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ONCOLOGY NURSES QUALITY Improvement Series

Updates for Oncology Nurses—Optimizing the Paradigm Shift Driven by CKD 4/6 Inhibitors in Metastatic HR-Positive, HER2-Negative Breast Cancer

FACULTY

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Director and Lead, Breast Center of Advanced Oncology
Medical Oncologist and Hematologist
Cancer Treatment Centers of America
Philadelphia, PA

PROGRAM OVERVIEW

This case-based live virtual activity will cover the treatment and management of patients with HER2-negative breast cancer.

TARGET AUDIENCE

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

LEARNING OBJECTIVES

Upon completion of the 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
- Review the various roles for oncology nurses in the management of patients with breast cancer

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Purpose: This program would be beneficial for nurses involved in the long-term treatment and management of patients with hormone receptor-positive, HER2-negative metastatic breast cancer. **CNE Credits:** 1 ANCC Contact Hour.

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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 for RNs and APNs.

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The reviewer of this activity has nothing to disclose.

CNE Content Review

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1. Read the CME/CNE information and faculty disclosures
2. Participate in the live virtual activity
3. Complete the posttest and online evaluation form

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ONCOLOGY NURSES QUALITY Improvement Series

Updates for Oncology Nurses—Optimizing the Paradigm Shift Driven by CDK 4/6 Inhibitors in Metastatic HR-Positive, HER2-Negative Breast Cancer

I. Clinical Trial Data from Cyclin dependent kinase (CDK) 4/6 Inhibition in Breast Cancer

a. Summary of pivotal CDK 4/6 trials data updates – First line treatment
b. regimens and efficacy
c. Summary of pivotal CDK 4/6 trials data updates – Second and subsequent line treatment regimens and efficacy
d. Toxicity profiles and safety signal updates of approved CDK 4/6 agents

II. Optimizing CDK 4/6 Inhibition: Patient with Advanced Breast Cancer

a. Who is a candidate for CDK 4/6 inhibition?
    i. Line of therapy - 1st line or 2nd line of treatment
    ii. Prior therapy, metastatic sites – patient's response
        a) Primary endocrine resistance
        b) Visceral disease
        c) Prognostic markers and their interpretation and their past medical history - CDK 4/6 adverse event (AE) profile: Which agent to use?
    iii. Considerations when incorporating a CDK 4/6 inhibitor into the treatment regimen
        a) Making the switch to a CDK 4/6 inhibitor
        b) Choosing an endocrine partner with CDK 4/6 therapy
        c) Premenopausal vs. postmenopausal status
        d) Next steps after progression on a CDK 4/6 inhibitor

III. Monitoring and Managing Toxicities Associated with CDK 4/6 Inhibition – Its Application to Clinical Practice

a. Toxicities commonly associated with CDK 4/6 inhibitor use and their management considerations
    i. Co-morbid conditions and tolerability
    ii. Required monitoring (laboratory and clinical) while on treatment
    iii. Appropriate intervention and management of CDK 4/6 inhibitor associated AEs

IV. Multidisciplinary Team Tools in Optimizing Care and Adverse Event Management

a. The educated patient as a critical team member
    i. Key knowledge to optimize care
        a) Disease state and disease course
        b) Medication use – dosing regimen (how and when to take, adherence, dosing options)
        c) Special considerations for oral oncolytic medications
        d) Potential AEs: recognition, reporting, management and prevention
        e) Past medical history and how it relates to AEs
        f) Review of treatment plan – initially and ongoing
    ii. How decisions are made
        a) The shared decision-making (SDM) model supported with the use of decision aids
        b) How SDM impacts AE recognition and management
b. Cancer survivorship tools that foster multidisciplinary team engagement
    i. Survivorship care plan and how it aligns the patient care team across specialties, from the oncologist, oncology nurse and beyond
        a) Collaborative monitoring and management of adverse events
        b) Medication adherence
        c) Communication of acute events

V. Case Study

VI. Question and Answer

Updates for Oncology Nurses— Optimizing the Paradigm Shift Driven by CDK 4/6 Inhibitors in Metastatic HR-Positive, HER2-Negative Breast Cancer

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

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Disclosures

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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
- 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
- Review the various roles for oncology nurses in the management of patients with breast cancer

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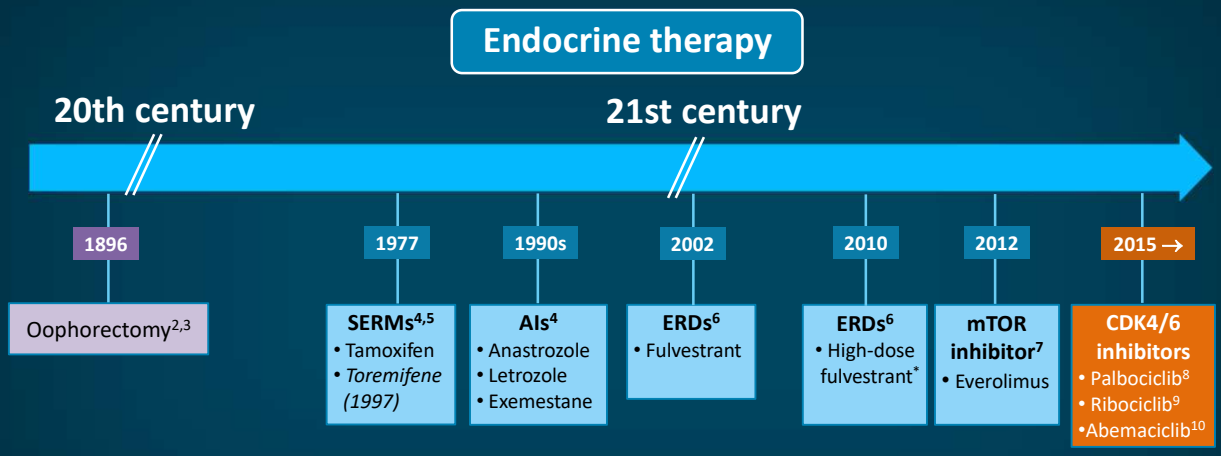
Historical Timeline of Therapies for HR+ Advanced Breast Cancer (ABC)



* 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.Toremifine (Fareston®) prescribing information (PI), 2017 (http://fareston.com/uploads/documents/fareston-pi.pdf). 6. Fulvestrant (Faslodex®) prescribing information (PI), 2019 (https://medicalinformation.astrazeneca-us.com/home/prescribing-information/faslodex-pi.html) . 7. Baselga J, et al. *N Engl J Med*. 2012;366:520-529. 8. Finn RS, et al. *Lancet Oncol*. 2015;16:25-35. 9. Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748. 10. Sledge GW Jr, et al. *J Clin Oncol*. 2017;35:2875-2884. URLs accessed 8/7/2020.

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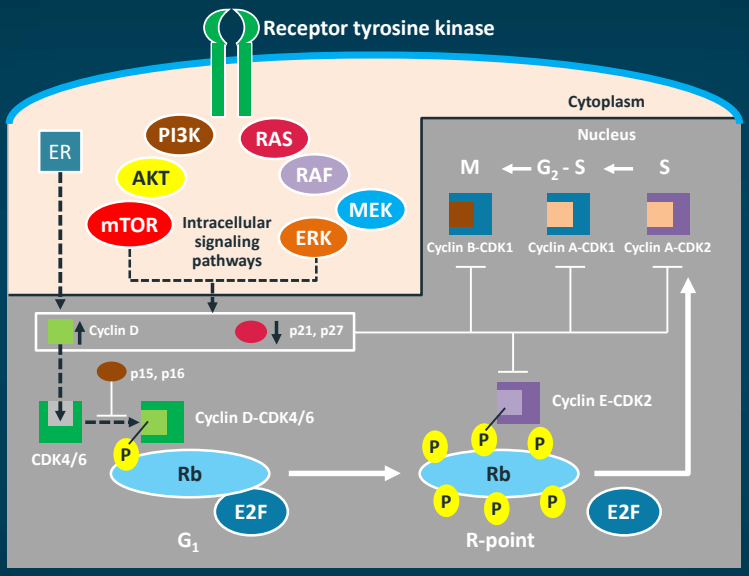
Regulation of G1/S Checkpoint in Breast Cancer



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

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

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Frequent Alterations in Cyclin D/CDK4/6 in BC

- **Amplification of cyclin D1** (11q13) in ER+ breast cancer
  - Non-catalytic effects of cyclin D1 on transcription, DNA repair, etc.
- Cyclin-dependent kinase 4 **(CDK4) amplification/overexpression**
- Rb loss is uncommon in ER+ disease.
- **Loss of negative regulators** (p16, p27)
- Association of above with antiestrogens' response and prognosis
- Growth-factor signaling (steroid and peptide) and cell-cycle progression

DNA = deoxyribonucleic acid; ER+ = estrogen receptor positive.

Musgrove EA et al. *Nat Rev Cancer.* 2011;11:558-572. Yu Q et al. *Cancer Cell.* 2006;9:23-32. Arnold A, Papanikolaou A. *J Clin Oncol.* 2005;23:4215-4224.

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CDK4/6 Inhibitors: Clinical Trials 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	**PALOMA-2** *(1st line)* **PALOMA-3** *(2nd line)*	**MONALEESA-2** *(1st line)* **MONALEESA-7** *(1st line)* **MONALEESA-3** *(1st/2nd line)*	**MONARCH-3** *(1st line)* **MONARCH-2** *(2nd line)* **MONARCH-1** *(2nd line)*
FDA approval status for HR-positive, HER2-negative advanced or metastatic breast cancer	1st-line therapy in combination with an AI 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 ET and prior chemotherapy in metastatic setting

FDA = US Food and Drug Administration; HR = hormone receptor; HER = human epidermal growth factor receptor; AI = aromatase inhibitor; BID = twice daily; ET = endocrine therapy.

1. Ibrance [package insert]. New York, NY: Pfizer Inc; 2019. 2. Kisqali [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2020. 3. Verzenio [package insert]. Indianapolis, IN: Eli Lilly & Co;2020. URLS accessed 3/2/2020.

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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.

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1st Line Treatment with CDK 4/6 Inhibitors

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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	41
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).

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.

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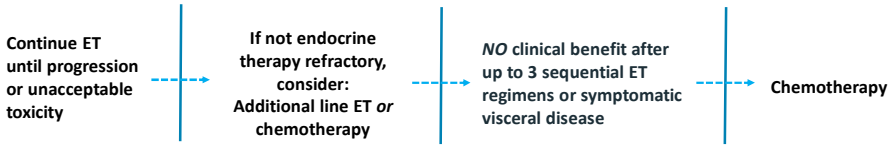
Systemic ET Is Preferred for Patients With HR+, HER2– ABC

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend *3 lines of consecutive ET* for patients with HR+ ABC without visceral symptoms.
  - **Preferred FDA-approved systemic ETs or combination therapies** include:

First line:
- **AI or Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib or ribociclib)**
- Fulvestrant ± anastrozole or letrozole
- Anastrozole or letrozole
- Tamoxifen or toremifene
- Exemestane

Second/subsequent line:
- **Fulvestrant + CDK4/6 inhibitor *(if no previous CDK4/6 inhibitor use)***
- Everolimus + exemestane, fulvestrant or tamoxifen
- Anastrozole or letrozole
- Exemestane
- Fulvestrant
- Tamoxifen or toremifene

Treatment algorithm for recurrent or stage IV BC



ET = endocrine therapy; HR = hormone receptor; HER = human epidermal growth receptor. **denotes category 1 treatment.*

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Breast cancer. Version 5.2020, 7/15/20

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Endocrine Resistance

Challenge of endocrine resistance

- ~ 50% of HR+ ABC patients do not respond to initial ET.
- The majority (if not all) patients will ultimately progress despite ET.

Overcoming resistance to ET

- Signaling pathways alteration and checkpoint regulation
  - mTOR/PI3K vs CDK
- CDK4/6 + PI3K inhibition is synergistic

PI3K = = phosphatidylinositol 3-kinase.

Osborne CK, Schiff R. *Ann Rev Med.* 2011;62:233-247. Fan W et al. *Future Med Chem.* 2015;7:1511-1519.

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CDK4/6 Inhibitors As Initial Therapy In ER+ Advanced Breast Cancer: A Story Of Success

- Four Phase III trials

- ER+/HER2 negative
- Advanced disease
- No prior ET for M+

→ Endocrine Therapy + Placebo

→ Endocrine Therapy + CDK4/6 inhibitor

- Consistent improvement in Progression-free Survival (PFS) with CDK4/6 inhibitors (Median PFS from ± 12 to ± 24 months)
- Similar results in pre- (MONALEESA-7) and in post-menopausal (PALOMA-2, MONALEESA-2, MONARCH-3) patients

Finn RS, et al. *New Engl J Med* 2016;375:1925-1936. Hortobagyi GN, et al. *New Engl J Med* 2016;375:1738-1748. Goetz MP, et al. *J Clin Oncol* 2017;35:3638-3646. Tripathy D, et al. *Lancet Oncol.* 2018;19:904-915

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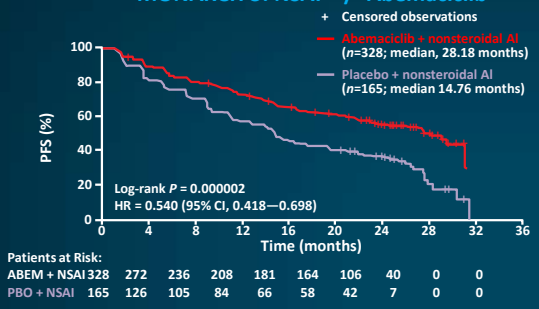
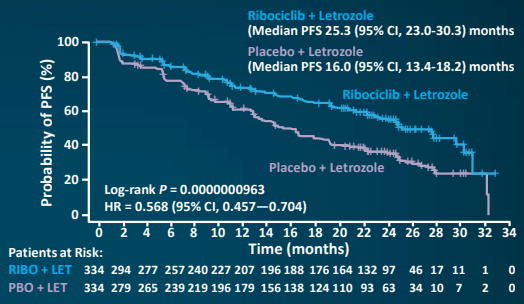
CDK4/6i + AI: 1L Therapy for HR+/HER2- MBC

MONARCH 3: NSAI + /- Abemaciclib

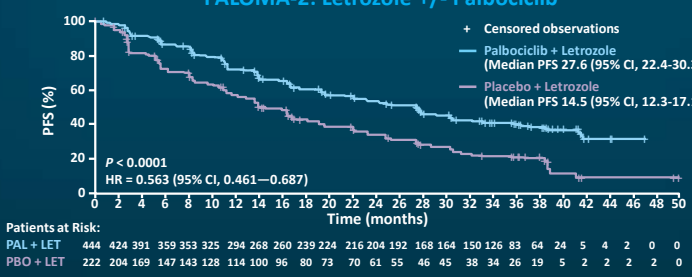


CDK 4/6i + ET	Median PFS (months)
Abemaciclib + NSAI	28.2
Palbociclib + Letrozole	27.6
Ribociclib + Letrozole	25.3

MONALEESA-2: Letrozole +/- Ribociclib



PALOMA-2: Letrozole +/- Palbociclib



1. Johnston S, et al. *npj Breast Cancer. 2019;*5:5. 2. Hortobagyi GN, et al. *Ann Oncol* . 2018;29:1541-1547. 3. Rugo HS, et al. *Breast Cancer Res Treat*. 2019;174:719-729.

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Ribociclib in Premenopausal 1st-Line Metastatic Breast Cancer

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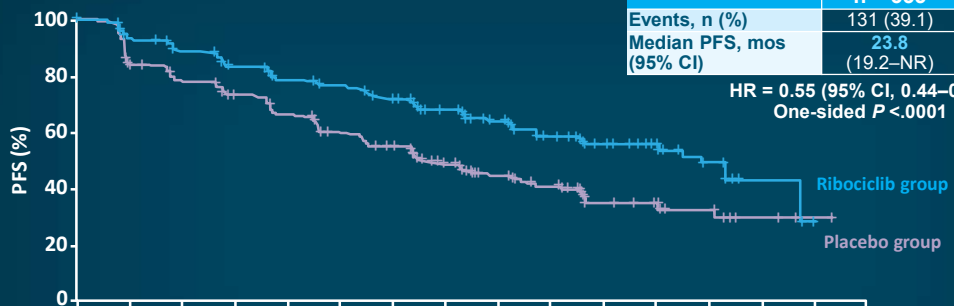
MONALEESA-7: Primary Endpoint PFS (Investigator-Assessed)

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

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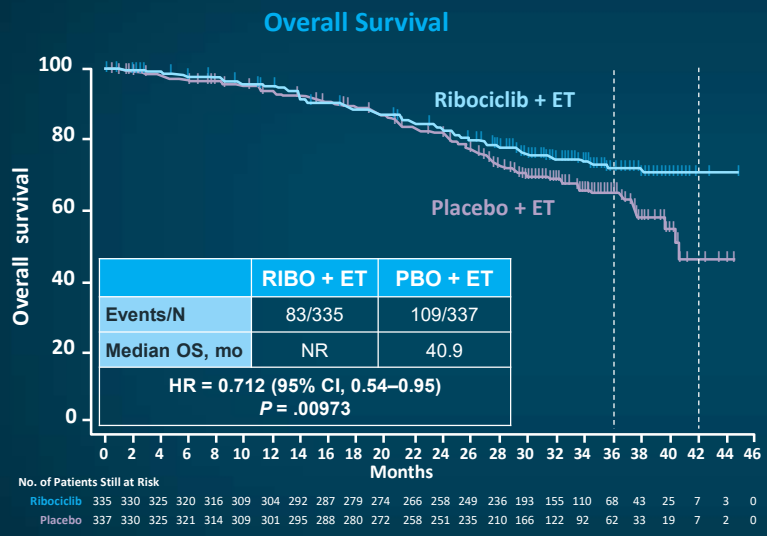
MONALEESA-7 Trial: Overall Survival



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

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ESR1 Mutations in Breast Cancer

Trial	Study Treatment	Patient Population	Patients (n study/ total N on trial)	ESR1 Mutation Frequency
MONALEESA-2[1]	Letrozole +/- Ribociclib	1st line ER+ MBC	494/668	4.0%
BOLERO-2[2]	Exemestane +/- Everolimus	ER+ MBC after PD on ET	541/724	28.8%
FERGI[3]	Fulvestrant +/- Pictilisib	ER+ MBC after PD on ET	153/168	40.0%
PALOMA-3[4]	Fulvestrant +/- Palbociclib	ER+ MBC after PD on ET	195/521	25.3%

1. Hortobagyi GN,et al. *Ann Oncol*. 2018;29:1541-1547. 2. Chandarlapaty S, et al. *JAMA Oncol*. 2016;2:1310-1315.
3. Spoerke JM, et al. *Nat Commun*. 2016;7:11579. 4. Fribbens C, et al. *J Clin Oncol*. 2016;34:2961-2968.

**Pictilisib is not FDA-approved.*

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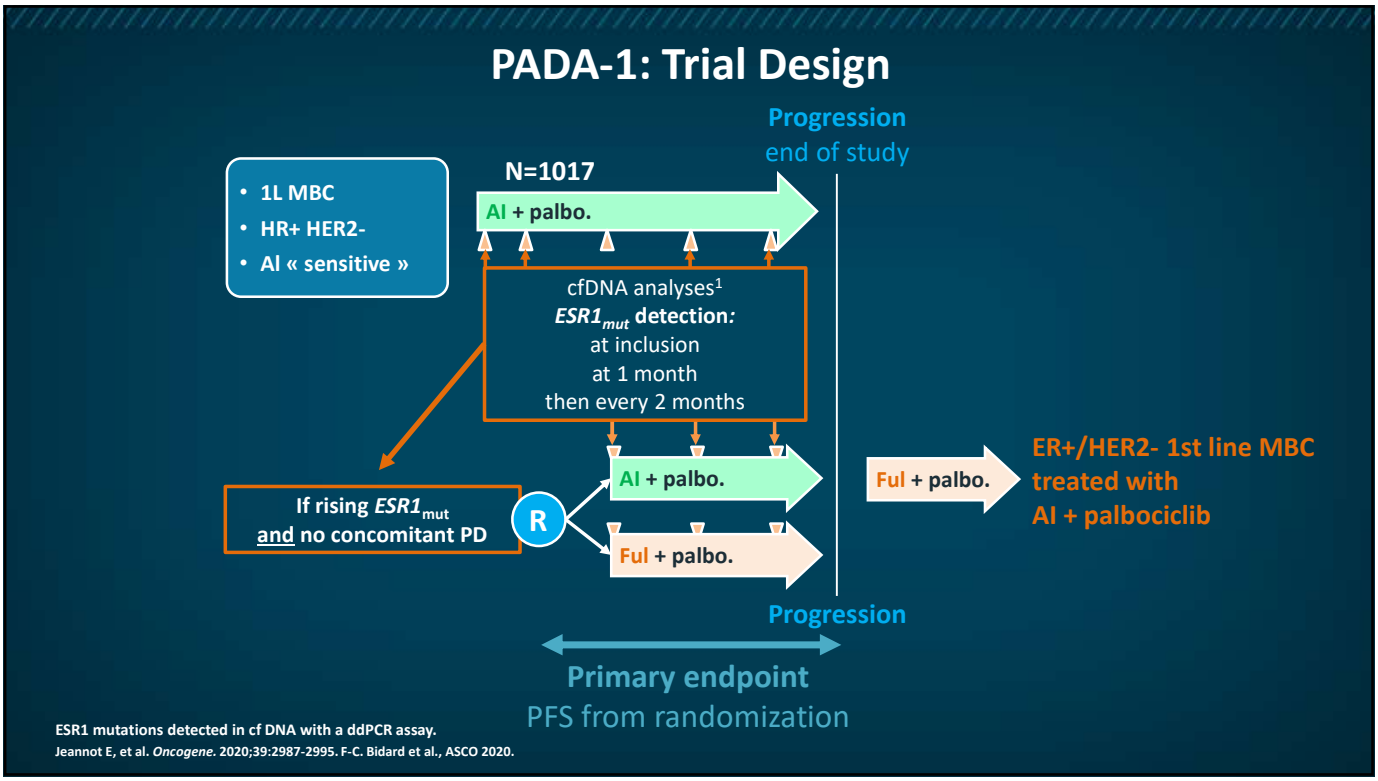
PADA-1: Trial Design



ESR1 mutations detected in cf DNA with a ddPCR assay.

Jeannot E, et al. *Oncogene.* 2020;39:2987-2995. F-C. Bidard et al., ASCO 2020.

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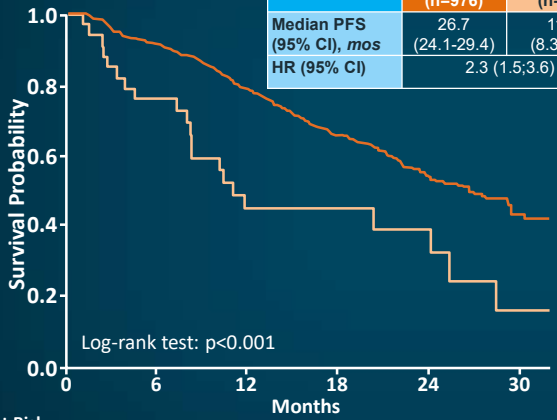
PADA-1: ESR1 is a Poor Prognosticator...but

Progression-free Survival

	ESR1 WT (n=976)	ESR1 mut (n=33)
Median PFS (95% CI), *mos*	26.7 (24.1-29.4)	11.0 (8.3-NR)
HR (95% CI)	2.3 (1.5;3.6)	

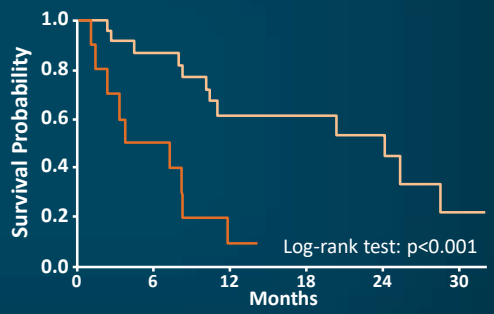


No. at Risk

ESR1 WT	976	877	710	452	179	39
ESR1 mut	33	23	12	9	6	1

Early clearance (MAF <0.1%) **at 4 weeks**

- Observed in 23/33 patients
- Followed by a later "resurgence" of ***ESR1$_{mut}$*** in 15/23 patients (at time of analysis)



Estimated PFS[1] by *ESR1$_{mut}$* status at 1 month:

- *ESR1$_{mut}$* "cleared": median 24.1 mo (10.5-NR)
- *ESR1$_{mut}$* detected: median 7.4 mo [2.5-NR)

Bidard FC, et al. ASCO 2020 (https://meetinglibrary.asco.org/record/185414/abstract).

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CDK4/6 Inhibitors Combined with Fulvestrant

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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*= .01**

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;382:514-524. 6. Sledge GW Jr, et al. *J Clin Oncol*. 2017;35:2875-2884. 7. Sledge GW Jr, et al. *JAMA Oncol*. 2020;6:116-124.

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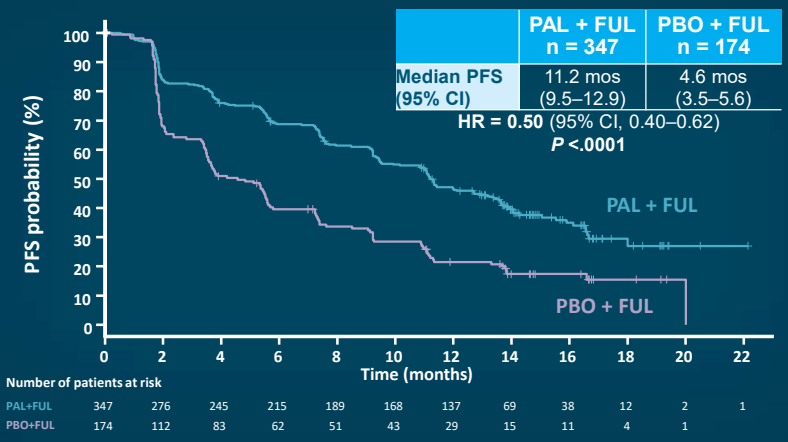
PALOMA-3: FINAL PFS (ITT)
Palbociclib + Fulvestrant



	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.

23

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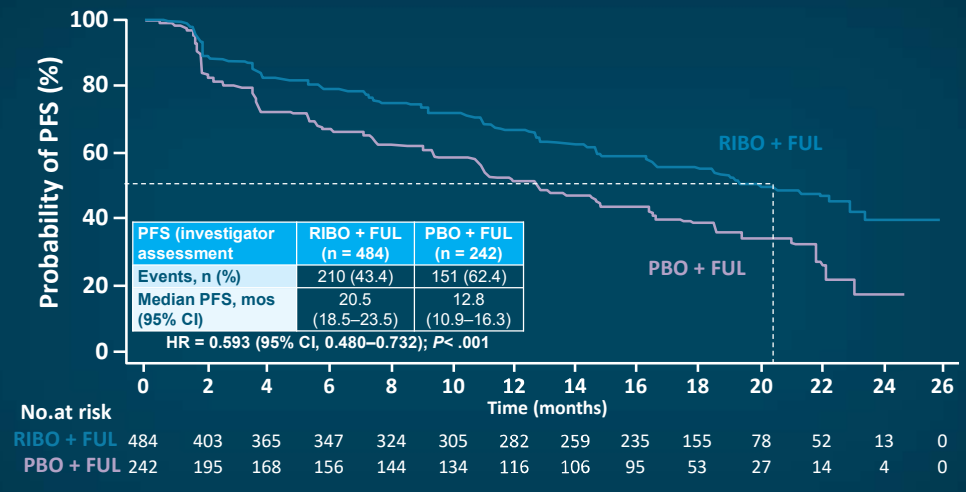
MONALEESA-3: Primary Endpoint PFS (Investigator-Assessed)
Ribociclib + Fulvestrant



PFS (investigator assessment	RIBO + FUL (n = 484)	PBO + FUL (n = 242)
Events, n (%)	210 (43.4)	151 (62.4)
Median PFS, mos (95% CI)	20.5 (18.5–23.5)	12.8 (10.9–16.3)

HR = 0.593 (95% CI, 0.480–0.732); *P*< .001

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.

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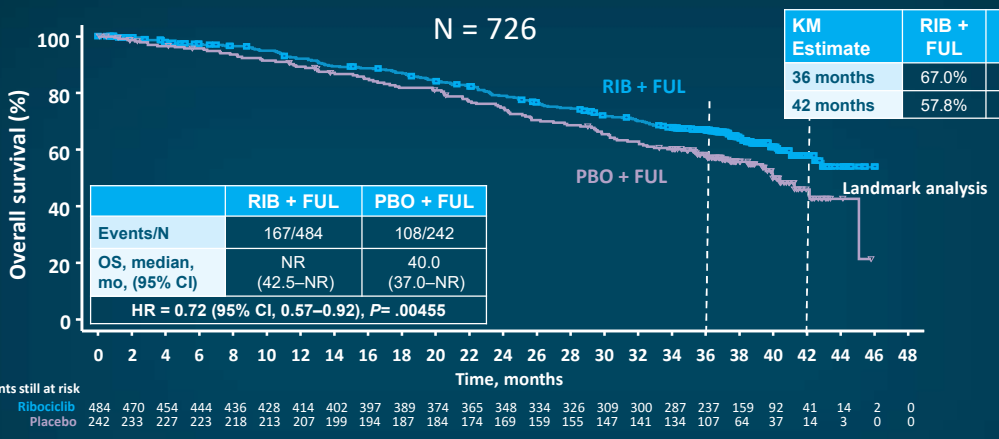
MONALESSA-3: Overall Survival



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.

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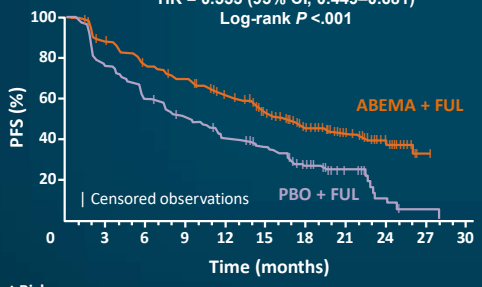
MONARCH-2: Primary Endpoint PFS Abemaciclib + Fulvestrant

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

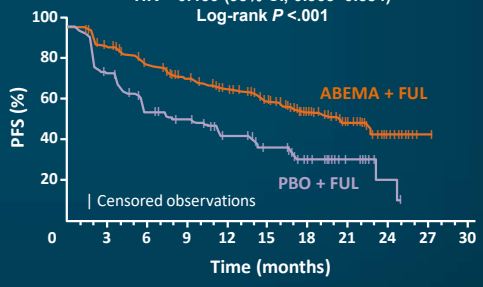
Investigator assessment	ABEMA + FUL (n = 446)	PBO + FUL (n = 223)
Median PFS, mos	16.4	9.3

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



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



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

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.

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But What About When You Combine With CDK4/6i for 1st Line MBC?

Key inclusion criteria:

1. ER[+]/HER2[-] MBC
2. No prior therapy for advanced disease
3. Postmenopausal or premenopausal*
4. Endocrine sensitive criteria:
   - Relapse >12 mo. from end of endocrine therapy, or
   - "de novo" metastatic

Stratification factors:

- Visceral involvement (N/Y)
- "de novo" /recurrent

N=486

Randomization (1:1)

Fulvestrant
500 mg IM, on Days 1, 14 & monthly thereafter
+ Palbociclib
125 mg PO, once daily, 3 weeks on, 1 week off

Letrozole
2.5 mg PO, once daily, continuously
+ Palbociclib
125 mg PO, once daily, 3 weeks on, 1 week off

Treatment until progressive disease per investigator

or

intolerable toxicity

PARSIFAL: Fulvestrant or Letrozole in combination with Palbociclib

Prior Therapies

Characteristics	All Patients (N=486)	Fulvestrant + Palbociclib (N=243)	Letrozole + Palbociclib (N=243)
Prior therapies in EBC, n (%)			
Chemotherapy			
Neoadjuvant	46 (9.5)	25 (10.3)	21 (8.6)
Adjuvant	144 (29.6)	73 (30)	71 (29.2)
Endocrine therapy			
Tamoxifen	177 (36.4)	87 (35.8)	90 (37.0)
Aromatase inhibitors	117 (24.1)	65 (26.7)	52 (21.4)
Both	70 (14.4)	39 (16.0)	31 (12.8)

* If premenopausal, ovarian suppression was required.

Llombart-Cussac A, et al. *J Clin Oncol.* 2020;38:15(suppl 15):1007.

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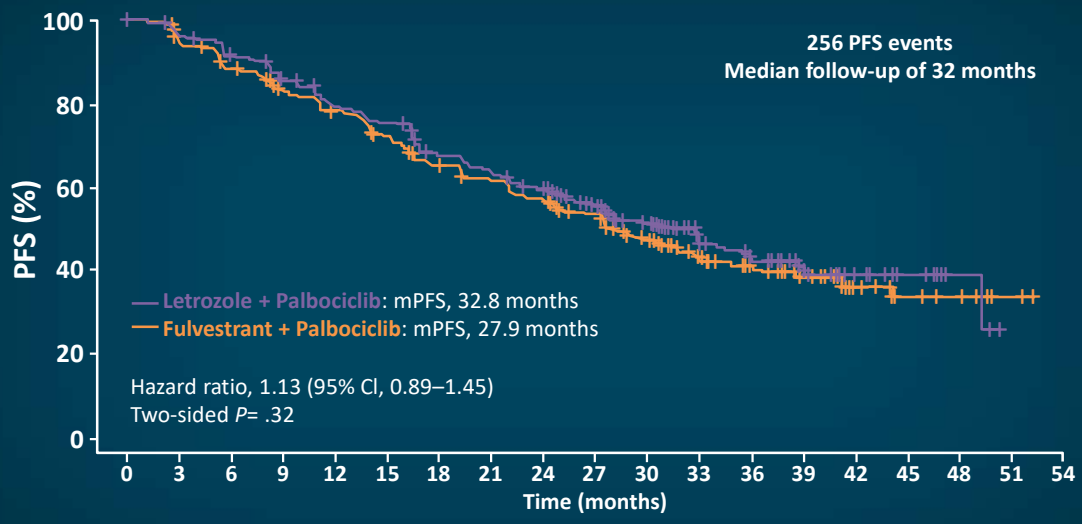
PARSIFAL: PFS ITT Analysis



Fulvestrant/palbociclib > letrozole/palbociclib

Llombart-Cussac A, et al. *J Clin Oncol.* 2020;38(suppl 15):1007. Jhaveri KL. ASCO Daily News. May 2020 (https://dailynews.ascopubs.org/do/10.1200/ADN.20.200189/full/). Accessed August 17, 2020.

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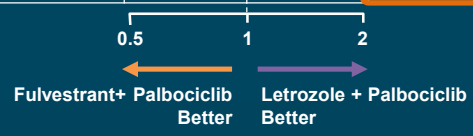
PARSIFAL: Outcomes Based On Prior AI Therapy

Pre-specified subgroup analysis

Subgroup	Fulvestrant+ Palbociclib	Letrozole + Palbociclib	Hazard Ratio (95% CI)	Interaction p-value	Fulvestrant+ Palbociclib	Letrozole + Palbociclib
Prior aromatase inhibitors therapy						
No	178 (73.3)	191 (78.6)	1.21 (0.90-1.61)	0.2409	28.9	32.8
Yes	65 (26.7)	52 (21.4)	0.86 (0.54-1.39)		27.5	19.3



Llombart-Cussac A, et al. *J Clin Oncol.* 2020;38(suppl 15):1007

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Abemaciclib

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nextMONARCH 1: Endpoint Analysis

Investigator-Assessed

Randomized, open-label, phase 2 study of safety and efficacy of ABEMA ± TAM or ABEMA monotherapy in women (n = 234) with previously treated HR+/HER2– *metastatic* breast cancer

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	0.551-1.177	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

NCT02747004 (nextMONARCH1). Hamilton E, et al. SABCS 2018: poster PD1-11.

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CDK 4/6 Inhibitors vs Chemotherapy

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PEARL: Study Objectives

Randomized phase 3 study of safety and efficacy of PAL + EXE *or* FUL vs CAPE in postmenopausal women (n = 601) with previously treated HR+/HER2– *metastatic* breast cancer

- 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).

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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.

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Monitoring and Managing Toxicities associated with CDK 4/6 Inhibition

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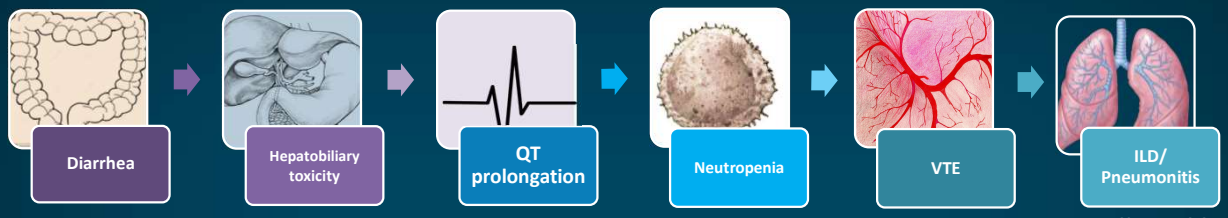
Adverse Events for CDK4/6 Inhibitors



Diarrhea	Hepatobiliary toxicity	QT prolongation	Neutropenia	VTE	ILD/ Pneumonitis
Abemaciclib Palbociclib Ribociclib	Abemaciclib Ribociclib	Ribociclib	Palbociclib Ribociclib Abemaciclib	Abemaciclib	Palbociclib Ribociclib Abemaciclib
Antidiarrheal therapy Increase oral hydration Notify HCP	LFTs before initial cycle, Q2 weeks x 2 cycles, then at start of cycle x 4 cycles (RIBO) or Qmonth x 2 months (ABEMA)	EKG before initial cycle, repeat at Day 14 of cycle 1 and start of cycle 2. Electrolytes before initial cycle, then at start of each cycle x 6 cycles	CBC before initial cycle, Q2 weeks x 2 cycles/months (ABEMA) or at start of each cycle x 6 (RIBO)	Monitor for signs and symptoms of thrombosis or pulmonary embolism	Monitor regularly for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)

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

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

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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. Ibrance [package insert]. New York, NY: Pfizer Inc; 2019.

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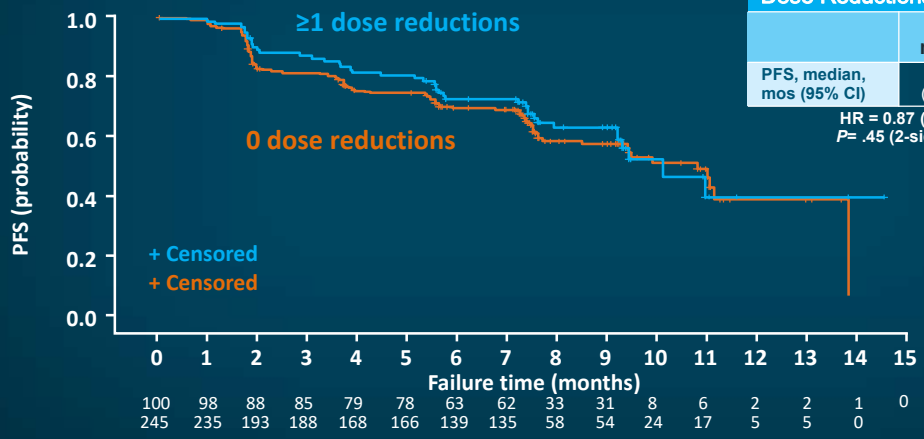
PALOMA-3: Effect on PFS of Dose Reductions Due to Neutropenia

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 log-rank test)

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

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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	35.0	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.

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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.

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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®).

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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.

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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

Ibrance [package insert]. New York, NY: Pfizer Inc; 2019.

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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®).

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Multidisciplinary Team Tools

Optimizing Care and Adverse event Management

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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).

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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).

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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.

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Oncology Nurses in Decision Making Processes

- ONS has a tool kit for Nurses to help with oral therapy monitoring and adherence
- Information and training available in the areas of :
  - Education such as drug-drug and food-drug interactions
  - Management of adverse effects
  - Lab monitoring
  - Pharmacy and reimbursement
  - Financial assistance programs and resources
  - Methods of Monitoring of adherence
  - Motivational interviewing and counseling

Ref: Adherence to Oral Therapies for Cancer: Helping Your Patients Stay on Course Toolkit by ONS

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Patient Education

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

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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	
Second solid tumors	Bowel and bladder dysfunction
Myelodysplasia and acute myelogenous leukemia	Sexual dysfunction
Cardiovascular disease and accelerated atherosclerosis	Pain syndromes
Lung disease	Lymphedema
Osteoporosis	Economic hardship
Hypothyroidism, other endocrinopathies, and metabolic syndrome	Psychosocial problems, including anxiety, depression, posttraumatic stress disorder, suicide

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

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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.

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Case Study 1 – Question 1

- Sandra is a 74 yo retired special needs teacher, initially diagnosed with early stage left breast cancer 8 years ago, with a 2 cm mass in the left breast. She underwent left sided lumpectomy with no evidence of nodal involvement. Oncotype Dx assay showed a low risk of recurrence and she did not receive adjuvant chemotherapy, but was treated with radiation and endocrine therapy with anastrozole for 5 years.
- She remained without any disease for close to 3 years when she presented with left hip pain. Further work up led to diagnosis of metastatic breast cancer with bone only involvement, ER PR positive and HER2neu is negative.
- Comorbid conditions include hypertension, intermittent diarrhea, atrial fibrillation controlled with amiodarone and diabetes.
- What are her options of therapy?
  a) Fulvestrant
  b) Letrozole with palbociclib
  c) Letrozole with ribociclib
  d) Letrozole with abemaciclib
  e) Chemotherapy
  f) Fulvestrant with alpelisib
  g) Exemestane and everolimus

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Case Study 1 – Question 2

- Sandra received first line therapy with letrozole for ER/PR +, HER2-negative metastatic breast cancer for 28 months. Follow up CT chest, abdomen and pelvis showed new and multiple lung nodules, solitary liver lesion and mediastinal adenopathy. No brain lesions noted on MR Brain. She remains asymptomatic and does her routine activities. Upon starting her next line of treatment with abemaciclib + fulvestrant, she reports watery, non-bloody stools of 6/day, which she attributes to her history of intermittent diarrhea.
- What do you recommend as the next line of treatment?
  a) Start anti-diarrheal agent
  b) Encourage oral hydration
  c) Triage for symptoms that would prompt emergency evaluation (dizziness, palpitations, etc)
  d) B and C
  e) All of the above

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Case Study 2 – Question 1

- Sonia is a nurse practitioner who at age 40 was diagnosed with Stage II Right Breast Invasive Ductal Carcinoma, when she presented with palpable right breast mass. She was initially treated with lumpectomy and sentinel node biopsy, which was negative for germline BRCA mutation, PT2, N1, M0, Gr II, ER/PR positive, Her2neu negative. She received adjuvant chemotherapy, radiation to the right breast and nodal areas, and endocrine therapy with tamoxifen for 5 years.
- 10 years from her diagnosis, she developed right hip pain and was diagnosed with solitary bone metastasis after biopsy confirmation. Being post menopausal, she was placed on letrozole monotherapy after radiation to that site, which she took for 18 months.
- Increasing cough led to imaging studies which showed multiple lung nodules and adenopathy, numerous sclerotic osseous lesions and confirmed progression of metastatic disease.
- What is the next step in treatment?
  a) Fulvestrant with Abemaciclib
  b) Fulvestrant
  c) Fulvestrant with Palbociclib
  d) Capecitabine
  e) Fulvestrant with Alpelesib if *PIK3CA* mutation is present

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Case Study 2 – Question 2

- On follow-up from cycle 3 of treatment with CDK4/6i + fulvestrant, she presents with fatigue, chills, and urinary frequency. She is afebrile with a temperature of 96.2F in the clinic, is slightly tachycardic at 110 bpm with a regular rhythm.
- What is the next step in assessment?

  a) Obtain sputum cultures
  b) Check CBC with ANC
  c) Obtain EKG
  d) Check LFTs

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Summary: CDK4/6 Inhibitors in ER+ mBC

- The **three CDK4/6 inhibitors seem to be consistent and comparable in prolonging PFS *in combination with ET in the metastatic setting***, with acceptable toxicity
- CDK4/6 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; based on side effect profiles, most patients in US are receiving CDK4/6i + AI
- **Abemaciclib** and **ribociclib** in ***combination with endocrine therapy*** have demonstrated **significant improvements in OS**
- Looking into the future: a *biomarker driven* approach?
- 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

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Thank You

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