WILEY

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Ask-the-Expert Webinar

Mechanisms of endocrine therapy resistance and treatment options in hormone receptor positive breast cancer

Conflicts of Interest

Gustavo Werutsky

Institutional financial interest

Research grants/ Local PI/ Steering Committee: AstraZeneca, Astellas, BeiGene, BMS, Roche, Ipsen, Janssen, Libbs, Lilly, MSD, Novartis, Roche, Pfizer and Takeda.

Personal financial interest

Honoraria/ Advisory: AstraZeneca, MSD, Novartis, Daiichi, Roche. Wiley related to this presentation.

Non-financial interest

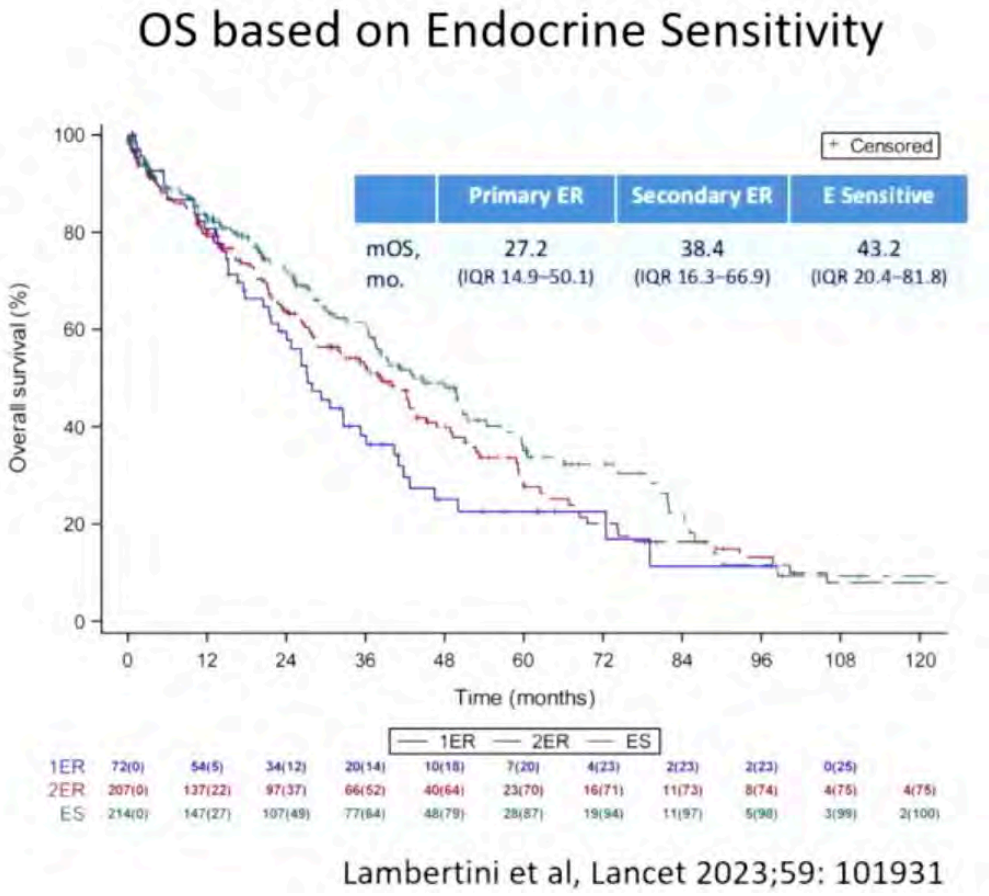
LACOG Executive Director, member of the Breast International Group (BIG) Executive Board and the EORTC Breast Cancer Group Steering Committee.

Learning Objectives

- Overview of the mechanisms of endocrine resistance in breast cancer
- Development of CDK 4/6 inhibitors in breast cancer and its clinical benefit in early and metastatic disease
- Understand the mechanisms of acquired resistance to endocrine therapy plus CDK4/6 inhibitors and potential treatment combinations to overcome resistant luminal tumors
- Treatment selection in clinical practice after disease progression on a CDK4/6 inhibitor and future areas of research

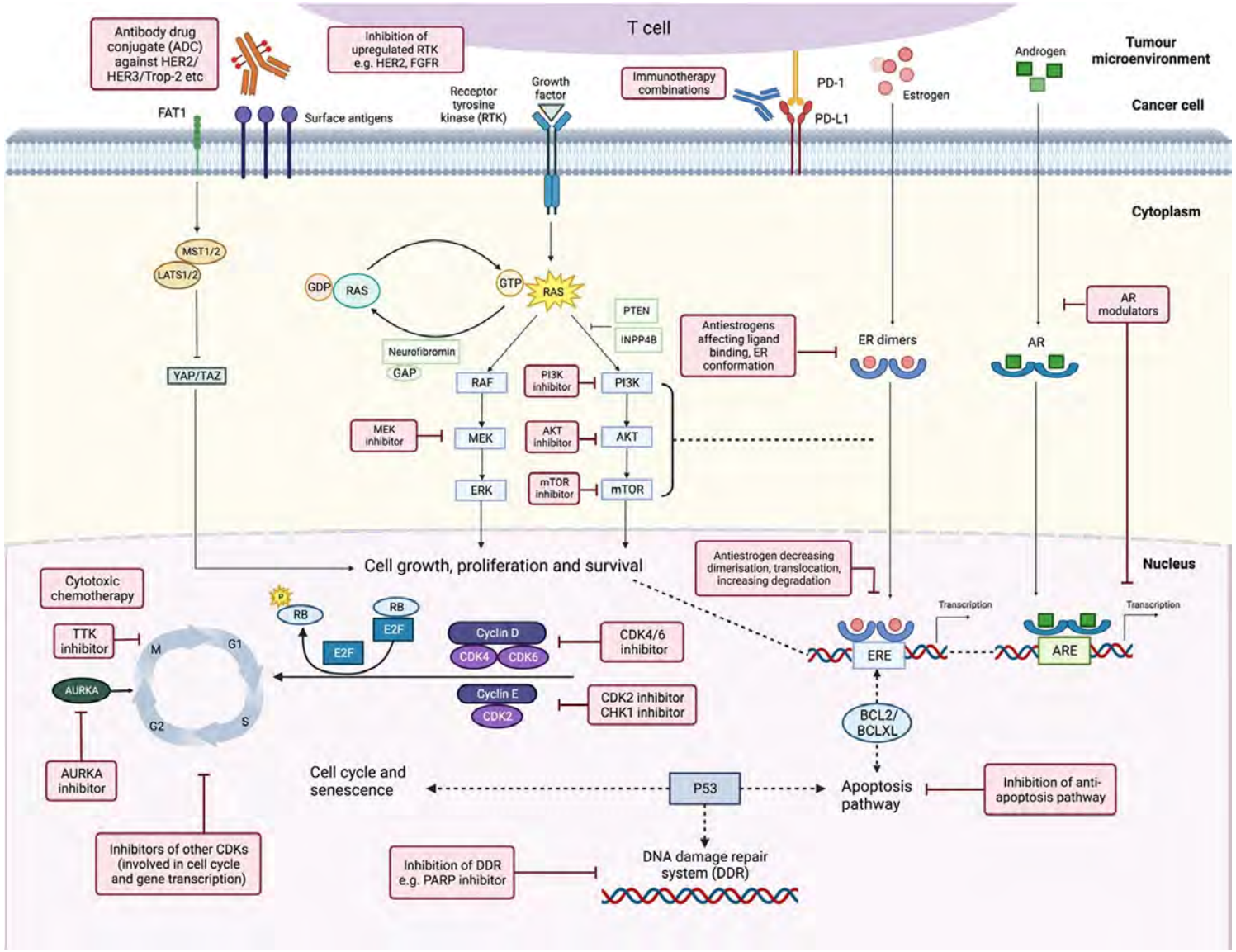
Individual patient-level analysis from the Mammella Intergruppo (MIG) and Grupo Italiano Mammella (GIM) Studies (1992-2012)

- Using ESO/ESMO definitions, evaluated outcome in 6612 pts with HR+/HER2- ESBC enrolled in 4 ph III randomized trials evaluating chemo, ET and duration of ET
  - Median age 60, median FU 9 years; 9.7% with DR, primarily in bone
- 493 had DR as first DFS event
  - 14.6% primary endocrine resistant, 42% secondary endocrine resistant, 43.4% endocrine sensitive
  - Primary ER: more often young, and with higher incidence of visceral mets (particularly liver)



Lambertini et al, Lancet 2023;59: 101931

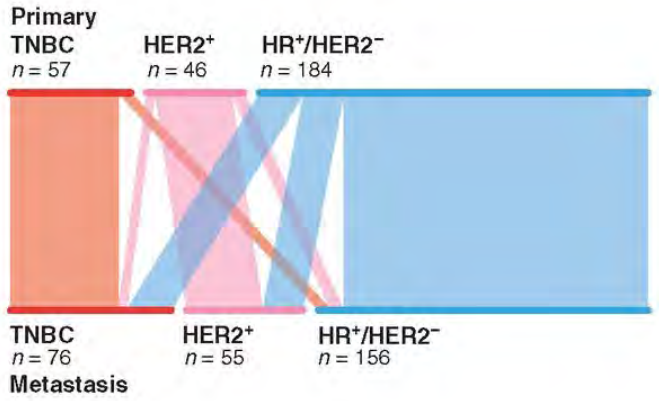
Oncogenic signaling pathways in HR + /HER2– ABC with potential therapeutic strategies post CDK4/6 inhibitors



Ma J. npj Breast Cancer, 9: 74 (2023)

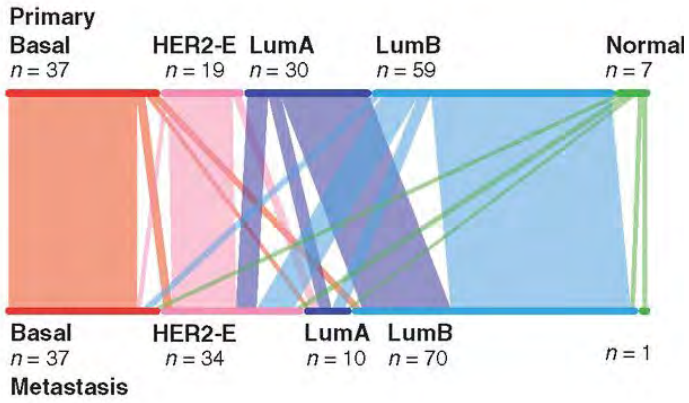
AURORA RNA-seq of paired primary tumors and metastatic samples

A Subtype switching, on IHC subtypes



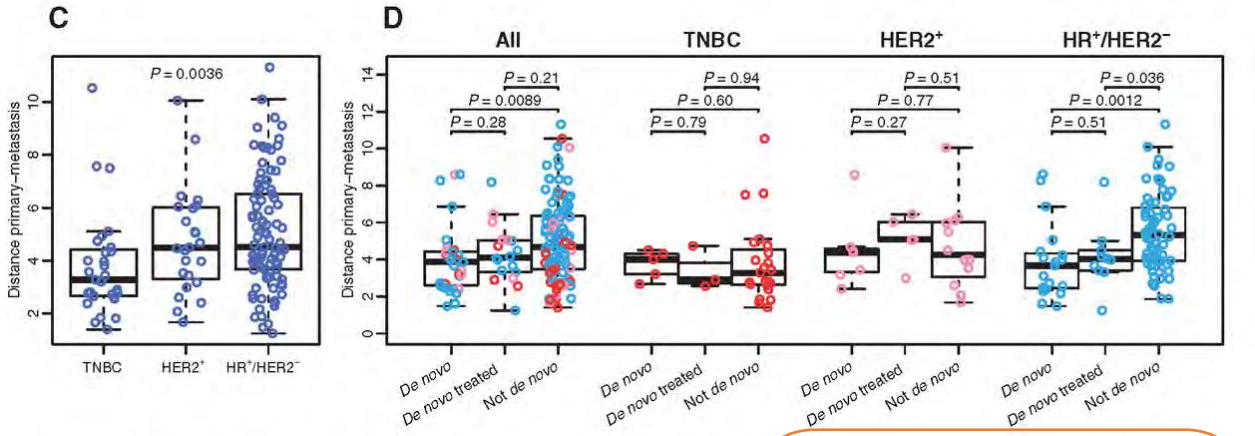
Luminal A primaries switched in metastatic samples (90% of cases)

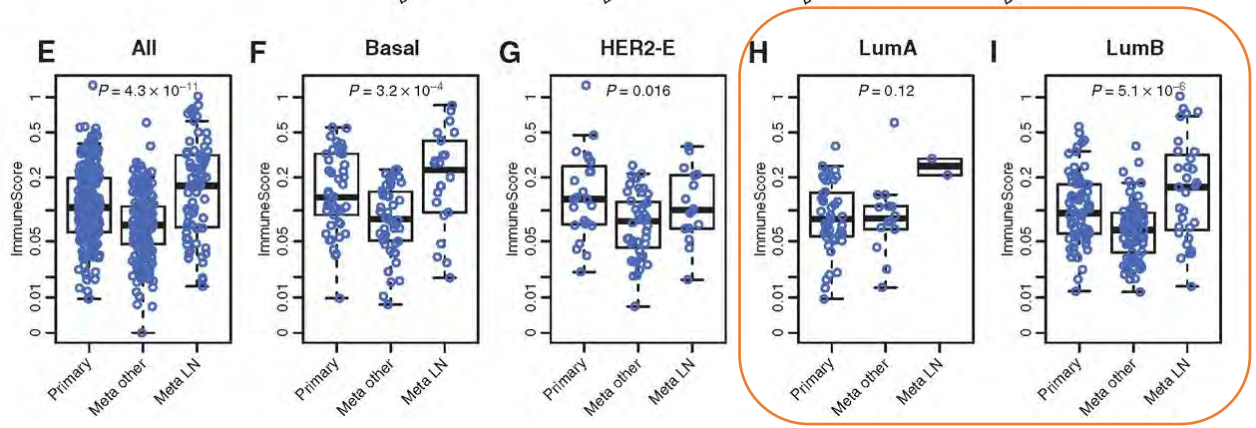
B Subtype switching, on PAM50



Intrinsic subtype switching 55 (36%) cases

Distribution of the distances between primaries and metastases in term of expression of the PAM50 genes, in function of the clinical subtype

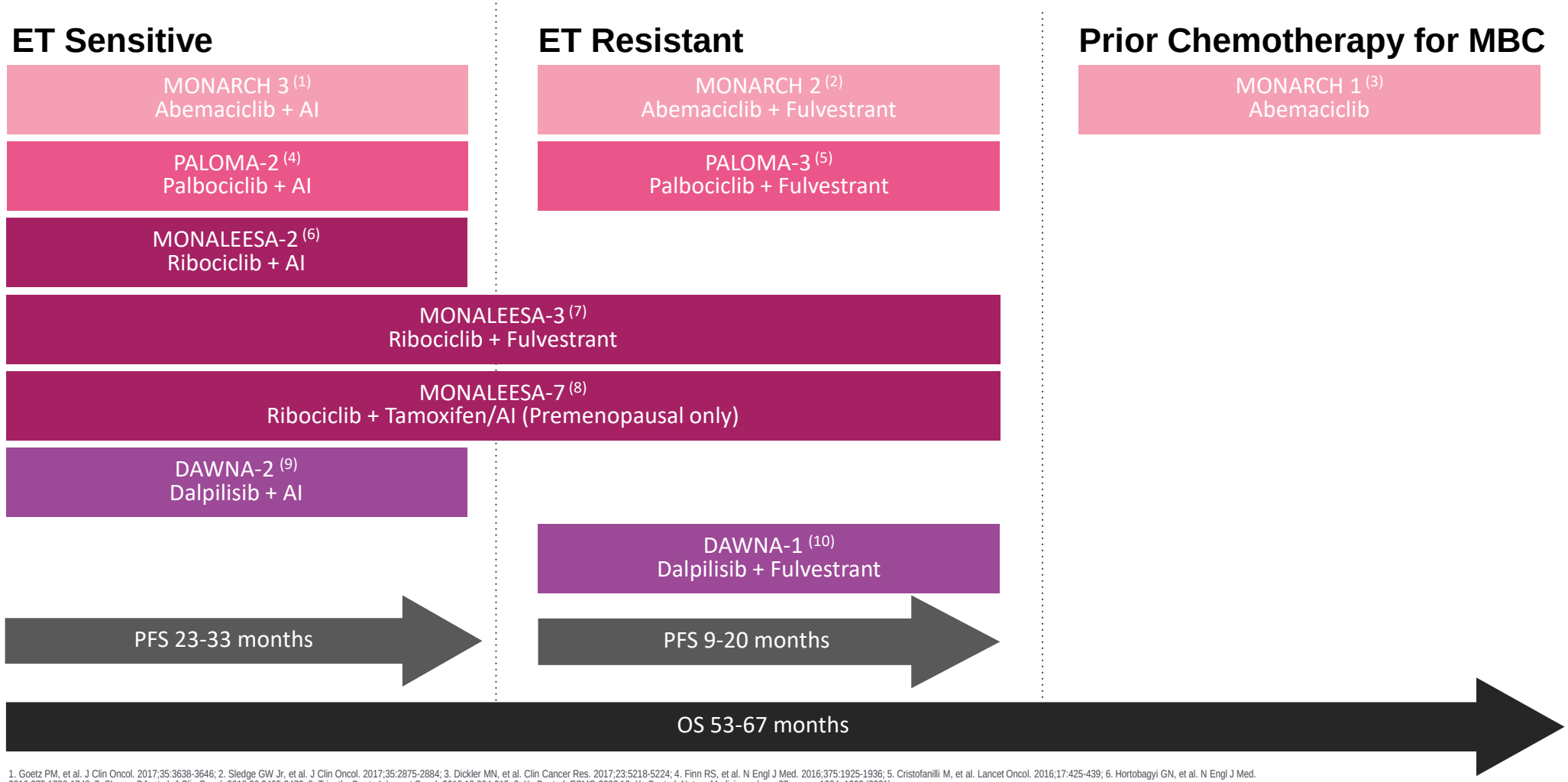




Difference in immune signal between primary and metastasis across PAM50 subtypes

Cancer Discov 2021 Nov;11(11):2796-2811

Overview of Clinical Trials with CDK 4/6 Inhibitors in Advanced Breast Cancer

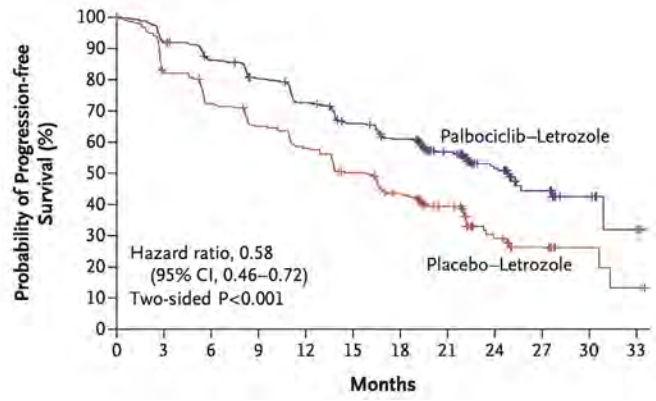


1. Goetz PM, et al. J Clin Oncol. 2017;35:3638-3646; 2. Sledge GW Jr, et al. J Clin Oncol. 2017;35:2875-2884; 3. Dickler MN, et al. Clin Cancer Res. 2017;23:5218-5224; 4. Finn RS, et al. N Engl J Med. 2016;375:1925-1936; 5. Cristofanilli M, et al. Lancet Oncol. 2016;17:425-439; 6. Hortobagyi GN, et al. N Engl J Med. 2016;375:1738-1748; 7. Slamon DJ, et al. J Clin Oncol. 2018;36:2465-2472; 8. Tripathy D, et al. Lancet Oncol. 2018;19:904-915. 9. Xu B, et al. ESMO 2022 10. Xu B, et al. Nature Medicine volume 27, pages 1904–1909 (2021)

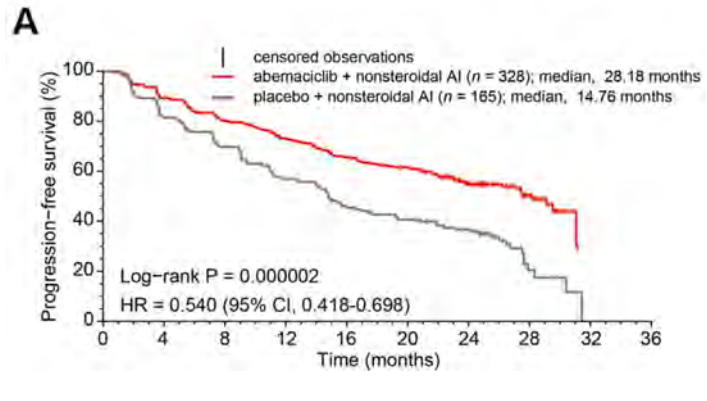
Werutsky G. unpublished

Consistent PFS Results in First-line CDK 4/6 Inhibitors Trials

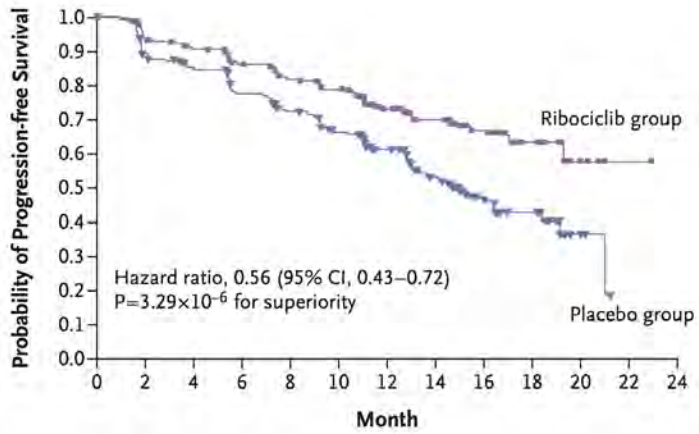
PALOMA-2



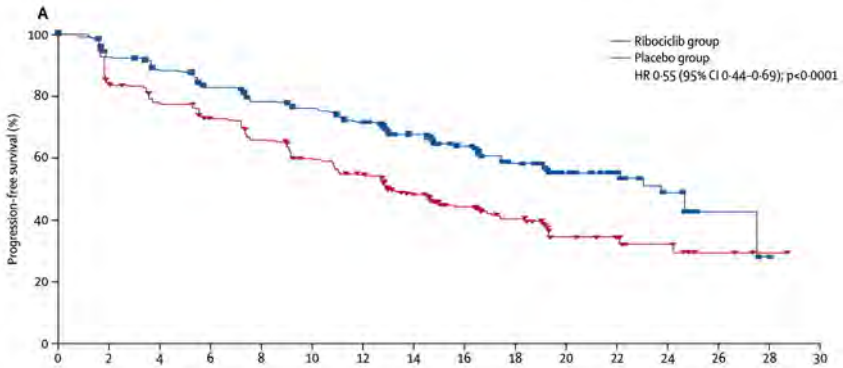
MONARCH-3



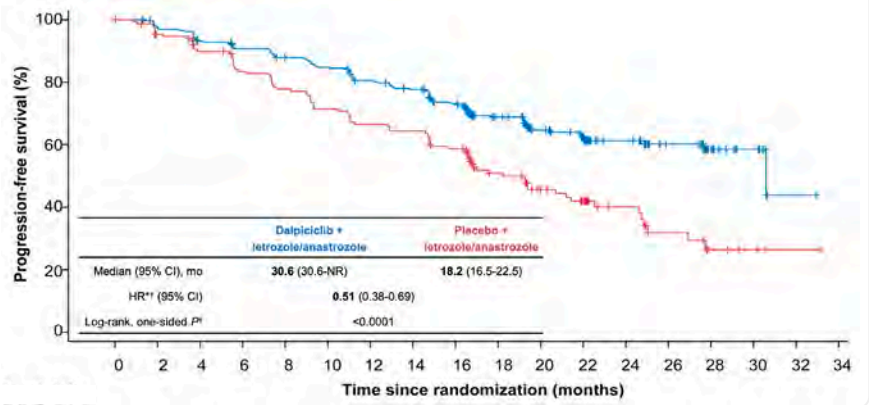
MONALEESA-2



MONALEESA-7



DAWNA-2



Finn N Engl J Med 2016; Goetz J Clin Oncol 2017; Hortobagyi N Engl J Med 2016; Tripathy Lancet Oncol 2018; Xu ESMO 2022; Johnston npj Breast Cancer (2019)5:5

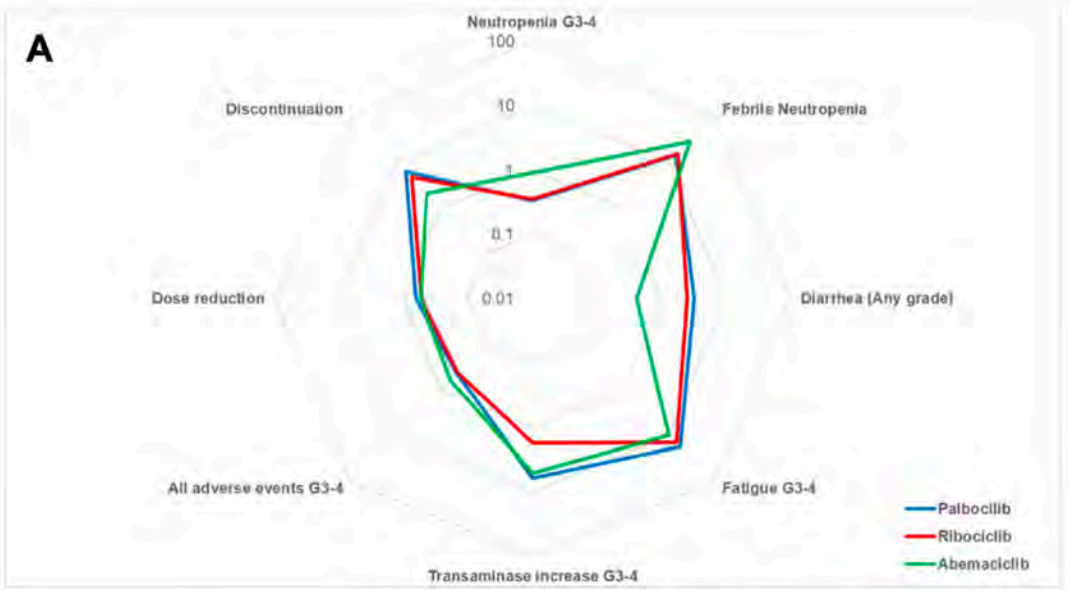
Differences in Pharmacokinetics and Toxicity Between CDK 4/6 Inhibitors

	Palbociclib	Ribociclib	Abemaciclib
IC_{50} (nM)			
Cyclin D1–CDK4	11	10	2
Cyclin D1/2/3–CDK6	16	39	10
Cyclin B–CDK1	>10 000	113 000	1627
Cyclin A/E–CDK2	>10 000	76 000	504
Cyclin T–CDK9	NR	NR	57
Mean terminal half-life (h)	26	36	17–38
Standard dosing	125 mg daily (3 weeks on, 1 week off)	600 mg daily 3 weeks on, 1 week off)	150 mg twice daily in combination with antioestrogen; 200 mg twice daily as monotherapy

Trial Details	PALOMA-2	MONALEESA-2	MONALEESA-3	MONALEESA-7	MONARCH-3
CDK 4/6 Inhibitor	Palbociclib	Ribociclib	Ribociclib	Ribociclib	Abemaciclib
Endocrine therapy	Letrozole	Letrozole	Fulvestrant	Gosrelin plus tamoxifen or NSAI	NSAI
% ≥1 dose reduction due to AE (combination arm)	36%	50.6%	n/a	31%	46.5%
% treatment discontinuation (combination arm)	9.7%	7.5%	n/a	4%	16.5%

Adapted Spring LM. Lancet 2020; 395: 817–27; A. Grinshpun et al. npj Breast Cancer (2023) 15; Mastrantoni L. eClinicalMedicine 2023;56: 101824

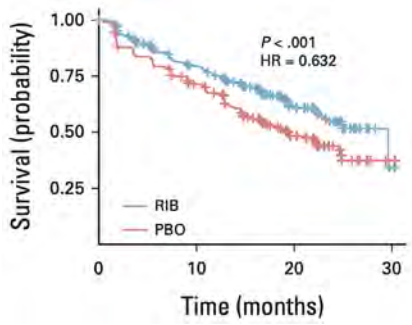
Likelihood of being helped or harmed (LHH) for PFS



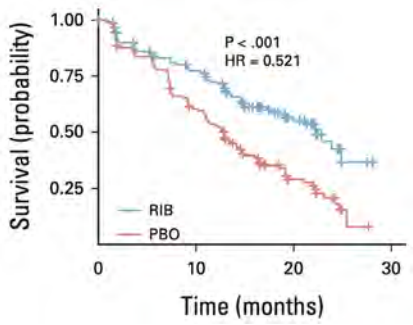
	Palbociclib [95% CI]	Ribociclib [95% CI]	Abemaciclib [95% CI]
Neutropenia (G3-4)	0·33 [0·24-0·43]	0·35 [0·26-0·46]	0·90 [0·57-1·38]
Febrile neutropenia	14·27 [6·66-55·65]	15·52 [7·89-48·74]	28·53 [9·74-∞]
Diarrhea (Any grade)	3·22 [1·42-13·91]	2·52 [1·04-30·46]	0·42 [0·27-0·60]
Fatigue (G3-4)	17·56 [6·19-∞]	14·41 [6·86-48·74]	9·92 [4·74-27·73]
Transaminase increase (G3-4)	6·01 [2·84-18·55]	1·75 [0·94-3·93]	5·07 [1·91-∞]
All adverse events (G3-4)	0·45 [0·31-0·61]	0·43 [0·31-0·58]	0·62 [0·41-0·89]
Dose reduction	0·65 [0·43-0·94]	0·54 [0·32-0·97]	0·56 [0·39-0·75]
Discontinuation	6·17 [2·48-92·76]	4·69 [1·81-∞]	2·09 [1·25-3·60]

PAM50 Intrinsic Subtype and PFS Across the MONALEESA 2, 3 and 7 Trials

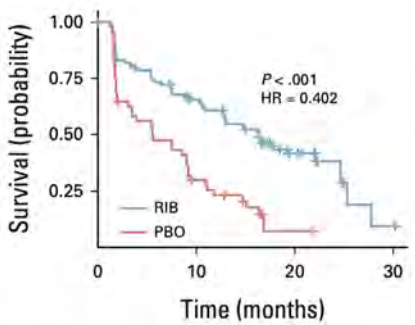
Luminal A



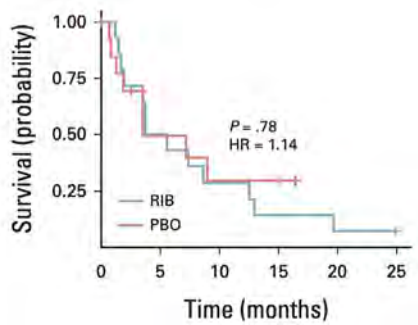
Luminal B



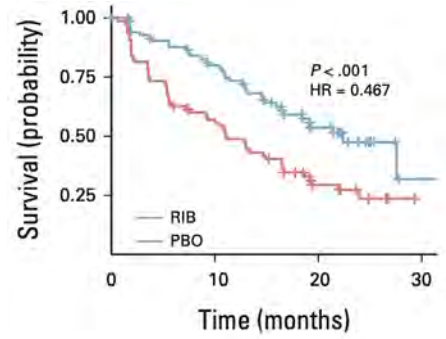
HER2 E



Basal-Like

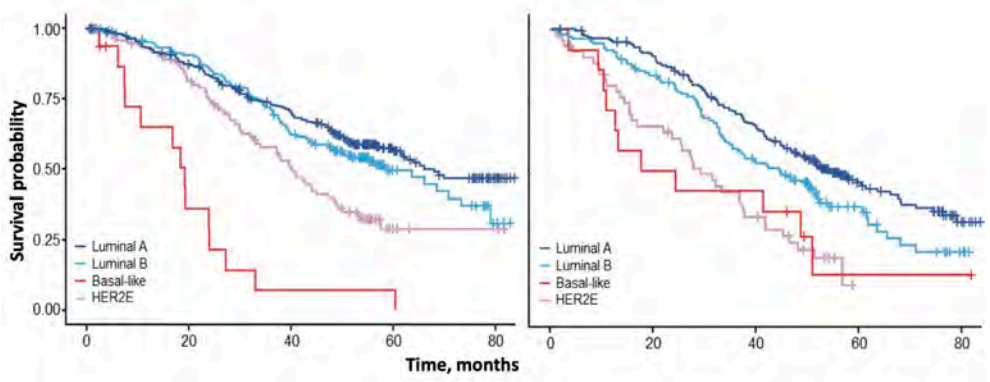


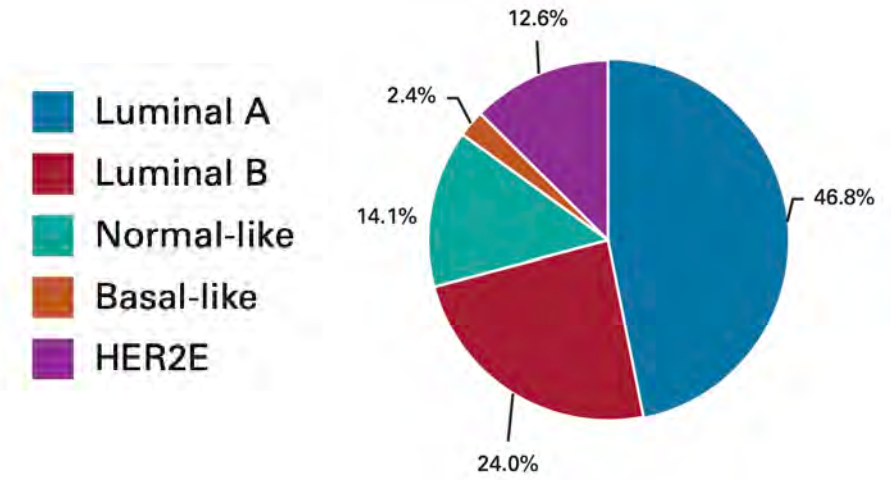
Normal-like



Ribo + ET

ET

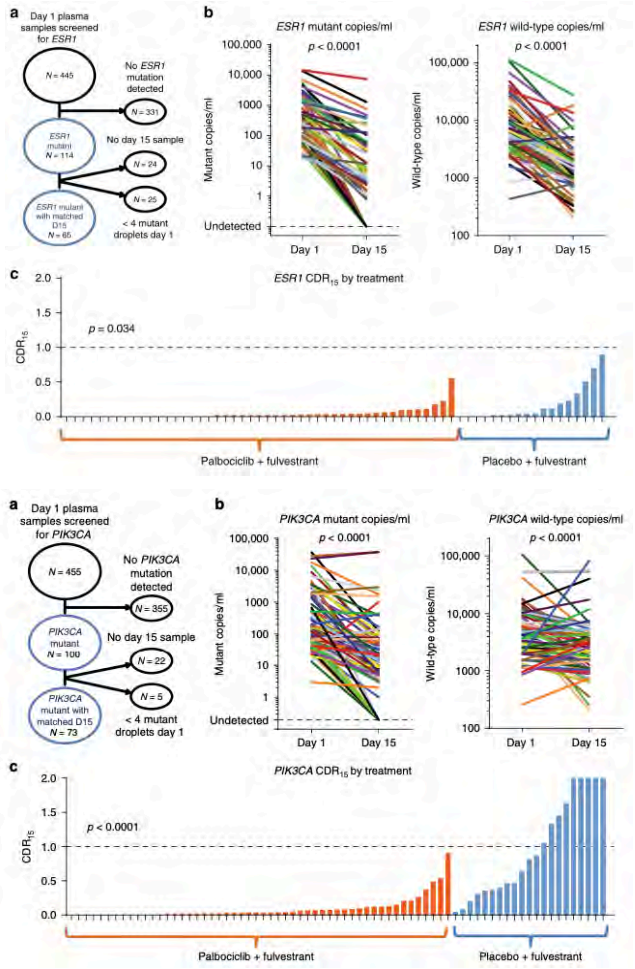


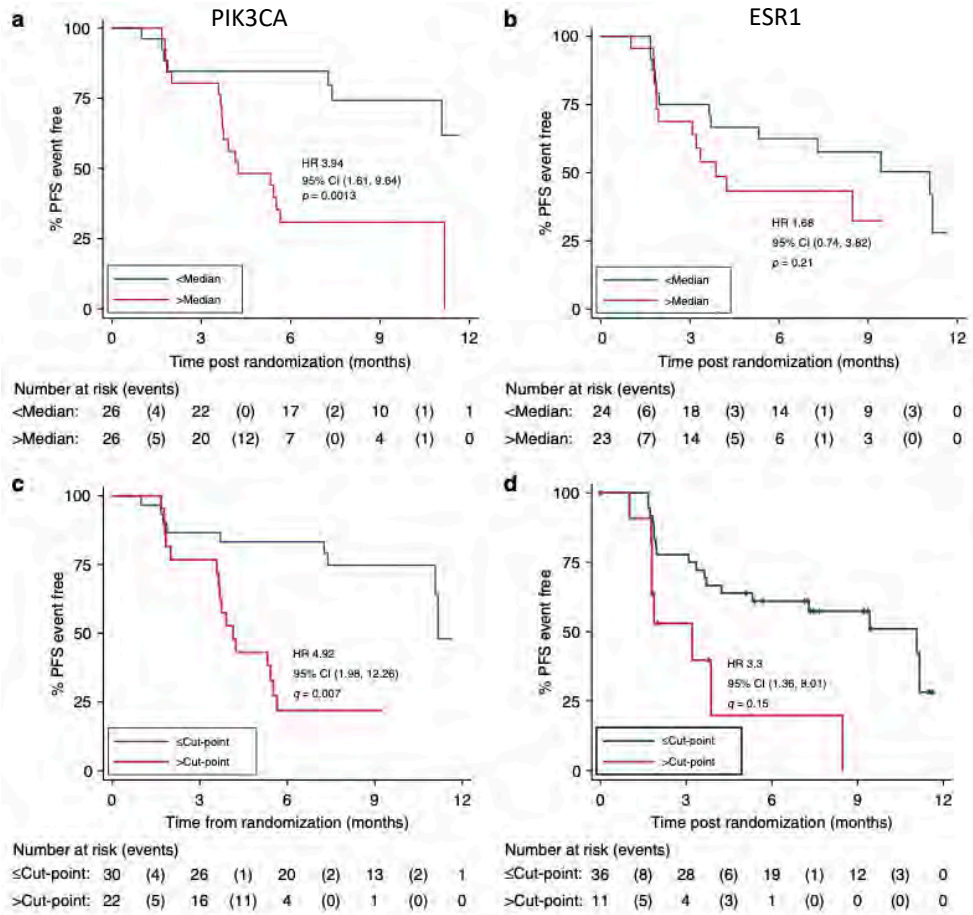


Prat A. J Clin Oncol 2021. 39:1458-1467; Carey, L. et al. Cancer Res. 2022. 82, GS2-00

Early drop in ctDNA levels correlates with prognostic in patients treated with CDK4/6i + ET

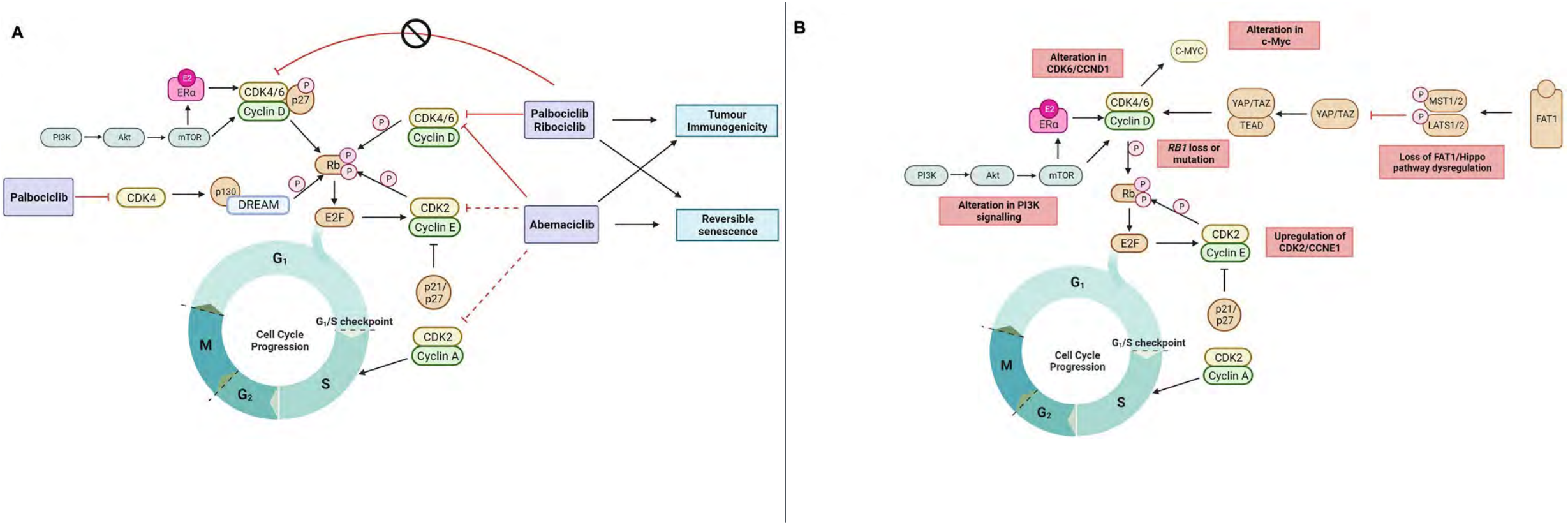
Early PIK3CA ctDNA dynamics predict progression-free survival (PFS) on palbociclib and fulvestrant more strongly than ESR1 dynamics





o'leary b. nature communications | (2018)9:896

Mechanisms of ET and CDK 4/6 inhibitor acquired resistance



Zhou F. Front Cell Dev iol 2023

MAINTAIN: continuing CDK 4/6 inhibitors post progression

Key Entry Criteria
- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

1:1

N=120

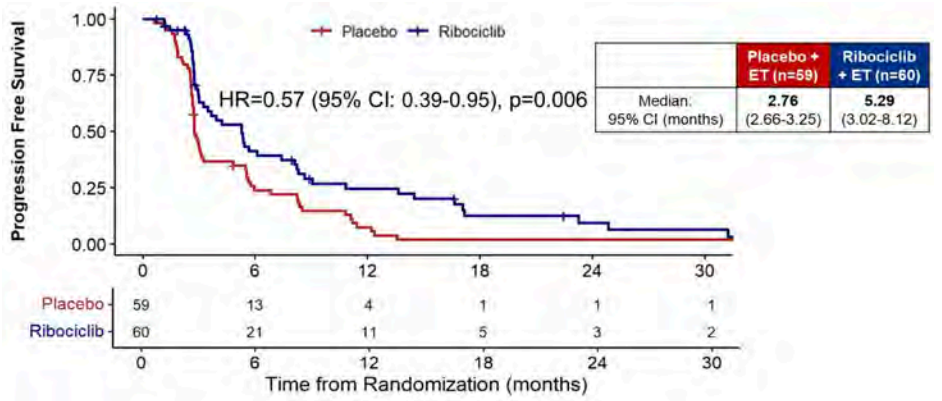
Arm 1
Ribociclib + Switch Endocrine Therapy*

Arm 2
Placebo + Switch Endocrine Therapy*

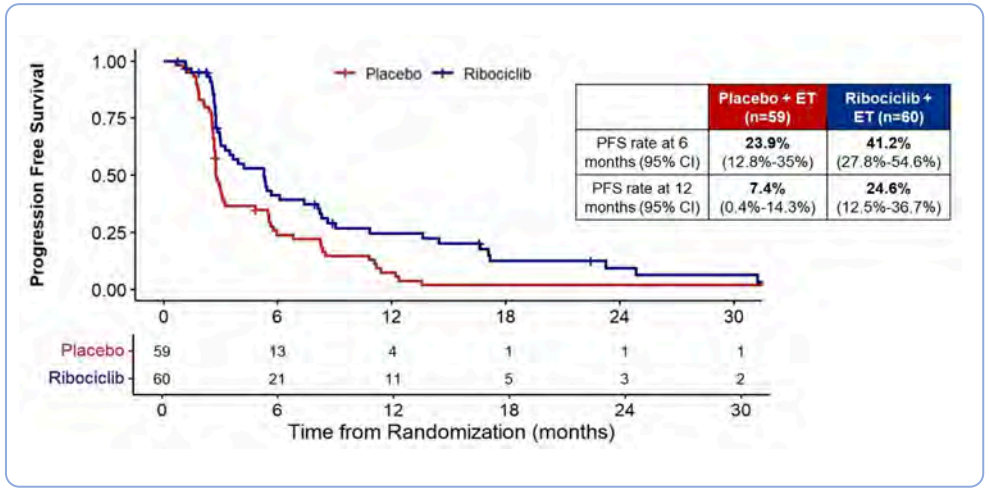
Primary Endpoint
- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints
- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

• Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median, 95% CI (months)	2.76 (2.66-3.25)	5.29 (3.02-8.12)



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
PFS rate at 6 months (95% CI)	23.9% (12.8%-35%)	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%)

- Prior CDK4/6 inhibitor: 87% Palbociclib
- Prior duration of CDK 4/6 inhibitor: 15.5 vs 17months
- 60% visceral metastasis

Kalinsky K. LBA 1004 ASCO 2022

PACE: Palbociclib After CDK 4/6i and Endocrine Therapy

Luminal BC patients progressing to CDK 4/6i benefit from immunotherapy?

Eligibility Criteria
- HR+/HER2- MBC
- Progression on CDK4/6i and ET, with ≥6mo SD on prior regimen
- ≤2 prior lines ET for MBC
- No prior fulvestrant
- 0-1 prior chemo for MBC

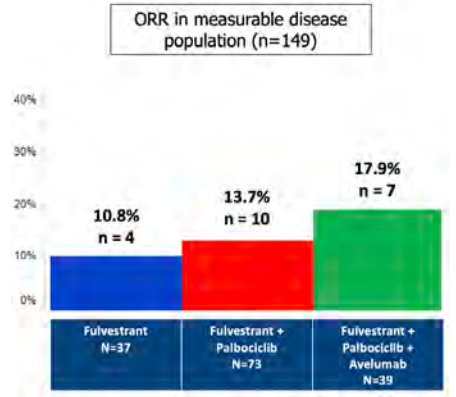
→ 1:2:1 randomization; stratified by exposure to chemo between CDK4/6i and entry onto trial

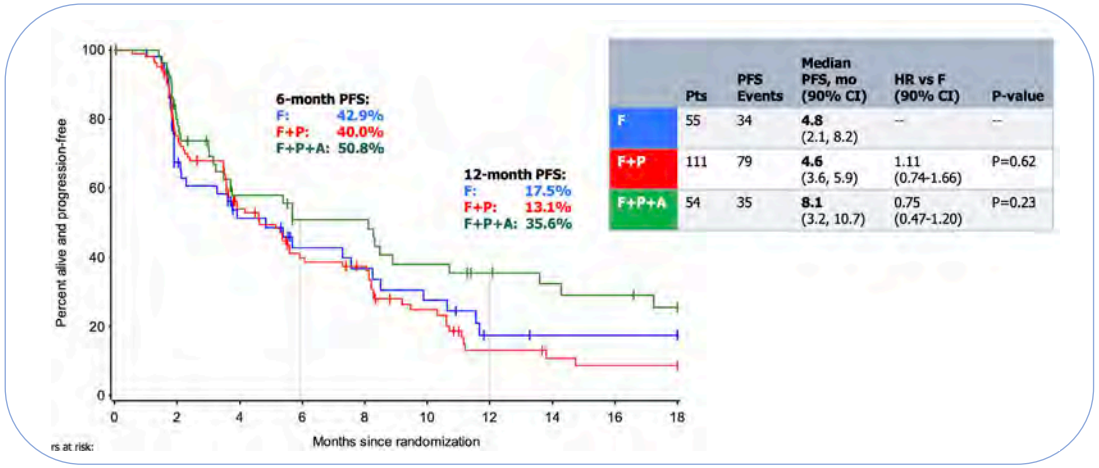
N=220

RANDOMIZE

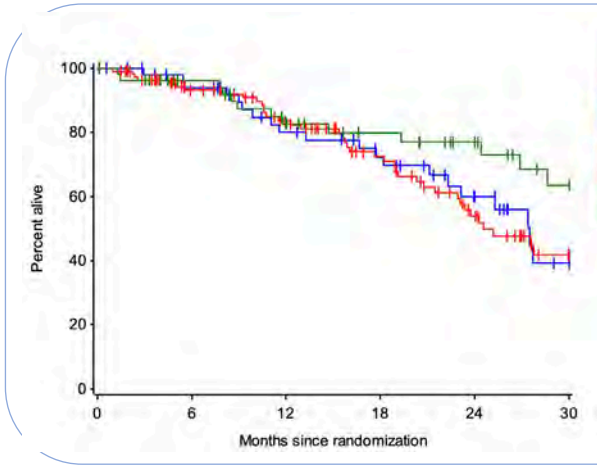
- **Fulvestrant:** 500 mg IM C1D1,15, then q28d
- **Fulvestrant:** 500 mg IM C1D1,15, then q28d **Palbociclib:** 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment)
- **Fulvestrant:** 500 mg IM C1D1,15, then q28d **Palbociclib:** 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment) **Avelumab:** 10 mg/kg IV q14d

- 90% received prior Palbociclib





	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	4.8 (2.1, 8.2)	--	--
F+P	111	79	4.6 (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	8.1 (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

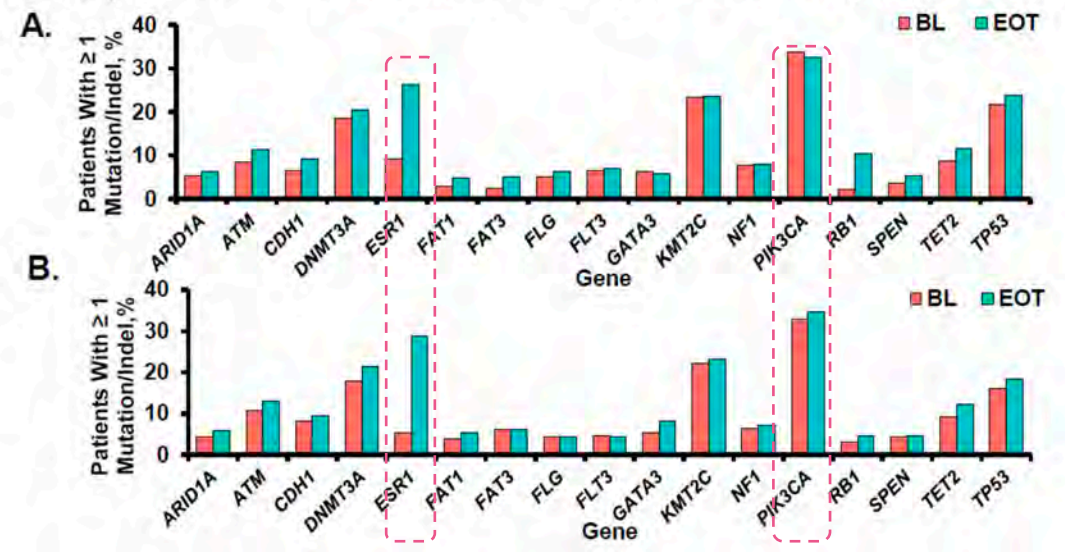


	Pts	OS Events	Median OS, mo (90% CI)	HR vs F (90% CI)
F	55	23	27.5 (21.1, 38.0)	--
F+P	111	43	24.6 (21.5, 33.3)	1.02 (0.67-1.56)
F+P+A	54	17	42.5 (26.8, 46.0)	0.68 (0.40-1.15)

Mayer EL GS3-06 SABCS 2022

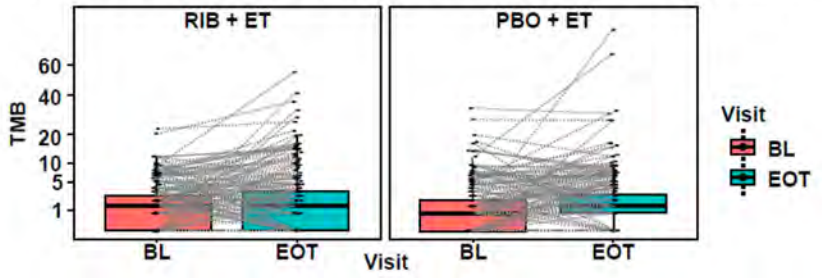
MONALESSA 2, 3, -7: Mechanisms of Acquired Resistance to Ribocilib Plus Endocrine Therapy

Frequency of Gene Alterations at BL and EOT for (A) RIB and (B) PBO Arms



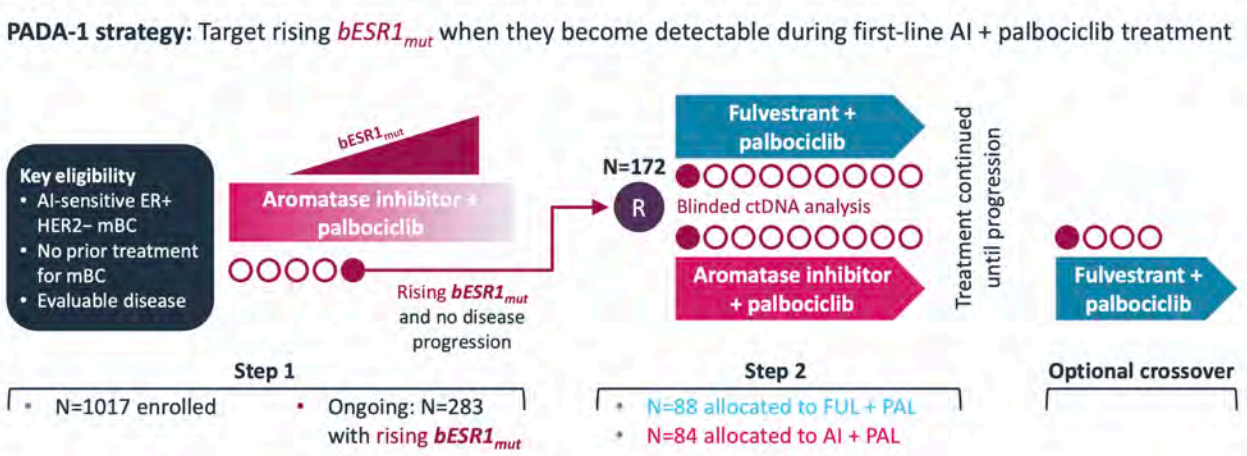
- In the RIB arm, the frequency of alterations in RB1 (10.4% vs 2.0%), ATM (11.3% vs 8.4%), FAT1 (4.8% vs 3.0%), FAT3 (5.0% vs 2.5%), and TET2 (11.6% vs 8.6%) was higher at EOT vs BL (FDR-adj P < .10)
- *GATA3* was higher at EOT vs BL in the ET alone arm but not with the combination of RIB + ET
- **In both arms, the frequency of alterations in ESR1 was also higher at EOT vs BL for RIB (26.3% vs 9.1%) and PBO (28.9% vs 5.4%) (FDR-adj P < .0001)**

Figure 6. TMB at BL and EOT in RIB and PBO Arms

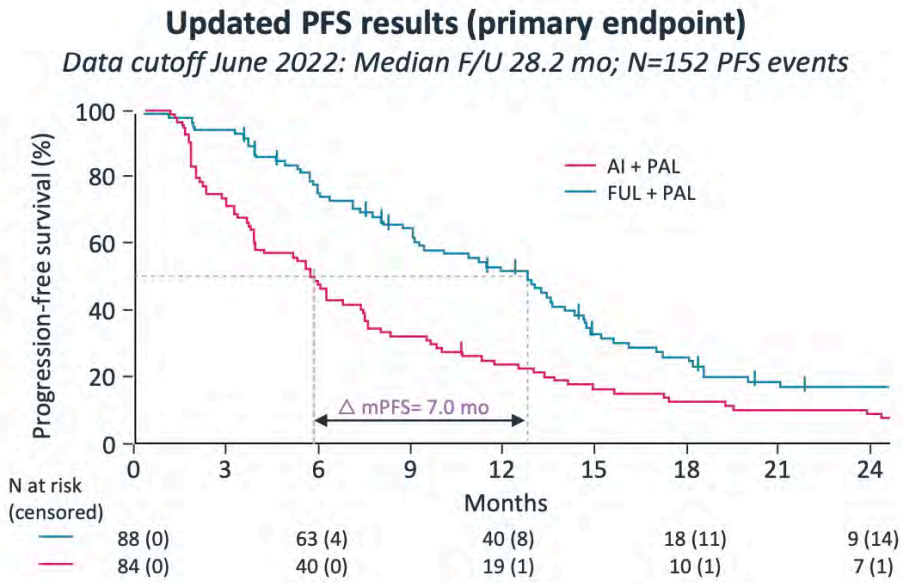


- An increase in TMB from BL to EOT was observed in both arms (*P* < .0001)
- **In the RIB arm, the percentage of patients with high TMB (> 10 mutations/Mb) increased from BL (1.1%) to EOT (5.7%) (McNemar P = .0001)**

PADA-1: characterization of ESR1 mutations with aromatase inhibitor or fulvestrant + palbociclib therapy



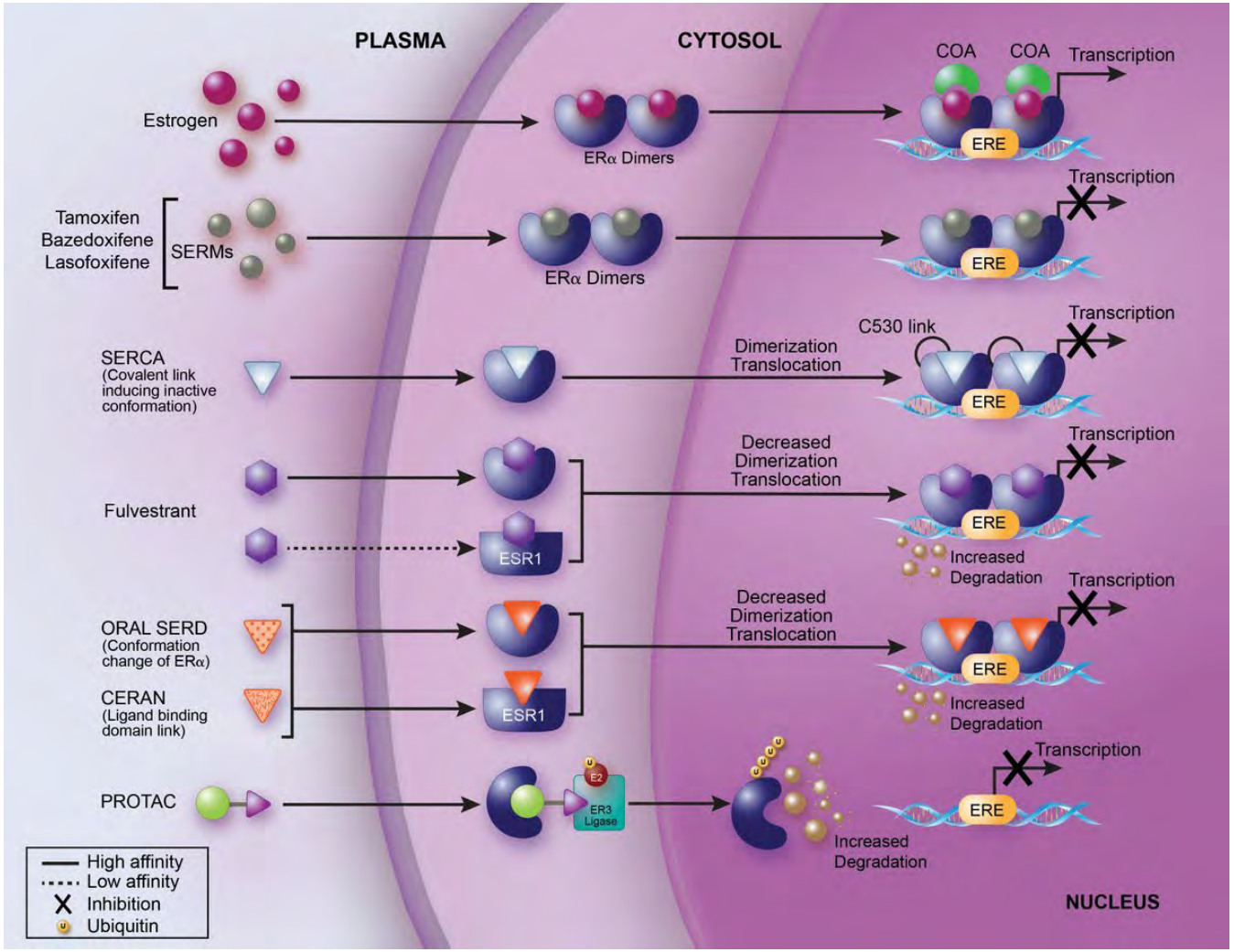
PADA-1: Updated PFS results



	ASCO 2023 analysis		2021 analysis[1]	
	FUL + PAL	AI + PAL	FUL + PAL	AI + PAL
mPFS, mo (95% CI)	12.8 (9.3–14.7)	5.8 (3.9–7.5)	11.9	5.7
HR (95% CI)	0.54 (0.38–0.75)		0.61	
Optional crossover (n=49) mPFS (95% CI)	3.5 (2.4–5.4)			

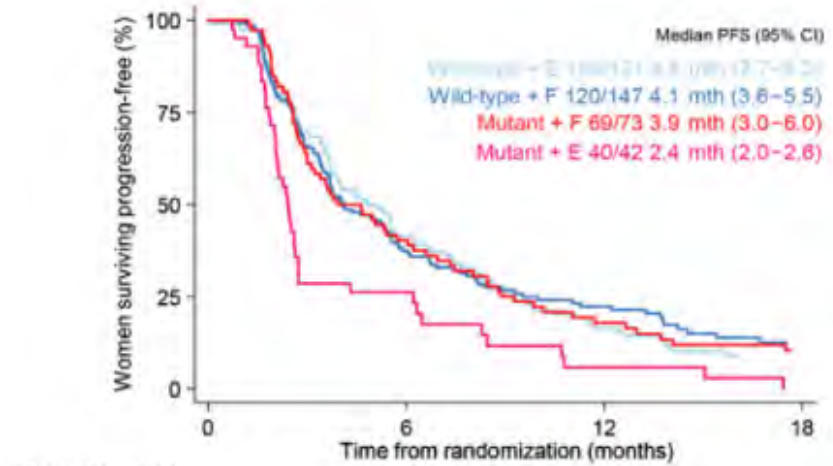
Bidard FC. ASCO 2023. Abst 1002

New frontiers for ER inhibition and drug development



Ferraro; Cancer Treat Rev 2022

ESR1 Mutations and OS on Fulvestrant vs Exemestane in Advanced HR+ Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT

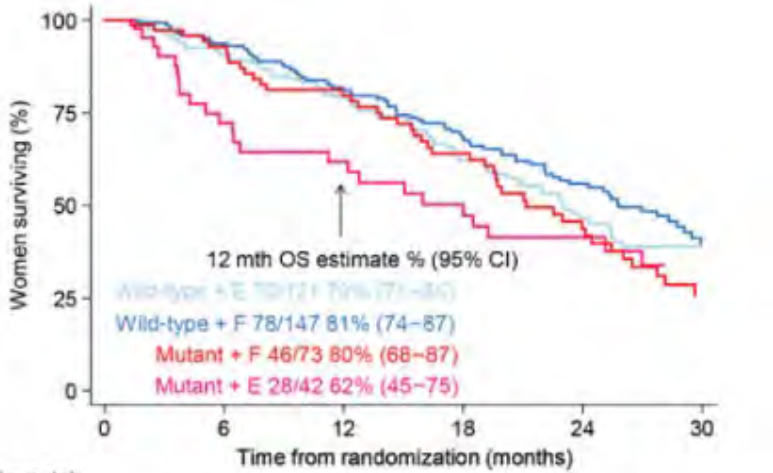


N at risk (events)

Wild-type + E	121	(70)	49	(28)	17	(8)	7
Wild-type + F	147	(87)	50	(19)	25	(10)	8
Mutant + E	42	(31)	9	(7)	2	(2)	0
Mutant + F	73	(43)	29	(16)	12	(5)	6

Figure 2.

PFS in the combined analysis of SoFEA and EFECT by *ESR1* mutation status and treatment. Patients with *ESR1* mutation detected: HR, 0.59; 95% CI, 0.39–0.89; $P = 0.01$. Patients without *ESR1* mutation detected: HR, 1.05, 95% CI, 0.81–1.37; $P = 0.69$. Interaction test $P = 0.02$. E, exemestane; F, fulvestrant; mth, month; mutant, *ESR1* mutation detected; wild-type, *ESR1* mutation not detected.



N at risk (events)

Wild-type + E	121	(11)	109	(14)	93	(19)	68	(15)	37	(6)	21
Wild-type + F	147	(9)	134	(18)	113	(17)	89	(15)	59	(13)	26
Mutant + E	42	(11)	28	(4)	22	(4)	17	(3)	11	(2)	6
Mutant + F	73	(5)	64	(9)	52	(10)	38	(11)	23	(8)	9

Figure 3.

OS in the combined analysis of SoFEA and EFECT by *ESR1* mutation status and treatment. Patients with *ESR1* mutation detected: restricted mean survival analysis $P = 0.04$. Patients without *ESR1* mutation detected: restricted mean survival analysis $P = 0.69$. E, exemestane; F, fulvestrant; mth, month; mutant, *ESR1* mutation detected; wild-type, *ESR1* not detected.

Turner N, et al. Clin Cancer Res 2020;26:5172–7

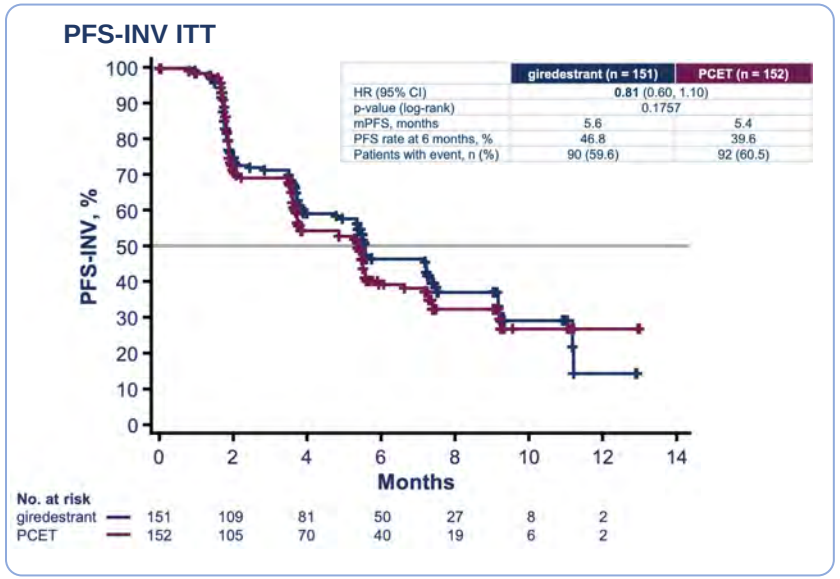
Oral SERD trial landscape in pretreated HR+/HER2- metastatic breast cancer

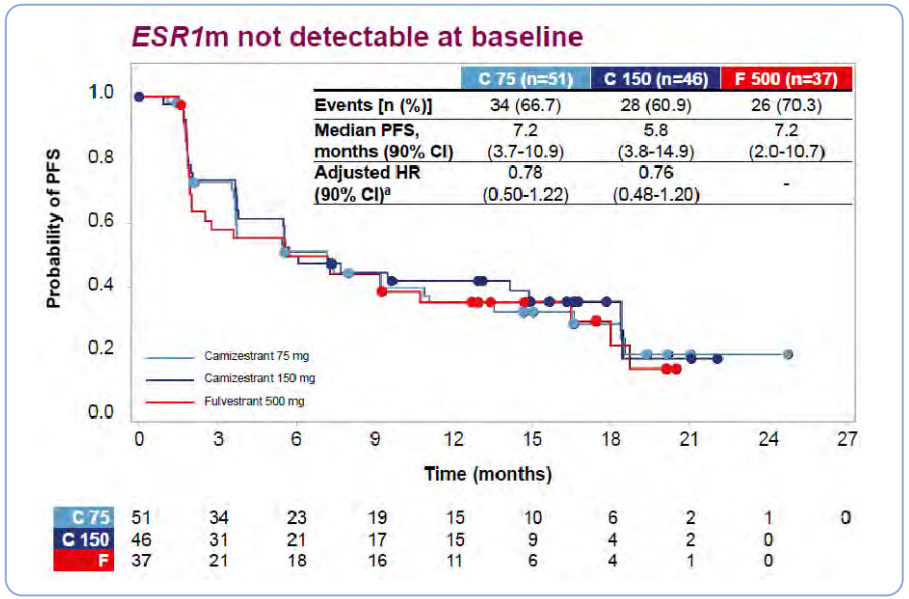
	EMERALD[1]	SERENA-2[2]	EMBER-3[3]	AMEERA-3[4-6]	acelERA[6-9]
Treatment	**Elacestrant**	**Camizestrant**	**Imlunestrant** +/- abemaciclib	**Amcenestrant**	**Giredestrant**
Control Arm	fulvestrant / AIs	fulvestrant	fulvestrant / exemestane	fulvestrant / AIs / tamoxifen	fulvestrant / AIs
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	**Required (100%)**	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	**YES**	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	**YES**	YES	NO	YES	YES
Data readout	**Positive (Registrational)**	Positive (Non-Registrational)	Ongoing	Negative	Negative

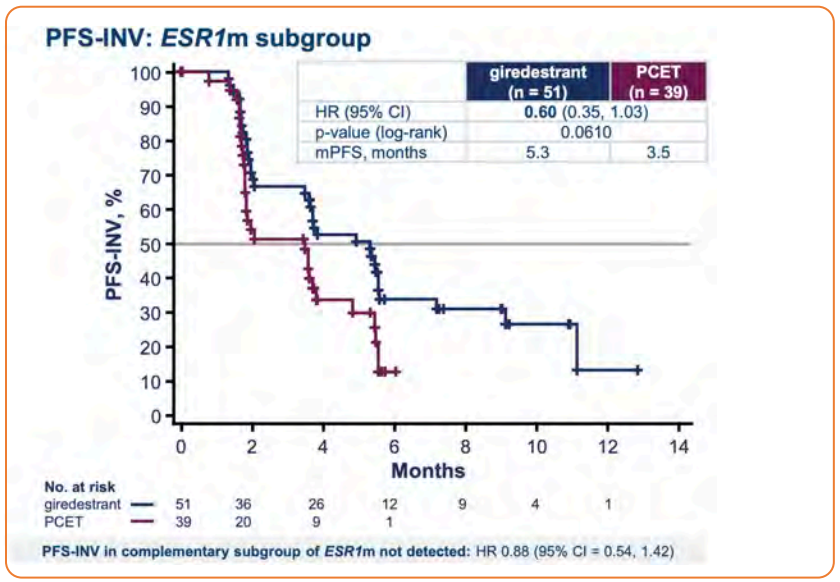
1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, https://clinicaltrials.gov/ct2/show/NCT04214288; 3. EMBER-3. Clinical Trials.gov identifier: NCT04975308. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04975308; 4. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04059484; 5. Tolaney SM, et al. *Ann Oncol.* 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback. Accessed July 20, 2022; 7. acelERA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04576455; 8. Martin M, et al. *J Clin Oncol*. 2021;39(15):abstr TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol.* 2022;33(7):S88-S121 (abstr 211MO).

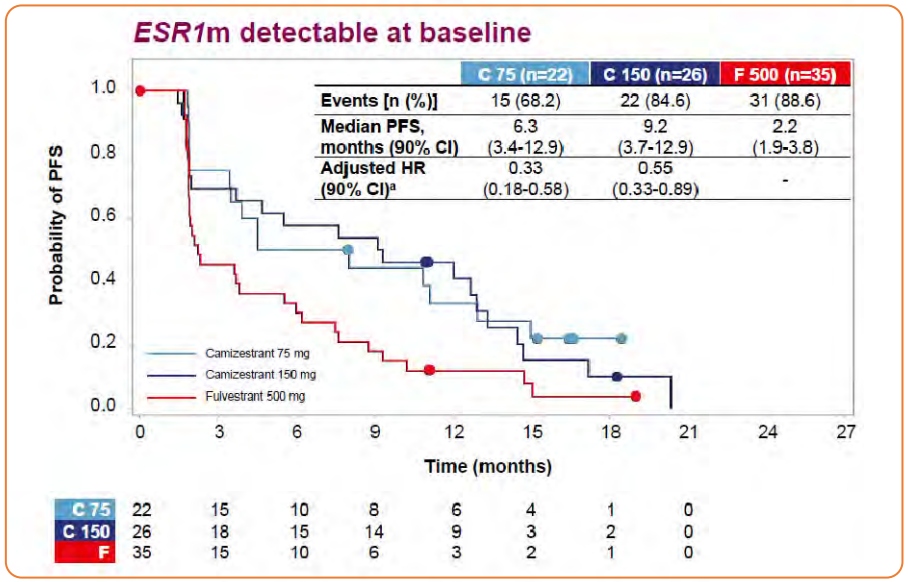
Study design: acelERA BC (NCT04576455)

SERENA-2 study overview









Martin M. ESMO 2022; Oliveira M SABCS 2022

EMERALD Phase 3 Study Design

International, multicenter, randomized, open-label, active-controlled, event-driven, phase III study

Patient Inclusion Criteria (N = 466)

- Aged ≥ 18 years
- Locally advanced or metastatic breast adenocarcinoma not amenable to curative therapy
- ER+/HER2- disease
- Postmenopausal
- Measurable disease or non-measurable bone-only disease
- 1 to 2 lines of previous ET and 0 to 1 lines of chemotherapy for metastatic disease
- Prior CDK4/6 inhibitor treatment with fulvestrant or an aromatase inhibitor (AI)
- Appropriate candidate for ET
- Confirmed estrogen receptor 1 (*ESR1*) mutation status

1:1 randomization

Elacestrant 400 mg orally, once daily

Investigator's choice of anastrozole 1 mg/d, exemestane 25 mg/d, letrozole 2.5 mg/d, fulvestrant 500 mg (cycle 1: d1, 15; cycle 2: d1; cycle3+: d1)

End Points

Primary:

- **PFS in all patients**
- **PFS in patients with *ESR1* mutations only**

Secondary:

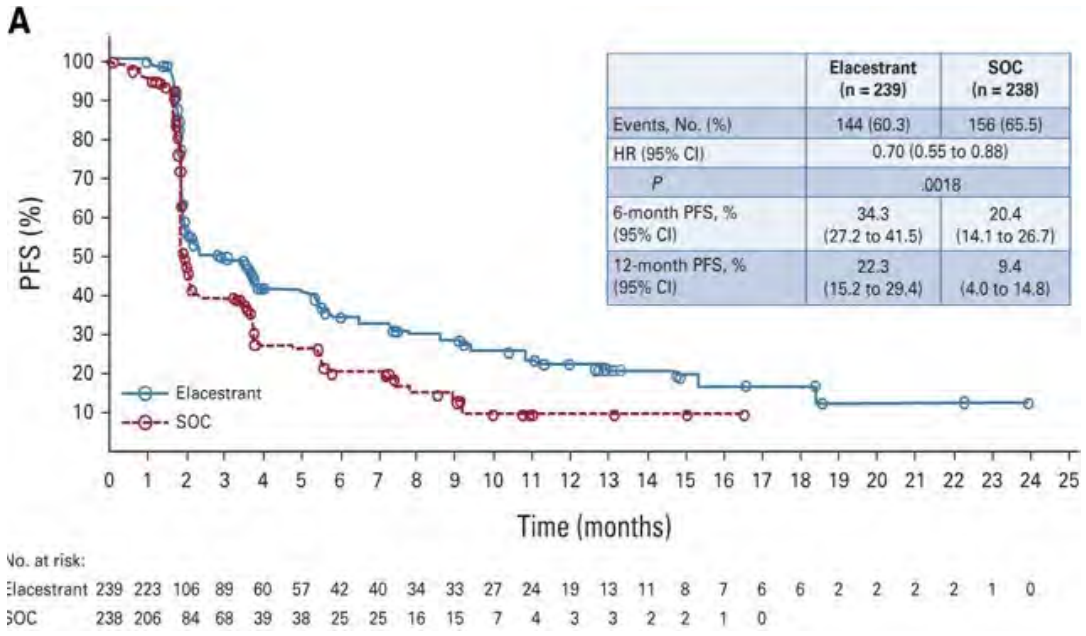
- **Overall survival (OS) in all patients**
- **OS in patients with *ESR1* mutations only**

Stratification factors: *ESR1* mutation status, presence of visceral metastases, previous fulvestrant treatment

Bidard FC et al. J Clin Oncol 40:3246-3256

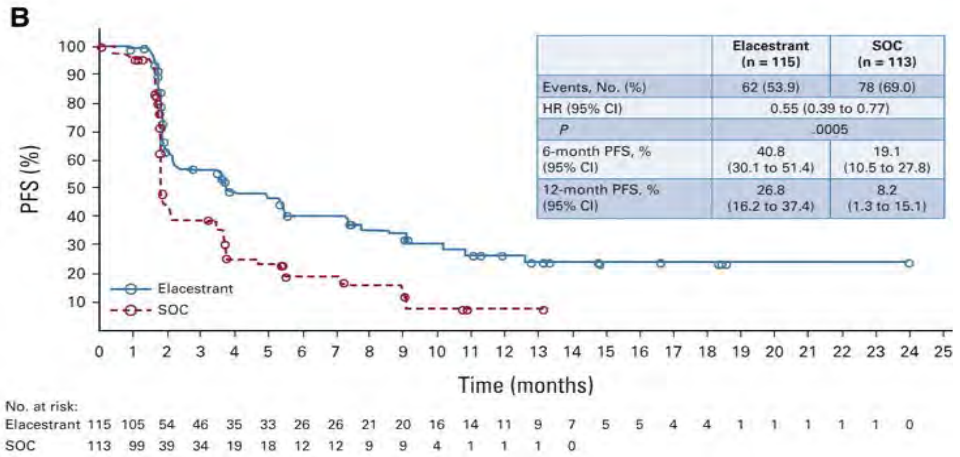
EMERALD: Primary endpoint PFS in all pts and ESR1 mut only

All pts (ITT)

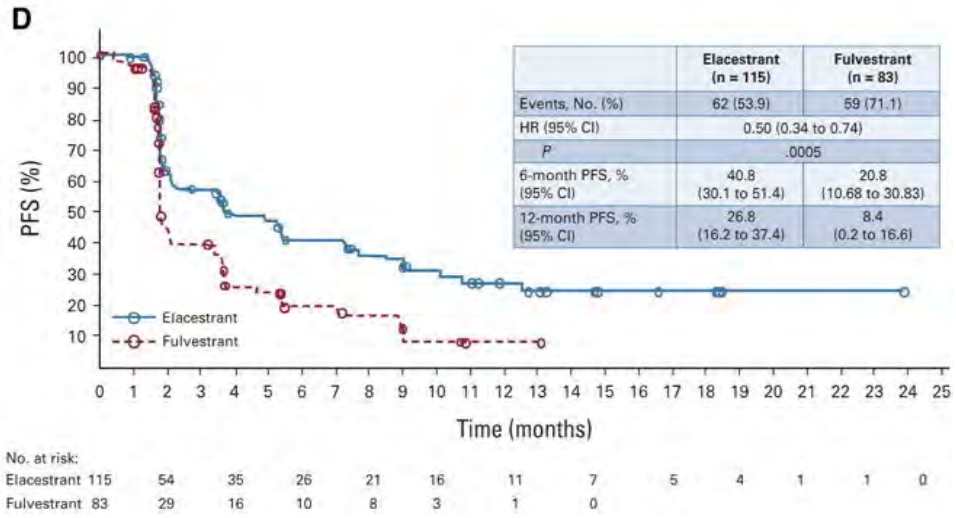


	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

Patients with ESR1mut



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

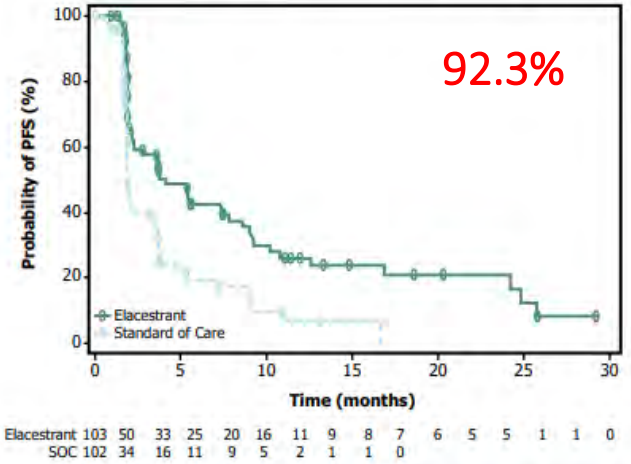


	Elacestrant (n = 115)	Fulvestrant (n = 83)
Events, No. (%)	62 (53.9)	59 (71.1)
HR (95% CI)	0.50 (0.34 to 0.74)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	20.8 (10.68 to 30.83)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.4 (0.2 to 16.6)

Bidard et al. ; J Clin Oncol 2022 403246-3256.

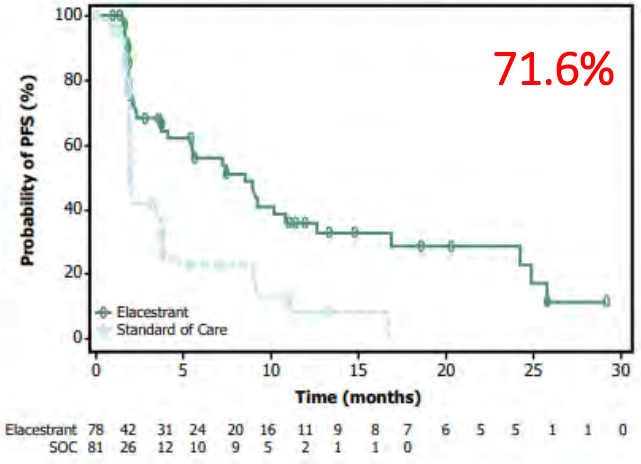
EMERALD: PFS by duration prior CDK4/6i (ESR1mut)

At least 6 mo CDK4/6i



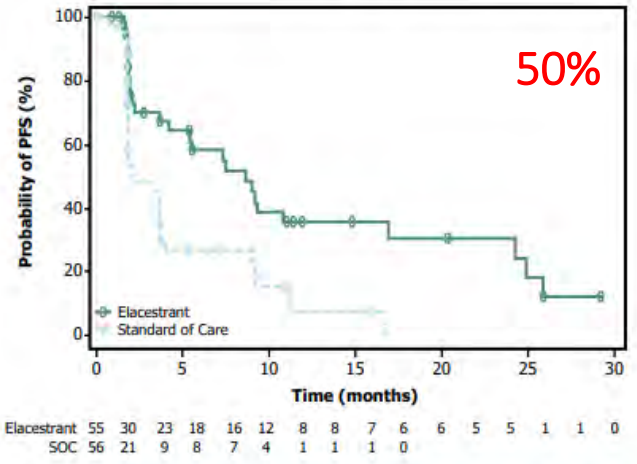
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i

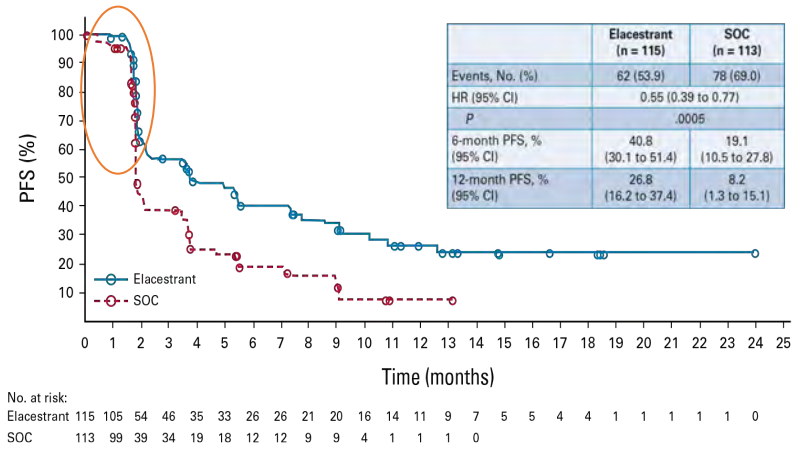


	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Bardia et al; SABCS 2022 GS3-01

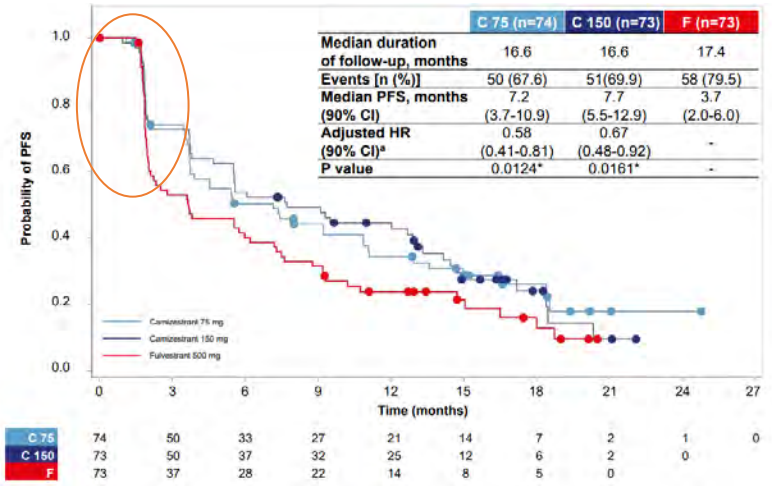
ET resistance and impact on sequential use of ET +- combinations or new agents

EMERALD



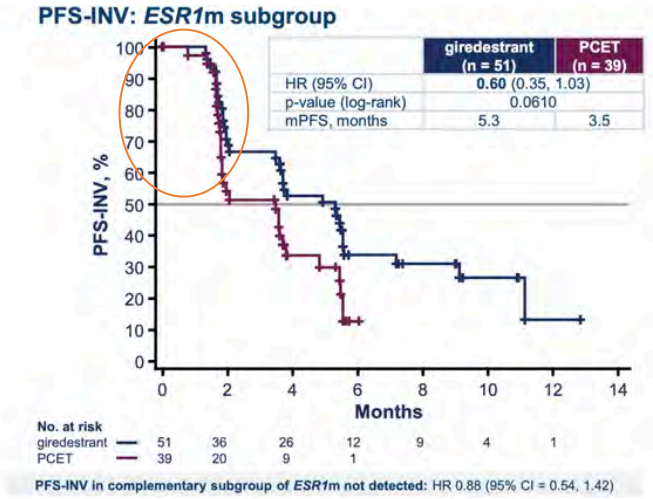
	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

SERENA-2



	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

acelERA



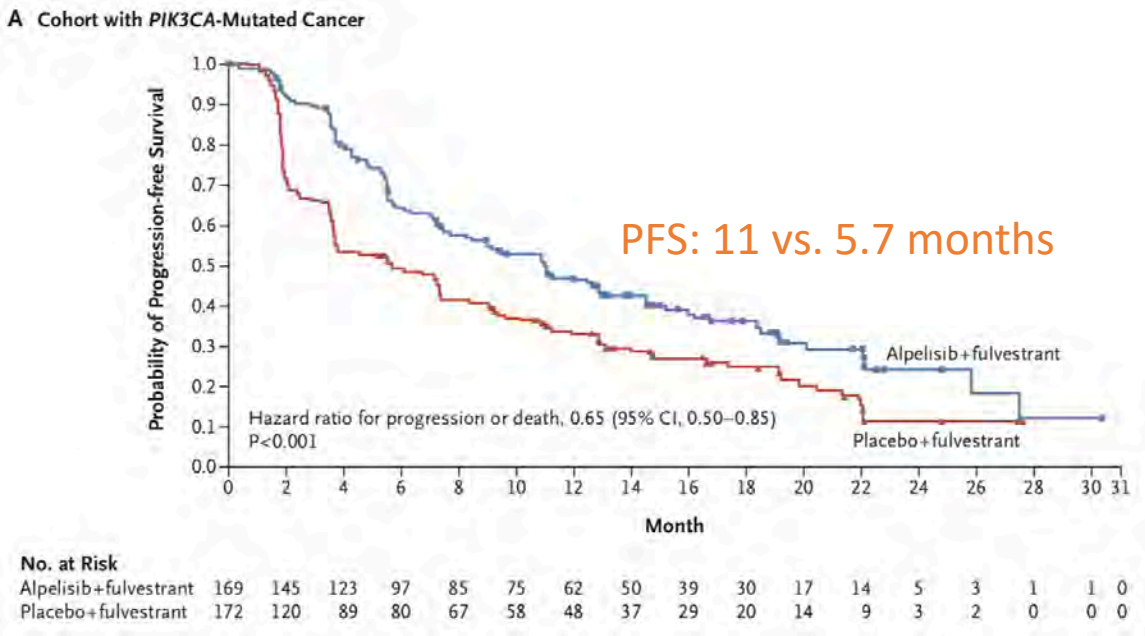
	giredestrant (n = 51)	PCET (n = 39)
HR (95% CI)	0.60 (0.35, 1.03)	
p-value (log-rank)	0.0610	
mPFS, months	5.3	3.5

Non-candidates to ET

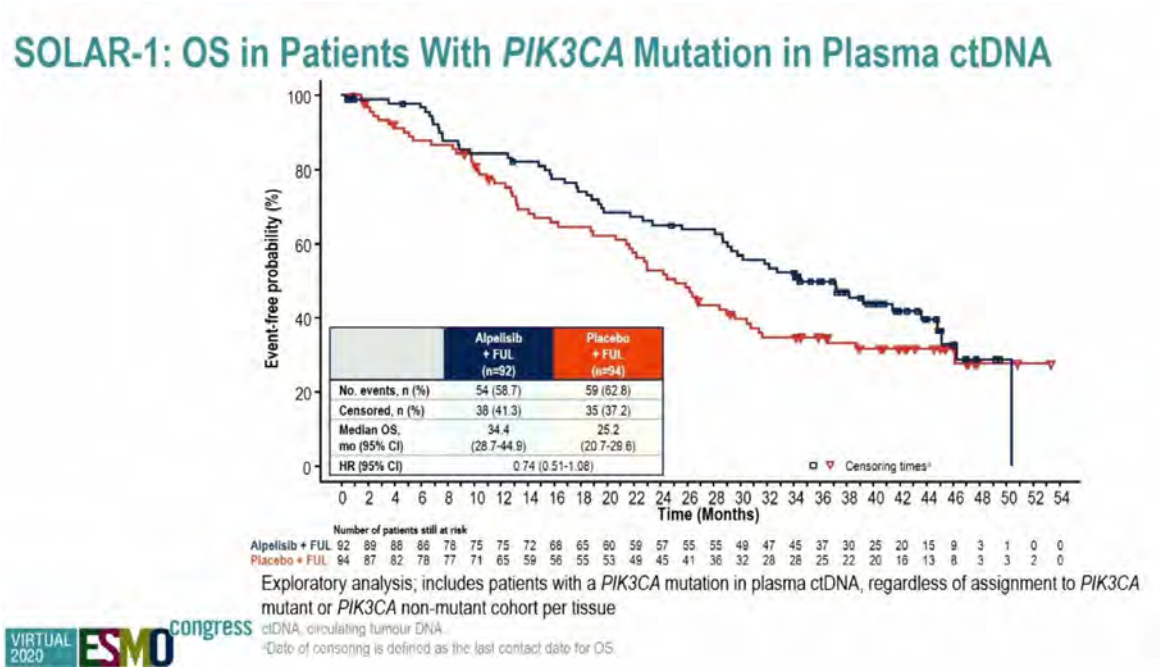
How do we select from our available treatments?
Fulvestrant
Rechallenge CDK4/6 inhibitors (+ ET)
Fulvestrant + Capivasertib
Exemestane (Fulvestrant) + Everolimus
Fulvestrant + Alpelisib (in PIK3CAmut)
Elacestrant (in ESR1mut)
Olaparib – Talazoparib in gBRCA1/2mut
ADCs

Bidard FC et al. J Clin Oncol 40:3246-3256; Martin M. ESMO 2022; Oliveira M SABCS 2022

SOLAR-1: Alpelisib in *PIK3CA*-Mutated HR+/HER2- MBC



PFS: 11 vs. 5.7 months



ORR: 35.7% vs. 16.3%

PIK3CA mutation by means of polymerase-chain-reaction analysis of mutation hot spots in the C2, helical, and kinase domains of PI3K (corresponding to exons 7, 9, and 20, respectively) with the use of a tumor-tissue sample

Andre F. NEJM 2019

CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

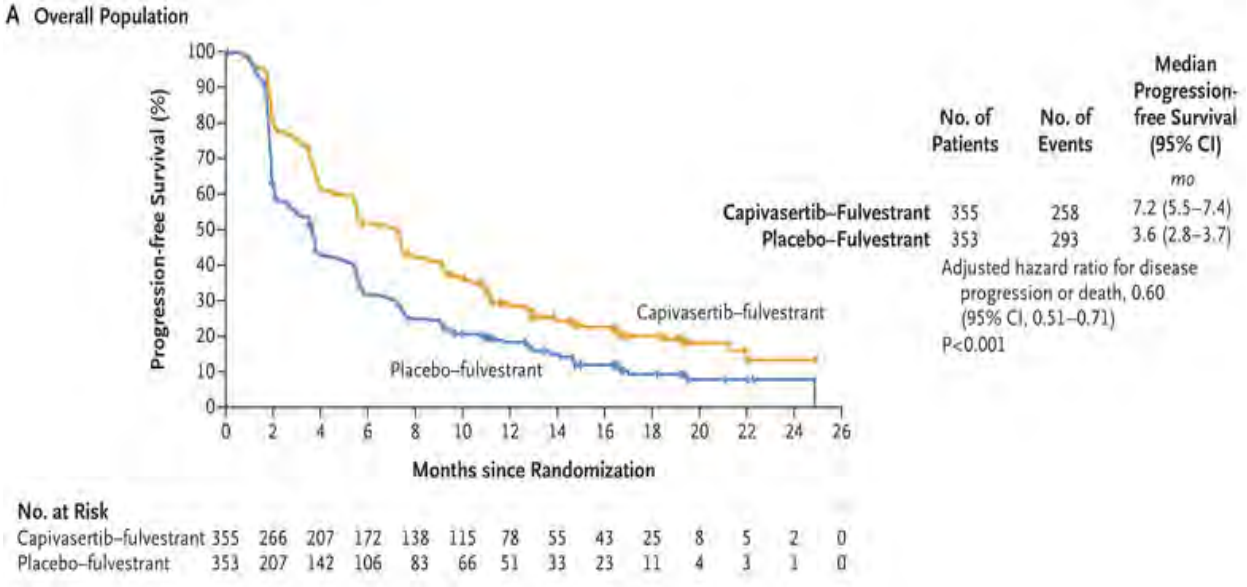
Key secondary endpoints

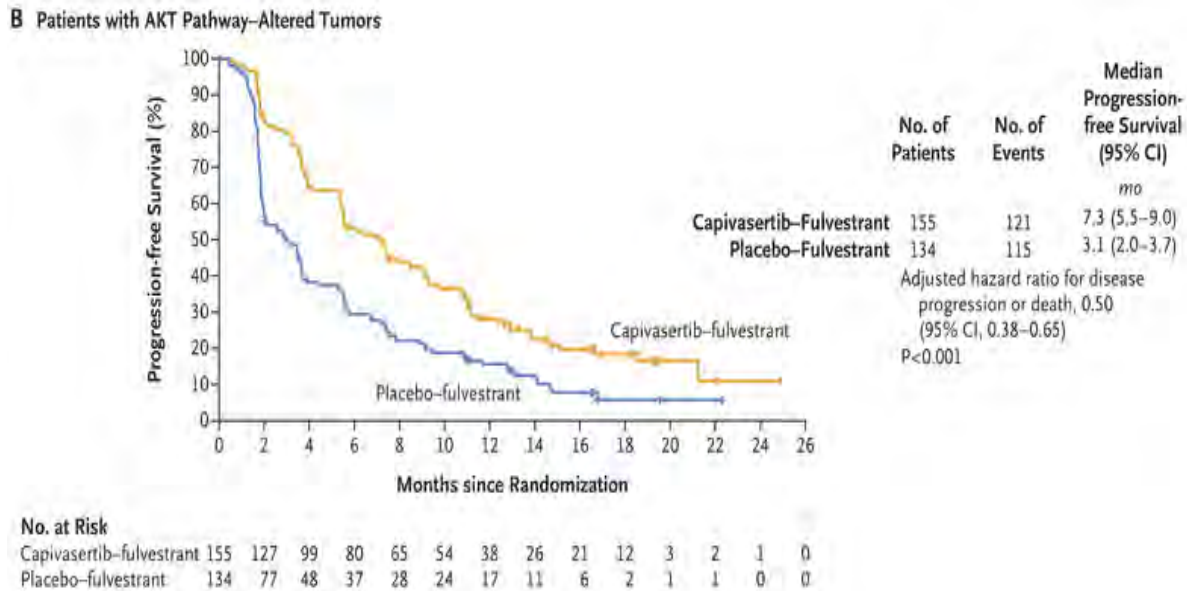
Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

CAPItello-291: Primary endpoint PFS in ITT and AKT pathway alterations





- **Visceral metastasis: 66% vs73%**
- **Endocrine resistance: primary 38% vs 41% secondary 61% vs 59%**
- **Prior ET for ABC: ≥1 90% vs 85%**
- **Previous CDK 4/6i for ABC: 72% vs 67%**

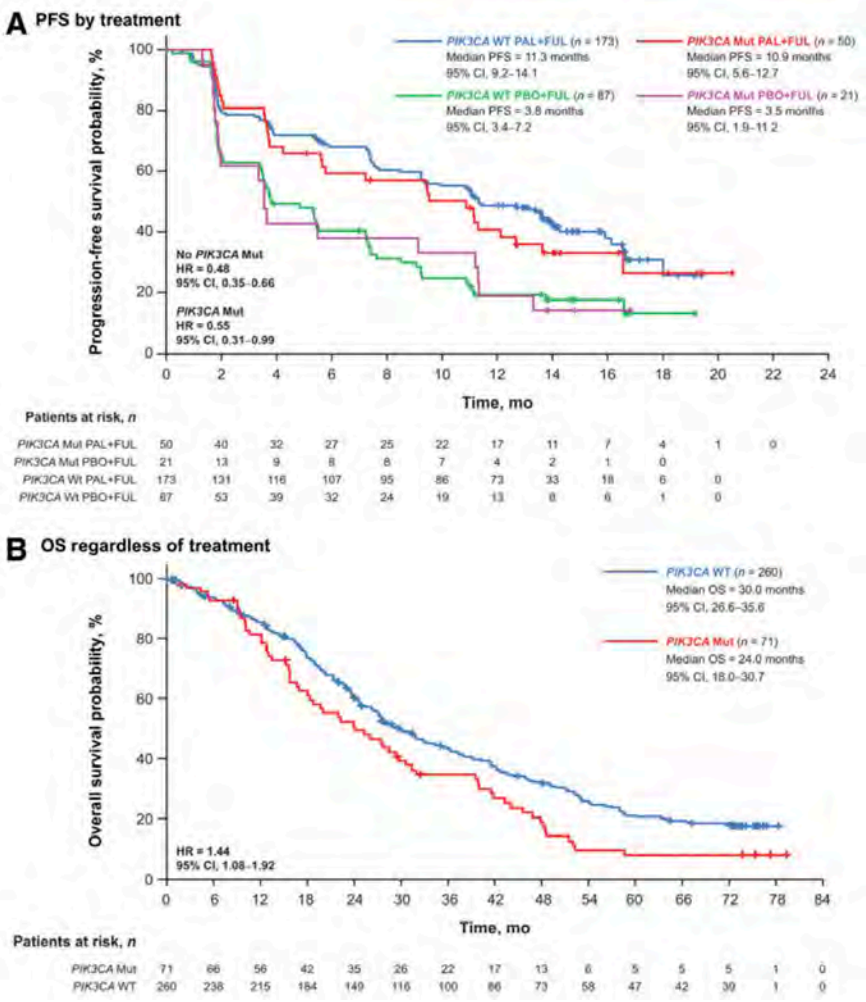
Any AKT pathway alterations 43.7% vs 38%

- **PIK3CA only 31% vs 26.1%**
- PIK3CA and AKT1 0.6% vs 0.6%
- PIK3CA and PTEN 1.1% vs 1.5%
- AKT1 only 5.1% vs 4.2%
- PTEN only 5.9% vs 4.5%

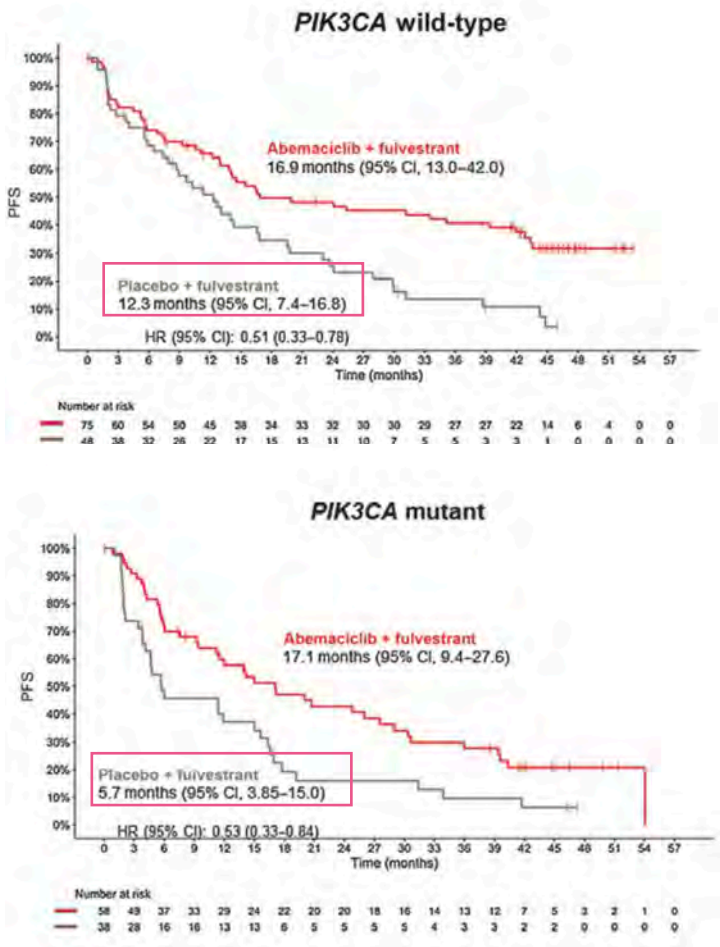
Turner GS3-04, SABCS2022 N Engl J Med 2023; 388:2058-2070

Exploratory analysis of CDK 4/6 inhibitor efficacy by PIK3CA mutation status

PALOMA 3

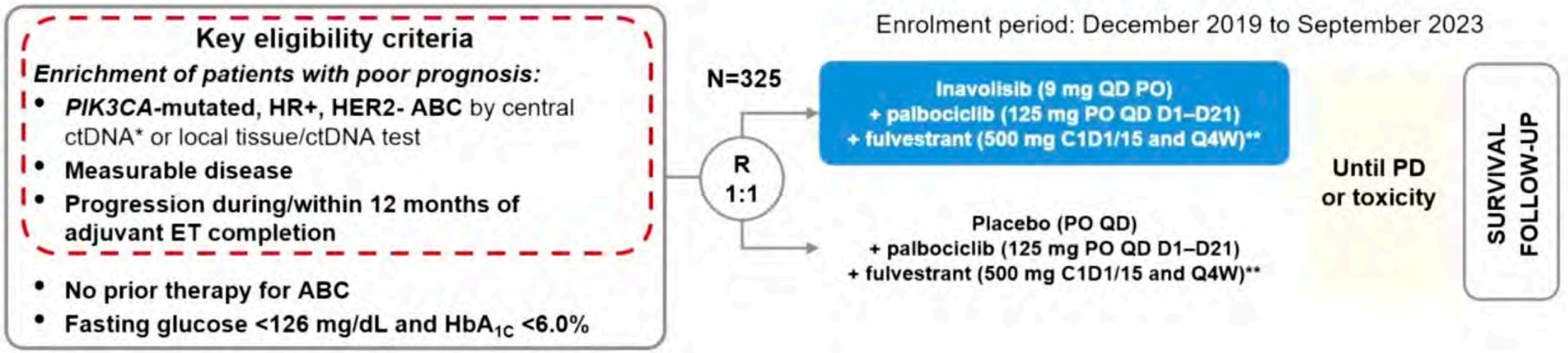


MONARCH 2



Modified Hope Hugo; Cristofanilli. Clin Cancer Res 2022; 28:3433. Tonaley Clin Cancer Res 2022:28;1500

INAVO120: Study Design



Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

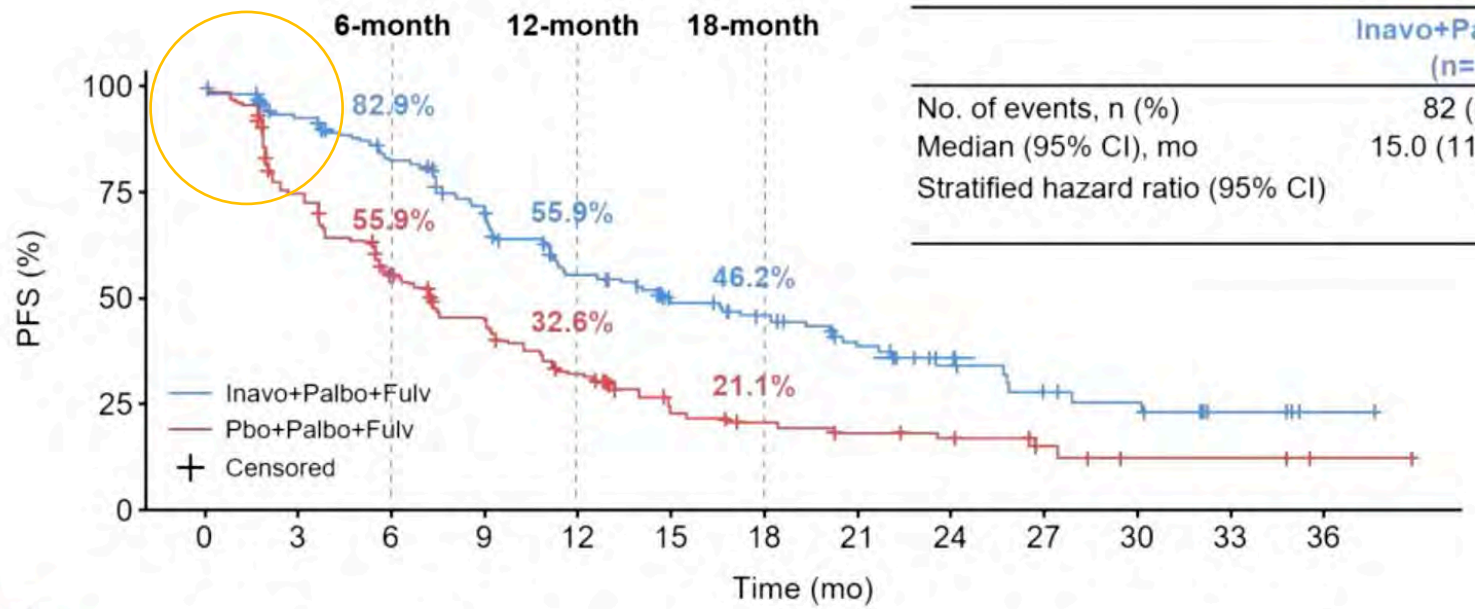
Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; ** Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29**:1634–1657.

Javheri K. SABCS 2023

INAVO120: Primary endpoint PFS (investigator-assessed)



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)** **p<0.0001**	

Median follow-up:
21.3 months

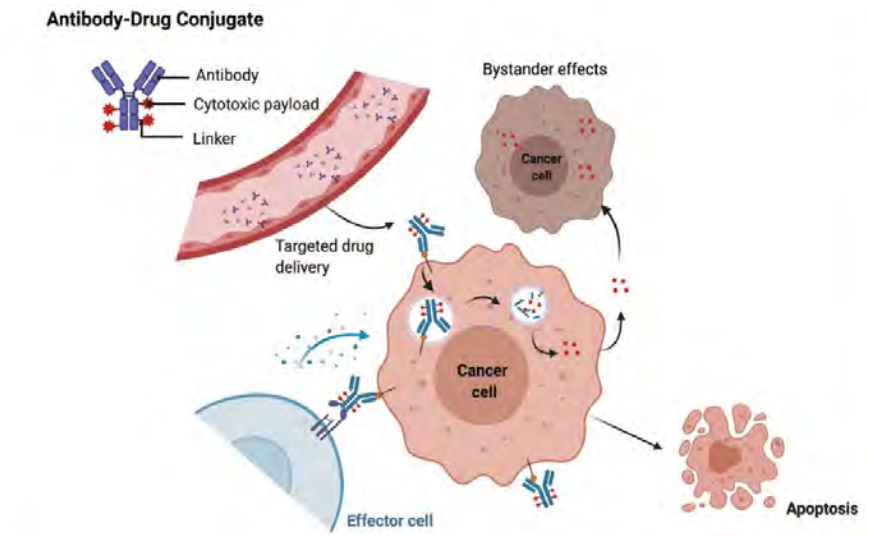
CCOD: 29th September 2023
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

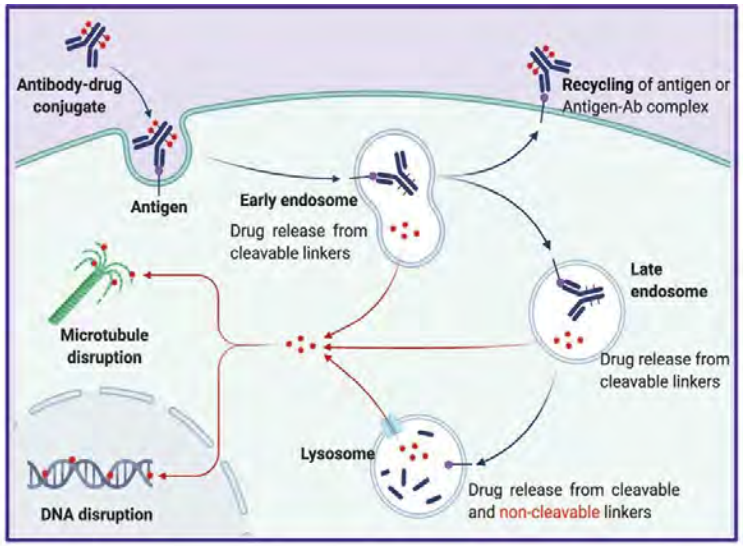
Endocrine resistance:
- 34% primary
- 66% secondary

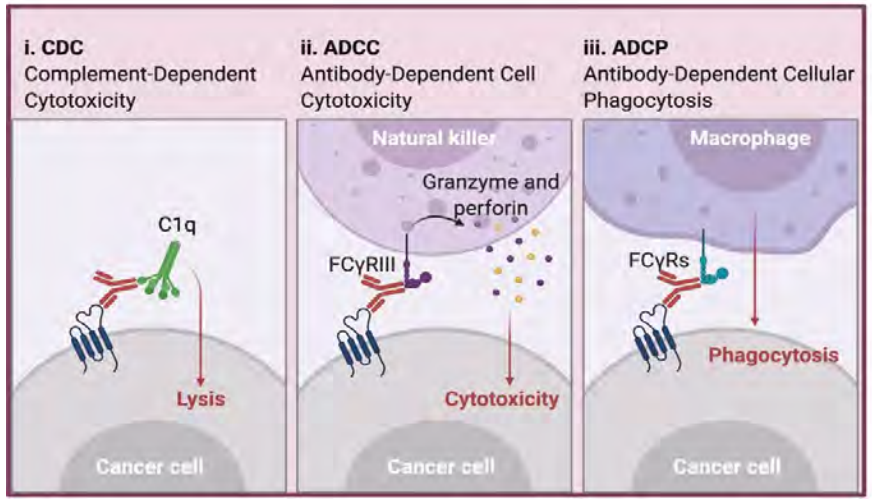
High risk features:
- 48% premenopausal
- 80% visceral mets, 50% liver mets

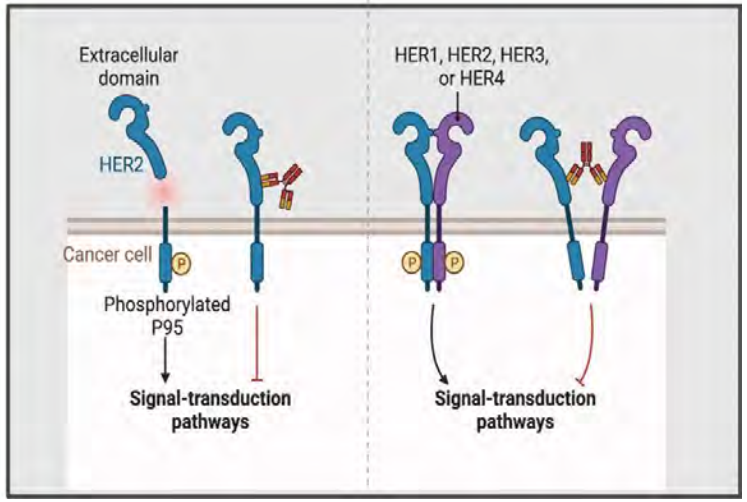
Javheri K. GS03-14, SABCS 2023

Antibody-Drug Conjugates mechanism of action





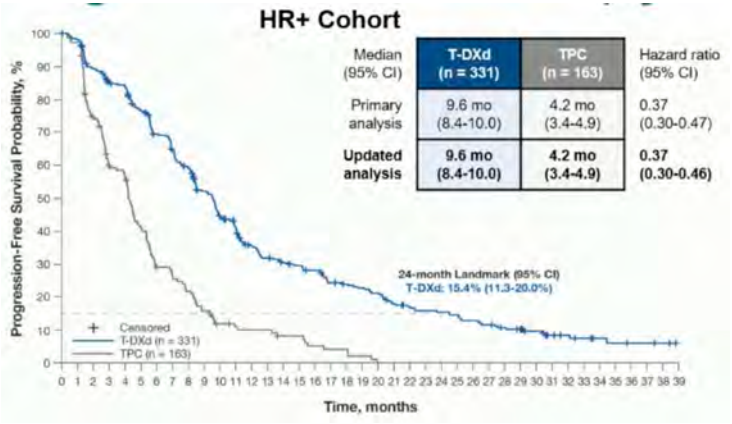




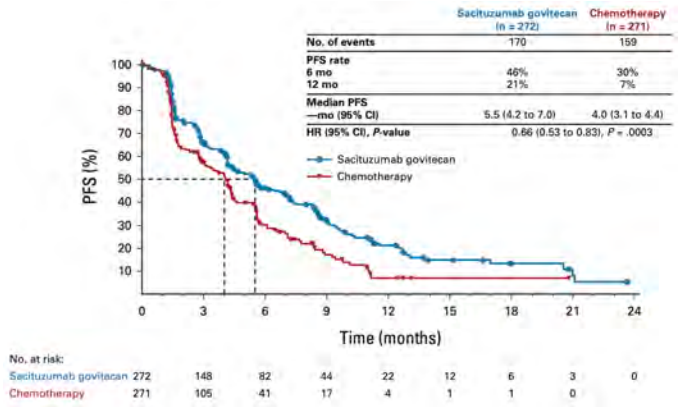
Signal Transduction and Targeted Therapy 2022

Antibody-drug conjugates for the treatment of luminal MBC progressing to prior chemotherapy

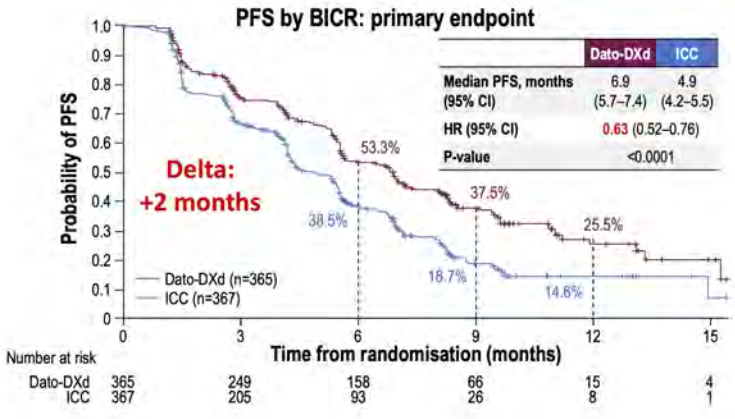
DESTINY-Breast04
Trastuzumab-DXd



TROPiCS-02
Sacituzumab Govitecan



TROPION-Breast01
Datopotamab-DXd



Anti HER2

Anti Trop2

Modi S. ESMO 2023; Rugo H J Clin Oncol 2022; Bardia A ESMO 2023;

DESTINY-Breast06: Trastuzumab deruxtecan HR+, HER2 low metastatic breast cancer whose progressed on endocrine

POPULATION

- Advanced/metastatic HR+ breast cancer
- HER2 IHC >0 <1+ or 1+ or 2+ (determined based on central IHC assessment of archival tissue collected at time of diagnosis of first metastatic disease or later)

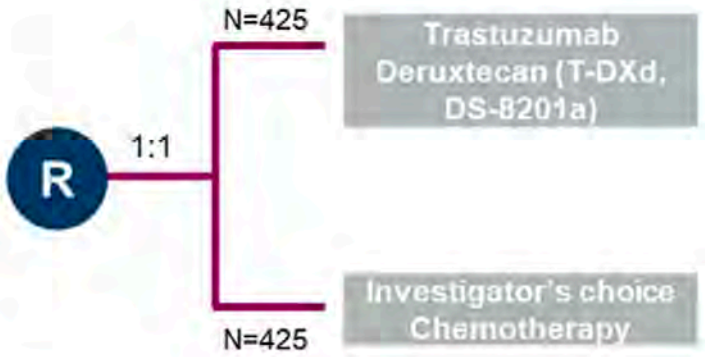
Prior lines of therapy in MBC:

Progression after 2 prior ET+/- targeted therapy, **or** within 6 months of 1st line ET+CDK4/6i

Stratification factors:

- Prior CDK4/6 inhibitor
- HER2 IHC 2+ v. 1+ v. >0 <1+
- Prior taxane in non-metastatic setting

TREATMENT



- Chemotherapy options: capecitabine, paclitaxel, nab-paclitaxel
- Treatment continues until progressive disease or toxicity
- HER2 IHC >0 <1+ defined by tumor membrane expression characterized as faint or barely perceptible and incomplete membrane staining that is seen in 10% or fewer tumor cells (HER2 >0 <1+ population N=150)
- Futility analysis in HER2 IHC >0 <1+ cohort will be done

ENDPOINTS

Primary:
- PFS (BICR) in HER2-low population

Key Secondary:
- OS in HER2-low population
- PFS in ITT population
- OS in ITT population

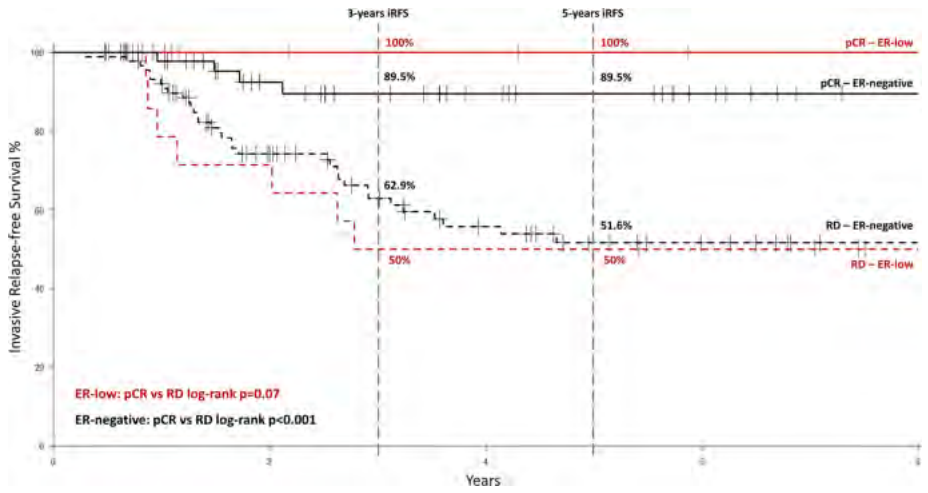
Secondary:
- PFS (investigator assessed) in HER2-low
- ORR and DOR of HER2-low and ITT populations
- Safety and tolerability
- Symptoms, functioning and HRQoL

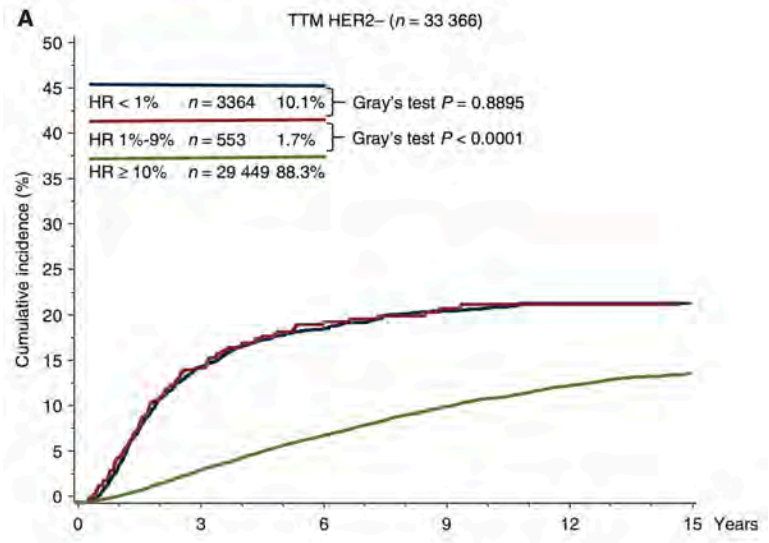
Exploratory:
- Protein expression
- ctDNA
- Patient Reported Outcomes

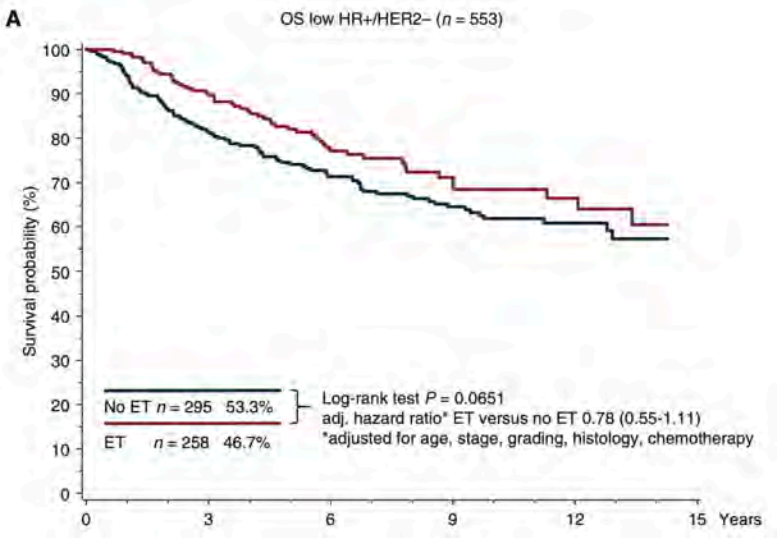
Bardia A. OT-03-09 SABCS 2020

Outcome of early breast cancer patients with low hormone receptor positivity

Invasive relapse-free survival according to ER-status and response to neoadjuvant chemotherapy







Dieci MV. npj Breast Cancer 7, 101; Schrodi S. Ann Oncol. 2021 Nov;32(11):1410-1424

ER Low Positive (1% to 10%)

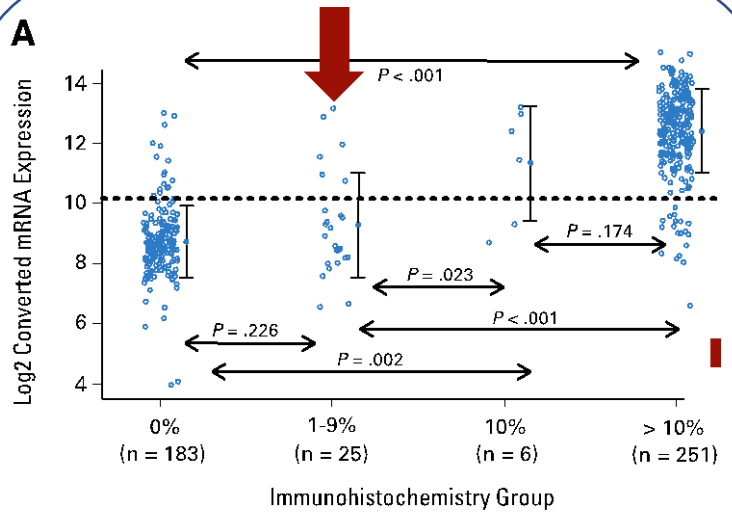


Table 2. Molecular Class of Borderline ER-Positive Patients

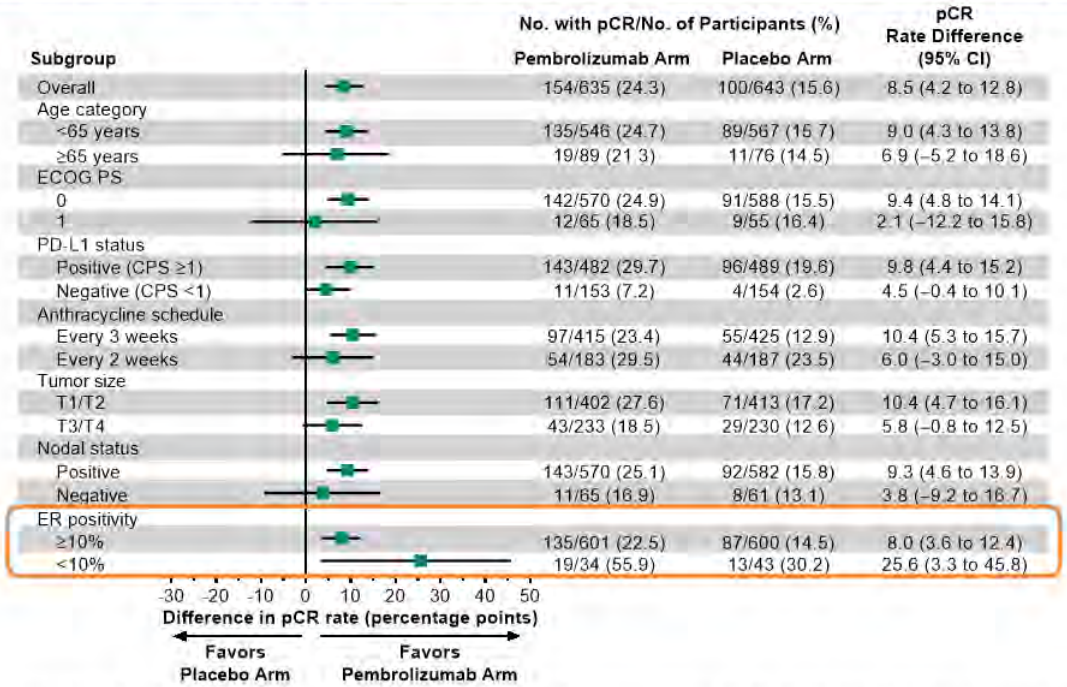
IHC		Molecular Subtypes by PAM50				
IHC Level (%)	No. of Patients	Luminal A	Luminal B	HER2 Amplified	Basal	Normal
0	183	2	1	51	111	18
1-9	25	0	2	8	12	3
10	6	2	1	1	1	1
> 10	251	120	61	38	16	16

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PAM50, multigene test used to assign molecular class to individual breast cancers.[16]

Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

Kimberly H. Allison, MD[1]; M. Elizabeth H. Hammond, MD[2]; Mitchell Dowsett, PhD[3]; Shannon E. McKernin[4]; Lisa A. Carey, MD[5]; Patrick L. Fitzgibbons, MD[6]; Daniel F. Hayes, MD[7]; Sunil R. Lakhani, MD[8,9]; Mariana Chavez-MacGregor, MSc[10]; Jane Perlmutter, PhD[11]; Charles M. Perou, PhD[5]; Meredith M. Regan, ScD[12]; David L. Rimm, MD, PhD[13]; W. Fraser Symmans, MD[10]; Emina E. Torlakovic, MD, PhD[14,15]; Leticia Varella, MD[16]; Giuseppe Viale, MD[17,18]; Tracey F. Weisberg, MD[19]; Lisa M. McShane, PhD[20]; and Antonio C. Wolff, MD[21]

Pathological Complete Response (ypT0/Tis ypN0) in Subgroups

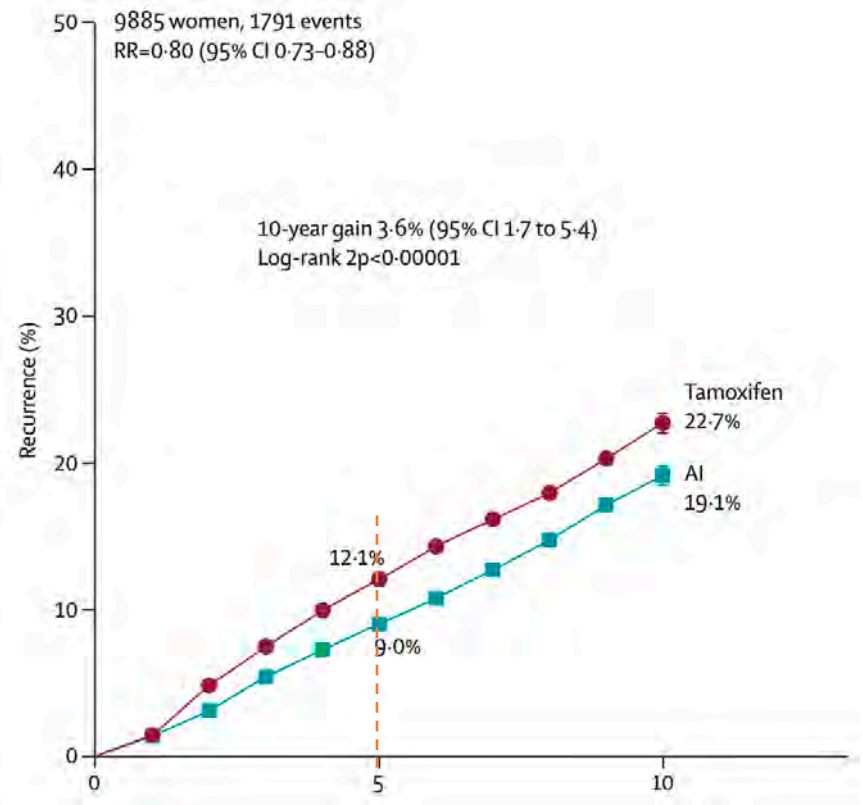


For the overall population, analysis is based on Miettinen and Nurminen method stratified by the analysis randomization stratification factors. For other subgroups, analysis is based on unstratified Miettinen and Nurminen method. Data cutoff date: May 25, 2023.

Allison JCO 2020; Iwamoto JCO 2012; Cardoso ESMO 2023

Impact of adjuvant aromatase inhibitors and duration of treatment

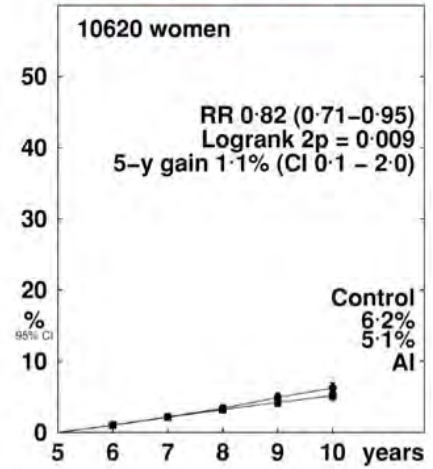
Carryover effect



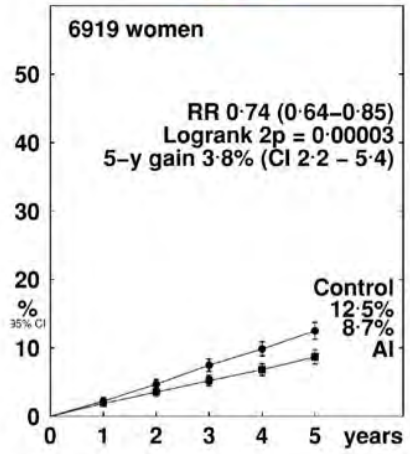
Lancet. 2015 Oct 3;386(10001):1341-1352
SABCS 2028 Abst. GS3-03

Extended Aromatase Inhibitor

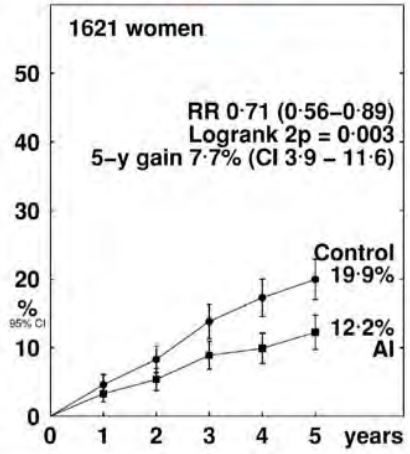
Node-negative



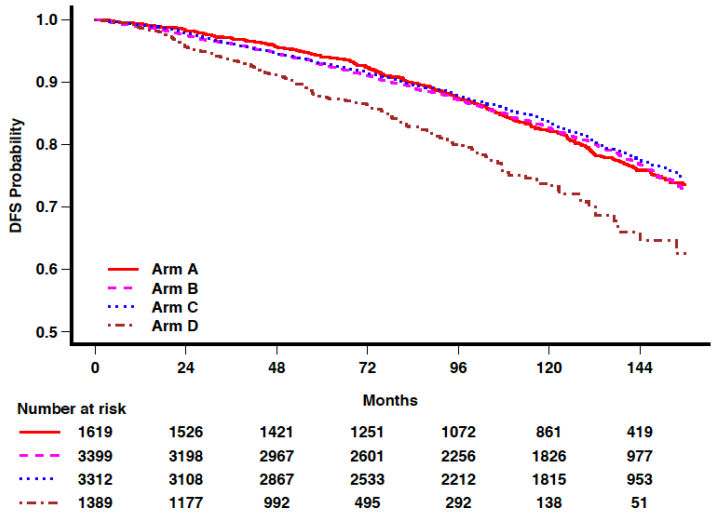
N 1-3

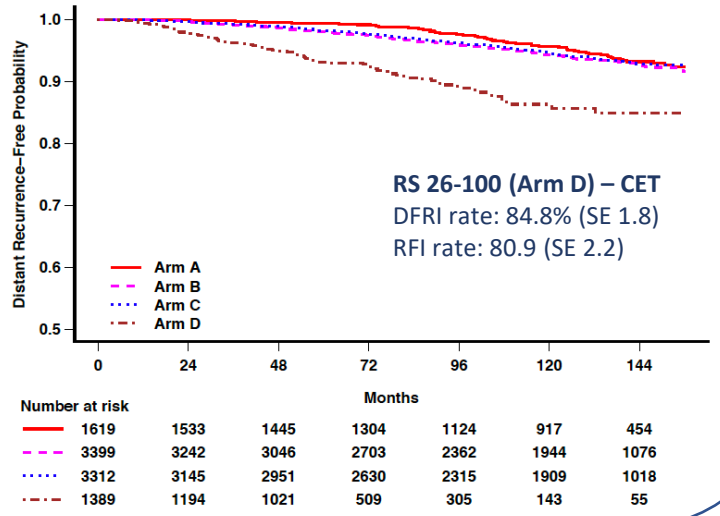


N 4+



Trial Assigning Individualized Options for Treatment (TAILORx): An Update Including 12-Year Event Rates





RS 26-100 (Arm D) – CET
DFRI rate: 84.8% (SE 1.8)
RFI rate: 80.9 (SE 2.2)

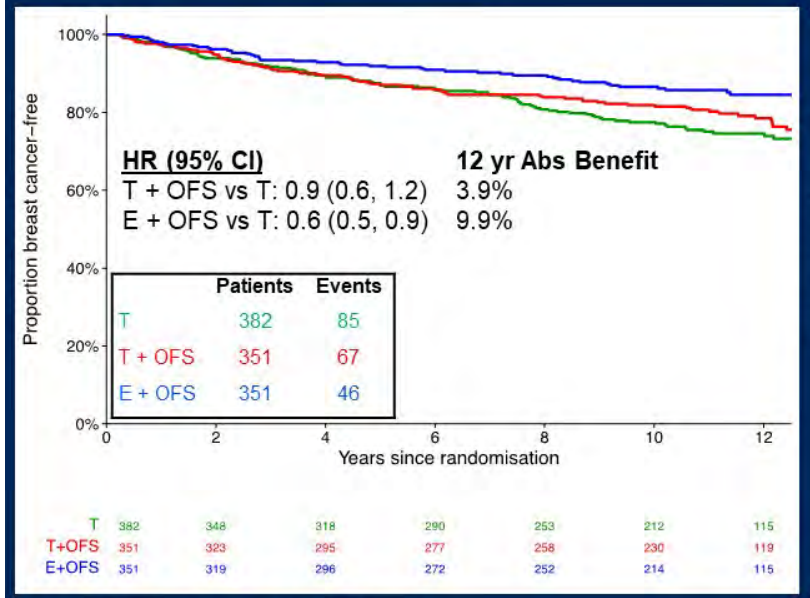
End-point	Event Rate	Arm B RS 11-25 ET (n=3399)	Arm C RS 11-25 CET (n=3312)
IDFS	5 years	92.8% (0.5)	93.1% (0.5)
	12 years	76.8% (0.9)	77.4% (0.9)
DRFI	5 years	98.0% (0.3)	98.2% (0.2)
	12 years	92.6% (0.5)	92.8% (0.5)
RFI	5 years	96.9% (0.3)	97.0% (0.3)
	12 years	89.6% (0.6)	90.5% (0.6)
OS	5 years	98.0% (0.2)	98.1% (0.2)
	12 years	89.8% (0.6)	89.8% (0.6)

Sparano SABCS2022

PAM50 ROR Predictive results– overall cohort

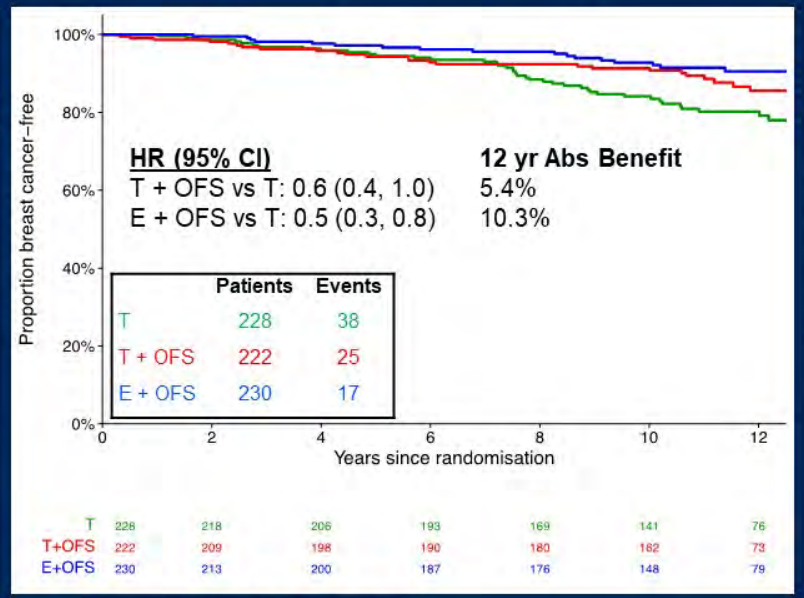
[Endpoint = BCFI]

Unselected (N=1084)



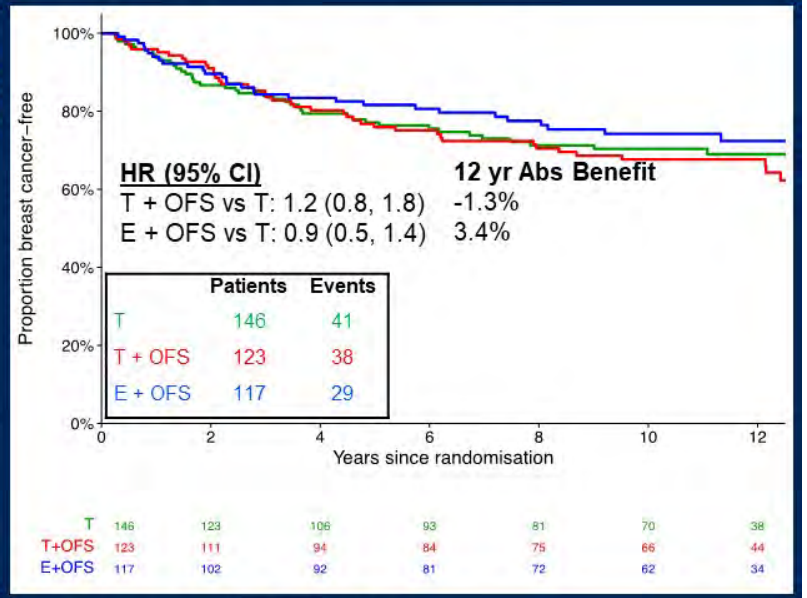
Chemo n=543 (50.1%)

ROR low/int (N=680, 64%)



Chemo n=212 (31.1%)

ROR high (N=386, 36%)



Chemo n=315 (81.6%)

p_{int} (E + OFS) = 0.1; (T + OFS) = 0.2

PRESENTED BY: LAUREN C. BROWN, LAURENC.BROWN@PETERMAC.ORG

PENELOPE-B: prognosis according to BC subtype and effect of palbociclib

Figure 2: iDFS by AIMS subtype (treatment arms combined)

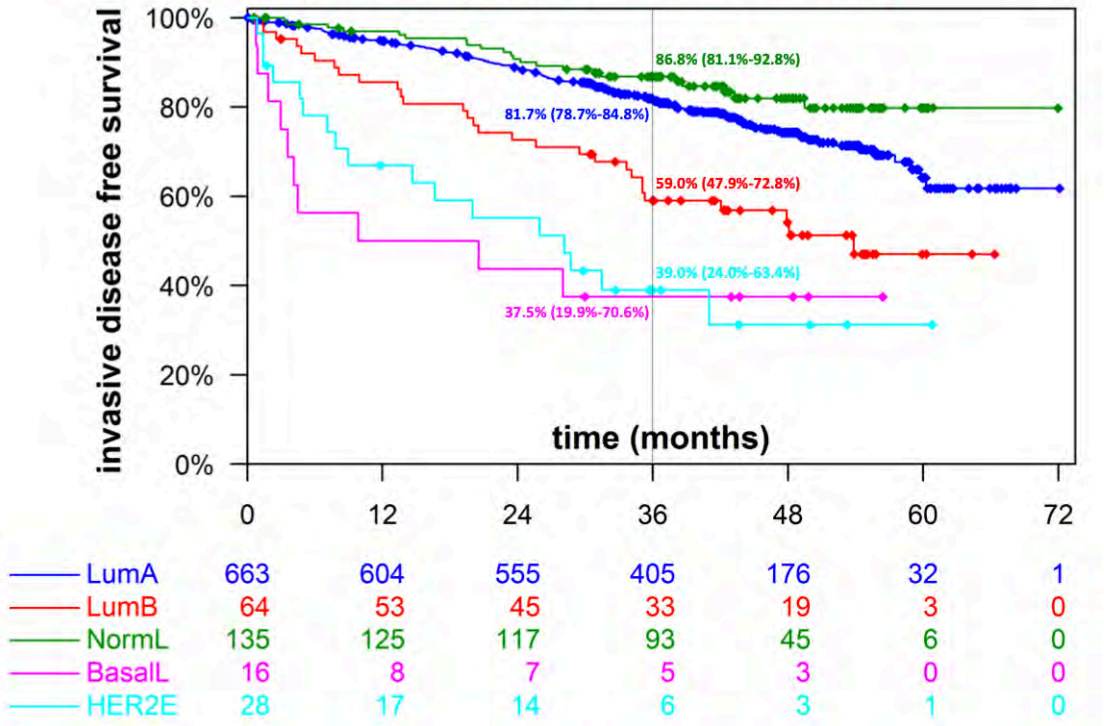
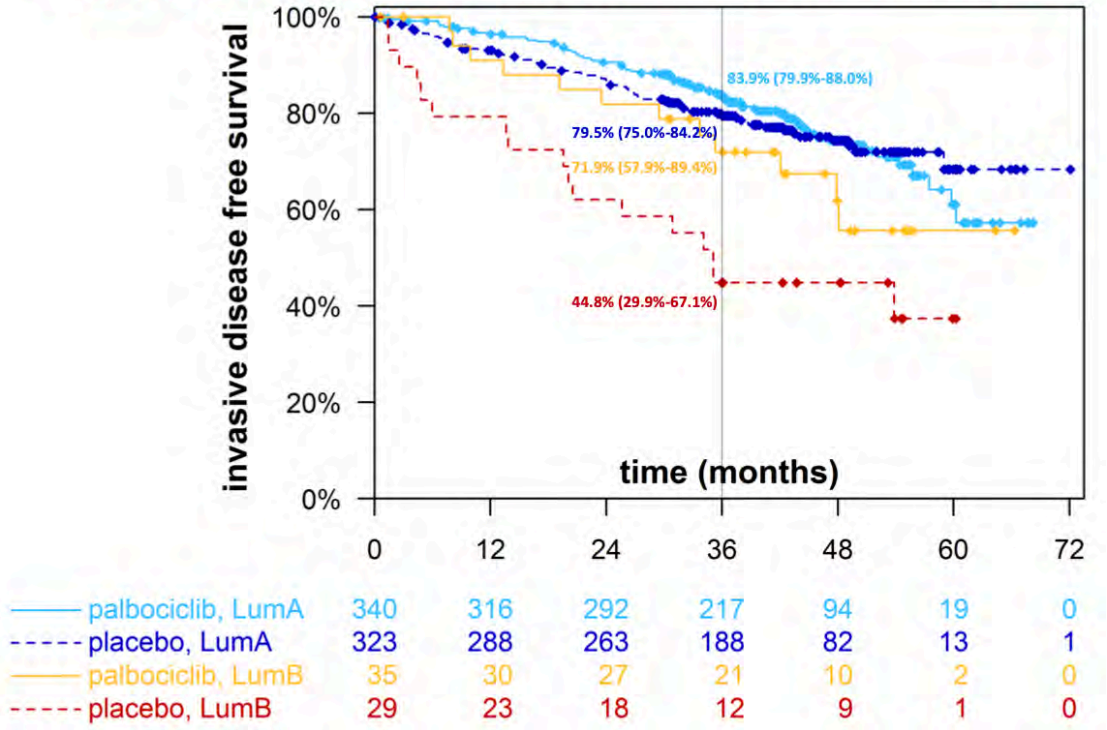
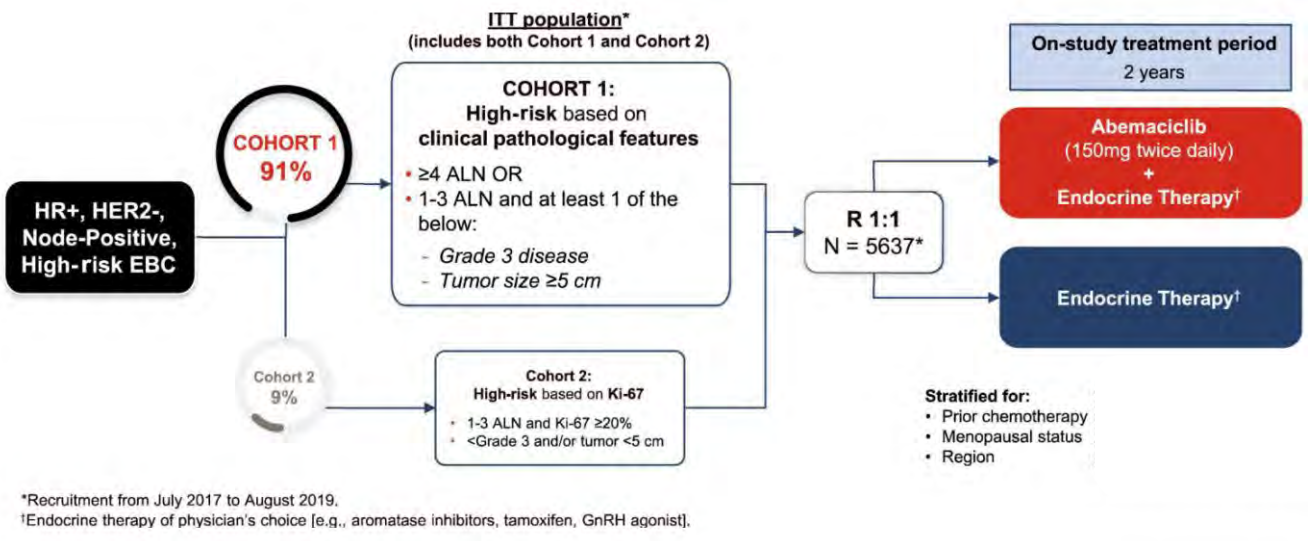


Figure 3: iDFS by AIMS subtype and treatment in the AIMS-luminal cohort

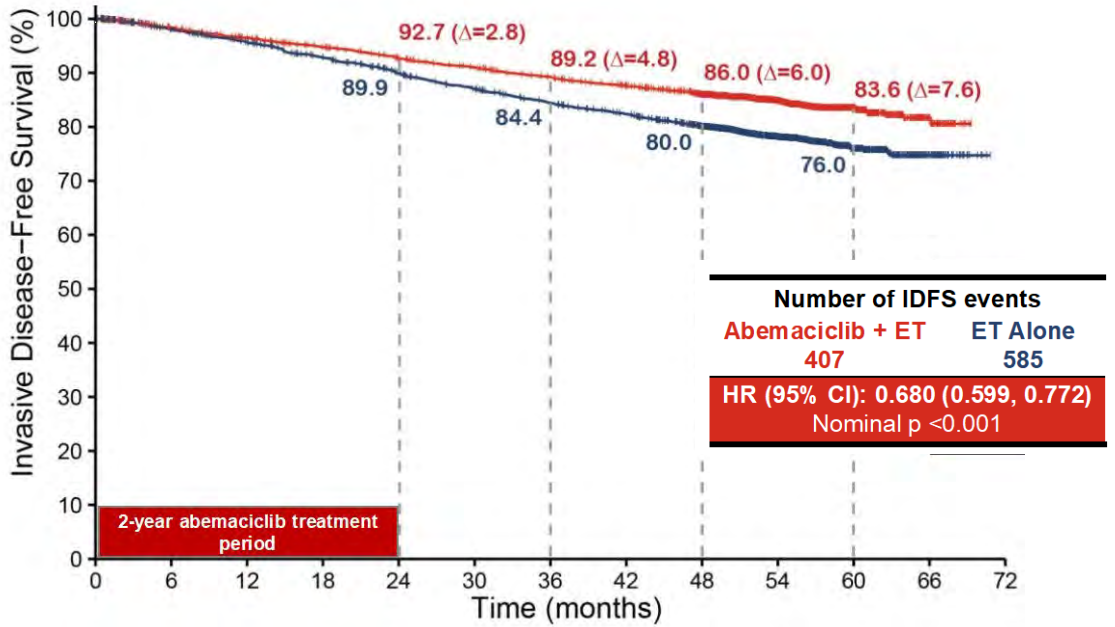


Denkert C. ASCO 2021 Poster No.519

monarchE Study Design and Primary Endpoint Results



IDFS benefits persists beyond completion of abemaciclib



32% reduction in the risk of developing an IDFS event.
The KM curves continue to separate and the absolute difference in IDFS rates between arms was 7.6% at 5 years

Harbeck N. ESMO2023

NATALEE Study Design and Primary Endpoint Results

NATALEE Study Design[1-3]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 ***or***
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N=5101[b]

R 1:1[c]

Ribociclib 400 mg/d
3 wk on/1 wk off
for 3 y
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d] for ≥5 y
+ goserelin in men and premenopausal women

Primary End Point
– iDFS using STEEP criteria

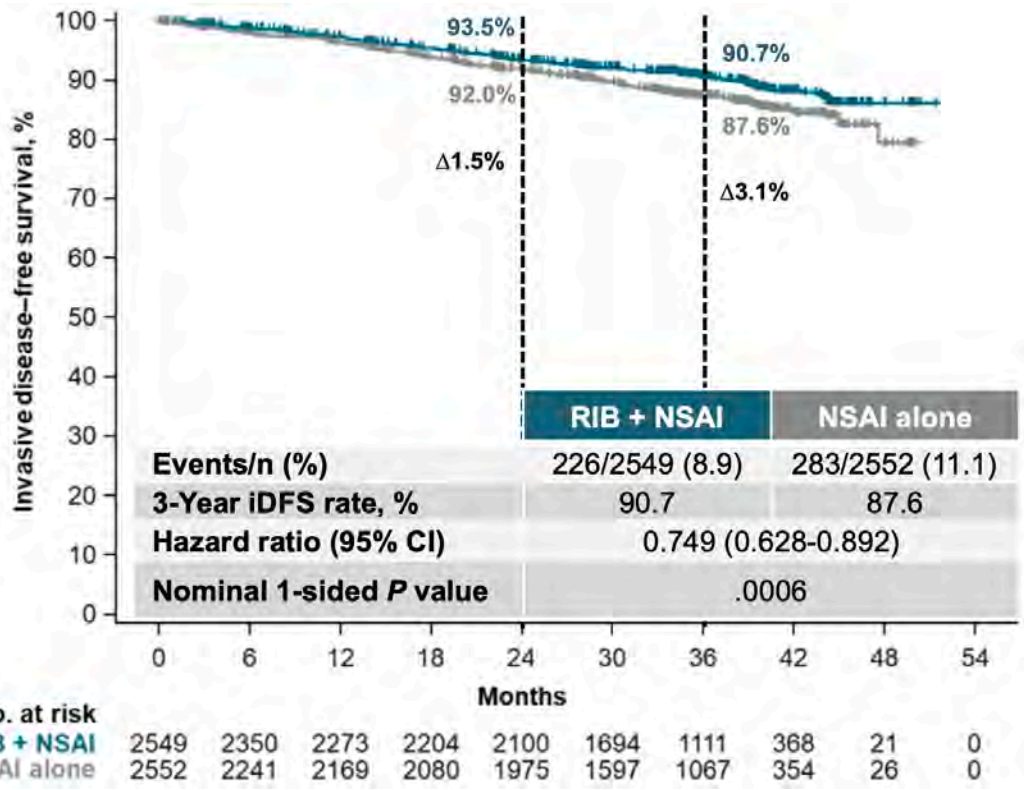
Secondary End Points
– Recurrence-free survival
– Distant disease–free survival
– OS
– PROs
– Safety and tolerability
– PK

Exploratory End Points
– Locoregional recurrence–free survival
– Gene expression and alterations in tumor ctDNA/ctRNA samples

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

ct, circulating tumor; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from Jan 10, 2019 to April 20, 2021. [c] Open-label design. [d] Per investigator choice.

1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl). Abstract TPS597. 3. Slamon DJ, et al. *Ther Adv Med Oncol.* 2023;15:17588359231178125.



Hortobagyi. SABCS2023: NEJM 2024

OlympiA: Olaparib for BRCA 1/2 mutated early BC patients

OlympiA: Trial schema

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC*: non-pCR
- *Hormone receptor–positive*: non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → Surgery → +/- Radiotherapy

Adjuvant Group
- *TNBC*: ≥ pT2 or ≥ pN1
- *Hormone receptor–positive*: ≥ 4 positive lymph nodes

Surgery → ≥ 6 cycles Adjuvant Chemotherapy → +/- Radiotherapy

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

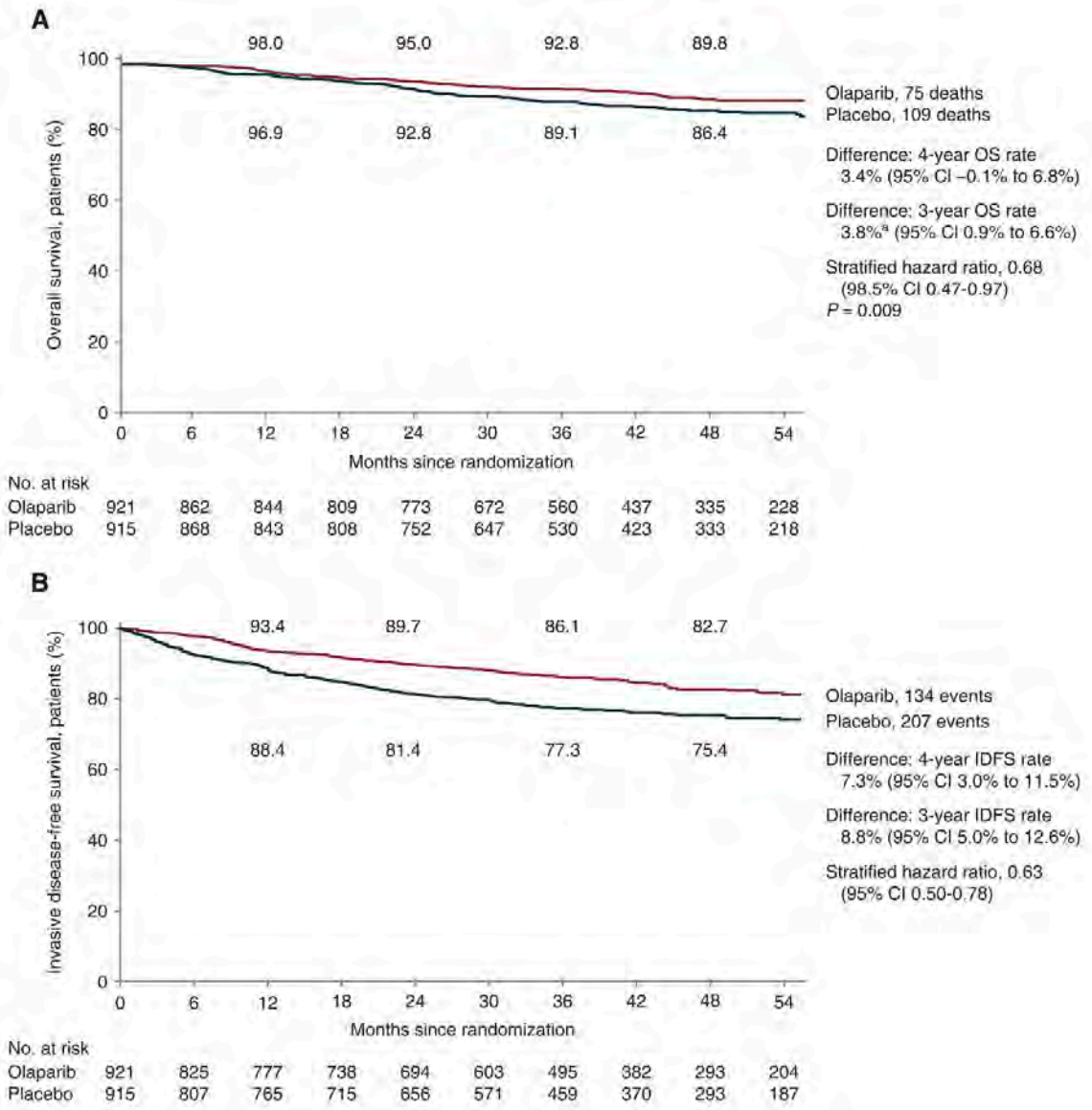
Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

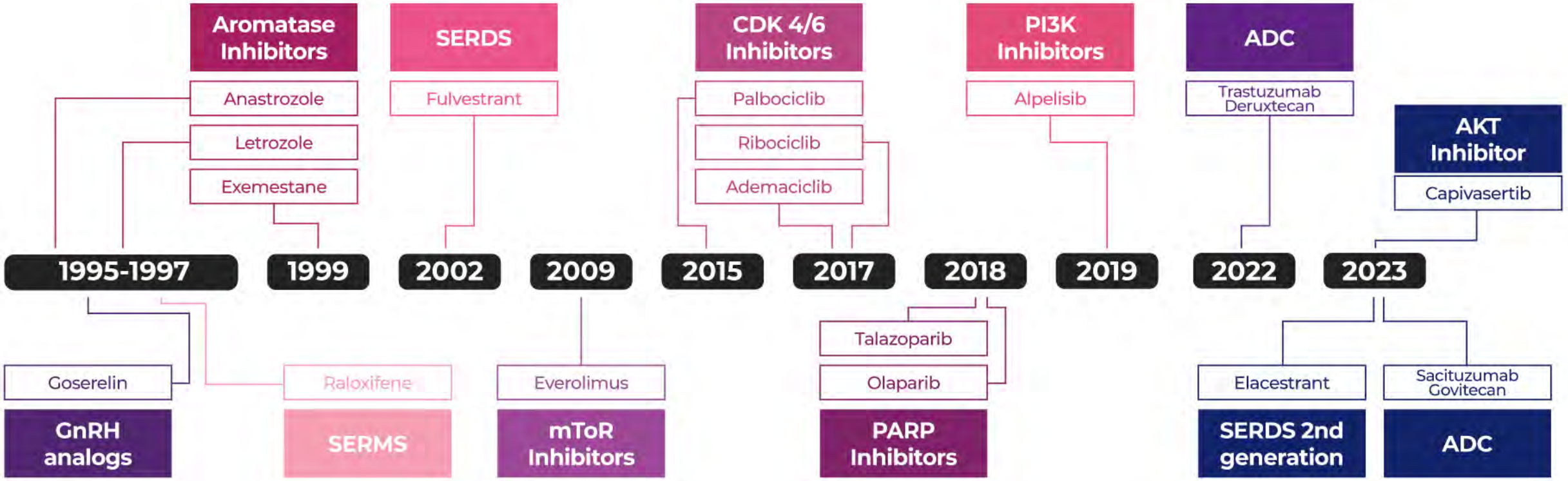
Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy



Tutt. ASCO 2021: Geyer. Ann Oncol 2022

Timeline of Targeted Therapies Approval for HR+ HER2- Metastatic Breast Cancer



Werutsky, G. Unpublished

THANK YOU

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mama

Instituto Projeto cura.

LACOG
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In Affiliation with JOHNS HOPKINS MEDICINE INTERNATIONAL

WILEY

Ask-the-Expert Webinar

CDK4/6i: side effects and impact on QoL

Valentina Guarneri, MD, PhD

Department of Surgery, Oncology and Gastroenterology
University of Padova Istituto Oncologico Veneto IRCCS, Padova, Italy

Learning objectives

1. Understand the common side effects associated with CDK4/6 inhibitors, including hematologic and non-hematologic adverse events
2. Evaluate the available evidence regarding the impact of CDK4/6 inhibitor therapy on quality of life
3. Recognize the strategies to prevent and manage CDK4/6 inhibitor-related side effects
4. Recognize the unique considerations for managing CDK4/6 inhibitor-related side effects in elderly patients

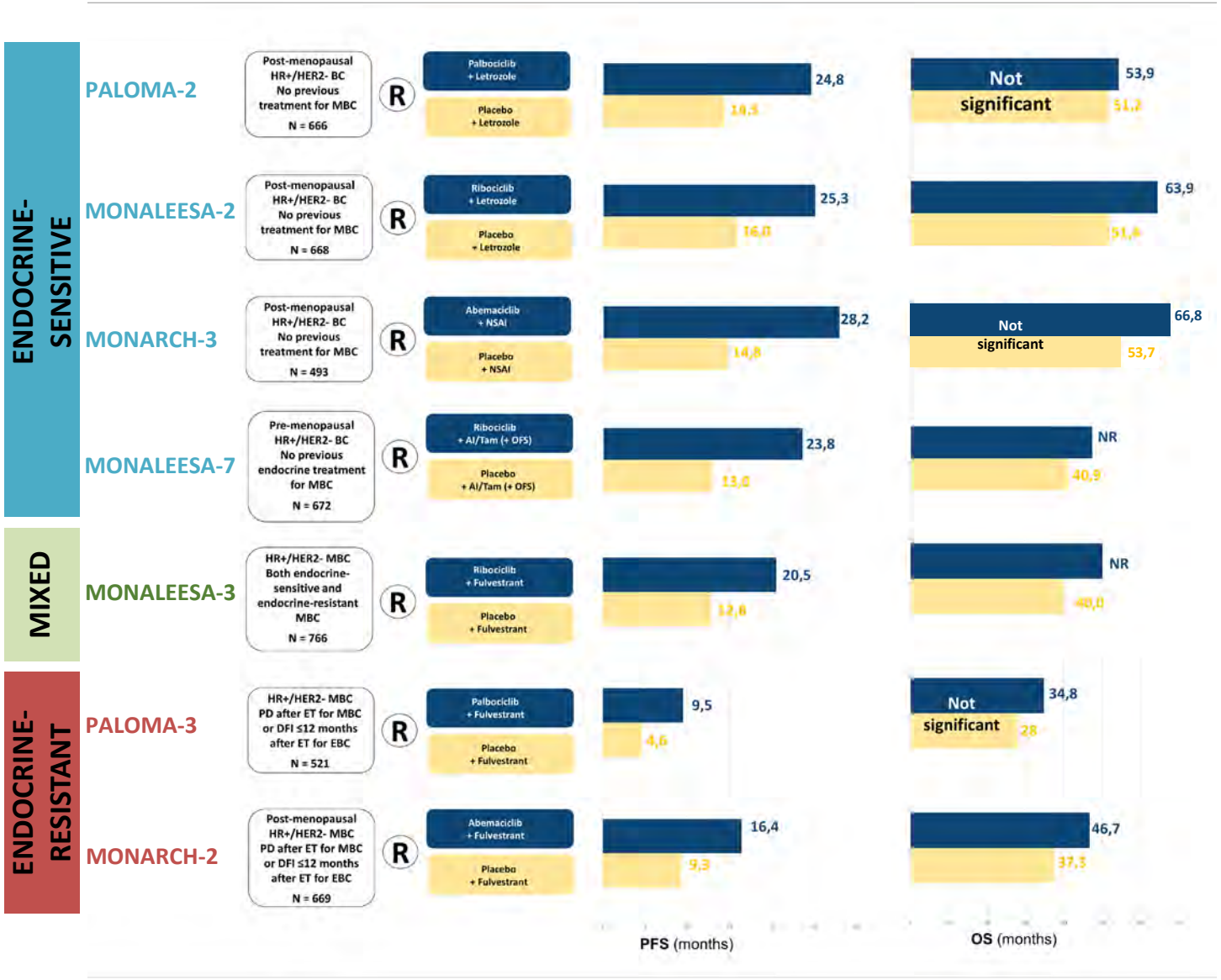
DECLARATION OF INTERESTS

Advisory Board:
EliLilly, Novartis, MSD, Gilead, Eisai, Merck Serono, Exact Sciences, Pfizer, Olema Oncology, Daiichi-Sankyo, Astra Zeneca, PierreFabre, Zentiva, Menarini Stemline

Speaker's Bureau:
EliLilly, Novartis, GSK, Amgen, Gilead, Astra Zeneca, Exact Sciences, Menarini Stemline

Expert Testimony:
EliLilly

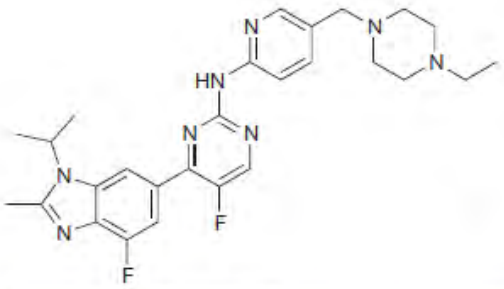
CDK 4/6i-based tx for HR+/HER2- MBC: crystallized first-line



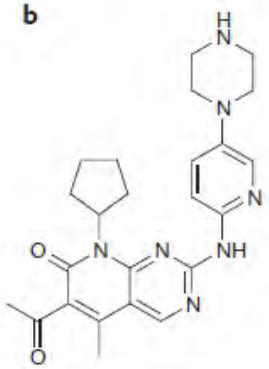
Modified from Miglietta F et al, ESMO Open 2022

Chemical structure of selective CDK 4/6i

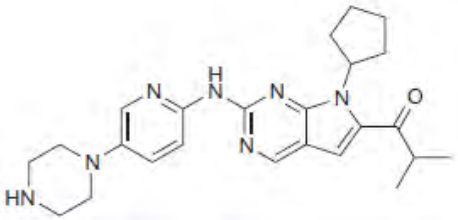
a



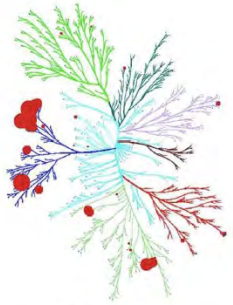
b



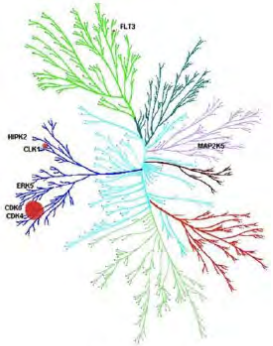
c



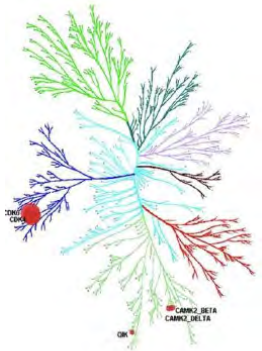
	Abemaciclib (LY-2835219)	Palbociclib (PD-0332991)	Ribociclib (LEE011)
IC_{50}	CDK1: >1 μM	CDK1: >10 μM	CDK1: >100 μM
	CDK2: >500 nM	CDK2: >10 μM	CDK2: >50 μM
	CDK4: 2 nM	CDK4: 9–11 nM	CDK4: 10 nM
	CDK5: ND	CDK5: >10 μM	CDK5: ND
	CDK6: 5 nM	CDK6: 15 nM	CDK6: 39 nM
	CDK7: 300 nM	CDK7: ND	CDK7: ND
	CDK9: 57 nM	CDK9: ND	CDK9: ND



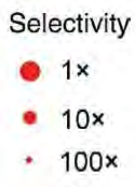
Abemaciclib



Palbociclib



Ribociclib



O'Leary Nat Rev Oncol 2016

Hematological AEs

	Palbociclib^			Ribociclib°			Abemaciclib*		
	All	G3	G4	All	G3	G4	All	G3	G4
Neutropenia	80	56	10	74	50	9.6	41	19.6	1.5
Leukopenia	39	24	1	33	20	1.2	20.8	7.3	0.3
Anemia	24	5	<1	19	0.9	0.3	28.4	5.8	0
Thrombocytopenia	16	1	<1	9.0	0.6	0	-	-	-

Febrile neutropenia: palbociclib 1.8%; ribociclib 1.5%.

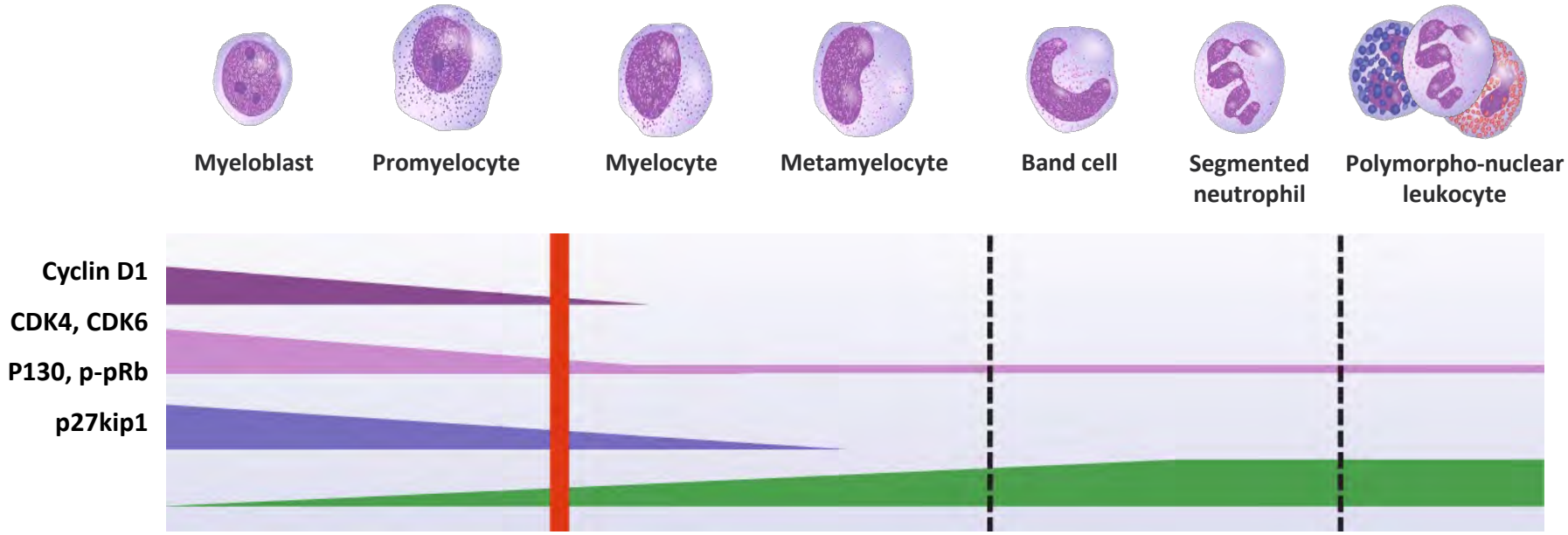
^ AEs ≥10% of study population
◦AEs ≥5% of study population
*AEs ≥15% of study population

Finn et al NEJM 2016; Cristofanilli et al, Lancet Onc 2017; Hortobagyi et al, NEJM 2016; Slamon et al, JCO 2018; Tripathy et al, Lancet Onc 2018 Sledge et al, JCO 2017; Goetz et al, JCO 2017

Biological drivers of CDK 4/6i-related neutropenia

CDK4/6 inhibitors arrest the cell cycle at G1 preventing cyclin D–CDK4/6 activity
However, **neutrophils depend on cyclin D–CDK4/6 activity to enter the cell cycle and proliferate**
The effect on neutrophil proliferation is **reversible** with CDK4/6 inhibitors

Cell cycle proteins during granulopoiesis[1]



p130, Rb-like protein 2; p-pRb, phosphorylated retinoblastoma protein; p27kip1, CDK inhibitor

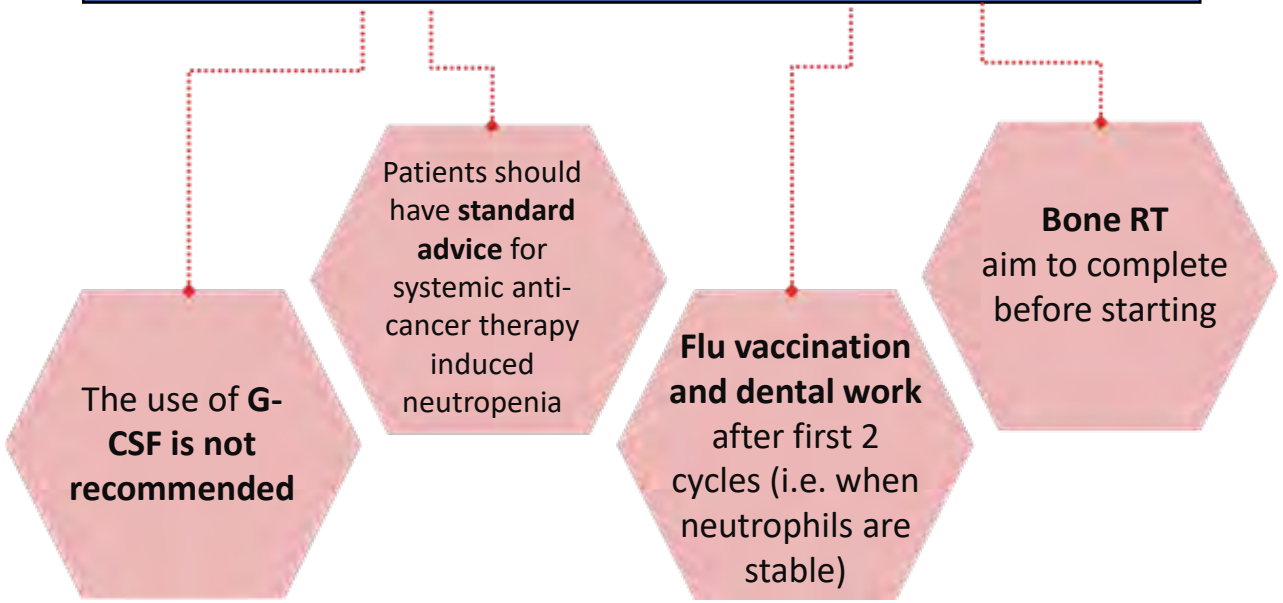
1. Klausen P, et al. J Leukoc Biol. 2004;75:569−578;
2. Kumar S, Fillippi M-D. In Gabrilovich D, ed. The Neutrophils. 3rd ed. London: Imperial College Press; 2013:1−41;
3. Roberts PJ, et al. J Natl Cancer Inst. 2012;104:476−487;
Graphic adapted from: Klausen P, et al. J Leukoc Biol. 2004;75:569−578.

Management of neutropenia in clinical practice

MONITORING & DOSE ADJUSTMENT

- **No dose adjustment is required for G1-2** neutropenia
- Consider **dose reduction in cases of recurrent uncomplicated G3** neutropenia in subsequent cycles
- Consider **dose reduction in cases of prolonged (>1 wk) recovery from G3** neutropenia
- In case of **febrile neutropenia**, hold until recovery to G2, then restart at the next lower dose

PRACTICAL TIPS



Verma S et al. The Oncologist 2016

NON-hematological AEs

Adverse Event	Palbociclib^			Ribociclib°			Abemaciclib*		
	All	G3	G4	All	G3	G4	All	G3	G4
Nausea	35	<1	0	52	2.4	0	38.5	0.9	–
Infections§				50	3.6	0.6	39	4	0.9
Fatigue	37	2	0	37	2.1	0.3	40	1.8	–
Diarrhea	26	1	0	35	1.2	0	81	9.5	0
Alopecia	33	0	0	33	–	–	26.6	–	–
Vomiting	16	<1	0	29	3.6	0	28.4	5.8	0
Constipation	19	<1	0	25	1.2	0	15.9	0.6	0
Headache	21	<1	0	22	0.3	0	15.6	0.6	–
↓ Appetite	15	1	0	19	1.5	0	24.5	1.2	0
Rash	18	1	0	17	0.6	0			
ALT increased				16	7.5	1.8	15.6	5.8	0.3
AST increased				15	4.8	0.9			

§Paloma 2: upper respiratory tract infection 13.3% G1-2
Urinary tract infection 11.9% G1-2, 1.1% G3
^AEs ≥10% of study population; ◦AEs ≥5% of study population; *AEs ≥15% of study population

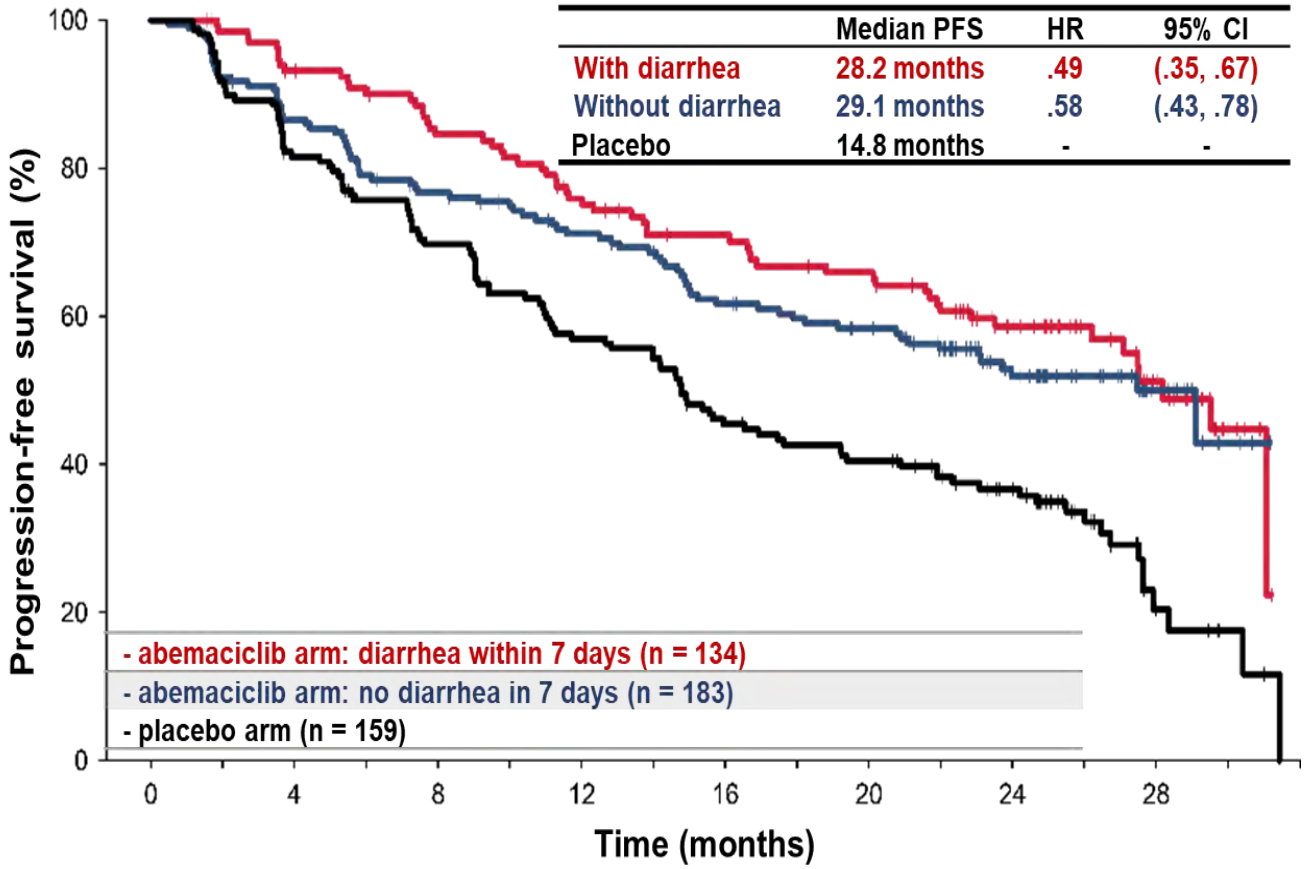
Finn et al NEJM 2016; Cristofanilli et al, Lancet Onc 2017; Hortobagyi et al, NEJM 2016; Slamon et al, JCO 2018; Tripathy et al, Lancet Onc 2018; Sledge et al, JCO 2017; Goetz et al, JCO 2017

Abemaciclib-related diarrhea - ABC

Characteristics of diarrhea within MONARCH 2 and MONARCH 3 trials

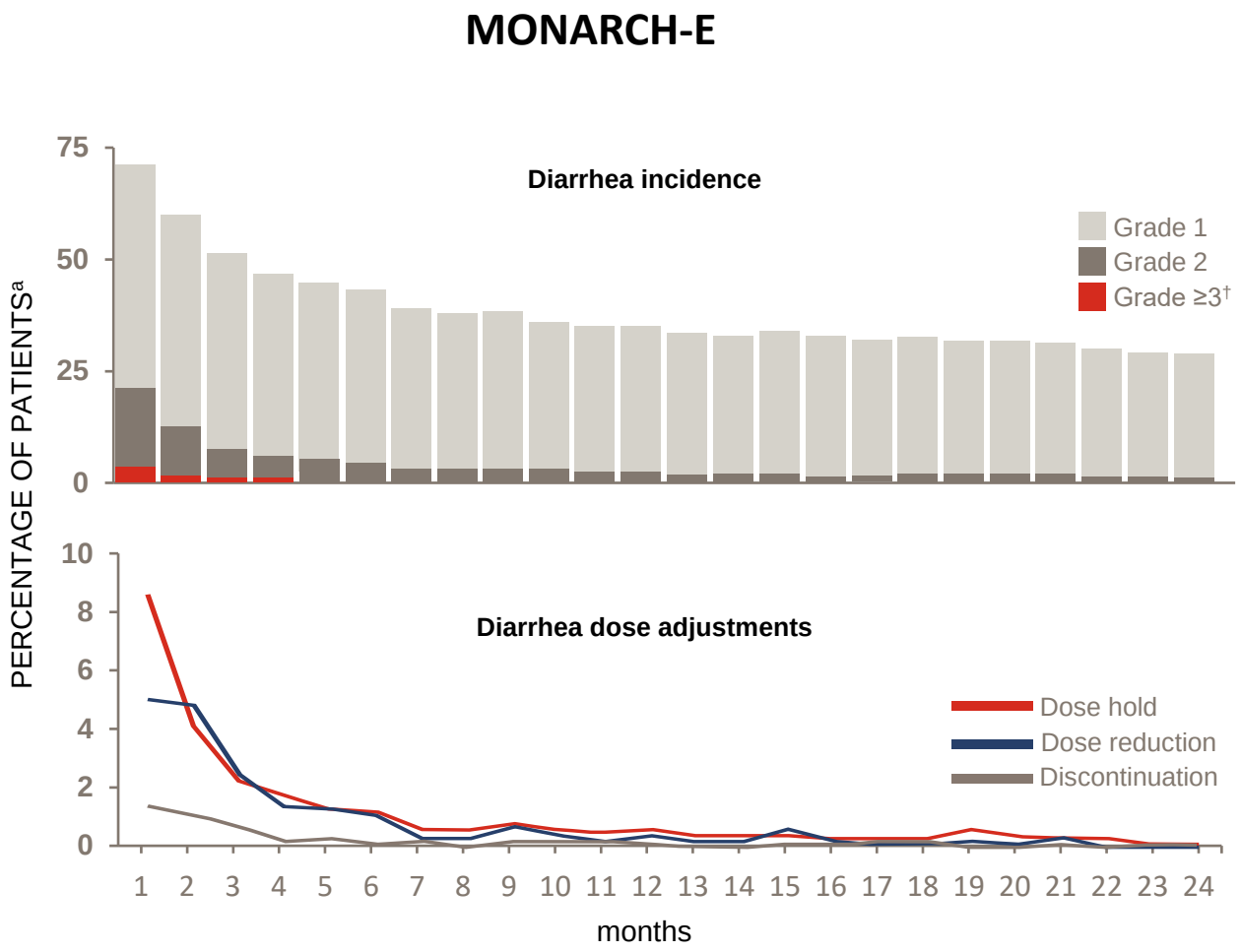
	MONARCH 2 (N=441)	MONARCH 3 (N=327)
Median Time of Onset	6 days	8 days
Duration		
Grade 2 (days)	9 days	10.5 days
Grade 3 (days)	6 days	8 days
Dose Reduction Due to Diarrhea		
Median Time to 1st Dose Reduction	29 days	37.5 days
Dose Reductions Due to Diarrhea	83 (18.8%)	42 (15.8%)
Discontinuations Due to Diarrhea	13 (2.9%)	6 (1.8%)
Hospitalizations Due to Diarrhea	4 (1%)	4 (1.2%)

MONARCH 3: Landmark analysis of PFS with/without diarrhea (any grade) within 7 days



Dickler MN et al. Clin Care Res 2017; Rugo H R et al, ASCO 2018; Johnston et al, NPJ Breast Cancer 2019

Abemaciclib-related diarrhea - EBC



DIARRHEA ONSET, SEVERITY AND DURATION

- Median time to onset of diarrhea was 8 days and incidence decreased over time
- Diarrhea was mostly low grade (Grade1/2: 76%)
- Grade 2/3 events were highest in the first few months, mostly lasting ≤7 days and did not recur

DISCONTINUATION OF ABEMACICLIB DUE TO DIARRHEA

- Discontinuation rate due to diarrhea was low (5.3%) – most were due to low grade events
- Most discontinuations occurred within the first 3 months (74% of those without a prior dose reduction)

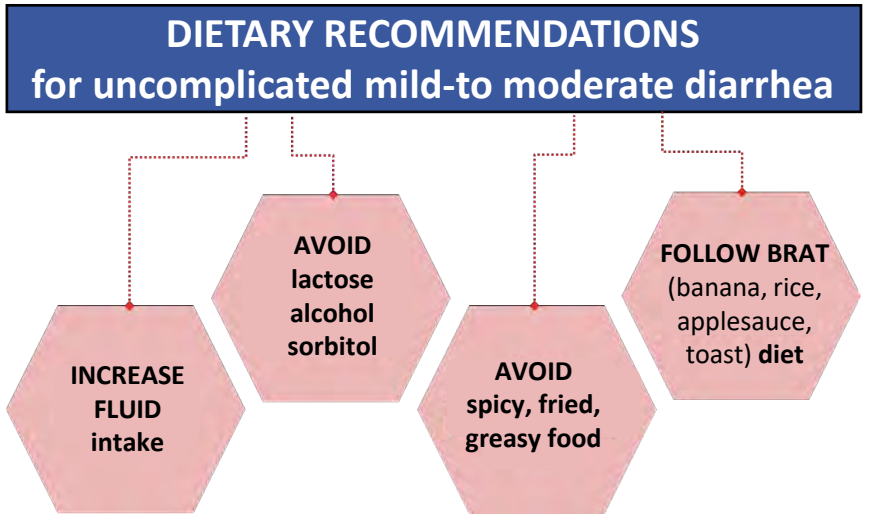
- ~30% of patients had Grade 1 diarrhea in second year of treatment, but ≤0.6% patients had dose adjustments

*In the by month analyses, number of patients at risk each month is used as the denominator to calculate % of events. †There were no Grade 4 events and 1 Grade 5 event.
AFU1: Additional Follow-Up 1.

Rugo HS, et al. Ann Oncol. 2022;33(6):616-627.

Management of diarrhea

NCI-CTCAE Grade or Profile	Dose Modification
At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide	
Grade 1 *Increase of <4 stools/day over baseline (BL); mild increase in ostomy output compared to BL*	**No dose modification** is required
Grade 2 *Increase of 4-6 stools/day over BL; moderate increase in ostomy output compared to BL*	If toxicity does not resolve within 24 hours to Grade ≤1, **suspend** dose until resolution; **dose reduction is not required**
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	**Suspend** dose until toxicity resolves to Grade ≤1; **resume at *next lower dose***
Grade 3 or 4 or requires hospitalization *G3: Increase of ≥7 stools/day over BL; incontinence; hospitalization indicated; severe increase in ostomy output compared to BL; limiting self-care activities of daily living* *G4: Life-threatening consequences; urgent intervention indicated*	**Suspend** dose until toxicity resolves to Grade ≤1; **resume at *next lower dose***



National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0
Johnston SRD, et al. J Clin Oncol. 2020;38(34):3987-3998. Rugo HS, et al. Poster presented at: SGBCS 2021. Poster PO13.

Abemaciclib-related effect of creatinine

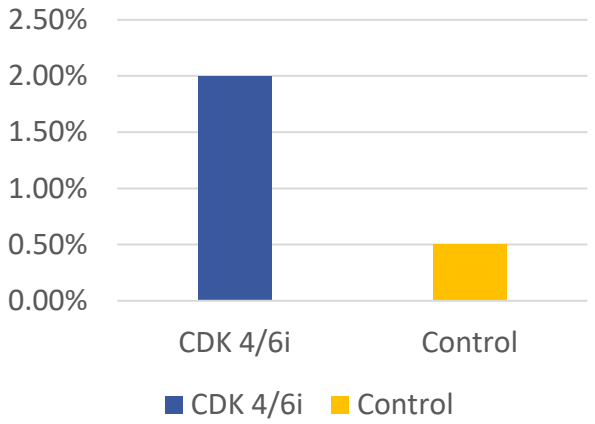
- The increase in SCr due to abemaciclib results from **inhibition of a molecular pump** that transports creatinine from the blood to the urine
- One consequence of this inhibition is the **potential for drug-drug interactions** with compounds that use this pathway for elimination (eg, metformin)
- The increase in SCr occurs **within the first 28-day cycle of abemaciclib**, remains elevated but stable throughout the treatment period and is **reversible** upon treatment discontinuation[1-3]
- **Renal function (GFR) is not impacted**, as other measures of GFR that do not rely on SCr (such as cystatin C-calculated GFR) are not affected by abemaciclib treatment[1,2,4]

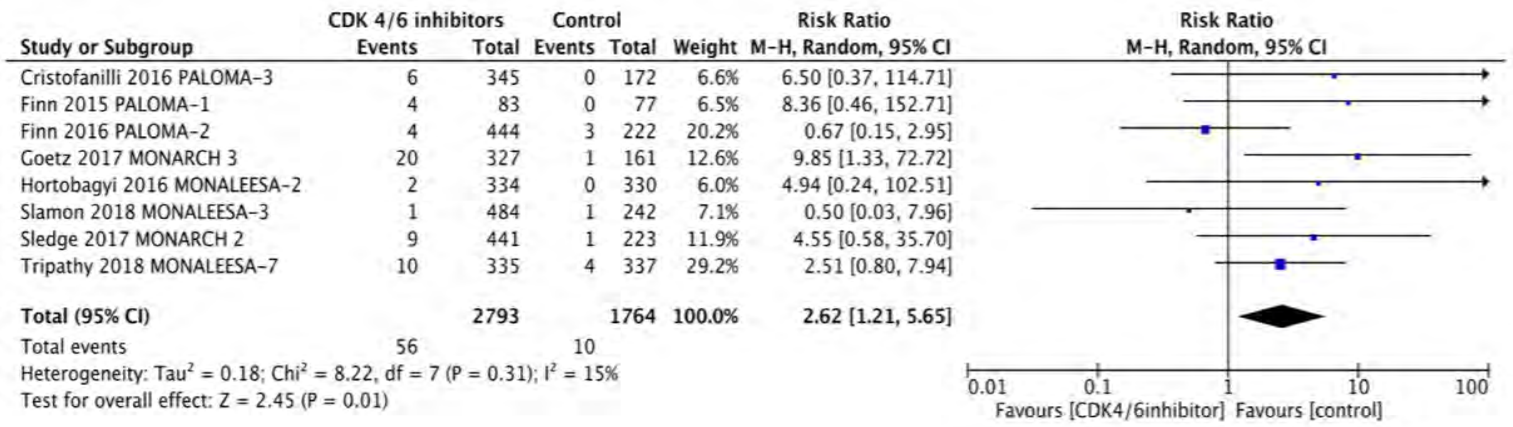
1. Patnaik A et al. *Cancer Discov* 2016;6:740-53
2. Dickler MN et al. *Clin Care Res* 2017;(Ahead of print)
3. Data on file; Eli Lilly and Company
4. Sledge GW et al. *J Clin Oncol* 2017;(Ahead of print)
5. Milburn J et al. *Nephrol Dial Transplant* 2017;32: 434–439

VTE events

RCT trials (n=4557) = PALOMA 1-2-3, MONARCH 2-3, MONALEESA 2-3-7

- VTE events: **56 (2%) in the CDK 4/6+HT** vs **10 (0.5%) in HT alone**.
- Pooled **RR 2.62** (95% CI 1.21-5.659)





Subgroup	Number of studies (number of patients)	VTE events/number of patients (CDKI arm)	VTE events/number of patients (control arm)	Pooled RR (95% CI)	I^2 (%), P value
Palbociclib containing regimen	3 (1343)	14/872	3/471	2.33 (0.36, 15.19)	48%, 0.38
Abemaciclib containing regimen	2 (1152)	29/768	2/384	6.77 (1.61, 28.43)	0%, 0.009*
Ribociclib containing regimen	3 (2062)	13/1153	5/909	2.19 (0.80, 5.97)	0%, 0.13
First line treatment	5 (2650)	40/1523	8/1127	2.75 (0.98, 7.75)	34%, 0.06
Second line treatment	2 (1181)	15/786	1/395	5.14 (0.96, 27.38)	0%, 0.06
Fulvestrant ET	3 (1907)	16/1270	2/637	2.73 (0.63, 11.91)	5%, 0.18
Non-fulvestrant ET	5 (2650)	40/1523	8/ 1127	2.75 (0.98, 7.75)	34%, 0.06

Thein BCRT 2020

VTE events: focus on abemaciclib

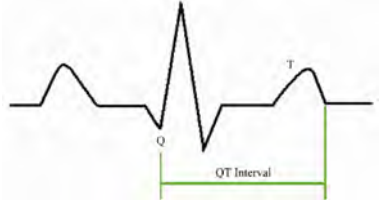
	MONARCH 2		MONARCH 3		MONARCH E*	
	Abemaciclib + Fulvestrant (N=441)	Placebo + Fulvestrant (N=223)	Abemaciclib + NSAI (N=327)	Placebo + NSAI (N=161)	Abemaciclib + HT (N=2791)	HT (N=2800)
VTE (all grade)	21 (4.8%)	2 (0.9%)	20 (6.1%)	1 (0.6%)	71 (2.5%)	17 (0.6%)
PE	11 (2.5%)	0	11 (3.4%)[a]	1 (0.6%)	28 (1.0%)	4 (0.1%)
DVT	10 (2.3%)	2 (0.9%)	9 (2.8%)	0		
Grade ≥3	9 (2.0%)	1 (0.4%)	10 (3.1%)	1 (0.6%)		
Death	0	0	3 (0.9%)[b]	0	0	0
SAE	8 (1.8%)	1 (0.4%)	9 (2.8%)	1 (0.6%)	34 (1.2%)	8 (0.3%)
Treatment discontinuation	2 (0.5%)	0	4 (1.2%)[c]	0	14 (0.5%)	-
Dose reduction	2 (0.5%)	0	0	1 (0.6%)	-	-

* **VTE with abema+tam vs tam**: 34 (4.3) vs 6 (0.7); **VTE with abema+AI vs AI**: 34 (1.8) vs 11 (0.6)
Approximately 50% (33 of 71) of the VTE events occurred **within the first 180 days**; trend for higher incidence of PE and G3/4 VTE with increasing BMI

Abbreviations: DVT = deep vein thrombosis; N = number in study population; NFI = no further information ; NSAI = nonsteroidal aromatase inhibitor; PE = pulmonary embolism; SAE = serious adverse event; VTE = venous thromboembolic event.
a 3 patients experienced both PE and DVT
b PE and DVT; thromboembolism NFI; respiratory failure
c includes 3 patients who died

Rugo et al, Annals Oncology 2022; Toi et al, ESMO BC 2021; Johnston et al, NPJ Breast Cancer 2019; Neven et al, CCR 2021

QTc prolongation



- Uncomplicated prolongation of the **QT interval has been associated with palbociclib and ribociclib treatment** in a dose-dependent manner, while based on evaluation of the QTc interval in pts and healthy volunteer study, **abemaciclib did not cause large mean increase** (i.e. 20 ms) in the QTc interval

Focus on RIBOCICLIB

	MONALEESA 2 (600mg)	MONALEESA 3 (600 mg)	MONALEESA 7 (600 mg)	NATALEE (400 mg)
	Ribociclib + letrozole	Ribociclib + Fulv	Ribociclib + HT	Ribociclib + NSAI
QTcF prolongation any grade	4.5%	6.2%	12.5%	5.2
QTcF prolongation grade ≥3/>480 msec	3.3%	5.6%	1.8	1.0
QTcF prolongation grade ≥3/>500 msec	--	1.7%	0	0.1

- Any concomitant medication administered to the patient for side-effect management should be carefully reviewed to avoid the co-administration of medications known to increase the risk of QTcF prolongation

Sammons SL, et al. Current Cancer Drug Targets, 2017; Hortobagyi et al, NEJM 2016; Slamon et al, JCO 2018; Tripathy et al, Lancet Onc 2018 ; Slamon et al, ASCO 2023

ILD: scale of the problem

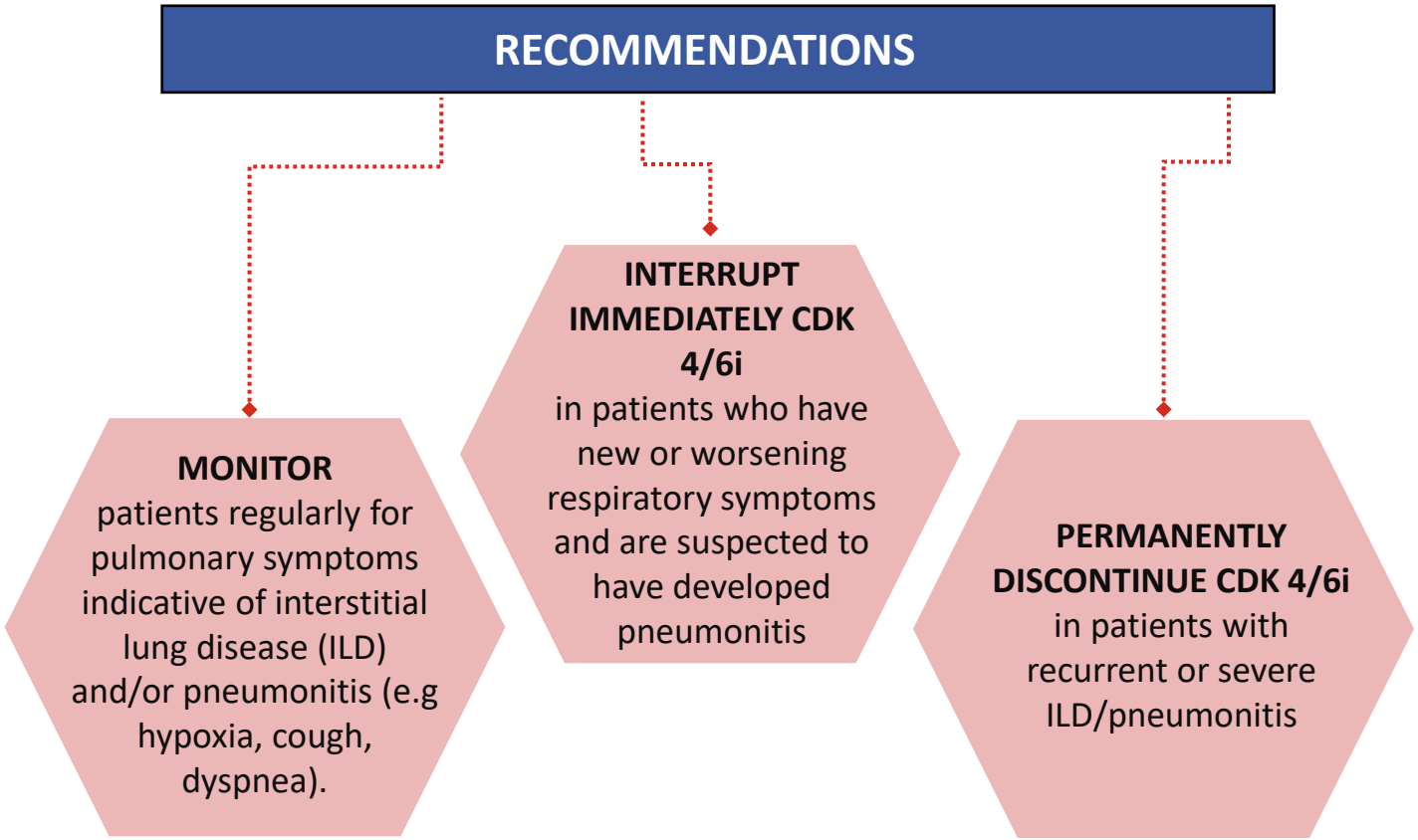
- **FDA safety announcement**

  [9-13-2019] The U.S. Food and Drug Administration (FDA) is warning that […]palbociclib, […] ribociclib, and […] abemaciclib used to treat some patients with advanced breast cancers may cause **rare but severe inflammation of the lungs**. We have approved new warnings about this risk to the prescribing information and Patient Package Insert for the entire class of these cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor medicines. The overall benefit of CDK 4/6 inhibitors is still greater than the risks when used as prescribed.

	PALBOCICLIB	RIBOCICLIB	ABEMACICLIB
	PALOMA 1-2-3	MONALEESA 2-3-7	MONARCH 1-2-3
Registration trials for ABC	Any grade: 1% G3-G4: 0.1% G5: no cases	Any grade: 1.1% G3-G4: 0.3% G5: 1 case	Any grade: 3.3% G3-G4: 0.6% G5: 0.4%
Post-marketing (ABC)	Additional cases with fatalities reported	Additional cases with fatalities reported	Additional cases with fatalities reported

Ibrance prescribing information, Ribociclib prescribing information, Abemaciclib prescribing information; Rugo HS, et al. *Ann Oncol.* 2022

ILD: management



Ibrance prescribing information, Ribociclib prescribing information, Abemaciclib prescribing information

CDK 4/6i-related quality of life (QoL) – ESMO-MCBS

ESMO-MCBS v1.0 (June 2015)

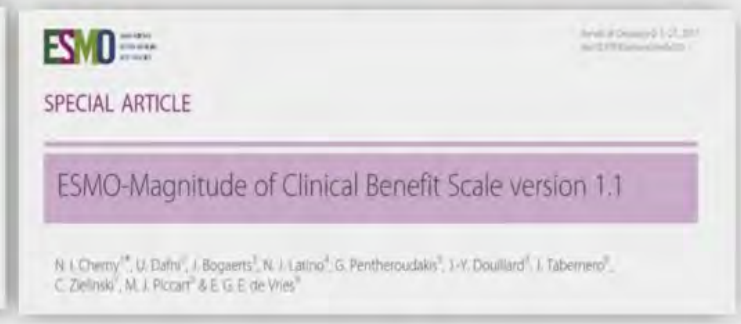
EDITOR'S CHOICE

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny, R. Sullivan, U. Dafni, J. M. Kerst, A. Sobrero, C. Zielinski, E. G. E. de Vries, M. J. Piccart

Field tested and validated in 78 studies
Google Scholar citations 580: 9/2020

ESMO-MCBS v1.1 (Sept 2017)



ESMO

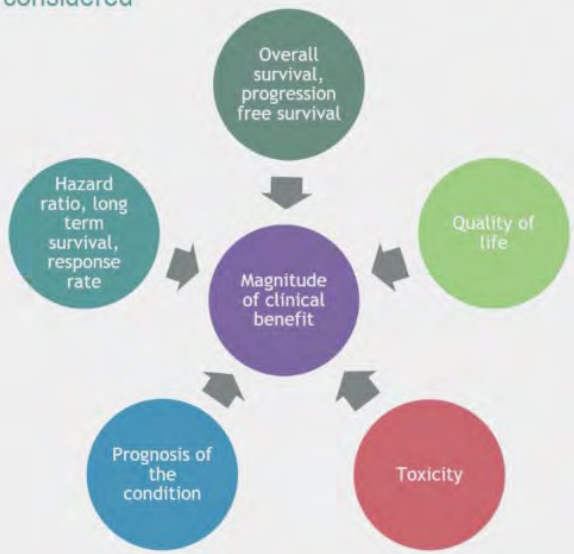
SPECIAL ARTICLE

ESMO-Magnitude of Clinical Benefit Scale version 1.1

N. I. Cherny, U. Dafni, J. Bogaerts, N. J. Latino, G. Pentheroudakis, J-Y. Douillard, I. Tabernero, C. Zielinski, M. J. Piccart & E. G. E. de Vries

Field tested and validated in 128 studies
Google Scholar citation 211: 9/2020

ESMO-MCBS factors considered



Relevance and coherence: clear statement of underlying premises

1. Cure takes precedence over deferral of death
2. Direct endpoints such as survival and QoL take precedence over surrogates such as PFS or RR
3. DFS in curative disease is a more valid surrogate than PFS in non-curative disease
4. Interpretation of the evidence for benefit derived from surrogate outcomes (such as PFS or RR) may be influenced by secondary outcome data
5. Tail of curve data may sometimes indicate important gain for a minority of responders
6. Data from RCTs are more credible than from single arm studies

Cherny NI et al, Ann Oncol 2015; Cherny NI et al, Ann Oncol 2017

CDK 4/6i-related quality of life (QoL) - ABC

Drug	Trial	CDK4/6i > control*		CDK4/6i = control		CDK4/6i < control**
PALBOCICLIB	PALOMA 2	Pain scores GHS TTD		GHS/QoL		-
	PALOMA 3					Hair loss
RIBOCICLIB	MONALEESA 2	TTD (pain, emotional, funct.)	Pain scores	EORTC QLQ-C30 GHS/QoL	EORTC QLQ-C30 GHS/QoL	-
	MONALEESA 3		TTD (HR-QoL and EORTC QLQ-C30 - functioning)		EORTC QLQ-C30 GHS/QoL	-
	MONALEESA 7		TTD (HR-QoL and EORTC QLQ-C30 – pain, fatigue, emotional, social funct.)		Work productivity	-
ABEMACICLIB	MONARCH 3	Financial difficulties		GHS		Symptoms (diarrhea, nausea/vomiting, appetite loss)
	MONARCH 2	Pain scores (TTD) Role functioning				

In the **ADVANCED SETTING**, overall, adding CDK 4/6i did not worsen patients' HR-QoL

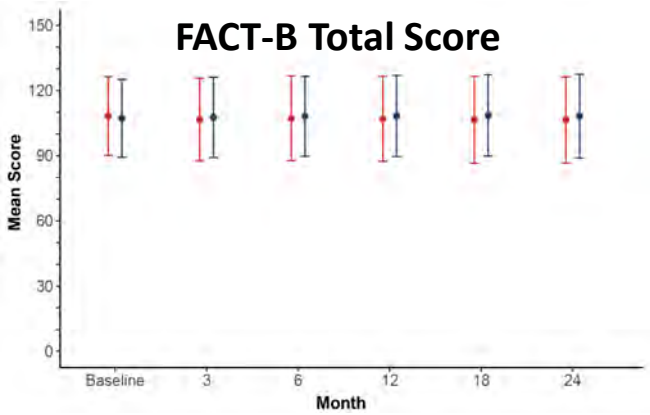
- Positive trend towards pain improvement
- Gastrointestinal scores favored the control arm in abemaciclib-containing trials

Di Lauro et al, ESMO Open 2022; Tolaney et al, Lancet Oncol 2020; Kaufman et al, Oncologist 2020; Rugo et al, Ann Oncol 2018; Rugo et al, Br Cancer Res and Treat 2019;Harbeck et al, Ann Oncol 2016; Rugo et al, EJC 2018; Verma et al, Br Cancer Res and Treat 2016; Janni et al, Br Cancer Res and Treat 2018; Fashing et al, The Breast 2020; Harbeck et al, Ther Adv Med Oncol 2016; Lu et al, Ann Oncol 2019; Harbeck et al, Cancer Res 2020; Tripathy et al, JCO Fashing et al, Ann Oncol 2021; Fashing et al, Ann Oncol 2021

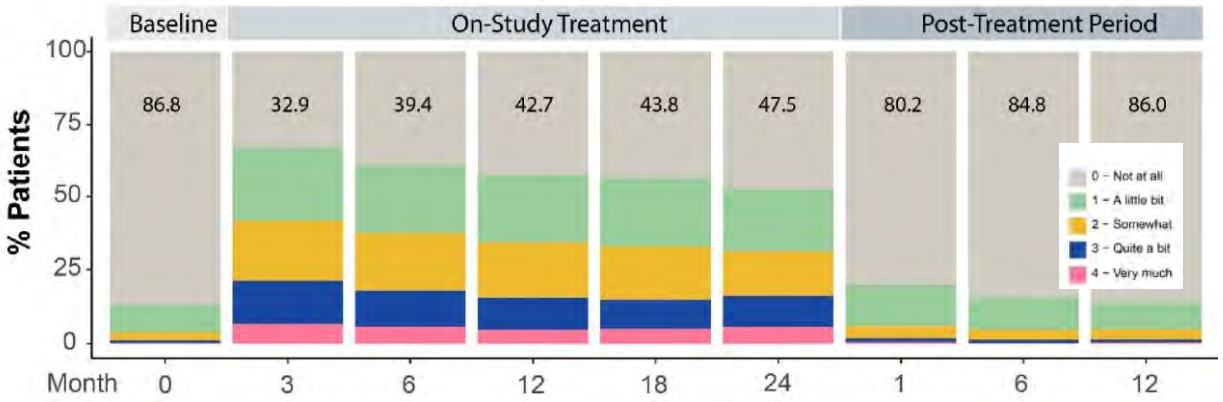
CDK 4/6i-related quality of life (QoL) - EBC

MONARCH-E

FACT-B Total Score

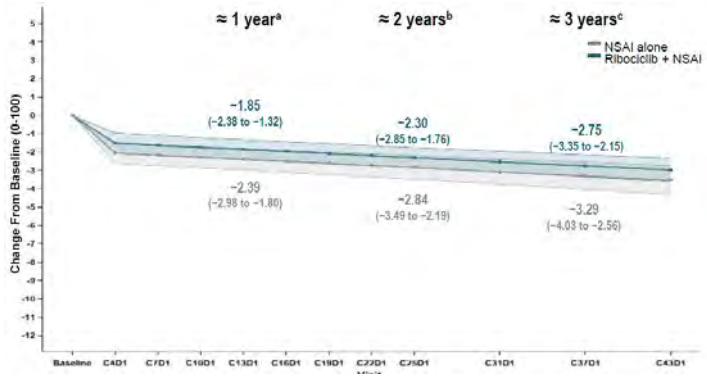


FACT-ES C5 “I have diarrhea”

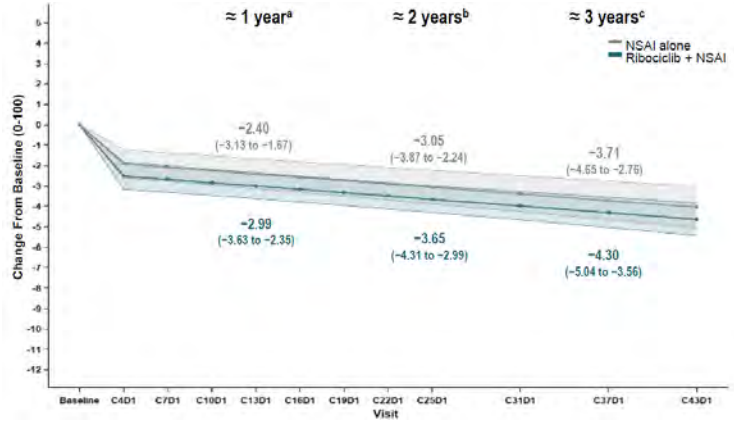


NATALEE

EORTC-QLQ C30 Physical functioning



EORTC-QLQ C30 Global Health Status

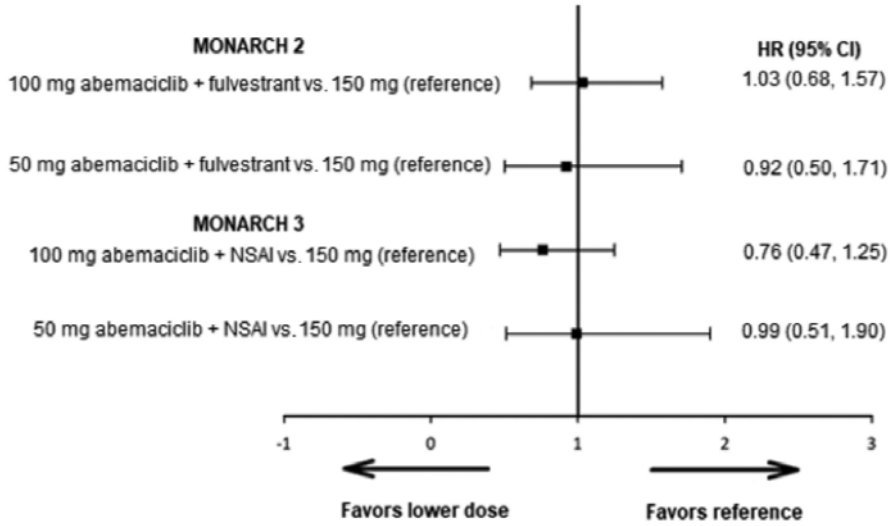


- In the **EARLY SETTING**, the HR-QoL was maintained with CDK 4/6i added to adjuvant ET
  - The only exception was represented by diarrhea with abemaciclib within the Monarch-E trial (FACT-B C5), however, no significant differences were observed in patients being bothered by treatment side effects (FACT-B GP5)

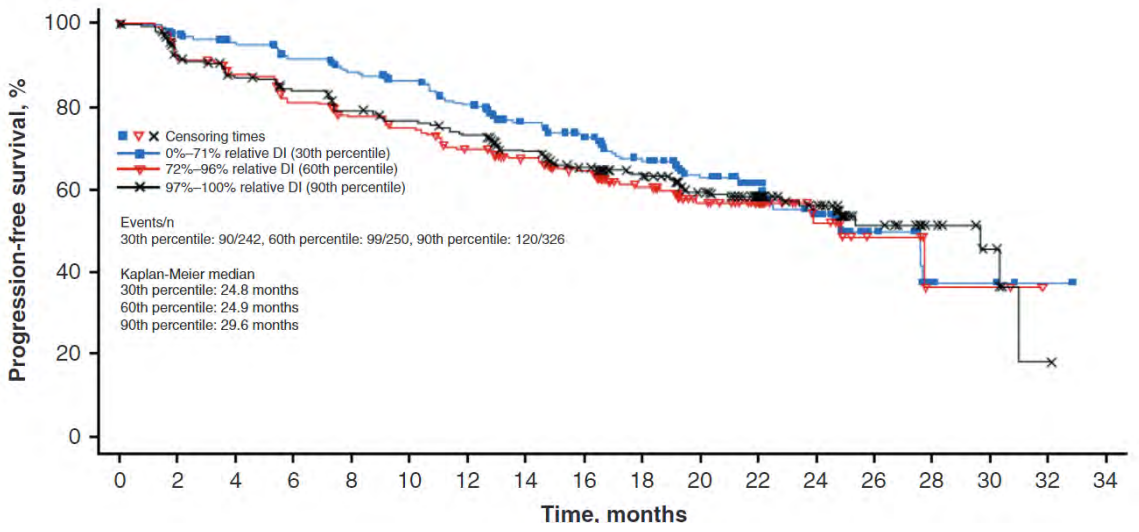
Tolaney S, et al. Poster presented at: SGBCS 2021; Rugo et al, Ann Oncol 2022; Fasching et al, ESMO Plenary

Impact of dose reduction: ABC

MONARCH-2 and MONARCH-3



MONALEESA-2, MONALEESA-3 and MONALEESA-7*



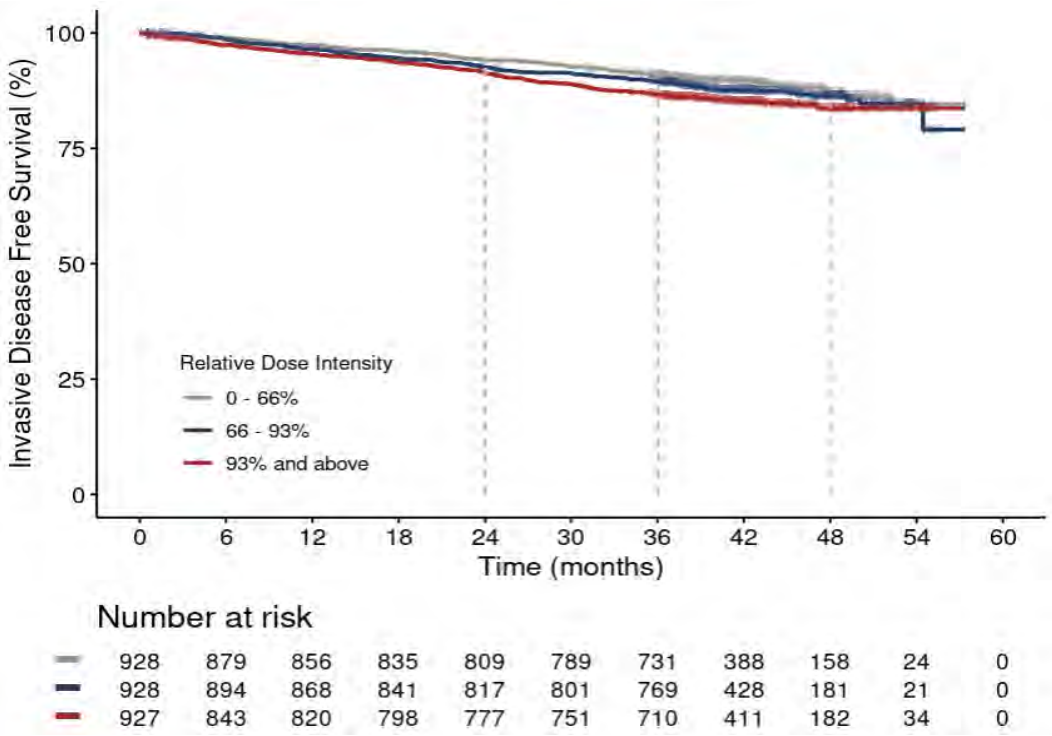
*Also NO detrimental effect on OS of dose reduction and RDI

NO detrimental effect of dose reduction/RDI on CDK 4/6 magnitude of benefit

Rugo et al, The Oncologist 2021; Burris et al, British J Canc 2021, Hart et al ASCO 2022

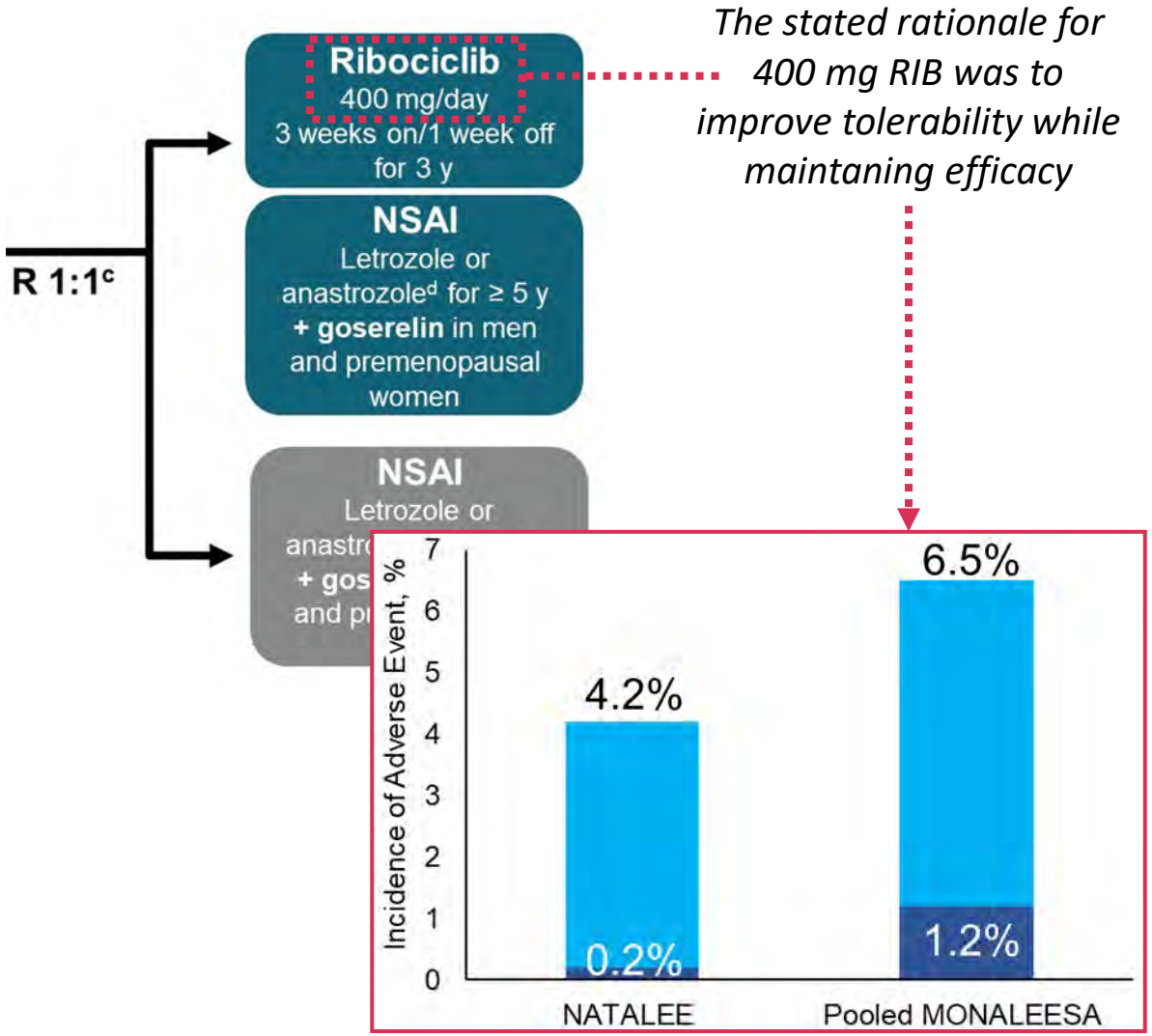
Impact of dose reduction: EBC

MONARCH-E



4-year IDFS rates were generally consistent across 3 equal-sized subgroups based on RDI (87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest)

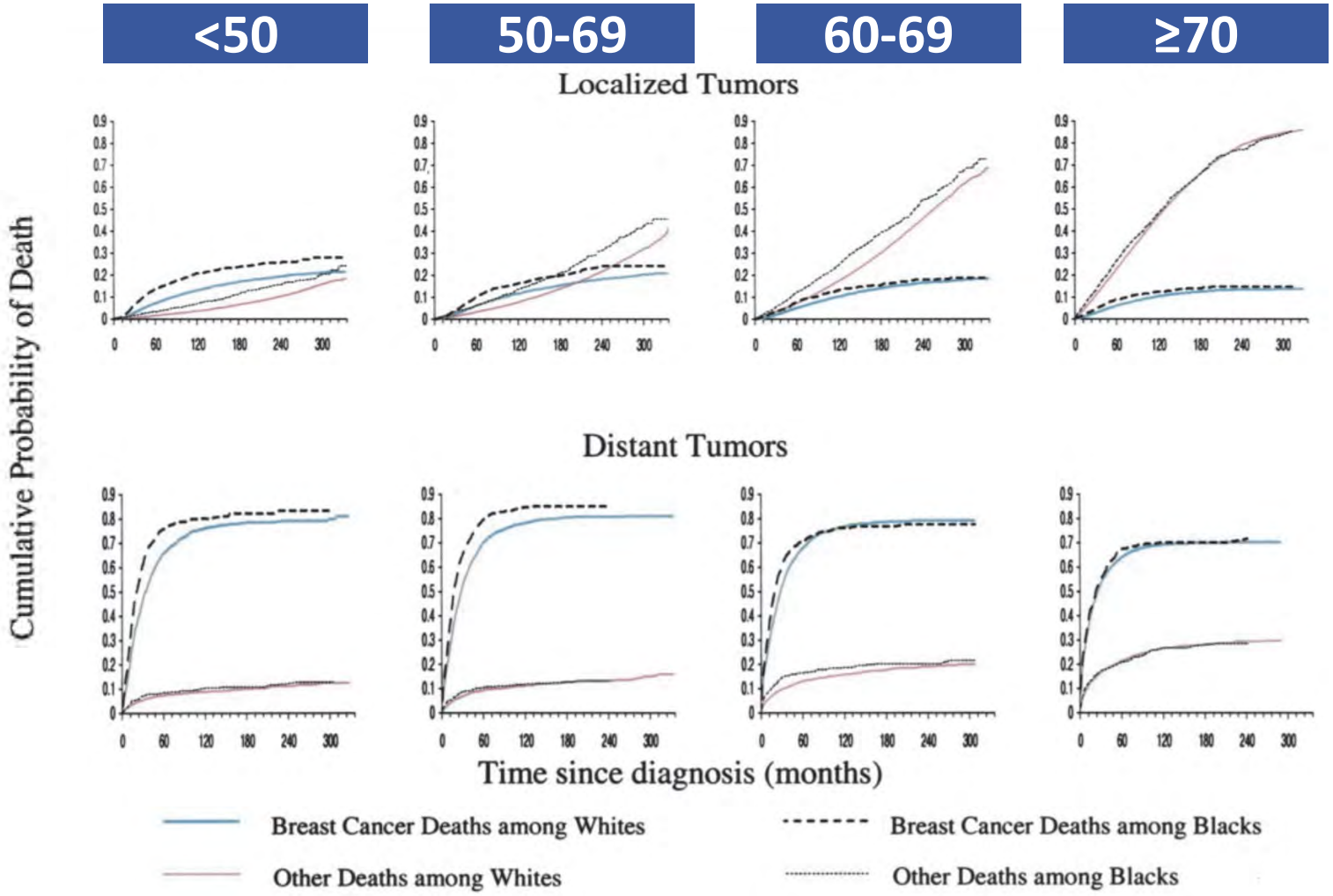
NATALEE



Hamilton et al. ASCO 2023; O'Shaughnessy et al, ESMO 2023; Slamon et al, ASCO 2023

Breast cancer: impact of AGE according to disease setting

430,210 patients from the SEER database



EARLY BC: death from BC

- predominant cause of death for pts <50 yy.
- predominant cause of death for at least 13-17 yy after diagnosis in pts 50-59 yy
- at older ages, the probability of competing causes of death becomes increasingly important.

METASTATIC BC:

- death from BC is the overwhelming cause of death regardless of age at diagnosis, with most deaths occurring within the first 5 years from diagnosis.

Schairer J Nat Can Inst 2004

ELDERLY patients - ABC

		Palbociclib PALOMA trials	Ribociclib MONALEESA trials	Abemaciclib MONARCH trials
TREATMENT NAIVE	PFS	PALOMA-2: 65+ years: HR 0.57 (95% CI 0.39–0.84)	MONALEESA-2: +AI, 65+ years: HR 0.658 (95% CI 0.466–0.928) MONALEESA-3: +fulvestrant, over 65 years: HR 0.597 (95% CI 0.436–0.818)*	MONARCH-3: 65+ years: HR 0.57 (95% CI 0.36–0.90)
	Toxicity	65+ years: any grade neutropenia 81%; febrile neutropenia 1%	65+ years: nausea, alopecia, diarrhea and vomiting in >10% of patients; >10% increase in fatigue and grade 1–2 anemia	Age-specific data not available
PRE TREATED	PFS	PALOMA-3: 65+ years: HR 0.35 (95% CI 0.19–0.62)	MONALEESA-3:* +fulvestrant, 65+ years: HR 0.597 (95% CI 0.436– 0.818)*	MONARCH-2: 65+ years: 0.620 (95% CI 0.447–0.860)
	Toxicity	70+ years: grade 3–4 neutropenia 13.9%	Age-specific data not available	Age-specific data not available

*The MONALEESA-3 study included treatment-naïve and pretreated patients.
AI, aromatase inhibitor; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

- CDK 4/6 inh. + ET appears to be **equally effective** in older pts as in younger pts.
- Older pts seem to experience **similar to slightly increased toxicity** than younger pts.
- QOL DATA ARE LACKING: some older patients (typically subject to a shorter life expectancy, competing comorbidities, polypharmacy) may value **QoL as important or even more important than survival**.

Battisti et al, Therapeutic Advances in Medical Oncology 2018

ELDERLY patients- EBC

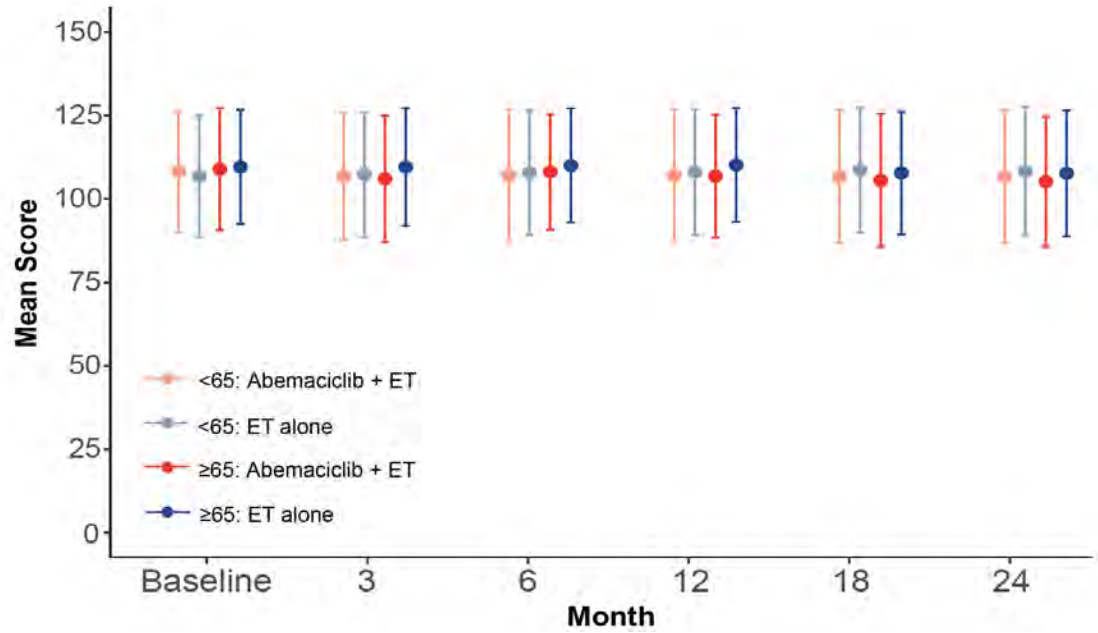
MONARCH-E

- Older Patients had more comorbidities, higher baseline ECOG PS Scores, and received less prior (neo) adjuvant CT
- Older Patients derived **similar abemaciclib benefit** to ITT Population *(also within Cohort 1)*
- **Adverse Event rates** were similar between age groups
- **Dose Adjustments** were more common in older patients
- **QoL** was similar between arms and across age subgroups

		Abemaciclib + ET		
AE, %	**Grade**	**Overall** n=2791	**<65** n=2361	**≥65*** n=430
Any AE	Any	98	98	99
	G≥3	50	49	54
Clinically relevant AEs				
Diarrhea	G1	45	46	37
	G2	31	31	30
	G3	8	7	12
Fatigue	G1	23	23	21
	G2	15	14	20
	G3	3	2	6
Neutropenia	G1/2	26	27	22
	G≥3	20	20	19
ALT increase	G1/2	10	10	7
	G≥3	3	3	3
VTE	Any	3	2	3
	G≥3	1	1	1
ILD	Any	3	3	3
	G≥3	<1	<1	<1

	IDFS			DRFS		
	ITT	**<65**	**≥65**	**ITT**	**<65**	**≥65**
Events/N						
Abemaciclib + ET	**336**/2808	**270**/2371	**66**/437	**281**/2808	**230**/2371	**51**/437
ET alone	**499**/2829	**414**/2416	**85**/413	**421**/2829	**353**/2416	**68**/413
HR (95% CI)	**0.664** (0.578, 0.762)	**0.646** (0.554, 0.753)	**0.767** (0.556, 1.059)	**0.659** (0.567, 0.767)	**0.647** (0.548, 0.764)	**0.748** (0.520, 1.077)
Interaction p-val.	NA	0.35		NA	0.49	

QoL FACT-B Total Score



Hamilton et al. ASCO 2023

Conclusions

- Safety profile of CDK4/6i is now well characterized
- Data support dose reduction as an effective measure to manage treatment related Aes
- Despite dose reduction, treatment efficacy remains uncompromised
- QoL is preserved, despite the higher incidence of AEs as compared to endocrine monotherapy
- Patient education and proactive management are essential components of successful CDK4/6 inhibitor therapy.