Triple Negative Breast Cancer

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UCDAVIS
COMPREHENSIVE
CANCER CENTER

HELEN CHEW, MD

TRIPLE NEGATIVE BREAST CANCER

NO RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

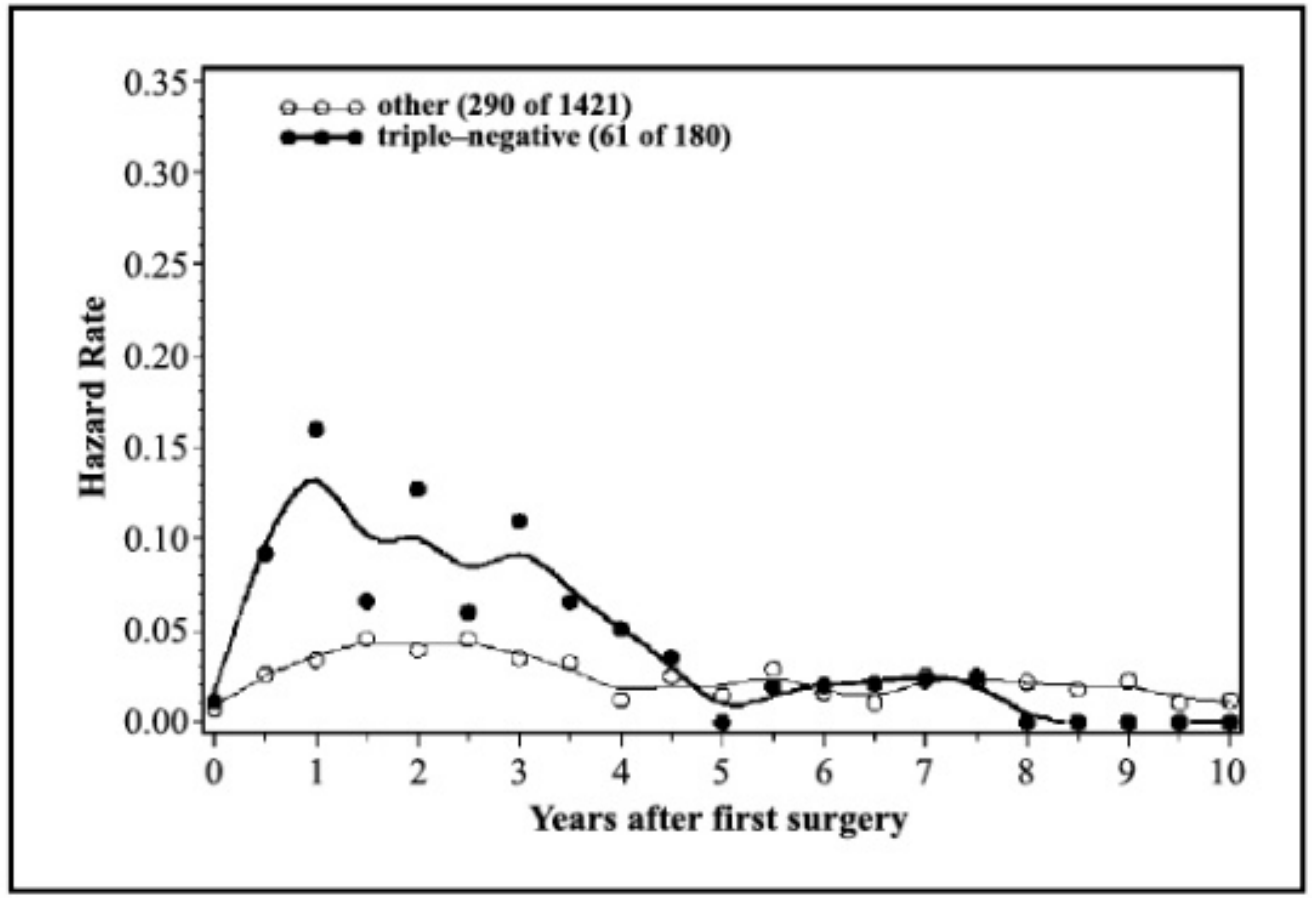
Today's talk

- Classification of triple negative breast cancers (TNBC)
- Review current standard and emerging therapies
- *BRCA*-mutated breast cancer
- Current trials

Triple negative breast cancers

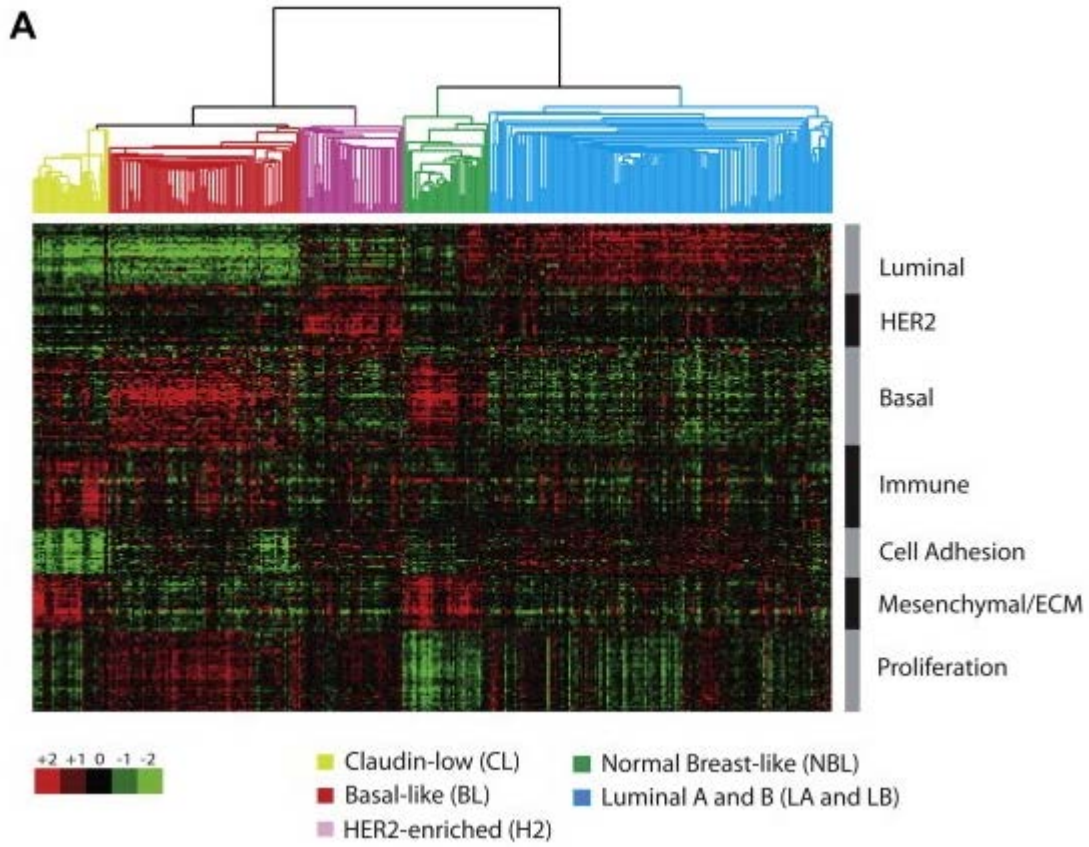
- Lack expression of ER, PgR or HER (non amplified)
- 15-20% of all breast cancers
- Clinically aggressive
- No “targeted” therapy proven

Rates of distant recurrences following surgery in triple-negative and other breast cancers.



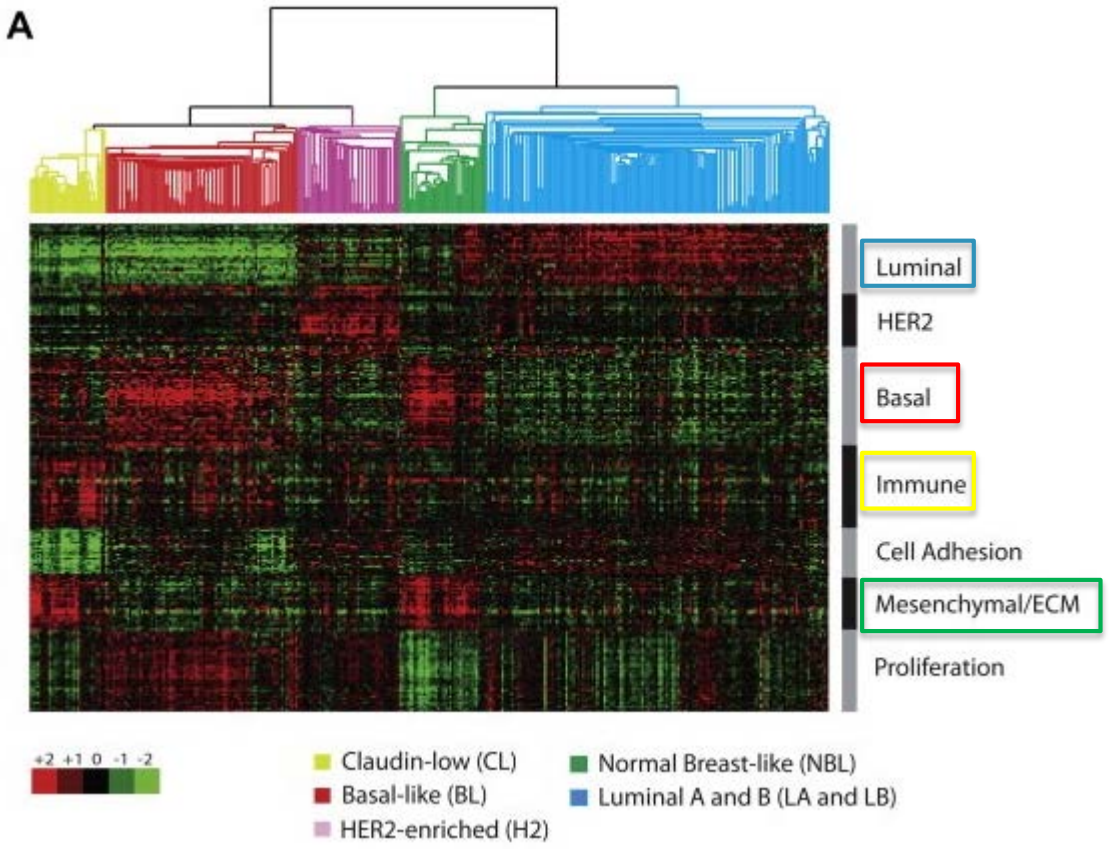
Dent R et al. Clin Canc Res 2007

Triple negative breast cancers



Prat and Perou, Molec Oncol 2010

Triple negative breast cancers



- Platinum agents, DNA repair
- PI3K and MEK pathways
- Checkpoint inhibitors
- Androgen receptor

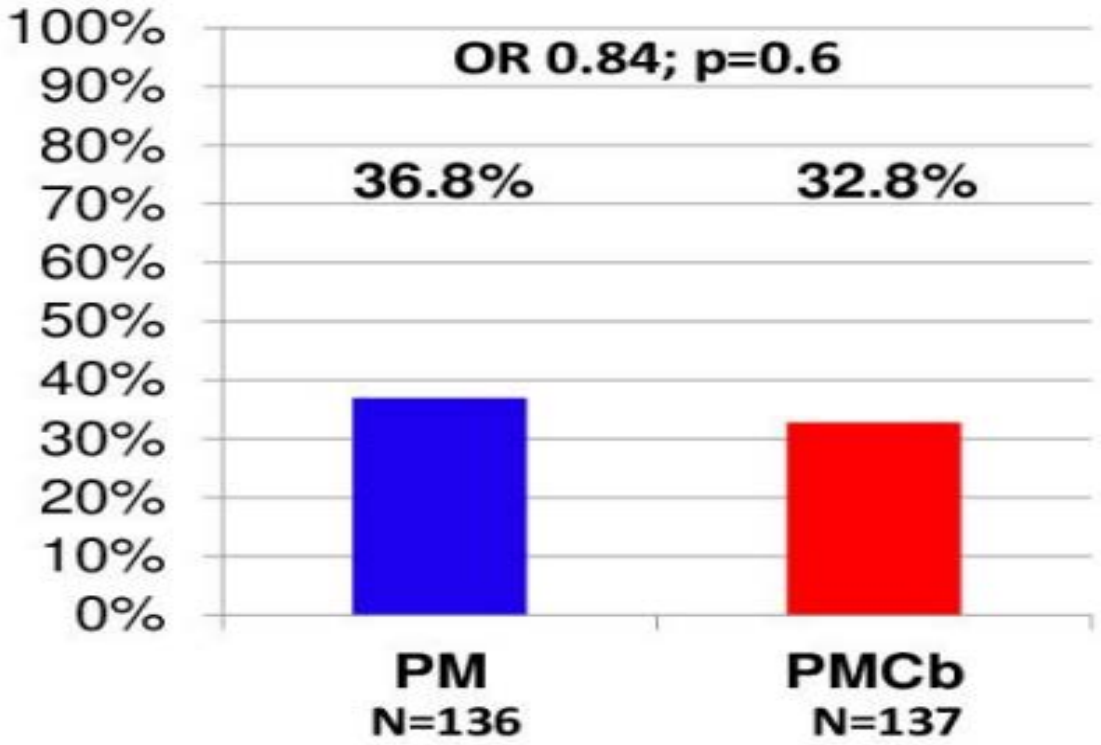
Prat and Perou, Molec Oncol 2010

GBG GERMAN BREAST GROUP

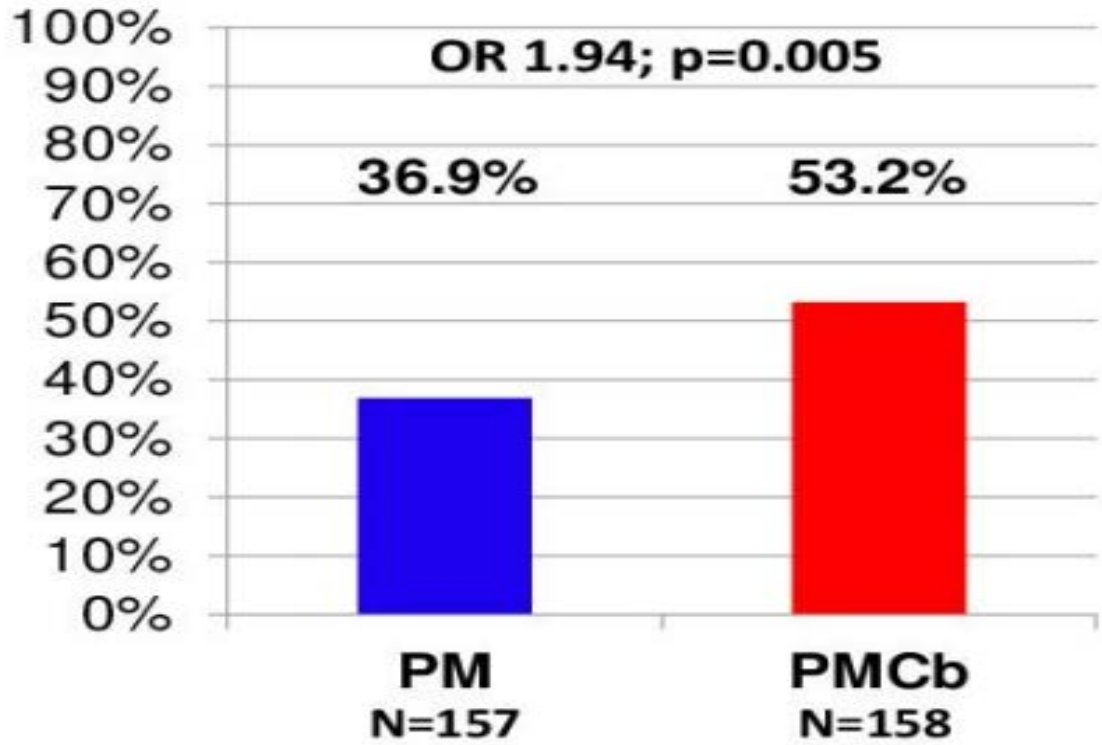
pCR Rates by Subtype

ypT0 ypN0

HER2-pos. BC



TNBC



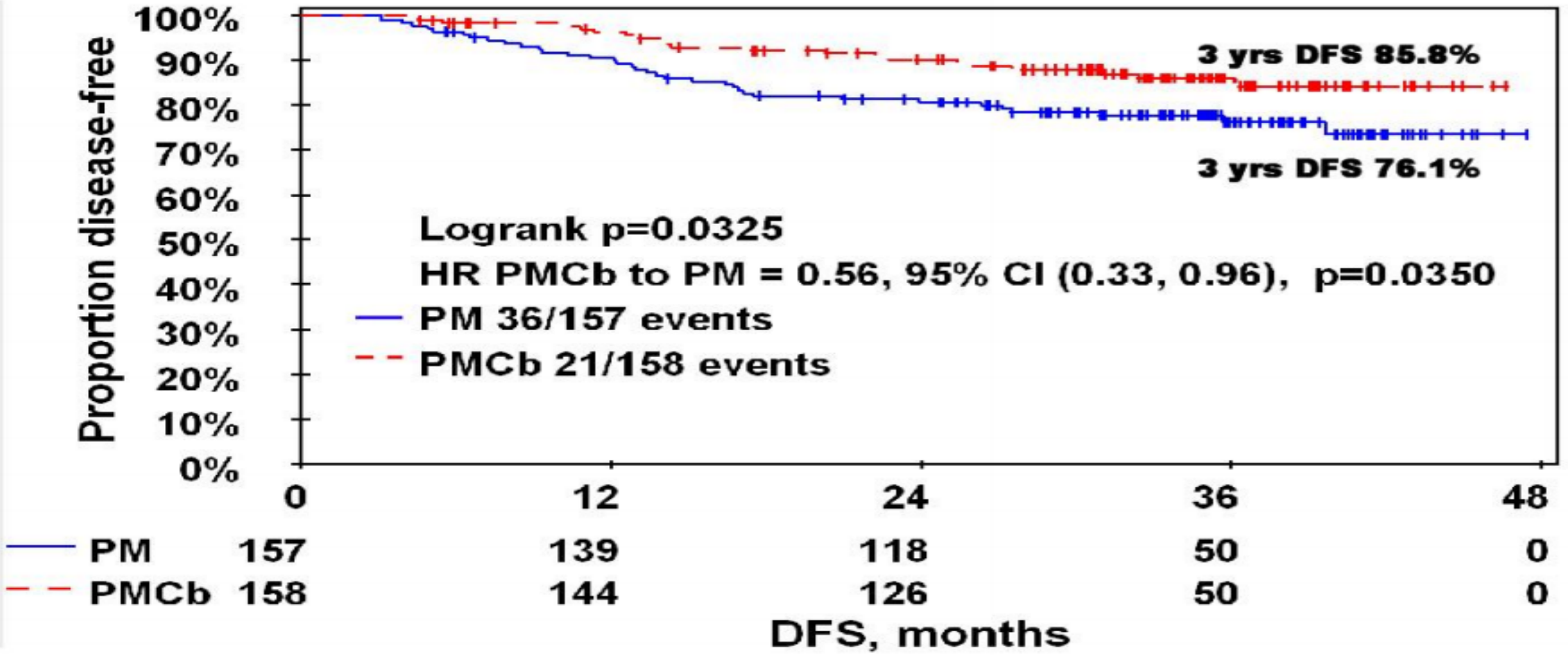
Test for interaction p=0.015

AGO-B BREAST STUDY GROUP

von Minckwitz et al. Lancet Oncology 2014

GBG GERMAN BREAST GROUP

DFS: Effect of Carboplatin in TNBC



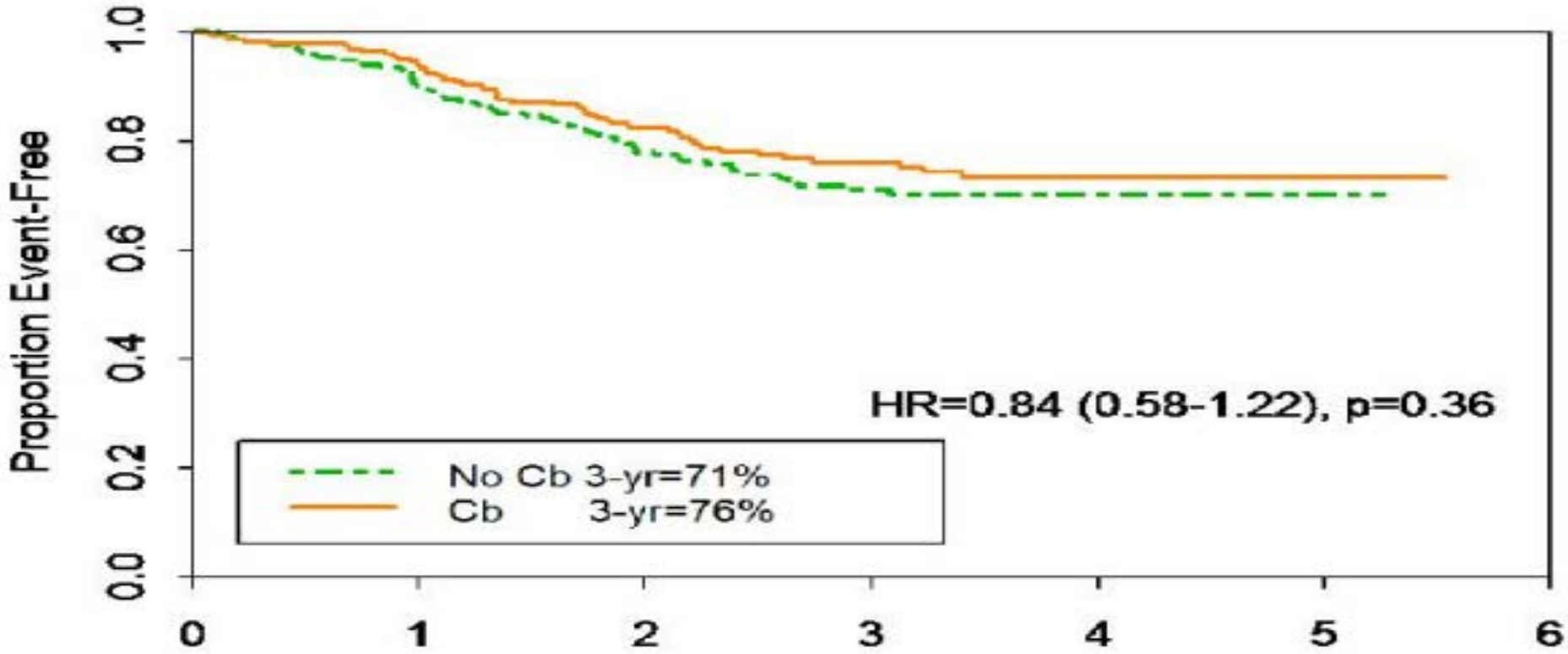
AGO-B BREAST STUDY GROUP

CALGB 40603 – pCR Results by factor

pCR Breast ypT0/is (%, 95% CI)				
Overall	Carbo	No Carbo	OR	p-value
53 (49-58)	60 (54-66)	46 (40-53)	1.76	0.0018
	Bev	No Bev	OR	p-value
	59 (52-65)	48 (41-54)	1.58	0.0089
pCR Breast/Axilla ypT0/is ypN0 (%, 95% CI)				
Overall	Carbo	No Carbo	OR	p-value
48 (43-53)	54 (48-61)	41 (35-48)	1.71	0.0029
	Bev	No Bev	OR	p-value
	52 (45-58)	44 (38-51)	1.29	0.0570

Sikov et al, J Clin Oncol 2015

CALGB 40603 – EFS for carboplatin vs. not



Number at Risk

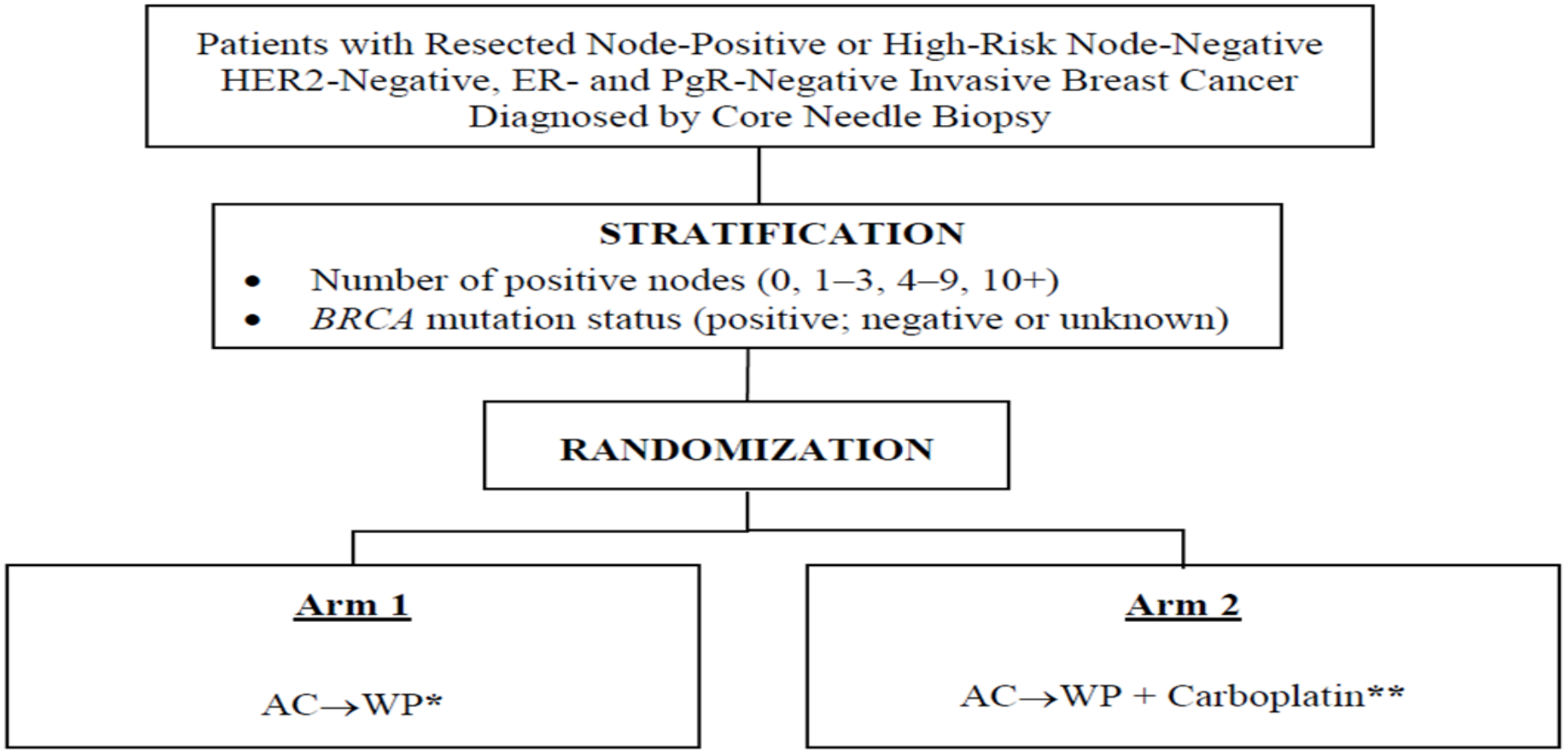
No Cb	218	185	145	94	31	2	0
Cb	225	202	162	101	37	2	0

Triple negative breast cancers

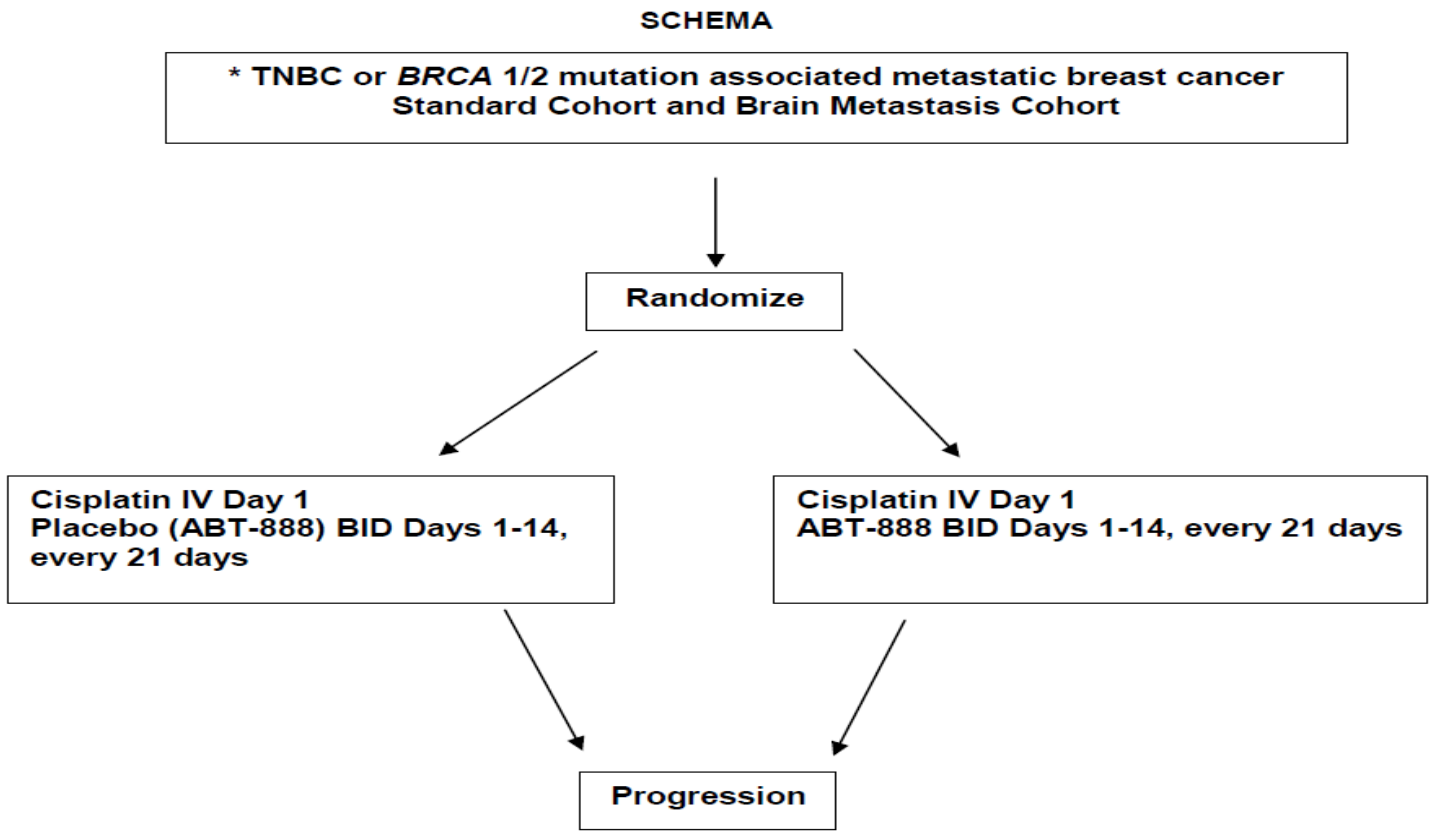
- Metastatic: platinum agents incorporated sequentially
- Neoadjuvant: consider adding carboplatin for pCR; capecitabine?
- Adjuvant: no data that additional agents improve DFS or OS

NRG BR003

Figure 1. NRG-BR003 SCHEMA



SWOG 1416 in TNBC or *BRCA*-mutated



PI: Eve Rodler, MD

AZD5363 plus Paclitaxel versus Placebo plus Paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial.

Peter Schmid[1], Jacinta Abraham[2], Stephen Chan[3], Duncan Wheatley[4], Adrian Murray Brunt[5], Gia Nemsadze[6], Richard Baird[7], Yeon Hee Park[8], Peter Hall[9], Timothy Perren[10], Rob Stein[11], Mangel László[12], Jean-Marc Ferrero[13], Melissa Phillips[14], John Conibear[14], Javier Cortes[15], Shah-Jalal Sarker[1], Aaron Prendergast[1], Hayley Cartwright[1], Kelly Mousa[1], Nick Turner[16]

[1]Barts Cancer Institute, St Bartholomew's Hospital, Queen Mary University of London, UK; [2]Velindre NHS Trust, UK; [3]Nottingham University Hospitals NHS Trust, UK, [4]Royal Cornwall Hospitals NHS Trust, UK; [5]University Hospitals of North Midlands NHS Trust, UK; [6]Institute of Clinical Oncology, Georgia; [7]Cambridge University Hospitals NHS Foundation Trust, UK; [8]Samsung Medical Centre, Republic of Korea; [9]NHS Lothian, UK; [10]Leeds Teaching Hospitals NHS Trust, UK; [11]University College London Hospitals NHS Foundation Trust, UK; [12]Medical University of Pécs, Hungary; [13]Centre Antoine Lacassagne, France; [14]Barts Health NHS Trust; UK; [15]Ramon Y Cajal University Hospital, Spain; [16]Royal Marsden NHS Foundation Trust; UK

Presented By Peter Schmid at 2018 ASCO Annual Meeting

Background

- The PI3K/AKT signalling pathway is frequently activated in TNBC through activating mutations in *PIK3CA* or *AKT1* and alterations in *PTEN*[1-3]
- In addition, deficient expression of PTEN is a common finding in TNBC and has been associated with a higher degree of AKT pathway activation[4]
- Capivasertib (AZD5363) is a highly-selective, oral, small molecule AKT inhibitor.
- Capivasertib has shown preclinical activity in TNBC models with and without alterations of *PIK3CA, AKT1* and *PTEN,* but sensitivity was associated with activation of *PI3K* or *AKT* and/or deletions of *PTEN*.

1. Cancer Genome Atlas Network, Nature 2012; 490: 61–70.; 2. Curtis C, et al.. Nature 2012; 486: 346–52.; 3. Pereira B, et al. Nat Commun 2016; 7: 11479.; 4Millis SZ, et al. Clin Breast Cancer 2015; 15: 473–81.

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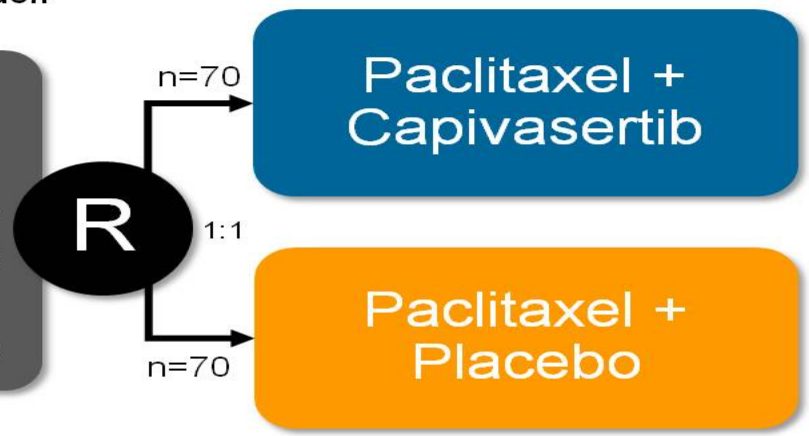
PAKT Study Design

Trial Sponsor: Queen Mary University of London

- Metastatic breast cancer
- Triple-negative disease:
  - ER/PR <1%
  - HER2 IHC0-2 and/or ISH negative
- Measurable or evaluable disease
- No prior treatment for MBC
- No taxane treatment <12 months



Primary endpoint:

- Investigator-assessed PFS (ITT)

Secondary endpoints:

- PFS in patients with/without *PIK3CA/AKT1/PTEN* alterations
- Overall Survival
- Response rates (ORR)
- Clinical benefit rate (CBR)
- Duration of response
- Safety
- Health-related quality of life

Stratification factors:

- Number of metastatic sites (<3, ≥3)
- DFI (end of (neo)adjuvant chemotherapy ≤12 months ago, end of (neo)adjuvant) chemotherapy >12 months or no prior chemotherapy)

Treatment:

- **Paclitaxel, 90 mg/m^2, IV, days 1, 8, & 15, q4 weeks**
- **Capivasertib/Placebo, 400mg orally BD, days 2-5, 9-12, 16-19**
- Paclitaxel for ≥6 cycles, Capivasertib/Placebo until PD
- If paclitaxel stopped prior to PD, Capivasertib/Placebo to be continued until PD
- Tumour assessments every 8 weeks

ER = Estrogen Receptor; PR = Progesterone Receptor; IHC = Immunohistochemistry; ISH = In situ Hybridisation; PFS = Progression-free survival

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Safety: Reported Adverse Events

	Paclitaxel + Capivasertib (N=68)				Paclitaxel + Placebo (N=70)			
	All Grades		Grade 3/4		All Grades		Grade 3/4	
Number of patients with at least one AE	66	97.1%	-	-	64	91.4%	-	-
Diarrhoea	49	72.1%	9	13.2%	19	27.1%	1	1.4%
Fatigue	30	44.1%	3	4.4%	18	25.7%	0	-
Nausea	24	35.3%	1	1.5%	23	32.9%	0	-
Rash	28	41.2%	3	4.4%	11	15.7%	0	-
Neuropathy	17	25.0%	1	1.5%	13	18.6%	0	-
Stomatitis	18	26.5%	1	1.5%	10	14.3%	0	-
Infection	15	22.1%	3	4.4%	10	14.3%	1	1.4%
Decreased appetite	14	20.6%	0	-	8	11.4%	0	-
Alopecia	11	16.2%	0	-	9	12.9%	0	-
Vomiting	13	19.1%	1	1.5%	6	8.6%	1	1.4%
Constipation	5	7.4%	0	-	10	14.3%	0	-
Abdominal pain	7	10.3%	0	-	7	10.0%	0	-
Dry skin	10	14.7%	0	-	2	2.9%	0	-
Dyspnoea	6	8.8%	0	-	5	7.1%	0	-
Headache	8	11.8%	0	-	3	4.3%	0	-
Oedema	6	8.8%	0	-	4	5.7%	0	-
Dysgeusia	7	10.3%	0	-	3	4.3%	0	-
Joint pain	2	2.9%	0	-	6	8.6%	0	-
Neutropenia	6	8.8%	2	2.9%	2	2.9%	2	2.9%
Cough	1	1.5%	0	-	6	8.6%	0	-
Hyperglycaemia	6	8.8%	1	1.5%	1	1.4%	0	-

AEs occurring in ≥8% in at at least one of the treatment groups

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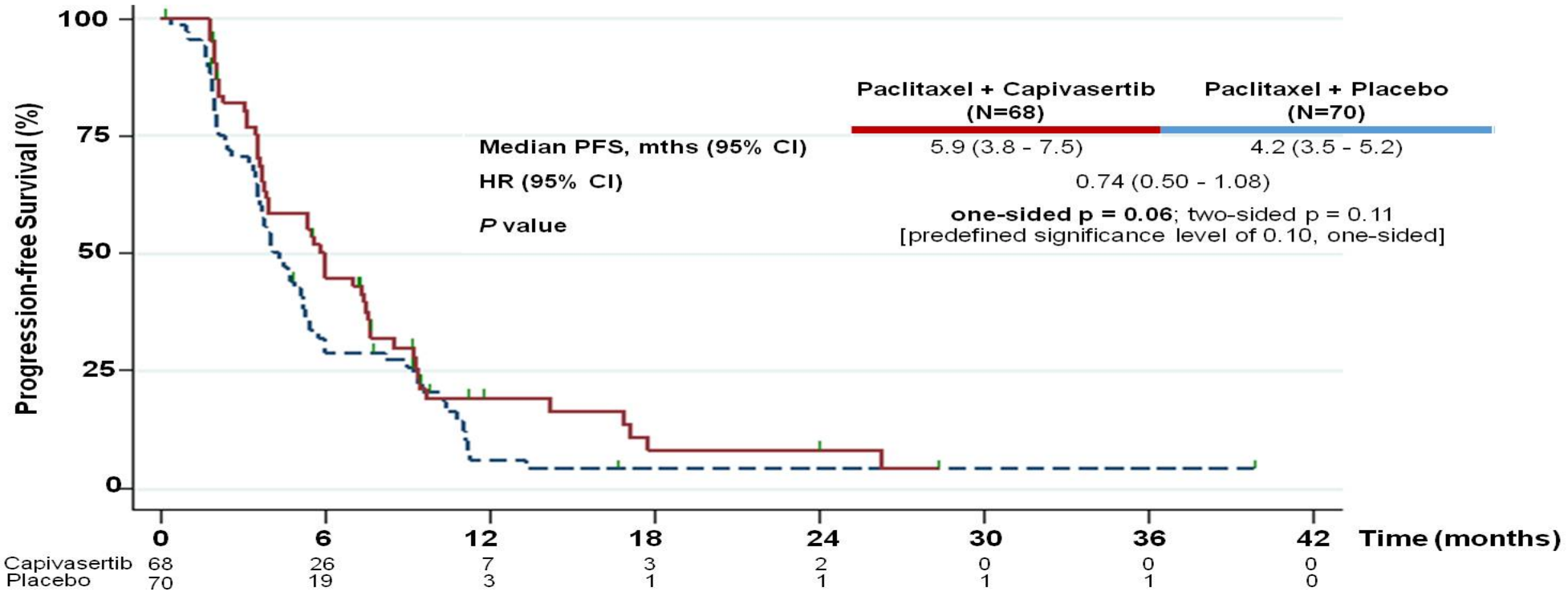
PFS by investigator assessment (ITT)



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mths = months; PFS = progression-free survival

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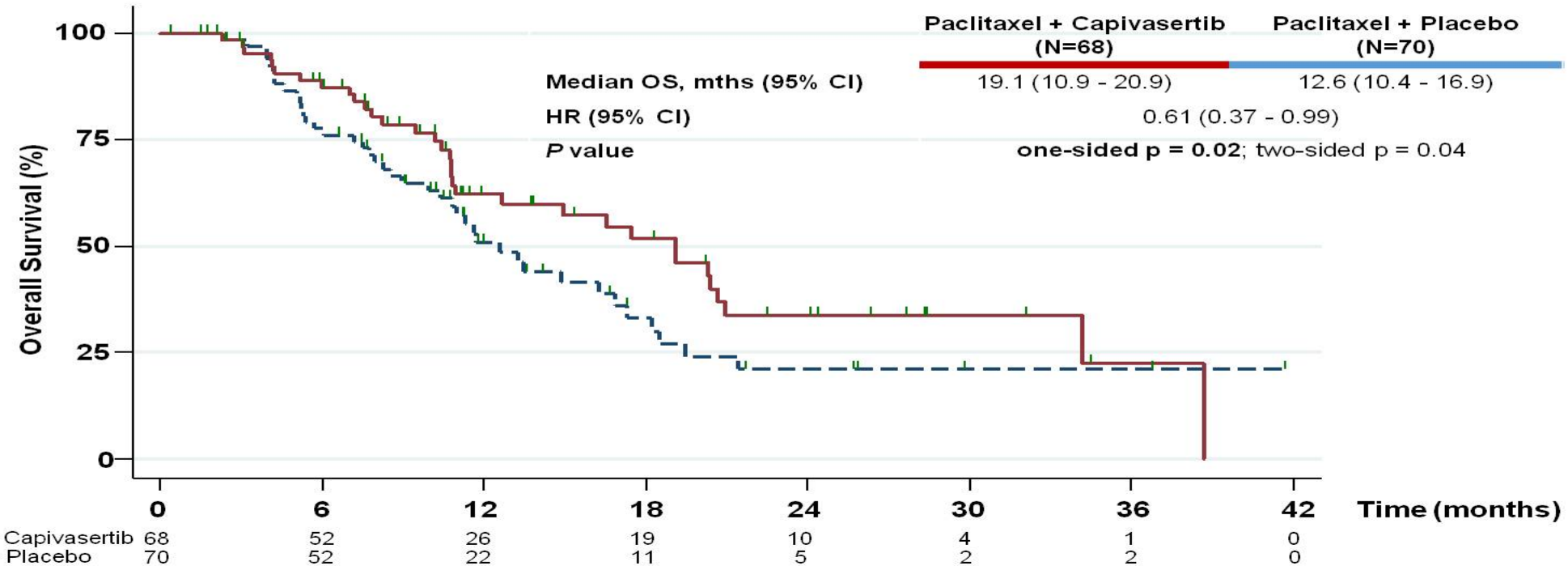
Overall Survival (ITT Population)



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mths = months; OS = overall survival

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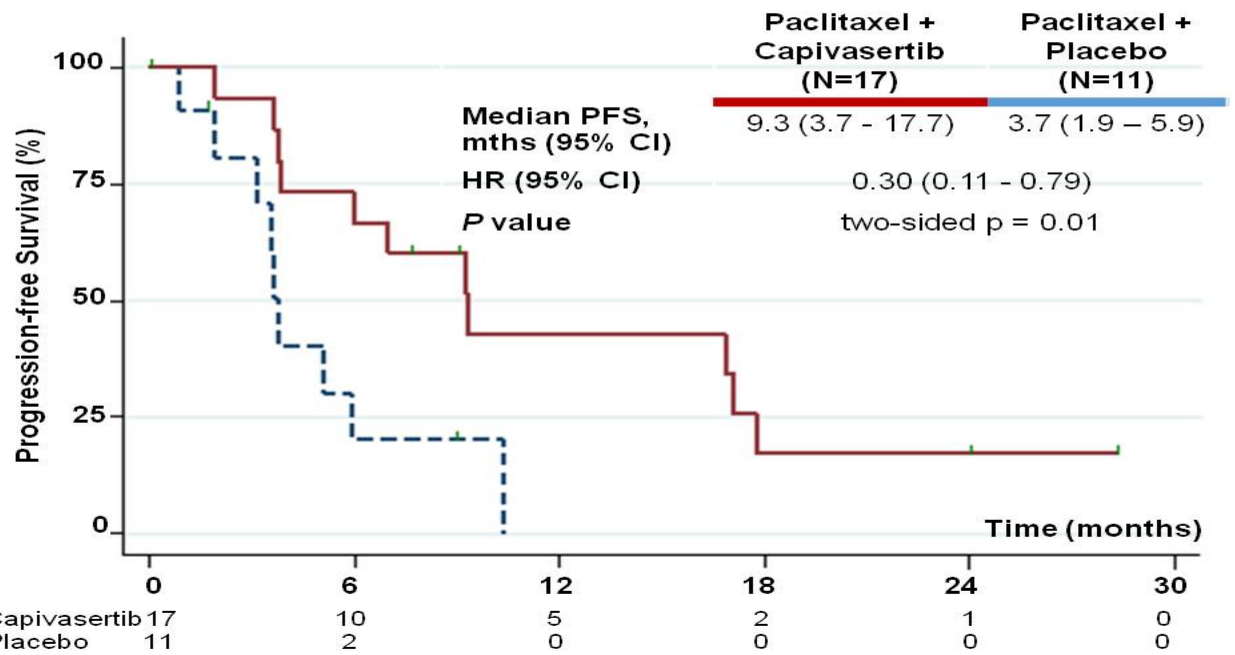
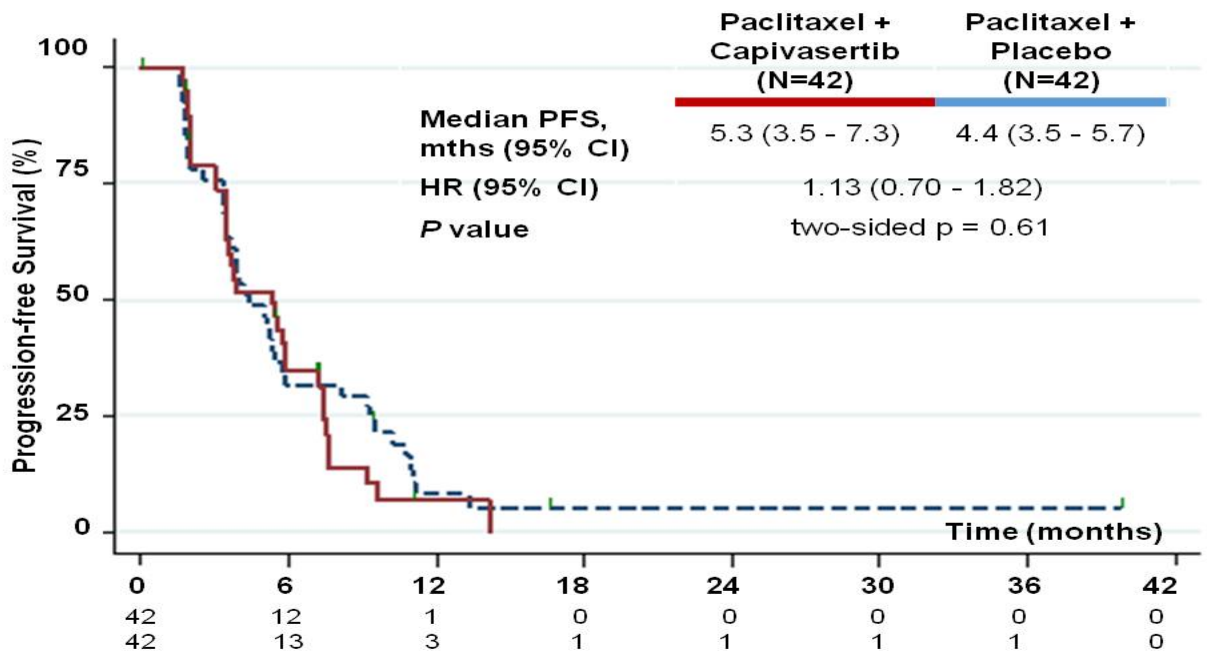
PFS by tumour *PIK3CA/AKT1/PTEN* status

PIK3CA/AKT1/PTEN altered



PIK3CA/AKT1/PTEN not altered



CI = confidence interval; HR = hazard ratio; mths = months; PFS = progression-free survival

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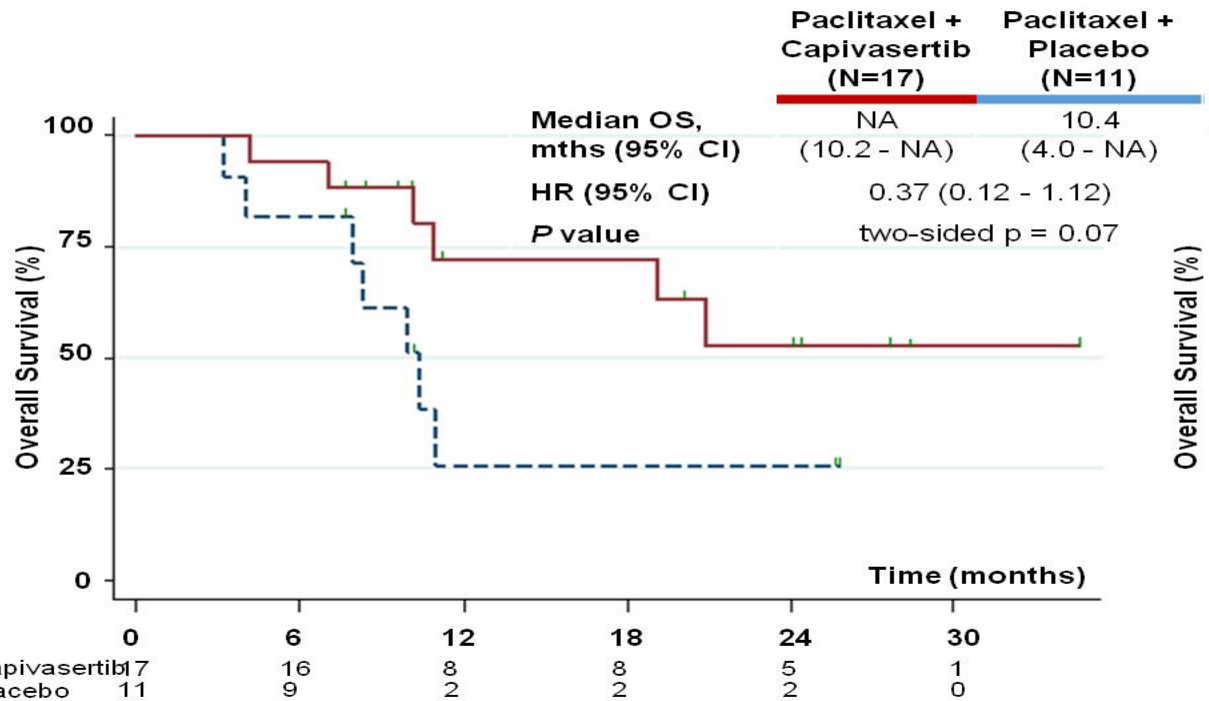
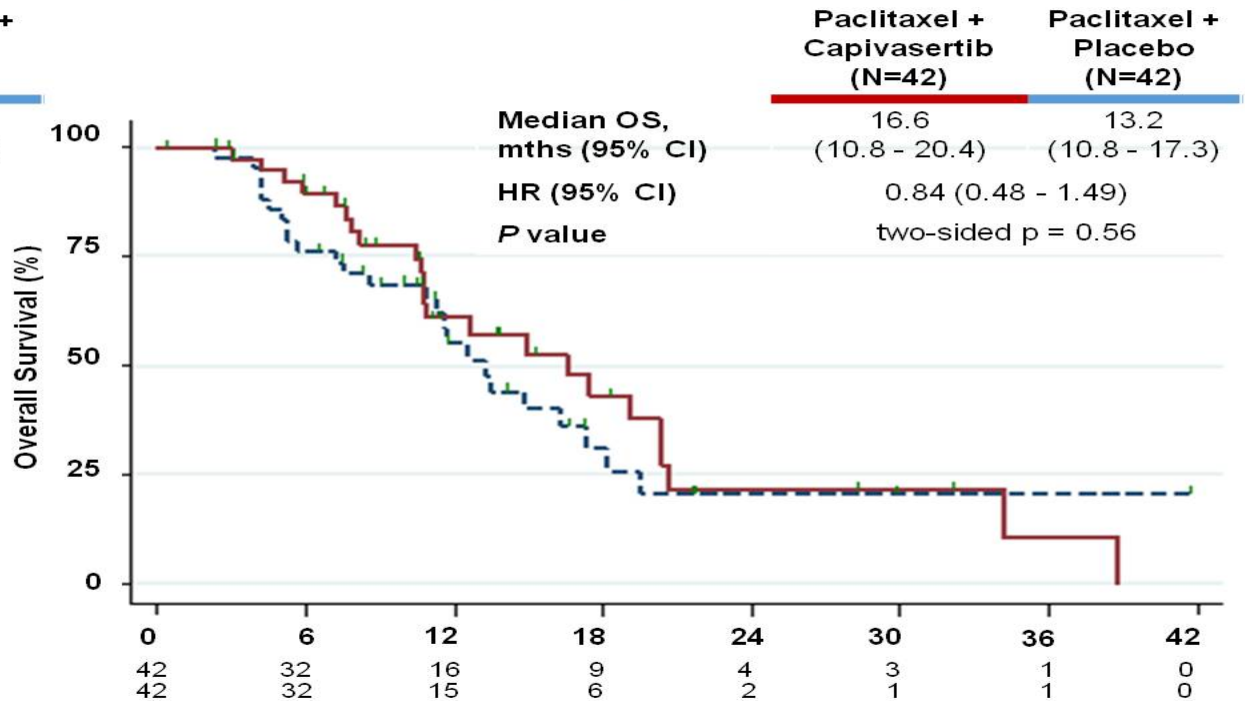
Overall Survival by *PIK3CA/AKT1/PTEN* status

PIK3CA/AKT1/PTEN altered



PIK3CA/AKT1/PTEN not altered



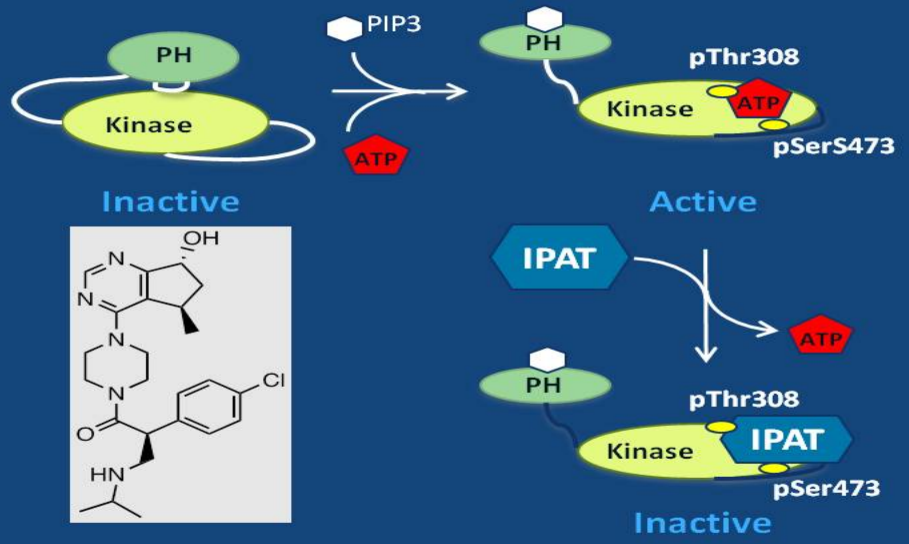
CI = confidence interval; HR = hazard ratio; mths = months; OS = overall survival

Ipatasertib: selective targeting of AKT

IPAT enzymatic potency

Enzyme	IC_{50} (nM)
Akt1	5
Akt2	18
Akt3	8
PKA	3100 (620x)

IPAT targets only active AKT



Selective targeting of AKT may allow a greater therapeutic window in patients

LOTUS (NCT02162719) randomized phase II trial

- Measurable locally advanced/metastatic TNBC[a] not amenable to curative resection
- No prior systemic therapy for advanced/metastatic disease
- Chemotherapy-free interval ≥6 months
- ECOG performance status 0/1
- Archival or newly obtained tumor tissue for central PTEN assessment

(n=124)

R 1:1

PAC 80 mg/m^2 days 1, 8, & 15 + IPAT 400 mg qd days 1-21 q28d

Treatment until disease progression, intolerable toxicity,[b] or withdrawal of consent

PAC 80 mg/m^2 days 1, 8, & 15 + PBO days 1-21 q28d

Stratification factors

- (Neo)adjuvant chemotherapy
- Chemotherapy-free interval
- Tumor IHC PTEN status

Endpoints

- Co-primary: PFS in ITT and PTEN-low populations
- Secondary: ORR, DoR, OS (ITT, PTEN-low, and PI3K/AKT pathway-activated populations), safety

[a]Defined as <1% tumor cell expression of estrogen and progesterone receptors and negative HER2 status (FISH/CISH HER2:CEP17 ratio <2.0, or locally assessed IHC 0 or 1+ [or 2+ but negative by FISH/CISH]). [b]Patients discontinuing PAC or IPAT/PBO due to toxicity could continue on single-agent treatment. Protocol did not specify primary prophylactic antidiarrheal use

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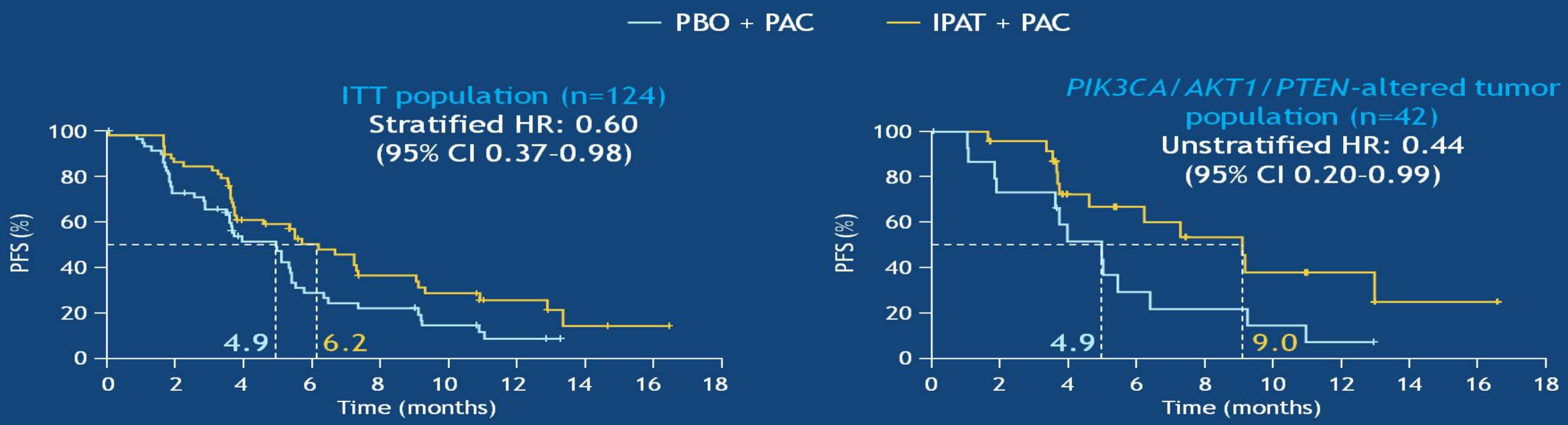
DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; FISH/CISH = fluorescence/chromogenic in situ hybridization; IHC = immunohistochemistry; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PAC = paclitaxel; PBO = placebo; PFS = progression-free survival; q28d = every 28 days; qd = once daily; R = randomization

Primary analysis: IPAT effect on PFS enhanced in *PIK3CA/AKT1/PTEN*-altered subgroup (Foundation Medicine[a])

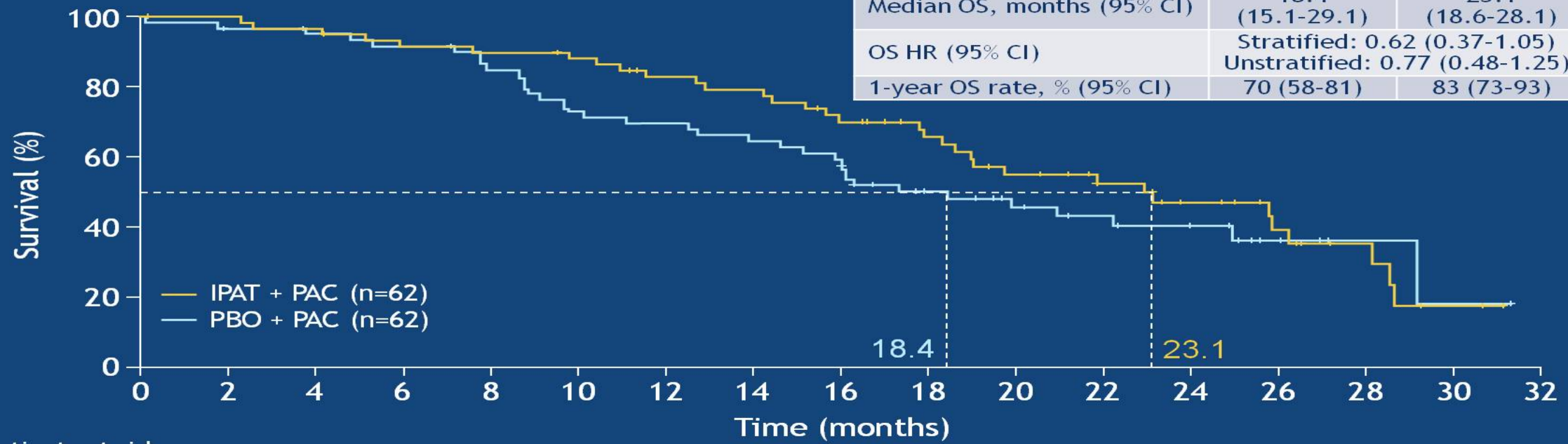


[a]FoundationOne
CI = confidence interval; HR = hazard ratio

Kim et al. Lancet Oncol 2017

OS in the ITT population

	PBO + PAC (n=62)	IPAT + PAC (n=62)
OS events, n (%)	35 (56)	33 (53)
Median OS, months (95% CI)	18.4 (15.1-29.1)	23.1 (18.6-28.1)
OS HR (95% CI)	Stratified: 0.62 (0.37-1.05) Unstratified: 0.77 (0.48-1.25)	
1-year OS rate, % (95% CI)	70 (58-81)	83 (73-93)



No. of patients at risk

IPAT + PAC	62	60	58	54	53	51	46	44	37	31	25	20	15	10	6	2
PBO + PAC	62	59	57	55	50	43	41	38	32	24	19	16	13	6	2	1

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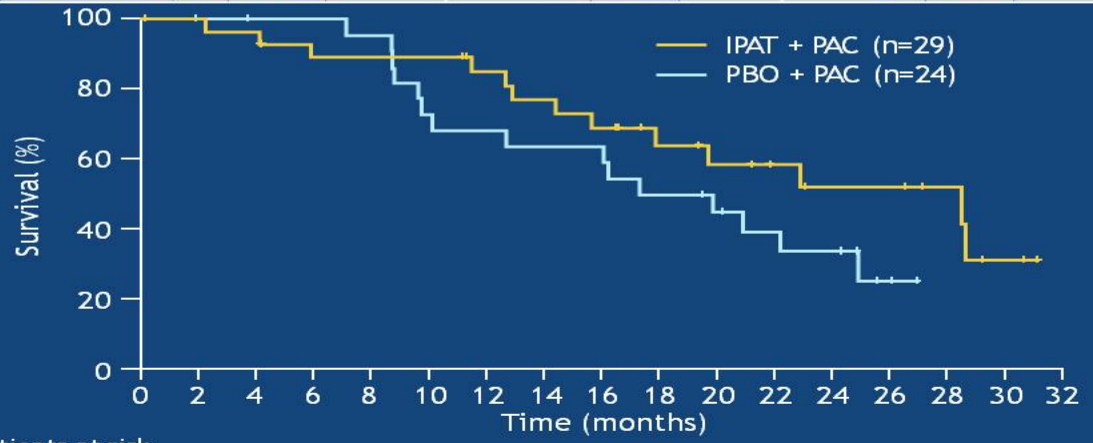
OS according to IHC PTEN status (Ventana)

PTEN normal

	PBO + PAC (n=24)	IPAT + PAC (n=29)
OS events, n (%)	15 (63)	13 (45)
Median OS, months (95% CI)	18.6 (10.1-24.9)	28.5 (17.8-NE)
Unstratified OS HR (95% CI)	0.56 (0.26-1.23)	
1-year OS rate, % (95% CI)	68 (49-88)	85 (72-99)

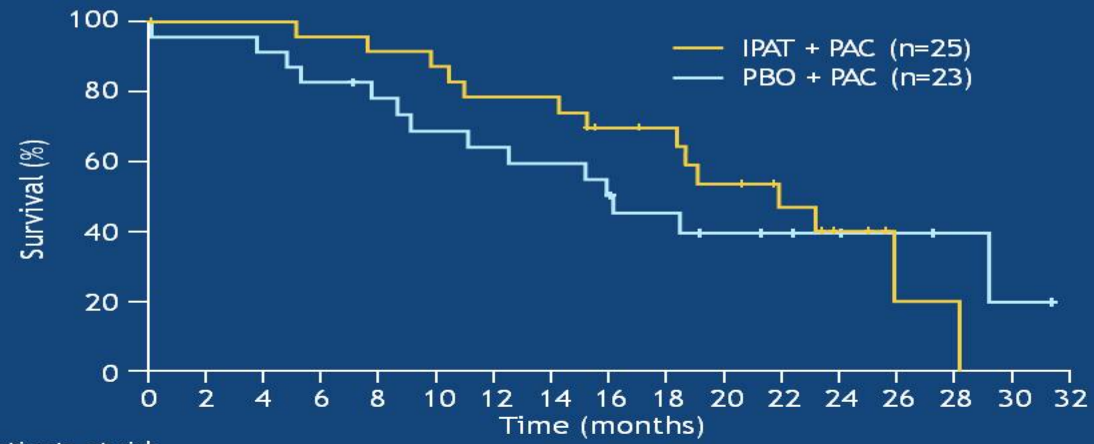


No. of patients at risk

IPAT + PAC	29	28	27	24	21	19	17	13	11	9	7	7	5	2
PBO + PAC	24	23	22	22	21	16	15	14	14	11	9	7	6	2

PTEN low[a]

	PBO + PAC (n=23)	IPAT + PAC (n=25)
OS events, n (%)	14 (61)	14 (56)
Median OS, months (95% CI)	16.1 (9.0-29.1)	21.8 (18.3-28.1)
Unstratified OS HR (95% CI)	0.86 (0.40-1.83)	
1-year OS rate, % (95% CI)	64 (44-84)	79 (62-95)



No. of patients at risk

IPAT + PAC	25	24	24	23	22	20	18	18	14	13	10	7	4	1	1
PBO + PAC	23	22	21	19	17	15	14	13	10	8	6	5	3	3	2	1

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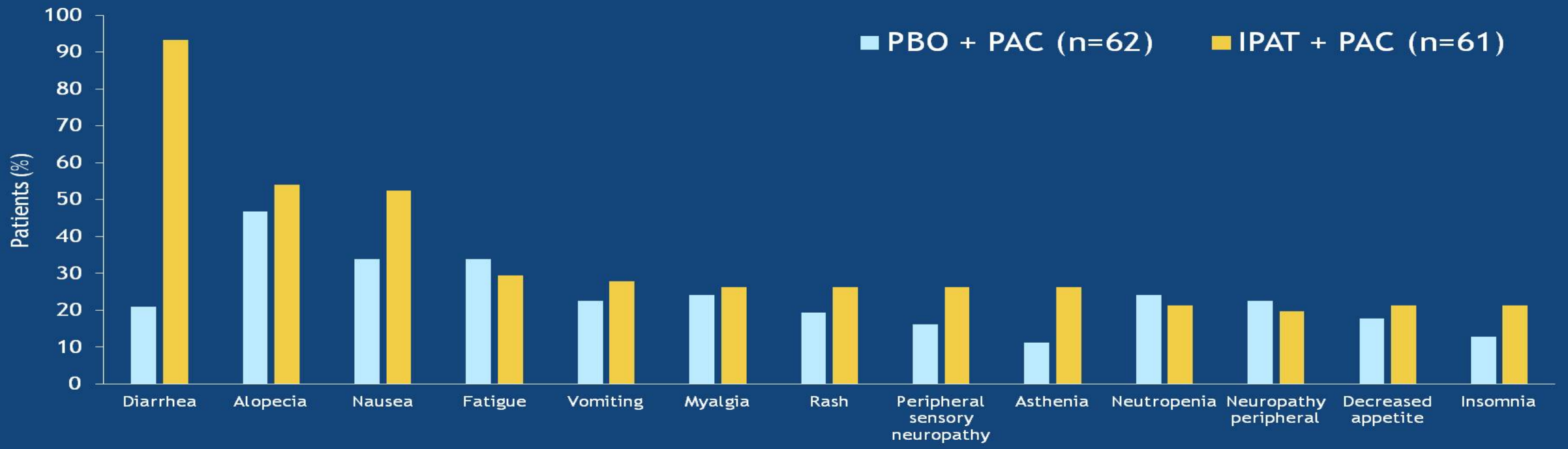
[a]Defined as IHC 0 in ≥50% of tumor cells

Updated safety: Most common[a] adverse events (all grades)



[a]Adverse events occurring in >20% of patients in either treatment arm

Study Design – KEYNOTE-086 Cohort A

Patients

- Age ≥18 y
- Centrally confirmed TNBC[a]
- ≥1 prior systemic treatment for mTNBC with documented PD
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample for PD-L1 evaluation
- No radiographic evidence of CNS metastases
- Measurable disease per RECIST v1.1 by central review

N = 170

Pembrolizumab 200 mg IV Q3W

for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

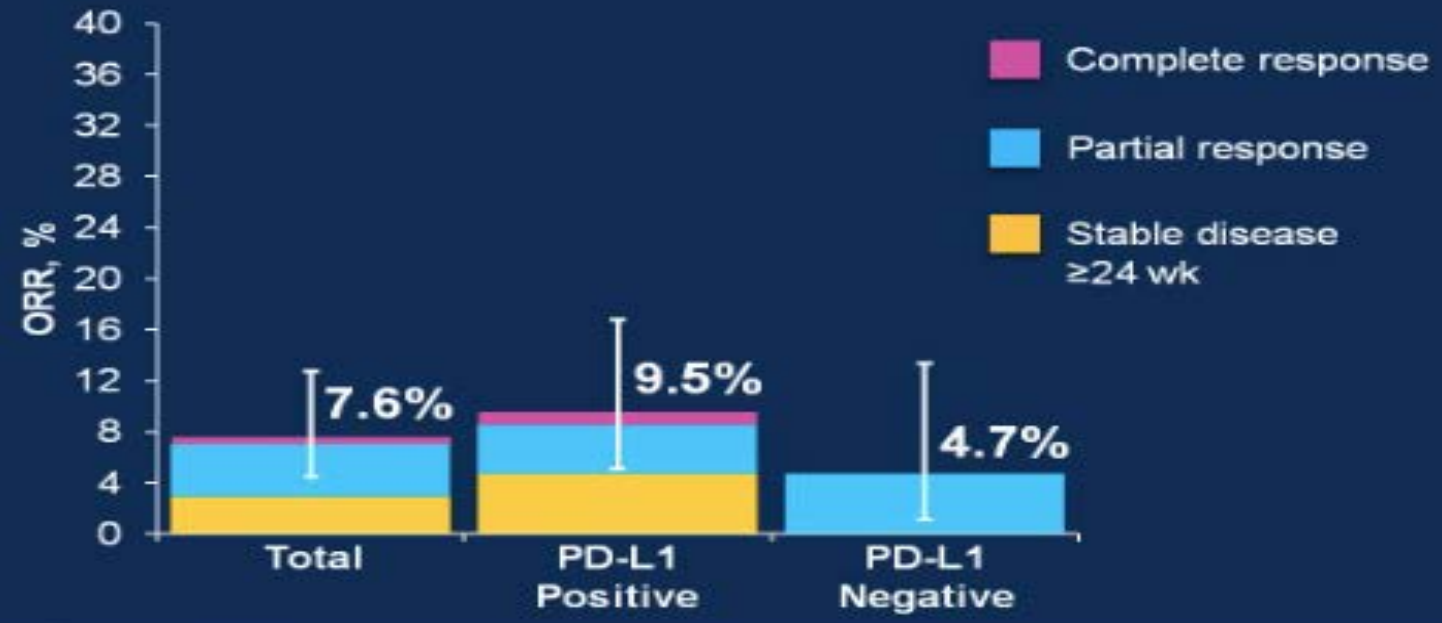
Protocol-specified follow-up

- **Primary end points: ORR[b] and safety**
- **Secondary end points[b]: DOR, DCR,[c] PFS, OS**

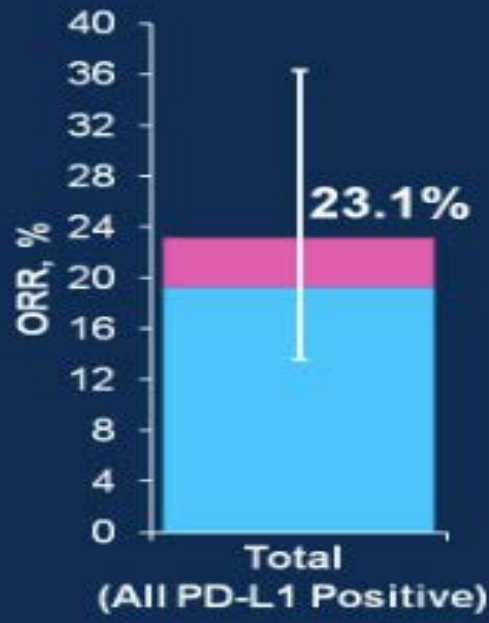
[a]<1% tumor cells positive for ER and PR by IHC, irrespective of intensity, and HER2 IHC 0 or 1+ or FISH negative. [b]Assessed in the total population and in the PD-L1–positive population [c]DCR = disease control rate = SD ≥24 wk + CR + PR

Pembrolizumab Antitumor Activity in Previously Treated and Previously Untreated mTNBC

Cohort A (N = 170): Previously Treated, Regardless of PD-L1 Expression



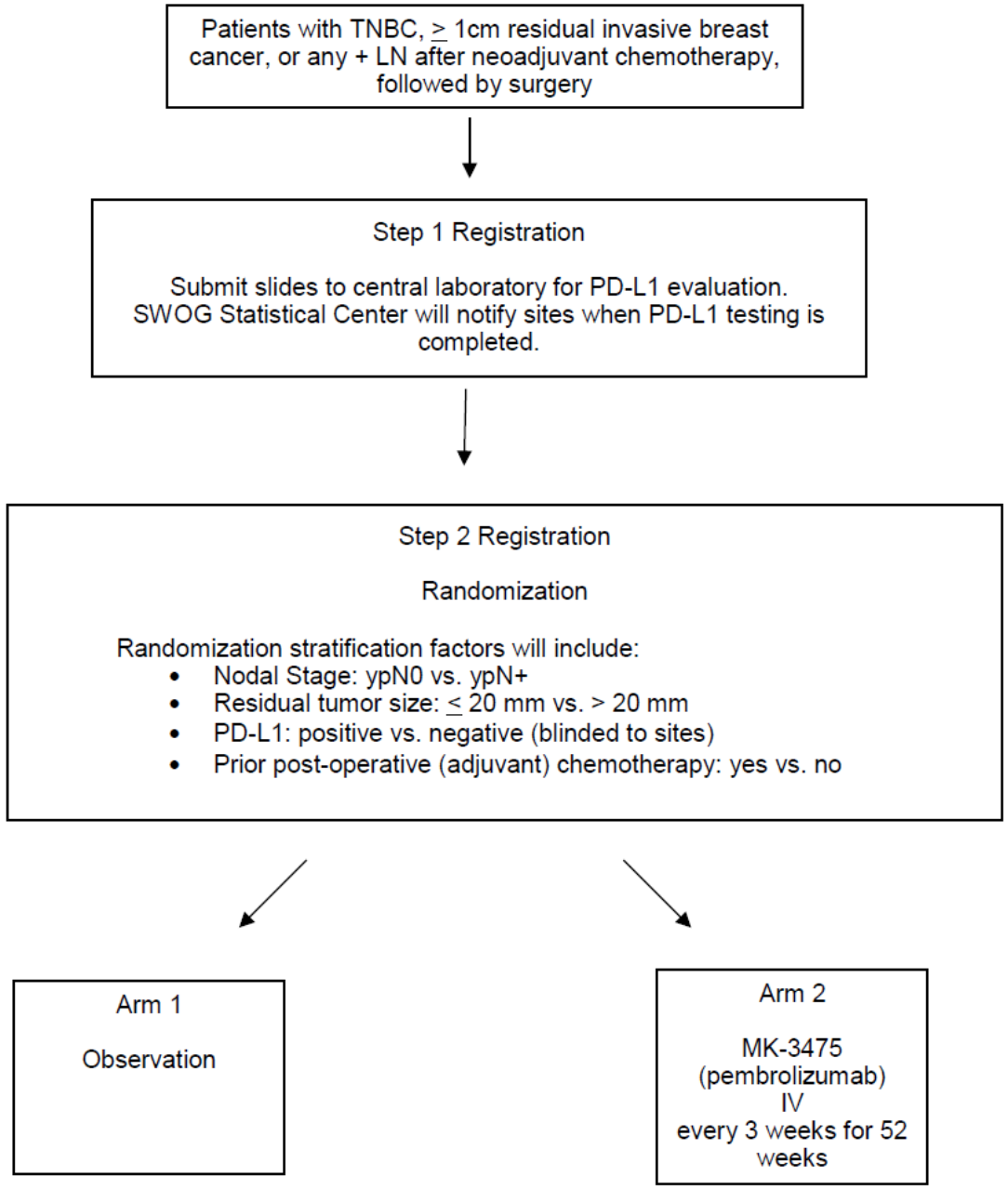
Cohort B (N = 52)[1]: Previously Untreated, PD-L1 Positive



1. Adams S et al. ASCO Annual Meeting, Jun 2-6, 2017, Chicago, IL; abstr 1088; presented Sunday, Jun 4, from 8:00-11:30 am on poster board #80.

S1418

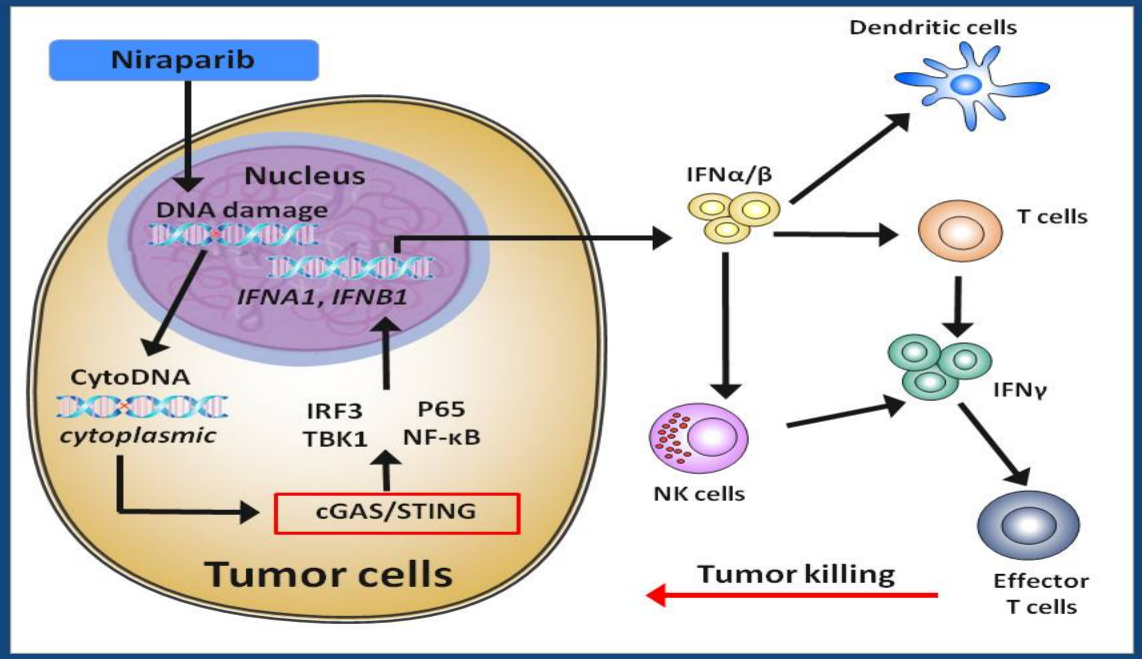
SCHEMA



Rationale for Niraparib (PARPi) + anti-PD-1 Combination

Preclinical studies demonstrated synergistic activity of PARPi + anti-PD-1, regardless of *BRCA* mutational status or PD-1 sensitivity

- Potential Mechanism of Action
  - Unrepaired DNA damage resulting from niraparib treatment leads to the abnormal presence of DNA in the cytoplasm, activating Stimulator of Interferon Genes (STING) pathway
  - Activation of the STING pathway leads to increased expression and release of type 1 interferons, subsequent induction of γ-interferon, and intratumoral infiltration of effector T-cells



1. Huang J et al. Biochem Biophys Res Commun. 2015 Aug 7;463(4):551-6; 2. Jiao SP et al. Clin Cancer Res. 2017 Jul 15;23(14):3711-3720; 3. Sato H et al. Nat Commun. 2017 Nov 24;8(1):1751

TOPACIO Phase 2 Design

Objective: Evaluate niraparib and anti-PD-1 combination therapy in metastatic TNBC patients

Phase 2

Recommended Phase 2 Dose
Niraparib 200 mg orally daily + Pembrolizumab 200 mg IV every 21 days (21 day cycle)

↓

Endpoint Assessment

Primary Endpoint	Objective Response Rate (ORR) by RECIST 1.1
Secondary Endpoints	Progression-free Survival (PFS) Duration of Response (DOR)

Statistical Plan

Hypothesis	Null: ORR ≤ 15%
Power to reject null with N=48 patients (alpha=10%, two-sided)	82% - assuming true ORR=30% 94% - assuming true ORR=35%

*ER and PR < 1% per ASCO/CAP guidelines
#Prior amendment allowed up to 3 prior lines of cytotoxic therapy for advanced disease
**Prior amendment had no restriction on platinum for inclusion or exclusion criteria

Key Inclusion Criteria

- TNBC (ER-negative, PR-negative, and HER-2 negative)*
- Disease recurrence or progression following neoadjuvant/adjuvant therapy
- ≤2 prior lines of cytotoxic treatment for advanced disease (not including neoadjuvant/adjuvant therapies or targeted small molecules)#
- Prior platinum allowed in metastatic setting if no progression documented while on or within 8 weeks of last platinum**

Key Exclusion Criteria

- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or PARP inhibitor

Response Assessments

- Scans every 9 weeks

Best Overall Response and Objective Response Rate (ORR)

Response	Response Rate, n (%) Efficacy Evaluable (N=46)*
Complete Response (CR)	3 (7%)
Partial Response (PR)**	10 (22%)
Stable Disease (SD)	10 (22%)
Progressive Disease (PD)	23 (50%)
ORR (CR+PR)	13 (28%)
DCR (CR+PR+SD)	23 (50%)

9 Patients still on treatment
- 2 CR
- 6 PR
- 1 SD

*9 pts did not have evaluable post-baseline tumor assessments and were not included in the evaluable population (6 pts discontinued due to AE; 1 due to clinical progression and 2 for other reasons).

**Responses include both confirmed and unconfirmed; DCR: Disease Control Rate; Data as of April 02, 2018

Biomarker Status for Efficacy Evaluable Patients (N=46)

Biomarker Status	n (%)
t*BRCA*mut	15 (33%)
HRRmut (excluding t*BRCA*mut)	5 (11%)
Both HRRwt and t*BRCA*wt	20 (43%)
PD-L1 Positive	25 (54%)
PD-L1 Negative	13 (28%)

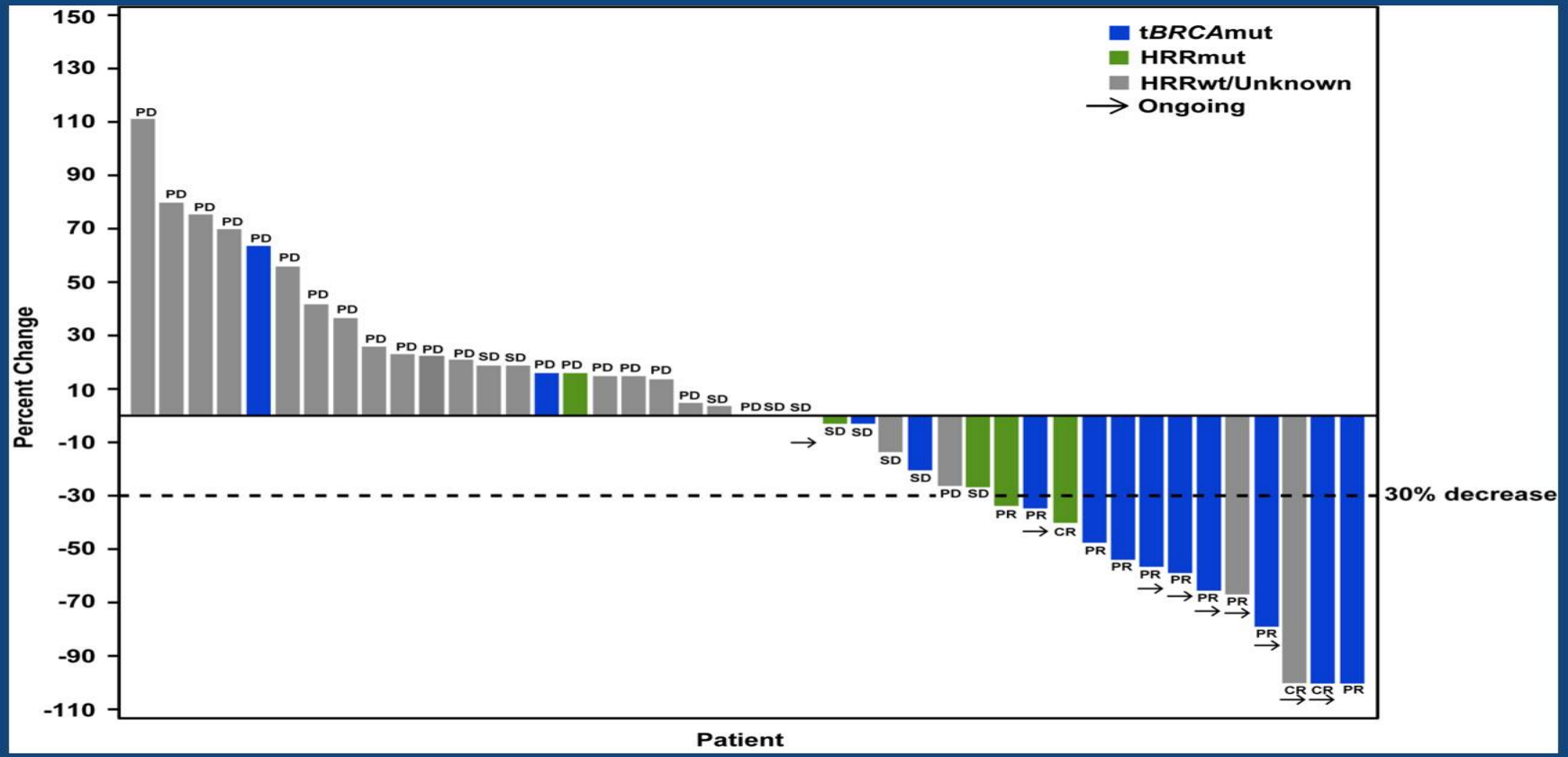
t*BRCA:* tumor *BRCA* (Myriad assay)
HRR: Mutational status of 16 Homologous Recombination Repair pathway genes excluding *BRCA*1/2 (Myriad assay)
PD-L1 positive: ≥1% combined proportionality score (Dako 22C3 Clinical Trial Assay)
Excludes patients whose biomarker status is unknown

Biomarker-Selected Populations

Efficacy Evaluable Patients	ORR (CR+PR)	DCR (CR+PR+SD)
t*BRCA*mut patients (n=15)	9 (60%)	12 (80%)
HRRmut + t*BRCA*mut (n=20)	11 (55%)	16 (80%)
PD-L1 positive patients (n=25)	9 (36%)	13 (52%)

- Overall Response Rate in all evaluable (biomarker-unselected) patients (N=46): ORR 28%, DCR=50%

Observed Best Responses



VOLUME 36 · NUMBER 9 · MARCH 20, 2018
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Enzalutamide for the Treatment of Androgen Receptor–Expressing Triple-Negative Breast Cancer

Tiffany A. Traina, Kathy Miller, Denise A. Yardley, Janice Eakle, Lee S. Schwartzberg, Joyce O'Shaughnessy, William Gradishar, Peter Schmid, Eric Winer, Catherine Kelly, Rita Nanda, Ayca Gucalp, Ahmad Awada, Laura Garcia-Estevez, Maureen E. Trudeau, Joyce Steinberg, Hirdesh Uppal, Iulia Cristina Tudor, Amy Peterson, and Javier Cortes

Table 2. Clinical Benefit

Benefit	Evaluable Subgroup (n = 78)	ITT Population (N = 118)
CBR16		
No.	26	29
% (95% CI)	33 (23 to 45)	25 (17 to 33)
CBR24		
No.	22	24
% (95% CI)	28 (19 to 39)	20 (14 to 29)
CR or PR		
No.	6	7
%	8	6

Abbreviations: CBR16, clinical benefit rate at 16 weeks; CBR24, clinical benefit rate at 24 weeks; CR, complete response; ITT, intent-to-treat; PR, partial response.

Table 2. Clinical Benefit

Published in: Tiffany A. Traina; Kathy Miller; Denise A. Yardley; Janice Eakle; Lee S. Schwartzberg; Joyce O'Shaughnessy; William Gradishar; Peter Schmid; Eric Winer; Catherine Kelly; Rita Nanda; Ayca Gucalp; Ahmad Awada; Laura Garcia-Estevez; Maureen E. Trudeau; Joyce Steinberg; Hirdesh Uppal; Iulia Cristina Tudor; Amy Peterson; Javier Cortes; *JCO* **2018,** 36, 884-890.
DOI: 10.1200/JCO.2016.71.3495

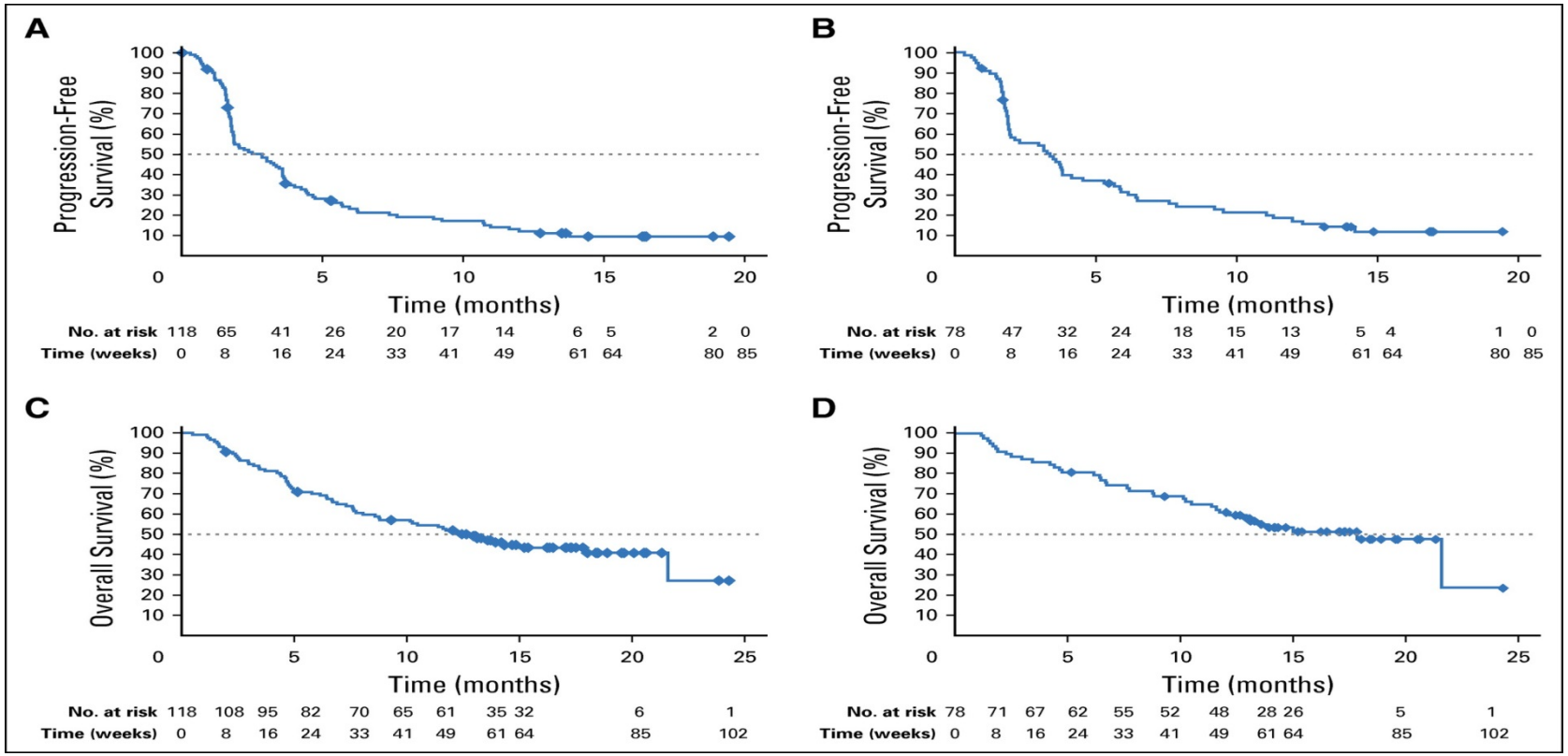


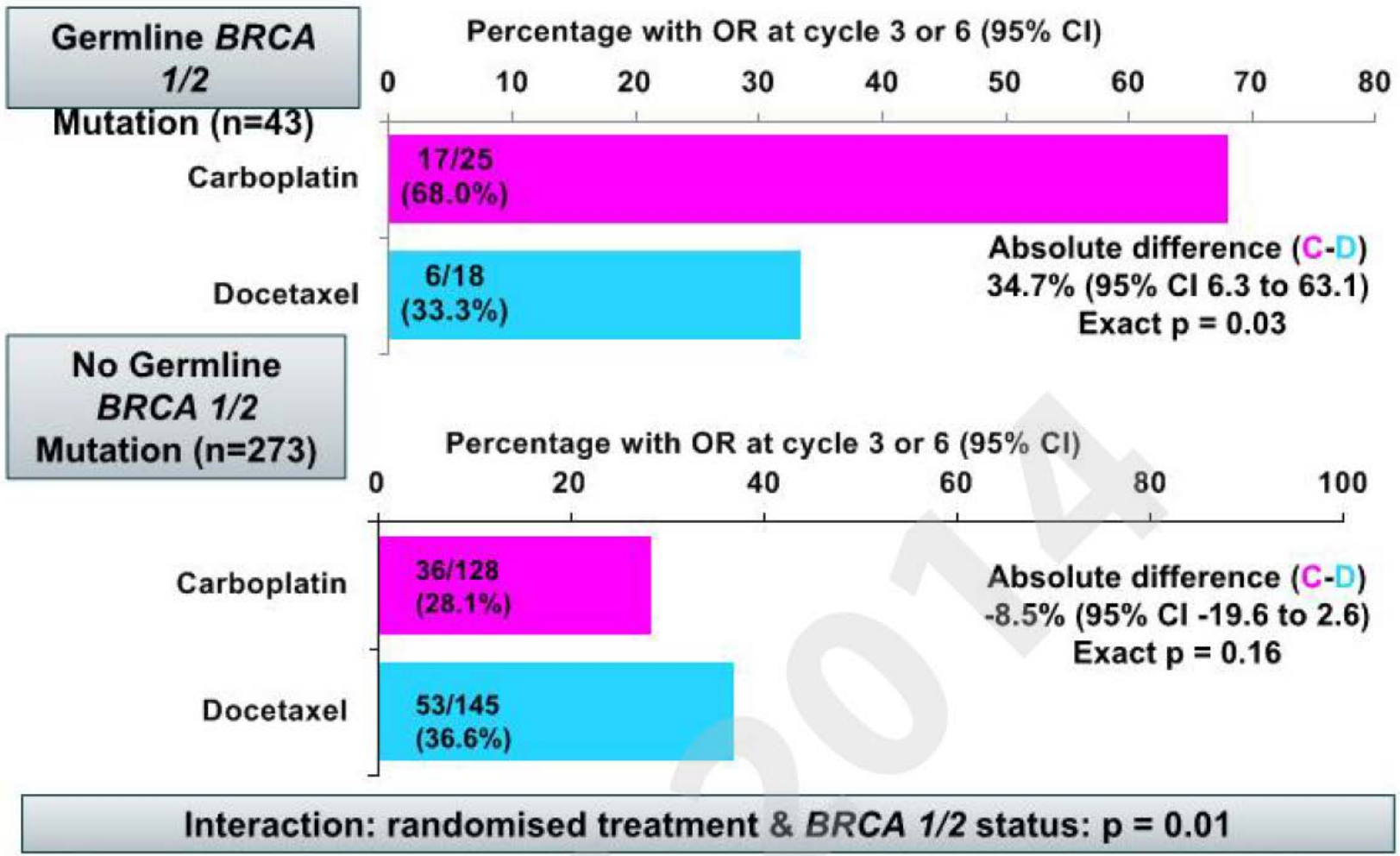
Fig 2. Kaplan-Meier plots of primary analysis of progression-free survival (PFS) in the (A) intent-to-treat (ITT) population and (B) evaluable subgroup and of overall survival (OS) in the (C) ITT population and (D) evaluable subgroup.

Published in: Tiffany A. Traina; Kathy Miller; Denise A. Yardley; Janice Eakle; Lee S. Schwartzberg; Joyce O'Shaughnessy; William Gradishar; Peter Schmid; Eric Winer; Catherine Kelly; Rita Nanda; Ayca Gucalp; Ahmad Awada; Laura Garcia-Estevez; Maureen E. Trudeau; Joyce Steinberg; Hirdesh Uppal; Iulia Cristina Tudor; Amy Peterson; Javier Cortes; *JCO* **2018,** 36, 884-890.
DOI: 10.1200/JCO.2016.71.3495

BRCA-mutated breast cancers

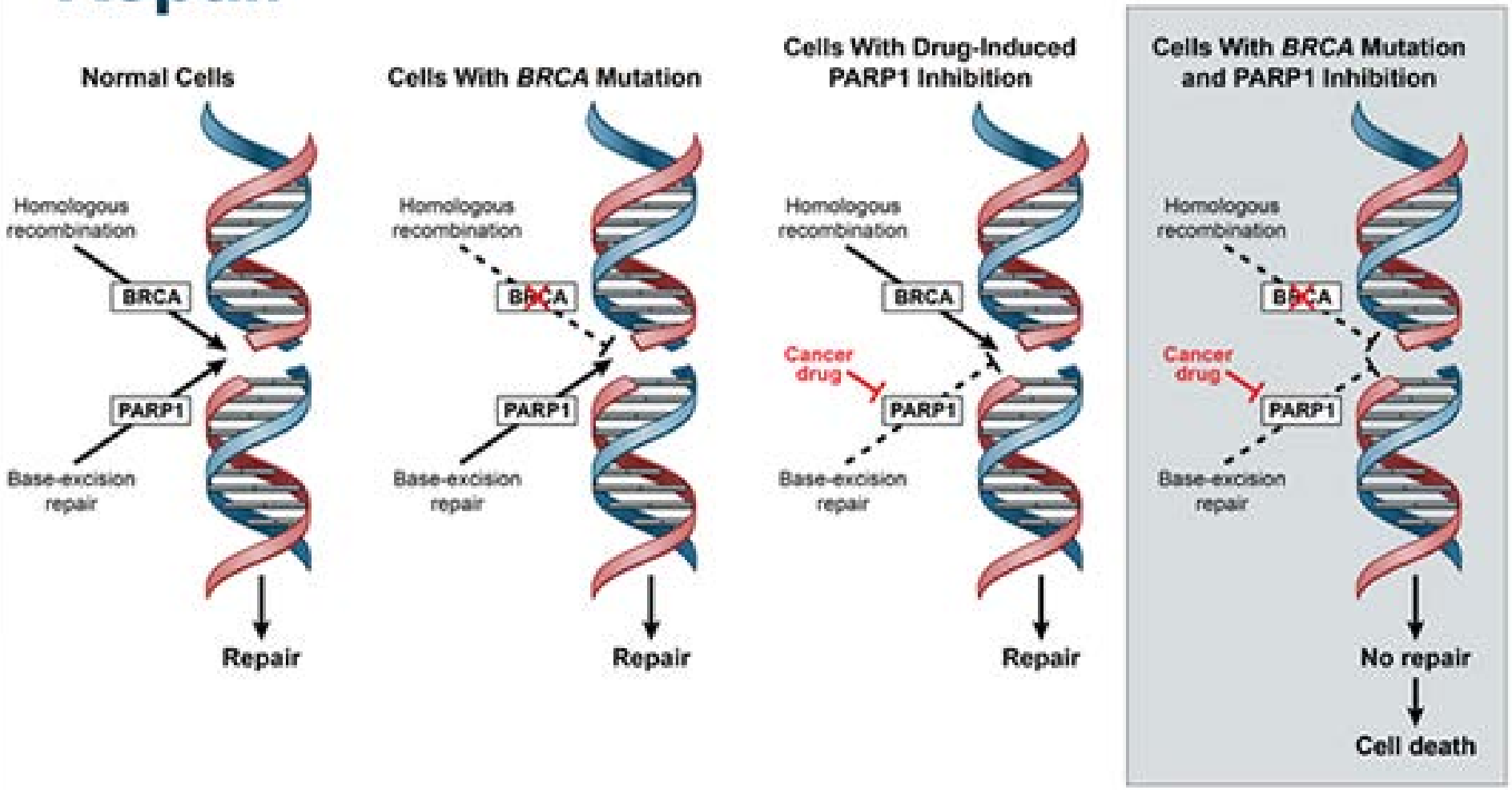
- Most g*BRCA*m carriers will develop TNBC, but most TNBC are not in g*BRCA*m carriers

Objective response – *BRCA 1/2* status



Interaction: randomised treatment & *BRCA 1/2* status: p = 0.01

DNA Repair: Role of Homologous Recombination and Base-Excision Repair



Iglehart JD, et al. *N Engl J Med*. 2009;361:189-191.[3]

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

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

Primary endpoint

- Progression-free survival by RECIST by central review

Key secondary efficacy endpoints

- Overall survival
- ORR by investigator
- Safety

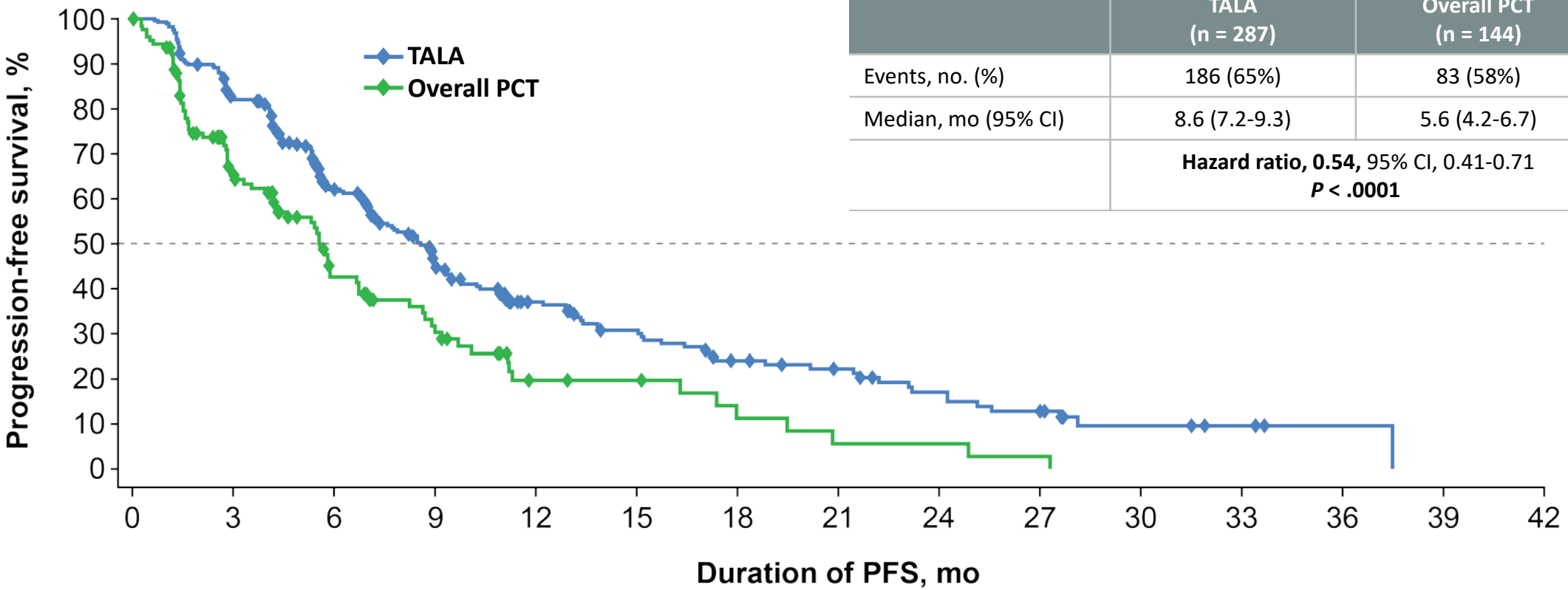
Exploratory endpoints

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

Litton et al. EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced germline BRCA-mutation breast cancer. Abs. GS6-07.

Primary Endpoint: PFS by 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)

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

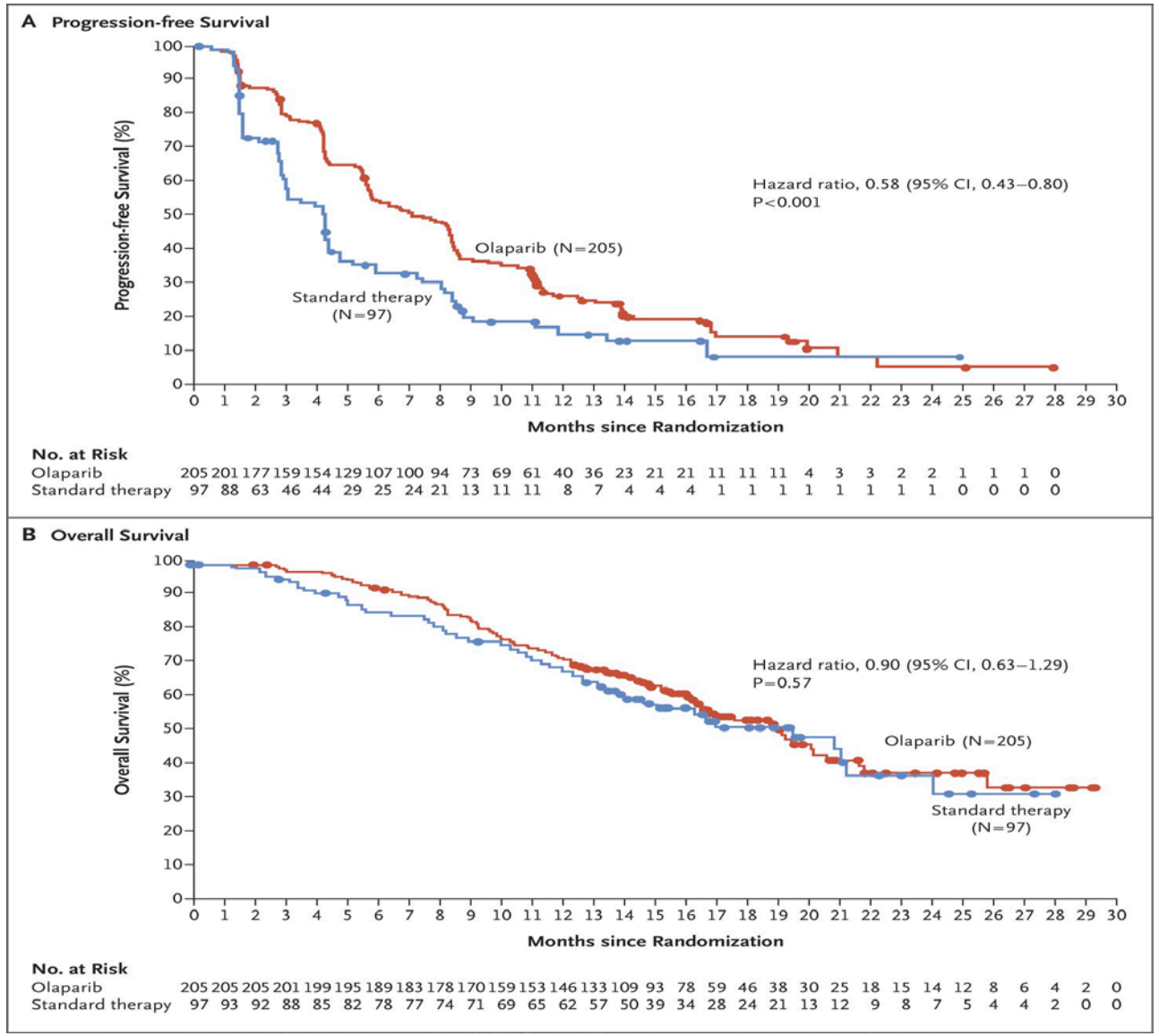
Treat until progression

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

Kaplan–Meier Estimates of Progression-free Survival and Overall Survival.



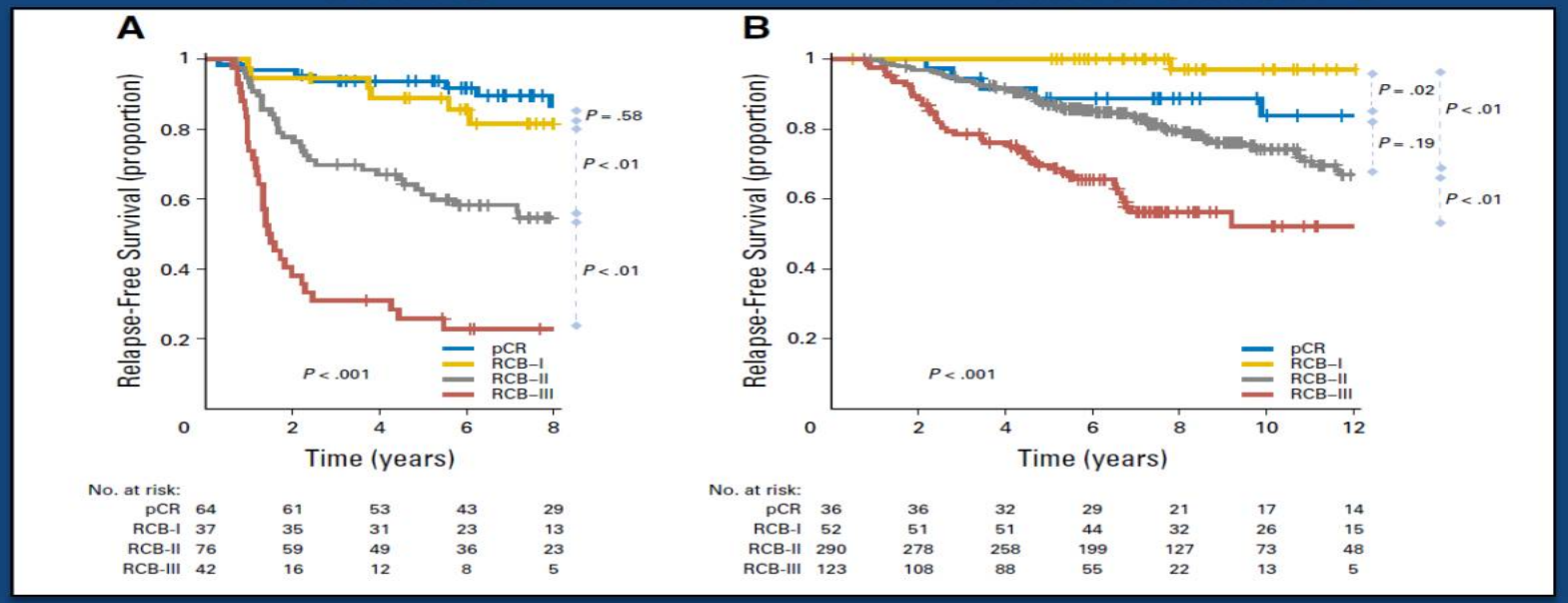
Robson M et al. N Engl J Med 2017;377:523-533

The NEW ENGLAND JOURNAL of MEDICINE

Background- Residual Cancer Burden (RCB)

TNBC

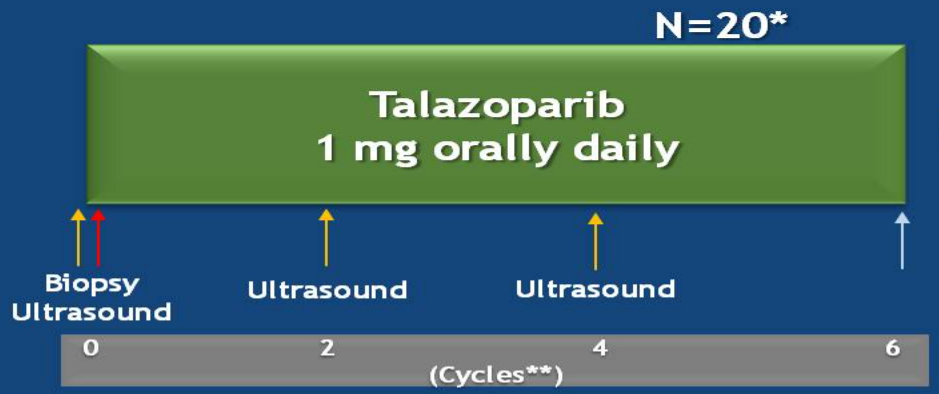
HR Positive



Excellent pathologic response (RCB-0 or -I) is associated with good prognosis in HR+ and TNBC.

Symmans WF J Clin Oncol 2017;35:1049-60

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

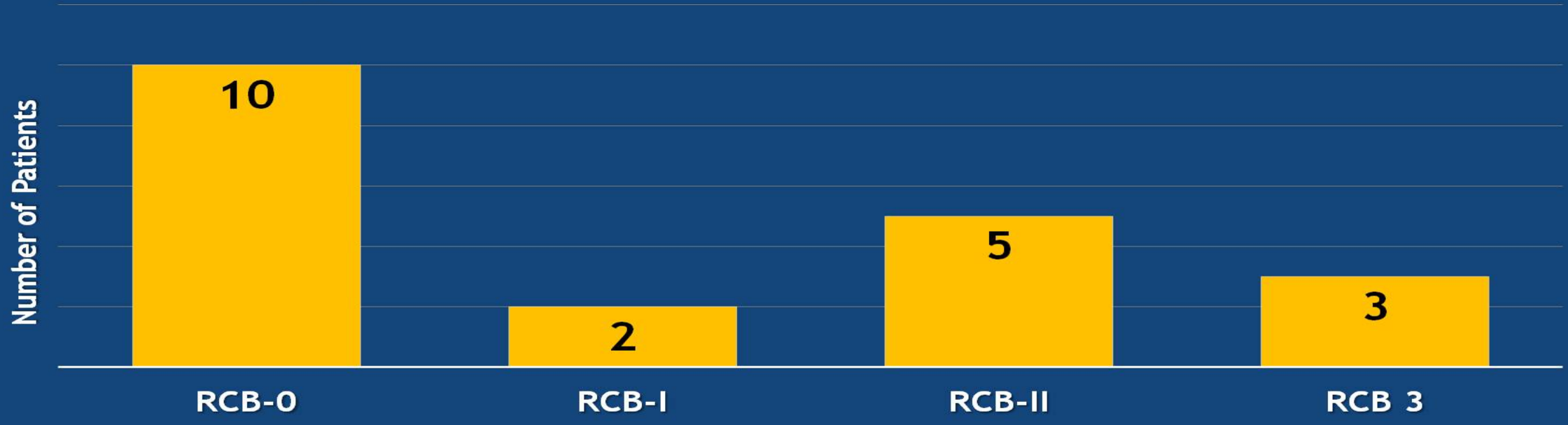
Primary Objectives

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

Secondary Objective

- Evaluate toxicity

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 Litton at 2018 ASCO Annual Meeting

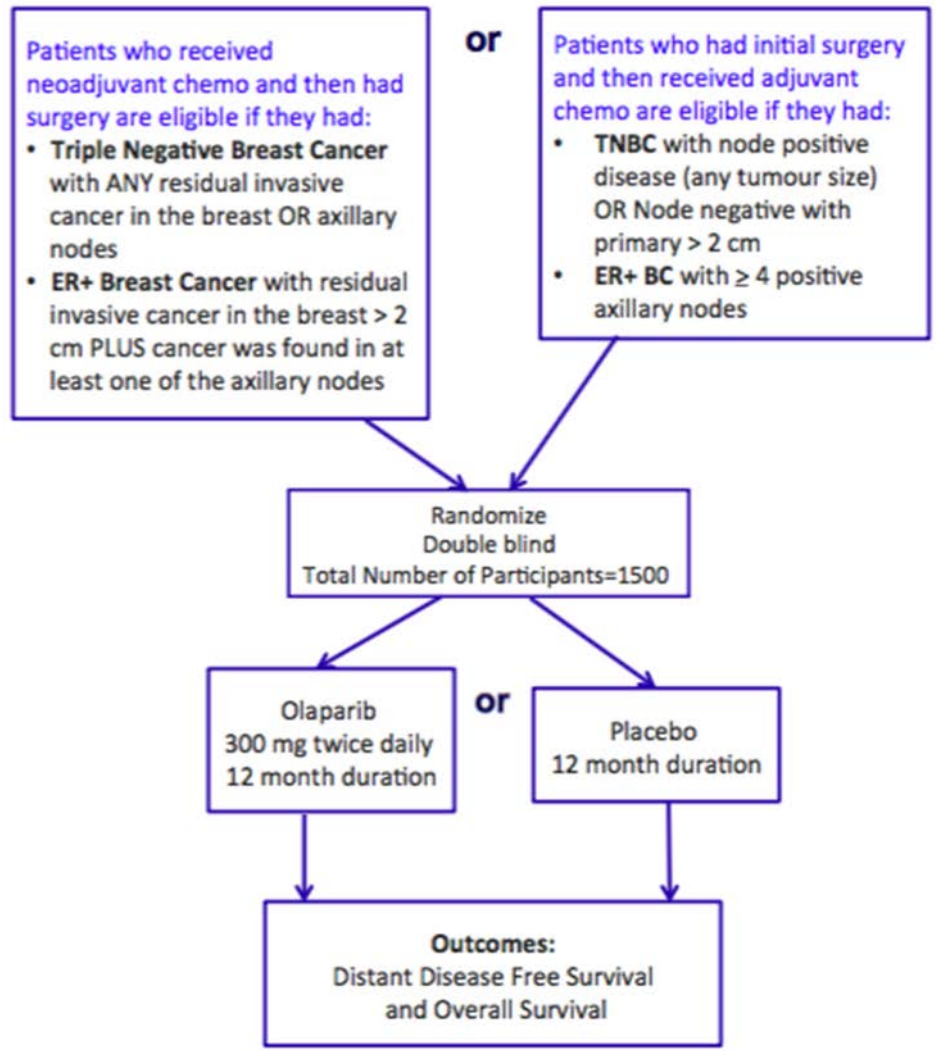
Pathologic Results- Number of Patients

Variable	RCB-0	RCB-I	RCB-II	RCB-III
BRCA1 (n=16)	8	1	5	2
BRCA2 (n=3)	2	1	0	0
TNBC (n=14)	7	1	4	2
HR+ (n=5)	3	1	1	0
Stage 1 (n=5)	4	0	1	0
Stage 2 (n=12)	5	2	4	1
Stage 3 (n=2)	1	0	0	1

Presented By Jennifer Litton at 2018 ASCO Annual Meeting

OlympiA Schema

Patients with stage II or III breast cancer who
- are HER2 negative
- have a *BRCA* mutation
- have received chemotherapy for treatment:



Conclusions

- Continued unmet need in heterogenous TNBC
- PARP inhibitors in *BRCA*-mutated cancers

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