Eighth Annual Wisconsin Review of San Antonio Breast Cancer Symposium

Triple-Negative Breast Cancer and others

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Disclosure Information

- **I have no financial relationships to disclose.**

Topics

- Triple Negative Breast Cancer
- Pregnancy in Breast Cancer
- Non-invasive Breast Cancer

Triple Negative Breast Cancer

- **GS5-01: Addition of platinum to sequential taxane-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: A phase III randomized controlled trial**
- **GS5-02: Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative early breast cancer and homologous recombination deficiency – long-term survival of the GeparOLA study**
- **GS5-03: Evaluation of anti-PD-1 Cemiplimab plus anti-LAG-3 REGN3767 in Combination with Paclitaxel in Early-Stage, High-Risk HER2-negative Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL**

San Antonio Breast Cancer Symposium®, December 6-10, 2022

Addition of platinum to sequential taxane-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: A phase III randomized controlled trial

Sudeep Gupta, M.D., D.M.; on behalf of

Nita S Nair, Rohini W Hawaldar, Vaibhav Vanmali, Vani Parmar, Seema Gulia, Jaya Ghosh, Shalaka Joshi, Rajiv Sarin, Tabassum Wadasadawala, Tejal Panhale, Sangeeta Desai, Tanuja Shet, Asawari Patil, Garvit Chitkara, Sushmita Rath, Jyoti Bajpai, Meenakshi Thakur, and Rajendra A Badwe.

Breast Cancer Working Group, Tata Memorial Centre, Mumbai

Funded by Tata Memorial Centre, Mumbai

TMC Neoadjuvant Platinum TNBC Study

- TNBC (1% cutoff for ER & PR)
- No evidence of M1
- Fit for anthracycline
- T1-T4, N0-3

R

Platinum
Pacli+Carbo → AC/EC

Control
Pacli → AC/EC

Surgery → Radiotherapy

Breast conserving surgery
OR
Mastectomy

Stratification

Menopausal Status
(Pre+Peri, Post)

Clinical Stage
OBC (cT_{1-3},N_{0-1}, M_0)
LABC (cT_4/N_{2-3}, M_0)

Platinum Arm:
Paclitaxel 100/m2 + Carboplatin (AUC-2) once per week X 8w*
followed by
[Doxorubicin (60/m2) or Epirubicin (90/m2)] + Cyclo (600/m2) every 2 weeks or 3 weeks X 4 cycles

Control Arm: Same as above, without carboplatin

Endpoint

- **Primary endpoint: Event-free survival**
- **Secondary endpoints: Overall survival**

  pCR rate

Patient & Tumor Characteristics

	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Age (years)			
Median (Range)	46 (26-69)	46 (25-67)	46 (25-69)
≤ 50 years	245 (68.8%)	255 (70.6%)	500 (69.7%)
> 50 years	111 (31.2%)	106 (29.4%)	217 (30.3%)
Menopausal Status			
Pre- or Peri-menopausal	209 (58.7%)	209 (57.9%)	418 (58.3%)
Post-menopausal	147 (41.3%)	152 (42.1%)	299 (41.7%)
Family History of Any Cancer			
Yes	72 (20.2%)	62 (17.2%)	134 (18.7%)
No	284 (79.8%)	299 (82.8%)	583 (81.3%)

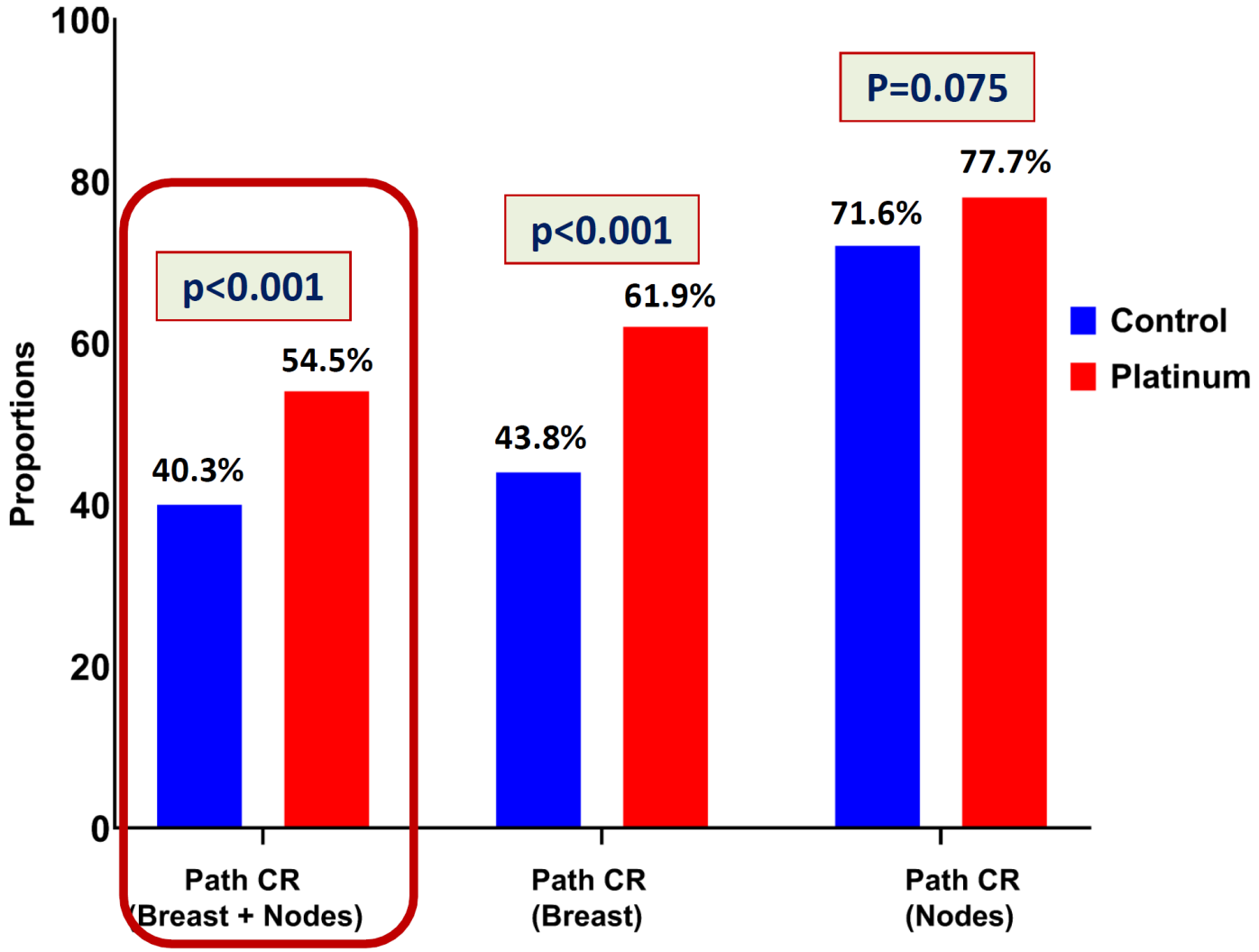
Patient & Tumor Characteristics

	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Clinical Stage (pre-NACT)			
Operable (cT1-3, N0-1)	142 (39.9%)	143 (39.6%)	285 (39.7%)
Locally Advanced (cT4 / N2-3)	214 (60.1%)	218 (60.4%)	432 (60.3%)
Clinical Node Status (pre-NACT)			
Negative	39 (11.0%)	41 (11.4%)	80 (11.2%)
Positive	317 (89.0%)	320 (88.6%)	637 (88.8%)
Clinical T-size (pre-NACT) (cm)			
Median (Range)	6.0 (1.2-20.0)	6.0 (1.5-20.0)	6.0 (1.2-20.0)
≤ 5 cm	79 (22.2%)	81 (22.4%)	160 (22.3%)
> 5 cm	277 (77.8%)	280 (77.6%)	557 (77.7%)

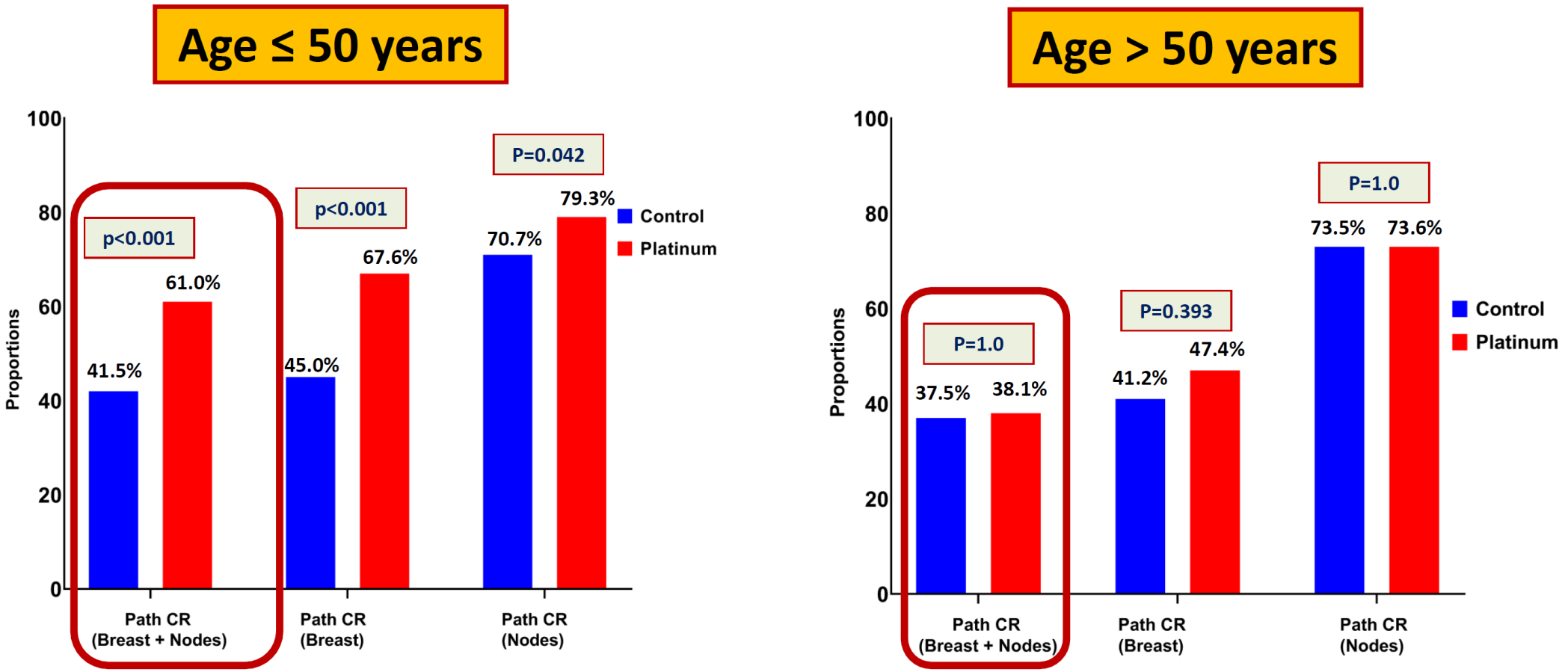
Patient & Tumor Characteristics

	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Receptor Status			
TNBC	356 (100%)	361 (100%)	717 (100%)
Other	0 (0%)	0 (0%)	0 (0%)
Pathological Subtype			
Invasive Duct Carcinoma	310 (87.1%)	331 (91.7%)	641 (89.4%)
Metaplastic	33 (9.3%)	22 (6.1%)	55 (7.7%)
Others	13 (3.7%)	8 (2.2%)	21 (2.9%)
Grade			
II	2 (0.6%)	3 (0.8%)	5 (0.7%)
III	354 (99.4%)	358 (99.2%)	712 (99.3%)

ITT: Pathological Response to NACT by Rx-Arm

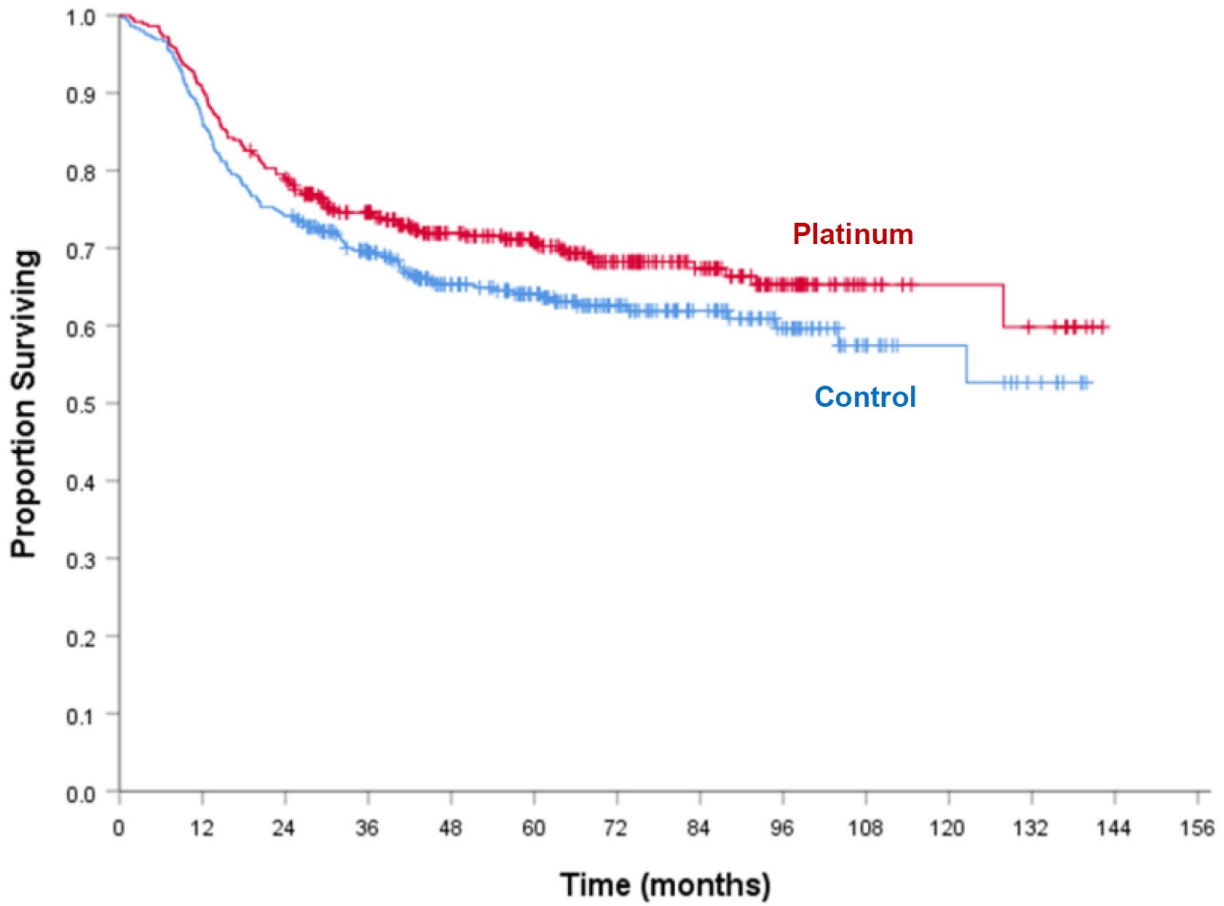


Pathological Response to NACT by Age & Rx-Arm



Multivariable (binary logistic) analysis for factors affecting pCR: Rx-Arm X Age interaction significant in a model including Rx-Arm, Age, cT size, cN status, Family History

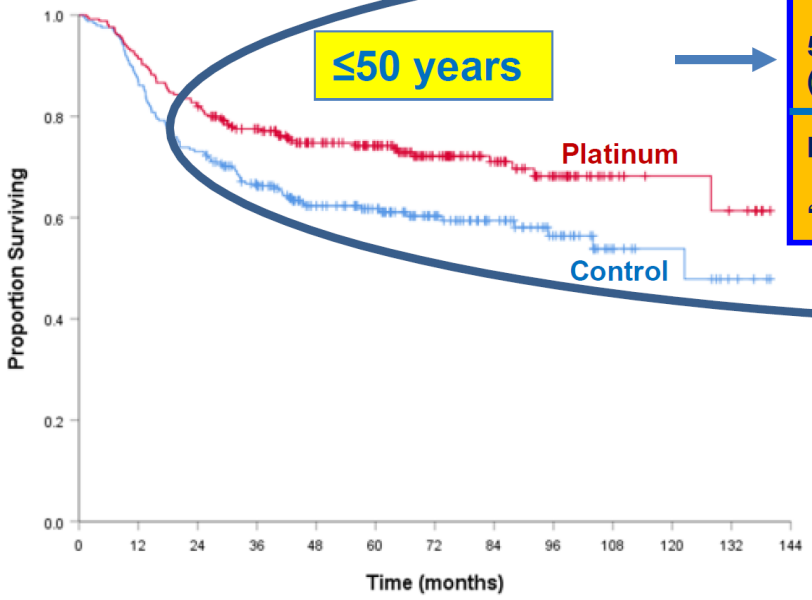
Event-free Survival in ITT (N=717)



Control	356	308	264	218	169	141	101	70	45	19	12	7
Platinum	361	326	284	239	190	159	112	79	47	17	12	10

Event-free Survival in Younger and Older Patients

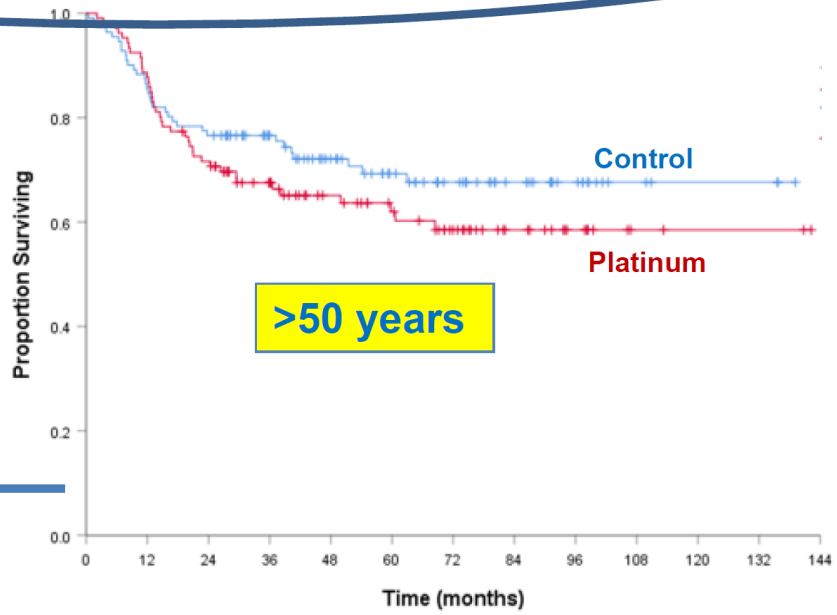
≤50 years



	Platinum	Control
5-year EFS (95% CI)	74.2% (68.71 - 79.69%)	61.7% (55.43 - 67.97%)
HR (95% CI)	0.642 (0.473 - 0.871)	
'p'	0.004	

Control	245	213	179	149	115	98	69	49	32	14	9	4
Platinum	255	233	209	180	145	122	85	62	37	14	10	8

>50 years

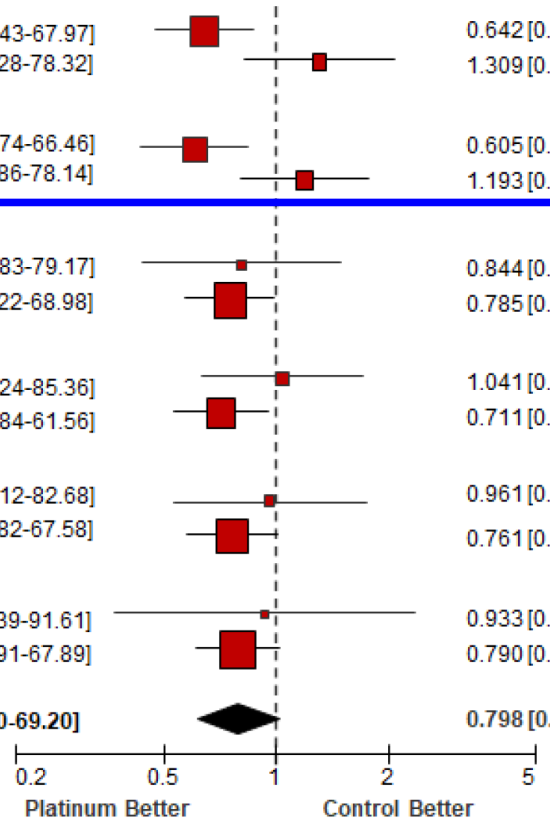


	Platinum	Control
5-year EFS (95% CI)	62.0% (52.2 - 71.8%)	69.3% (60.28 - 78.32%)
HR (95% CI)	1.309 (0.825-2.076)	
'p'	0.253	

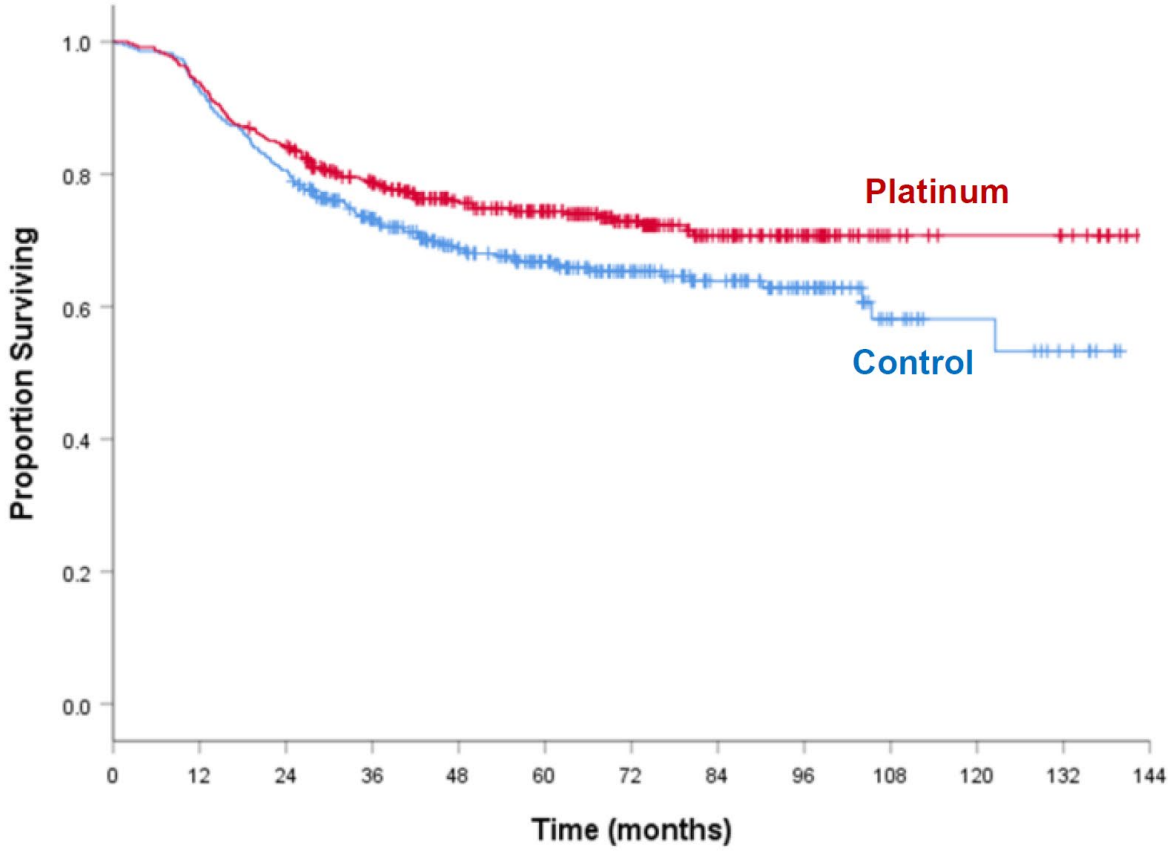
Control	111	95	85	69	54	43	32	21	13	5	3	3
Platinum	106	93	75	59	45	37	27	17	10	3	2	2

Event-free Survival: Subgroup Analysis

Subgroup	No. of patients with an event/total Platinum	Control	5-Yr Event-free Survival % [95% CI] Platinum	Control	Hazard Ratio [95% CI]	'P' value for Interaction
Age						
<=50 years	71/255	98/245	74.2 [68.71-79.69]	61.7 [55.43-67.97]	0.642 [0.473, 0.871]	0.010
>50 years	40/106	33/111	62.0 [52.20-71.80]	69.3 [60.28-78.32]	1.309 [0.825, 2.076]	
Menopausal Status						
Pre/peri-menopausal	58/209	87/209	75.0 [69.12-80.88]	59.6 [52.74-66.46]	0.605 [0.434, 0.843]	0.010
Post-menopausal	53/152	44/147	64.7 [56.66-72.74]	70.5 [62.86-78.14]	1.193 [0.800, 1.780]	
Family History of Cancer						
Yes	18/62	24/72	75.4 [64.62-86.18]	68.0 [56.83-79.17]	0.844 [0.457, 1.558]	0.836
No	93/299	107/284	69.7 [64.41-74.99]	63.1 [57.22-68.98]	0.785 [0.595, 1.037]	
Clinical Stage						
OBC (T1-3/N0-1)	32/143	31/142	78.6 [71.35-85.85]	78.3 [71.24-85.36]	1.041 [0.635, 1.706]	0.190
LABC (T4/N2-3)	79/218	100/214	65.4 [58.93-71.87]	54.7 [47.84-61.56]	0.711 [0.529, 0.955]	
Clinical T Size						
<=5 cm	21/81	22/79	78.3 [69.09-87.51]	71.9 [61.12-82.68]	0.961 [0.528, 1.749]	0.469
>5 cm	90/280	109/277	68.6 [63.11-74.09]	61.7 [55.82-67.58]	0.761 [0.575, 1.006]	
Clinical Node Status						
Negative	9/41	9/39	76.8 [63.47-90.13]	77.5 [63.39-91.61]	0.933 [0.370, 2.352]	0.744
Positive	102/320	122/317	70.0 [64.90-75.10]	62.4 [56.91-67.89]	0.790 [0.608, 1.028]	
All Patients	**111/361**	**131/356**	**70.7 [65.80-75.60]**	**64.1 [59.0-69.20]**	**0.798 [0.620, 1.028]**	



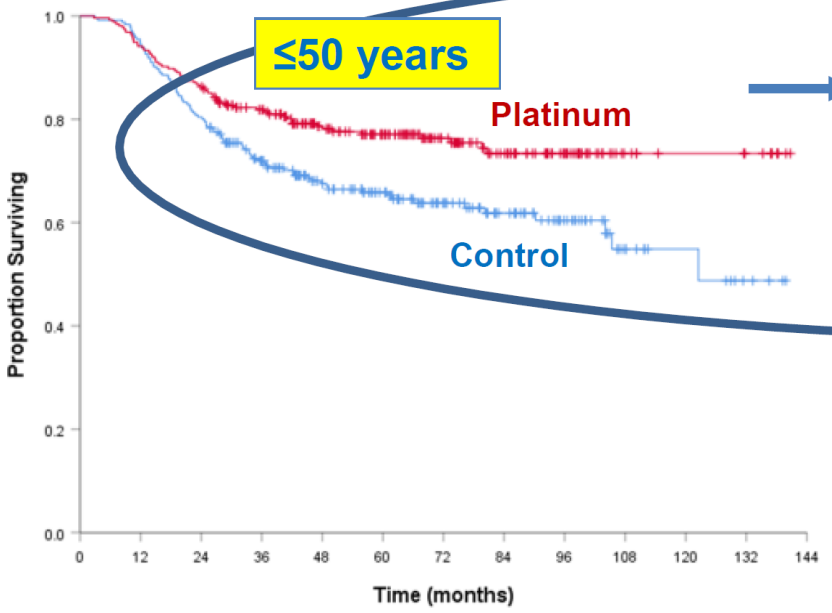
Overall Survival in ITT (N=717)



Control	356	330	287	229	179	147	106	74	48	20	12	7
Platinum	361	339	303	252	201	168	122	83	51	19	14	12

Overall Survival in Younger and Older Patients

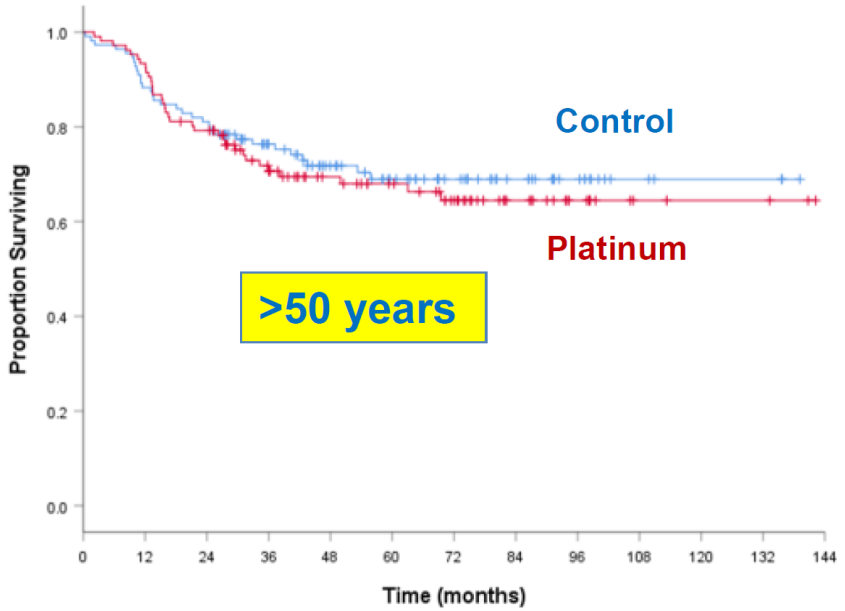
≤50 years



	Platinum	Control
5-year OS (95% CI)	77.1% (71.81 - 82.39%)	65.9% (59.82 - 71.98%)
HR (95% CI)	0.611 (0.440 - 0.848)	
'p'	0.003	

Control	245	232	197	160	125	104	74	53	35	15	9	4
Platinum	255	240	220	190	153	127	91	64	40	15	11	9

>50 years

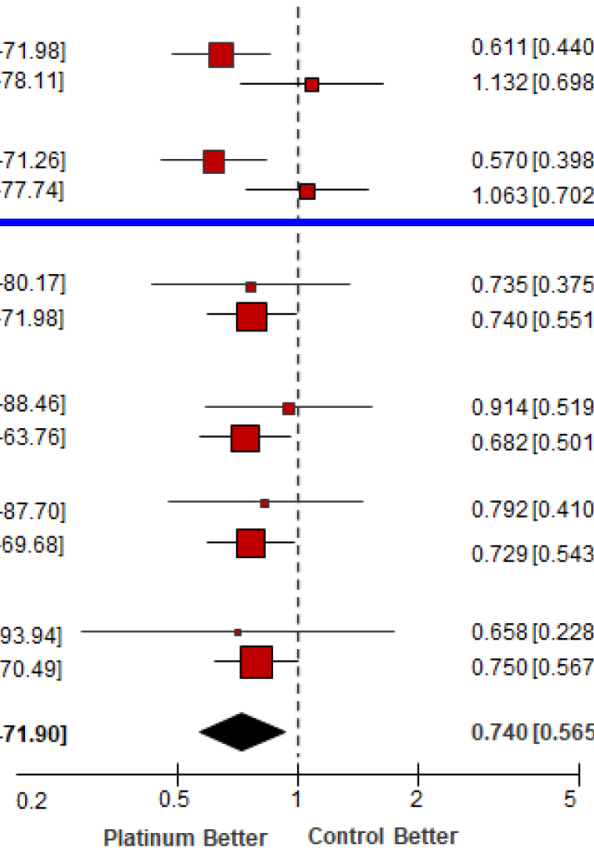


	Platinum	Control
5-year OS (95% CI)	68.0% (58.79 - 77.21%)	68.9% (59.69 - 78.11%)
HR (95% CI)	1.132 (0.698 - 1.835)	
'p'	0.615	

Control	111	98	90	69	54	43	32	21	13	5	3	3
Platinum	106	99	83	62	48	41	31	19	11	4	3	3

Overall Survival: Subgroup Analysis

Subgroup	No. of patients with an event/total Platinum	Control	5-Yr Event-free Survival % [95% CI] Platinum	Control	Hazard Ratio [95% CI]	'P' value for Interaction
Age						
<=50 years	60/255	89/245	77.1 [71.81-82.39]	65.9 [59.82-71.98]	0.611 [0.440, 0.848]	0.038
>50 years	34/106	32/111	68.0 [58.79-77.21]	68.9 [59.69-78.11]	1.132 [0.698, 1.835]	
Menopausal Status						
Pre/peri-menopausal	48/209	78/209	78.2 [72.52-83.88]	64.6 [57.94-71.26]	0.570 [0.398, 0.817]	0.027
Post-menopausal	46/152	43/147	69.0 [61.16-76.84]	69.9 [62.06-77.74]	1.063 [0.702, 1.612]	
Family History of Cancer						
Yes	14/62	22/72	77.0 [66.42-87.58]	68.8 [57.43-80.17]	0.735 [0.375, 1.438]	0.930
No	80/299	99/284	73.9 [68.80-79.0]	66.3 [60.62-71.98]	0.740 [0.551, 0.994]	
Clinical Stage						
OBC (T1-3/N0-1)	23/143	25/142	84.6 [78.33-90.87]	81.8 [75.14-88.46]	0.914 [0.519, 1.610]	0.354
LABC (T4/N2-3)	71/218	96/214	67.7 [61.23-74.17]	56.9 [50.04-63.76]	0.682 [0.501, 0.927]	
Clinical T Size						
<=5 cm	16/81	20/79	81.2 [72.18-90.22]	77.9 [68.10-87.70]	0.792 [0.410, 1.528]	0.823
>5 cm	78/280	101/277	72.5 [67.21-77.79]	63.8 [57.92-69.68]	0.729 [0.543, 0.980]	
Clinical Node Status						
Negative	6/41	8/39	86.5 [75.33-97.67]	81.4 [68.86-93.94]	0.658 [0.228, 1.897]	0.829
Positive	88/320	113/317	72.9 [67.80-78.00]	65.0 [59.51-70.49]	0.750 [0.567, 0.991]	
All Patients	94/361	121/356	**74.4 [69.70-79.10]**	**66.8 [61.70-71.90]**	0.740 [0.565, 0.969]	



Toxicity

Toxicity	Platinum (N=361)	Control (N=356)		Platinum (N=361)	Control (N=356)
	Any Grade			Grade III or Worse	
Neutropenia	56 (15.5%)	18 (5.1%)		31 (8.6%)	7 (2.0%)
Anemia	23 (6.4%)	9 (2.5%)		7 (1.9%)	1 (0.3%)
Thrombocytopenia	21 (5.8%)	4 (1.1%)		7 (1.9%)	0 (0%)
Neutropenic Fever	-	-		16 (4.4%)	10 (2.8%)
Nausea	24 (6.6%)	26 (7.3%)		0 (0%)	1 (0.3%)
Vomiting	37 (10.2%)	34 (9.6%)		1 (0.3%)	1 (0.3%)
Diarrhea	22 (6.1%)	16 (4.5%)		4 (1.1%)	3 (0.8%)
Mucositis	21 (5.8%)	21 (5.9%)		1 (0.3%)	3 (0.8%)
Peripheral Neuropathy	65 (18.0%)	65 (18.3%)		3 (0.8%)	3 (0.8%)
Skin	10 (2.8%)	15 (4.2%)		3 (0.8%)	3 (0.8%)
Cardiac	3 (0.8%)	0 (0%)		0 (0%)	0 (0%)
Hepatic	1 (0.3%)	2 (0.6%)		0 (0%)	0 (0%)
Renal	0 (0%)	0 (0%)		0 (0%)	0 (0%)
Any SAE	53 (14.7%)	46 (12.9%)			

CONCLUSIONS

- **Addition of carboplatin to taxane-anthracycline neoadjuvant chemotherapy should be the standard treatment in patients with TNBC who are ≤50 years or who are pre-menopausal.**

Comments

- The total dose of Paclitaxel was lower (800 mg/m2 vs 960 mg/m2)
- Similar outcomes to other studies

Platinum arm	GeparSixto	BrighTNess	CALGB 40603	Current study
pCR	53.2%	58%	54%	54.5%
EFS	86.1% (3-yr)	79% (4-yr)	70.1% (5-yr)	70.7% (5-yr)

- No immunotherapy
- No Capecitabine after surgery

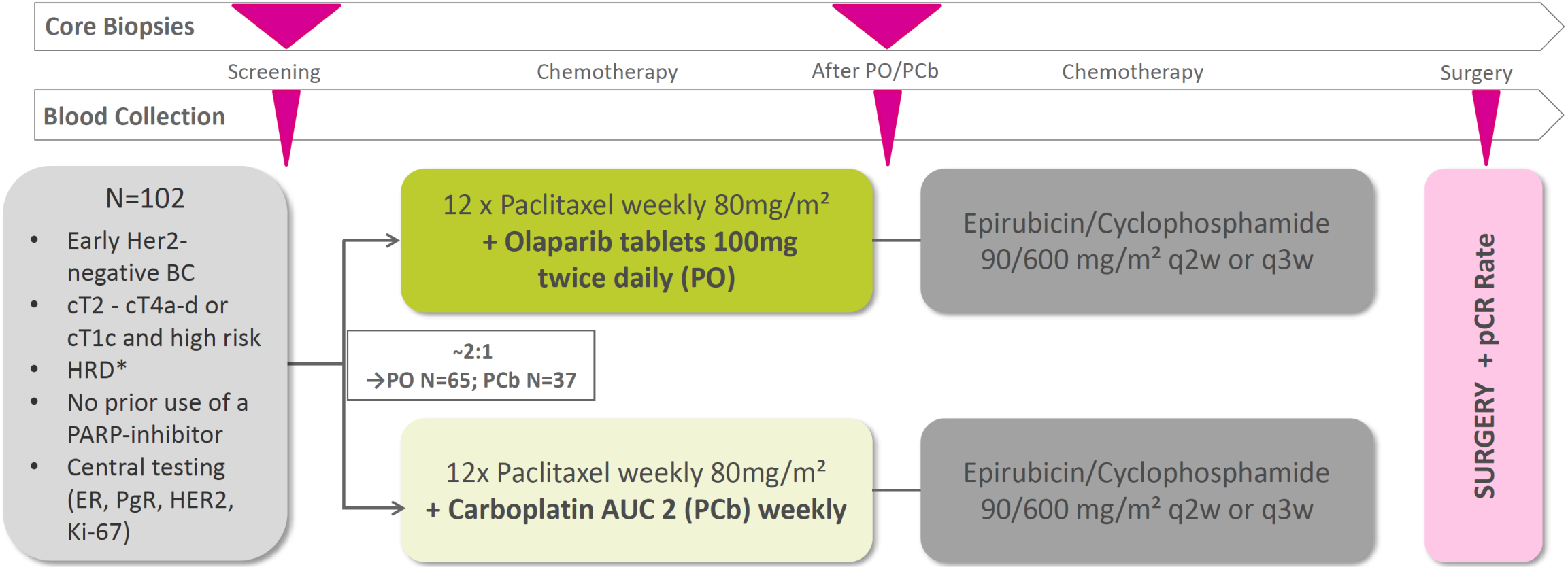
GeparOLA - GBG 90

Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative early breast cancer and homologous recombination deficiency – long-term survival of the GeparOLA study

Peter A. Fasching, Sabine Schmatloch, Jan Hauke, Julia Rey, Christian Jackisch, Peter Klare, Theresa Link, Claus Hanusch, Jens Huober, Andrea Stefek, Sabine Seiler, Christoph Uleer, Wolfgang D. Schmitt, Gabriele Doering, Kerstin Rhiem, Andreas Schneeweiss, Carsten Denkert, Rita K. Schmutzler, Eric Hahnen, Michael Untch, Valentina Nekljudova, Jens-Uwe Blohmer, Sibylle Loibl

-This is a joint study by GBG and AGO-B-

GeparOla Study Design



Stratification Factors:

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

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

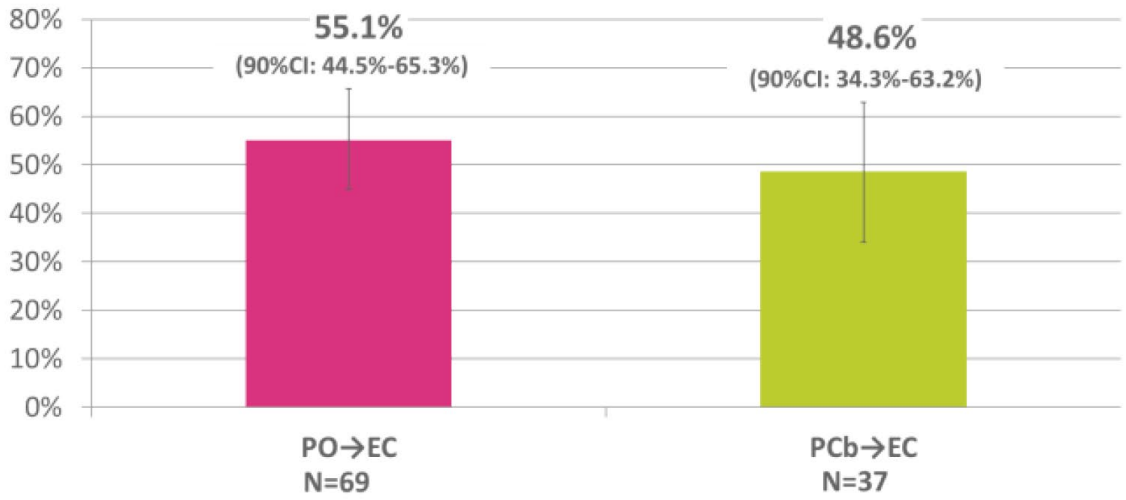
Fasching et *al*. Ann Oncol. 2020
[1]Timms et al. Breast Cancer Res 2014

Previously Reported Results of Primary Outcome

Primary efficacy endpoint:

- to assess the pathological complete response rate of breast and lymph nodes (ypT0/is ypN0) of neoadjuvant treatment of olaparib and paclitaxel followed by epirubicin and cyclophosphamide (PO→EC) in patients with early BC and HR deficient tumors (defined as either t*BRCA1/2* mutation and/or HRD score high and/or known g*BRCA* mutation).

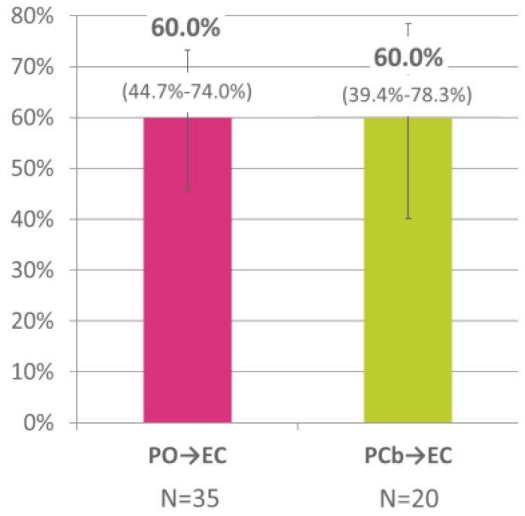
Primary Endpoint – pCR (ypT0/is ypN0) rates in the two treatment arms:

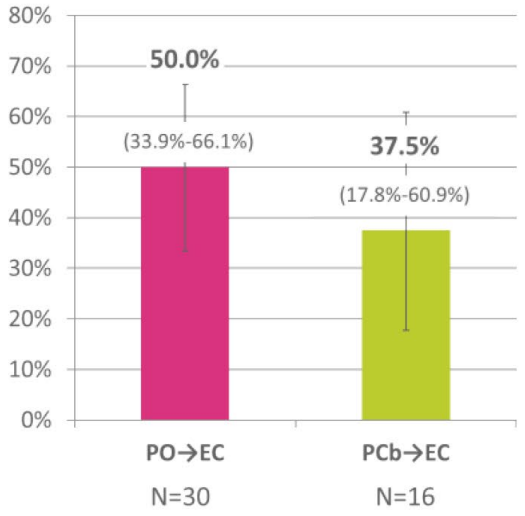


Fasching et *al*. Ann Oncol. 2020

Previous Results of pCR Rates in Subgroups

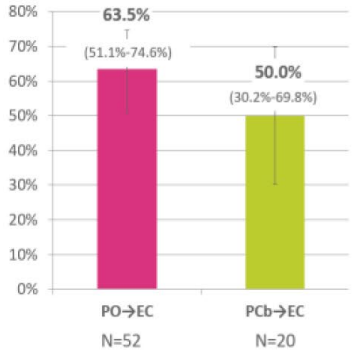
g/tBRCA mutated (N=55)



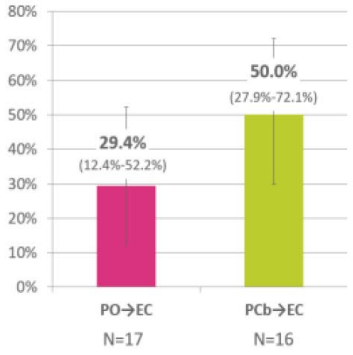


g/tBRCA wildtype (N=46)

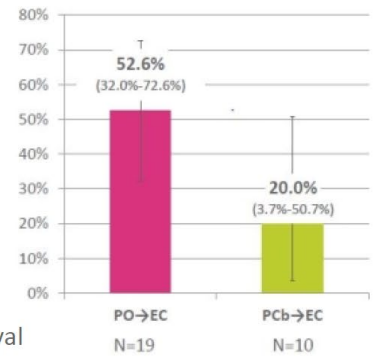
cN0 (N=72)



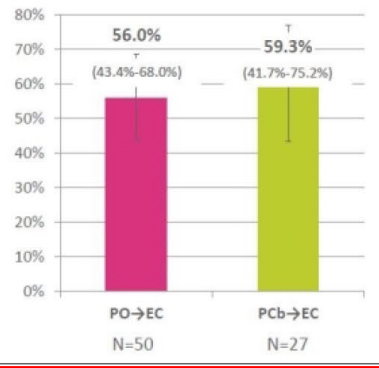
cN+ (N=33)



HR-positive (N=29)



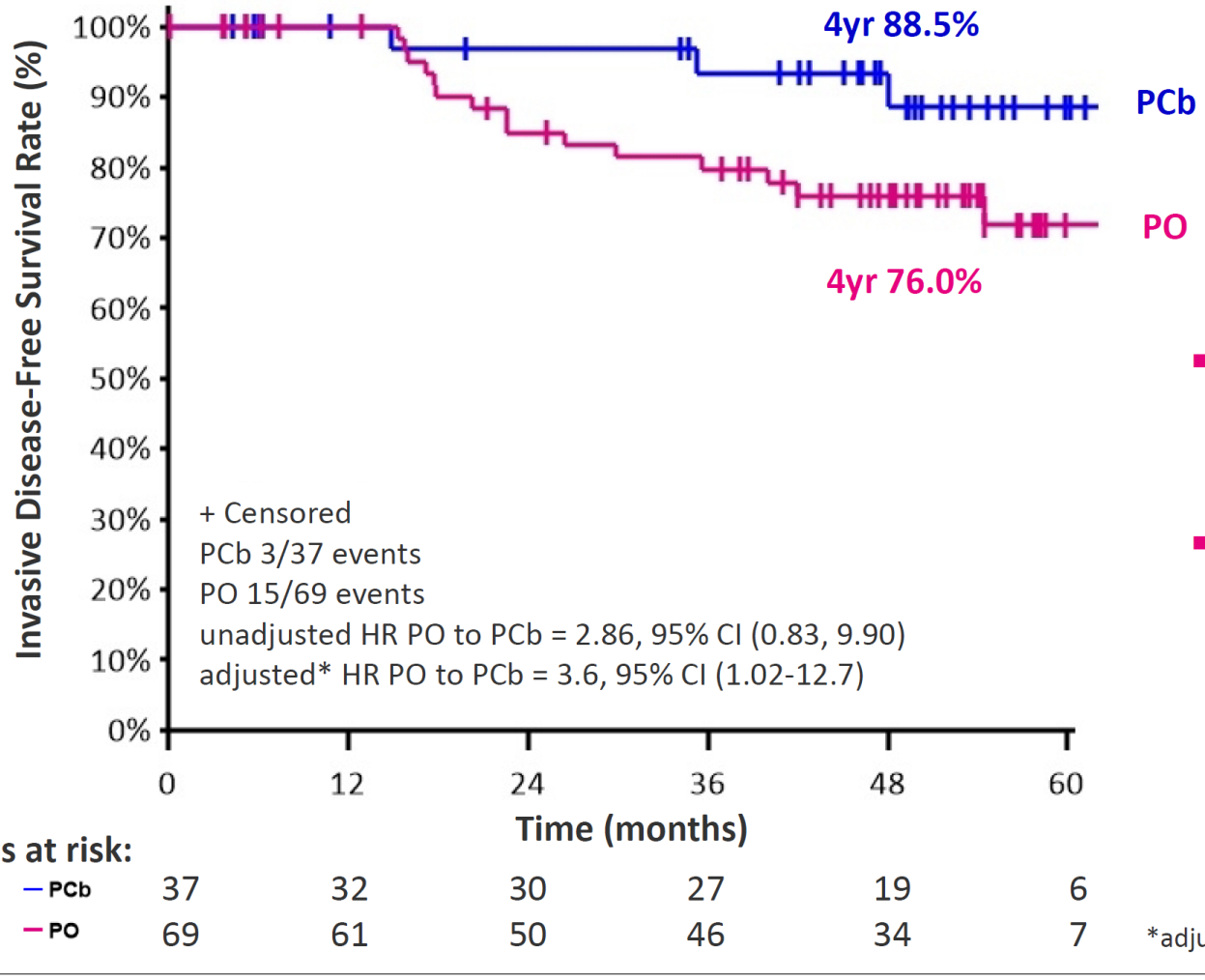
HR-negative (N=77)



90% confidence interval

Fasching et *al*. Ann Oncol. 2020

Results: iDFS in the Overall Study Population

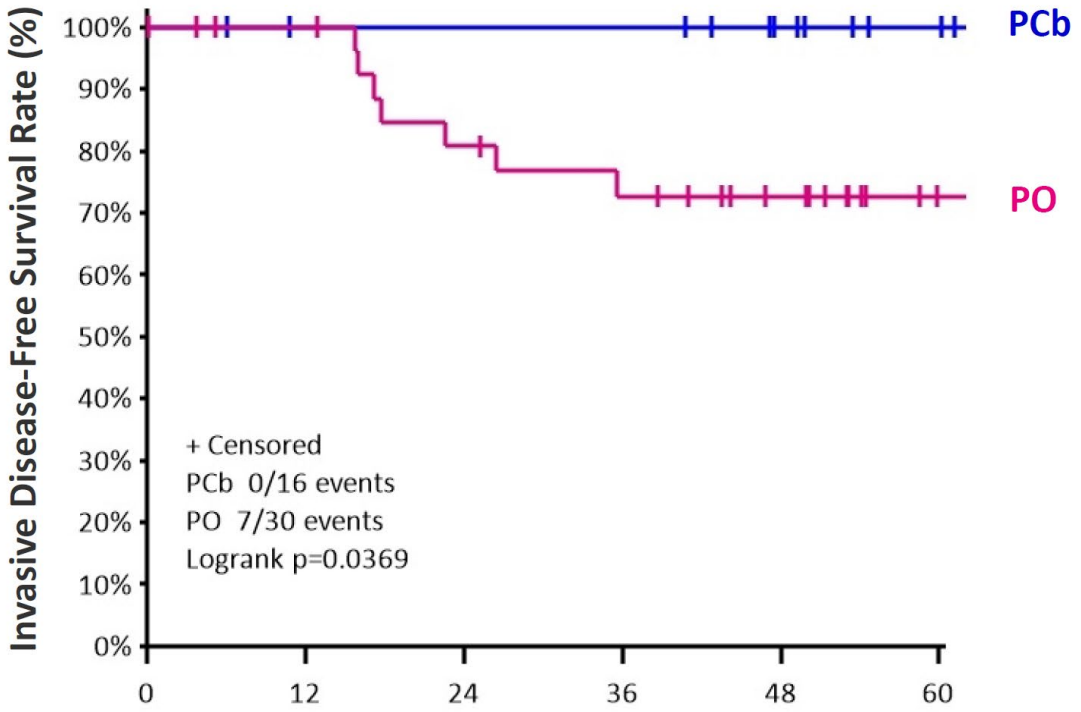


- Median follow-up of 49.8 (range 0.1 – 69.1) months
- 4-year loco-regional recurrence rate after PO treatment was higher (10.3%) compared to PCb treatment (4.9%)

*adjusted for nodal status and gen mutation status

Results: iDFS Stratified by *BRCA*1/2-Mutation Status

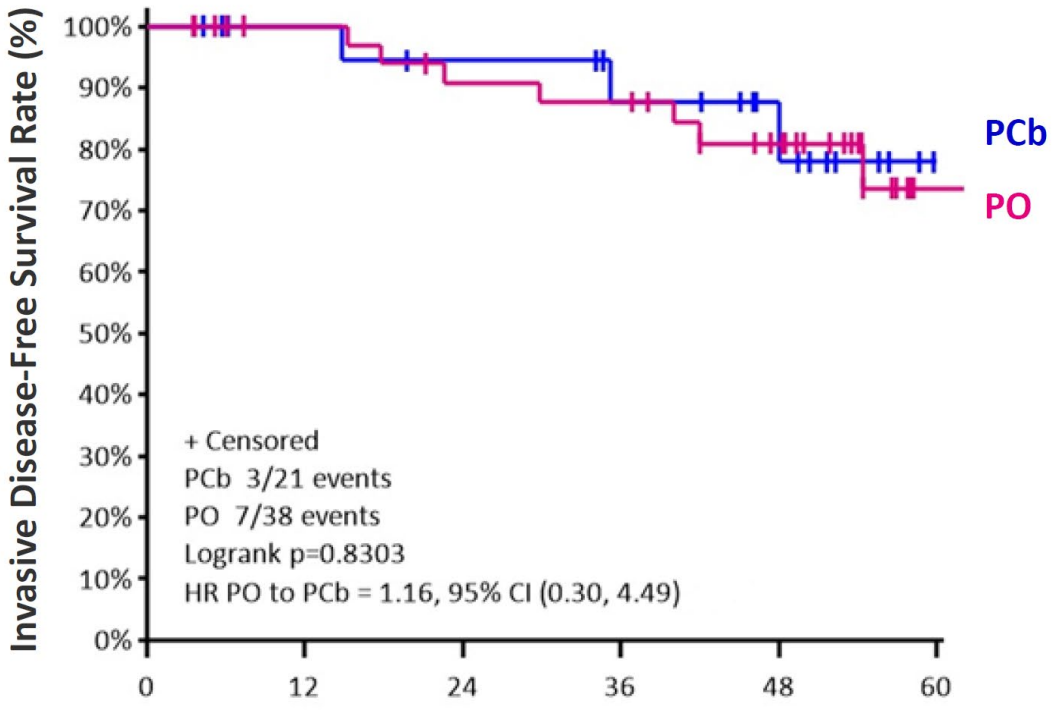
with g/t*BRCA* wildtype (HRD score high)



Patients at risk:

PCb	16	14	14	14	10	6
PO	30	27	21	18	13	4

with g/*tBRCA* mutation

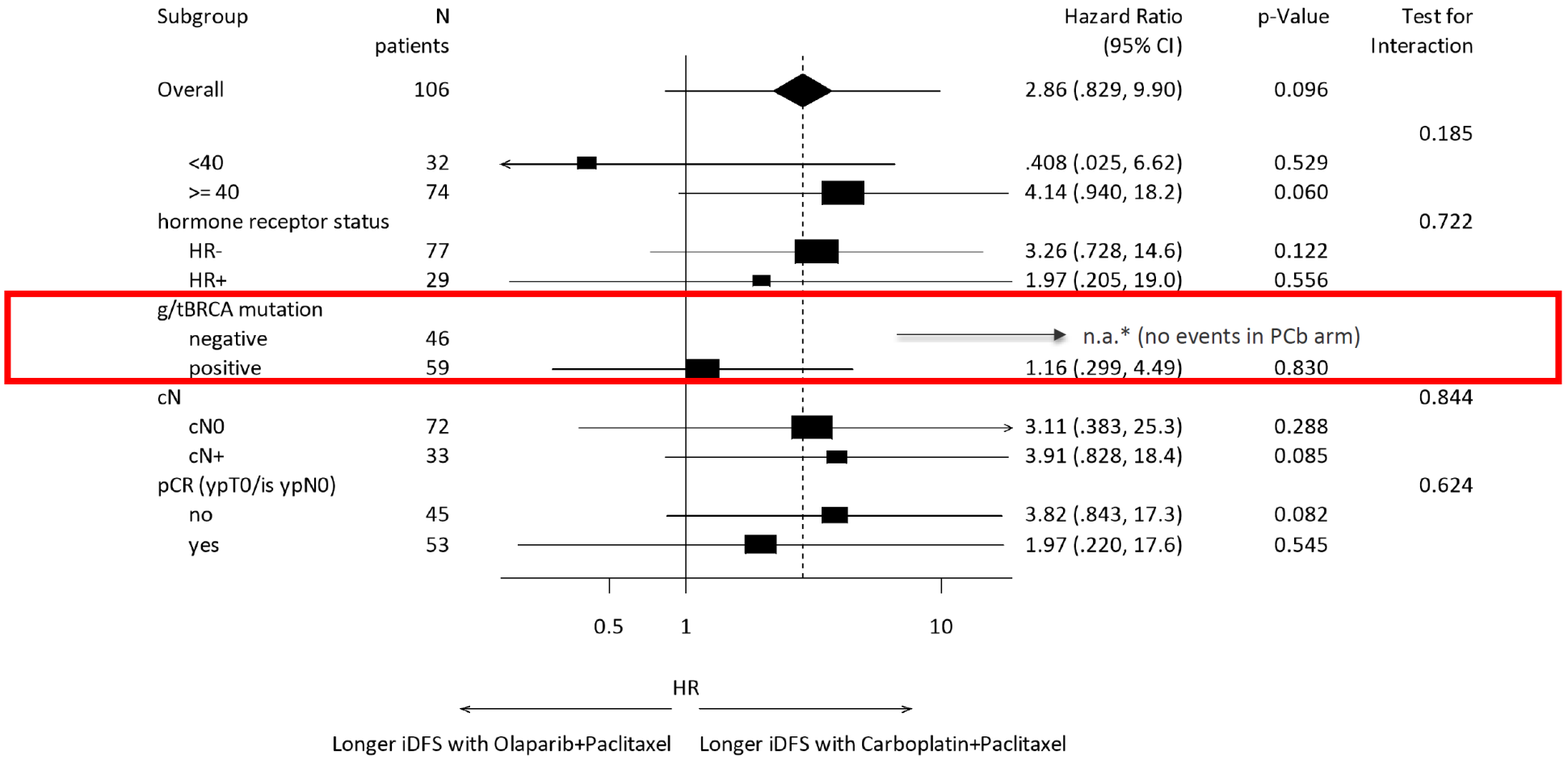


Patients at risk:

PCb	21	18	16	13	9	0
PO	38	33	29	28	21	3

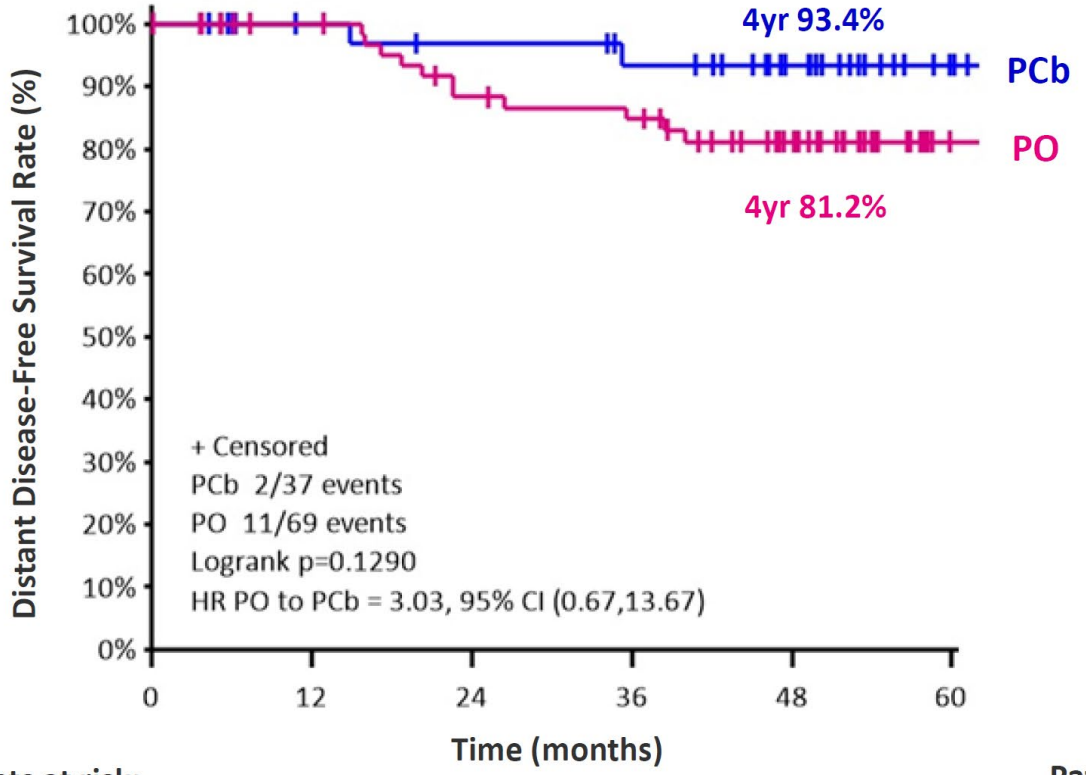
Results: iDFS in Subgroups with *BRCA*1/2-Mutation Status

(Univariate Cox Regression Model)



Results: DDFS and OS in the Overall Study Population

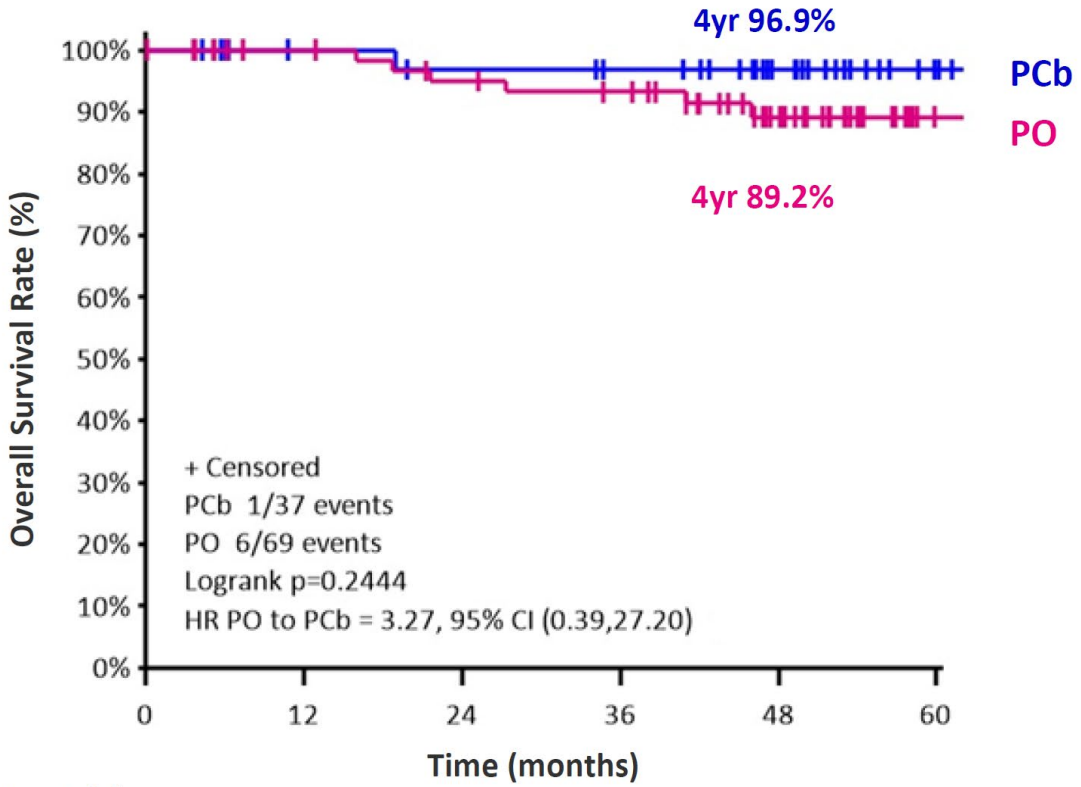
DDFS



Patients at risk:

PCb	37	32	30	27	19	6
PO	69	61	52	49	36	7

OS

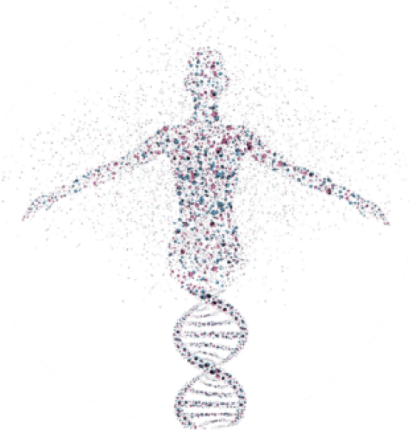


Patients at risk:

PCb	37	32	30	28	19	6
PO	69	61	56	53	37	7

Comments

- **In mutated BRCA, Olaparib had the same pCR and survival benefit as Carboplatin**
- **In wild type BRCA but high HRD, Olaparib had increased pCR than Carboplatin but did not translate into survival benefit**

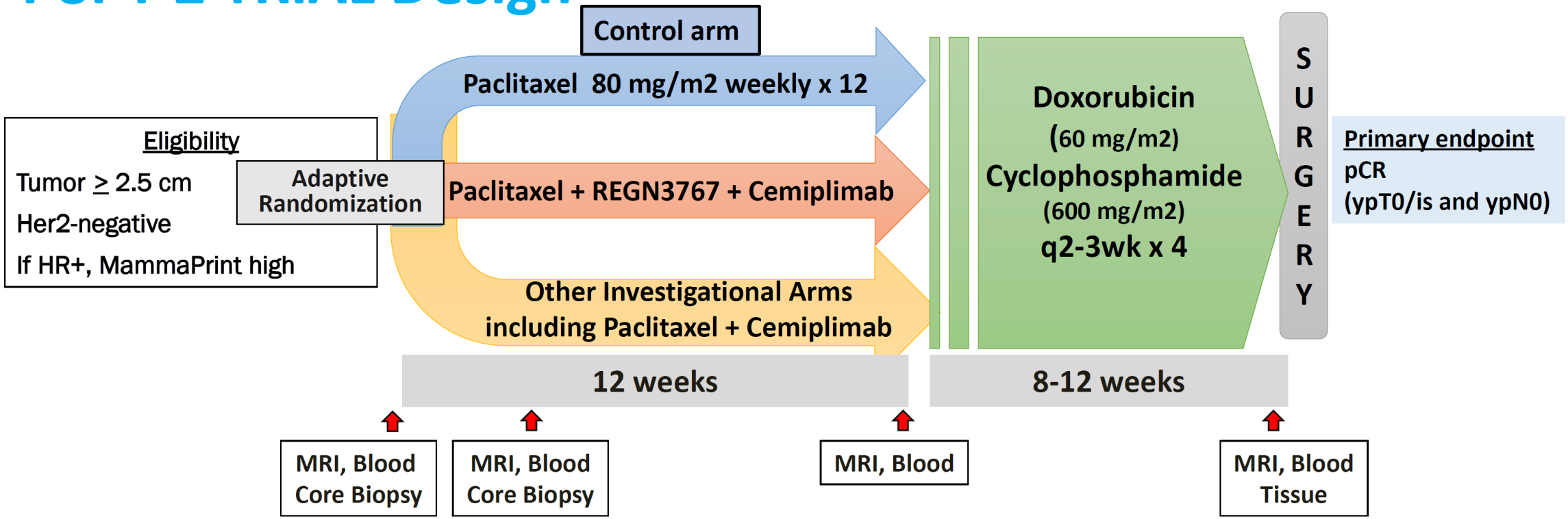


Evaluation of anti-PD-1 Cemiplimab plus anti-LAG-3 REGN3767 in Combination with Paclitaxel in Early-Stage, High-Risk HER2-negative Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

Claudine Isaacs, Rita Nanda, Christina Yau, Jo Chien, Megna Trivedi, Erica Stringer-Reasor, Christos Vaklavas, Judy Boughey, Amy Sanford, Anne Wallace, Amy Clark, Alexandra Thomas, Kathy Albain, Laura Kennedy, Tara Sanft, Kevin Kalinsky, Heather Han, Williams N, Mili Arora, Anthony Elias, Carla Falkson, Smita Asare, Ruixiao Lu, Maria Pitsiouni, Amy Wilson, Jane Perlmutter, Hope S Rugo, Richard Schwab, Frasier Symmans, Nola Hylton, Laura Van 't Veer, Douglas Yee, Angela DeMichele, Don Berry, Laura Esserman

on behalf of the I-SPY 2 TRIAL Consortium

I-SPY 2 TRIAL Design



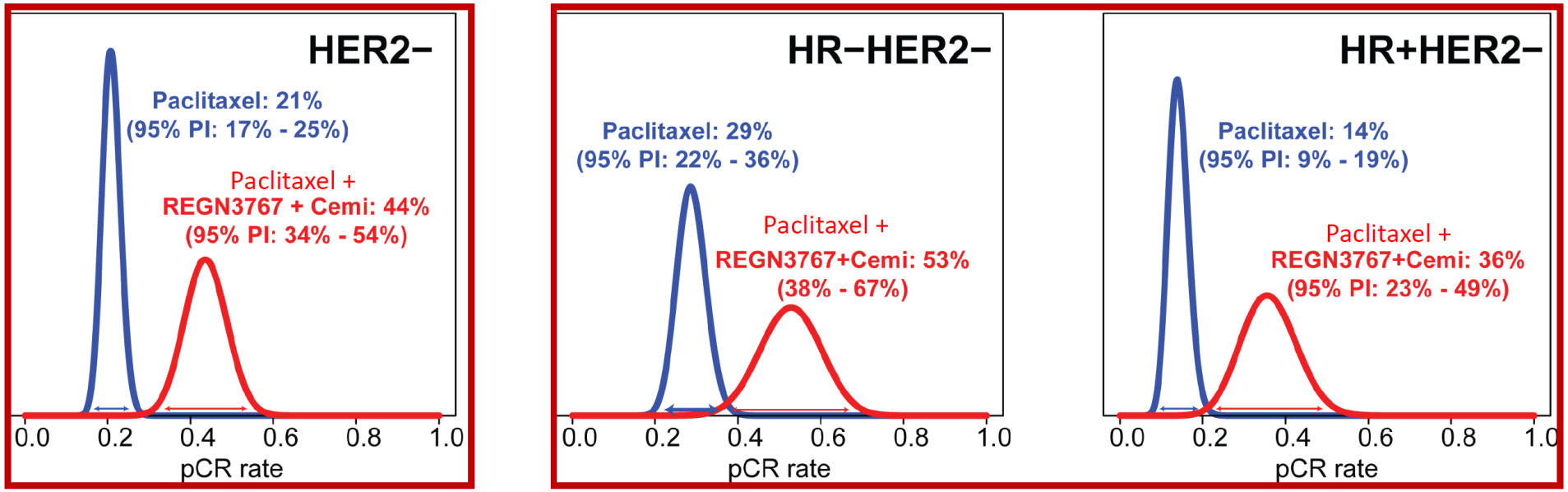
- REGN3767 + Cemiplimab was studied in **3 HER2-negative** biomarker signatures: **all HER2-; TNBC; HR+/HER2**
- Agent Graduation:
  - ≥85% predicted probability of success in a 300-patient phase 3 neoadjuvant trial
- Graduation is assessed for each pre-specified biomarker signature

Demographics (all HER2-negative)

	Randomization period
REGN3767 + Cemiplimab	Feb. 13, 2020 – Dec. 9, 2021
Paclitaxel (control)	Apr. 12, 2010 – Dec. 9, 2021

Patient characteristics	REGN 3767 + Cemiplimab (n=76)	Control (n=350)
Age, yrs		
Median (Range)	47 (26-78)	48 (19-80)
Race, n (%)		
White	57 (75%)	273 (78%)
African American	11 (14%)	46 (13%)
Asian	5 (7%)	30 (9%)
Other	3 (4%)	1 (0%)
HR status, n (%)		
Positive	40 (53%)	195 (56%)
Negative	36 (47%)	155 (44%)
Tumor size by MRI, cm		
Median (Range)	3.45 (1.6 - 10.9)	3.8 (1.2 - 15.0)
Clinical nodal status		
Node positive	31(41%)	151(43%)

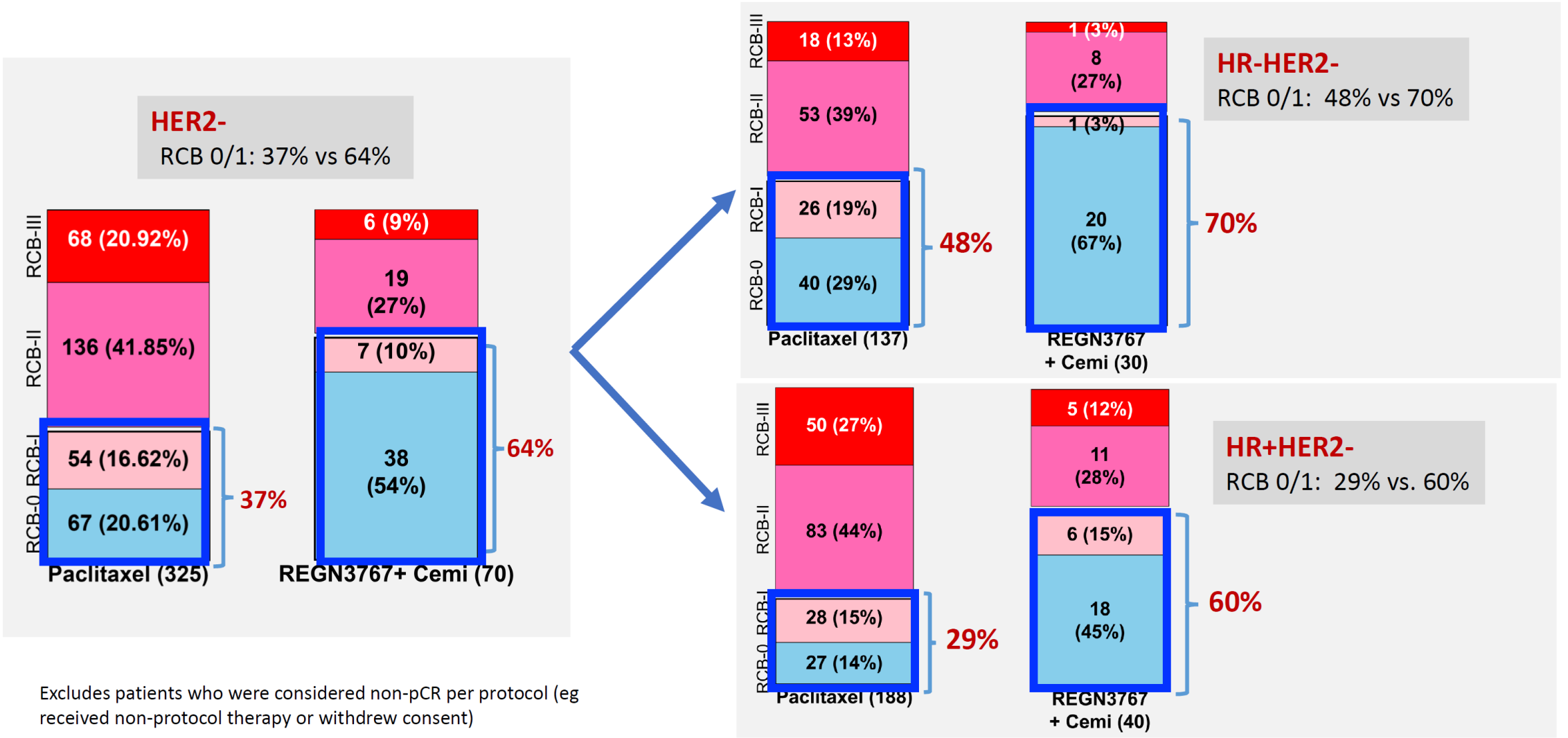
Efficacy Analysis



Signature	Estimated pCR Rate (95% Probability Interval)		Probability Pac + REGN3767 + Cemi Superior to Control	Predictive Probability of Success in Phase 3 (relative to Control)
	Pac + REGN3767 + Cemi (n=76)	Control (n=350)		
HER2-	44% (34% - 54%)	21% (17% - 25%)	>0.999	0.955
HR-HER2-	53% (38% - 67%)	29% (22% - 36%)	0.999	0.915
HR+HER2-	36% (23% - 49%)	14% (9% - 19%)	>0.999	0.940

Pac + REGN3767 + Cemiplimab graduated in all 3 eligible biomarker signatures by demonstrating increased pCR

Cemiplimab + REGN 3767 downshifted residual cancer burden class (RCB)[1] across all subtypes



Excludes patients who were considered non-pCR per protocol (eg received non-protocol therapy or withdrew consent)

Treatment-Emergent Adverse Events (non-immune) (≥ 10% difference)

Adverse Event	REGN3767 + Cemi (n=76)		Control (n=350)	
	Grade>=3	All Grade	Grade>=3	All Grade
Blood and lymphatic system disorders				
Anemia	1 (1%)	24 (32%)	14 (4%)	67 (19%)
General Disorders				
Fatigue	3 (4%)	64 (84%)	4 (1%)	238 (68%)
Headache	2 (3%)	35 (46%)	3 (1%)	105 (30%)
Fever	0	20 (26%)	1 (<1%)	40 (11%)
Pain	0	22 (29%)	0	50 (14%)
Dizziness	0	21 (28%)	0	58 (17%)
Gastrointestinal disorders				
Diarrhea	1 (1%)	37 (49%)	6 (2%)	118 (34%)
Constipation	0	37 (49%)	0	137 (39%)
Dry mouth	0	13 (17%)	0	23 (7%)
Decreased appetite/dysgeusia	0	26 (34%)	0	77 (22%)
Laboratory/Investigations				
Alanine aminotransferase increased	1 (1%)	16 (21%)	4 (1%)	36 (10%)
Other				
Peripheral neuropathy	0	27 (36%)	6 (2%)	174 (50%)
Alopecia	na	52 (68%)	na	202 (58%)
Hot flashes	0	31 (41%)	1 (<1%)	94 (27%)

Pulmonary embolism 2 (3%) vs 1 (0.3%); Sepsis 5 (7%) vs 2 (1%)

Immune-Related Adverse Events (irAEs)

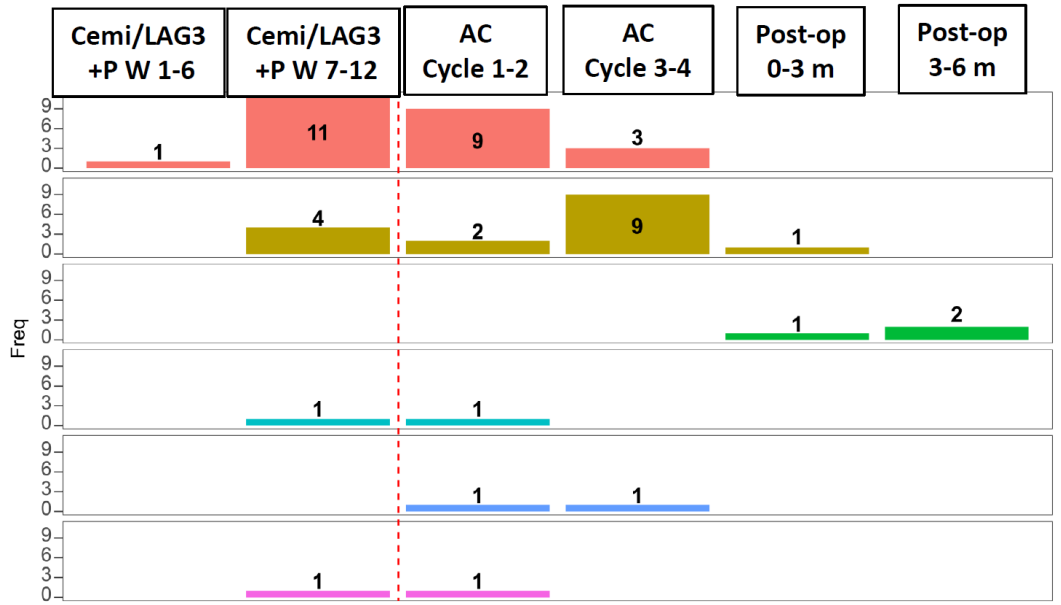
40 (53%) patients in REGN3767 + Cemi arm experienced irAE

- 63% of irAEs occurred after > 12 weeks of treatment start
- Timing of irAE onset similar to prior I-SPY2 experience with other immune-targeting agents

irAE	Grade 1/2	Grade 3	All Grade
Hypothyroidism	24 (32%)	0 (0%)	24 (32%)
Adrenal insufficiency/ Hypophysitis	10 (12%)	6 (5%)	16 (21%)
Type 1 diabetes mellitus	0	3 (4%)	3 (4%)
Autoimmune hepatitis	0	2 (3%)	2 (3%)
Pneumonitis	2 (3%)	0 (0%)	2 (3%)
Renal failure acute	1 (1%)*	1 (1%)	2 (3%)

1 case of arthritis (G3)
1 case of immune-related rash maculo-papular (G3)
1 case of thyroiditis (G2)
No Grade 4+ irAEs

Timing of irAE onset by Time from Treatment Start



Based on available data as of October 15th, 2022

Conclusions

- Cemiplimab + REGN 3767 highly effective combination in both TNBC and HR+/HER2 negative breast cancer

- ImPrint signature identified greatest benefit from checkpoint inhibitor based therapy
  - In Immune+ signature, Cemiplimab + Paclitaxel (84%) performed very similarly to Cemiplimab + REGN3767 + paclitaxel (91%)

- Addition of REGN3767 associated with increased incidence of AI as well as 3 cases (5%) of Type 1 diabetes
  - This rate has not been observed in other patient populations
  - Small studies have suggested lower irAEs with lower doses of immunotherapy

- Given activity, evaluating safety profile of lower dose REGN3767 given in combination with cemiplimab + paclitaxel

Comments

- **Together with KN522, it showed that checkpoint inhibitor immunotherapy is beneficial in TNBC**
- **No obvious benefit adding anti-LAG-3**

Pregnancy in Breast Cancer

- **GS4-09: POSITIVE Trial: P**regnancy **O**utcome and **S**afety of **I**nterrupting **T**herapy for women with endocrine respons**IVE** breast cancer

Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVE breast cancer

Initial Results from the **POSITIVE Trial**
(IBCSG 48-14 / BIG 8-13 / Alliance A221405)

Ann Partridge on behalf of the POSITIVE Consortium

A H Partridge, S M Niman, M Ruggeri, F A Peccatori, H A Azim Jr, M Colleoni, C Saura, C Shimizu, A Barbro Sætersdal, J R Kroep, A Mailliez, E Warner, V F Borges, F Amant, A Gombos, A Kataoka, C Rousset-Jablonski, S Borstnar, J Takei, J Eon Lee, J M Walshe, M Ruíz Borrego, H CF Moore, C Saunders, V Bjelic-Radisic, S Susnjar, F Cardoso, K L Smith, T Ferreiro, K Ribi, K J Ruddy, S El-Abed, M Piccart, L A Korde, A Goldhirsch†, R D Gelber, O Pagani

ELIGIBILITY

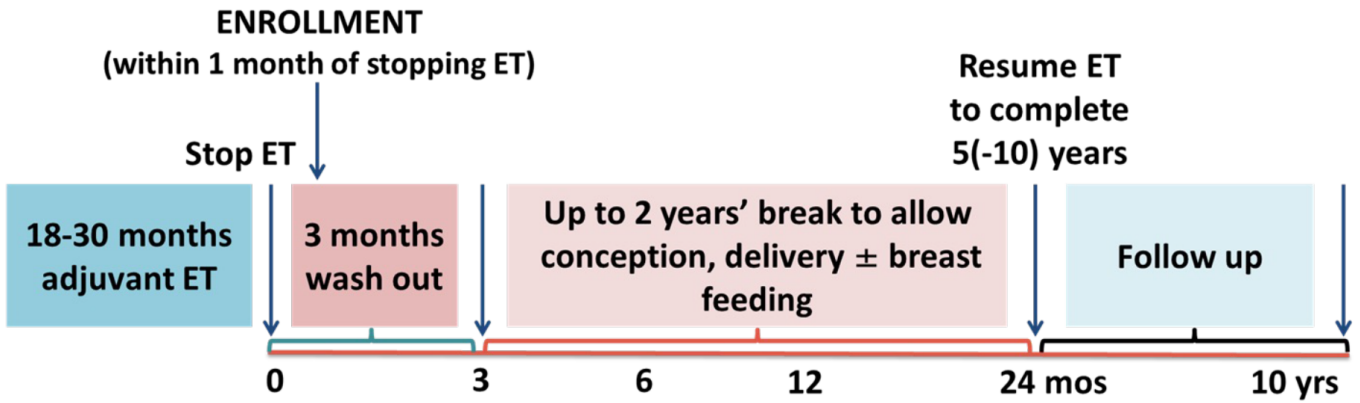
IBCSG

- Premenopausal women wishing to become pregnant
- Age ≤42 years at study entry
- At least 18 months and no more than 30 months of prior adjuvant ET for stage I-III HR+ BC
  - Prior neo/adjuvant chemotherapy ± fertility preservation allowed
- No clinical evidence of recurrence

TRIAL PROCEDURES

IBCSG

- Planned ET interruption (within 1 month of trial enrollment):
- Up to 2 years to attempt pregnancy, conceive, deliver, and breastfeed, including 3-months washout period
  - If no pregnancy by 1 year, fertility assessment strongly recommended
- ET resumption strongly recommended after pregnancy to complete planned 5-10 yrs
- Long-term follow-up



ENDPOINTS

IBCSG

- **Primary**
  - **Breast cancer-free interval (BCFI)** = time from enrollment (after 18-30 months of ET) to the first ipsilateral / locoregional / contralateral invasive disease or distant recurrence
- **Secondary**
  - Pregnancy outcomes
  - Offspring outcomes
  - Breastfeeding
  - Use of assisted reproductive technology (ART)
  - Adherence to endocrine treatment
  - Distant recurrence-free interval (DRFI) = time from enrollment to the first BC distant recurrence

KEY PATIENT CHARACTERISTICS

	N	%
	516	**100**
Age at enrollment ***Median 37 years (range 27-43 years)***		
<35	177	34%
35-39	221	**43%**
40-42	118	23%
Number of prior births		
0	387	**75%**
1	107	21%
≥ 2	22	4%
TNM stage		
I	242	**47%**
II	240	**47%**
III	31	6%
Unknown	3	1%

Partridge AH et al. Breast 2021;59:327-338.
DOI: 10.1016/j.breast.2021.07.021

TREATMENT PATTERNS

IBCSG

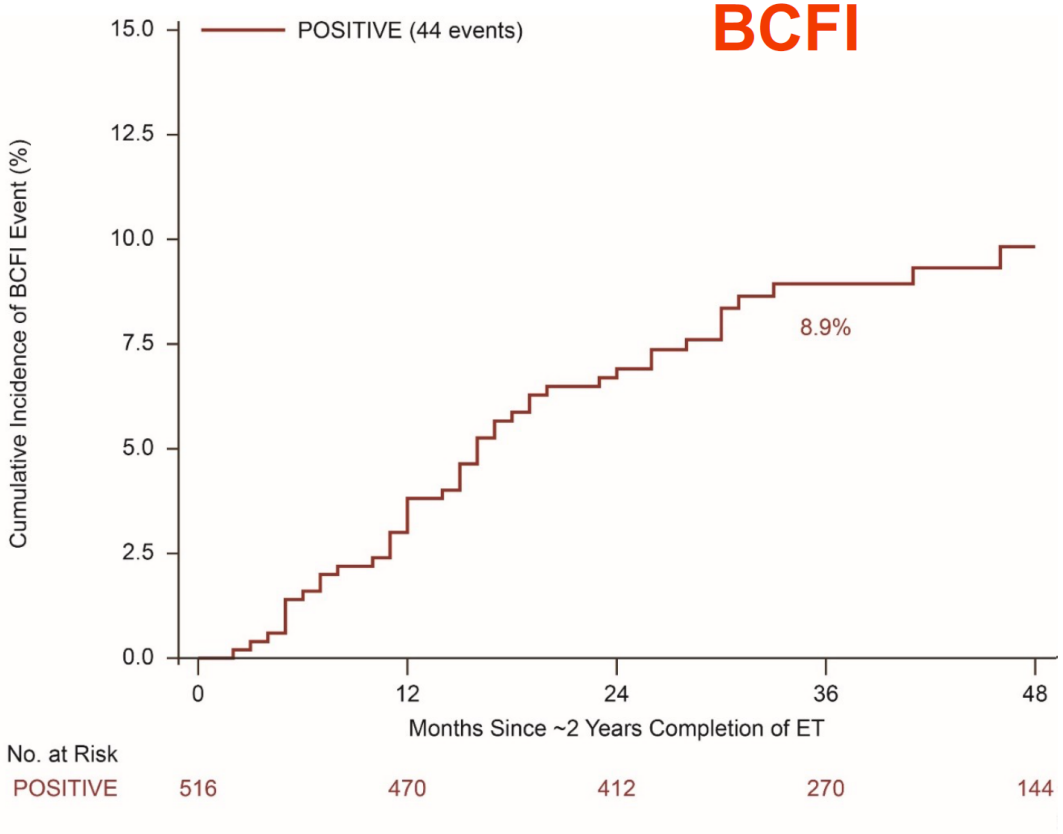
	N	%
	516	**100**
Endocrine therapy prior to enrollment *Median duration: 23.4 months*		
SERM alone	215	**42%**
SERM+OFS	184	**36%**
AI+OFS	82	16%
Other	35	7%
Prior (neo-)adjuvant chemotherapy		
None	196	38%
Yes	320	**62%**
Breast surgery		
Mastectomy	233	45%
Breast conserving procedure	283	55%

Partridge AH et al. Breast 2021;59:327-338. DOI: 10.1016/j.breast.2021.07.021

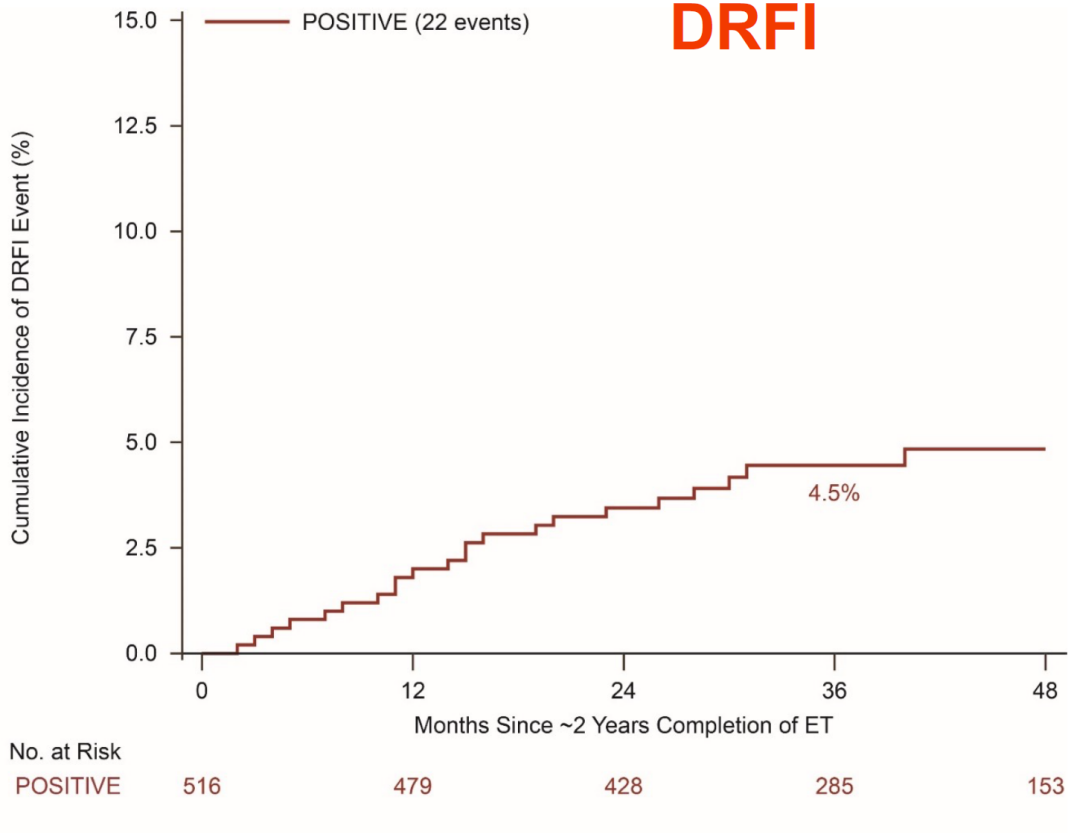
BREAST CANCER OUTCOMES – POSITIVE only

IBCSG

BCFI



DRFI

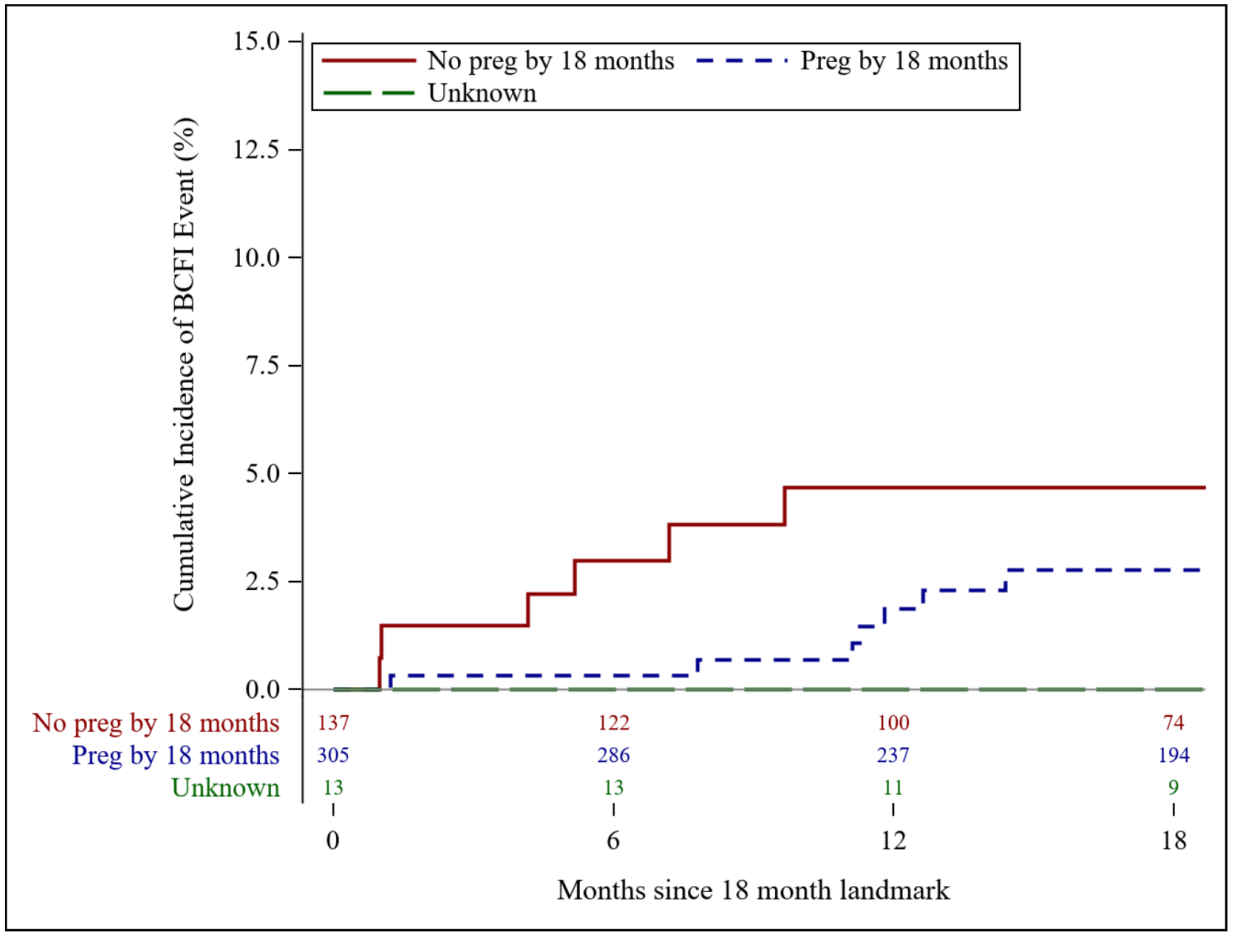


1638 patient-years of follow-up (41 months median follow-up)

BCFI FOR PREGNANT vs NON PREGNANT PATIENTS

IBCSG

18-month Landmark Analysis



Time-dependent Cox Models

BCFI hazard ratios

(pregnant vs. not pregnant):

0.55 (95% CI: 0.28 to 1.06) – univariable

0.53 (95% CI: 0.27 to 1.04) – multivariable*

* including age, BMI, lymph node status, prior chemo, and prior AI

PREGNANCY OUTCOMES

IBCSG

- 368 (74%) of the 497 women in the secondary endpoint population had at least one pregnancy (70% within 2 years) for a total of 507 pregnancies
- 317 had at least one live birth (64% of all women, 86% of those who became pregnant)

	N	% of 497	% of 368
Secondary endpoint population	497	100%	
At least one on trial pregnancy	368	**74%**	100%
At least one live birth (full-term or preterm)	317	**64%**	**86%**
At least one miscarriage	93	19%	25%
At least one elective abortion	16	3%	4%
At least one stillbirth/neonatal death	1/1	0.2% / 0.2%	0.3% / 0.3%

Note: 110 women had more than one pregnancy, and may contribute information to more than one row

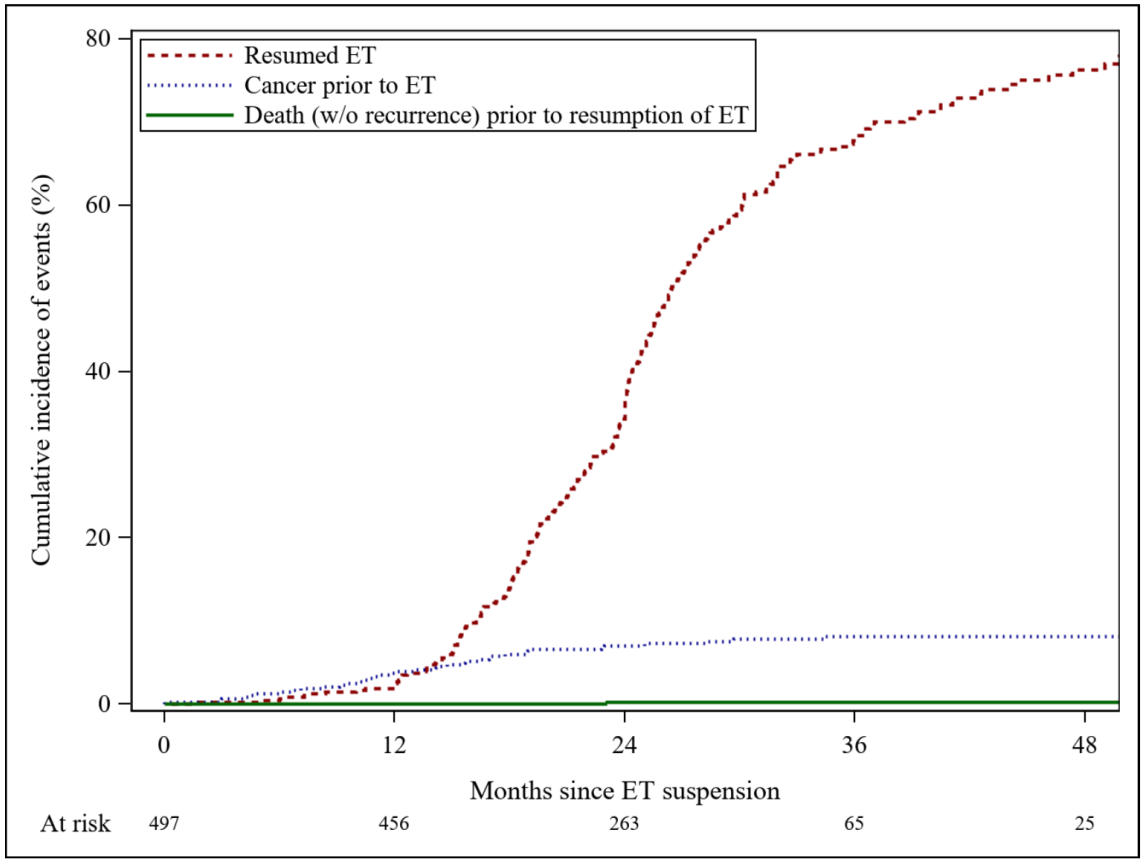
- **Delivery**
  - Vaginal 66%
  - Cesarean section 34%
- **Pregnancy complications**
  - 11% of pregnancies
  - Most common:
    Hypertension/preeclampsia 3%
    Diabetes 2%

OFFSPRING OUTCOMES

- 350 live births for the 317 women who had at least 1 live birth
- 335 singleton births and 15 sets of twins (365 offspring)
- 62% of 317 women reported breastfeeding

	N	%
Total offspring	365	100%
Low birth weight (<2500g)		
Yes	29	8%
No	**334**	**92%**
Missing/Unknown	2	0.5%
Birth defects		
Yes	8	2%
No	**350**	**96%**
Missing/Unknown	7	2%

ET RESUMPTION: COMPETING RISK ANALYSIS



Cumulative incidences at 48 months:

- 8% had cancer recurrence/death before resuming ET
- 76% resumed ET
- 15% had not yet resumed ET

79% of women disease-free at 2 years who have not yet resumed ET reported continuing pursuit of pregnancy, active/recent pregnancy or breastfeeding at most recent follow-up.

CONCLUSIONS

IBCSG

- In POSITIVE, temporary interruption of ET to attempt pregnancy among women who desire pregnancy does not impact short-term disease outcomes
- 74% of women had at least one pregnancy, most (70%) within 2 years
- Birth defects were low (2%), not clearly associated with treatment exposure
- Follow-up to 2029 planned to monitor ET resumption and disease outcomes
- **These data stress the need to incorporate patient-centered reproductive healthcare in the treatment and follow-up of young women with breast cancer**

Comments

- **This is the first prospective study looking at pregnancy in early stage breast cancer**
- **It is safe and not increasing the risk of recurrence**

Non-Invasive Breast Cancer

- **GS4-08: 10 YEAR RESULTS OF A PHASE 3 TRIAL OF LOW-DOSE TAMOXIFEN IN NONINVASIVE BREAST CANCER**

GS408

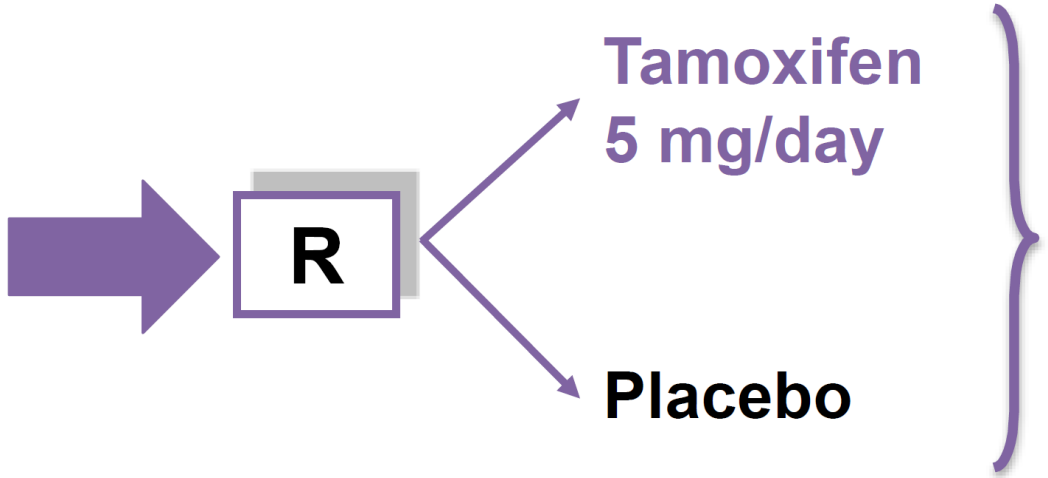
10 YEAR RESULTS OF A PHASE 3 TRIAL OF LOW-DOSE TAMOXIFEN IN NONINVASIVE BREAST CANCER

Andrea De Censi[1], Matteo Lazzeroni[2], Matteo Puntoni[3], Luca Boni[4], Aliana Guerrieri Gonzaga[2], Tania Buttiron Webber[1], Marianna Fava[1], Irene Maria Briata[1], Livia Giordano[5], Maria Digennaro[6], Laura Cortesi[7], Katia Cagossi[8], Elisa Gallerani[9], Alessia De Simone[10], Anna Cariello[11], Giuseppe Aprile[12], Maria Renne[13], Bernardo Bonanni[2]

(1) E.O. Ospedali Galliera, Genova, Italy; (2) IEO - European Institute of Oncology IRCCS, Milan; (3) Clinical & Epidemiological Research Unit, University Hospital of Parma; (4) IRCCS Ospedale Policlinico San Martino, Genoa; (5)Azienda Ospedaliera-Universitaria Città della Salute e della Scienza di Torino; (6) IRCCS Istituto Tumori Giovanni Paolo II, Bari; (7) Azienda Ospedaliera-Universitaria Policlinico di Modena; (8) Ospedale Bernardino Ramazzini, Carpi; (9) ASST Settelaghi Varese; (10) ICS Maugeri -Centro Medico di Pavia; (11) Ospedale Santa Maria delle Croci, Ravenna; (12) Azienda ULSS8 Berica- Ospedale di Vicenza; (13) Chirurgia Generale Azienda Ospedaliera Mater Domini Catanzaro.

TAM 01- Study Design

Women aged <75 yrs with IEN (ADH or LCIS or ER+ve or unknown DCIS)



3 yr treatment + at least 7 yr FU

Primary endpoint:
Incidence of invasive breast cancer or DCIS

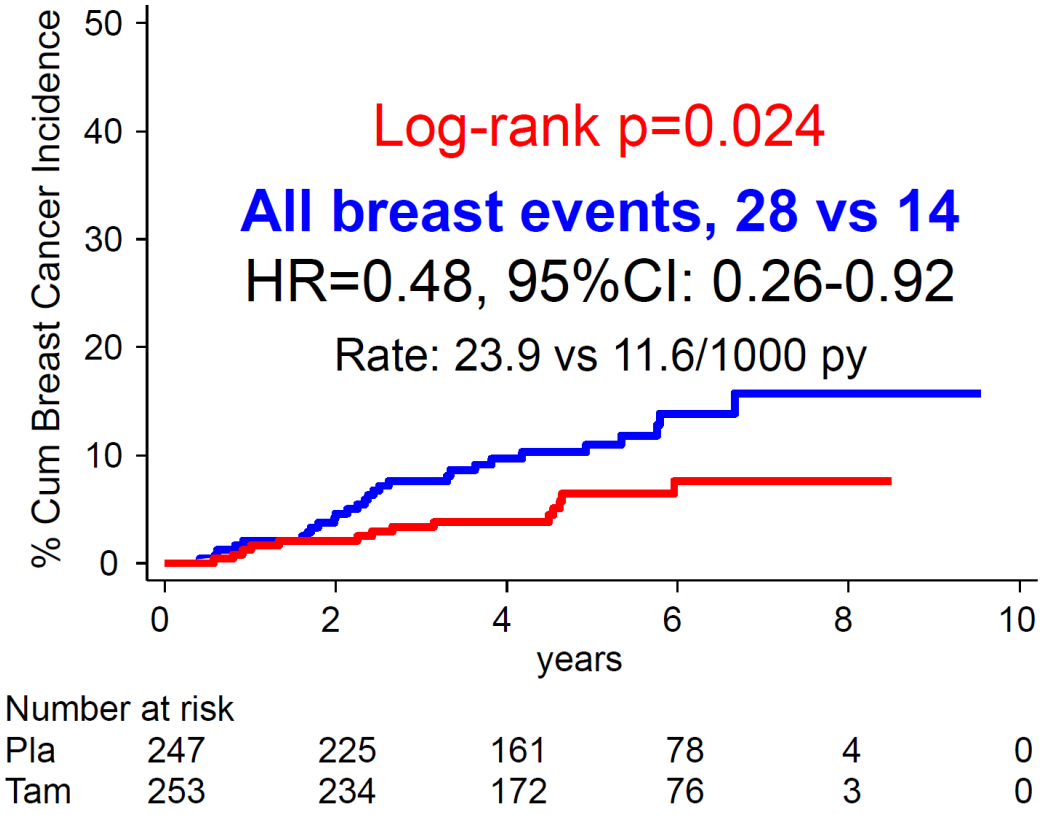
- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months for 3 yrs, Mx every year for 10 yrs

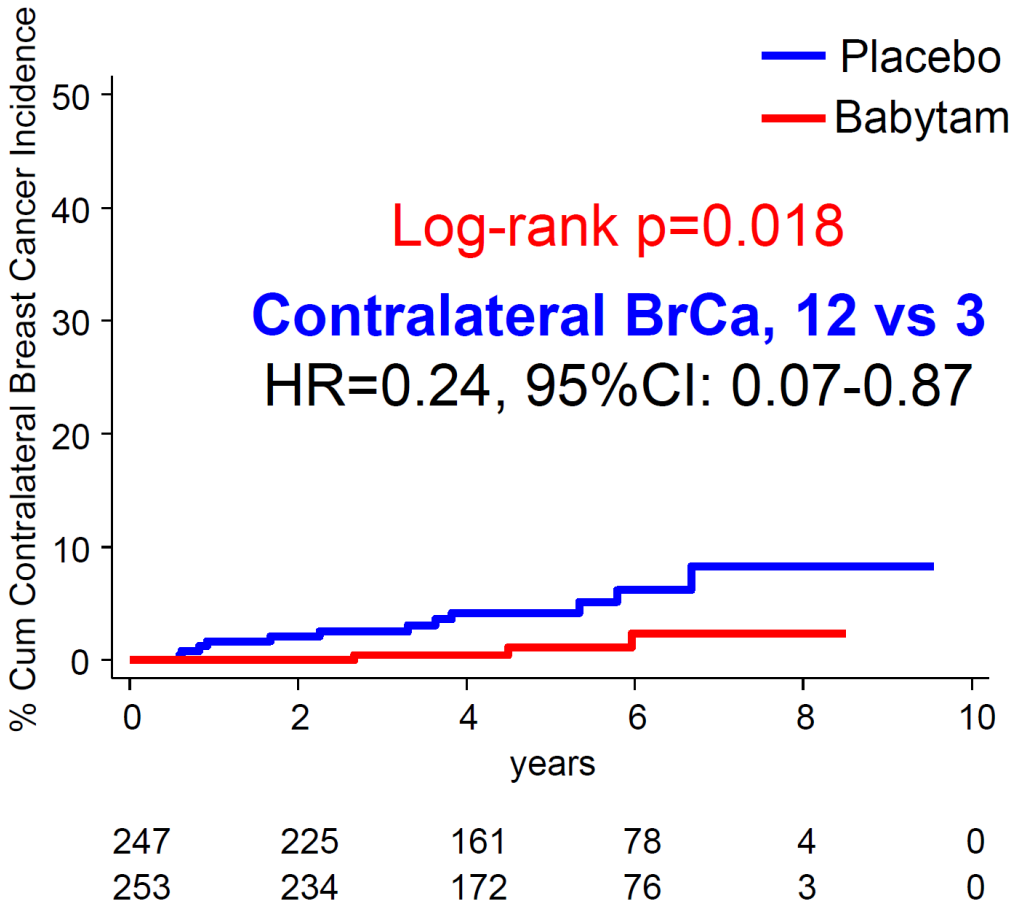
Main subject and tumor characteristics (n=500)

	Babytam N=253	Placebo N=247
Age, mean (SD)	54 (9.6)	54 (9.1)
Pre-menopausal, %	43	40
BMI, mean (SD)	25.7 (4.8)	25.3 (4.2)
ADH, %	20	20
LCIS, %	11	10
DCIS, %	69	70
ER/PR+ve/unk DCIS, %	66 / 34	67 / 33
Radiotherapy for DCIS, %	61	61

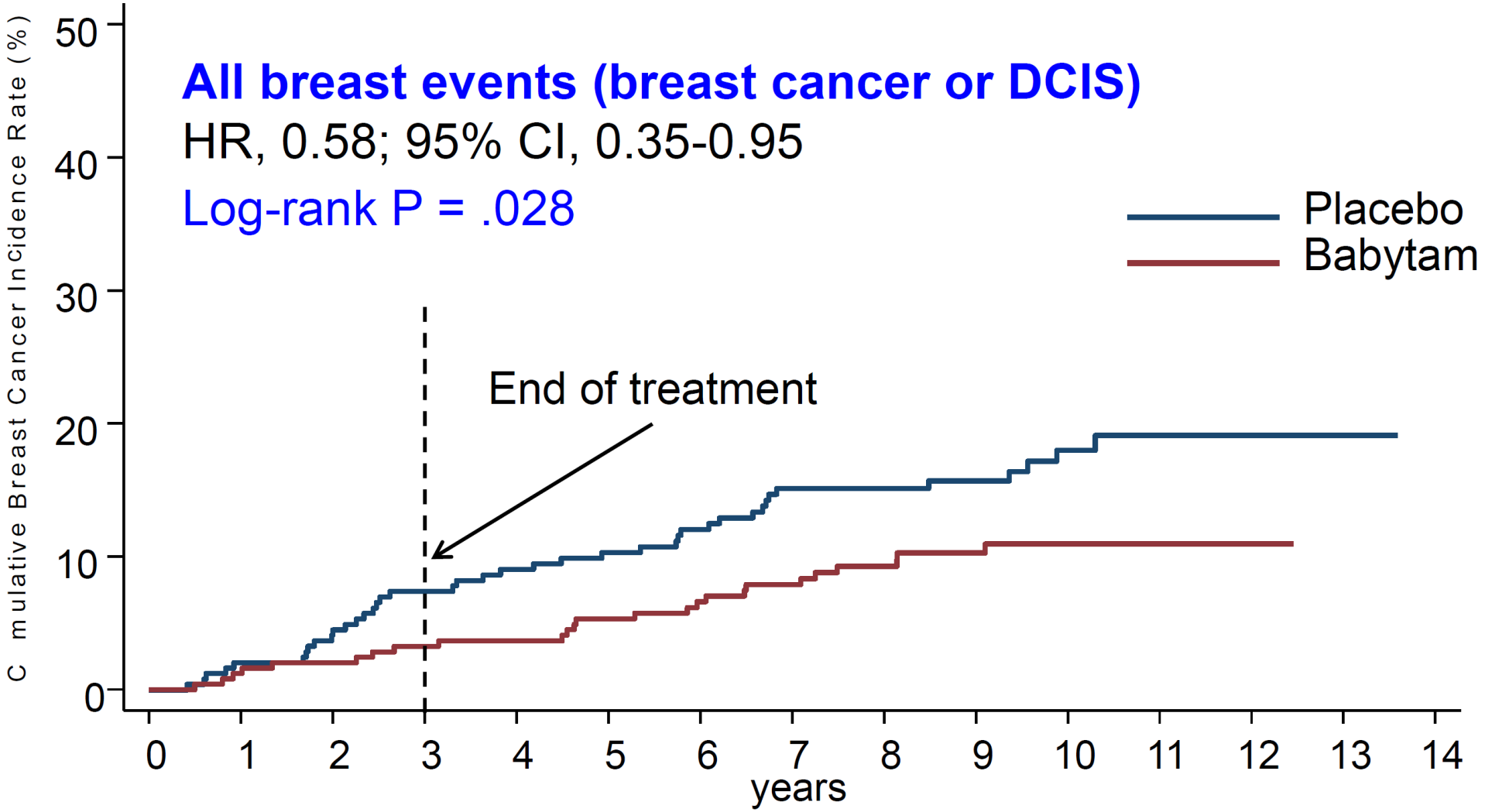
DeCensi et al. *J Clin Oncol.* 37(19):1629-1637, 2019

Babytam decreased breast cancer events (n=42) after a median of 5 years (SABCS 2018)





DeCensi et al. *J Clin Oncol.* 37(19):1629-1637, 2019



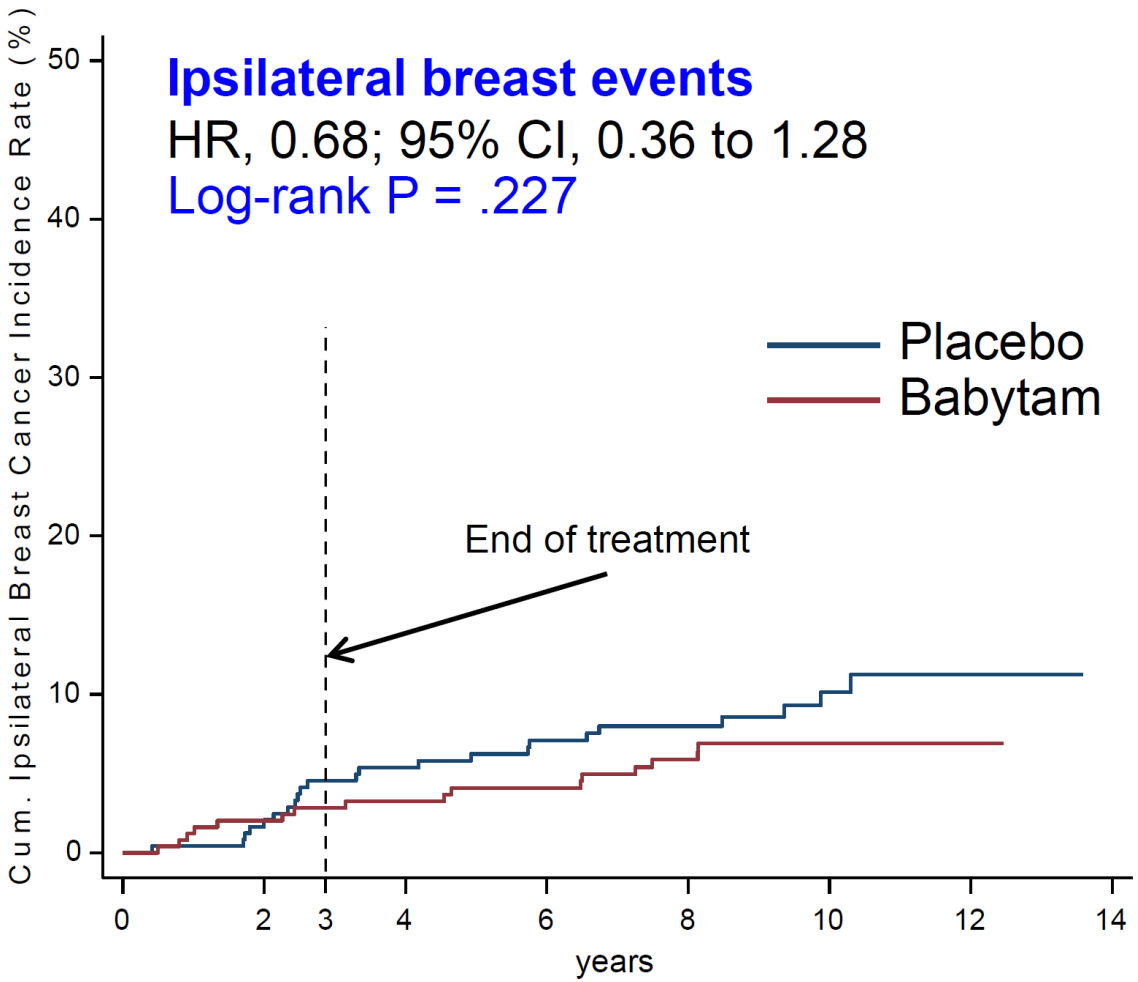
Number at risk

Placebo	247	(5)	240	(6)	233	(7)	224	(4)	218	(3)	213	(4)	202	(7)	190	(0)	170	(1)	134	(3)	92	(1)	51	(0)	12	(0)	2	(0)	0
Tamoxifen	253	(3)	245	(2)	241	(3)	236	(1)	232	(4)	227	(3)	218	(3)	210	(3)	179	(2)	141	(1)	102	(0)	46	(0)	10	(0)	0	(0)	0

Ipsilateral breast events

HR, 0.68; 95% CI, 0.36 to 1.28

Log-rank P = .227



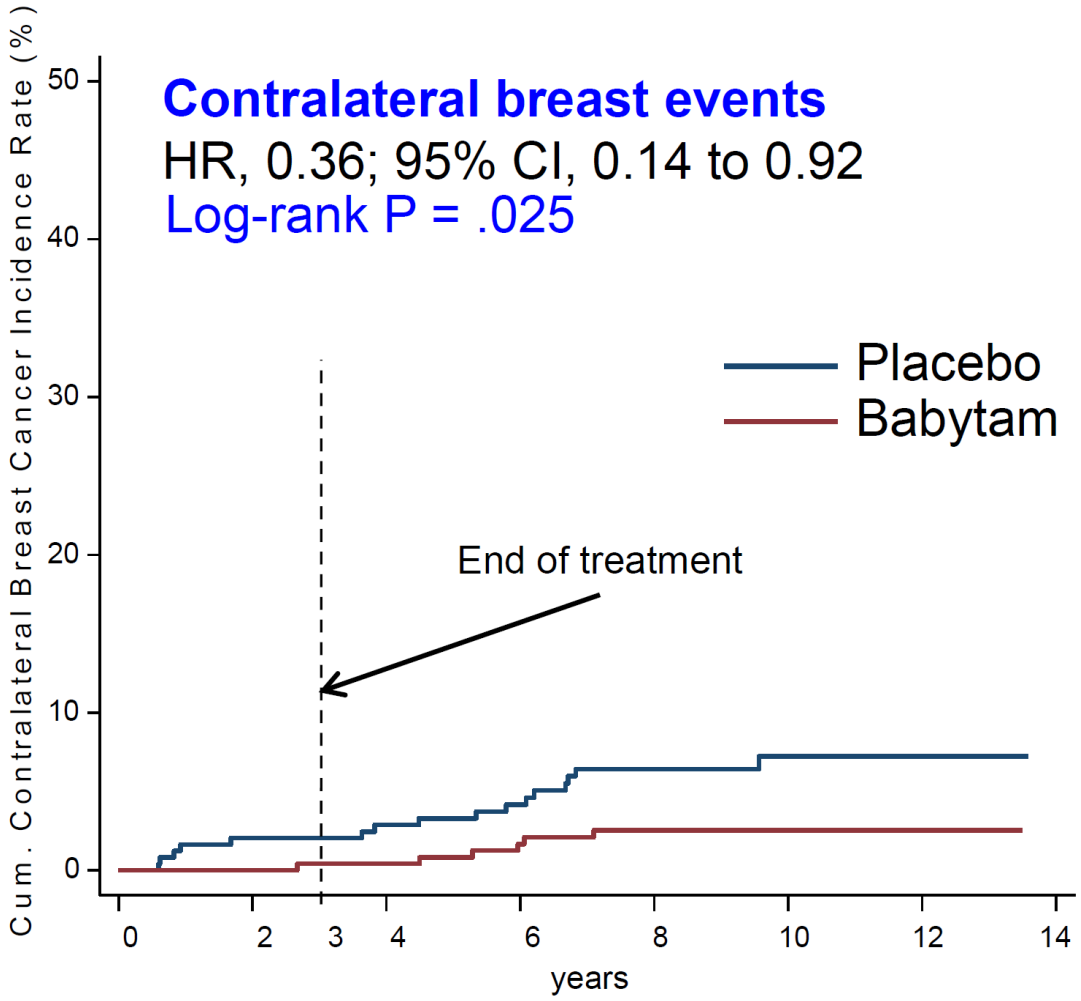
Number at risk

Placebo	247	(5)	238	(8)	225	(4)	212	(2)	182	(3)	100	(1)	12	(0)	0
Tamoxifen	253	(5)	241	(3)	233	(2)	223	(4)	183	(2)	105	(0)	10	(0)	0

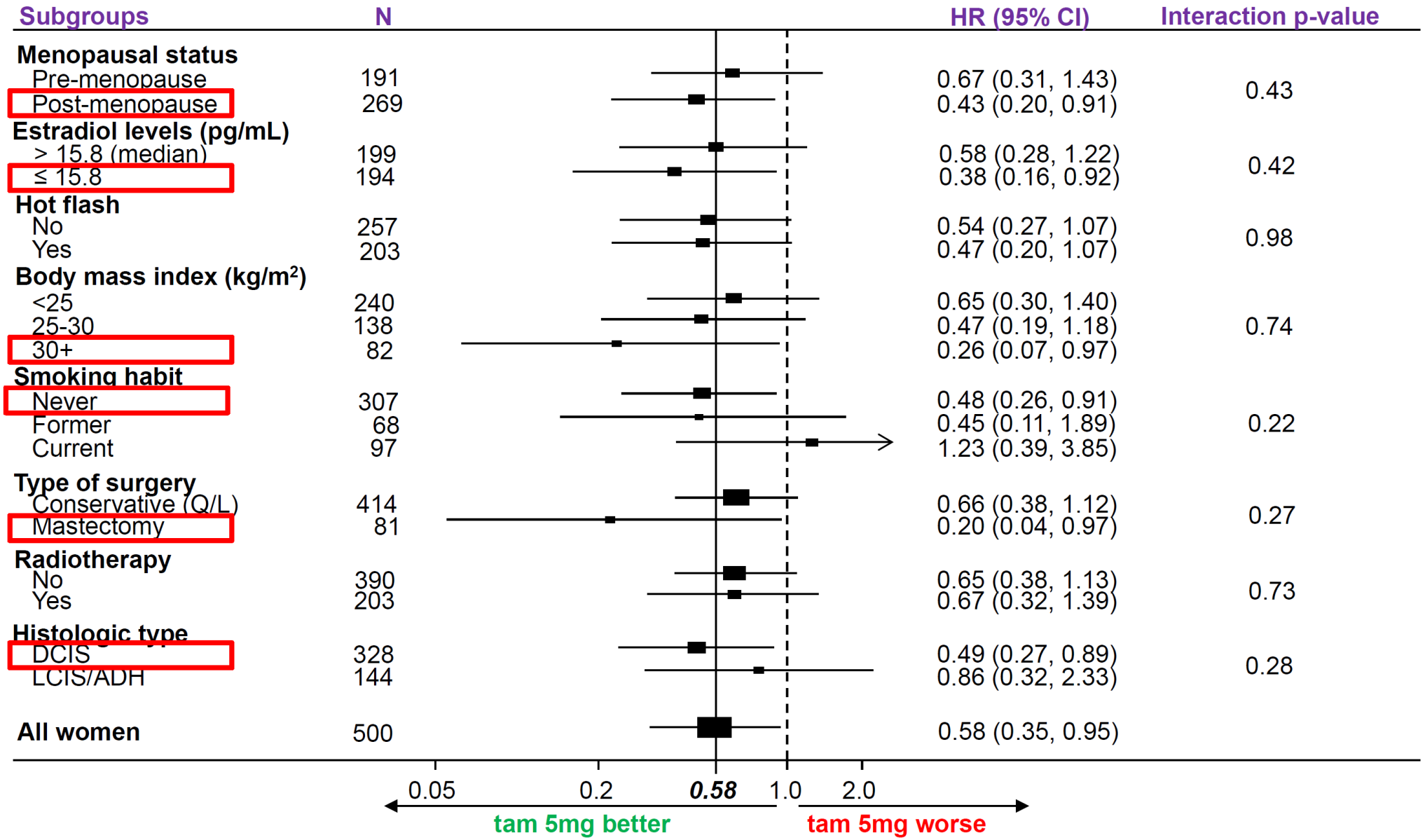
Contralateral breast events

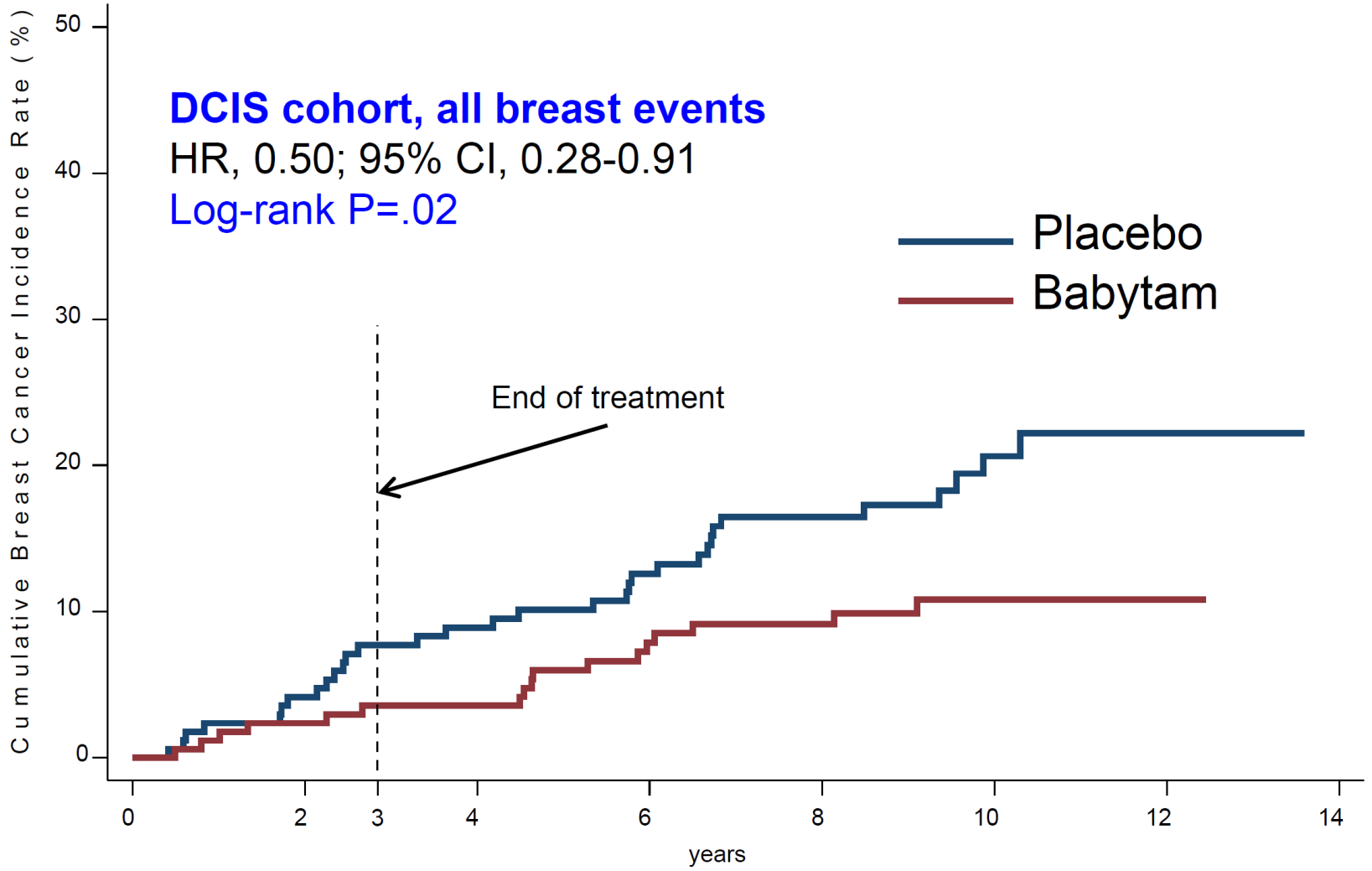
HR, 0.36; 95% CI, 0.14 to 0.92

Log-rank P = .025



	247	(5)	239	(2)	230	(3)	218	(5)	185	(1)	102	(0)	12	(0)	0
	253	(0)	246	(1)	240	(3)	229	(2)	192	(0)	109	(0)	12	(0)	0


Subgroups
N
HR (95% CI)
Interaction p-value
Menopausal status
Pre-menopause 191 0.67 (0.31, 1.43)
Post-menopause 269 0.43 (0.20, 0.91)
0.43
Estradiol levels (pg/mL)
> 15.8 (median) 199 0.58 (0.28, 1.22)
≤ 15.8 194 0.38 (0.16, 0.92)
0.42
Hot flash
No 257 0.54 (0.27, 1.07)
Yes 203 0.47 (0.20, 1.07)
0.98
Body mass index (kg/m²)
<25 240 0.65 (0.30, 1.40)
25-30 138 0.47 (0.19, 1.18)
30+ 82 0.26 (0.07, 0.97)
0.74
Smoking habit
Never 307 0.48 (0.26, 0.91)
Former 68 0.45 (0.11, 1.89)
Current 97 1.23 (0.39, 3.85)
0.22
Type of surgery
Conservative (Q/L) 414 0.66 (0.38, 1.12)
Mastectomy 81 0.20 (0.04, 0.97)
0.27
Radiotherapy
No 390 0.65 (0.38, 1.13)
Yes 203 0.67 (0.32, 1.39)
0.73
Histologic type
DCIS 328 0.49 (0.27, 0.89)
LCIS/ADH 144 0.86 (0.32, 2.33)
0.28
All women 500 0.58 (0.35, 0.95)
0.05
0.2
0.58
1.0
2.0
tam 5mg better
tam 5mg worse



Number at risk															
Placebo	172	(7)	162	(8)	151	(6)	139	(6)	116	(4)	61	(1)	4	(0)	0
Tamoxifen	174	(4)	165	(2)	159	(7)	146	(2)	124	(2)	77	(0)	6	(0)	0

Main characteristics of breast neoplastic events, by arm

	Tamoxifen (N=25)	Placebo (N=41)	p-value
Invasiveness, *n*			0.38
Invasive	21	30	
DCIS	4	11	
Site of recurrence, *n*			0.35
Ipsilateral	16	23	
Contralateral	6	16	
Distant	3	2	
Tumor stage, *n*			0.19
Tis	4	11	
T1	15	23	
T2-4	2	6	
Tx	4	1	
Nodes, *n*			0.89
Node-negative	21	33	
Node-positive	2	5	
Molecular phenotype, *n*			
Luminal	6	12	0.78
HER2+	15	22	0.80
Triple negative	0	3	0.28
Ki-67 %, *median (IQR)*	17 (11-30)	20 (13-30)	0.57

Adverse events by allocated arm

	Tamoxifen N=249	Placebo N=246	P Value
Adverse Events, n			
Endometrial cancer	1	0	1.0
Other neoplasms	16	9	0.22
Deep vein thrombosis or pulmonary embolism	1	1	1.0
Superficial phlebitis	2	0	0.50
Coronary heart disease	2	2	1.0
Bone fracture	4	2	0.69
Cataract	5	5	1.00
Endometrial polyps	20	13	0.28
Death from other causes	5	2	0.45
Death from breast cancer	1	2	0.62
Other serious adverse events	3	6	0.34

Conclusions

- Babytam 5 mg/day for 3 years lowers recurrence from non-invasive breast cancer at 10 y without AEs
- Effect on contralateral ca. opens door for primary prevention
- Benefit seen across all subgroups, though with low power
- Low-risk of death (0.6% at 10 y) supports treatment de-escalation in DCIS.
- Tamoxifen another example of a missed optimal dose for a targeted agent[1]

1. Shah M. *N Engl J Med* 2021;385:1445

Comments

- **Lack of standard arm in the study**
- **Tamoxifen 20 mg daily dose remains as the standard**
- **Confirm the presence of “carry-over” benefit of Tamoxifen**

Take Home Messages

- Carboplatin and immunotherapy should be considered in neoadjuvant regimen in triple negative breast cancer if not contraindicated
- Discussion of pregnancy should be opened up with young patients
- Low dose Tamoxifen could be considered in chemoprevention if patient cannot tolerate full dose of Tamoxifen or not a candidate for aromatase inhibitor