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DE CÂNCER DE MAMA 2018
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Treatment options with CDK4/6 in hormone refractory advanced breast cancer

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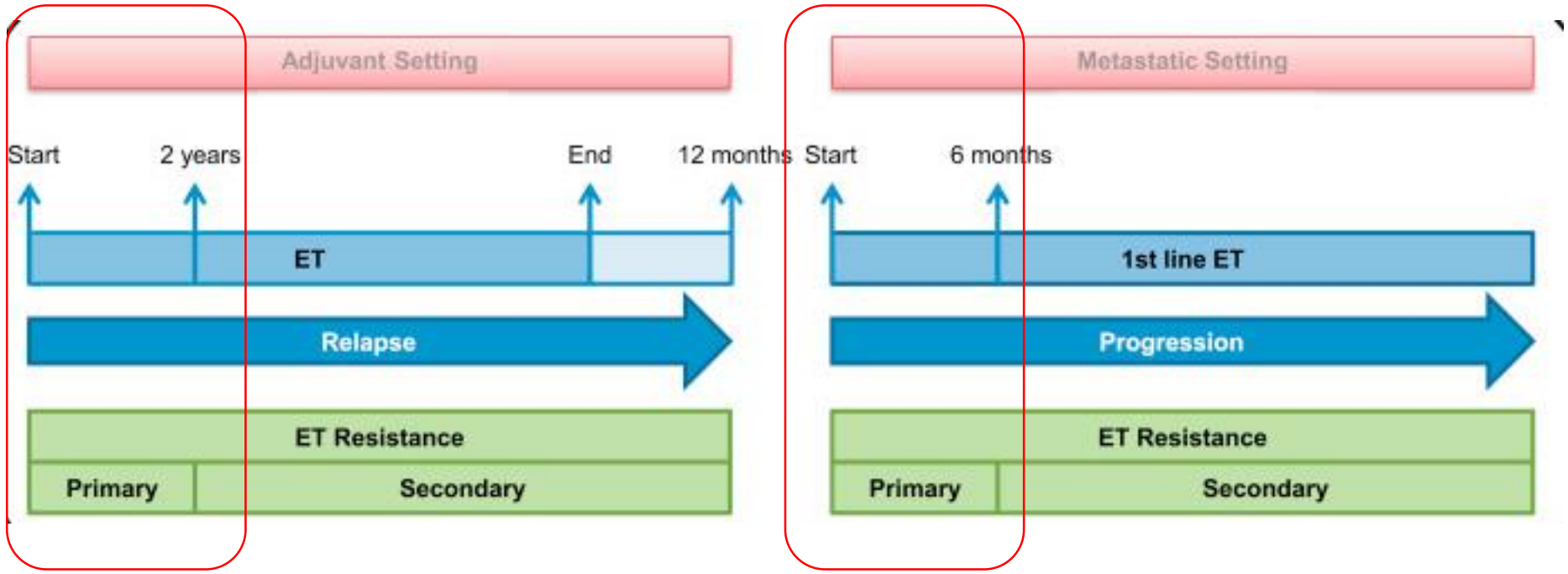
Porto Alegre, Brazil

Projeto cura.

LACOG
LATIN AMERICAN COOPERATIVE ONCOLOGY GROUP

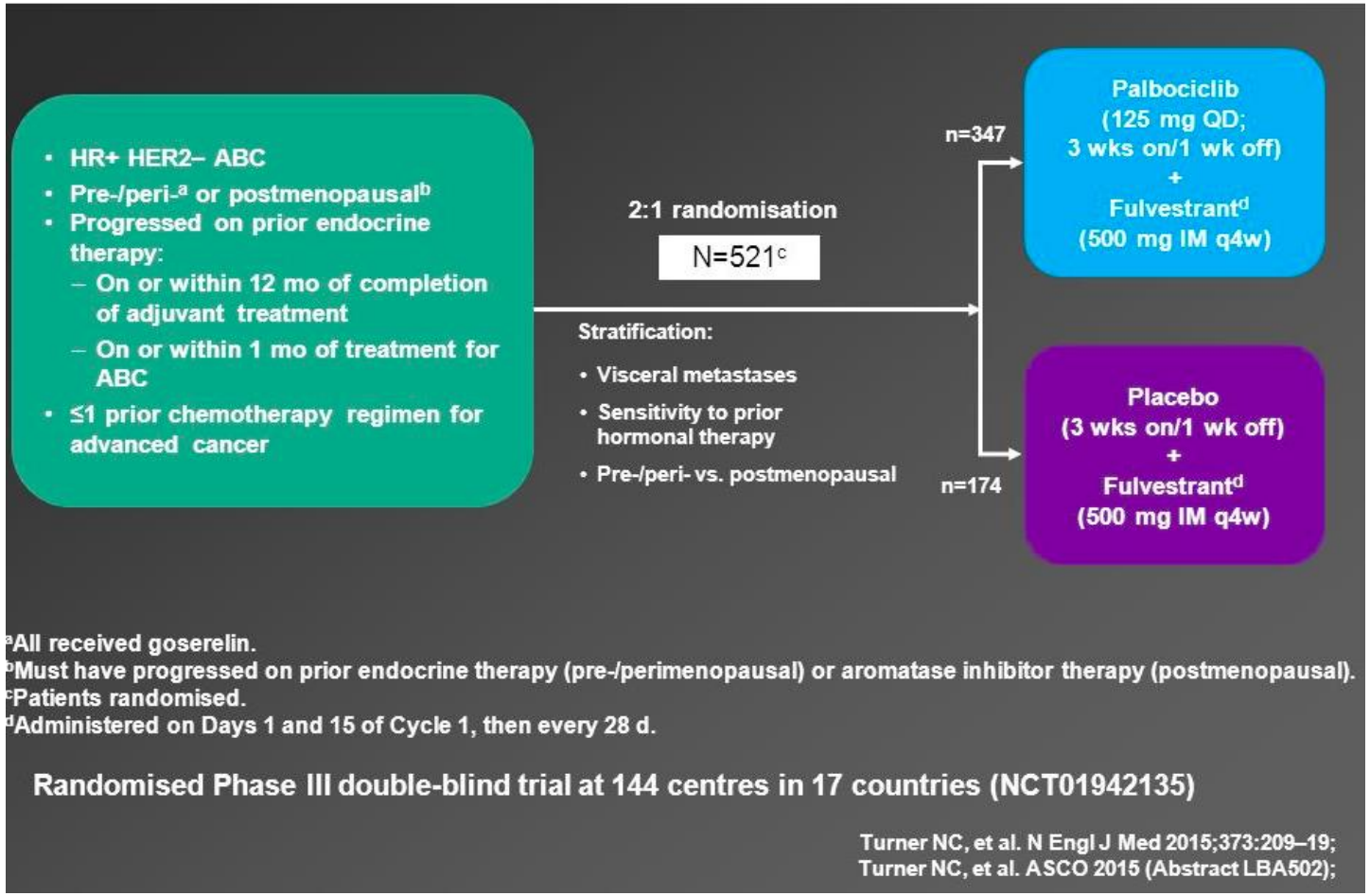
Defining Hormone Refractory Breast Cancer



Secondary = Sensitive

Treatment options for HR refractory BC

PALOMA-3: Study design

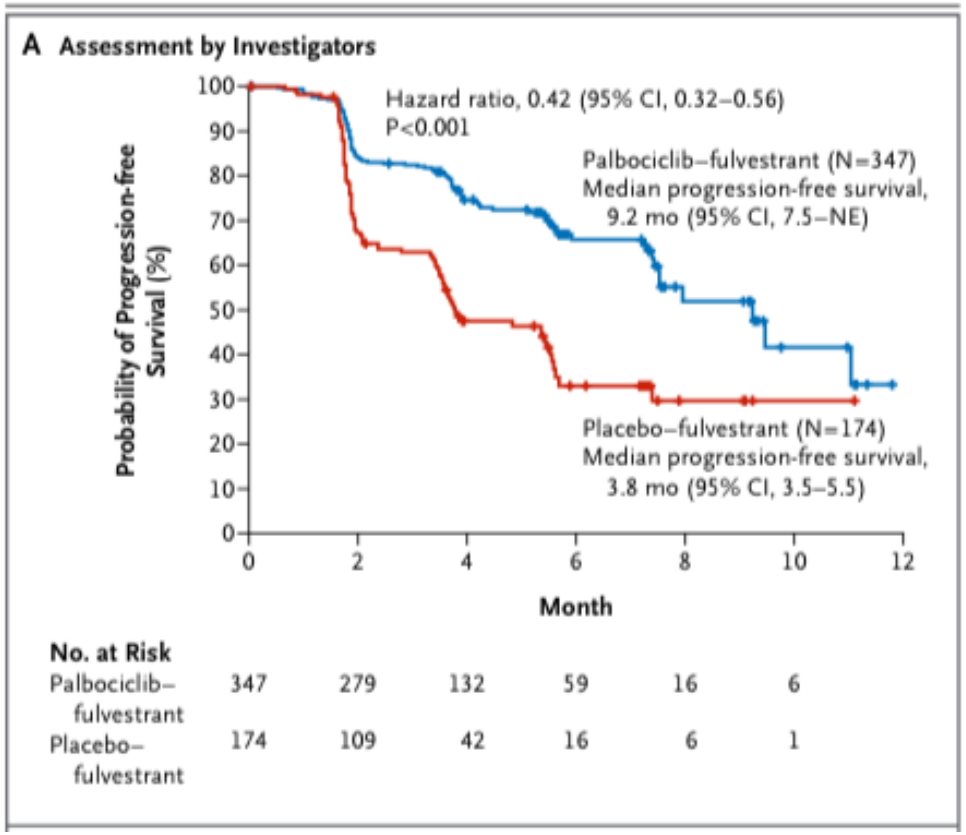


[a]All received goserelin.
[b]Must have progressed on prior endocrine therapy (pre-/perimenopausal) or aromatase inhibitor therapy (postmenopausal).
[c]Patients randomised.
[d]Administered on Days 1 and 15 of Cycle 1, then every 28 d.

Randomised Phase III double-blind trial at 144 centres in 17 countries (NCT01942135)

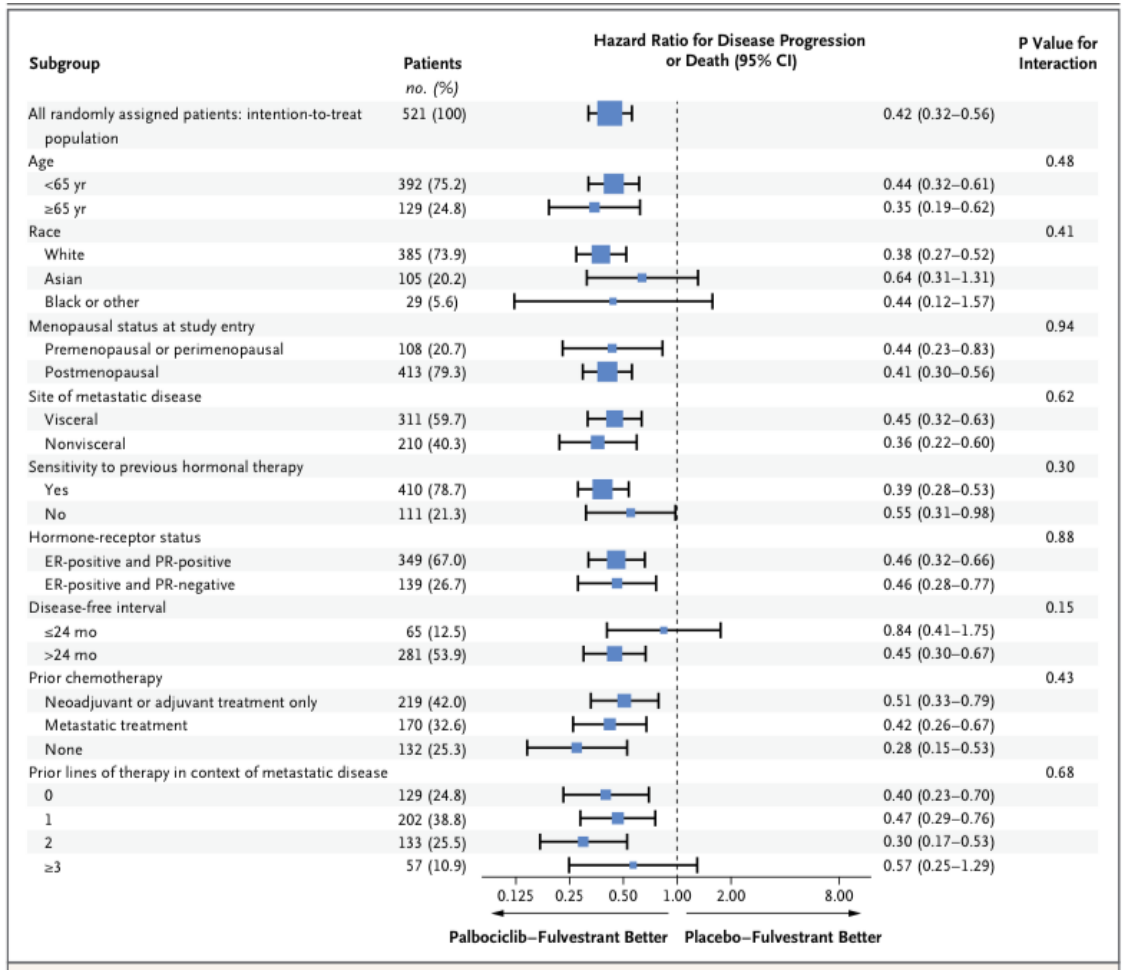
Turner NC, et al. N Engl J Med 2015;373:209–19;
Turner NC, et al. ASCO 2015 (Abstract LBA502);

PALOMA 3



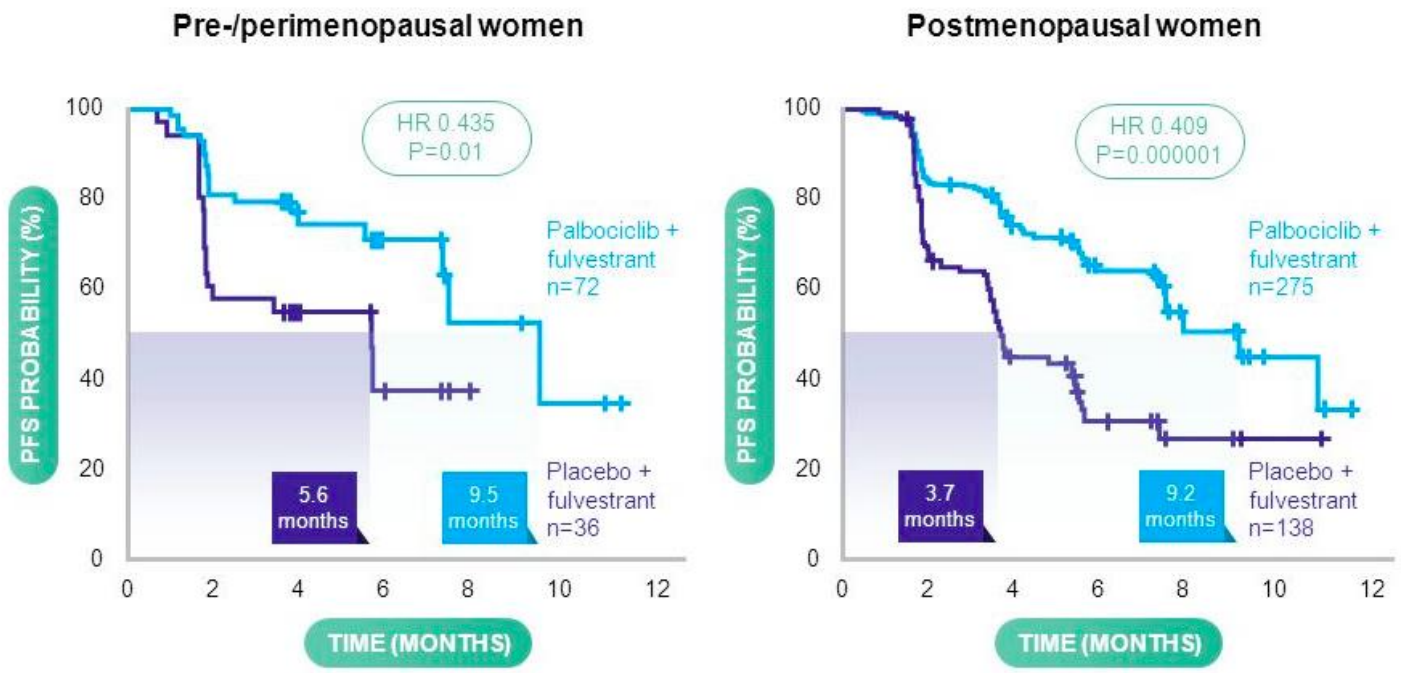
Outcome, % (95% CI)	Palbociclib + Fulvestrant (n = 345)	Placebo + Fulvestrant (n = 172)	Odds Ratio (95% CI)	*P* Value
ITT population				
▪ ORR	19.0 (15.0-23.6)	8.6 (4.9-13.8)	2.47 (1.36-4.91)	.0019
▪ CBR	66.6 (61.3-71.5)	39.7 (32.3-47.3)	3.05 (2.07-4.61)	< .0001
Pts with measurable disease at BL				
▪ ORR	24.6 (19.6-30.2)	10.9 (6.2-17.3)	2.69 (1.43-5.26)	.0012
▪ CBR	NR	NR	3.10 (1.99-4.92)	< .0001

PALOMA 3



Subgroup	Patients *no. (%)*	Hazard Ratio for Disease Progression or Death (95% CI)	P Value for Interaction
All randomly assigned patients: intention-to-treat population	521 (100)	0.42 (0.32–0.56)	
Age			0.48
<65 yr	392 (75.2)	0.44 (0.32–0.61)	
≥65 yr	129 (24.8)	0.35 (0.19–0.62)	
Race			0.41
White	385 (73.9)	0.38 (0.27–0.52)	
Asian	105 (20.2)	0.64 (0.31–1.31)	
Black or other	29 (5.6)	0.44 (0.12–1.57)	
Menopausal status at study entry			0.94
Premenopausal or perimenopausal	108 (20.7)	0.44 (0.23–0.83)	
Postmenopausal	413 (79.3)	0.41 (0.30–0.56)	
Site of metastatic disease			0.62
Visceral	311 (59.7)	0.45 (0.32–0.63)	
Nonvisceral	210 (40.3)	0.36 (0.22–0.60)	
Sensitivity to previous hormonal therapy			0.30
Yes	410 (78.7)	0.39 (0.28–0.53)	
No	111 (21.3)	0.55 (0.31–0.98)	
Hormone-receptor status			0.88
ER-positive and PR-positive	349 (67.0)	0.46 (0.32–0.66)	
ER-positive and PR-negative	139 (26.7)	0.46 (0.28–0.77)	
Disease-free interval			0.15
≤24 mo	65 (12.5)	0.84 (0.41–1.75)	
>24 mo	281 (53.9)	0.45 (0.30–0.67)	
Prior chemotherapy			0.43
Neoadjuvant or adjuvant treatment only	219 (42.0)	0.51 (0.33–0.79)	
Metastatic treatment	170 (32.6)	0.42 (0.26–0.67)	
None	132 (25.3)	0.28 (0.15–0.53)	
Prior lines of therapy in context of metastatic disease			0.68
0	129 (24.8)	0.40 (0.23–0.70)	
1	202 (38.8)	0.47 (0.29–0.76)	
2	133 (25.5)	0.30 (0.17–0.53)	
≥3	57 (10.9)	0.57 (0.25–1.29)	

PALOMA 3: PFS by Menopausal Status



Menopausal status interaction test P=0.94

All pre-/peri-menopausal patients also received goserelin.

Winer EP. ASCO 2015. 'Highlights of the Day: Breast Cancer

PALOMA 3: Adverse Events

Grade 3/4 Hematologic Event, n (%)	Palbociclib + Fulvestrant (n = 345)	Placebo + Fulvestrant (n = 172)
Neutropenia	223 (65)	1 (< 1)
Anemia	10 (3)	3 (2)
Leukopenia	95 (28)	2 (1)
Thrombocytopenia	8 (2)	0

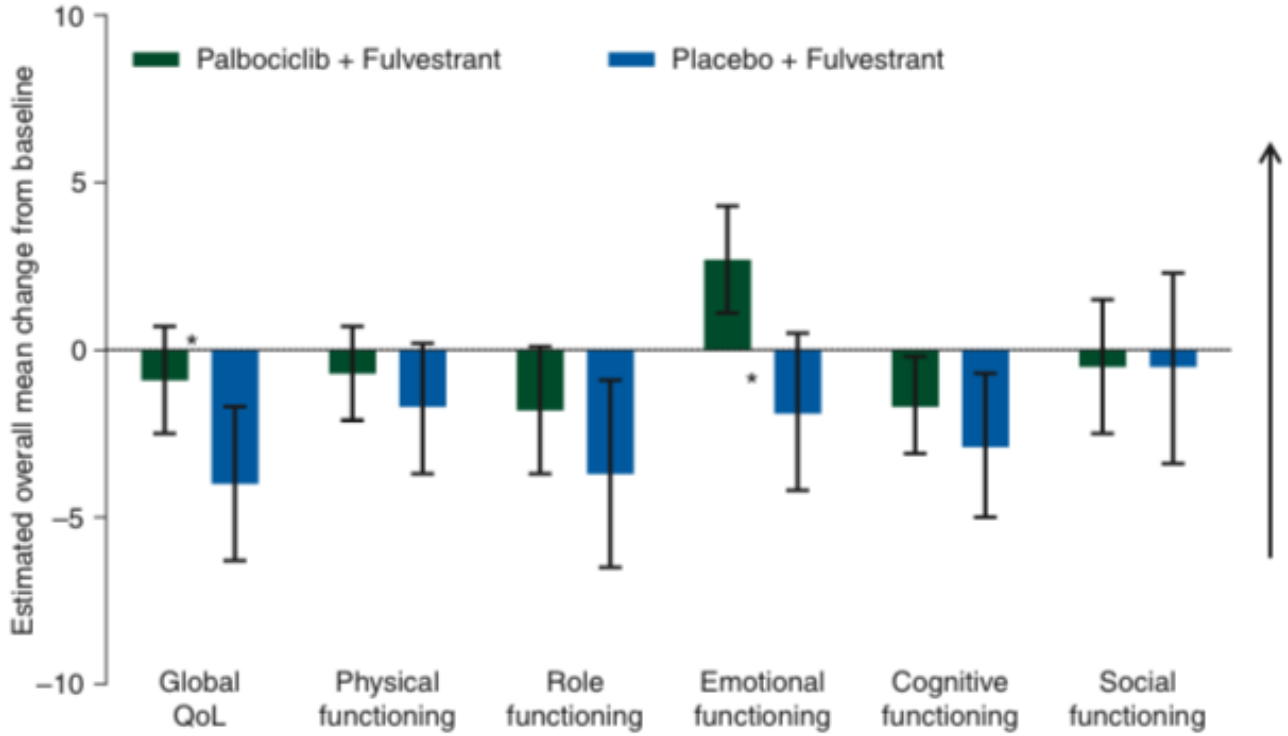
- Febrile neutropenia was uncommon in both groups (3 pts vs 1 pt, respectively)
- The most common nonhematologic AEs included infections, fatigue, nausea, headache, and diarrhea
  - Incidence of grade 3/4 AEs was comparable between arms, with no more than 2% of pts experiencing grade 3/4 toxicities
- Discontinuations due to AEs were similar with palbociclib + fulvestrant and placebo + fulvestrant (4% vs 2%, respectively)

Cristofanilli M, et al. Lancet Oncol. 2016;17:425-439.

Slide credit: clinicaloptions.com

Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial

N. Harbeck[1*], S. Iyer[2], N. Turner[3], M. Cristofanilli[4], J. Ro[5], F. André[6], S. Loi[7], S. Verma[8], H. Iwata[9], H. Bhattacharyya[2], K. Puyana Theall[10], C. H. Bartlett[2] & S. Loibl[11]



Ann Oncol. 2016 Jun;27(6):1047-54.

Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial

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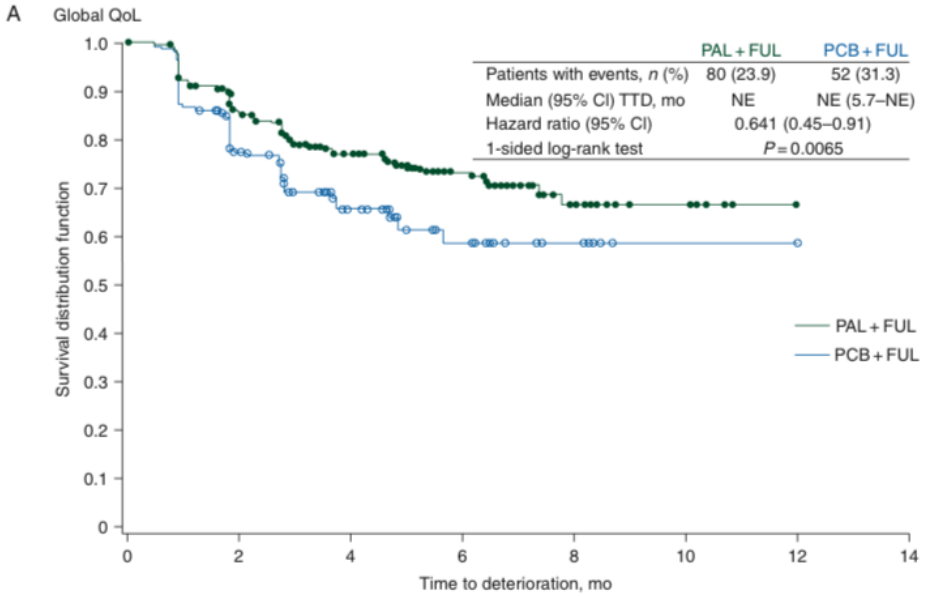
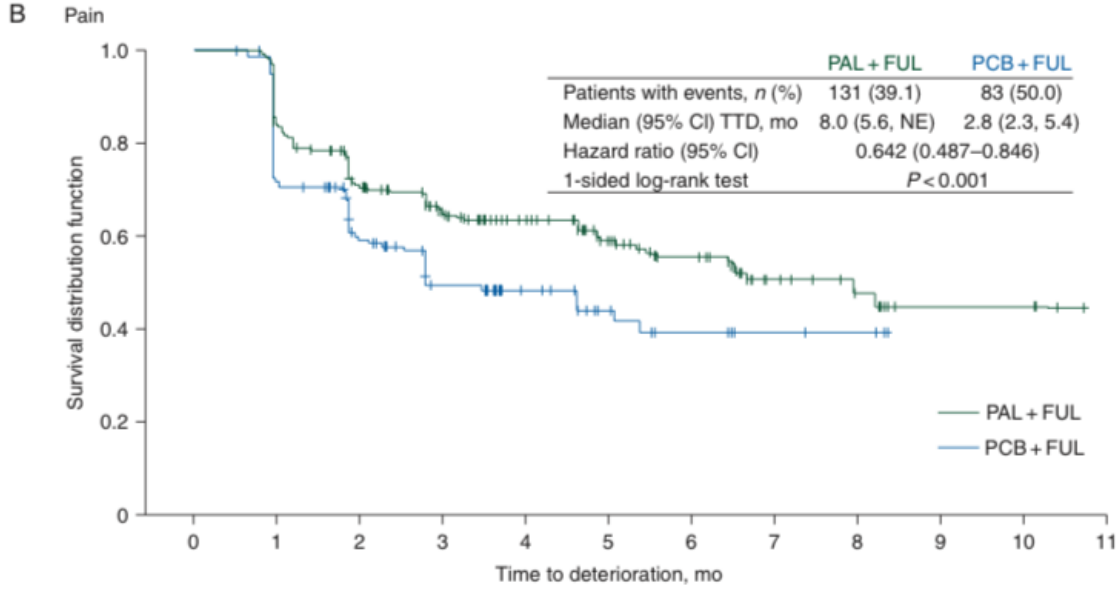




Ann Oncol. 2016 Jun;27(6):1047-54.

MONARCH 2: Study Design

Stratified by metastatic site,
ET resistance (primary vs secondary)

Patients with HR+/HER2- advanced breast cancer who progressed on 1 line of ET (neoadjuvant, adjuvant, or first line); pre/peri/post menopausal; no prior chemo for metastatic disease; ECOG PS 0/1
(N = 669)

Abemaciclib 150 mg BID* +
Fulvestrant 500 mg on Days 1, 15, 29
and once monthly thereafter
(n = 446)

Placebo +
Fulvestrant 500 mg on Days 1, 15, 29
and once monthly thereafter
(n = 223)

Median follow-up: 19.5 mos

*Dose reduced from 200 mg to 150 mg after 178 pts enrolled.

- Pts enrolled at 142 centers in 19 countries
- Primary endpoint: PFS (investigator assessed)
- Secondary endpoints: OS, ORR, clinical benefit rate, safety

Sledge GW, et al. ASCO 2017. Abstract 1000.

Slide credit: clinicaloptions.com

MONARCH 2

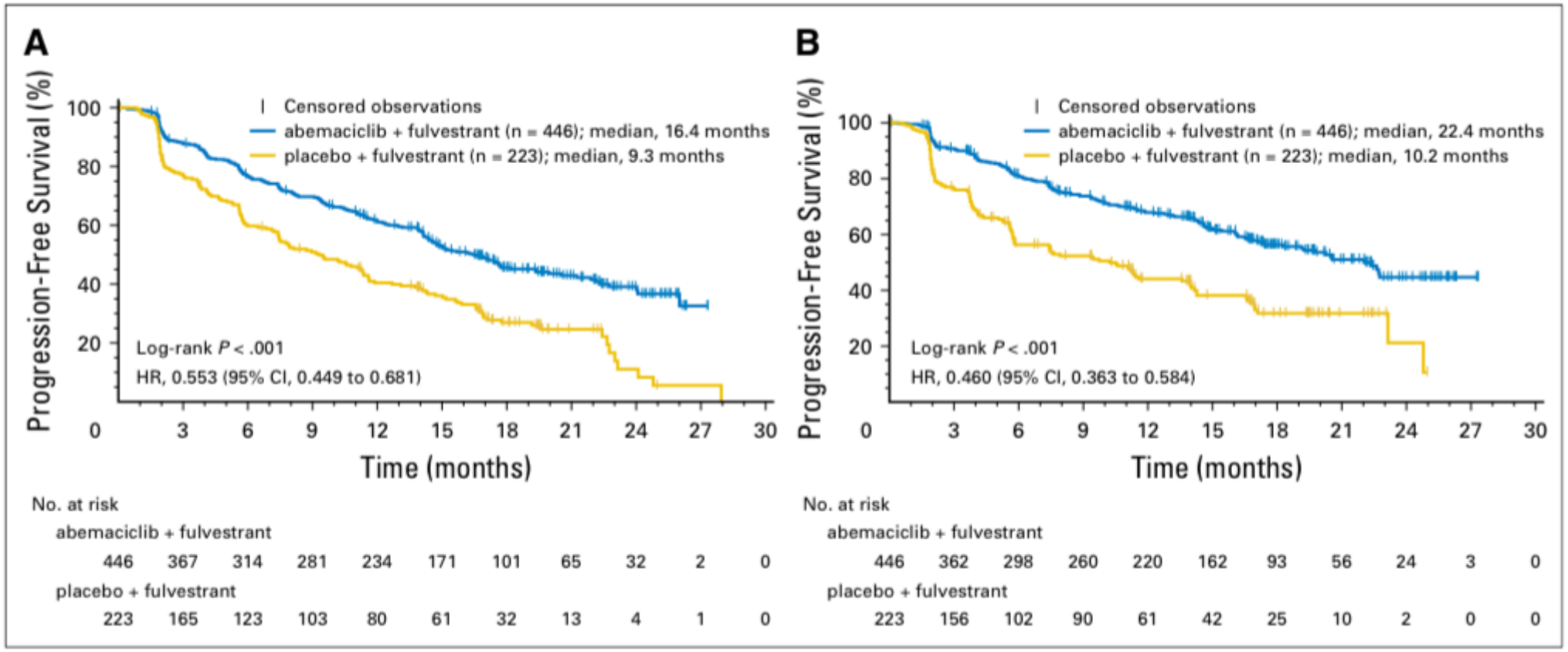


Fig 2. Kaplan-Meier plots of progression-free survival. (A) Investigator-assessed and (B) independent central review of intent-to-treat population. HR, hazard ratio.

Sledge. J Clin Oncol 2017; 35:2875-2884

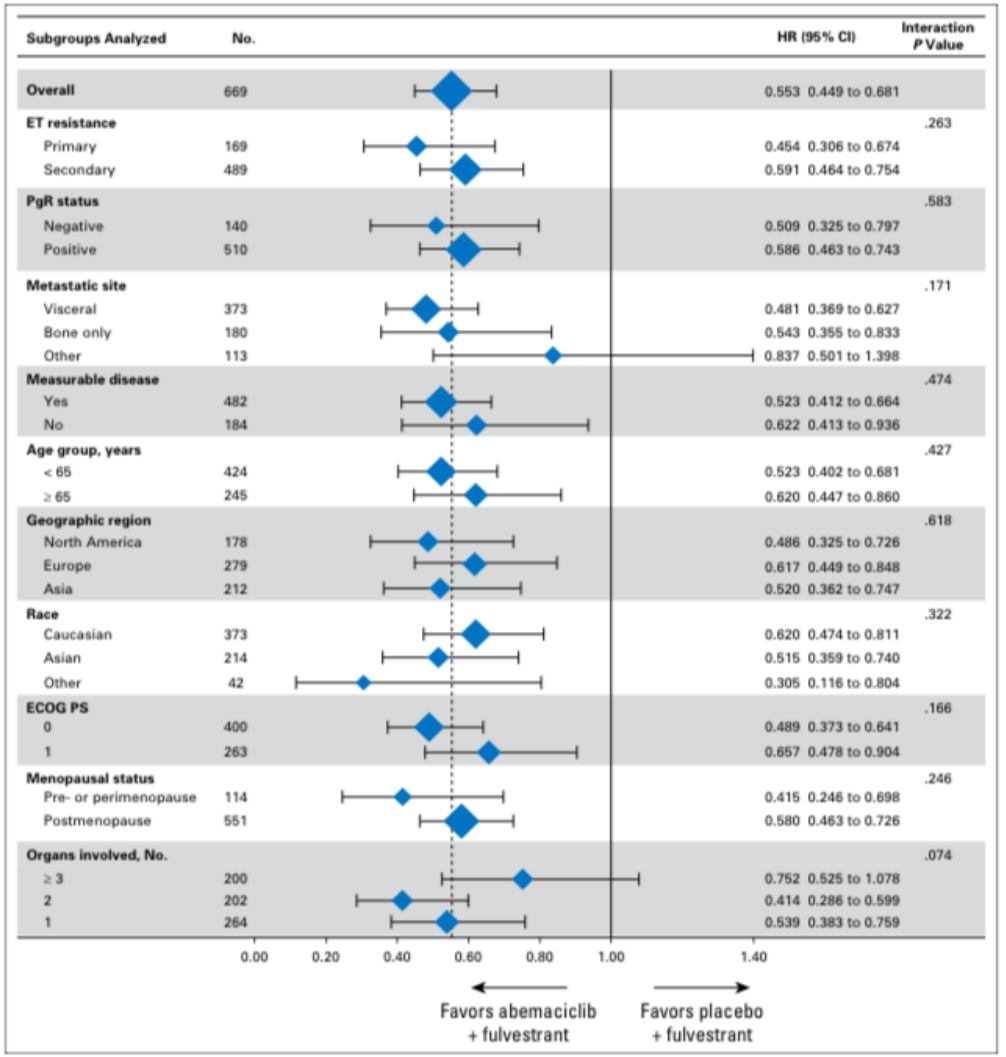
MONARCH 2

Table 2. Best Overall Response

Best Overall Response*	Abemaciclib + Fulvestrant (n = 446) No. (%)	Abemaciclib + Fulvestrant (n = 446) 95% CI†	Placebo + Fulvestrant (n = 223) No. (%)	Placebo + Fulvestrant (n = 223) 95% CI†	Odds Ratio	*P* Value
Intent-to-treat population						
CR	14 (3.1)	1.5 to 4.8	1 (0.4)	−0.4 to 1.3		
PR	143 (32.1)	27.7 to 36.4	35 (15.7)	10.9 to 20.5		
SD	213 (47.8)	43.1 to 52.4	133 (59.6)	53.2 to 66.1		
≥ 6 months	165 (37.0)	32.5 to 41.5	89 (39.9)	33.5 to 46.3		
Progressive disease	40 (9.0)	6.3 to 11.6	45 (20.2)	14.9 to 25.4		
Not evaluable	36 (8.1)	5.5 to 10.6	9 (4.0)	1.5 to 6.6		
Overall response rate (CR + PR)	157 (35.2)	30.8 to 39.6	36 (16.1)	11.3 to 21.0	2.82	< .001
Disease control rate (CR + PR + SD)	370 (83.0)	79.5 to 86.4	169 (75.8)	70.2 to 81.4	1.56	0.025
Clinical benefit rate (CR + PR + SD ≥ 6 months)	322 (72.2)	68.0 to 76.4	125 (56.1)	49.5 to 62.6	2.04	< .001
Measurable disease						
CR	11 (3.5)	1.5 to 5.5	0	NA		
PR	142 (44.7)	39.2 to 50.1	35 (21.3)	15.1 to 27.6		
SD	109 (34.3)	29.1 to 39.5	84 (51.2)	43.6 to 58.9		
≥ 6 months	80 (25.2)	20.4 to 29.9	50 (30.5)	23.4 to 37.5		
Progressive disease	32 (10.1)	6.8 to 13.4	38 (23.2)	16.7 to 29.6		
Not evaluable	24 (7.5)	4.6 to 10.5	7 (4.3)	1.2 to 7.4		
Overall response rate (CR + PR)	153 (48.1)	42.6 to 53.6	35 (21.3)	15.1 to 27.6	3.42	< .001
Disease control rate (CR + PR + SD)	262 (82.4)	78.2 to 86.6	119 (72.6)	65.7 to 79.4	1.77	0.012
Clinical benefit rate (CR + PR + SD ≥ 6 months)	233 (73.3)	68.4 to 78.1	85 (51.8)	44.2 to 59.5	2.55	< .001

Sledge. J Clin Oncol 2017; 35:2875-2884

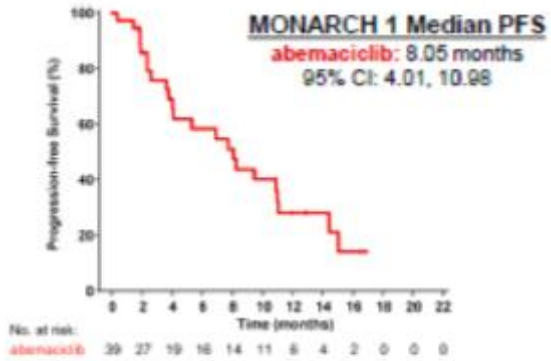
MONARCH 2



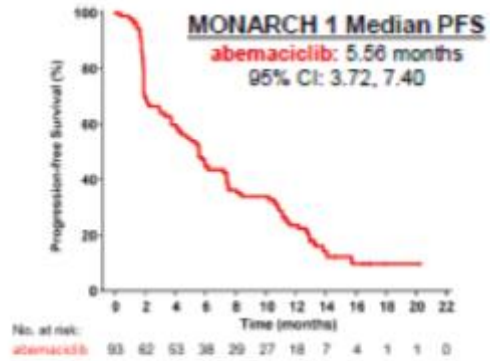
Sledge. J Clin Oncol 2017; 35:2875-2884

Progression-Free Survival

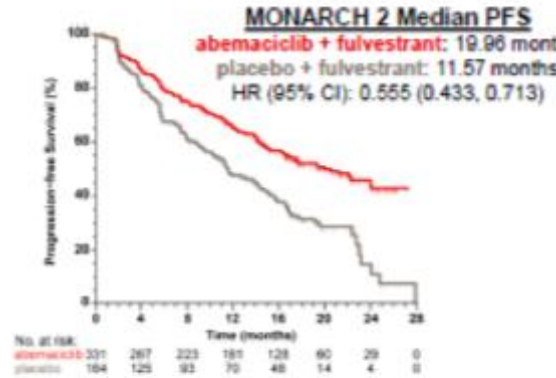
Liver Metastases - No



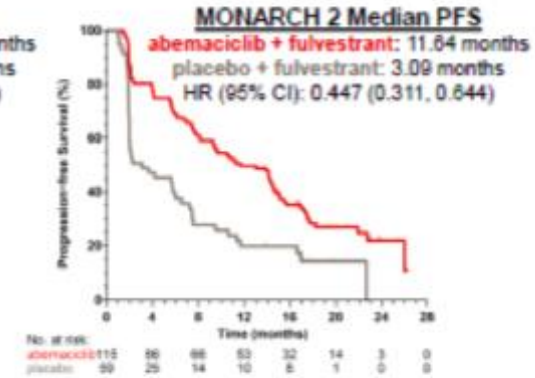
Liver Metastases - Yes



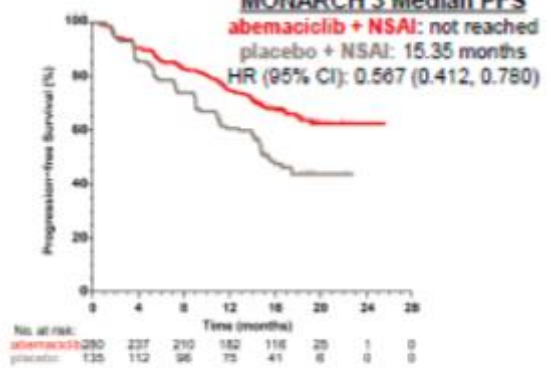
Liver Metastases - No



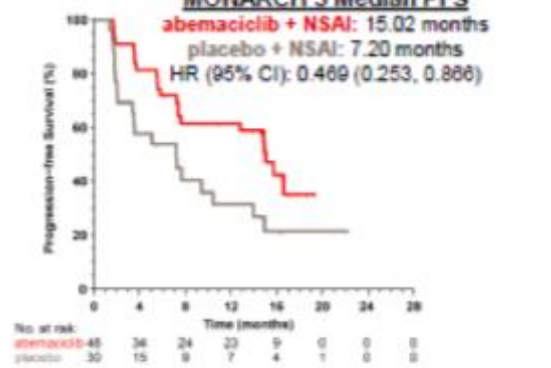
Liver Metastases - Yes



Liver Metastases - No



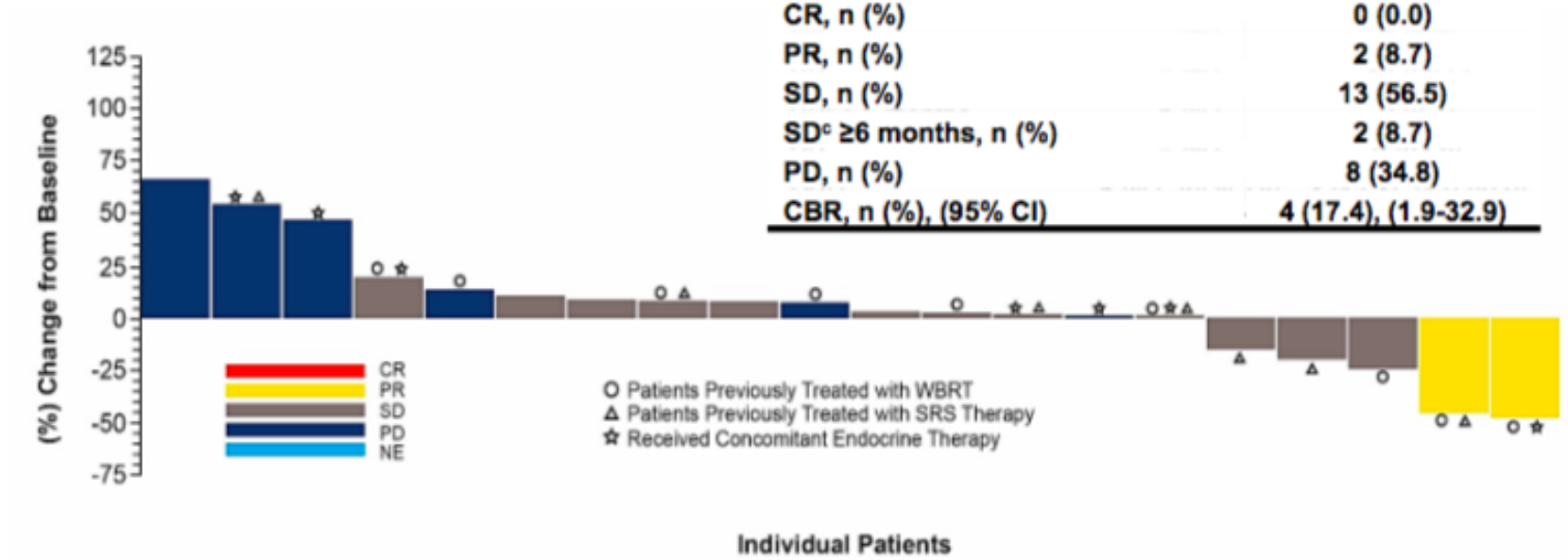
Liver Metastases - Yes



Di Leo A, et al. Presented at: 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, Texas. Abstract P5-21-02.

CNS Response[a] Summary[b] for Part B (HR+, HER2-)

Patients With Response	N = 23
OIRR, n (%), (95% CI)	2 (8.7), (0.0-20.2)
CR, n (%)	0 (0.0)
PR, n (%)	2 (8.7)
SD, n (%)	13 (56.5)
SD[c] ≥6 months, n (%)	2 (8.7)
PD, n (%)	8 (34.8)
CBR, n (%), (95% CI)	4 (17.4), (1.9-32.9)



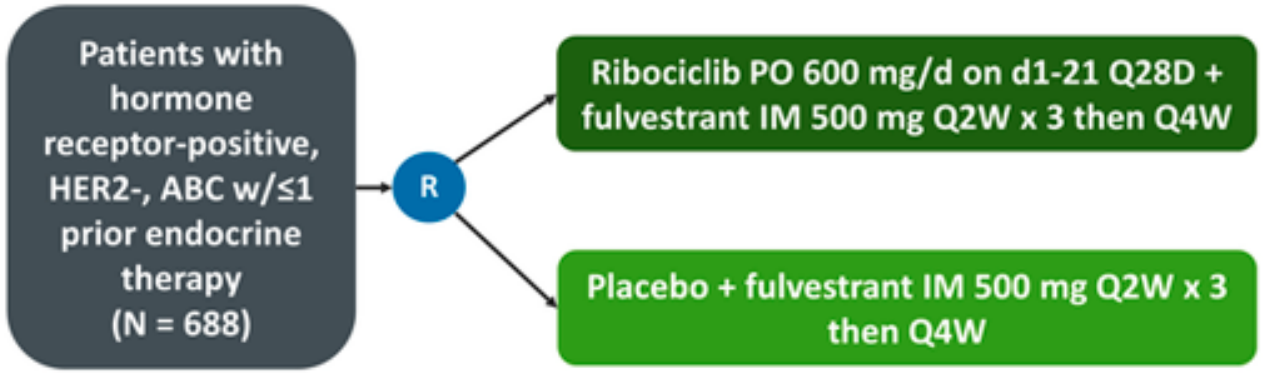
[a]Response criteria per RANO-BM; [b]3 patients had no post-baseline tumor measurements and therefore were not included in this waterfall plot; [c]Patients with SD ≥6 months are included in the number of patients with SD

Bachelot T, et al. Presented at: 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, Texas. Abstract P1-17-03.

Ongoing Studies

Ribociclib + Fulvestrant in First-Line MBC: MONALEESA-3 Trial

- Randomized, double-blind, phase 3 trial

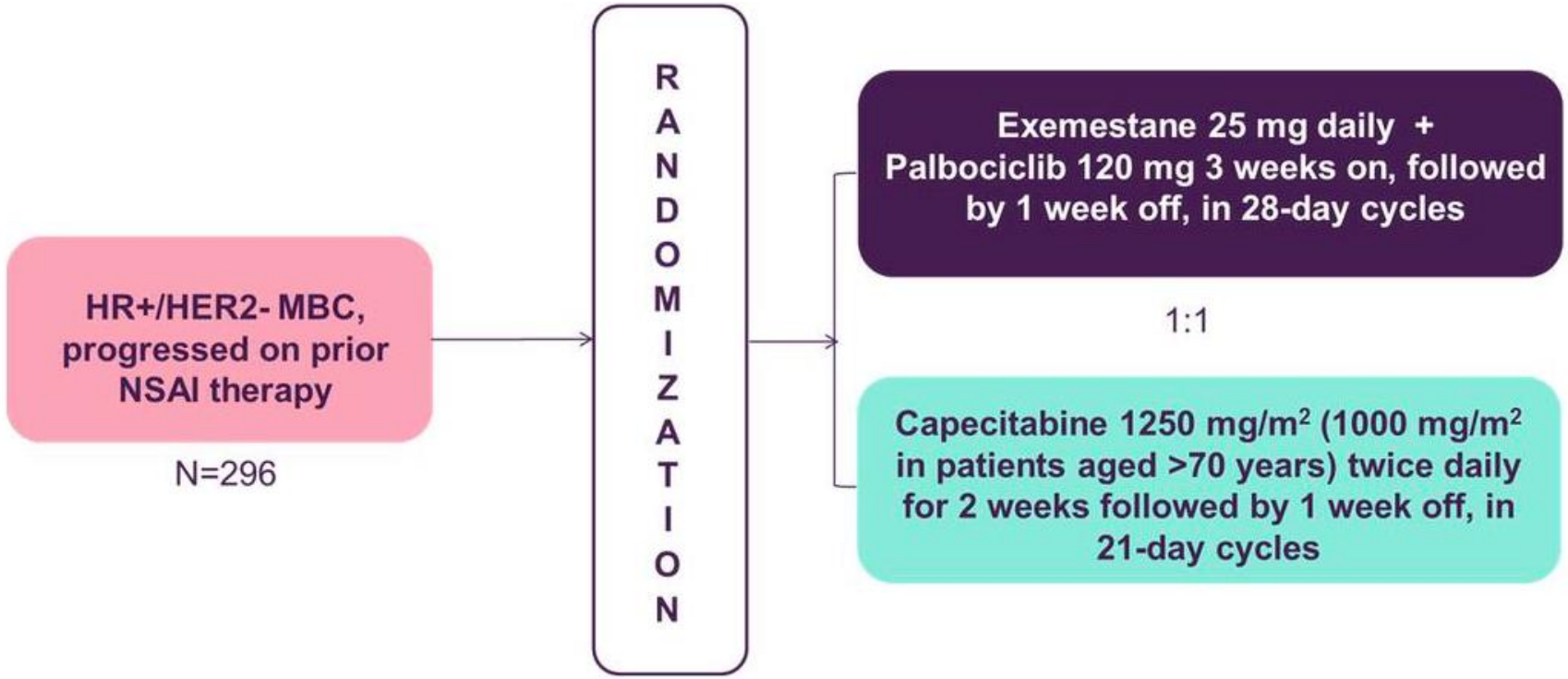


Primary endpoint: PFS

Estimated primary completion date February 2020.

ClinicalTrials.gov. NCT02422615.

PEARL Trial



Primary Endpoint: PFS

Clinical trial information: NCT0208507

Selective CDK 4/6 Inhibitors: Comparison of Key Clinical Characteristics

	Palbociclib	Ribociclib	Abemaciclib
Route	PO	PO	PO
Dose, mg	125 QD	600 QD	200 BID
Schedule	3 wks on/1 wk off	3 wks on/1 wk off	Continuous
Half-life, hr	27	32.6	17-38
ORR (monotherapy), %	6	2.3	19.7
Key grade 3/4 toxicities, %	Neutropenia, 51 Thrombocytopenia, 22	Neutropenia, 28 Thrombocytopenia, 9	Neutropenia, 27 Diarrhea, 20 Fatigue, 13
CNS penetration	Uncertain	No	Yes

DeMichele A, et al. Clin Cancer Res. 2015;21:995-1001. Hamilton E, et al. Cancer Treatment Rev. 2016;45:129-138. Infante JR, et al. Clin Cancer Res. 2016;22:5696-5705. Dickler MN, et al. ASCO 2016. Abstract 510. Barroso-Sousa R, et al. Breast Care. 2016;11:167-173.

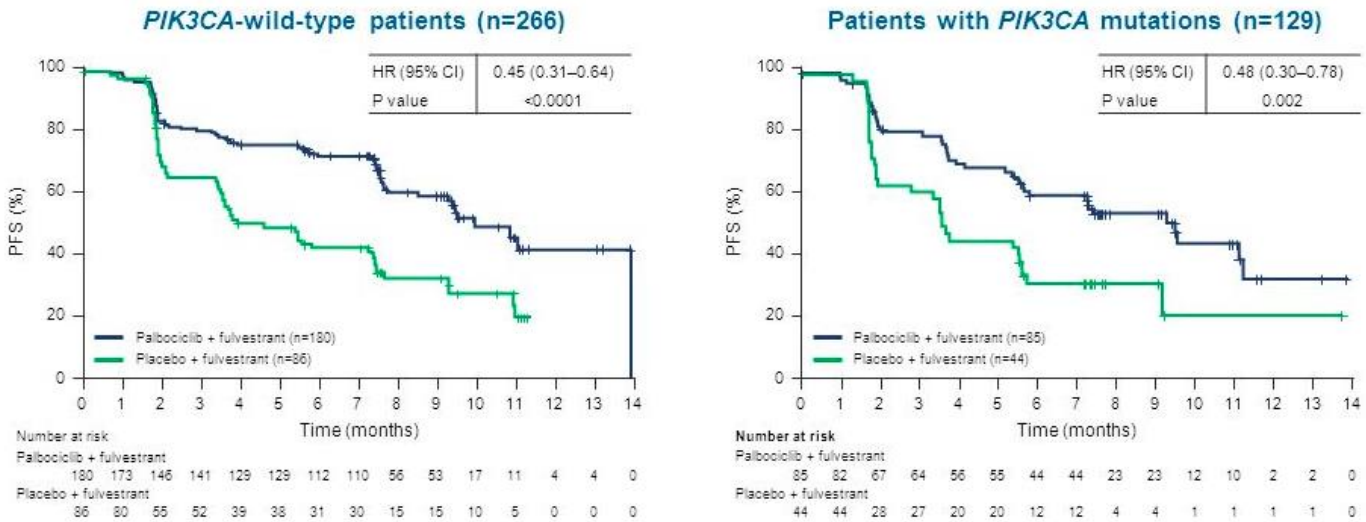
Slide credit: clinicaloptions.com

Predictive Factors for CDK 4/6 inhibitors

PALOMA 3: Treatment effect by PIK3CA status

- ***PIK3CA*** **mutations were detected in 33% of patients who provided baseline plasma samples for cell-free DNA analysis (129/395)**

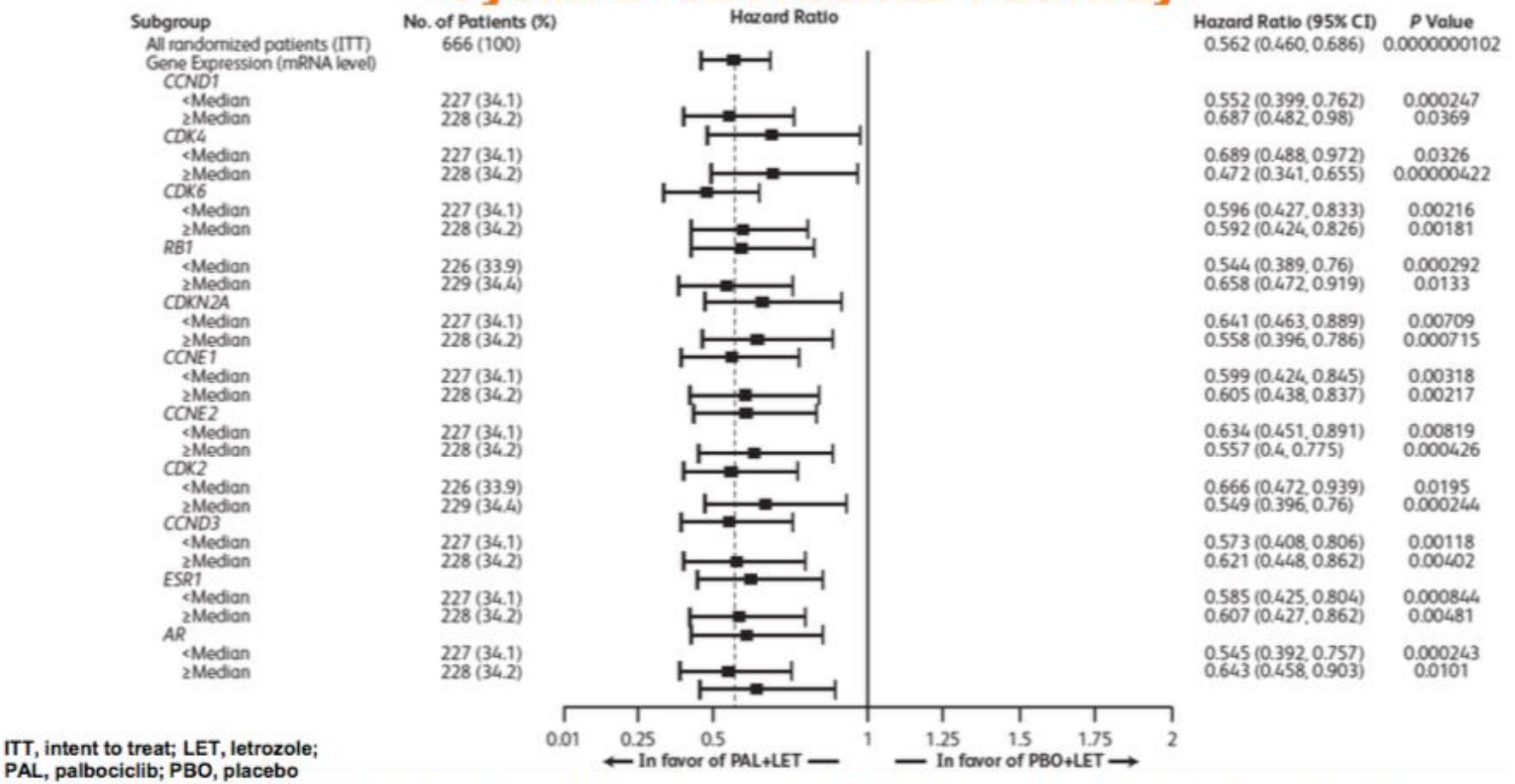
PIK3CA status did not influence the magnitude of PFS benefit from palbociclib (HR=0·45 for _PIK3CA_ wild-type, HR=0·48 for _PIK3CA_ mutation positive, $P_{interaction}$ = 0·83)



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

Cristofanilli M, et al. Lancet Oncol. 2016

Subgroup Analysis Based on Target Gene Expression in the Cyclin D-CDK4/6-RB Pathway



ITT, intent to treat; LET, letrozole; PAL, palbociclib; PBO, placebo

Finn RS, et al. Presented at: 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017: San Antonio, TX. Abstract P2-09-10.

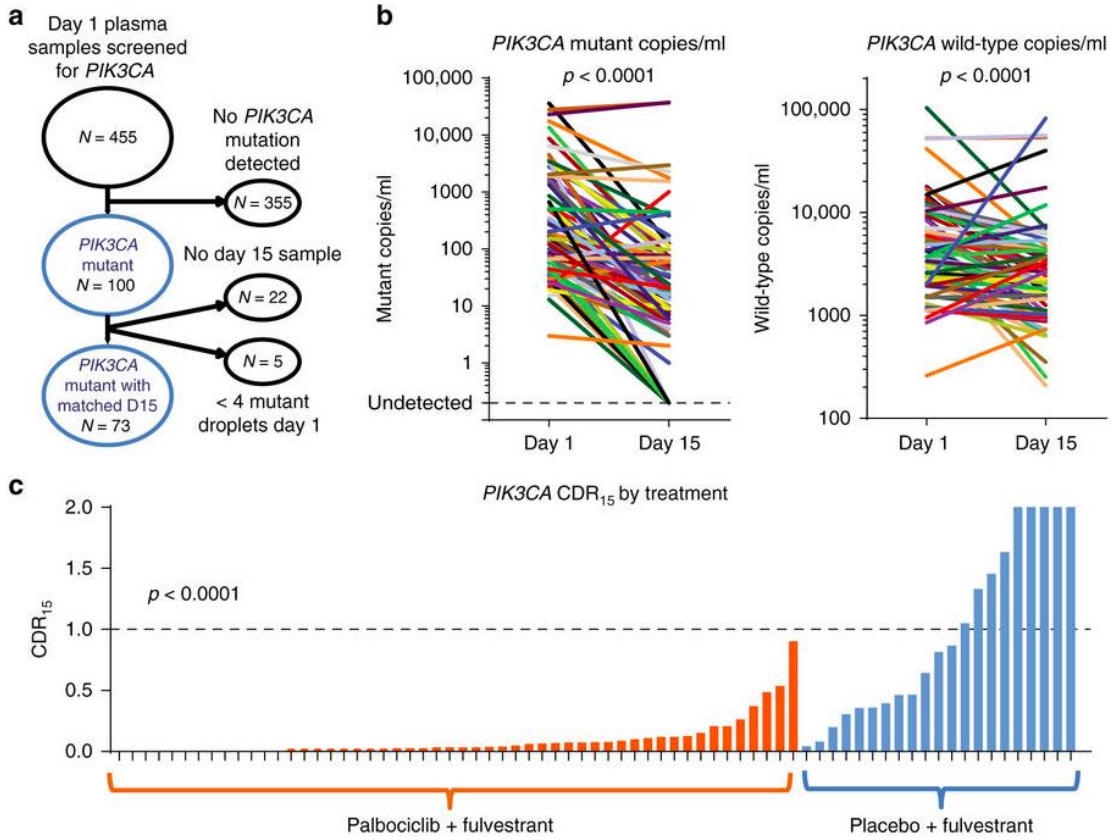
Treatment effects of palbociclib in combination with endocrine therapy were consistent across all the analyzed biomarker subgroups.

ARTICLE

DOI: 10.1038/s41467-018-03215-x OPEN

Early circulating tumor DNA dynamics and clonal selection with palbociclib and fulvestrant for breast cancer

Ben O'Leary[1,2], Sarah Hrebien[1], James P. Morden[3], Matthew Beaney[1], Charlotte Fribbens[1,2], Xin Huang[4], Yuan Liu[4], Cynthia Huang Bartlett[4], Maria Koehler[4], Massimo Cristofanilli[5], Isaac Garcia-Murillas[1], Judith M. Bliss[3] & Nicholas C. Turner[1,2]



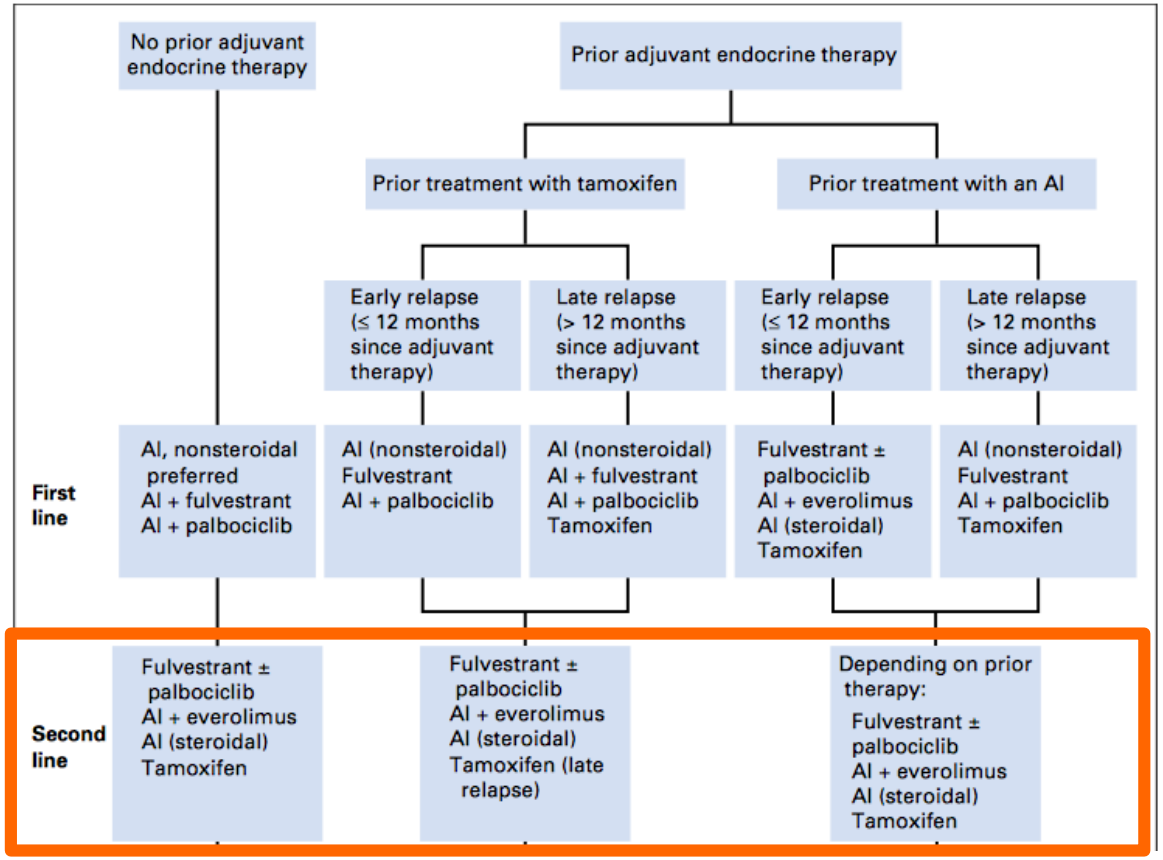
O'Leary B. Nat Commun. 2018 Mar 1;9(1):896.

Guidelines for Treatment of HR positive metastatic BC

VOLUME 34 · NUMBER 25 · SEPTEMBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline



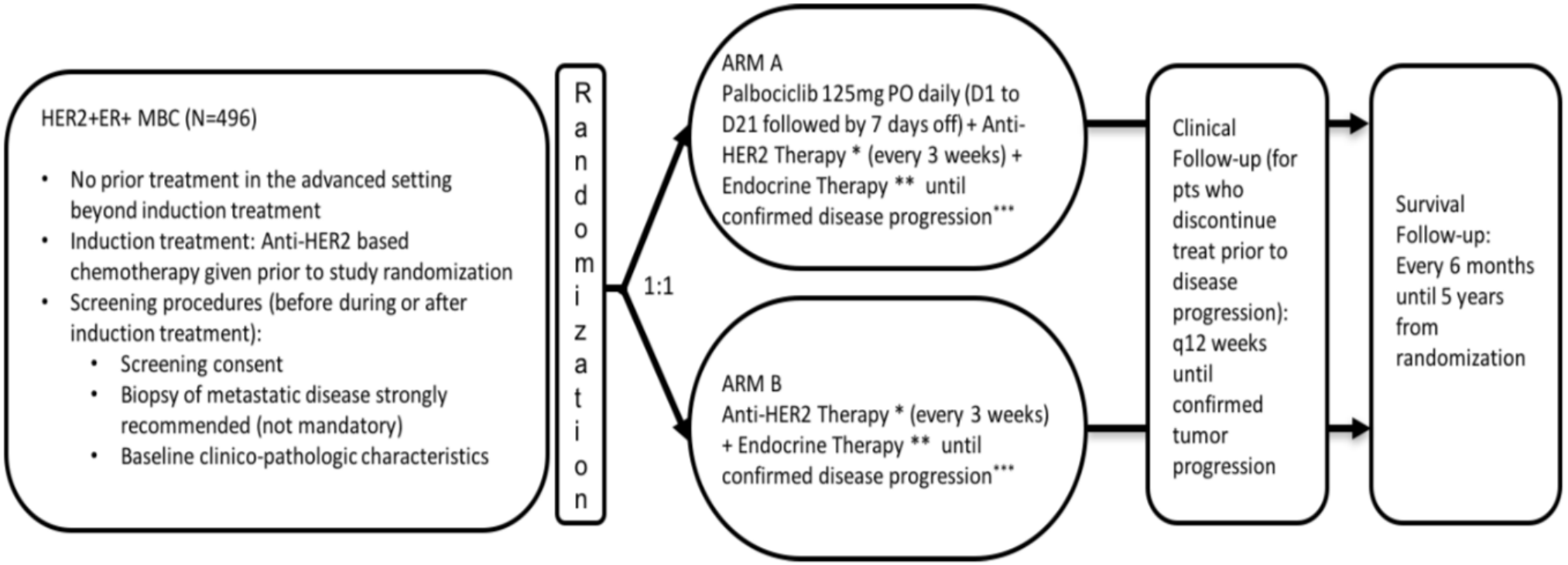
Rugo HS. J Clin Oncol. 2016 Sep 1;34(25):3069-103.

How Are Physicians Treating ER+/HER2– BC in Real Life?

		First-Line Treatment for ABC		Number of ET Lines Before First CT		
Analysis	Nº ER+/ HER2–	CT	ET	1 Line	2 Lines	≥3 Lines
US[1]	19,120	40%	60%	44%	12%	4%
Europe[2]	355	31%	69%	62%	7%	0%
Brazil[3]	690	53%	47%	-	-	-
UK[4]	209	50%	50%	-	-	-

1. Swallow E, et al. Curr Med Res Opin 2014;30:1537–1545;
2. Andre F, et al. Curr Med Res Opin 2014;30:1007–1016.
3. Barrios CH, et al. Can Res 76, P06,-16,-04, 2016;
4. Kurosky S, et al. Presented at the International Society for Pharmacoeconomics and Outcomes Research 18th Annual European Congress, 2015; Milan, Italy (PCN352)

PATINA TRIAL - HER2 Positive



COLLABORATORS

ALLIANCE FOUNDATION TRIALS, LLC

Australia & New Zealand Breast Cancer Trials Group

GBG GERMAN BREAST GROUP

ECOG

SOLTI

Pfizer Oncology

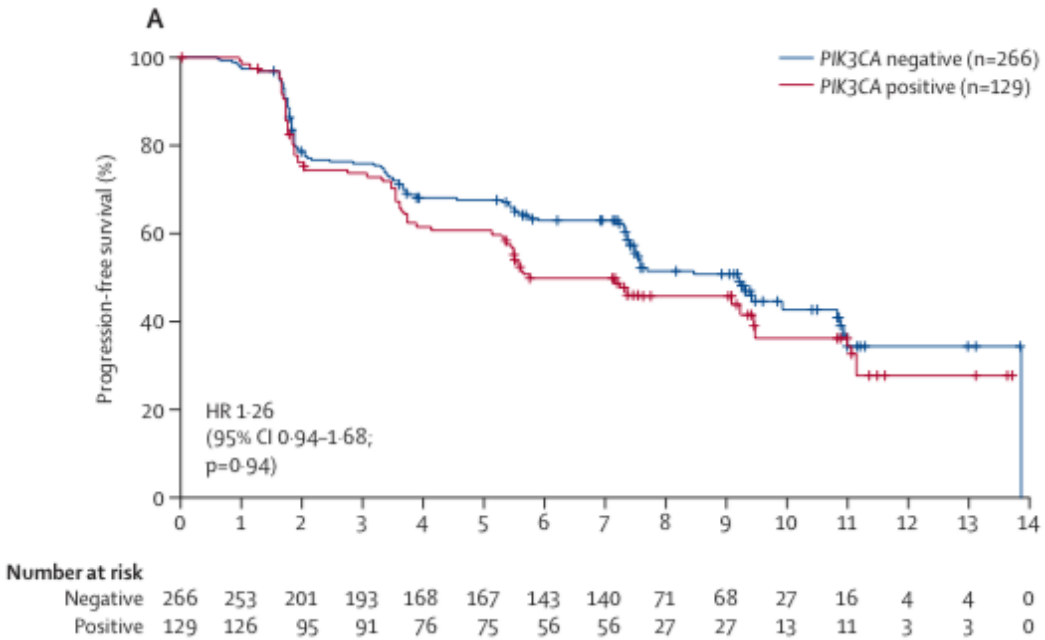
cura.

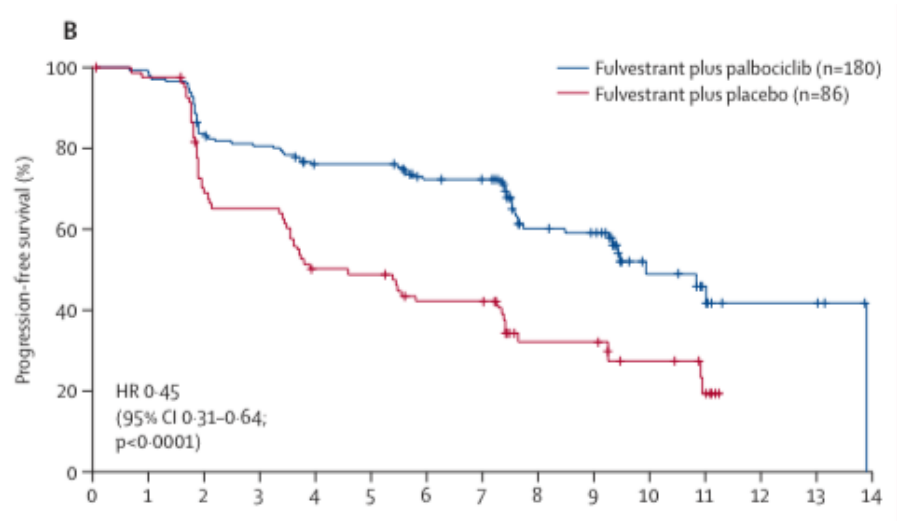
LACOG LATIN AMERICAN COOPERATIVE ONCOLOGY GROUP

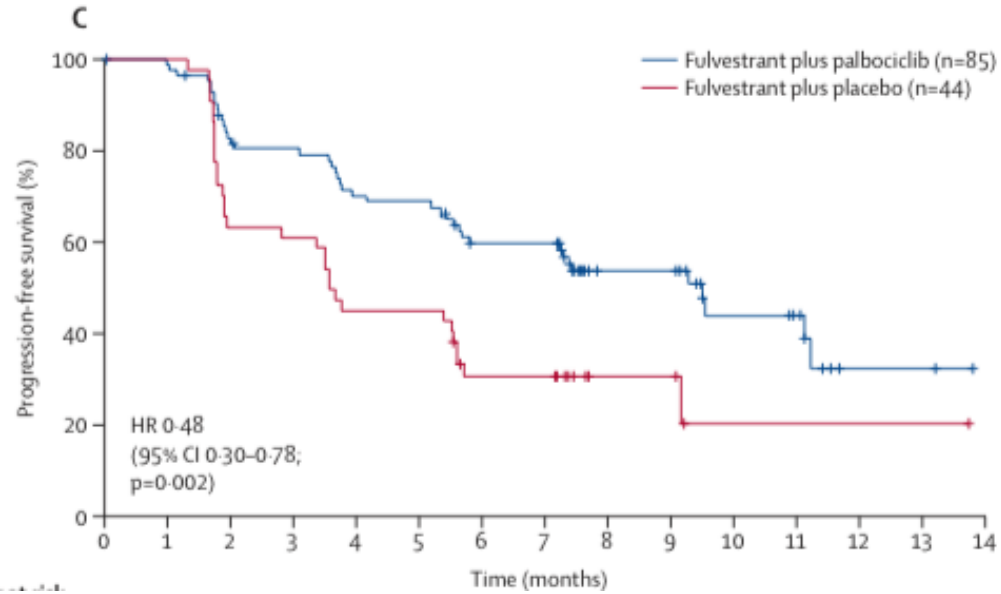
Conclusion

- CDKs 4/6 double the benefit in terms of PFS in hormone refractory metastatic breast cancer
- All subgroups of patients benefit
- To date only ER positivity is a predictive factor for CDKs 4/6 benefit
- Question: when to start CDK4/6 inhibitors with ET – first x second-line

Back up

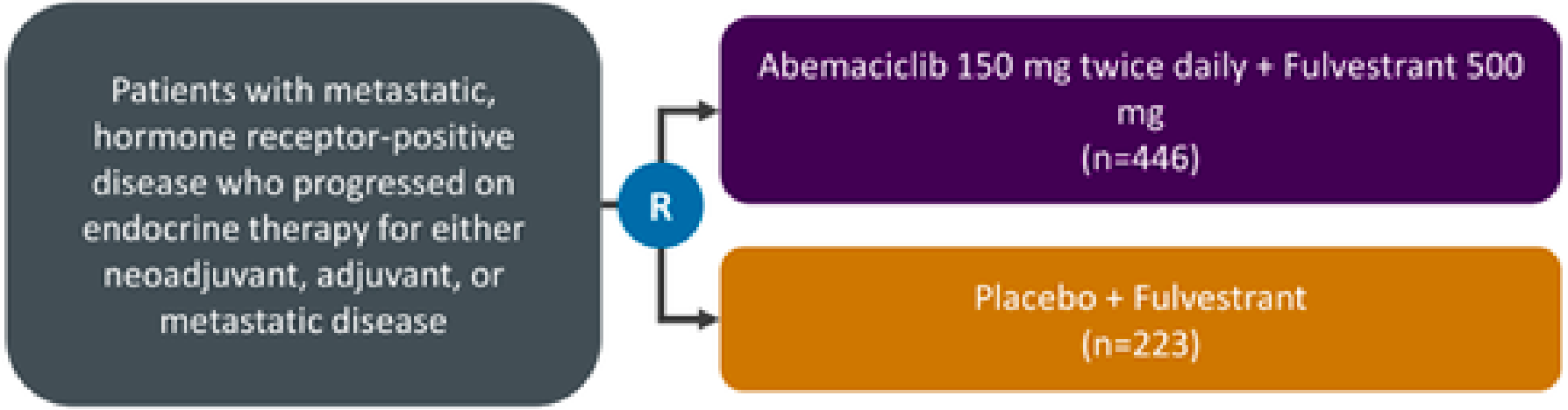

A
PIK3CA negative (n=266)
PIK3CA positive (n=129)
Progression-free survival (%)
HR 1·26
(95% CI 0·94–1·68;
p=0·94)
Number at risk
Negative 266 253 201 193 168 167 143 140 71 68 27 16 4 4 0
Positive 129 126 95 91 76 75 56 56 27 27 13 11 3 3 0


B
Fulvestrant plus palbociclib (n=180)
Fulvestrant plus placebo (n=86)
Progression-free survival (%)
HR 0·45
(95% CI 0·31–0·64;
p<0·0001)


C
Fulvestrant plus palbociclib (n=85)
Fulvestrant plus placebo (n=44)
Progression-free survival (%)
HR 0·48
(95% CI 0·30–0·78;
p=0·002)
Time (months)

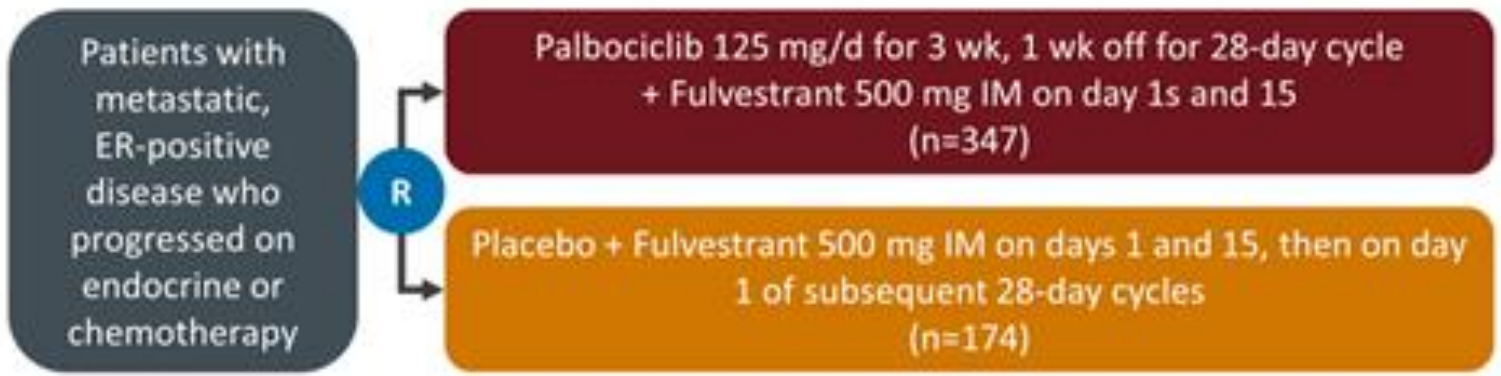
MONARCH 2: Abemaciclib in Progressive Disease

- Randomized phase 3 trial (N = 669)



PALOMA-3: Palbociclib in Progressive Disease

- Randomized phase 3 trial



Efficacy and Safety of Abemaciclib in Patients With Liver Metastases in the MONARCH 1, 2, and 3 Studies

Abstract P5-21-02

Di Leo A, Dickler M, Sledge GW, Toi M, Forrester T, Nanda S, Koustenis A, Bourayou N, Johnston S

Study Design Overview of the MONARCH 1, 2, and 3 Trials

Key Enrollment Criteria	MONARCH 1	MONARCH 2	MONARCH 3
Prior endocrine therapy	Progress on or after ET	Progressed while receiving adjuvant or first-line ET of ≤12 months from the end of adjuvant ET	ET naïve or disease relapse >12 months after (neo)adjuvant ET
Chemotherapy regimens in advanced setting	1 or 2	0	0
Visceral crisis[1,2]	No restriction	Not permitted	Not permitted
ECOG PS	0 or 1	0 or 1	0 or 1
Dose and schedule			
Abemaciclib	200 mg, twice daily, continuous	150 mg[a], twice daily, continuous	150 mg, twice daily, continuous
Fulvestrant	-	500 mg, per label	
Anastrozole[b]	-	-	1 mg, daily
Letrozole[b]	-	-	2.5 mg, daily

[a]post-amendment; [b]physician's choice of NSAI (anastrozole or letrozole)

1. Cardoso F, et al. *Ann Oncol.* 2014;25(10):1871-1888; 2. Cardoso F, et al. *Breast.* 2014;23(5):489-502.
Di Leo A, et al. Presented at: 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, Texas. Abstract P5-21-02.

Incidence of Patients With Liver Metastases

	MONARCH 1	MONARCH 2		MONARCH 3	
Presence of Liver Metastases	Abemaciclib N = 132	Abemaciclib + Fulvestrant N = 446	Placebo + Fulvestrant N = 223	Abemaciclib + NSAI N = 328	Placebo + NSAI N = 165
Yes	93 (70.5%)	115 (25.8%)	59 (26.5%)	48 (14.6%)	30 (18.2%)
No	39 (29.5%)	332 (74.2%)	164 (73.5%)	280 (85.4%)	135 (81.8%)

Di Leo A, et al. Presented at: 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, Texas. Abstract P5-21-02.

Response Rates (Measurable Disease)

	MONARCH 1	MONARCH 2		MONARCH 3	
Treatment Arm	Abemaciclib	Abemaciclib + Fulvestrant	Placebo + Fulvestrant	Abemaciclib + NSAI	Placebo + NSAI
Liver metastases - Yes	n = 93	n = 111	n = 59	n = 48	n = 29
Objective response rate, n (%)	20 (21.5)	54 (48.6)	9 (15.3)	26 (54.2)	6 (20.7)
Complete response, n (%)	0	2 (1.8)	0	0	0
Partial response, n (%)	20 (21.5)	52 (46.8)	9 (15.3)	26 (54.2)	6 (20.7)
Clinical benefit rate, n (%)	39 (41.9)	76 (68.5)	21 (35.6)	32 (66.7)	12 (41.4)
Disease control rate, n (%)	59 (63.4)	85 (76.6)	29 (49.2)	41 (85.4)	18 (62.1)
Liver metastases - No	n = 39	n = 207	n = 105	n = 219	n = 101
Objective response rate, n (%)	6 (15.4)	99 (47.8)	26 (24.8)	132 (60.3)	51 (50.5)
Complete response, n (%)	0	9 (4.3)	0	5 (2.3)	0
Partial response, n (%)	6 (15.4)	90 (43.5)	26 (24.8)	127 (58.0)	51 (50.5)
Clinical benefit rate, n (%)[b]	17 (43.6)	157 (75.8)	64 (61.0)	180 (82.2)	78 (77.2)
Disease control rate, n (%)	30 (76.9)	177 (85.5)	90 (85.7)	199 (90.9)	94 (93.1)

Di Leo A, et al. Presented at: 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, Texas. Abstract P5-21-02.

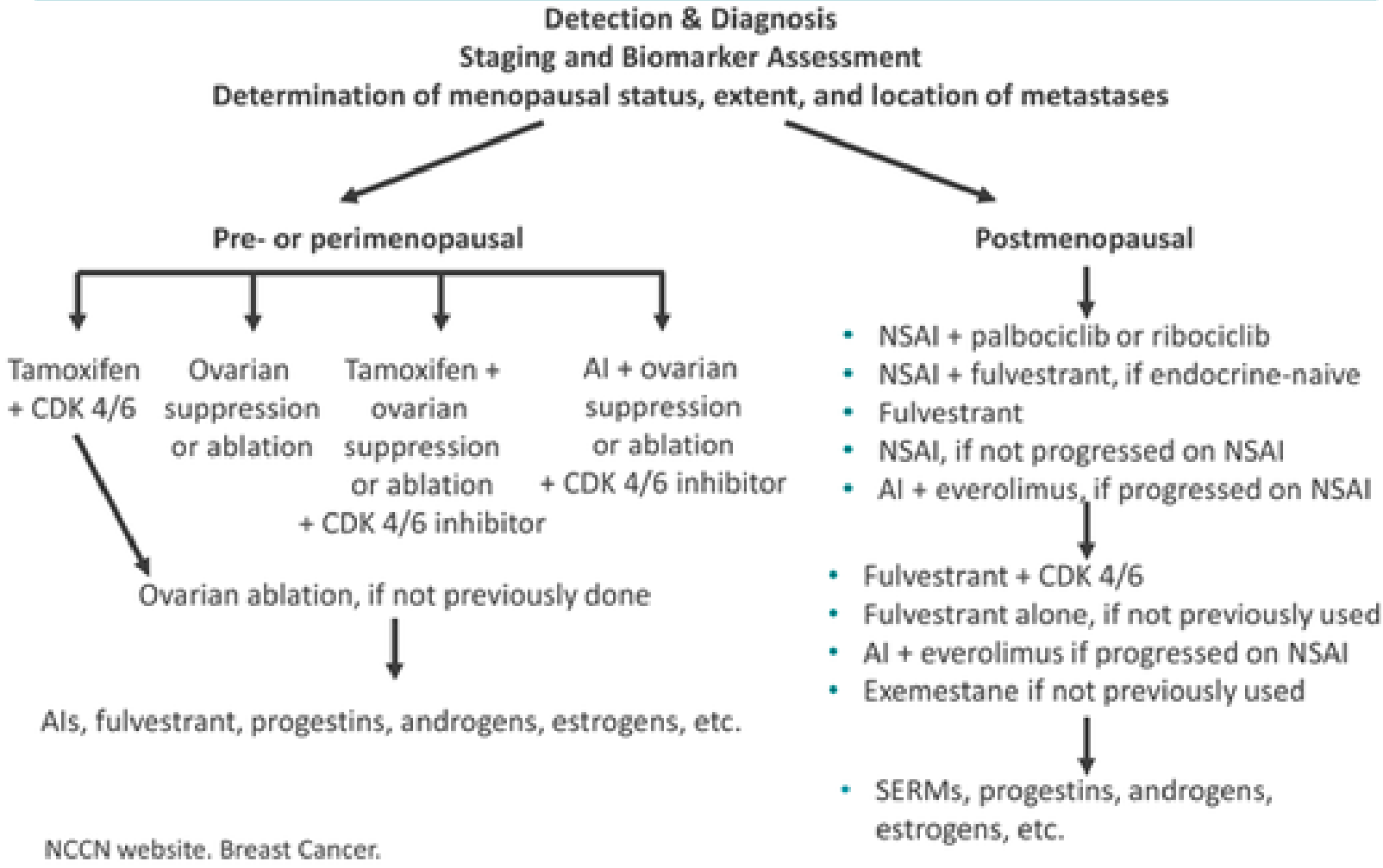
Treatment with CDK 4/6 beyond progression

Abemaciclib

- Phase 1 trial with abemaciclib alone or in combination with pre-existing endocrine therapy[a] (N = 55)
  - Acceptable safety and early clinical activity as a single agent
- Phase 2 MONARCH 1 trial of single agent abemaciclib[b] (N = 132)
  - ORR was 19.7%
  - Clinical benefit rate was 42.4%
  - Median duration of response was 8.6 months

a. Shapiro J, et al. ASCO 2013. Abstract 2500. b. Dickler M, et al. *J Clin Oncol*. 2016;34(suppl). Abstract 510.

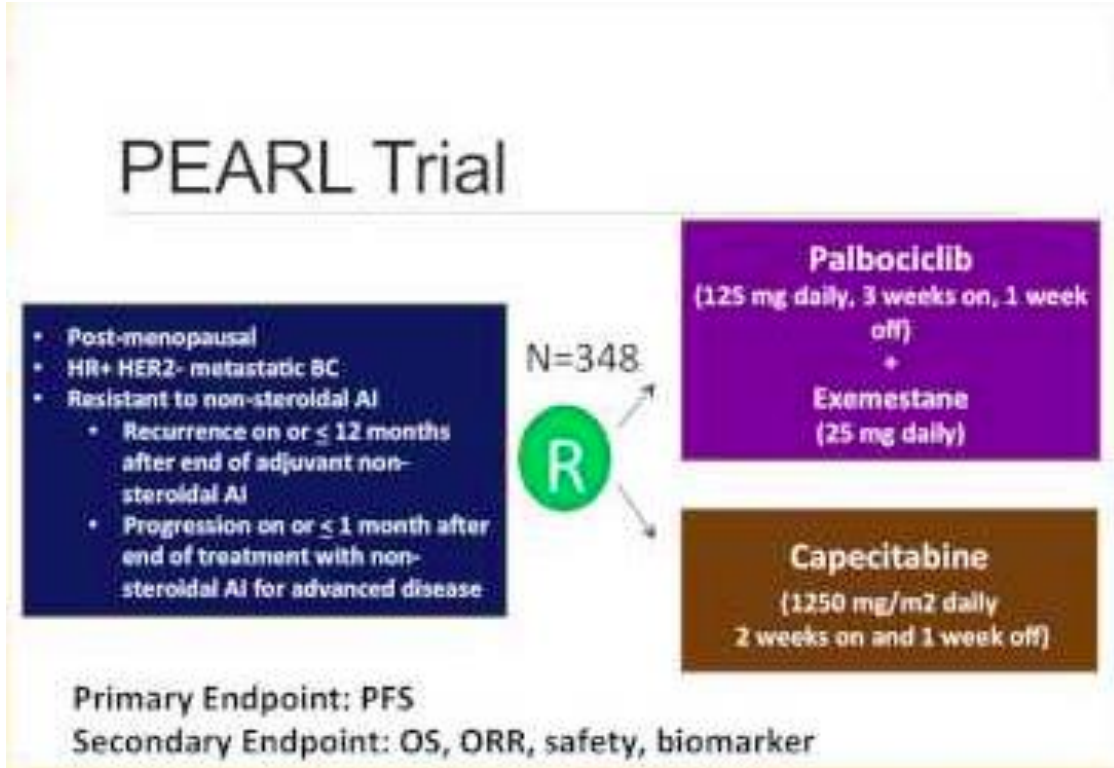
Management of ER+ Metastatic Breast Cancer in 2017



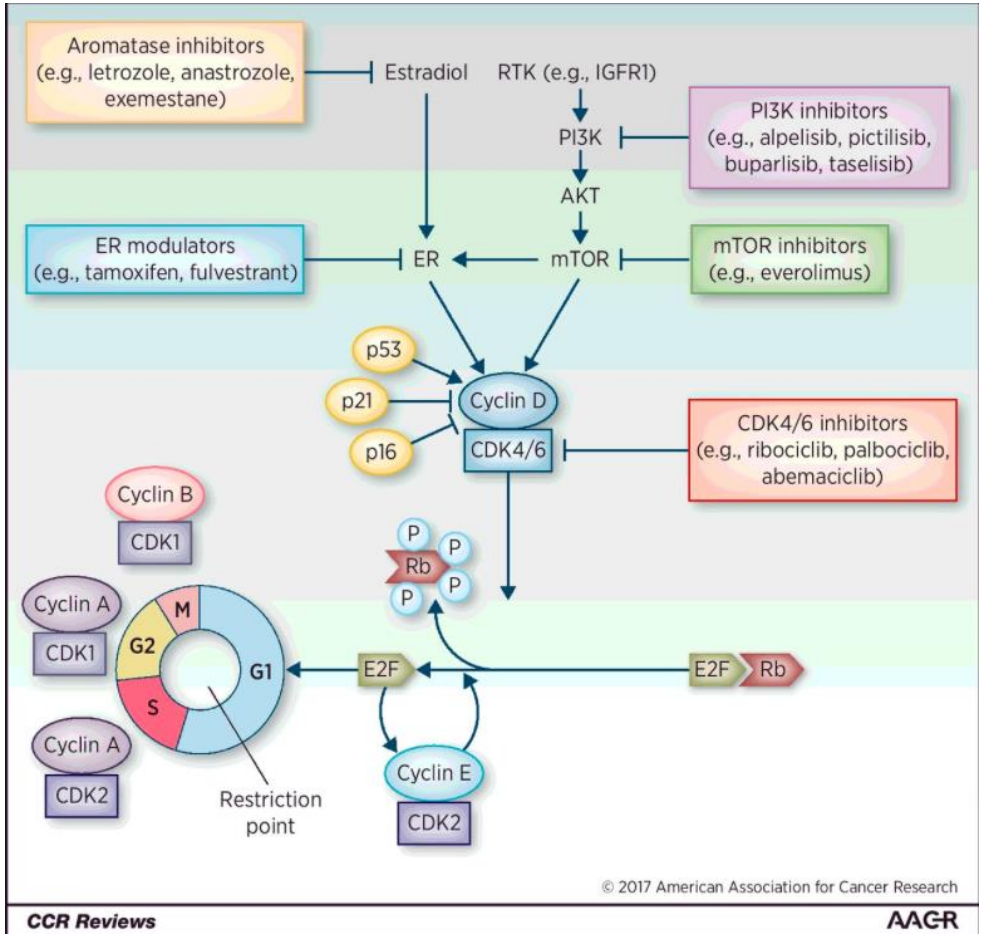
NCCN website. Breast Cancer.

Table 2. Adverse Events with an Incidence of 10% or More in the Palbociclib–Fulvestrant Group, Regardless of Relationship to Study Drugs.*

Event	Palbociclib–Fulvestrant (N=345)			Placebo–Fulvestrant (N=172)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	337 (97.7)	202 (58.6)	37 (10.7)	153 (89.0)	28 (16.3)	3 (1.7)
Neutropenia	272 (78.8)	184 (53.3)	30 (8.7)	6 (3.5)	0	1 (0.6)
Leukopenia	157 (45.5)	85 (24.6)	2 (0.6)	7 (4.1)	0	1 (0.6)
Fatigue	131 (38.0)	7 (2.0)	0	46 (26.7)	2 (1.2)	0
Nausea	100 (29.0)	0	0	45 (26.2)	1 (0.6)	0
Anemia	90 (26.1)	9 (2.6)	0	17 (9.9)	3 (1.7)	0
Headache	73 (21.2)	1 (0.3)	0	30 (17.4)	0	0
Thrombocytopenia	67 (19.4)	6 (1.7)	2 (0.6)	0	0	0
Upper respiratory infection†	67 (19.4)	1 (0.3)	0	28 (16.3)	0	0
Diarrhea	66 (19.1)	0	0	30 (17.4)	1 (0.6)	0
Constipation	58 (16.8)	0	0	24 (14.0)	0	0
Alopecia	51 (14.8)‡	NA	NA	10 (5.8)	NA	NA
Hot flushes	51 (14.8)	0	0	28 (16.3)	0	0
Vomiting	50 (14.5)	1 (0.3)	0	21 (12.2)	1 (0.6)	0
Arthralgia	45 (13.0)	1 (0.3)	0	28 (16.3)	0	0
Cough	45 (13.0)	0	0	18 (10.5)	0	0
Decreased appetite	44 (12.8)	3 (0.9)	0	13 (7.6)	0	0
Stomatitis	40 (11.6)	2 (0.6)	0	4 (2.3)	0	0
Back pain	39 (11.3)	3 (0.9)	0	26 (15.1)	4 (2.3)	0
Dizziness	37 (10.7)	1 (0.3)	0	16 (9.3)	0	0
Dyspnea	37 (10.7)	0	1 (0.3)	11 (6.4)	1 (0.6)	0
Pain in extremity	34 (9.9)	0	0	19 (11.0)	3 (1.7)	0


PEARL Trial
Post-menopausal
HR+ HER2- metastatic BC
Resistant to non-steroidal AI
Recurrence on or ≤ 12 months after end of adjuvant non-steroidal AI
Progression on or ≤ 1 month after end of treatment with non-steroidal AI for advanced disease
N=348
R
Palbociclib
(125 mg daily, 3 weeks on, 1 week off)
+
Exemestane
(25 mg daily)
Capecitabine
(1250 mg/m2 daily
2 weeks on and 1 week off)
Primary Endpoint: PFS
Secondary Endpoint: OS, ORR, safety, biomarker

The role of cyclin–CDK complexes and the cyclin D–CDK4/6–p16–Rb pathway in the cell cycle.



Pre-clinical comparison of CDK 4/6 inhibitors

MONARCH 2

Table 1. Patient and Disease Baseline Characteristics

Characteristic	Abemaciclib + Fulvestrant (n = 446)	Placebo + Fulvestrant (n = 223)
Age, years, median (range)	59 (32-91)	62 (32-87)
ET resistance*		
Primary	111 (24.9)	58 (26.0)
Secondary	326 (73.1)	163 (73.1)
Most recent ET†		
Neoadjuvant or adjuvant	263 (59.0)	133 (59.6)
Metastatic	171 (38.3)	85 (38.1)
Prior AI		
Yes	316 (70.9)	149 (66.8)
No	130 (29.1)	74 (33.2)
PgR status‡		
Positive	339 (76.0)	171 (76.7)
Negative	96 (21.5)	44 (19.7)
Metastatic site§		
Visceral	245 (54.9)	128 (57.4)
Bone only	123 (27.6)	57 (25.6)
Other	75 (16.8)	38 (17.0)
Measurable disease		
Yes	318 (71.3)	164 (73.5)
No	128 (28.7)	59 (26.5)
Race‖		
Asian	149 (33.4)	65 (29.1)
Caucasian	237 (53.1)	136 (61.0)
Other	29 (6.5)	13 (5.8)
ECOG performance status¶		
0	264 (59.2)	136 (61.0)
1	176 (39.5)	87 (39.0)
Prior chemotherapy for neoadjuvant or adjuvant treatment		
Yes	267 (59.9)	134 (60.1)
No	179 (40.1)	89 (39.9)
Menopausal status#		
Pre- or perimenopause	72 (16.1)	42 (18.8)
Postmenopause	371 (83.2)	180 (80.7)

Sledge. J Clin Oncol 2017; 35:2875-2884