empower

EMPOWER

Optimizing the Paradigm Shift Driven by CDK 4/6 Inhibition in
METASTATIC HR-POSITIVE, HER2-NEGATIVE BREAST CANCER

THURSDAY
AUGUST 27, 2020

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

Supported by an educational grant from Lilly.

Agenda

1. **Clinical Trial Data from Cyclin dependent kinase (CDK) 4/6 Inhibition in Breast Cancer**
    - i. Efficacy of first-line treatment regimens
    - ii. Efficacy of second- and subsequent-line treatment regimens
    - iii. Clinical trial data on CDK 4/6 inhibitors vs chemotherapy
    - ***iv. (VR animation) – The mechanism of action of CDK 4/6 inhibitors***
    - v. Toxicity profiles and safety of approved CDK 4/6 inhibitors

2. **Optimizing CDK 4/6 Inhibition: Patient with Advanced Breast Cancer**
    - i. Identifying candidates for CDK 4/6 inhibition
    - ii. Line of therapy - 1st line or 2nd line of treatment
    - iii. Patient-specific factors
        - a. Pre- vs postmenopausal status
        - b. Primary endocrine resistance
        - c. Visceral disease
        - d. Prior therapy
        - e. Metastatic sites
    - iv. Considering the safety profile of CDK 4/6 inhibitors in therapy selection
    - v. Choosing an endocrine partner

3. **Monitoring and Managing Toxicities Associated with CDK 4/6 Inhibition - Its Application to Clinical Practice**
    - i. Toxicities commonly associated with each CDK 4/6 inhibitor use
    - ***ii. (VR animation) – Potential adverse events with CDK 4/6 inhibitors***
    - iii. Required monitoring (laboratory and clinical) while on treatment
    - iv. Appropriate intervention and management of CDK 4/6 inhibitor- associated AEs

4. **Multidisciplinary Team Tools in Optimizing Care and Adverse Event Management**
    - i. Improving patient education
    - ii. Incorporating shared decision-making strategies into clinical practice
    - iii. Cancer survivorship tools that foster multidisciplinary team engagement

5. **Shared Decision-Making Case Study Video**

6. **Conclusions**

7. **Question and Answer**

Optimizing the Paradigm Shift Driven by CDK 4/6 Inhibition in Metastatic HR-positive, HER2-negative Breast Cancer

PROGRAM CHAIRS & FACULTY

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PROGRAM OVERVIEW

This program will review the use of CDK 4/6 inhibitors in the treatment of HR+/HER2-negative breast cancer and the management of treatment-related adverse events.

TARGET AUDIENCE

This CME initiative is designed to meet the educational needs of medical oncologists, advanced practice clinicians, oncology nurses, pharmacists, and other healthcare providers involved in the treatment of patients with hormone receptor-positive, HER2-negative metastatic breast cancer.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Identify the patient who will benefit from CDK 4/6 inhibitor therapy with consideration of patient and disease characteristics and appropriately time its use in the course of the disease
- Recognize commonly associated toxicities of CDK4/6 inhibition, and apply strategies for both the monitoring and management of adverse events associated with their use in patients with metastatic breast cancer

- Utilize methodologies to activate all members of the healthcare team, encourage collaboration, and incorporate shared decision-making and survivorship tools to assist in optimizing patient outcomes and management of adverse events

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Purpose: This program would be beneficial for nurses involved in the treatment of patients with hormone receptor-positive, HER2-negative metastatic breast cancer. Credits: 2.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 2.0 contact hour of continuing nursing education of RNs and APNs.

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Dr. O'Shaughnessy received honoraria for consulting and advisory boards for AbbVie Inc., Agendia, Amgen Biotechnology, AstraZeneca, Bristol-Myers Squibb, Celgene Corporation, Eisai, Genentech, Genomic Health

GRAIL, Immunomedics, Heron Therapeautics, Ipsen Biopharmaceuticals, Jounce Therapeutics, Lilly, Merck, Myriad, Novartis, Ondonate Therapeutics, Pfizer, Puma Biotechnology, Prime Oncology, Roche, Seattle Genetics, Syndax Pharmaceuticals, and Takeda.

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CNE Content Review

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3. Submit the evaluation form to Med Learning Group

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Provided by Med Learning Group

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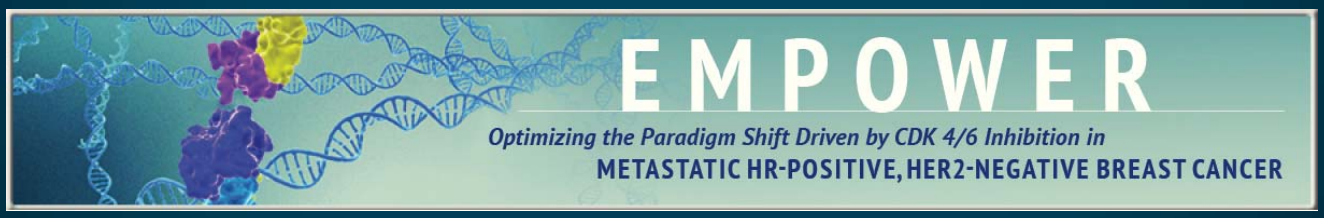

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EMPOWER:

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Learning Objectives

- Identify the patient who will benefit from CDK 4/6 inhibitor therapy with consideration of patient and disease characteristics and appropriately time its use in the course of the disease
- Recognize commonly associated toxicities of CDK4/6 inhibition, and apply strategies for both the monitoring and management of adverse events associated with their use in patients with metastatic breast cancer
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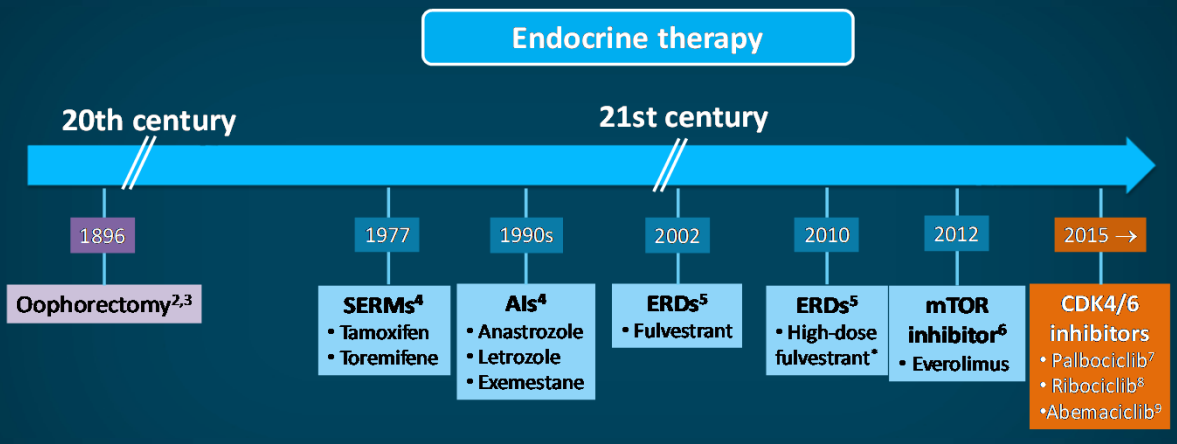
An Overview of CDK4/6 Inhibitors

Joyce O'Shaughnessy, MD

Historical Timeline of Therapies for HR+ Advanced Breast Cancer (ABC)

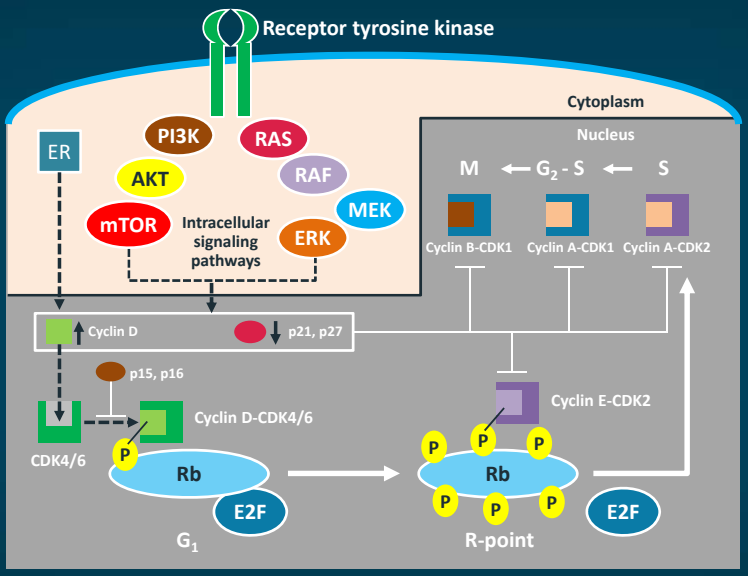


* Marginal improvement over lower-dose fulvestrant.

HR+ = hormone-receptor positive; SERM = selective estrogen receptor modulator; AI = aromatase inhibitor; ERD = estrogen-receptor downregulator; mTOR = mammalian target of rapamycin; CDK = cyclin-dependent kinase.

1. Advanced Breast Cancer Community (www.advancedbreastcancercommunity.org/understanding-abc). 2. Beatson GT. *Lancet*. 1896;148:104-107. 3. Beatson GT. *Lancet*. 1896;148:162-165. 4. Cohen MH, et al. *Oncologist*. 2001;6:4-11. 5. Fulvestrant (Faslodex®) prescribing information (PI), 2019 (https://medicalinformation.astrazeneca-us.com/home/prescribing-information/faslodex-pi.html) . 6. Baselga J, et al. *N Engl J Med*. 2012;366:520-529. 7. Finn RS, et al. *Lancet Oncol*. 2015;16:25-35. 8. Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748. 9. Sledge GW Jr, et al. *J Clin Oncol*. 2017;35:2875-2884. URLs accessed 3/2/2020.

Regulation of G1/S Checkpoint in Breast Cancer



BC = breast cancer; ER = estrogen receptor; ERK = extracellular signal-regulated kinase; MEK = mitogen-activated protein kinase kinase; P = phosphate; Rb = retinoblastoma; P = phosphate; PI3K = phosphatidylinositol 3-kinase.

Ingham M, Schwartz GK. *J Clin Oncol.* 2017;35:2949-2959.

CDK4/6 Inhibitors: Status Overview

	Palbociclib[1] (PAL)	Ribociclib[2] (RIBO)	Abemaciclib[3] (ABEMA)
Dose/ schedule	125 mg daily 3 weeks on/1 week off	600 mg daily 3 weeks on/1 week off	Combination: 150 mg BID Monotherapy: 200 mg BID Continuous
Completed phase 3 trials	1st line—PALOMA-2 2nd line—PALOMA-3	1st line—MONALEESA-2 MONALEESA-7 1st/2nd line—MONALEESA-3	1st line—MONARCH-3 2nd line—MONARCH-2 MONARCH-1
FDA approval status for HR-positive, HER2-negative advanced or metastatic breast cancer	1st-line therapy in combination with an aromatase inhibitor in postmenopausal women or in men 2nd-line therapy in combination with fulvestrant in postmenopausal patients	1st-line therapy in combination with an AI in pre/perimenopausal or postmenopausal women 1st- or 2nd-line therapy in combination with fulvestrant in postmenopausal women	1st-line therapy in combination with an AI in postmenopausal women 2nd-line therapy with fulvestrant Monotherapy in adults with disease progression following endocrine therapy and prior chemotherapy in metastatic setting

FDA = US Food and Drug Administration; HR = hormone receptor; HER = human epidermal growth factor receptor; BID = twice daily.

1. Palbociclib (Ibrance®) prescribing information (PI) 2019 (www.accessdata.fda.gov/drugsatfda_docs/label/2019/207103Orig1s012lbl.pdf). 2. Ribociclib (Kisqali®) PI 2020 (www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kisqali.pdf). 3. Abemaciclib (Verzenio™) PI 2019 (http://pi.lilly.com/us/verzenio-uspi.pdf). URLS accessed 3/2/2020.

Characteristics Relaying Potential Benefit from CDK4/6 Inhibitors

- **Estrogen receptor positivity**
- ***Outside of estrogen receptor expression, no specific biomarkers have been identified*** that are predictive of CDK4/6 inhibitor response or resistance.
- Exploratory analyses of clinical trials indicate *consistent benefits* in multiple patient subgroups including:
  - Poor prognostic subgroups (high tumor grade, visceral metastases, liver metastases)
  - Younger (<65 years old) and older (≥65 years old) patient subgroups with advanced breast cancer

Lynce F, et al. *Pharmacol Ther*. 2018;191:65-73.

Video about MOA of CDK4/6 inhibitors

CDK 4/6 Inhibitors for 1st-Line Therapy

CDK4/6 Inhibitors Phase 3 Trials: 1st Line

	Palbociclib[1]	Ribociclib[2,3]	Abemaciclib[4]
	PALOMA-2	MONALEESA-2	MONARCH-3
Partner	Letrozole	Letrozole	Letrozole or anastrozole
Eligibility	No prior treatment for advanced disease	No prior treatment for advanced disease No adjuvant NSAI if disease-free interval <12 months	No prior treatment for advanced disease No adjuvant NSAI if disease-free interval <12 months
Population	N = 666	N = 668	N = 493
De novo stage IV, %	31	34	40
Relapse ≤12 mos, %	22	2	-
Bone only, %	23	22	22
Response rate (%)			
• ORR	42.1 vs 34.7	53 vs 37	48.2 vs 34.5
• CBR	84.9 vs 70.3	80 vs 72	78.0 vs 71.5

ORR = overall/objective response rate; mos = months; CBR = clinical benefit rate (CR [complete response] + PR [partial response] + SD [stable disease] ≥24 weeks); ET = endocrine therapy.

1. Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936. 2. Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748. 3. O'Shaughnessy J, et al. *Breast Cancer Res Treat*. 2018;168:127-134. 4. Goetz MP, et al. *J Clin Oncol*. 2017;35(32):3638-3646.

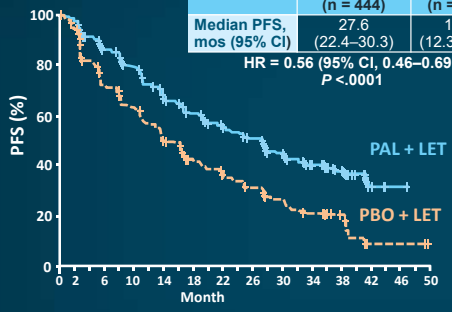
PALOMA-2 and MONALEESA-2: PFS Update

Investigator Assessment

PALOMA-2

	PAL + LET (n = 444)	PBO + LET (n = 222)
Median PFS, mos (95% CI)	27.6 (22.4–30.3)	14.5 (12.3–17.1)

HR = 0.56 (95% CI, 0.46–0.69)
P <.0001



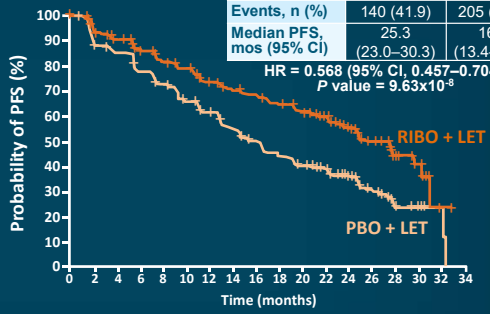
No. at risk

PAL + LET	444	424	359	325	268	239	216	192	164	126	64	5	2	0
PBO + LET	222	204	147	128	100	80	70	55	45	34	19	2	2	0

MONALEESA-2

	RIBO + LET (n = 334)	PBO + LET (n = 334)
Events, n (%)	140 (41.9)	205 (61.4)
Median PFS, mos (95% CI)	25.3 (23.0–30.3)	16.0 (13.4–18.2)

HR = 0.568 (95% CI, 0.457–0.704)
P value = 9.63×10^{-8}



No. at risk

RIBO + LET	334	294	277	257	240	227	207	196	188	176	164	132	97	46	17	11	1	0
PBO + LET	334	279	265	239	219	196	179	156	138	124	110	93	63	34	10	7	2	0

Demonstrated continued treatment benefit for PAL + LET (PALOMA-2) and RIBO + LET (MONALEESA-2) vs PBO

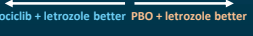
PFS = progression-free survival; PAL = palbociclib; LET = letrozole; PBO = placebo; RIBO = ribociclib; NR = not reached; HR = hazard ratio; CI = confidence interval; n = number.

Rugo HS, et al. *Breast Cancer Res. Treat.* 2019;174:719-729. Hortobagyi GN, et al. *Ann Oncol.* 2018;29:1541-1547.

PALOMA-2 and MONALEESA-2: Subgroup Analyses

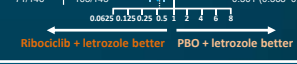
PALOMA-2

Subgroup	PAL + LET No. of patients (%)	PBO + LET No. of patients (%)	Hazard Ratio (95% CI)
All randomly assigned patients	444 (100)	222 (100)	0.58 (0.46–0.72)
Age			
<65 yr	263 (59.2)	141 (63.5)	0.57 (0.43–0.74)
≥65 yr	181 (40.8)	81 (36.5)	0.57 (0.39–0.84)
Race			
White	344 (77.5)	172 (77.5)	0.58 (0.45–0.74)
Asian	65 (14.6)	30 (13.5)	0.48 (0.27–0.87)
Site of metastatic disease at baseline			
Visceral	214 (48.2)	110 (49.5)	0.63 (0.47–0.85)
Nonvisceral	230 (51.8)	112 (50.5)	0.50 (0.36–0.70)
Prior hormonal therapy			
Yes	249 (56.1)	126 (56.8)	0.53 (0.40–0.70)
No	195 (43.9)	96 (43.2)	0.63 (0.44–0.90)
Disease-free interval			
Newly metastatic disease	167 (37.6)	81 (36.5)	0.67 (0.46–0.99)
≤12 mos	99 (22.3)	48 (21.6)	0.50 (0.33–0.76)
>12 mos	178 (40.1)	93 (41.9)	0.52 (0.36–0.73)
Region			
North America	168 (37.8)	99 (44.6)	0.60 (0.43–0.85)
Europe	212 (47.7)	95 (42.8)	0.57 (0.41–0.80)
Asia Pacific	64 (14.4)	28 (12.6)	0.49 (0.27–0.87)
ECOG performance status			
0	257 (57.9)	102 (45.9)	0.65 (0.47–0.90)
1 or 2	187 (42.1)	120 (54.1)	0.53 (0.39–0.72)
Bone-only disease at baseline			
Yes	103 (23.2)	48 (21.6)	0.36 (0.22–0.59)
No	341 (76.8)	174 (78.4)	0.65 (0.51–0.84)
Measurable disease			
Yes	338 (76.1)	171 (77.0)	0.66 (0.52–0.85)
No	106 (23.9)	51 (23.0)	0.35 (0.22–0.57)
Prior chemotherapy			
Yes	213 (48.0)	109 (49.1)	0.53 (0.40–0.72)
No	231 (52.0)	113 (50.9)	0.61 (0.44–0.84)
Most recent therapy			
Aromatase inhibitor	91 (20.5)	44 (19.8)	0.55 (0.34–0.88)
Antiestrogen	154 (34.7)	75 (33.8)	0.56 (0.39–0.80)
No. of disease sites			
1	138 (31.1)	66 (29.7)	0.51 (0.34–0.77)
≥2	306 (68.9)	156 (70.3)	0.61 (0.47–0.79)
Histopathological classification			
Ductal carcinoma	356 (80.2)	184 (82.9)	0.59 (0.46–0.75)
Lobular carcinoma	68 (15.3)	30 (13.5)	0.46 (0.26–0.78)



MONALEESA-2

Subgroup	RIBO + LET Events n/n	PBO + LET Events n/n	Hazard Ratio (95% CI)
All patients	140/334	205/334	0.568 (0.457–0.704)
US patients	38/100	63/113	0.527 (0.351–0.793)
ECOG PS			
0	82/205	123/202	0.581 (0.439–0.769)
1	58/129	82/132	0.543 (0.385–0.766)
Age			
<65 years	82/184	127/189	0.518 (0.392–0.684)
≥65 years	58/150	78/145	0.658 (0.466–0.928)
Race			
Asian	14/28	19/23	0.370 (0.180–0.760)
Non-Asian	121/281	171/287	0.614 (0.486–0.775)
HR status			
ER+ and PgR+	109/269	162/277	0.606 (0.475–0.774)
Other	31/65	43/57	0.358 (0.217–0.591)
Liver or lung metastases			
No	59/152	80/143	0.597 (0.426–0.837)
Yes	81/182	125/191	0.561 (0.424–0.743)
Bone-only disease			
No	114/265	159/256	0.551 (0.432–0.702)
Yes	26/69	46/78	0.642 (0.393–1.048)
De novo disease			
No	97/220	144/221	0.579 (0.447–0.749)
Yes	43/114	61/113	0.569 (0.384–0.843)
Previous ET			
NSAI and others	15/30	17/23	0.430 (0.205–0.901)
TAM and/or EXE	63/146	102/149	0.516 (0.376–0.708)
None	62/158	86/162	0.651 (0.468–0.904)
Previous chemotherapy			
No	69/188	102/189	0.640 (0.470–0.871)
Yes	71/146	103/145	0.501 (0.368–0.681)

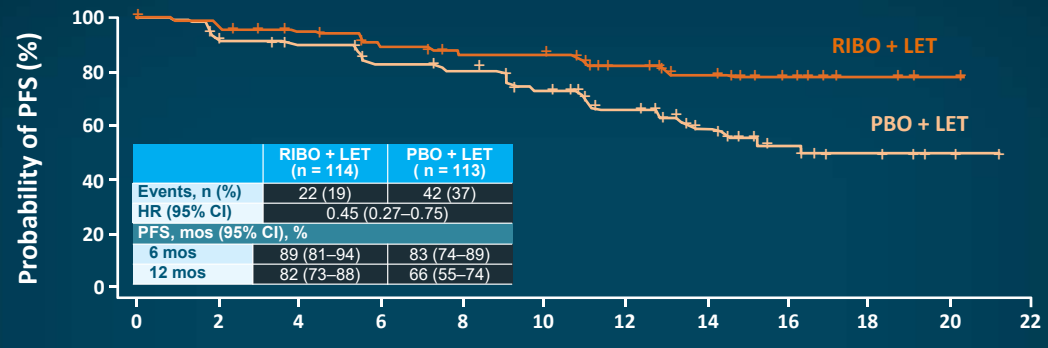


Demonstrated consistent PFS benefit for all predefined subgroups in the PAL + LET (PALOMA-2) and RIBO + LET arms (MONALEESA-2)

Finn RS, et al. *N Engl J Med.* 2016;375:1925-1936. Hortobagyi GN. *Breast Cancer Res.* 2018;20:123.

MONALEESA-2 *de novo* Subgroup

Locally Assessed PFS



	RIBO + LET (n = 114)	PBO + LET (n = 113)
Events, n (%)	22 (19)	42 (37)
HR (95% CI)	0.45 (0.27–0.75)	
PFS, mos (95% CI), %		
6 mos	89 (81–94)	83 (74–89)
12 mos	82 (73–88)	66 (55–74)

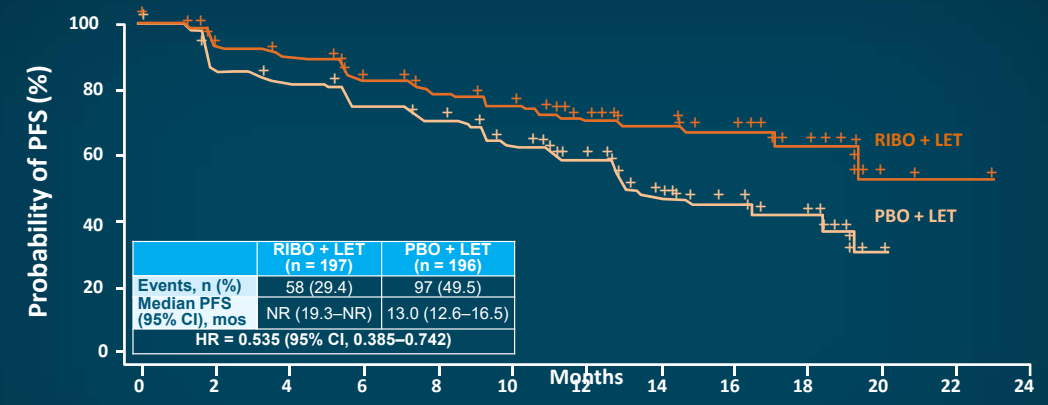
No. at risk												
RIBO + LET	114	106	100	92	87	87	66	50	29	5	1	0
PBO + LET	113	99	93	85	81	70	52	32	16	7	3	0

- Efficacy of ribociclib in *de novo* disease was consistent with findings from overall population.
- Results support PFS results from PALOMA-2 (PAL + LET) in a similar patient population, demonstrating the benefit of CDK4/6 inhibition in 1L treatment of HR+ metastatic BC.

O'Shaughnessy J, et al. *Breast Cancer Res Treat*. 2018;168:127-134. Hortobagyi GN. *Breast Cancer Res*. 2018;20:123.

MONALEESA-2

Analyses in Patients with Visceral Metastases



	RIBO + LET (n = 197)	PBO + LET (n = 196)
Events, n (%)	58 (29.4)	97 (49.5)
Median PFS (95% CI), mos	NR (19.3–NR)	13.0 (12.6–16.5)
HR = 0.535 (95% CI, 0.385–0.742)		

No. at risk:												
RIBO + LET	197	175	163	148	137	129	94	67	38	13	3	1	0
PBO + LET	196	162	152	137	128	111	83	50	27	14	1	0	0

RIBO + LET treatment benefit was maintained in patients with visceral metastases.

Burris H, et al. San Antonio Breast Cancer Symposium (SABCS) 2016: abstract P4-22-16. Hortobagyi GN. *Breast Cancer Res*. 2018;20:123

MONALEESA-2: Efficacy by Biomarker Analyses

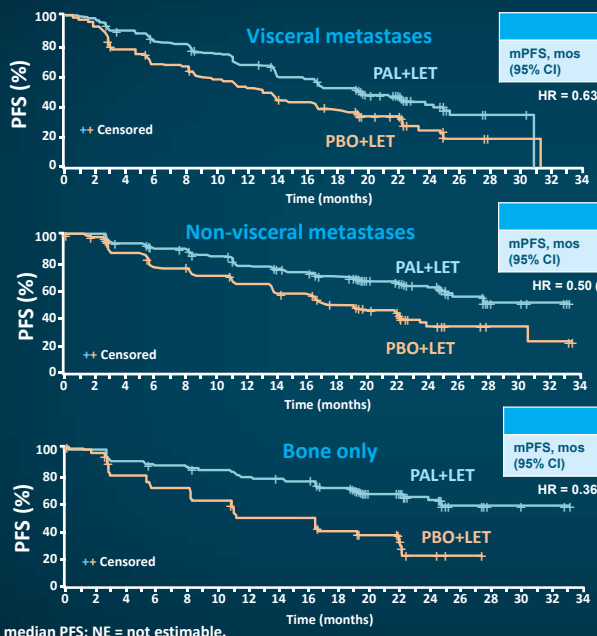
- Ribociclib treatment benefit was maintained irrespective of baseline Rb, p16, or Ki67 protein expression, or *CDKN2A*, *CCND1*, or *ESR1* gene expression levels.
- *PIK3CA* alterations were detected in the ctDNA of 34% of evaluable patients; ribociclib treatment benefit was similar among *PIK3CA*–wild type and *PIK3CA*-altered groups.

Biomarker		Status	n (%)	HR (95% CI)	*P*-value
All patients				0.56 (0.43–0.72)	.00000326
Protein level	Total Rb (n = 479)	≤10th percentile	59 (12)	0.55 (0.25–1.25)	.16
		>10th percentile	420 (88)	0.51 (0.37–0.71)	.000061
	p16 (n = 405)	Low H-score	213 (53)	0.56 (0.34–0.91)	.02
		High H-score	192 (47)	0.54 (0.34–0.86)	.01
	Ki67 (n = 463)	≤14% of tumor cells	216 (47)	0.64 (0.39–1.04)	.071
		>14% of tumor cells	247 (53)	0.44 (0.29–0.66)	.000077
Gene expression	*CDKN2A* (386)	Low expression	193 (50)	0.51 (0.32–0.83)	.006
		High expression	193 (50)	0.62 (0.39–1.00)	.052
	CCND1 (386)	Low expression	193 (50)	0.50 (0.31–0.80)	.0038
		High expression	193 (50)	0.65 (0.40–1.06)	.083
	ESR1 (386)	Low expression	193 (50)	0.68 (0.43–1.05)	.082
		High expression	193 (50)	0.48 (0.28–0.82)	.0072
	PIK3CA (417)	Wildtype	276 (66)	0.51 (0.34–0.78)	.0016
		Altered	141 (34)	0.52 (0.31–0.86)	.0120

PIK3CA = phosphatidylinositol 3-kinase catalytic alpha polypeptide.

Andre F, et al. *Cancer Res.* 2017;77(13 suppl): abstract CT045. Modified from Campone M, et al. IMPAKT Breast Cancer Conference 2017: abstract 160.

PALOMA-2: mPFS Based on Disease Location



	PAL + LET	PBO + LET
mPFS, mos (95% CI)	19.3 (16.4–22.2)	12.9 (8.4–16.6)

HR = 0.63 (95% CI, 0.47–0.85), *P* <.01

	PAL + LET	PBO + LET
mPFS, mos (95% CI)	NR (25.1–NE)	16.8 (13.7—22.2)

HR = 0.50 (95% CI, 0.36–0.70), *P* <.0001

	PAL + LET	PBO + LET
mPFS, mos (95% CI)	NR (24.8–NE)	11.2 (8.2—22.0)

HR = 0.36 (95% CI, 0.22–0.59), *P* <.0001

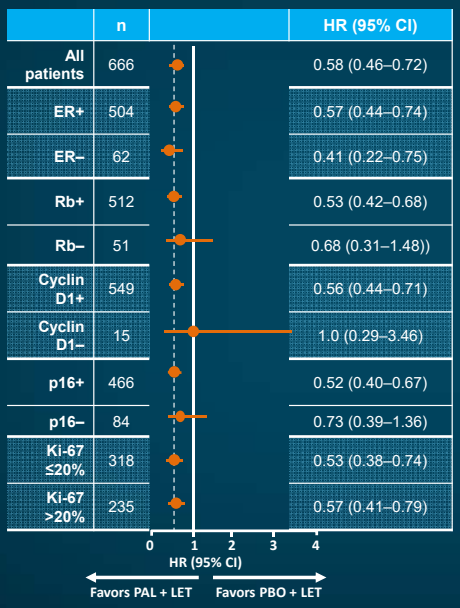
mPFS was significantly longer in those treated with PAL + LET vs PBO + LET in subgroups with +/– visceral metastases (any lung/pleura +/– liver involvement) and bone-only disease.

mPFS = median PFS; NE = not estimable.

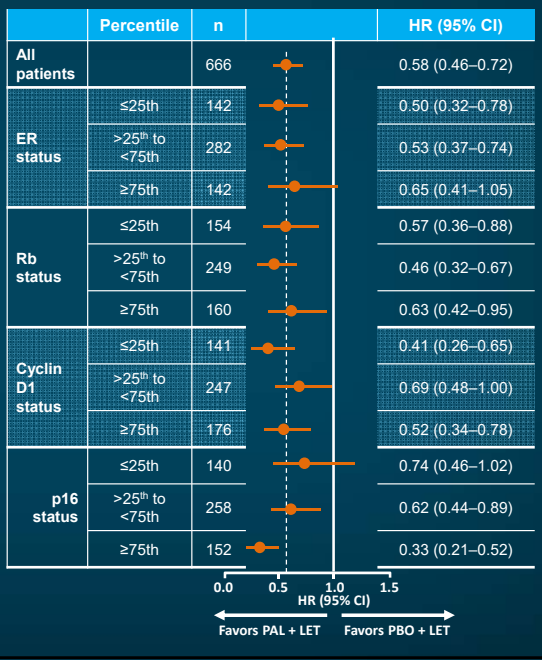
Turner NC, et al. *Ann Oncol.* 2018;29:669-680.

Biomarker Analyses from PALOMA-2

Qualitative analysis



Quantitative analysis



Finn RS, et al. *Ann Oncol.* 2016;27(6):abstract LBA15.

MONARCH-3 Study Design

Abemaciclib as Initial Therapy for ABC

- HR+, HER2– ABC
- Postmenopausal
- Metastatic or locally recurrent disease with no prior systemic therapy in this setting
- If neoadjuvant or adjuvant ET administered, a disease free interval of >12 months since completion of ET
- ECOG PS ≤1

N = 493

2 :1 Randomization

Abemaciclib
150 mg BID (continuous schedule) +
ANA 1 mg or*
LET 2.5 mg QD until PD

Placebo
BID (continuous schedule) +
ANA 1 mg or*
LET 2.5 mg QD until PD

Primary endpoint:
Investigator-assessed PFS

Secondary endpoint:
OS, response rates, safety

Stratification factors:
- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

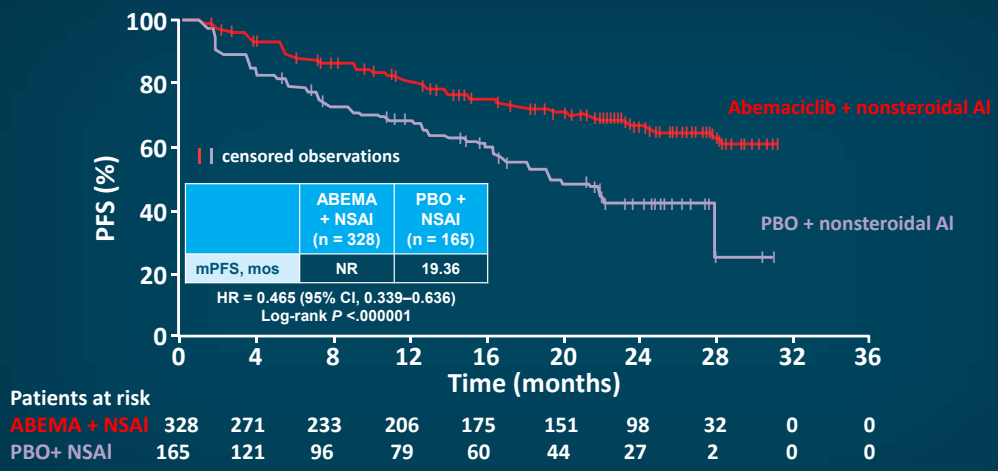
*** per physician's choice: 79.1% received letrozole, 19.9% received anastrozole**

- **Statistics:** Study powered to 80% at one-sided alpha of 0.025 assuming HR of 0.67 with analyses at 189 and 240 PFS events. Positive study at the interim required a HR <0.56 and two-sided *P* <.0005.
- **Median follow-up:** 17.8 months (interim analysis).

ECOG = Eastern Cooperative Oncology Group; PS = performance status; PD = progressive disease; ANA = anastrozole; LET = letrozole.

Goetz MP, et al. *J Clin Oncol*. 2017;35:3638-3646.

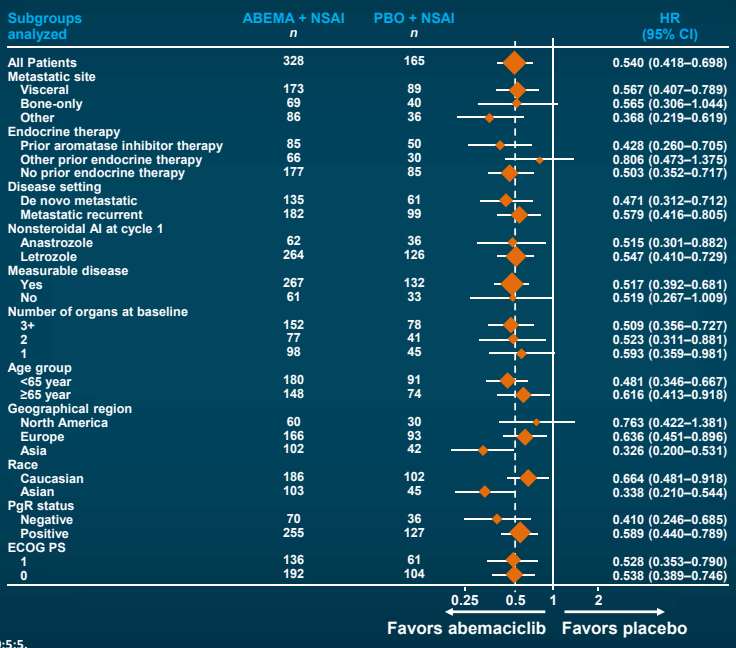
MONARCH-3: Final PFS by ICR in ITT Population



ICR = independent central review ; ITT = intention to treat; NSAI = nonsteroidal AI.

Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5.

MONARCH-3: PFS Subgroup Analysis



PgR = progesterone receptor.

Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5.

MONARCH-3: Objective Response Rates

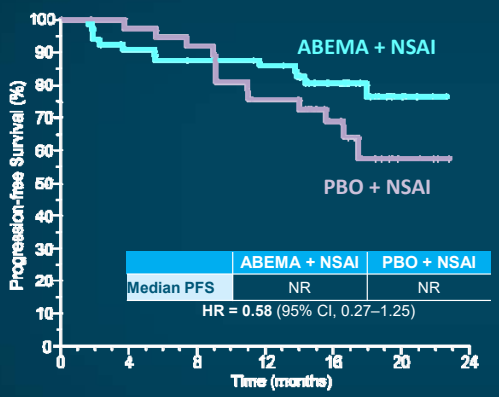
Best Overall Response	Abemaciclib + NSAI		Placebo + NSAI		*P*-value
	n	% (95% CI)	n	% (95% CI)	
All patients, *n*	328		165		
CR	9	2.7 (1.0–4.5)	1	0.6 (–0.6 to 1.8)	
PR	154	47.0 (41.6–52.4)	60	36.4 (29.0–43.7)	
Objective response rate (CR/PR)	163	49.7 (44.3–55.1)	61	37.0 (29.6–44.3)	.005
Disease control rate (CR/PR/SD)	291	88.7 (85.3–92.1)	143	86.7 (81.5–91.9)	.501
Clinical benefit rate (CR/PR/SD ≥6 months)	256	78.0 (73.6–82.5)	118	71.5 (64.6–78.4)	.101
Patients with measurable disease at baseline, n	267		132		
CR	9	3.4 (1.2–5.5)	0	N/A	
PR	154	57.7 (51.8–63.6)	60	45.5 (37.0–53.9)	
Objective response rate (CR/PR)	163	61.0 (55.2–66.9)	60	45.5 (37.0–53.9)	.003
Disease control rate (CR/PR/SD)	239	89.5 (85.8–93.2)	114	86.4 (80.5–92.2)	.310
Clinical benefit rate (CR/PR/SD ≥6 months)	211	79.0 (74.1–83.9)	92	69.7 (61.9–77.5)	.037

Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5.

MONARCH-3: Exploratory PFS Analysis

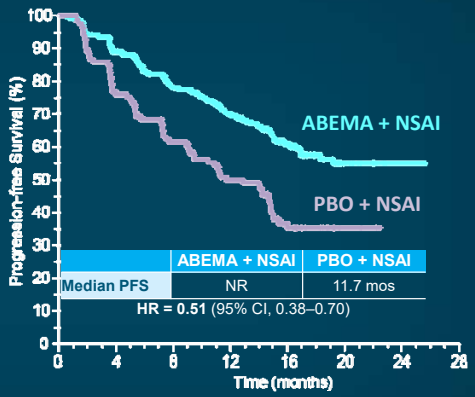
Bone-Only Disease

Patients with bone-only disease



PFS Rate	6 mos	12 mos	18 mos
ABEMA + NSAI (n = 70)	87.6%	86.0%	76.5%
PBO + NSAI (n = 39)	94.6%	75.7%	57.6%

Patients without bone-only disease



PFS Rate	6 mos	12 mos	18 mos
ABEMA + NSAI (n = 258)	82.7%	69.5%	57.5%
PBO + NSAI (n = 126)	68.4%	49.9%	35.4%

Goetz MP, et al. *J Clin Oncol*. 2017;35:3638-3646.

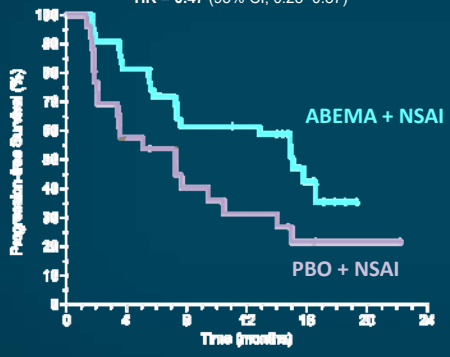
MONARCH-3: Exploratory PFS Analysis

Liver Metastases

Patients with liver metastases

	ABEMA + NSAI	PBO + NSAI
Median PFS	15.0 mos	7.2 mos

HR = 0.47 (95% CI, 0.25–0.87)

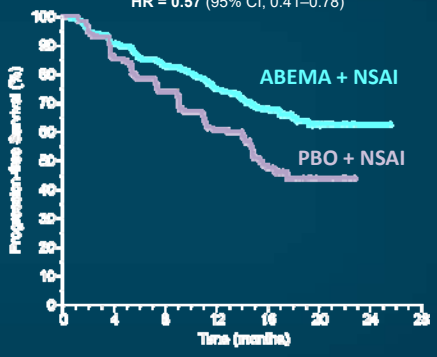


PFS Rate			
	6 mos	12 mos	18 mos
ABEMA + NSAI (n = 48)	71.8%	61.5%	35.3%
PBO + NSAI (n = 30)	53.8%	31.4%	21.5%

Patients without liver metastases

	ABEMA + NSAI	PBO + NSAI
Median PFS	NR	15.4 mos

HR = 0.57 (95% CI, 0.41–0.78)



PFS Rate			
	6 mos	12 mos	18 mos
ABEMA + NSAI (n = 280)	85.6%	74.8%	64.9%
PBO + NSAI (n = 135)	78.7%	60.7%	43.9%

Goetz MP et al. *J Clin Oncol*. 2017;35:3638-3646.

Case Study 1—Question 1

- A 58-year-old woman has been treated for stage II ER+ PR– HER2– breast cancer with 5 years of an aromatase inhibitor. Two years after completing AI, she develops painful bone metastases at multiple sites. Staging is otherwise negative for metastases.
- Biopsy of bone lesion confirms ER+ PR– HER2– carcinoma.
- In addition to an anti-osteoclast agent, you recommend:
  - A. Fulvestrant
  - B. Letrozole + ribociclib
  - C. Letrozole + palbociclib
  - D. Fulvestrant + abemaciclib
  - E. Fulvestrant + palbociclib

Case Study 1—Question 2

- The patient is treated with letrozole plus ribociclib, in addition to zoledronic acid, and has improvement in her bone pain and resolution of areas of active disease on bone scan for 30 months.
- After 30 months on treatment, she develops new left-hip and lumbar-spine pain, and bone scan shows progression of disease. Restaging shows no other areas of metastasis. Genotyping revealed wild-type PIK3CA status.
- You recommend:
  - A. Fulvestrant
  - B. Fulvestrant or exemestane + everolimus
  - C. Fulvestrant + ribociclib
  - D. Fulvestrant + palbociclib
  - E. Fulvestrant + abemaciclib
  - F. Capecitabine
  - G. Abemaciclib

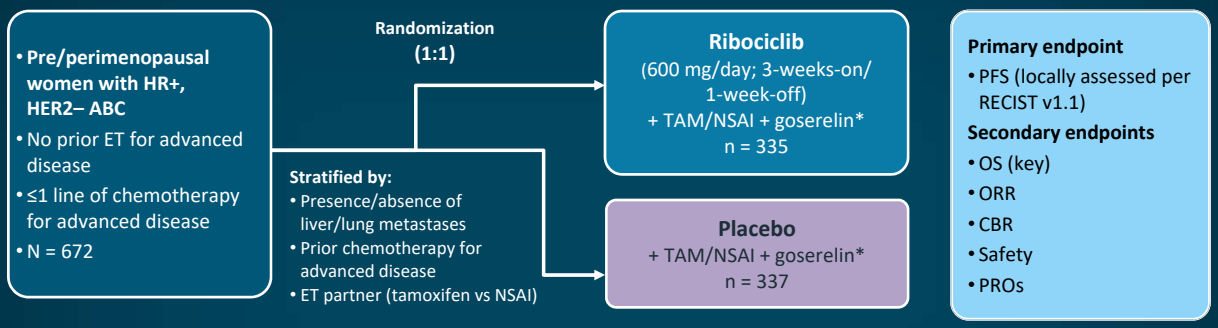
Case Study 1—Question 3

If this patient had asymptomatic liver metastases with mildly elevated liver function tests instead of bone-only disease and was diagnosed with metastases while receiving adjuvant anastrozole, your recommendation for therapy would be:

- A. Letrozole + palbociclib
- B. Letrozole + ribociclib
- C. Fulvestrant + palbociclib
- D. Fulvestrant + abemaciclib
- E. Fulvestrant + ribociclib
- F. Taxane
- G. Capecitabine

Ribociclib in Premenopausal 1st-Line Metastatic Breast Cancer

MONALEESA-7: Phase 3 Placebo-Controlled Study of RIBO and Tamoxifen/NSAI + Goserelin



***Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg subcutaneous injection every 28 days.**

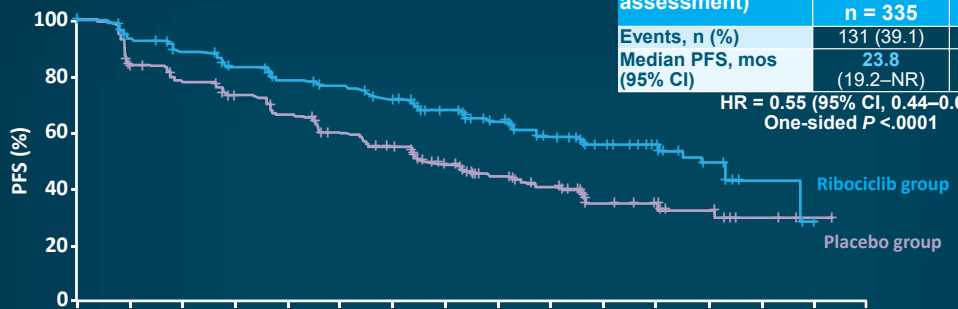
- Tumor assessments performed every 8 weeks for 18 months, then every 12 weeks
- Primary analysis planned after ~329 PFS events
  - 95% power to detect a 33% risk reduction (HR = 0.67) with one-sided α=2.5%, corresponding to increase in median PFS to 13.4 mos (median PFS of 9 mos for placebo arm), and a sample size of 660 patients

RECIST = Response Evaluation Criteria in Solid Tumors; PRO = patient-reported outcome.
NCT02278120 (MONALEESA-7). Tripathy D, et al. SABCS 2017: abstract GS2-05.

MONALEESA-7: Primary Endpoint PFS (Investigator-Assessed)

PFS (investigator assessment)	RIBO + TAM/NSAI* n = 335	PBO + TAM/NSAI* n = 337
Events, n (%)	131 (39.1)	187 (55.5)
Median PFS, mos (95% CI)	23.8 (19.2–NR)	13.0 (11.0–16.4)

HR = 0.55 (95% CI, 0.44–0.69)
One-sided *P* <.0001



No. at risk (number censored)																			
Ribociclib group	335 (0)	301 (9)	264 (12)	264 (15)	245 (20)	235 (23)	219 (25)	178 (55)	136 (88)	90 (124)	54 (156)	40 (170)	20 (187)	3 (202)	1 (203)	0 (204)
Placebo group	337 (0)	273 (12)	248 (15)	230 (19)	207 (21)	183 (25)	165 (27)	124 (50)	94 (72)	62 (97)	31 (121)	24 (128)	13 (138)	3 (147)	1 (149)	0 (150)

Demonstrated improved median PFS of 23.8 months with RIBO + ET (TAM/NSAI) vs placebo arms (13 mos)

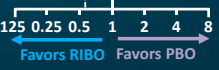
*Both groups also received goserelin.

Tripathy D, et al. *Lancet Oncol.* 2018;19:904-915

MONALEESA-7: PFS Subgroup Analysis

- Demonstrated PFS benefit in RIBO arms for most prespecified subgroups vs placebo.
- The patient proportion with overall response and clinical benefit was greater in RIBO arms, with probability of response at 6 months of 35.1% vs placebo (24.6%).*

		Events n/N			HR (95% CI)	HR (95% CI)
		RIBO	PBO	Total		
Endocrine therapy partner	Tamoxifen	39/87	55/90	94/177		0.59 (0.39–0.88)
	NSAI	92/248	132/247	224/495		0.57 (0.44–0.74)
Age	<40 years	42/98	61/88	103/186		0.44 (0.29–0.67)
	≥40 years	89/237	126/249	215/486		0.59 (0.45–0.78)
Race	Asian	33/99	62/99	95/198		0.40 (0.26–0.63)
	Non-Asian	84/200	112/213	196/413		0.66 (0.49–0.88)
Region	Asia	33/92	56/88	89/180		0.42 (0.27–0.66)
	Europe and Australia	55/136	75/139	130/275		0.63 (0.44–0.91)
	Latin America	12/31	11/25	23/56		0.76 (0.31–1.86)
	North America	19/47	27/50	46/97		0.54 (0.29–1.01)
	Other	12/29	18/35	30/64		0.84 (0.39–1.82)
ECOG PS	0	87/245	134/255	221/500		0.55 (0.42–0.72)
	≥1	43/87	51/79	94/166		0.50 (0.32–0.77)
Hormone receptor status	ER and PgR positive	105/286	149/286	254/572		0.57 (0.45–0.74)
	Other	26/49	38/51	64/100		0.44 (0.26–0.77)
Liver or lung metastases	Yes	75/173	109/170	184/343		0.50 (0.38–0.68)
	No	56/162	78/167	134/329		0.64 (0.45–0.91)
Bone-only disease	Yes	25/81	33/78	58/159		0.70 (0.41–1.19)
	No	106/254	154/259	260/513		0.53 (0.42–0.69)
No. of metastatic sites	<3	76/219	106/216	182/435		0.60 (0.44–0.81)
	≥3	55/116	81/121	136/237		0.50 (0.35–0.72)
Prior chemo for advanced disease	Yes	22/47	29/47	51/94		0.55 (0.31–0.95)
	No	109/288	158/290	267/578		0.57 (0.44–0.72)
Prior neoadjuvant or adjuvant chemo	Yes	64/138	76/138	140/276		0.68 (0.48–0.96)
	No	45/150	82/152	127/302		0.41 (0.28–0.60)
Prior neoadjuvant or adjuvant ET	Yes	58/127	79/141	137/268		0.62 (0.44–0.89)
	No	73/208	108/196	181/404		0.52 (0.38–0.70)
Disease-free interval after diagnosis	≤12 months	12/23	9/13	24/36		0.56 (0.21–1.49)
	>12 months	76/176	106/190	182/366		0.62 (0.46–0.83)
	Newly diagnosed	40/136	72/134	112/270		0.43 (0.29–0.64)
Treatment-free interval after neoadjuvant or adjuvant ET	≤12 months	51/100	65/105	116/205		0.59 (0.40–0.87)
	>12 months	7/25	14/35	21/60		0.75 (0.28–2.02)
All patients		131/335	187/337	318/672		0.55 (0.44–0.69)



*ITT population and measurable disease at baseline.
n/N = number/number in population.

Tripathy D, et al. *Lancet Oncol.* 2018;19:904-915.

MONALEESA-7

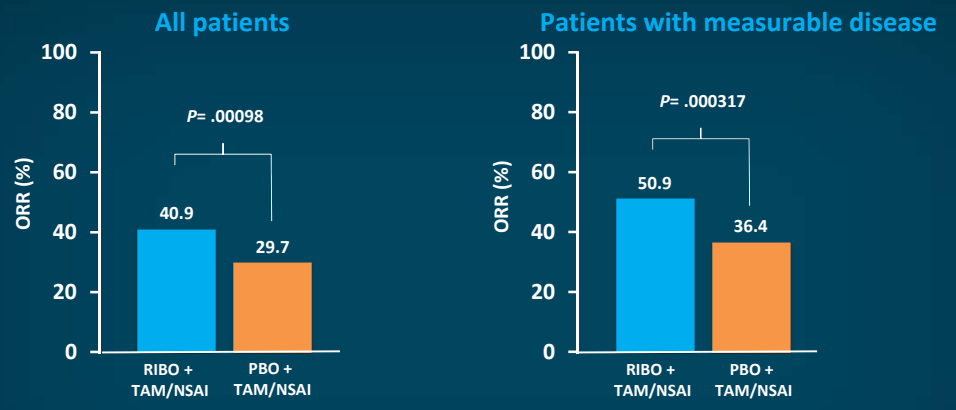
PFS by Endocrine Therapy Partner

PFS (investigator assessment)	Tamoxifen*		NSAI	
	RIBO arm† n = 87	PBO arm† n = 90	RIBO arm† n = 248	PBO arm† n = 247
Events, n	39	55	92	132
Median PFS, mos (95% CI)	22.1 (16.6–24.7)	11.0 (9.1–16.4)	27.5 (19.1–NR)	13.8 (12.6–17.4)
HR (95% CI)	0.585 (0.387–0.884)		0.569 (0.436–0.743)	

*Tamoxifen should not be given with ribociclib due to concerns about QTc prolongation; †Goserelin included in all combinations.

Tripathy D, et al. SABCS 2017:abstract GS2-05.

MONALEESA-7: Secondary Endpoints



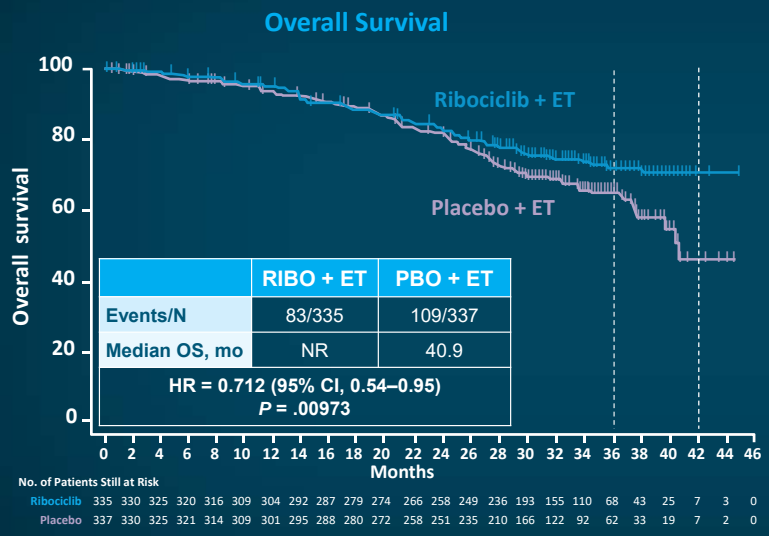
CBR in patients with measurable disease was 79.9% for ribociclib + tamoxifen/NSAI vs 67.3% for placebo + tamoxifen/NSAI (*P*= .00034).

Goserelin included in all combinations.

CBR = CR + PR + (SD + non-complete response/non-progressive disease ≥24 weeks).

Tripathy D, et al. SABCS 2017:abstract GS2-05.

MONALEESA-7 Trial: Overall Survival



	RIBO + ET	PBO + ET
Events/N	83/335	109/337
Median OS, mo	NR	40.9
HR = 0.712 (95% CI, 0.54–0.95) *P* = .00973		

- RIBO + ET had ≈29% relative reduction in risk of death
- The *P* value of 0.00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis		
Kaplan-Meier Estimate	RIBO + ET	PBO + ET
36 mo	71.9%	64.9%
42 mo	70.2%	46.0%

Hurvitz SA, et al. *J Clin Oncol.* 2019;37(18 suppl): abstract LBA1008. Im SA, et al. *N Engl J Med*. 2019;381:307-316.

Case 2—Question 1

- A 33-year-old woman presents with painful vertebral metastases. Biopsies of a breast mass and bone metastasis reveal grade 3 ER+ PR+ HER2– breast cancer. Staging evaluation shows bone-only mBC.
- In addition to an anti-osteoclast agent, you recommend:
  - A. LHRH agonist + tamoxifen
  - B. LHRH agonist + AI
  - C. LHRH agonist + tamoxifen + ribociclib
  - D. LHRH agonist + AI + palbociclib
  - E. LHRH agonist + AI + ribociclib
  - F. LHRH agonist + AI + abemaciclib

mBC = metastatic breast cancer; LHRH = luteinizing hormone-releasing hormone.

CDK4/6 Inhibitors Combined with Fulvestrant

Sara Hurvitz, MD

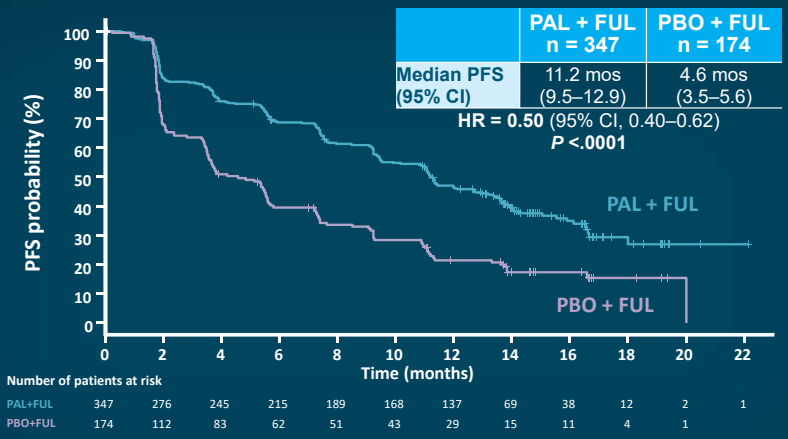
CDK4/6 Inhibitors in Combination with Fulvestrant

	Palbociclib[1–3]	Ribociclib[4,5]	Abemaciclib[6,7]
	PALOMA-3	MONALEESA-3	MONARCH-2
Endocrine partner	Fulvestrant	Fulvestrant	Fulvestrant
Eligibility	PD on prior met ET	Tx-Naïve or ≤1 met ET	PD on neoadj/adj ET, ≤12 mo from end of adj ET, or ≤1 met ET
Population	N = 521	N = 726	N = 669
ORR (%)	19.0 vs 9.0	32.4 vs 21.5	35.2 vs 16.1
Median PFS (mo)	9.5 vs 4.6 HR = 0.46; *P* <0.0001	20.5 vs 12.8 HR = 0.59; *P* <.001	16.4 vs 9.3 HR = 0.553; *P* <.001
Median OS (mo)	34.9 vs 28.0 HR = 0.81; *P*= .09	NE vs 40.0 HR = 0.72; P = 0.00455	46.7 vs 37.3 HR = 0.757; *P*= .0137

1. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936. 2. Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439. 3. Cristofanilli M, et al. European Society for Medical Oncology (ESMO) 2018: abstract LBA2_PR. 4. Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472. 5. Slamon DJ, et al. *N Engl J Med*. 2020;382(6):514-524. 6. Sledge GW Jr, et al. *J Clin Oncol*. 2017;35:2875-2884. 7. Sledge GW Jr, et al. *JAMA Oncol*. 2020;6(1):116-124.

Palbociclib + Fulvestrant

PALOMA-3: FINAL PFS (ITT)



	PAL + FUL n = 347	PBO + FUL n = 174
Median PFS (95% CI)	11.2 mos (9.5–12.9)	4.6 mos (3.5–5.6)

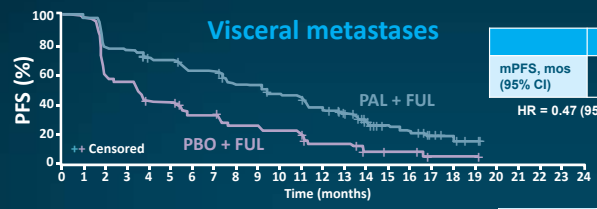
HR = 0.50 (95% CI, 0.40–0.62)
***P* <.0001**

Absolute improvement in median PFS in the palbociclib arm vs the placebo arm was 6.6 months.

FUL = fulvestrant.

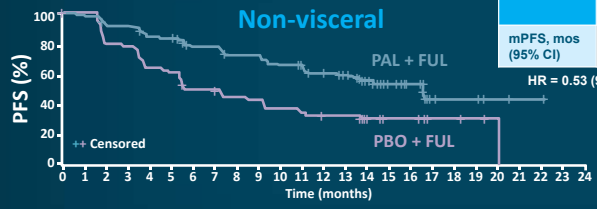
Turner NC, et al. *N Engl J Med* 2018;379:1926-1936 and supplement.

PALOMA-3: mPFS Based on Disease Location



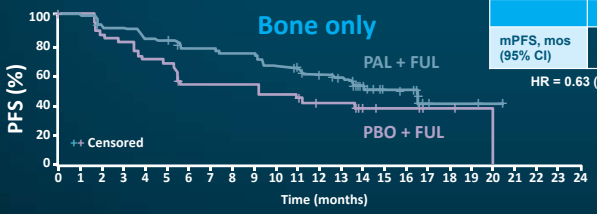
	PAL + FUL	PBO + FUL
mPFS, mos (95% CI)	9.2 (7.5–11.1)	3.4 (1.9–5.1)

HR = 0.47 (95% CI, 0.35–0.61), *P* <.0001



	PAL + FUL	PBO + FUL
mPFS, mos (95% CI)	16.6 (13.2–NE)	17.3 (4.8–10.9)

HR = 0.53 (95% CI, 0.36–0.77), *P* <.001



	PAL + FUL	PBO + FUL
mPFS, mos (95% CI)	14.3 (11.2–NE)	9.2 (4.8–20.0)

HR = 0.63 (95% CI, 0.38–1.06), *P* <.05

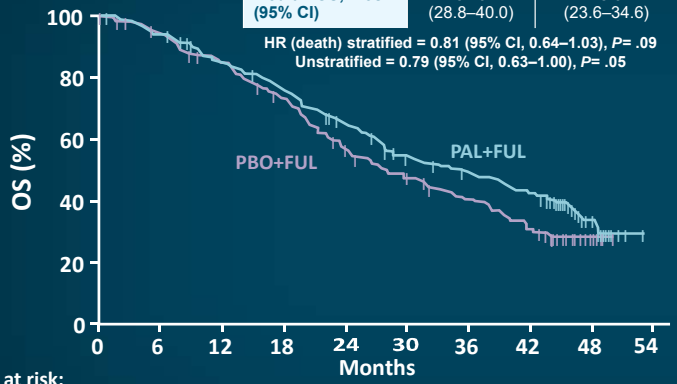
mPFS was significantly longer in those treated with PAL + FUL vs PBO + FUL in subgroups +/– visceral metastases (lung/pleura, liver, brain and peritoneal involvement) as well as bone-only disease.

Turner NC, et al. *Ann Oncol.* 2018;29:669-680.

PALOMA-3: Overall Survival (OS) in ITT Group

	PAL + FUL n = 347	PBO + FUL n = 174
Median OS, mos (95% CI)	34.9 (28.8–40.0)	28.0 (23.6–34.6)

HR (death) stratified = 0.81 (95% CI, 0.64–1.03), *P*= .09
Unstratified = 0.79 (95% CI, 0.63–1.00), *P*= .05



No. at risk:

PAL + FUL	347	321	286	247	209	165	148	126	17	0
PBO + FUL	174	155	135	115	86	68	57	43	7	0

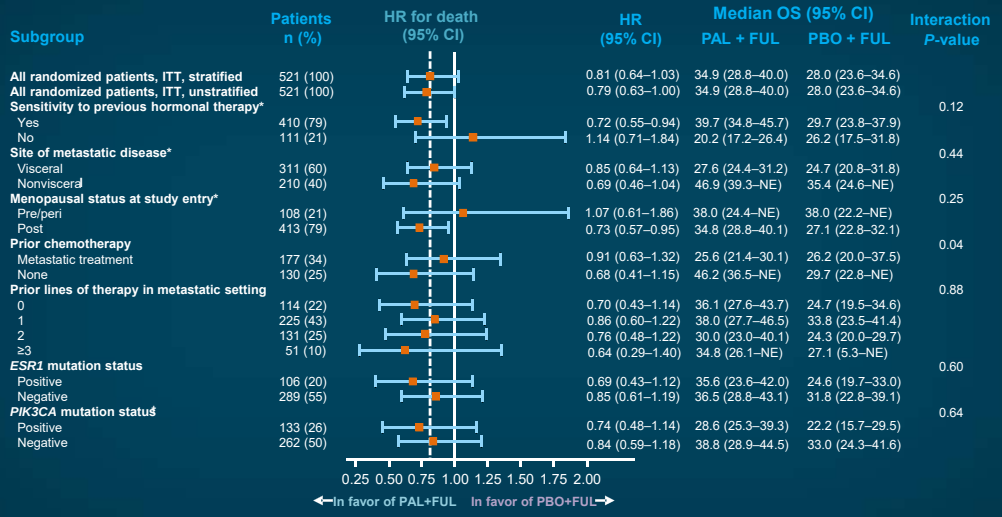
Statistical analysis design

- PALOMA-3 study was powered for primary endpoint, PFS, but was not optimized for secondary endpoint, OS.
- Planned final OS analysis was performed at 310 events in 521 randomized patients with a median follow-up of 44.8 mos and approximately 60% data maturity (data cutoff date: April 13, 2018).
- Prespecified significance threshold was 2-sided P-value of 0.047, which was adjusted for interim analyses.

Absolute improvement in median OS in palbociclib arm vs placebo arm was 6.9 months.

Turner NC, et al. *N Engl J Med.* 2018;379:1926-1936.

PALOMA-3: OS Subgroup Analysis



*Prespecified stratification factors.

ESR1 = estrogen receptor 1.

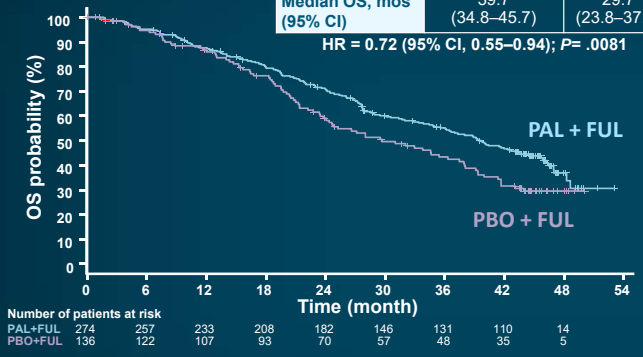
Turner NC, et al. *N Engl J Med.* 2018;379:1926-1936.

PALOMA-3: OS by Prior ET Sensitivity

Patients with Sensitivity to Prior ET

	PAL + FUL (n = 274)	PBO + FUL (n = 136)
Median OS, mos (95% CI)	39.7 (34.8–45.7)	29.7 (23.8–37.9)

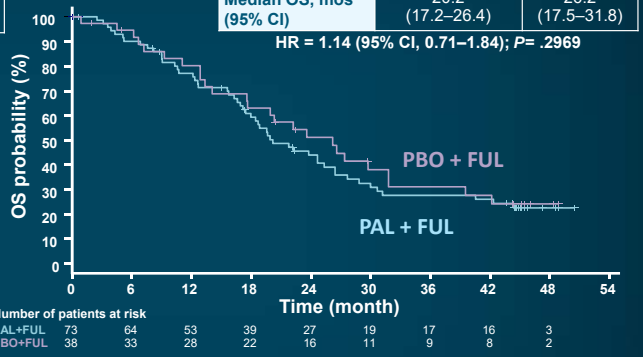
HR = 0.72 (95% CI, 0.55–0.94); *P*= .0081



Patients Without Sensitivity to Prior ET

	PAL + FUL (n = 73)	PBO + FUL (n = 38)
Median OS, mos (95% CI)	20.2 (17.2–26.4)	26.2 (17.5–31.8)

HR = 1.14 (95% CI, 0.71–1.84); *P*= .2969

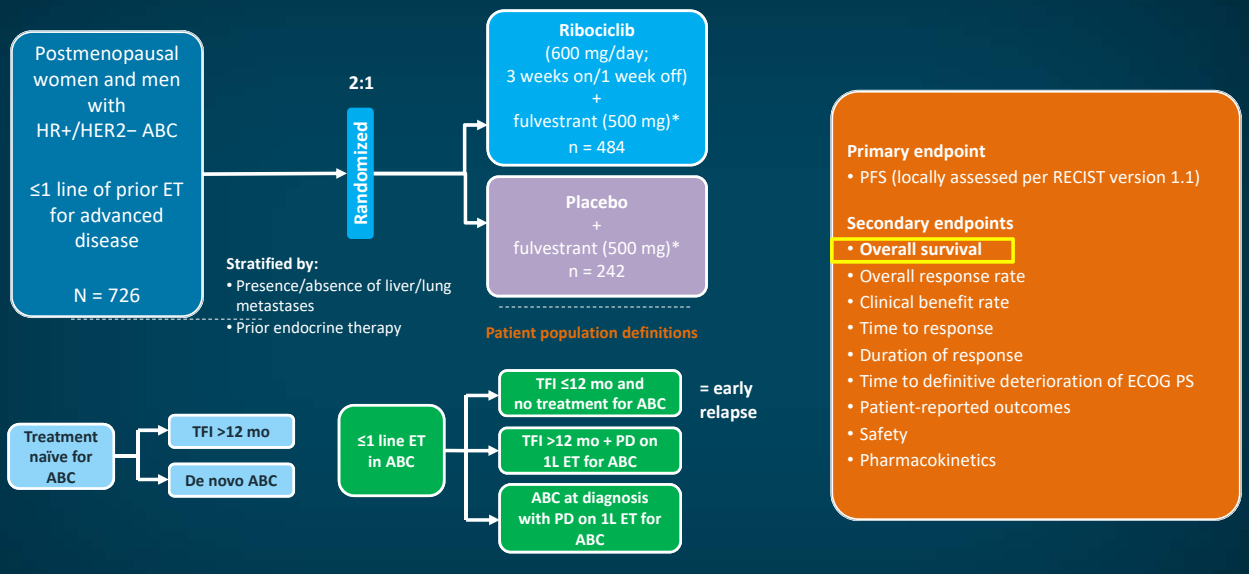


- In patients with sensitivity to prior ET, absolute improvement in median OS in the palbociclib vs placebo arm was 10.0 months.
- Sensitivity to previous ET defined as either documented clinical benefit (CR, PR, or SD for >24 weeks) from ≥1 prior endocrine therapy regimen for metastatic disease or ≥24 months of adjuvant ET before recurrence

Turner NC, et al. *N Engl J Med.* 2018;379:1926-1936.

Ribociclib + Fulvestrant

MONALEESA-3 Study Design



Primary endpoint
- PFS (locally assessed per RECIST version 1.1)

Secondary endpoints
- **Overall survival**
- Overall response rate
- Clinical benefit rate
- Time to response
- Duration of response
- Time to definitive deterioration of ECOG PS
- Patient-reported outcomes
- Safety
- Pharmacokinetics

*Fulvestrant 500 mg intramuscularly every 28 days plus an additional dose on cycle 1, day 15.

1L = first line; 2L = second line; TFI = treatment-free interval.

Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472. NCT02422615 (MONALEESA-3).

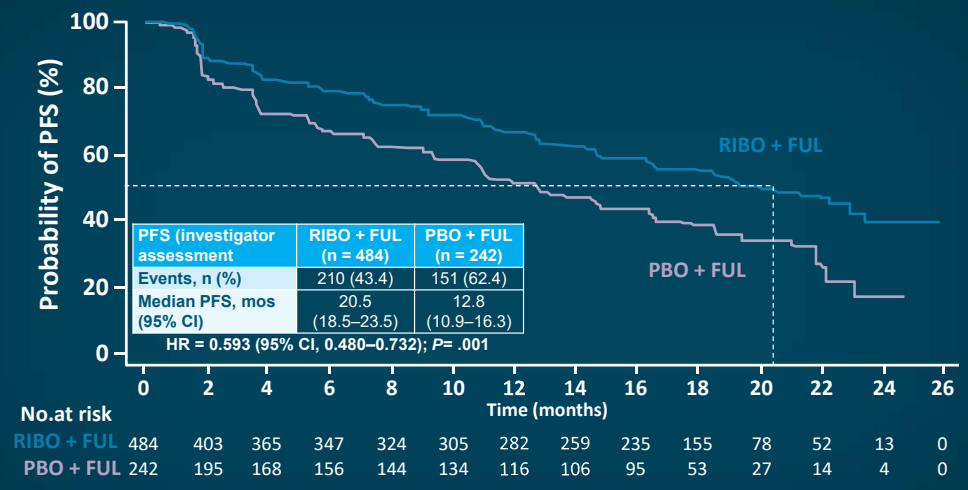
MONALEESA-3: Prior ET Status Criteria

Prior Endocrine Therapy Status Criteria	
First line **(ie, treatment-naïve for ABC)**	**Second line + early relapsers** **(ie, received up to 1 line of prior ET for ABC)**
• **Relapse** *>12 months* after completion of (neo)adjuvant ET **OR** • *De novo* advanced/metastatic disease (no prior exposure to ET)	• **Early relapse** *on or ≤12 months* from completion of (neo)adjuvant ET **OR** • **Relapse** *>12 months* from completion of (neo)adjuvant ET with **subsequent progression** *after 1 line* of ET (antiestrogen /AI) for ABC **OR** • ABC at diagnosis with **progression** *after 1 line* of ET (antiestrogen/AI)

Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472.

MONALEESA-3: Primary Endpoint PFS

Investigator-Assessed

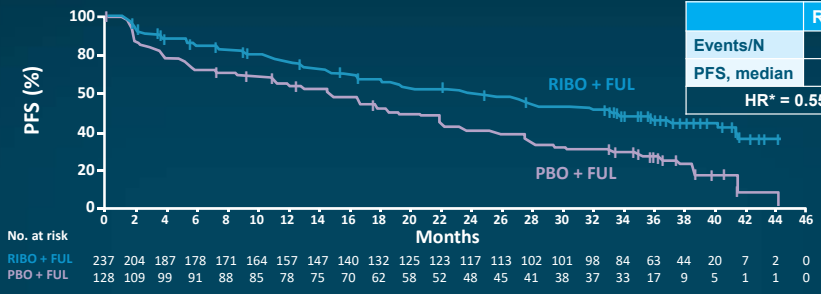


HR of 0.593 corresponds to a 41% reduction in risk of progression in ribociclib vs placebo arm.

Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472.

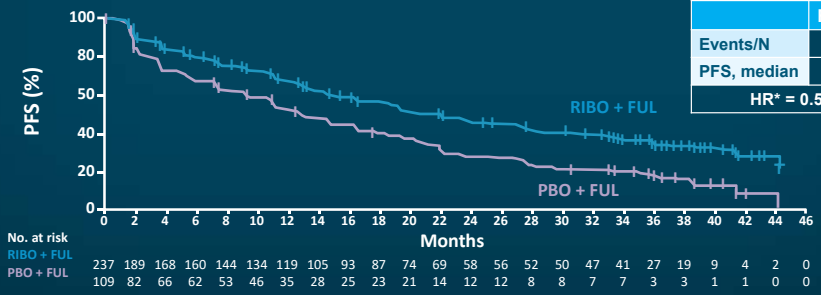
MONALEESA-3: PFS by Line of Therapy

Patients receiving first-line treatment



	RIBO + FUL	PBO + FUL
Events/N	112/237	95/128
PFS, median	33.6 mo	19.2 mo
HR* = 0.55 (95% CI, 0.42–0.72)		

Patients with early relapse or receiving second-line treatment



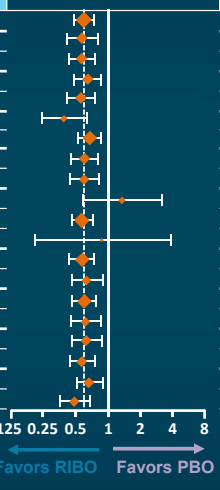
	RIBO + FUL	PBO + FUL
Events/N	167/237	95/109
PFS, median	14.6 mo	9.1 mo
HR* = 0.57 (95% CI, 0.44–0.74)		

*HR for disease progression or death.

Slamon DJ, et al. *N Engl J Med* 2020;382:514-524.

MONALEESA-3: PFS Subgroup Analysis

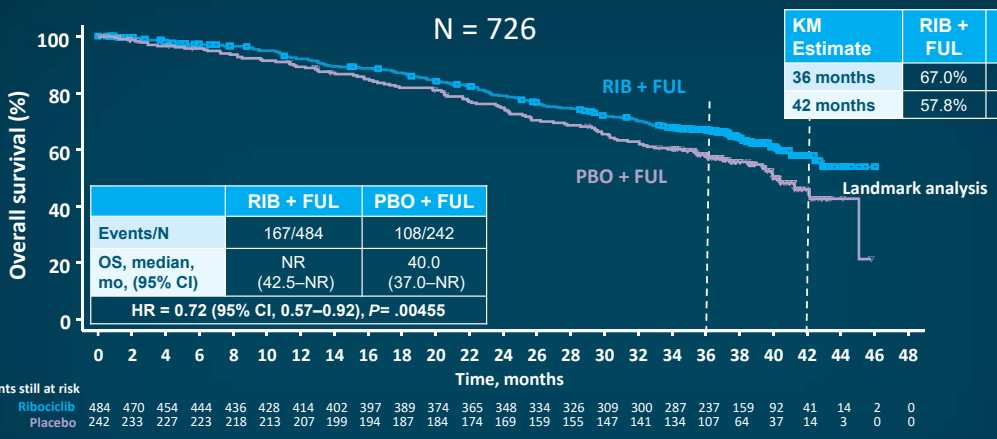
		Events, n/n		Hazard ratio (95% CI)	HR	95% CI
		RIBO+FUL	PBO+FUL			
All patients		210/484	151/242		0.593	0.480–0.732
Prior ET*	1st line*	76/238	66/129		0.577	0.415–0.802
	2nd line+early relapsers†	131/236	34/109		0.565	0.428–0.744
Liver or lung involvement	Yes	116/242	77/121		0.645	0.483–0.861
	No	94/242	74/120		0.563	0.415–0.764
Bone lesion only	Yes	36/103	35/51		0.379	0.234–0.613
	No	174/381	116/190		0.658	0.519–0.833
Age	<65 years	115/258	81/129		0.607	0.454–0.810
	≥65 years	95/226	70/113		0.597	0.436–0.818
Race	Asian	22/45	7/18		1.353	0.574–3.186
	Caucasian	174/406	136/213		0.562	0.448–0.704
	Other	8/18	3/6		0.881	0.199–3.907
ECOG PS	0	126/310	95/158		0.559	0.427–0.733
	1	83/173	56/83		0.633	0.450–0.890
Metastatic sites, no.	<3	126/309	92/149		0.586	0.447–0.768
	≥3	84/175	59/92		0.621	0.441–0.874
Prior tamoxifen	Yes	79/193	63/104		0.620	0.443–0.866
	No	131/291	88/137		0.562	0.428–0.738
Prior AI	Yes	135/257	80/118		0.670	0.507–0.886
	No	75/227	71/123		0.481	0.345–0.669



*Treatment naive for ABC; †Received up to 1 line of prior endocrine therapy for ABC.

Slamon DJ, et al. *J Clin Oncol.* 2018;36:2465-2472.

MONALESSA-3: Overall Survival



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

	RIB + FUL	PBO + FUL
Events/N	167/484	108/242
OS, median, mo, (95% CI)	NR (42.5–NR)	40.0 (37.0–NR)
HR = 0.72 (95% CI, 0.57–0.92), *P*= .00455		

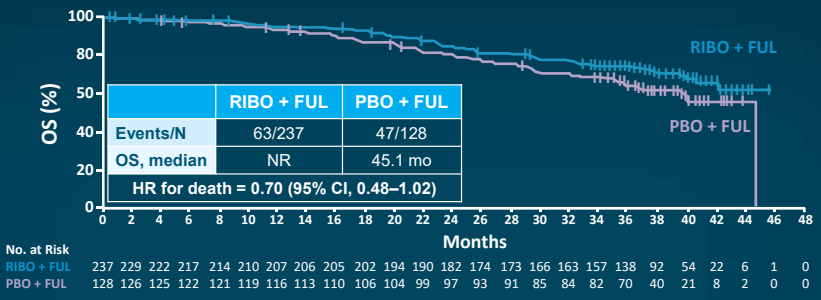
- Reduction in relative risk of death with ribociclib was 28%.
- The *P* value of 0.00455 crossed the prespecified boundary to claim superior efficacy (*P* <.01129).

KM = Kaplan-Meier.

Slamon DJ, et al. *N Engl J Med.* 2020;382:514-524.

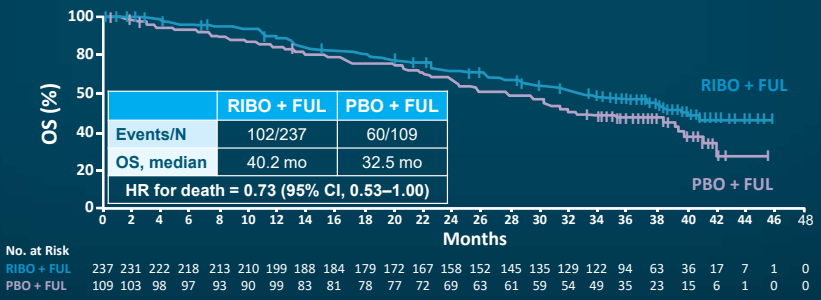
MONALEESA-3: OS by Line of Therapy

Patients receiving first-line treatment



	RIBO + FUL	PBO + FUL
Events/N	63/237	47/128
OS, median	NR	45.1 mo
HR for death = 0.70 (95% CI, 0.48–1.02)		

Patients with early relapse or receiving second-line treatment



	RIBO + FUL	PBO + FUL
Events/N	102/237	60/109
OS, median	40.2 mo	32.5 mo
HR for death = 0.73 (95% CI, 0.53–1.00)		

Slamon DJ, et al. *N Engl J Med* 2020;382:514-24

MONALEESA-3: OS by Prior Response to ET

Degree of Response to Prior ET	Ribociclib n	Placebo n	Hazard Ratio (95% CI)
Endocrine naïve	139	74	0.64 (0.38–1.05)
Endocrine resistant	53	25	0.70 (0.37–1.33)
Endocrine sensitive	289	140	0.74 (0.55–1.01)

- Endocrine naïve—patients who did not receive any ET in any setting
- Endocrine resistant
  - Progressive disease within first 6 months of first-line ET for ABC while on endocrine therapy
  - **OR** relapse within the first 2 years of (neo)adjuvant therapy
- Endocrine sensitive—all remaining patients

Slamon DJ, et al. *N Engl J Med.* 2020;382:514-524 supplement.

Abemaciclib + Fulvestrant

MONARCH 2: Study Design

- HR+, HER2– ABC
- Pre/peri-* or postmenopausal
- ET resistant:
  - Relapsed on neoadjuvant or on/within 1 year of adjuvant ET
  - Progressed on first-line ET for ABC
- No chemo for ABC
- No more than 1 ET for ABC
- ECOG PS ≤1

N = 669

2 :1 Randomization

abemaciclib (n = 446): 150 mg† BID (continuous schedule) + **fulvestrant:** 500 mg‡

Placebo (n = 223): BID (continuous schedule) + **fulvestrant:** 500 mg‡

Primary endpoint:
- Investigator-assessed PFS

Secondary endpoint:
- Overall survival

Exploratory analysis:
- Time to chemotherapy (TTC)

Stratification factors
- Metastatic site (visceral, bone only, or other)
- ET resistance (primary or secondary)

- Median follow-up: 47.7 months
- 17% patients (abemaciclib arm) vs 4% (placebo arm) remained on treatment

Data cut-off: 20 June 2019

*Required to receive gonadotrophin-releasing hormone (GnRH) agonist; †Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled; ‡ Fulvestrant administered per label.

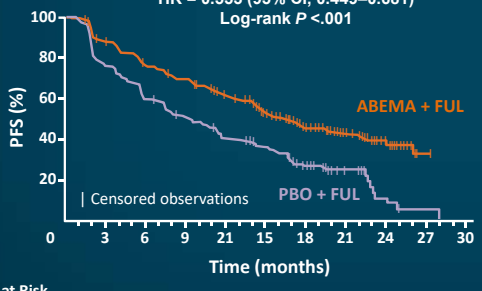
Sledge GW Jr, et al. *JAMA Oncol.* 2020;6:116-124. Sledge GW Jr, et al. *J Clin Oncol.* 2017;35:2875-2884.

MONARCH-2: Primary Endpoint PFS

ABEMA + FUL demonstrated median PFS of 22.4 months (compared with 10.2 months with PBO + FUL) with consistent PFS results on blinded central analysis.

Investigator assessment	ABEMA + FUL (n = 446)	PBO + FUL (n = 223)
Median PFS, mos	16.4	9.3

HR = 0.553 (95% CI, 0.449–0.681)
Log-rank *P* <.001

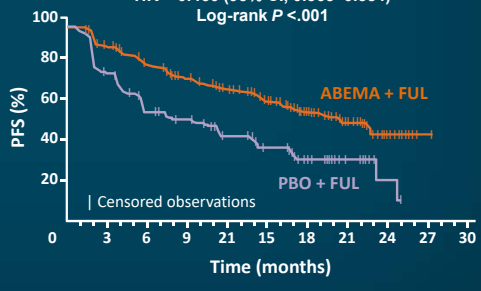


No. at Risk

ABEMA + FUL	446	367	314	281	234	171	101	65	32	2	0
PBO + FUL	223	165	123	103	80	61	32	13	4	1	0

Independent assessment	ABEMA + FUL (n = 446)	PBO + FUL (n = 223)
Median PFS, mos	22.4	10.2

HR = 0.460 (95% CI, 0.363–0.584)
Log-rank *P* <.001

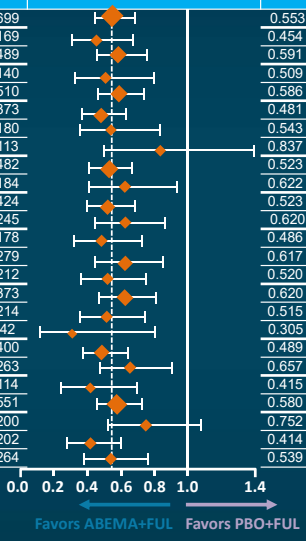


	446	362	298	260	220	162	93	56	24	3	0
	223	156	102	90	61	42	25	10	2	0	0

Sledge GW Jr, et al. *J Clin Oncol.* 2017;35:2875-2884.

MONARCH-2: PFS Subgroup Analysis

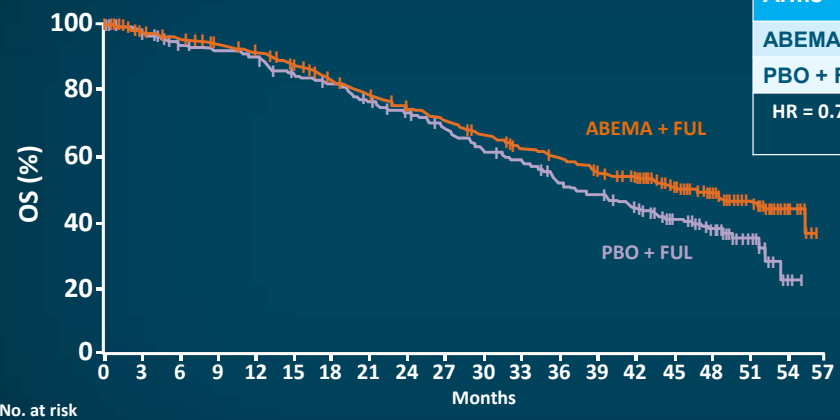
Subgroup Analyzed		No.	HR (95% CI)	Interaction *P* Value
Overall		699	0.553 (0.449–0.681)	
ET resistance	Primary	169	0.454 (0.306–0.674)	.263
	Secondary	489	0.591 (0.464–0.754)	
PgR status	Negative	140	0.509 (0.325–0.797)	.583
	Positive	510	0.586 (0.463–0.743)	
Metastatic site	Visceral	373	0.481 (0.369–0.627)	.171
	Bone only	180	0.543 (0.355–0.833)	
	Other	113	0.837 (0.501–1.398)	
Measurable disease	Yes	482	0.523 (0.412–0.664)	.474
	No	184	0.622 (0.413–0.936)	
Age group, years	<65	424	0.523 (0.402–0.681)	.427
	≥65	245	0.620 (0.447–0.860	
Geographical region	North America	178	0.486 (0.325–0.726)	.618
	Europe	279	0.617 (0.449–0.848)	
	Asia	212	0.520 (0.362–0.747)	
Race	Caucasian	373	0.620 (0.474–0.811)	.322
	Asian	214	0.515 (0.359–0.740)	
	Other	42	0.305 (0.116–0.804)	
ECOG PS	0	400	0.489 (0.373–0.641)	.166
	1	263	0.657 (0.487–0.904)	
Menopausal status	Pre- or perimenopause	114	0.415 (0.246–0.698)	.246
	Postmenopausal	551	0.580 (0.463–0.726)	
Organs involved, no.	≥3	200	0.752 (0.525–1.078)	.074
	2	202	0.414 (0.286–0.599)	
	1	264	0.539 (0.383–0.759)	



Addition of ABEMA to FUL demonstrated improvement in PFS across all patient subgroups.

Sledge GW Jr, et al. *J Clin Oncol*. 2017;35:2875-2884.

MONARCH-2: Overall Survival



Arms	Median OS
ABEMA + FUL	46.7 mo
PBO + FUL	37.3 mo
HR = 0.757 (95% CI, 0.606–0.945) Log-rank *P*= .01	

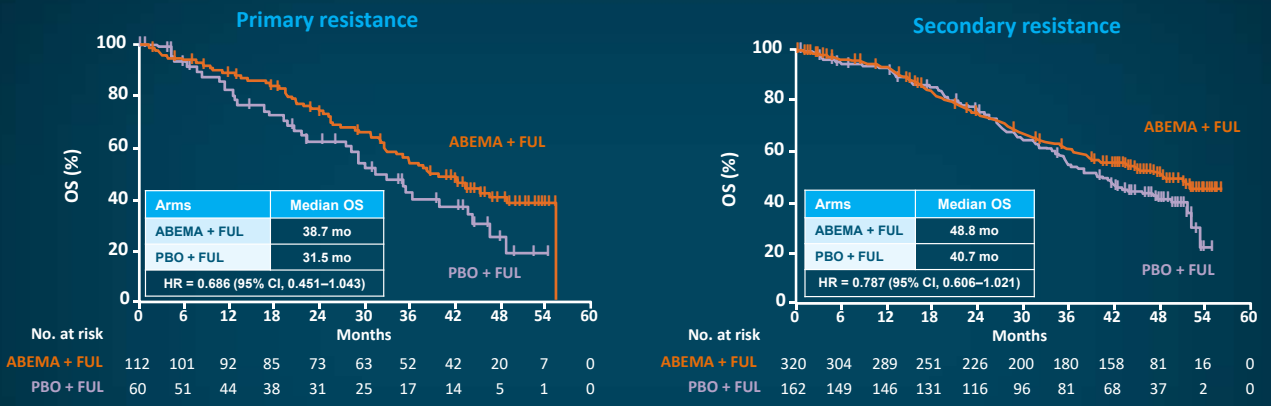
No. at risk

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

Sledge GW Jr, et al. *JAMA Oncol*. 2020;6:116-124.

MONARCH-2: Overall Survival

Resistance to ET



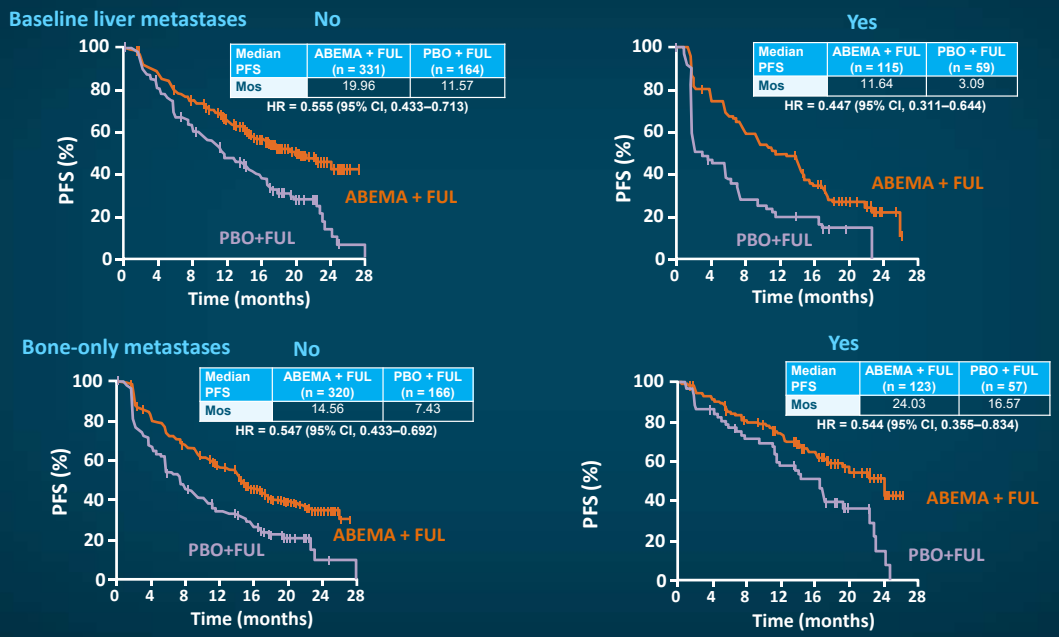
Statistically significant improvements also noted with abemaciclib + FUL compared with PBO + FUL in:

- Time to second disease progression (median, 23.1 vs 20.6 months)
- Time to chemotherapy (median, 50.2 vs 22.1 months)
- Chemotherapy-free survival (25.5 vs 18.2 months)

Sledge GW Jr, et al. *JAMA Oncol*. 2020;6:116-124.

Abemaciclib Benefit in Poor-Prognostic Subgroups

MONARCH-2



Goetz MP, et al. SABCS 2017:abstract GS6-02.

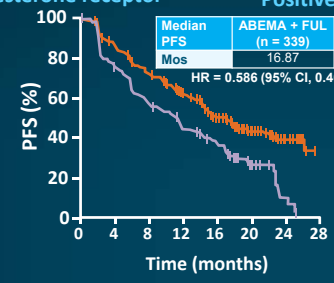
Abemaciclib in Poor-Prognostic Subgroups

MONARCH-2

Progesterone receptor: Positive

Median PFS	ABEMA + FUL (n = 339)	PBO + FUL (n = 171)
Mos	16.87	11.24

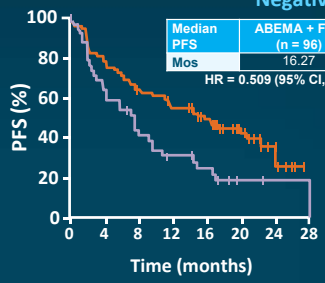
HR = 0.586 (95% CI, 0.463–0.743)



Progesterone receptor: Negative

Median PFS	ABEMA + FUL (n = 96)	PBO + FUL (n = 44)
Mos	16.27	7.43

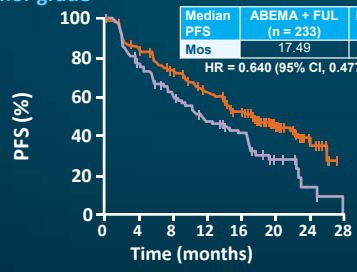
HR = 0.509 (95% CI, 0.325–0.797)



Tumor grade: Low/intermediate

Median PFS	ABEMA + FUL (n = 233)	PBO + FUL (n = 112)
Mos	17.49	11.57

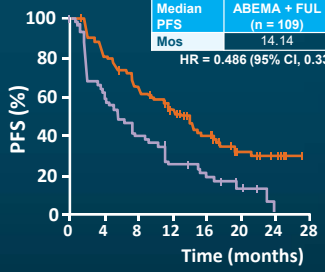
HR = 0.640 (95% CI, 0.477–0.860)



Tumor grade: High

Median PFS	ABEMA + FUL (n = 109)	PBO + FUL (n = 60)
Mos	14.14	5.72

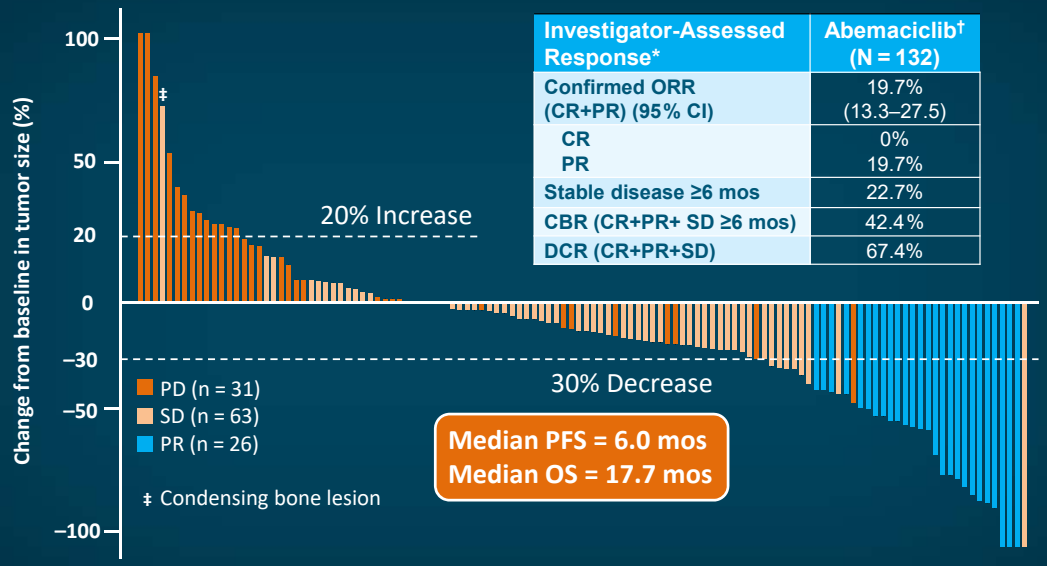
HR = 0.486 (95% CI, 0.335–0.706)



Goetz MP, et al. SABCS 2017:abstract GS6-02.

Abemaciclib

MONARCH 1: Late-Line Abemaciclib ER+ mBC



Investigator-Assessed Response*	Abemaciclib† (N = 132)
Confirmed ORR (CR+PR) (95% CI)	19.7% (13.3–27.5)
CR	0%
PR	19.7%
Stable disease ≥6 mos	22.7%
CBR (CR+PR+ SD ≥6 mos)	42.4%
DCR (CR+PR+SD)	67.4%

Trial dates: 6/2014–10/2018 (estimated study)

*Assessments based on independent review were comparable. †200 mg monotherapy dose.

Dickler MN, et al. *Clin Cancer Res.* 2017;23:5218-5224. NCT02102490 (MONSRCH 1).

nextMONARCH 1 Study Schema

Randomized, open-label, phase 2 study of safety and efficacy of ABEMA ± TAM or ABEMA monotherapy in women with previously treated HR+/HER2– *metastatic* breast cancer.

- HR+, HER2– BC
- Relapsed or progressed following ET
- No prior treatment with CDK4/6 inhibitor
- No pre-existing condition resulting in chronic diarrhea
- At least 2 prior chemotherapy regimens (at least 1 but no more than 2 in the metastatic setting)

Target N = 225

RANDOMIZE

- ABE (150 mg) + TAM
- ABE (150 mg)
- ABE (200 mg) + prophylactic loperamide

Trial dates: 9/2016–6/2019 (estimated study)

- **Primary outcome measure**: PFS baseline to objective disease progression or death (any cause, ~14 mos)
- **Secondary outcome measures**: ORR, DoR, OS, PK, safety profile, pain, and symptom burden changes

DoR = duration of response; PK = pharmacokinetics.

NCT02747004 (nextMONARCH1).

nextMONARCH 1: Endpoint Analysis

Investigator-Assessed

Therapeutic Arm	Median PFS	HR	95% CI	ORR	CBR
ABEMA (150 mg) + TAM	9.1 mos	0.815	0.556–1.193	25.6%	61.5%
ABEMA (150 mg)	6.5 mos	1.045	0.711–1.535	19.0%	49.4%
ABE (200 mg) + loperamide	7.4 mos	0.805	—	28.6%	51.9%

- ABEMA + TAM arm demonstrated longer PFS interval.
- Reduced incidence/severity of grades 2 and 3 diarrhea noted with dose reduction and prophylactic loperamide.
- ORR of ABEMA (200 mg) + loperamide was higher compared with ABEMA (200 mg) monotherapy in MONARCH 1.
- No new safety signals were identified.

Hamilton E, et al. SABCS 2018: poster PD1-11.

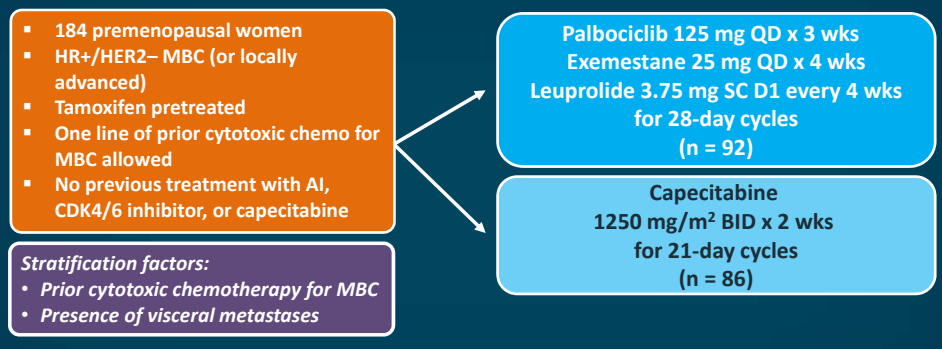
Q&A

CDK 4/6 Inhibitors vs Chemotherapy

Joyce O'Shaughnessy, MD

Young-PEARL: Study Design

- Prospective, multicenter, open-label, randomized phase 2 study by Korean Cancer Study Group

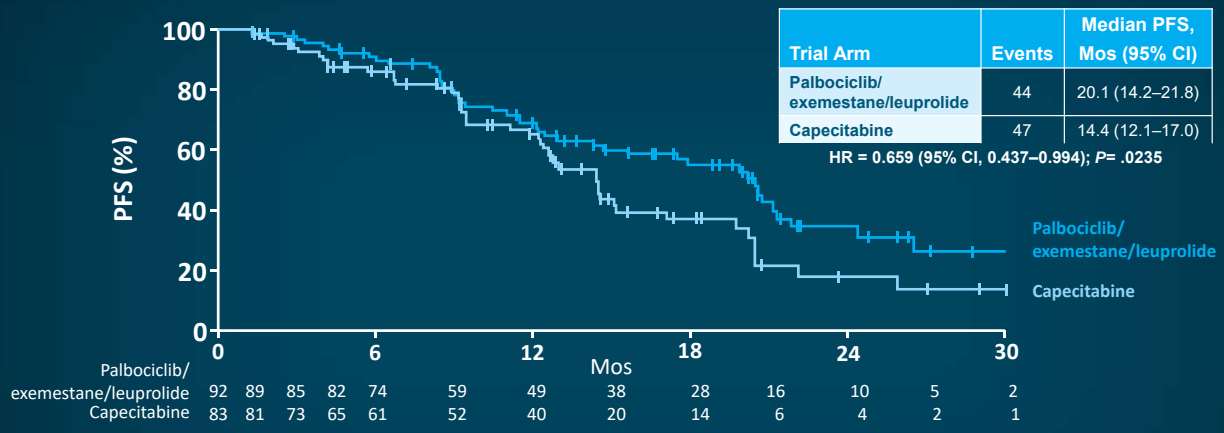


- Primary endpoint: Investigator-assessed PFS
- Secondary endpoints: DCR, OS, toxicity, QoL, biomarkers

QoL = quality of life.

Park YH, et al. *Lancet Oncol.* 2019;20:1750-1759. Park YH, et al. *J Clin Oncol.* 2019;37(15 suppl):abstract 1007. NCT02592746 (YoungPEARL).

Young-PEARL: PFS (Investigator Assessed)



Trial Arm	Events	Median PFS, Mos (95% CI)
Palbociclib/ exemestane/leuprolide	44	20.1 (14.2–21.8)
Capecitabine	47	14.4 (12.1–17.0)

HR = 0.659 (95% CI, 0.437–0.994); *P*= .0235

Palbociclib/ exemestane/leuprolide	92	89	85	82	74	59	49	38	28	16	10	5	2
Capecitabine	83	81	73	65	61	52	40	20	14	6	4	2	1

- Median follow-up: 17 mos
- Treatment ongoing in 47.8% of patients receiving palbociclib/exemestane/leuprolide, 39.5% of patients receiving capecitabine

Park YH, et al. *Lancet Oncol.* 2019;20:1750-1759. Park YH, et al. *J Clin Oncol.* 2019;37(15 suppl):abstract 1007.

Young-PEARL: Response Rates

	Palbociclib + Exemestane + Leuprolide (n = 92) n (%)	Capecitabine (n = 86) n (%)	P-value
ORR (n = 178)	34 (37.0%)	29 (34%)	.781
ORR (measurable n = 119)	31 (51%)	26 (45%)	.387
DCR (n = 178)	89 (97%)	78 (91%)	.480
DCR (measurable n = 119)	58 (95%)	51 (88%)	.262
CBR (n = 178) (CR + PR + SD ≥24 weeks)	74 (80%)	58 (67%)	.105
CBR (measurable n = 119) (CR + PR + SD ≥24 weeks)	48 (79%)	38 (66%)	.134

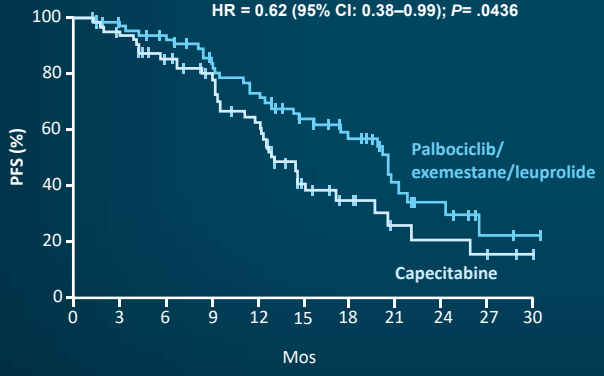
Park YH, et al. *Lancet Oncol.* 2019;20:1750-1759. Park YH, et al. *J Clin Oncol.* 2019;37(15 suppl):abstract 1007.

Young-PEARL: PFS Subgroup Analyses

No prior chemotherapy for MBC (n = 138)

Trial Arm	Median PFS Mo (95% CI)
Palbociclib/ exemestane/GnRH	20.4 (17.3–23.6)
Capecitabine	13.0 (10.7–15.3)

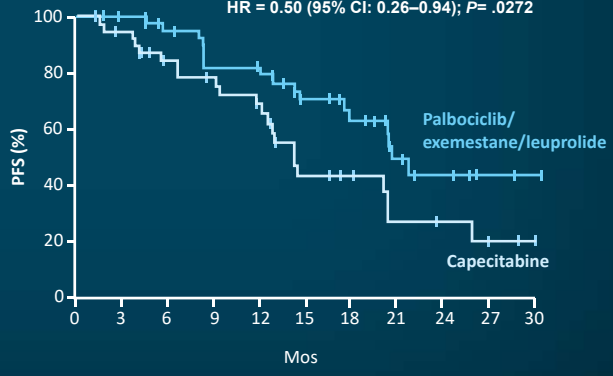
HR = 0.62 (95% CI: 0.38–0.99); *P*= .0436



No visceral metastases (n = 90)

Trial Arm	Median PFS Mo (95% CI)
Palbociclib/ exemestane/GnRH	20.7 (18.9–22.4)
Capecitabine	14.4 (12.1–16.7)

HR = 0.50 (95% CI: 0.26–0.94); *P*= .0272



Park YH, et al. *Lancet Oncol.* 2019;20:1750-1759. Park YH, et al. *J Clin Oncol.* 2019;37(15 suppl):abstract 1007.

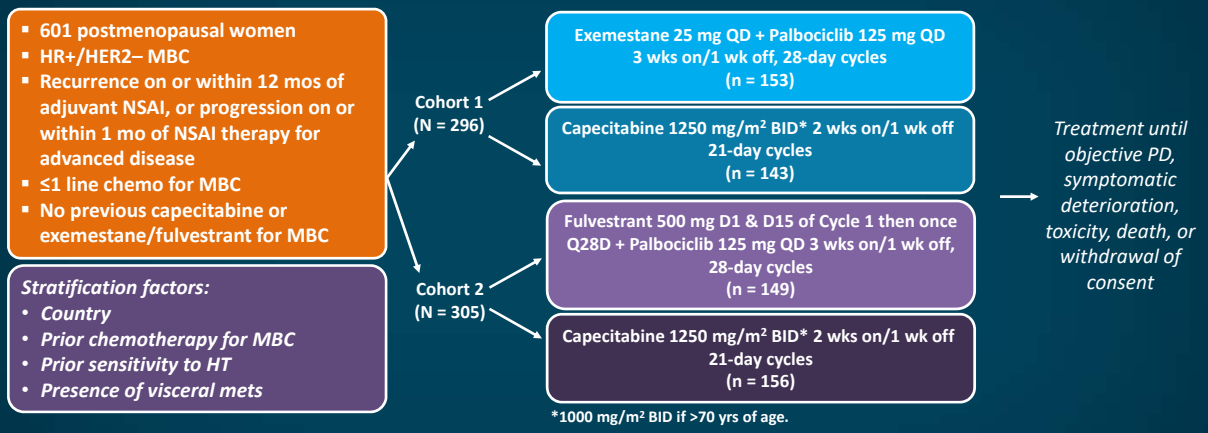
Young PEARL: Adverse Events

Adverse events, n (%)	Palbociclib + Exemestane + Leuprolide (n = 92)			Capecitabine (n = 86)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Neutropenia	61(62.0%)	46 (50%)	13 (14%)	29 (33%)	14 (16%)	0
Febrile neutropenia	3 (3%)	3 (3%)	0	1 (1%)	1 (1%)	0
Leukopenia	46 (50%)	10 (11%)	0	10(12%)	0	0
Anemia	7 (7%)	4 (4%)	0	6 (7%)	2 (2%)	0
Thrombocytopenia	2 (2%)	1 (1%)	1 (1%)	0	0	0
Arthralgia	20 (22%)	0	0	5 (6%)	0	0
Headache	21 (23%)	0	0	8 (9%)	0	0
Fatigue	26 (28%)	0	0	17 (20%)	0	0
Mucositis	36 (39%)	1 (1%)	0	19 (22%)	3 (3%)	0
Nausea	11 (12%)	0	0	30 (35%)	1 (1%)	0
Diarrhea	12 (13%)	1 (1)	0	36 (39%)	0	0
Hand-foot syndrome	1 (1%)	0	–	86 (100%)	12 (14%)	–

Park YH, et al. *Lancet Oncol.* 2019;20:1750-1759.

PEARL: Study Design

- Phase 3, international, randomized study with 2 cohorts



*1000 mg/m² BID if >70 yrs of age.

- **Cohort 2 was added to the trial based on a report that ESR1 mutations may induce resistance to AIs but not to fulvestrant.**

Martín M, et al. *SABCS* 2019:abstract GS2-07. NCT02028507 (PEARL).

PEARL: Study Objectives

- Coprimary objectives
  - Cohorts 1 and 2: PFS with palbociclib + ET (EXE or FUL) vs CAPE in patients with ESR1 wild-type tumors (presumed hormonal sensitivity)
  - Cohort 2: PFS with palbociclib + FUL vs CAPE regardless of ESR1 mutational status
- Secondary objectives
  - PFS with palbociclib + ET vs CAPE in all patients regardless of ESR1 mutational status
  - OS, ORR, CBR, response duration
  - Safety/tolerability
  - Health-related quality of life (EORTC QLQ-C30, QLQ-BR23, and EQ-5D-3L)
  - Biomarkers

EXE = exemestane; CAPE = capecitabine; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = quality of life questionnaire.

Martín M, et al. *SABCS* 2019:abstract GS2-07. NCT02028507 (PEARL).

PEARL: PFS

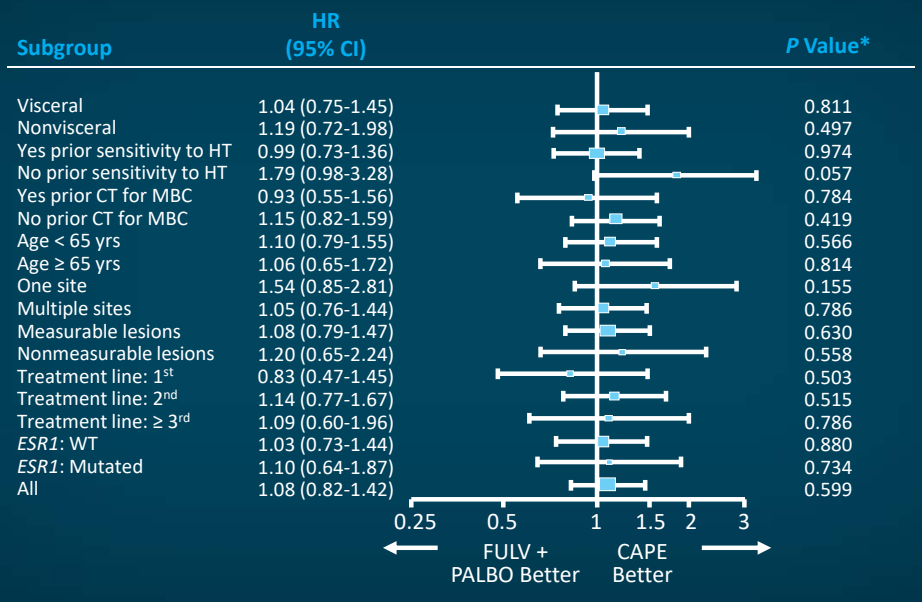
Comparison	Median PFS Mos (95% CI)	HR (95% CI)	*P*-Value
Cohort 2: FUL + PALBO (n = 149) vs CAPE (n = 156)	7.5 (5.7–10.9) vs 10.0 (6.3–12.9)	1.09 (0.83–1.44)	.537
ESR1 wt: ET + PALBO (n = 206) vs CAPE (n = 187)	8.0 (6.5–10.9) vs 10.6 (7.4–13.0)	1.08 (0.85–1.36)	.526
Cohorts 1 and 2: ET + PALBO (n = 302) vs CAPE (n = 299)	7.4 (5.9–9.3) vs 9.4 (7.5–11.3)	1.09 (0.90–1.31)	.380

2 co-primary endpoints were not met.

- Palbociclib + fulvestrant demonstrated similar PFS vs capecitabine in women with MBC resistant to AIs.
- Palbociclib + endocrine therapy demonstrated similar PFS vs capecitabine in women with ESR1 wildtype tumors.

Martín M, et al. *SABCS* 2019:abstract GS2-07.

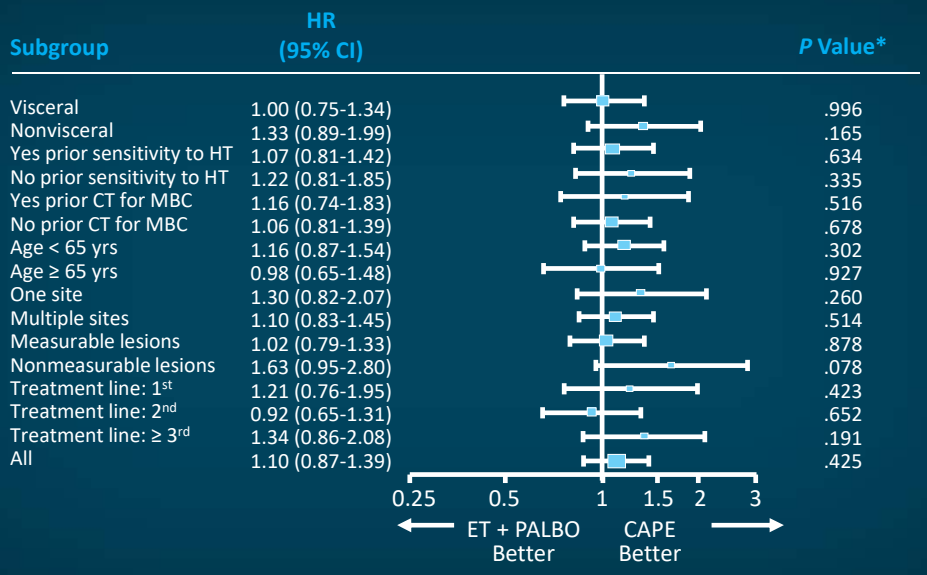
PEARL: PFS by Subgroup for Cohort 2



*Unadjusted Cox *P*-value comparing FUL + PALBO vs CAPE in each subgroup.

Martín M, et al. *SABCS* 2019:abstract GS2-07.

PEARL: PFS by Subgroup for *ESR1* WT



*Unadjusted Cox *P*-value comparing ET + PALBO vs CAPE in each subgroup.

Martín M, et al. *SABCS* 2019:abstract GS2-07.

PEARL: Response

Response, %	Cohort 2			*ESR1* WT		
	FUL + PALBO (n = 149)	CAPE (n = 156)	Odds Ratio (95% CI)	ET + PALBO (n = 206)	CAPE (n = 187)	Odds Ratio (95% CI)
ORR (CR + PR)	27	33	0.73 (0.42–1.27)	28	37	0.67 (0.42–1.08)
CBR	49.0	48.1	1.06 (0.67–1.66)	50.5	50.3	1.03 (0.69–1.53)

Martín M, et al. *SABCS* 2019:abstract GS2-07.

Toxicity Monitoring and Management

Sara Hurvitz, MD

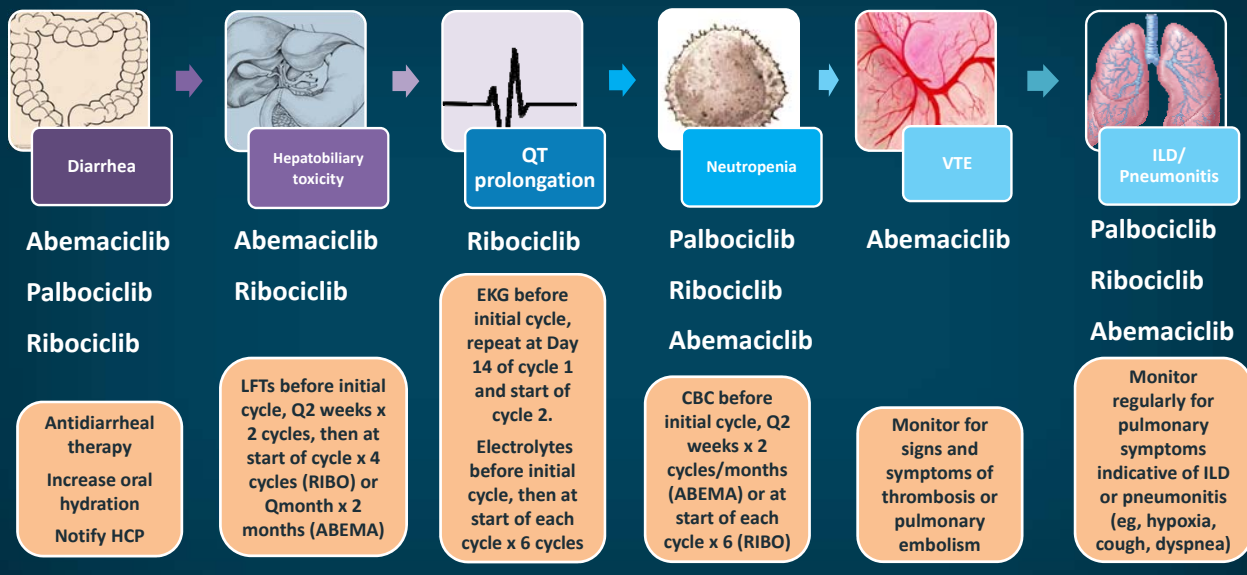
Case Study 3—Question 1

- A 65-year-old woman has had ER+ HER2– mBC generally responsive to several endocrine therapies, everolimus, and to capecitabine and paclitaxel. She has not received a CDK4/6 inhibitor.
- Her disease is progressing in her liver with mildly elevated LFTs.
- You recommend:
  - A. Eribulin
  - B. Abemaciclib
  - C. Endocrine therapy + abemaciclib
  - D. Endocrine therapy + ribociclib
  - E. Gemcitabine or vinorelbine

LFT = liver-function test.

Video about safety of CDK4/6 inhibitors

Adverse Events for CDK4/6 Inhibitors



VTE = venous thromboembolism; HCP = healthcare provider; EKG = electrocardiogram; CBC = complete blood count.

Prescribing information for abemaciclib (Verzenio®), palbociclib (Ibrance®), and ribociclib (Kisqali®).

Adverse Events: Palbociclib

PALOMA-2: LET + PAL (n = 444)[1]			
Grade	Any %	G3 %	G4 %
Toxicity			
Neutropenia*	79.5	56.1	10.4
Fatigue	37.4	1.8	0
Nausea	35.1	0.2	0
Diarrhea	26.1	1.4	0
Anemia	24.1	5.2	0.2
Thrombocytopenia	15.5	1.4	0.2

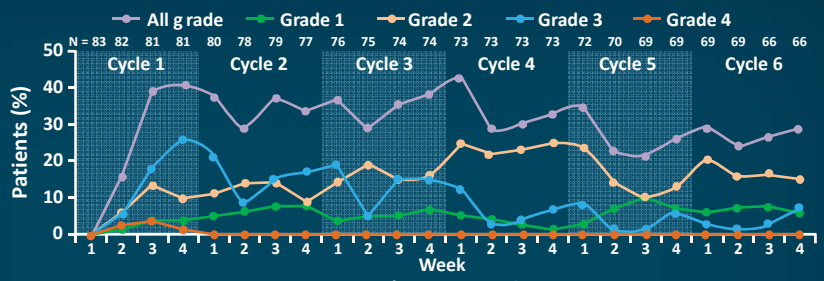
PALOMA-3: FUL + PAL (n = 345)[2]			
Grade	Any %	G3 %	G4 %
Toxicity			
Neutropenia*	81	55	10
Fatigue	39	2	0
Anemia	28	3	0
Thrombocytopenia	22	2	1

***CBC should be assessed prior to initiation of palbociclib therapy, at beginning of each cycle, on day 15 of first 2 cycles, and as clinically indicated.[3]**

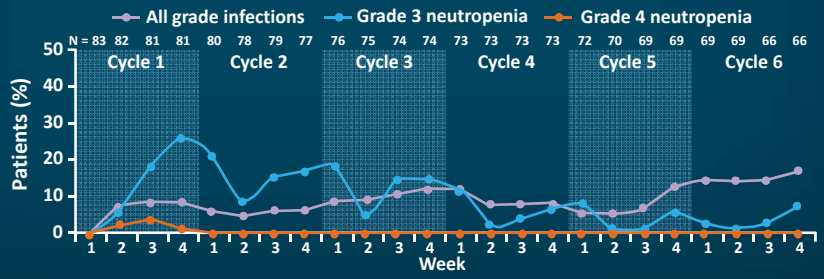
1. Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936. 2. Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439. 3. Palbociclib (Ibrance®) PI, 2017.

PALOMA-1: CDK4/6 Inhibitor-Induced Neutropenia Declines Over Time

Neutropenia by grade in palbociclib + letrozole arm



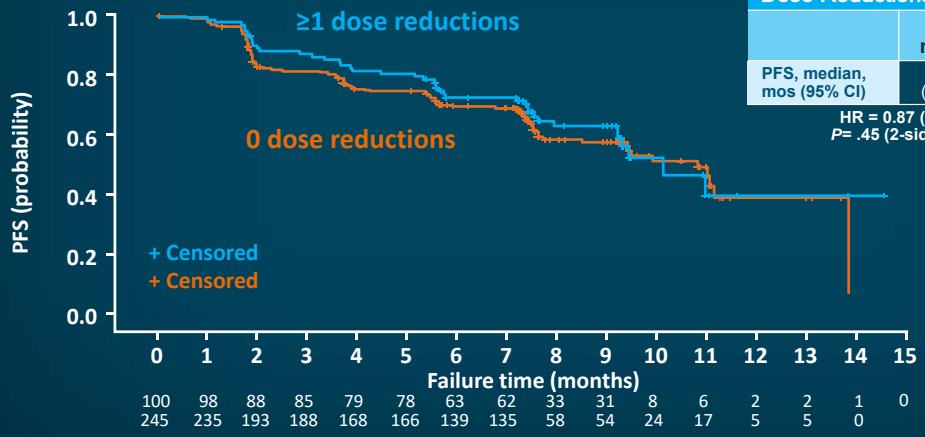
Grade 3–4 neutropenia and all grade infections in palbociclib + letrozole arm



Finn RS, et al. *Breast Cancer Res*. 2016;18:67.

PALOMA-3: Effect on PFS of Dose Reductions Due to Neutropenia

No difference in PFS was observed between patients who had ≥1 dose reduction because of neutropenia vs no dose reduction.



Dose Reductions Due to Neutropenia	≥1 n = 100	0 n = 245
PFS, median, mos (95% CI)	9.5 (8.0–NE)	9.5 (7.6–11.2)

HR = 0.87 (95% CI, 0.61–1.25
P= .45 (2-sided long-rank test)

Verma S, et al. *Oncologist*. 2016;21:1165-1175.

Adverse Events: Ribociclib

- QTc prolongation
  - 11 patients (3.3%) in the letrozole + ribociclib arm
  - Reversible and early
- 1 sudden cardiac death: hypokalemia and grade 2 QTc prolongation

MONALEESA-2: Letrozole + ribociclib (n = 334)			
Grade	Any %	G3 %	G4 %
Toxicity			
Neutropenia	74.3	49.7	9.6
Nausea	51.5	2.4	0
Diarrhea	35	1.2	0
Anemia	18.6	0.9	0.3
Elevated ALT	15.6	7.5	1.8
Elevated AST	15.0	4.8	0.9

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748.

Adverse Events: Abemaciclib

≥20% occurrence in abemaciclib arm, n (%)	Abemaciclib + nonsteroidal AI (n = 327)				Placebo + nonsteroidal AI (n = 161)			
	All Grades	Grade 2	Grade 3	Grade 4	All Grades	Grade 2	Grade 3	Grade 4
Any adverse event	323 (98.8)	102 (31.2)	169 (51.7)	22 (6.7)	152 (94.4)	70 (43.5)	36 (22.4)	4 (2.5)
Diarrhea	269 (82.3)	99 (30.3)	31 (9.5)	0	52 (32.3)	14 (8.7)	2 (1.2)	0
Neutropenia	143 (43.7)	53 (16.2)	72 (22.0)	6 (1.8)	3 (1.9)	1 (0.6)	1 (0.6)	1 (0.6)
Fatigue	135 (41.3)	59 (18.0)	6 (1.8)	–	54 (33.5)	21 (13.0)	0	–
Nausea	135 (41.3)	40 (12.2)	4 (1.2)	–	33 (20.5)	1 (0.6)	2 (1.2)	–
Anemia	103 (31.5)	49 (15.0)	23 (7.0)	0	13 (8.1)	3 (1.9)	2 (1.2)	0
Abdominal pain	102 (31.2)	24 (7.3)	6 (1.8)	–	21 (13.0)	6 (3.7)	2 (1.2)	–
Vomiting	99 (30.3)	28 (8.6)	5 (1.5)	0	21 (13.0)	2 (1.2)	4 (2.5)	0
Alopecia	90 (27.5)	7 (2.1)	–	–	18 (11.2)	0	–	–
Decreased appetite	86 (26.3)	30 (9.2)	5 (1.5)	0	17 (10.6)	3 (1.9)	1 (0.6)	0
Leukopenia	72 (22.0)	31 (9.5)	27 (8.3)	1 (0.3)	4 (2.5)	1 (0.6)	0	1 (0.6)
Blood creatinine increased	67 (20.5)	25 (7.6)	6 (1.8)	1 (0.3)	7 (4.3)	1 (0.6)	0	0

- Deaths due to AEs in MONARCH-3:
  - Abemaciclib arm: lung infection (n = 4), embolism (n = 2), respiratory failure (n = 2), cerebral ischemia (n = 1), cerebrovascular accident (n = 1), pneumonitis (n = 1);
  - Placebo arm: general physical health deterioration (n = 1), sudden death (n = 1)

Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5.

Dose Modifications

	Palbociclib	Ribociclib	Abemaciclib
Recommended starting dose	125 mg/day	600 mg/day	200 mg twice daily
First dose reduction	100 mg/day	400 mg/day	150 mg twice daily
Second dose reduction	75 mg/day	200 mg/day	100 mg twice daily
Further dose reductions	Discontinue if further dose reductions needed beyond 75 mg/day	Discontinue if further dose reductions needed beyond 200 mg/day	50 mg twice daily

- Palbociclib should be taken with food.
- Ribociclib and abemaciclib can be taken with or without food.
- Medication should be taken at approximately the same time each day.
- Avoid concomitant use of strong CYP3A4 inhibitors and inducers.

Prescribing information for abemaciclib (Verzenio®), palbociclib (Ibrance®), and ribociclib (Kisqali®).

Management of AEs with CDK 4/6 Inhibitors

- At the first sign of loose stools with abemaciclib, start treatment with antidiarrheal agents and increase intake of oral fluids.

Monitor CBC, creatinine, bilirubin, AST:

- Before therapy start
- Every 2 weeks for the first 2 cycles
- At the beginning of each subsequent cycle
- When clinically indicated

An ECG should be performed:

- Before starting treatment with **ribociclib**
- On day 14 of the first cycle
- At the beginning of the second cycle
- As clinically required
- More frequent ECG monitoring is recommended in the event of QTc prolongation during treatment.

Dose Modification for Hematologic Toxicities with Palbociclib

- **Grades 1 and 2:** no adjustment required
- **Grade 3:**
  - Day 1 of cycle: withhold palbociclib; repeat CBC within 1 week. When recovered to grade ≤2, start the next cycle at the same dose.
  - Day 15 of first 2 cycles: if grade 3 on day 15, continue at current dose to complete cycle and repeat CBC on day 22. If grade 4 on day 22, see grade 4 dose modification guidelines below.
  - Consider dose reduction if >1 week recovery from grade 3 or recurrent grade 2 neutropenia on day 1 of subsequent cycles.
  - If absolute neutrophil count 500 to <1000 mm^3 + fever or infection: hold palbociclib until recovery to grade ≤2 and reduce dose
- **Grade 4:** hold palbociclib until recovery to grade ≤2; reduce dose

Palbociclib (Ibrance®) PI 2019.

Managing Hematologic Toxicities with Ribociclib and Abemaciclib

- No dose adjustments needed if grade 1 or 2
- If afebrile grade 3 with ribociclib, hold until recovery to grade ≤2 and resume at same dose
- If recurrent or febrile grade 3 or grade 4, hold until recovery to grade ≤2; decrease dose with next cycle
- If blood-cell growth factors are required, hold abemaciclib dose for at least 48 hours after last dose of blood-cell growth factor and until toxicity resolves to ≤grade 2; resume at next lower dose (if not already done).

Prescribing information for ribociclib (Kisqali®) and abemaciclib (Verzenio®).

Managing Hepatobiliary Toxicity with Ribociclib

	Grade 1	Grade 2	Grade 3	Grade 4
	(>ULN to 3x ULN)	(>3 to 5 x ULN)	(>5 to 20 x ULN)	(>20 x ULN)
AST and/or ALT elevations from baseline, WITHOUT increase in total bilirubin above 2x ULN	No dose adjustment is required.	Baseline at < Grade 2: Dose interruption until recovery to ≤ baseline grade, then resume ribociclib at same dose. If Grade 2 recurs, resume ribociclib at next lower dose level. Baseline at Grade 2: No dose interruption.	Dose interruption until recovery to ≤ baseline grade, then resume at next lower dose level. If Grade 3 recurs, discontinue ribociclib.	Discontinue ribociclib
Combined elevations in AST and/or ALT WITH total bilirubin increase, in the absence of cholestasis	If patients develop ALT and/or AST > 3 x ULN along with total bilirubin > 2x ULN irrespective of baseline grade, discontinue ribociclib.			

ULN = upper limit of normal.

Ribociclib (Kisqali®) PI 2020.

Risk of Interstitial Lung Disease or Pneumonitis

- Rate of ILD or pneumonitis ranges from 1% to 3.3%
  - Grade 3 or 4 events occurred in 0.1% to 0.6% of patients in trials
- Patients should be counseled on importance of contacting HCP in case of dry cough with/without fever
- Monitor regularly for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)
  - If pneumonitis suspected, interrupt therapy immediately
  - Seek pulmonary consultation and consider early institution of corticosteroids
  - Permanently discontinue if recurrent or severe ILD/pneumonitis

ILD = interstitial lung disease.

Prescribing information for abemaciclib (Verzenio®), palbociclib (Ibrance®), and ribociclib (Kisqali®).

Case Study 4—Question 1

- A 65-year-old woman with mBC who has been pretreated with several endocrine therapies, everolimus, and capecitabine receives treatment with abemaciclib 200 mg PO bid.
- Which supportive therapy should the patient be advised to have on hand if needed?

A. G-CSF
B. Loperamide
C. Prochlorperazine
D. I would not recommend a prophylactic therapy.

G-CSF = granulocyte-colony stimulating factor.

Multidisciplinary Team Tools

Decision Aids and Communication Strategies to Enhance Patient Education and Communication

Joyce O'Shaughnessy, MD

Shared Decision-Making (SDM)

Shared decision-making involves the patient and healthcare provider working together to make a healthcare decision that is *best* for the patient, using:

- **Evidence-based information** about available options (including no intervention) and the associated risks and benefits
- The **provider's expertise** in communicating and tailoring evidence to the individual
- The **patient's *values, goals, concerns, expertise*** (of living with the condition) ***and preferences*** (including treatment burdens)

Studies of SDM in practice have demonstrated better health outcomes, improved QoL, increased compliance with treatment regimens, and lower demand for healthcare resources.

SHARE approach workshop curriculum (www.ahrq.gov/sites/default/files/wysiwyg/professionals/education/curriculum-tools/shareddecisionmaking/tools/tool-1/share-tool1.pdf). Agency for Healthcare Research and Quality (AHRQ). Strategy 6I: shared decision-making (www.ahrq.gov/sites/default/files/wysiwyg/cahps/quality-improvement/improvement-guide/6-strategies-for-improving/communication/cahps-strategy-section-6-i.pdf). Both URLs accessed 3/4/2020.

5 Essential Steps of SDM

SHARE Approach

It's all about communication!

AHRQ Share Approach (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf).

Video case study on shared decision-making

Decision Aids (DAs)

- DAs are tools utilized to **assist the communication** between patient and provider, augmenting the shared decision-making process.
- They provide information on *relevant risks, benefits, alternatives, and burdens,* without favoring any particular option.
- DAs should be designed to address modifiable factors such as *knowledge, support, unclear values, expectations, and psychological factors* (eg, anxiety).

- Reference guides
- Posters
- Questionnaires

- Patient checklists
- Outline of options
- Videos

Stacey D, et al. *Cochrane Database Syst Rev.* 2017;4:CD001431.

Patient Education

Educational discussion	• Review mechanisms of treatment(s) • Utilize educational material and decision aids if available
Assess communication	• Assess patient's ability to communicate symptoms • Language barrier • Access to phone/computer
Provide tools	• Provide treatment-plan details • Utilize tools to remember dosing schedules and appointments • Encourage patients to keep treatment diary
Reminders	• Medications for anticipated adverse events • Loperamide, acetaminophen, diphenhydramine

*Wallet card part of Oncology Nursing Society (ONS) publications.

Treating the Cancer Survivor

- There were >15.5 million cancer survivors in US in 2016, expected to be 20.3 million by 2026.
- Cancer survivors are susceptible to a multitude of complications from cancer and its treatment that must be managed.

Complications	Etiology
Second solid tumors	Genetic susceptibility, lifestyle (smoking, drinking), radiation therapy, especially immunosuppression (stem cell-transplant survivors)
Myelodysplasia and acute myelogenous leukemia	Chemotherapy, especially alkylating agents and topoisomerase II inhibitors
Cardiovascular disease and accelerated atherosclerosis	Anthracyclines, trastuzumab, taxanes, biological therapy, chest radiation, steroids, nilotinib, herceptin
Lung disease	Bleomycin, busulfan, chest radiation, stem-cell transplantation
Osteoporosis	Myeloma, androgen deprivation, steroids, AIs, radiation, methotrexate
Hypothyroidism, other endocrinopathies, and metabolic syndrome	Radiation, steroids, stem-cell transplantation, androgen deprivation, alkylating agents, imatinib, thalidomide
Infertility	Chemotherapy and radiation
Bowel and bladder dysfunction	Urinary and rectal surgery
Sexual dysfunction	Surgery on prostate, rectum, vagina
Pain syndromes	Surgery, such as thoracotomy
Psychosocial problems, including anxiety, depression, posttraumatic stress disorder, suicide	Cancer and cancer treatment
Economic hardship	Cancer treatment, disability, discrimination in employment and insurance
Lymphedema	Lymph node surgery and/or radiation

American Cancer Society. Cancer Treatment & Survivorship Facts & Figures 2016–2017. Mehta P, et al. *Fed Pract*. 2011;28(suppl 6):43S-49S.

Cancer Survivorship Care

Ensure patients have a comprehensive treatment summary that can be provided to other clinicians

- Detailed list of drugs, doses, frequencies, and complications can help determine risks of long-term complications.

Provide a cancer survivorship transition plan

- Allows patients to transition from oncology care to other providers
- Include recommendations for screening, surveillance, wellness, and referrals for physical rehabilitation, nutrition, fertility treatment, etc.

Deliver cancer survivorship care

- Observational data from SEER-Medicare suggest that ~30% of breast cancer survivors do not see an oncologist >1 year after diagnosis.

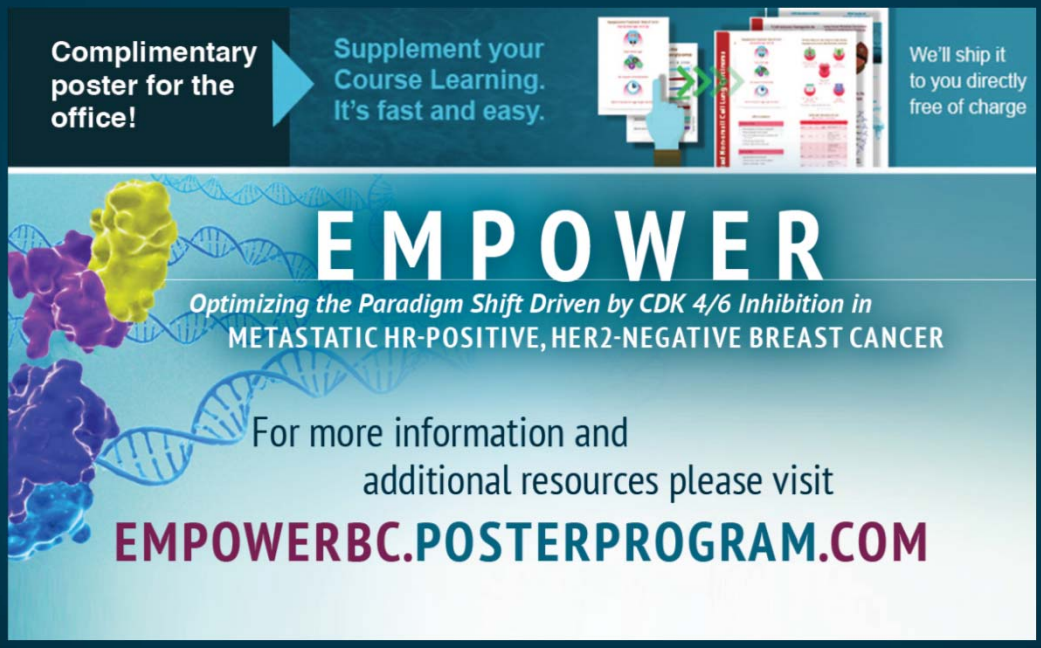
Mehta P, et al. *Fed Pract*. 2011;28(suppl 6):43S-49S.

Summary: CDK4/6 Inhibitors in ER+ mBC

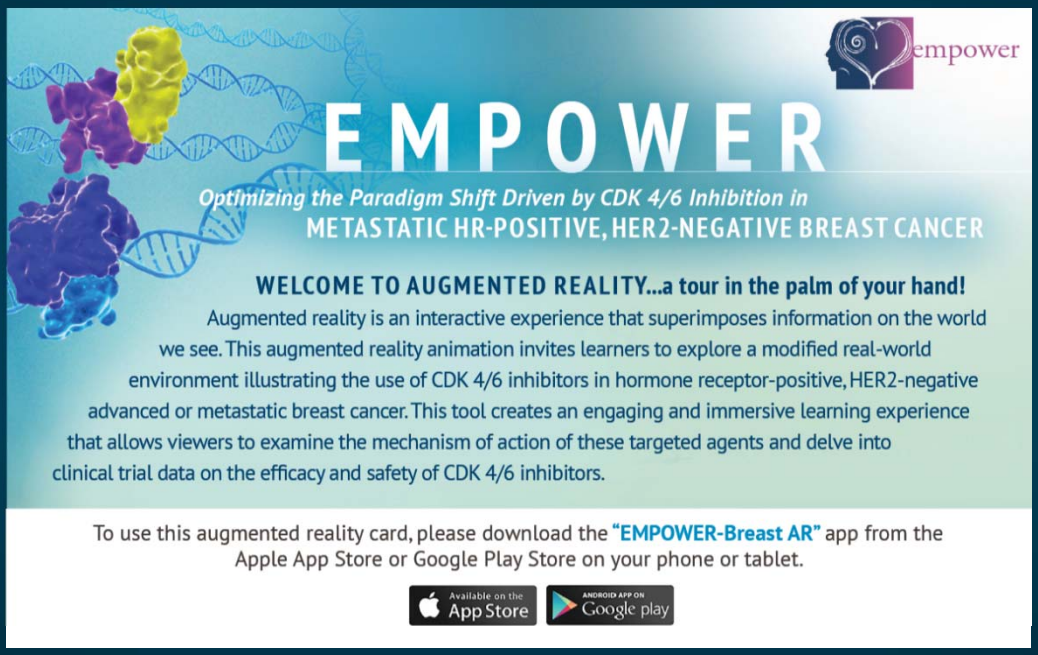
- The 3 CDK4/6 inhibitors seem to be consistent and comparable in prolonging PFS in combination with endocrine therapy in the metastatic setting, with acceptable toxicity.
- CDK 4/6 inhibitors improve the durability of both first- and second-line endocrine responses in patients with metastatic, HR+/HER2-negative BC and increase overall survival.
- Selection of agent, sequence, and number of drugs should be patient-specific; most patients in US are receiving CDK4/6i + AI.
- Abemaciclib and ribociclib in combination with endocrine therapy have demonstrated significant improvements in OS.
- Resistance is universal.
  - Next generation of trials is looking at switching ET or CDK4/6 inhibitors with addition of other drugs to inhibit resistance pathways.

EMPOWER Website

EMPOWER Poster Portal



EMPOWER Augmented Reality



Thank You

Optimizing the Paradigm Shift Driven by CDK 4/6 Inhibition in Metastatic HR-Positive, HER2-Negative Breast Cancer

Resource	Address
Ingham M, Schwartz GK. Cell-cycle therapeutics come of age. *J Clin Oncol.* 2017;35:2949-2959.	https://ascopubs.org/doi/full/10.1200/JCO.2016.69.0032
Lynce F, et al. CDK4/6 inhibitors in breast cancer therapy: Current practice and future opportunities. *Pharmacol Ther.* 2018;191:65-73.	https://www.sciencedirect.com/science/article/abs/pii/S0163725818301104
Finn RS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med.* 2016;375:1925-1936.	https://www.nejm.org/doi/10.1056/NEJMoa1607303
Hortobagyi GN, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. 2016;375:1738-1748.	https://www.nejm.org/doi/full/10.1056/NEJMoa1609709
O'Shaughnessy J, et al. Ribociclib plus letrozole versus letrozole alone in patients with de novo HR+, HER2- advanced breast cancer in the randomized MONALEESA-2 trial. *Breast Cancer Res Treat.* 2018;168:127-134.	https://link.springer.com/article/10.1007%2Fs10549-017-4518-8
Rugo HS, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res. Treat.* 2019;174:719-729.	https://link.springer.com/article/10.1007%2Fs10549-018-05125-4
Hortobagyi GN, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol.* 2018;29:1541–1547.	https://www.annalsofoncology.org/article/S0923-7534(19)32105-2/fulltext
Hortobagyi GN. Ribociclib for the first-line treatment of advanced hormone receptor-positive breast cancer: a review of subgroup analyses from the MONALEESA-2 trial. *Breast Cancer Res.* 2018;20:123.	https://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-018-1050-7
Turner NC, et al. Clinical considerations of the role of palbociclib in the management of advanced breast cancer patients with and without visceral metastases. *Ann Oncol.* 2018;29:669-680.	https://www.annalsofoncology.org/article/S0923-7534(19)35508-5/fulltext
Goetz MP, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35:3638-3646.	https://ascopubs.org/doi/full/10.1200/JCO.2017.75.6155
Johnston S, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer*. 2019;5:5.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6336880/
Tripathy D, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19:904-915.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30292-4/fulltext

Im SA, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med.* 2019;381:307-316.	https://www.nejm.org/doi/full/10.1056/NEJMoa1903765
Turner NC, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med.* 2018;379:1926-1936.	https://www.nejm.org/doi/full/10.1056/NEJMoa1810527
Slamon DJ, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol*. 2018;36:2465-2472.	https://ascopubs.org/doi/full/10.1200/JCO.2018.78.9909
Slamon DJ, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382:514-524.	https://www.nejm.org/doi/full/10.1056/NEJMoa1911149
Sledge GW Jr, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol.* 2017;35:2875-2884.	https://ascopubs.org/doi/full/10.1200/JCO.2017.73.7585
Sledge GW Jr, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy—MONARCH 2. *JAMA Oncol.* 2020;6:116-124.	https://jamanetwork.com/journals/jamaoncology/fullarticle/2752266
Cristofanilli M, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016;17:425-439.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00613-0/fulltext