Evolving Oral Cancer Therapies - Focus on Crowded Spaces

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Disclosure Statement

- I confirm that I have no relevant financial relationship(s) with ineligible companies to disclose.

and

- None of the planners for this activity have relevant financial relationships with ineligible companies to disclose.

Learning Objectives

At the completion of this activity, the participant will be able to:

1. Explain the rationale behind the use of small molecule, kinase-inhibitors across cancer treatment
2. Discuss the National Comprehensive Cancer Network (NCCN) recommendations for use of CDK4/6 inhibitors in the treatment paradigm of patients with advanced or metastatic breast cancer;
   a) Differentiate between sub-populations that were evaluated in each of the hallmark trials of these agents in metastatic breast cancer;
   b) Recognize the difference in pharmacokinetics, toxicity profiles of these agents, and
   c) Apply, based on evidence presented, a patient-tailored approach to the use of these agents.

Overview of Small Molecules (Kinase Inhibitors) Used in Cancer Treatment

Background

- *Kinases* are enzymes that, by transferring a phosphate group from ATP to a substrate, play an integral role in cell metabolism, cell-cycle regulation, differentiation, and survival.[1]
- As of the date of the referenced publication, there were 72 FDA-approved therapeutic agents that target these enzymes, of which, 69 are oral agents.[2]
- Many of the newer agents are coming in to spaces that already have approved agents
  - As therapeutic spaces become more crowded, it is important as pharmacists to be able to differentiate the data

References:
1) Naik RR, et al. Front. Pharmacol. 2023; 13:1064472. 2) Roskoski R Jr. *Pharmacol Res*. 2023 Jan;187:106552.

Examples of Crowded Spaces . . . Not by any means all-inclusive

Chronic Lymphocytic Leukemias

Target kinase: BTK

- Ibrutinib
- Acalabrutinib
- Zanubrutinib

Breast Cancer

Target kinase: CDK4/6

- Palbociclib
- Abemaciclib
- Ribociclib

Renal Cell Cancer

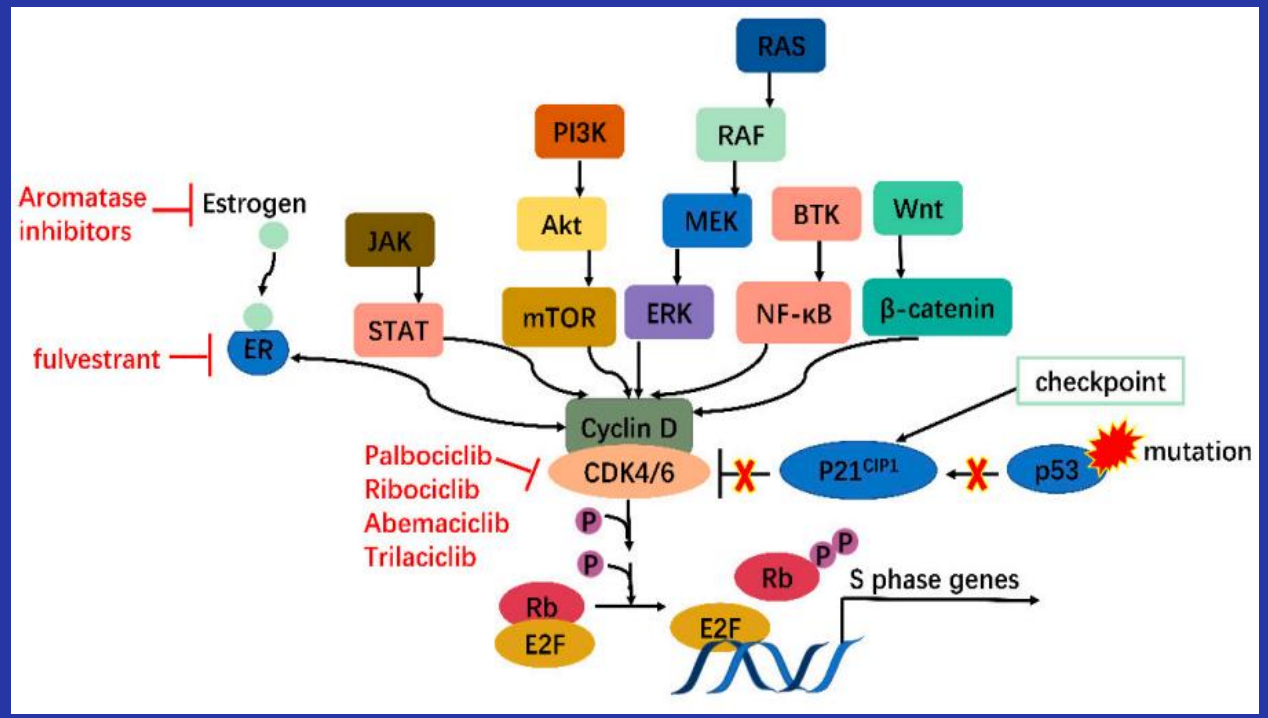
Target kinase: VEGF (and others)

- Axitinib
- Pazopanib
- Sunitinib
- Cabozantinib
- Lenvatinib
- Sorafenib

References:
Roskoski R Jr. *Pharmacol Res*. 2023 Jan;187:106552.

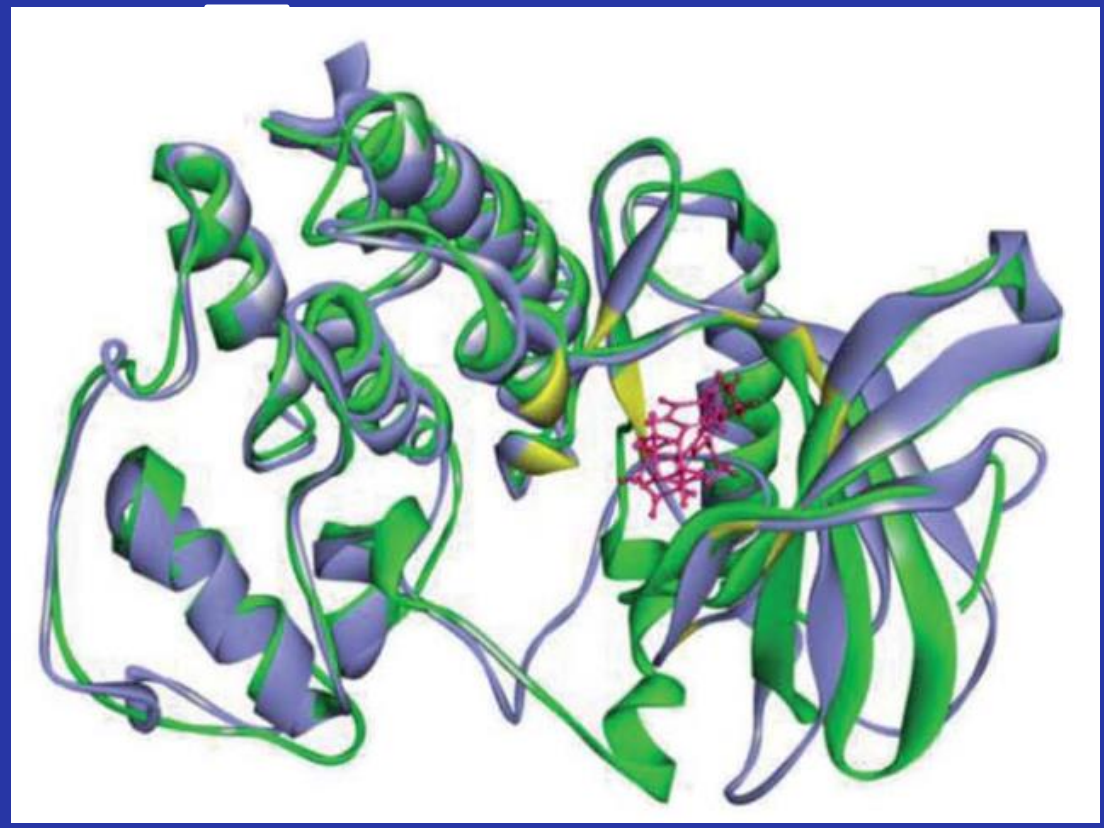
Virtual vs Actual Reality

Virtual



Reference: Qi J, et al. *Biomedicines*. 2022 Mar 16;10(3):685.

Reality



Reference: Adon T, et al. *RSC Adv.,* 2021, 11, 29227

Focus on the CDK 4/6 Inhibitors in the Treatment of Metastatic Breast Cancer

CKD 4/6 Inhibitors in the Treatment of Breast Cancer

- There are currently three different CDK 4/6 inhibitors in the "same space" for treating advanced or metastatic breast cancer (mBC):
  - Ribociclib (Kisquali)
  - Abemaciclib (Verzenio)
  - Palbociclib (Ibrance)

The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer looks at these agents in parity.[1]

- However, at the end of a patient-physician interaction, one is ultimately chosen.

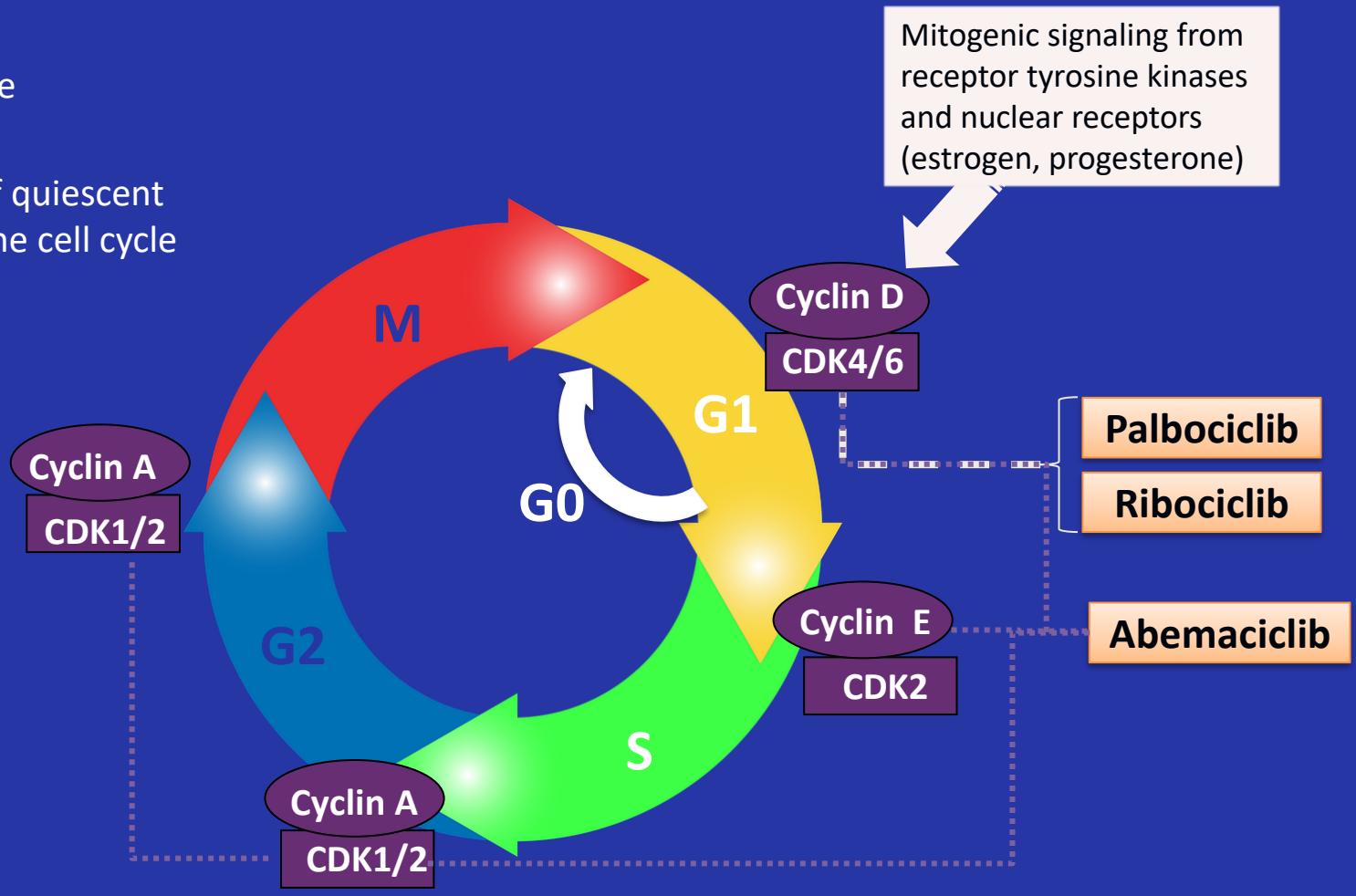
1. NCCN clinical practice guidelines in oncology: Breast Cancer. v.4.2022. nccn.org.

Similarities and Differences Between the Three CDK4/6 Inhibitors

1. Cyclins and CDKs (serine/threonine kinases) regulate progression through the phases of the cell[1]
2. Signaling from ER/PR receptors drive progression of quiescent cells from G0 or G1 into the S phase, and through the cell cycle through the CDK4 or CDK6 complex[1]

<u>DIFFERENCES[1]</u>

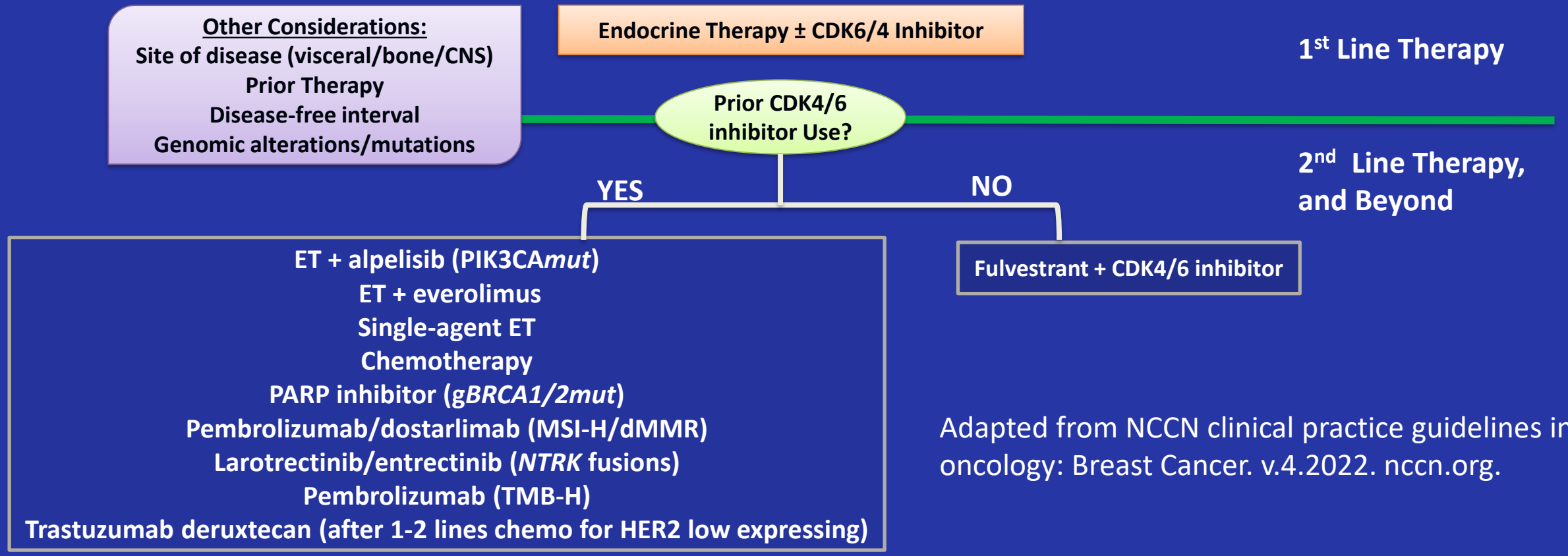
- Ribociclib and palbociclib are more lipophilic than abemaciclib
- Palbociclib has equal affinity for CDK4 and CDK6; while abemaciclib and ribociclib have greater potency for CDK4 than for CDK6
- Abemaciclib has in-vivo inhibition of a broader array of CDKs



Key: ER/PR – Estrogen Receptor / Progesterone Receptor; MOA – mechanism of action

1. George MA, et al. Front. Oncol. 2021; 11:693104. doi: 10.3389/fonc.2021.693104

Treatment Pathway for HR+/HER2- Metastatic Breast Cancer



Adapted from NCCN clinical practice guidelines in oncology: Breast Cancer. v.4.2022. nccn.org.

Key: BRCA - BReast CAncer gene; CNS – central nervous system; dMMR - mismatch repair deficient; ET - endocrine therapy; HR – hormone receptor; HER2 - human epidermal growth factor receptor 2; MSI-H, microsatellite instability–high; mut – mutated; NTRK - Neurotrophic tyrosine receptor kinase; PARP - Poly (ADP-ribose) polymerase; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TMB-H, tumor mutational burden–high.

NCCN Endorses Parity in Metastatic Breast Cancer Between All Current CDK4/6 Inhibitors

CDK 4/6 Inhibitor		IBRANCE (Palbociclib)[2]	KISQALI (Ribociclib)[3]	VERZENIO (Abemaciclib)[4]
NCCN Compendia[1]	**1st or 2nd Line in combination with additional hormonal agent**	Advanced/Metastatic Breast Cancer, HR+, HER2- without visceral crisis post- and pre-menopausal (with ovarian suppression/ablation) **(ALL CATEGORY 1)** • 1st line with fulvestrant (preferred regimen) • 1st line with an aromatase inhibitor (preferred regimen) • 2nd + line with fulvestrant (preferred regimen) if CDK4/6 inhibitor not previously used		
	Monotherapy in 2nd+ line, post endocrine therapy *and* chemotherapy	N/A	N/A	Recurrent, unresectable, metastatic breast cancer, HR+, HER2-, non- or asymptomatic-visceral disease **(CATEGORY 2A)**
FDA approval **THIS IS WHAT PHARMACY- BENEFITS ADMINISTRATORS USE FOR AUTHORIZATION**		Advanced/Metastatic Breast Cancer HR+, HER2- • 1st line in combination with an AI as initial endocrine therapy in postmenopausal women (or men) • In combination with fulvestrant in patients with disease progression following endocrine therapy	Advanced/Metastatic Breast Cancer HR+, HER2- • 1st line in combination with an AI • In combination with fulvestrant as initial endocrine therapy or following disease progression on endocrine therapy in postmenopausal women or in men.	Advanced/Metastatic Breast Cancer HR+, HER2- • 1st line in combination with an AI as initial endocrine therapy in postmenopausal women (or men) • In combination with fulvestrant in patients with disease progression following endocrine therapy • Monotherapy following disease progression on endocrine and chemo

Key: FDA – Food and Drug Administration; HR – hormone receptor; HER2 - human epidermal growth factor receptor 2; NCCN - National Comprehensive Cancer Network

References: 1. National Comprehensive Cancer Network (NCCN) Breast Cancer Guidelines v4.2022.; 2. IBRANCE Package Insert. Pfizer, NY, NY 11/2019; 3. KISQUALI Package Insert. Novartis, East Hanover, NJ. 12/2021; 4. VERZENIO Package Insert. Lilly USA, Indianapolis, IN. 10/2021

CDK 4/6 Inhibitors in HR(+) HER2(-)

Early Breast Cancer

CDK 4/6 Inhibitor	IBRANCE Palbociclib	KISQALI Ribociclib	VERZENIO Abemaciclib

NCCN Compendia
 	
(Based on the patient population within the registrational trials)[1,2]
	N/A	N/A	Adjuvant in combination with endocrine therapy in high risk, defined as:
			• ≥ 4 lymph nodes
			<OR>
			• 1-3 lymph nodes + one of the following:
			  • Grade 3 disease
			  • Tumor ≥ 5 cm
			  • Ki-67 score ≥ 20%

FDA approval **THIS IS WHAT PHARMACY-BENEFITS ADMINISTRATORS USE FOR AUTHORIZATION**	N/A	N/A	Adjuvant in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment hormone receptor (+), HER2 (-), node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% This was recently revised as of March 3, 2023: The FDA-approved label expansion removed the Ki-67 score requirement

Brief side-bar on Adjuvant Treatment

Key: FDA – Food and Drug Administration; HR – hormone receptor; mBC – metastatic breast cancer; NCCN - National Comprehensive Cancer Network

References: 1. Johnson. *J Clin Oncol*. 2020 ;38 :34 : 3987-3997. (monarchE trial); 2. Harbeck. *Ann Oncol.* 2021 ;32 : 1571-1581. (monarchE update Ki-67 analysis)

Trial Data, To Date, First-Line Setting

Variable	PALOMA-2[1-3] (N = 666)	MONARCH-3[4] (N = 493)	MONALEESA-2[5,6] (N = 668)	MONALEESA-7[7,8] (N = 672)
Patient population	postmenopausal women with ER+/HER2- advanced breast cancer	postmenopausal women with ER+/HER2- advanced breast cancer	postmenopausal women with ER+/HER2- advanced breast cancer	**Pre/peri-menopausal** women with ER+/HER2- advanced breast cancer
ET therapy partner	Letrozole	Letrozole	Letrozole	Letrozole, anastrozole, or tamoxifen + LHRH agonist
CDK4/6 inhibitor	Palbociclib	Abemaciclib	Ribociclib	Ribociclib
Median PFS, CDK4/6 inhibitor + ET vs ET, months	27.6 vs 14.5	28.2 vs 14.8	25.3 vs 16.0	23.8 vs 13.0
Hazard ratio	0.58 (p<0.001)	0.54 (p<0.001)	0.57 (p<0.001)	0.55 (p<0.001)
Median OS, CDK4/6 inhibitor + ET vs ET, months	53.9 vs 51.2	67.1 vs 54.5[9]	63.9 vs 51.4	58.7 vs 48.0
Hazard ratio	0.956	0.75[ǂ]	**0.76***	**0.76***

[ǂ]Statistical Significance not yet reached; *Significant

Key: ER – estrogen receptor; ET - endocrine therapy; LHRH – luteinizing hormone releasing hormone; NR - not reached; OS - overall survival; PFS - progression-free survival;

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Finn. ASCO 2022. Abstr LBA1003. 4. Goetz. JCO. 2017;35:3638; 5. Hortobagyi. NEJM. 2016;375:1738; 6. Hortobagyi. NEJM. 2022;386:942. 7. Tripathy. Lancet Oncol. 2018;19:904. 8. Lu. Clin Cancer Res. 2022;28:851. 9. Goetz MP, et al. Abstract LBA15. Presented at: European Society for Medical Oncology Congress; Sept. 9-13, 2022

Potential Rational for Reported OS Differences

Randomized Phase III Trials	PALOMA-2 Palbociclib[1]	MONALEESA-2 Ribociclib[2]	MONALEESA-7 Ribociclib[3]
De novo MBC	38%	34%	41%
Disease-free interval prior to randomization			
≤ 12 months	**22%**	1%	7%
>12 months	40%	NR	53%
>24 months	NR	60%	NR

PALOMA-1: **33%**

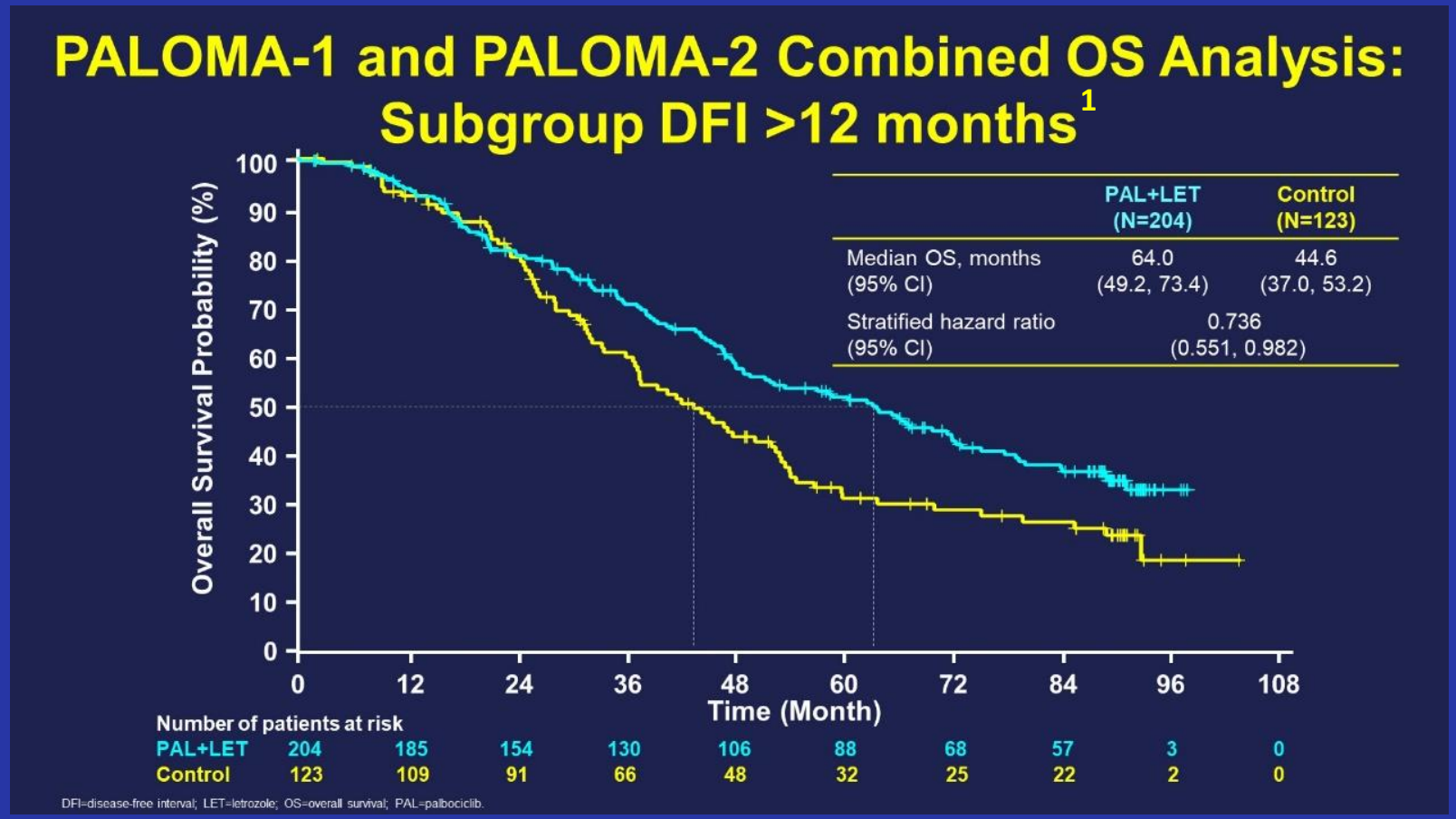
No *other* substantial differences in:

- prior therapy,
- visceral disease,
- subsequent CDK4/6 inhibitor use (ie, subsequent therapy) in placebo arm (~1/3 of patients across trials)
- other variables

- PALOMA-1 trial was the "precursor", Phase 2, open-label trial of palbociclib plus letrozole vs letrozole alone (N=165 post menopausal women with HR+/HER2- mBC).[4]
  - Palbociclib plus letrozole significantly prolonged PFS vs letrozole alone HR: 0.488; 95% CI: 0.319, 0.748; *P* = 0.0004; median PFS, 20.2 vs 10.2 months, respectively), but failed in the general population to show an OS advantage.[4]

1. Finn. NEJM. 2016;375:1925. 2. Hortobagyi. NEJM. 2016;375:1738. 3. Tripathy. Lancet Oncol. 2018;19:904. 4. Finn. Breast Cancer Research and Treatment . 2020; 183:419–428

Palbociclib Survival Results in the Subgroup of Patients with a Prolonged Disease-Free Interval



Ribociclib Reported Survival:

Variable	MONALEESA-2[2,3] (N = 668)	MONALEESA-7[4,5] (N = 672)
Median OS, Ribociclib + ET vs ET, months	63.9 vs 51.4	58.7 vs 48.0
Hazard ratio	0.76*	0.76*

*Significant

1. Finn. [ORAL PRESENTATION] ASCO 2022. Abstract LBA1003. 2. Hortobagyi. NEJM. 2016;375:1738; 3. Hortobagyi. NEJM. 2022;386:942. 4. Tripathy. Lancet Oncol. 2018;19:904. 5. Lu. Clin Cancer Res. 2022;28:851.

So ***IS*** There an Efficacy Difference, Overall? Summary:

- Unable to definitively say with current overall survival data[1-4]
  - Paloma-1 and Paloma-2 had higher proportions of patients with more “aggressive” disease (defined by a disease-free interval of ≤12 months from last line of therapy)
  - For trials of both drugs (ribociclib and palbociclib), overall survival was a secondary endpoint
    - Paloma-2 had “missing survival data” in 13% of the palbociclib/letrozole group and in 21% of the placebo/letrozole group, and not well-defined as to why
- The overall survival results with abemaciclib (Monarch-3) were *just* reported; however, the proportion with a disease-free interval of ≤12 months has not been reported[5]

1. Finn. NEJM. 2016;375:1925. 2. Hortobagyi. NEJM. 2016;375:1738. 3. Tripathy. Lancet Oncol. 2018;19:904. 4. Finn. [ORAL PRESENTATION] ASCO 2022. Abstract LBA1003. 5. Goetz. JCO. 2017;35:3638;

Bottom Line on Survival:

- When you exclude the “more aggressive disease” patients from the palbociclib trials, overall survival benefit appears comparable to what is seen in both ribociclib trials.
- Further those with more aggressive disease probably will have a shorter PFS (and OS) regardless of CDK 4/6 agent chosen.
- Currently, abemaciclib and ribociclib are the only agents with proven overall survival benefit in an intent-to-treat population.

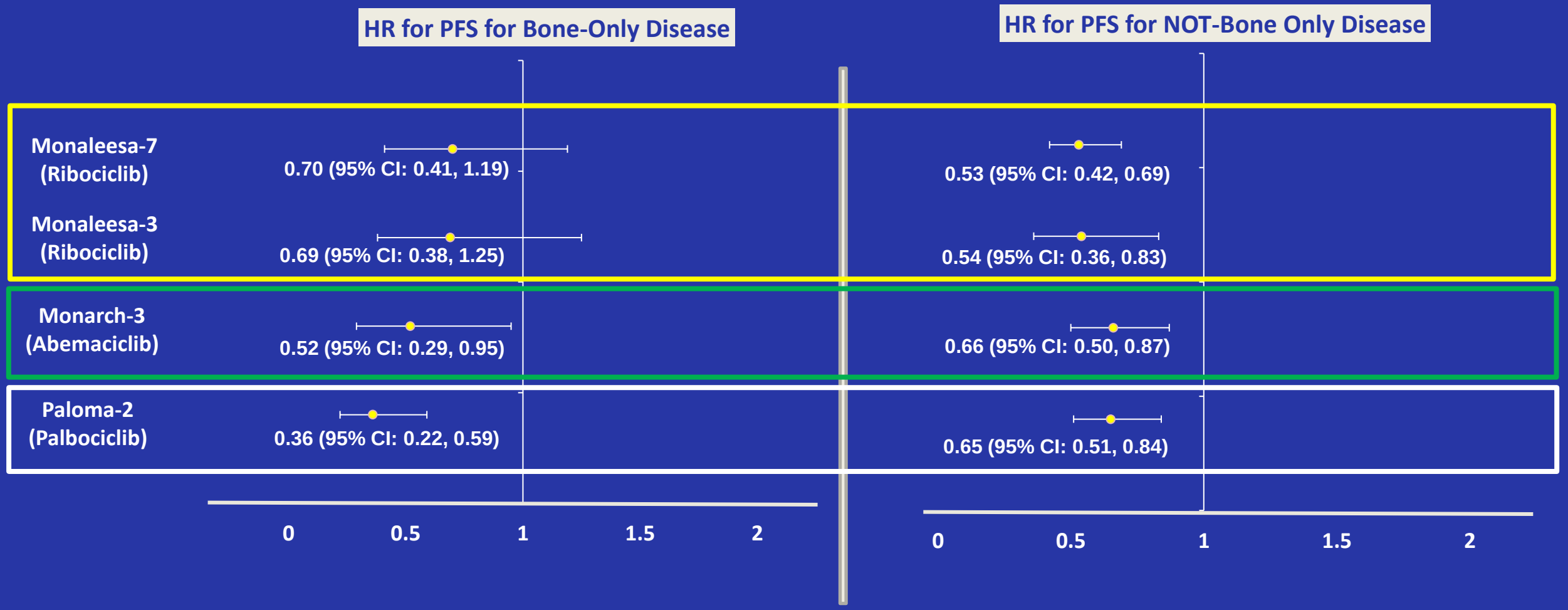
1. Finn. NEJM. 2016;375:1925. 2. Hortobagyi. NEJM. 2016;375:1738. 3. Tripathy. Lancet Oncol. 2018;19:904. 4. Finn. [ORAL PRESENTATION] ASCO 2022. Abstract LBA1003. 5. Goetz. JCO. 2017;35:3638;

Bone Only vs Visceral Disease

Variable	PALOMA-2[1-3] (N = 666)	MONARCH-3[4] (N = 493)	MONALEESA-2[5,6] (N = 668)	MONALEESA-7[7,8] (N = 672)
CDK4/6 inhibitor	Palbociclib	Abemaciclib	Ribociclib	Ribociclib
Site of Metastases, Study arm vs placebo, %				
Bone Any Only	 Not reported 23.2 vs 21.6	 Not reported 21.3 vs 23.6	 73.7 vs 73.1 20.7 vs 23.4	 75 vs 73 24 vs 23
Visceral	48.2 vs 49.5	52.4 vs 53.9	59.0 vs 58.8	58 vs 56
Non-Visceral	51.8 vs 50.5	Not reported	Not reported	Not reported
Lymph Nodes	Not reported	Not reported	39.8 vs 36.8	42 vs 47
Other	Not reported	26.2 vs 22.4	10.5 vs 6.6	2 vs 2 (skin)

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Finn. ASCO 2022. Abstr LBA1003. 4. Goetz. JCO. 2017;35:3638; 5. Hortobagyi. NEJM. 2016;375:1738; 6. Hortobagyi. NEJM. 2022;386:942. 7. Tripathy. Lancet Oncol. 2018;19:904. 8. Lu. Clin Cancer Res. 2022;28:851.

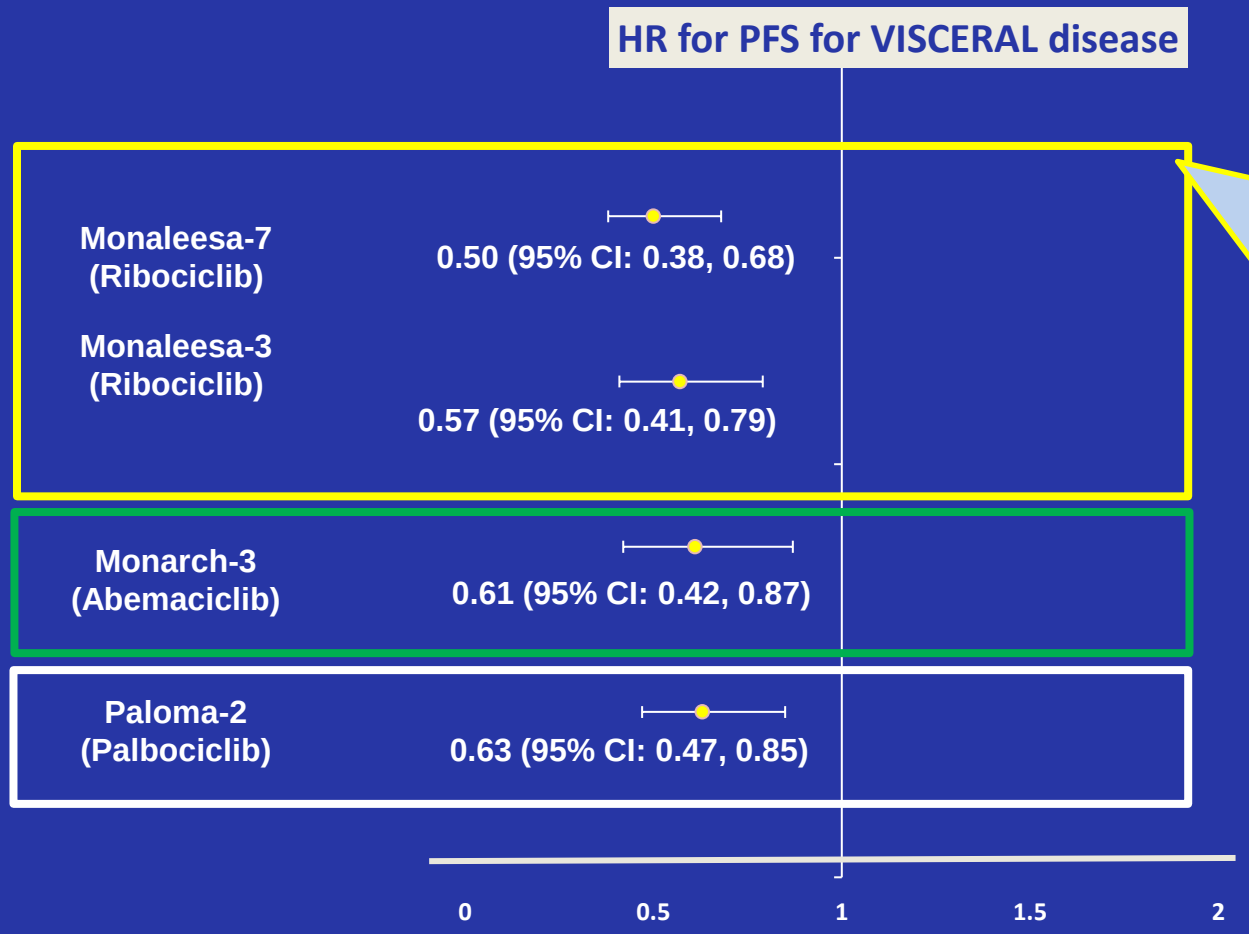
PFS Based on Bone-Only Metastases vs Not



Key: HR – hazard ratio; PFS – progression-free survival

1. Finn. NEJM. 2016;375:1925. 2. Goetz. JCO. 2017;35:3638; 3. Hortobagyi. NEJM. 2016;375:1738; 4. Tripathy. Lancet Oncol. 2018;19:904.

PFS Based on Visceral Metastases



Additional Updated Data:

Phase 2 RIGHT Choice Trial evaluated Ribociclib plus ET vs Combination Chemotherapy as first-line treatment [5]

Patients had "aggressive disease" defined as:

- symptomatic visceral disease,
- rapid disease progression or impending visceral compromise, or
- markedly symptomatic non-visceral disease.

	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

Key: HR – hazard ratio; PFS – progression-free survival

1. Finn. NEJM. 2016;375:1925. 2. Goetz. JCO. 2017;35:3638; 3. Hortobagyi. NEJM. 2016;375:1738; 4. Tripathy. Lancet Oncol. 2018;19:904. 5. Lu, et al. [ORAL PRESENTATION] SABC. San Antonio, December 6th, 2022.

Central Nervous System Metastases

- In a xenograft model, both palbociclib and abemaciclib were shown to cross the blood-brain-barrier; however, abemaciclib brain levels were reached at lower doses than palbociclib[1]
  - In a Phase 1 study in solid tumor patients, abemaciclib was detected in the cerebrospinal fluid at similar concentrations to what was found in the plasma in patients with glioblastoma[2]
- Finally, in a Phase 2 study of abemaciclib in metastatic breast cancer patients with CNS metastases (HR+/HER2- patients, n=58):[3]
  - Intracranial disease overall response rate: 5.2% (95% CI: 0-10.9%)
  - However, including stable disease, the intracranial disease control rate was 65.5% (95% CI: 53.3-77.7%)
  - Median PFS: 4.9 months (95% CI: 2.9-5.6) – *notably this was in a heavily pretreated population (median # of lines of previous therapy: 3 [range: 1-10], with a median time since initial diagnosis of 7 years [range: 1-18])*
  - *Previous CDK 4/6 inhibitor therapy was not allowed*

1. Raub et al. *Drug Metab Dispos*. 2015 Sep;43(9):1360-71; 2. Patnaik et al. *Cancer Discov* . 2016; 6 (7): 740–753; 3. Tolaney, et al. *Clin Cancer Res.* 2020; 26 (20): 5310–5319.

Unanswered Questions in CNS Disease

- Does abemaciclib (or any CDK 4/6 inhibitor) have activity in patients with CNS metastases that have been previously treated with a CDK 4/6 inhibitor?

- Why is this important specifically for CNS disease?
    - Patients with metastatic, hormone receptor-positive breast cancer tend to present with CNS disease later in their course.

Is Continued CDK 4/6 Inhibition Beneficial After Progression on a CDK 4/6 Inhibitor

Abemaciclib:[1]

- In a case-series report of n=58 patients that had progressed on palbociclib
- Given abemaciclib (24% as monotherapy / 76% in combination with an anti-estrogen agent):
  - 34% of patients (n=20) had early progression of <90 days
  - 36% of patients (n=21) had a treatment duration exceeding 6 months, with a median PFS overall of 5.8 months (95% CI: 3.4, 8.0)

Palbociclib:[2]

- Two on-going trials:
  - NCT03147287 (palbociclib after progression on endocrine therapy + another CDK 4/6 inhibitor)
  - NCT03809988 (palbociclib after progression on palbociclib [switch endocrine therapy])

1. Wander et al. *J Clin Oncol. 2019 37:15_suppl, 1057-1057*; 2. ClinicalTrials.gov

Is Continued CDK 4/6 Inhibition Beneficial After Progression on a CDK 4/6 Inhibitor

Ribociclib (the MAINTAIN trial)[1]

Key Inclusion:
- ER/PR+ and HER2-
- Progression on ET + any CDK 4/6i
- ≤1 line of prior therapy
- Stable brain metastases allowed

R 1:1

N=120

Arm 1
Ribociclib plus switch endocrine therapy

Arm 2
Placebo plus switch endocrine therapy

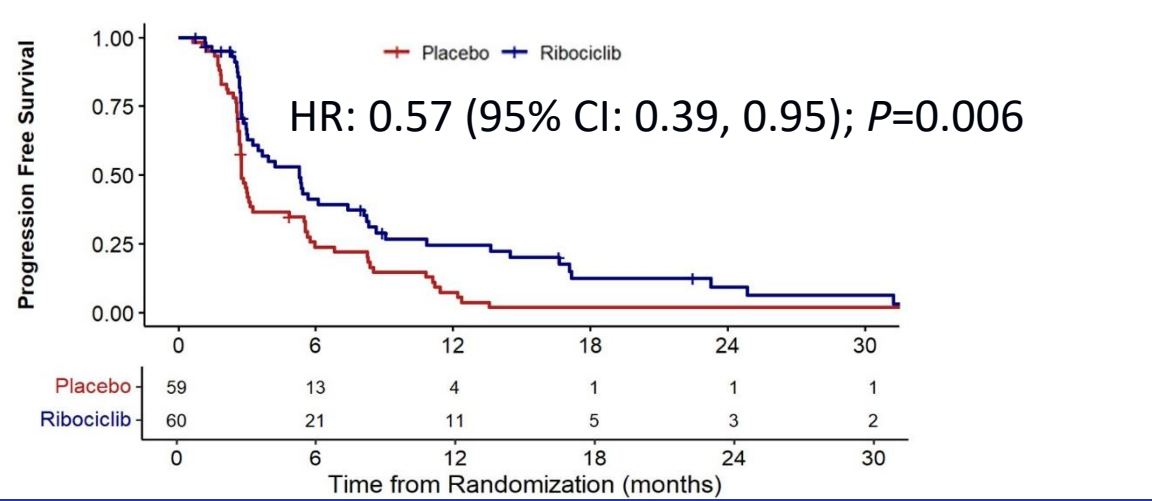
Primary Endpoint: PFS

Variable	Placebo (n=59)	Ribociclib (n=60)
Disease characteristics		
De novo mets at diagnosis	32 (54%)	21 (35%)
Visceral mets	35 (59%)	36 (60%)
Bone-only mets	9 (15%)	13 (22%)
Treatment Characteristics		
Prior chemotherapy for met disease	7 (12%)	4 (7%)
Prior CDK 4/6 inhibitor		
Palbociclib	51 (86%)	52 (87%)
Ribociclib	8 (14%)	6 (10%)
Abemaciclib	0 (0%)	2 (3%)
Prior CDK 4/6 inhibitor duration		
≤12 months	21 (36%)	18 (30%)
>12 months	38 (64%)	42 (70%)

Key: met – metastasis

1. Kalinsky et al. *J Clin Oncol 40, 2022 (suppl 17; abstr LBA1004)*

Ribociclib Post-CDK 4/6i Progression (MAINTAIN trial)[1]



	Placebo + Switch Endocrine Therapy	Ribociclib + Switch Endocrine Therapy
PFS rate at 6 months (95% CI)	23.9% (12.8, 35.0)	41.2% (27.8, 54.6)
PFS rate at 12 months (95% CI)	7.4% (0.4, 14.3)	24.6% (12.5, 36.7)

Subgroup	N	HR (95% CI)
Prior Palbociclib	103	0.58 (0.38, 0.90)
Prior Ribociclib	14	0.50 (0.15, 1.70)
Prior duration of CDK 4/6i ≤12 months	39	0.36 (0.1, 0.74)
Prior duration of CDK 4/6i >12 months	80	0.76 (0.47, 1.24)
Visceral disease present	71	0.49 (0.29, 0.83)
Visceral disease absent	48	0.69 (0.37, 1.29)
Bone-only disease	22	0.54 (0.20, 1.49)
Not Bone-only disease	97	0.58 (0.38, 0.90)

1. Kalinsky et al. *J Clin Oncol 40, 2022 (suppl 17; abstr LBA1004)*

So ***DO*** Sub-Populations Matter? Summary:

- Palbociclib and abemaciclib may be a better options for patients with bone-only disease at initial metastatic presentation based on progression-free survival data
- In terms of PFS, none of the hazard ratios crossed “1” for the subpopulations with visceral disease, with any of the CDK 4/6 inhibitors
- CNS metastases, at presentation, may warrant abemaciclib
  - However, how to treat these post-progression on a previous CDK 4/6 inhibitor is not yet known
- Ribociclib is the only CDK 4/6 inhibitor, to date, with randomized data to support it’s use post progression on a previous CDK 4/6 inhibitor (although not yet approved)

1. Finn. NEJM. 2016;375:1925. 2. Hortobagyi. NEJM. 2016;375:1738. 3. Tripathy. Lancet Oncol. 2018;19:904. 4. Finn. [ORAL PRESENTATION] ASCO 2022. Abstract LBA1003. 5. Goetz. JCO. 2017;35:3638;

PHARMACOLOGIC & AE DIFFERENCES

Pharmacokinetics / Dosing Considerations

		Palbociclib (IBRANCE)	Ribociclib (KISQALI)	Abemaciclib (VERZENIO)
Target		CDK4/6	CDK 4/6	CDK4/6 + 1,2,5,9,4,16-18
Half-life		29 (+/-5) hours	32 hours	18.3 hour
Starting Dose		125 mg daily D1-21 Q28D	600 mg daily D1-21 Q28D	150 mg twice daily (in combination) 200 mg twice daily (monotherapy)
Metabolism		All are Hepatic – CYP3A4 – Drug interactions and dose reductions		
Recommended Dose Adjustments				
Liver dysfunction	Childs-Pugh B	No Adjustment	400 mg dose	No adjustment
	Childs-Pugh C	75 mg dose	400 mg dose	Once daily dosing
Concomitant meds	Strong 3A4 Inhibitor	75 mg dose	400 mg dose	100 mg BID
	Strong 3A4 Inducer	Avoid concomitant use		
Renal dysfunction		No adjustment	200 mg dose for CrCl < 30	No adjustment

George MA, et al. Front. Oncol. 2021; 11:693104. doi: 10.3389/fonc.2021.693104; IBRANCE Package Insert. Pfizer, NY, NY 11/2019; KISQUALI Package Insert. Novartis, East Hanover, NJ. 12/2021; VERZENIO Package Insert. Lilly USA, Indianapolis, IN. 10/2021

Side Effect Profile Differences

Diarrhea	Liver Toxicity	QT Prolongation	Neutropenia	VTE	ILD / Pneumonitis
**Abemaciclib (81-90%; G≥3, 9-20%) Palbociclib (24-26%; G≥3, 1% Ribociclib (29-35%; G ≥3, 1%)	Abemaciclib Ribociclib	**Ribociclib	**Palbociclib (80-83%; G≥3, 66%) **Ribociclib (69-78%; G ≥3, 53-65%) Abemaciclib (37-46%; G≥3, 22-27%)	Abemaciclib	Abemaciclib (RARE) Palbociclib (RARE) Ribociclib (RARE)
MANAGEMENT					
Patient Counseling • Antidiarrheal therapy • Increase oral hydration • When to notify healthcare team	LFTs before starting treatment, Q2W x 2 months, then: • Abemaciclib, Qmonth x 2 months & as indicated • Ribociclib, at start of cycle x 4 cycles & as indicated	ECG before cycle 1, Day 14 of cycle 1, start of cycle 2, then as indicated Electrolytes at start of each cycle x 6 cycles, then as indicated	CBC before starting treatment, then: • Abemaciclib, Q2W x 2 months, qDay 1 x 2, then as indicated • Palbociclib, Days 1 and 15 of cycles 1-2, *qDay 1* • Ribociclib, Q2W x 2 cycles, *qDay 1*	Patient Counseling • Signs / symptoms of VTE or pulmonary thrombosis • When to notify healthcare team	Patient Counseling • Signs / symptoms of ILD/Pneumonitis • hypoxia • cough • dyspnea • When to notify healthcare team

Key: AE - adverse event; CBC - complete blood count; G – Grade; ILD, - interstitial lung disease; LFT, - liver function test; VTE - venous thromboembolism

References: CCO, Clinicaloptions.com; Gillespie, et al. J Adv Pract Oncol 2020;11(1):81–96; IBRANCE Package Insert. Pfizer, NY, NY 11/2019; KISQUALI Package Insert. Novartis, East Hanover, NJ. 12/2021; VERZENIO Package Insert. Lilly USA, Indianapolis, IN. 10/2021; . George MA, et al. Front. Oncol. 2021; 11:693104. doi: 10.3389/fonc.2021.693104

Dose Reductions for Neutropenia – Focus on Palbociclib and Ribociclib[1]

Palbociclib: monitor CBC prior to start of *each* cycle, mid-cycle for the first 2 cycles, and as clinically indicated
Ribociclib: monitor CBC prior to start and mid-cycle for the first 2 cycles, then at the start of each cycle for the next 4 cycles, then as clinically indicated

Grade 3 ANC (<1000 to 500/mm^3) withOUT fever

Day 1 of cycle:
- Withhold dosing
- Repeat CBC within 1 week
- Start next cycle when ANC >1000/mm^3 at the same dose

Day 15 of first 2 cycles:
- Continue at same dosing to complete cycle
- Repeat CBC at Day 21 (and prior to next cycle)

Grade 3 ANC (<1000 to 500/mm^3) WITH fever
OR
Grade 4 ANC (<500/mm^3)

Interrupt dosing
- Initiate new cycle when ANC is ≤Grade 2 (≥1000/mm^3)
- Follow FN guidelines, if necessary
- Resume next cycle at 1 dose level lower

Diarrhea with Abemaciclib

Percentage of Patients with “Significant” (ie, Grade ≥2) Diarrhea in Monarch-3, By Cycle[1]

Characteristic	Abemaciclib + ET (n=327)
Diarrhea (all grades), n (%) Grade 1 Grade 2 Grade 3	269 (82.3) 139 (42.5) 99 (30.3) 31 (9.5)
Time to onset, median (days)	8.0
Duration of Grade 2, median (days)	12.0
Duration of Grade 3, median (days)	8
Antidiarrheal medication, n (%)	226 (69.1%)

Management of Diarrhea with Abemaciclib

<u>First Sign of Loose Stool:</u>

Start antidiarrheal agent (ie, loperamide vs diphenoxylate/atropine)

Grade 1
(Increase of <4 stools over baseline)

→ No dose modification indicated

Grade 2

(Increase of 4 to 6 stools over baseline)

→ Hold dosing until resolution to Grade ≤1

Reduce dose if resolution took >24 hours, if it recurs after holding and reinitiating same dose

Grade 3

(Increase of ≥7 stools over baseline)

Grade 4

Life-threatening consequences/Urgent intervention indicated

→ Hold dosing until resolution to Grade ≤1

MUST reduce dose

References: 1. Rugo, et al. The Oncologist 2021;26:e53–e65

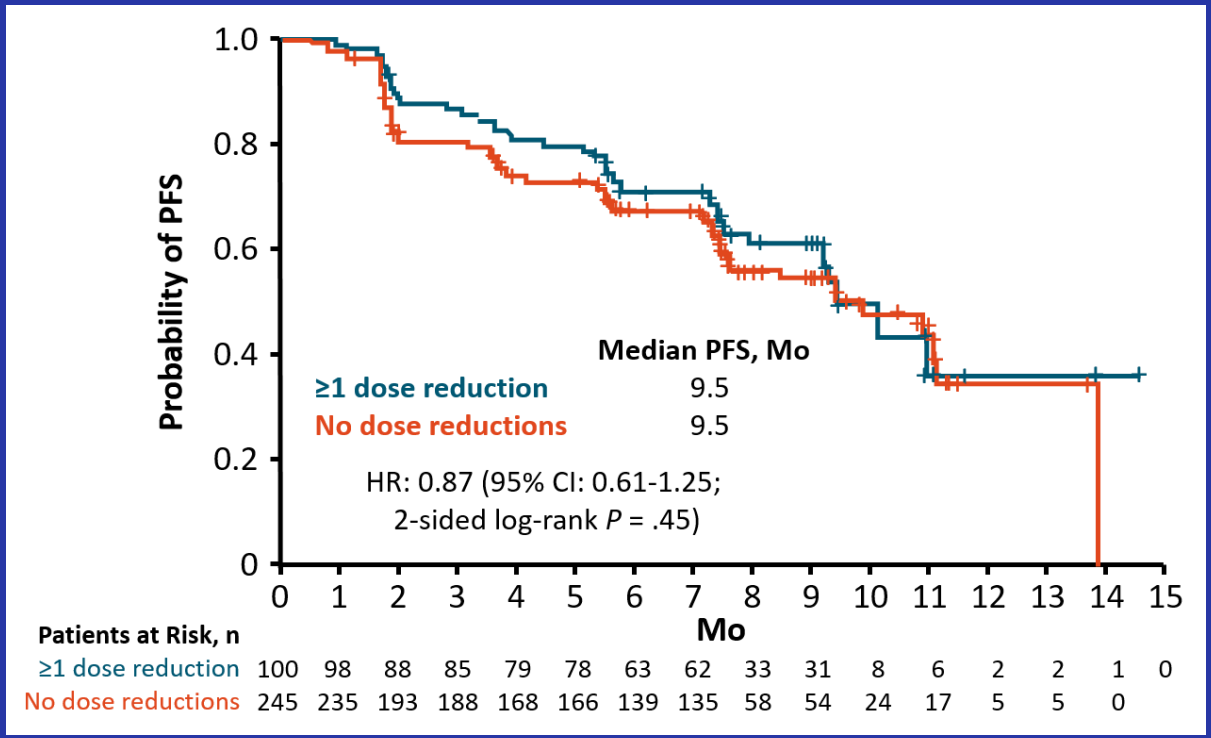
Dose Reductions

Variable	PALOMA-2[1] (N = 666)	MONARCH-3[2] (N = 493)	MONALEESA-2[3] (N = 668)	MONALEESA-7[4] (N = 672)
CDK4/6 inhibitor	Palbociclib	Abemaciclib	Ribociclib	Ribociclib
Dose Reduction During Study Due to AE, %				
Any	36%	46.5%	50.6%	35%
Predominant AE(s) implicated in dose reductions	24% due to neutropenia	16.7% due to diarrhea	Neutropenia (% not reported)	Not reported, although 4% were due to QTC interval prolongation

1. Finn. NEJM. 2016;375:1925. 2. Johnston et al. *NPJ Breast Cancer*. 2019 Jan 17;5:5. doi: 10.1038/s41523-018-0097-z. 3. . Hortobagyi. NEJM. 2016;375:1738; 4. Tripathy. Lancet Oncol. 2018;19:904.

Dose Reductions – Do They Matter

Palbociclib (from Paloma-3, 2nd line trial)[1]



Abemaciclib (Monarch-3)[2]

Reduced dose vs protocol dose (150 mg bid)	HR (95% CI)	Pvalue
100 mg vs 150 mg	0.764 (0.467, 1.251)	0.2849
50 mg vs 150 mg	0.985 (0.511, 1.902)	0.9650

Take home message for patients: dose reductions due to toxicities that cannot otherwise be managed do not appear to effect efficacy.

1. Verma, et al. *Oncologist.* 2016 Oct;21(10):1165-1175; adapted from CCO. Clinicaloptions.com; 2. Johnston et al. *NPJ Breast Cancer*. 2019 Jan 17;5:5

Final Summary:

- All three CDK 4/6 Inhibitors have a place in therapy in the treatment of metastatic, hormone receptor positive breast cancer.
    - Palbociclib and abemaciclib appear to perform better in bone-only disease in terms of progression-free survival benefit
    - Abemaciclib may have better activity, given published data, in CNS-disease
    - Ribociclib is the only one, thus far, with prospective published data for use after progression on a prior CDK 4/6 inhibitor, although this is not yet FDA approved
- Dose reductions are common, although toxicity profiles and reasons for dose reductions differ between agents
    - Dose reductions do not seem to affect efficacy

Need More Information?

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