BREAST CANCER: C'E QUALCOSA DI NUOVO ?

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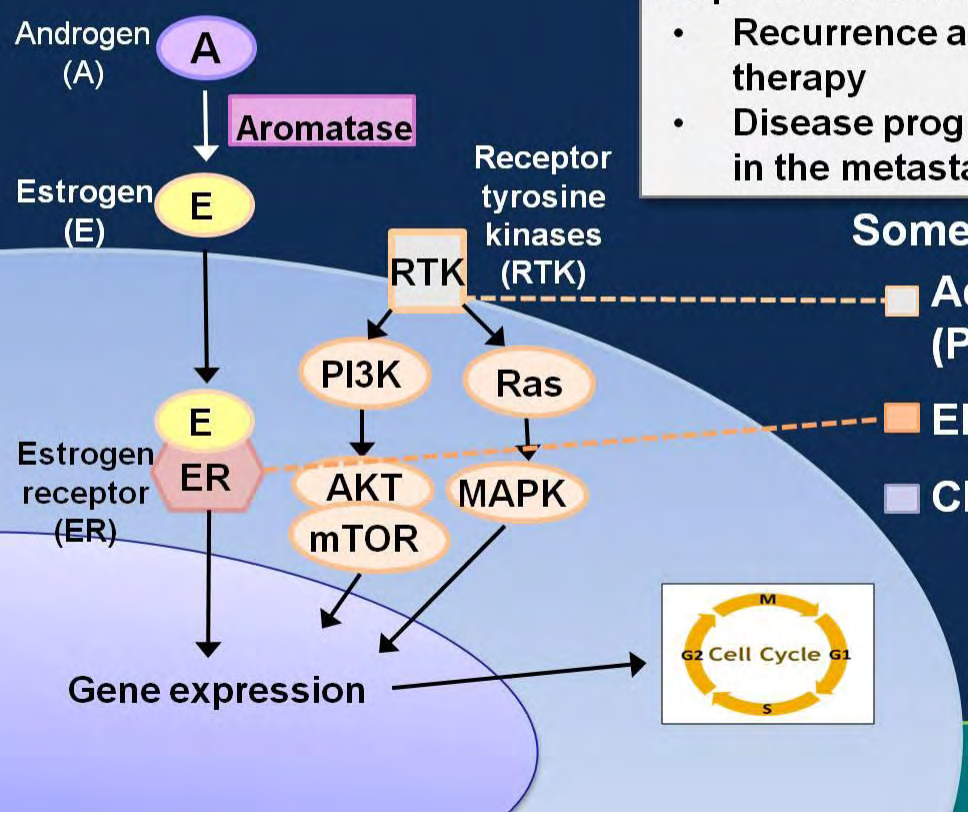
HR POSITIVE

Acquired resistance to endocrine therapy in ER+ BC

Acquired resistance is defined as:

- Recurrence at least 12 months after completion of adjuvant therapy
- Disease progression ≥ 6 months after endocrine therapy initiated in the metastatic setting



Some ways acquired resistance may occur:

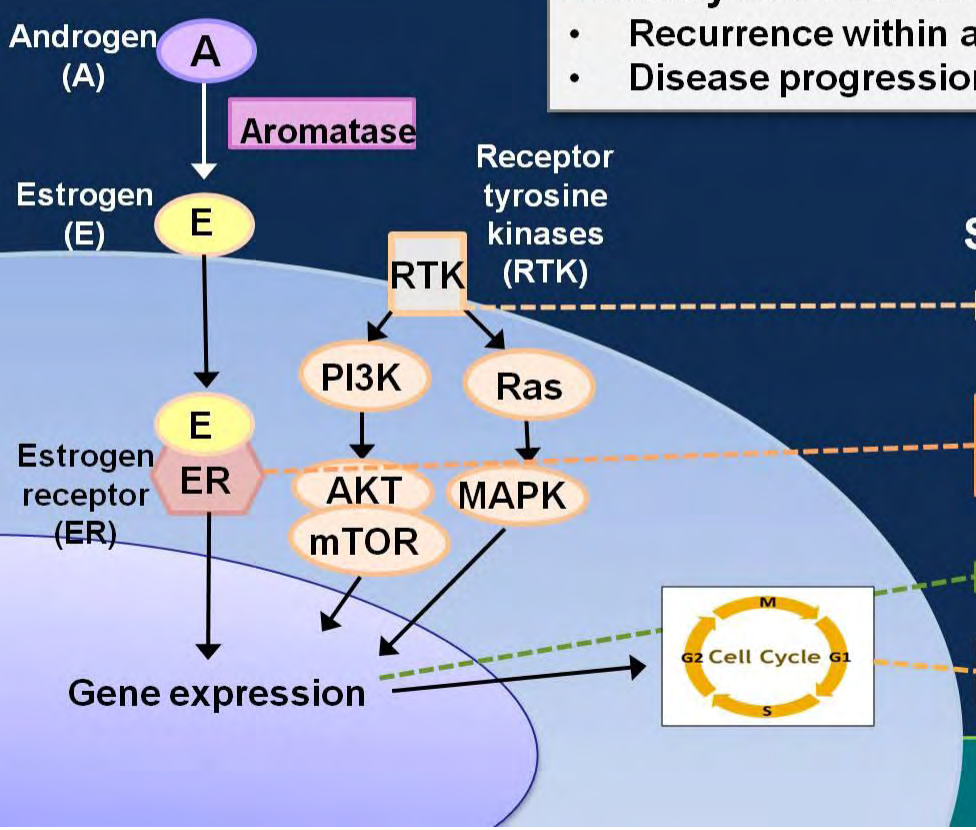
- Activation of growth factor signaling pathways (PI3K/ AKT/ mTOR; MAPK/ ERK; etc.)
- ER mutations
- Changes in the tumor microenvironment

1. Bachelot T, et al. *J Clin Oncol.* 2012;30(22):2718-2724;
2. Bedard PL, et al. *Breast Cancer Res Treat.* 2008;108(3):307-317

Primary resistance to endocrine therapy in ER+BC

Primary resistance is defined as

- Recurrence within adjuvant therapy
- Disease progression < 6 months after treatment in the metastatic setting

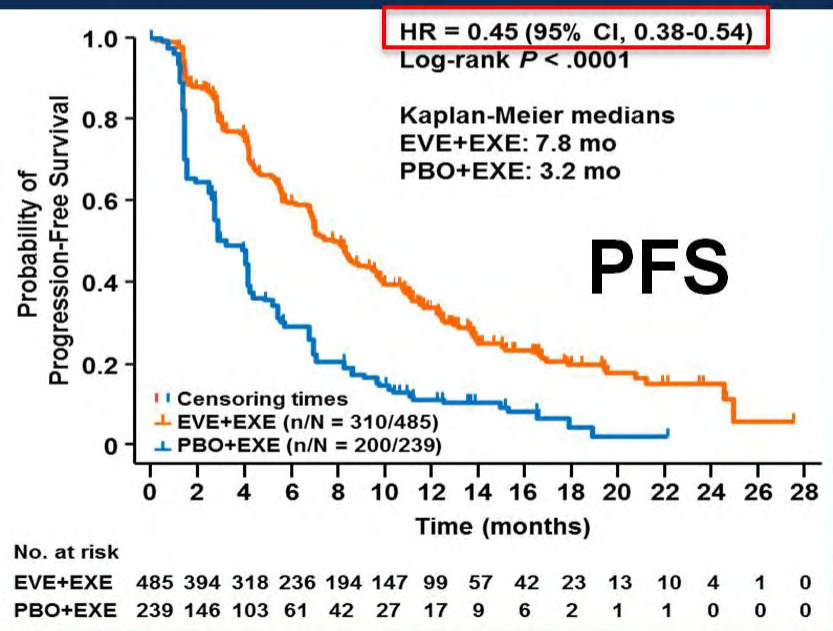


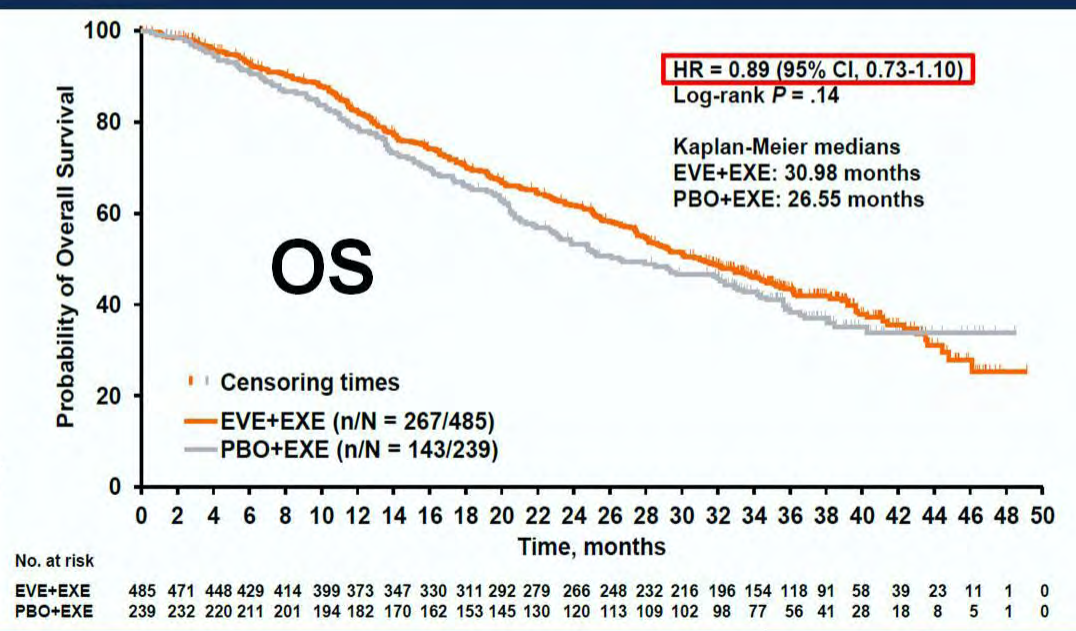
Some ways primary resistance may occur:

- FGFR amplifications
- Loss of ERα
  Post-translational modification of ERα
  Expression of ER cofactors
- MYC amplification and overexpression
- Cyclin D1 amplification or expression

1. Bachelot T, et al. *J Clin Oncol.* 2012;30(22):2718-2724;
2. Bedard PL, et al. *Breast Cancer Res Treat.* 2008;108(3):307-317

mTOR Inhibition: BOLERO-2





Baselga J, et al. *N Engl J Med.* 2012;366(6):520-529
Piccart M, et al. *Ann Oncol.* 2014;25(12):2357-2362.

Pan-PI3K Inhibition: BELLE-2

Phase 3 Study in ER+ HER2− MBC; AI Resistant and mTORi Naive

Full Population (N=1047)	Buparlisib + Fulvestrant n=576	Placebo + Fulvestrant n=571
Median PFS, months (95% CI)	6.9 (6.8–7.8)	5.0 (4.0–5.2)
HR (95% CI)	0.78 (0.67–0.89)	
One-sided *P* value	<0.001	

ctDNA *PIK3CA* Mutant n=200	Buparlisib + Fulvestrant n=87	Placebo + Fulvestrant n=113
Median PFS, months (95% CI)	7.0 (5.0–10.0)	3.2 (2.0–5.1)
HR (95% CI)	0.56 (0.39–0.80)	
One-sided nominal *P* value	<0.001	

ctDNA *PIK3CA* Non-mutant n=387	Buparlisib + Fulvestrant n=199	Placebo + Fulvestrant n=188
Median PFS, months (95% CI)	6.8 (4.7–8.5)	6.8 (4.7–8.6)
HR (95% CI)	1.05 (0.82–1.34)	
One-sided nominal *P* value	0.642	

Pan-PI3K Inhibition: BELLE-3

Phase 3 Study in ER+ HER2− MBC; AI and mTORi Resistant

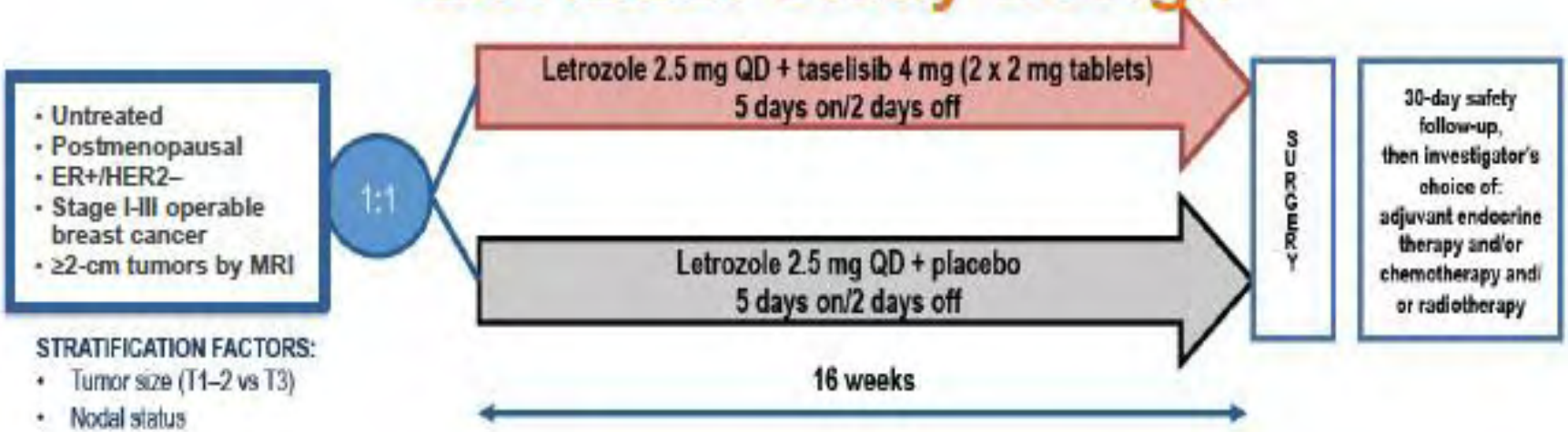
Full Population (N=432)	Buparlisib + Fulvestrant n=289	Placebo + Fulvestrant n=143
Median PFS, months (95% CI)	3.9 (2.8–4.2)	1.8 (1.5–2.8)
HR (95% CI)	0.67 (0.53–0.84)	
One-sided *P* value	<0.001	

ctDNA *PIK3CA* Mutant	Buparlisib + Fulvestrant	Placebo + Fulvestrant
Median PFS, months (95% CI)	4.2 (2.8–6.7)	1.6 (1.4-2.8)
HR (95% CI)	0.46 (0.29–0.73)	
One-sided nominal *P* value	<0.001	

ctDNA *PIK3CA* Non-mutant	Buparlisib + Fulvestrant	Placebo + Fulvestrant
Median PFS, months (95% CI)	3.9 (2.8–4.3)	2.7 (1.5–3.6)
HR (95% CI)	0.73 (0.53–1.00)	
One-sided nominal *P* value	0.026	

Baselga et al. SABCS 2015
Di Leo et al. SABCS 2016

LORELEI Study Design



STRATIFICATION FACTORS:

- Tumor size (T1–2 vs T3)
- Nodal status

KEY INCLUSION CRITERIA:

- Multifocal disease allowed
- Sample for centralized *PIK3CA* genotyping
- Fasting glucose ≤125 mg/dL

KEY EXCLUSION CRITERIA:

- cT4 or cN3 stage breast cancer
- Bilateral invasive or multicentric breast cancer
- Excisional biopsy of primary tumor and/or sentinel lymph node biopsy prior to study treatment
- Stage IV breast cancer

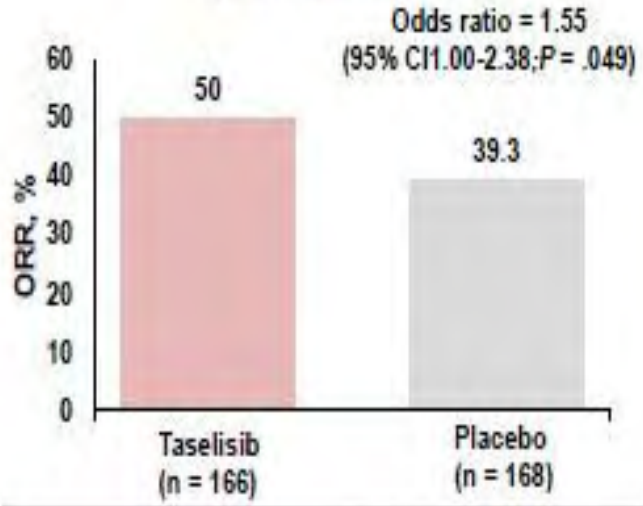
	Pre treatment	Week 3	Week 9	Week 16	Surgery (Week 17–18)
Tumor tissue					
MRI			*		
Breast U/S					
Mammogram					

* MRI @ Week 9: only required if suspicion of progression or if unevaluable by U/S at baseline

Saura C, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA_10.

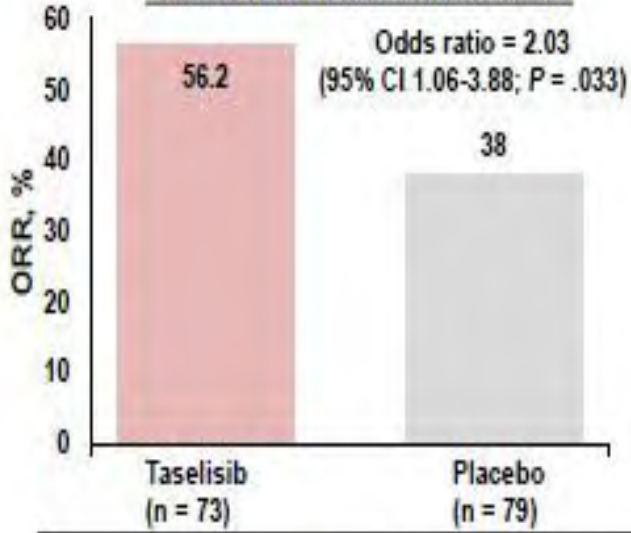
Efficacy: Response Rate

All Randomized Patients



Response, n (%)	Taselisib (n = 166)	Placebo (n = 168)
CR	8 (4.8)	3 (1.8)
PR	75 (45.2)	63 (37.5)
SD	67 (40.2)	86 (51.2)
Non-CR/Non-PD	0	1 (0.6)
PD	6 (3.6)	5 (3.0)
Missing/ND/NE	10 (6.0)	10 (6.0)

Patients With *PIK3CA*-Mutant Tumors

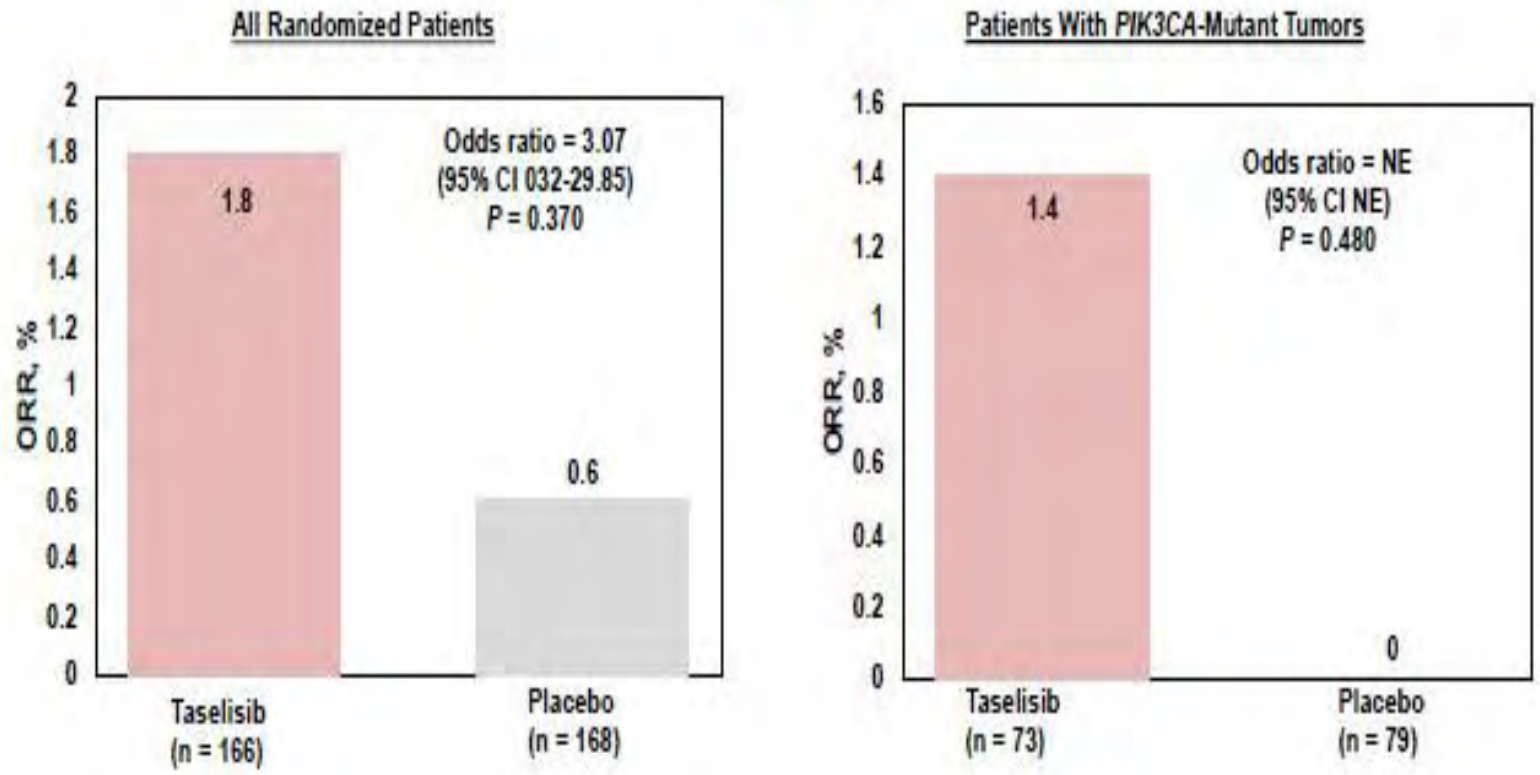


Response, n (%)	Taselisib (n = 73)	Placebo (n = 79)
CR	5 (6.8)	2 (2.5)
PR	36 (49.3)	28 (35.4)
SD	28 (38.4)	39 (49.4)
Non-CR/Non-PD	0	1 (1.3)
PD	1 (1.4)	3 (3.8)
Missing/ND/NE	3 (4.1)	6 (7.6)

Taselisib dose reductions: 11.4%; Taselisib discontinuations: 10.8%

Saura C, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA_10.

Efficacy: pCR



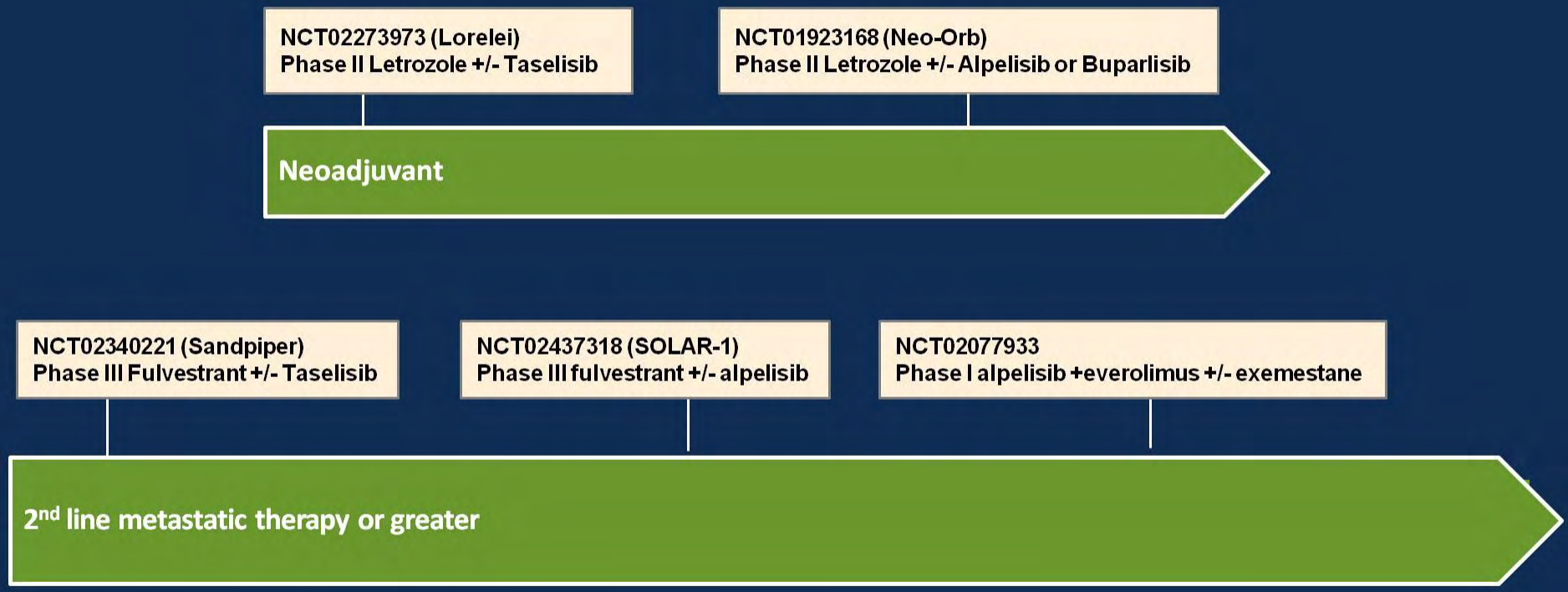
Safety: G3-4 Adverse Events in ≥1%

AE, n (%)	Taselisib (n = 167)	Placebo (n = 167)
Number of patients with at least one G3-4 AE	43 (25.7)	13 (7.8)
Gastrointestinal disorders	13 (7.8)	2 (1.2)
Diarrhea	8 (4.8)	1 (0.6)
Colitis	2 (1.2)	0
Stomatitis ≥5%	2 (1.2)	0
Infections and infestations	8 (4.8)	2 (1.2)
Postoperative wound infection	2 (1.2)	1 (0.6)
Erysipelas	2 (1.2)	0
Skin and subcutaneous tissue disorders	8(4.8)	0
Rash	3 (1.8)	0
Vascular disorders	6 (3.6)	4 (2.4)
Hypertension	5 (3.0)	4 (2.4)
Metabolism and nutrition disorders	6 (3.6)	0
Hyperglycemia	2 (1.2)	0
Hypokalemia	2 (1.2)	0
Investigations	4 (2.4)	2 (1.2)
Lipase increased	2 (1.2)	1 (0.6)
Amylase increased	2 (1.2)	0
General disorders and administration site conditions	2 (1.2)	0

One sudden death (G5) occurred in the taselisib arm, but was considered unrelated to study treatment

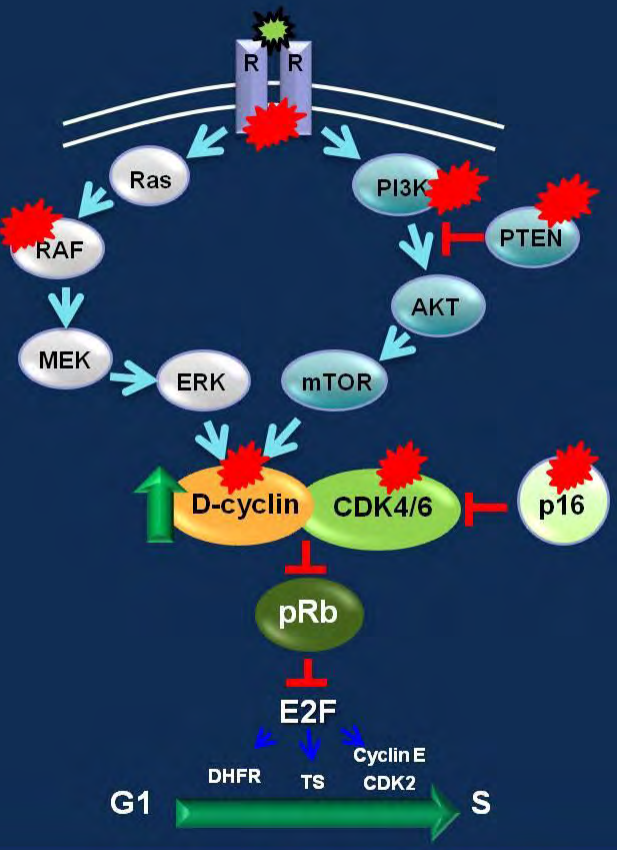
Saura C, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA_10.

Ongoing trials: α-specific PI3K inhibitors



CDK 4/6 Inhibition

	Palbociclib		Abemaciclib		Ribociclib	
IC_{50}	CDK 4: 9-11 mM CDK 6: 15 mM		CDK 4: 2 mM CDK 6: 5 mM		CDK 4: 11 mM CDK 6: 39 mM	
Dosing	125 mg daily (3 weeks on, 1 week off)		200 mg twice daily (continuously)		600 mg daily (3 weeks on, 1 week off)	
ORR in monotherapy*	6%		17%		3%	
CNS penetration	No		Yes		No	
Common adverse events (%)*	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Neutropenia	95	54	88	27	46	29
Thrombocytopenia	76	19	42	2	37	10
Fatigue	68	0	65	13	29	3
Diarrhea	16	0	90	20	22	3
Nausea	23	0	65	5	46	2
Vomiting	5	0	35	2	25	0
QTc prolongation	NR	NR	NR	NR	8	0



Barros-Sousa et al. Breast Care, 2016

Clinical Benefit with CDK4/6 Inhibitors

	PALOMA-1	PALOMA-2	MONALEESA-2	PALOMA-3	MONARCH-2
Design	Phase II open label, 1st line	Phase III placebo control, 1st line	Phase III placebo control, 1st line	Phase III placebo control, 2nd line	Phase III placebo control, 2nd line
Endocrine partner	Letrozole	Letrozole	Letrozole	Fulvestrant	Fulvestrant
CDK4/6 Inhibitor	Palbociclib	Palbociclib	Ribociclib	Palbociclib	Amebaciclib
Patients on study, n	165	666	668	521	669
Efficacy (CDK4/6 inhibitor vs. control arm)					
Primary end point: PFS					
HR	0.49	0.58	0.56	0.46	ASCO 2017
Median PFS, months	20.2 vs 10.2 (10 mo)	24.8 vs 14.5 (10.3 mo)	25.3 vs 16 (9.3 mo)	9.5 vs 4.6 (4.9 mo)	Oral session 6/3 1:15 PM

Finn et al, 2015; Cristofanilli et al, 2016; Finn et al, 2016; Hortobagyi et al., 2016

Impact of Prior Treatment on Palbociclib Plus Letrozole (P+L) Efficacy and Safety in Patients (pts) With Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2–) First-Line Advanced Breast Cancer (ABC): A PALOMA-2 Subgroup Analysis

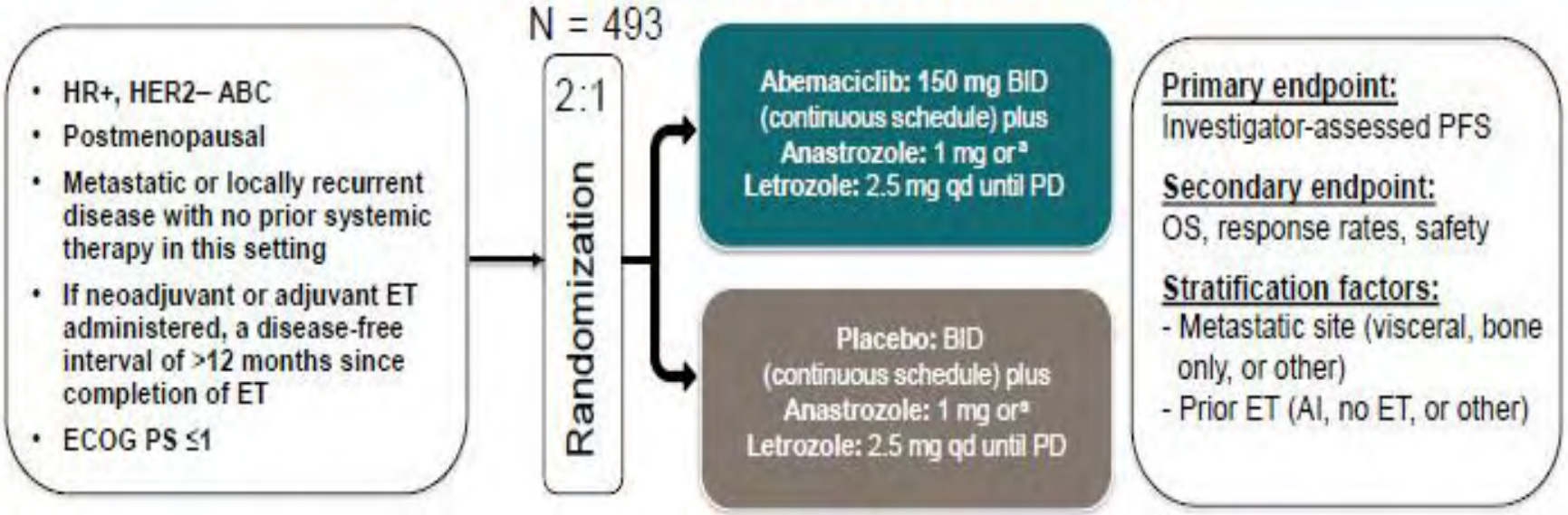
Summary of Treatment Efficacy by Patient Subgroups

	Prior Endocrine Therapy		Prior Chemotherapy	
Efficacy Endpoints for Palbociclib plus Letrozole vs Placebo plus Letrozole	Yes n = 249 vs n = 126	No n = 195 vs n = 96	Yes n = 213 vs n = 109	No n = 231 vs n = 113
Median PFS, months	22.2 vs 11.3	25.7 vs 19.6	22.4 vs 13.7	25.7 vs 17.0
Hazard ratio (95% CI)	0.53 (0.40-0.70)	0.63 (0.44-0.90)	0.53 (0.40-0.72)	0.61 (0.44-0.84)
ORR, %	33.7 vs 27.0	52.8 vs 44.8	36.2 vs 30.3	47.6 vs 38.9
Odds ratio (95% CI)	1.38 (0.84-2.29)	1.38 (0.82-2.33)	1.30 (0.78-2.22)	1.43 (0.88-2.32)
CBR, %	81.5 vs 66.7	89.2 vs 75.0	81.7 vs 70.6	87.9 vs 69.9
Odds ratio (95% CI)	2.21 (1.31-3.70)	2.76 (1.37-5.56)	1.85 (1.04-3.29)	3.12 (1.71-5.71)
Patients with a response (CR/PR), n	84 vs 34	103 vs 43	77 vs 33	110 vs 44
Median DOR (CR/PR), months	22.5 vs 22.5	28.0 vs 16.7	20.1 vs 20.9	28.0 vs 16.7
(95% CI)	(16.6-NE) vs (11.2-NE)	(19.3-28.0) vs (15.4-22.3)	(16.7-NE) vs (11.1-NE)	(20.1-28.0) vs (13.8-NE)

NE, not evaluable; PR, partial response

Finn R, et al. *Ann Oncol*. 2017;28(Suppl 5): Abstract 248P.

MONARCH 3: Study Design



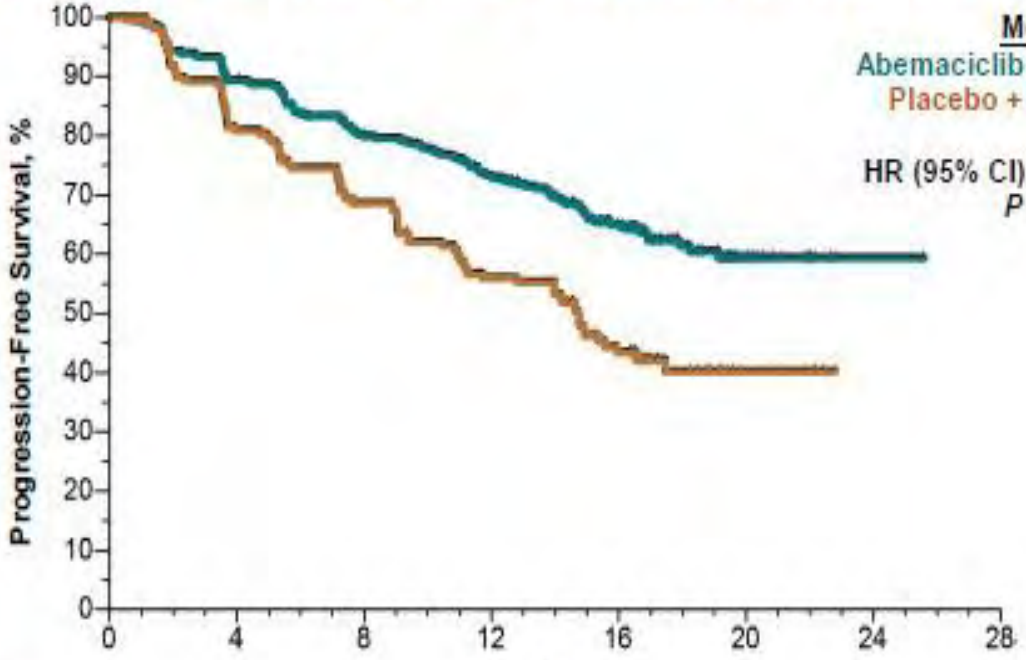
[a]per physician's choice: 79.1% received letrozole, 19.9% received anastrozole

- **Statistics**: Study powered to 80% at one-sided alpha of 0.025 assuming a hazard ratio of 0.67 with analyses at 189 and 240 PFS events. Positive study at the interim required a hazard ratio <0.56 and two-sided $P<.0005$
- **Enrollment:** From November 2014 to November 2015 patients enrolled in 158 centers from 22 countries
- **Median follow-up:** 17.8 months (interim analysis)

ABC, advanced breast cancer; AI, aromatase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HR+, hormone receptor–positive; OS, overall survival; PD, progressive disease; PFS, progression-free survival

Di Leo A, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract 236O_PR.

Primary Endpoint (PFS) Met at Interim Analysis



Median PFS
Abemaciclib + NSAI: Not reached
Placebo + NSAI: 14.7 months

HR (95% CI): 0.543 (0.409, 0.723)
P = .000021

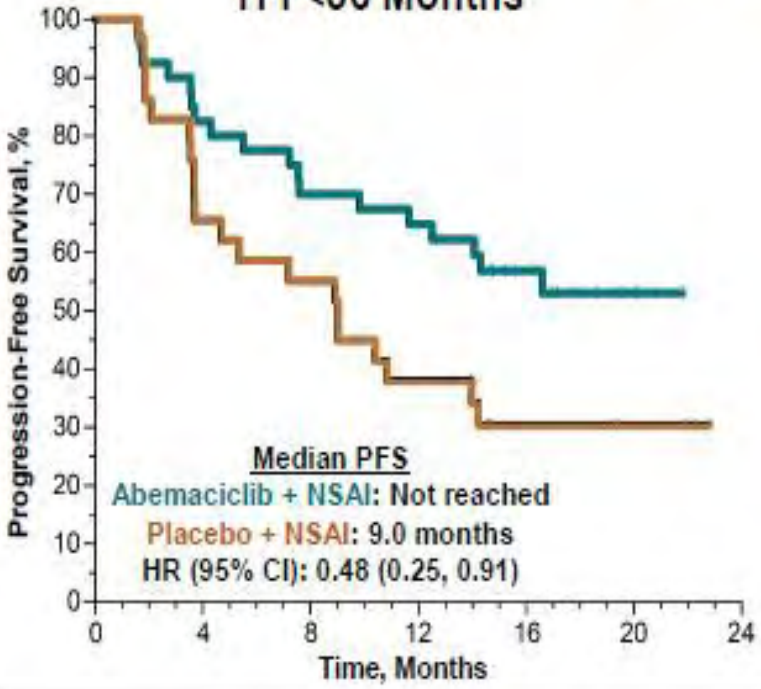
Patients at Risk:								
abemaciclib arm	328	271	234	205	125	25	1	0
placebo arm	165	127	105	82	45	7	0	0

PFS benefit confirmed by blinded independent central review:
HR (95% CI): 0.508 (0.359, 0.723); *P* = .000102

CI, confidence interval; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor
Di Leo A, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract 236O_PR.

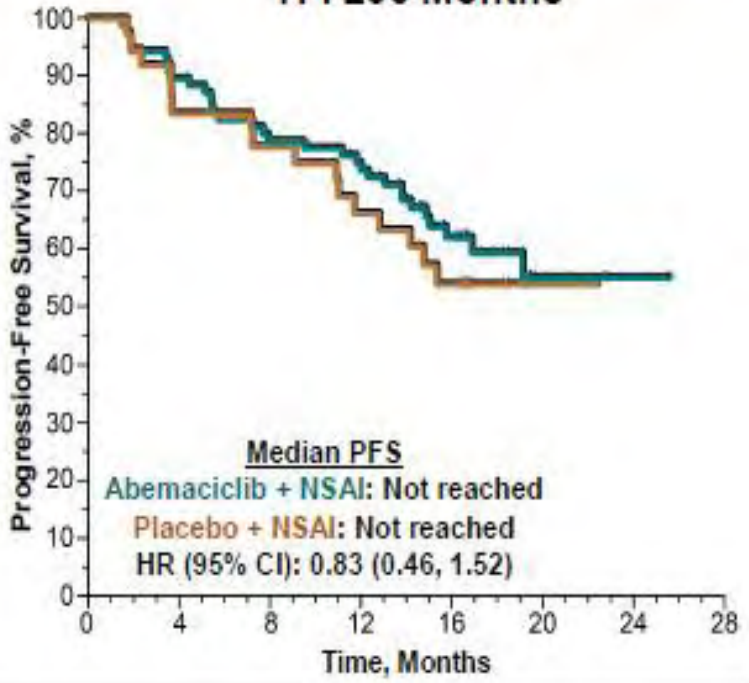
Exploratory PFS Analysis: Treatment-Free Interval (TFI)

TFI <36 Months



Landmark PFS Rate			
Arm	6 Months	12 Months	18 Months
Abemaciclib (n = 42)	77.5%	64.8%	53.0%
Placebo (n = 32)	58.6%	37.9%	30.3%

TFI ≥36 Months

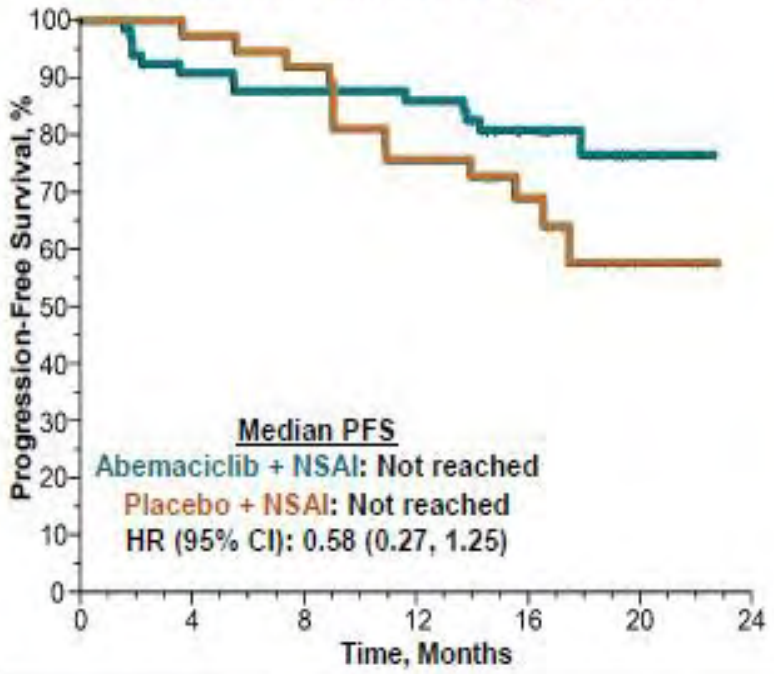


Landmark PFS Rate			
Arm	6 Months	12 Months	18 Months
Abemaciclib (n = 94)	82.4%	73.7%	59.4%
Placebo (n = 40)	83.5%	66.2%	53.9%

Di Leo A, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract 236O_PR.

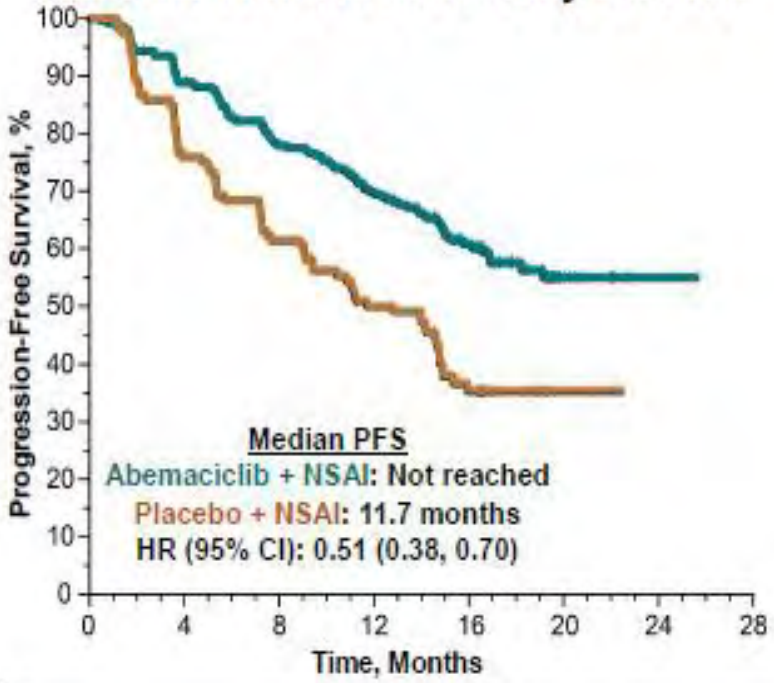
Exploratory PFS Analysis: Bone-Only Disease

Patients With Bone-Only Disease



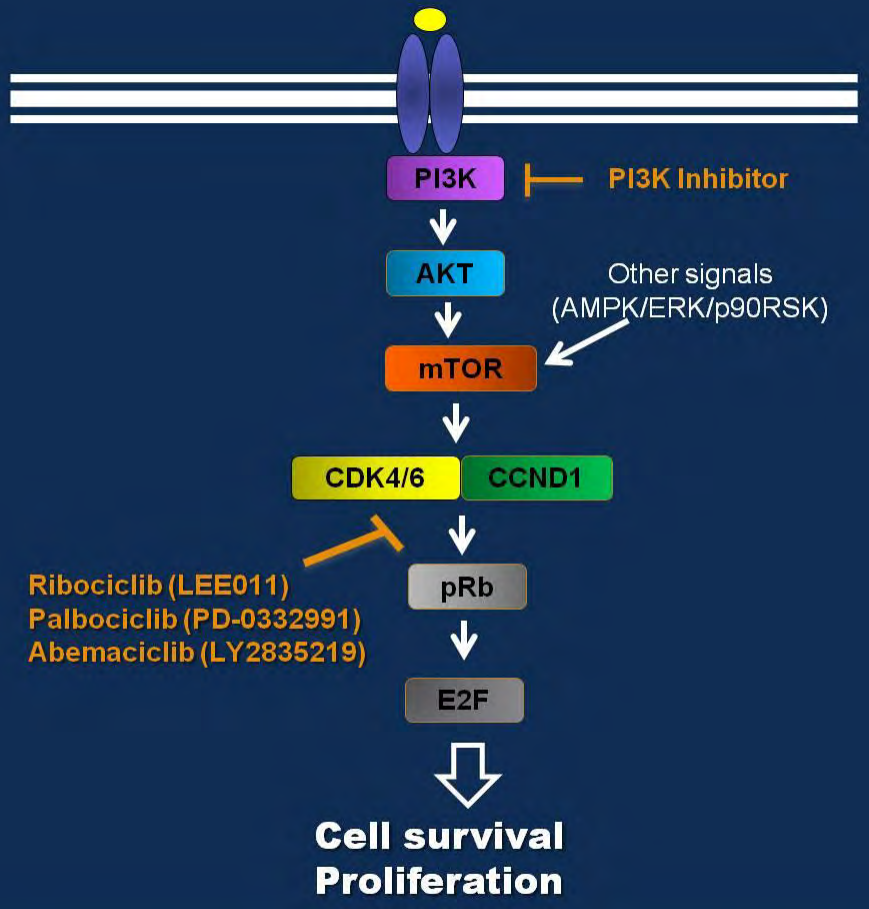
Landmark PFS Rate			
Arm	6 Months	12 Months	18 Months
Abemaciclib (n = 70)	87.6%	86.0%	76.5%
Placebo (n = 39)	94.6%	75.7%	57.6%

Patients Without Bone-Only Disease



Landmark PFS Rate			
Arm	6 Months	12 Months	18 Months
Abemaciclib (n = 258)	82.7%	69.5%	57.5%
Placebo (n = 126)	68.4%	49.9%	35.4%

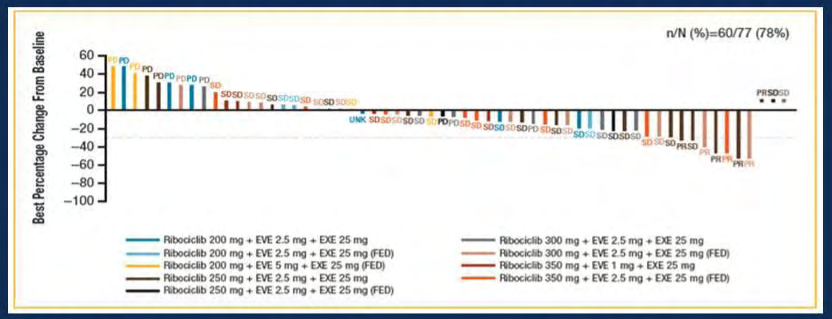
Di Leo A, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract 236O_PR.



CDK4/6 inhibition + α-PI3K inhibition combinations could reverse resistance to endocrine therapy as well as CDK4/6 therapy

Exemestane + Everolimus + Ribociclib

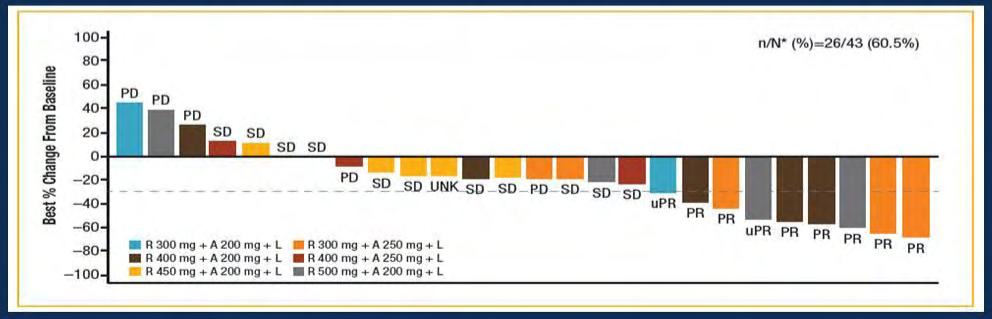
Phase Ib/II study of postmenopausal women with AI-resistant ER+ MBC



Bardia et al. SABCS 2015.

Letrozole + Alpelisib + Ribociclib

Phase Ib study of postmenopausal women with ER+ MBC

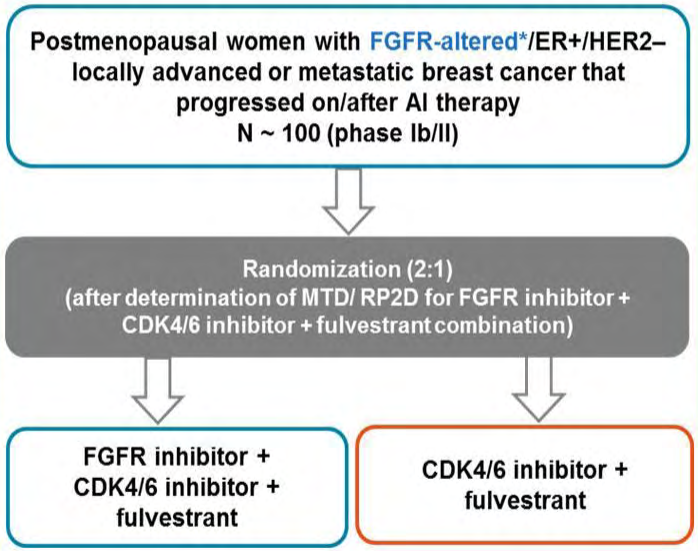


Juric et al. SABCS 2015.

Targeting *FGFR*

Completed	Safety and Efficacy of TKI258 in FGFR1 Amplified and Non-amplified Metastatic HER2 Negative Breast Cancer	
	Condition:	Metastatic Breast Cancer
	Intervention:	Drug: TKI258
Completed	A Phase II Trial Testing Oral Administration of Lucitanib in Patients With Fibroblast Growth Factor Receptor (FGFR)1-amplified or Non-amplified Estrogen Receptor Positive Metastatic Breast Cancer	
	Condition:	Breast Cancer
	Intervention:	Drug: lucitanib
Completed Has Results	Safety and Efficacy of AZD4547 in Combination With Fulvestrant vs. Fulvestrant Alone in ER+ Breast Cancer Patients	
	Conditions:	FGFR Inhibition, Pharmacokinetics, Biomarkers; ER+ Breast Cancer
	Interventions:	Drug: AZD4547; Drug: Exemestane; Drug: Placebo; Drug: Fulvestrant
Active, not recruiting	AZD4547 & Anastrozole or Letrozole (NSAIs) in ER+ Breast Cancer Patients Who Have Progressed on NSAIs (RADICAL)	
	Condition:	Breast Cancer
	Intervention:	Drug: AZD4547 / anastrozole or letrozole
Recruiting	Open-Label, Dose-Escalation Study of INCB054828 in Subjects With Advanced Malignancies	
	Conditions:	Malignant Solid Tumour; Carcinoma, Non-Small-Cell Lung; Stomach Neoplasms; Urothelial Carcinoma; Endometrial Neoplasms; Multiple Myeloma; MPN; Breast Cancer; Cholangiocarcinoma
	Interventions:	Drug: INCB054828; Drug: Gemcitabine+Cisplatin; Drug: Pembrolizumab; Drug: Docetaxel
Recruiting	NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma	
	Conditions:	Advanced Malignant Solid Neoplasm; Lymphoma; Recurrent Malignant Solid Neoplasm; Recurrent Plasma Cell Myeloma; Refractory Malignant Neoplasm; Refractory Plasma Cell Myeloma

Phase Ib/II trial of FGFR TKI erdafitinib + fulvestrant + CDK4/6 inhibitor in endocrine-resistant ER+/HER2– metastatic breast cancer with FGF pathway alterations (Mayer, I)

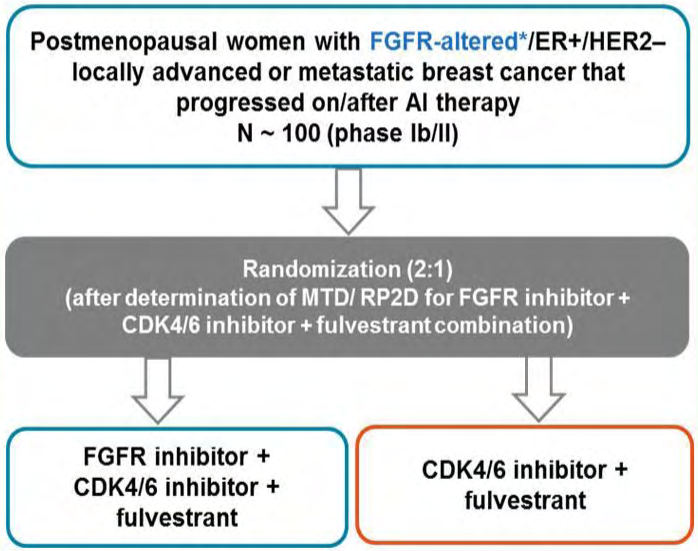


* FGFR alteration = *FGFR1-4 amplification*

Targeting *FGFR*

Completed	Safety and Efficacy of TKI258 in FGFR1 Amplified and Non-amplified Metastatic HER2 Negative Breast Cancer	
	Condition:	Metastatic Breast Cancer
	Intervention:	Drug: TKI258
Completed	A Phase II Trial Testing Oral Administration of Lucitanib in Patients With Fibroblast Growth Factor Receptor (FGFR)1-amplified or Non-amplified Estrogen Receptor Positive Metastatic Breast Cancer	
	Condition:	Breast Cancer
	Intervention:	Drug: lucitanib
Completed Has Results	Safety and Efficacy of AZD4547 in Combination With Fulvestrant vs. Fulvestrant Alone in ER+ Breast Cancer Patients	
	Conditions:	FGFR Inhibition, Pharmacokinetics, Biomarkers; ER+ Breast Cancer
	Interventions:	Drug: AZD4547; Drug: Exemestane; Drug: Placebo; Drug: Fulvestrant
Active, not recruiting	AZD4547 & Anastrozole or Letrozole (NSAIs) in ER+ Breast Cancer Patients Who Have Progressed on NSAIs (RADICAL)	
	Condition:	Breast Cancer
	Intervention:	Drug: AZD4547 / anastrozole or letrozole
Recruiting	Open-Label, Dose-Escalation Study of INCB054828 in Subjects With Advanced Malignancies	
	Conditions:	Malignant Solid Tumour; Carcinoma, Non-Small-Cell Lung; Stomach Neoplasms; Urothelial Carcinoma; Endometrial Neoplasms; Multiple Myeloma; MPN; Breast Cancer; Cholangiocarcinoma
	Interventions:	Drug: INCB054828; Drug: Gemcitabine+Cisplatin; Drug: Pembrolizumab; Drug: Docetaxel
Recruiting	NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma	
	Conditions:	Advanced Malignant Solid Neoplasm; Lymphoma; Recurrent Malignant Solid Neoplasm; Recurrent Plasma Cell Myeloma; Refractory Malignant Neoplasm; Refractory Plasma Cell Myeloma

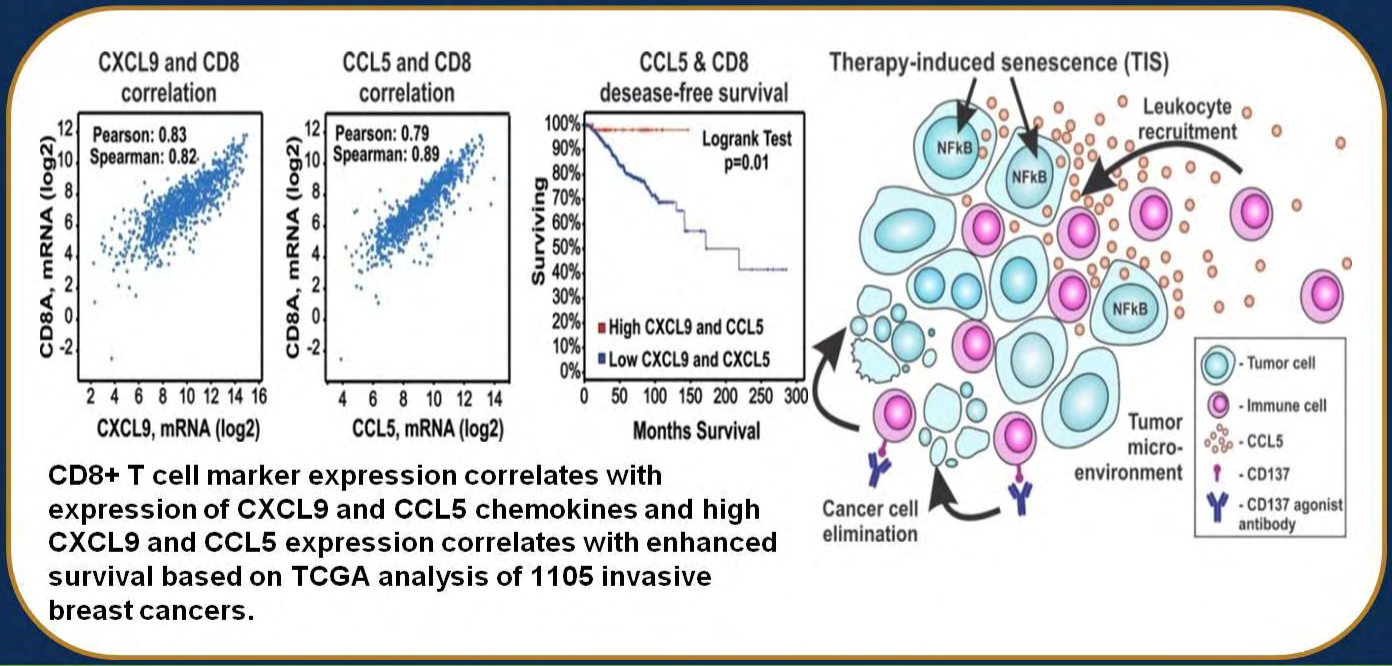
Phase Ib/II trial of FGFR TKI erdafitinib + fulvestrant + CDK4/6 inhibitor in endocrine-resistant ER+/HER2– metastatic breast cancer with FGF pathway alterations (Mayer, I)



* FGFR alteration = *FGFR1-4 amplification*

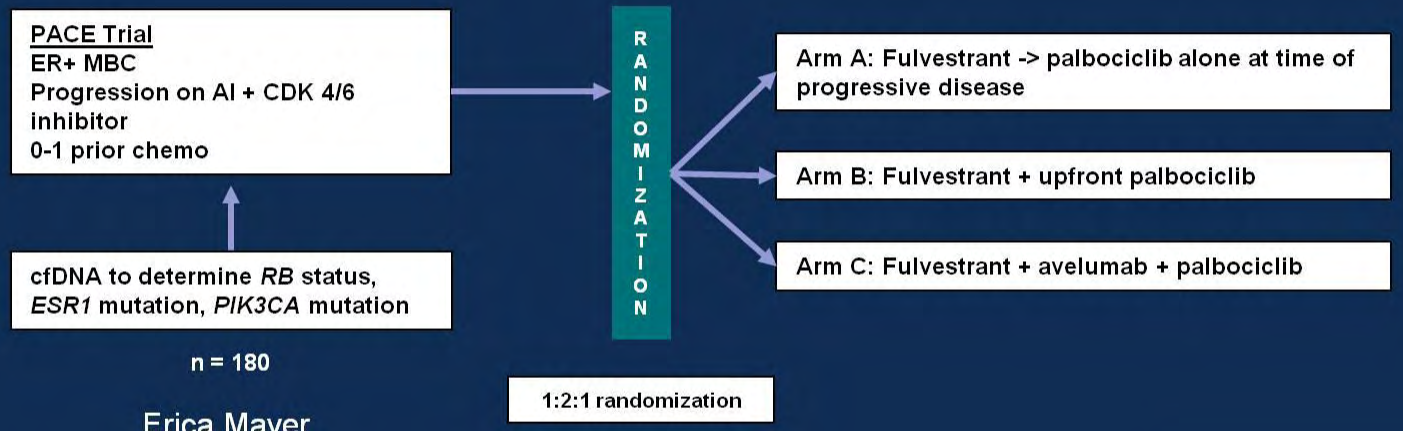
Immunotherapy combination strategies in ER+ MBC – CDK4/6 inhibition

- Inhibition of CDK4/6 in ER+ breast cancer → Induction of senescence and enhanced recruitment of immune cells
- This may result in increased sensitivity checkpoint inhibitors



CD8+ T cell marker expression correlates with expression of CXCL9 and CCL5 chemokines and high CXCL9 and CCL5 expression correlates with enhanced survival based on TCGA analysis of 1105 invasive breast cancers.

Immunotherapy combination strategies in ER+ MBC – CDK4/6 inhibition



JPCE Trial
Patients with Stage IV NSCLC or ER+ MBC
(N = 75)
NCT02779751

→ Abemaciclib + Pembrolizumab

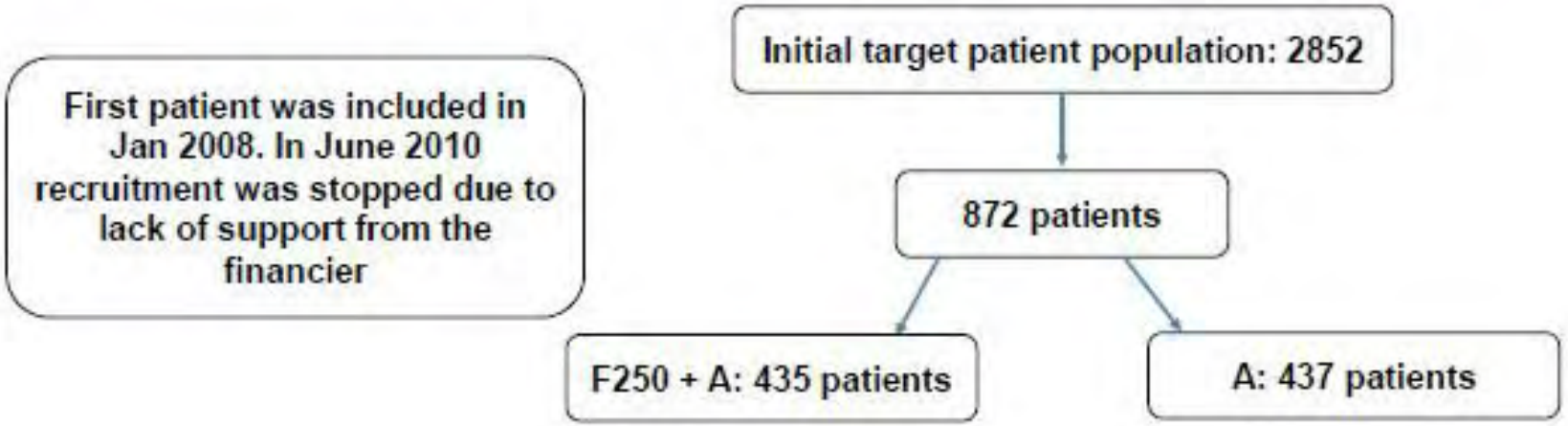
Phase III Evaluating the Addition of Fulvestrant (F) to Anastrozole (A) As Adjuvant Therapy in Postmenopausal Women With Hormone Receptor Positive HER2 Negative (HR+/HER2-) Early Breast Cancer (EBC): Results From the GEICAM/2006-10 Study

Study Design

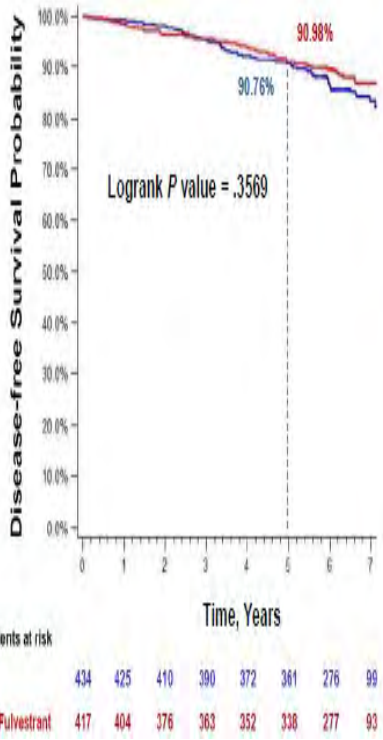
HR+/HER2- postmenopausal patients with early breast cancer who have undergone surgery with or without neoadjuvant chemotherapy

Early End Recruitment Rationale

FACT trial comparing fulvestrant + anastrozole to anastrozole alone in 1st relapse showed no difference in time to progression at more than 40 months follow-up[1]



Disease-Free Survival



Number of patients at risk

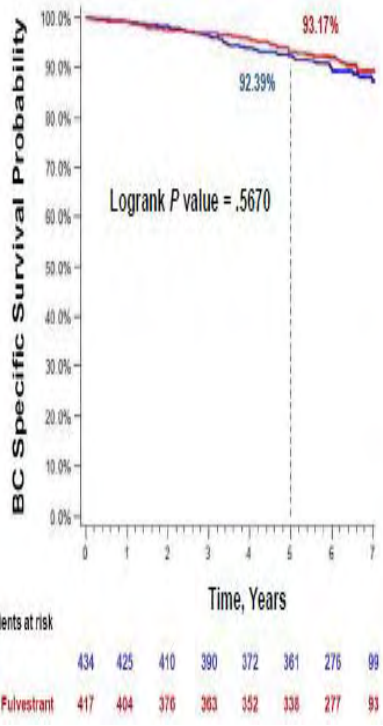
Anastrozole	434	425	410	390	372	361	276	99
Anastrozole + Fulvestrant	417	404	376	363	352	338	277	93

Median follow-up: 6.41 years

Arm	Events
Anastrozole	62
Anastrozole + Fulvestrant	49

HR: 0.839 (95% CI: 0.576-1.220)

BC Specific Survival



Number of patients at risk

Anastrozole	434	425	410	390	372	361	276	99
Anastrozole + Fulvestrant	417	404	376	363	352	338	277	93

Median follow-up: 6.41 years

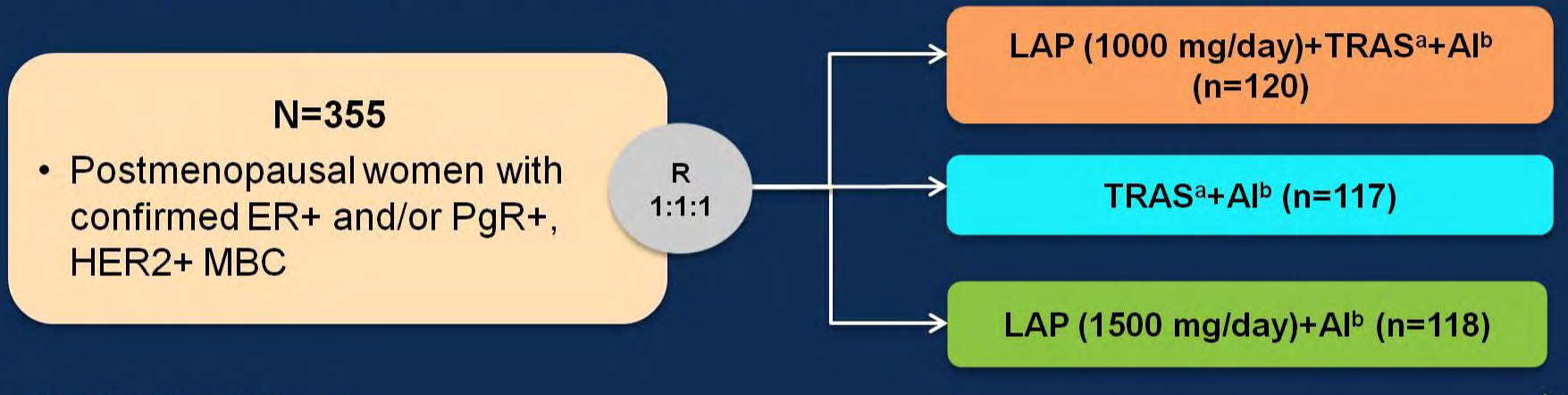
Arm	Events
Anastrozole	47
Anastrozole + Fulvestrant	39

HR: 0.884 (95% CI: 0.578-1.352)

HER 2 POSITIVE :
ESCALATE
OR
DE-ESCALATE ?

ALTERNATIVE: Study Design

- Global study conducted across 112 sites, 29 countries; Data cutoff: March 11, 2016



Stratification factors:

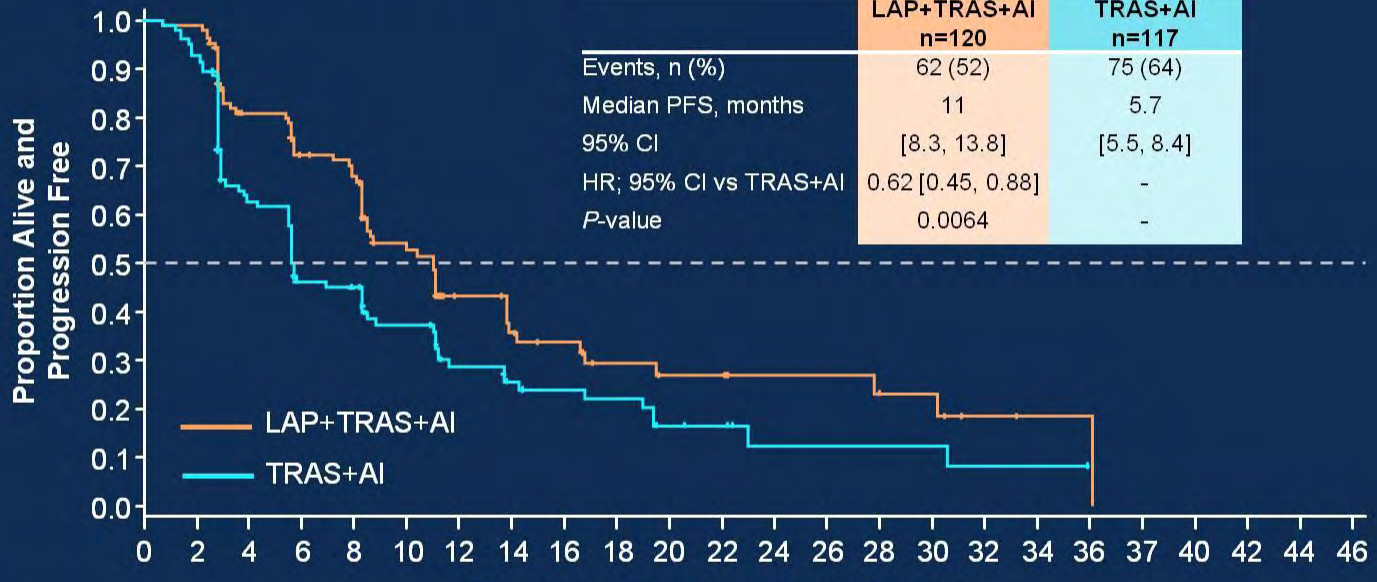
- Prior TRAS in neo/adjuvant or metastatic setting
- Investigator's choice of AI (steroidal/nonsteroidal)

[a]TRAS 8 mg/kg IV loading dose followed by 6 mg/kg IV q3weeks; [b]Investigator's choice of AI included LET (2.5 mg/day), ANA (1 mg/day) or EXE (25 mg/day).

AI, aromatase inhibitor; ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; LAP, lapatinib; MBC, metastatic breast cancer; PgR+, progesterone receptor-positive; TRAS, trastuzumab.

ALTERNATIVE: Primary Endpoint

PFS With LAP+TRAS+AI vs TRAS+AI (ITT Population)



	LAP+TRAS+AI n=120	TRAS+AI n=117
Events, n (%)	62 (52)	75 (64)
Median PFS, months	11	5.7
95% CI	[8.3, 13.8]	[5.5, 8.4]
HR; 95% CI vs TRAS+AI	0.62 [0.45, 0.88]	-
P-value	0.0064	-

Subjects at risk

LAP+TRAS+AI	120	109	77	64	59	39	24	19	16	12	10	10	7	7	5	5	2	1	1	0	0	0	0	0
TRAS+AI	117	98	57	39	37	28	19	15	13	12	7	6	3	3	3	3	2	2	0	0	0	0	0	0

AI, aromatase inhibitor; HR, hazard ratio; ITT, intent-to-treat; LAP, lapatinib; PFS, progression-free survival; TRAS, trastuzumab;

ALTERNATIVE: Secondary Endpoint

OS in All Treatment Arms

	LAP+TRAS+AI n=120	TRAS+AI n=117	LAP+AI n=118
Events, n (%)	21 (18)	30 (26)	31 (26)
Median OS, months	46.0	40.0	45.1
95% CI	[46.0, -]	[23.0, -]	[22.3, -]
HR; 95% CI vs TRAS+AI	0.60 [0.35, 1.04]	-	0.82 [0.49, 1.36]
P-value	0.070	-	0.440

Subjects at risk

LAP+TRAS+AI	120	115	109	100	93	80	68	62	58	48	39	38	28	23	19	15	13	11	8	6	6	4	2	1	1	1	0
TRAS+AI	117	109	96	87	81	71	61	51	47	40	35	27	21	18	13	13	12	10	7	5	4	2	2	1	1	1	0
LAP+AI	118	114	104	99	90	73	63	54	52	45	36	30	27	22	20	20	13	13	12	10	6	6	6	1	0	0	0

ALTERNATIVE: Response Rates

	LAP+TRAS+AI (n=120)	TRAS+AI (n=117)	LAP+AI (n=118)
Best response, (%)			
CR	5	<1	7
PR	27	13	12
SD	43	45	53
PD	15	31	24
Clinical benefit rate	41	31	33
Overall response rate[a]			
CR+PR, (%), 95% CI (%)	31.7 (23.5, 40.8)	13.7 (8.0, 21.3)	18.6 (12.1, 26.9)

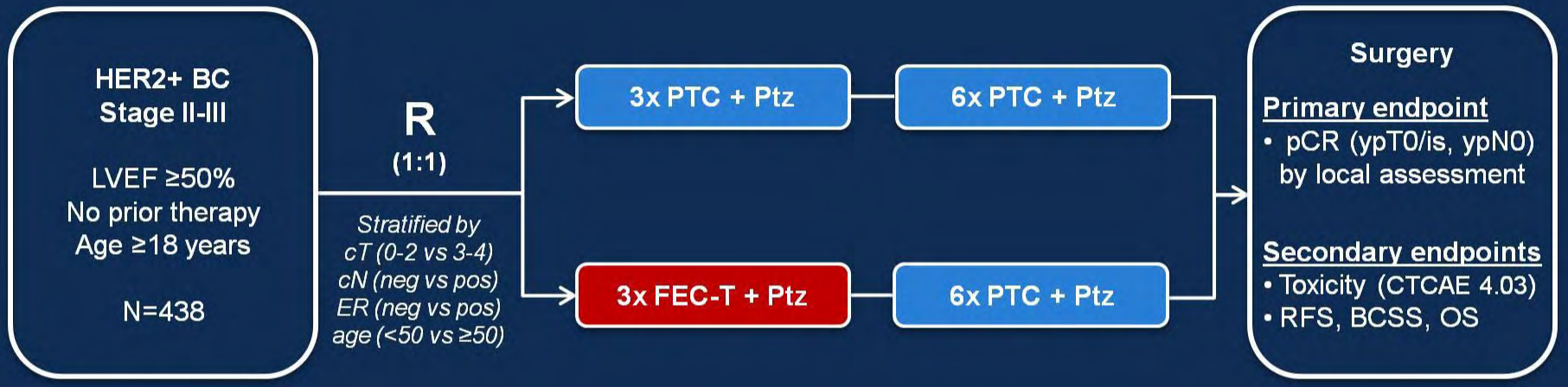
OR[b]: 2.83: 1.43, 5.89 (0.0017)

OR[b]: 1.492: 0.69, 3.3 (0.2829)

[a]Subjects with unknown or missing response are treated as nonresponders.
[b]95% CI (*P*-value[c]).
[c]*P*-value from exact test shows that common odds ratio equals to 1.

AI, aromatase inhibitor; CR, complete response; LAP, lapatinib; OR, odds ratio; PD, progressive disease; PR, partial response; SD, stable disease; TRAS, trastuzumab.

TRAIN-2 study design

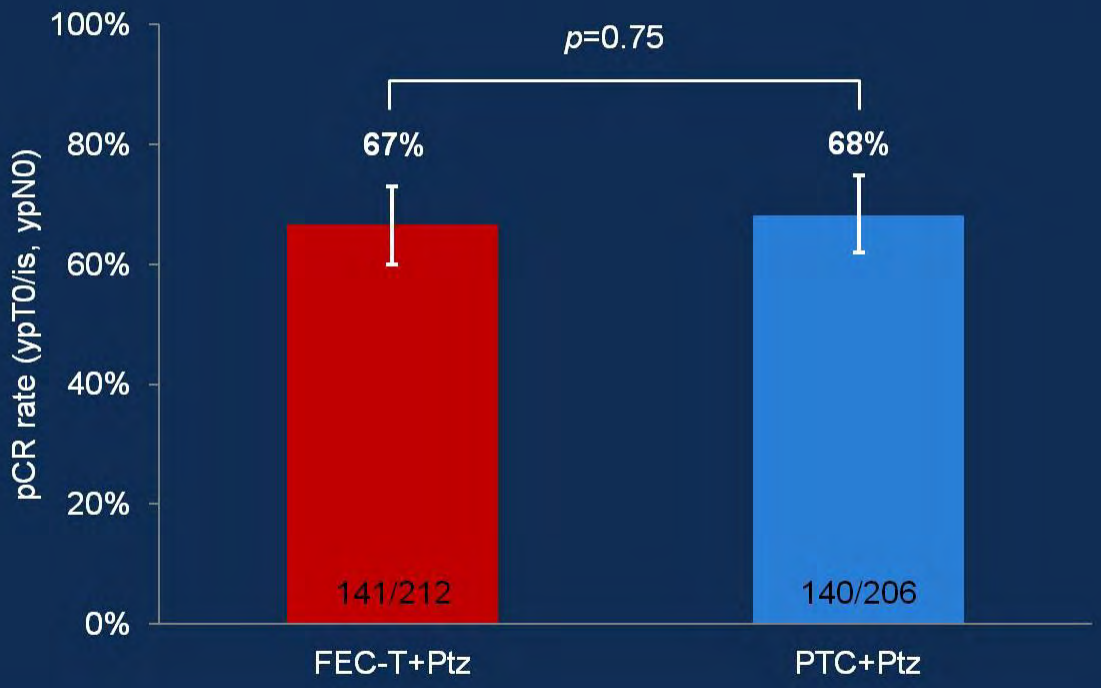


Adjuvant trastuzumab to complete one year of treatment and endocrine therapy for ER+ and/or PR+ tumors

PTC+Ptz cycle of 3 weeks, day 1 PTC+Ptz, day 8 only P; P = paclitaxel 80mg/m^2; T = trastuzumab 6mg/kg (loading dose 8mg/kg); C = carboplatin AUC = 6mg·min/ml; Ptz = pertuzumab, 420mg (loading dose 840mg)

FEC-T+Ptz cycle of 3 weeks: F = 5-fluorouracil 500mg/m^2; E = epirubicin 90mg/m^2; C = cyclophosphamide 500mg/m^2; T = trastuzumab 6mg/kg (loading dose 8mg/kg); Ptz = pertuzumab, 420mg (loading dose 840mg)

Primary endpoint: pCR breast & axilla



Grade ≥3 hematological adverse events

	FEC-T+Ptz (n=220*)		PTC+Ptz (n=218)		
AE term	Grade 3	Grade 4	Grade 3	Grade 4	*p*-value†
Neutropenia, %	41%	18%	47%	6%	0.34
Anemia, %	20%	<1%	21%	0%	0.91
Thrombocytopenia, %	14%	3%	16%	3%	0.71
Febrile neutropenia, %	10%	<1%	1%	0%	<0.0001

One patient randomized to FEC-T+Ptz developed acute myeloid leukemia
*One patient randomized to PTC+Ptz received FEC-T+Ptz
†*p*-value for difference in incidence of grade≥3 toxicity

CTCAE V4.03

Cardiac safety

Ejection fraction decrease

AE term	FEC-T+Ptz (n=220*)	PTC+Ptz (n=218)	*p*-value
LVEF decrease ≥10% or LVEF <50%†, %	29%	17%	0.003
LVEF decrease ≥10% and LVEF <50%, %	5%	3%	0.32

*One patient randomized to PTC+Ptz received FEC-T+Ptz
†CTCAE definition of grade 2 ejection fraction decrease

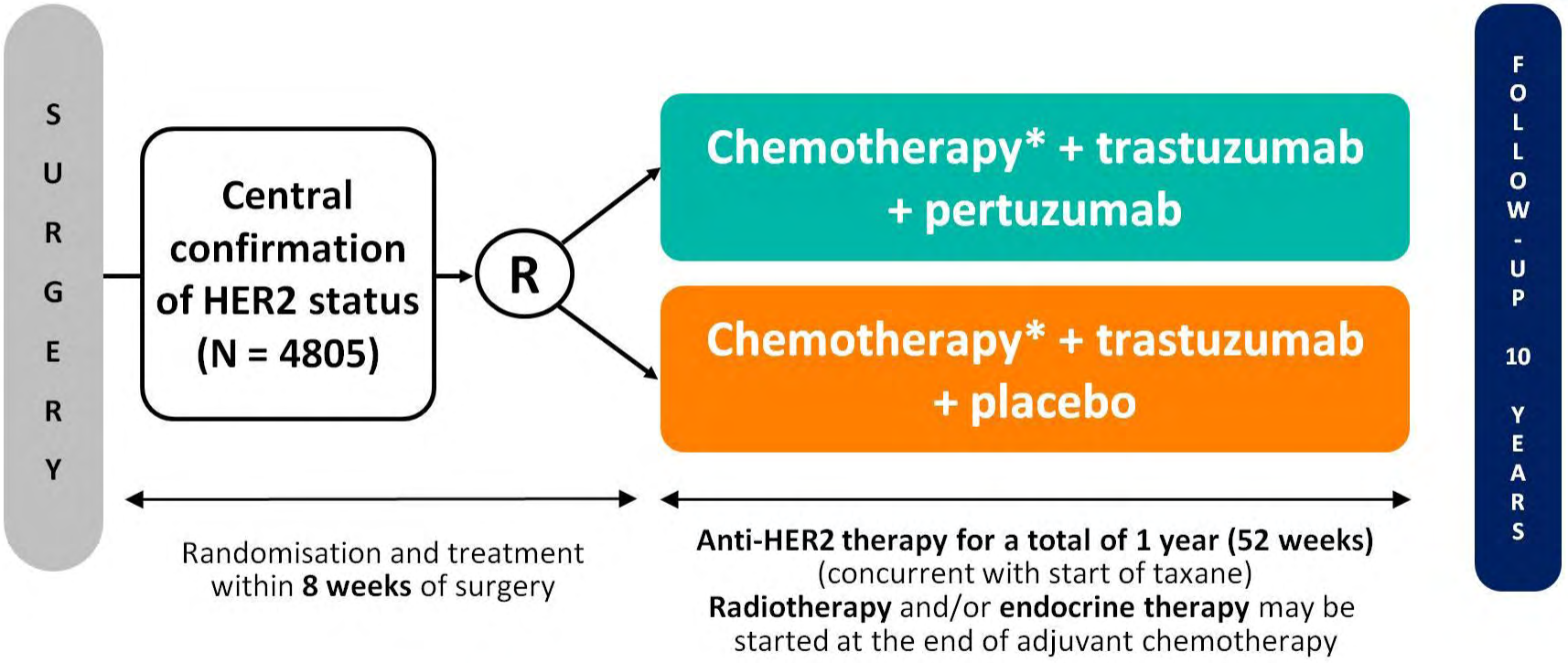
Other cardiac adverse events grade ≥2

AE term	FEC-T+Ptz (n=220*)	PTC+Ptz (n=218)
Symptomatic left ventricular systolic dysfunction, n	2	1
Myocardial infarction, n	0	2
Acute coronary syndrome, n	0	1
Arrhythmias, n	2	1

*One patient randomized to PTC+Ptz received FEC-T+Ptz

CTCAE V4.03

APHINITY: Trial Design



*A number of standard anthracycline-taxane-sequences or a non-anthracycline (TCH) regimen were allowed

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Breast International Group

APHINITY: Key Eligibility Criteria

Inclusion Criteria

- HER2-positive status confirmed by a central review (IHC 3+ or FISH-/CISH-positive)*
- Node-positive, any tumour size except T0
- Node-negative
  - Tumour size >1 cm

  OR
  - For tumours >0.5 and ≤1 cm, at least 1 of:
    - histological/nuclear grade 3

    OR
    - ER- and PR-negative

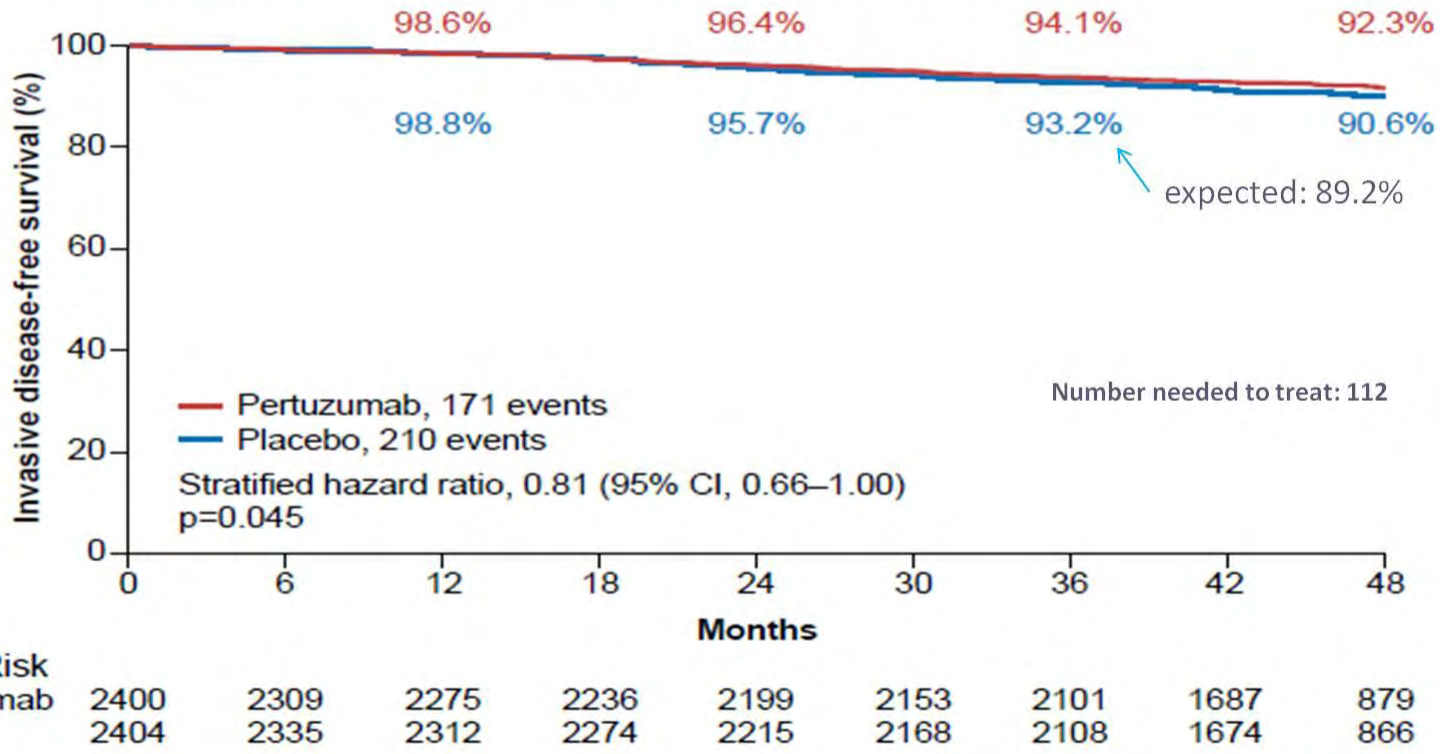
    OR
    - age <35
- Baseline LVEF ≥55%

Exclusion Criteria

- Prior invasive breast cancer
- Non-operable breast cancer
- Metastatic disease (stage IV)
- Previous non-breast malignancies (except for the following: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinomas of the skin)
- Previous or current anti-cancer therapy or previous radiotherapy for any malignancy
- Cardiac dysfunction or serious medical conditions

* Wolff A et al, J Clin Oncol 2013

APHINITY: Intent-to-Treat Primary Endpoint Analysis Invasive Disease-free Survival



No. at Risk									
Pertuzumab	2400	2309	2275	2236	2199	2153	2101	1687	879
Placebo	2404	2335	2312	2274	2215	2168	2108	1674	866

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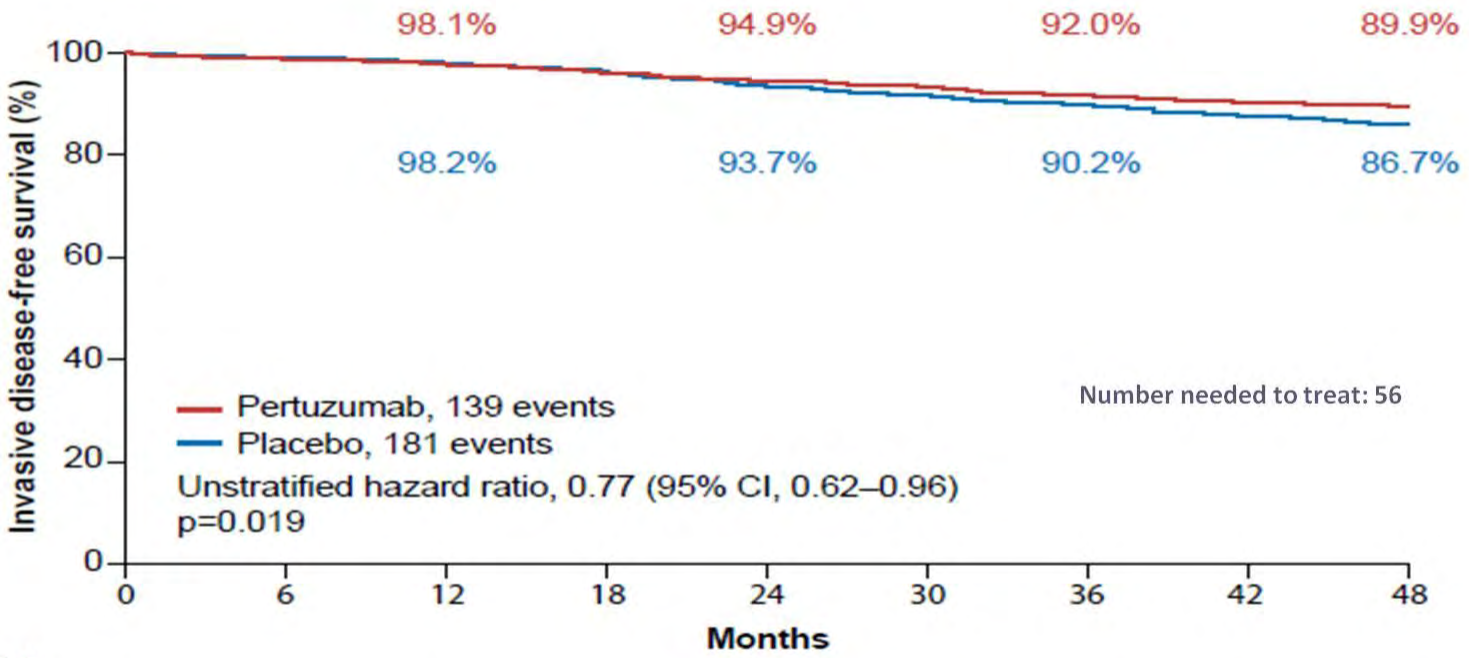
APHINITY: Node-positive Subgroup



No. at Risk									
Pertuzumab	1503	1444	1419	1387	1358	1327	1283	912	423
Placebo	1502	1453	1439	1408	1359	1319	1264	882	405

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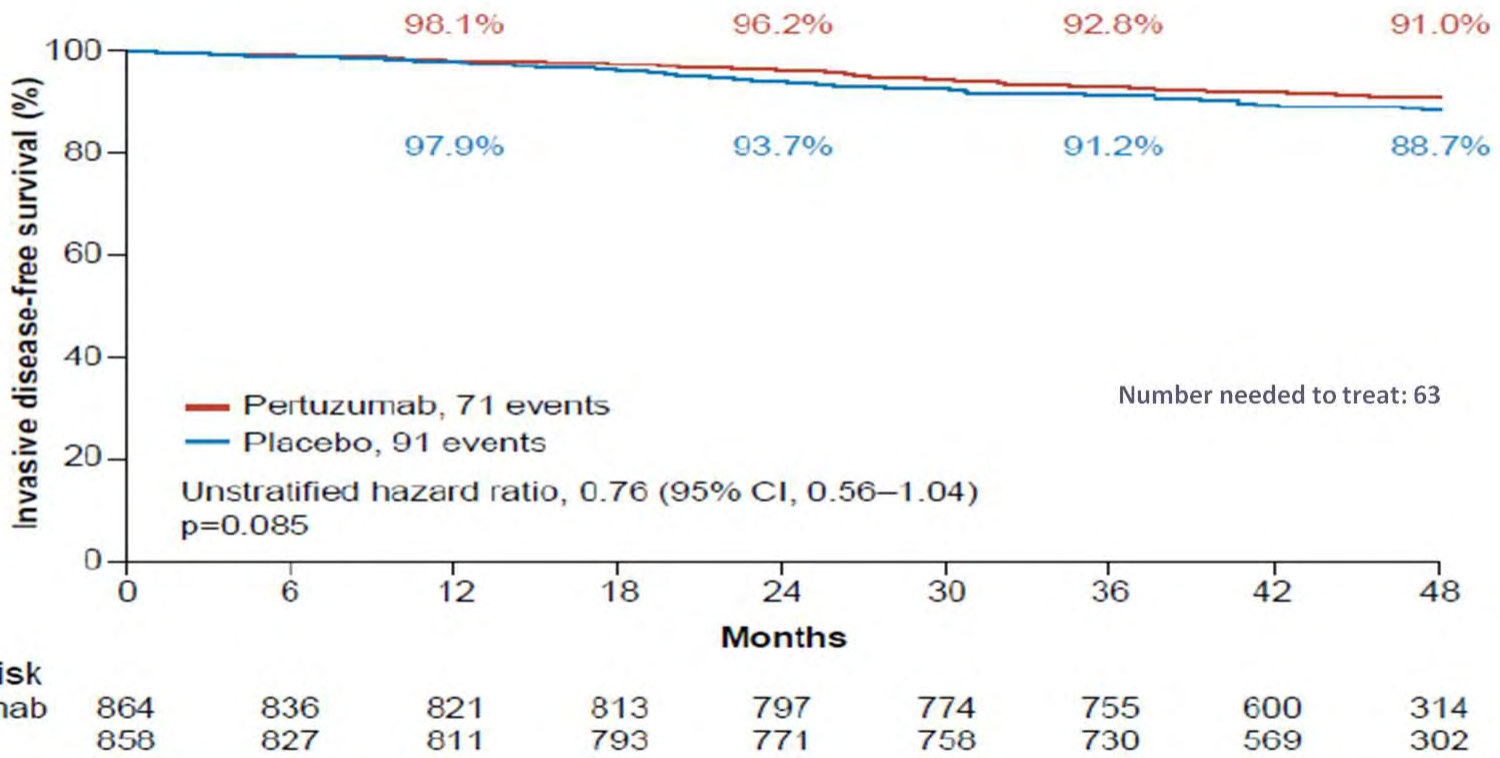
APHINITY: Hormone Receptor-negative Subgroup



No. at Risk									
Pertuzumab	864	836	821	813	797	774	755	600	314
Placebo	858	827	811	793	771	758	730	569	302

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Breast International Group

APHINITY: Secondary Efficacy Endpoints

3-year	Pertuzumab n=2400	Placebo n=2404	Hazard ratio (95% CI)	p value
IDFS (primary endpoint), %	94.1	93.2	**0.81 (0.66, 1.00)**	**0.045**
Secondary efficacy endpoints, %				
IDFS incl. second primary non-BC events (STEEP definition)	93.5	92.5	**0.82 (0.68, 0.99)**	**0.043**
Disease-free interval	93.4	92.3	**0.81 (0.67, 0.98)**	**0.033**
Recurrence-free interval	95.2	94.3	**0.79 (0.63, 0.99)**	**0.043**
Distant recurrence-free interval	95.7	95.1	**0.82 (0.64, 1.04)**	**0.101**
Overall survival (first interim analysis)*	97.7	97.7	**0.89 (0.66, 1.21)**	**0.467**

* 1st interim analysis at 26% of the target events for the final overall survival analysis

APHINITY: Cardiac Endpoints

N (%)	Pertuzumab n=2364	% Treatment difference (95% CI)	Placebo n=2405
Primary cardiac endpoint	**17 (0.7)**	**0.4 (0.0, 0.8)**	**8 (0.3)**
• Heart failure NYHA III/IV + LVEF drop* • Cardiac death**	15 (0.6) 2 (0.08)		6 (0.2) 2 (0.08)
• Recovered according to LVEF	7		4
Secondary cardiac endpoint Asymptomatic or mildly symptomatic LVEF drop*	**64 (2.7)**	**-0.1 (-1.0, 0.9)**	**67 (2.8)**

*LVEF drop = ejection fraction drop ≥10% from baseline AND to below 50%;
**Identified by the Cardiac Advisory Board for the trial according to a prospective definition

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APHINITY: Common Grade ≥ 3 Adverse Events

	Pertuzumab n=2364	Placebo n=2405
Neutropenia	**385 (16.3%)**	**377 (15.7%)**
Febrile Neutropenia	**287 (12.1%)**	**266 (11.1%)**
Anaemia	**163 (6.9%)**	**113 (4.7%)**
Diarrhoea	**232 (9.8%)**	**90 (3.7%)**
- with chemotherapy and targeted therapy	232 (9.8%)	90 (3.7%)
- with targeted therapy (post-chemotherapy)	12 (0.5%)	4 (0.2%)
- with AC->T (N=1834; 1894)	137 (7.5%)	59 (3.1%)
- with TCH (N= 528; 510)	95 (18.0%)	31 (6.1%)

9 weeks vs 1 year adjuvant trastuzumab in combination with chemotherapy: results of the phase III multicentric Italian Short-HER study

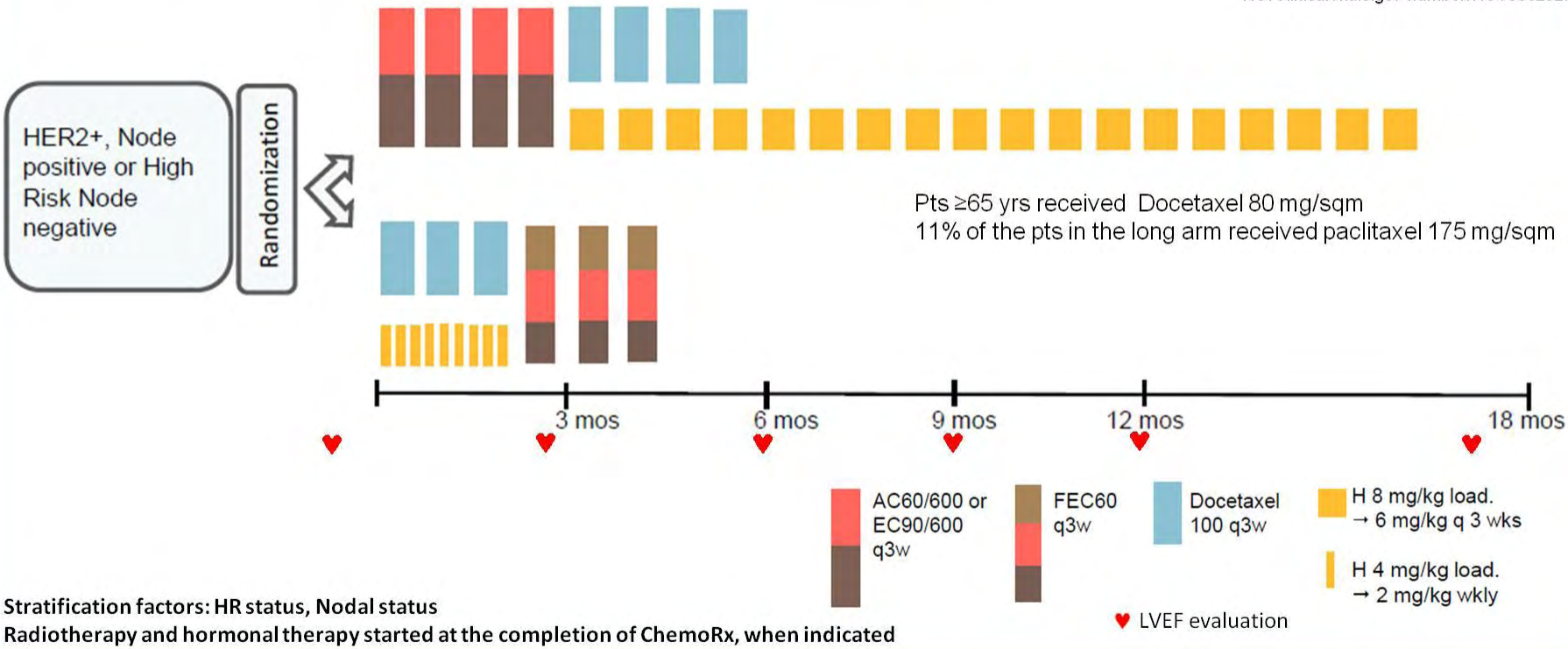
PF Conte, G. Bisagni, A. Frassoldati, A. Brandes, E. Anselmi, F. Giotta, M. Aieta, V. Gebbia, A. Musolino, O. Garrone, C. Taverniti, G. Cavazzini, A. Turletti, D. Rubino, A. Ferro, E. Picardo, F. Piacentini, S. Balduzzi, R. D'Amico, V. Guarneri

Medical Oncology 2, Istituto Oncologico Veneto IRCCS
DiSCOG-University of Padova, Italy
On behalf of the Short-HER Study Team

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Short-HER: Study Design

EUDRACT number: 2007-004326-25
NCI ClinicalTrials.gov number: NCT00629278

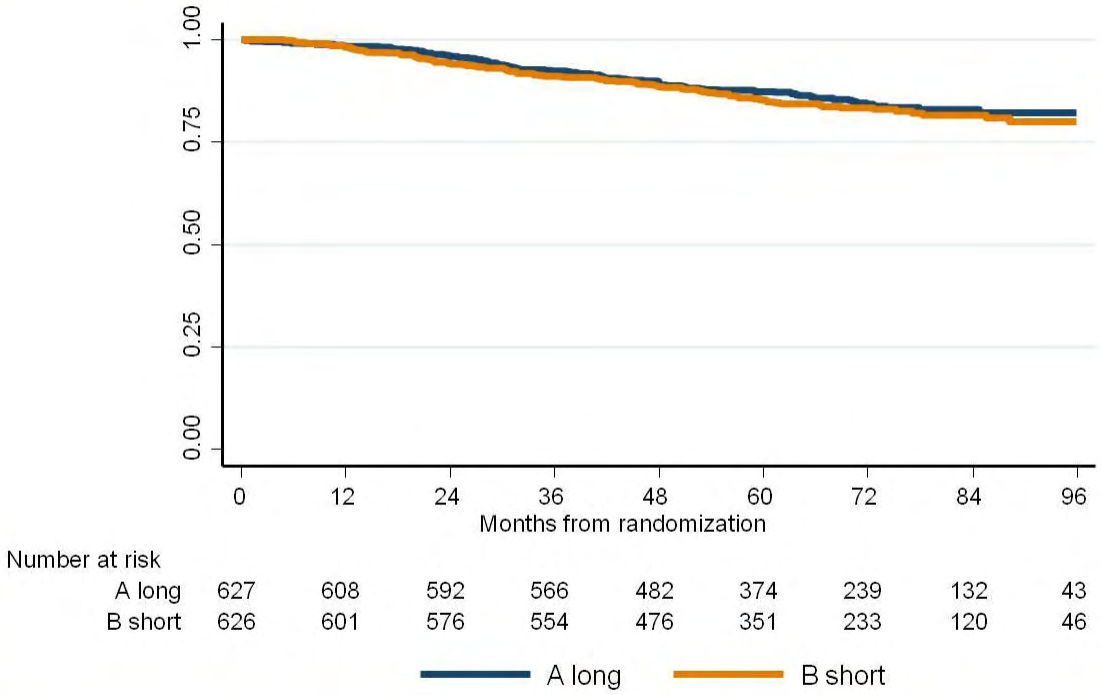


Stratification factors: HR status, Nodal status
Radiotherapy and hormonal therapy started at the completion of ChemoRx, when indicated

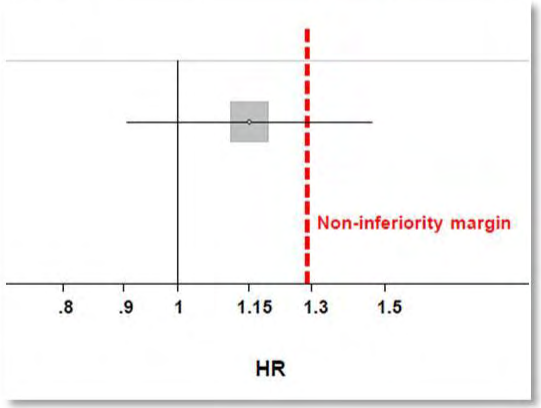
Main Inclusion Criteria

- Surgically resected infiltrating primary breast cancer
- HER2+ (either IHC 3+ or FISH+)
- Node positive
- Node negative and at least one of the following: T > 2 cm, Grade 3, lymphovascular invasion, Ki 67> 20%, age < 35, HR negative (< 10%)
- Age >18, < 75 years
- ECOG PS 0-1
- Normal organ and marrow function
- LVEF within the institutional normal range
- Written informed consent

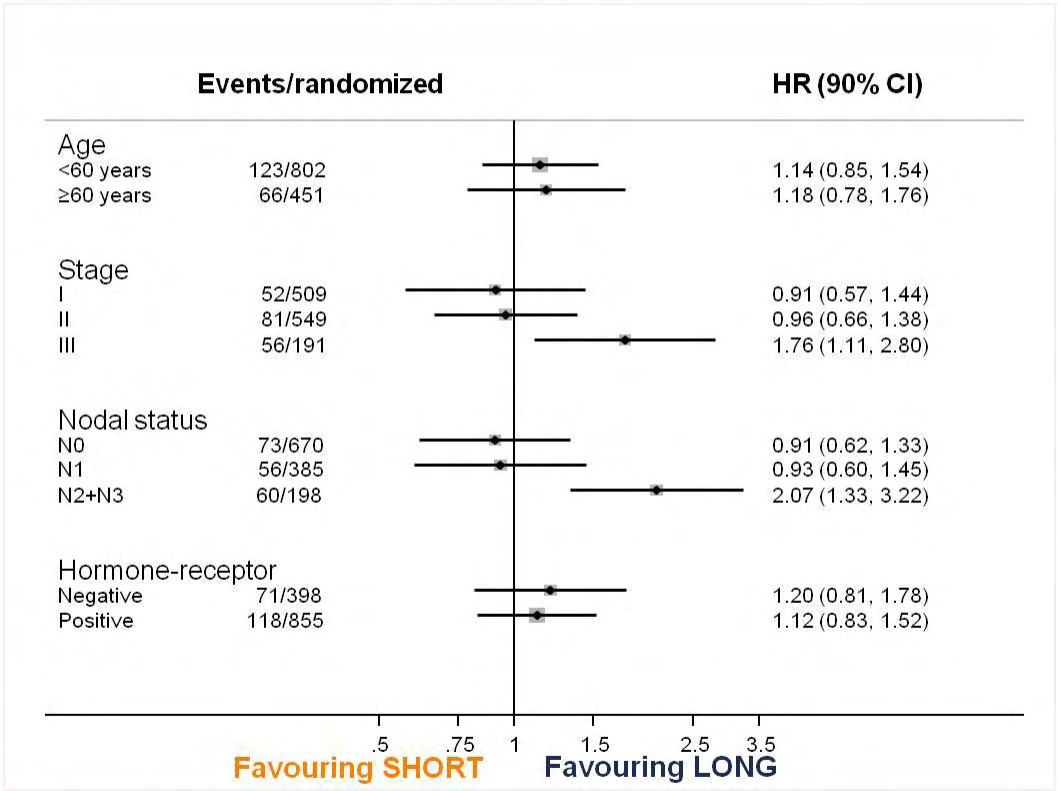
Short-HER: Disease Free Survival



	Long (N=627)	Short (N=626)
DFS events #	89	100
5y DFS %	87.5	85.4
HR (90% CI)	1.15 (0.91-1.46)	

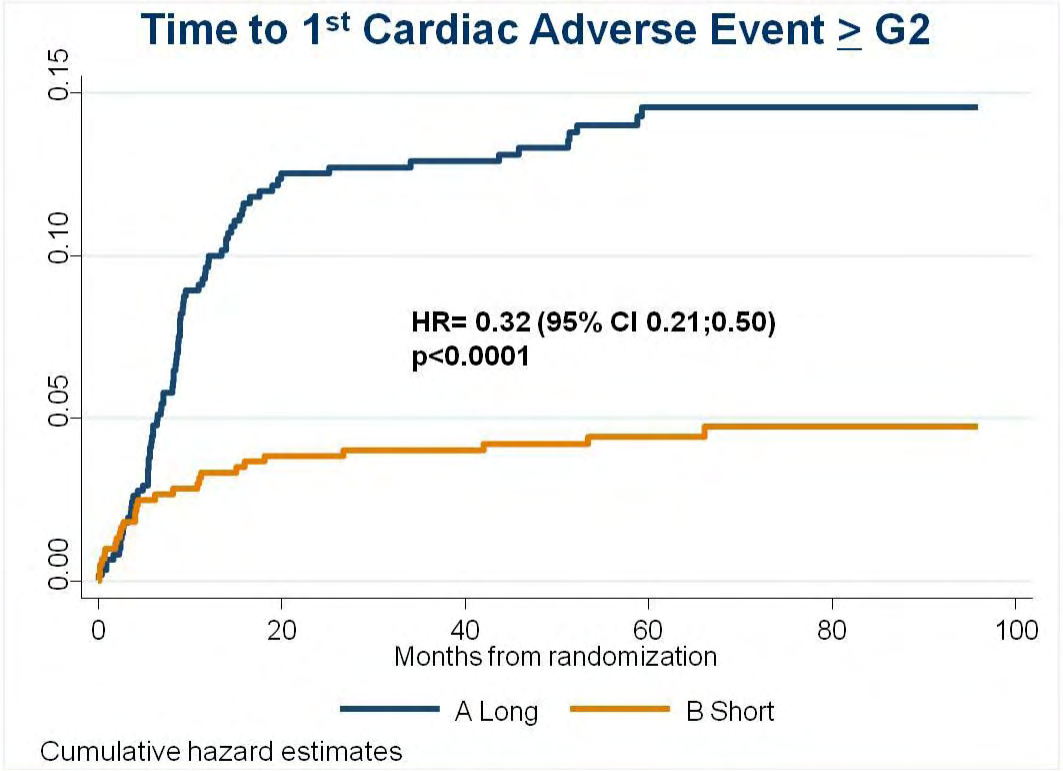


DFS – Subgroup analysis



	Ratio of HRs (90%CI)	p-value
Stage **III vs I+II**	**2.30** (1.35, 3.94)	**< 0.001**
Nodal status **N2+N3 vs N0+N1**	**2.25** (1.33, 3.83)	**< 0.001**

Cardiac Adverse Events



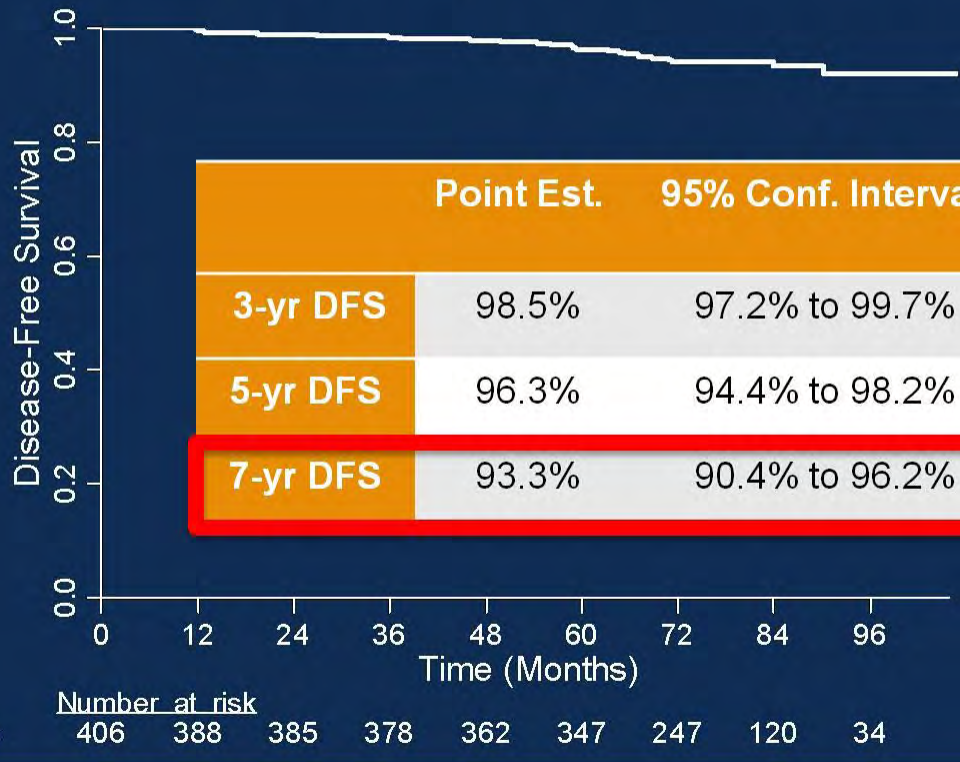
Number of cardiac events

Grade	Long N(%)	Short N(%)
2	70 (11.2)	22 (3.5)
3	17 (2.7)	7 (1.1)
4	3 (0.5)	3 (0.5)
Total	**90 (14.4)**	**32 (5.1)**

Trastuzumab and Paclitaxel for Stage I HER2+ disease (Tolaney et al. abstract 511)

N=406
HR+ 67%
91% T≤2 cm
98.5% N0

2,390 patient-years of follow-up (5.9 years/patient)

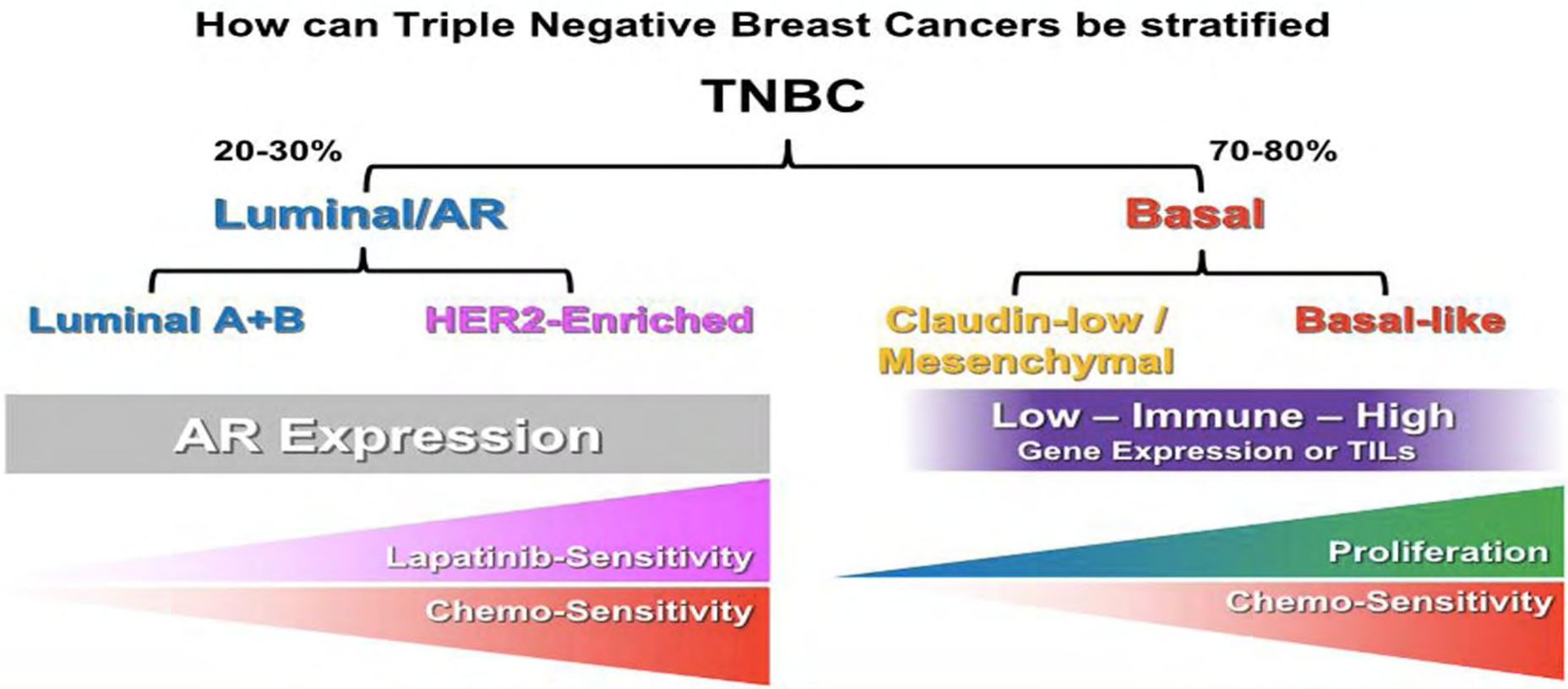


	Point Est.	95% Conf. Interval	No. of events
3-yr DFS	98.5%	97.2% to 99.7%	6
5-yr DFS	96.3%	94.4% to 98.2%	14
7-yr DFS	93.3%	90.4% to 96.2%	23

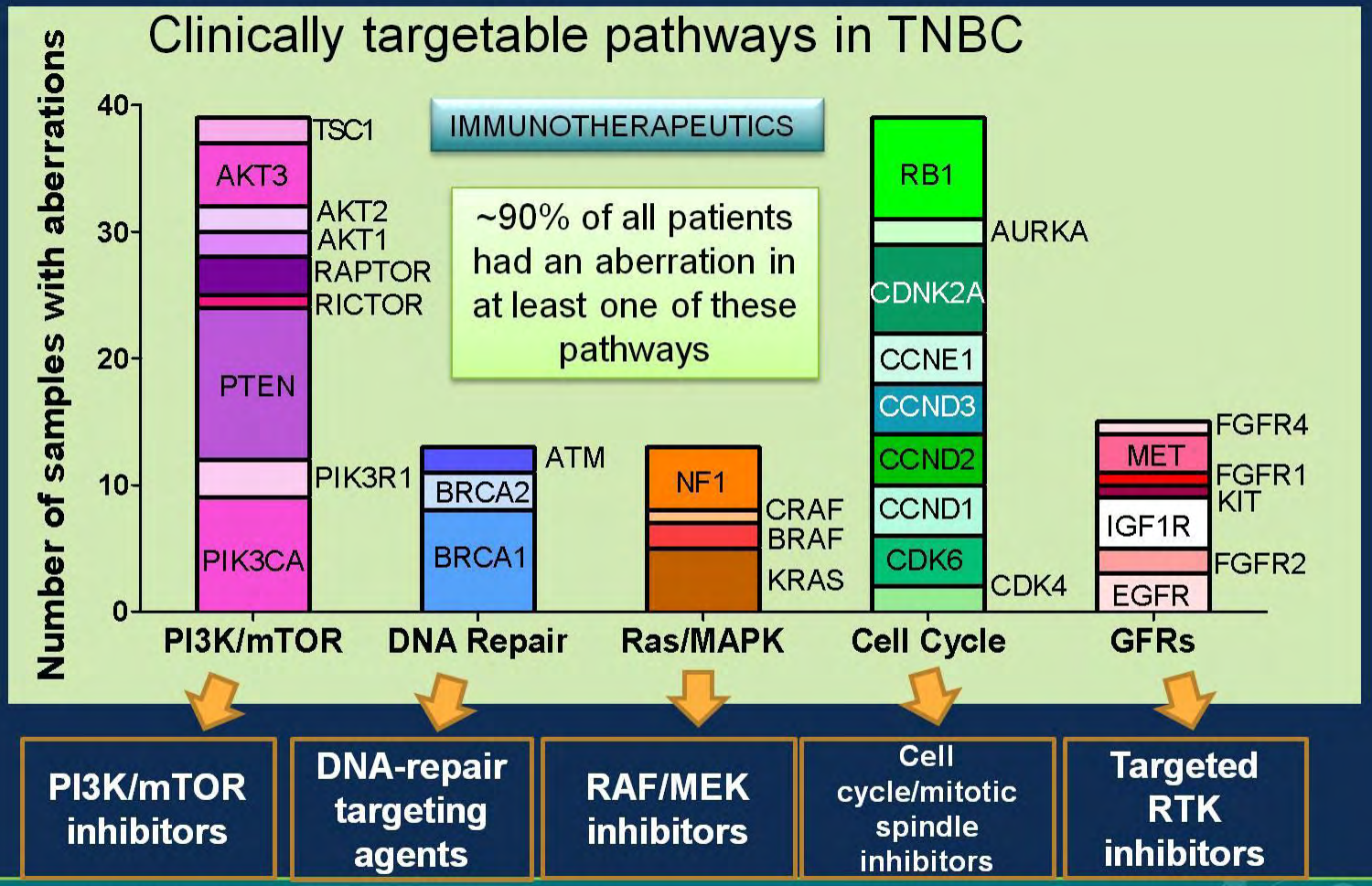
Trastuzumab and Paclitaxel for Stage I HER2+ disease (Tolaney et al. abstract 511)

DFS Event	N (%)	Time to event [months; mean(range)]
Any recurrence or death	23 (5.7)	
Local/Regional Recurrence	5 (1.2)	
Ipsilateral axilla (HER2+)	3	29 (12-54)
Ipsilateral breast (HER2+)	2	51 (37-65)
New Contralateral Primary Breast Cancer	6 (1.5)	
HER2+	1	56
HER2-	3	36 (12-59)
Unknown	2	87 (84-90)
Distant Recurrence	4 (1.0)	49 (27-63)
Death		
Non-breast cancer related	8 (2.0)	58 (13-71)

TRIPLE NEGATIVE



Perou C SABCS 2016



Balko Cancer Discovery 2014

Immune checkpoint inhibitors in metastatic TNBC

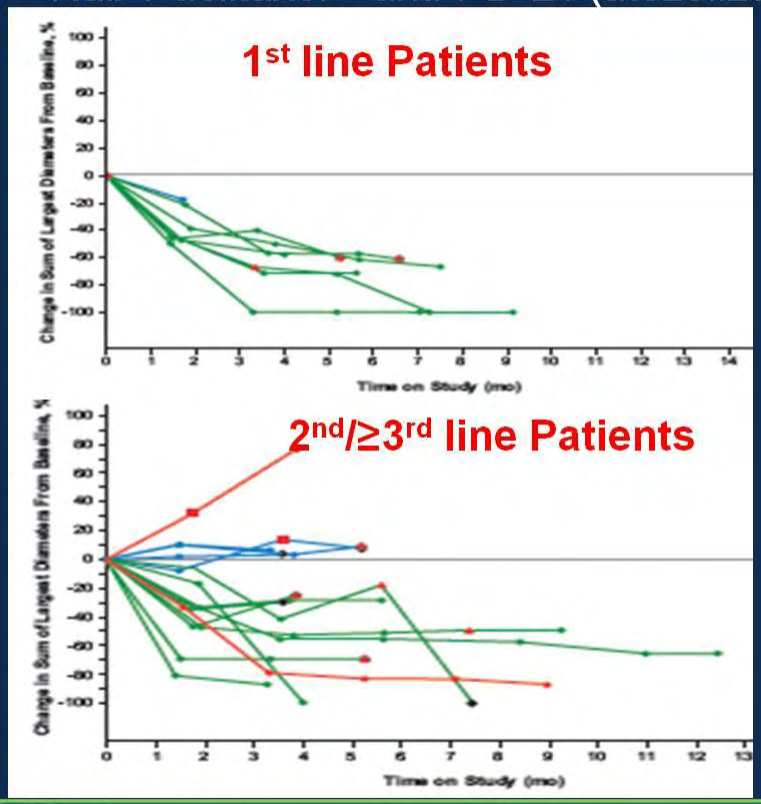
Immune checkpoint inhibitors have shown durable responses in heavily pretreated patients with metastatic TNBC

	Pembrolizumab (n = 32)	Atezolizumab (n = 71)	Avelumab (n=58 /9)
Target	PD-1	PD-L1	PD-L1
Tumour PD-L1	≥1% (58%+)	≥5%	All / ≥1%
ORR	18.5%	13%	8.6% / 44.4%
SD	25.9%	18%	22.4%

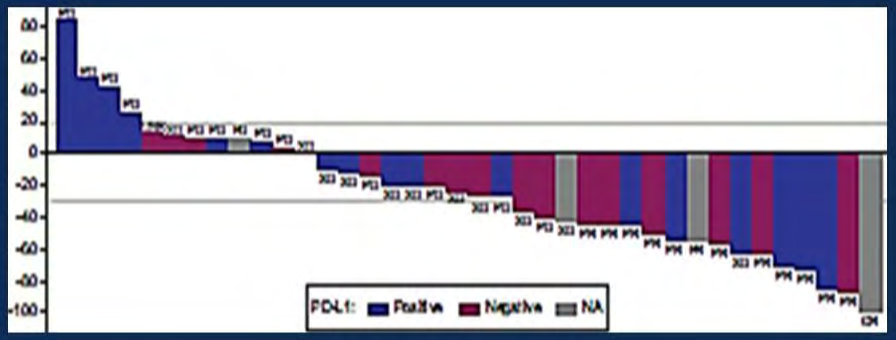
Nanda et al. JCO 2016, Schmid et al. AACR 2017, Dirix et al SABCS 2015

Combination Immune-and Chemotherapy in TNBC

Nab-Paclitaxel + anti-PD-L1 (atezolizumab)



Eribulin + anti-PD-1 (pembrolizumab)

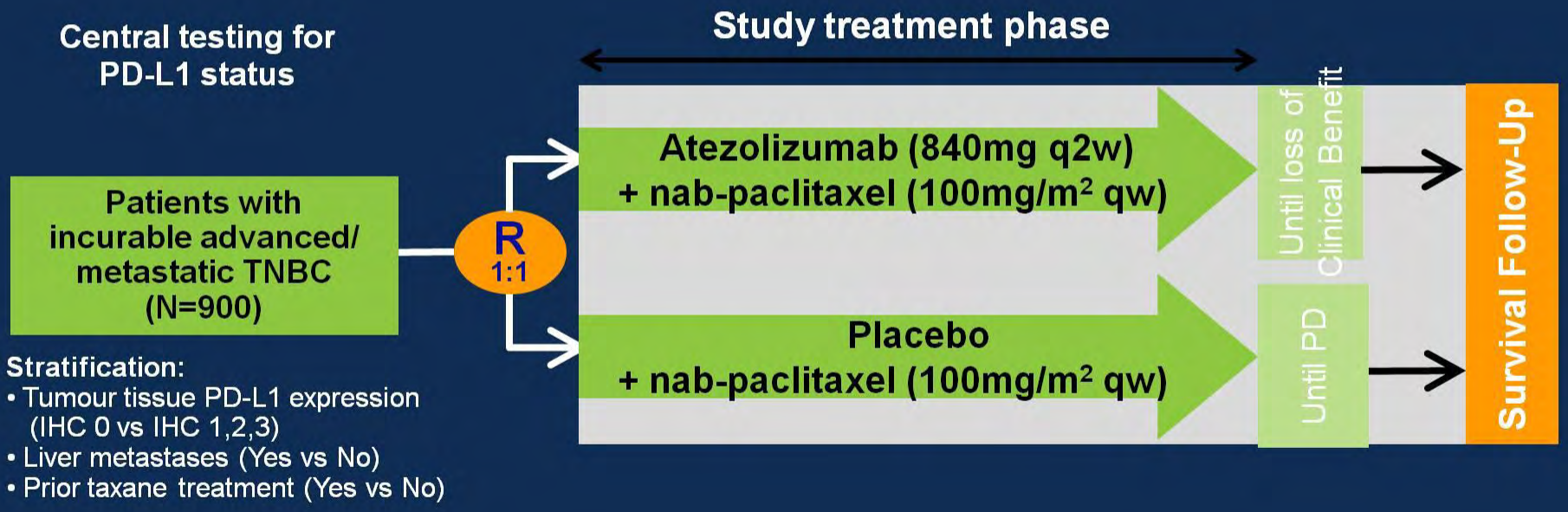


	All	1st line (n=17)	2nd/3rd L (n=18)
ORR	34.4%	41.2%	27.3%
CBR	40.6%	47.1%	36.4%

Adams S, SABCS 2015; Tolaney, S SABCS 2016

IMpassion130: Atezolizumab in 1st line mTNBC

DESIGN: DOUBLE-BLIND | MULTICENTRE | RANDOMIZED | PLACEBO-CONTROLLED



Study Design – KEYNOTE 522 Trial

Stratified by
1. T1/T2 vs T3/T4
2. N0 vs N+
3. Carbo Q1 vs Q3

Primary Endpoints:
- pCR rate (ypT0/Tis ypN0)
- EFS

Secondary Endpoints:
- pCR rate in PD-L1+
- EFS in PD-L1+
- OS

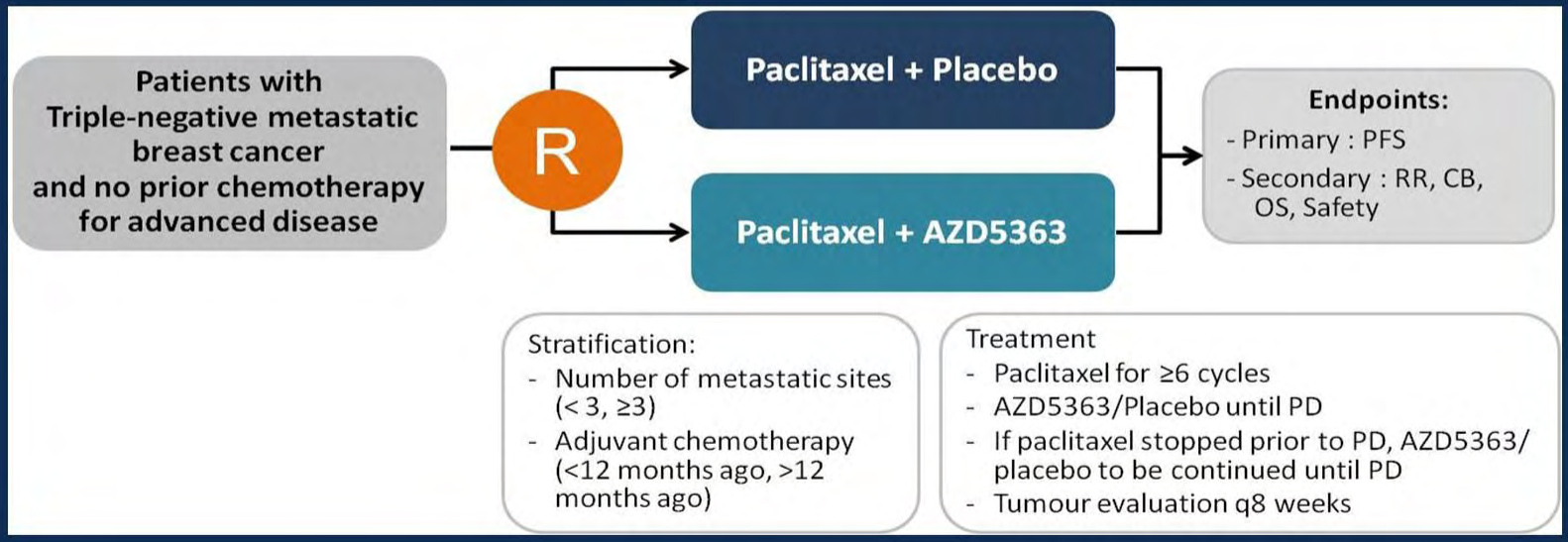
Study Treatment

Paclitaxel 80 mg/m^2 IV weekly,
Carboplatin weekly (AUC 1.5) or 3-weekly (AUC5)
Doxorubicin 60 mg/m^2 IV 3-weekly
(Epirubicin 90 mg/m^2 IV 3-weekly)
Cyclophosphamide 600 mg/m^2 IV 3-weekly
Pembrolizumab **200 mg IV q3weeks**

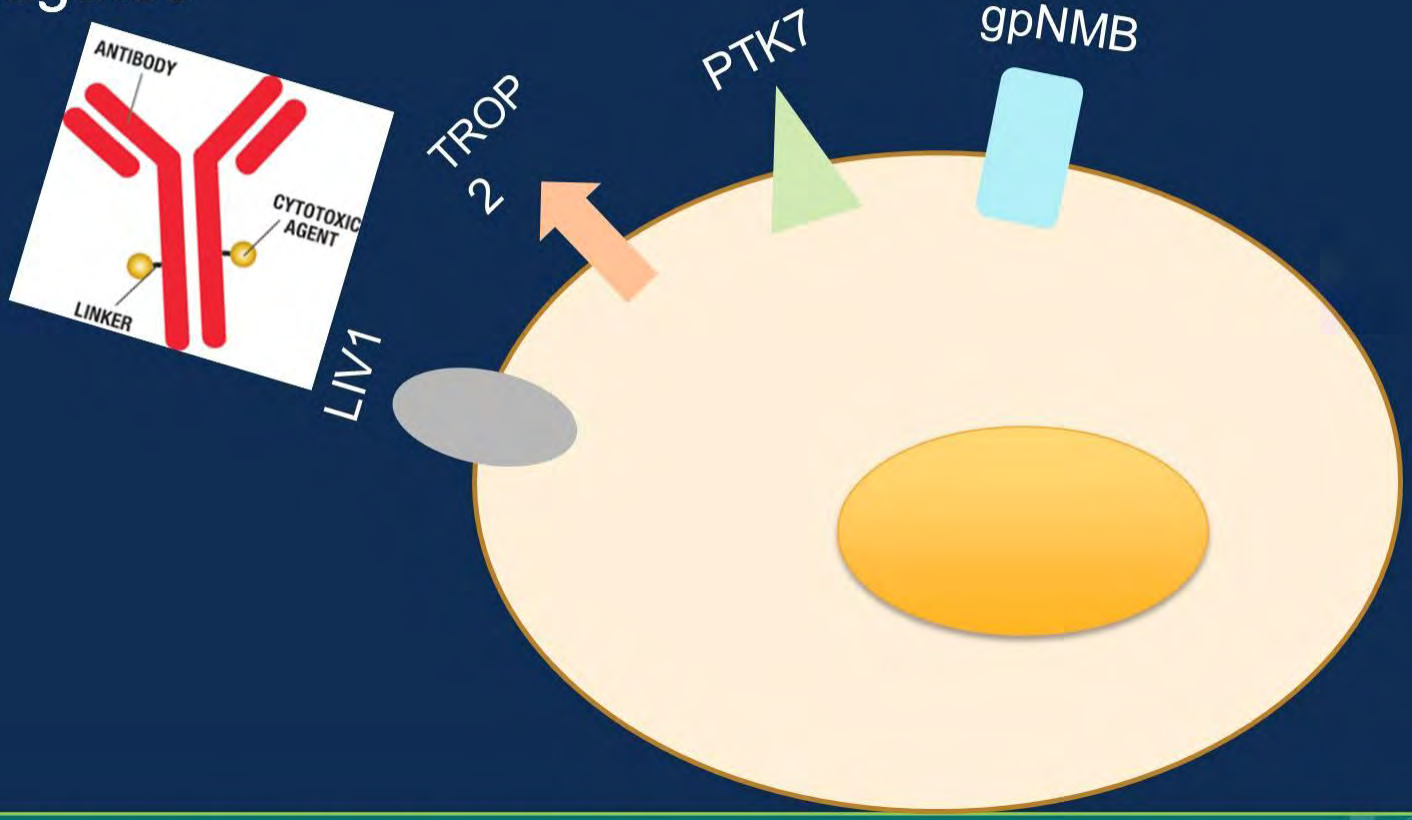
Targeting the PI3K/AKT pathway in TNBC

PAKT Trial: Paclitaxel +/- AKT inhibitor AZD5363 in metastatic TNBC

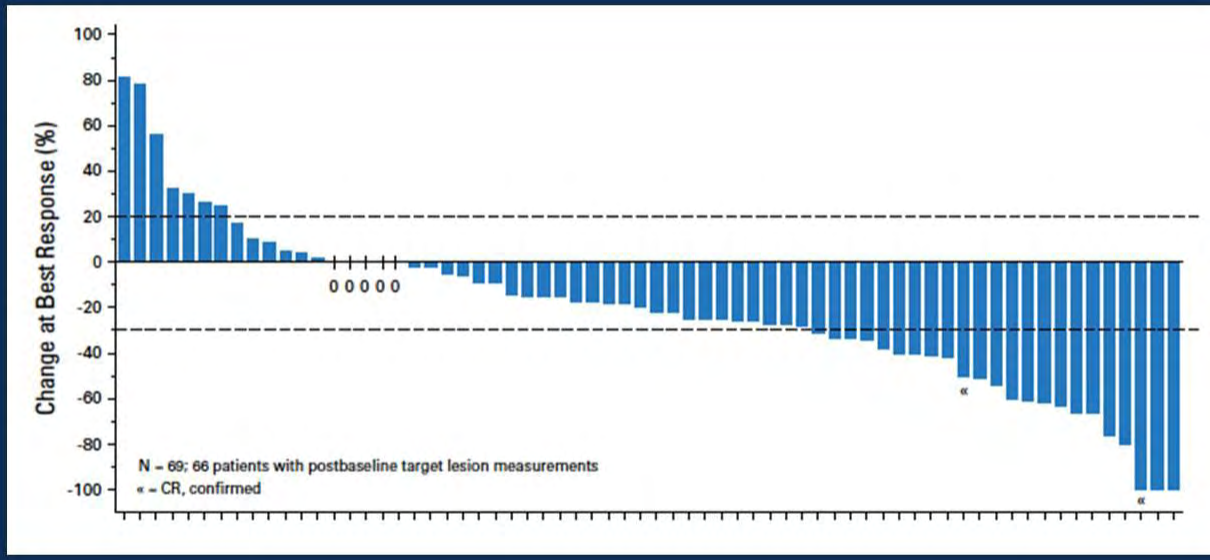
Investigator-initiated academic Trial (Sponsor: QMUL); funding from AstraZeneca
Coordinating centre: Barts Cancer Institute

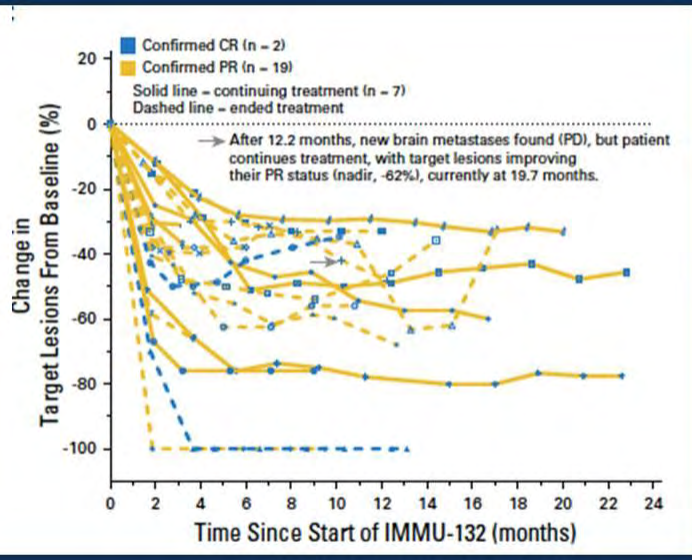


Cell surface markers: Targets for Antibody-Drug Conjugates



Sacituzumab Govitecan:
Breakthrough Designation by FDA





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

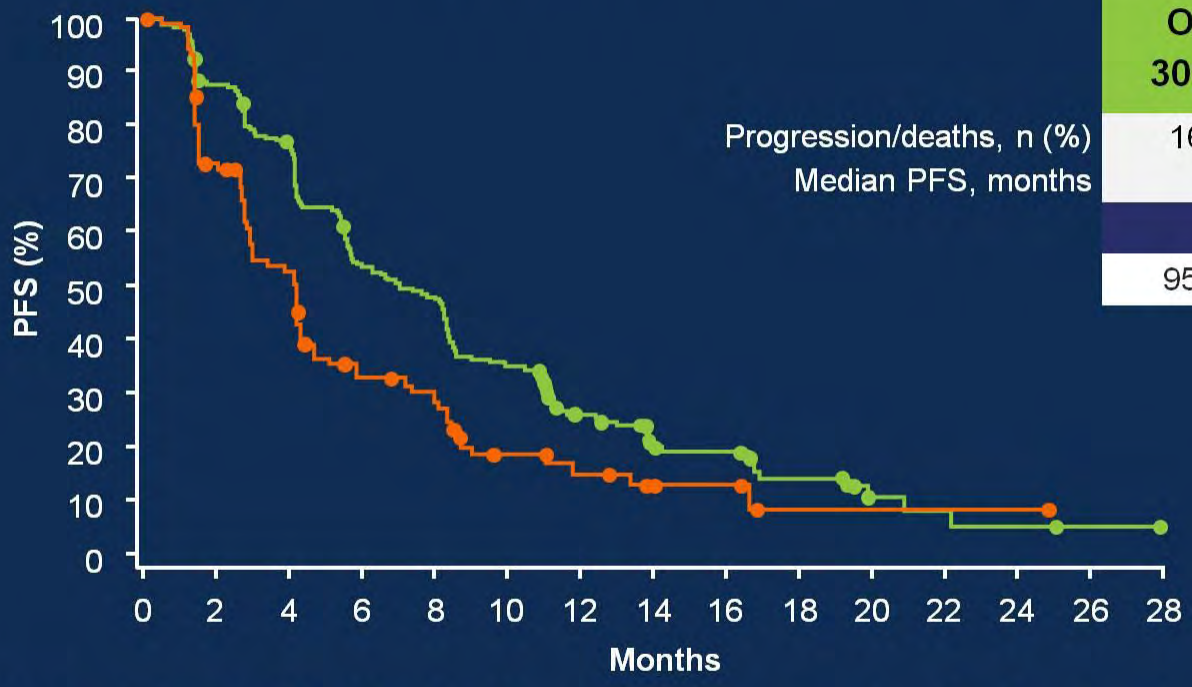
Treat until progression

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

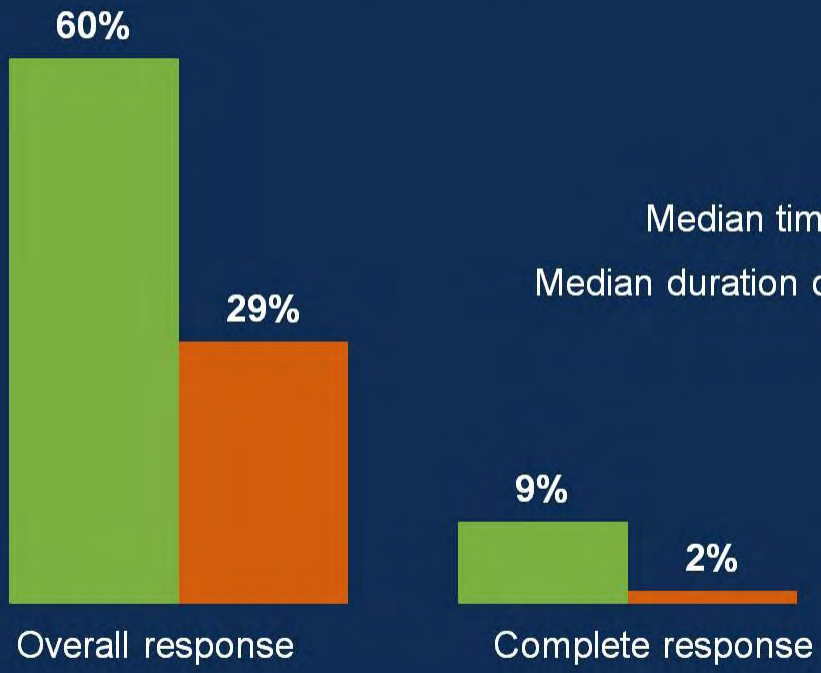
Primary endpoint: progression-free survival by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

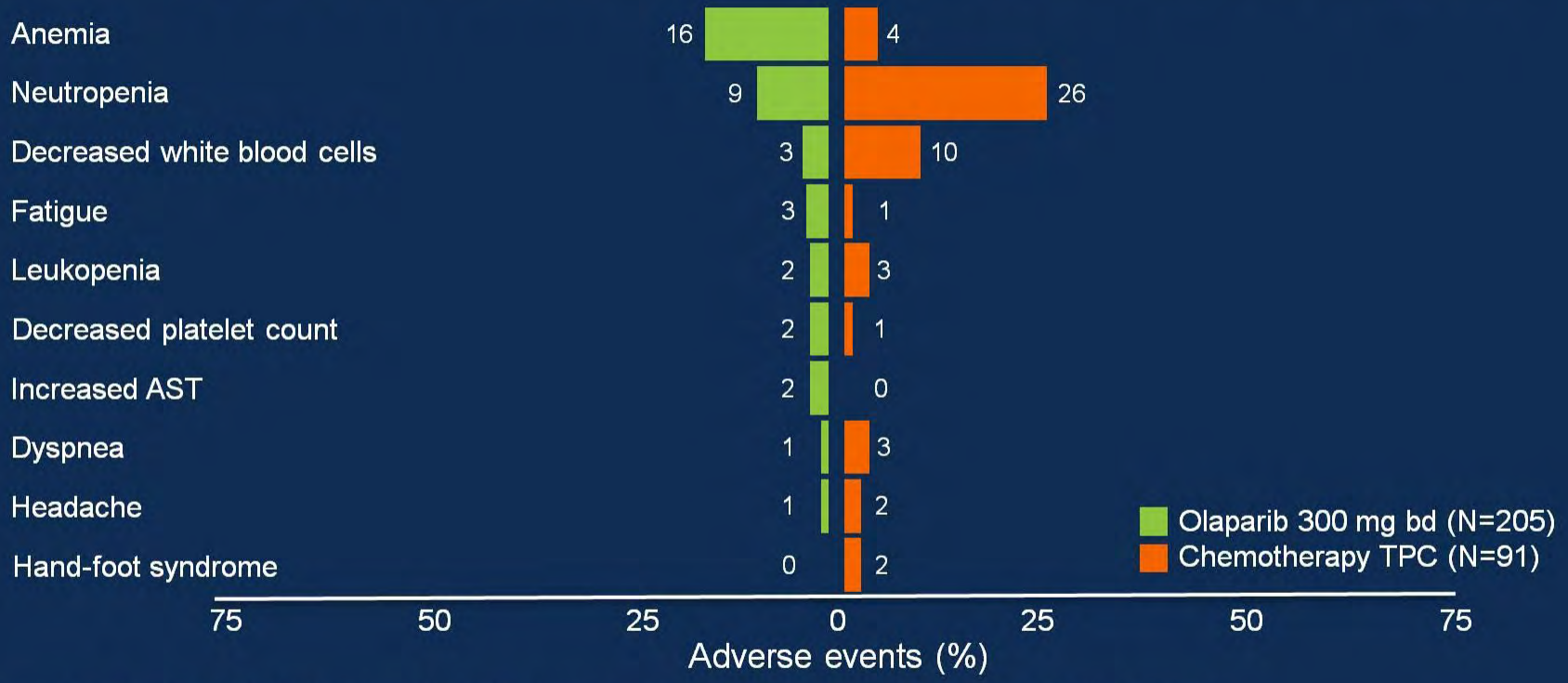
At risk, n															
Olaparib 300 mg bd	205	177	154	107	94	69	40	23	21	11	4	3	2	1	0
Chemotherapy TPC	97	63	44	25	21	11	8	4	4	1	1	1	1	0	0

Objective response by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
n	167	66
Median time to response, days	47	45
Median duration of response, months	6.2 (4.6–7.2)	7.1 (2.8–12.2)

Grade ≥3 adverse events in ≥2% patients in either arm



Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia

ALT, alanine aminotransferase; AST, aspartate aminotransferase