I EDIZIONE

BREAST talk

20 MAGGIO
2021
ORE 15.00 - 18.00

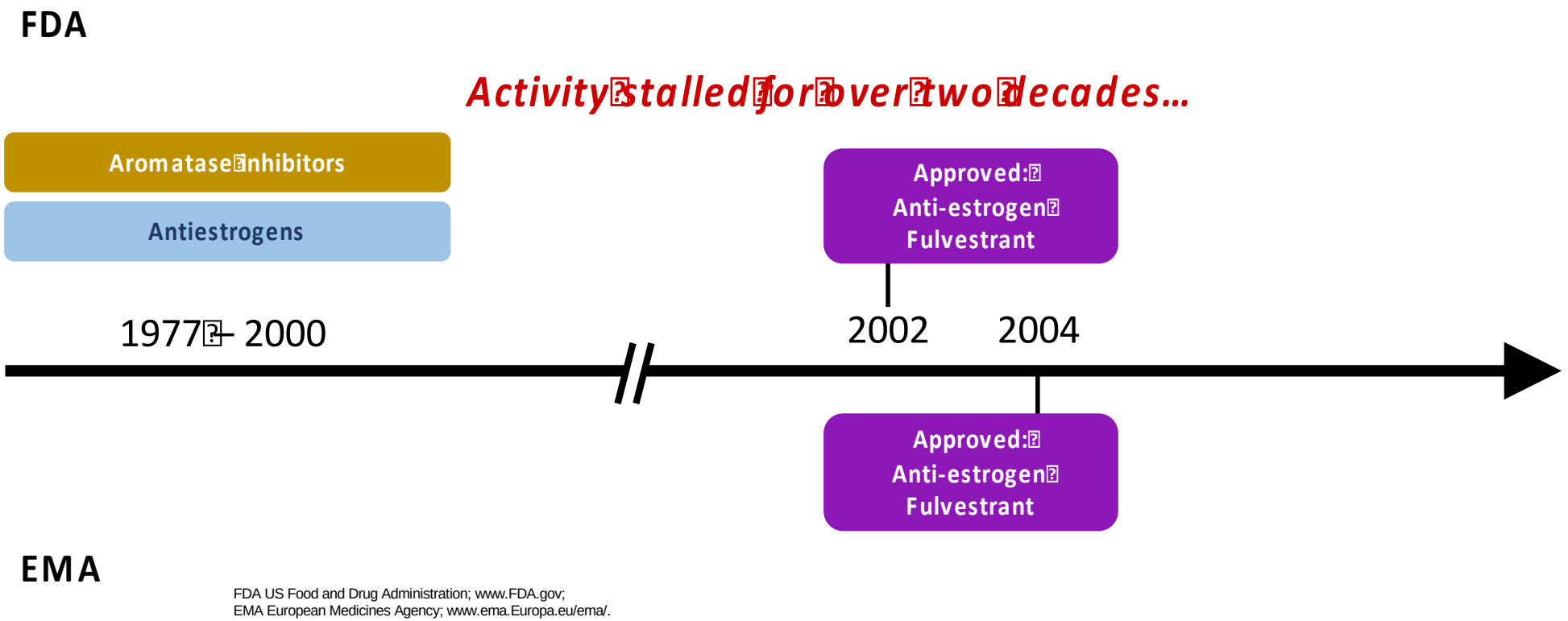
mBC HR+/Her2
Update dagli studi clinici

Mario Giuliano

Università Federico II

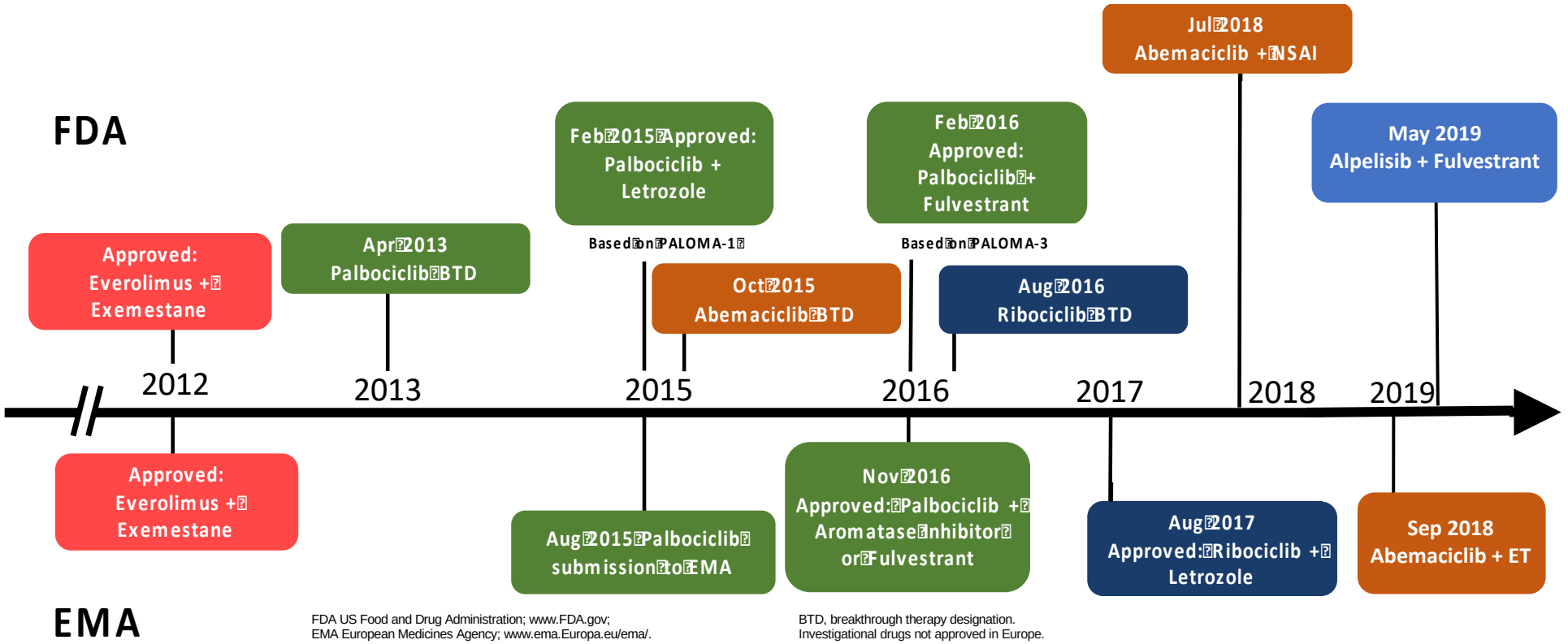
Napoli

Drugs approved for the management of HR+/HER2– MBC



FDA US Food and Drug Administration; www.FDA.gov;
EMA European Medicines Agency; www.ema.Europa.eu/ema/.

Drugs approved for the management of HR+/HER2– MBC

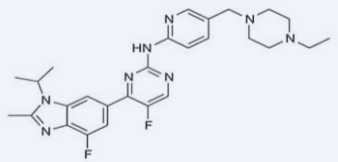


FDA US Food and Drug Administration; www.FDA.gov;
EMA European Medicines Agency; www.ema.Europa.eu/ema/.

BTD, breakthrough therapy designation.
Investigational drugs not approved in Europe.

Pivotal phase III trials with CDK4/6 inhibitors

Abemaciclib

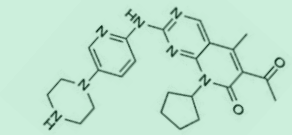


MONARCH Program

MONARCH-3 — Endocrine-sensitive — R 2:1 → Abemaciclib + NSAI / Placebo + NSAI

MONARCH-2 — Endocrine-resistance (ACQUIRED) Endocrine-resistance (PRIMARY) — R 2:1 → Abemaciclib + Fulvestrant / Placebo + Fulvestrant

Palbobociclib

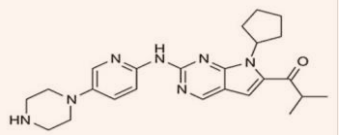


PALOMA Program

PALOMA-2 — Endocrine-sensitive — R 2:1 → Palbociclib + letrozole / Placebo + letrozole

PALOMA-3 — Endocrine-resistance (ACQUIRED) Endocrine-resistance (PRIMARY) — R 1:1 → Palbociclib + fulvestrant / Placebo + fulvestrant

Ribociclib



MONALEESA Program

MONALEESA-2 — Endocrine-sensitive — R 1:1 → Ribociclib + letrozole / Placebo + letrozole

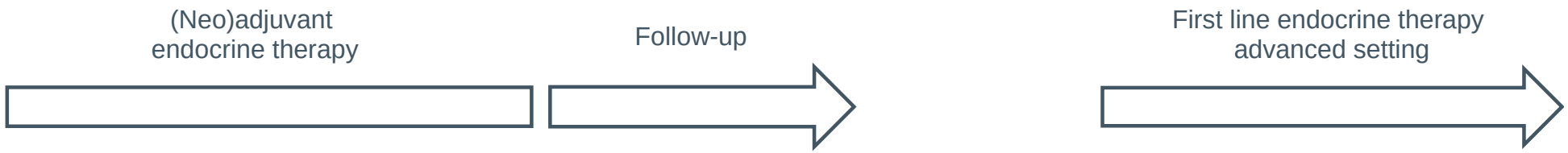
MONALEESA-3 — Endocrine-sensitive Endocrine-resistance (ACQUIRED) Endocrine-resistance (PRIMARY) — R 2:1 → Ribociclib + Fulvestrant / Placebo + Fulvestrant

MONALEESA-7 — Endocrine-sensitive Endocrine-resistance (ACQUIRED) Endocrine-resistance (PRIMARY) — R 1:1 → Ribociclib + NSAI/TAM + GOS / Placebo + + NSAI/TAM + GOS

Overall 4415 patients with HR+/HER2- MBC enrolled in pivotal trials

1. Finn RS, et al. *Lancet Oncol.* 2015 2. Finn RS, et al. N Engl J Med. 2016 3. G.N. Hortobagyi et al, NEJM 2016 4. Goetzet a. JCO 2017 5. Slamon et al, JCO 2018 6. Tripathy D, et al. Lancet Oncol. 2018

ER+/HER2- mBC is heterogeneous according to endocrine resistance

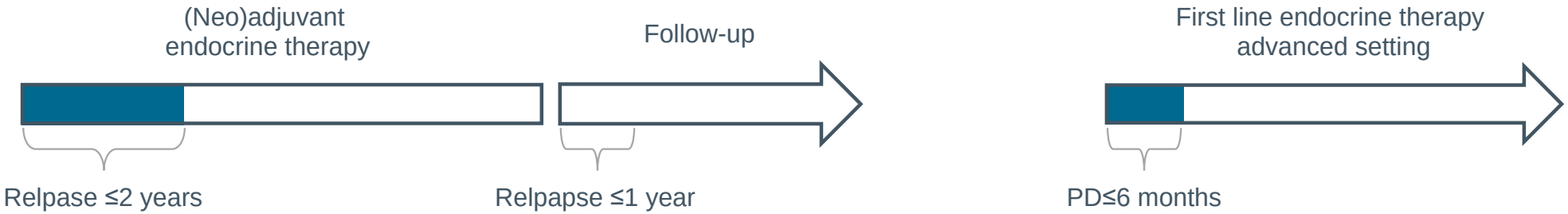


Cardoso F Ann Oncol 2014; Cardoso F Breast 2014;
Cardoso F et al. Ann Oncol 2017;
Cardoso F Ann Oncol 2018

ER+/HER2- mBC is heterogeneous according to endocrine resistance

ENDOCRINE RESISTANCE

PRIMARY



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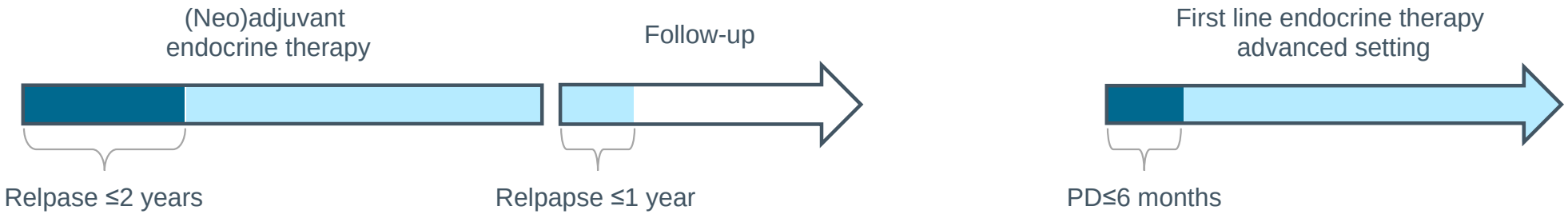
ER+/HER2- mBC is heterogeneous according to endocrine resistance

ENDOCRINE RESISTANCE

PRIMARY | **SECONDARY (ACQUIRED)**



Cardoso F Ann Oncol 2014; Cardoso F Breast 2014;
Cardoso F et al. Ann Oncol 2017;
Cardoso F Ann Oncol 2018

ER+/HER2- mBC is heterogeneous according to endocrine resistance

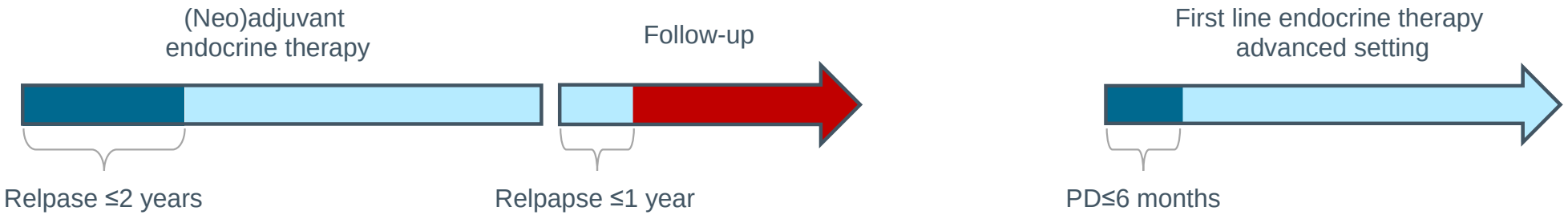
ENDOCRINE RESISTANCE

PRIMARY

SECONDARY (ACQUIRED)

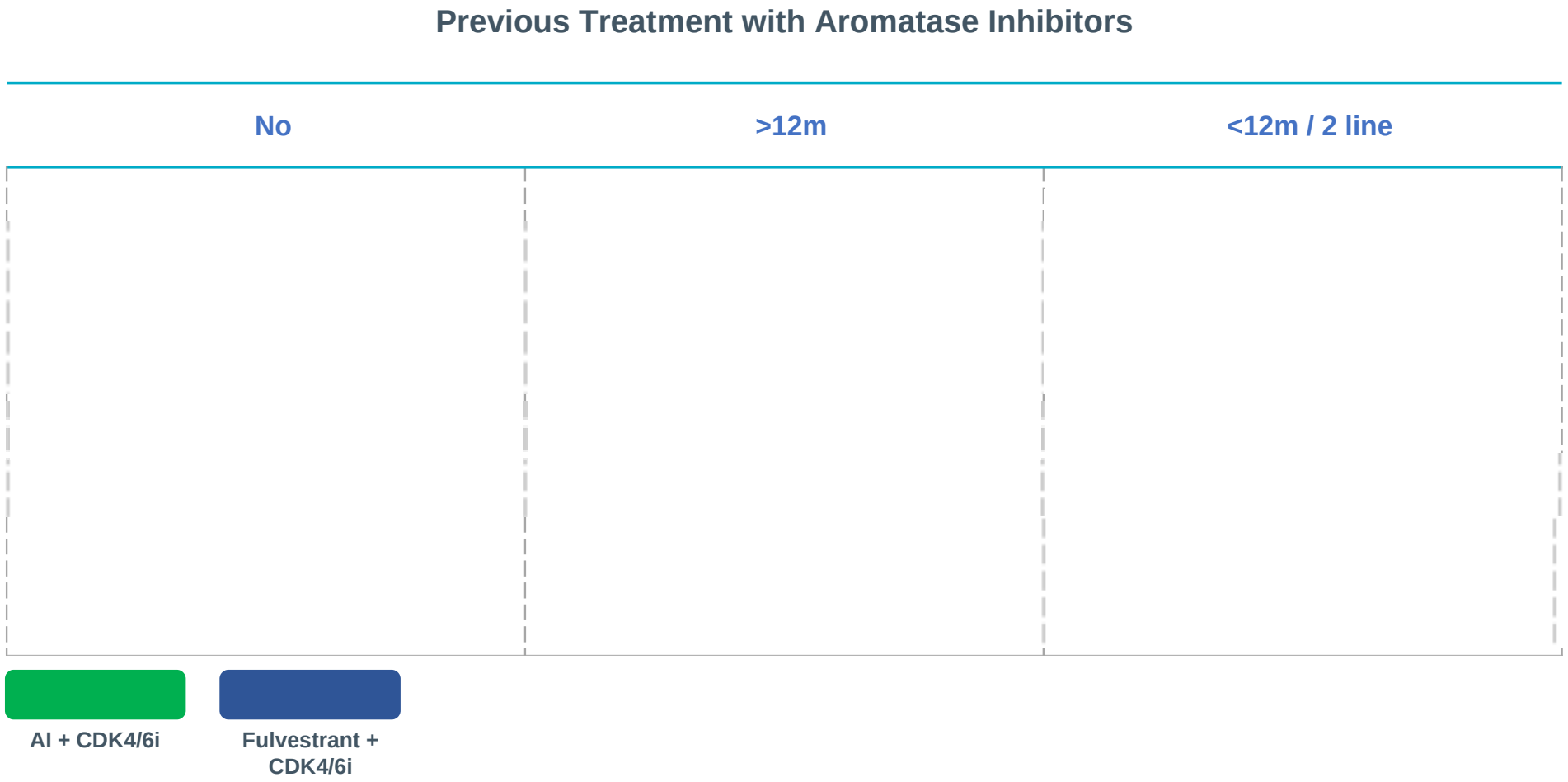
ENDOCRINE SENSITIVE

+ De Novo disease



Cardoso F Ann Oncol 2014; Cardoso F Breast 2014;
Cardoso F et al. Ann Oncol 2017;
Cardoso F Ann Oncol 2018

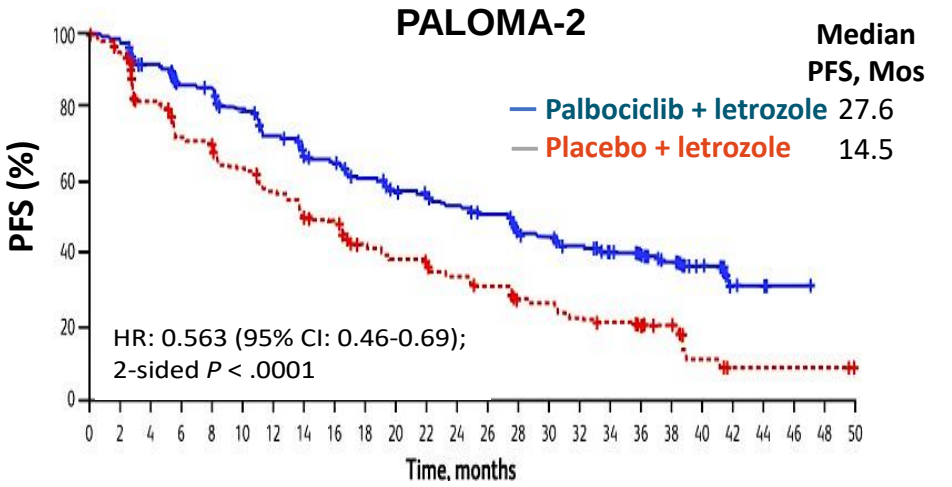
Differences across CDK4/6 inhibitors trials

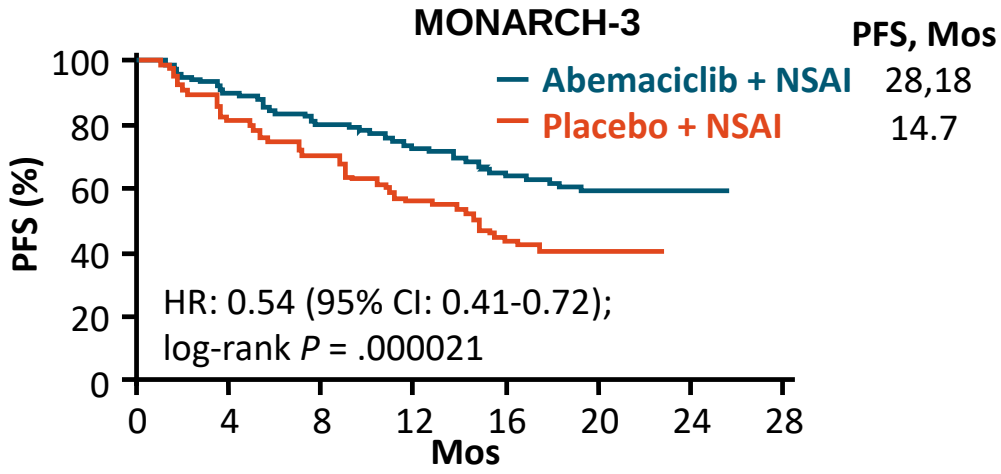


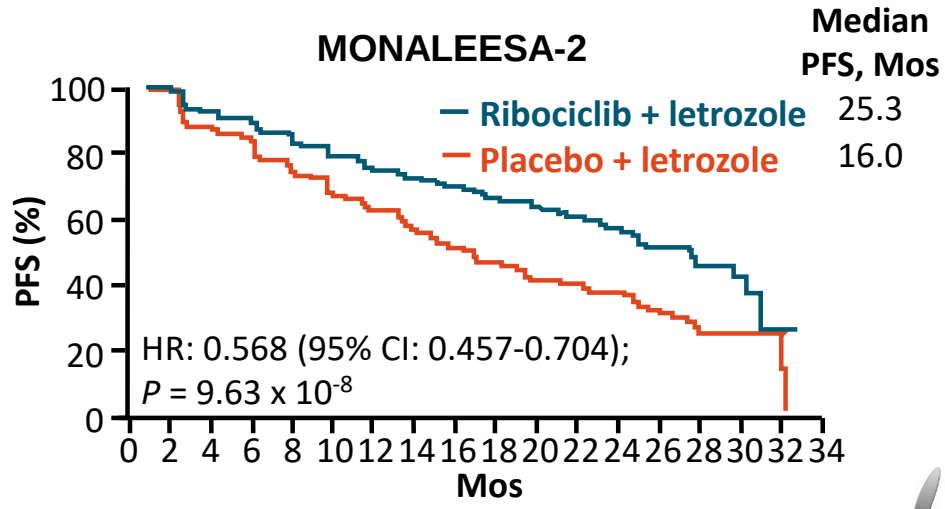
[1]Finn, et al. *N Engl J Med.* 2016. 375:1925-1936; [2]Goetz, et al. *J Clin Oncol.* 2017. 35:3638-3646; [3]Hortobagyi, et al. *N Engl J Med.* 2016. 375:1738-1748; [4]Tripathy, et al. *Lancet Oncol.* 2018; 19: 904–15; [5]Slamon, et al. *J Clin Oncol.* 2018. 36:2465-2472; [6]Sledge, et al. J Clin Oncol. 2017. 35:2875-2884; [7]Cristofanilli, et al. *Lancet Oncol.* 2016. 17: 425–39.

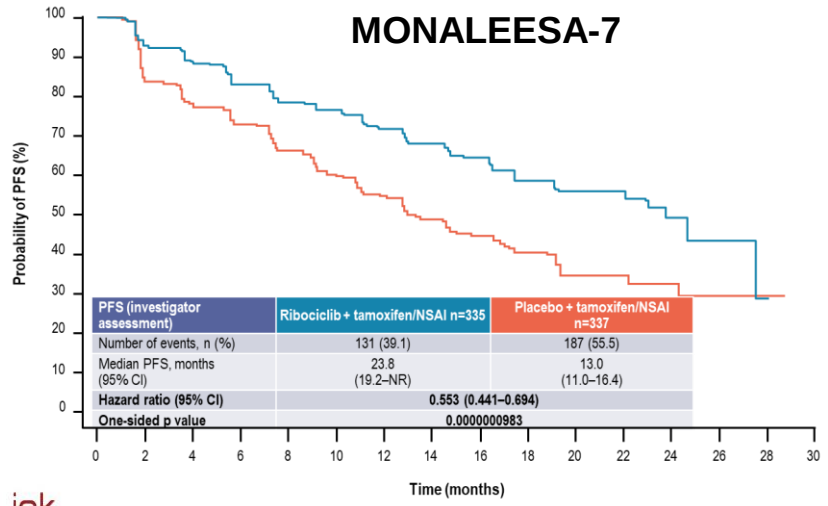
KLink profitablesolutions

1st line Trials: Updated PFS





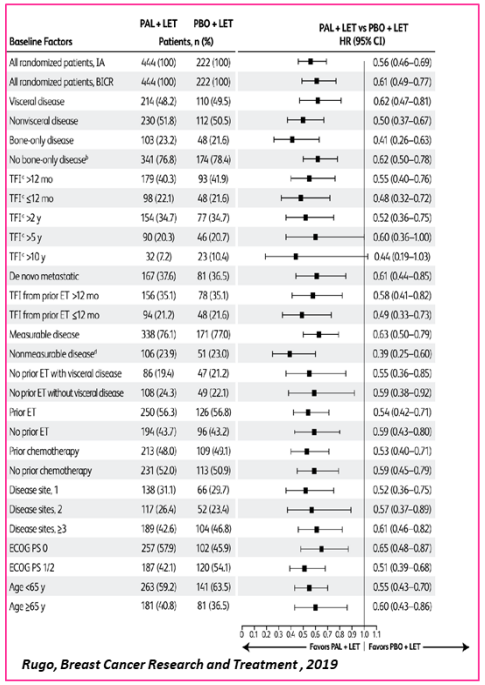




Rugo H et al, BCRT 2019; Hortobagyi GN et al, Ann Oncol 2018;
Johnston S et al, NPJ Breast Cancer 2019; 1.
Tripathy D et al SABCS17 oral presentation Abstract GS2-05 2. Tripathy D. et al. Lancet Oncol. 2018 Jul;19(**7**):904-915

PFS benefit in 1st line trials across patient subgroups

PALOMA-2



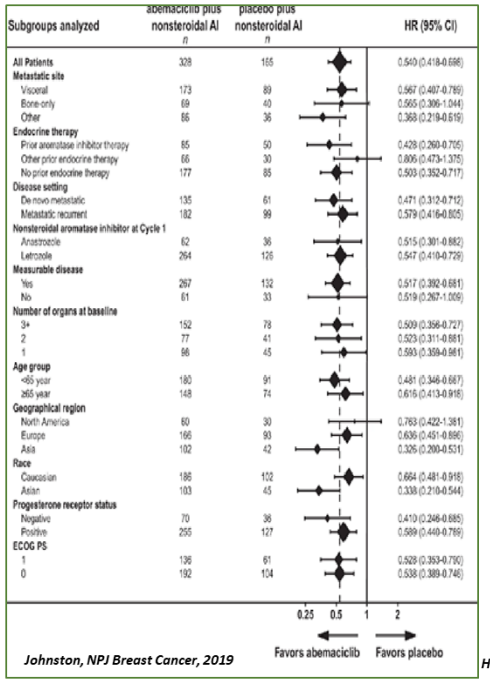
Baseline Factors	PAL + LET Patients, n (%)	PBO + LET Patients, n (%)	PAL + LET vs PBO + LET HR (95% CI)
All randomized patients, IA	444 (100)	222 (100)	0.56 (0.46–0.69)
All randomized patients, BICR	444 (100)	222 (100)	0.61 (0.49–0.77)
Visceral disease	214 (48.2)	110 (49.5)	0.62 (0.47–0.81)
Nonvisceral disease	230 (51.8)	112 (50.5)	0.50 (0.37–0.67)
Bone-only disease	103 (23.2)	48 (21.6)	0.41 (0.26–0.63)
No bone-only disease[3]	341 (76.8)	174 (78.4)	0.62 (0.50–0.78)
TFI[4] >12 mo	179 (40.3)	93 (41.9)	0.55 (0.40–0.76)
TFI[4] ≤12 mo	98 (22.1)	48 (21.6)	0.48 (0.32–0.72)
TFI[4] >2 y	154 (34.7)	77 (34.7)	0.52 (0.36–0.75)
TFI[4] >5 y	90 (20.3)	46 (20.7)	0.60 (0.36–1.00)
TFI[4] >10 y	32 (7.2)	23 (10.4)	0.44 (0.19–1.03)
De novo metastatic	167 (37.6)	81 (36.5)	0.61 (0.44–0.85)
TFI from prior ET >12 mo	156 (35.1)	78 (35.1)	0.58 (0.41–0.82)
TFI from prior ET ≤12 mo	94 (21.2)	48 (21.6)	0.49 (0.33–0.73)
Measurable disease	338 (76.1)	171 (77.0)	0.63 (0.50–0.79)
Nonmeasurable disease[5]	106 (23.9)	51 (23.0)	0.39 (0.25–0.60)
No prior ET with visceral disease	86 (19.4)	47 (21.2)	0.55 (0.36–0.85)
No prior ET without visceral disease	108 (24.3)	49 (22.1)	0.59 (0.38–0.92)
Prior ET	250 (56.3)	126 (56.8)	0.54 (0.42–0.71)
No prior ET	194 (43.7)	96 (43.2)	0.59 (0.43–0.80)
Prior chemotherapy	213 (48.0)	109 (49.1)	0.53 (0.40–0.71)
No prior chemotherapy	231 (52.0)	113 (50.9)	0.59 (0.45–0.79)
Disease site, 1	138 (31.1)	66 (29.7)	0.52 (0.36–0.75)
Disease sites, 2	117 (26.4)	52 (23.4)	0.57 (0.37–0.89)
Disease sites, ≥3	189 (42.6)	104 (46.8)	0.61 (0.46–0.82)
ECOG PS 0	257 (57.9)	102 (45.9)	0.65 (0.48–0.87)
ECOG PS 1/2	187 (42.1)	120 (54.1)	0.51 (0.39–0.68)
Age <65 y	263 (59.2)	141 (63.5)	0.55 (0.43–0.70)
Age ≥65 y	181 (40.8)	81 (36.5)	0.60 (0.43–0.86)

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1

Favors PAL + LET | Favors PBO + LET

Rugo, Breast Cancer Research and Treatment , 2019

MONARCH 3



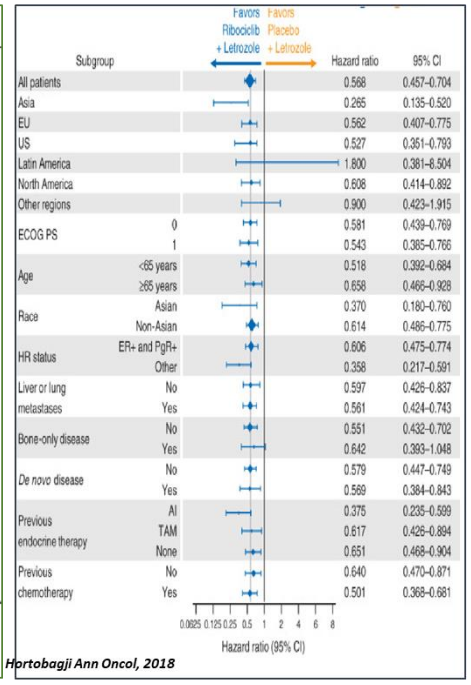
Subgroups analyzed	abemaciclib plus nonsteroidal AI n	placebo plus nonsteroidal AI n	HR (95% CI)
All Patients	328	165	0.540 (0.418-0.698)
Metastatic site			
Visceral	173	89	0.567 (0.407-0.789)
Bone-only	69	40	0.565 (0.306-1.044)
Other	86	36	0.368 (0.219-0.619)
Endocrine therapy			
Prior aromatase inhibitor therapy	85	50	0.428 (0.260-0.705)
Other prior endocrine therapy	66	30	0.806 (0.473-1.375)
No prior endocrine therapy	177	85	0.503 (0.352-0.717)
Disease setting			
De novo metastatic	135	61	0.471 (0.312-0.712)
Metastatic recurrent	182	99	0.579 (0.416-0.805)
Nonsteroidal aromatase inhibitor at Cycle 1			
Anastrozole	62	36	0.515 (0.301-0.882)
Letrozole	264	126	0.547 (0.410-0.729)
Measurable disease			
Yes	267	132	0.517 (0.392-0.681)
No	61	33	0.519 (0.267-1.009)
Number of organs at baseline			
3+	152	78	0.509 (0.356-0.727)
2	77	41	0.523 (0.311-0.881)
1	98	45	0.593 (0.359-0.981)
Age group			
<65 year	180	91	0.481 (0.346-0.667)
≥65 year	148	74	0.615 (0.413-0.916)
Geographical region			
North America	60	30	0.783 (0.422-1.381)
Europe	166	93	0.636 (0.451-0.896)
Asia	102	42	0.326 (0.200-0.531)
Race			
Caucasian	186	102	0.664 (0.481-0.918)
Asian	103	45	0.338 (0.210-0.544)
Progesterone receptor status			
Negative	70	36	0.410 (0.248-0.685)
Positive	255	127	0.589 (0.440-0.789)
ECOG PS			
1	136	61	0.528 (0.353-0.790)
0	192	104	0.538 (0.389-0.746)

0.25 0.5 1 2

Favors abemaciclib | Favors placebo

Johnston, NPJ Breast Cancer, 2019

MONALEESA-2



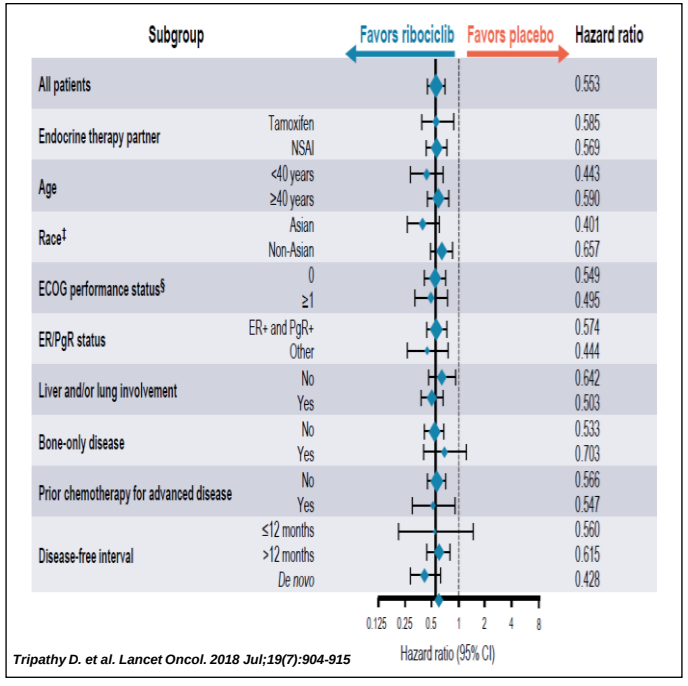
Subgroup		Favors Ribociclib + Letrozole	Favors Placebo + Letrozole	Hazard ratio	95% CI
All patients				0.568	0.457–0.704
Asia				0.265	0.135–0.520
EU				0.562	0.407–0.775
US				0.527	0.351–0.793
Latin America				1.800	0.381–8.504
North America				0.608	0.414–0.892
Other regions				0.900	0.423–1.915
ECOG PS	0			0.581	0.439–0.769
	1			0.543	0.385–0.766
Age	<65 years			0.518	0.392–0.684
	≥65 years			0.658	0.466–0.928
Race	Asian			0.370	0.180–0.760
	Non-Asian			0.614	0.486–0.775
HR status	ER+ and PgR+			0.606	0.475–0.774
	Other			0.358	0.217–0.591
Liver or lung metastases	No			0.597	0.426–0.837
	Yes			0.561	0.424–0.743
Bone-only disease	No			0.551	0.432–0.702
	Yes			0.642	0.393–1.048
De novo disease	No			0.579	0.447–0.749
	Yes			0.569	0.384–0.843
Previous endocrine therapy	AI			0.375	0.235–0.599
	TAM			0.617	0.426–0.894
	None			0.651	0.468–0.904
Previous chemotherapy	No			0.640	0.470–0.871
	Yes			0.501	0.368–0.681

0.0625 0.125 0.25 0.5 1 2 4 6 8

Hazard ratio (95% CI)

Hortobagji Ann Oncol, 2018

MONALEESA-7



Subgroup		Favors ribociclib	Favors placebo	Hazard ratio
All patients				0.553
Endocrine therapy partner	Tamoxifen			0.585
	NSAI			0.569
Age	<40 years			0.443
	≥40 years			0.590
Race‡	Asian			0.401
	Non-Asian			0.657
ECOG performance status§	0			0.549
	≥1			0.495
ER/PgR status	ER+ and PgR+			0.574
	Other			0.444
Liver and/or lung involvement	No			0.642
	Yes			0.503
Bone-only disease	No			0.533
	Yes			0.703
Prior chemotherapy for advanced disease	No			0.566
	Yes			0.547
Disease-free interval	≤12 months			0.560
	>12 months			0.615
	De novo			0.428

0.125 0.25 0.5 1 2 4 8

Hazard ratio (95% CI)

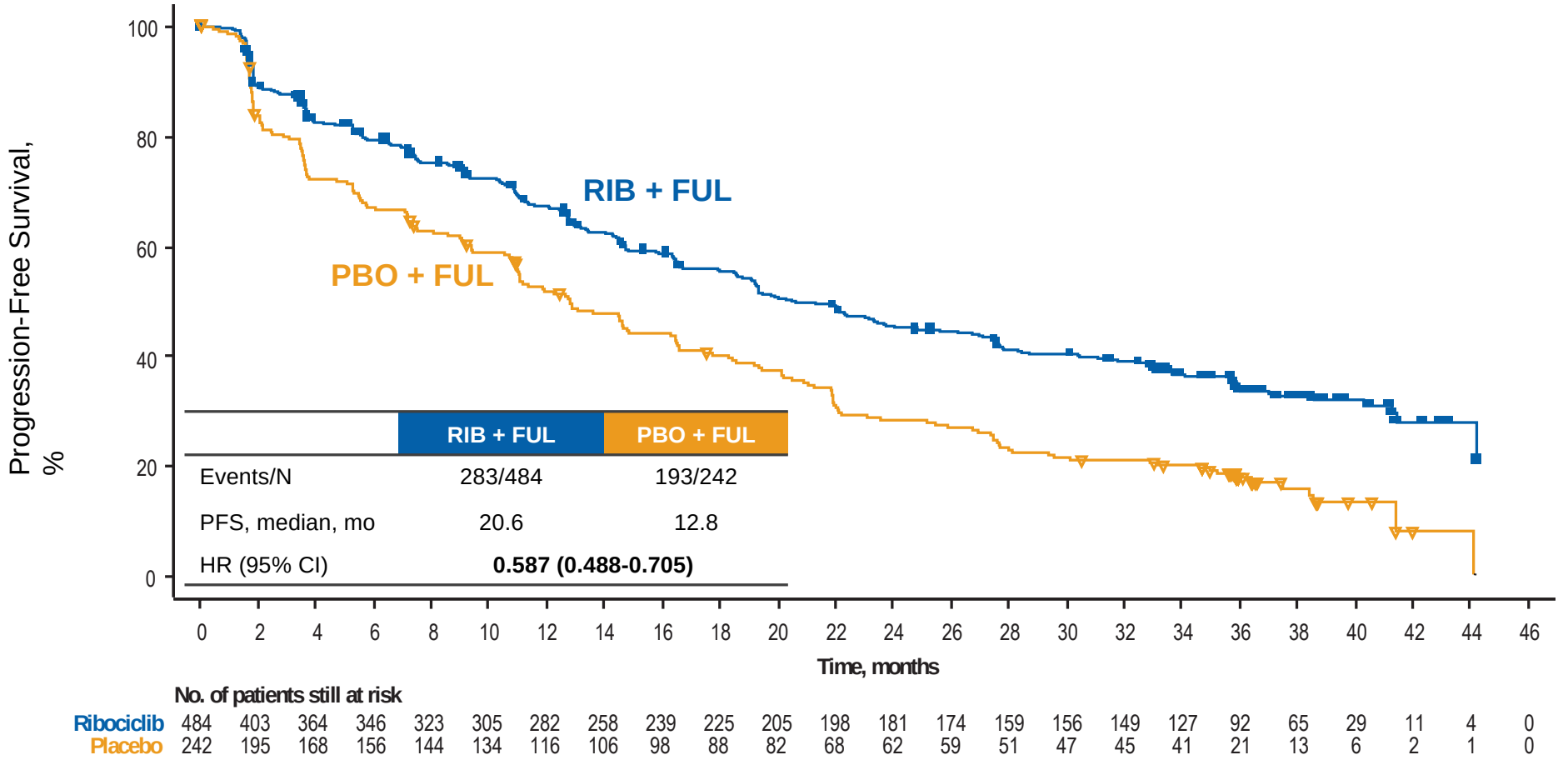
Tripathy D. et al. Lancet Oncol. 2018 Jul;19(7):904-915

Different populations across CDK4/6 inhibitors trials

Study	Line	Sensitivity	Primary ET resistance	Secondary ET resistance
PALOMA-2[1]	1st	▯ 100%		
MONARCH-3[2]	1st	▯ 100%		
MONALEESA-2[3]	1st	▯ 100%		
MONALEESA-7[4]	1st	▯ 70%		▯ 30%
MONALEESA-3[5]	1st & 2nd	▯ 50%	▯ 50% (% of pts with secondary resistance not provided)	
MONARCH-2[6]	2nd		▯ 25%	▯ 75%
PALOMA-3[7]	2nd		▯ 21%	▯ 79%

[1]Finn, et al. *N Engl J Med.* 2016. 375:1925-1936; [2]Goetz, et al. *J Clin Oncol.* 2017. 35:3638-3646; [3]Hortobagyi, et al. *N Engl J Med.* 2016. 375:1738-1748; [4]Tripathy, et al. *Lancet Oncol.* 2018; 19: 904–15; [5]Slamon, et al. *J Clin Oncol.* 2018. 36:2465-2472; [6]Sledge, et al. J Clin Oncol. 2017. 35:2875-2884; [7]Cristofanilli, et al. *Lancet Oncol.* 2016. 17: 425–39.

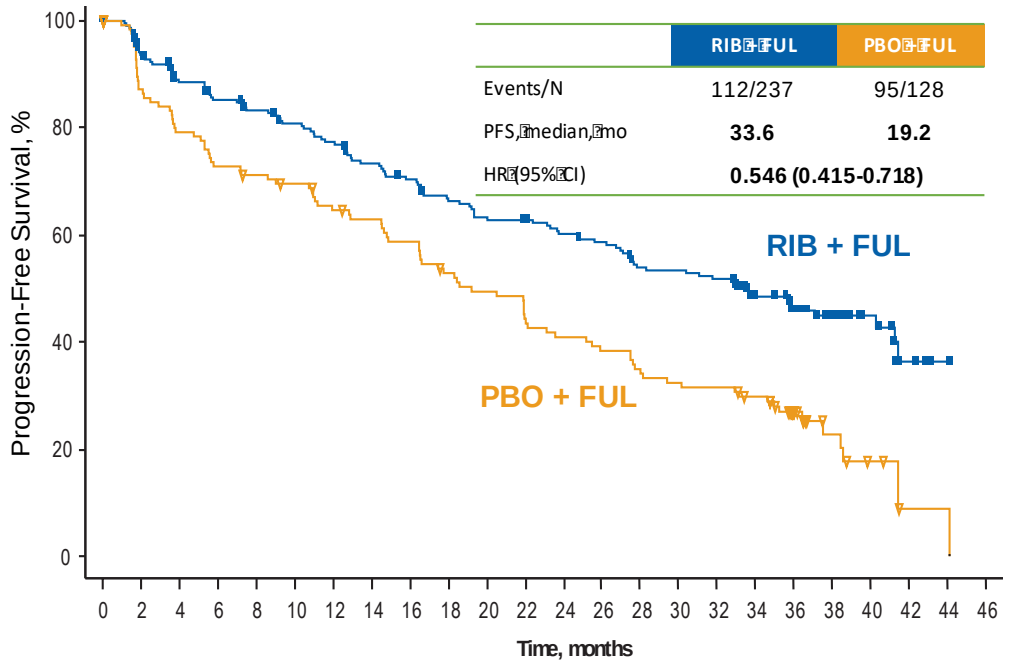
Mixed population: MONALEESA-3 Trial Updated PFS



Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-247.

PFS benefit in MONALEESA-3 trial according to endocrine sensitivity

Endocrine-sensitive

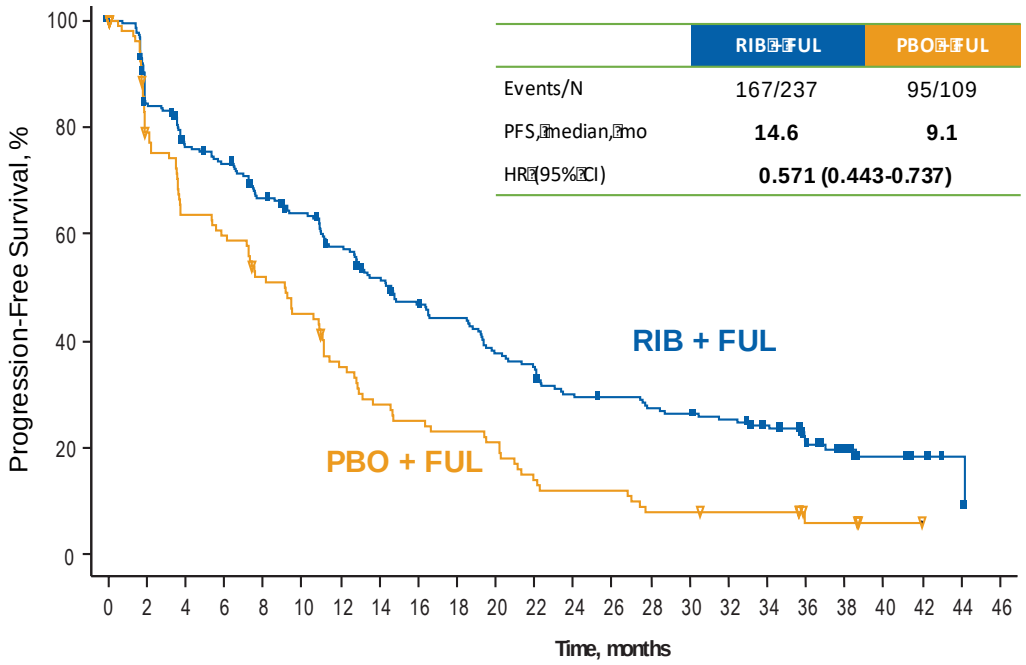


	RIB + FUL	PBO + FUL
Events/N	112/237	95/128
PFS, median, mo	**33.6**	**19.2**
HR (95% CI)	**0.546 (0.415-0.718)**	

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

Endocrine-resistant



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

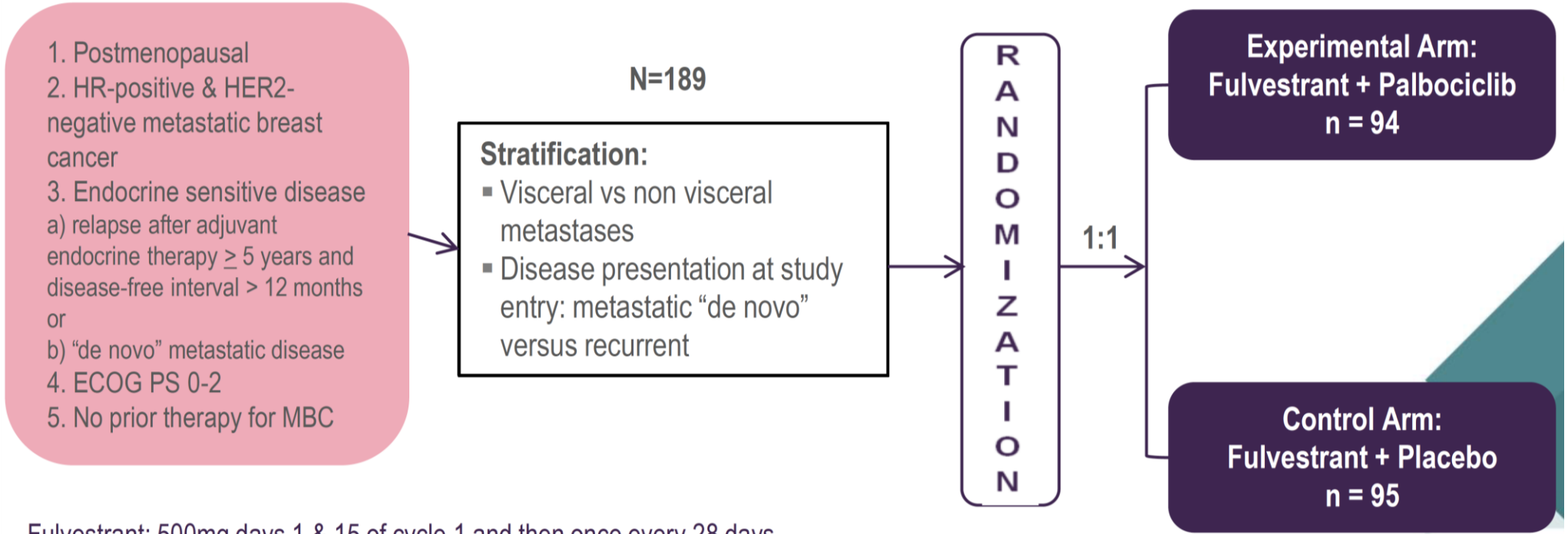
No. of patients still at risk

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

Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-247.

FLIPPER Trial

Randomized, double-blind, parallel-group, multicenter, international phase II study

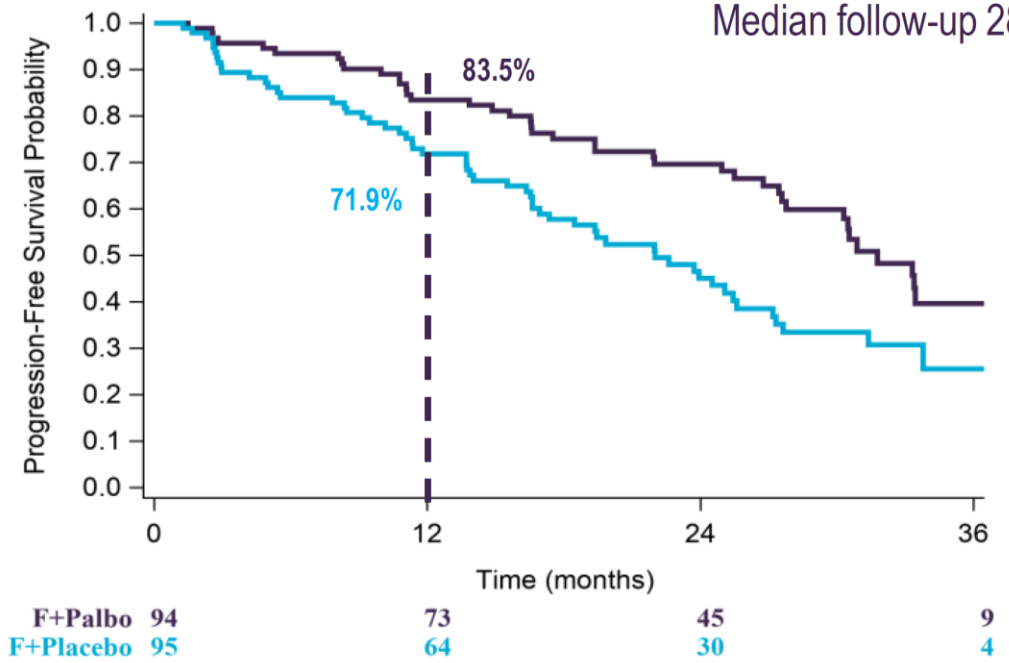


Fulvestrant: 500mg days 1 & 15 of cycle 1 and then once every 28 days
Palbociclib/Placebo: 125mg, 3 weeks on/1week off, q 28-days
Treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent

Abbreviations: HR=hormone receptor; HER2=human epidermal growth factor receptor 2; BC=breast cancer; ET=endocrine therapy. PD=progressive disease.

Albanell J et al, ESMO 2020

FLIPPER Trial: primary endpoint



	Fulvestrant + Palbociclib n=94	Fulvestrant + Placebo n=95
PFS rate at 1 year in ITT population (primary objective)		
No. of events (%)	15 (16.0)	26 (27.4)
No. of censored patients (%)	79 (84.0)	69 (72.6)
K-M **estimates** (80% CI)	**83.5% (78.5-88.5)**	**71.9% (65.8 - 77.9)**

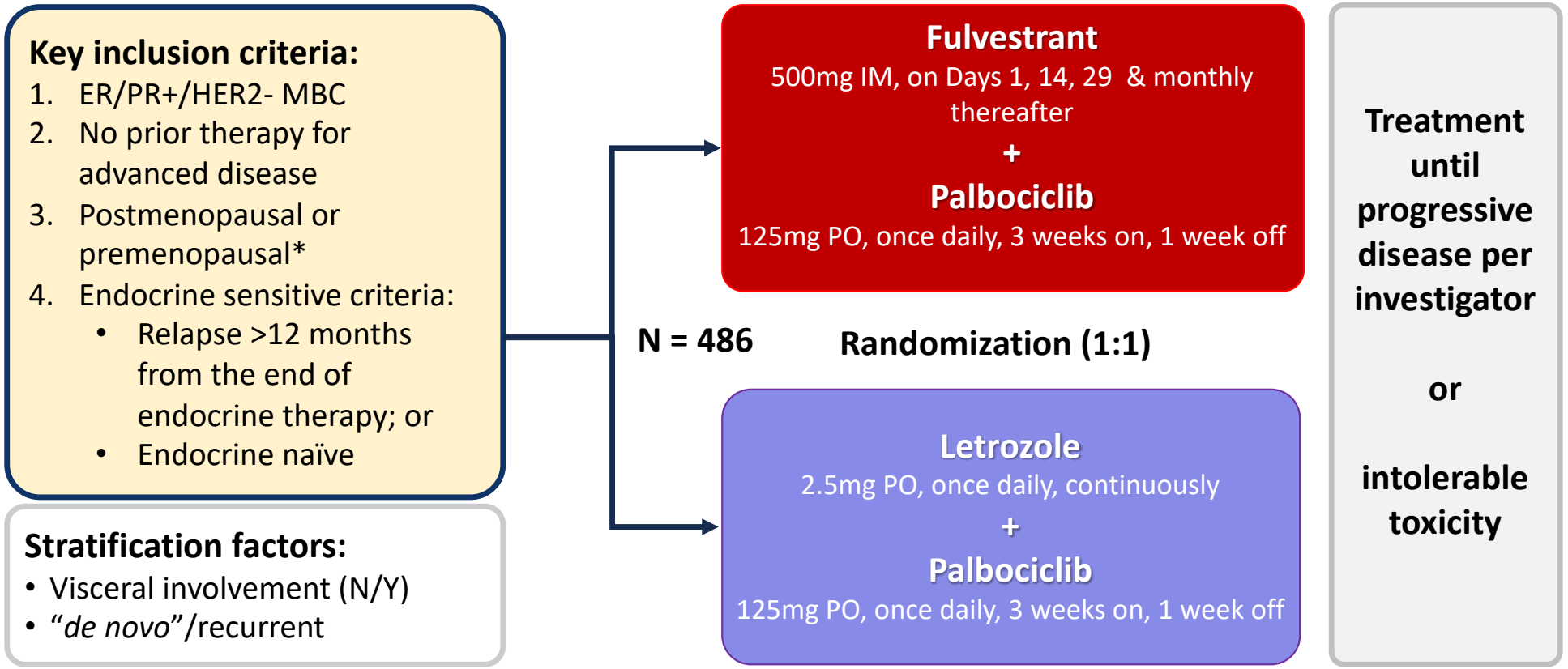
HR (80% CI): 0.55 (0.36-0.83) **p=0.064**

Statistical design; Hazard Ratio (HR): 0.6; Power: 80%; Two-sided alpha: 0.2

PFS in ITT population (secondary objective)		
No. of events (%)	40 (42.6)	56 (58.9)
No. of censored patients (%)	54 (57.4)	39 (41.1)
Median no. of **months** (80% CI)	**31.8 (30.3 - 33.4)**	**22 (18.5 - 25.1)**

Albanell J et al, ESMO 2020

Endocrine partner: PARSIFAL Trial

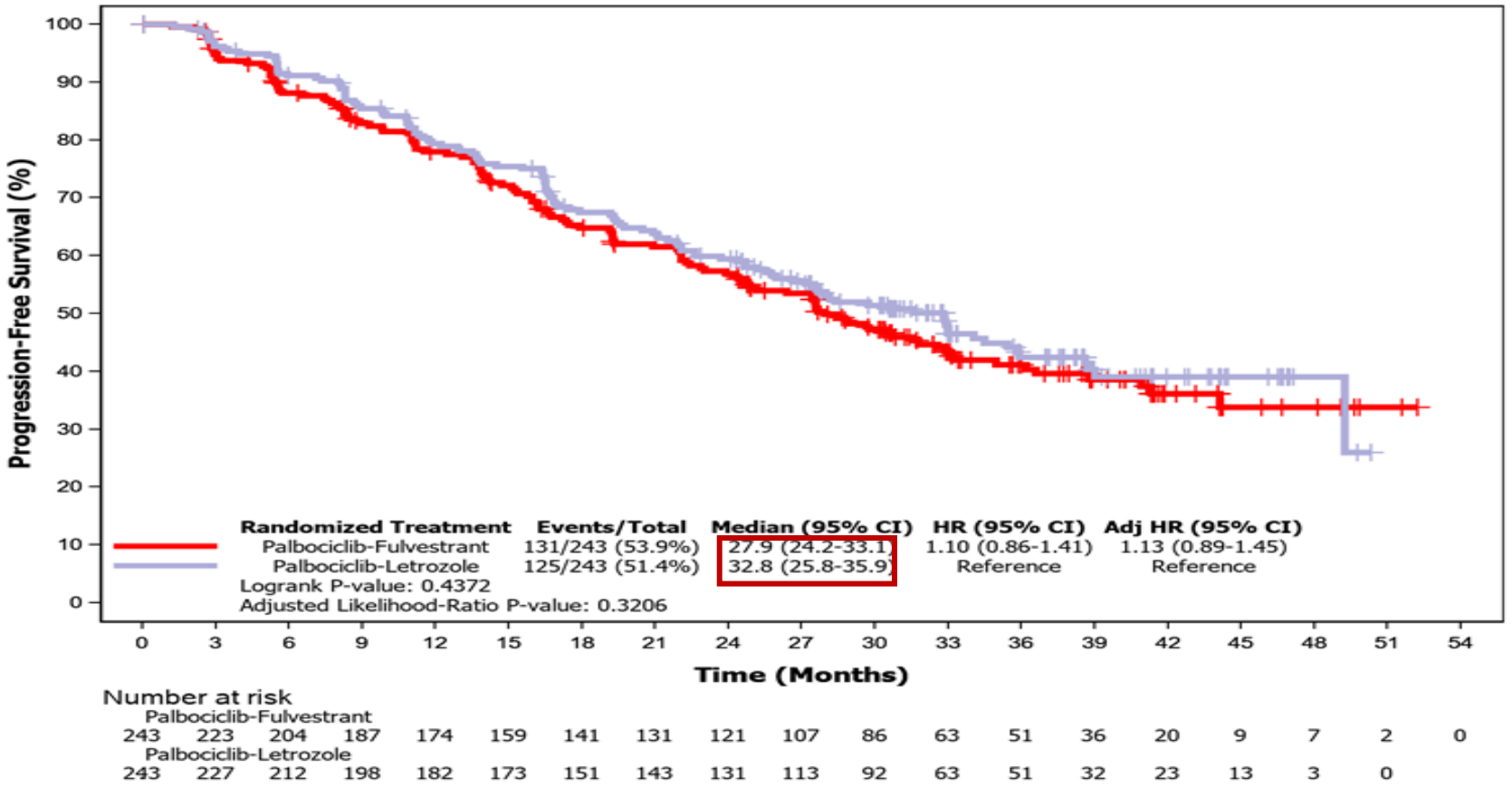


*If pre-menopausal, an ovarian suppression method was required.

ER: Estrogen receptor; HER2: Human Epidermal Growth Factor Receptor 2; IM: Intramuscular; MBC: Metastatic breast cancer; PO: Oral administration; PR: Progesterone receptor.

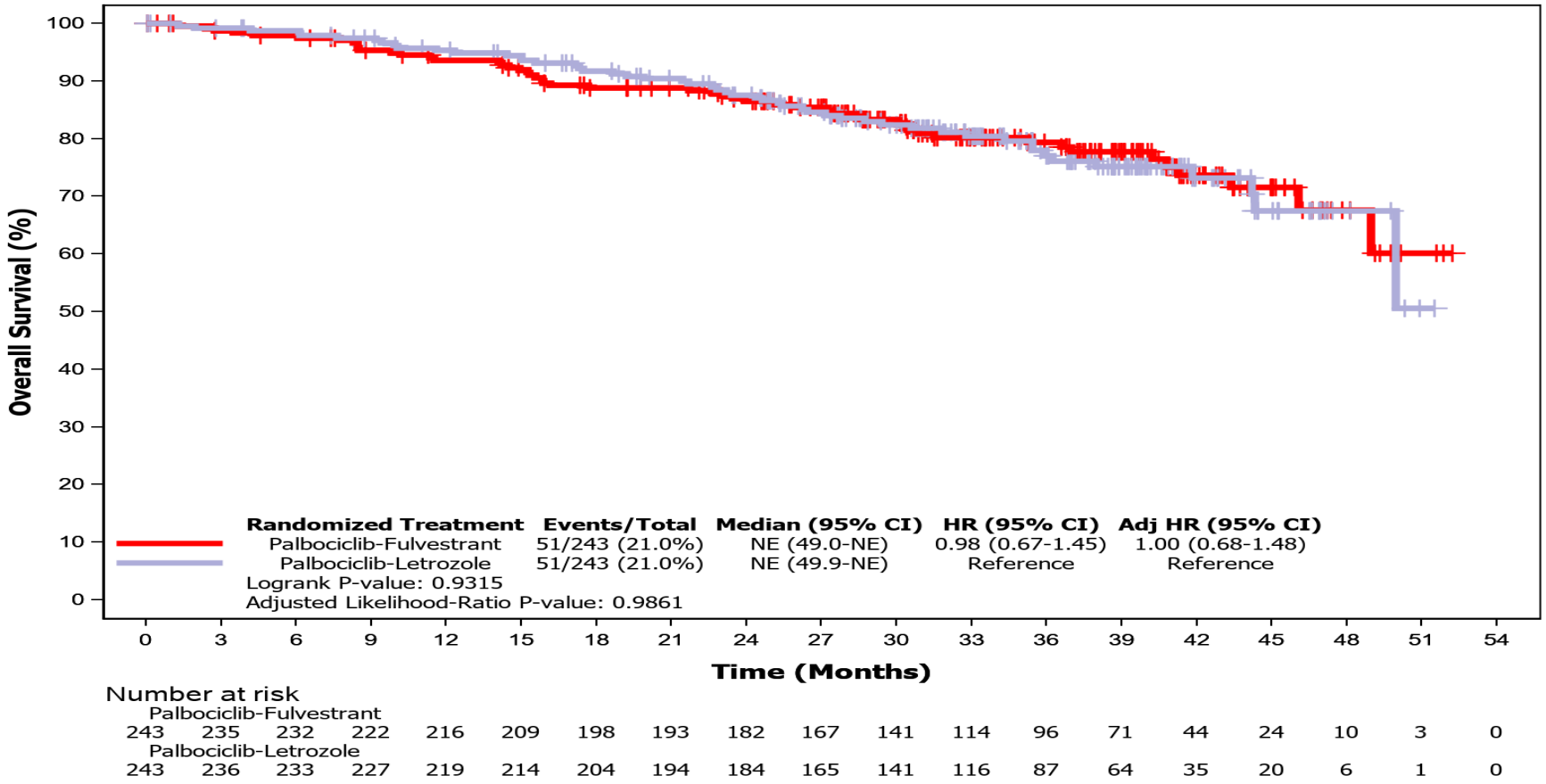
Llombart-Cussac A et al, ASCO 2020

Primary objective: PFS in ITT population



Llombart-Cussac A et al, ASCO 2020

OS in ITT population



Llombart-Cussac A et al, ASCO 2020

Different populations across CDK4/6 inhibitors trials

Study	Line	Sensitivity	Primary ET resistance	Secondary ET resistance
PALOMA-2[1]	1st	▯ 100%		
MONARCH-3[2]	1st	▯ 100%		
MONALEESA-2[3]	1st	▯ 100%		
MONALEESA-7[4]	1st	▯ 70%		▯ 30%
MONALEESA-3[5]	1st & 2nd	▯ 50%	▯ 50% (% of pts with secondary resistance not provided)	
MONARCH-2[6]	2nd		▯ 25%	▯ 75%
PALOMA-3[7]	2nd		▯ 21%	▯ 79%

[1]Finn, et al. *N Engl J Med.* 2016. 375:1925-1936; [2]Goetz, et al. *J Clin Oncol.* 2017. 35:3638-3646; [3]Hortobagyi, et al. *N Engl J Med.* 2016. 375:1738-1748; [4]Tripathy, et al. *Lancet Oncol.* 2018; 19: 904–15; [5]Slamon, et al. *J Clin Oncol.* 2018. 36:2465-2472; [6]Sledge, et al. J Clin Oncol. 2017. 35:2875-2884; [7]Cristofanilli, et al. *Lancet Oncol.* 2016. 17: 425–39.

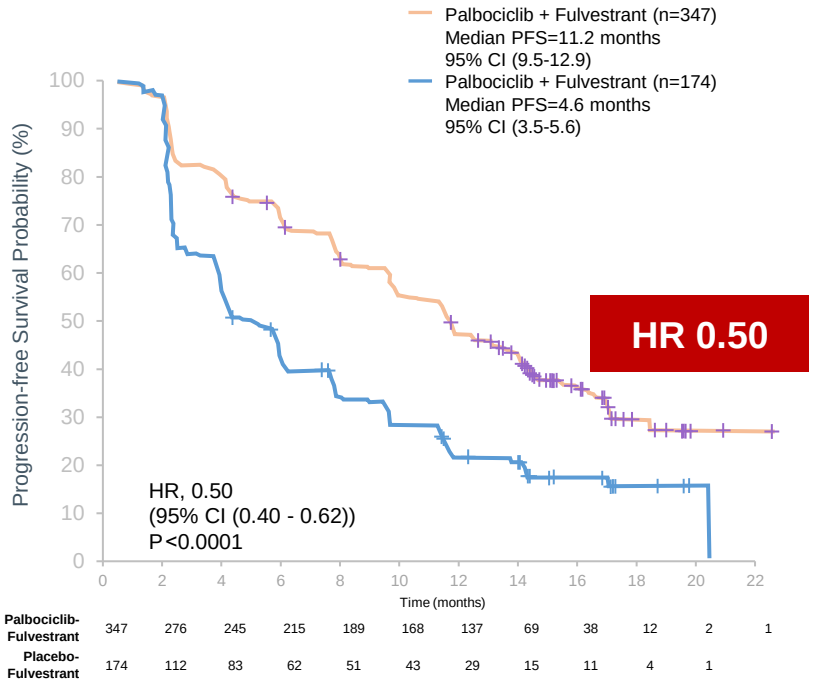
PFS benefit: Endocrine resistant

MONARCH-2[1]

	Abemaciclib + fulvestrant	Placebo + fulvestrant
No. of patients	446	223
No. of events	297	193
mPFS (months)	16.9	9.3

Abemaciclib-fulvestrant	446	365	312	280	242	208	176	158	147	132	121	114	104	97	78	53	28	18	4	0
Placebo-fulvestrant	223	165	124	103	81	72	54	47	36	31	26	18	17	14	9	7	0	0	0	0

PALOMA-3[2]

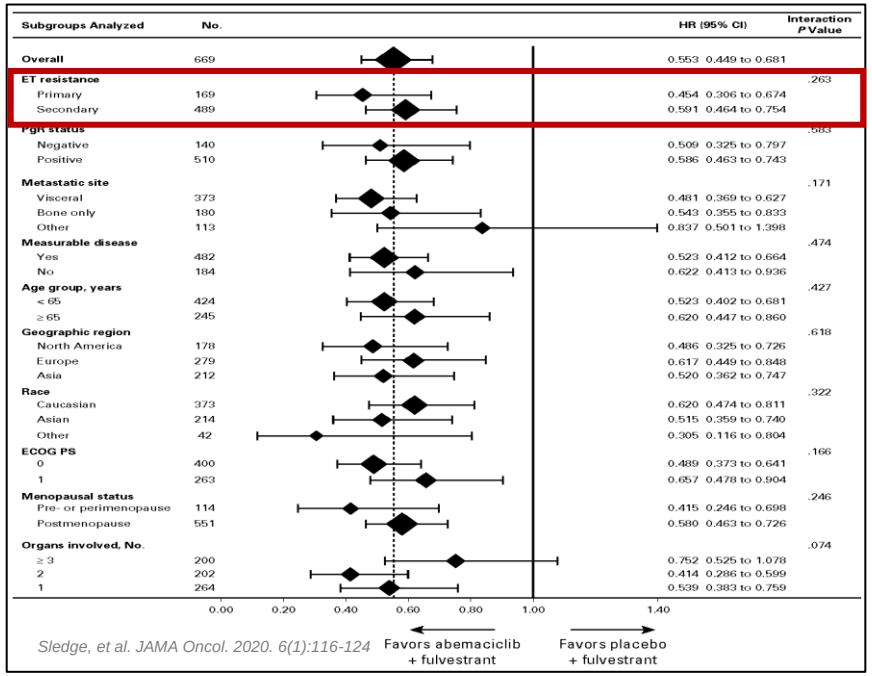


Palbociclib-Fulvestrant	347	276	245	215	189	168	137	69	38	12	2	1
Placebo-Fulvestrant	174	112	83	62	51	43	29	15	11	4	1	

[1]Sledge, et al. *JAMA Oncol.* 2020. 6(1):116-124; [2]Turner NC, et al. *N Engl J Med*. 2018. 379:1926-1936.

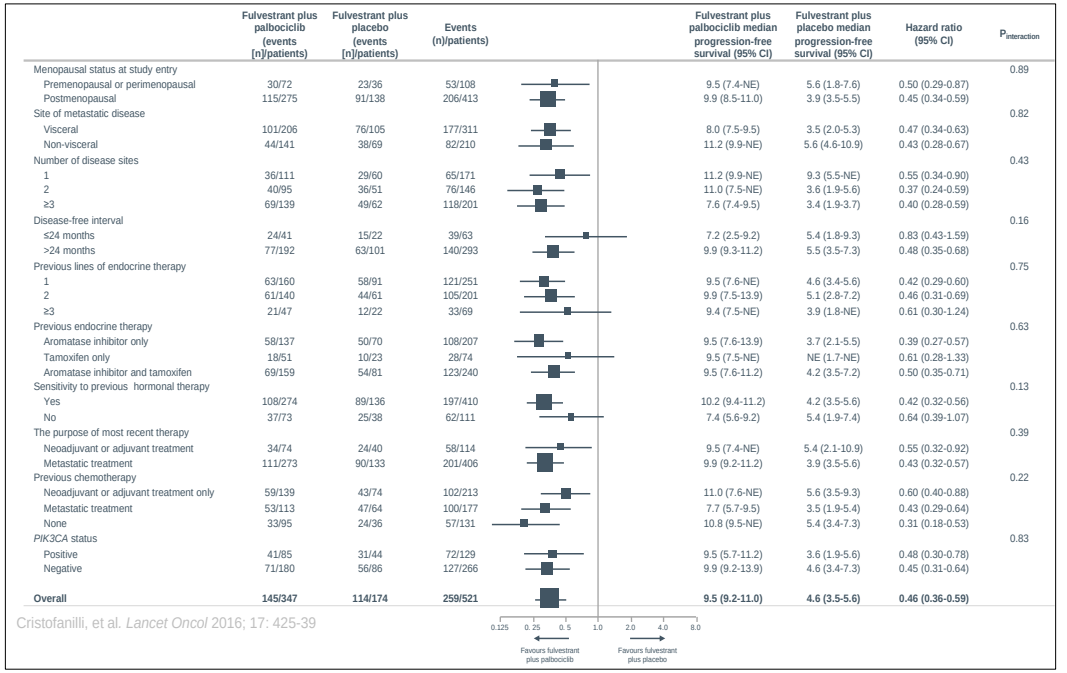
PFS benefit in endocrine resistant across patient subgroups

MONARCH-2



Sledge, et al. *JAMA Oncol.* 2020. 6(1):116-124

PALOMA-3



Cristofanilli, et al. *Lancet Oncol* 2016; 17: 425-39

FDA Pooled Analysis of CDK4/6 Inhibition in Patient Subgroups

Methods:

- Pooled, raw patient-level data from 5 Phase 3, randomized, controlled registration trials of CDK inhibitors with either:
  - An AI in first-line settings
  - Fulvestrant in second-line settings
- Median investigator-assessed PFS examined using KM plots

Overall Results of Median PFS

Subset	AI or fulvestrant	N	CDK4/6 inhibitor	Placebo (months)	Difference (months)	HR	95% CI
ITT population	Both	3002	20.5	11.8	8.7	0.59	0.53–0.65
ITT population	AI	1817	26.5	15.1	11.4	0.56	0.49–0.64
PR-negative disease	Both	490	16.5	7.4	9.1	0.50	0.40–0.64
Lobular cancer	Both	264	16.1	9.2	6.9	0.58	0.42–0.80
Bone-only metastases	Both	875	27.9	15.5	12.4	0.55	0.45–0.67
De novo metastatic disease*	AI	617	27.8	16.8	11.0	0.59	0.46–0.76
Disease-free interval >12 months	AI	929	25.7	14.2	11.5	0.55	0.46–0.67

*De novo metastatic disease defined as stage IV disease at diagnosis.
AI=aromatase inhibitor.

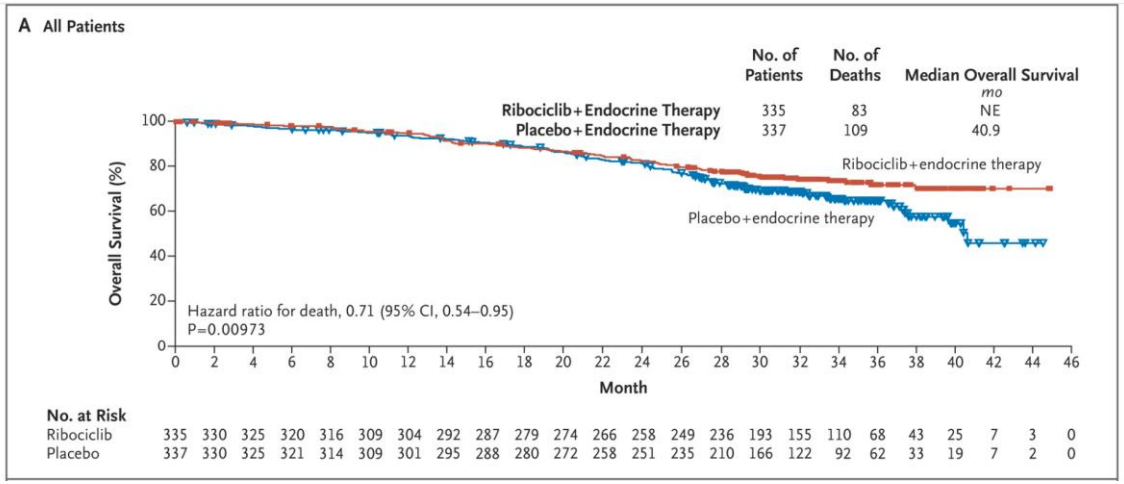
Gao JJ, et al. Abstract 1024. ASCO 2018.

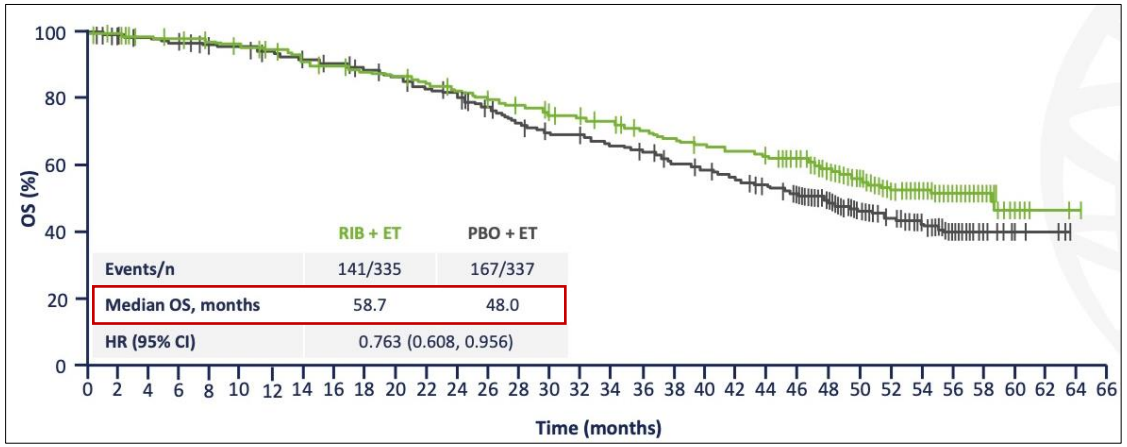
CDK4/6 inhibitor trials with available OS data

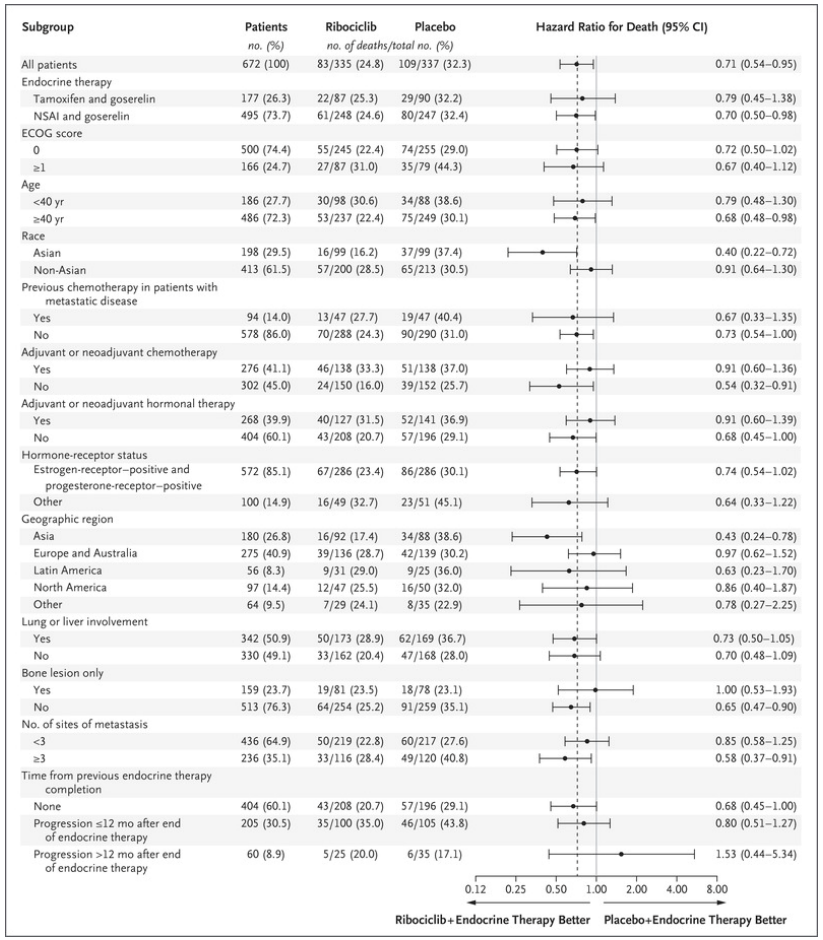
Study	Line	Sensitivity	Primary ET resistance	Secondary ET resistance
PALOMA-2[1]	1st	▯ 100%		
MONARCH-3[2]	1st	▯ 100%		
MONALEESA-2[3]	1st	▯ 100%		
MONALEESA-7[4]	1st	▯ 70%		▯ 30%
MONALEESA-3[5]	1st & 2nd	▯ 50%	▯ 50% (% of pts with secondary resistance not provided)	
MONARCH-2[6]	2nd		▯ 25%	▯ 75%
PALOMA-3[7]	2nd		▯ 21%	▯ 79%

[1]Finn, et al. *N Engl J Med.* 2016. 375:1925-1936; [2]Goetz, et al. *J Clin Oncol.* 2017. 35:3638-3646; [3]Hortobagyi, et al. *N Engl J Med.* 2016. 375:1738-1748; [4]Tripathy, et al. *Lancet Oncol.* 2018; 19: 904–15; [5]Slamon, et al. *J Clin Oncol.* 2018. 36:2465-2472; [6]Sledge, et al. J Clin Oncol. 2017. 35:2875-2884; [7]Cristofanilli, et al. *Lancet Oncol.* 2016. 17: 425–39.

OS benefit in 1st line MONALEESA-7 Trial



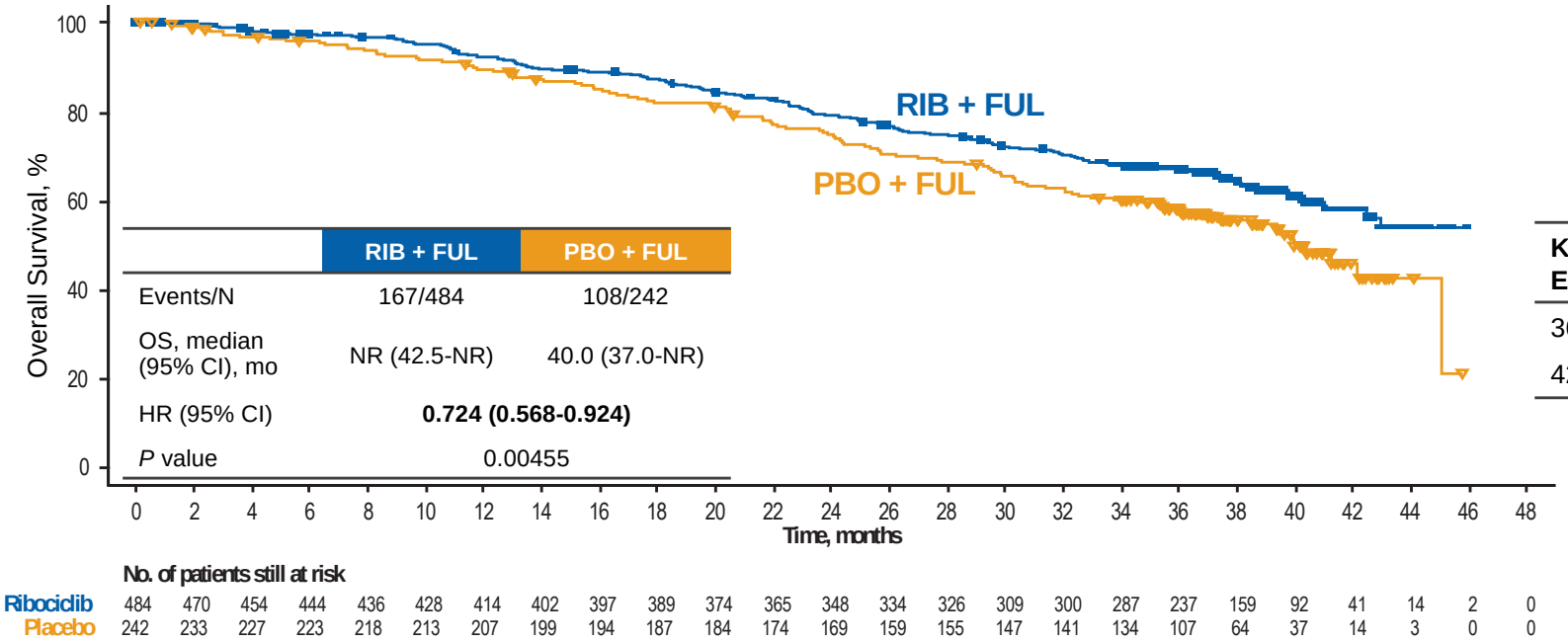




Seock-Ah Im, NEJM 2019; Tripathy D, et al, SABCS 2020

OS benefit in mixed population MONALEESA-3

The reduction in relative 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

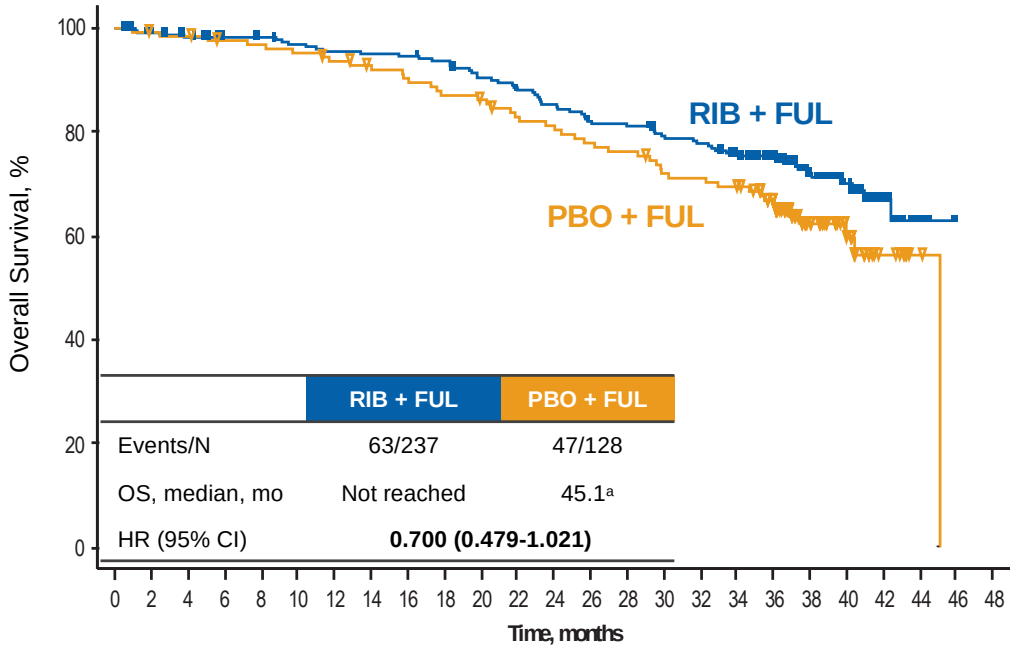
KM Estimate	RIB + FUL	PBO + FUL
36 months	67.0%	58.2%
42 months	57.8%	45.9%

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

Slamon et al, NEJM 2020 ; Tripathy D, et al, SABCS 2020

OS benefit in mixed population MONALEESA-3

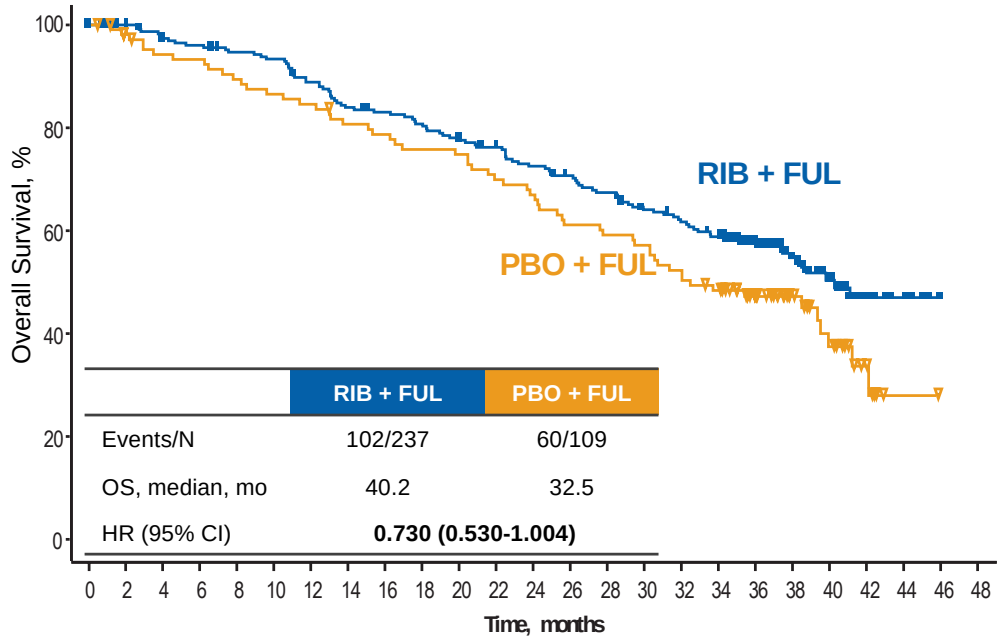
First line



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

Early relapse + second line



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

Slamon et al, NEJM 2020 ; Tripathy D, et al, SABCS 2020

Flatiron EHR Database: Overall Survival for First-Line Palbociclib + Letrozole vs Letrozole for HR+/HER2- MBC in US

Objective: Retrospective analysis of EHRs conducted using de-identified patient data from the Flatiron Health Analytic database to determine whether real-world data could demonstrate improved PFS and/or OS with PAL+LET compared with letrozole alone as first-line treatment for HR+/HER2– MBC

Inclusion

- Women ≥18 years old at MBC diagnosis
- Diagnosis of MBC at any point in patient history
- HR+/HER2– breast cancer
- Date of first prescription (index date) for palbociclib + letrozole or letrozole alone as first-line therapy for MBC between February 3, 2015, and February 28, 2019
- Potential follow-up of ≥3 months from index date to the study cutoff date of May 31, 2019

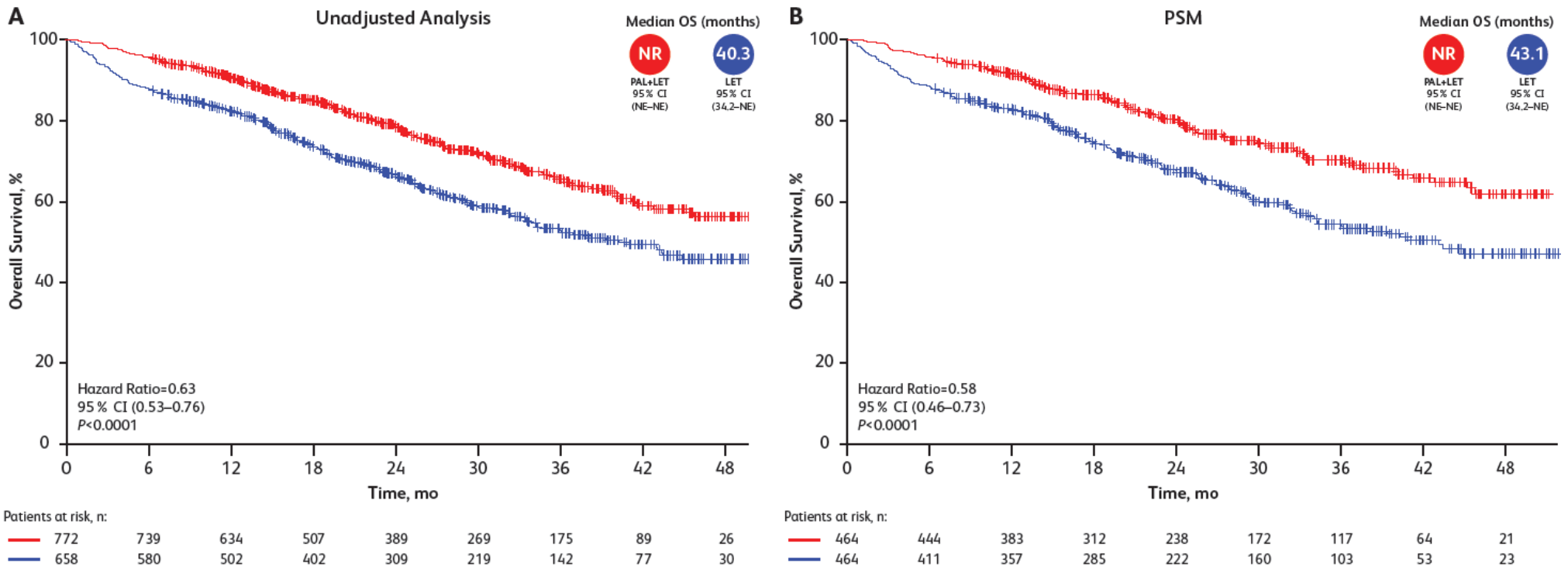
Exclusion

- Evidence of prior treatment with CDK4/6 inhibitors, aromatase inhibitors, tamoxifen, raloxifene, toremifene, or fulvestrant in the metastatic setting
- First structured activity >90 days after MBC diagnostic date
- Treatment with a CDK4/6 inhibitor as part of a clinical trial

- Number of patients (N=1430): PAL+ LET (n=772); LET (n=658)

DeMichele A et al, SABCS 2019

FLATIRON Study: OS



LET=letrozole; NE=not estimable; NR=not reached; OS=overall survival; PAL=palbociclib; PFS=progression-free survival; PSM=propensity score matching.

A consistent OS benefit of palbociclib plus letrozole versus letrozole alone was observed generally across all studied subgroups

DeMichele A et al, SABCS 2019

CDK4/6 inhibitor trials with available OS data

Study	Line	Sensitivity	Primary ET resistance	Secondary ET resistance
PALOMA-2[1]	1st	▯ 100%		
MONARCH-3[2]	1st	▯ 100%		
MONALEESA-2[3]	1st	▯ 100%		
MONALEESA-7[4]	1st	▯ 70%		▯ 30%
MONALEESA-3[5]	1st & 2nd	▯ 50%	▯ 50% (% of pts with secondary resistance not provided)	
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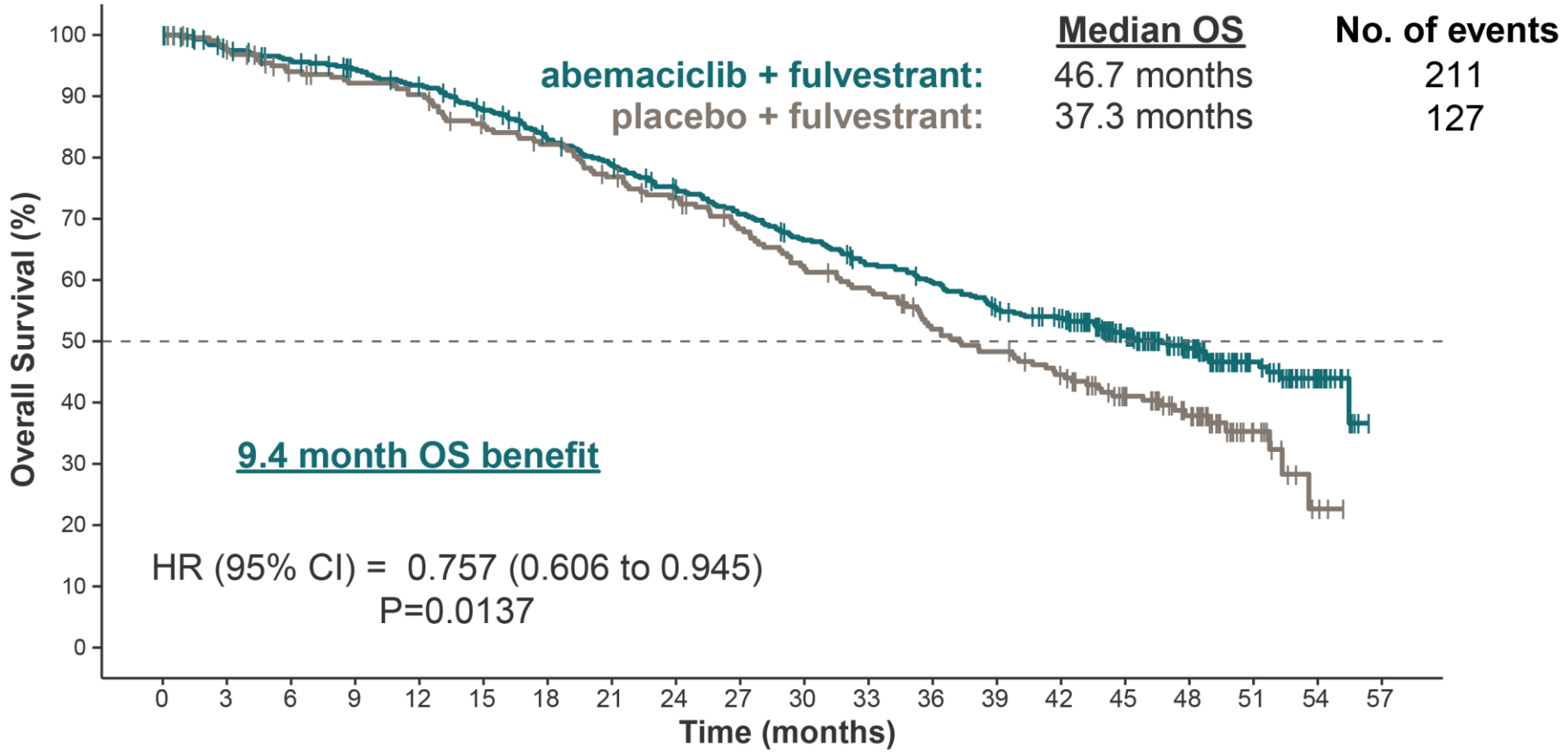
OS benefit in endocrine resistant MONARCH-2 Trial



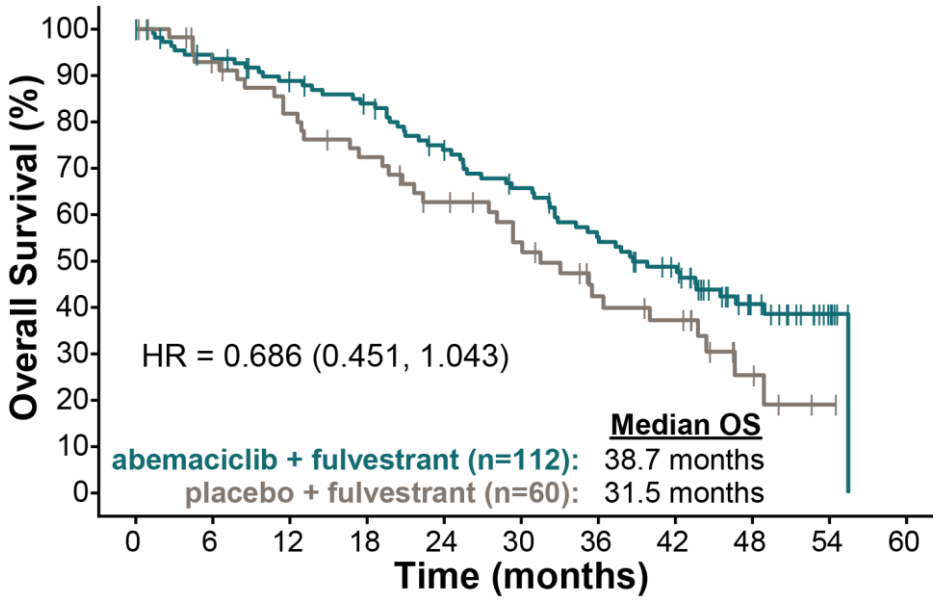
No. at risk

abemaciclib + fulvestrant	446	422	410	397	384	364	339	321	302	284	265	246	234	214	202	157	101	58	23	0
placebo + fulvestrant	223	214	201	195	191	178	170	158	148	135	122	115	99	92	82	62	42	15	3	0

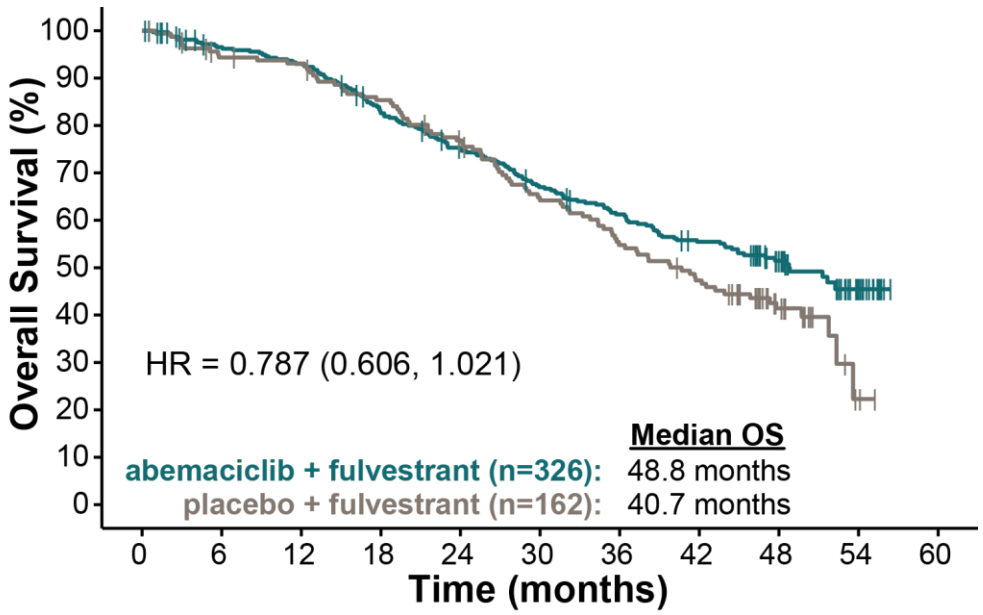
Sledge GW et, JCO 2017

MONARCH-2: OS benefit by endocrine resistance

Primary resistance



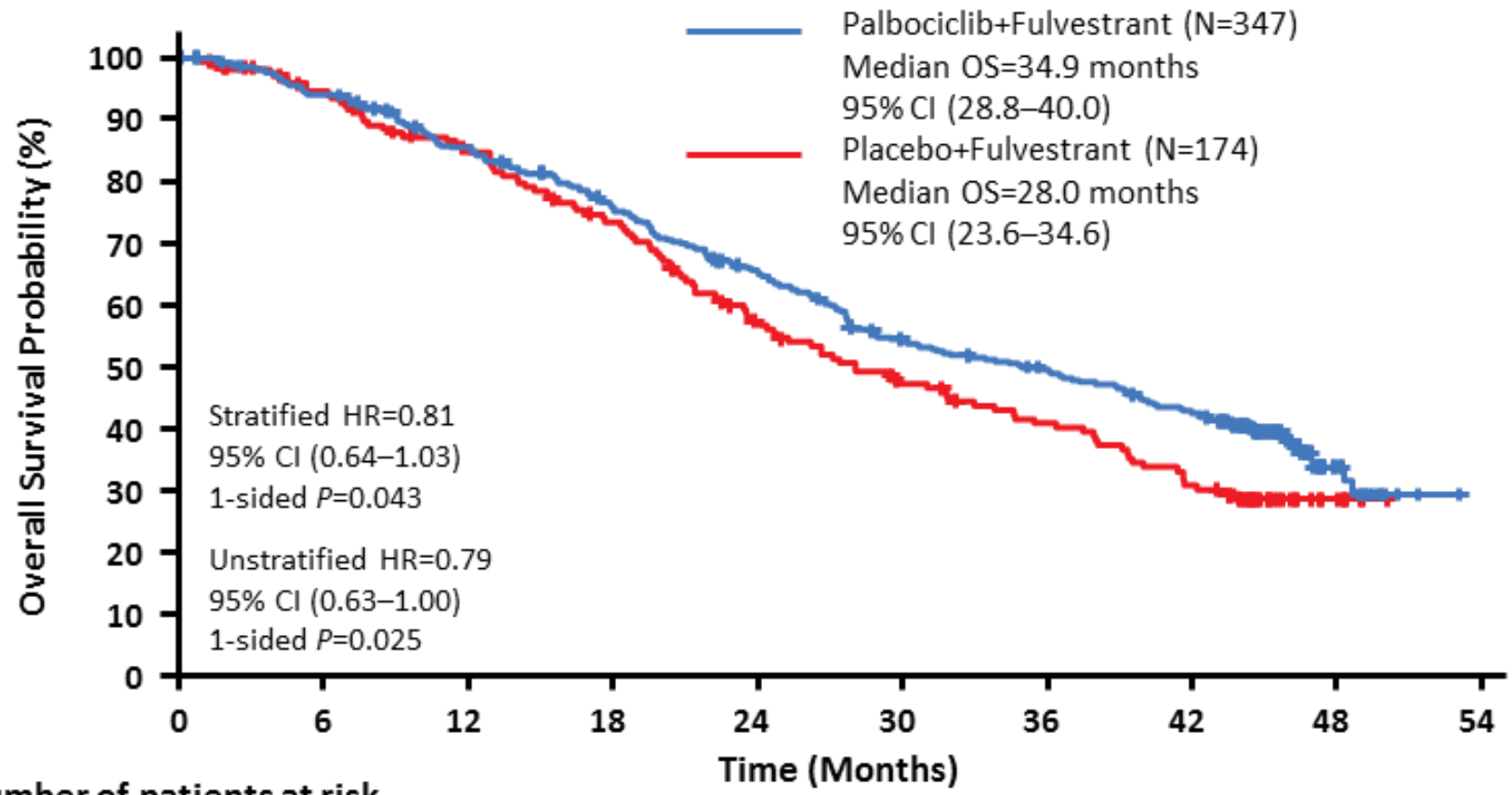
Secondary resistance



[a]Interaction p-value: 0.588

Sledge et al. JAMA Oncol. 2020;6(1):116-124.

OS benefit in endocrine resistant PALOMA-3 Trial



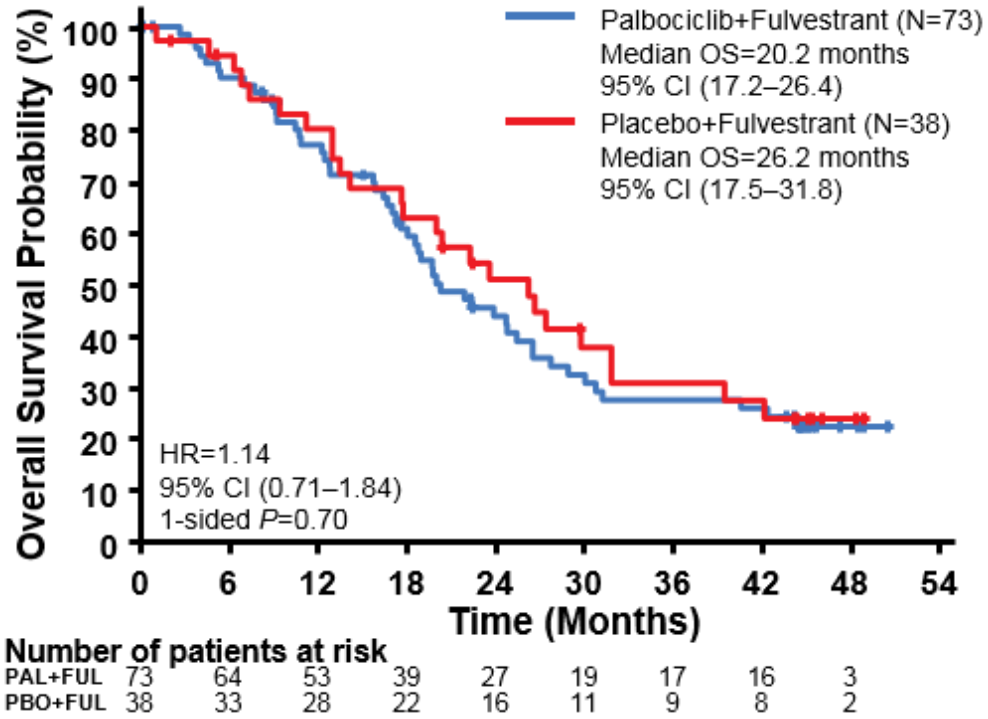
Number of patients at risk

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

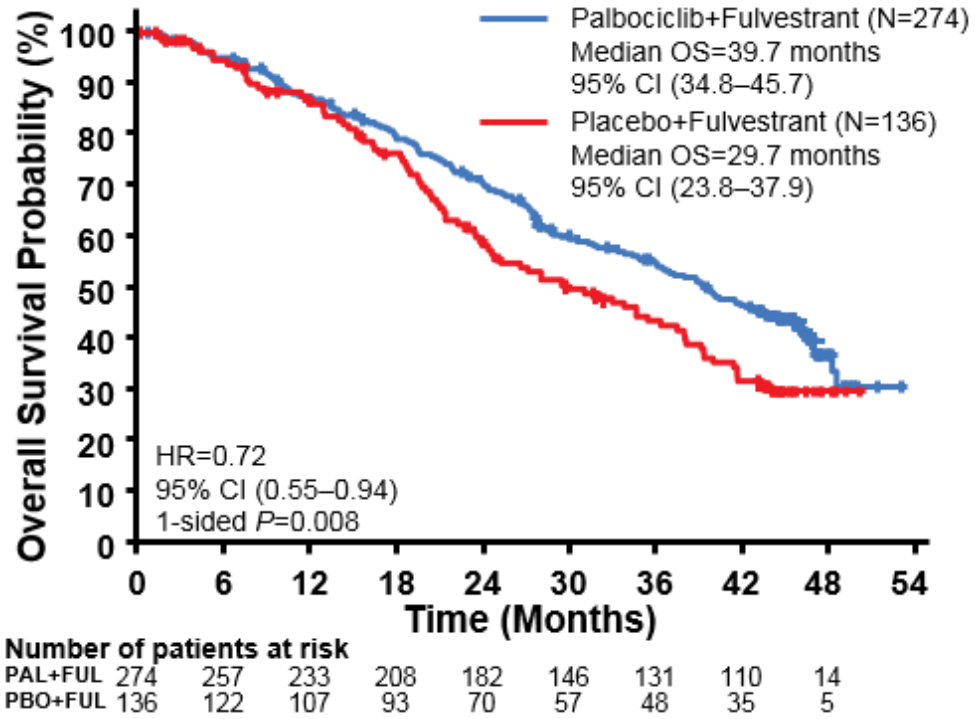
Turner NC et al, NEJM 2018

PALOMA-3: OS by sensitivity to prior ET

No sensitivity to prior ET



Sensitivity to prior ET



Turner NC et al, NEJM 2018

Differences in study population

Table 2: Comparison of eligibility criteria.

Selected Criteria	PALOMA-3	MONARCH 2	MONALEESA-3
Inclusion Criteria			
Menopausal status[a]	Pre, peri, or post	Pre, peri, or post	Post
Receptor status	HR+/HER2-	HR+/HER2-	HR+/HER2-
ECOG PS	0,1	0,1	0,1
Measurable disease	Required[b], or bone-only disease	Required, or bone-only disease	Required[b], or ≥1 predominantly lytic bone lesion
Progressed on or after endocrine therapy in the adjuvant or metastatic setting	Required	Required	Not required
Number of prior lines of endocrine therapy for MBC	Any[c]	≤1	≤1
Exclusion Criteria			
Visceral crisis	Excluded	Excluded	Excluded
Central nervous system metastasis (uncontrolled/symptomatic)	Excluded	Excluded	Excluded
Prior chemotherapy for MBC	>1 excluded	Excluded	Excluded

Matched-adjusted indirect comparison: MAIC Study

156P

Matching-adjusted indirect comparison of palbociclib versus ribociclib and abemaciclib in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer

Objective

To determine the relative efficacy of palbociclib + fulvestrant (PAL+FUL) versus abemaciclib + fulvestrant (ABM+FUL) and ribociclib + fulvestrant (RIB+FUL) in patients with human epidermal growth factor receptor 2-negative advanced breast cancer (HR+/HER2- ABC) in terms of overall survival (OS) using matching-adjusted indirect comparison (MAIC).

Conclusion

Overall survival was similar between PAL+FUL vs ABM+FUL and PAL+FUL vs RIB+FUL after adjusting for cross-trial differences. Differences in baseline characteristics between patient populations highlight the importance of conducting MAICs.

Context

There are no head-to-head clinical trials comparing PAL+FUL with ABM+FUL and RIB+FUL for the treatment of HR+/HER2- ABC.

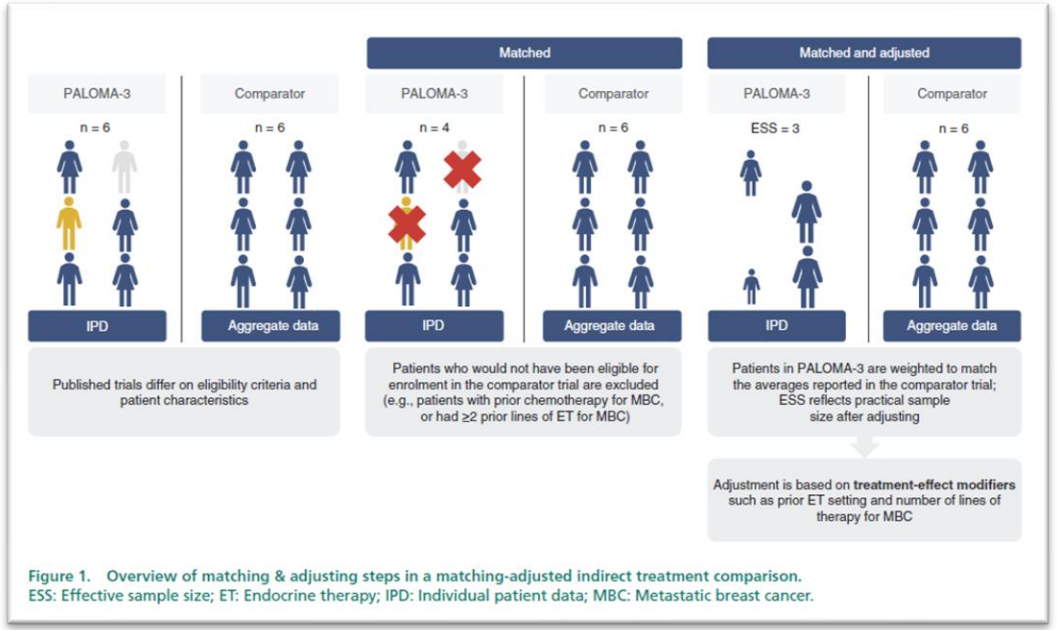


Figure 1. Overview of matching & adjusting steps in a matching-adjusted indirect treatment comparison.
ESS: Effective sample size; ET: Endocrine therapy; IPD: Individual patient data; MBC: Metastatic breast cancer.

Traditional ITC methods based only on summary-level data may be biased due to such inherent differences in patient populations. Matching-adjusted indirect comparisons (MAICs) are used to indirectly compare a treatment effect across studies by leveraging individual patient data (IPD) from one study to reduce cross-trial differences. This is achieved through matching and adjusting of the IPD to the summary-level data of the comparator trial's population. When a common comparator is present, anchored MAICs can be used to further adjust for cross-trial differences. By anchoring through the control arm, differences in known and unknown prognostic factors across trials are accounted for when determining the relative treatment effect.

The present study uses anchored MAICs, which are designed to reduce cross-trial differences that would otherwise undermine the validity of traditional ITCs. By leveraging IPD from PALOMA-3 and summary-level data from MN 2 and ML-3, separate anchored MAICs were conducted to compare PAL+FUL to ABM+FUL and RIB+FUL in terms of OS in patients with HR+/HER2- ABC.

Matching-adjusted indirect comparison of palbociclib versus ribociclib and abemaciclib in hormone receptor-positive/HER2-negative advanced breast cancer. H. Rugo 2021

Matched-adjusted indirect comparison: MAIC Study

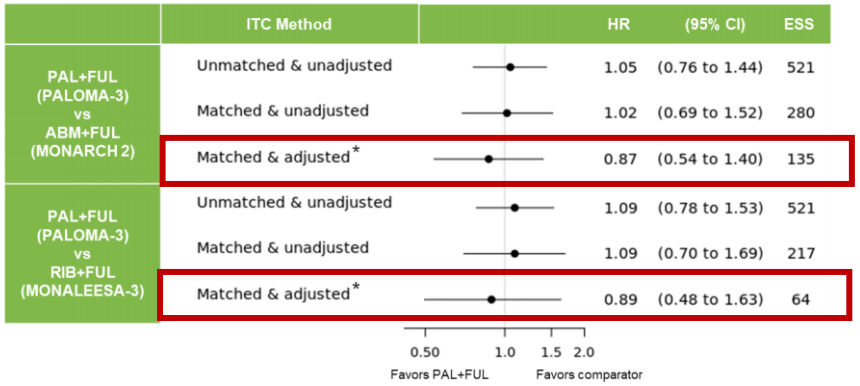
Table 1: OS results in randomized controlled trials.

Study	Median OS (months)	HR (95% CI)
PALOMA-3[1]	PAL+FUL: 34.9 PBO+FUL: 28.0	0.79 (0.63-1.00)
MONARCH 2[2]	ABM+FUL: 46.7 PBO+FUL: 37.3	0.76 (0.61-0.95)
MONALEESA-3[3]	RIB+FUL: not reached PBO+FUL: 40.0	0.72 (0.57-0.92)

Table 2: Comparison of eligibility criteria.

Selected Criteria	PALOMA-3	MONARCH 2	MONALEESA-3
Inclusion Criteria			
Menopausal status[a]	Pre, peri, or post	Pre, peri, or post	Post
Receptor status	HR+/HER2-	HR+/HER2-	HR+/HER2-
ECOG PS	0,1	0,1	0,1
Measurable disease	Required[b], or bone-only disease	Required, or bone-only disease	Required[b], or ≥1 predominantly lytic bone lesion
Progressed on or after endocrine therapy in the adjuvant or metastatic setting	Required	Required	Not required
Number of prior lines of endocrine therapy for MBC	Any[c]	≤1	≤1
Exclusion Criteria			
Visceral crisis	Excluded	Excluded	Excluded
Central nervous system metastasis (uncontrolled/symptomatic)	Excluded	Excluded	Excluded
Prior chemotherapy for MBC	>1 excluded	Excluded	Excluded

Figure 2: Executive summary of ITC results.



Limitations

- When the comparator trial included a broader population (eg, MONALEESA-3 did not require progression on or after ET in the adjuvant or metastatic setting), IPD from PALOMA-3 could not be matched.
- MAIC methodology assumes that all treatment-effect modifiers are balanced across trials; however, differences in characteristics accounted for in the analysis were limited by those reported in the comparator publications.
- There were considerable differences in baseline characteristics between PALOMA-3 and MONALEESA-3 study populations, which resulted in a lower ESS compared to the MAIC with MONARCH 2.

Matching-adjusted indirect comparison of palbociclib versus ribociclib and abemaciclib in hormone receptor-positive/HER2-negative advanced breast cancer. H. Rugo 2021

Take-Home messages

- Consistent survival benefit (PFS) achieved by CDK 4/6i in patients with both endocrine-sensitive and endocrine-resistant tumors, in HR+/HER2- mBC
- First time that any targeted agent + ET has demonstrated significantly longer OS vs ET alone as initial endocrine-based therapy
- Heterogeneous OS results in endocrine-resistant disease across different trials may be due in part to different study population
- All patient with HR+/HER2- mBC should receive a CDK 4/6i as earlier as possible in the course of their disease