Review of triple negative breast cancer and new agents

GASCO Review of SABCS 2014

January 10th 2015, Atlanta, GA

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Chief of Hematology and Medical Oncology, Georgia Cancer Center for Excellence, Grady Memorial Hospital

Topics to be covered

- Triple negative breast cancer
  - Neo-adjuvant: S2-07 (Nab-paclitaxel), S4-04 (carboplatin/bevacizumab)
  - Metastatic: (S3-01)
- New agents:
  - PI3-kinase inhibition: S2-02, S2-03
  - PD-1 anibody S1-09
  - IMMU-132 P5-18-09

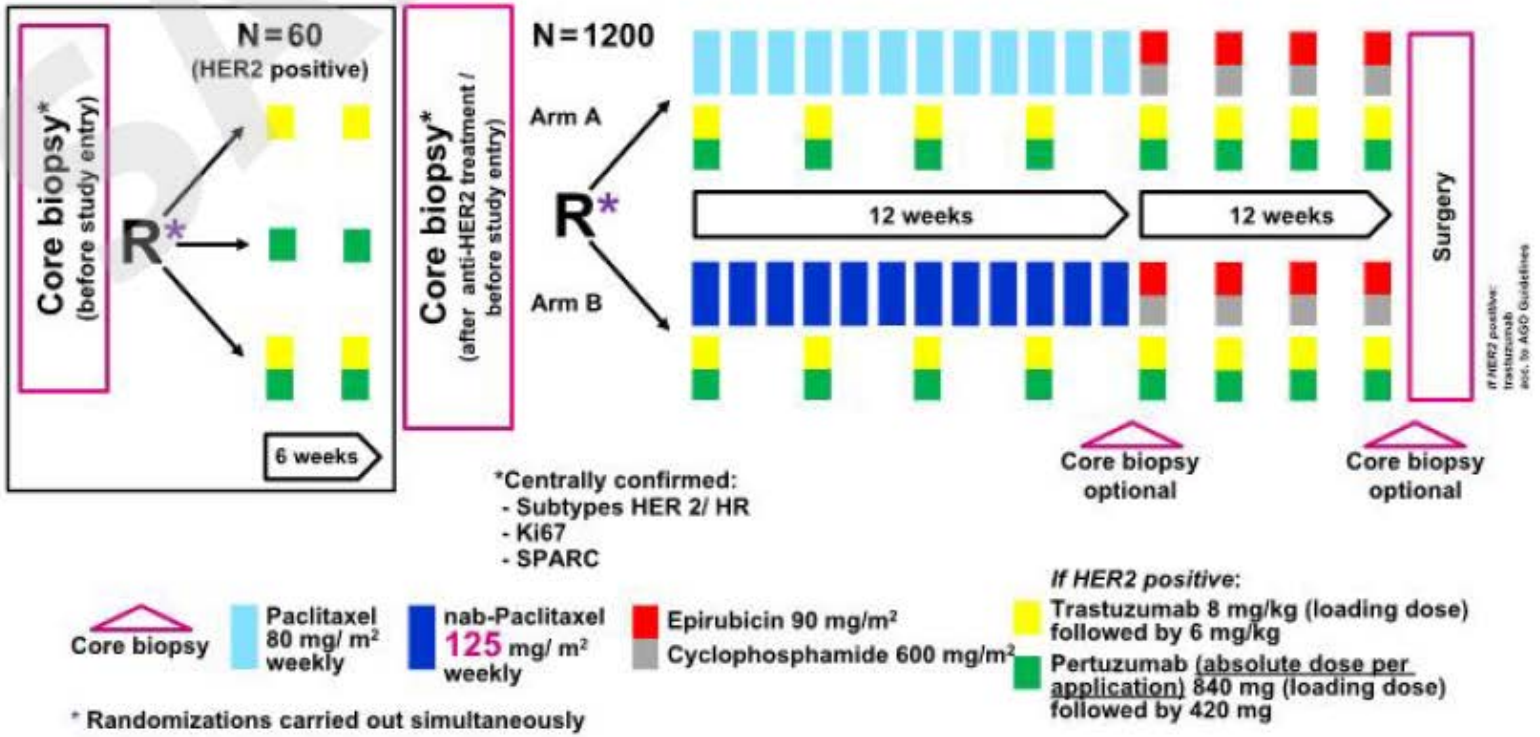
A randomized phase III trial comparing nanoparticle-based (nab) paclitaxel with solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer GBG 69 - GeparSepto

Michael Untch, Christian Jackisch, Andreas Schneeweiss, Bettina Conrad, Bahriye Aktas, Carsten Denkert, Holger Eidtmann, Hermann Wiebringhaus, Sherko Kümmel, Jörn Hilfrich, Mathias Warm, Stefan Paepke, Marianne Just, Claus Hanusch, John Hackmann, Jens-Uwe Blohmer, Michael Clemens, Serban Dan Costa, Bernd Gerber, Valentina Nekljudova, Sibylle Loibl, Gunter von Minckwitz

- A joint study of the AGO Breast and the German Breast Group (GBG) -

Gepar septo

Final Study Design
(after 400 patients recruited)



AGO-B BREAST STUDY GROUP

GBG GERMAN BREAST GROUP

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Main Baseline Characteristics
(recruitment period Jul 12 - Jan 14)

	Paclitaxel N (%) N=598	Nab-paclitaxel N (%) N=606	Overall N (%) N=1204
Age, median (range), yrs	48 (22 - 76)	49 (21 - 75)	49 (21 - 76)
Palpable tumor size, median (range), mm	30 (5 - 150)	30 (4 -150)	30 (4 - 150)
cT3 / 4	86 (16.6)	82 (16.0)	168 (16.3)
cN+	264 (45.1)	275 (46.3)	539 (45.7)
G 3	336 (56.2)	318 (52.5)	654 (54.3)
Breast cancer subtype			
HER 2-	402 (67.2)	407 (67.1)	809 (67.2)
HER 2+	196 (32.7)	199 (32.8)	395 (32.8)
Ki 67 >20%	414 (69.2)	418 (69.0)	832 (69.1)
SPARC +	94 (15.7)	97 (16.0)	191 (15.9)

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Taxane Discontinuation

Reason for taxane discontinuation	Paclitaxel N (%) N=598	Nab-paclitaxel N (%) N=606	p-value
Completed	**516 (86.3)**	**479 (79.0)**	**<.001**
AEs	37 (6.2)	103 (17.0)	
Progression	30 (5.0)	10 (1.7)	
Patient's decision	6 (1.0)	7 (1.2)	
Investigators decision	7 (1.2)	6 (1.0)	
Death	1 (0.2)	0 (0.0)	
Unknown/ missing	1 (0.2)	1 (0.2)	

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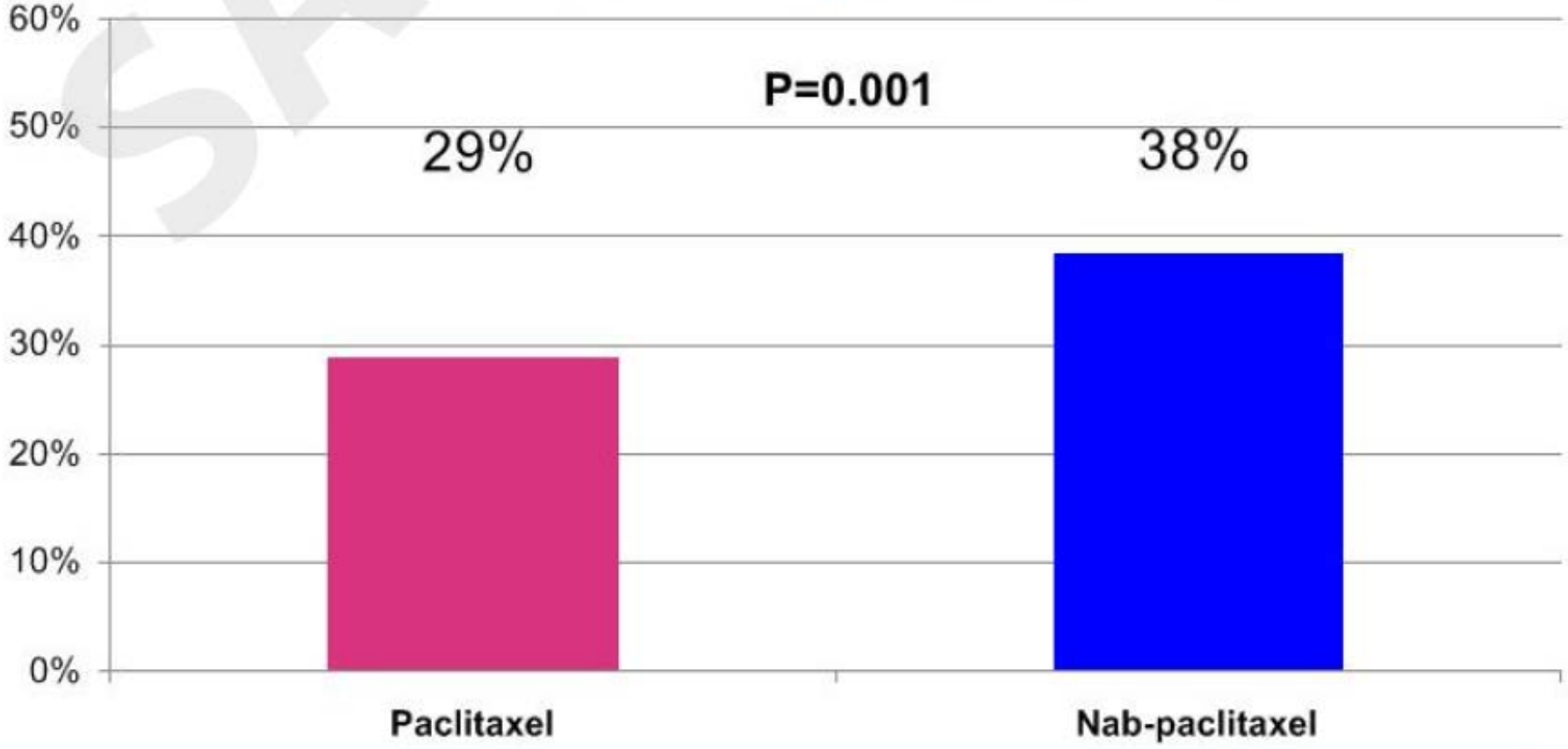
Primary endpoint (pCR: ypT0 ypN0)



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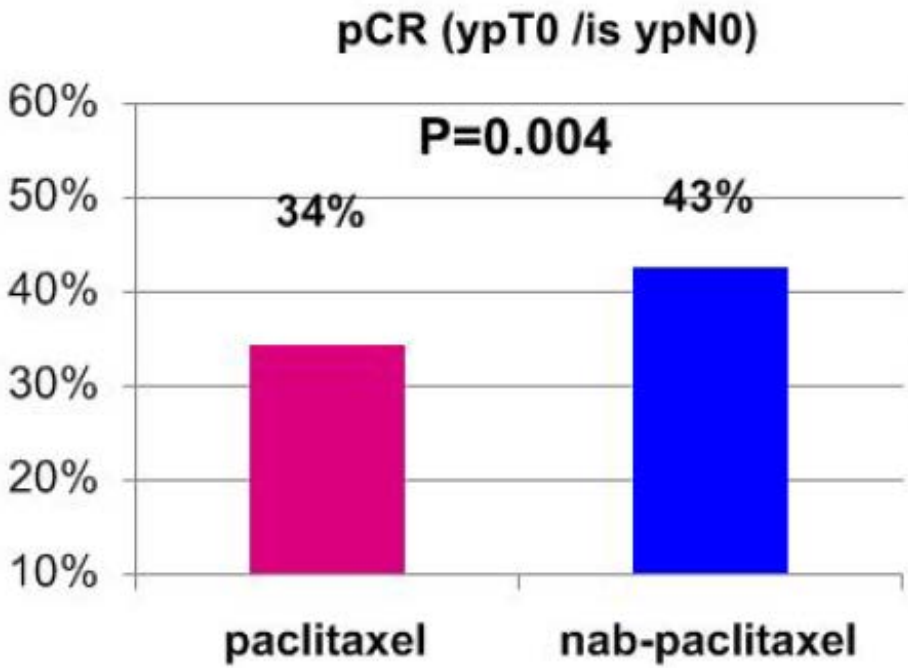
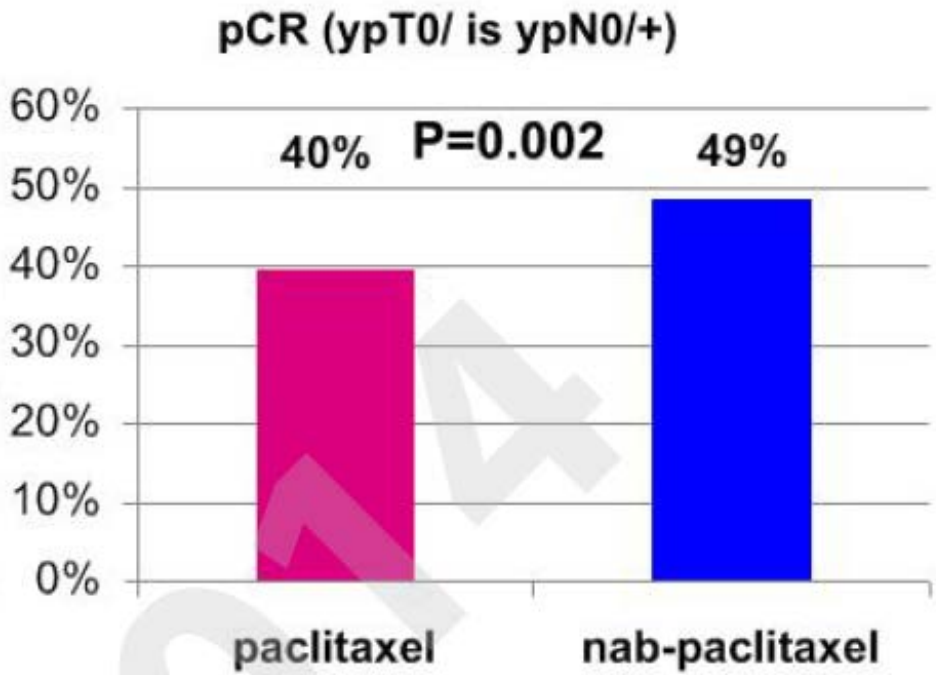
Secondary Endpoints
pCR rates according to other definitions





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pCR in Stratified Subgroups

Parameter	Subgroup	pCR (%)	p-value
SPARC	SPARC negative	28.8 vs 37.7	.003
	SPARC positive	29.8 vs 48.3	.074
Ki67	Ki67<=20%	19.6 vs 26.1	.137
	Ki67>20%	**33.1 vs 44.0**	**.001**
Biological subtype	HER2-, HR+	12.0 vs 16.0	.183
	HER2-, HR-	**25.7 vs 48.2**	**<.001**
	HER2+, HR+	50.0 vs 56.4	.275
	HER2+, HR-	66.7 vs 74.6	.371
HER2	**HER2-**	**17.7 vs. 27.0**	**<.001**
	HER2+	**54.1 vs 61.8**	**.120**
HR-status	HR-	36.1 vs. 56.1	<.001
	HR+	25.6 vs. 29.9	.169

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Selected Hematological Toxicities

AE	Grade	Paclitaxel N (%) N=598	Nab-paclitaxel N (%) N=606	p-value
Anemia	any	526 (88.3)	560 (92.4)	.019
	3-4	6 (1.0)	15 (2.5)	.076
Neutropenia	any	485 (81.5)	528 (87.3)	.007
	3-4	368 (61.8)	366 (60.5)	.636
Febrile neutropenia		25 (4.2)	28 (4.6)	.779

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Non-hematological Toxicities

AE	Grade	Paclitaxel N (%) N=598	Nab-paclitaxel N (%) N=606	p-value
Fatigue	any	465 (77.8)	502 (82.8)	.030
	3-4	**28 (4.7)**	**36 (5.9)**	**.369**
Diarrhea	any	264 (44.1)	310 (51.2)	.015
	3-4	**17 (2.8)**	**20 (3.3)**	**.739**
Rash	any	138 (23.1)	201 (33.2)	<.001
	3-4	**4 (0.7)**	**7 (1.2)**	**.547**
Hand-foot syndrome	any	105 (17.6)	168 (27.7)	<.001
	3-4	**6 (1.0)**	**14 (2.3)**	**.112**
Peripheral sensory neuropathy	any	390 (65.2)	511 (84.3)	<.001
	3-4	**16 (2.7)**	**62 (10.2)**	**<.001**
Myalgia	any	145 (24.2)	189 (31.2)	.008
	3-4	0 (0.0)	3 (0.5)	.249

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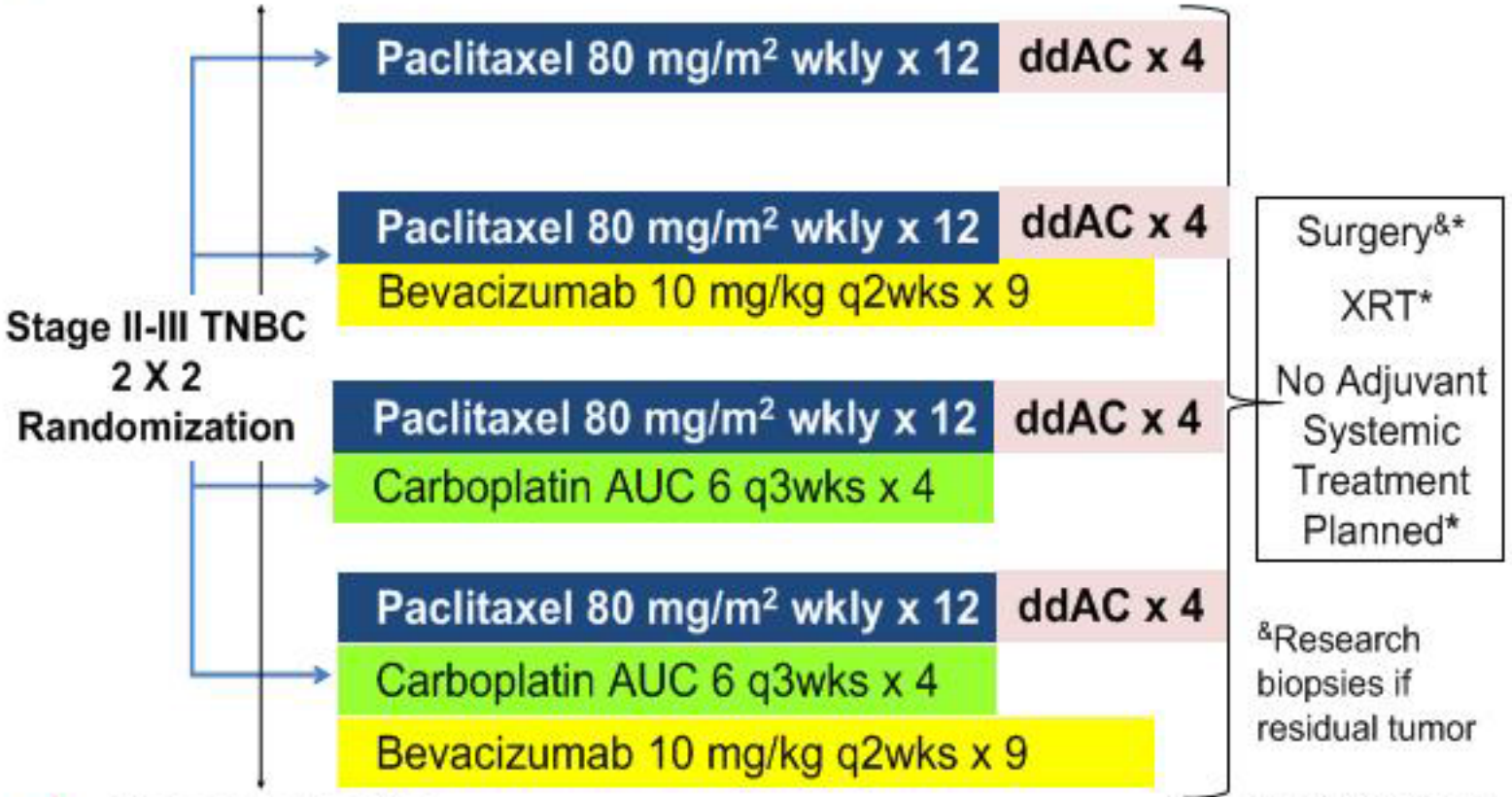
Conclusion

- **Primary study endpoint was reached: Nab- paclitaxel increased significantly the pCR rate compared to Paclitaxel (OR 1.53; p<0.001)**
- **This effect was seen in all subgroups, especially in patients with triple-negative tumors (OR 2.69)**
- **Nab-paclitaxel was associated with a higher rate of sensory neuropathy than Paclitaxel**
- **Long term follow-up is needed to validate if the increase in pCR rate translates into a better DFS and OS**

Impact of intrinsic subtype by PAM50 and other gene signatures on pathologic complete response rates in triple-negative breast cancer after neoadjuvant chemotherapy +/- carboplatin or bevacizumab: CALGB/Alliance 40603

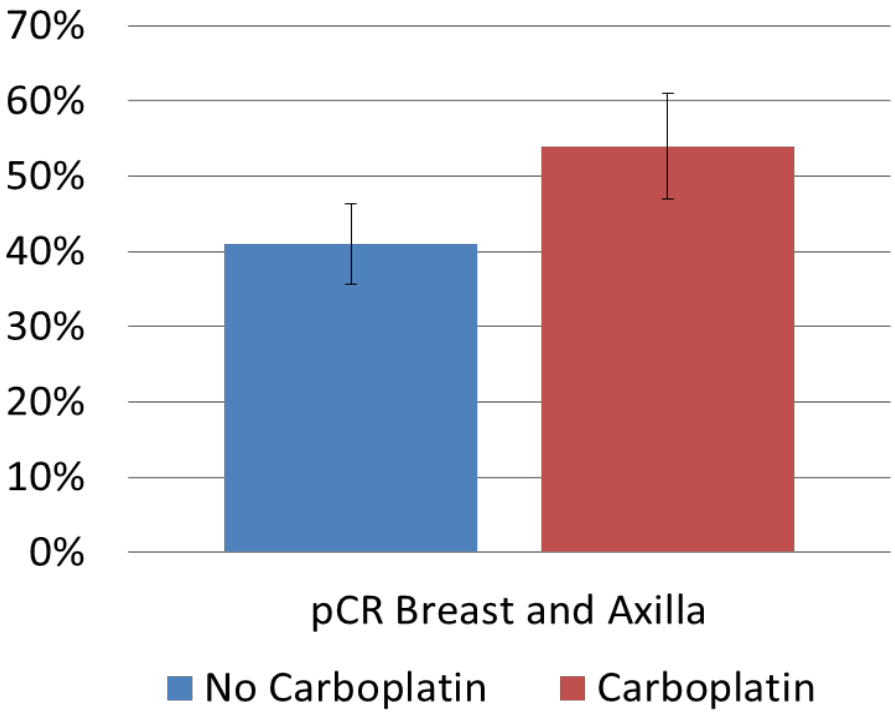
William M. Sikov, William T. Barry, Katherine A. Hoadley, Brandelyn N. Pitcher, Baljit Singh, Sara M. Tolaney, Charles S. Kuzma, Timothy J. Pluard, George Somlo, Elisa R. Port, Mehra Golshan, Donald A. Berry, Olwen M. Hahn, Lisa A. Carey, Charles M. Perou, Clifford A. Hudis and Eric P. Winer for the CALGB/Alliance

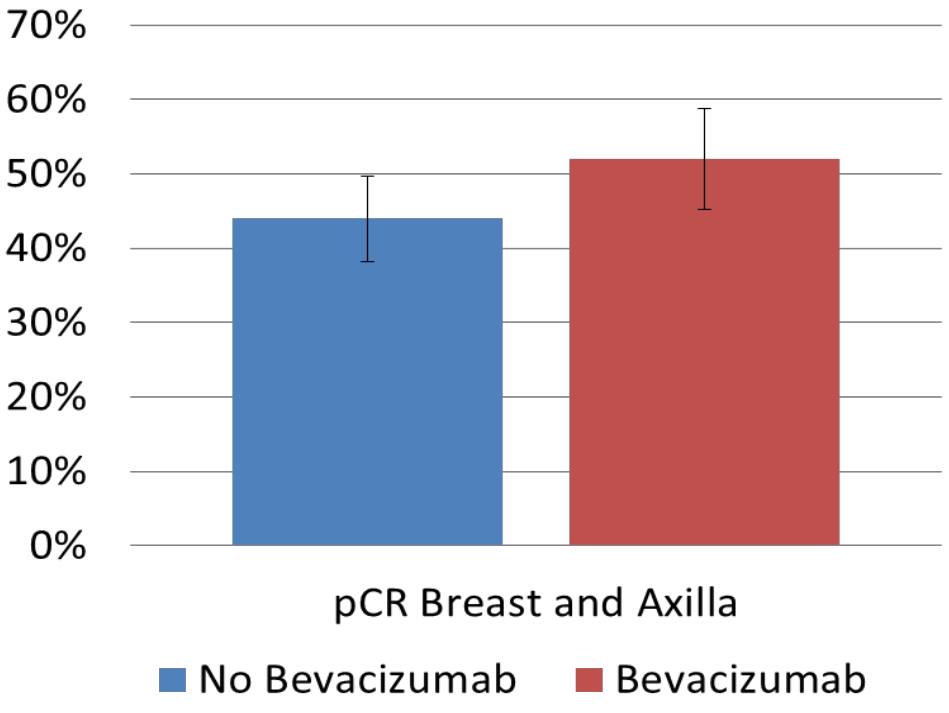
CALGB 40603: Schema – Randomized Phase II



CALGB 40603: pCR Breast/Axilla (ypT0/is N0)

41% (35-48%)	54% (48-61%)	44% (38-51%)	52% (45-58%)



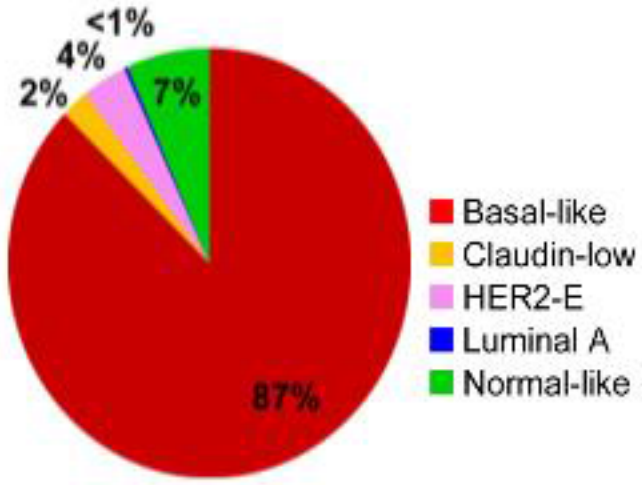


N=212	N=221	N=218	N=215

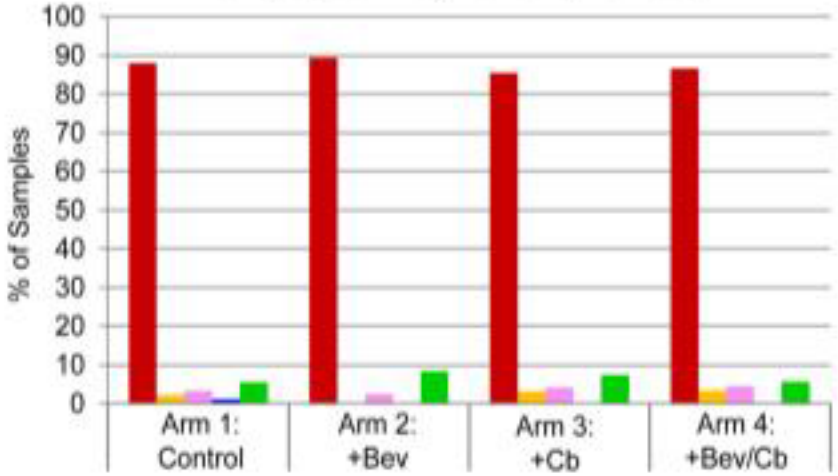
Odds ratio: 1.71	p = 0.0029	Odds ratio: 1.36	p = 0.0570

Intrinsic Subtype of Pre-treatment Samples

All samples (n=360)

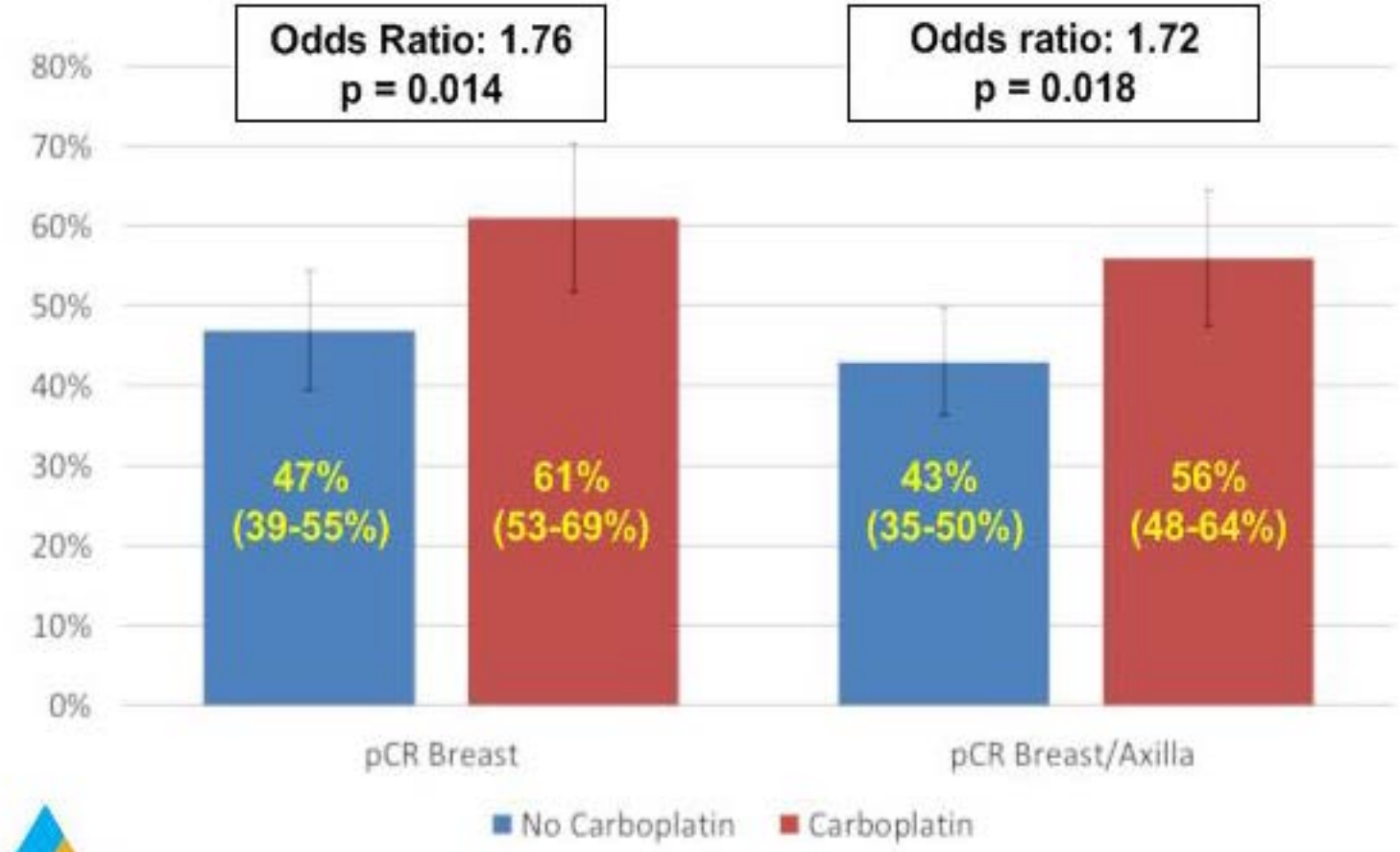


Distribution of subtypes did not vary by arm (Fisher p=0.88)

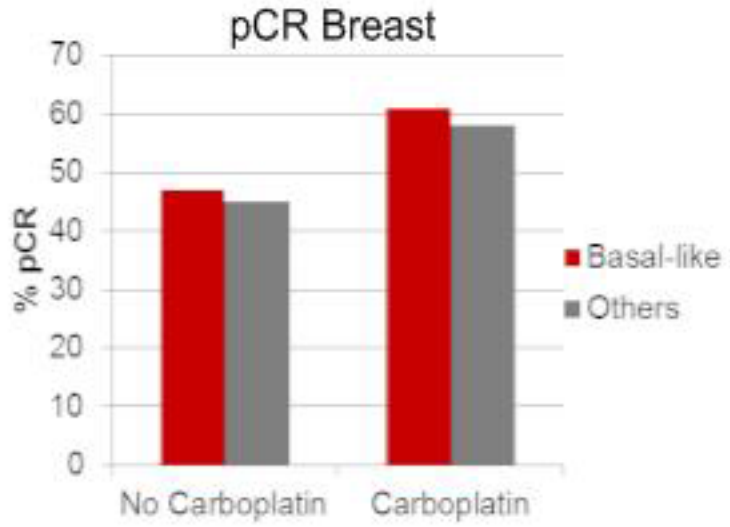


- Overall pCR breast rate in subtyped samples did not differ between Basal-like (170/314) (54%) and non-Basal-like (24/46) (52%) cancers

pCR in Basal-like subtype + / - Carboplatin



Carboplatin: Association of Subtype and pCR



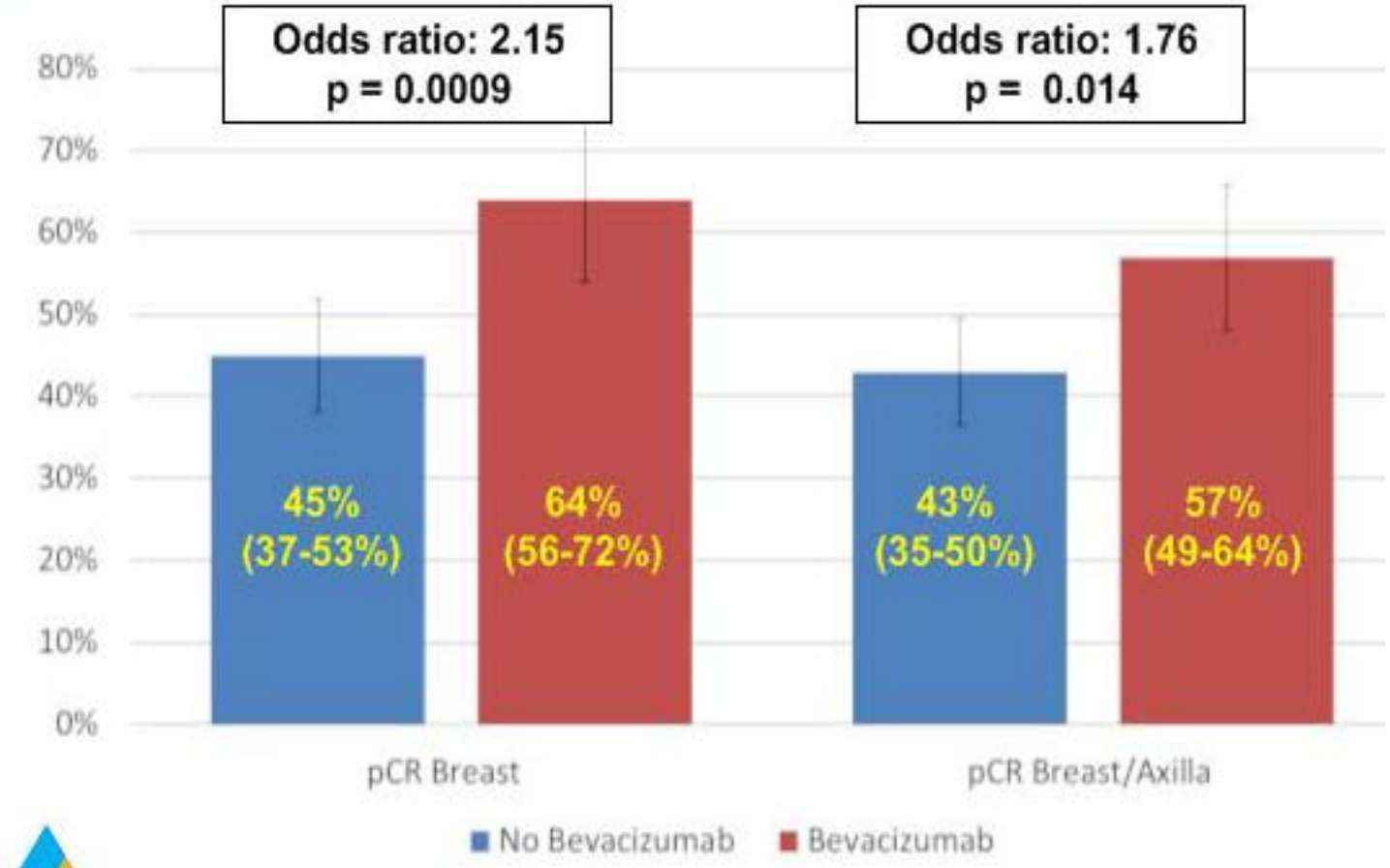
	n	No Carbo	Carbo
Basal-like	**314**	**73/155 (47%)**	**97/159 (61%)**
Others	**46**	**9/20 (45%)**	**15/26 (58%)**

Carboplatin benefit did not vary by subtype (interaction p=0.93)

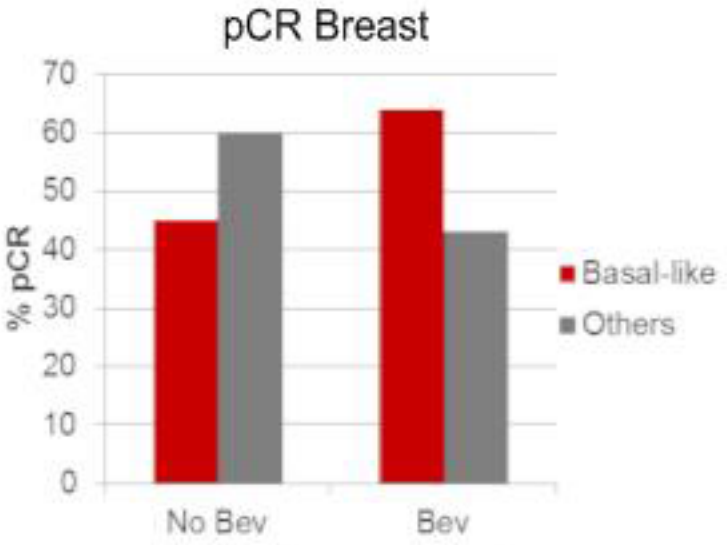
pCR Breast:

Patient group	N	OR	p-value
All patients	443	1.76	0.0018
All subtyped	360	1.74	0.009
Basal-like	314	1.76	0.014
Non-Basals	46	1.67	0.55

pCR in Basal-like subtype + / - Bevacizumab



Bevacizumab: Association of Subtype and pCR



	n	No Bev	Bev
Basal-like	**314**	**73/162 (45%)**	**97/152 (64%)**
Others	**46**	**15/25 (60%)**	**9/21 (43%)**

Bevacizumab benefit was significantly greater in Basal-like subtype (interaction p=0.024)

pCR Breast:

Patient group	N	OR	p-value
All patients	443	1.58	0.0089
All subtyped	360	1.78	0.0081
Basal-like	314	2.15	0.0009
Non-Basals	46	0.50	0.25

Gene Expression Proliferation and ER Signatures

	All Samples			Basal-like only		
Variable	Overall pCR rate	Carboplatin benefit	Bevacizumab benefit	Overall pCR rate	Carboplatin benefit	Bevacizumab benefit
High Proliferation[1]	**0.0099**	0.8068	**0.031**	**0.0041**	0.2674	0.8491
Low Estrogen Signature[2]	**0.0032**	0.8738	**0.0002**	**0.0002**	0.9615	**0.0216**

[1]Parker et al, JCO 2007 (PMID:19204204); [2]Oh et al, JCO 2006 (PMID:16505416)

- High proliferation signature was predictive of pCR in all patients and in the Basal-like subset, and was predictive of greater pCR benefit for bevacizumab in all patients
- Low estrogen signature was predictive of pCR and predictive of greater pCR benefit for bevacizumab in all patients and in the Basal-like subset
- Neither of these signatures was predictive of greater pCR benefit for carboplatin

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Conclusions: CALGB 40603

- Large percentage of basal-like cancers by intrinsic subtyping (almost 90%)
- No difference in PCR based in basal-like and non basal-like phenotype
- Higher PCR noted for the addition of bevazicumab in basal-like cancers but lower PCR noted with bevacizumab in non basal-like
- High proliferation, low ER signaling associated with higher PCR rate with bevacizimab

Optimal pre-operative therapy for TNBC?

- Addition of carboplatin to paclitaxel increases PCR in TNBC (both basal and non-basal) but increased hematologic toxicity and decreased dose intensity of paclitaxel without growth factors
- No profile identified as yet that predicts which patients need carboplatin
- Is Nab-paclitaxel an alternative to paclitaxel plus carboplatin (certainly less toxic)?

ICR The Institute of Cancer Research in partnership with KING'S College LONDON CANCER RESEARCH UK BREAKTHROUGH BREAST CANCER

TNT: 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

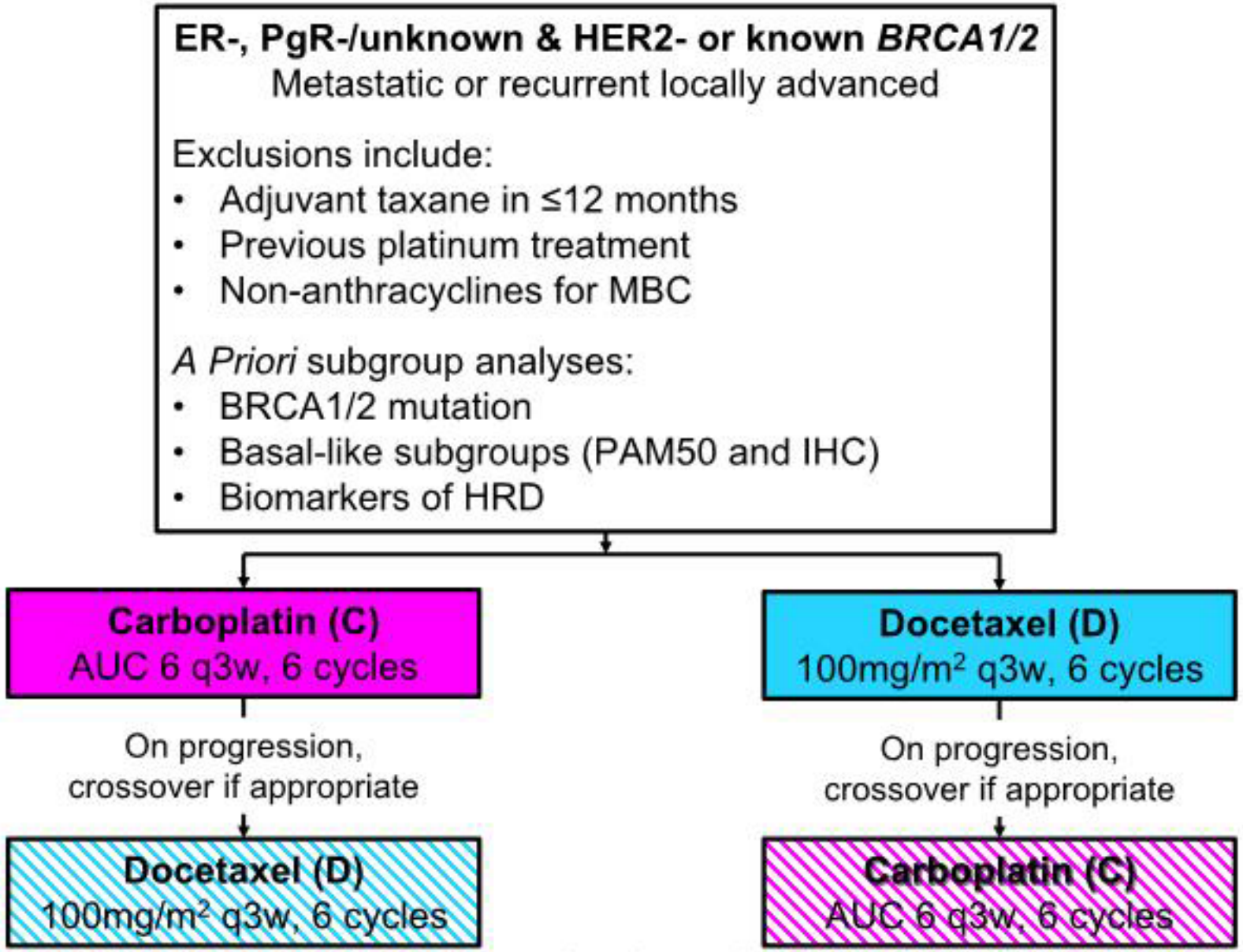
Andrew Tutt, *Paul Ellis, Lucy Kilburn, Cheryl Gillett, Sarah Pinder, Jacinta Abraham, Sophie Barrett, Peter Barrett-Lee, Stephen Chan, Maggie Cheang, Mitch Dowsett, Lisa Fox, Patrycja Gazinska, Anita Grigoriadis, Alexander Gutin, Catherine Harper-Wynne, Matthew Hatton, Sarah Kernaghan, Jerry Lanchbury, James Morden, Julie Owen, Jyoti Parikh, Peter Parker, Nazneen Rahman, Rebecca Roylance, Adam Shaw, Ian Smith, Rose Thompson, Kirsten Timms, Holly Tovey, Andrew Wardley, Gregory Wilson, Mark Harries, Judith Bliss*

on behalf of the TNT trial management group and investigators

CRUK/07/012

Making the discoveries that defeat cancer

Trial design



Baseline characteristics

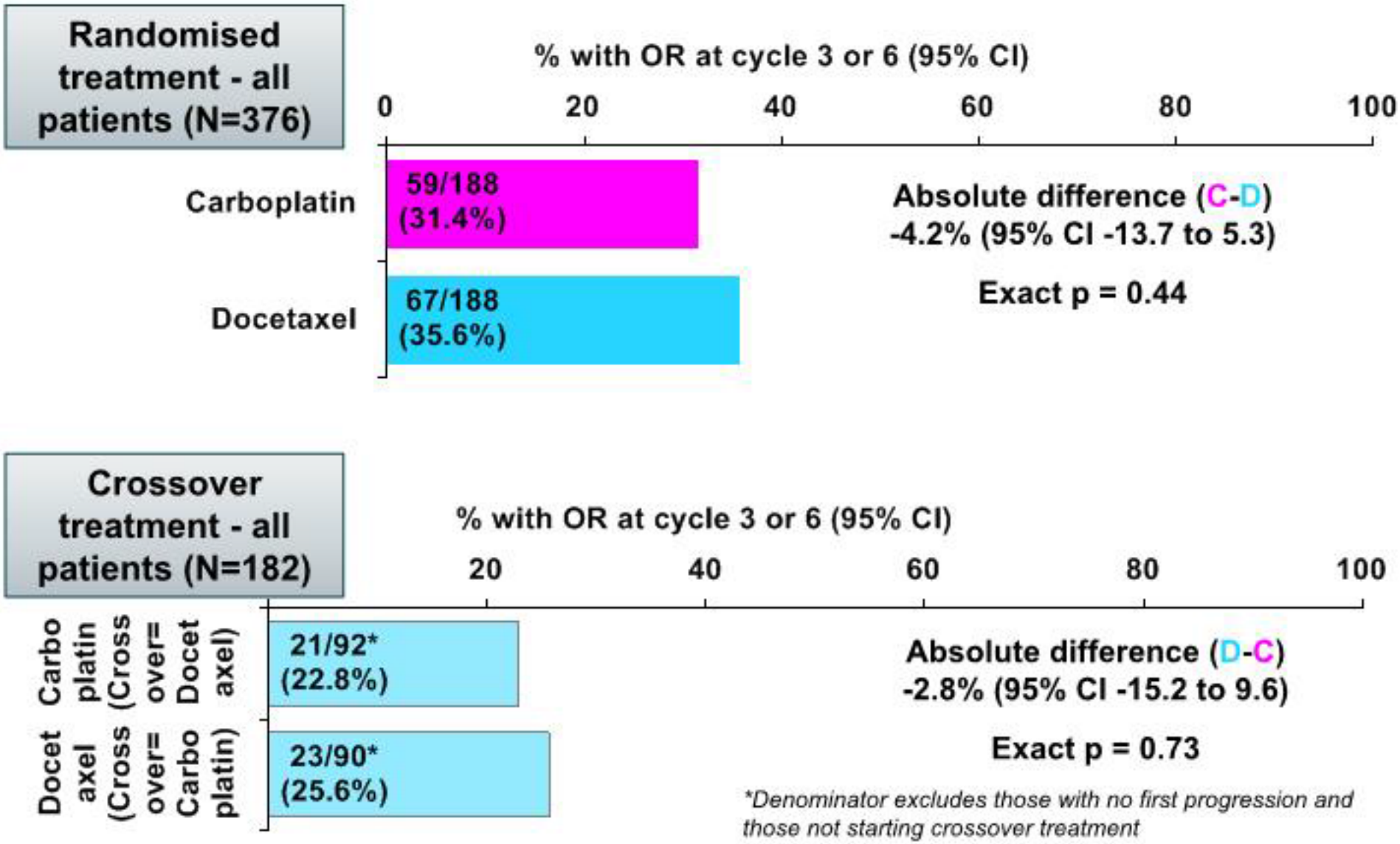
376 patients/74 UK centres between 08/08-03/14

		Carboplatin (N=188)		Docetaxel (N=188)	
Patient status at baseline*, n(%)	TN – no known mutation	166	*88.3*	171	*91.0*
	Known BRCA1/2 mutation	17	*9.0*	12	*6.4*
Stage , n(%)	Locally advanced	15	*8.0*	20	*10.6*
	Metastatic	173	*92.0*	168	*89.4*
ECOG PS, n(%)	0 or 1	174	*92.6*	176	*93.6*
	2	14	*7.5*	12	*6.4*
Taxane in adjuvant setting, n(%)		65	*34.6*	61	*32.5*
Liver or parenchymal lung metastases, n(%)		98	*52.1*	100	*53.2*
Age, median (IQR)		55.7 *47.6-62.9*		54.9 47.9-63.5	
Time to relapse, median (IQR)		2.1 *1.5-3.4*		2.1 *1.3-3.5*	

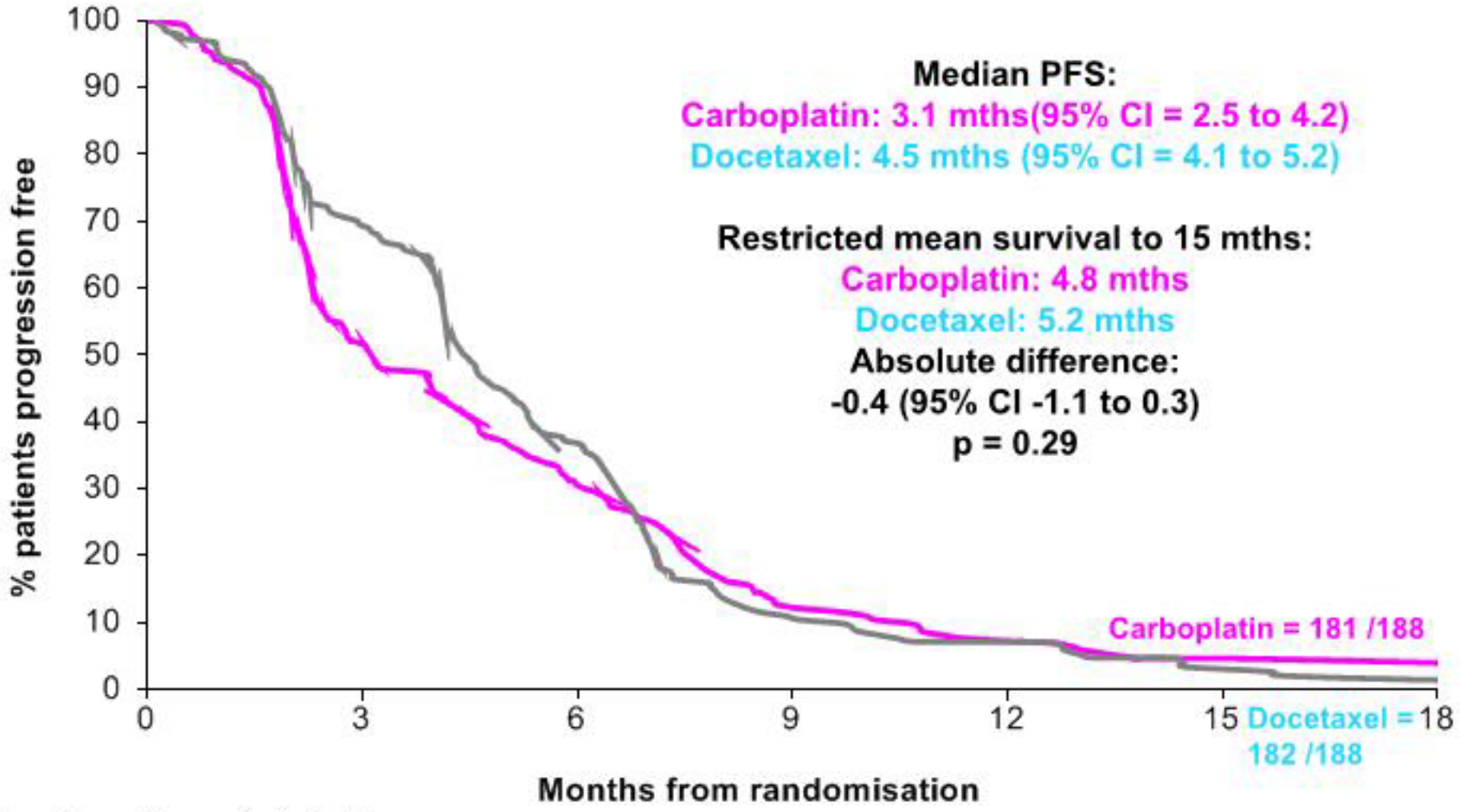
Minimisation balancing factors

** 10 pts (5 C, 5 D) subsequently declared ineligible by local centre (but included in ITT analysis)*

Objective response



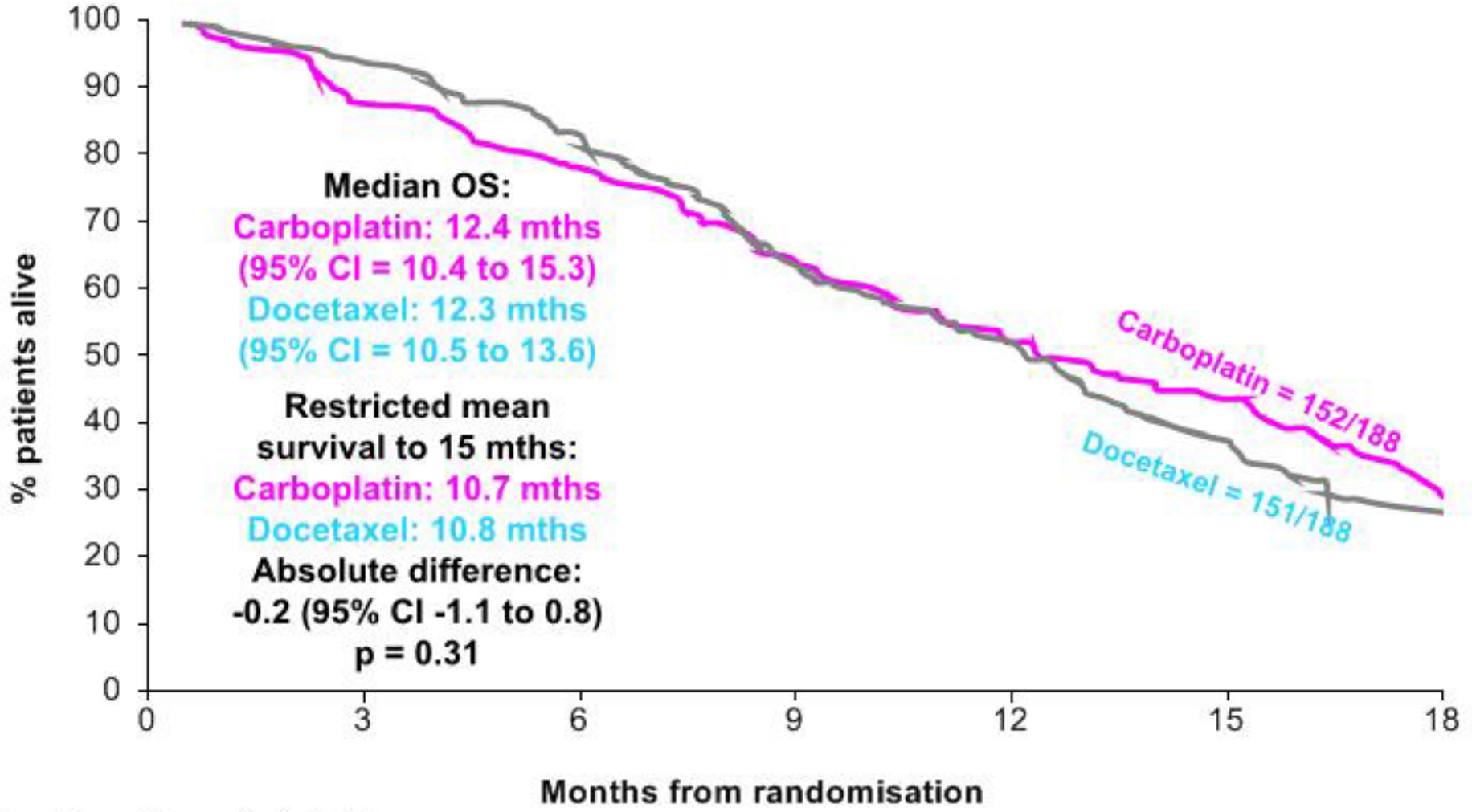
Progression-free survival



Number of events/at risk

C:	*0/188*	*90/98*	*40/56*	*32/22*	*9/13*	*5/8*	*0/7*
D:	*0/188*	*57/130*	*60/69*	*48/20*	*7/13*	*6/5*	*2/3*

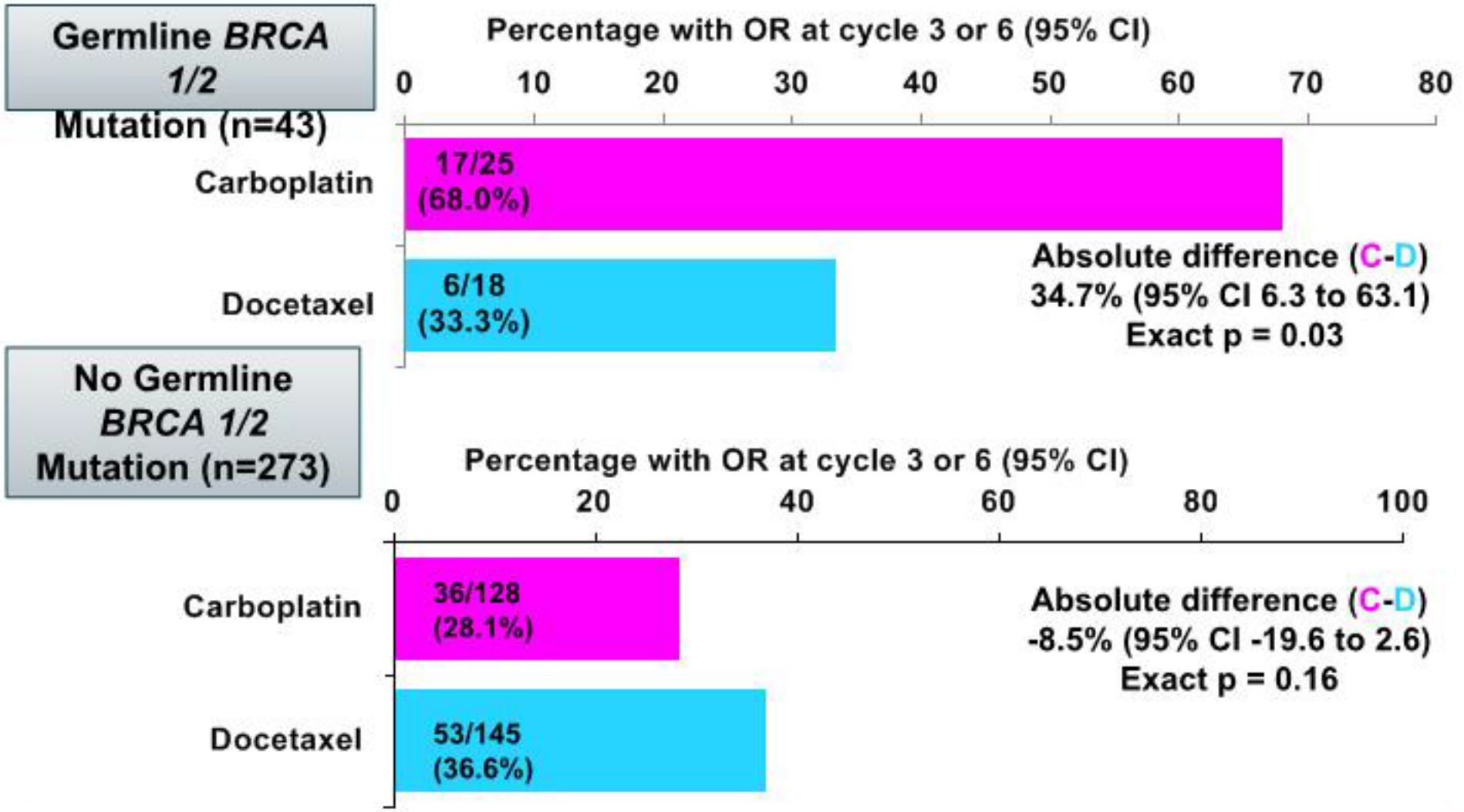
Overall survival



Number of events/at risk

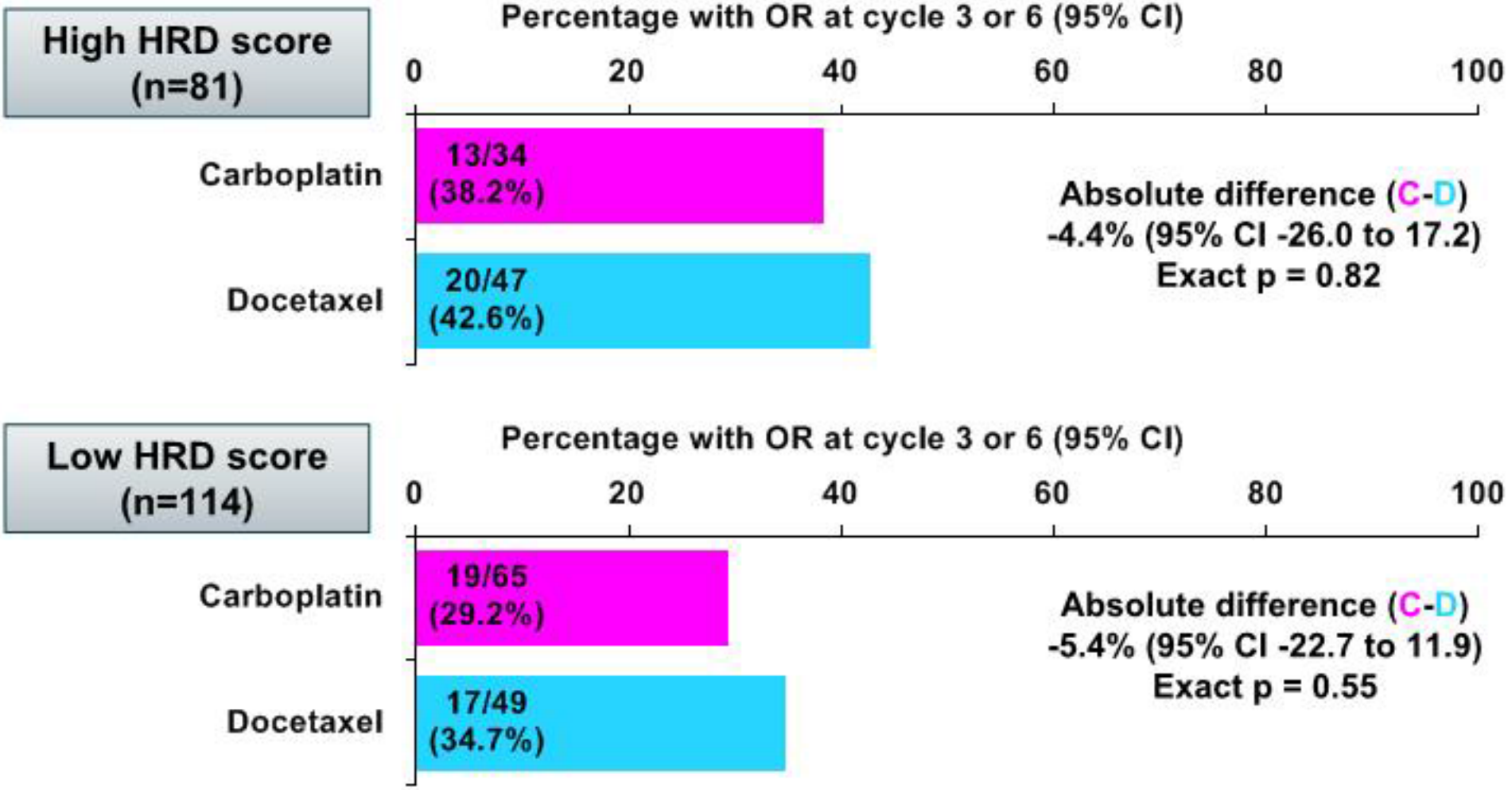
C:	*0/188*	*23/165*	*18/141*	*24/11*	*22/89*	*14/71*	*22/44*

Objective response – *BRCA 1/2* status



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

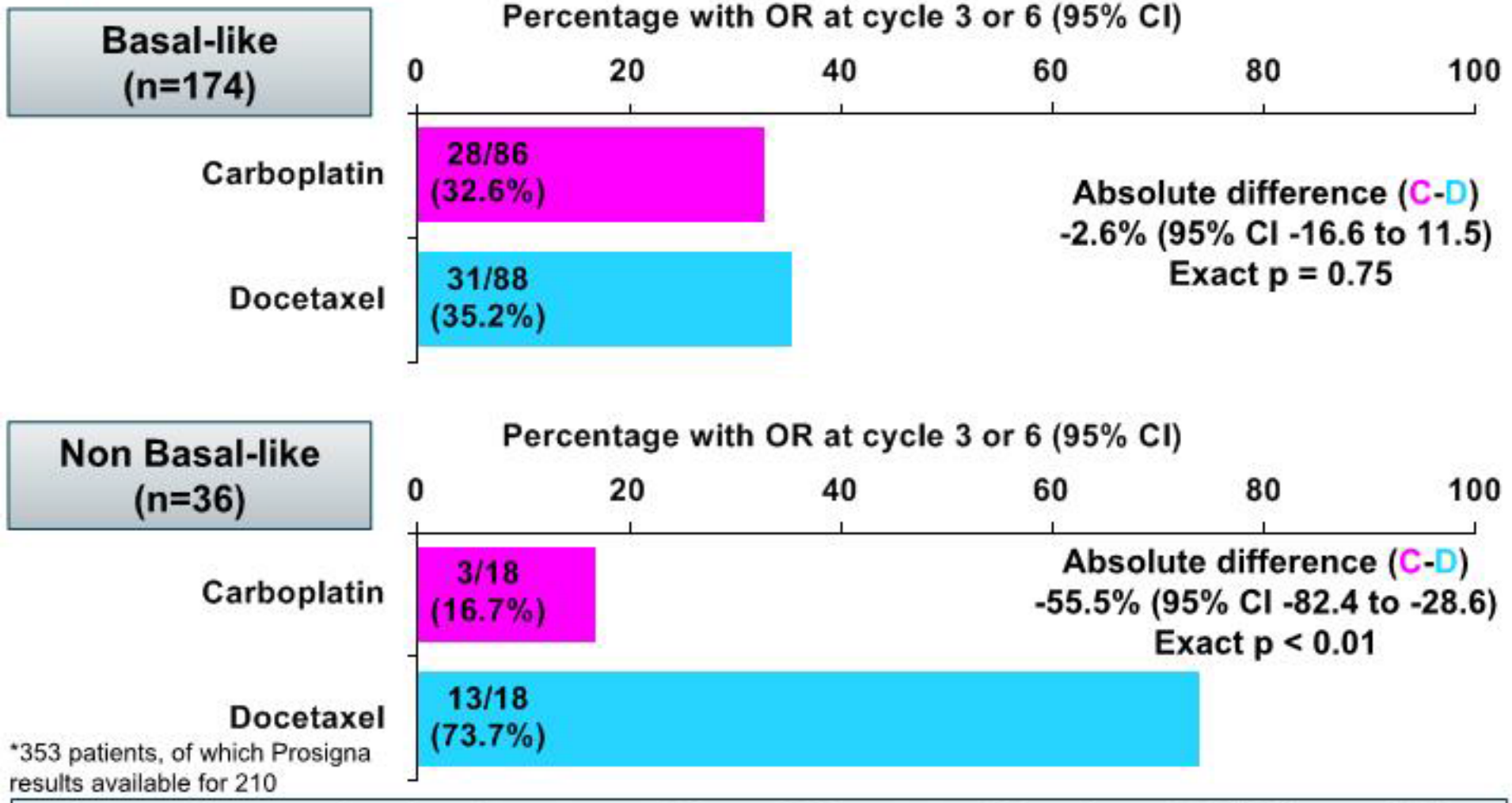
Objective response – HRD score



Interaction: randomised treatment & dichotomised HRD score: p = 0.91

Objective response – Basal-like (Prosigna PAM50)[24]

All patients entered by site as TNBC*



*353 patients, of which Prosigna results available for 210

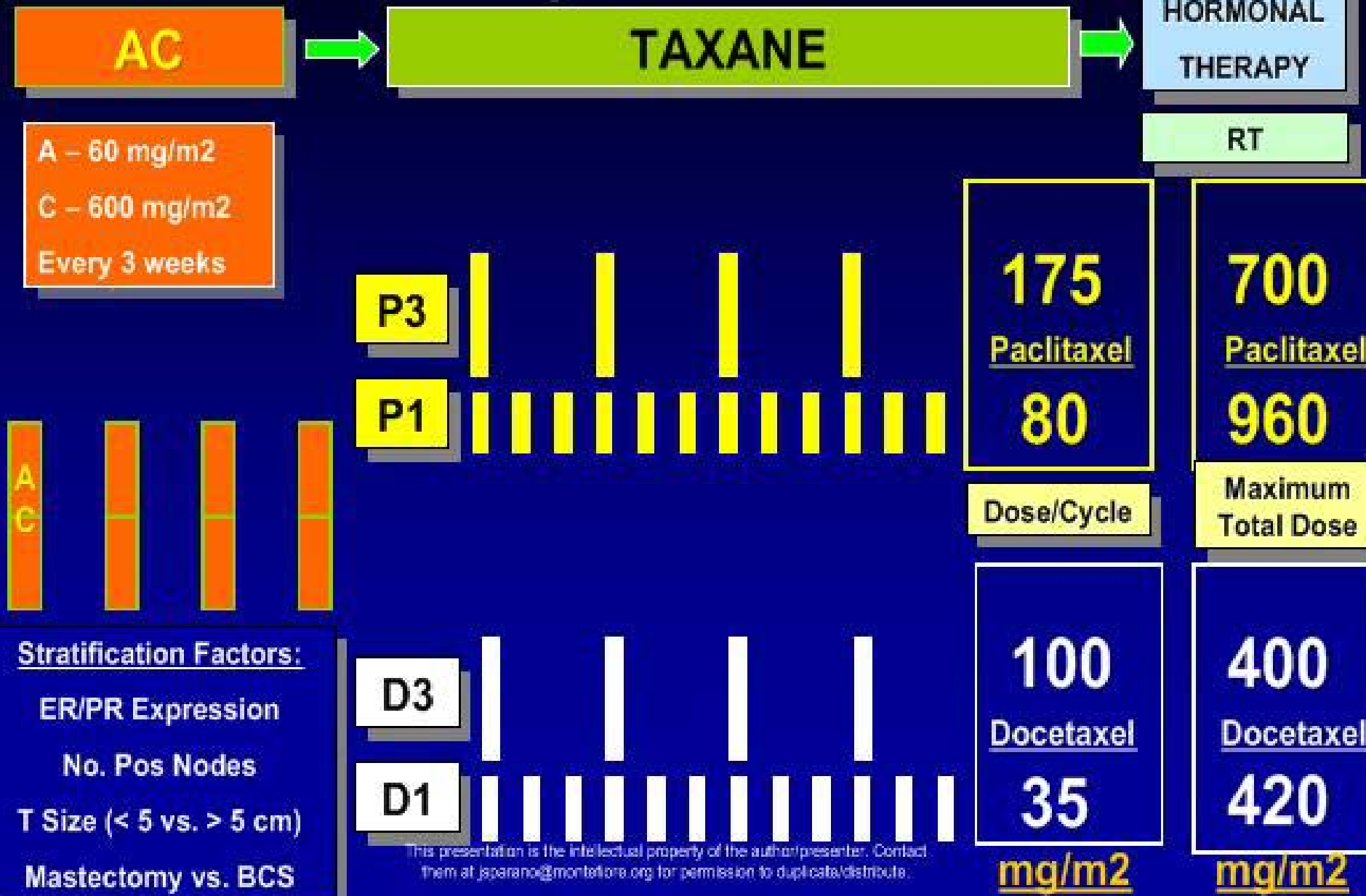
Interaction: randomised treatment & basal-like status (Prosigna PAM50): p = 0.01

Conclusions: TNT trial

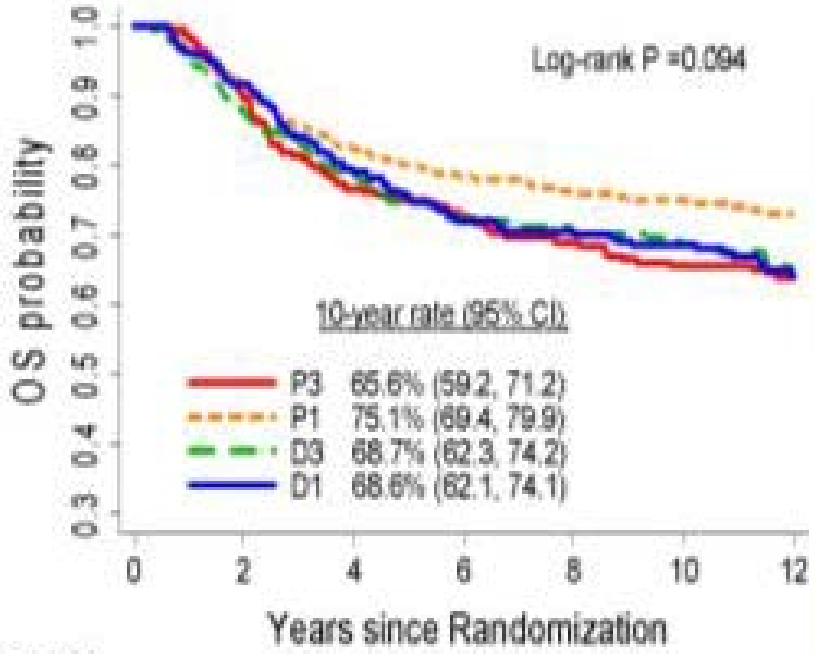
- In the overall population of patients with TNBC carboplatin did not offer an advantage over docetaxel
  - Carboplatin superior to docetaxel in patients with known BRCA germline mutations
  - No difference between agents based on HRD score
  - Superiority of docetaxel over carboplatin in non basal-like TNBC interesting and requires further study

Methods - E1199 - Schema & Patient Population:

Stage IIA-IIIA Breast Cancer

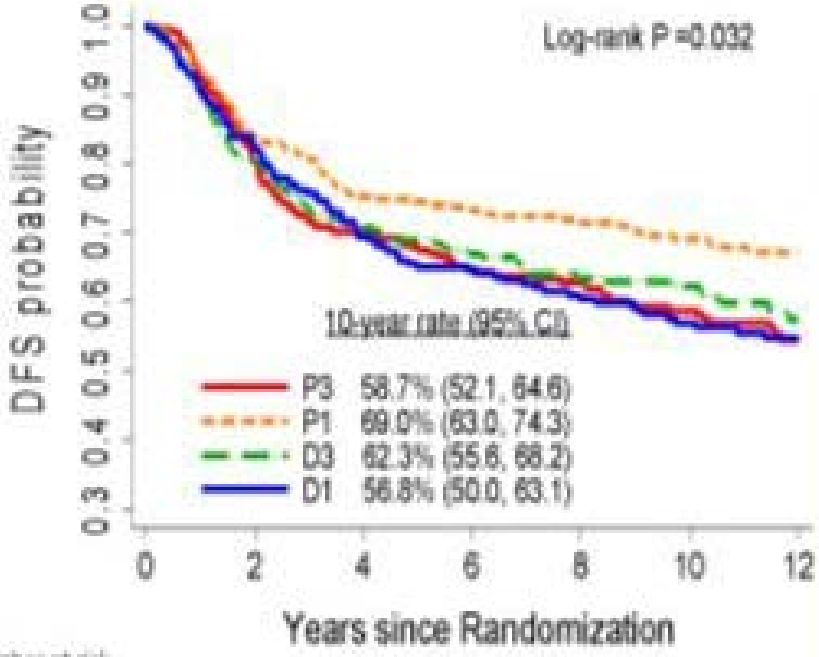


Results – Exploratory Analysis in Triple Negative Disease (N=1025)



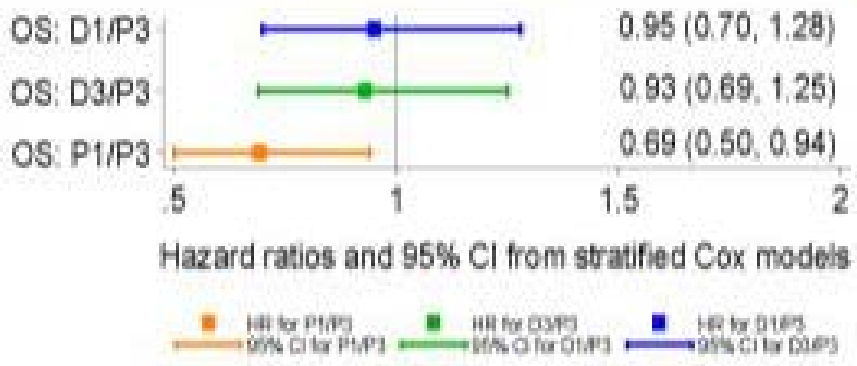
Number at risk

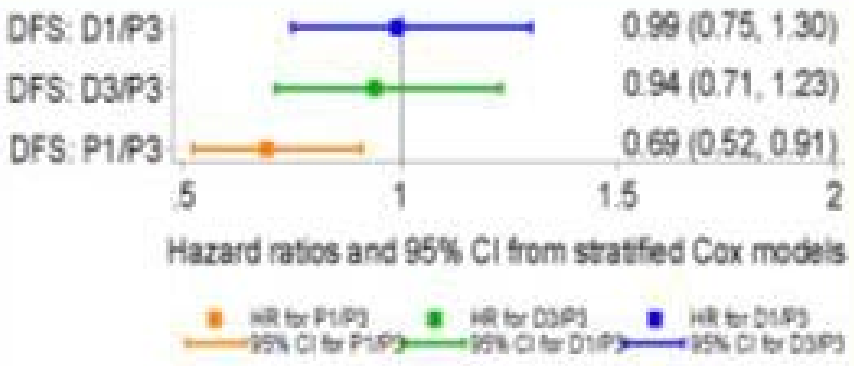
P3	261	232	190	168	149	134	84
P1	274	245	218	196	179	167	102
D3	248	214	186	159	144	139	87
D1	243	218	184	156	143	129	77



Number at risk

P3	261	207	166	138	126	102	47
P1	274	226	197	175	159	127	61
D3	248	195	160	134	120	106	52
D1	243	197	160	133	109	88	49





San Antonio Breast Cancer Symposium, Dec 9-13, 2014

FERGI Phase II Study of PI3K Inhibitor Pictilisib (GDC-0941) plus Fulvestrant vs Fulvestrant plus Placebo in Patients with ER+, Aromatase Inhibitor-(AI)-Resistant Advanced or Metastatic Breast Cancer – Part I Results

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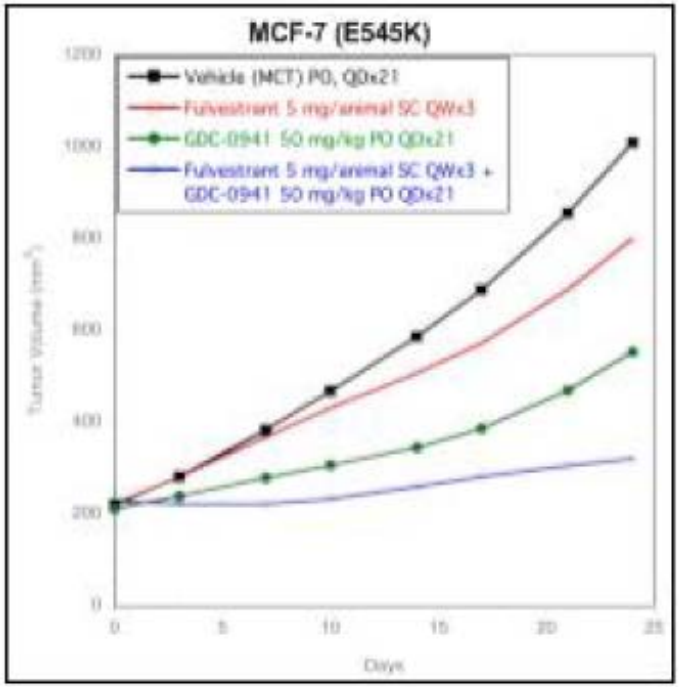
PI3K Pathway Activation in MBC

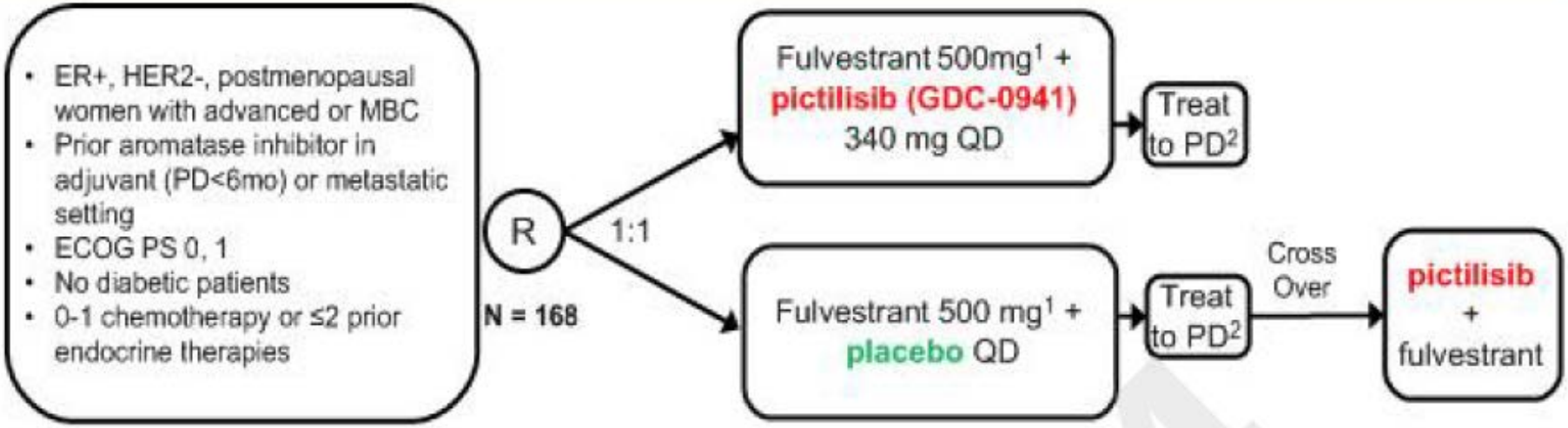
- 40-45% of ER+ BC tumors harbor a *PIK3CA* mutation
- PI3K/mTOR signaling has been implicated as a resistance mechanism to anti-estrogen therapies both *in vitro*[1] and in the clinical setting[2]

- Pictilisib is a orally bioavailable, potent and selective inhibitor of Class I PI3K[3]
- Oncogenic alterations in PI3K pathway were predictive of sensitivity to pictilisib in vitro and in vivo
- The combination of pictilisib and fulvestrant is synergistic in ER+ BC xenograft models



1. Miller *et al.* JCO 2010
2. Baselga *et al.* NEJM 2012; Bachelot et al. JCO 2012
3. Raynaud et al., MCT 2009

FERGI Study Design – Part I



Stratification factors	1° objective	2° objectives
• *PIK3CA*-MT and *PTEN* loss[3] • Measurable disease • 1° vs. 2° resistance[4]	• PFS in the ITT • PFS in *PIK3CA*-MT pts • Safety	• Objective response rate • Duration of objective response • PK

[1] Administered on D1 of each 28 day cycle and C1D15; [2] Tumor assessments performed every 8 weeks; [3] Exons 9 and 20 in the codons encoding amino acids E542, E545, and H1047 were detected by RT-PCR; [4] Disease relapse during or within 6 months of completing AI treatment in the adjuvant setting, or disease progression within 6 months of starting AI treatment in the metastatic setting. [5] Data presented is with an additional year of follow up per-protocol primary analysis

- Median duration of follow up 17.5 months

Baseline Demographics

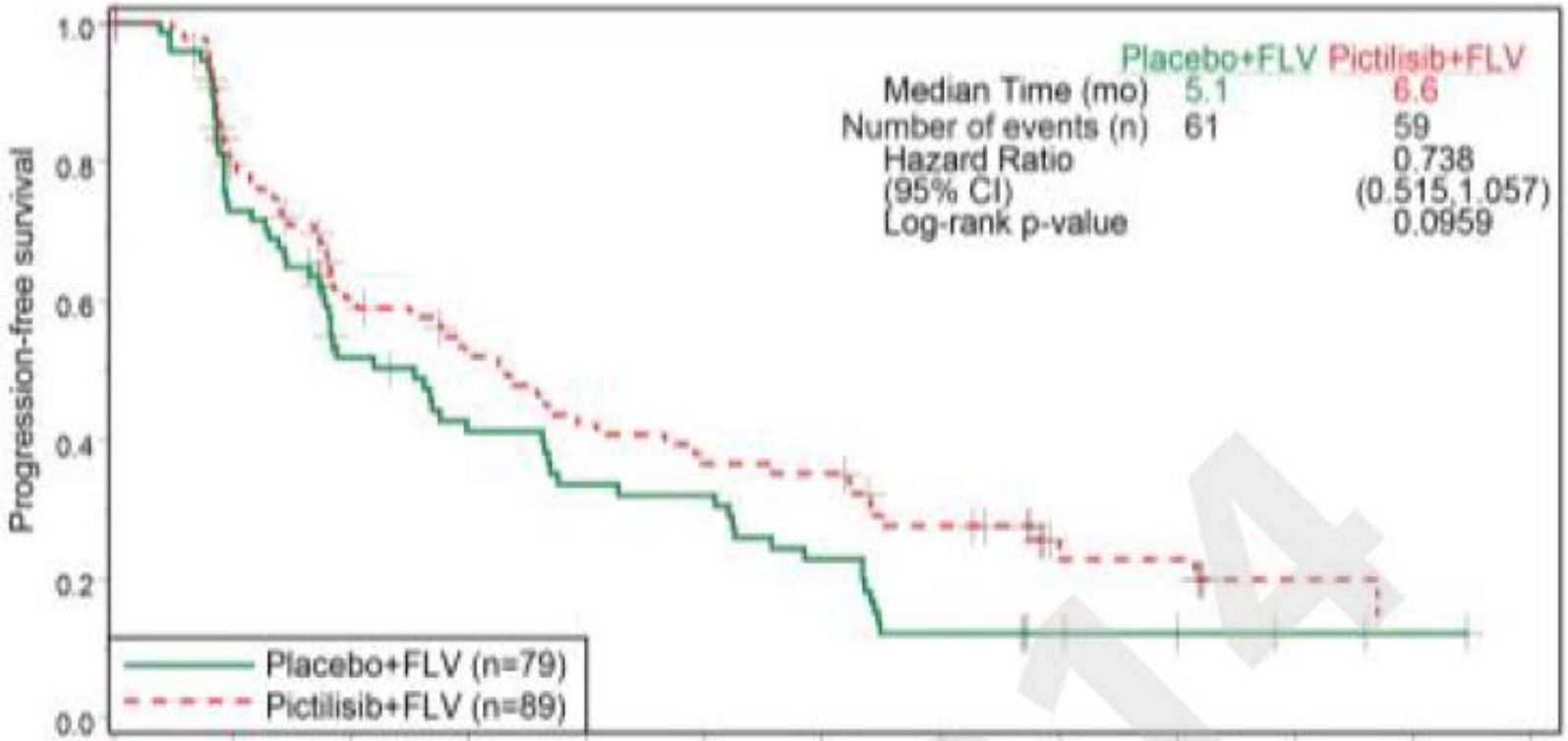
		Pictilisib (n=89)	Placebo (n=79)
Age	Median (Range)	60.0 (36-90)	63.0 (40-82)
	≥ 65	29 (33%)	29 (37%)
Race	White	78 (88%)	68 (86%)
	Asian	5 (6%)	8 (10%)
ECOG PS	0	61 (69%)	45 (57%)
	1	28 (32%)	33 (43%)
PIK3CA-mutation positive	n	38 (43%)	32 (41%)
Progesterone receptor[1]	PR positive (≥10%)	58 (65%)	58 (73%)
	PR negative (<10%)	21 (24%)	14 (18%)
Endocrine resistance (derived)[2]	Primary	43 (48%)	41 (52%)
	Secondary	46 (52%)	38 (48%)

[1]PR status based on central assessment; [2]Primary and secondary resistance

		Pictilisib (n=89)	Placebo (n=79)
Disease (n)	Measurable (derived)	51 (57%)	43 (54%)
	Visceral	51 (57%)	42 (53%)
	Bone-only	19 (21%)	17 (22%)
No. of metastatic sites	1	31 (35%)	26 (33%)
	2	34 (38%)	22 (28%)
	≥3	24 (27%)	31 (39%)
Purpose of most recent systemic therapy	Adjuvant	24 (27%)	20 (25%)
	Advanced/Metastatic	65 (73%)	59 (75%)
Previous chemo-therapy	n	64 (72%)	50 (63%)
	Neo- or Adjuvant	43 (48%)	35 (44%)
	Metastatic	21 (24%)	15 (19%)
No. of prior systemic therapies	n	65	59
	1	33 (37%)	36 (46%)
	2	23 (26%)	15 (19%)
	≥3	9 (10%)	8 (10%)

- Both arms appear to be well balanced

Progression-Free Survival in the ITT Population

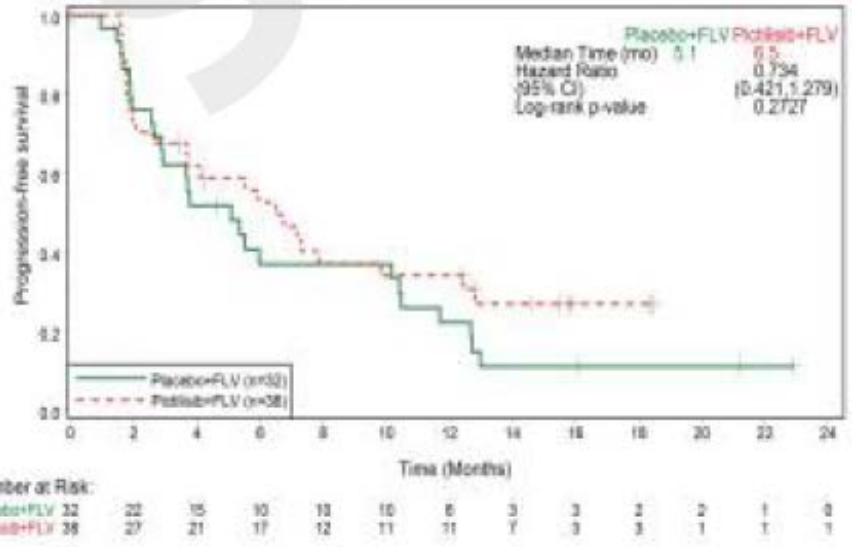


Number at Risk:

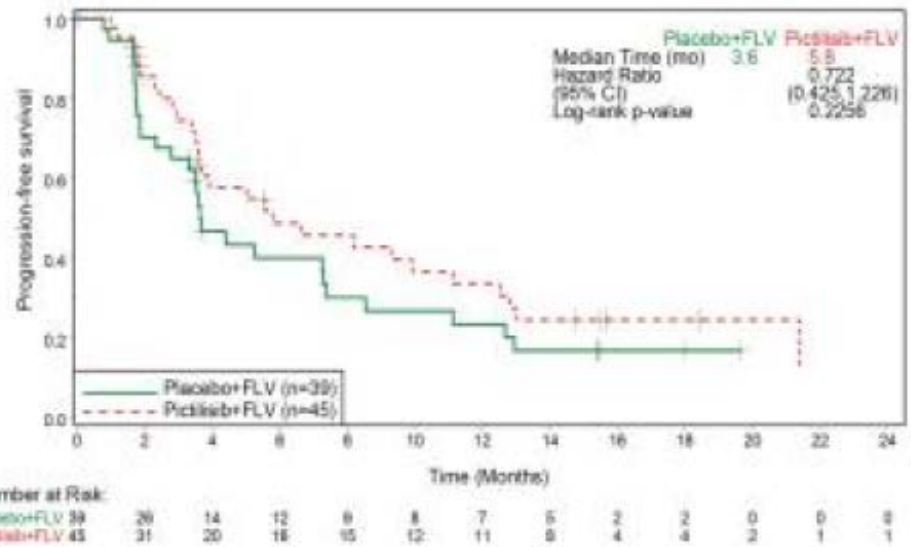
Placebo+FLV	79	54	35	27	22	21	15	8	5	4	2	1	0
Pictilisib+FLV	89	63	45	37	30	26	25	18	9	8	3	2	2

Progression-Free Survival Based on Tumor *PIK3CA* Mutation Status

PIK3CA-Mutant Population

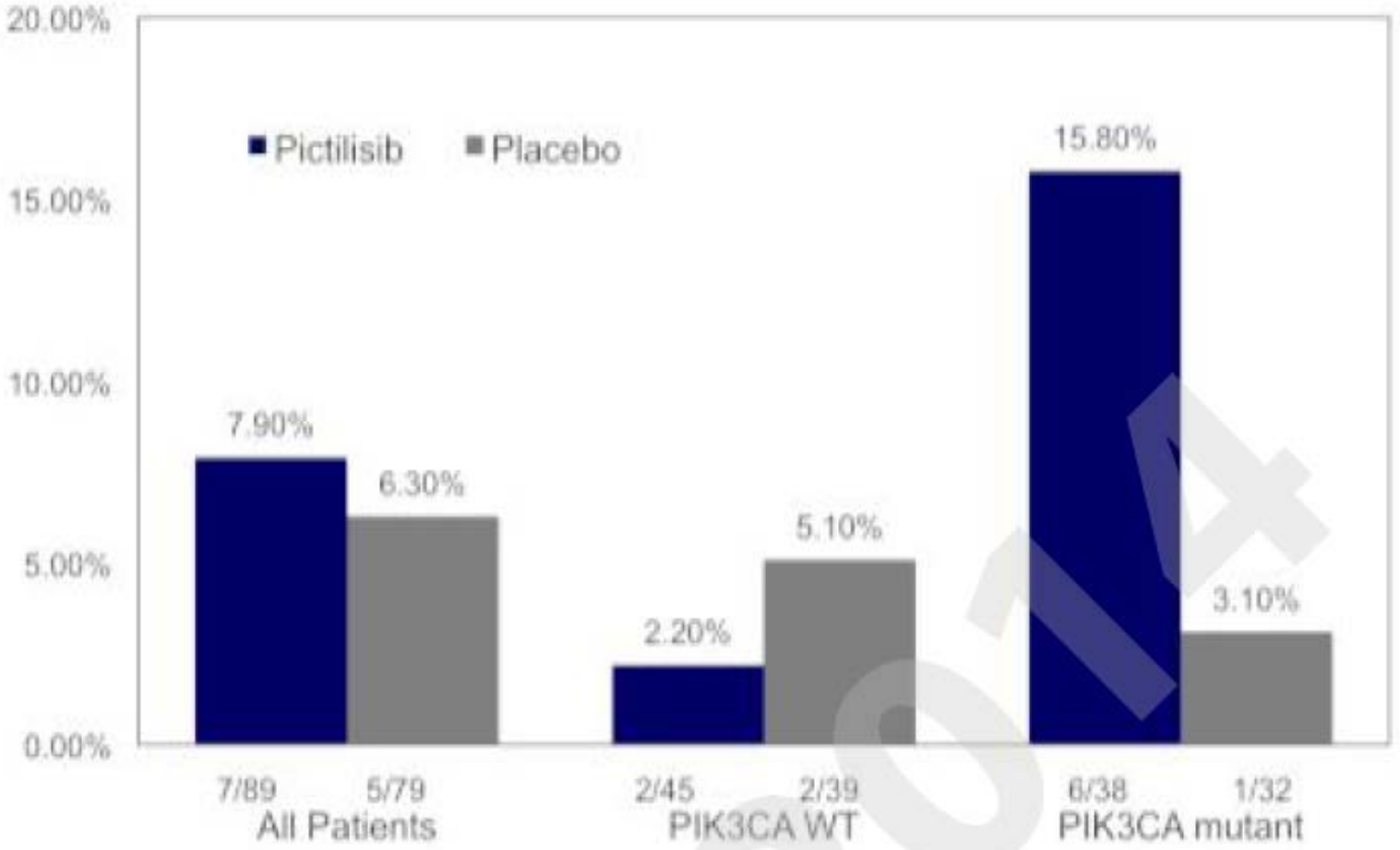


PIK3CA "Wild-Type" Population



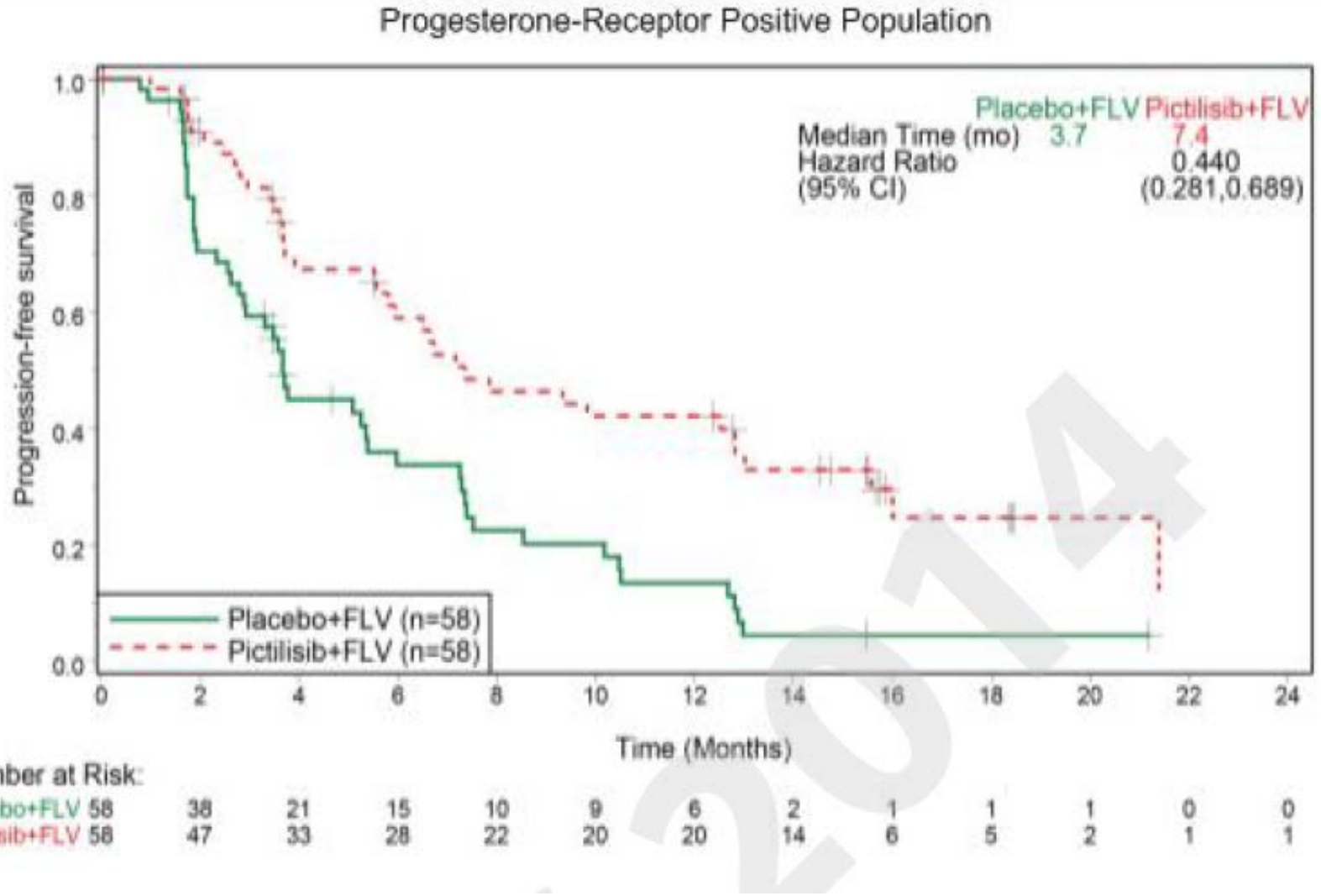
- PIK3CA mutation status does not predict benefit of the addition of pictilisib to fulvestrant

Objective Response Rate



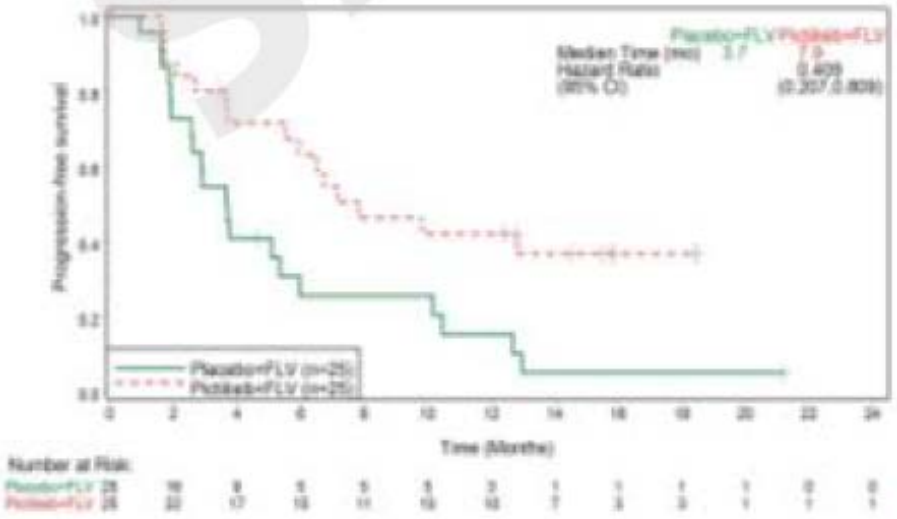
- ORR in the PIK3CA-mutant group treated with pictilisib numerically higher than placebo patients
  - Placebo ORR consistent with prior reports (Chia et al., JCO 2008)

Progression-Free Survival in Patients with ER and PR Positive Disease

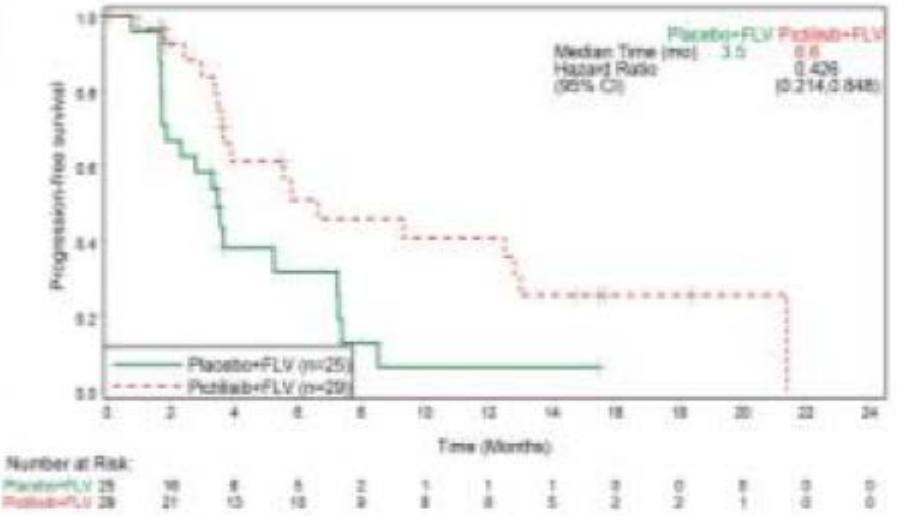


Progression-Free Survival in Patients with ER and PR Positive Disease Based on Tumor *PIK3CA* Mutation Status

PR+ and *PIK3CA* mutation



PR+ and *PIK3CA* "Wild-Type"



AEs Related to Any Study Drug

	Pictilisib (n=89)		Placebo (n=79)	
Adverse Event[1,2]	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhea	56 (63%)	5 (7%)	7 (9%)	-
Nausea	43 (48%)	3 (3.4%)	15 (19%)	-
Rash[3]	38 (43%)	15 (17%)	5 (6%)	-
Dysgeusia	31 (35%)	-	-	-
Fatigue	24 (27%)	5 (6%)	16 (20%)	-
Vomiting	18 (20%)	3 (3%)	3 (4%)	-
Decreased appetite	17 (19%)	1 (1%)	5 (6%)	-
Hyperglycemia	15 (17%)	4 (5%)	4 (5%)	-
Stomatitis	14 (16%)	2 (2%)	2 (2%)	-
Hot flush	10 (11%)	-	10 (13%)	-
AST increased	10 (11%)	3 (3%)	7 (8%)	2 (3%)
Dyspepsia	8 (9%)	-	2 (3%)	-
Mucosal inflammation	9 (10%)	-	2 (3%)	-
Pneumonitis	7 (8%)	1 (1%)	1 (1%)	-
Colitis	4 (5%)	3 (3%)	-	-

[1]Adverse events independent of attribution; based on CTCAE v.3
[2]Adverse events >10% except pneumonitis and colitis
[3]Includes all rash, generalized, maculo-papular, pruritic, erythematous and papular rash

- There were 28 (31%) SAEs in treatment arm vs 16 (20%) in placebo arm
- Safety is consistent with our single agent phase I experience
- No drug-drug interaction between pictilisib and fulvestrant
- There were no treatment related deaths reported

FERGI Part I Summary

- Safety
  - The safety profile in FERGI is consistent with Phase I experience
  - Toxicity (GI and dermatological) resulted in significant dose modifications and discontinuations of pictilisib

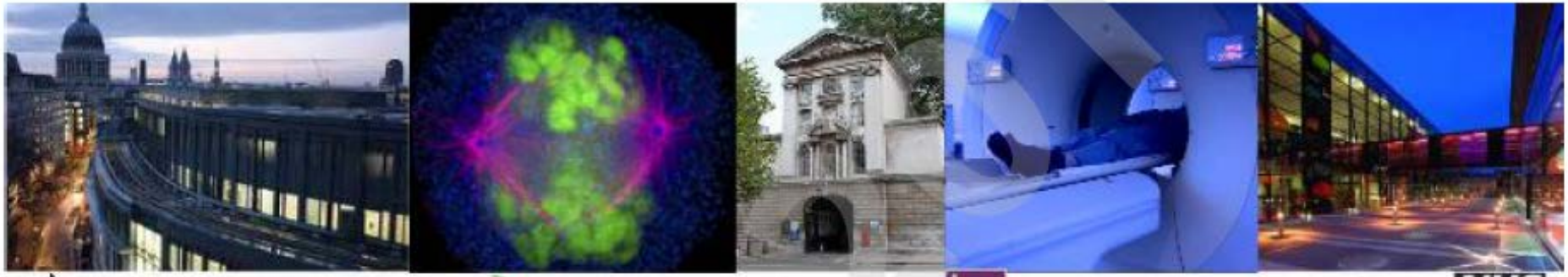
- Efficacy
  - In the ITT population, the addition of pictilisib to fulvestrant was associated with a non-statistically significant mPFS improvement (5.1m vs 6.6 m, HR 0.74)
  - PIK3CA mutation status does not predict benefit of the addition of pictilisib to fulvestrant
  - Exploratory subgroup analyses demonstrated potential activity in patients with ER+/PR+ tumors. Further studies warranted to explore this finding.

Preoperative window of opportunity study of the PI3K inhibitor Pictilisib (GDC-0941) plus Anastrozole vs Anastrozole alone in patients with ER+, HER2-negative breast cancer (OPPORTUNE study)

P. Schmid, S.E. Pinder, D. Wheatley, C. Zammit, J. Macaskill, J. Hu, R. Price, N Bundred, S. Hadad, A. Shia, S.-J. Sarker, L. Lim, P. Gazinska, N. Woodman, D. Korbie, M. Trau, P. Mainwaring, P. Parker, A. Purushotham, A.M. Thompson

on behalf of the OPPORTUNE study investigators

Barts Cancer Institute, St Bartholomew's Hospital; Queen Mary University of London



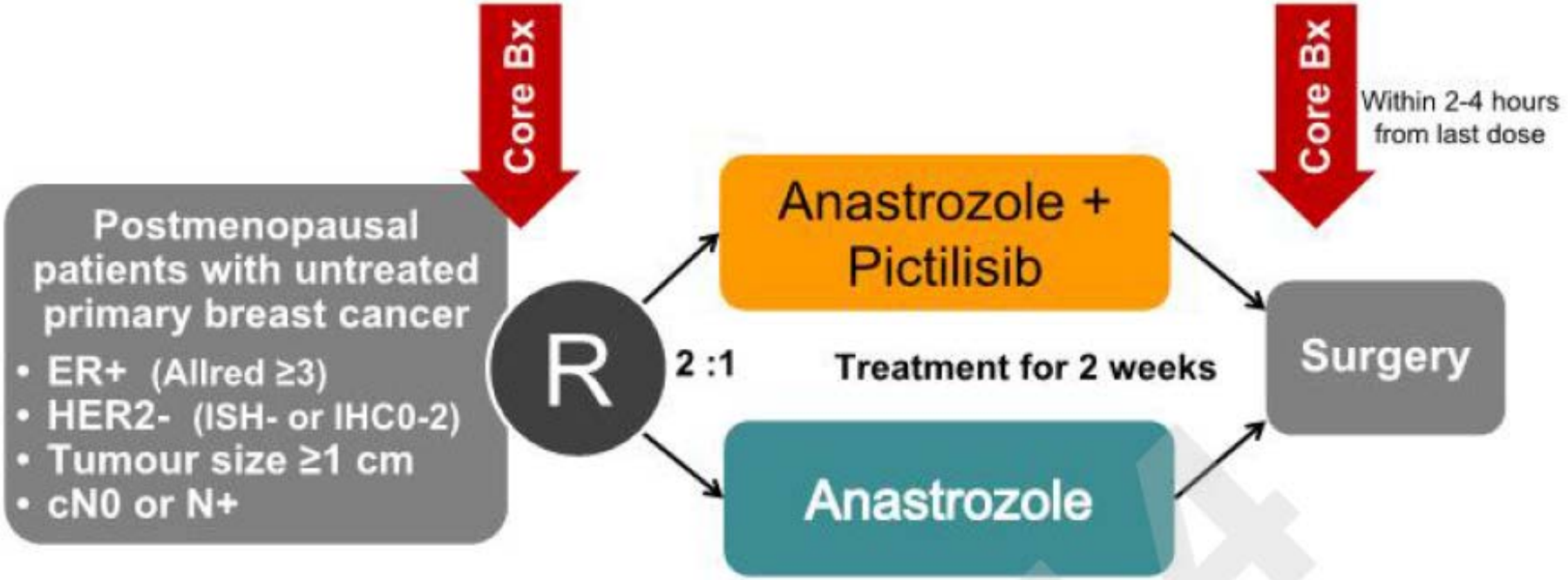
Queen Mary University of London

ECMC

NCRN

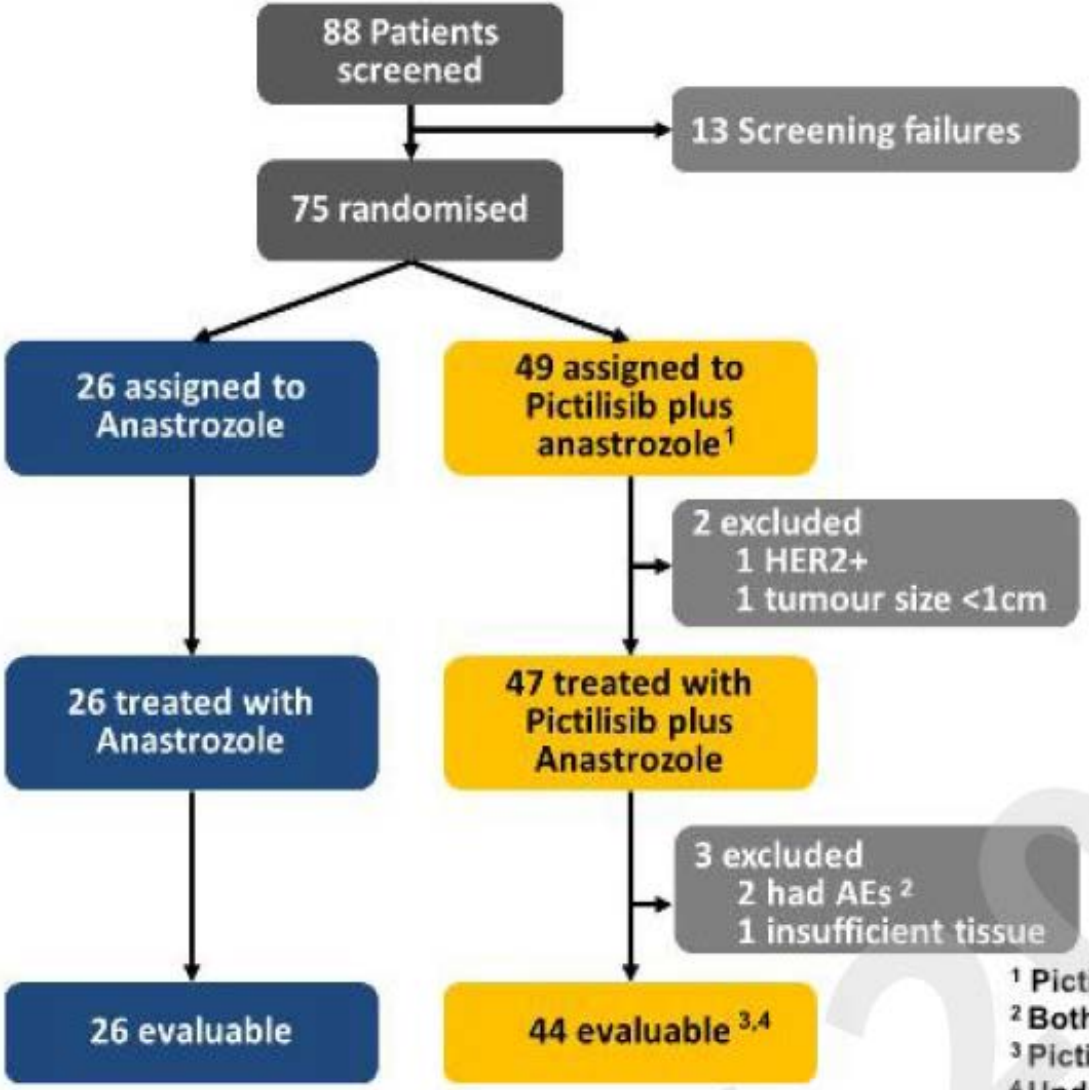
Barts Health NHS NHS Trust

OPPORTUNE Study Design



- **Randomisation (2:1) favouring the combination, stratified by Centre & Grade**
- **Study dosing once daily for 14 days (+/- 2 days)**
  - **Anastrozole: 1 mg**
  - **Pictilisib: initially 340 mg; changed to 260 mg in 08/2012**
- **Adjuvant therapy as indicated**
- **1st analysis of primary endpoint scheduled after 70 evaluable patients; 2nd analysis after 141 patients focusing on subset analyses and additional biomarkers**

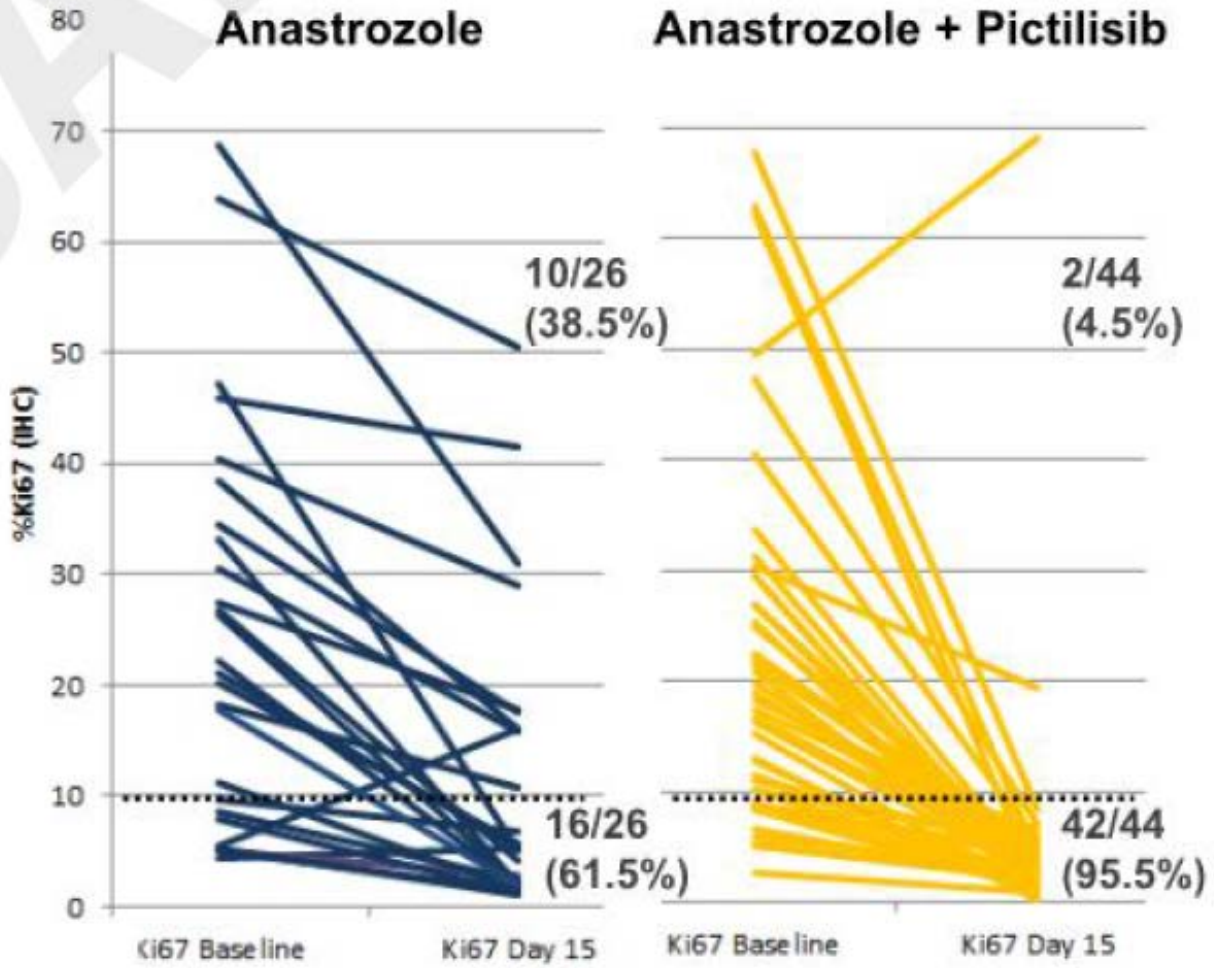
Study Population



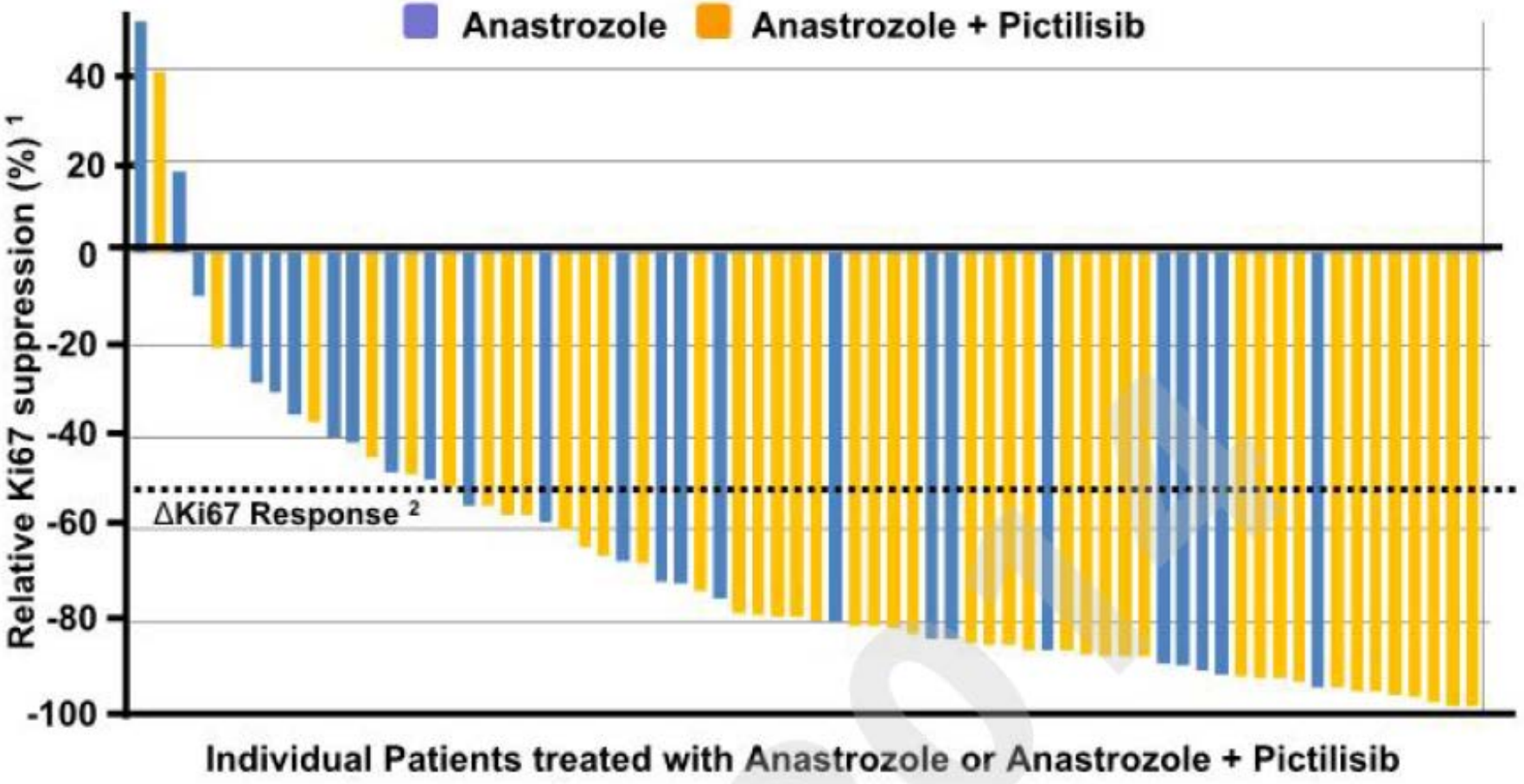
	A	A + P
N	26	44
Grade		
G1/2	85%	84%
G3	15%	16%
BL Ki67		
≤14%	35%	39%
>14%	65%	61%
PAM50		
Lum A	32%	41%
Lum B	68%	59%

[1] Pictilisib 340 mg, n = 8; Pictilisib 260 mg, n = 41
[2] Both patients on Pictilisib 340 mg
[3] Pictilisib 340 mg, n = 5; Pictilisib 260 mg, n = 39
[4] Updated from abstract; all patients now evaluable

Individual Change in Ki67



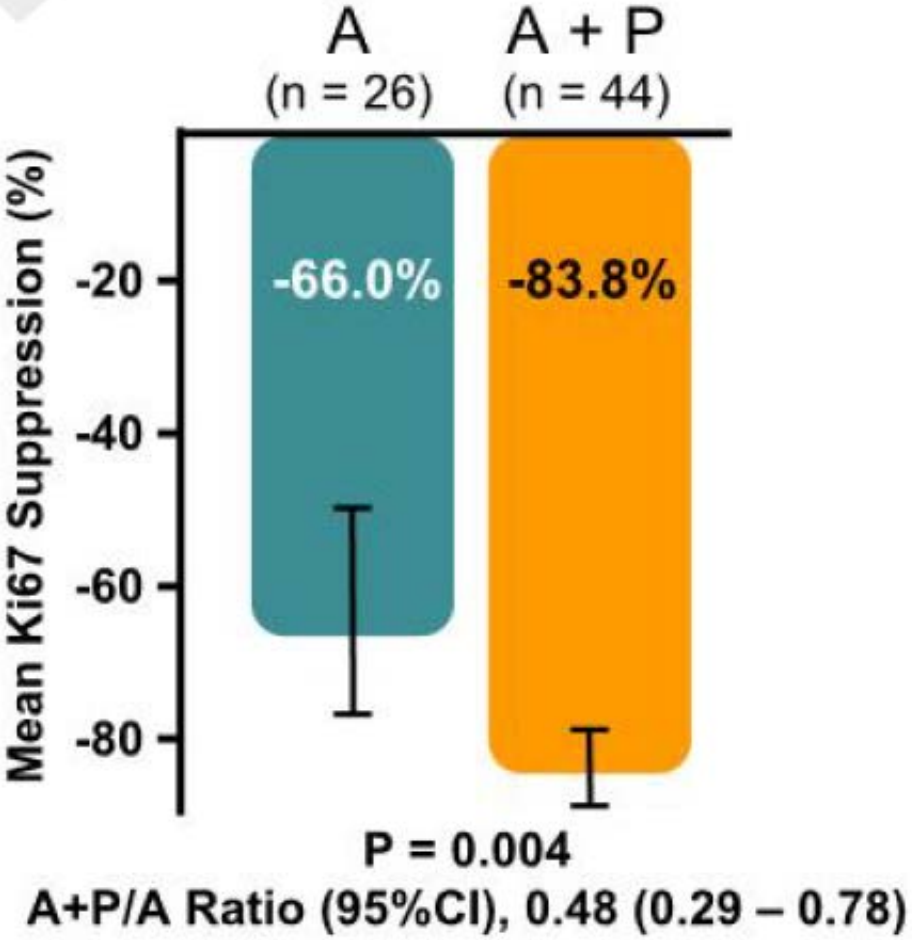
Individual Relative Ki67 Suppression



[1] Relative Ki67 Suppression, defined as $Ln(Ki67_{Day15}) - Ln(Ki67_{baseline})$;
[2] ΔKi67 Response, defined as ≥50% fall in Ki67 score between Day15 and Baseline

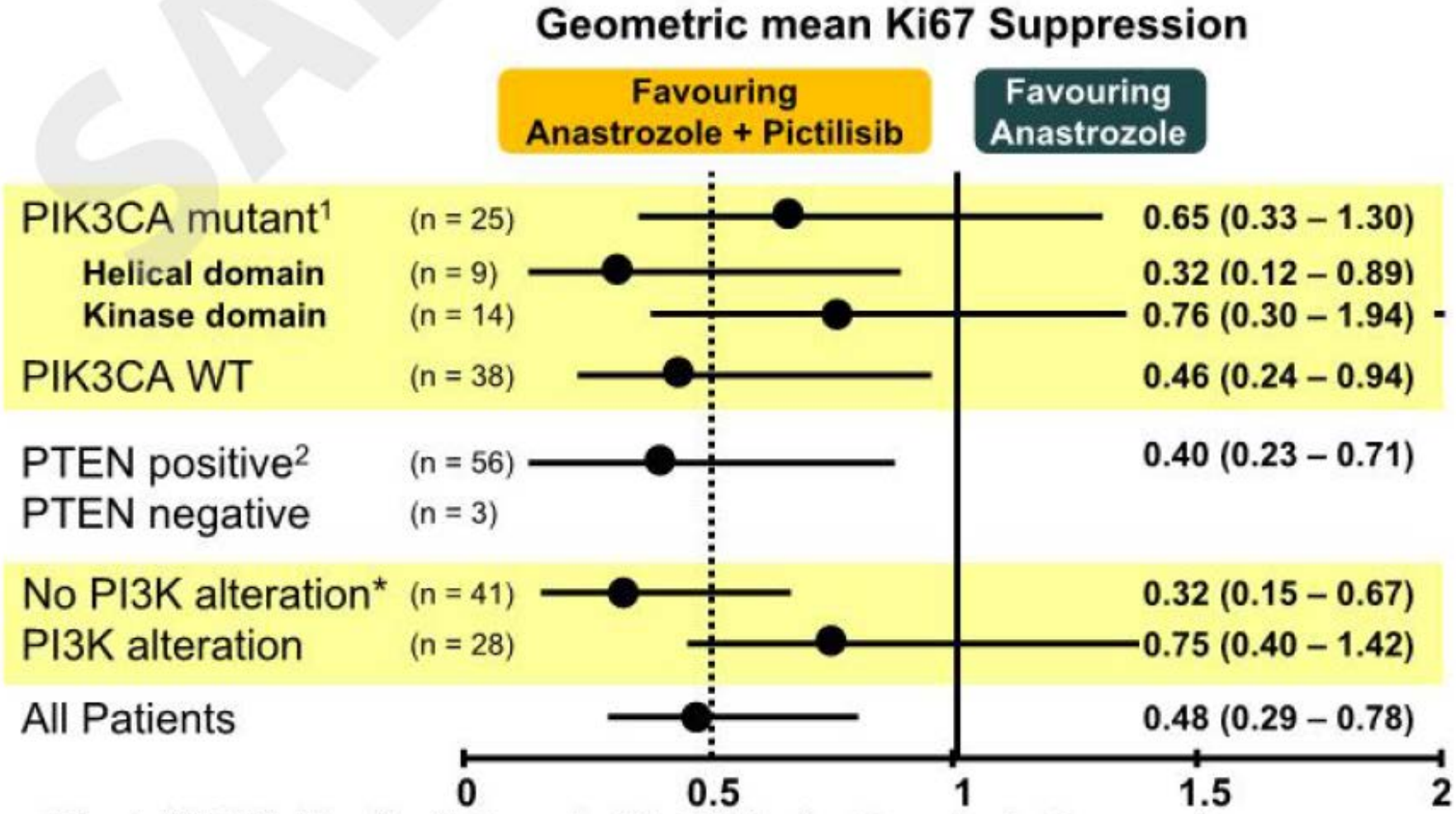
Primary Endpoint

Geometric mean Ki67 Suppression



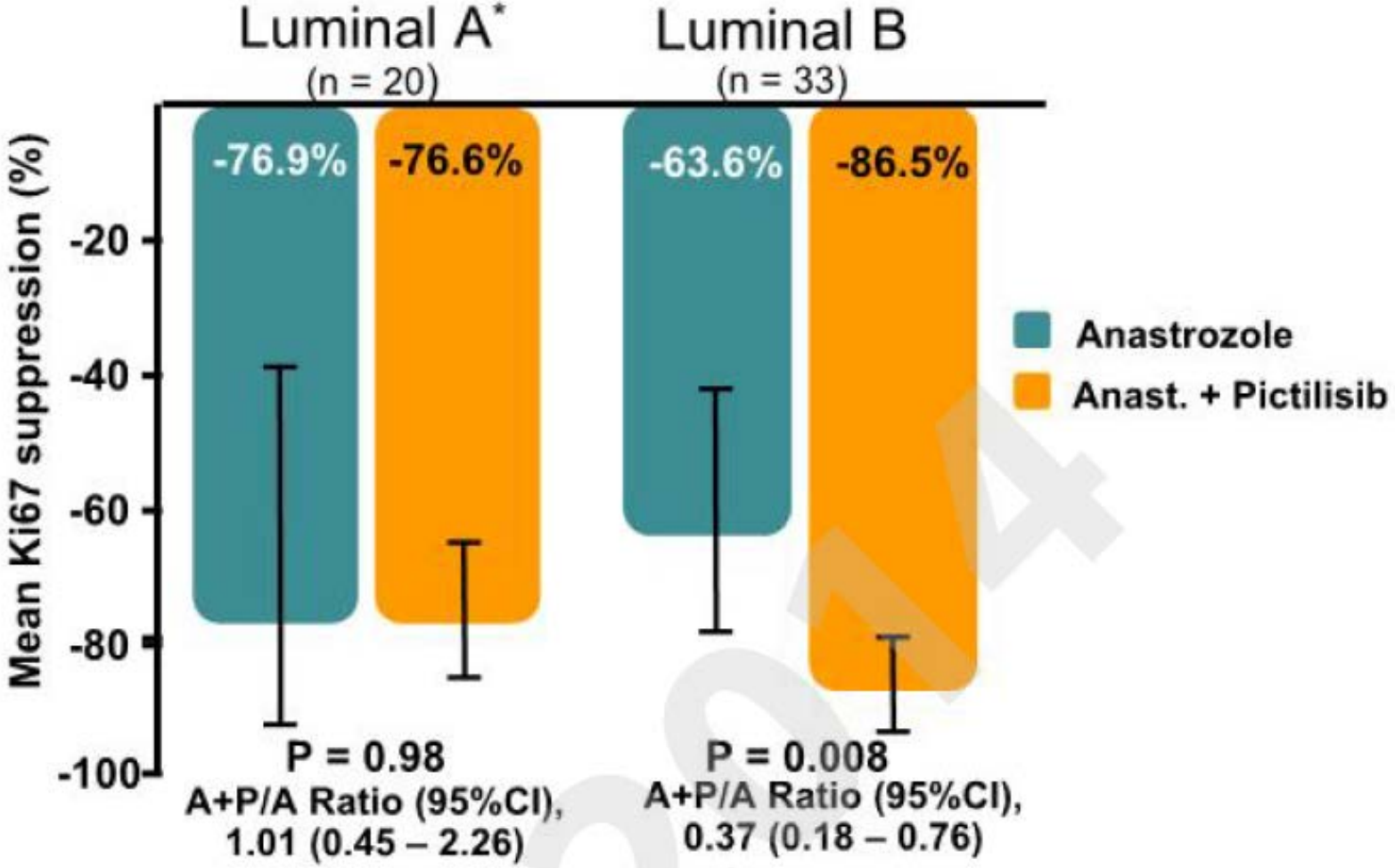
Geometric mean Ki67 Suppression defined as $Ln(Ki67_{Day15}) - Ln(Ki67_{baseline})$

PI3K Pathway Alterations & Response



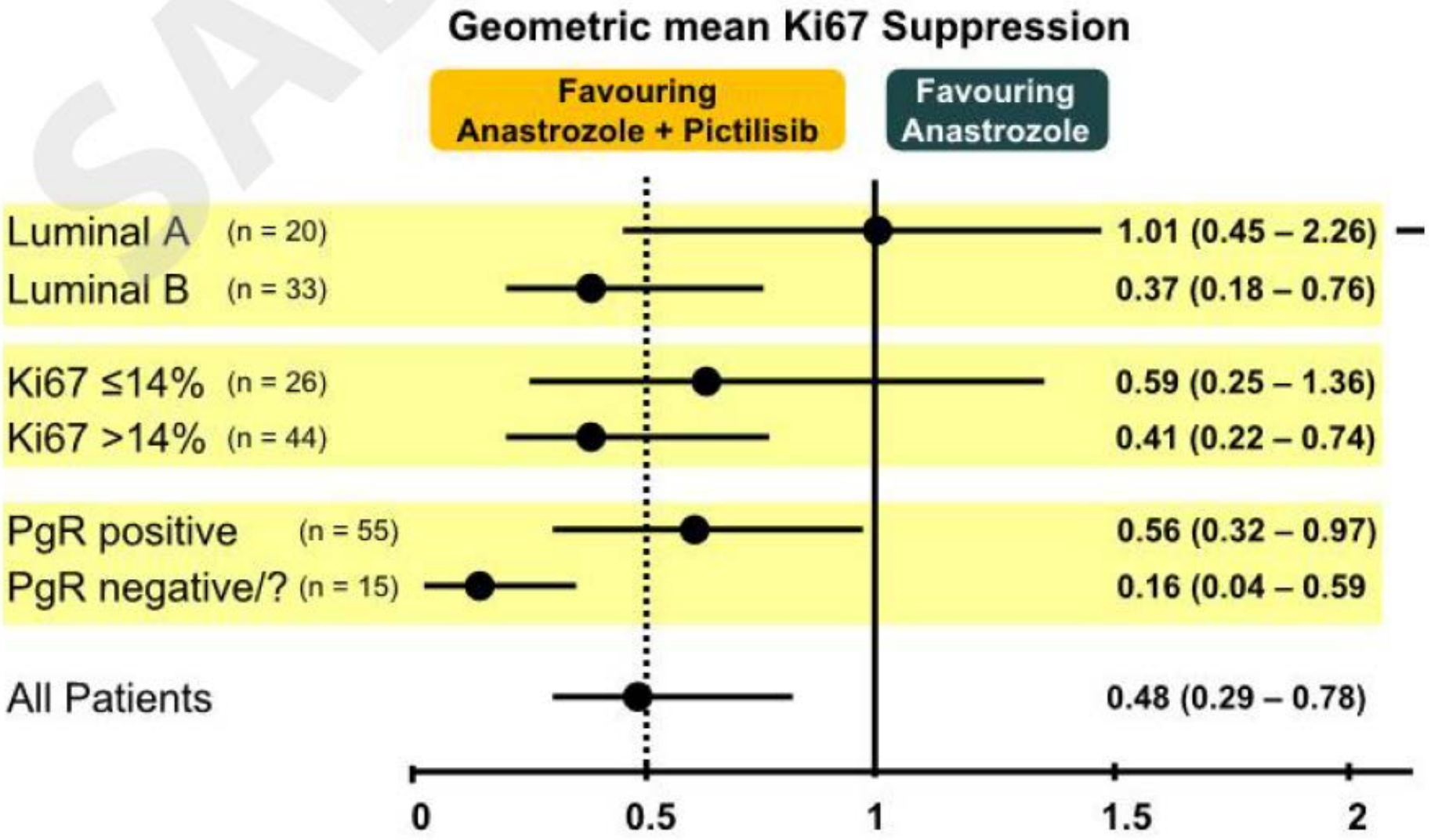
[1] Targeted NGS (P1 chip and Ion PI Sequencing 200 v3 Kit) Ampliseq Comprehensive Cancer panel;
[2] Central IHC analysis, Primary antibody: PTEN (138G6; Cell Signalling #9559)
[3] PIK3CA mutation and/or loss of PTEN

Geometric mean Ki67 Suppression by Subtype (PAM50)



* PAM50 Nanostring

Ki67 Suppression in Subgroups



Summary and Conclusions

- Addition of the PI3K inhibitor Pictilisib significantly increased the anti-proliferative response to Anastrozole in ER+ early breast cancer
- Subset analyses suggest increased benefit of Pictilisib for patients with Luminal B or highly-proliferative tumours
- PIK3CA mutations or PTEN status were not predictive of response to Pictilisib
- The addition of Pictilisib to Anastrozole was not associated with an increase in tumour cell apoptosis
- The safety profile of the combination is acceptable and consistent with other trials

A Phase Ib Study of Pembrolizumab (MK-3475) in Patients With Advanced Triple-Negative Breast Cancer

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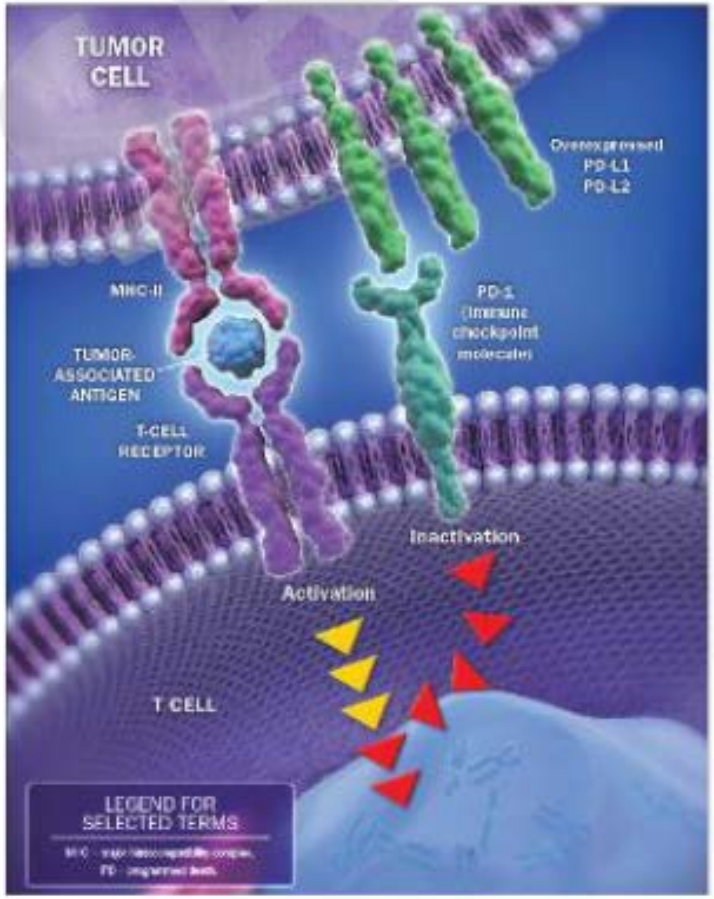
[6]Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; [7]Yale University School of Medicine, New Haven, CT;
[8]Merck & Co., Inc., Whitehouse Station, NJ; [9]Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles, Belgium

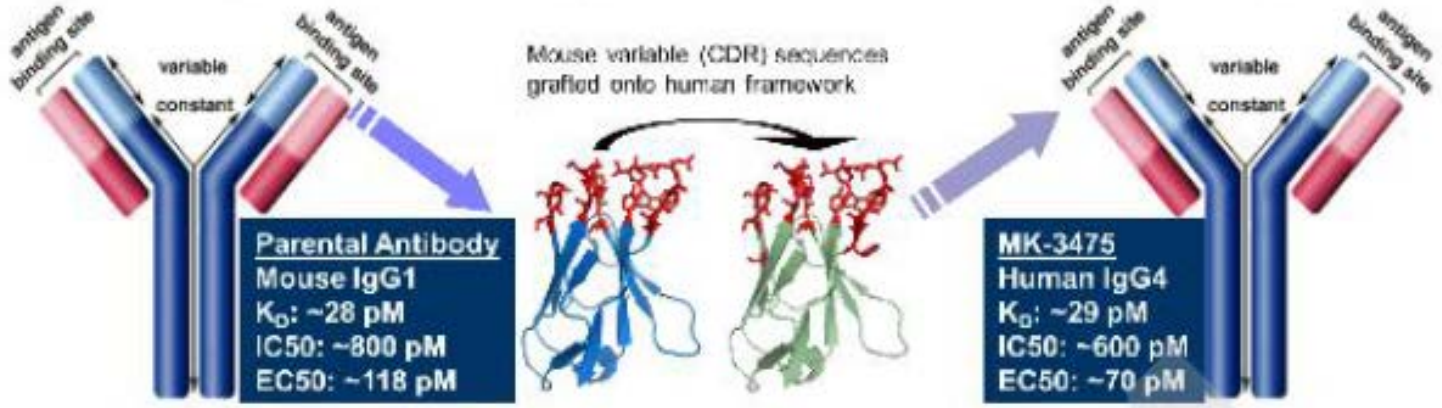
PD-1 Pathway and Immune Surveillance



- PD-1 is expressed primarily on activated T cells[1]
- Binding of PD-1 to its ligands PD-L1 and PD-L2 impairs T-cell function[1]
- PD-L1 is expressed on tumor cells and macrophages[2]
- Tumors can co-opt the PD-1 pathway to evade immune surveillance[2]

1. Keir ME et al. *Annu Rev Immunol.* 2008;26:677-704; 2. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64.

Pembrolizumab (MK-3475) Is a Humanized IgG4, High-Affinity, Anti-PD-1 Antibody



- High affinity for the PD-1 receptor (KD ≈ 29 pM)
- Dual ligand blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- PK supports dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Demonstrated clinical activity in multiple tumor types[1-6]
- Recently approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

1. Ribas A et al. *J Clin Oncol*. 2014;32(suppl 5):abstr LBA9000; 2. Rizvi N et al. *J Clin Oncol*. 2014;32(suppl 5): abstr 8007; 3. Garon EB et al. *J Clin Oncol*. 2014;32(suppl 5): abstr 8020; 4. Seiwert TY et al. *J Clin Oncol*. 2014;32(suppl 5):abstr 6011. 5. Plimack E et al. Abstr. LBA23. Presented at 2014 ESMO Congress, September 26-30, Madrid, Spain. 6. Muro K et al. LBA15. Presented at 2014 ESMO Congress, September 26-30, Madrid, Spain.

December 9-13, 2014
SAN ANTONIO BREAST CANCER SYMPOSIUM

KEYNOTE-012:
Triple-Negative Breast Cancer Cohort

- Recurrent or metastatic ER$^-$/PR$^-$/HER2$^-$ breast cancer
- ECOG PS 0-1
- PD-L1$^+$ tumor[a]
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No active brain metastases

→ Pembro 10 mg/kg Q2W

- Complete Response → Discontinuation Permitted
- Partial Response or Stable Disease → Treat for 24 months or until progression or intolerable toxicity
- Confirmed Progressive Disease[b] → Discontinue

- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

[a]PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.
[b]If clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.

Best Overall Response (RECIST v1.1, Central Review)

	Patients Evaluable for Response[a] n = 27
Overall response rate	5 (18.5%)
Best overall response	
Complete response[b]	1 (3.7%)
Partial response[b]	4 (14.8%)
Stable disease	7 (25.9%)
Progressive disease	12 (44.4%)
No assessment[c]	3 (11.1%)

[a]Includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and who had ≥1 post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE. 5 patients were excluded because they did not have any assessments per central review (n = 2) or because they did not have measurable disease per central review at baseline (n = 3).
[b]Confirmed responses only.
[c]"No assessment" signifies patients who discontinued therapy before the first post-baseline scan due to progressive disease or a treatment-related AE.

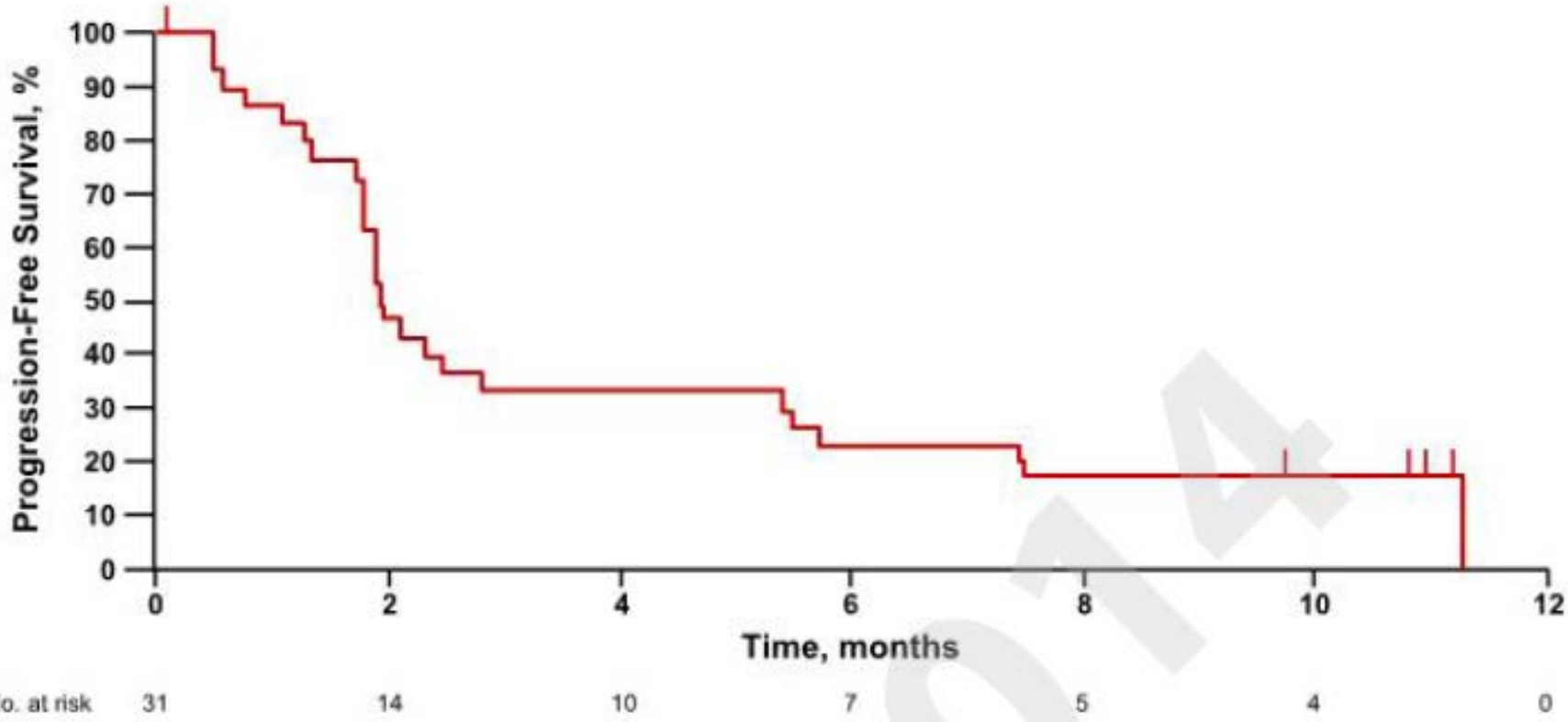
Best Overall Response By Previous Therapy (RECIST v1.1, Central Review)

	Evaluable Patients N = 27[a]	CR or PR[b]	SD	PD or No Assessment[c]
Neoadjuvant or adjuvant	24	4 (16.7%)	7 (29.2%)	13 (54.2%)
No. of lines for metastatic disease				
0	4	0 (0.0%)	1 (25.0%)	3 (75.0%)
1	4	1 (25.0%)	1 (25.0%)	2 (50.0%)
2	6	0 (0.0%)	2 (33.3%)	4 (66.7%)
3	4	1 (25.0%)	1 (25.0%)	2 (50.0%)
4	3	1 (33.3%)	0 (0.0%)	2 (66.7%)
≥5	6	2 (33.3%)	2 (33.3%)	2 (33.3%)

- Previous therapy among the 5 patients with CR or PR
  - Capecitabine: 5 (100.0%)
  - Taxane: 5 (100.0%)
  - Anthracycline: 4 (80.0%)
  - Platinum: 3 (60.0%)
  - Eribulin: 1 (20.0%)

[a]Includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and who had ≥1 post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE. 5 patients were excluded because they did not have any assessments per central review (n = 2) or because they did not have measurable disease per central review at baseline (n = 3).
[b]Confirmed responses only.
[c]"No assessment" signifies patients who discontinued therapy before the first scan due to progressive disease or a treatment-related AE.

Kaplan-Meier Estimate of PFS (RECIST v1.1, Central Review)



- Median PFS: 1.9 months (95% CI, 1.7-5.4)
- PFS rate at 6 months: 23.3%

Treatment-Related Adverse Events With Incidence ≥5%[a]

	N = 32	
	Any Grade	Grade 3-5
Arthralgia	6 (18.8%)	0 (0.0%)
Fatigue	6 (18.8%)	0 (0.0%)
Myalgia	5 (15.6%)	0 (0.0%)
Nausea	5 (15.6%)	0 (0.0%)
ALT increased	2 (6.3%)	0 (0.0%)
AST increased	2 (6.3%)	0 (0.0%)
Diarrhea	2 (6.3%)	0 (0.0%)
Erythema	2 (6.3%)	0 (0.0%)
Headache	2 (6.3%)	1 (3.1%)

- Adverse events of a potentially immune-mediated nature, regardless of attribution, included pruritus (n = 3; all grade 1-2), hepatitis[b] (n = 1; grade 3), and hypothyroidism (n = 1; grade 2)

Summary and Conclusions

- Pembrolizumab showed an acceptable safety and tolerability profile in patients with heavily pretreated, PD-L1-positive, advanced triple-negative breast cancer
- Pembrolizumab was associated with an ORR of 18.5%
- Responses were durable, with the median response duration not reached (range, 15 to 40+ weeks) and 3 of 5 responders on treatment for ≥11 months
- The acceptable safety and tolerability profile and promising antitumor activity support the further development of pembrolizumab in patients with advanced triple-negative breast cancer
- A phase II study of pembrolizumab for patients with advanced triple-negative breast cancer is planned for the first half of 2015

IMMU-132 (sacituzumab govitecan)

- IMMU-132 is a ADC targeting Trop-2, an antigen found in high prevalence in many epithelial cancers, including TNBC, and conjugated to SN-38, a topoisomerase inhibitor and active metabolite of irinotecan,
- Studies in mice bearing human pancreatic tumor xenografts (Capan-1) have shown IMMU-132 remains intact in the serum until internalized within the tumor cell where SN-38 is released resulting in selective cancer cell death.

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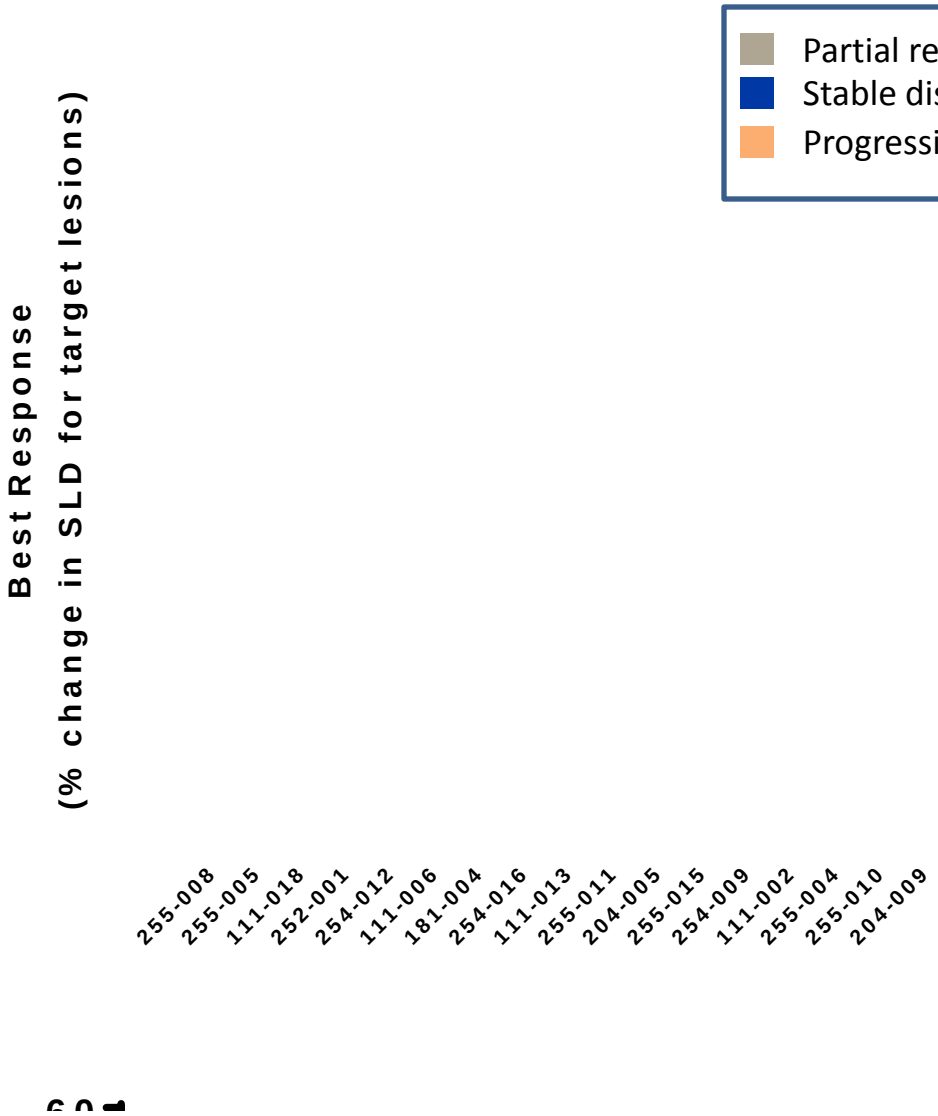
IMMU-132: Efficacy in Patients with Heavily Pretreated Metastatic TNBC



ORR = 30%

N = 23
7 PR
9 SD
7 PD

Disease stabilization = 70% (16/23)

CBR (PR + SD ≥ 4 mo) = 52%
CBR (PR + SD ≥ 6 mo) = 40%

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IMMU-132 AEs: Patient with TNBC (N=21 patients)

Criteria: Grade 1-4 Adverse Event for ≥ 14% or any Grade 3 or 4 Adverse Event.

Number of patients = 21	Total	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	11	7	3	1	0
Neutrophil count decreased	9	0	0	7	2
Nausea	9	7	2	0	0
Fatigue	9	7	2	0	0
Alopecia	6	2	4	NA	NA
Anemia	5	2	2	1	0
Vomiting	4	3	1	0	0
White blood count decreased	3	0	2	1	0
Dysgeusia	3	3	0	0	0
Pruritus	3	3	0	0	0
Skin hyperpigmentation	3	3	0	0	0
Lymphocyte count decreased	2	1	0	1	0
Febrile Neutropenia	1	0	0	0	1
Typhilitis	1	0	0	1	0

NA Not applicable.

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Practice changing?

- Maybe:
  - Substitution of Nab-paclitaxel for paclitaxel in pre-op TNBC is reasonable but no comparison to taxol plus carboplatin (less toxic option)
- Confirmatory:
  - Value of platinums in BRCA-related cancers
- Interesting and worthy of further study:
  - Predictive value of sub-typing of TNBC
  - PD1 inhibition in TNBC
  - IMMU-132 in refractory TBC