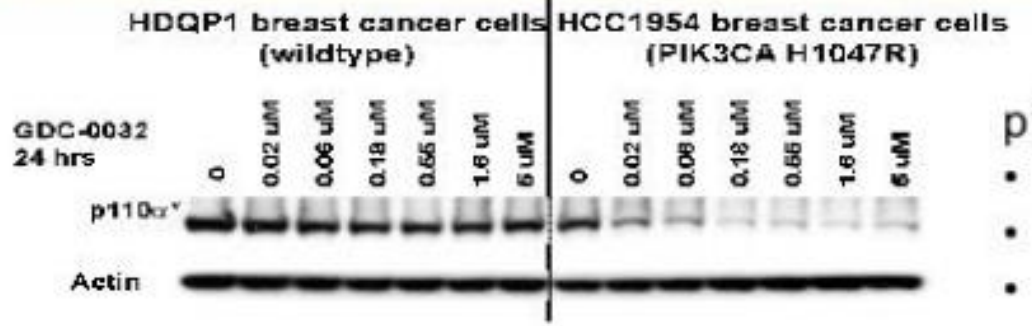


- Taselisib gains 3-4 fold shift in potency in PI3Kα mutant knock-ins
- PI3K inhibitors that do not shift include: GDC-0941, BYL719, BKM120

This unexpected result implies a unique mechanism of action for taselisib in mutant cells

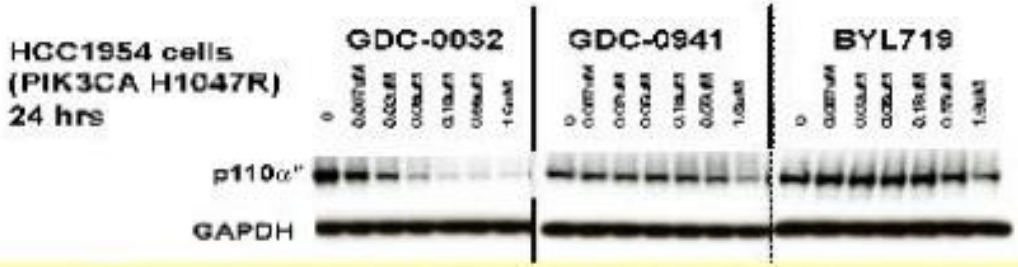
Kyle Edgar

Taselisib (GDC-0032) leads to degradation of mutant PI3Kα protein, uniquely among clinical compounds



p110a protein degradation is:

- dose-dependent
- time-dependent
- specific to PI3K mutants

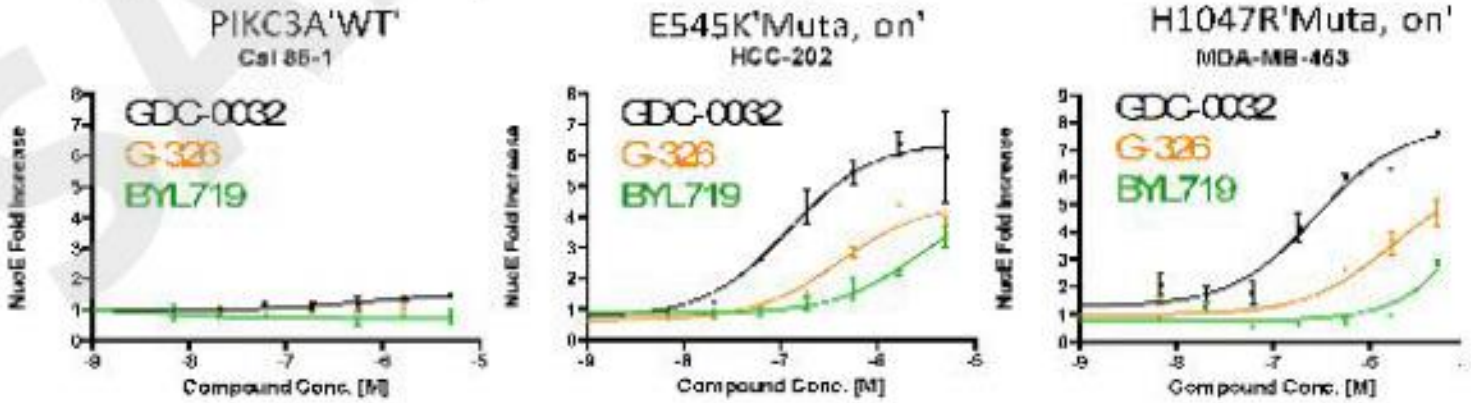


Other clinical compounds do not induce degradation of mutant protein

Hypothesis – PI3K inhibitors which induce degradation of the mutant protein will have greater efficacy which may widen the therapeutic index

Taselisib induces apoptotic cell death in PIK3CA mutant cells

- 3 day cell death assay
- Taselisib (GDC-0032) compared to PI3Kalpha inhibitors G-326 and BYL719

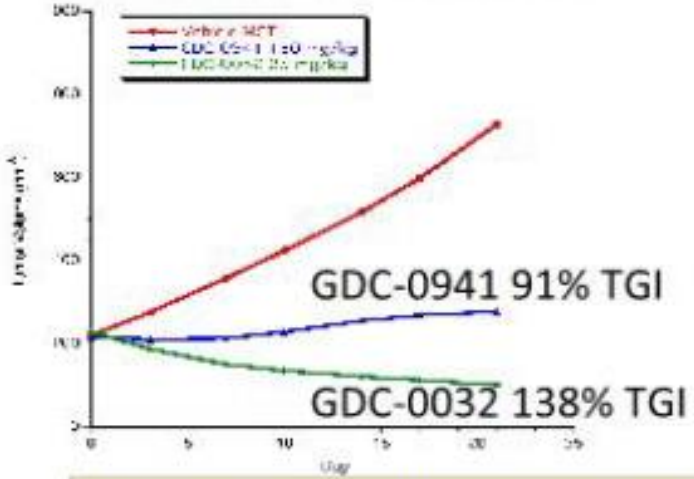


Taselisib (GDC-0032) shows strongest induction of apoptosis

- Stronger apoptosis is likely the impact of maintaining pathway suppression after feedback has occurred

Taselisib has greater maximal efficacy than other PI3K inhibitors, in PIK3CA mutant xenografts

HCC-1954 breast cancer xenograft
PIK3CA H1047R mutant



HCC-1954 breast cancer xenograft
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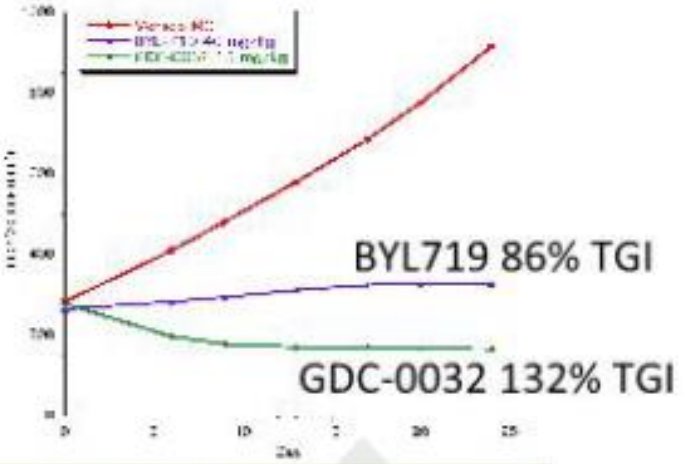


Drugs dosed daily in mice at the Maximum Tolerated Dose

- Taselisib (GDC-0032) induces regressions
  - Stasis observed for GDC-0941 and BYL719

Becky Hong,

PI3K Inhibitor Clinical Trials

- FERGI: Fulvestrant ± Pictilisib N=168
  - No difference in PFS (6.6 vs 5.1 months)
- BELLE3: Fulvestrant ± Buparlisib N=432
  - PFS 3.9 vs 1.8 months (HR 0.67) BUT side effects
- Multiple ongoing clinical trials
  - SANDPIPER: Fulvestrant ± Taselisib
  - Ph1b/2: Enzalutamide + Taselisib for AR+ TNBC
  - BYL719 in combination with letrozole, paclitaxel

San Antonio Breast Cancer Symposium—December 6-10, 2016

Double-blind Concordance Study of Breast Cancer Treatment Recommendations Between Manipal Multidisciplinary Tumor Board and an Artificial Intelligence Advisor for Oncology IBM's Watson For Oncology

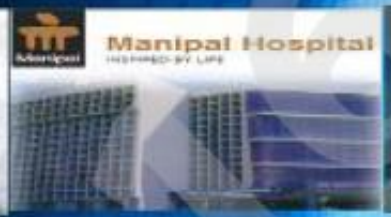
Somashekhar, Rohit, Arun K, Martin S, Andrew N, Amit R

San Antonio Breast Cancer Symposium
San Antonio, Texas, USA
December 6, 2016

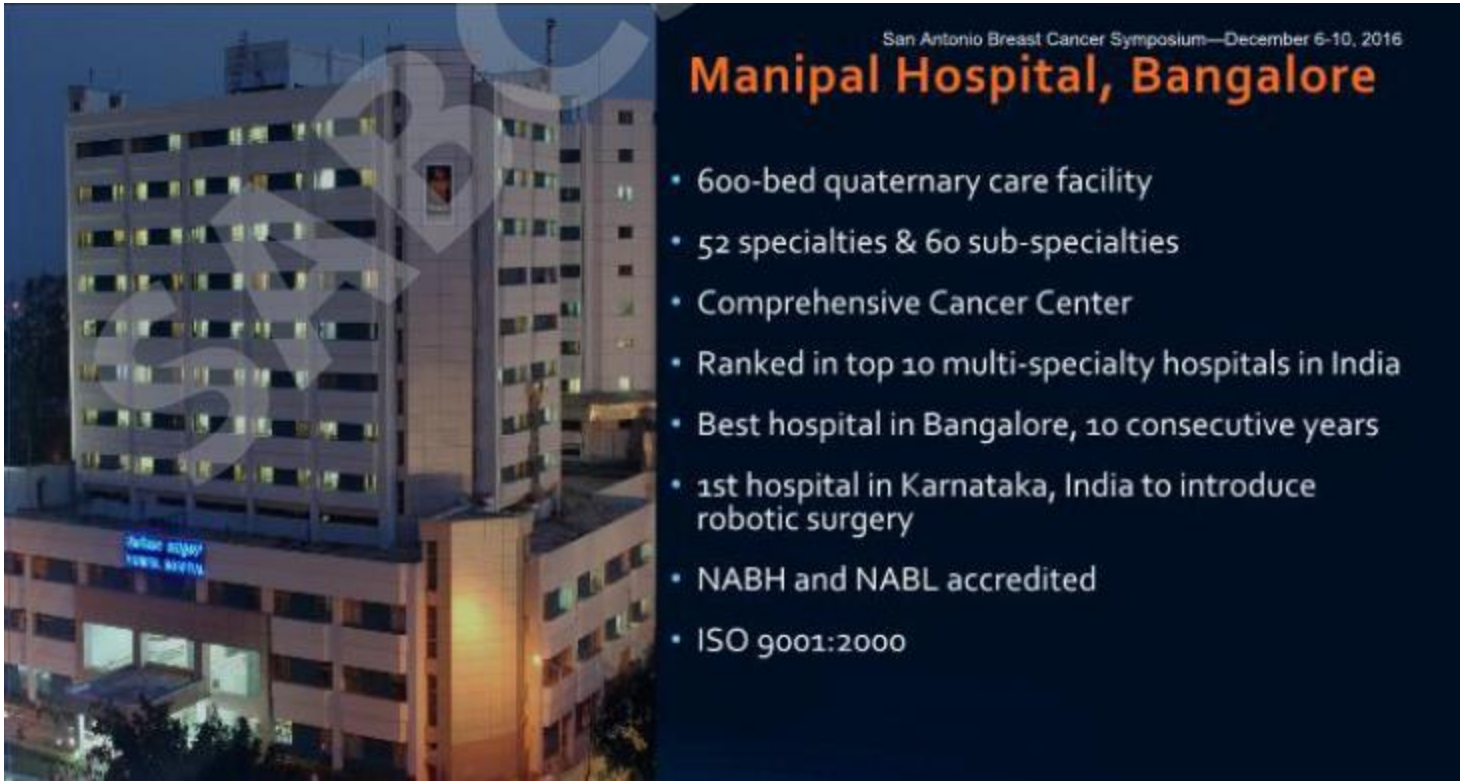
Prof.Dr. Somashekhar.S.P.
MS, MCh (Oncosurgery), FRCS.Ed

Chairman Oncology Manipal Health Enterprise MHEPL
Head Of Department
Department of Surgical & Gynec. Oncology , Robotics & HIPEC
Manipal Comprehensive Cancer Centre
Manipal Hospital, Bangalore, India

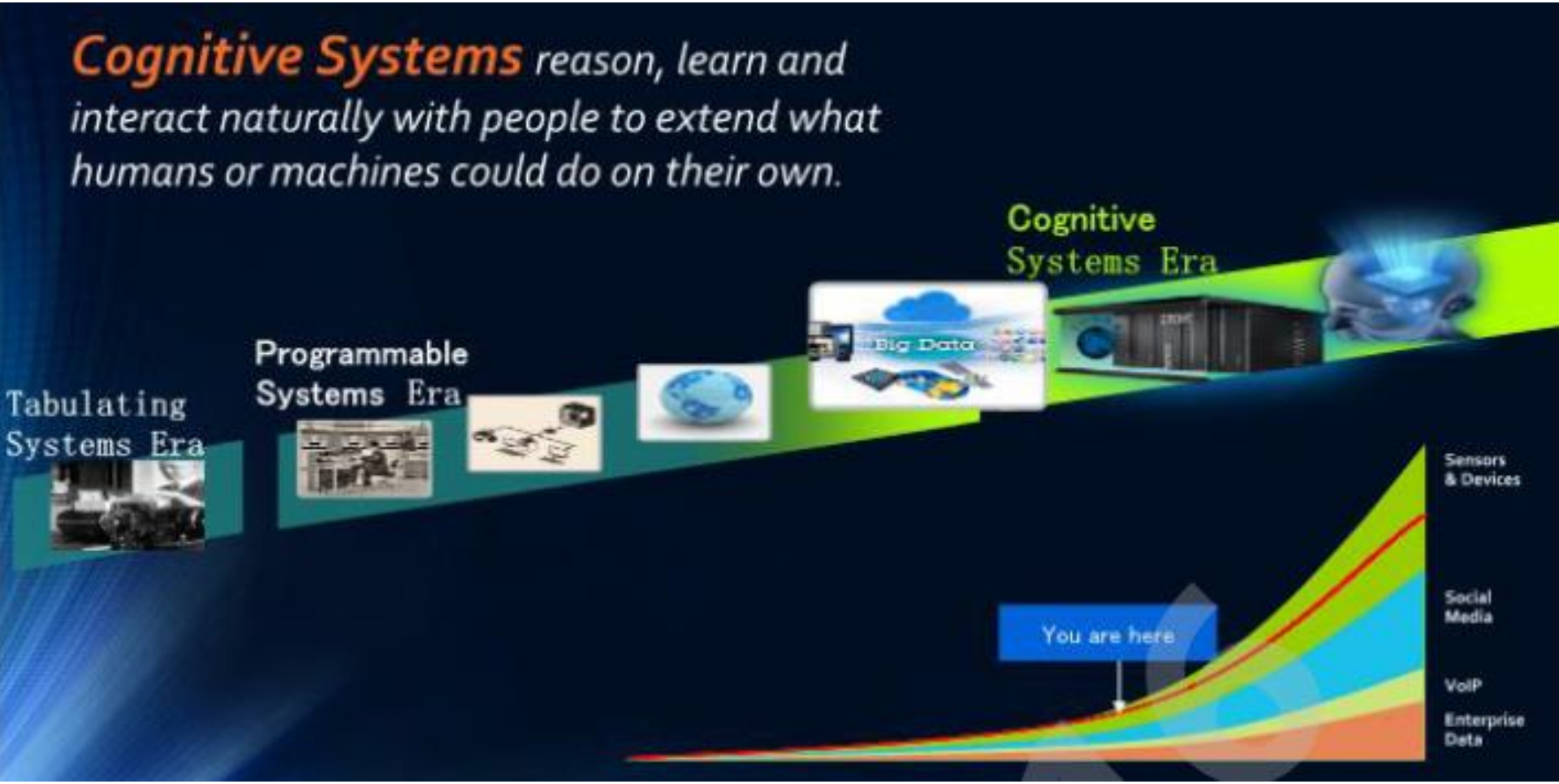


S6-07 Double blinded validation study to assess performance of IBM articial intelligence platfrom Watson for oncology in comparison to Manipal multidisciplinary tumour board – First study of 638 breast cancer cases



How do we stay up to date with ongoing research and treatment options?



Watson for Oncology: Evidence-based, personalized treatment plans

Dedicated

Dedicated Cloud
Triple redundancy
Speed

Corpus

The Corpus contains Healthline Medical Taxonomy to varied sources from:
ASCO, EBSCO information services Elsevier, MMS, NCCN guidelines, US Government, Wiley
- 250 textbooks
- 200 medical journals
- 15 million pages of Oncology text
- >10,000 oncology cases

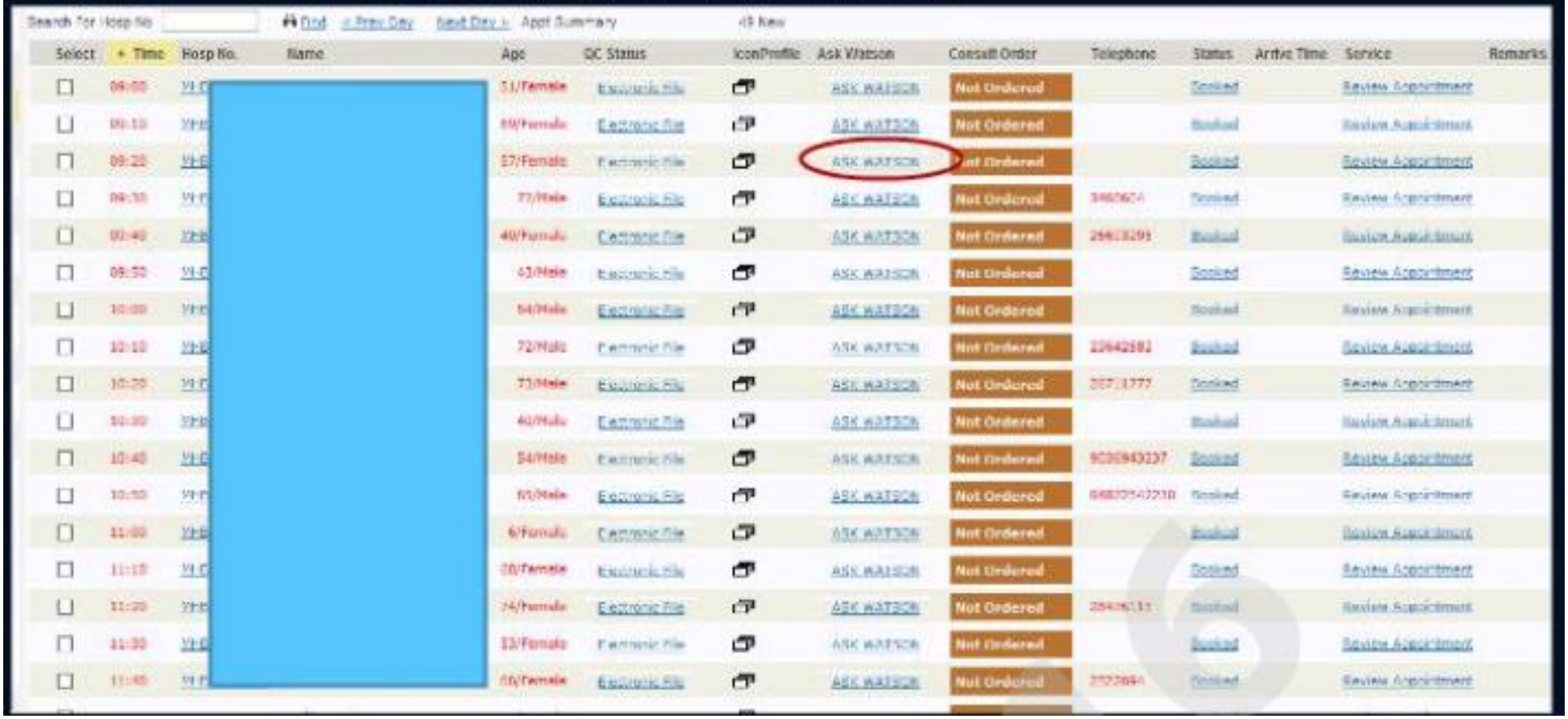
Expansion

Second and Third line treatment options
New cancers

Training **Refresh**

Continuous training by MSKCC oncologists
Refresh and Maintenance of corpus
New cases

Doctors appointment list active



WFO Output

- Analyzes >100 patient attributes for breast cancer
- Some user attribute abstraction and WFO entry
- RX recommendations ranked in 3 color categories:
  - Green: Recommended Rx (REC)
  - Amber: For Consideration (FC)
  - Red: Not RECommended (N-REC)
- Provides supporting evidence

40 seconds to analyze chart
60 seconds to generate recommendation report

Breast Cancer Concordance Study at Manipal Hospital

Evaluate concordance of treatment recommendations between WFO and local expertise (Manipal Multidisciplinary Tumour Board), MMDT

N = 638 cancer cases, last 3 years

T1*: Joint MMDT Best Decision

T2**: WFO Recommendation

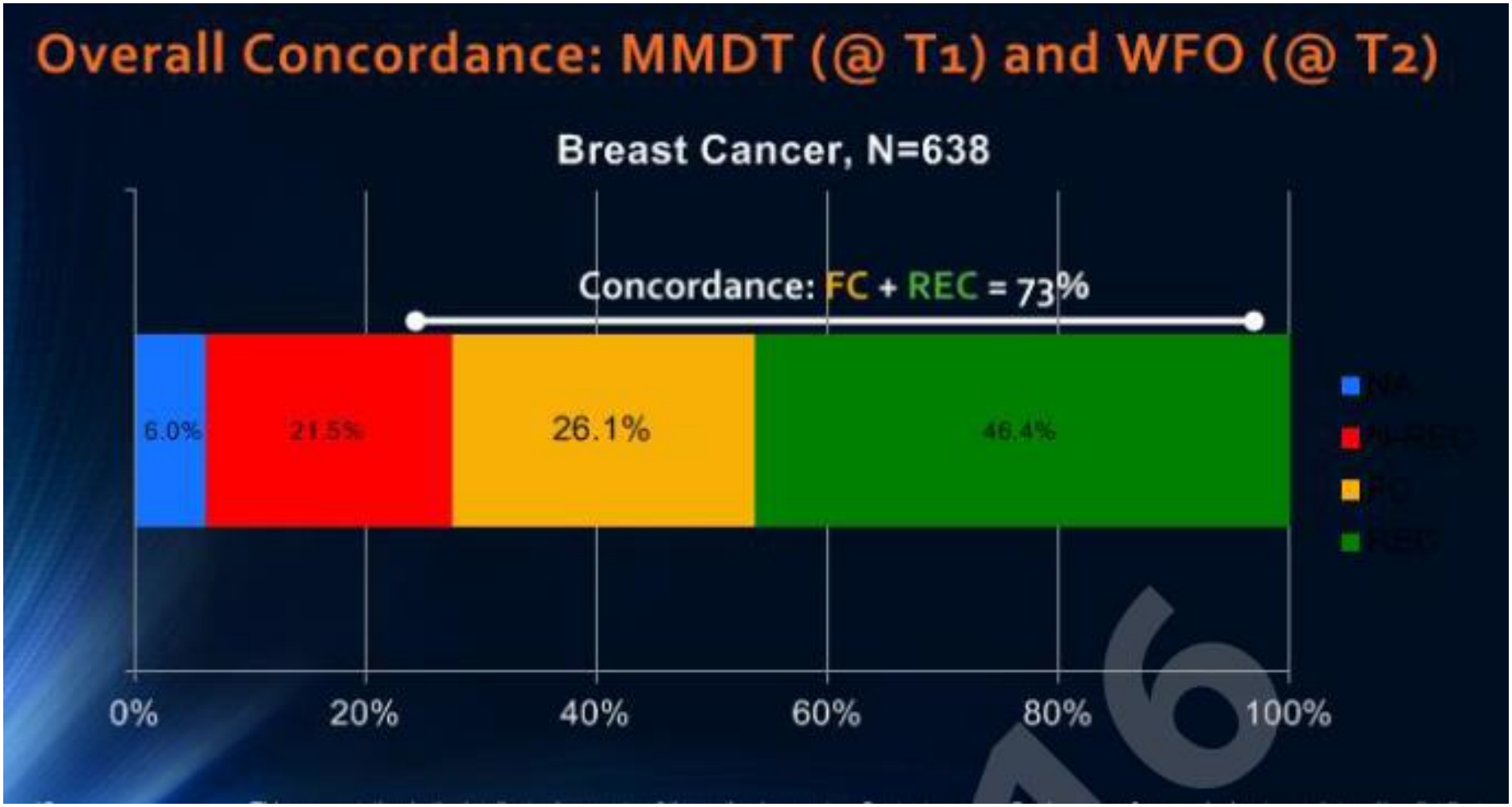
T2*: Joint MMDT Best Decision

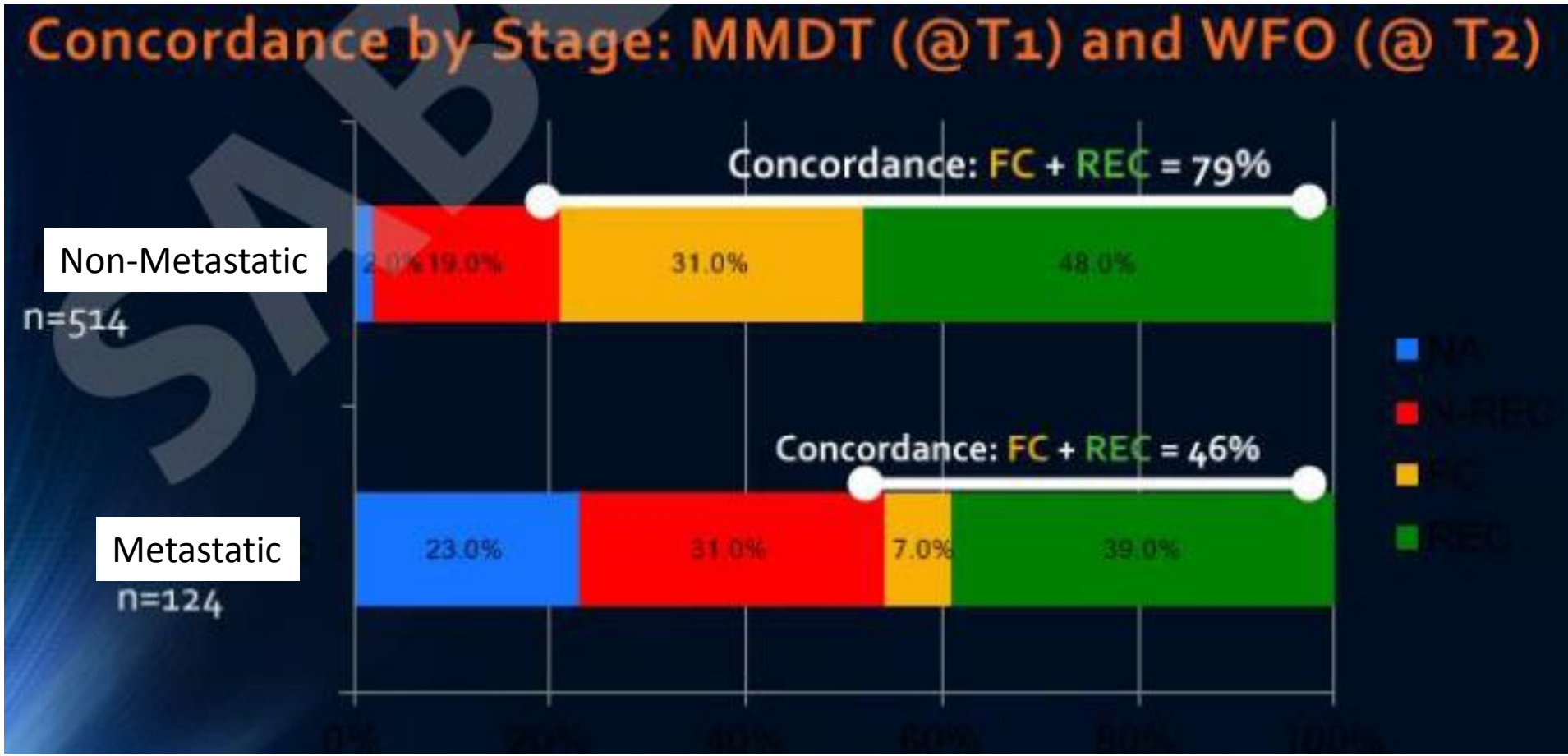
T1-T2 Blinded Concordance

T2-T2 Blinded Concordance

* T1 Time of original treatment decision by MMDT in the past (last 1-3 years)
** T2 Time (2016) of WFO's treatment advice and of MMDT's treatment decision upon blinded re-review of non-concordant cases

Overall Concordance: MMDT (@ T1) and WFO (@ T2)




Concordance by Stage: MMDT (@T1) and WFO (@ T2)
Concordance: FC + REC = 79%
Non-Metastatic
n=514
2.0%
19.0%
31.0%
48.0%
Concordance: FC + REC = 46%
Metastatic
n=124
23.0%
31.0%
7.0%
39.0%

Concordance WFO (@T2) and MMDT (@T1* v. T2**) (N= 638 Breast Cancer Cases)

Time Point/Concordance	REC		REC + FC	
	n	%	n	%
T1*	296	46	463	73
T2**	381	60	574	90

* T1 Time of original treatment decision by MMDT in the past (last 1-3 years)
** T2 Time (2016) of WFO's treatment advice and of MMDT's treatment decision upon blinded re-review of non-concordant cases

Comments:

- Study was not designed to assess why recommendations differed or inferiority/superiority
- Goal was to reduce "cognitive burden" on oncologists by providing clinically actionable insights to assist in treating patients
- Interesting concept but unclear how this impacts practice

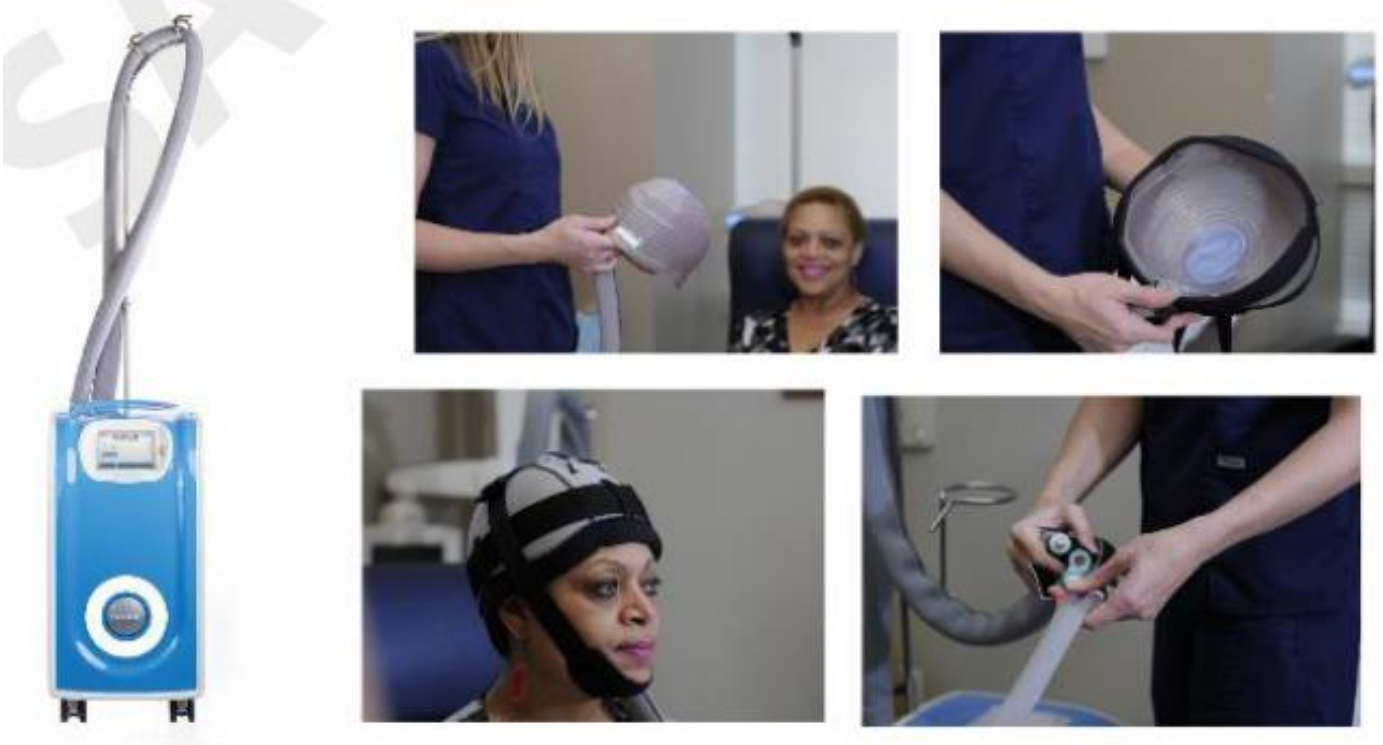
San Antonio Breast Cancer Symposium
December 6-10, 2016

Baylor College of Medicine

Scalp Cooling Alopecia Prevention Trial (SCALP)

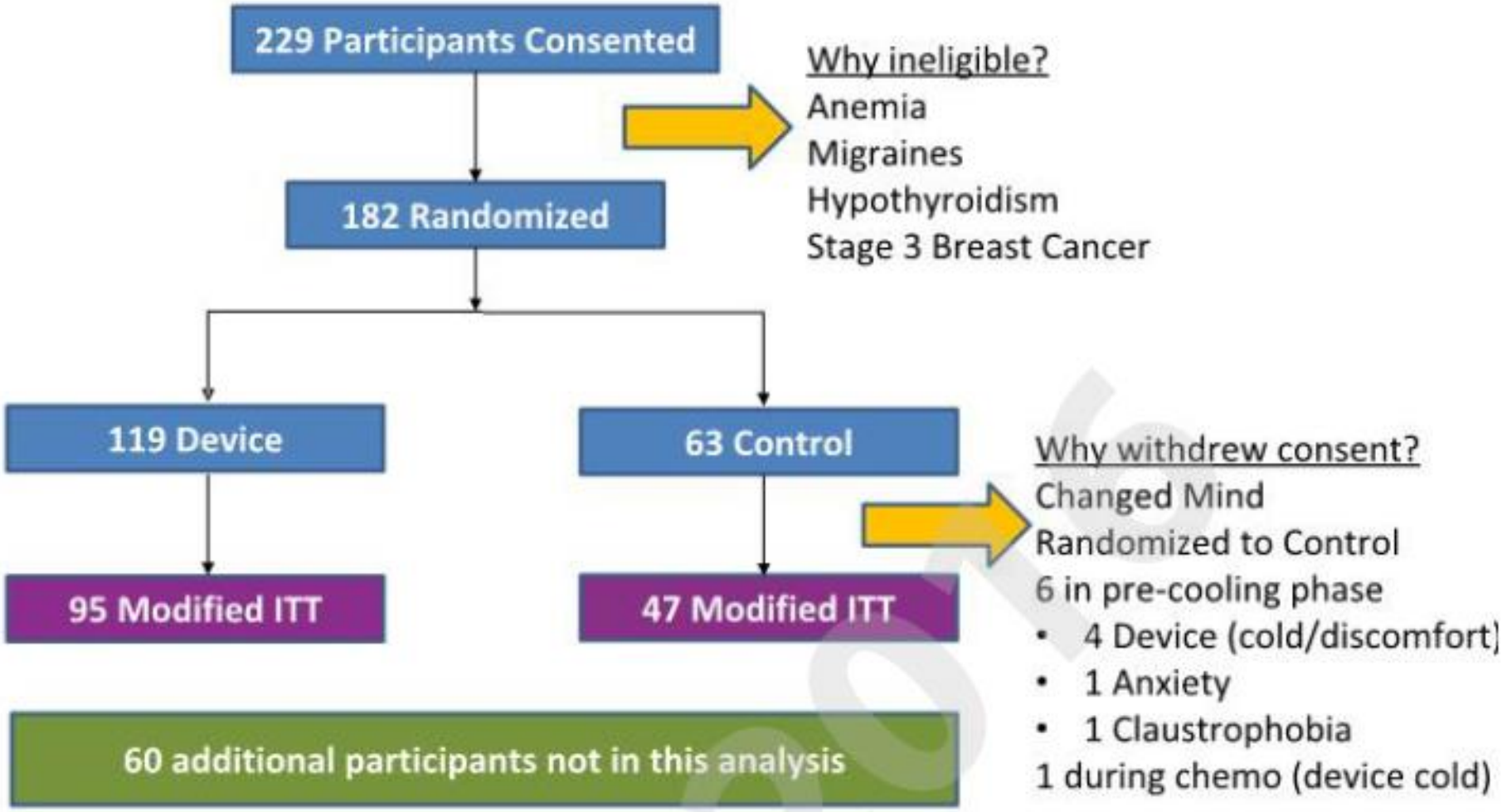
Julie Nangia, Tao Wang, Polly Niravath, Kristen Otte, Cynthia Osborne, Steven Papish, Frankie Holmes, Jame Abraham, Shari Goldfarb, Jay Courtright, Richard Paxman, Mari Rude, Susan Hilsenbeck, Kent Osborne, Mothaffar Rimawi

S5-02 Scalp Cooling Alopecia Prevention trial (SCALP) for patients with early stage breast cancer

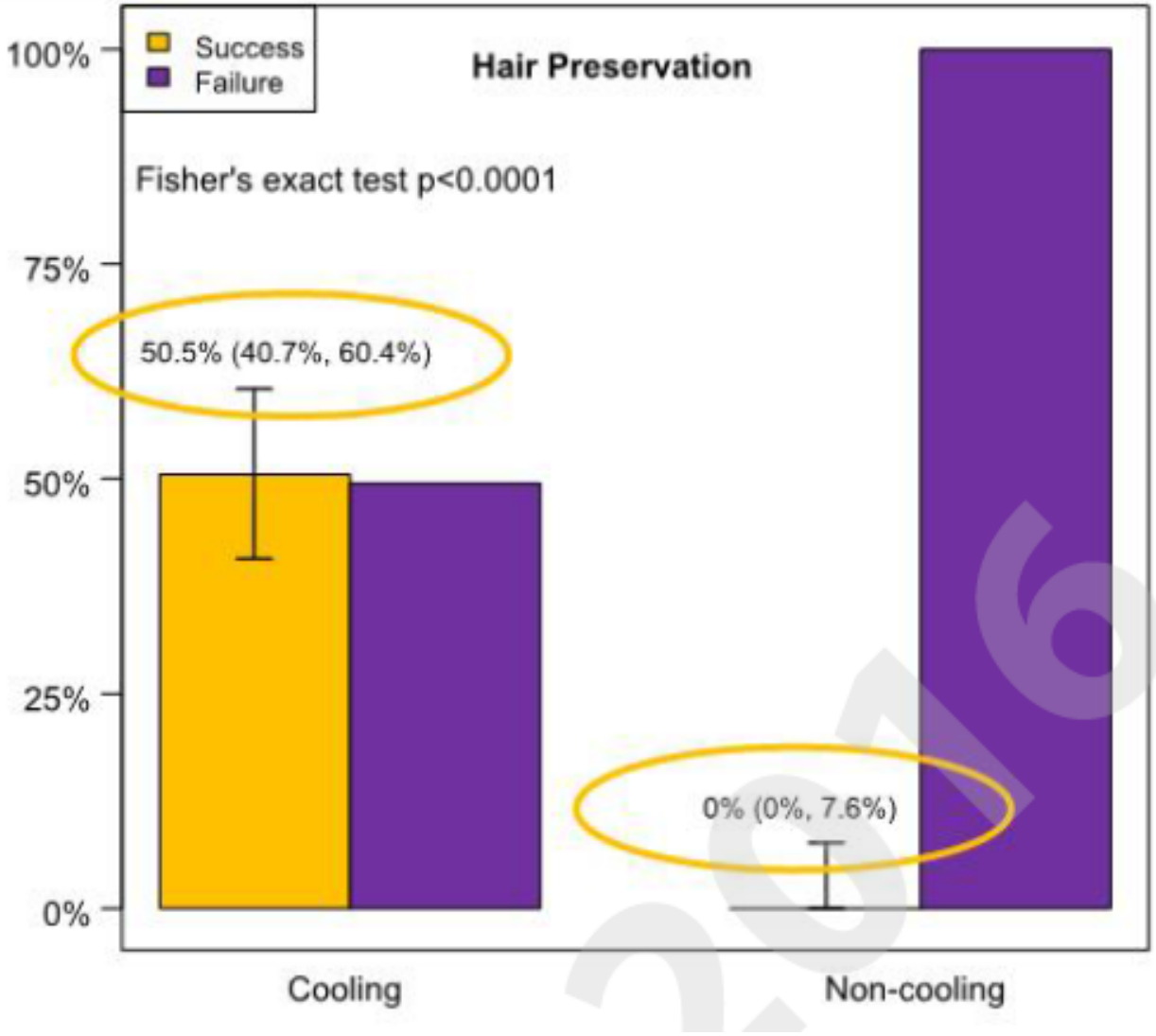


- 229 women from 12/2013 – 9/2016
- 7 US sites (3 academic, 4 community)
- Inclusion: Stage 1 or 2, neo/adjuvant
- Exclusion: migraines, anemia, hypothyroidism, uncontrolled medical condition

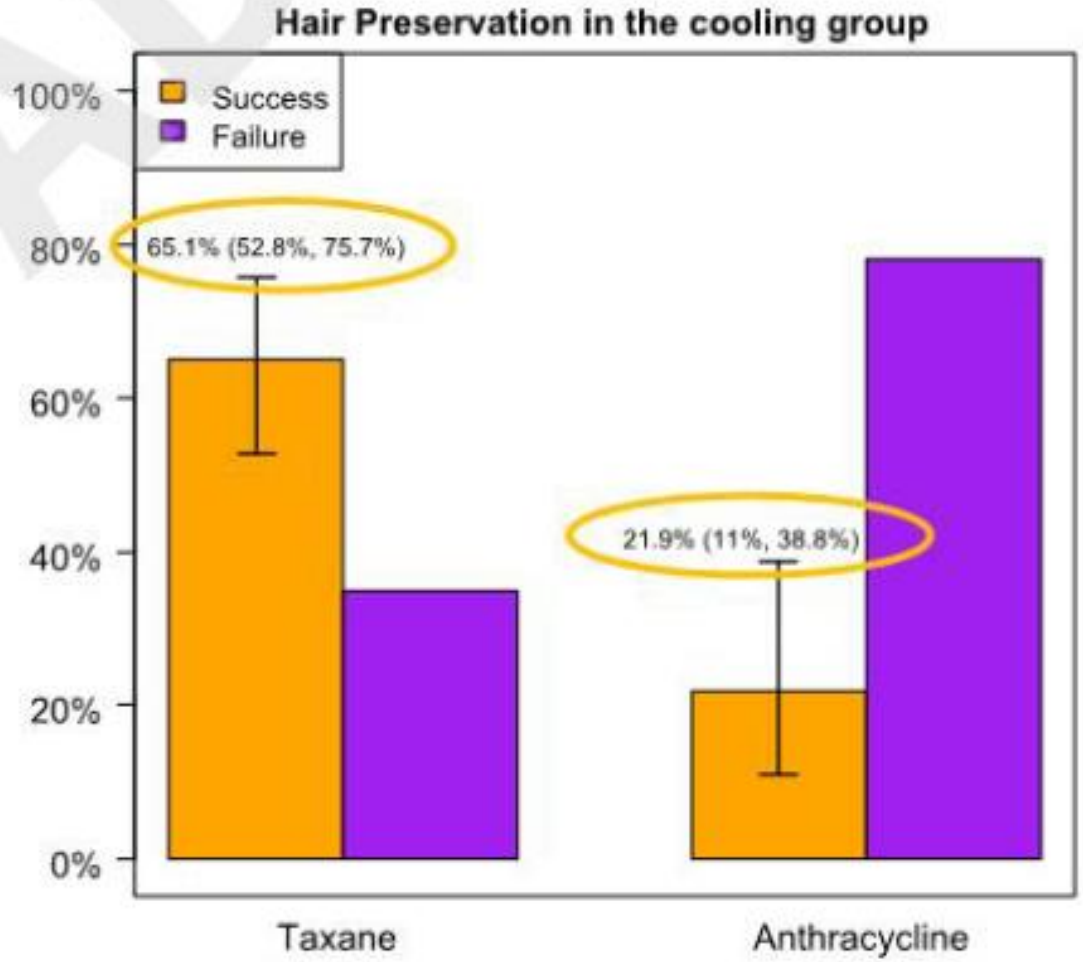
SCALP


229 Participants Consented
Why ineligible?
Anemia
Migraines
Hypothyroidism
Stage 3 Breast Cancer
182 Randomized
119 Device
63 Control
Why withdrew consent?
Changed Mind
Randomized to Control
6 in pre-cooling phase
• 4 Device (cold/discomfort)
• 1 Anxiety
• 1 Claustrophobia
1 during chemo (device cold)
95 Modified ITT
47 Modified ITT
60 additional participants not in this analysis

Results: Primary Outcome



Discussion


Hair Preservation in the cooling group
Success
Failure
100%
80%
60%
40%
20%
0%
65.1% (52.8%, 75.7%)
21.9% (11%, 38.8%)
Taxane
Anthracycline

Results: Adverse Events

Adverse Device Effects

AADEs (CTCAE V4.0)	Cooling N = 101			
	Cycle 1	Cycle 2	Cycle 3	Cycle 4
	n=101	n=84	n=66	n=62
Headache	11.9%	10.7%	1.5%	6.5%
Nausea	4%	2.4%	1.5%	1.6%
Dizziness	3%	1.2%		
Chills	1%			
Paresthesia	1%			
Pruritus	1%			
Sinus pain			1.5%	
Skin & SQ tissue disorders	1%			
Skin ulceration	1%			

Results: Quality of Life

Patient Reported Comfort Scale

Comfort Scale	Cooling (N = 101)			
	Cycle 1	Cycle 2	Cycle 3	Cycle 4
	n=101	n=84	n=66	n=62
Very Comfortable	11.9%	16.7%	16.7%	14.5%
Reasonable Comfortable	51.5%	39.3%	47%	50%
Comfortable	28.7%	26.2%	21.2%	24.2%
Uncomfortable	5.9%	13.1%	12.1%	9.7%
Very Uncomfortable	-	2.4%	-	-
Not Assessed	2%	2.4%	3%	1.6%

Quality of Life Assessments showed no difference

Thank you