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Comprehensive Cancer Center

Are all CDK4/6 Inhibitors the Same?

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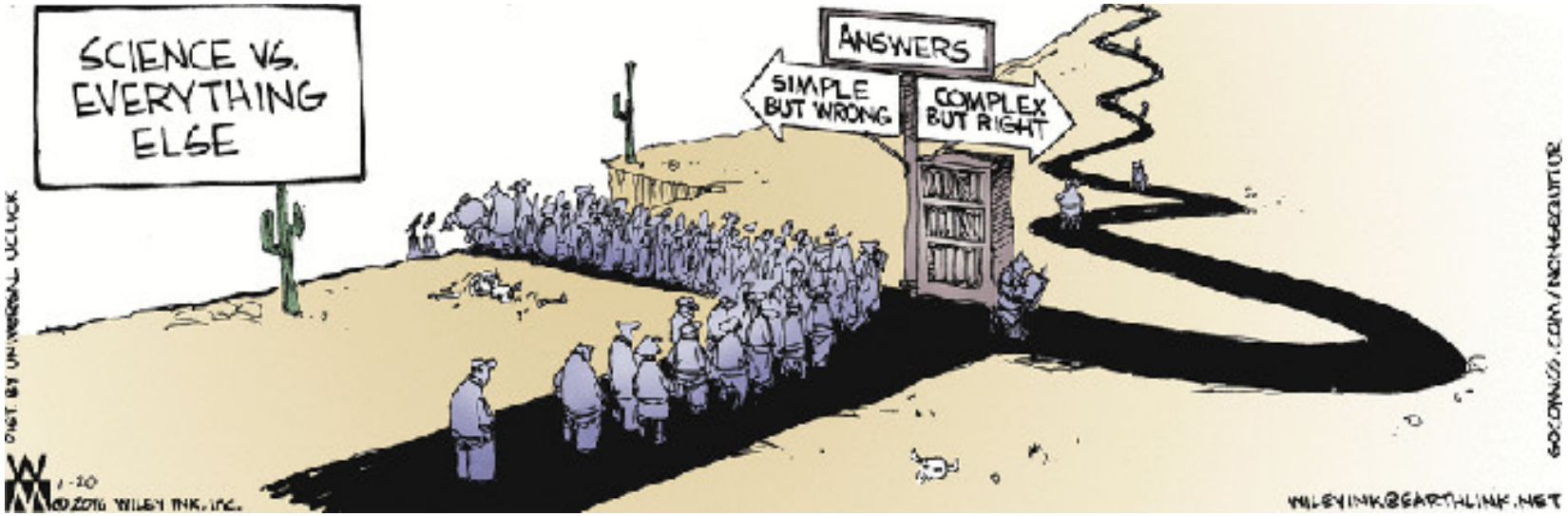
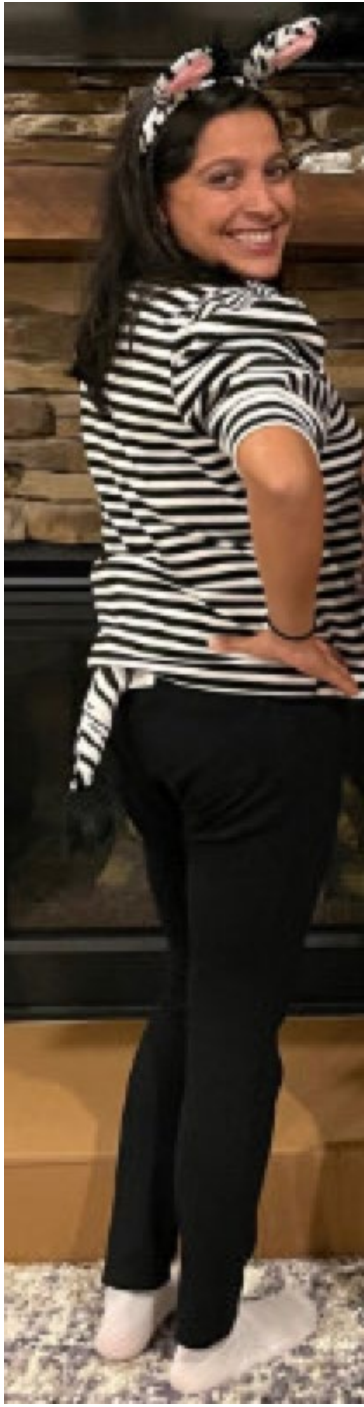
Are all CDK4/6 Inhibitors the Same?


SCIENCE VS. EVERYTHING ELSE
ANSWERS
SIMPLE BUT WRONG
COMPLEX BUT RIGHT
DIST. BY UNIVERSAL UCLICK
WILEYINK@EARTHLINK.NET

Dr. Bhave, however, is a simple creature.

She likes black and white.



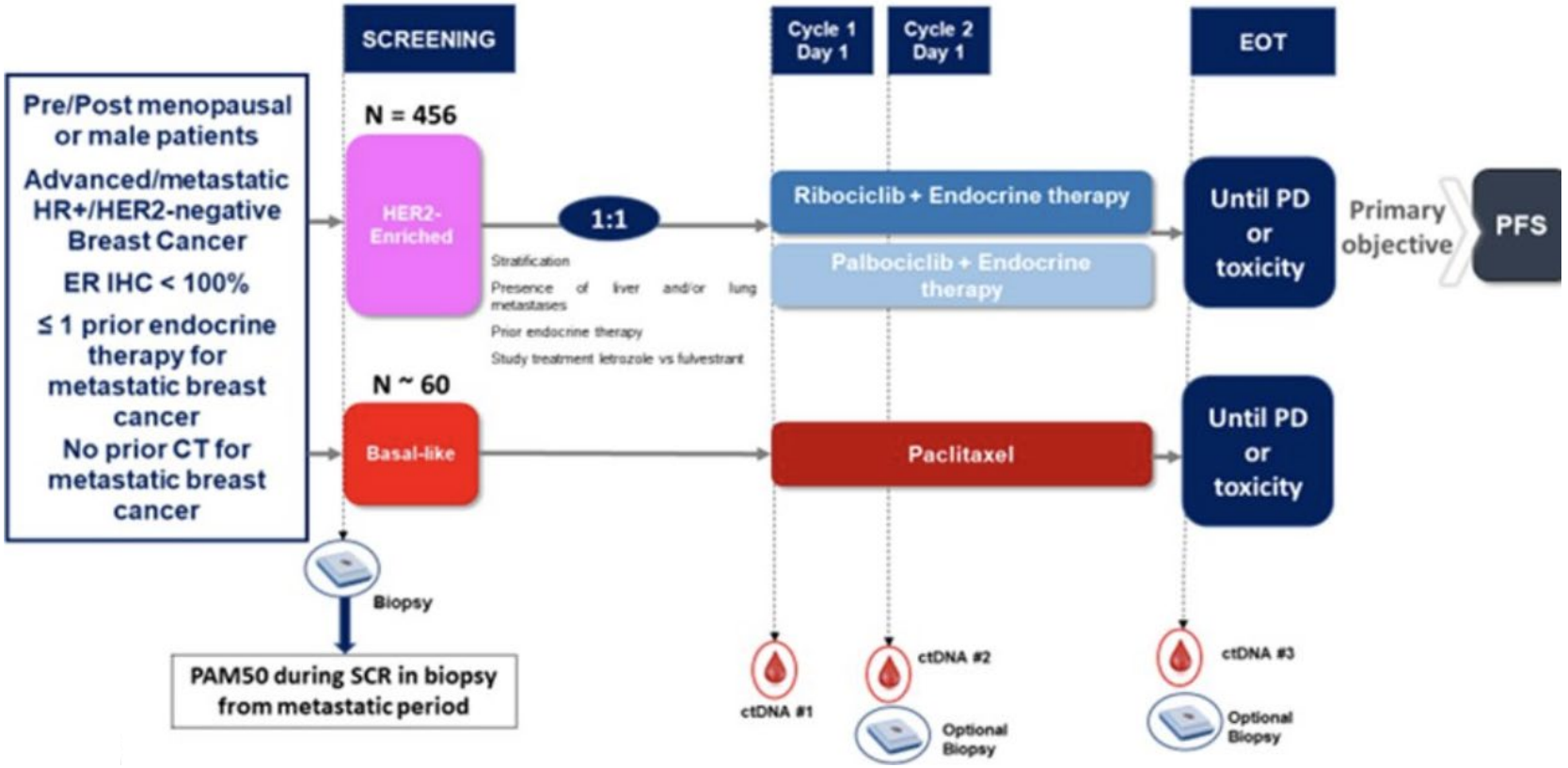
What Are We **Really** Asking?

- Is there a BEST CDK inhibitor?
- How do you define best? PFS? OS? Tolerability? Accessibility?
- Dr. Bhave is going to try to snow you with data that differentiates the efficacy of these drugs with respect to OS.

FACTS

NO head to head comparison between these agents.

HARMONIA SOLTI-2101/AFT-58



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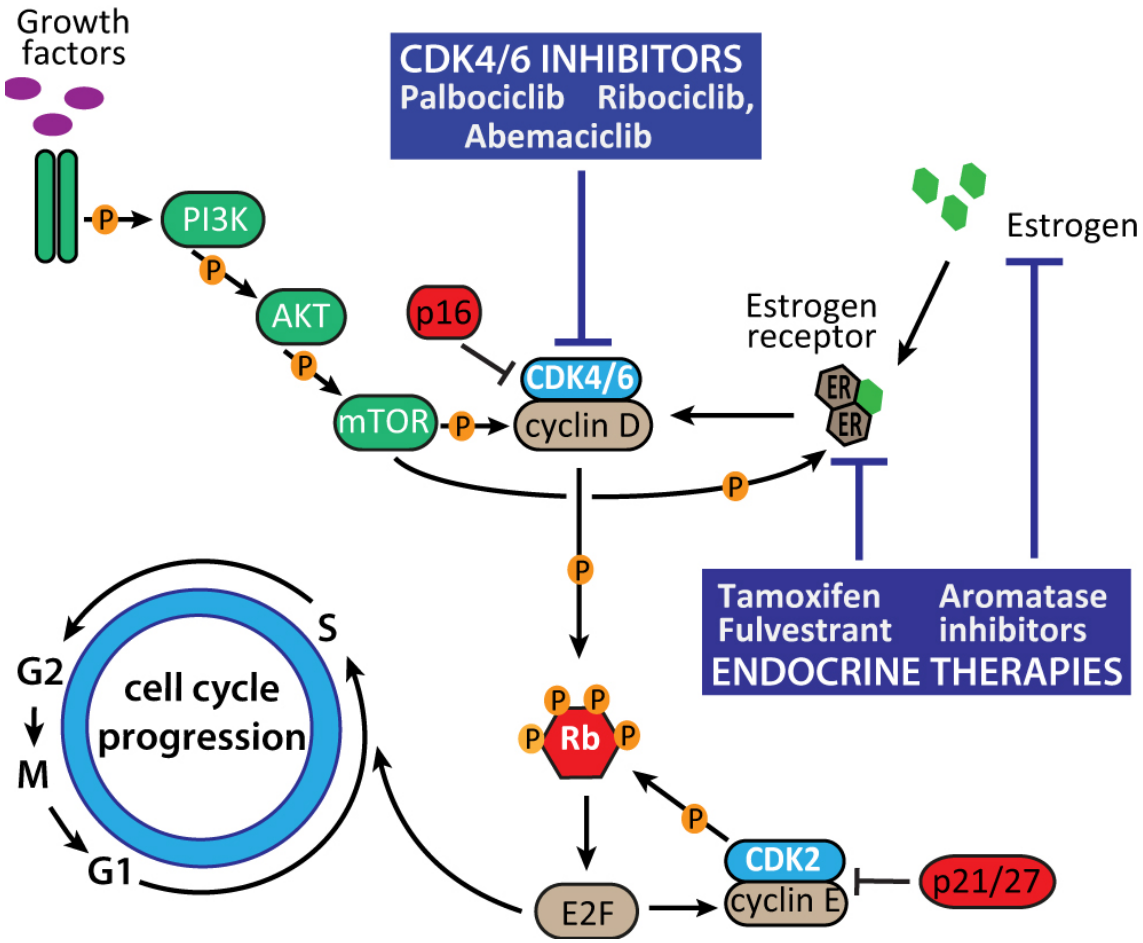
FACTS

This is a first world question.

Perfect should not be the enemy of the good.

There is more to life than death.

DYSREGULATION OF CDK 4/6 IN BREAST CANCER



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Portman. Endocrine-Related Cancer 26, 1; 10.1530/ERC-18-0317

CDK 4/6 INHIBITORS

Drug	Target	Dosing	Side Effects*	Monitoring	Pearls
PALBOCICLIB	CDK6/4	125mg daily D1-21 f/b 7d off	Neutropenia	CBC	
RIBOCICLIB	↑↑CDK6/4	600mg daily D1-21 f/b 7d off	Neutropenia LFT abnormalities Small risk QTc prolongation	CBC & LFTs & EKG	Watch out for QT prolonging con meds
ABEMACICLIB	↑CDK6/4 CDK2, CDK1	With ET: 150mg bid *continuous* Monotherapy: 200mg bid *continuous*	Less Neutropenia Diarrhea Small risk DVT	CBC & LFTs	Antidiarrheal CNS penetration? Single agent option

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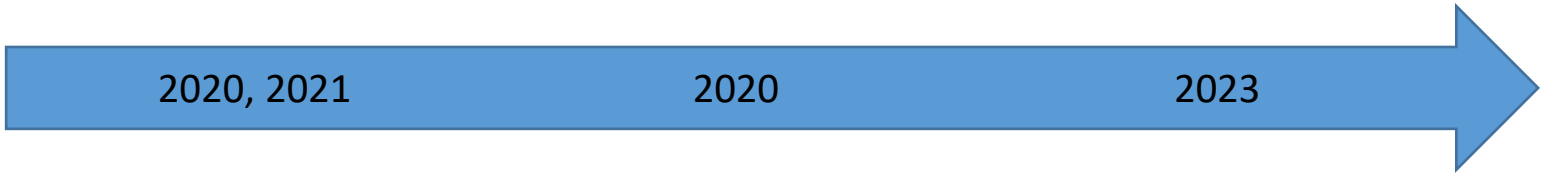
*All of these drugs could cause ILD/pneumonitis
*Avoid grapefruit

CDKi in High Risk Early Stage Hormone +, Her2 - BC



~~Palbociclib~~

Abemaciclib

FDA Approved

Ribociclib

CDK 4/6 INHIBITORS in EARLY STAGE ER+ BC

Study	Intervention	Population	HR IDFS
PENELOPE-B	PALBO x1y + ET	High risk post-neoadjuvant CTX	0.93
PALLAS	PALBO x2y + ET	Stage II & III	0.93
MONARCH-E	**ABEMA x2y + ET**	Stage II + high-risk, Stage III	**0.66**
NATALEE	RIBO x3y + ET	Stage II + high-risk, Stage III	**0.75**

Loibl JCO 2020; Mayer Lancet Oncology 2021; Johnston JCO 2021; Johnston Lancet Oncology 2023; Slamon ASCO 2023

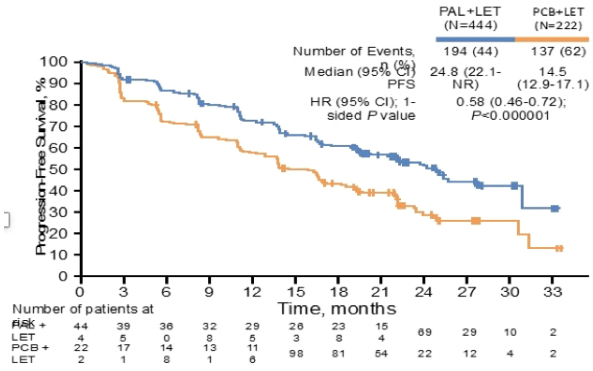
FDA Approvals for Hormone +, Her2 - MBC

Palbociclib	Ribociclib	Abemaciclib

1st Line (CDKi + AI): **Equivalent** PFS

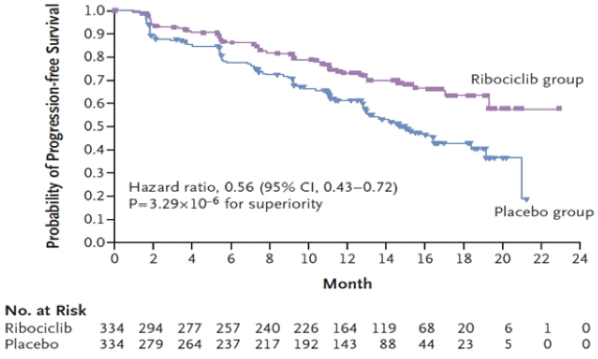
PALOMA2
palbociclib

HR 0.58, p<0.001



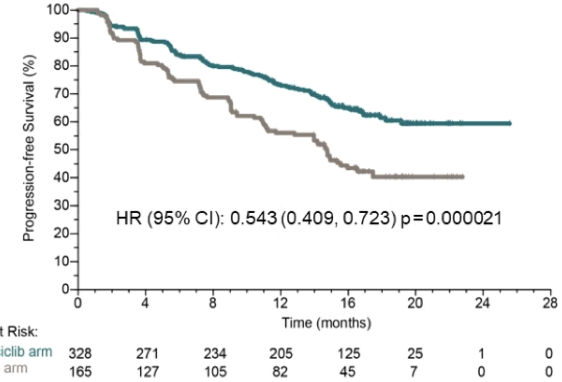
MONALEESA2
ribociclib

HR 0.56, p<0.001



MONARCH3
abemaciclib

HR 0.54, p<0.001



Finn NEJM 2016;Hortobagyi NEJM 2016; Di Leo JCO 2017

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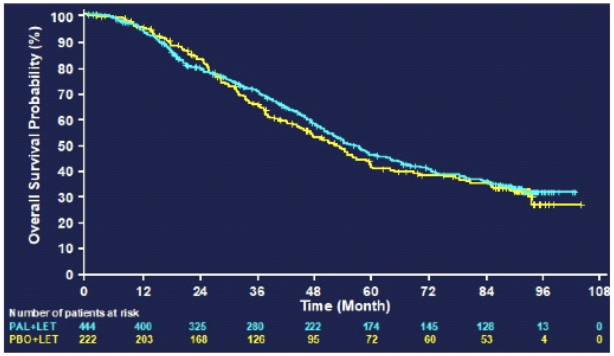
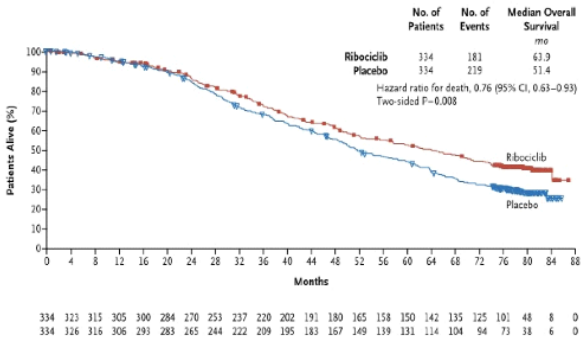
1st Line (CDKi + AI) RCT: OS

PALOMA2
palbociclib
HR 0.96, p=0.3



X

MONALEESA2
ribociclib
HR 0.76, p=0.008



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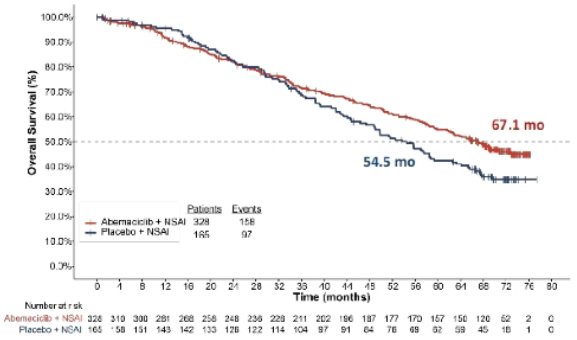
MONARCH3
abemaciclib
HR 0.754, p=0.03 NS



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Finn ASCO 2022;Hortobagyi NEJM 2022; Goetz ESMO 2022

CDK 4/6 INHIBITORS in ER+ MBC: FIRST-LINE STUDIES

Study	Intervention	Population	PFS (mo)	OS (mo)
MONALEESA-2*	RIBO + AI	Postmenopausal	25.3 vs 16	63.9 vs 51.4
MONALEESA-3#	RIBO + FULVESTRANT	Postmenopausal & men	33.6 vs 19.2	67.6 vs 51.8
MONALEESA-7*	RIBO + AI/TAM + OS	Premenopausal	23.8 vs 13	58.7 vs 48
MONARCH-3**	ABEMA + AI	Postmenopausal	29.0 vs 14.8	67.1 vs 54.5
PALOMA-2	PALBO + AI	Postmenopausal	24.8 vs 14.5	53.9 vs 51.2
PARSIFAL‡	PALBO + FULVESTRANT vs PALBO + AI	Post & Premenopausal	27.9 vs 32.8	*4y OS rate* 67.6% vs 67.5%

‡PhII- PFS results not significant; # ESMO 2022 update with 70.8 mo follow-up for 1st line; **ESMO 2022 Interim OS

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Neven ESMO 2022; Hortobagyi Annals of Oncology 2018; Seock-Ah NEJM 2019; Tripathy SABCS 2020; Goetz JCO 2017; Finn NEJM 2016; Finn Breast Cancer Res Treat 2020; Llombart-Cussac ASCO 2020; Hortobagyi NEJM 2022; Finn ASCO 2022

FACTS

Beware of cross-trial comparisons.

There were differences in the populations enrolled.

Trial populations rarely reflect the complexity of the real world.

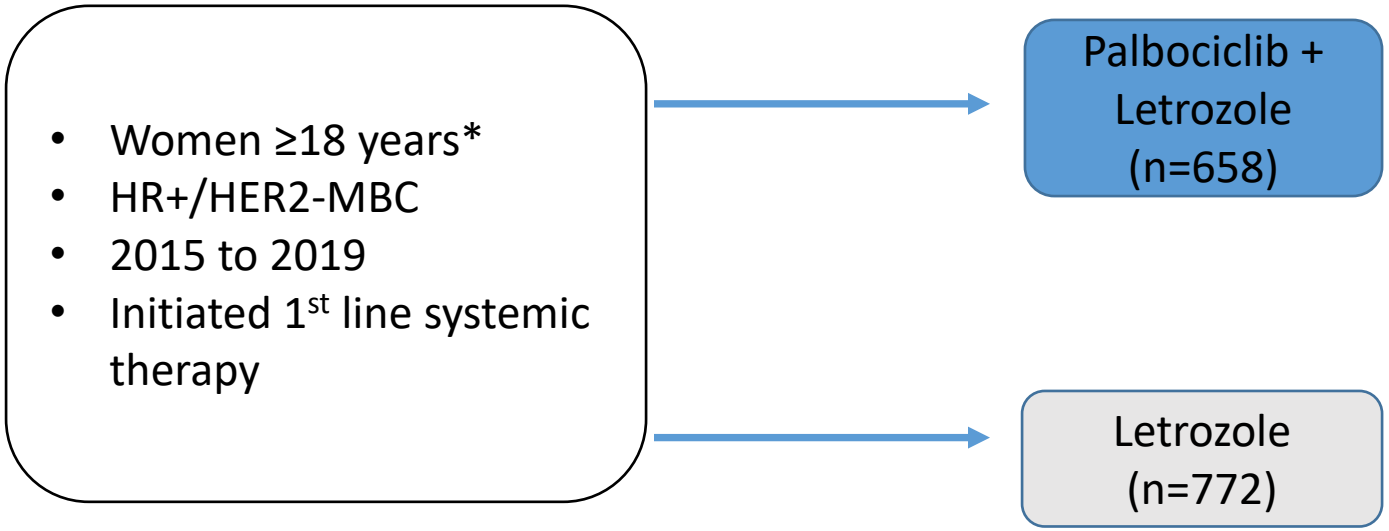
OS Differences in 1st Line RCT CDKi Studies

- PALOMA-2: Missing Survival Data
- Differences in disease-free intervals

	PALOMA-2 Palbo	MONALEESA-2 Ribo	MONALEESA-7 Ribo	MONALEESA-3 Ribo 1L Cohort
De Novo MBS	38%	34%	41%	20%
Disease-Free Interval				
≤12 mo	22%	1%	7%	5%
>12 mo	40%	NR	53%	75%

Finn NEJM 2016; Tripathy Lancet Onc 2018; Slamon NEJM 2020; Finn ASCO 2022; Cinicaloptions.com

OS in a Retrospective Flatiron Study



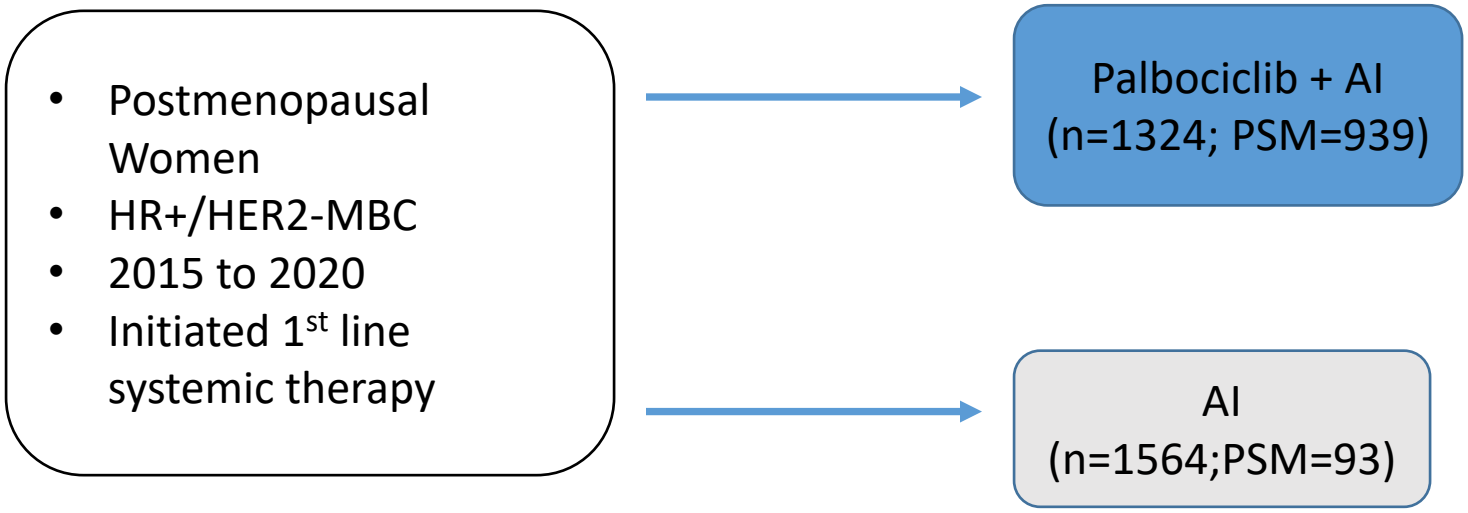
OS NR in Palbo + Letrozole vs 43 months Letrozole

Landmark OS analysis at 3y: 65% Palbo + Letrozole vs 53% Letrozole

*>60% age ≥65
HR 0.55 (age ≥70) vs 0.71 (age 18-50)

DeMichele Breast Cancer Research 2021

OS in a 2nd Retrospective Flatiron Study



PSM median OS 58 months Palbociclib + AI vs 44 mo AI alone

HR 0.72 [0.62–0.83]; P < 0.0001

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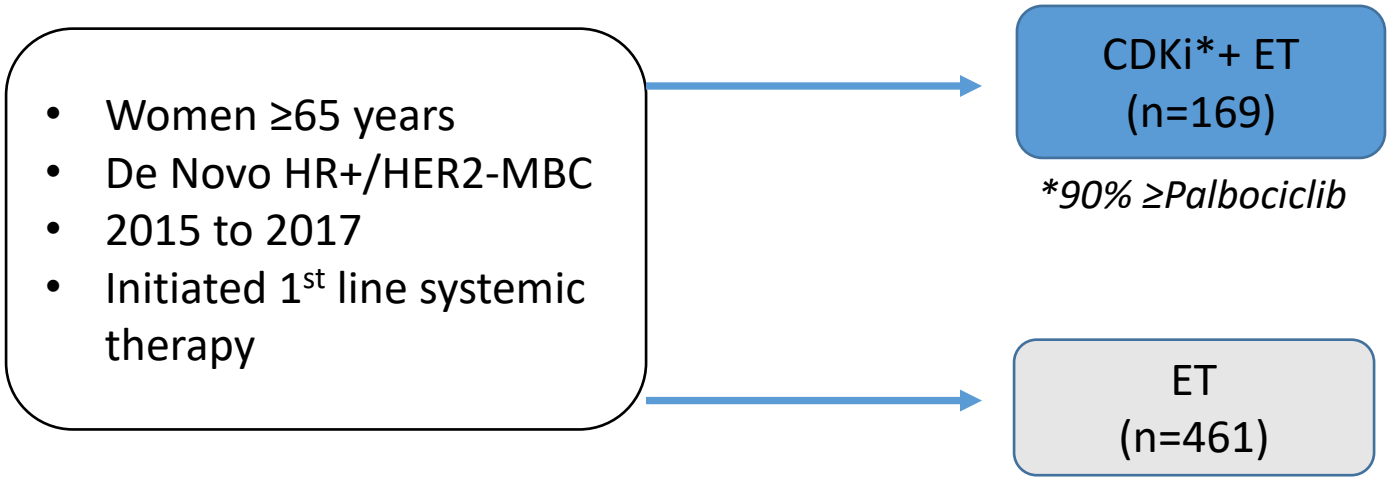
Rugo NPJ Breast Cancer 2022

OS in a Retrospective SEER-Medicare Study



OS rate at 3 years: 73% ET+CDKi vs 49% for ET alone (p<.0001)
41% lower rate of mortality (aHR, 0.590)

Goyal Cancer 2023

What Questions **Should** We Be Asking?

- Does *everyone* actually need a CDK inhibitor upfront in metastatic disease?
- Is efficacy *so* different that you should ignore patient specific variables that might affect the CDK inhibitor you select?
- Will all this matter in the long-run anyway?

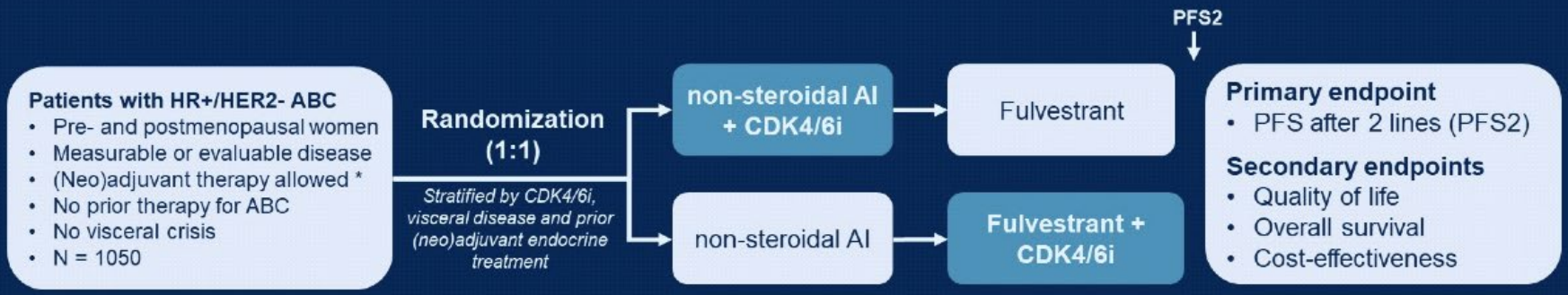
A Patient Story

- 65 yo retired woman enjoys travelling internationally. Has had bouts of recurrent cellulitis in the lower extremities.
- 4/2012: Screening MMG shows a L breast mass. Diagnosed with a grade 2 ER 100%, PR 97%, HER2 IHC 1+ negative L breast cancer.
- Undergoes lumpectomy and SLNB; pT2N1. Oncotype Dx RS 16 but PET-CT shows diffuse bone mets, confirmed on biopsy. Asymptomatic.
- 8/2012: Begins palliative Anastrazole and bisphosphonate; by 4/2014 her imaging is NED.
- 3/2020: PET shows subtle increases in metabolic uptake in her L femur. Asymptomatic. Switches from Anastrazole to Exemestane
- 5/2021: PET shows interval increase in uptake in humeral osseous met. Asymptomatic. Molecular testing + NTRK, BRCA2, NF1; germline negative. Switches from Exemestane to Tamoxifen.
- 9/2021: Increased osseous uptake in femur. Asymptomatic. Initiates Fulvestrant and Palbociclib.
- 3/2023: Restaging shows metabolic response.

She remained on single agent AI for ~9 years!

SONIA trial design

SONIA



- Tumor assessments every 12 weeks
- PFS locally assessed per RECIST v1.1
- Primary analysis planned after 574 PFS2 events
  - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤0.65 and Δ ≥3 months) with two-sided α=5%[1]

HR+, hormone receptor positive; HER2- , HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival
* disease-free interval after non-steroidal aromatase inhibitor >12 months. ClinicalTrials.gov (NCT03425838)
1. Cherny NI, et al. Ann Oncol 2017

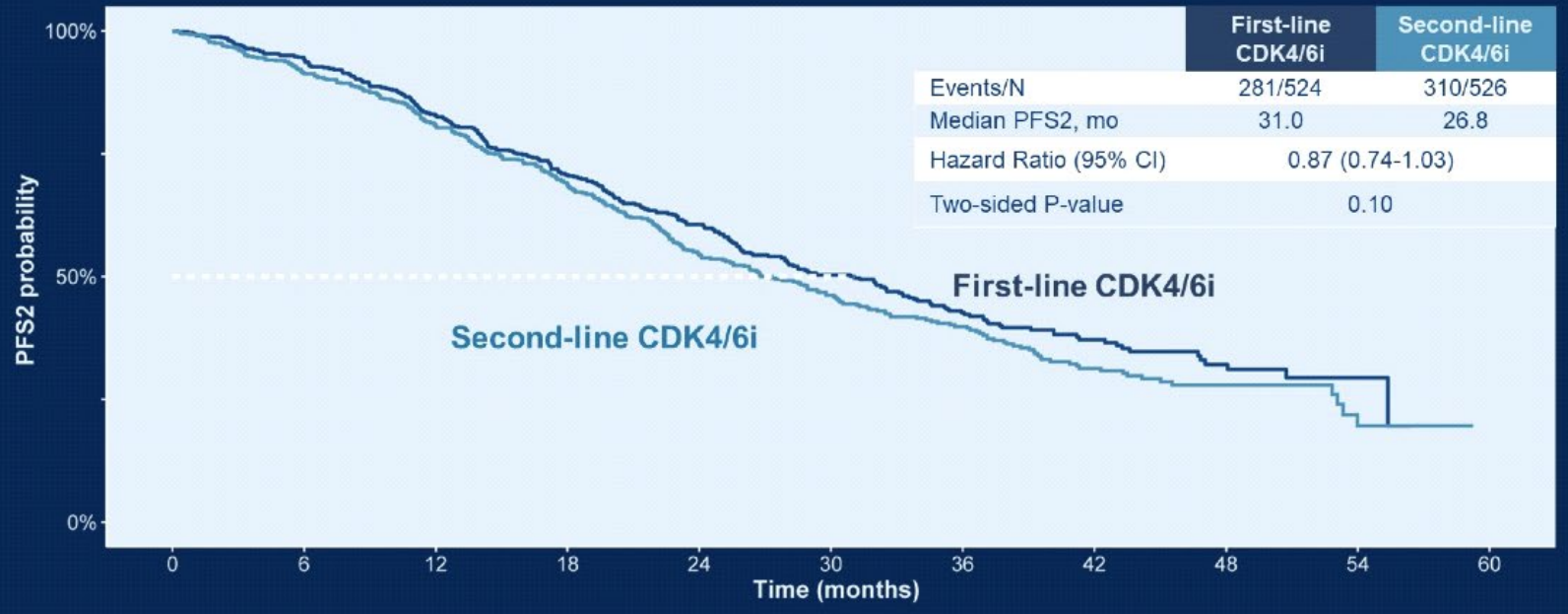
Baseline characteristics

SONIA

		First-line CDK4/6i N=524	Second-line CDK4/6i N=526
Median age, years (range)		64 (24-88)	63 (25-87)
WHO PS, n (%)	0	257 (49)	257 (49)
	≥1	267 (51)	269 (51)
Menopausal status, n (%)	Pre- / perimenopausal	69 (13)	76 (14)
	Postmenopausal	455 (87)	450 (86)
Disease-free interval, n (%)	Newly diagnosed	182 (35)	182 (35)
	≤24 months	96 (18)	98 (19)
	>24 months	246 (47)	246 (47)
Prior (neo)adjuvant therapy, n (%)	Chemotherapy	212 (40)	210 (40)
	Endocrine therapy	258 (49)	254 (48)
Metastatic site, n (%)	Visceral disease	291 (56)	292 (56)
	Bone-only disease	91 (17)	91 (17)
Measurable disease, n (%)		315 (60)	312 (59)
Type of CDK4/6i, n (%)	Palbociclib	479 (91)	479 (91)
	Ribociclib	42 (8)	44 (8)
	Abemaciclib	3 (1)	3 (1)

Primary endpoint: PFS2

SONIA



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	281/524	310/526
Median PFS2, mo	31.0	26.8
Hazard Ratio (95% CI)	0.87 (0.74-1.03)	
Two-sided P-value	0.10	

First-line	524 (0)	491 (3)	429 (5)	339 (34)	244 (84)	167 (123)	118 (148)	69 (184)	31 (215)	5 (239)	0 (243)
Second-line	526 (0)	478 (2)	418 (6)	330 (35)	225 (76)	164 (105)	115 (133)	65 (161)	30 (190)	9 (207)	0 (216)

Numbers at risk (censored)

1st vs 2nd line CDKi: Main Findings of SONIA

- **Did not improve** PFS, OS, or QOL
- **42% increase** of G3-4 toxicity
- **$200,000** increase in drug costs/patient

Does it matter that most of the CDKi used was Palbociclib?

Is Fulvestrant the optimal 2nd line?

How do we identify these good risk patients?

Sonke ASCO 2023

Racial Disparities in Use of 1st Line Treatment

Percentage initiating 1L CDK4/6 inhibitors.						
Year	2015	2016	2017	2018	2019	2020
NHW	46	60	69	73	72	48
NHB	41	50	57	62	66	43

Martei ASCO 2023

What Questions **Should** We Be Asking?

- Does *everyone* actually need a CDK inhibitor upfront in metastatic disease?
- Is efficacy *so* different that you should ignore patient specific variables that might affect the CDK inhibitor you select?
- Will all this matter in the long-run anyway?

What Questions **Should** We Be Asking?

Patient 1	Patient 2	Patient 3
48 yo patient with with ER/PR+ Her2- MBC and a history of bipolar disorder on olanzapine and citalopram.	65 yo patient with ER/PR+ Her2- MBC and a history of Chron's.	72 yo patient ER/PR+ Her2- MBC with cirrhosis due to ETOH. Lives 2 hours from the cancer center.
QTc Risk	Diarrhea Risk	LFTs Access to monitoring

What Questions **Should** We Be Asking?

- Does *everyone* actually need a CDK inhibitor upfront in metastatic disease?
- Is efficacy *so* different that you should ignore patient specific variables that might affect the CDK inhibitor you select?
- Will all this matter in the long-run anyway?

What Questions **Should** We Be Asking?

- New drugs, new biomarkers to predict response, & new combinations will affect selection and sequencing
  - Novel CDK inhibitors (CDK2; CDK7)
  - Novel combinations (PI3K-inhibitors; SERDs)
  - CDK post CDK
  - Molecular subtyping

- What CDKi will we select in the advanced disease setting when people relapse after adjuvant CDK inhibitors?
  - PACE, **MAINTAIN**, PALMIRA

Are All CDK4/6 Inhibitors The Same?

Are All CDK4/6 Inhibitors Useful?

Choose the right drug at the right time for the right patient

Efficacy, Convenience, Comorbidities, Toxicity, Drug interactions

Given their different indications, efficacy data, and side effect profiles, **all available CDK 4/6i are valuable therapy options** for patients with breast cancer