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

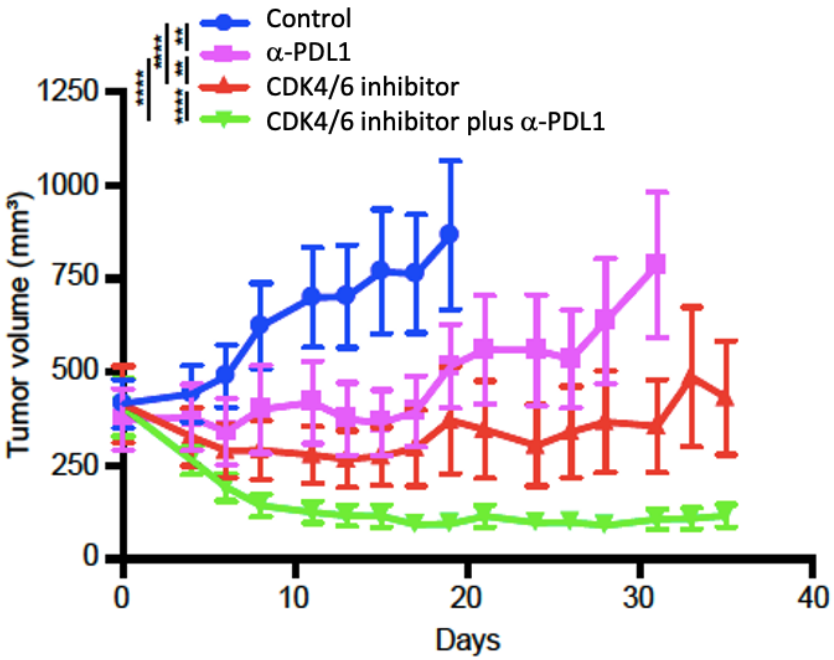
PACE: Palbociclib After CDK and Endocrine Therapy
A Randomized Phase II Study of Fulvestrant +/- Palbociclib after Progression on CDK4/6 inhibitor for HR+/HER2- Metastatic Breast Cancer

Erica L. Mayer[1]; Yue Ren[1]; Nikhil Wagle[1]; Reshma Mahtani[2]; Cynthia Ma[3]; Angela DeMichele[4]; Massimo Cristofanilli[5]; Jane Meisel[6]; Kathy D Miller[7]; Trevor Jolly[8]; Elizabeth Riley[9]; Rubina Qamar[10]; Priyanka Sharma[11]; Sonya Reid[12]; Natalie Sinclair[1]; Meredith Faggen[1]; Caroline Block[1]; Naomi Ko[13]; Ann Partridge[1]; Wendy Chen[1]; Michelle DeMeo[1]; Victoria Attaya[1]; Amanda Okpoebo[1]; Yuan Liu[14]; Eric Gauthier[14]; Harold J. Burstein[1]; Meredith Regan[1]; Sara M. Tolaney[1]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [2]Miami Cancer Institute, Miami, FL; [3]Washington University School of Medicine, St Louis, MO; [4]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [5]Weill Cornell Medicine, New York, NY; [6]Winship Cancer Institute, Emory University, Atlanta, GA; [7]Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN; [8]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [9]University of Louisville Health – Brown Cancer Center, Louisville, KY; [10]Aurora Cancer Care, Milwaukee, WI; [11]University of Kansas Medical Center, Westwood, KS; [12]Vanderbilt-Ingram Cancer Center, Nashville, TN; [13]Boston Medical Center, Boston, MA; [14]Pfizer, Inc, New York, NY.

PACE: Background and Rationale

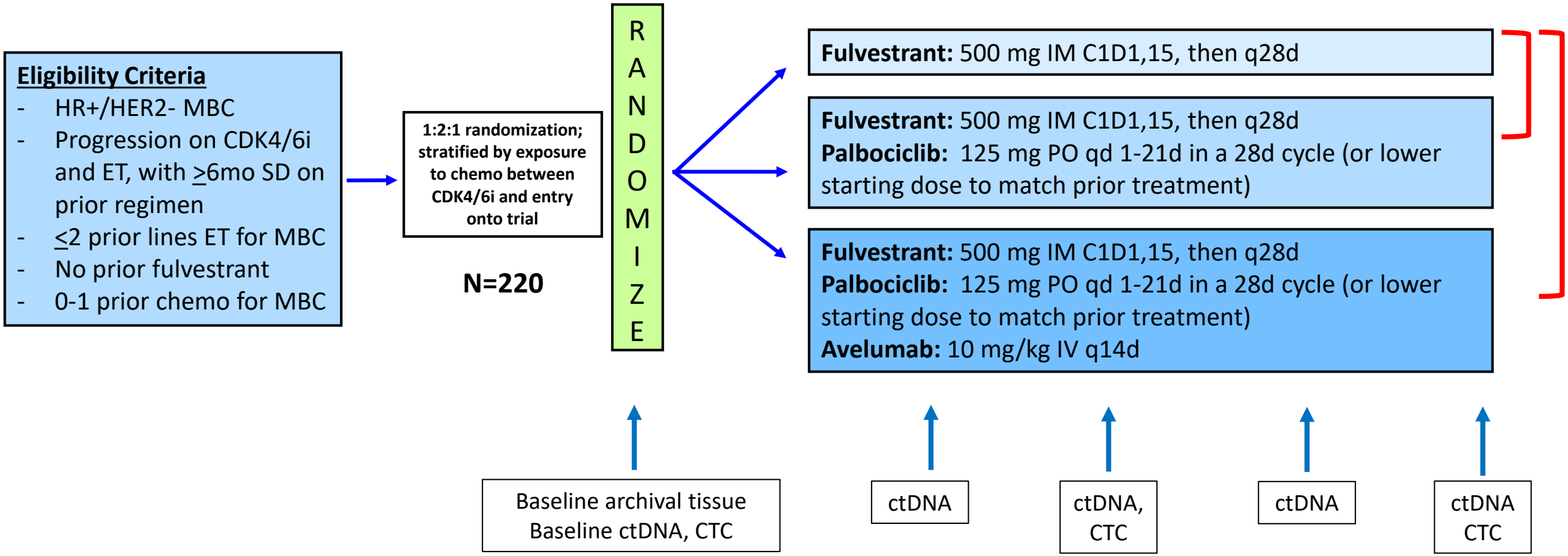
- CDK4/6 inhibitor (CDK4/6i) with endocrine therapy (ET) is a standard of care for metastatic and high-risk early HR+/HER2- breast cancer.
- Mechanisms for resistance to CDK4/6i are under study; it is not clear if alterations at time of progression provide resistance to CDK4/6i, ET, or both.
- Whether a CDK4/6 inhibitor should be continued at time of disease progression has been an open question.
- Preclinical data suggest combination therapy with CDK4/6i + checkpoint inhibition beyond prior progression may provide synergistic efficacy.



The PACE trial was designed to explore the activity of continuation of CDK4/6i beyond progression, with change of ET to fulvestrant, and to explore the addition of PD-L1 inhibition.

Goel et al, Nature 2017; Wander et al, JNCCN 2021; Kalinsky et al, ASCO 2022

PACE Trial: Schema



Primary objective: To compare PFS (RECIST-confirmed) for fulvestrant+palbociclib vs. fulvestrant alone

Secondary objectives: To compare PFS for fulvestrant+palbociclib+avelumab vs fulvestrant alone, response endpoints, safety, outcomes in predefined molecular subgroups including ESR1, PIK3CA, and Rb.

PACE: Statistical Plan

- Total planned enrollment was 220 patients.

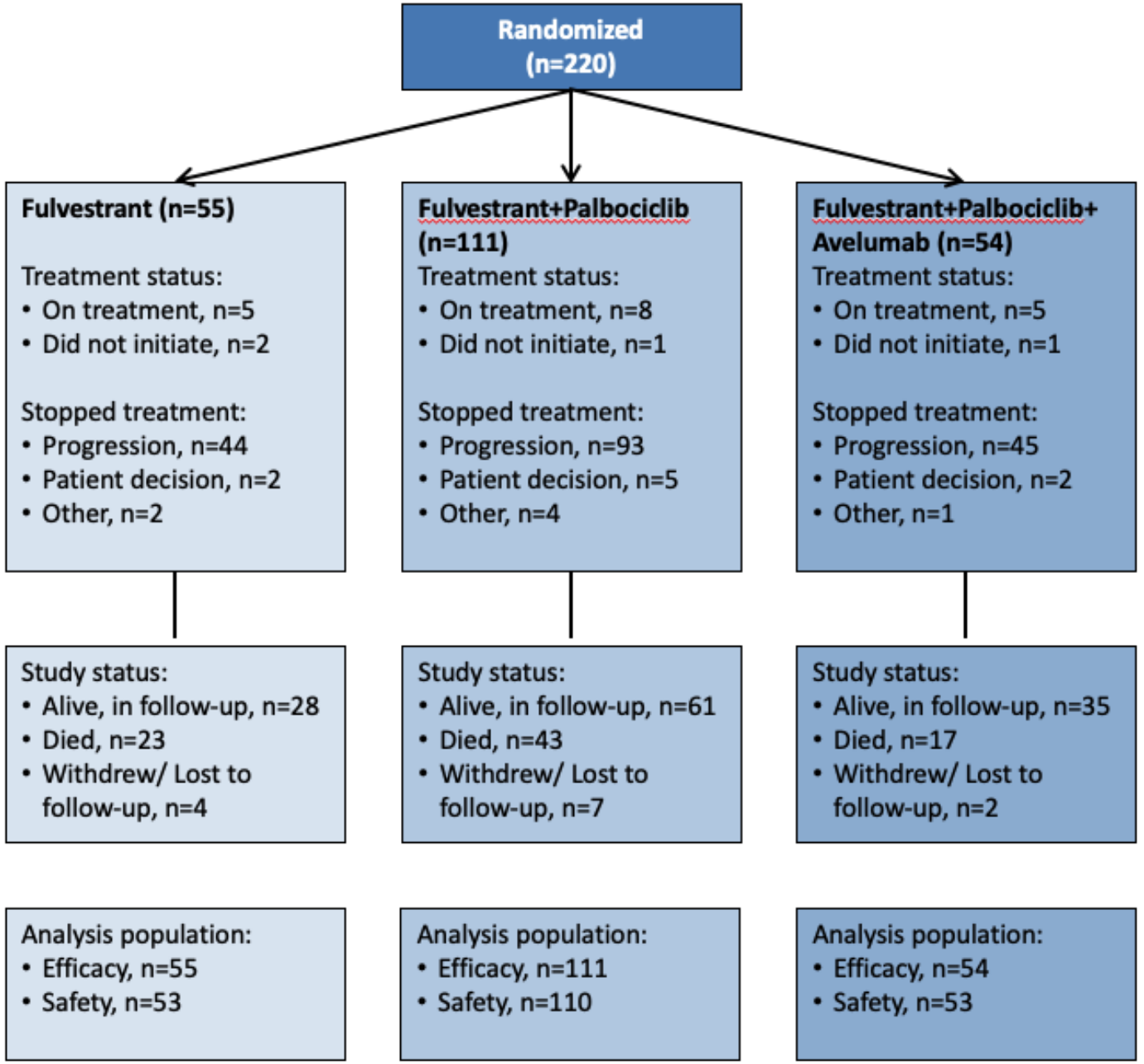
- **Primary objective**: superiority of fulvestrant+palbociclib vs fulvestrant alone:
  - 119 PFS events required for 80% power to detect an improvement in median PFS from 4 mo to 6.5 mo (HR=0.62), using one-sided α=0.05 logrank test; randomization of 165 patients to the two groups was planned over 2.5 years
  - HRs with two-sided 90% CIs and two-sided p-values are reported

- **Secondary objective**: superiority fulvestrant+palbociclib+avelumab vs fulvestrant alone:
  - 63 PFS events required for 80% power to detect an improvement in median PFS from 4 mo to 7.5 mo (HR=0.53), using one-sided α=0.05 logrank test

- DF/HCC DSMB reviewed the trial every 6 months for safety and one protocol-defined interim analysis for futility.

PACE: Study Conduct

- Between September 2017 and February 2022, 220 patients were enrolled from 13 centers; 216 initiated treatment.
- Median follow-up is 23.6 months; at time of datalock in July 2022, 18 patients continue on protocol therapy.
- Efficacy ITT population: n=220
- Safety population: n=216



PACE Trial: Patient Demographics

	Fulvestrant (n=55)		Fulvestrant + Palbociclib (N=111)		Fulvestrant + Palbociclib + Avelumab (N=54)		Overall (n = 220)	
	N	%	N	%	N	%	N	%
Female	55	**100.0**	109	**98.2**	54	**100.0**	218	**99.0**
Age (median, range)	58 (36-77)		55 (28-77)		58 (25-83)		57 (25-83)	
Race								
White	47	**85.5**	88	**79.3**	44	**81.5**	179	**81.4**
Black	3	**5.5**	13	**11.7**	4	**7.4**	20	**9.1**
Asian	0	**0**	4	**3.6**	3	**5.6**	7	**3.2**
Other	5	**9.1**	6	**5.4**	3	**5.6**	14	**6.4**
Post-menopausal	47	**85.5**	87	**78.4**	44	**81.5**	178	**80.9**
De novo MBC	28	**50.9**	40	**36.0**	20	**37.0**	88	**40.0**
Visceral disease	29	**52.7**	70	**63.1**	33	**61.1**	132	**60.0**
Bone only disease	4	**7.3**	18	**16.2**	8	**14.8**	30	**13.6**
Measurable disease	37	**67.3**	73	**65.8**	39	**72.2**	149	**67.7**

Unknown values are omitted from the table.

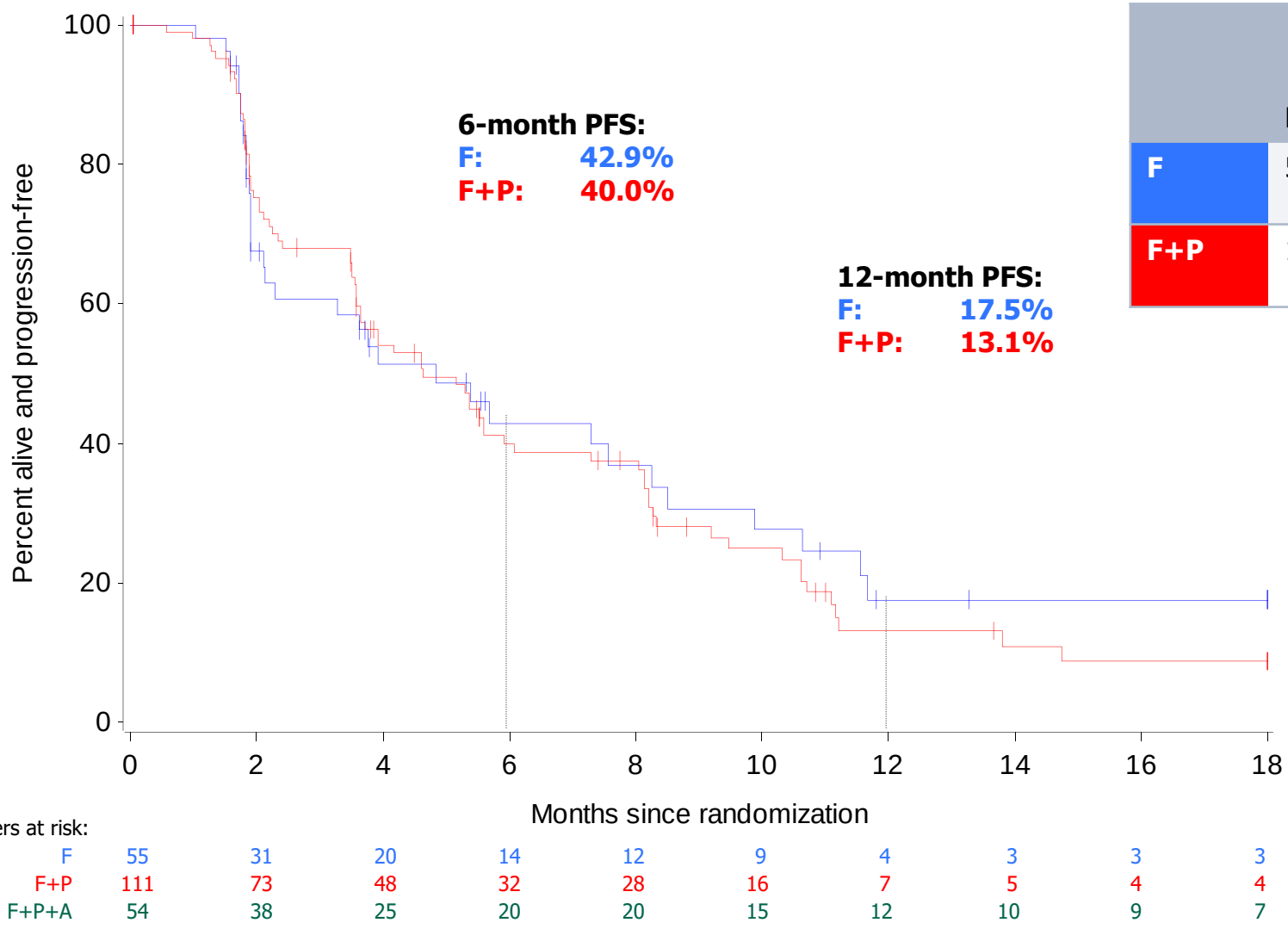
PACE: Prior Treatment Characteristics

	Fulvestrant (n=55)		Fulvestrant + Palbociclib (N=111)		Fulvestrant + Palbociclib + Avelumab (N=54)		Overall (n = 220)	
	N	%	N	%	N	%	N	%
Prior adjuvant endocrine exposure*								
Endocrine resistant	10	**18.2**	32	**28.8**	16	**29.6**	58	**26.4**
Endocrine sensitive	45	**81.8**	78	**70.3**	37	**68.5**	160	**72.7**
Prior CDK4/6i								
Palbociclib	52	**94.5**	102	**91.9**	46	**85.2**	200	**90.9**
Ribociclib	1	**1.8**	5	**4.5**	4	**7.4**	10	**4.5**
Abemaciclib	2	**3.6**	3	**2.7**	4	**7.4**	9	**4.1**
Duration of prior CDK4/6i + ET								
6-12 months	10	**18.2**	26	**23.4**	16	**29.6**	52	**23.6**
> 12 months	45	**81.8**	84	**75.7**	38	**70.4**	167	**75.9**
Prior chemotherapy for MBC	11	**20.0**	16	**14.4**	9	**16.7**	36	**16.4**
Line of MBC therapy initiated in PACE								
First line	3	**5.5**	5	**4.5**	2	**3.7**	10	**4.5**
Second Line	42	**76.4**	83	**74.8**	44	**81.5**	169	**76.8**
> Second Line	10	**18.2**	21	**18.9**	7	**13.0**	38	**17.3**
Any systemic therapy between prior CDK4/6i and randomization	5	**9.1**	16	**14.4**	5	**9.3**	26	**11.8**

Unknown values are omitted from the table.

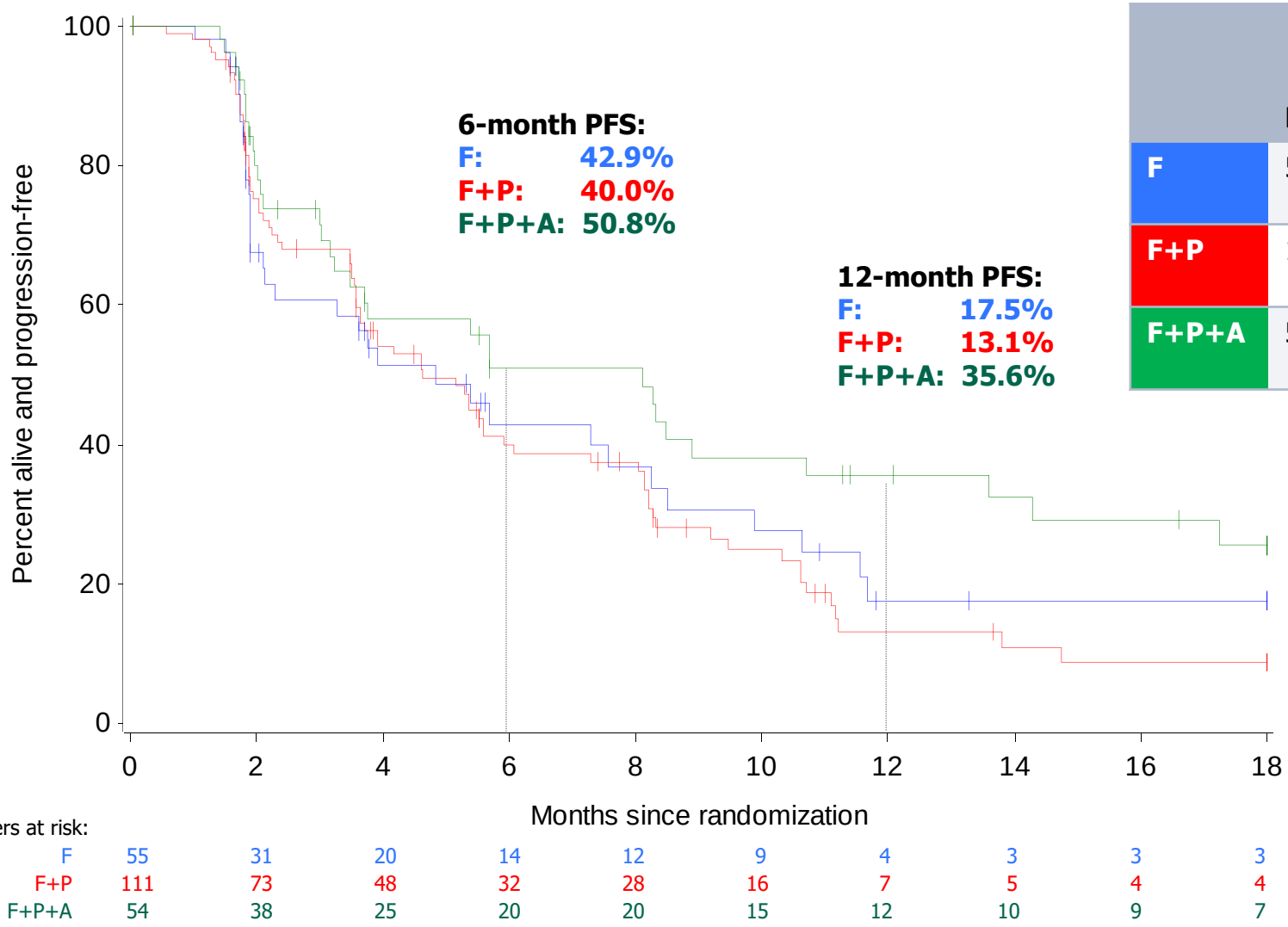
*Endocrine resistant: recur <1y of adj ET. Endocrine sensitive: *de novo* MBC, or no adj ET, or recur ≥1y after adj ET. Adapted from ESO-ESMO guidelines, Ann Oncol 2020

PACE: Progression Free Survival ITT



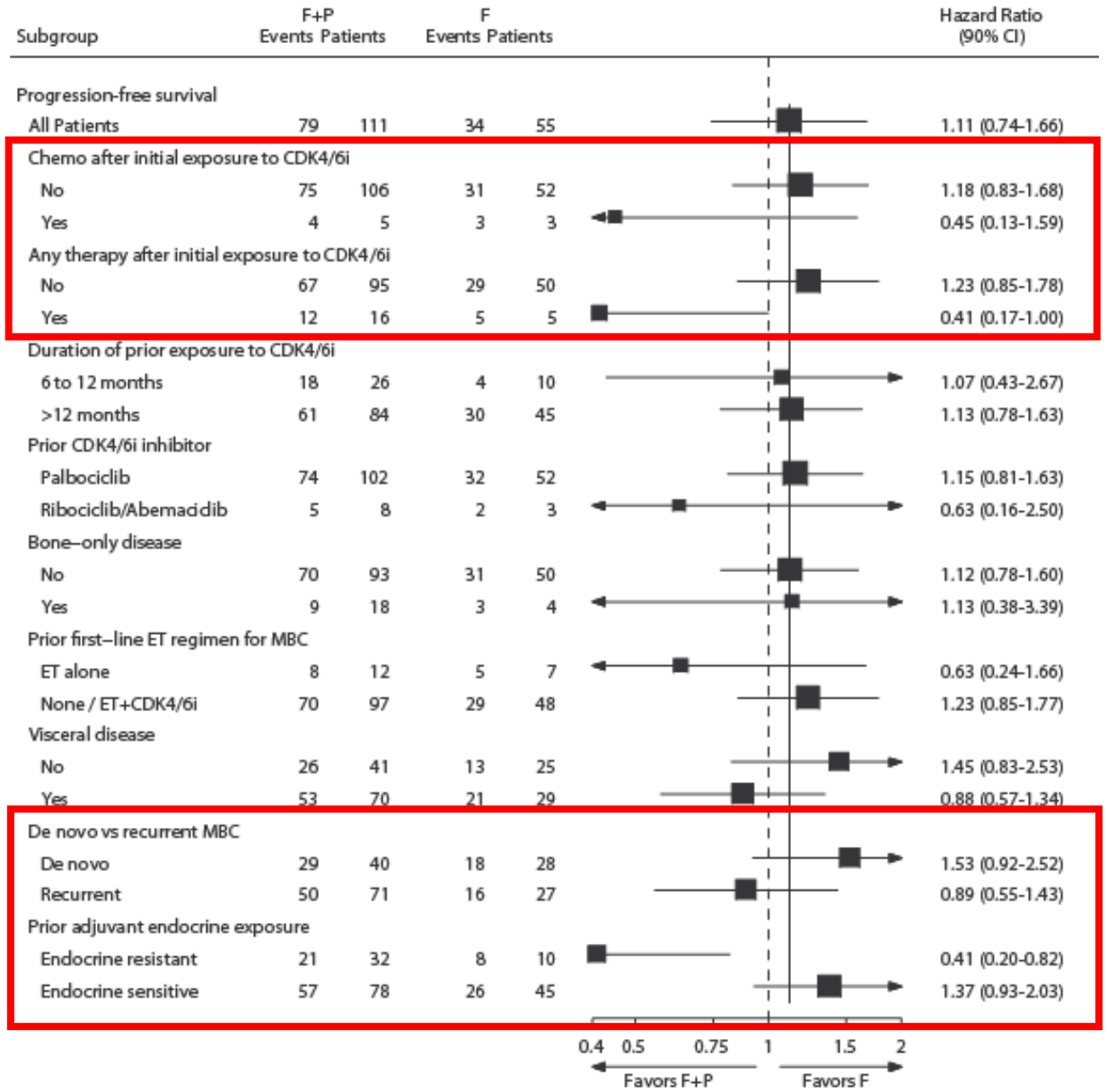
	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62

PACE: Progression Free Survival ITT



	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

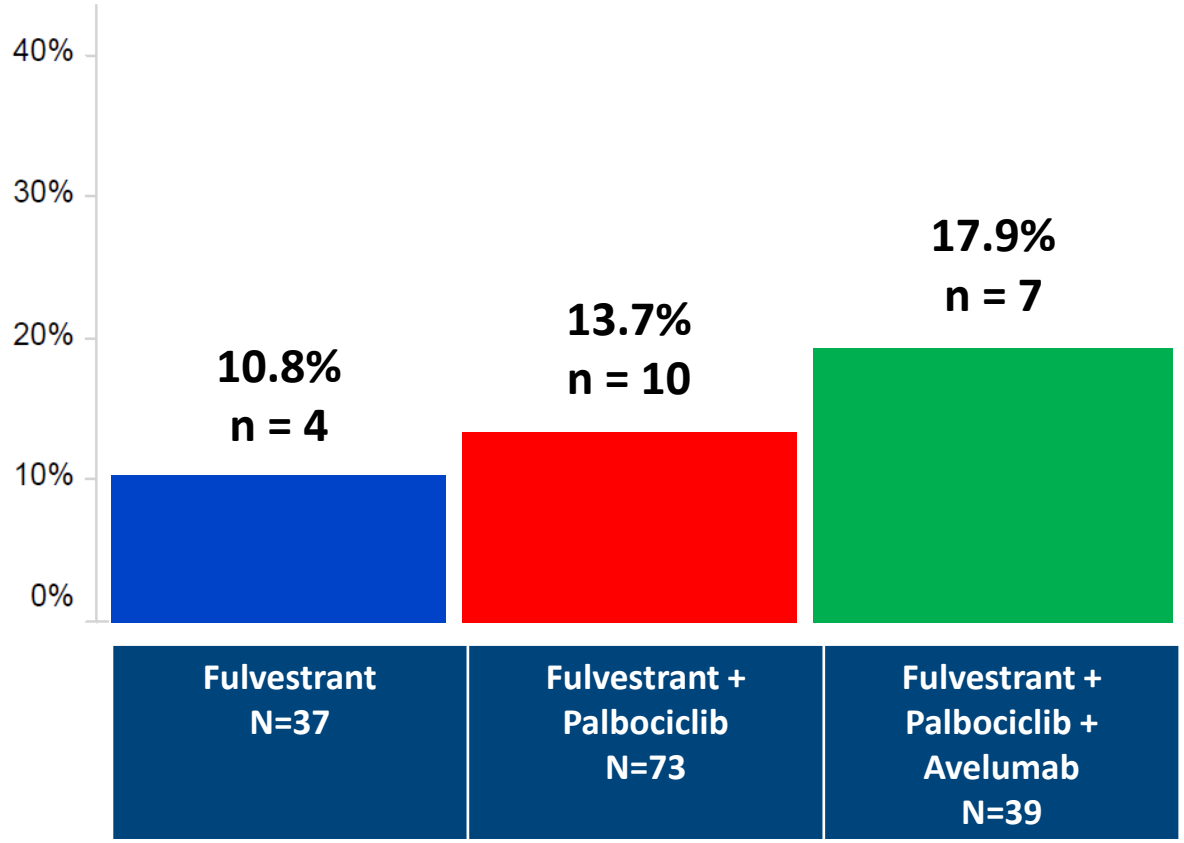
PACE: Subgroup analysis



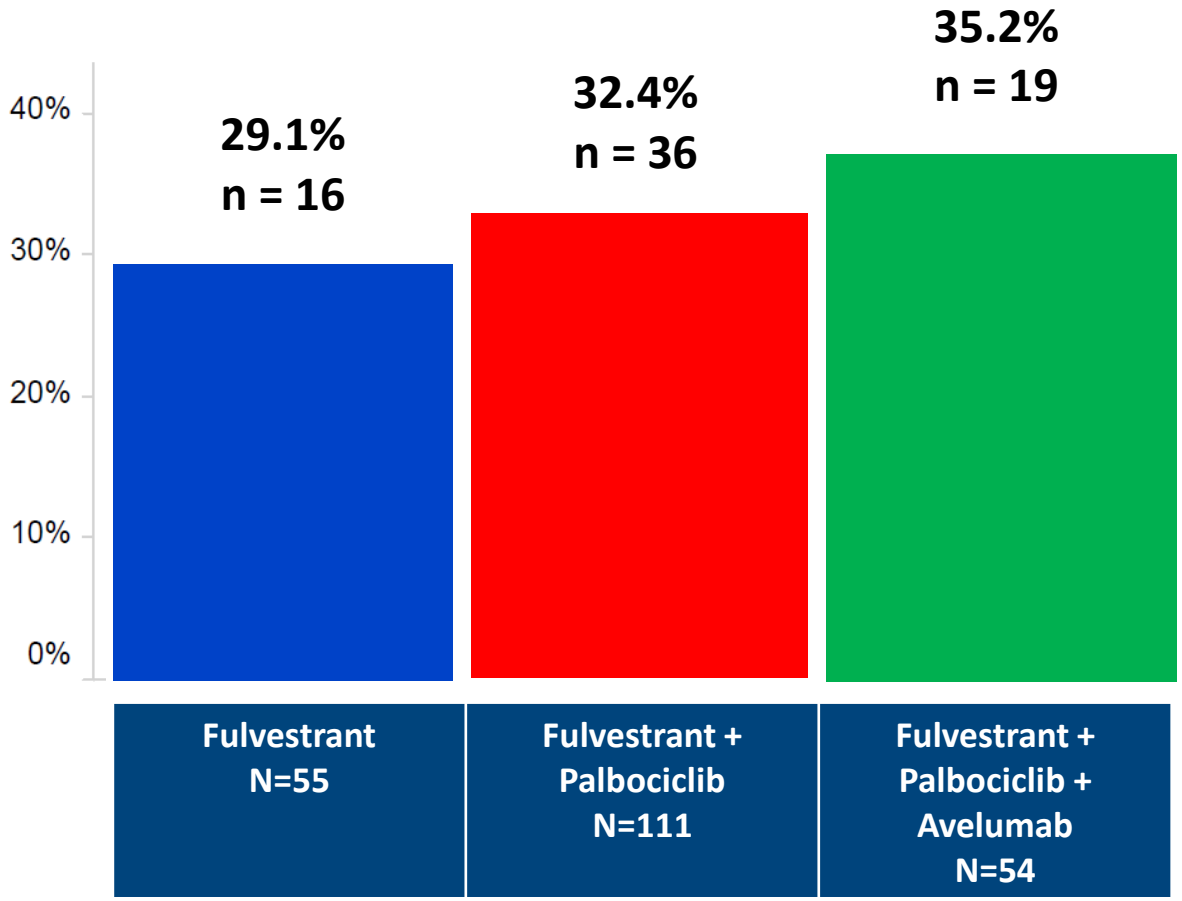
*Endocrine resistant: recur <1y of adj ET. Endocrine sensitive: do novo MBC, or no adj ET, or recur ≥1y after adj ET.

PACE: Response Endpoints

ORR in measurable disease population (n=149)

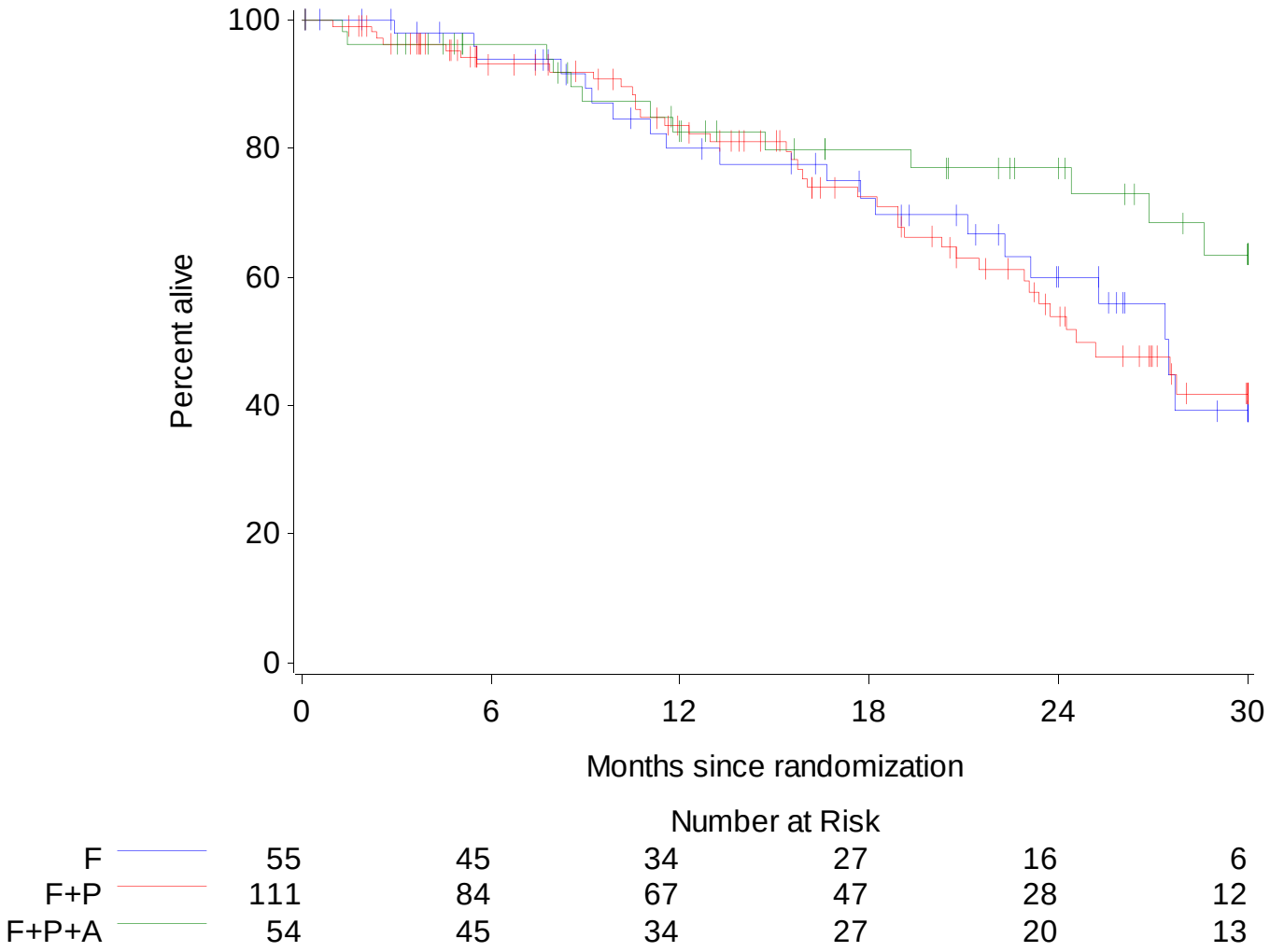


CBR in ITT Population (n=220)



Unknown values are omitted from the tables. ORR = objective response rate. CBR = clinical benefit rate: objective response or stage disease for > 24 weeks.

PACE: Overall Survival



	Pts	OS Events	Median OS, mo (90% CI)	HR vs F (90% CI)
F	55	23	**27.5** (21.1, 38.0)	--
F+P	111	43	**24.6** (21.5, 33.3)	1.02 (0.67-1.56)
F+P+A	54	17	**42.5** (26.8, 46.0)	0.68 (0.40-1.15)

PACE: Treatment Exposure and Toxicity

- No dose reductions of fulvestrant or avelumab were permitted.
- No patients were reported to have stopped all protocol therapy specifically due to unacceptable treatment-related toxicity.

	Fulvestrant + Palbociclib (N=111)		Fulvestrant + Palbociclib + Avelumab (N=54)	
	N	%	N	%
Palbociclib starting dose*				
125 mg qd	68	61.3	28	51.9
100 mg qd	29	26.1	15	27.8
75 mg qd	10	9.0	10	18.5
Palbociclib hold for toxicity	40	36.0	31	57.4
Palbociclib dose reduction	25	22.5	11	20.4
Avelumab hold for toxicity	n/a	n/a	21	38.9

*3 patients did not start protocol therapy

PACE: Treatment Related Adverse Events in ≥10% of Patients

	Fulvestrant (n=53)		Fulvestrant + Palbociclib (N=110)		Fulvestrant + Palbociclib + Avelumab (N=53)	
	All grades (n, %)	Grade 3/4 (n, %)	All grades (n, %)	Grade 3/4 (n, %)	All grades (n, %)	Grade 3/4 (n, %)
Hematologic						
Neutropenia*	2 (3.8)	.	72 (65.5)	36 (32.7)	39 (73.6)	26 (49.1)
Anemia	2 (3.8)	.	24 (21.8)	5 (4.5)	18 (34.0)	2 (3.8)
Platelet count decreased	1 (1.9)	.	16 (14.5)	1 (0.9)	17 (32.1)	2 (3.8)
Non-hematologic						
Fatigue	18 (34.0)	.	38 (34.5)	2 (1.8)	34 (64.2)	3 (5.7)
Nausea	5 (9.4)	.	13 (11.8)	.	10 (18.9)	.
Diarrhea	.	.	11 (10.0)	.	9 (17.0)	2 (3.8)
Anorexia	2 (3.8)	.	4 (3.6)	.	9 (17.0)	1 (1.9)
Mucositis	.	.	10 (9.1)	1 (0.9)	8 (15.1)	1 (1.9)
Increased AST	6 (11.3)	.	6 (5.5)	1 (0.9)	8 (15.1)	1 (1.9)
Pain in extremity	1 (1.9)	.	.	.	8 (15.1)	.
Pruritus	1 (1.9)	.	5 (4.5)	.	7 (13.2)	1 (1.9)
Constipation	2 (3.8)	.	7 (6.4)	.	7 (13.2)	.
Injection site reaction	6 (11.3)	.	12 (10.9)	.	35 (5.7)	.

*There were no episodes of febrile neutropenia. There were no Grade 5 toxicity events.

PACE: Potential Immune-Related Adverse Events

- Rates of immune related toxicity events were low, with no unexpected toxicities.

	Fulvestrant + Palbociclib + Avelumab (N=53)	
	All grades (n, %)	Grade 3/4 (n, %)
AST increased	6 (11.3)	1 (1.9)
ALT increased	5 (9.4)	1 (1.9)
Cardiac troponin T increased	1 (1.9)	1 (1.9)
Hypoxia	1 (1.9)	1 (1.9)
Bullous dermatitis	1 (1.9)	1 (1.9)
Infusion related reaction	4 (7.5)	1 (1.9)
Hypothyroidism	4 (7.5)	.
Fever	4 (7.5)	.
CPK increased	4 (7.5)	.
Arthralgia	4 (7.5)	.
Hyperglycemia	3 (5.7)	.
Rash maculo-papular	3 (5.7)	.
Colitis	2 (3.8)	.
Skin hypopigmentation	2 (3.8)	.
Alkaline phosphatase increased	2 (3.8)	.
Hyperthyroidism	2 (3.8)	.
Adrenal insufficiency	1 (1.9)	.
Rectal hemorrhage	1 (1.9)	.
Blood bilirubin increased	1 (1.9)	.
Rash acneiform	1 (1.9)	.

PACE: Mutation Frequency in Baseline ctDNA Analysis

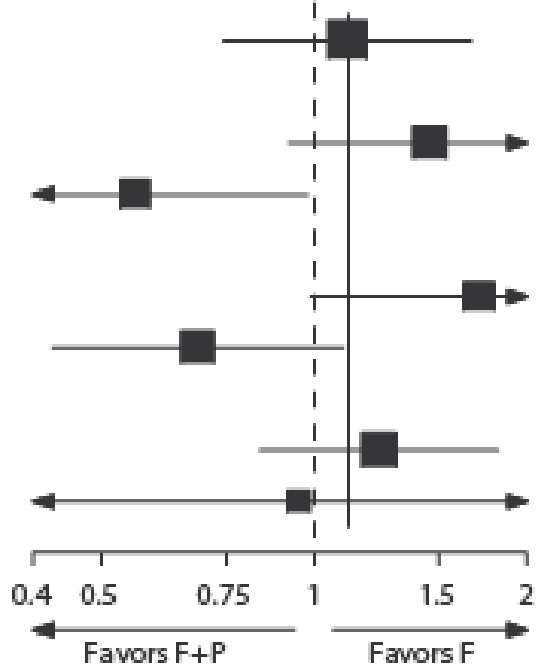
- ctDNA sample was obtained at baseline and evaluated using the Guardant360® platform.*
- 200 of 220 patients had baseline sample available for ctDNA analysis.

	Fulvestrant (n=48)		Fulvestrant + Palbociclib (N=102)		Fulvestrant + Palbociclib + Avelumab (N=50)		Overall (N=200)	
	N	%	N	%	N	%	N	%
Any ESR1 mutation	**23**	**47.9**	**55**	**53.9**	**30**	**60.0**	**108**	**54.0**
D538G	15		36		18		69	
Y537S	9		26		7		42	
Y537N	7		17		6		30	
E380Q	1		11		7		19	
Any PIK3CA mutation	**12**	**25.0**	**39**	**38.2**	**19**	**38.0**	**70**	**35.0**
H1047R	4		11		8		23	
E545K	3		12		4		21	
Any Rb mutation	**6**	**12.5**	**10**	**9.8**	**7**	**14.0**	**23**	**11.5**

* Next generation sequencing was performed evaluating somatic single-nucleotide variants in complete or critical exons of 73 genes. Analyses were limited to SNVs, indels, and high amplifications in the prespecified genes.

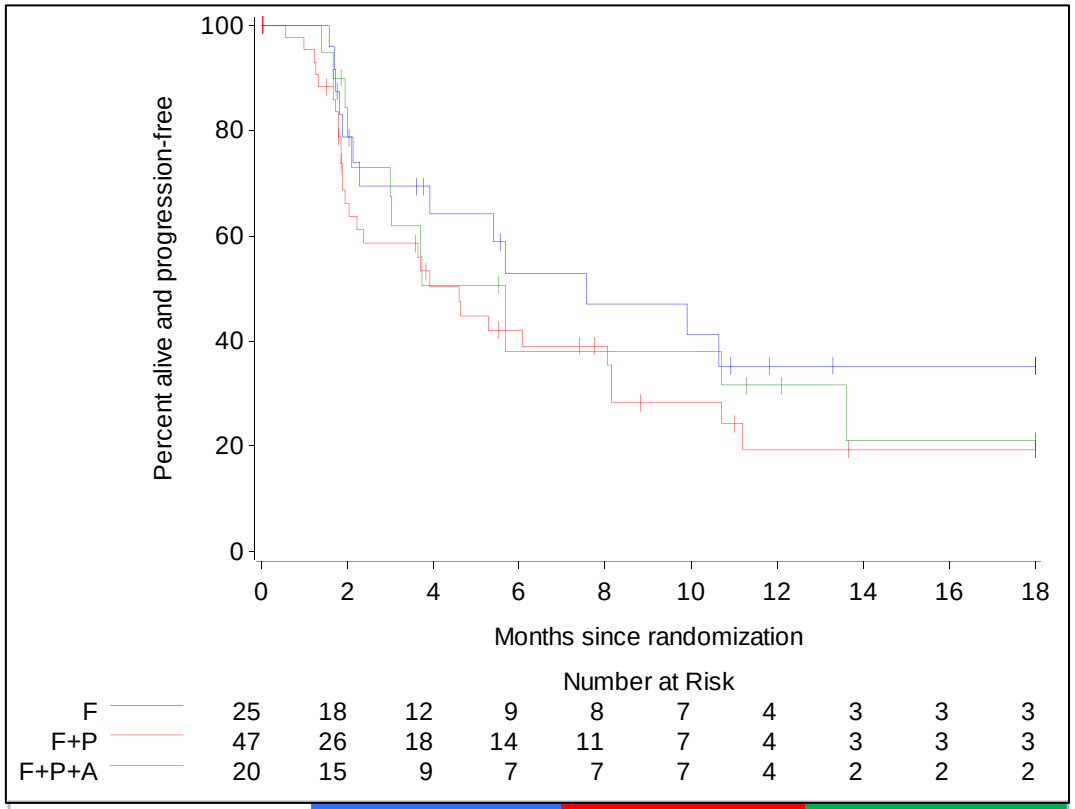
PACE: Exploratory Analysis of Baseline Mutation and Outcome

Subgroup	F+P Events	F+P Patients	F Events	F Patients	Hazard Ratio (90% CI)
Progression-free survival					
All Patients	79	111	34	55	1.11 (0.74-1.66)
Any PIK3CA mutation					
WT	45	63	18	36	1.44 (0.91-2.29)
Mutation	29	39	12	12	0.56 (0.32-0.99)
Any ESR1 mutation					
WT	31	47	13	25	1.70 (0.99-2.95)
Mutation	43	55	17	23	0.68 (0.42-1.09)
Any Rb1 mutation					
WT	67	92	25	42	1.23 (0.83-1.81)
Mutation	7	10	5	6	0.95 (0.36-2.49)



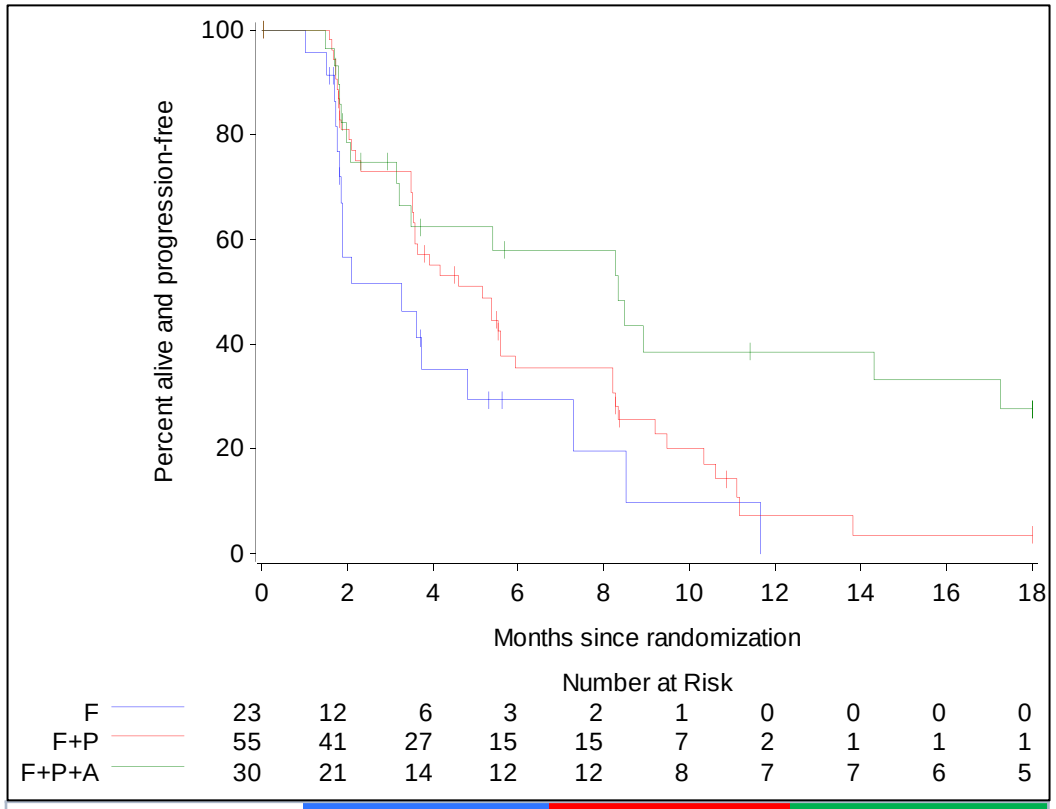
PACE: Exploratory Analysis of Baseline ESR1 Mutation and Outcome

ESR1 WT



	F	F+P	F+P+A
Median PFS, mo (90% CI)	**7.6** (2.3, NR)	**4.6** (1.9, 8.1)	**5.7** (2.1, 13.6)
HR F+P vs F (90% CI)		1.70 (0.99, 2.95)	

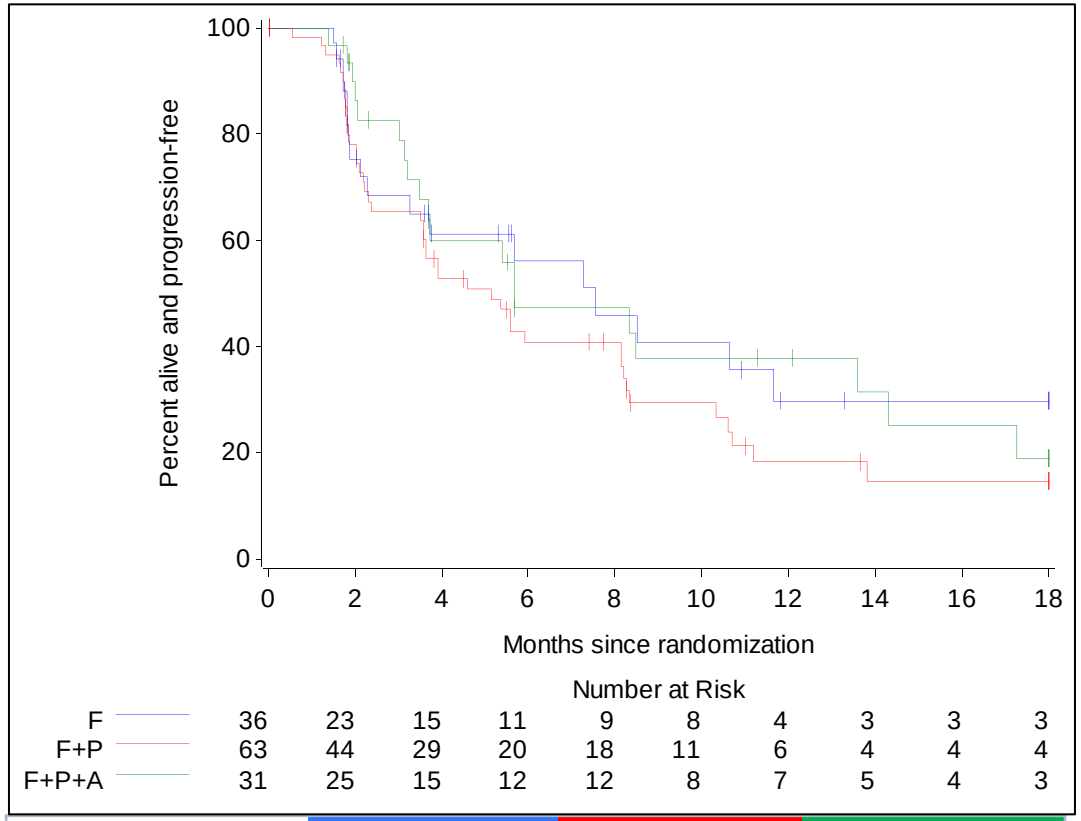
ESR1 altered



	F	F+P	F+P+A
Median PFS, mo (90% CI)	**3.3** (1.8, 7.3)	**5.2** (3.5, 5.9)	**8.3** (3.2, 17.2)
HR F+P vs F (90% CI)		0.68 (0.42, 1.09)	

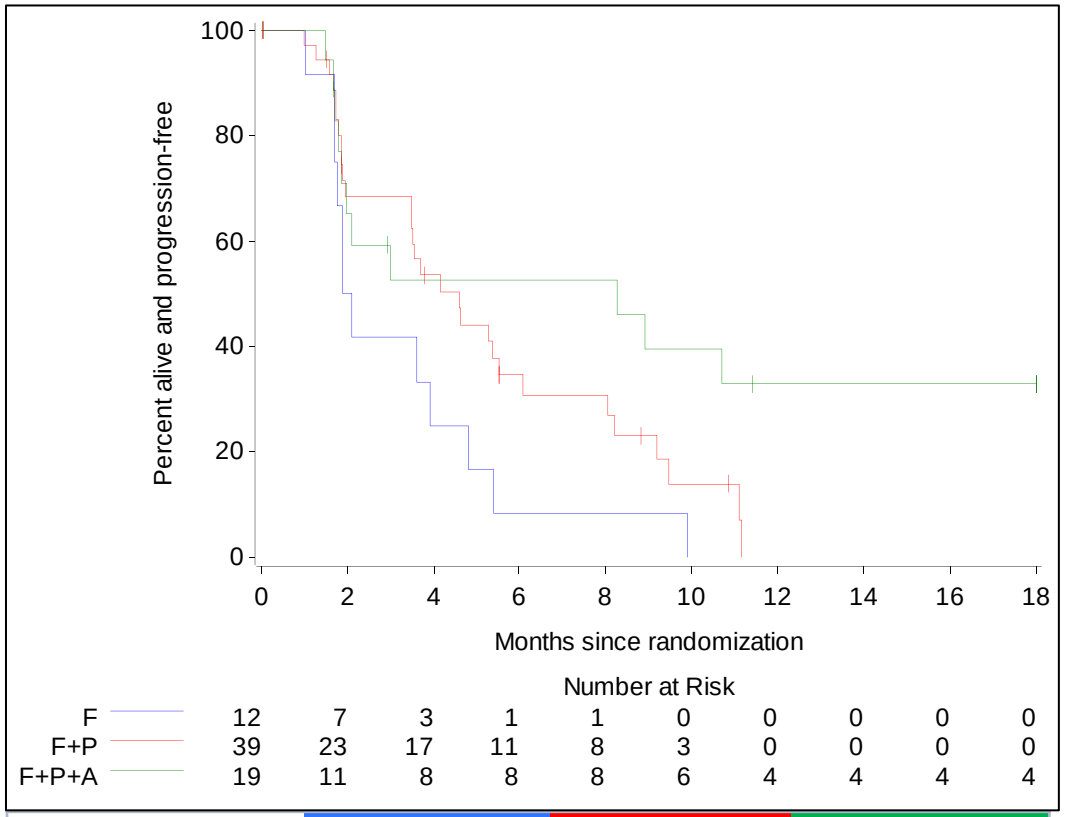
PACE: Exploratory Analysis of Baseline PIK3CA Mutation and Outcome

PIK3CA WT



	F	F+P	F+P+A
Median PFS, mo (90% CI)	**7.6** (2.3, 11.7)	**5.2** (3.6, 8.1)	**5.7** (3.5, 14.3)
HR F+P vs F (90% CI)		1.44 (0.91, 2.29)	

PIK3CA altered



	F	F+P	F+P+A
Median PFS, mo (90% CI)	**2.0** (1.7, 4.8)	**4.6** (3.5, 6.1)	**8.3** (1.8, 19.0)
HR F+P vs F (90% CI)		0.56 (0.32, 0.99)	

PACE: Conclusions

- Among patients with ER+/HER2- MBC, combining palbociclib with fulvestrant beyond progression on prior CDK4/6i did not significantly improve PFS compared with using fulvestrant alone.
- The observed longer PFS when a PD-L1 inhibitor was added to fulvestrant+palbociclib is an intriguing signal in this ER+ population and deserves further study.
- No new toxicity signals were seen in the study population, including no unexpected immune-related toxicity events and no protocol discontinuation for toxicity.
- Baseline ctDNA analysis suggests potential benefit of palbociclib after progression on prior CDK4/6i may be influenced by ESR1 or PIK3CA status.
- Ongoing evaluation of serial ctDNA and CTC samples will allow exploration of the mutational and resistance landscape as well as markers of sensitivity to IO therapy in ER+ disease.
- A better understanding of mechanisms driving progression post-CDK4/6i and ET will guide more rationale treatment selection for subsequent lines of therapy and improve outcomes for patients.

Acknowledgements

- **We would like to thank:**
  - **The patients and caregivers who volunteered to participate in the PACE trial.**
  - **The research staff and providers at the 13 participating cancer centers.**
  - **Funding support from Pfizer, Inc.**