empower

EMPOWER

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

PROGRAM CHAIR
Sara Hurvitz, MD
Associate Professor of Medicine
David Geffen School of Medicine at UCLA
Director, Breast Cancer Clinical Research Program
Co- Director, Santa Monica – UCLA Outpatient Oncology Practice
Santa Monica, CA

This activity is provided by Med Learning Group.
This activity is co-provided by Complete Conference Management (CCM).
This activity is supported by an educational grant from Lilly USA, LLC.

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

PROGRAM CHAIR

Sara Hurvitz, MD
Associate Professor of Medicine
David Geffen School of Medicine at UCLA
Director, Breast Cancer Clinical Research Program
Co- Director, Santa Monica – UCLA Outpatient Oncology Practice
Santa Monica, CA

FACULTY PRESENTERS

Sramila Aithal, MD
Director, Breast Center of Advanced Oncology
Medical Oncologist/Hematologist
Cancer Treatment Centers of America
Philadelphia, PA

Adam M. Brufsky, MD, PhD
Professor of Medicine
University of Pittsburgh
Pittsburgh, PA

Jennifer Diamond, MD
Associate Professor of Medical Oncology
Joyce M. Brown Chair for Developmental Therapeutics in Women's Cancers
Co-Director, Women's Cancer Developmental Therapeutics (WCDT) Program
University of Colorado Anschutz Medical Campus
Denver, CO

Monica Fornier, MD
Associate Professor
Memorial Sloan Kettering Cancer Center
Weill Cornell Medical College
New York, NY

Erica Hamilton, MD
Director, Breast and Gynecologic Research Program
Sarah Cannon Research Institute/Tennessee Oncology
Nashville, TN

Meghan Karuturi, MD
MD Anderson Cancer Center
Department of Breast Medical Oncology
Division of Cancer Medicine Division

Houston, TX

Peter A. Kaufman, MD
Professor of Medicine
Division of Hematology/Oncology
Larner College of Medicine, UVM
UVM Cancer Center
Burlington, VT

Shayma Master Kazmi, MD, RPh
CTCA Medical Director Thoracic Oncology
Philadelphia, PA

Reshma Mahtani, DO
Associate Professor of Medicine
Sylvester Cancer Center
University of Miami
Miami, FL

Erica L. Mayer, MD, MPH
Breast Oncology Center / Physican
Dana-Farber Cancer Institute
Boston, MA

Ruta D. Rao, MD
Associate Professor of Medicine
Medical Director, Rush University Cancer Center
Chicago, IL

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

ACCREDITATION STATEMENT

Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

CREDIT DESIGNATION STATEMENT

Med Learning Group designates this live activity for a maximum of 1.0 *AMA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the live activity.

NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the treatment of patients with hormone receptor-positive, HER2-negative metastatic breast cancer. Credits: 1.0 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 1.0 contact hour of continuing nursing education of RNs and APNs.

DISCLOSURE POLICY STATEMENT

In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educational programs sponsored by Med Learning Group must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, staff, and planning committee members participating in an MLG-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity.

DISCLOSURE OF CONFLICTS OF INTEREST

Dr. Hurvitz reports editorial support and research grants paid to UCLA: Ambrx, Amgen, Bayer, Daiichi Sankyo, GNE/Roche, GSK, Immunomedics, Lilly, Macrogenics, Novartis, Pfizer, OBI, Pieris, PUMA, Radius, Sanofi, Seattle Genetics, and Dignitana.

Dr. Aithal serves on the speakers' bureau for Pfizer, Novartis, and PUMA.

Dr. Brufsky serves on the speakers' bureau for Novartis, Pfizer, Lilly, and Sanofi; and has received consulting fees from AstraZeneca, Novartis, Roche, Lilly, and Pfizer.

Dr. Diamond has nothing to disclose.

Dr. Fornier has nothing to disclose.

Dr. Hamilton reports consulting fees paid to institution only (no personal fees) from: Pfizer, Genentech/Roche, Lilly, PUMA Biotechnology, Daiichi Sankyo, Mersana Therapeutics, Boehringer Ingelheim, AstraZeneca, Novartis, Silverback Therapeutics, Black Diamond; and research/clinical trial support paid to institution only (no personal fees) from: AstraZeneca, Hutchinson MediPharma, OncoMed, MedImmune, StemCentrx, Genentech/Roche, Curis, Verastem, Zymeworks, Syndax, Lycera, Rgenix, Novartis, Mersana, Millenium, TapImmune, Cascadian, Lilly, BerGenBio, Medivation, Pfizer, Tesaro, Boehringer Ingelheim, Eisai, H3 Biomedicine, Radius Health, Acerta, Takeda, Macrogenics, Abbvie, Immunomedics, FujiFilm, Effector, Merus, Nucana, Regeneron, Leap Therapeutics, Taiho Pharmaceutical, EMD Serono, Daiichi Sankyo, ArQule, Syros, Clovis, Cytomx, InventisBio, Deciphera, Unum Therapeutics, Sermonix Pharmaceuticals, Sutro, Aravive, Zenith Epigenetics, Arvinas, Torque, Harpoon, Fochon, Black Diamond, Orinove, Molecular Templates, Silverback Therapeutics.

Dr. Karuturi has received consulting fees from Pfizer.

Dr. Kaufman serves on the speakers' bureau for Lilly and has received consulting fees from Lilly, Eisai, Polyphor, Merck, Celgene, Macrogenics, Pfizer, Novartis, and Amgen; he has also received research grant support from Lilly, Eisai, Polyphor, Merck, Celgene, Macrogenics, Pfizer, Novartis, Amgen and Sanofi.

Dr. Kazmi has received consulting fees from Merck, Eisai, Takeda, and Lilly; and serves on the speakers' bureau for Merck, Eisai, Takeda, Lilly, and Immunomedics.

Dr. Mahtani has received consulting fees from Agendia, Biotheranostics, Lilly, Pfizer, Novartis, Eisai, Seattle Genetics, PUMA, and Genentech; and is contracted for research with Genentech.

Dr. Mayer has received consulting fees from Pfizer, Novartis, Elsai, CT, and Lilly; and has been sponsored for research with Pfizer, Elsai, and Myriad.

Dr. Rao has received consulting fees from Novartis, Genentech, PUMA, and Genomic Health.

CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

The reviewer of this activity has nothing to disclose.

Staff Planners and Managers

The staff, planners, and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:

Matthew Frese, MBA, General Manager of Med Learning Group, has nothing to disclose.

Christina Gallo, SVP, Educational Development for Med Learning Group, has nothing to disclose.

Diana Tommasi, PharmD, Medical Director for Med Learning Group, has nothing to disclose.

Lauren Welch, MA, VP, Accreditation and Outcomes for Med Learning Group, has nothing to disclose.

Jessica McMullen, MPH, Program Manager for Med Learning Group, has nothing to disclose.

Russie Allen, Accreditation and Outcomes Coordinator, has nothing to disclose.

DISCLOSURE OF UNLABELED USE

Med Learning Group requires that faculty participating in any CME activity disclose to the audience when discussing any unlabeled or investigational use of any commercial product or device not yet approved for use in the United States.

During this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

METHOD OF PARTICIPATION

There are no fees for participating and receiving CME credit for this live activity. To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures.
2. Participate in the live activity.
3. Submit the online evaluation form to Med Learning Group.

You will receive your certificate upon completion of your electronic evaluation form, as a downloadable file.

DISCLAIMER

Med Learning Group makes every effort to develop CME activities that are science based.

This activity is designed for educational purposes. Participants have a responsibility to use this information to enhance their professional development in an effort to improve patient outcomes. Conclusions drawn by the participants should be derived from careful consideration of all available scientific information. The participant should use his/her clinical judgment, knowledge, experience, and diagnostic decision making before applying any information, whether provided here or by others, for any professional use.

For CME questions, please contact Med Learning Group at info@medlearninggroup.com

Contact this CME provider at Med Learning Group for privacy and confidentiality policy statement information at http://medlearninggroup.com/privacy-policy/

AMERICANS WITH DISABILITY ACT

Event staff will be glad to assist you with any special needs (eg, physical, dietary, etc). Please contact Med Learning Group prior to the live event at info@medlearninggroup.com

Provided by Med Learning Group

This activity is co-provided by Ultimate Medical Academy/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. (Whiteboard animation) – The mechanism of action of CDK 4/6 inhibitors***
    - iv. Clinical trial data on CDK 4/6 inhibitors vs chemotherapy
    - 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**
    - i. Toxicities commonly associated with each CDK 4/6 inhibitor use
    - ii. Required monitoring (laboratory and clinical) while on treatment
    - iii. 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. **Conclusions**

6. **Question and Answer**

EMPOWER:

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

PROGRAM CHAIR:

Sara Hurvitz, MD

Associate Professor of Medicine
David Geffen School of Medicine at UCLA
Director, Breast Cancer Clinical Research Program
Co- Director, Santa Monica – UCLA Outpatient Oncology Practice
Santa Monica, CA

Program Overview

- We have an electronic evaluation process that you can complete by following the directions on the provided card.
- This program also has a complimentary poster portal where you can choose preselected images relevant to this presentation to create an office poster. Please refer to the provided card.

Disclosures

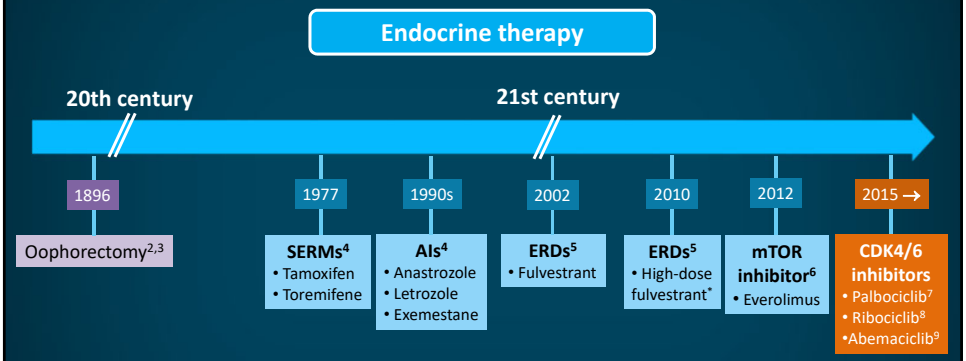
- Please see Program Overview for specific speaker disclosure information
- During the course of this lecture, faculty may mention the use of medications for both FDA-approved and non-approved indications

This activity is supported by an educational grant from Lilly.

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
- 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

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.

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 aromatase inhibitor 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 aromatase inhibitor in postmenopausal women 2nd line therapy with fulvestrant Monotherapy in adults with disease progression following endocrine therapy and prior chemotherapy in the 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

- ***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.

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
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. Di Leo A, et al. *Ann Oncol*. 2017;28(suppl 5):abstract 236O_PR.

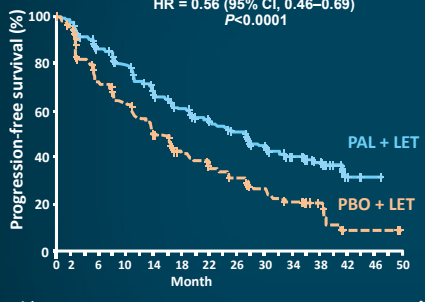
PALOMA-2 and MONALEESA-2: PFS Update

Investigator assessment

PALOMA-2

	PAL + LET	PBO + LET
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<0.0001



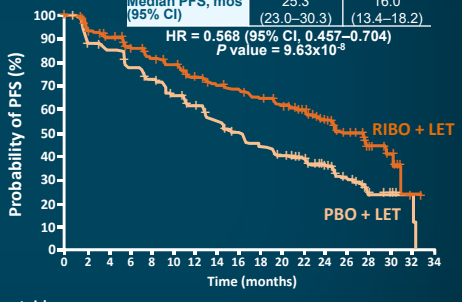
No. at risk

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

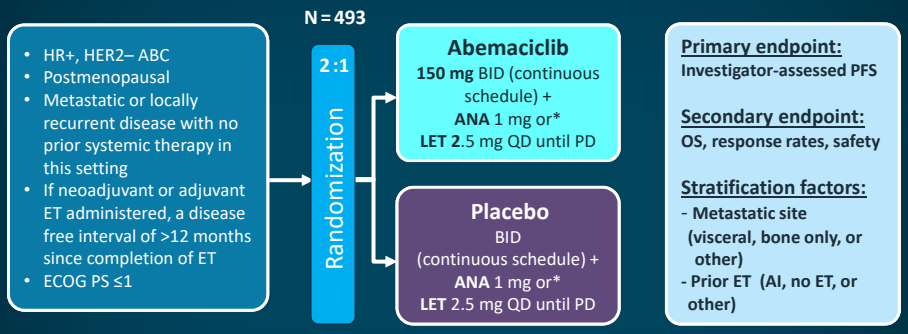
RIBO + LET	334	294	277	257	240	227	207	196	188	176	164	132	97	46	17	11	1	0
PBO + LET	334	279	265	239	219	196	179	156	138	124	110	93	63	34	10	7	2	0

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

PAL = palbociclib; LET = letrozole; RIBO = ribociclib; NR = not reached; CI = confidence interval.

Rugo H et al. *Breast Cancer Res. Treat.* 2019;174(3):719-729. Hortobagyi GN et al. *Ann Oncol.* 2018;29:1541–1547.

MONARCH-3 Study Design
Abemaciclib as Initial Therapy for ABC

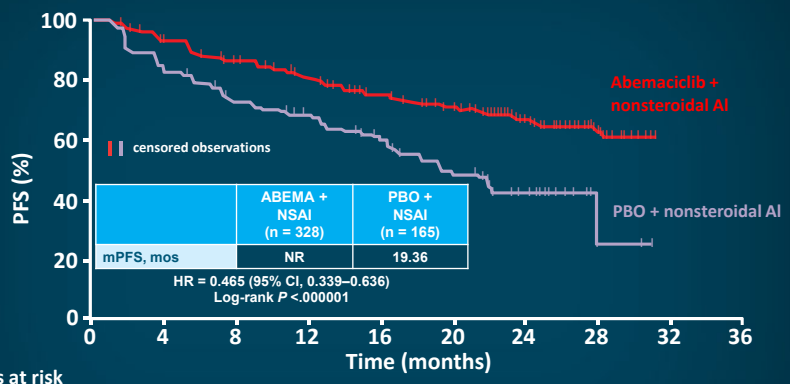


*per physician's choice: 79.1% received letrozole, 19.9% received anastrozole

- **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



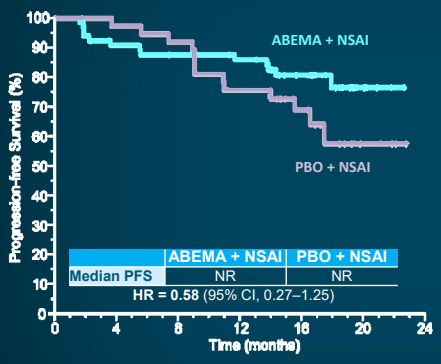
Patients at risk

ABEMA + NSAI	328	271	233	206	175	151	98	32	0	0
PBO+ NSAI	165	121	96	79	60	44	27	2	0	0

ICR = independent central review ; ITT = intention to treat; NSAI = nonsteroidal AI.
Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5.

MONARCH-3: Exploratory PFS Analysis
Bone-Only Disease

Patients with bone-only disease

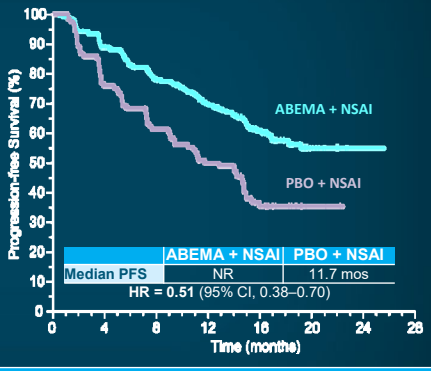


	ABEMA + NSAI	PBO + NSAI
Median PFS	NR	NR

HR = 0.58 (95% CI, 0.27–1.25)

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



	ABEMA + NSAI	PBO + NSAI
Median PFS	NR	11.7 mos

HR = 0.51 (95% CI, 0.38–0.70)

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%

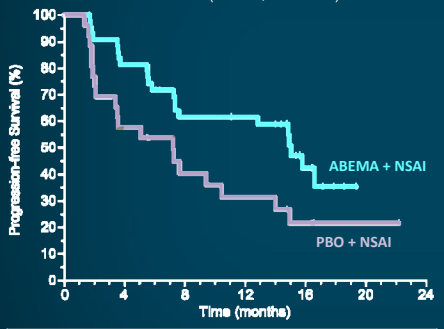
Goetz MP, et al. *J Clin Oncol*. 2017;35:3638-3646.

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)

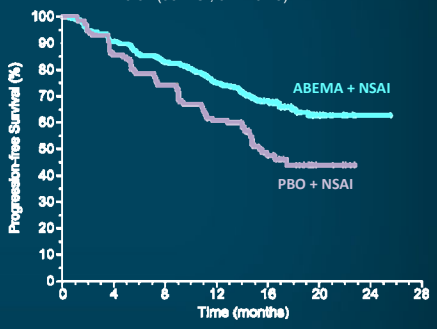


PFS Rate	6 mos	12 mos	18 mos
ABEMA + NSAI (n = 48)	71.8%	61.5%	35.3%
PBO + NSAI (n = 30)	53.8%	31.4%	21.5%

Patients without liver metastases

	ABEMA + NSAI	PBO + NSAI
Median PFS	NR	15.4 mos

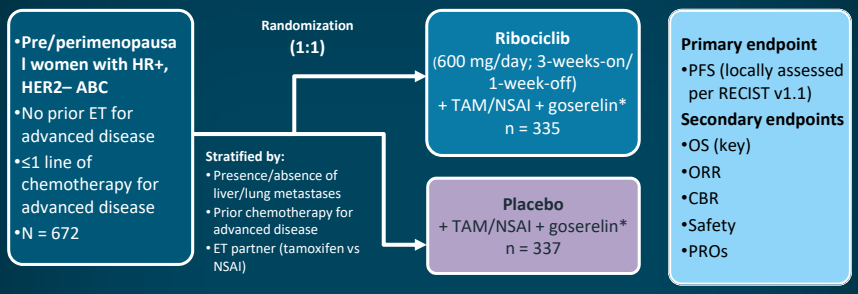
HR = 0.57 (95% CI, 0.41–0.78)



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.

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.

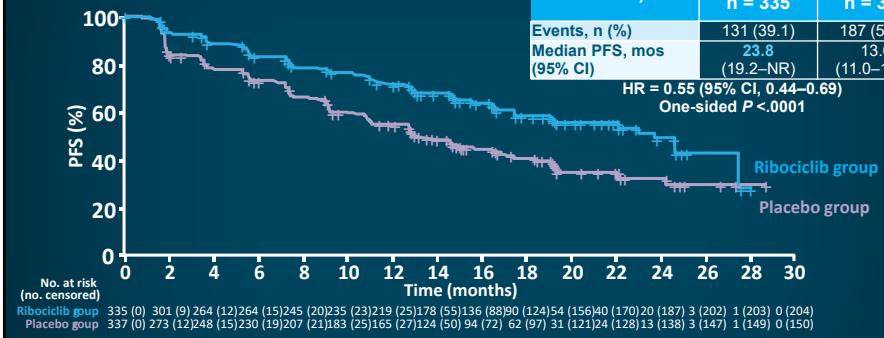
- Tumor assessments performed every 8 weeks for 18 months, then every 12 weeks
- Primary analysis planned after ~329 PFS events
  - 95% power to detect a 33% risk reduction (HR = 0.67) with one-sided α=2.5%, corresponding to increase in median PFS to 13.4 mos (median PFS of 9 mos for placebo arm), and 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 (no. 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

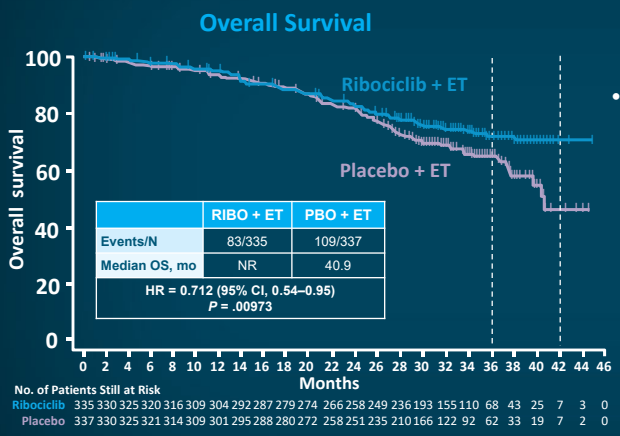
MONALEESA-7
PFS by Endocrine Therapy Partner

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 Trial: Overall Survival



- 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.

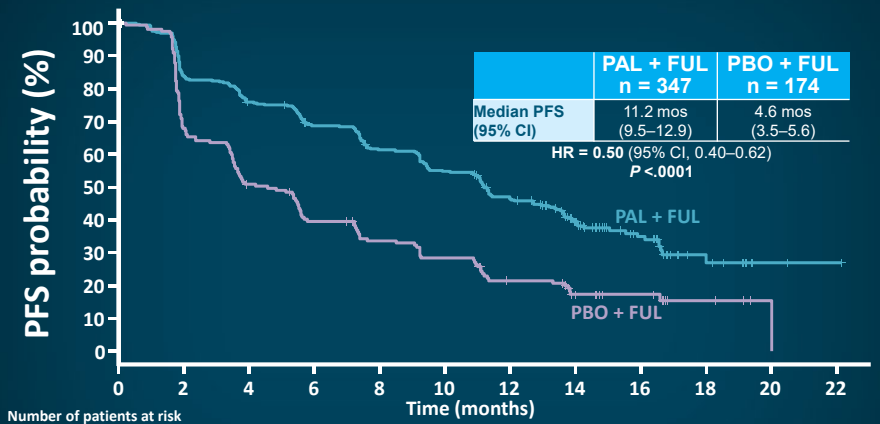
CDK4/6 Inhibitors Combined with Fulvestrant

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	Progression or relapse on prior ET	Treatment-naïve or ≤1 line of prior ET	Progression on neoadjuvant/adjuvant ET, ≤12 mo from end of adjuvant ET, or ≤1 line ET for metastatic disease
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* = 0.09	NE vs 40.0 HR = 0.72; *P* = 0.00455	46.7 vs 37.3 HR = 0.757; *P* = 0.0137

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.

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**

Number of patients at risk

PAL+FUL	347	276	245	215	189	168	137	69	38	12	2	1
PBO+FUL	174	112	83	62	51	43	29	15	11	4	1	

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

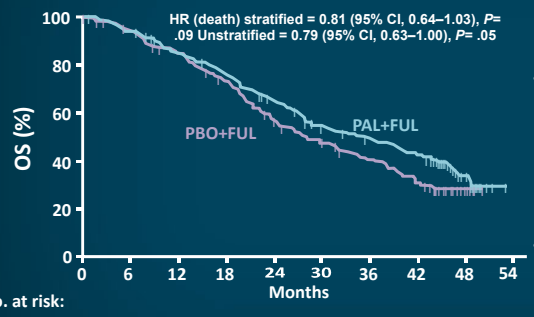
21

FUL = fulvestrant.

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

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)



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.

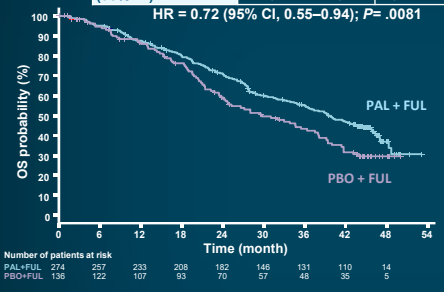
22

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

PALOMA-3: OS by Prior ET Sensitivity

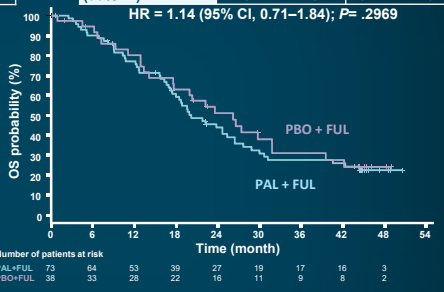
Patients with Sensitivity to Prior ET	PAL + FUL (n = 274)	PBO + FUL (n = 136)
Median OS, mos (95% CI)	39.7 (34.8–45.7)	29.7 (23.8–37.9)

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)

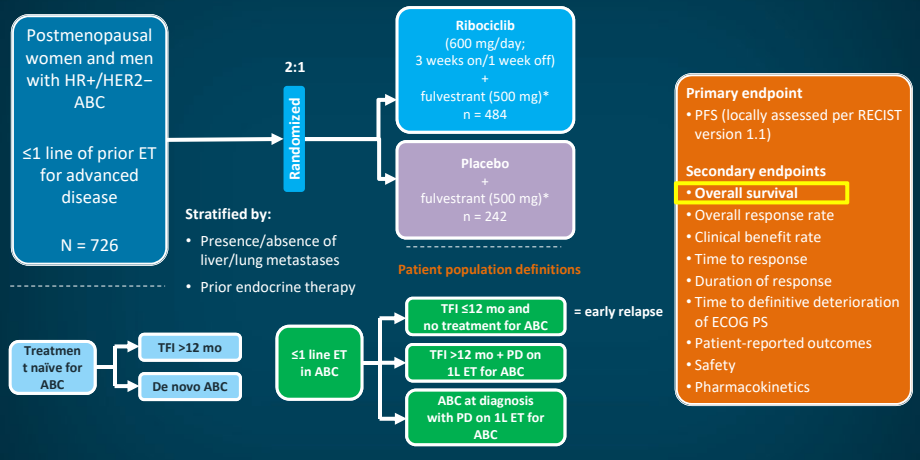
HR = 1.14 (95% CI, 0.71–1.84); *P*= .2969



- 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.

MONALEESA-3 Study Design

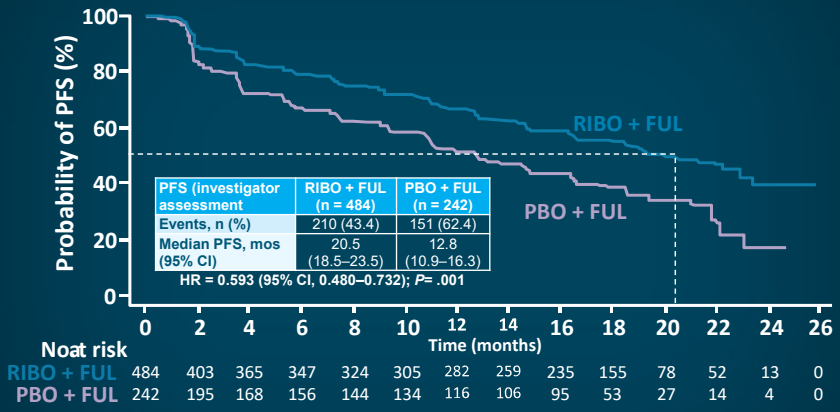


*Fulvestrant 500 mg intramuscularly every 28 days plus an additional dose on cycle 1, day 15.

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

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

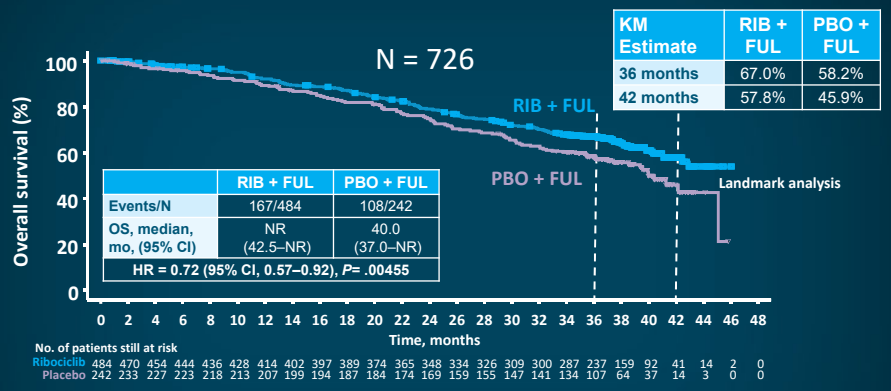
MONALEESA-3: Primary Endpoint PFS Investigator-Assessed



- 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.

MONALESSA-3: Overall Survival



- 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.

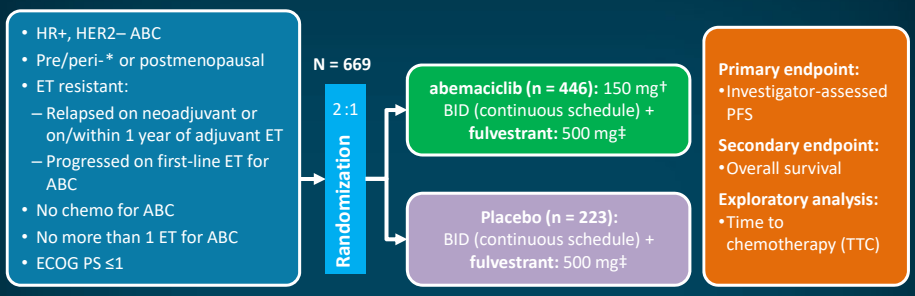
MONALEESA-3: OS by Prior Response to ET

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.

MONARCH 2: Study Design



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

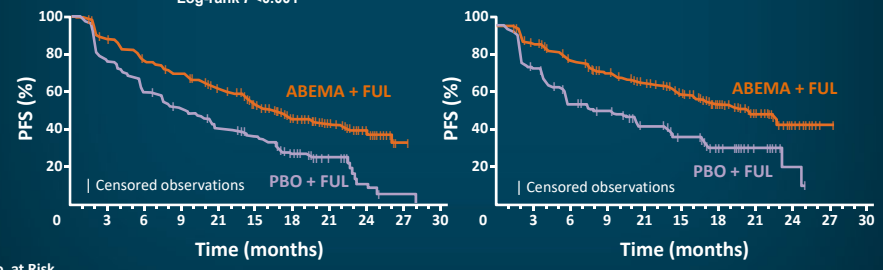
ABEMA + FUL demonstrated median PFS of 22.4 months (compared with 10.2 months with PBO + FUL) with consistent PFS results on blinded central analysis.

Investigator assessment	ABE + 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*<0.001

Independent assessment	ABE + 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*<0.001



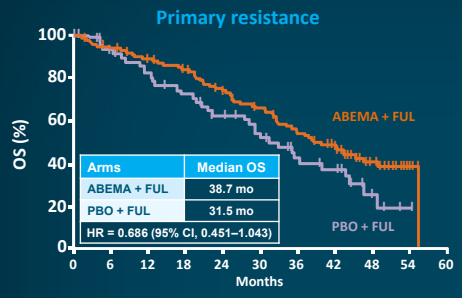
No. at Risk

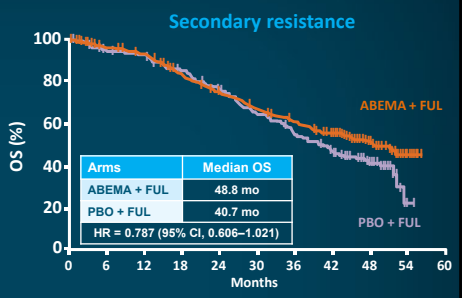
ABEMA + FUL	446	367	314	281	234	171	101	65	32	2	0
PBO + FUL	223	165	123	103	80	61	32	13	4	1	0

ABEMA + FUL	446	362	298	260	220	162	93	56	24	3	0
PBO + FUL	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: Overall Survival Resistance to ET





- Statistically significant improvements also noted with abemaciclib + FUL compared with PBO + FUL in:
- Median OS (46.7 vs 37.3 months; HR = 0.757 (95% CI, 0.606-0.945); P = .01)
- 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.

MONARCH-2: Objective Response Rates Measurable Disease

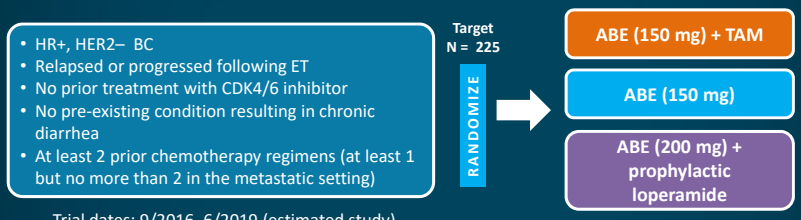
Objective Response Rate			
	PBO arm (%)	ABEMA arm (%)	Δ (%)
PgR: negative	9.68	43.94	34.26
Liver mets: yes	15.25	48.65	33.39
High-grade	20.83	51.32	30.48
Bone-only disease: no	21.79	49.50	27.70
Low/intermediate grade	19.51	47.06	27.55
ECOG PS: 0	20.59	47.47	26.89
ECOG PS: 1	22.58	49.17	26.59
PgR: positive	25.40	50.00	24.60
Liver mets: no	24.76	47.83	23.06

Response rates are not reported for bone-only disease since the majority of lesions were not measurable

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

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



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).

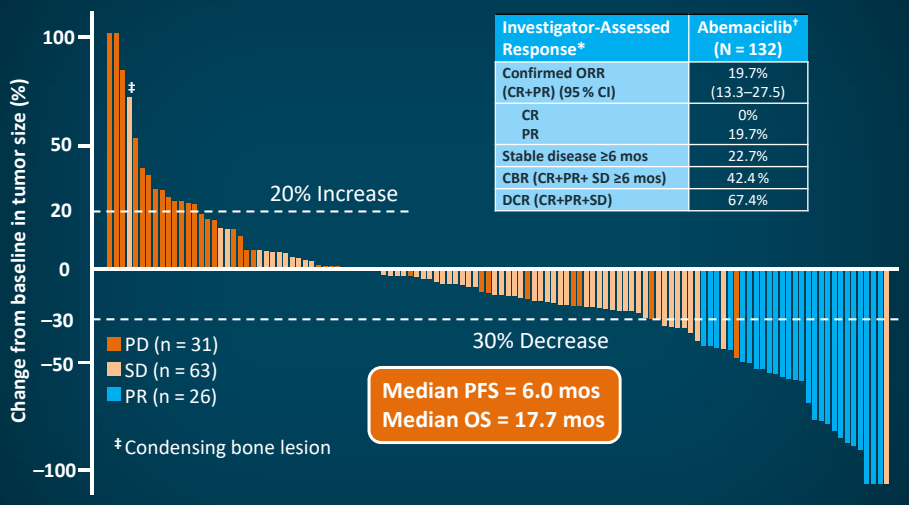
nextMONARCH 1: Endpoint Analysis Investigator-Assessed

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.

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%

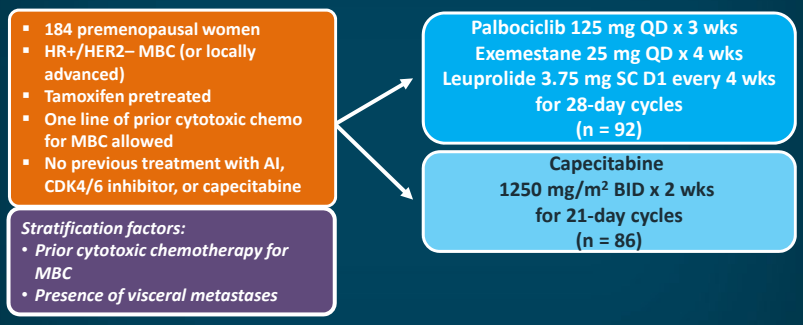
Trial dates: 6/2014–10/2018 (estimated study)

*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).

CDK 4/6 Inhibitors vs Chemotherapy

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

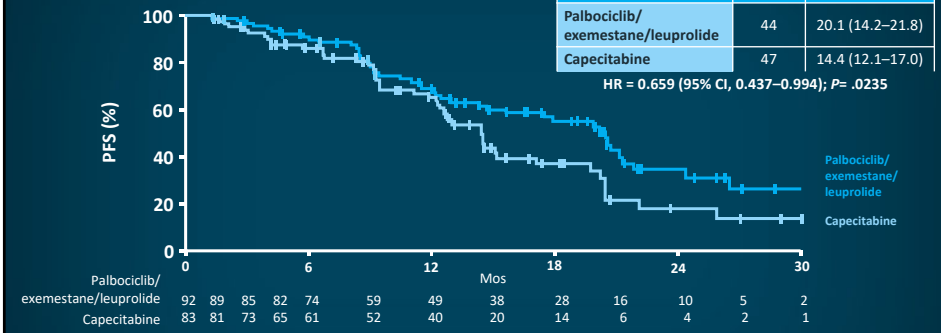
QoL = quality of life.

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. ASCO 2019. Abstr 1007.

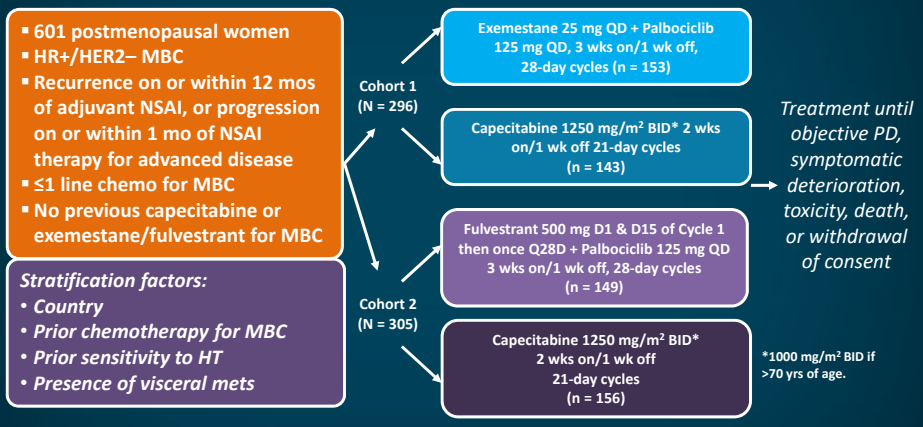
Young-PEARL: Response Rates

	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.

PEARL: Study Design

- Phase 3, international, randomized study with 2 cohorts



- 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: PFS

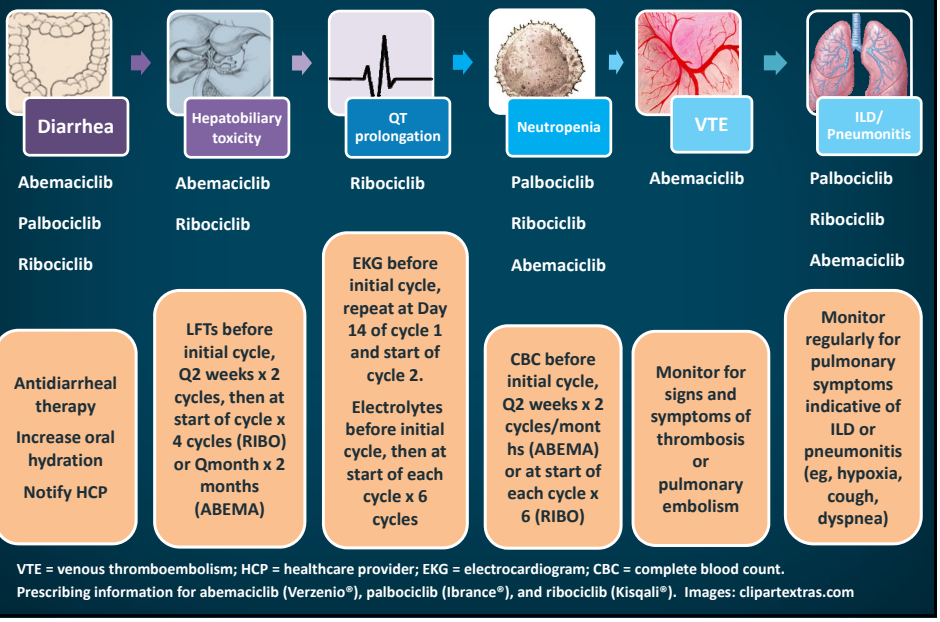
Comparison	Median PFS Mos (95% CI)	HR (95% CI)	*P*-Value
Cohort 2: FUL + PALBO (n = 149) vs CAPE (n = 156)	7.5 (5.7–10.9) vs 10.0 (6.3–12.9)	1.09 (0.83–1.44)	.537
ESR1 wt: ET + PALBO (n = 206) vs CAPE (n = 187)	8.0 (6.5–10.9) vs 10.6 (7.4–13.0)	1.08 (0.85–1.36)	.526
Cohorts 1 and 2: ET + PALBO (n = 302)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

Toxicity Monitoring and Management

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®). Images: clipartextras.com

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.

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

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

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®).

Multidisciplinary Team Tools

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

Its all about Communication!

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

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.

Case Study —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 —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 —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

Summary

	Palbociclib	Ribociclib	Abemaciclib
	PALOMA-2	MONALEESA-2	MONARCH-3
Partner	Letrozole	Letrozole	Letrozole or anastrozole
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

	Palbociclib	Ribociclib	Abemaciclib
	PALOMA-3	MONALEESA-3	MONARCH-2
Endocrine partner	Fulvestrant	Fulvestrant	Fulvestrant
ORR (%)	19.0 vs 9.0	32.4 vs 21.5	35.2 vs 16.1
Median PFS (mo)	9.5 vs 4.6	20.5 vs 12.8	16.4 vs 9.3
Median OS (mo)	34.9 vs 28.0	NE vs 40.0	46.7 vs 37.3

Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936. Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748. O'Shaughnessy J, et al. *Breast Cancer Res Treat*. 2018;168:127-134. Goetz MP, et al. *J Clin Oncol*. 2017;35(32):3638-3646. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936. Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439. Cristofanilli M, et al. European Society for Medical Oncology (ESMO) 2018: abstract LBA2_PR. Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472. Slamon DJ, et al. *N Engl J Med*. 2020;382(6):514-524. Sledge GW Jr, et al. *J Clin Oncol*. 2017;35:2875-2884. Sledge GW Jr, et al. *JAMA Oncol*. 2020;6(1):116-124.

Summary: CDK4/6 Inhibitors in ER+ mBC

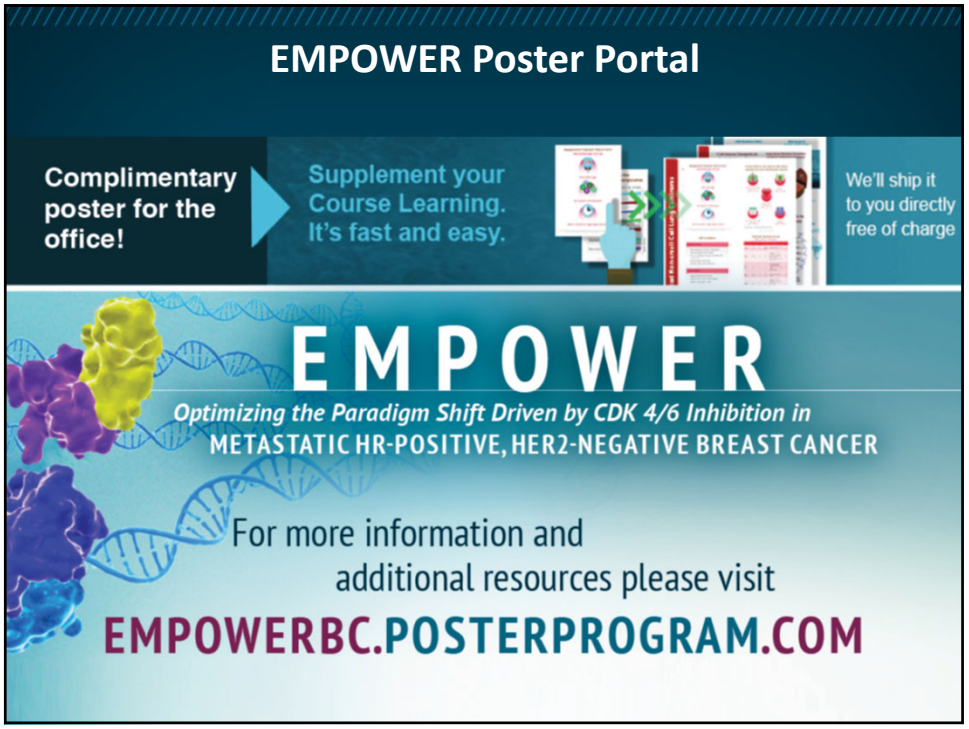
- The 3 CDK4/6 inhibitors seem to be consistent and comparable in prolonging PFS in combination with endocrine therapy in the metastatic setting, with acceptable toxicity.
  - Due to similarities in outcomes with all CDK 4/6 inhibitors, selection of therapeutic agents should consider differences in toxicities.
- 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.

Electronic Evaluation Form

- Before we move to Q&A, I want to remind you to fill out your evaluation form electronically by following the directions on the provided card at your seat.
- Once you complete your evaluation form, your CME certificate will be provided as a PDF that you can save for your records.
- You will also have the opportunity to download a PDF of the program slides.
- Even if you do not need credit, we appreciate you completing the evaluation form.

EMPOWER Website

EMPOWER Poster Portal



EMPOWER Augmented Reality

Thank You!

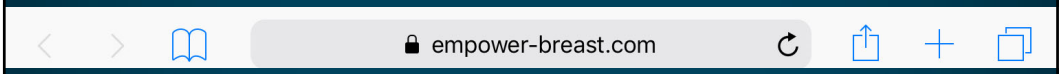
Questions and Answers

empower-breast.com

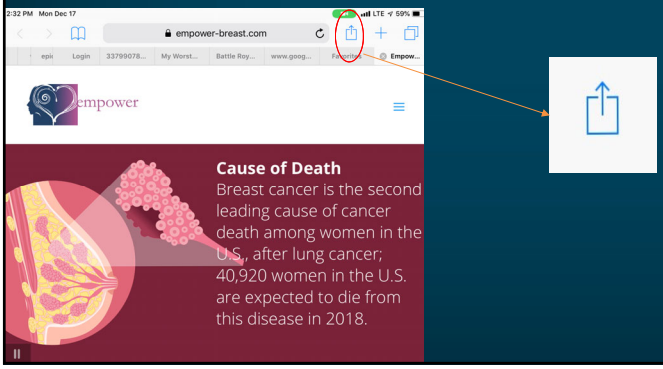
- A mobile website application that can be downloaded to any smart phone or device and can be viewed on a PC
- The mobile website application serves as a resource for both healthcare practitioners and patients
- This tool will be updated continuously with the following:
  - New meeting dates/locations
  - CME activities
  - References and links to educational resources

Directions to Download to a Smart Device

1. Open the browser on your smart device and visit empower-breast.com

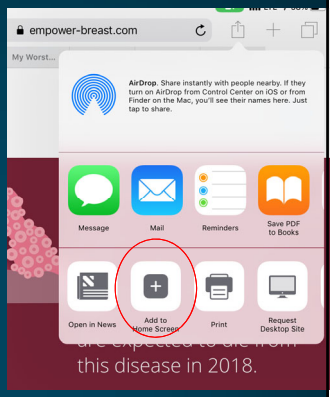


2. Select the box pictured here at the top or bottom of your mobile device screen and click on it



Directions to Download to a Smart Device

3. Touch “Add to Home Screen” Icon



4. Now find icon on home screen and touch to access

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