CDK 4/6 Inhibition in Metastatic ER+ Breast Cancer

Kimberly L. Blackwell

ASCO 2017

Research To Practice

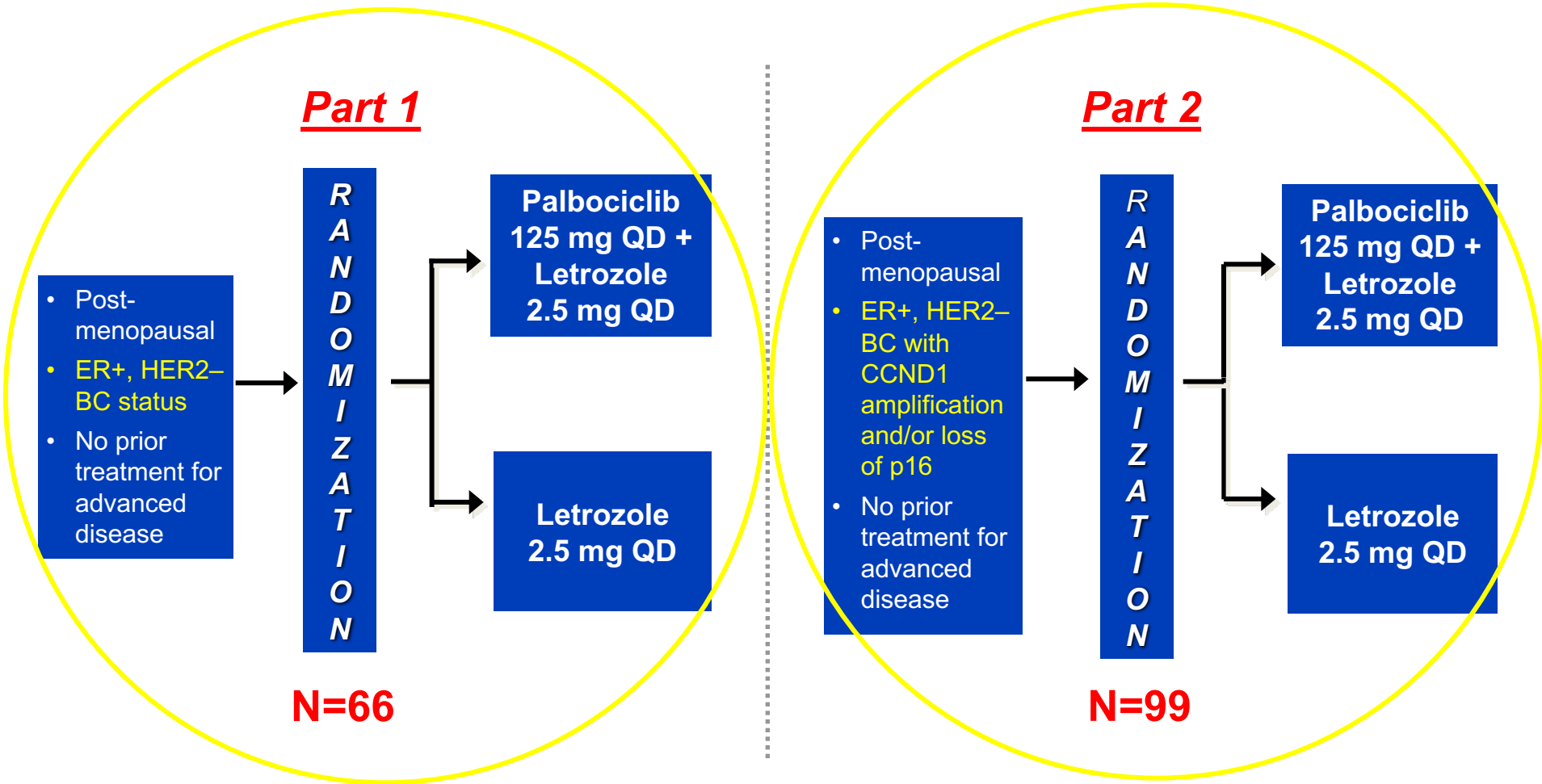
Disclosures

Advisory Committee	Eisai Inc, MacroGenics Inc, Merck, Novartis, Pfizer Inc, Pierian Biosciences, Syndax Pharmaceuticals Inc
Consulting Agreements	Celgene Corporation, Coherus BioSciences, G1 Therapeutics, Genentech BioOncology, Lilly, Puma Biotechnology, Sandoz, Novartis, Pfizer, Roche Laboratories Inc
Contracted Research	Celgene Corporation, Genentech BioOncology, Novartis, Pfizer Inc

CDK 4/6 Inhibitors in Clinical Development

Drug name	Status	Year
Palbociclib	FDA approved. 1st line therapy ER+, HER2- metastatic breast cancer, 2nd line	2015
Ribociclib (LEE011)	FDA approved, Phase III clinical trials.	2017
Abemaciclib (LY2853219)	Phase III clinical trials. FDA breakthrough designation.	?

PALOMA-1 Study Design
ER+, HER2– Locally Recurrent or Metastatic Breast Cancer



Key Eligibility Criteria

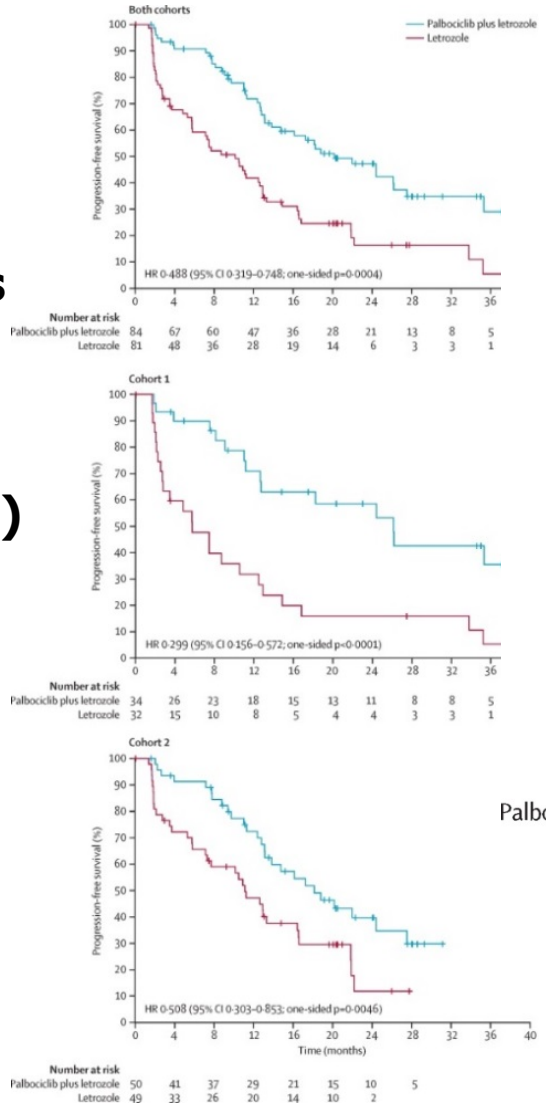
- Measurable disease (RECIST 1.0) or bone-only disease
- ECOG PS of 0 or 1
- Adequate blood counts and organ function
- No prior/current brain metastases

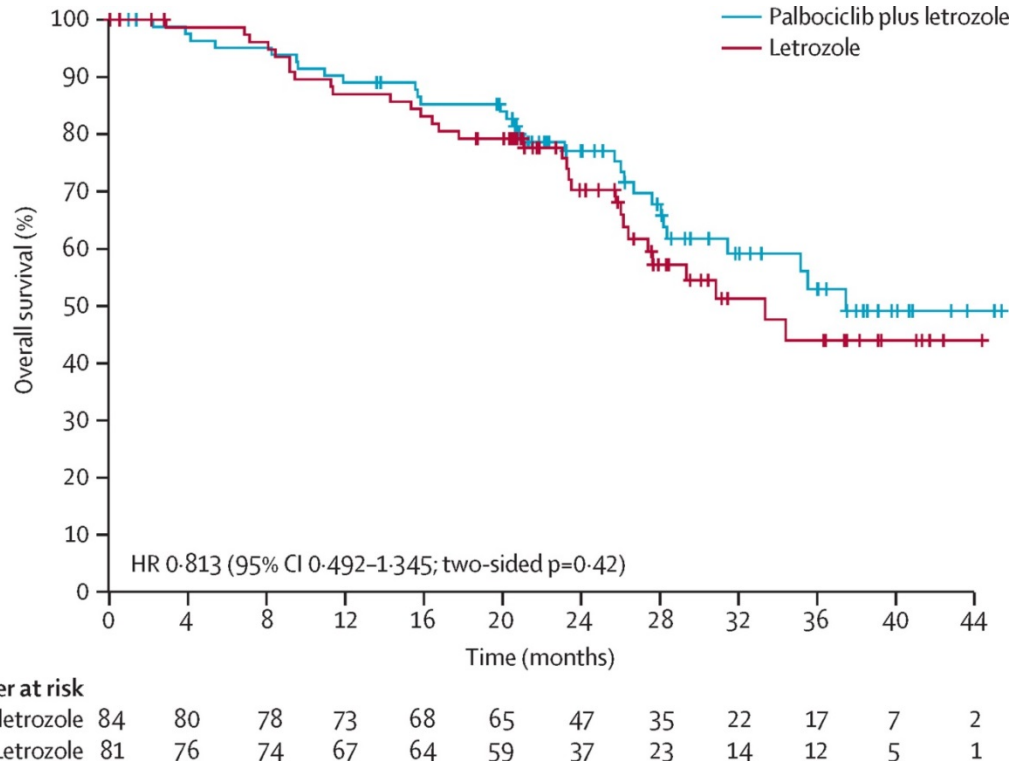
Stratification Factors

- Disease Site (Visceral vs Bone only vs Other)
- Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)

PALOMA-1 Study Design
ER+, HER2– Locally Recurrent or Metastatic Breast Cancer

PFS:
20.2 vs 10.2 mos (p= 0.0004)

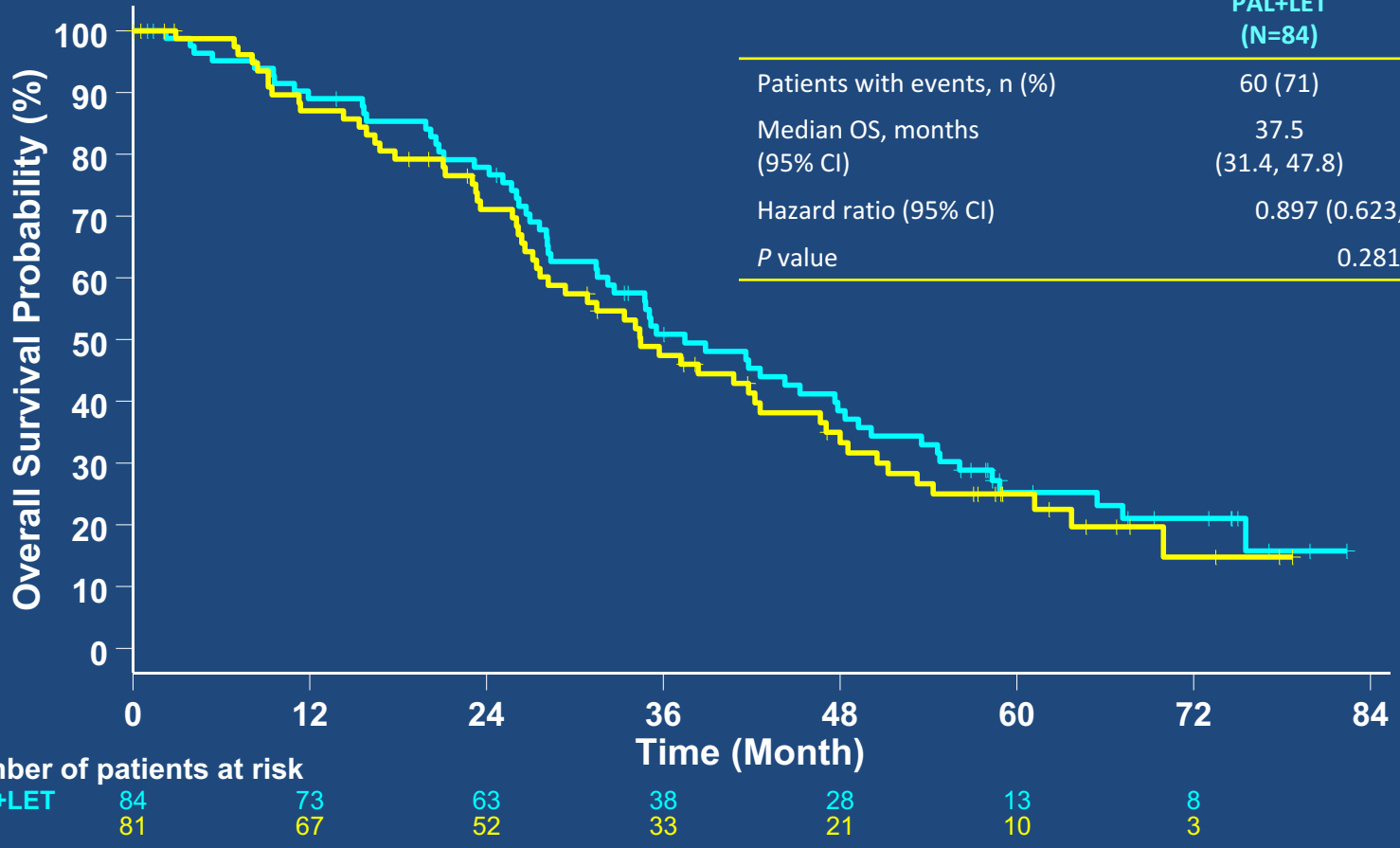




OS:
37 v 33 mos (p= 0.4)

The Lancet Oncology 2015 16, 25-35DOI: (10.1016/S1470-2045(14)71159-3)

PALOMA-1 OS: Phase 2 (ITT)



	PAL+LET (N=84)	LET (N=81)
Patients with events, n (%)	60 (71)	56 (69)
Median OS, months (95% CI)	37.5 (31.4, 47.8)	34.5 (27.4, 42.6)
Hazard ratio (95% CI)	0.897 (0.623, 1.294)	
P value	0.281	

Finn, ASCO, 2017

PALOMA-2: Phase 3 Study Palbociclib Plus Letrozole as First-Line Therapy in HR+, HER2– ABC

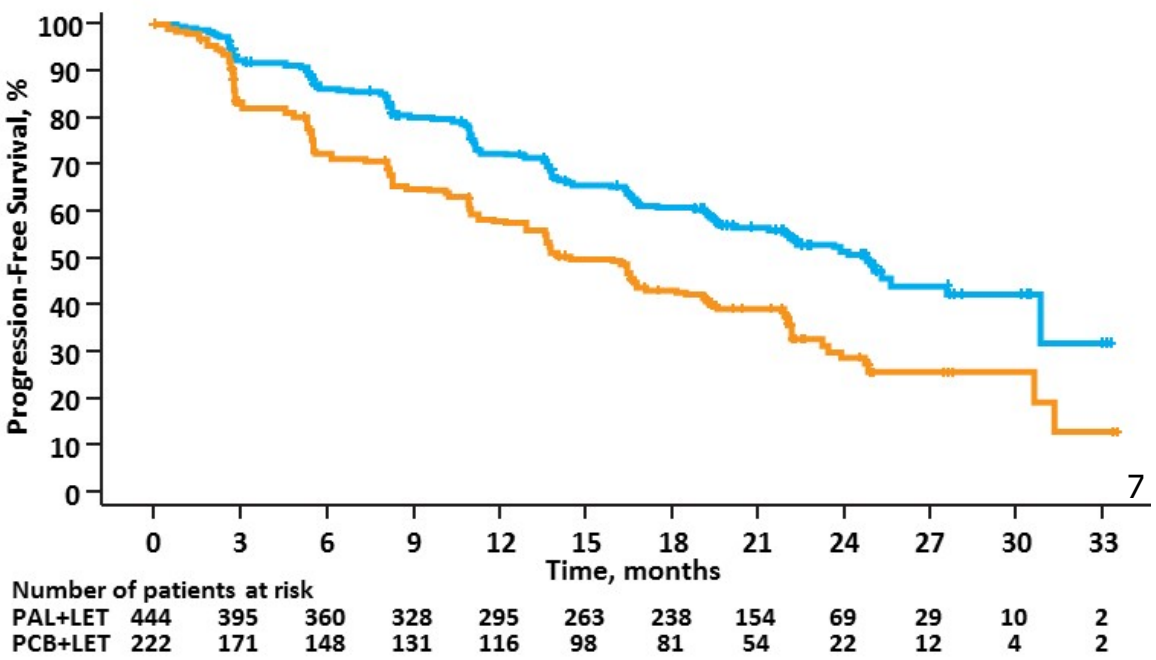
PALOMA-2
(N = 666)

- Postmenopausal women ≥ 18 years of age
- ER+, HER2– ABC
- No prior systemic treatment for advanced disease

Palbociclib + Letrozole
n = 444

Placebo + Letrozole
n = 222

PAL + LET vs PBO + LET
Median PFS 24.8 mo vs 14.5 mo
HR = 0.58 (95% CI, 0.46-0.72)
***P* < 0.001**



ABC, advanced breast cancer; ER+, estrogen receptor-positive; ET, endocrine therapy; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor-positive; mo, months.

Finn RS, et al. *N Engl J Med*. 2016;375(20):1925-1936.

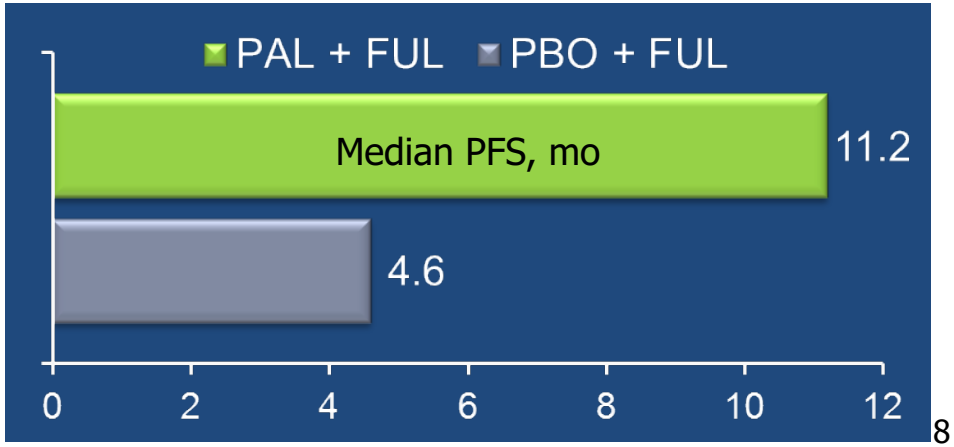
PALOMA-3: Phase 3 Study of CDKi (Palbociclib) Plus Fulvestrant in HR+, HER2– ABC

PALOMA-3
(N = 521)

- Women ≥ 18 years of age
- ER+, HER2– ABC
- Relapsed on or within 12 months after completion of adjuvant ET or on or within 1 month after therapy for advanced disease

Palbociclib + Fulvestrant

Placebo + Fulvestrant



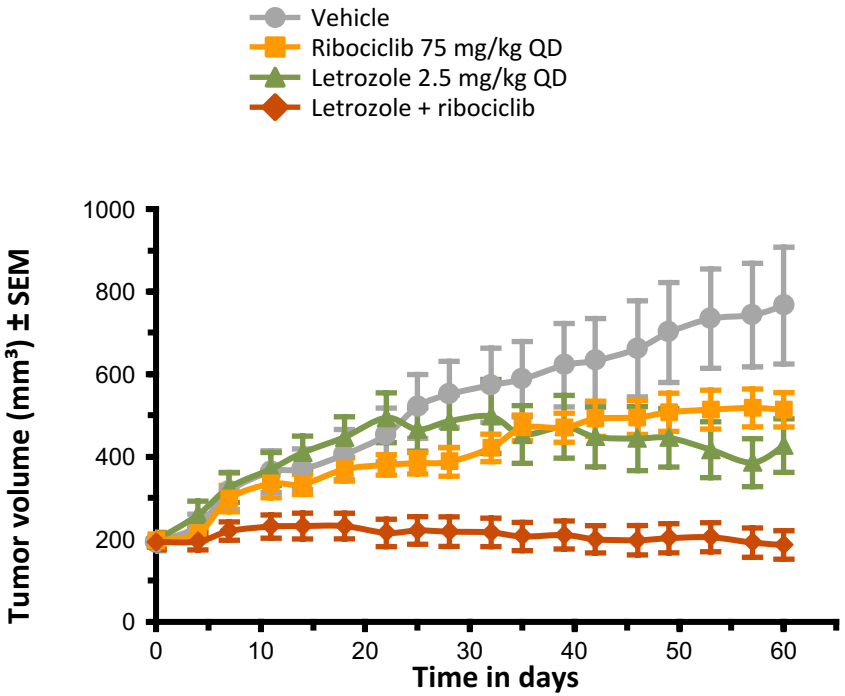
HR = 0.50 (95% CI, 0.40-0.62);
P < 0.0001

ABC, advanced breast cancer; AE, adverse event; CDKi, cyclin-dependent kinase inhibitor; CI, confidence interval; ET, endocrine therapy; FUL, fulvestrant; HT, hormonal therapy; LET, letrozole; HER2–, human epidermal growth factor receptor-2–negative; HR, hazard ratio; HR+, hormone receptor-positive; PAL, palbociclib; PBO, placebo; PFS, progression-free survival.

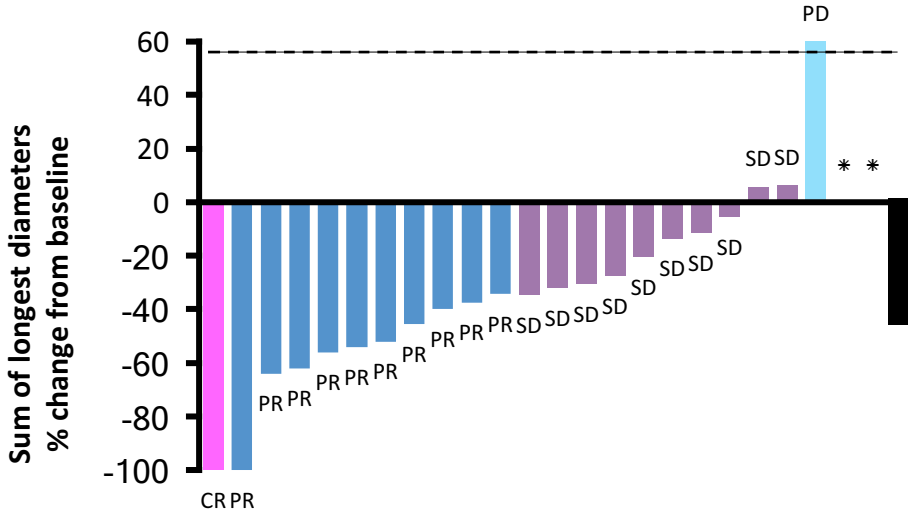
1. Cristofanilli M, et al. *Lancet Oncol.* 2016;17(4):425-439; 2. Turner NC, et al. SABCS 2016. Abstract P4-22-06 [poster].

Ribociclib + Letrozole Demonstrate Anti-Tumor Activity

Inhibition of tumor growth in ER+ breast cancer xenograft model HBX34[1]

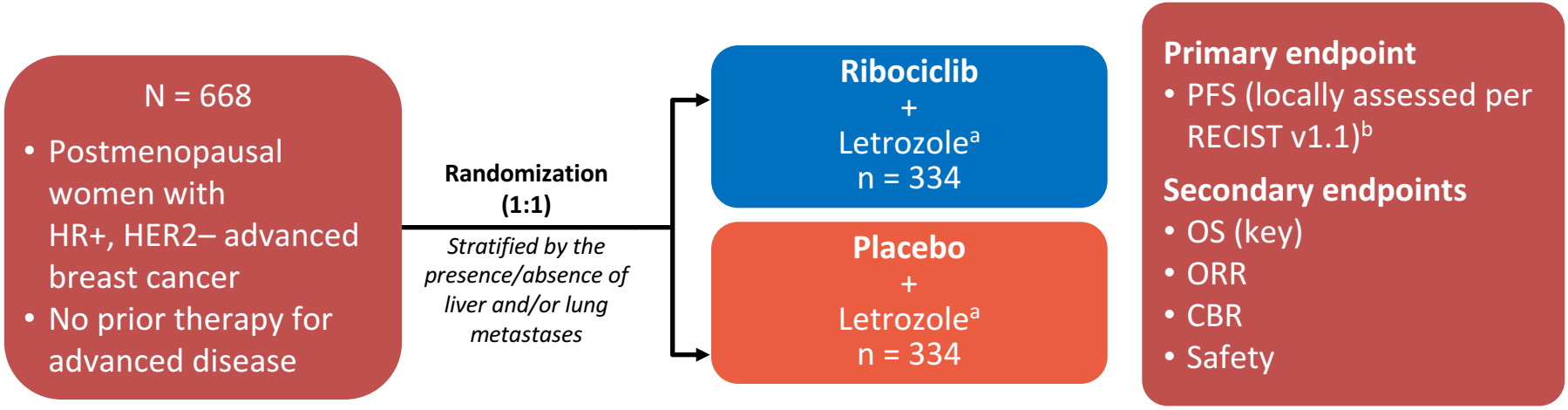


Patients with ER+/HER2– advanced breast cancer; first-line ribociclib + letrozole group[2] (n=24)



- ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive;
  PD, progressive disease; QD, once daily.
- 1. O'Brien NA, *et al. AACR* 2014, abstr 4756 (oral); 2. Juric D, *et al. ASCO* 2016, abstr 568 (poster).

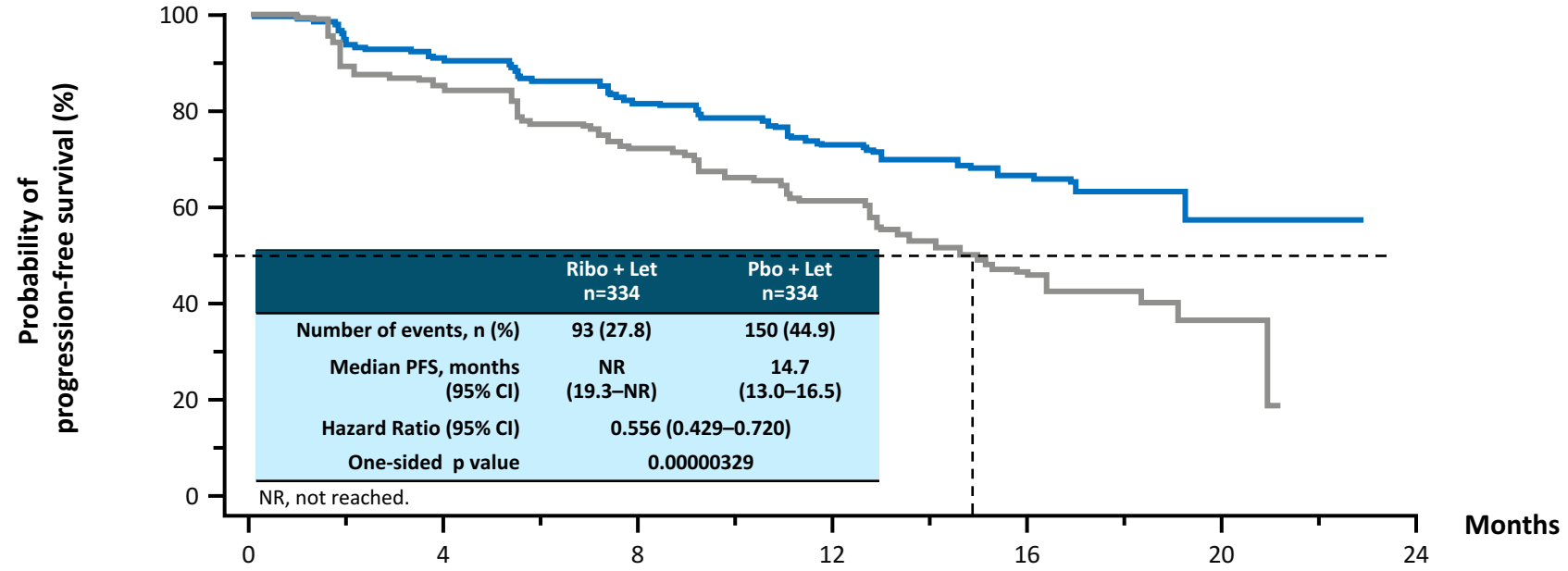
MONALEESA-2: A Phase 3, Double-Blind, Placebo-Controlled Study of Ribociclib + Letrozole



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Final analysis planned after 302 PFS events
  - 93.5% power to detect a 33% risk reduction (HR 0.67) with one-sided α=2.5%

[a] Ribociclib 600 mg per day, 3-weeks-on/1-week-off; letrozole 2.5 mg/day.
[b]With supportive independent central review; MONALEESA-2 is registered at ClinicalTrials.gov (NCT01958021).
CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.
Hortobagyi G, et al. *N Engl J Med.* 2016;375(18):1738-1748.

MONALEESA-2 Met the Primary Endpoint at Interim/ASCO 2017



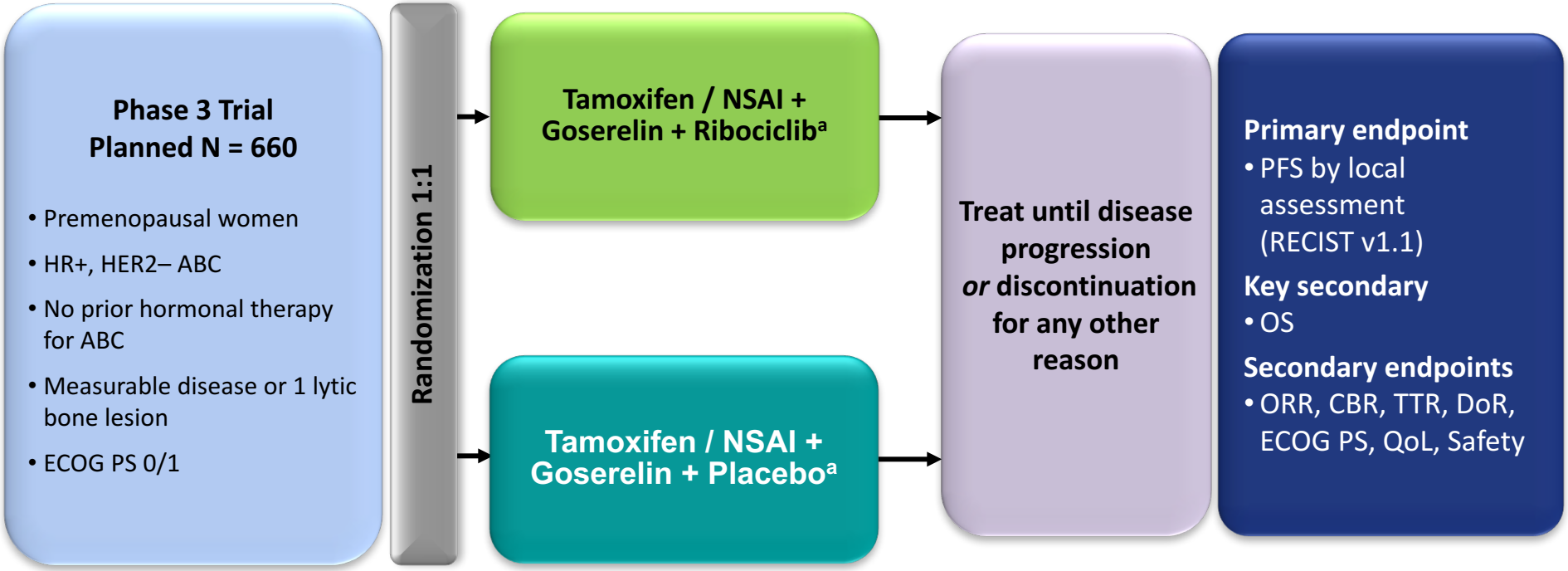
PFS results by independent central review: hazard ratio 0.592 (95% CI: 0.412–0.852; p=0.002)
PFS results (ASCO 2017): HR of 0.568; p=0.000000009 25.3 vs. 16.0 months
OS (ASCO 2017): HR of 0.746; p= 0.059 NR vs. 33.0 months

Hematologic Adverse Events

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	74.3	49.7	9.6	5.2	0.9	0
Leukopenia	32.9	19.8	1.2	3.9	0.6	0
Anemia	18.6	0.9	0.3	4.5	1.2	0
Lymphopenia	10.5	5.7	1.2	2.1	0.9	0
Thrombocytopenia	9.0	0.6	0	0.6	0	0

Febrile neutropenia occurred in 1.5% of patients in the ribociclib arm vs. none in the placebo arm

MONALEESA-7: Ribociclib + Letrozole + Goserelin for Premenopausal Women With HR+, HER2– ABC

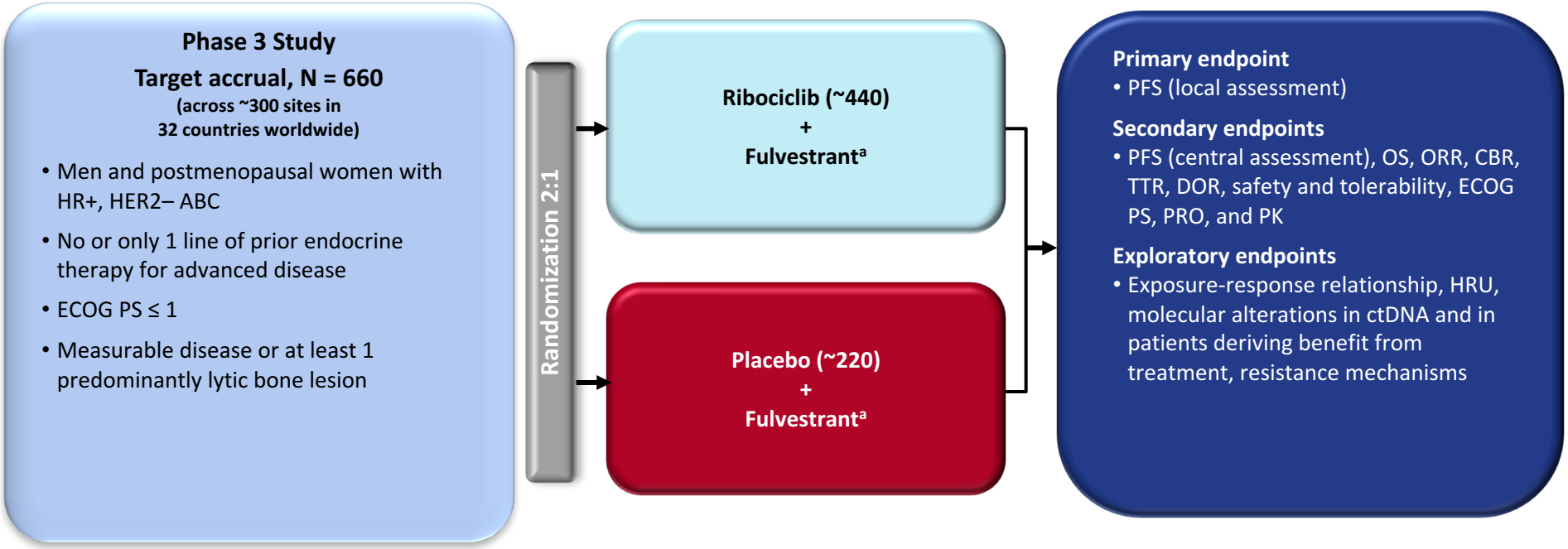


ABC, advanced breast cancer; CBR, clinical benefit rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor-positive; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

[a] Ribociclib or placebo (600 mg) given once daily for 21 days followed by a 7-day break (28-day cycle); letrozole (2.5 mg), anastrozole (1 mg), tamoxifen (20 mg) given on a continuous dosing schedule (28-day cycles); goserelin (3.6 mg) given on day 1 of each 28-day cycle.

www.clinicaltrials.gov (NCT02278120).

MONALEESA-3: Ribociclib + Fulvestrant for PreMenopausal and Postmenopausal Women With HR+, HER2– ABC



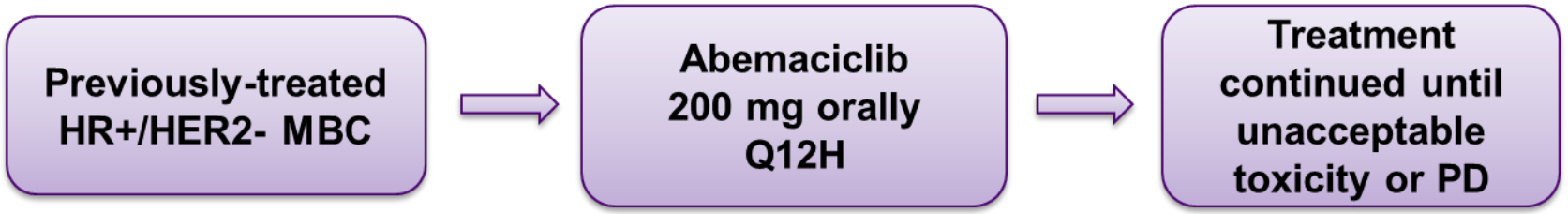
- Enrollment complete May 2016
- Stratification will be based on the presence of lung or liver metastases and prior ET

[a]Ribociclib or placebo (600 mg) given once daily for 21 days followed by a 7-day break (28-day cycle); fulvestrant (500 mg) given IM on Days 1 and 15 of Cycle 1 and Day 1 of each cycle thereafter

ABC, advanced breast cancer; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRU, hospital resource utilization; IM, intramuscular; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcomes; QD, once daily; RIB, ribociclib; TTR, time to response.

Fasching PA, et al. SABCS 2015; Abstract OT2-01-02 (poster); www.clinicaltrials.gov (NCT02422615).

MONARCH 1: Phase 2 Study Design



- Median number of prior systemic regimens (any setting) was 5 (range 2-11)
- 100% of patients received taxanes in any setting
- Median number of prior systemic regimens for metastatic disease was 3 (range 1-8)

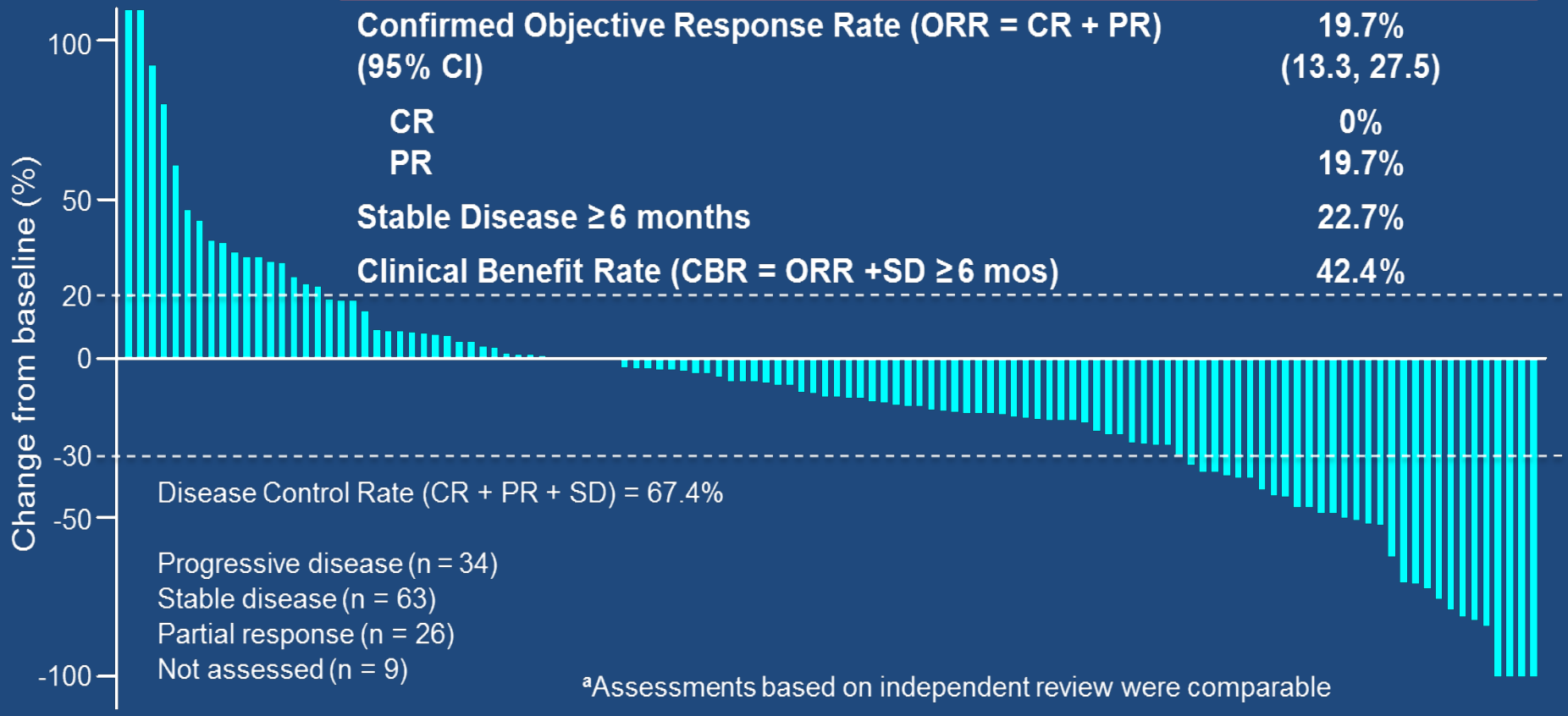
Endocrine Therapy for Metastatic Disease	N=132 n (%)
# of Regimens	
1	48 (36.4)
2	25 (18.9)
3	24 (18.2)
≥ 4	18 (13.6)
Prior fulvestrant	67 (50.8)

Chemotherapy for Metastatic Disease	N=132 n (%)
# of Regimens	
1	67 (50.8)
2	64 (48.5)
3	1 (0.8)
Taxanes	**91 (68.9)**
Capecitabine	**73 (55.3)**

Dickler, SABCS, 2016

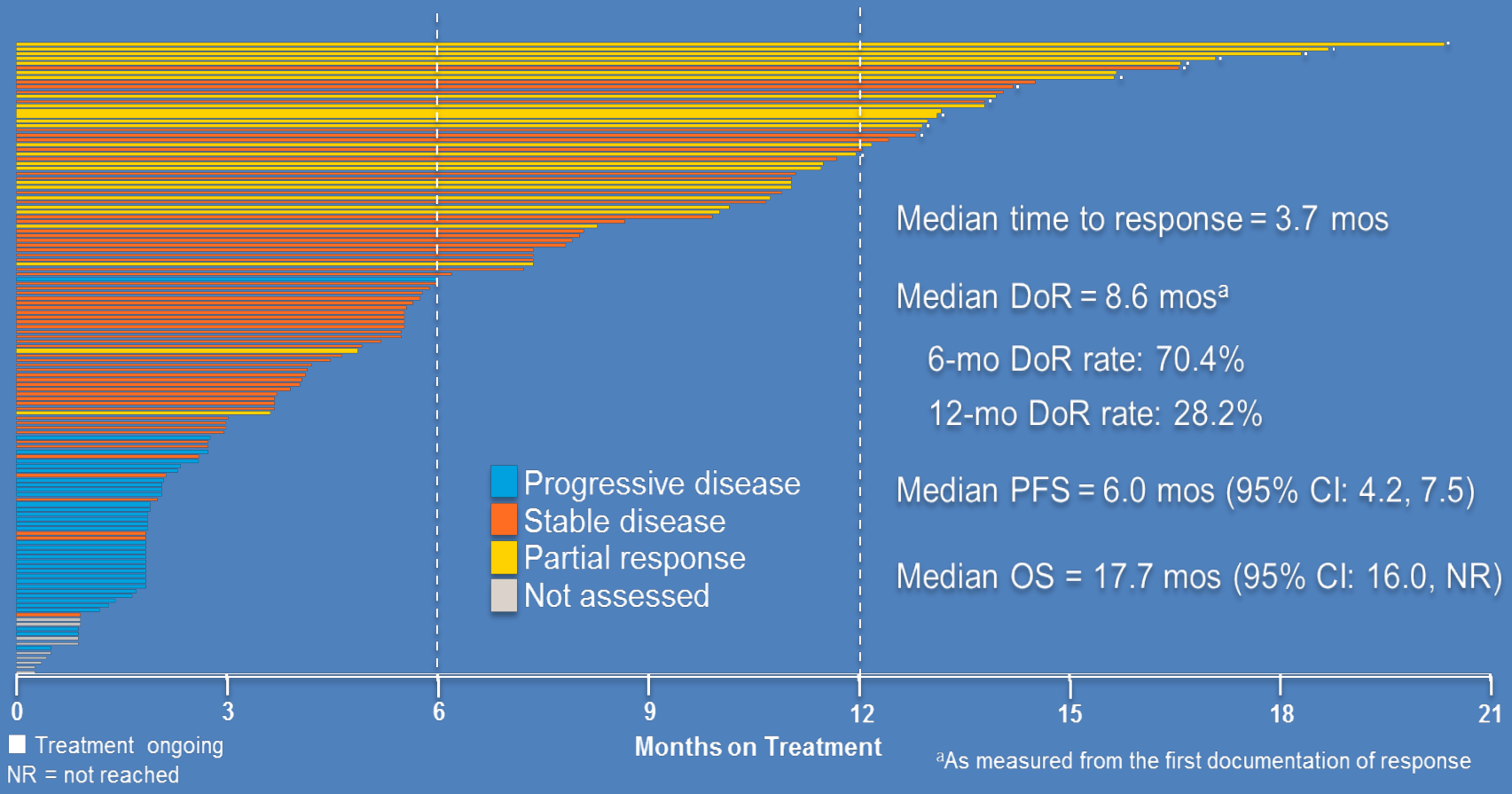
MONARCH 1: Response Summary

Investigator Assessed Response[a]	Abemaciclib 200 mg (N = 132)
Confirmed Objective Response Rate (ORR = CR + PR)	19.7%
(95% CI)	(13.3, 27.5)
CR	0%
PR	19.7%
Stable Disease ≥ 6 months	22.7%
Clinical Benefit Rate (CBR = ORR +SD ≥ 6 mos)	42.4%



[a]Assessments based on independent review were comparable

MONARCH 1: Treatment Duration



Median time to response = 3.7 mos

Median DoR = 8.6 mos[a]

6-mo DoR rate: 70.4%

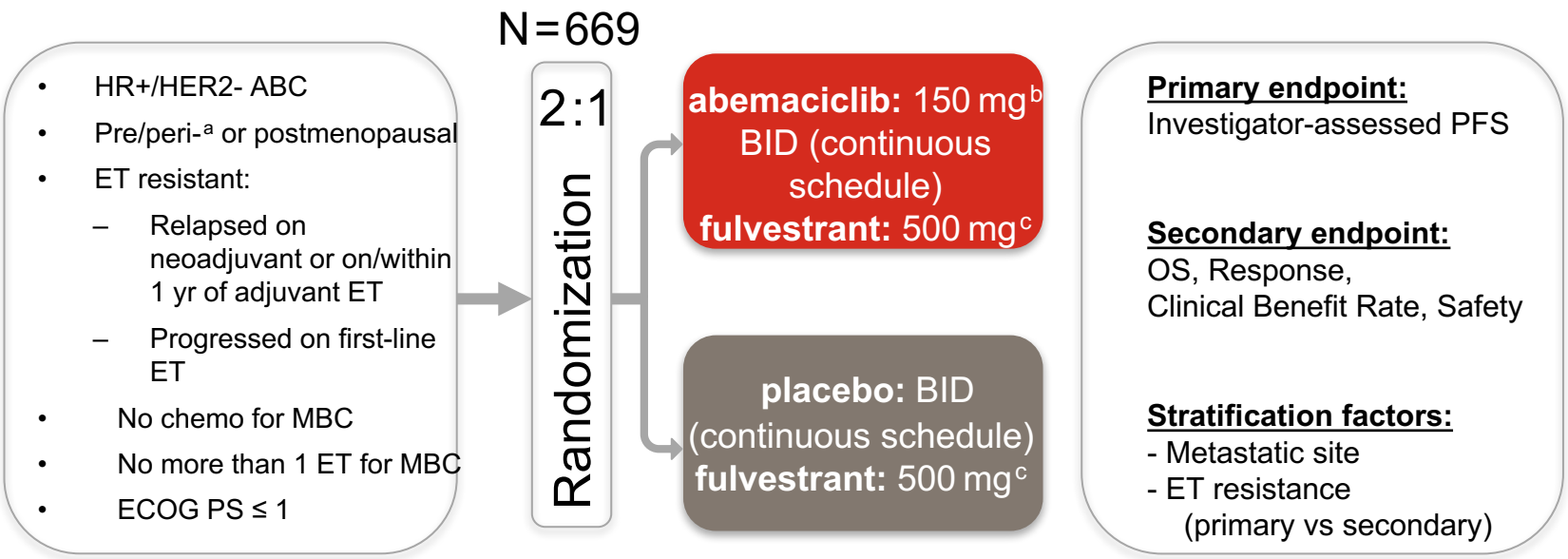
12-mo DoR rate: 28.2%

Median PFS = 6.0 mos (95% CI: 4.2, 7.5)

Median OS = 17.7 mos (95% CI: 16.0, NR)

[a]As measured from the first documentation of response

MONARCH-2 Study Design

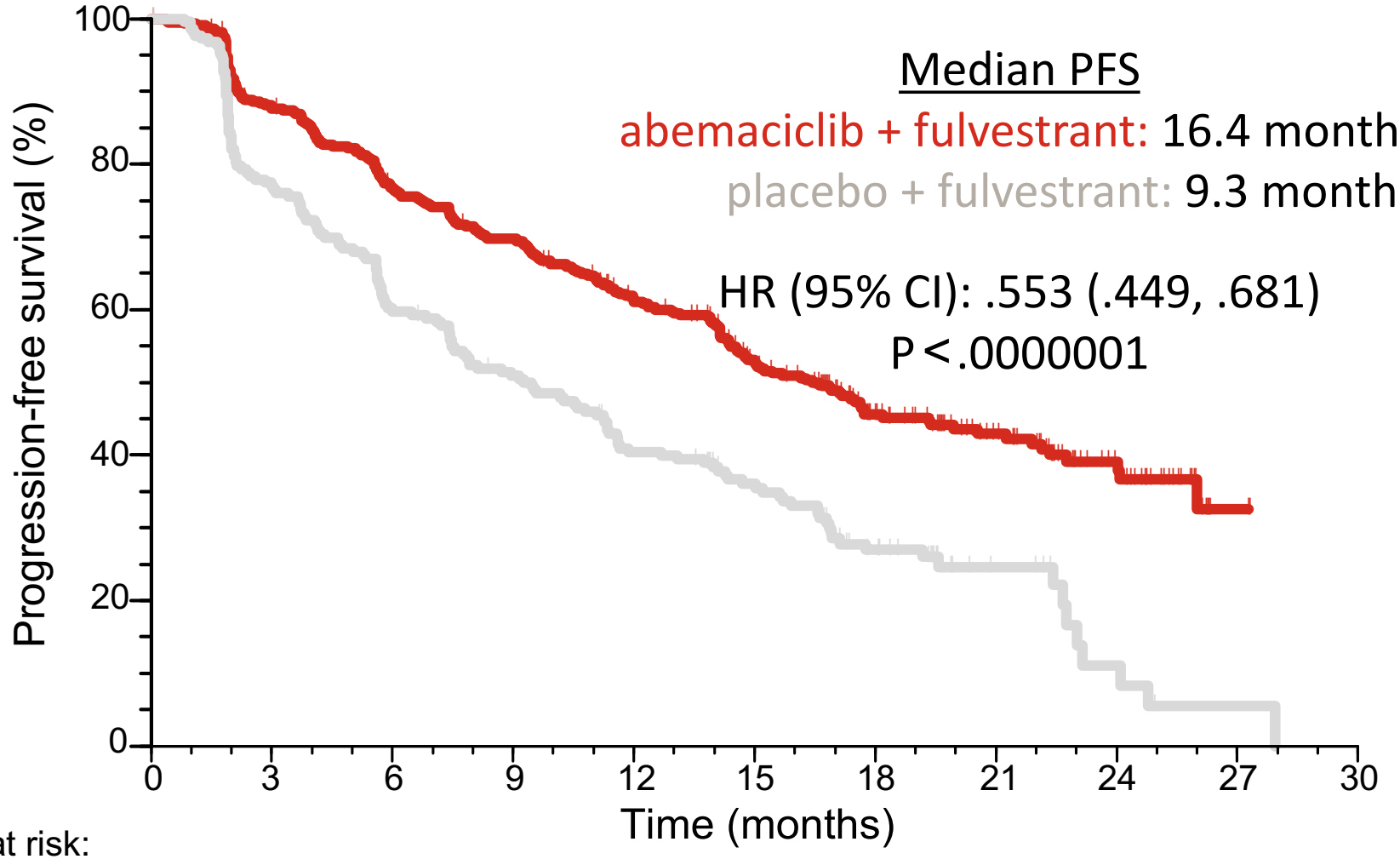


- **Statistics: 378 events for 90% power at one-sided α of .025 assuming a true HR of .703**

[a]Required to receive GnRH agonist
[b]Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled
[c]Fulvestrant administered per label

Sledge, ASCO, 2017

MONARCH 2: Primary Endpoint: PFS (ITT)



Patients at risk:											
abemaciclib	446	367	314	281	234	171	101	65	32	2	0
placebo	223	165	123	103	80	61	32	13	4	1	0

TEAE (Safety Population)

	abemaciclib + fulvestrant n = 441			placebo + fulvestrant n = 223		
≥ 20 % in either arm, n (%)	All	G3	G4	All	G3	G4
Any	**435 (98.6)**	**241 (54.6)**	**26 (5.9)**	**199 (89.2)**	**46 (20.6)**	**5 (2.2)**
Diarrhea[a]	**381 (86.4)**	**59 (13.4)**	**0**	**55 (24.7)**	**1 (0.4)**	**0**
Neutropenia[b]	**203 (46.0)**	**104 (23.6)**	**13 (2.9)**	**9 (4.0)**	**3 (1.3)**	**1 (0.4)**
Nausea	**199 (45.1)**	**12 (2.7)**	**-**	**51 (22.9)**	**2 (0.9)**	**-**
Fatigue	**176 (39.9)**	**12 (2.7)**	**-**	**60 (26.9)**	**1 (0.4)**	**-**
Abdominal pain	**156 (35.4)**	**11 (2.5)**	**-**	**35 (15.7)**	**2 (0.9)**	**-**
Anemia	**128 (29.0)**	**31 (7.0)**	**1 (0.2)**	**8 (3.6)**	**2 (0.9)**	**0**
Leukopenia	**125 (28.3)**	**38 (8.6)**	**1 (0.2)**	**4 (1.8)**	**0**	**0**
Decreased appetite	**117 (26.5)**	**5 (1.1)**	**0**	**27 (12.1)**	**1 (0.4)**	**0**
Vomiting	**114 (25.9)**	**4 (0.9)**	**0**	**23 (10.3)**	**4 (1.8)**	**0**
Headache	**89 (20.2)**	**3 (0.7)**	**-**	**34 (15.2)**	**1 (0.4)**	**-**

[a]Grade 2 diarrhea: abemaciclib + fulvestrant n = 140 (31.7 %); placebo + fulvestrant n = 11 (4.9 %).
[b]Febrile neutropenia was uncommon [6 patients in the abemaciclib arm (1 incorrectly coded; 1 post-chemotherapy)] and was not associated with severe infection