CDK 4/6 and PIK3CA Inhibitors in Breast Cancer Management

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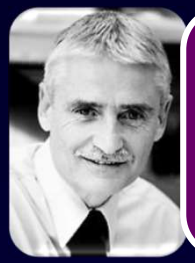
Disclosures

- Consultant: Astra Zeneca, Bayer, BMS, Eisai, Eli-Lilly, Merck, Novartis, Pfizer, Roche/ Genentech

CDKs: A Timeline



Early 1970s: **Leland Hartwell** identifies a number of genes involved in cell division "CDCs" (cell division cycle):

- Using yeast mutation model identified genes involved in the cell cycle
- Developed the concept of **"checkpoints"**

Early 1980s: **Tim Hunt**, using see urchins, identifies proteins that increase before cell division, then abruptly drop off (a cyclical pattern)

- **Cyclin D** and their degradation as a control mechanism in the cell cycle

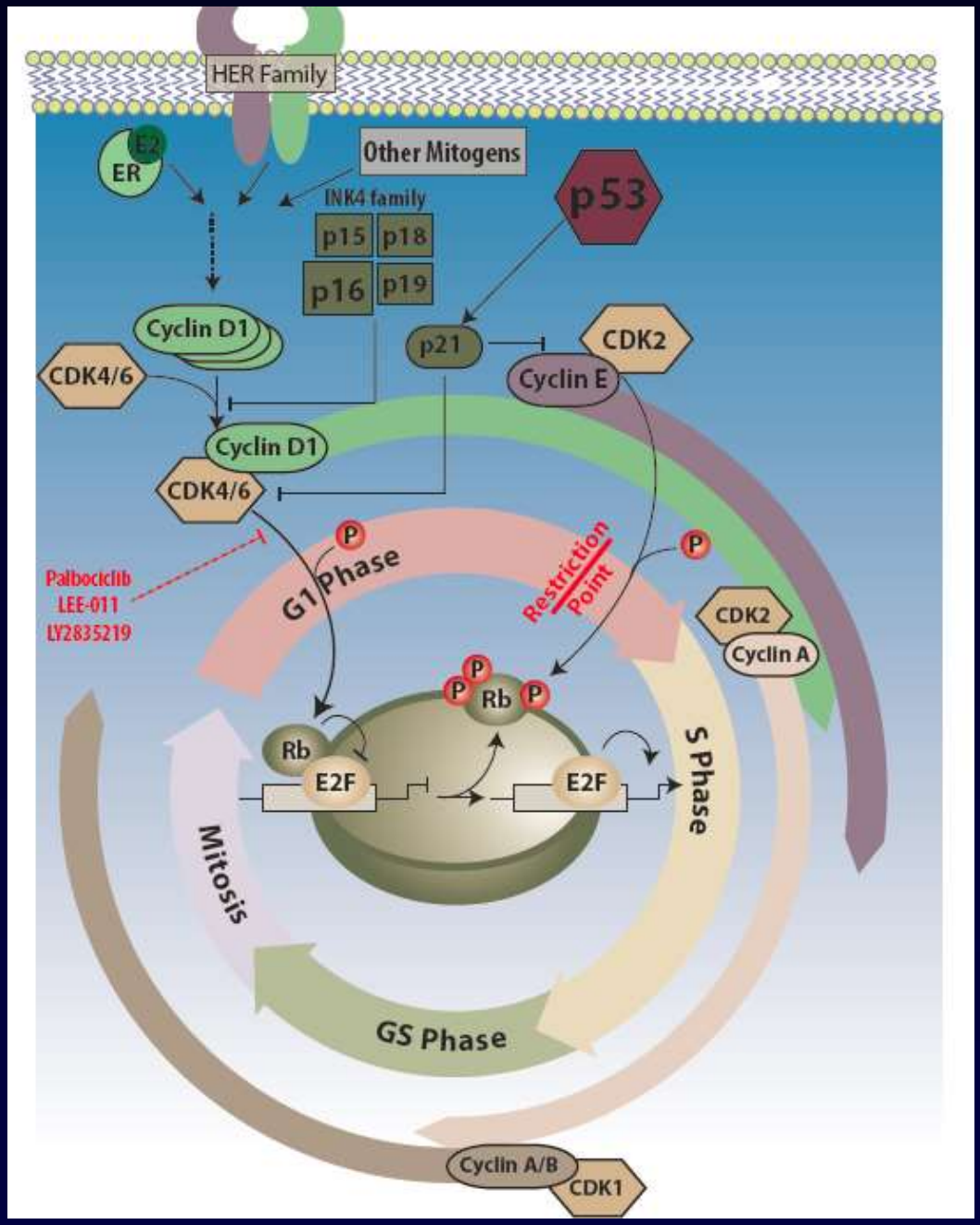
1970 1976 1980 2001

Late 1976: **Sir Paul Nurse**, again using yeast models, identifies other CDC2 and demonstrates its role in controlling the cell cycle

- Demonstrates the **function of CDKs** and their conservation

2001: **Hartwell, Nurse, and Hunt** win the **Noble Prize in Medicine and Physiology**

"The Nobel Prize in Physiology or Medicine 2001 – Presentation Speech.

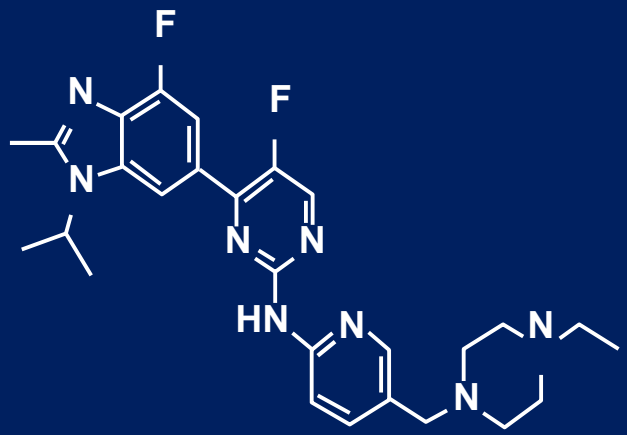


Finn RS et al Breast Can Res in press 2015

CDK4/6 Inhibitors in Clinical Trials

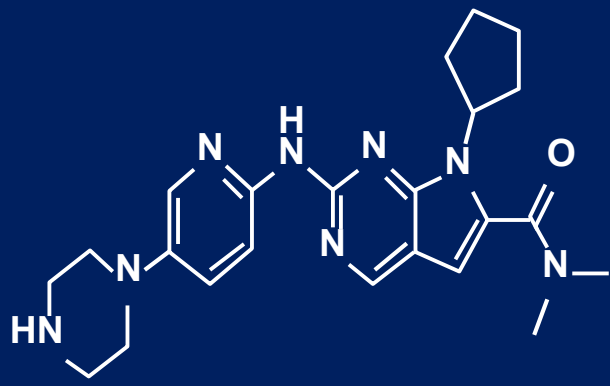
PD0332992
(Palbociclib)[1]
CDK4 IC_{50} = 11 nM
CDK6 IC_{50} = 16 nM

FDA Approved 2015



LY2835219
(Abemaciclib)[2]
CDK4 IC_{50} = 2 nM
CDK6 IC_{50} = 9.9 nM
CDK9 IC_{50} = 57 nM
CDK1 IC_{50} = 1,627 nM

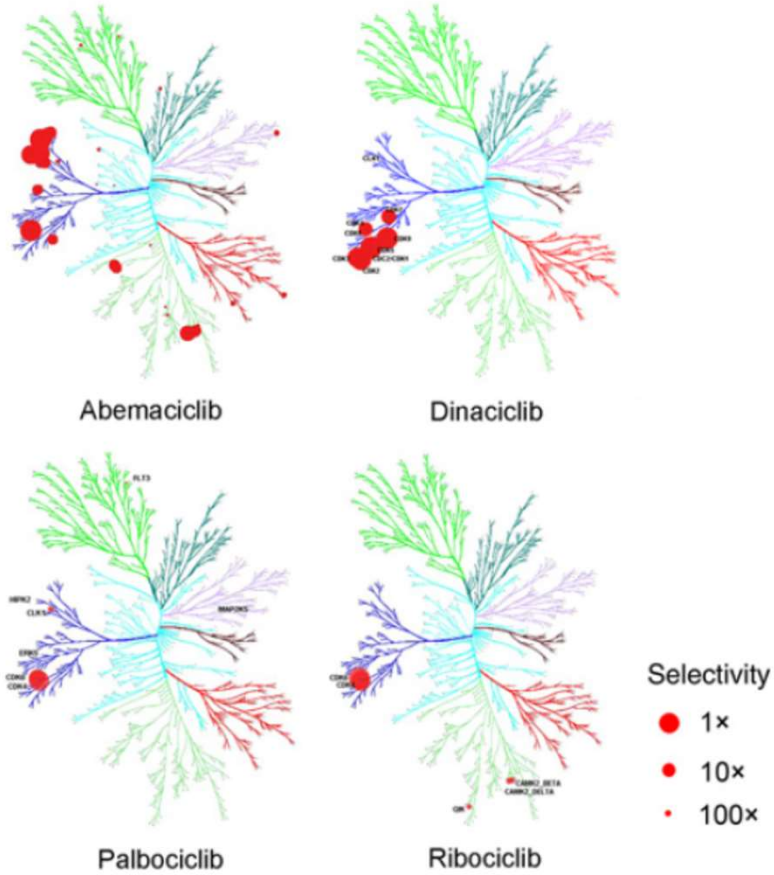
FDA Approved 2017



LEE011
(Ribociclib)[3]
CDK4 IC_{50} = 10 nM
CDK6 IC_{50} = 39 nM

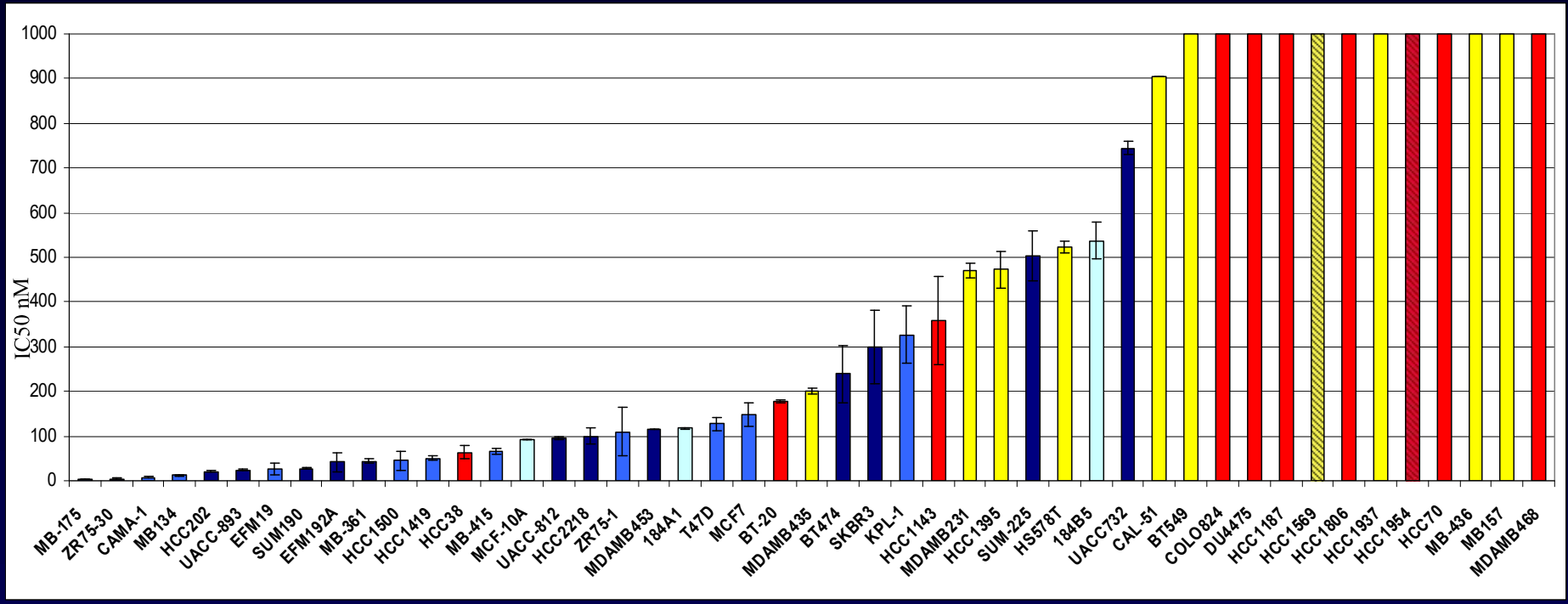
FDA Approved 2017

1. Fry DW et al. *Mol Cancer Ther*. 2004;3:1427.2 Gelbert LM et al. *Invest New Drugs*. 2014;32:825. 3 Kim S et al. *Mol Cancer Ther*. 2013;12(11 Suppl):PR02.



Chen et al Mol Can Ther 2016

Palbociclib: CDK 4/6 Inhibitor – Breast Panel

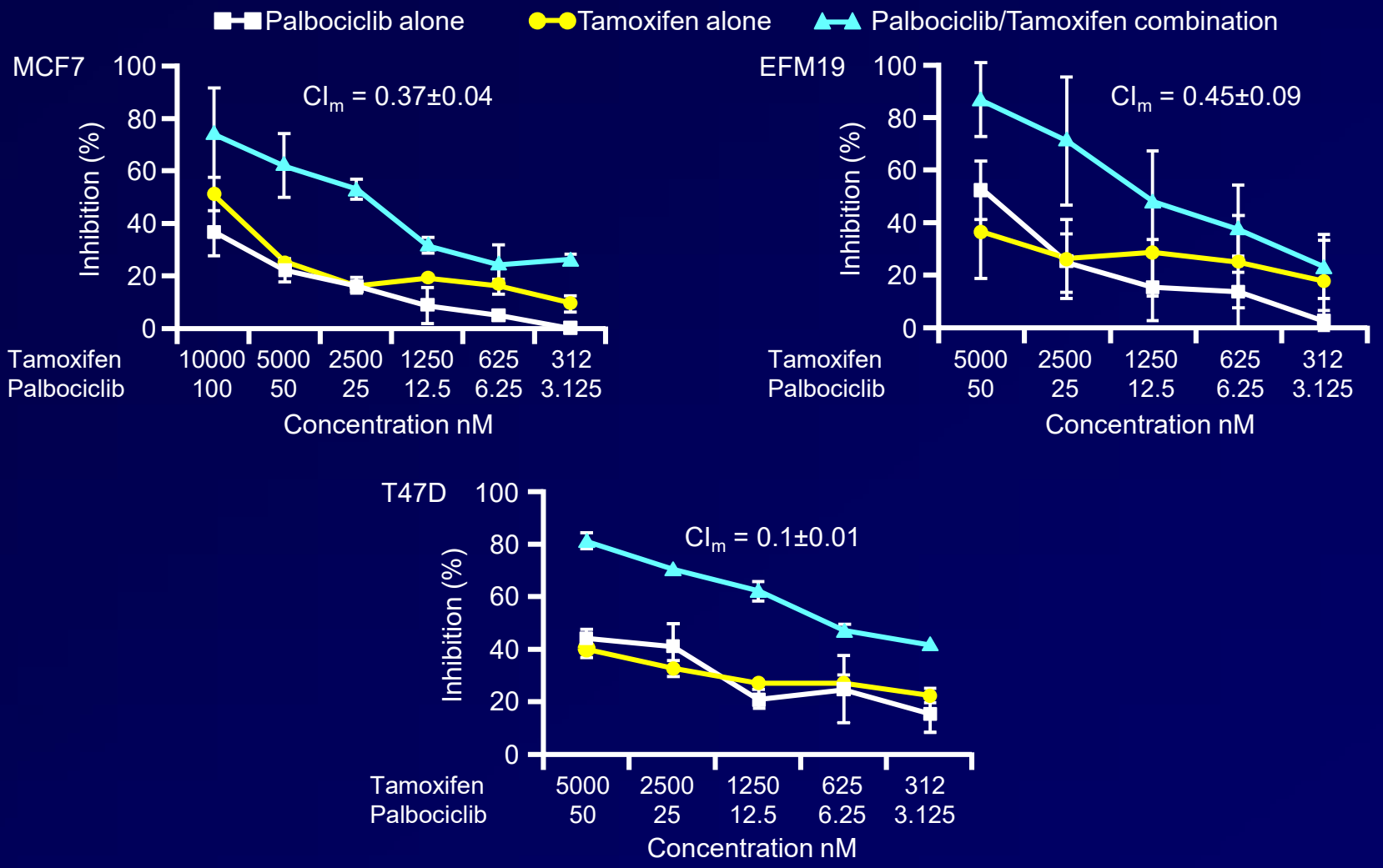


Subtype

- Luminal
- HER2 amplified
- Immortalized
- Non-luminal/post EMT
- Non-luminal

Finn R et al SABCS 2008, Finn RS, et al. *Breast Cancer Res.* 2009;11(5):R77.

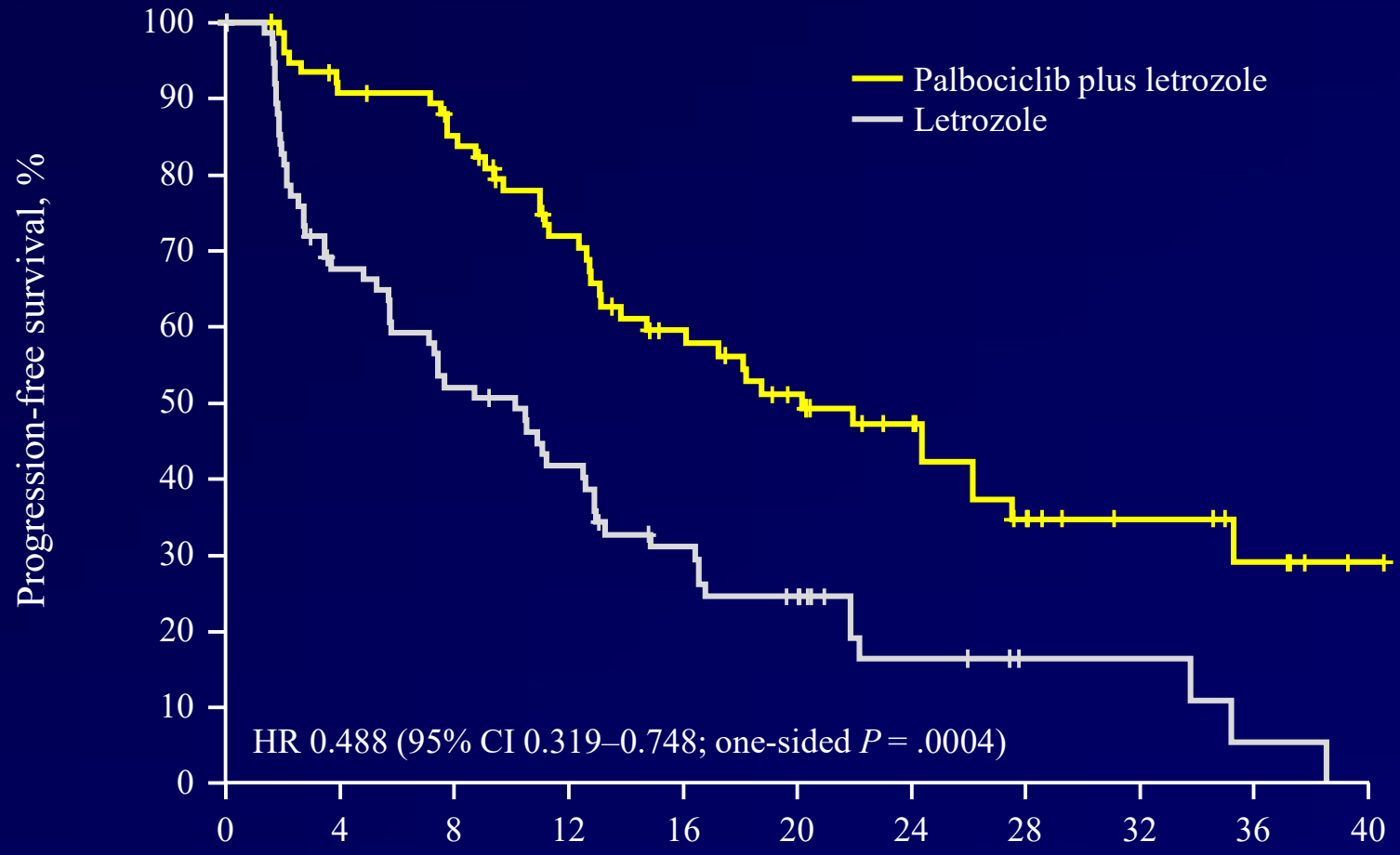
Palbociclib Acts Synergistically with Tamoxifen in ER+ Breast Cancer Cell Lines



- **Mean combination index (CI_m) <1 indicates synergy for the combinations**

Finn RS, et al. *Breast Cancer Res.* 2009;11(5):R77

PALOMA-1/TRIO-18: PFS (ITT Population)



Number at risk											
Palbociclib plus letrozole	84	67	60	47	36	28	21	13	8	5	1
Letrozole	81	48	36	28	19	14	6	3	3	1	

Finn RS, et al. *Lancet Oncol*. 2015;16(1):25-35.

PALOMA-1/TRIO-18: All-Causality AEs Occurring in ≥10% of Patients (Safety Population)

	PAL + LET (n=83)		LET (n=77)	
Adverse event, %	All grades	Grade 3/4	All grades	Grade 3/4
Any adverse event	99	76	84	21
Neutropenia	75	54	5	1
Leukopenia	43	19	3	0
Fatigue	41	5	23	1
Anemia	35	6	6	1
Nausea	25	2	13	1
Arthralgia	23	1	16	3
Alopecia	22	n/a	3	n/a
Diarrhea	20	4	10	0
Hot flush	21	0	12	0
Thrombocytopenia	17	2	1	0
Decreased appetite	16	1	7	0
Dyspnea	16	2	8	1
Nasopharyngitis	16	0	10	0
Back pain	11	0	16	1

- No cases of febrile neutropenia were reported

One (1%) grade 5 event occurred in the PAL + LET group (from disease progression); none occurred in the LET group.

Finn RS, et al. *Lancet Oncol*. 2015;16(1):25-35.

February 3rd 2015

- U.S. Food and Drug Administration (FDA) granted accelerated approval of palbociclib (IBRANCE®)
- Indicated in combination with letrozole, for the treatment of postmenopausal women with ER+/ HER2- advanced breast cancer as initial endocrine-based therapy
- This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial (PALOMA-2)

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Palbociclib and Letrozole in Advanced Breast Cancer

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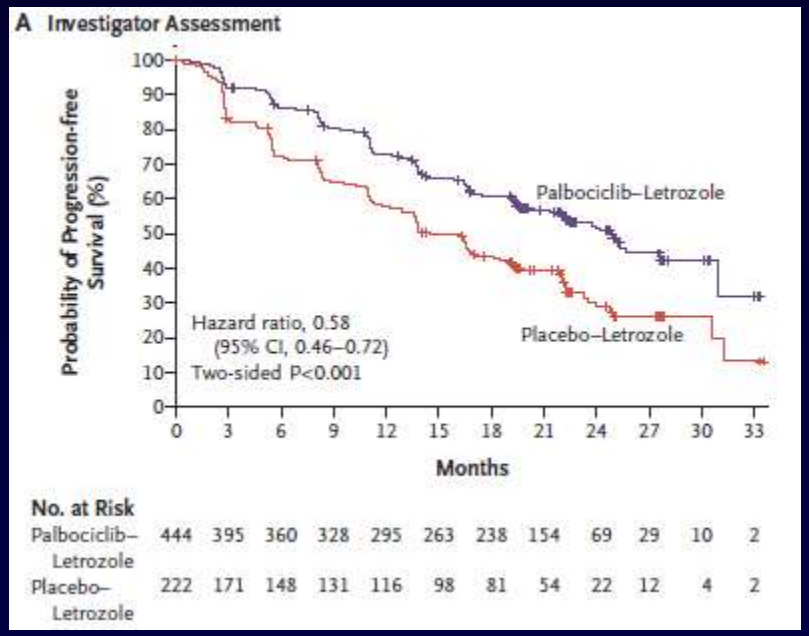
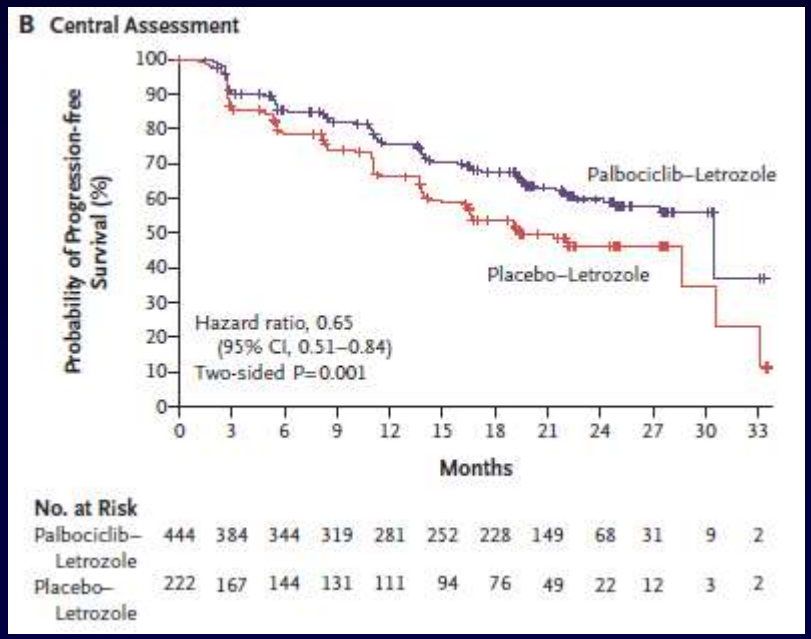
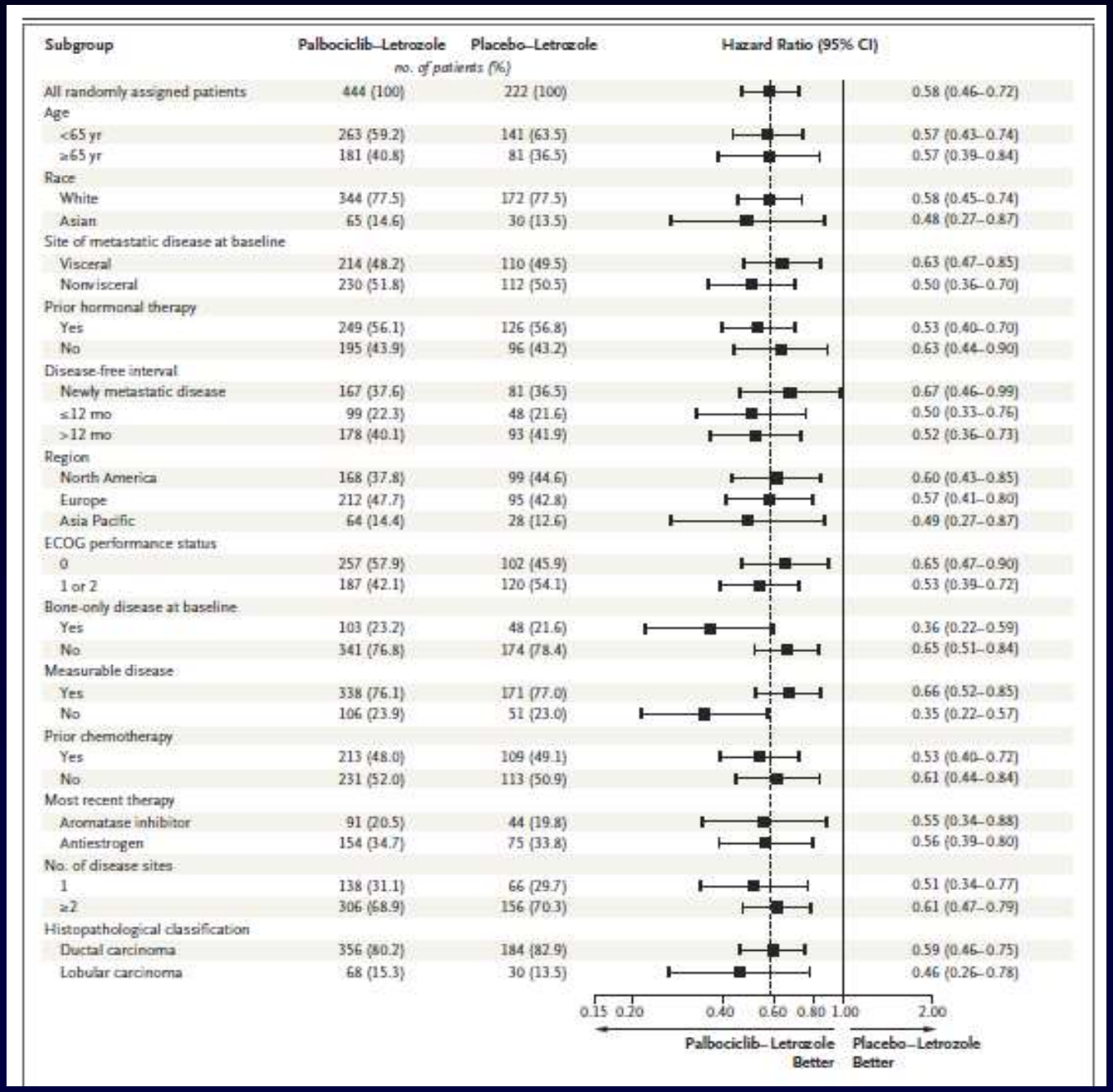






Finn RS et al NEJM 2016

PALOMA-2: Overall Response (ITT Population)

- As initial therapy for postmenopausal ER+/HER2– advanced breast cancer, palbociclib + letrozole improves ORR and CBR over letrozole alone

	Palbociclib + letrozole (N=444)	Placebo + letrozole (N=222)	Odds ratio (95% CI)	2-sided P value (exact)
All randomized patients, n	444	222		
ORR,[a] % (95% CI)	**42.1** (37.5–46.9)	**34.7** (28.4–41.3)	1.40 (0.98–2.01)	0.06
CBR,[b] % (95% CI)	**84.9** (81.2–88.1)	**70.3** (63.8–76.2)	2.39 (1.58–3.59)	<0.0001
Median DoR, months	**22.5** (19.8–28.0)	**16.8[c]** (14.2–28.5)	NR	NR
Patients with measurable disease	338	171		
ORR,[a] % (95% CI)	**55.3** (49.9–60.7)	**44.4** (36.9–52.2)	1.55 (1.05–2.28)	0.03
CBR,[b] % (95% CI)	**84.3** (80.0–88.0)	**70.8** (63.3–77.5)	2.23 (1.39–3.56)	<0.001
Median DoR, months	**22.5** (19.8–28.0)	**16.8** (15.4–28.5)	NR	NR

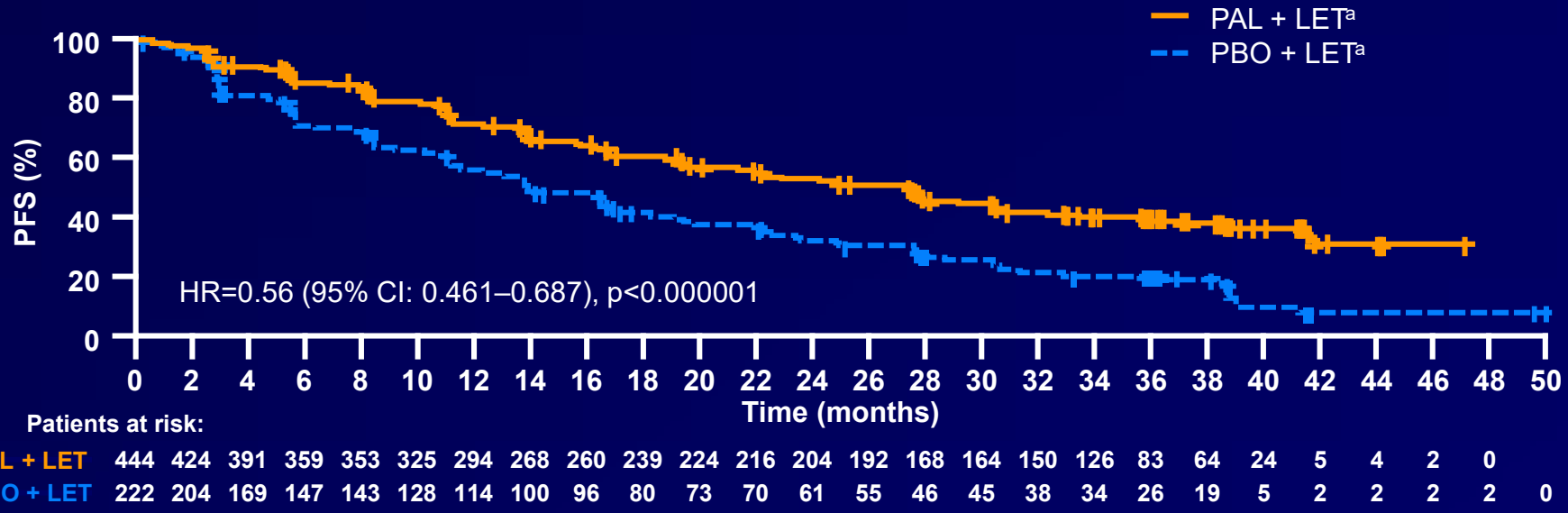
[a]Confirmed complete response + partial response
[b]Confirmed complete response + partial response + stable disease ≥24 weeks
[c]One patient with bone-only disease at baseline was included; all other patients had measurable disease at baseline
CI, confidence interval; CBR, clinical benefit rate; DoR, duration of response; ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; ITT, intention to treat; NR, not reported; NS, not significant; ORR, overall response rate

Finn RS, et al. *N Engl J Med* 2016;375(20):1925–36

PALOMA-2: Investigator-Assessed PFS

Investigator-assessed PFS[a]

	Data cutoff date: February 26, 2016[b]		Data cutoff date: May 31, 2017[c]	
	PAL + LET	PBO + LET	PAL + LET	PBO + LET
mPFS, months (95% CI)	24.8 (22.1–NE)	14.5 (12.9–17.1)	27.6 (22.4–30.3)	14.5 (12.3–17.1)
PFS HR (95% CI)	0.576 (0.463–0.718)		0.563 (0.461–0.687)	
1-sided p value	<0.000001		<0.000001	



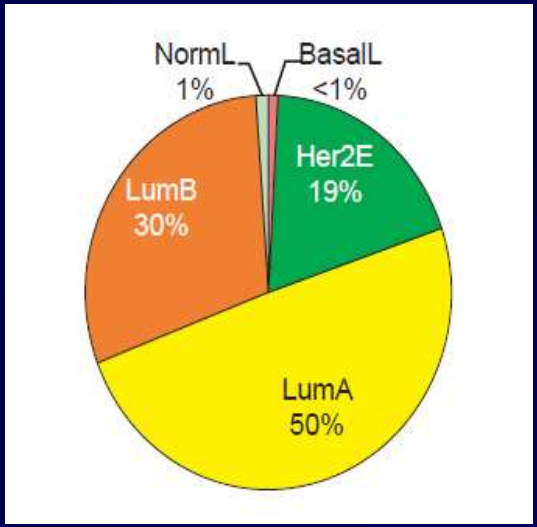
Patients at risk:

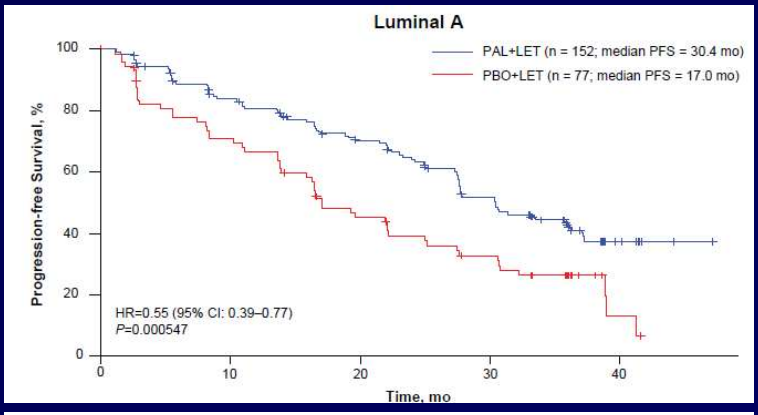
PAL + LET	444	424	391	359	353	325	294	268	260	239	224	216	204	192	168	164	150	126	83	64	24	5	4	2	0
PBO + LET	222	204	169	147	143	128	114	100	96	80	73	70	61	55	46	45	38	34	26	19	5	2	2	2	0

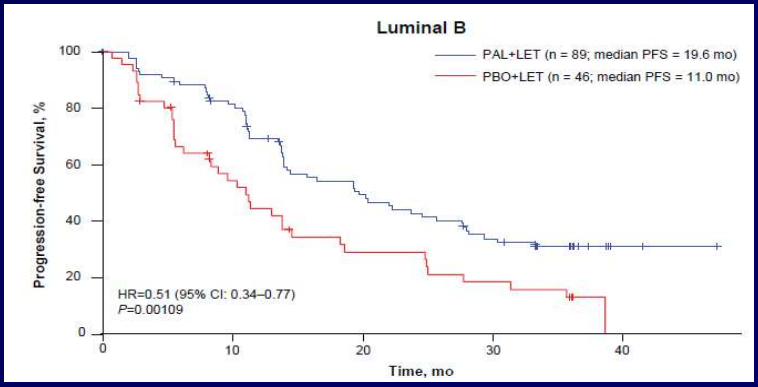
[a]Data cutoff, May 31, 2017
[b]Median follow-up duration was 23.0 months in the palbociclib + letrozole arm and 22.3 months in the placebo + letrozole arm; [c]Median follow-up duration was 37.6 months in the palbociclib + letrozole arm and 37.3 months in the placebo + letrozole arm
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; LET, letrozole; mPFS, median PFS; NE, not estimable; PAL, palbociclib; PBO, placebo; PFS, progression-free survival

Rugo HS, Finn RS et al. Presented at SABCS 2017 (Abstract P5-21-03)

PALOMA-2 in Patients with ER+/HER2– ABC/MBC: Intrinsic Subtypes







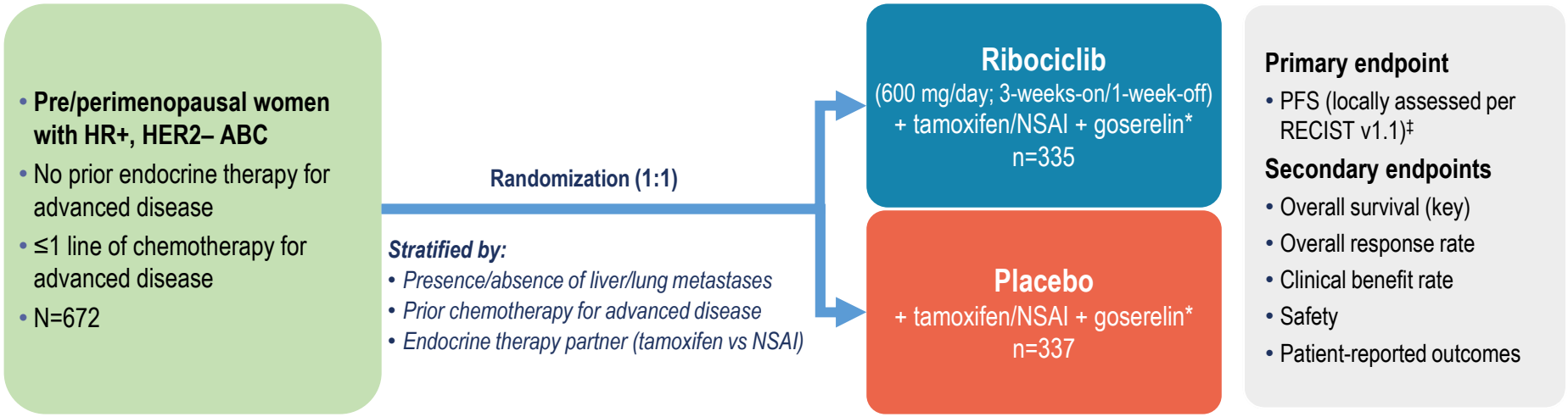
Finn RS et al SABCS 2017

Consistent Findings in 1st Line CDK 4/6-I Treatment

	PALOMA-2	MONALEESA-2	MONARCH 3
Design	Phase 3 (1:1)	Phase 3 (1:1)	Phase 3 (2:1)
CDK 4/6 Agent	Palbociclib	Ribociclib	Abemaciclib
Endocrine partner	Letrozole	Letrozole	Anastrozole or letrozole
Patients on study, N	N = 666	N = 668	N = 493
Primary Endpoints (PFS)			
HR	0.563	0.568	0.543
Median PFS, months	**27.6 vs 14.5**	**25.3 vs 16.0**	**NR vs. 14.7**

CBR = clinical benefit response; ITT = intent-to-treat; ORR – objective response rate

MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 PFS events

– 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm[1,2]), and a sample size of 660 patients

- NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.
- *Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days;
‡PFS by Blinded Independent Review Committee conducted to support the primary endpoint.

1. Klijn JG, *et al*. *J Clin Oncol* 2001;19:343–353; 2. Mourisden H, *et al*. *J Clin Oncol* 2001;19:2596–2606.

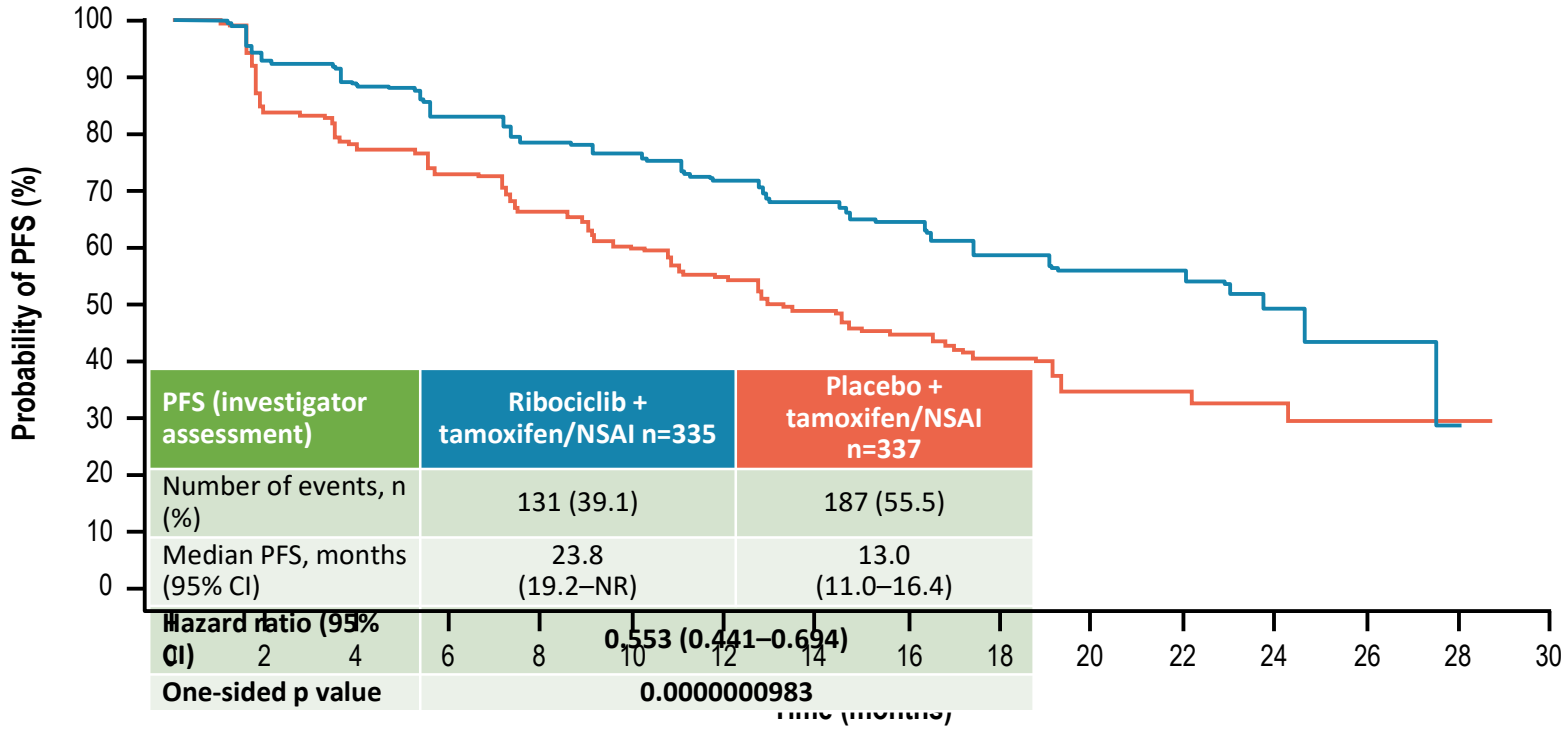
Patient demographics and baseline characteristics

Characteristic*	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Median age, years (range)	43 (25–58)	45 (29–58)
Race		
Caucasian	187 (55.8)	201 (59.6)
Asian	99 (29.6)	99 (29.4)
Other‡	29 (8.7)	19 (5.6)
Unknown	20 (6.0)	18 (5.3)
ECOG performance status§		
0	245 (73.1)	255 (75.7)
1	87 (26.0)	78 (23.1)
Missing	3 (0.9)	3 (0.9)
Metastatic sites		
Visceral disease	193 (57.6)	188 (55.8)
Bone-only disease	81 (24.2)	78 (23.1)
***De novo* metastatic disease**	136 (40.6)	134 (39.8)
Non-*de novo* metastatic disease	199 (59.4)	203 (60.2)
Disease-free interval		
≤12 months	23 (6.9)	13 (3.9)
>12 months	176 (52.5)	190 (56.4)
Prior (neo)adjuvant endocrine therapy	127 (37.9)	141 (41.8)
Prior chemotherapy		
For advanced disease	47 (14.0)	47 (13.9)
(Neo)adjuvant only	138 (41.2)	138 (40.9)
None	150 (44.8)	152 (45.1)

*All values are n (%), unless stated otherwise; ‡'Other' includes Black, Native American, and other;
§ One patient in the placebo arm had an ECOG performance status of 2.
Goserelin included in all combinations.

Tripathy D, al. Lancet Oncol. 2018 Jul;19(7):904-915.

Primary endpoint: PFS (investigator-assessed)



PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	131 (39.1)	187 (55.5)
Median PFS, months (95% CI)	23.8 (19.2–NR)	13.0 (11.0–16.4)
Hazard ratio (95% CI)	0.553 (0.441–0.694)	
One-sided p value	0.0000000983	

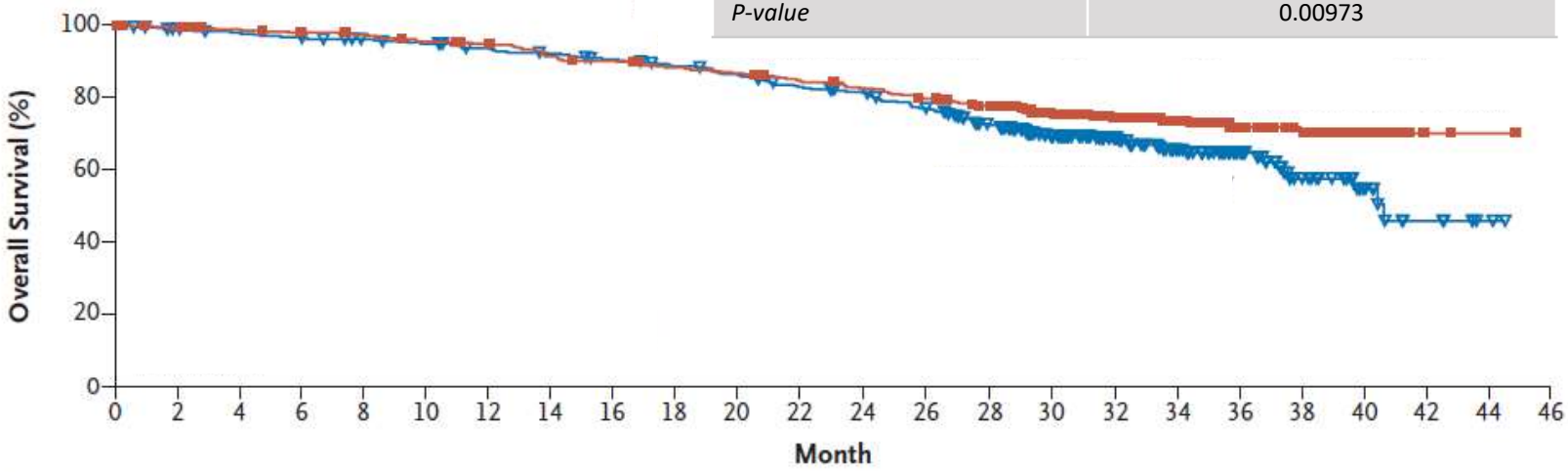
No. at risk																
Ribociclib + tamoxifen/NSAI	335	301	284	264	245	235	219	178	136	90	54	40	20	3	1	0
Placebo + tamoxifen/NSAI	337	273	248	230	207	183	165	124	94	62	31	24	13	3	1	0

- CI, confidence interval; NR, not reached. Goserelin included in all combinations.

Tripathy D, al. Lancet Oncol. 2018 Jul;19(7):904-915.

MONALEESA 7 SURVIVAL

	Ribociclib group	Placebo group
Events/N	83/335	109/337
Median OS, mo	Not evaluable	40.9
HR (95% CI) *P-value*	0.71 (0.535–90.948) 0.00973	



No. at Risk																								
Ribociclib	335	330	325	320	316	309	304	292	287	279	274	266	258	249	236	193	155	110	68	43	25	7	3	0
Placebo	337	330	325	321	314	309	301	295	288	280	272	258	251	235	210	166	122	92	62	33	19	7	2	0

- Median f/u 34.6 months, 35% on ribo, 17 % on placebo arm
- At 42 months, OS rate was 70% ribo arm, 46% placebo arm
- Post-treatment therapt equal in both arms 68.9% ribo arm, 73.2% placebo arm

Im SA, ET AL. N Engl J Med. 2019 Jun 4.

HEMATOLOGIC ADVERSE EVENTS

Regardless of study treatment relationship

Adverse Event ≥5% in Either Arm, %	Ribociclib + Letrozole n=334			Placebo + Letrozole n=330		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Neutropenia	74	50	9.6	5.2	0.9	0
Leukopenia	33	20	1.2	3.9	0.6	0
Anemia	19	0.9	0.3	4.5	1.2	0
Lymphopenia	11	5.7	1.2	2.1	0.9	0
Thrombocytopenia	9.0	0.6	0	0.6	0	0

- Febrile neutropenia occurred in 5 (1.5%)* patients in the ribociclib arm vs. none in the placebo arm

COPENHAGEN 2016 ESMO congress

Hortabagyi G et al NEJM 2016

*5 cases, which includes 1 case of febrile neutropenia recorded incorrectly.

NON-HEMATOLOGIC ADVERSE EVENTS

Regardless of study treatment relationship

Adverse Event ≥15% in Either Arm, %	Ribociclib + Letrozole n=334			Placebo + Letrozole n=330		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Nausea	52	2.4	0	29	0.6	0
Infections	50	3.6	0.6	42	2.1	0.3
Fatigue	37	2.1	0.3	30	0.9	0
Diarrhea	35	1.2	0	22	0.9	0
Alopecia	33	–	–	16	–	–
Vomiting	29	3.6	0	16	0.9	0
Arthralgia	27	0.6	0.3	29	0.9	0
Constipation	25	1.2	0	19	0	0
Headache	22	0.3	0	19	0.3	0
Hot flush	21	0.3	0	24	0	0
Back pain	20	2.1	0	18	0.3	0
Cough	20	0	–	18	0	–
Decreased appetite	19	1.5	0	15	0.3	0
Rash	17	0.6	0	7.9	0	0
ALT increased	16	7.5	1.8	3.9	1.2	0
AST increased	15	4.8	0.9	3.6	1.2	0

- In the ribociclib arm 10 (3.0%) patients experienced Grade 2 QTcF (481–500 ms) and 1 (0.3%) patient experienced Grade 3 QTcF (>500 ms); no dose reductions were required

Hortabagyi G et al NEJM 2016

Central Laboratory Abnormalities (Safety Population) ≥30% Occurrence

	abemaciclib + NSAI n = 327				placebo + NSAI n = 161			
Grade, n (%)	**Any**	**2**	**3**	**4**	**Any**	**2**	**3**	**4**
Any laboratory abnormality	315 (99.7)	146 (46.2)	121 (38.3)	21 (6.6)	150 (94.9)	38 (24.1)	14 (8.9)	1 (0.6)
Creatinine increased[a]	308 (98.1)	166 (52.9)	7 (2.2)	0	131 (84.0)	7 (4.5)	0	0
White blood cell decreased	258 (82.4)	134 (42.8)	40 (12.8)	0	42 (26.9)	11 (7.1)	1 (0.6)	0
Anemia	256 (81.8)	122 (39.0)	5 (1.6)	0	43 (27.6)	14 (9.0)	0	0
Neutrophil count decreased	251 (80.2)	120 (38.3)	60 (19.2)	9 (2.9)	32 (20.5)	4 (2.6)	4 (2.6)	0
Lymphocyte count decreased	165 (52.7)	63 (20.1)	23 (7.3)	2 (0.6)	40 (25.6)	15 (9.6)	3 (1.9)	0
Alanine aminotransferase increased	149 (47.6)	29 (9.3)	20 (6.4)	2 (0.6)	39 (25.2)	3 (1.9)	3 (1.9)	0
Aspartate aminotransferase increased	115 (36.7)	12 (3.8)	12 (3.8)	0	36 (23.2)	6 (3.9)	1 (0.6)	0
Platelet count decreased	113 (36.2)	10 (3.2)	4 (1.3)	2 (0.6)	18 (11.6)	0	1 (0.6)	0
Hypercalcemia	96 (30.6)	0	0	2 (0.6)	50 (32.1)	1 (0.6)	0	0

[a]CTCAE version 4.0 defines Grade 1 creatinine increased as >1-1.5x baseline or >ULN-1.5x ULN

Di Leo et al ESMO 2017

Treatment-emergent Adverse Events (Safety Population) ≥20% Occurrence

	abemaciclib + NSAI n = 327				placebo + NSAI n = 161			
Grade, n (%)	**Any**	**2**	**3**	**4**	**Any**	**2**	**3**	**4**
Any adverse event	322 (98.5)	111 (33.9)	159 (48.6)	21 (6.4)	145 (90.1)	61 (37.9)	32 (19.9)	3 (1.9)
Diarrhea	266 (81.3)	89 (27.2)	31 (9.5)	0	48 (29.8)	11 (6.8)	2 (1.2)	0
Neutropenia	135 (41.3)	53 (16.2)	64 (19.6)	5 (1.5)	3 (1.9)	1 (0.6)	1 (0.6)	1 (0.6)
Fatigue	131 (40.1)	55 (16.8)	6 (1.8)	—	51 (31.7)	20 (12.4)	0	—
Nausea	126 (38.5)	36 (11.0)	3 (0.9)	—	32 (19.9)	1 (0.6)	2 (1.2)	—
Abdominal pain	95 (29.1)	21 (6.4)	4 (1.2)	—	19 (11.8)	4 (2.5)	2 (1.2)	—
Anemia	93 (28.4)	45 (13.8)	19 (5.8)	0	8 (5.0)	2 (1.2)	2 (1.2)	0
Vomiting	93 (28.4)	26 (8.0)	4 (1.2)	0	19 (11.8)	3 (1.9)	3 (1.9)	0
Alopecia	87 (26.6)	5 (1.5)	—	—	17 (10.6)	0	—	—
Decreased appetite	80 (24.5)	26 (8.0)	4 (1.2)	0	15 (9.3)	2 (1.2)	1 (0.6)	0
Leukopenia	68 (20.8)	31 (9.5)	24 (7.3)	1 (0.3)	4 (2.5)	1 (0.6)	0	1 (0.6)

- 1 patient experienced non-serious febrile neutropenia in the abemaciclib arm.
- Venous thromboembolic events occurred in 16 (4.9%) of patients in the abemaciclib arm versus 1 (0.6%) in the placebo arm.

Di Leo et al ESMO 2017

Design of Phase III Study in Recurrent MBC (1023)-PALOMA-3

- HR+, HER2– ABC
- Pre-/peri-* or post-menopausal
- Progressed on prior endocrine therapy:
  - On or within 12 mo adjuvant
  - On therapy for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

*All received goserelin.

2:1 Randomization

N=521

Stratification:

- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-/peri- vs Post-menopausal

n=347

Palbociclib (125 mg QD; 3 wks on/1 wk off) + Fulvestrant† (500 mg IM q4w)

n=174

Placebo (3 wks on/ 1wk off) + Fulvestrant† (500 mg IM q4w)

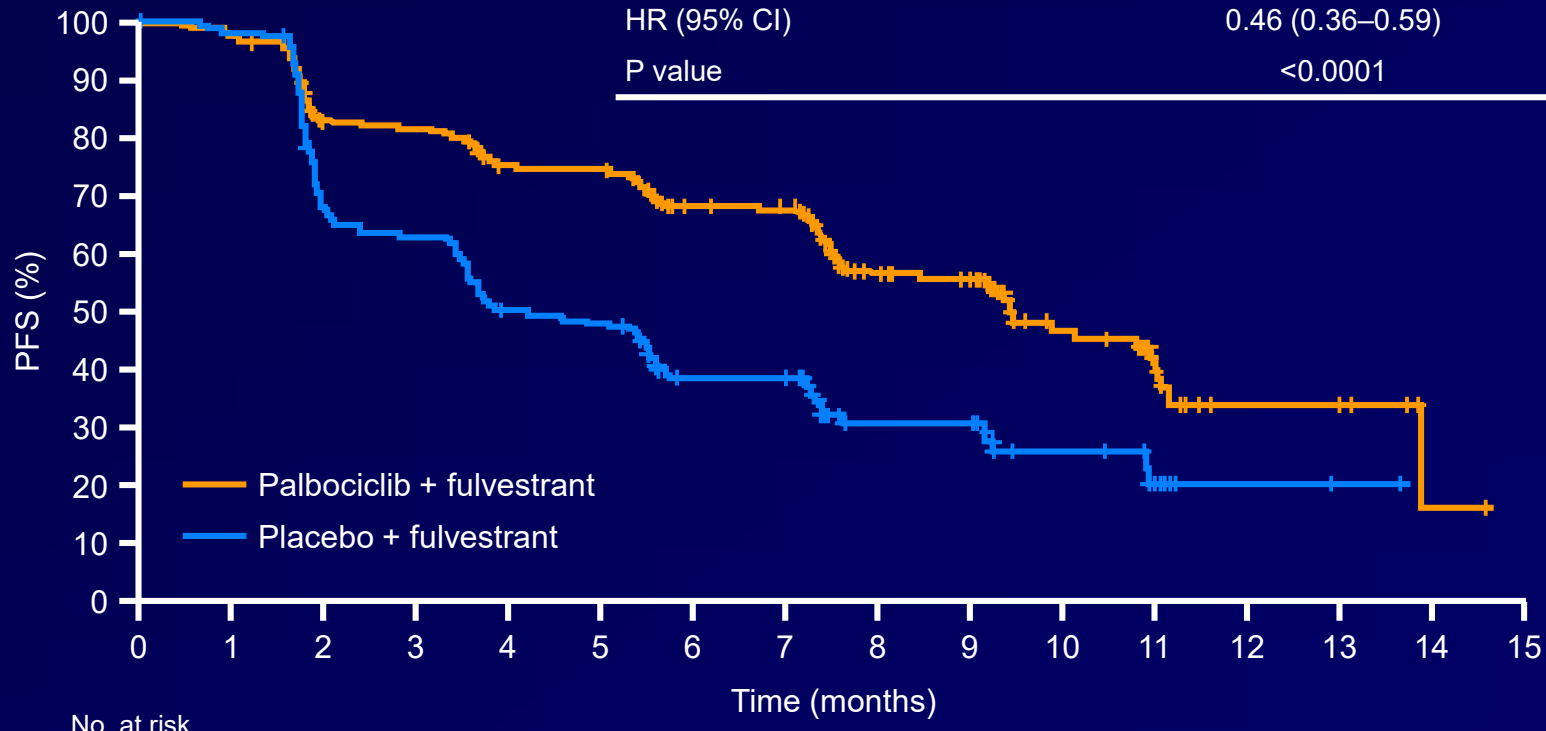
- ***Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.***

†administered on Days 1 and 15 of Cycle 1.

Clinicaltrials.gov NCT01942135

PALOMA-3 Final Analysis: Investigator-assessed PFS (ITT Population)

	PAL + FUL (n=347)	PBO + FUL (n=174)
Median PFS, months (95% CI)	9.5 (9.2–11.0)	4.6 (3.5–5.6)
HR (95% CI)	0.46 (0.36–0.59)	
P value	<0.0001	



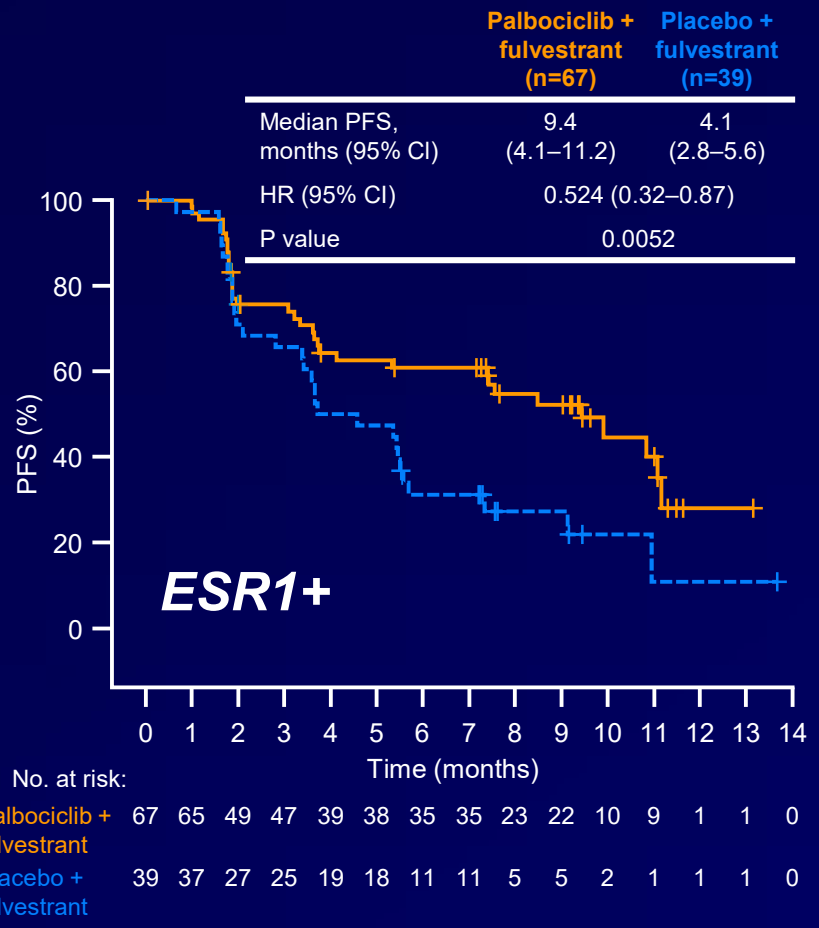
No. at risk																
Palbociclib + fulvestrant	347	333	281	273	247	244	202	197	91	85	32	23	7	7	1	0
Placebo + fulvestrant	174	165	112	105	83	80	59	58	22	22	13	7	2	1	0	0

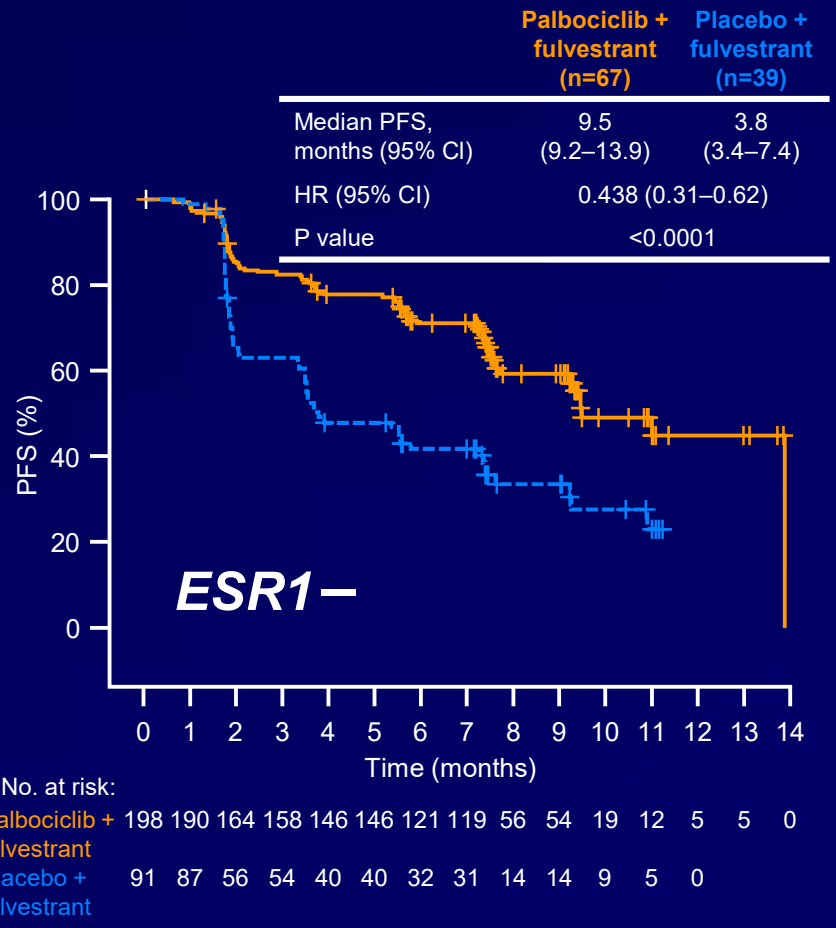
FUL, fulvestrant; HR, hazard ratio; PAL, palbociclib; PBO, placebo

Turner etal NEJM 2015
Cristofanilli M, et al. *Lancet Oncol* 2016 2016 Apr;17(4):425–39

ESR1 Mutations in PALOMA-3: Response by *ESR1* Mutation Status

- The PFS benefit associated with the addition of palbociclib to fulvestrant was demonstrated regardless of *ESR1* mutation status



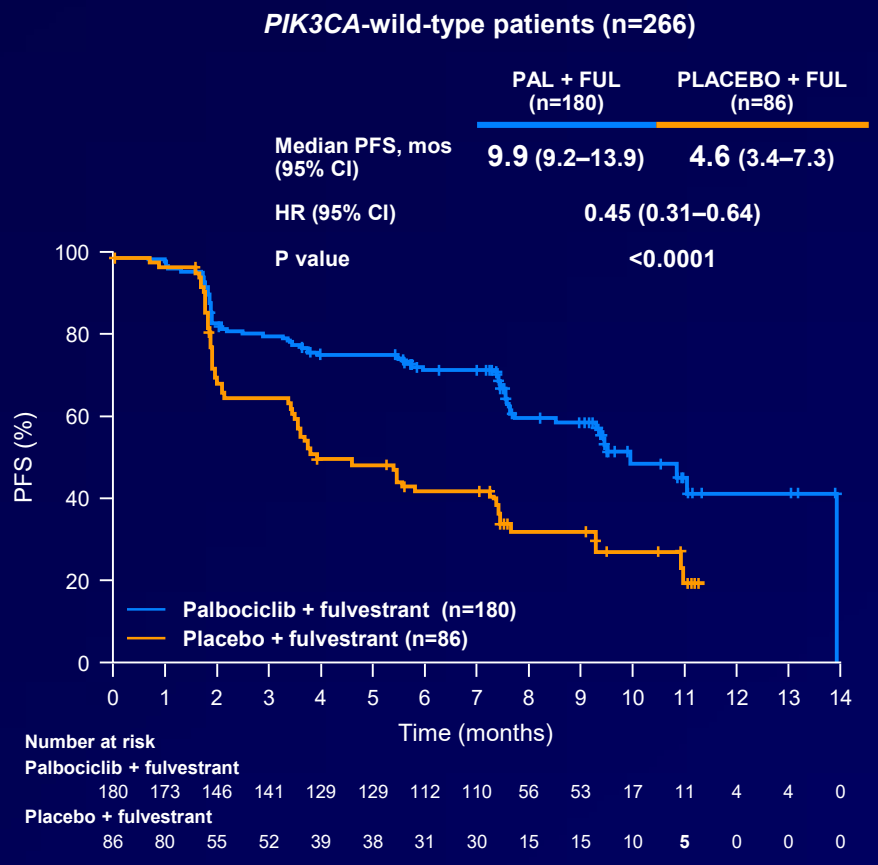


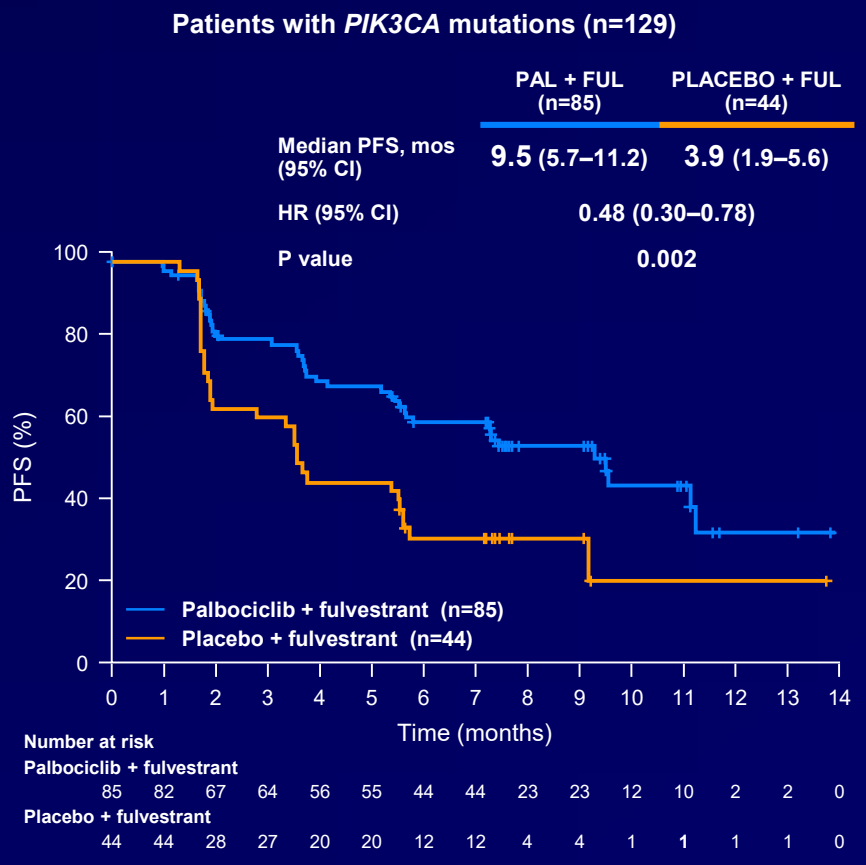
HR, hazard ratio

Turner NC, et al. *J Clin Oncol* 2016;34(Suppl.) (Abstract 512)

PALOMA-3 Final Analysis: PFS in Patients by *PIK3CA* Status

- *PIK3CA* status did not influence the magnitude of PFS benefit from palbociclib (HR=0·45 for *PIK3CA* wild-type, HR=0·48 for *PIK3CA* mutation positive, $P_{interaction}$ = 0·83)



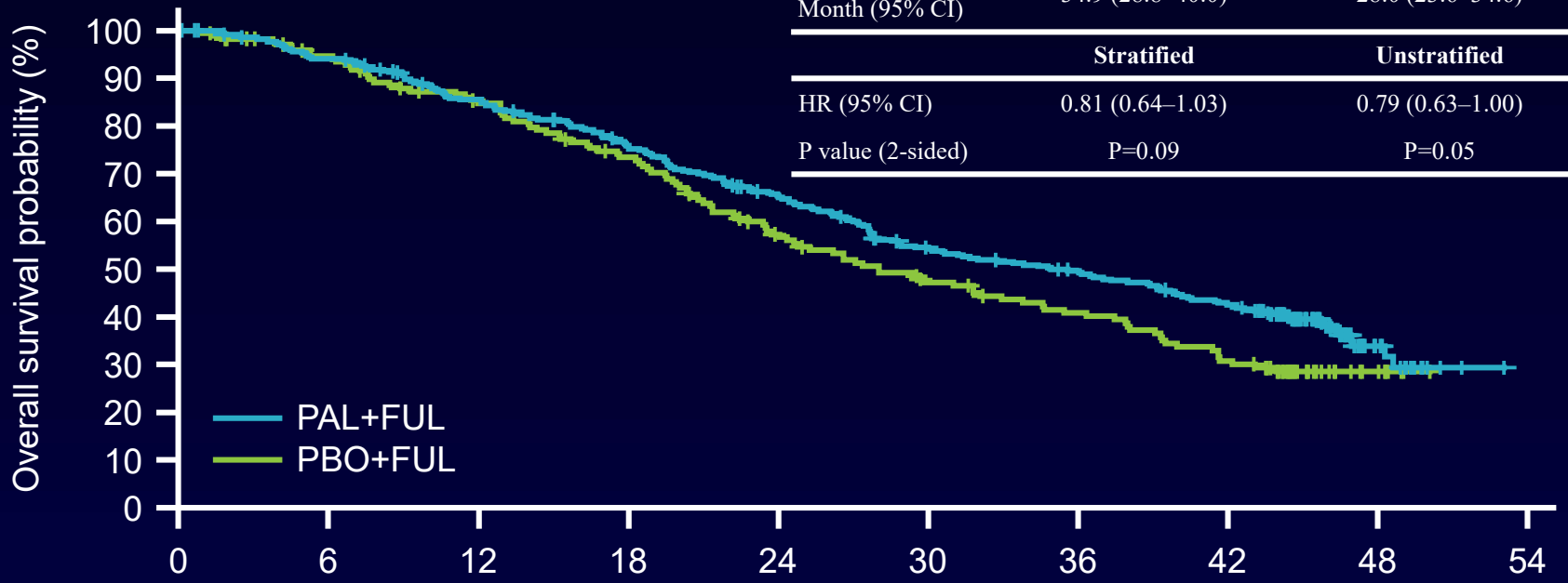


PFS, progression-free survival; HR, hazard ratio; CI, confidence interval

Cristofanilli M, et al. Lancet Oncol 2016 [Published online 2 March 2016; http://dx.doi.org/10.1016/S1470-2045(15)00613-0]

Overall Survival in PALOMA-3 (ITT)

	PAL+FUL (n=347)	PBO+FUL (n=174)
Median OS, Month (95% CI)	34.9 (28.8–40.0)	28.0 (23.6–34.6)
	Stratified	**Unstratified**
HR (95% CI)	0.81 (0.64–1.03)	0.79 (0.63–1.00)
P value (2-sided)	P=0.09	P=0.05



Number of patients at risk									
PAL+FUL	347	321	286	247	209	165	148	126	17
PBO+FUL	174	155	135	115	86	68	57	43	7

- **Absolute improvement in median OS in the palbociclib arm versus the placebo arm was 6.9 months**

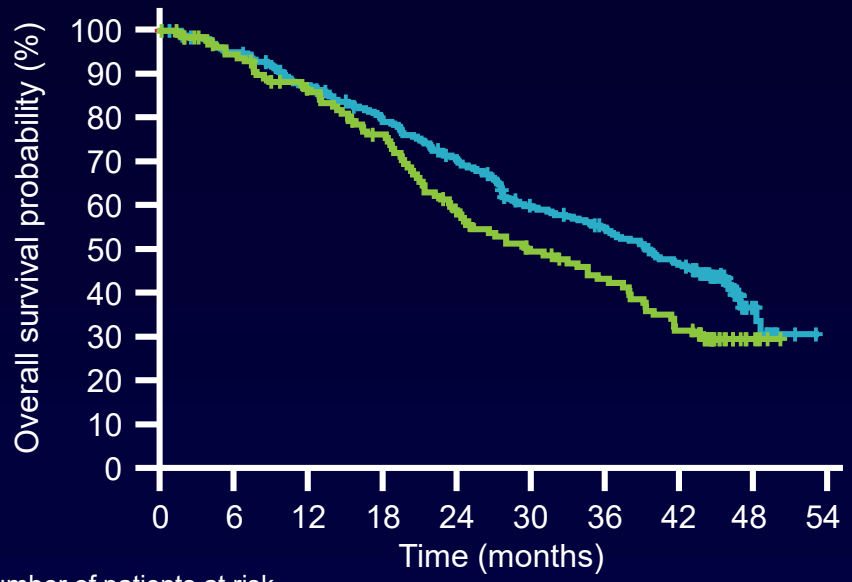
FUL=fulvestrant; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; PAL=palbociclib; PBO=placebo.

Turner, et al. N Engl J Med 2018

PALOMA3 Overall Survival By Sensitivity to Prior ET

Patients with sensitivity to prior ET

	PAL+FUL (n=274)	PBO+FUL (n=136)
Median OS, Month (95% CI)	39.7 (34.8–45.7)	29.7 (23.8–37.9)
HR (95% CI)	0.72 (0.55–0.94)	

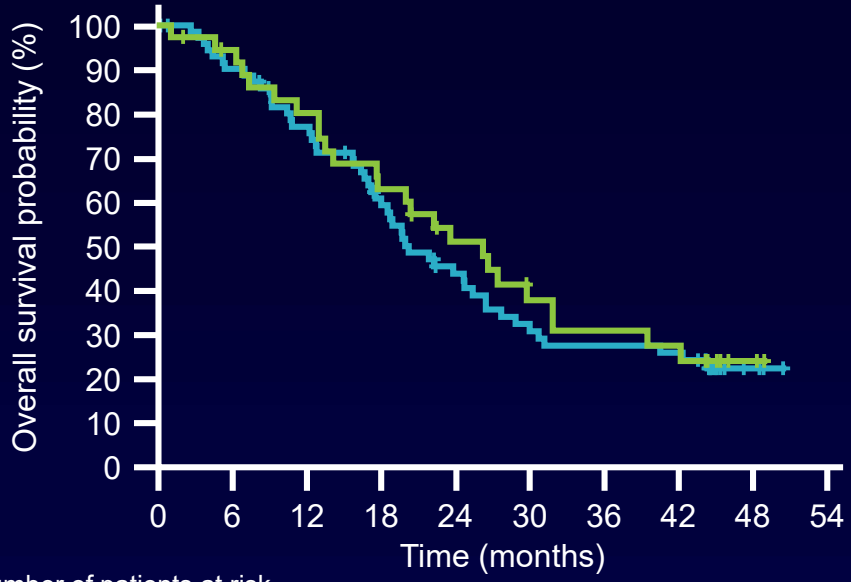


Number of patients at risk

PAL+FUL	274	257	233	208	182	146	131	110	14
PBO+FUL	136	122	107	93	70	57	48	35	5

Patients without sensitivity to prior ET

	PAL+FUL (n=73)	PBO+FUL (n=38)
Median OS, Month (95% CI)	20.2 (17.2–26.4)	26.2 (17.5–31.8)
HR (95% CI)	1.14 (0.71–1.84)	
P value (2-sided)	P=0.12	



Number of patients at risk

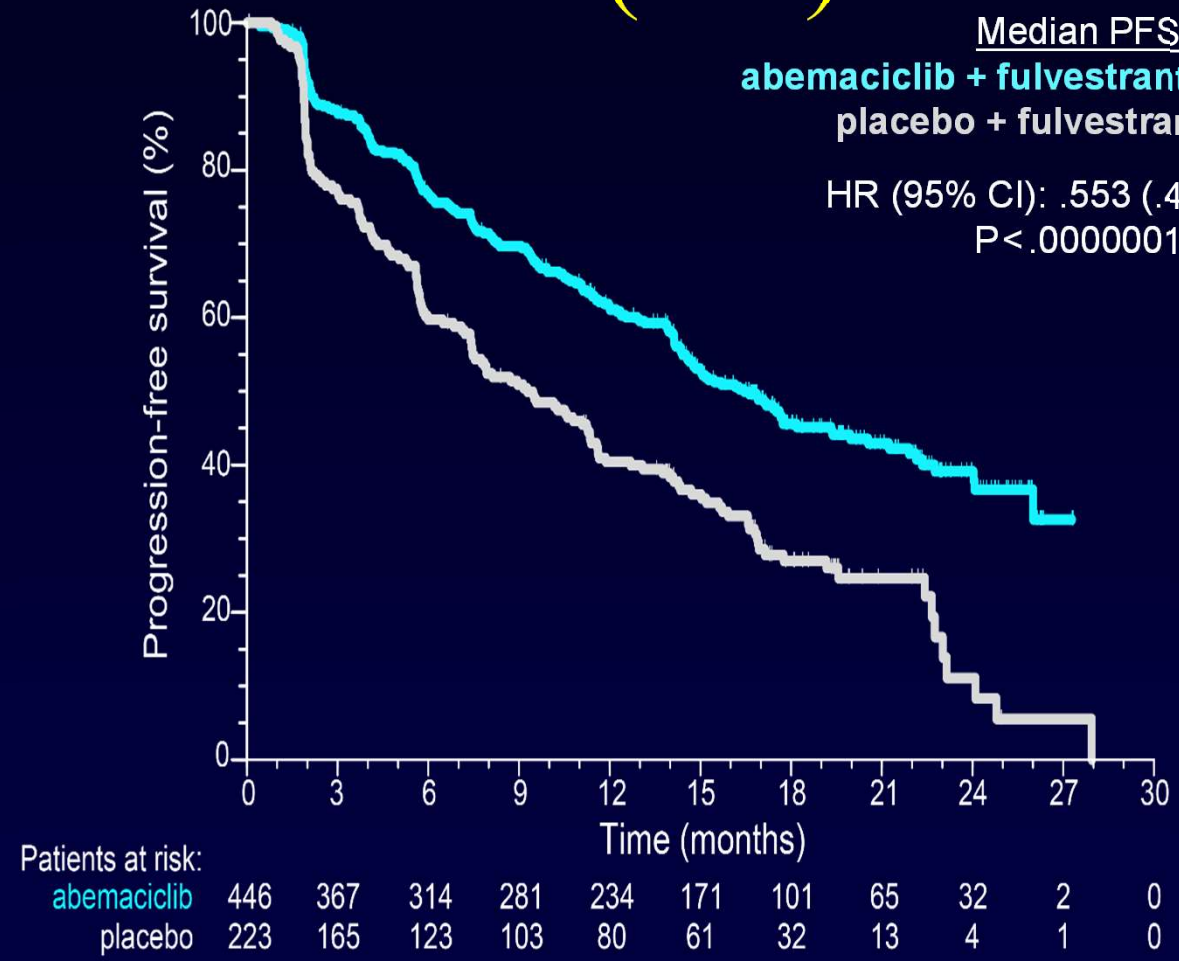
PAL+FUL	73	64	53	39	27	19	17	16	3
PBO+FUL	38	33	28	22	16	11	9	8	2

- **In patients with sensitivity to prior ET, absolute improvement in median OS in the palbociclib arm versus the placebo arm was 10.0 months**

CI=confidence interval; ET=endocrine therapy; FUL=fulvestrant; HR=hazard ratio; OS=overall survival; PAL=palbociclib; PBO=placebo.

Turner, et al. N Engl J Med 2018

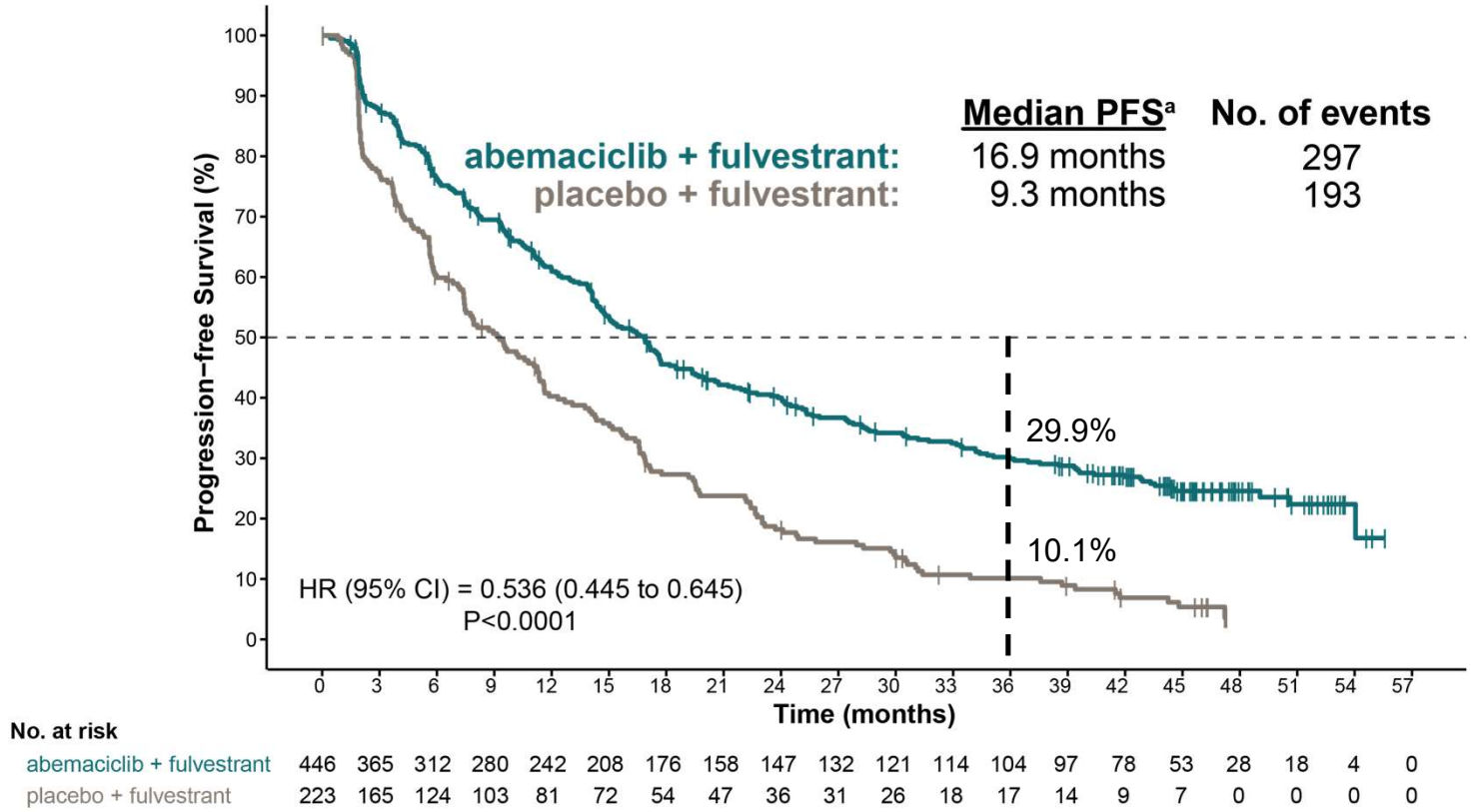
MONARCH 2Primary Endpoint: PFS (ITT)



PFS benefit confirmed by blinded independent central review (HR: .460; 95% CI: .363, .584; P<.000001)

Sledge et al ASCO 2017, Sledge et al JCO 2017

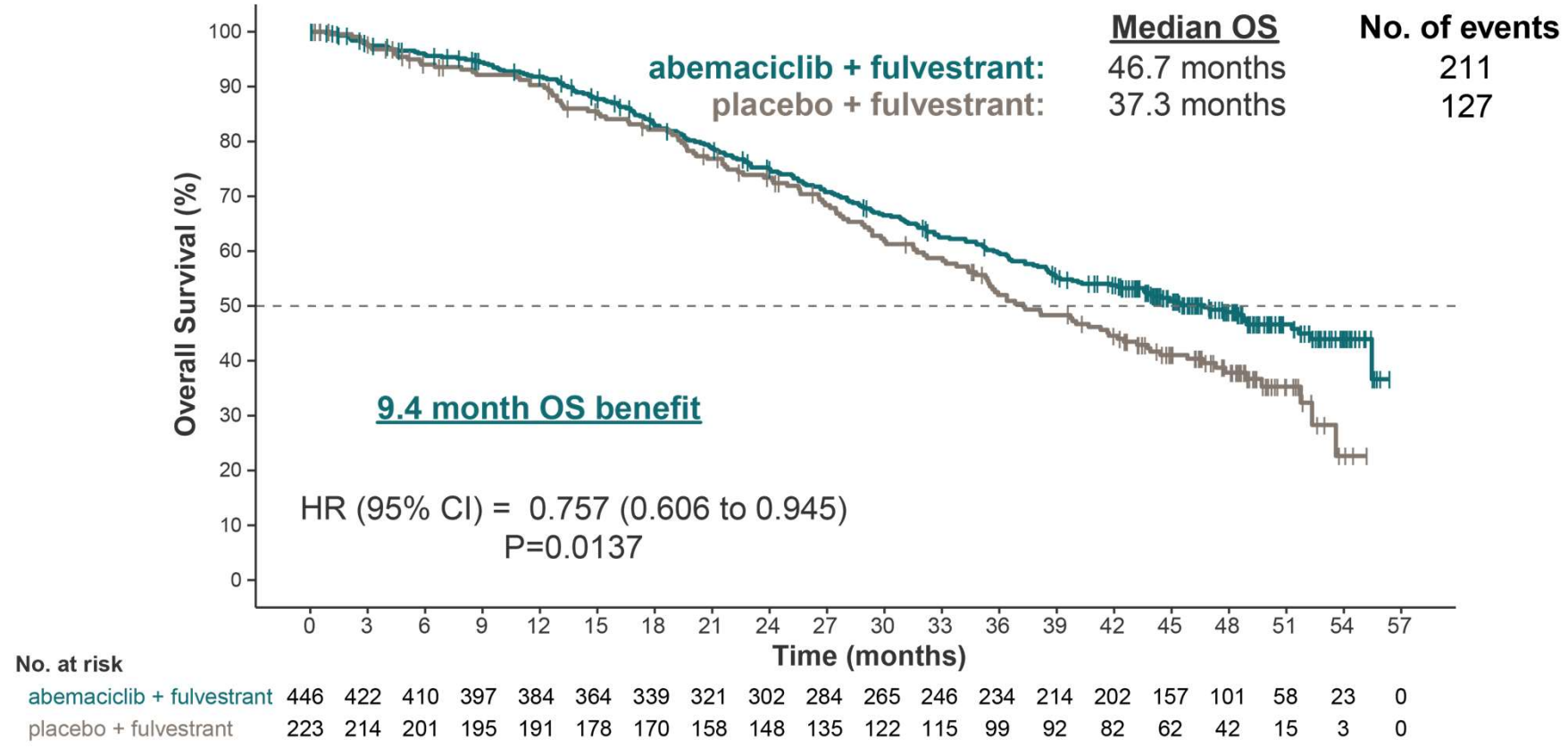
UPDATED PROGRESSION-FREE SURVIVAL



[a]PFS results at primary analysis: Median: 16.4 vs 9.3 months (HR: 0.553; 95% CI: 0.449, 0.681; P<0.001), 222 events abemaciclib arm vs 157 events placebo arm

Sledge et al JAMA Oncology 2019

OVERALL SURVIVAL



Sledge et al JAMA Oncology 2019

TREATMENT-EMERGENT ADVERSE EVENTS[a]

	abemaciclib + fulvestrant N = 441			placebo + fulvestrant N = 223		
≥20% in either arm, n (%)	**All**	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**
Any	435 (98.6)	259 (58.7)	32 (7.3)	203 (91.0)	51 (22.9)	9 (4.0)
Diarrhea	384 (87.1)	64 (14.5)	0	62 (27.8)	1 (0.4)	0
Neutropenia	219 (49.7)	118 (26.8)	13 (2.9)	9 (4.0)	3 (1.3)	1 (0.4)
Nausea	217 (49.2)	12 (2.7)	-	56 (25.1)	5 (2.2)	-
Fatigue	189 (42.9)	18 (4.1)	-	64 (28.7)	2 (0.9)	-
Abdominal pain	164 (37.2)	14 (3.2)	-	37 (16.6)	2 (0.9)	-
Anemia	153 (34.7)	39 (8.8)	1 (0.2)	10 (4.5)	3 (1.3)	0
Leukopenia	146 (33.1)	48 (10.9)	1 (0.2)	4 (1.8)	0	0
Decreased appetite	127 (28.8)	5 (1.1)	0	30 (13.5)	1 (0.4)	0
Vomiting	127 (28.8)	4 (0.9)	0	26 (11.7)	5 (2.2)	0
Headache	106 (24.0)	3 (0.7)	-	36 (16.1)	1 (0.4)	-

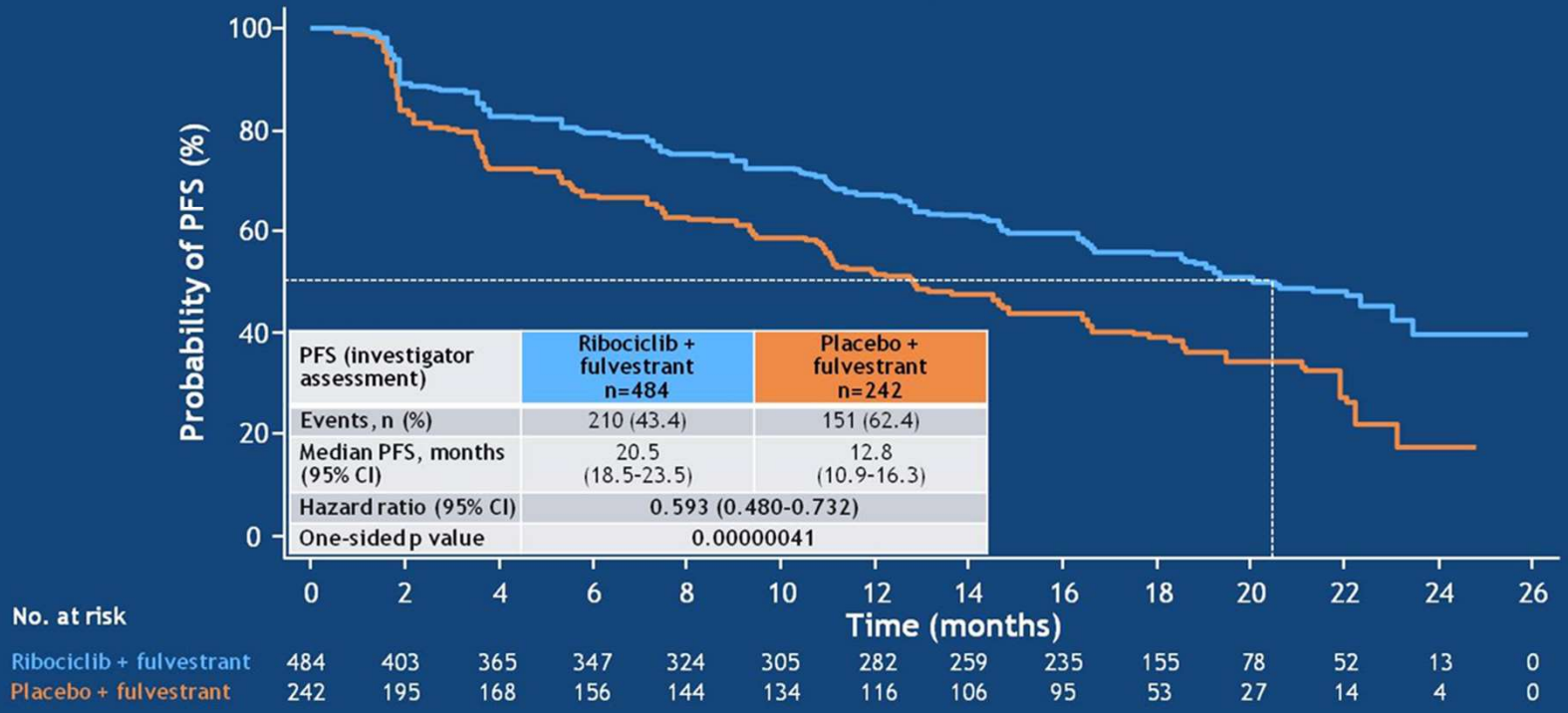
Abbreviations: N, number of patients in population; n, number of patients

[a]Death due to AEs was consistent with that of the primary analysis

Sledge et al JAMA Oncology 2019

MONALEESA 3 Ribociclib and Fulvestrant

Primary endpoint: PFS (investigator-assessed)



PFS (investigator assessment)	Ribociclib + fulvestrant n=484	Placebo + fulvestrant n=242
Events, n (%)	210 (43.4)	151 (62.4)
Median PFS, months (95% CI)	20.5 (18.5-23.5)	12.8 (10.9-16.3)
Hazard ratio (95% CI)	0.593 (0.480-0.732)	
One-sided p value	0.00000041	

No. at risk														
Ribociclib + fulvestrant	484	403	365	347	324	305	282	259	235	155	78	52	13	0
Placebo + fulvestrant	242	195	168	156	144	134	116	106	95	53	27	14	4	0

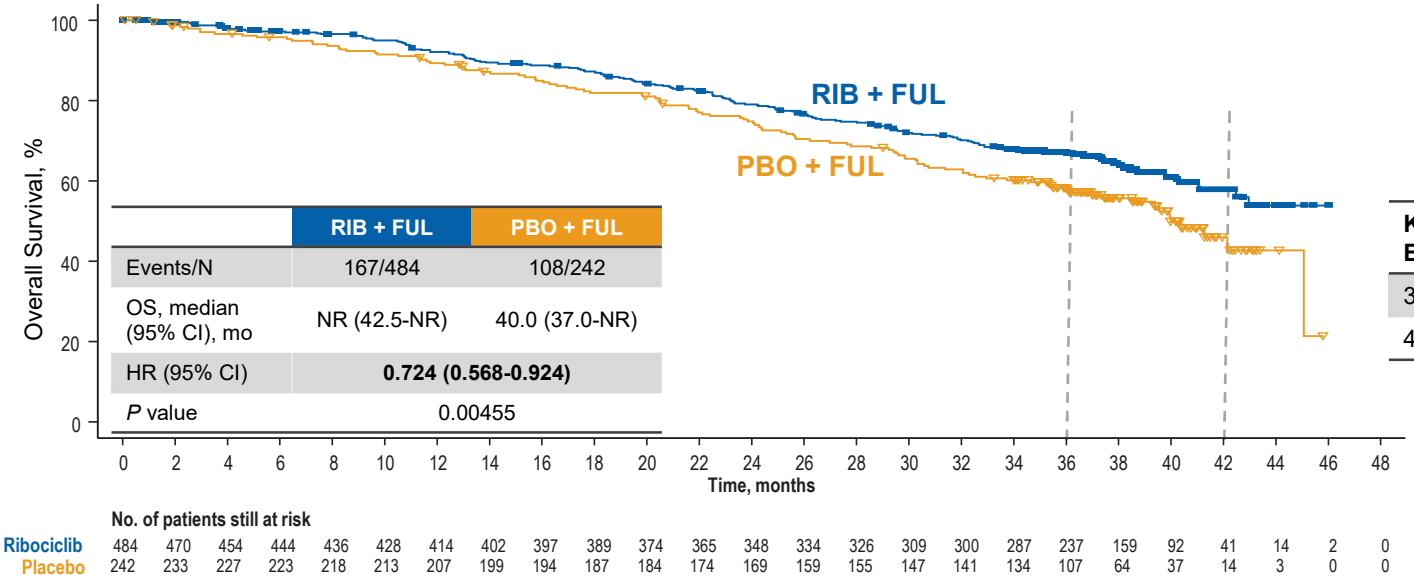
- The hazard ratio of 0.593 corresponds to a 41% reduction in risk of progression in the ribociclib vs placebo arm

CI, confidence interval.

Slamon et al JCO 2018

Overall Survival

The relative reduction in risk of death with RIB was 28%



	RIB + FUL	PBO + FUL
Events/N	167/484	108/242
OS, median (95% CI), mo	NR (42.5-NR)	40.0 (37.0-NR)
HR (95% CI)	**0.724 (0.568-0.924)**	
P value	0.00455	

Landmark Analysis

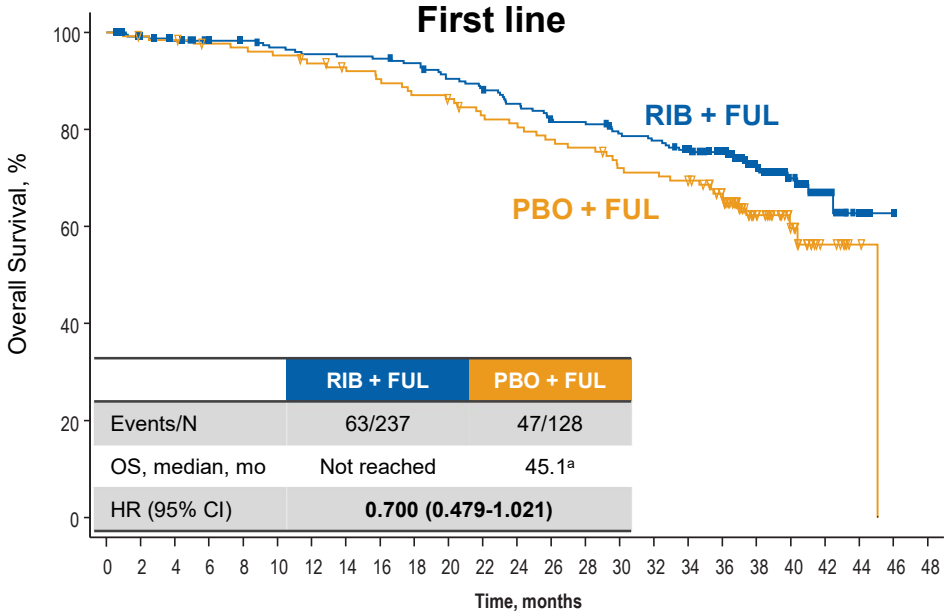
KM Estimate	RIB + FUL	PBO + FUL
36 months	67.0%	58.2%
42 months	57.8%	45.9%

- The *P* value of 0.00455 crossed the prespecified boundary to claim superior efficacy (*P* < 0.01129)

FUL, fulvestrant; HR, hazard ratio; KM, Kaplan-Meier; NR, not reached; OS, overall survival; PBO, placebo; RIB, ribociclib.

Overall Survival by Line of Therapy

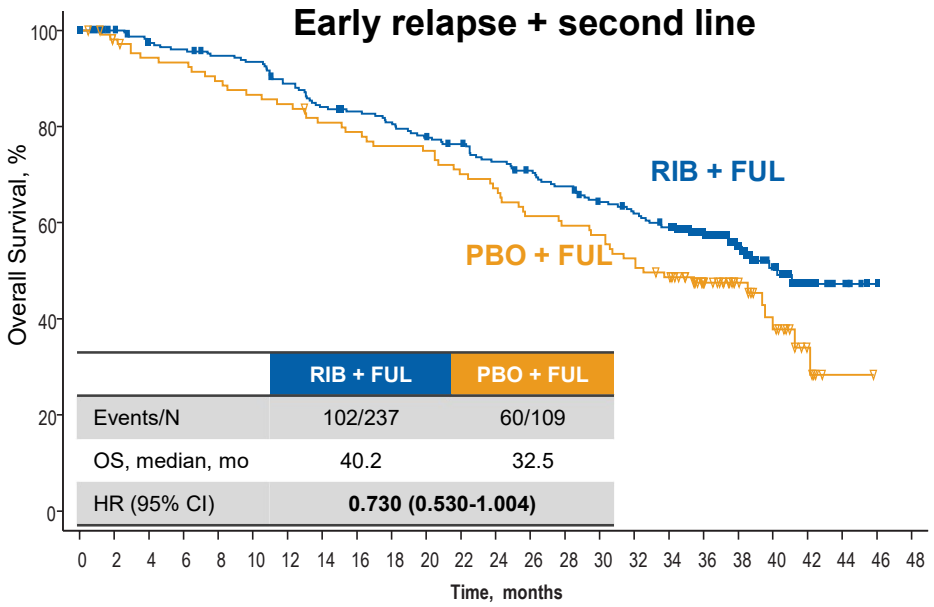
OS by line of therapy was consistent with overall population



	RIB + FUL	PBO + FUL
Events/N	63/237	47/128
OS, median, mo	Not reached	45.1[a]
HR (95% CI)	**0.700 (0.479-1.021)**	

No. of patients still at risk

Ribociclib	237	229	222	217	214	210	207	206	205	202	194	190	182	174	173	166	163	157	138	92	54	22	6	1	0
Placebo	128	126	125	122	121	119	116	113	110	106	104	99	97	93	91	85	84	82	70	40	21	8	2	0	0



	RIB + FUL	PBO + FUL
Events/N	102/237	60/109
OS, median, mo	40.2	32.5
HR (95% CI)	**0.730 (0.530-1.004)**	

No. of patients still at risk

Ribociclib	237	231	222	218	213	210	199	188	184	179	172	167	158	152	145	135	129	122	94	63	36	17	7	1	0
Placebo	109	103	98	97	93	90	88	83	81	78	77	72	69	63	61	59	54	49	35	23	15	6	1	0	0

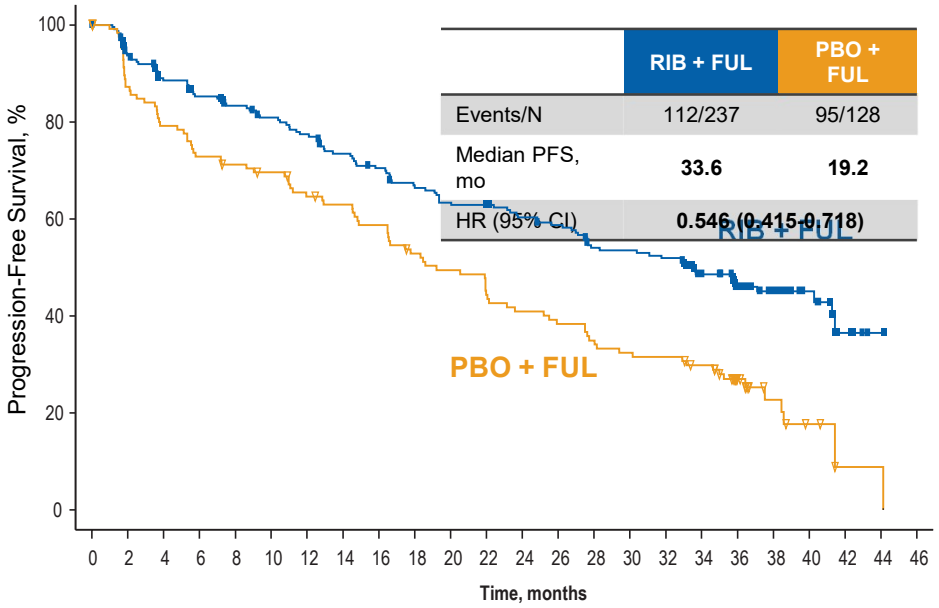
FUL, fulvestrant; HR, hazard ratio; OS, overall survival; PBO, placebo; RIB, ribociclib.
[a] This median value may not be estimated reliably due to the last patient on follow-up, who had an event at 45.1 months.

Slamon NEJM 2020

Progression-Free Survival by Line of Therapy

Median PFS for RIB + FUL is now reached in first line (33.6 months)

First line

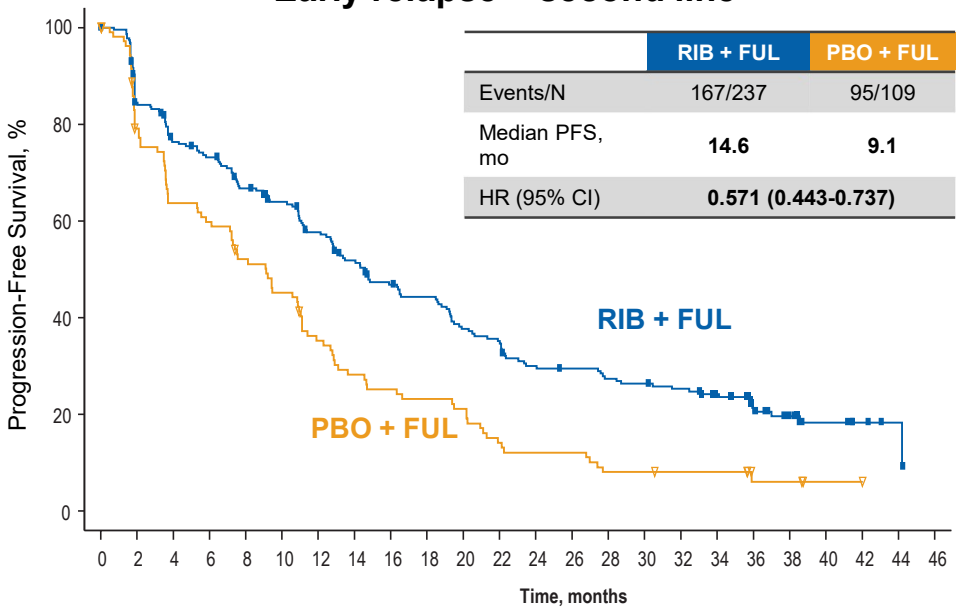


	RIB + FUL	PBO + FUL
Events/N	112/237	95/128
Median PFS, mo	**33.6**	**19.2**
HR (95% CI)	**0.546 (0.415-0.718)**	

No. of patients still at risk

Ribociclib	237	204	187	178	171	164	157	147	140	132	125	123	117	113	102	101	98	84	63	44	20	7	2	0
Placebo	128	109	99	91	88	85	78	75	70	62	58	52	48	45	41	38	37	33	17	9	5	1	1	0

Early relapse + second line



	RIB + FUL	PBO + FUL
Events/N	167/237	95/109
Median PFS, mo	**14.6**	**9.1**
HR (95% CI)	**0.571 (0.443-0.737)**	

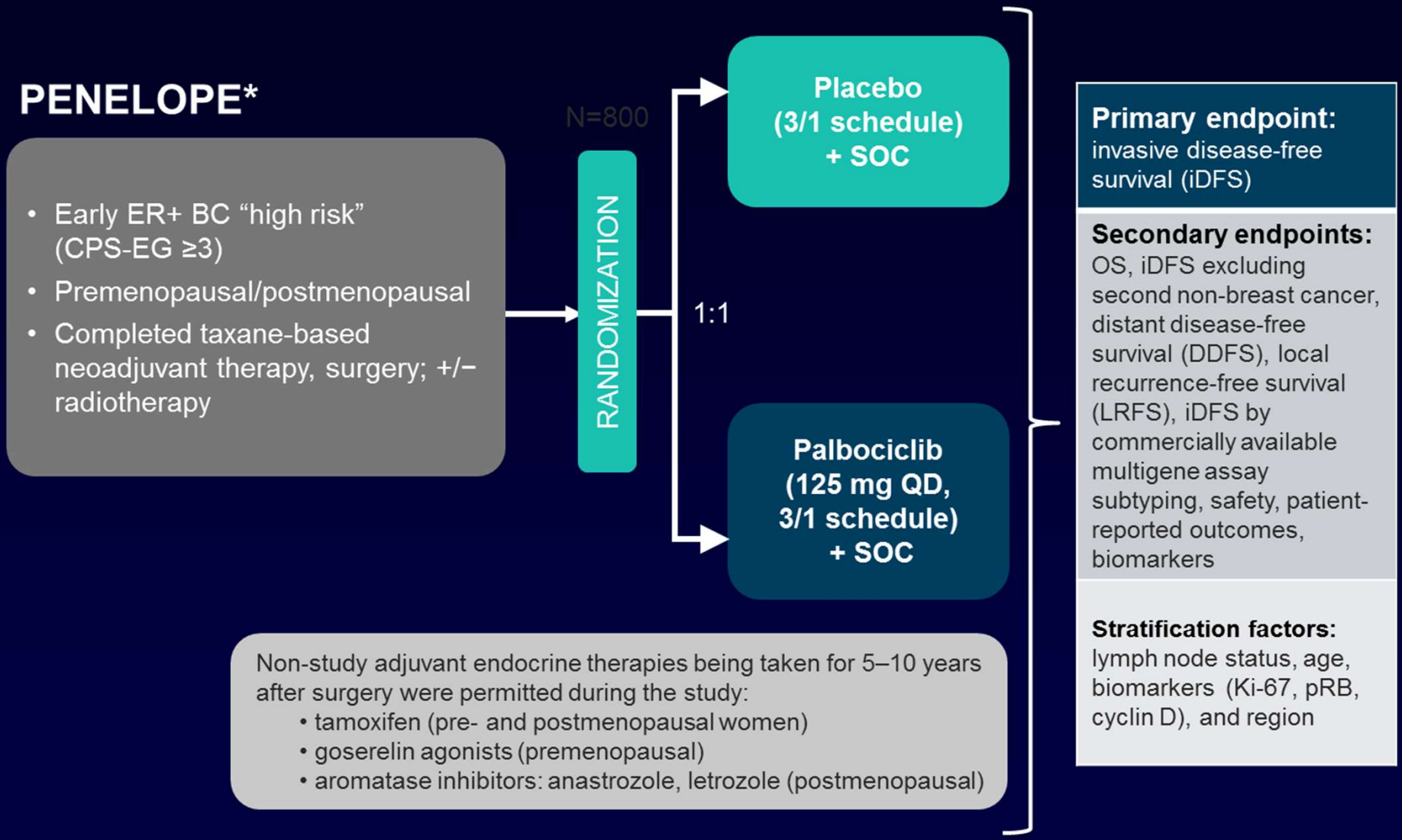
No. of patients still at risk

Ribociclib	237	189	168	160	144	134	119	105	93	87	74	69	58	56	52	50	47	41	27	19	9	4	2	0
Placebo	109	82	66	62	53	46	35	28	25	23	21	14	12	12	8	8	7	7	3	3	1	1	0	0

FUL, fulvestrant; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

Slamon NEJM 2020

Phase 3 Study of Palbociclib in High-risk Early BC: PENELOPE



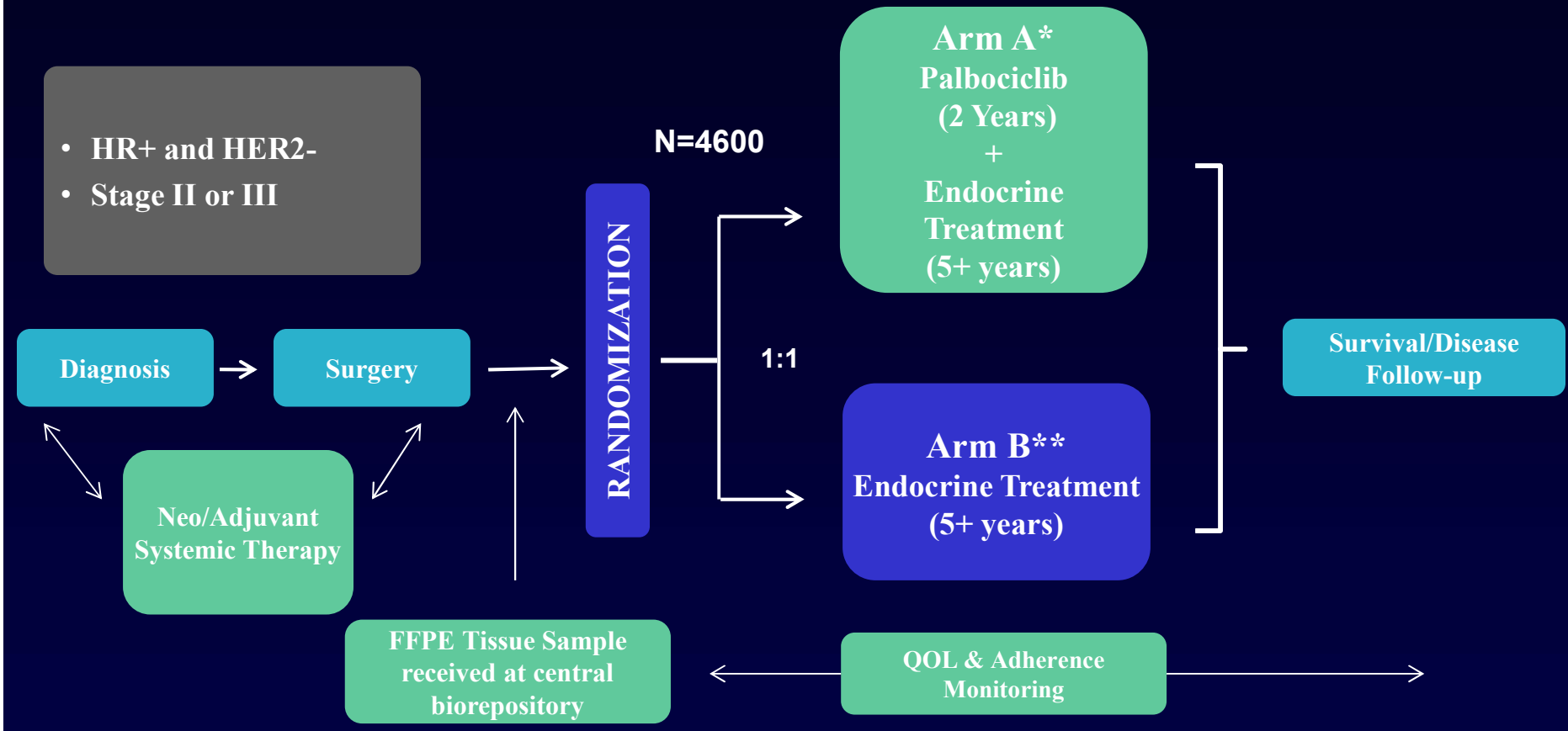
www.clinicaltrials.gov : NCT01864746

* In collaboration with GBG (Germany)

PALbociclib CoLlaborative Adjuvant Study: A Randomized Phase III Trial of Palbociclib With Standard Adjuvant Endocrine Therapy Versus Standard Adjuvant Endocrine Therapy Alone for Hormone Receptor Positive (HR+) / Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Early Breast Cancer (PALLAS)

Phase 3, PALLAS

Sponsor: Alliance for Clinical Trials in Oncology Foundation, ABCSG



*ARM A: palbociclib at a dose of 125 mg once daily, Day 1-21 in a 28-day cycle
**ARM B: standard adjuvant endocrine therapy (AI; tamoxifen)

www.clinicaltrials.gov : NCT02513394

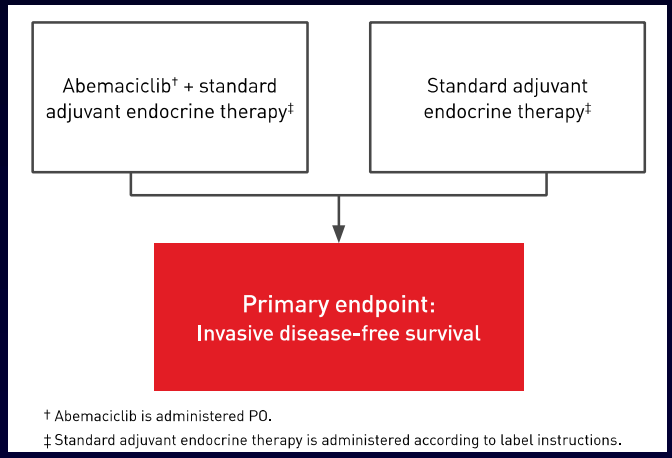
Stratification Factors:

- Pathologic stage (IIA vs IIB/III) or clinical stage if pre-operative therapy was given with the higher stage determining eligibility
- Neo/adjuvant chemotherapy (yes vs. no)
- Age (< 50 vs ≥ 50 years)
- Geographic region (North America vs. Europe vs. Asia)

NCT03155997, I3Y-MC-JPCF, monarchE: A Randomized, Open-Label, Phase 3 Study of Abemaciclib Combined With Standard Adjuvant Endocrine Therapy Versus Standard Adjuvant Endocrine Therapy Alone in Patients With High-Risk, Node-Positive, Early-Stage, Hormone-Receptor-Positive, Human Epidermal Receptor 2-Negative Breast Cancer*

Key Inclusion Criteria

- Hormone-receptor-positive (HR+), HER2-negative, node-positive, early-stage resected invasive breast cancer without evidence of distant metastases
- Underwent definitive surgical treatment for the current malignancy within 16 months of randomization
- Availability of tumor tissue from breast or lymph node for biomarker analysis prior to randomization
- Axillary lymph node involvement by tumor with one of the following:
  - Four or more axillary lymph nodes involved with cancer
  - Tumor size of at least 5 cm
  - Grade 3 histology
  - Ki67 index by central analysis of ≥20%
- Less than 12 weeks of endocrine therapy following the last nonendocrine therapy
- Full recovery from acute effects of chemotherapy and radiotherapy, and surgical side effects following definitive breast surgery
- Female (regardless of menopausal status) or male ≥18 years of age, or per local regulations
- Negative serum or plasma pregnancy status and must agree to use highly effective contraceptive methods
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Able to swallow oral medications



Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT03155997].

*This clinical trial is being conducted globally.

NATALEE Trial Design

NATALEE is a phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with ET as an adjuvant treatment in women and men with HR-positive, HER2-negative EBC

- Pre and postmenopausal women and men
- HR+, HER2 negative
- AJCC 8th Ed. Anatomic Stage:
  - III, or
  - II that is:
    - N1, or
    - N0 (T2-T3) with grade 2-3 and/or Ki67≥20% (excluding G1)
- Completed surgery, radiotherapy and chemotherapy (if indicated)

N≅ 4000

R (1:1)

Investigational

Ribociclib 400 mg/day 3 weeks on, 1 week off (D1-D21 of 28-day cycle), for 36 months

ET for 60 months:
- NSAI (all patients)
- + Goserelin (premenopausal women and men)

Control

ET for 60 months:
- NSAI (all patients)
- + Goserelin (premenopausal women and men)

Follow-up Phase

Stratification factors:
- Menopausal status: premenopausal women and men vs. postmenopausal women
- AJCC 8th edition Anatomic Stage Group: II vs. III
- Prior neo-/adjuvant chemotherapy: yes vs. no
- Geographical region: North America/Western Europe/Oceania vs. rest of the world

Enrollment of Stage II capped at ~ 40%, Stage III at ~60%

TRIO033-TRC-0008 R01

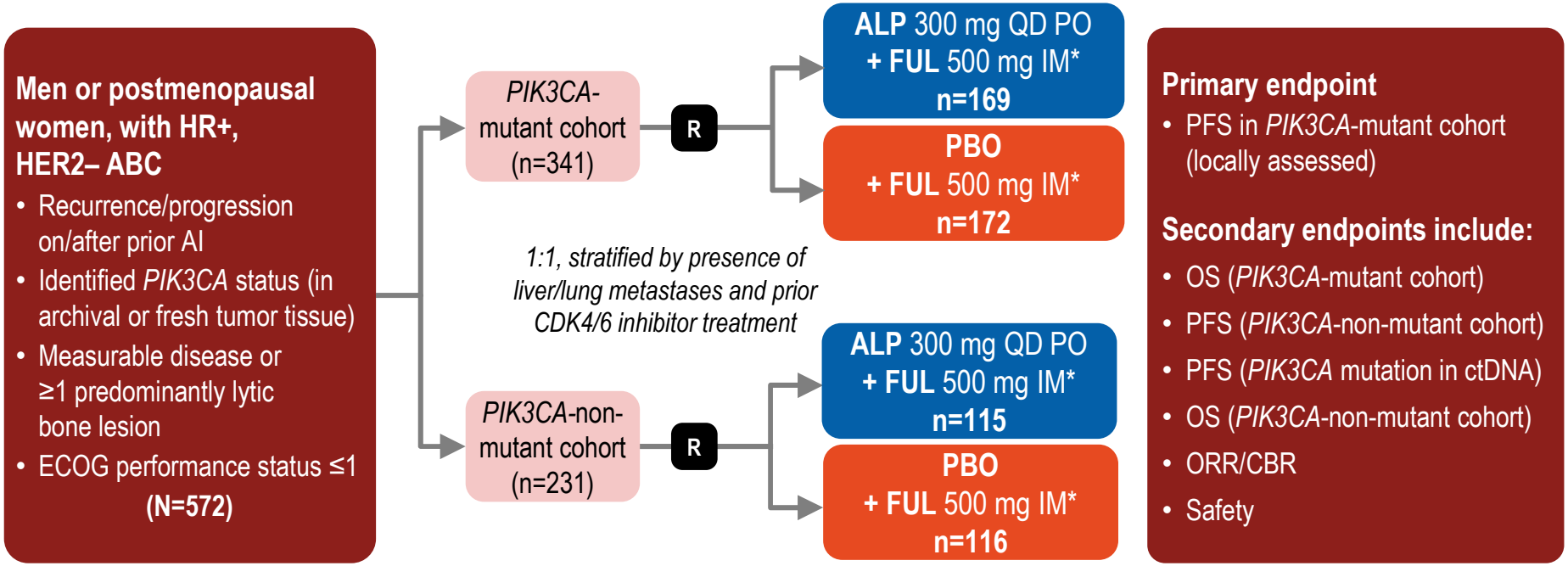
TRIO

Clinical trial information: NCT03701334.

8 Randomized Studies in Advanced ER+/ HER2 Negative Breast Cancer

Study Name	CDK/6 Inhibitor	Combination partner	Phase	N	Hazard ratio	Reference
PALOMA 1/ TRIO18	palbociclib	letrozole	II	165	0.49	Finn et al Lancet Oncology 2015
PALOMA2	palbociclib	letrozole	III	666	0.57	Finn et al NEJM 2016
MONALEESA 2	ribociclib	letrozole	III	668	0.56	Hortobagyi et al NEJM 2016
MONARCH 3	abemaciclib	Letrozole/ anastrazole	III	493	0.54	Goetz et al JCO 2017
MONALEESA 3	ribociclib	tamoxifen/ letrozole/ anastrazole	III	672	0.55	Tripathy et al Lancet Oncology 2018
PALOMA3	palbociclib	fulvestrant	III	521	0.42	Turner et al NEJM 2015
MONARCH 2	abemaciclib	fulvestrant	III	446	0.55	Sledge et al JCO 2017
MONALEESA7	ribociclib	fulvestrant	III	484	0.59	Slamon et al JCO 2018

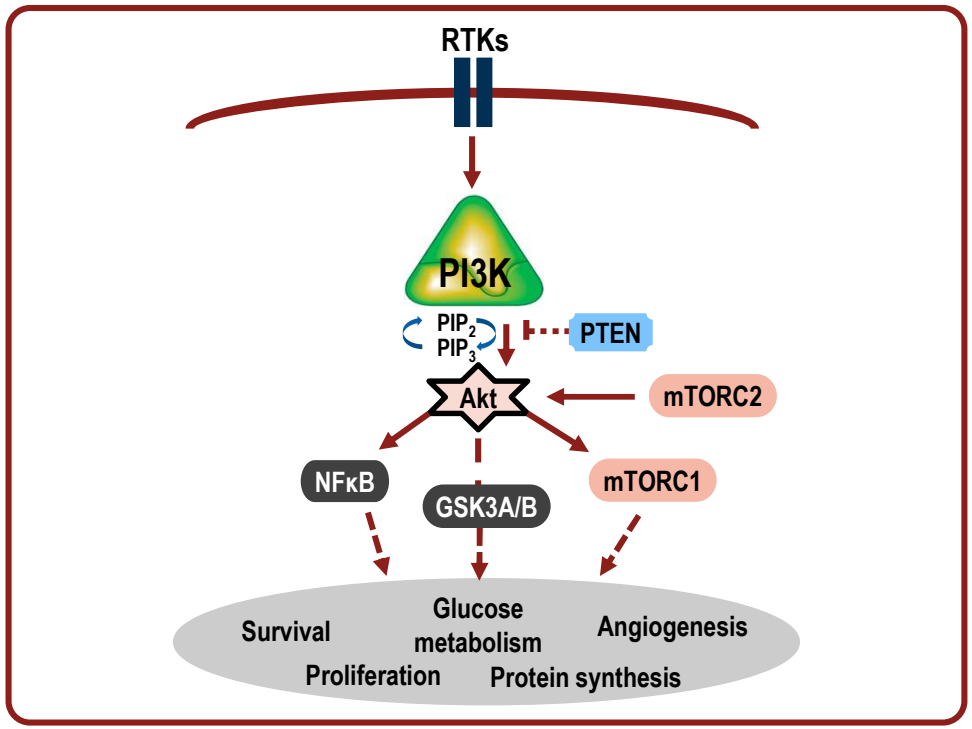
SOLAR-1: A Phase III randomized, controlled trial (NCT02437318)



*Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28 day cycles.

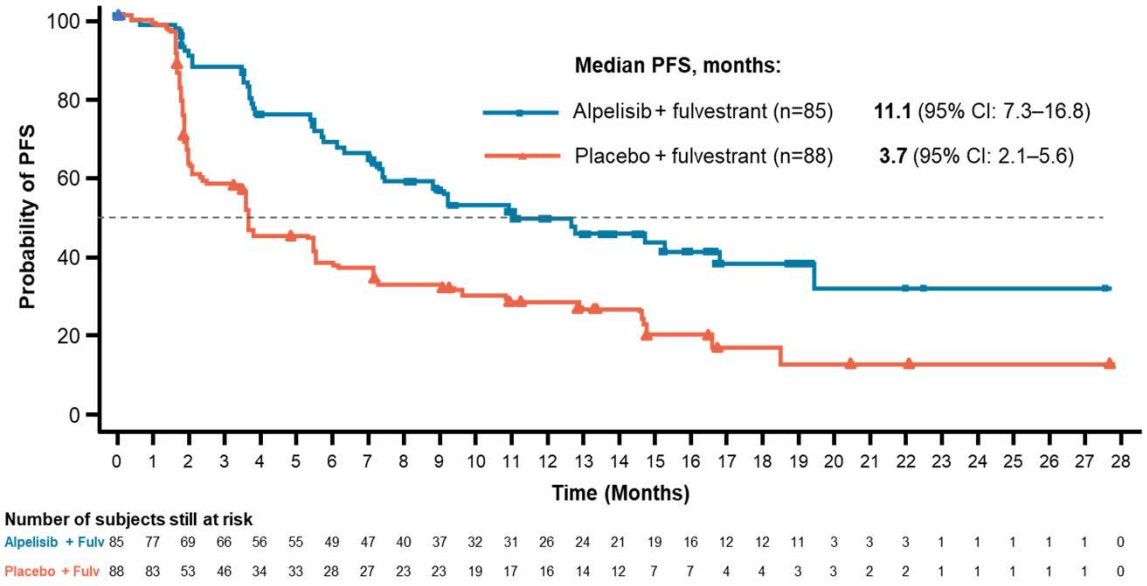
The PI3K pathway

- PI3K is involved in the production of PIP_3, which activates Akt[1]
- PI3K pathway hyperactivation is implicated in malignant transformation, cancer progression and endocrine therapy resistance[1–4]



1. Miller TW, et al. *J Clin Oncol* 2011;29:4452–4461; 2. Saal LH, et al. *Proc Natl Acad Sci U S A* 2007;104:7564–7569; 3. Hosford SR, Miller TW. *Pharmgenomics Pers Med* 2014;7:203–215; 4. Shaw RJ & Cantley LC. *Nature* 2006;441:424–430.

BIRC audit: Centrally assessed PFS in the *PIK3CA*-mutant cohort



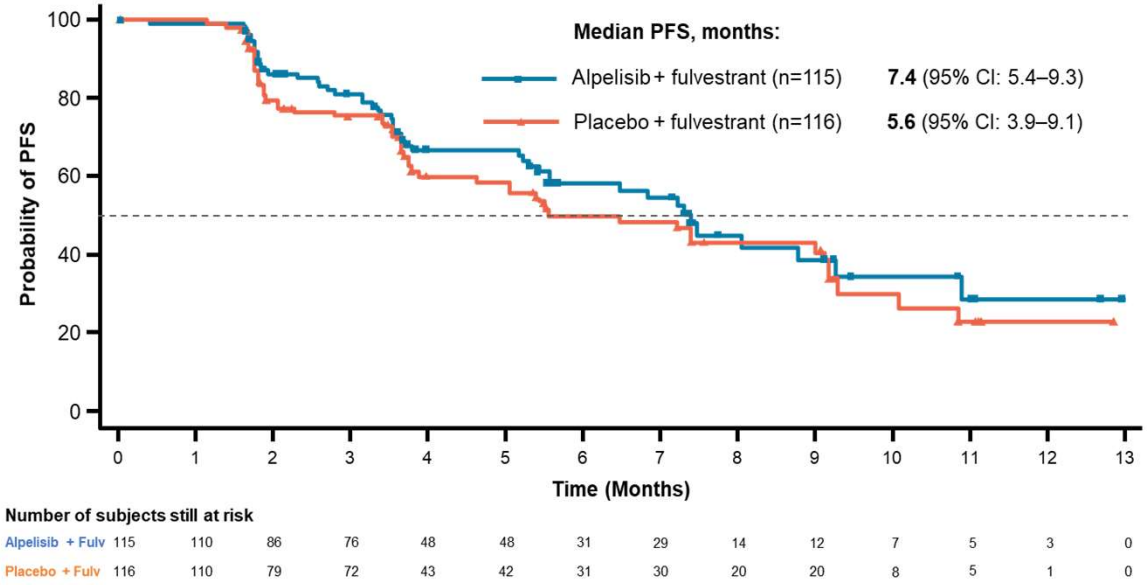
Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=85)	Placebo + fulvestrant (N=88)
Number of PFS events, n (%)	43 (50.6)	63 (71.6)
Median PFS (95% CI)	11.1 (7.3–16.8)	3.7 (2.1–5.6)
HR (95% CI)	0.48 (0.32–0.71)	

- Blinded independent review committee audit of 50% of randomized patients in the *PIK3CA*-mutant cohort (n=173)
- A full BIRC review of all patient data in the *PIK3CA*-mutant cohort was not required, based on prespecified thresholds

BIRC, blinded independent review committee.

Proof of Concept: PFS in the *PIK3CA*-non-mutant cohort

Proof of concept criteria were not met in the PIK3CA-non-mutant cohort



Data cut-off: Dec 23, 2016	Alpelisib + fulvestrant (N=115)	Placebo + fulvestrant (N=116)
Number of PFS events, n (%)	49 (42.6)	57 (49.1)
Progression	47 (40.9)	57 (49.1)
Death	2 (1.7)	0
Censored	66 (57.4)	59 (50.9)
Median PFS (95% CI)	7.4 (5.4–9.3)	5.6 (3.9–9.1)
HR (95% CI)	0.85 (0.58–1.25)	
Posterior probability HR<1, %	79.4	

- Proof of concept criteria: estimated hazard ratio ≤0.60 and posterior probability ≥90% that the hazard ratio was <1
- Patients with *PIK3CA*-non-mutant disease were followed up for safety alongside the *PIK3CA*-mutant cohort

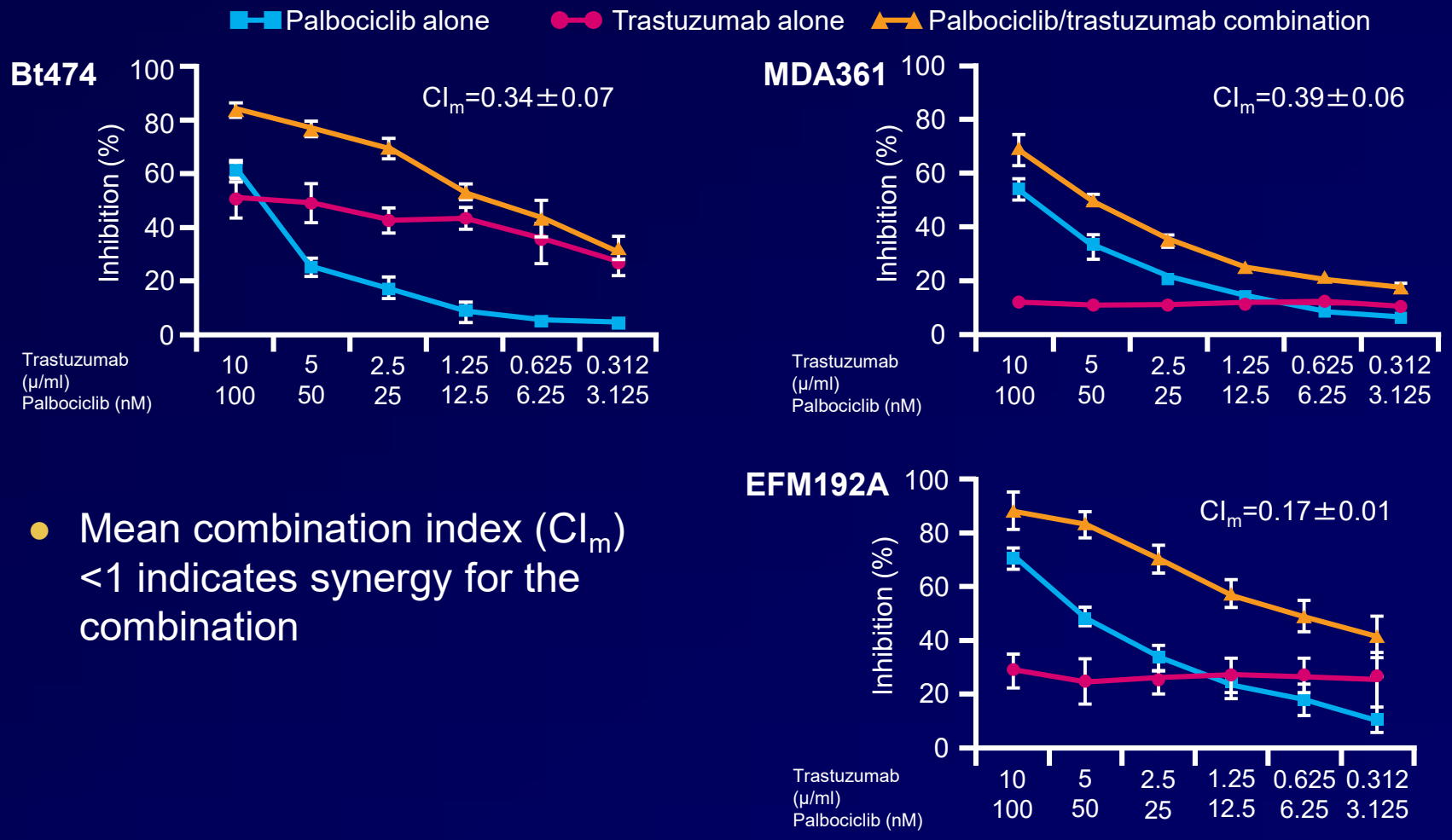
Adverse events in the total population

AEs ≥20% in either arm, %	Alpelisib + fulvestrant N=284			Placebo + fulvestrant N=287		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash*	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

- Eighteen patients (6.3%) discontinued alpelisib due to hyperglycemia and 9 patients (3.2%) due to rash; no patients discontinued placebo due to either hyperglycemia or rash
- Maculopapular rash was observed in 14.1% of patients (all-grade) and 8.8% (grade 3) in the alpelisib arm, vs 1.7% and 0.3%, respectively, in the placebo arm
- The safety profile of the alpelisib group and the placebo group was similar in *PIK3CA*-mutant and *PIK3CA*-non-mutant cohorts

*Single preferred term of "rash" does not include preferred term of "maculopapular rash".

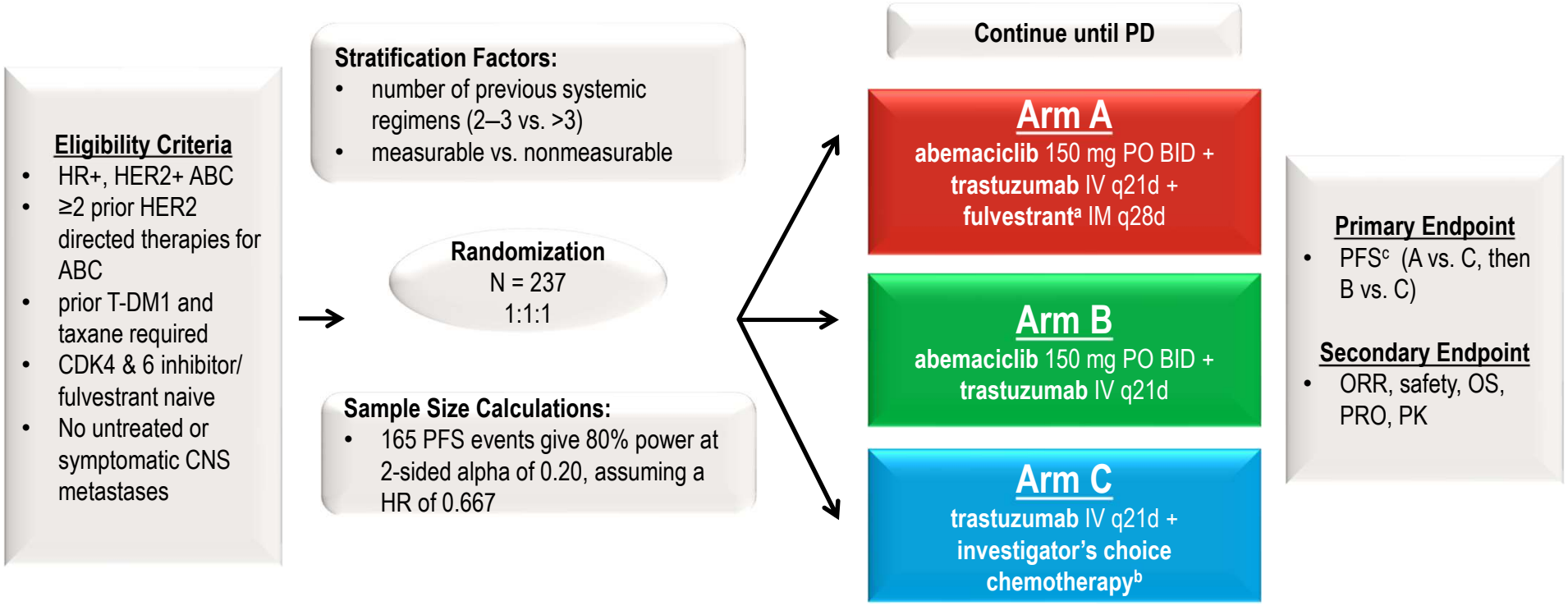
Palbociclib Acts Synergistically with Trastuzumab in HER2+ Breast Cancer Cell Lines



- Mean combination index (CI_m) <1 indicates synergy for the combination

Finn RS, et al. *Breast Cancer Res* 2009;11:R77

monarcHER STUDY DESIGN



Abbreviations: ABC = advanced breast cancer, HR+ = hormone receptor-positive, HER2(+) = human epidermal growth factor receptor-2 (positive), n = number of patients, PD = progressive disease, BID= twice daily, q21d= every 21 days, PFS = Progression Free Survival, ORR = Objective Response Rate, OS = Overall Survival, PRO = Patient Reported Outcomes, PK = pharmacokinetics

[a]Dosing per fulvestrant label

[b]Standard-of-care single-agent chemotherapy should include approved drug in breast cancer.

[c]investigator assessed

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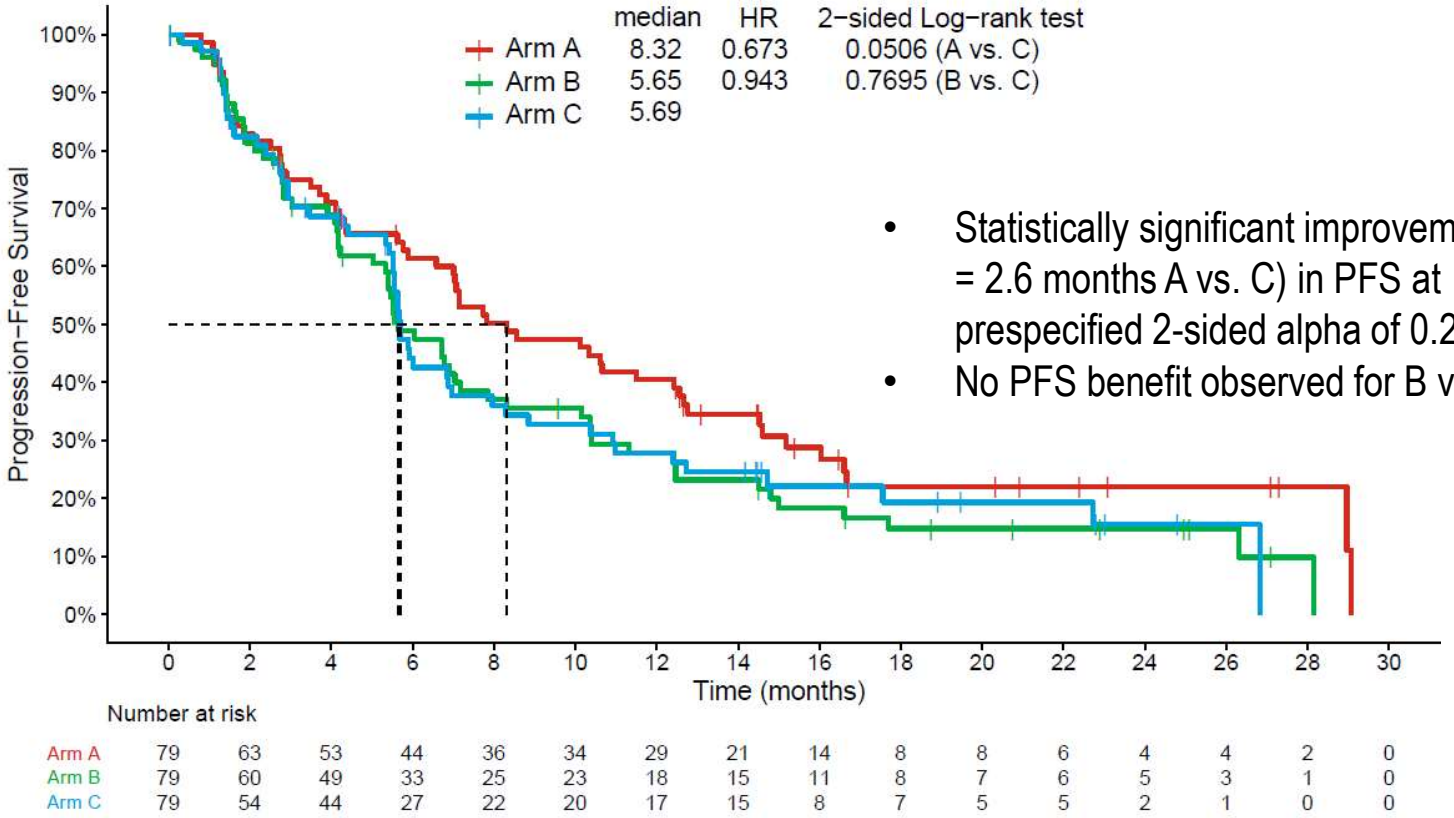
PRIMARY ENDPOINT: PFS

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

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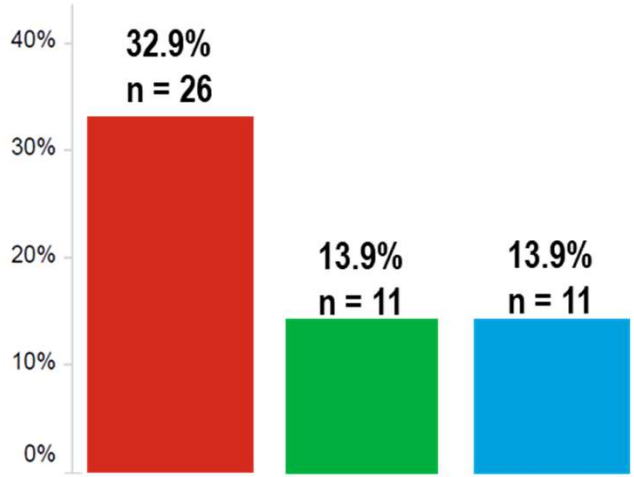
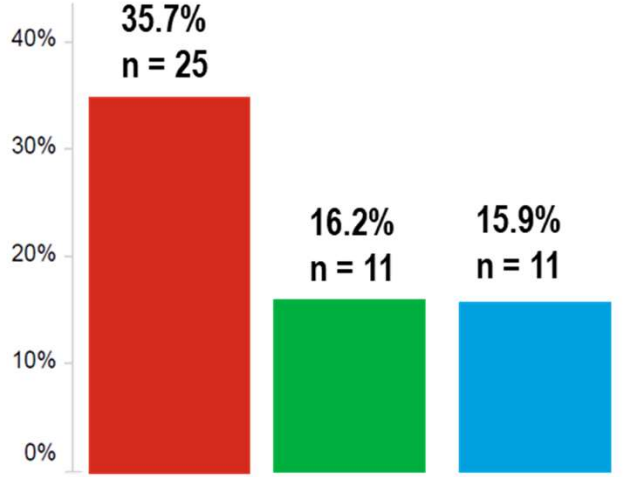
CONFIRMED BEST OVERALL RESPONSE RATE

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



ITT Population
Total N = 237

	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached



Measurable Disease
Total N = 207

	Arm A N=70	Arm B N=68	Arm C N=69
95% CI (%)	(24.5-46.9)	(7.4-24.9)	(7.3-24.6)
Stratified 2-sided p-value (vs Arm C)	0.0111	1.0000	-
Duration of Response, months	10.4	9.5	not reached

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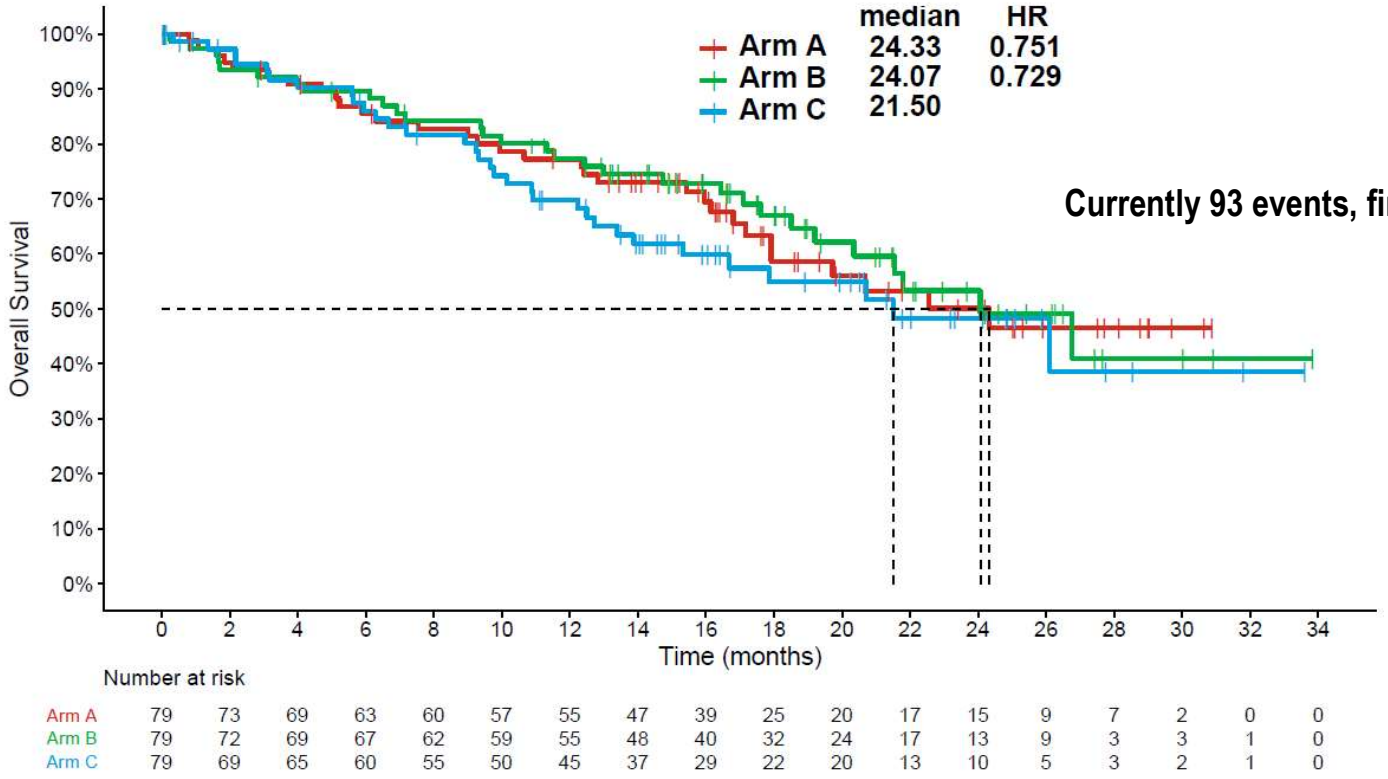
OVERALL SURVIVAL: EXPLORATORY ANALYSIS*

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



Currently 93 events, final at 158 (expected 2021)

* Pre-specified criteria for formal testing not met

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Conclusions:

- The development of CDK 4/6 inhibitors has changed the management of advanced ER+/ HER2 negative breast cancer
  - Consistent benefit across various clinical and pathologic subgroups
  - Role in early stage breast cancer and other subtypes is to be determined
  - Mechanisms of resistance and how to manage them is being studied
- Impact of PI3-kinase inhibitors is yet to be determined in the setting of prior CDK 4/6 inhibitor
- These drugs are improving OS for this group of patients

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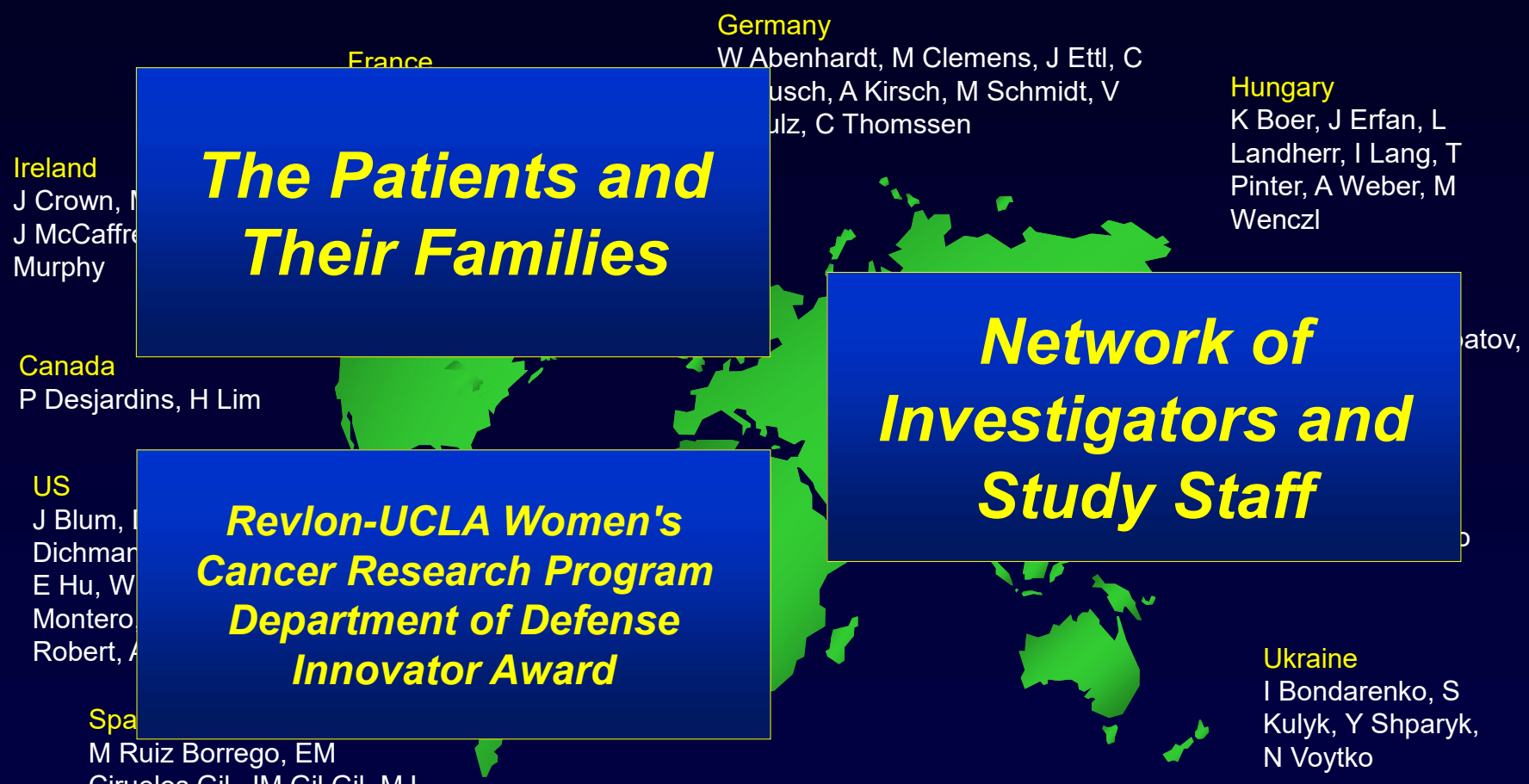

The Patients and Their Families

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Patients and their Families
that Participate in these studies