2024 Breast Cancer Congress

with Updates from the 2023 SABCS

Friday, February 2, 2024
3:35 PM – 4:00 PM CST

Advances in the Management of HR-Positive Metastatic Breast Cancer with SABCS Updates

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University of Wisconsin Carbone Cancer Center

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal

Agenda/Goals

- Understand the recent data regarding the role of CDK4/6 inhibitors in MBC including first line, those with visceral crisis and after prior CDK4/6i
- Discuss oral selective estrogen receptor degraders (SERDs) as a new treatment approach
- Review PI3K/Akt/mTOR pathway inhibitors as treatments approaches for MBC

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Summary of 1L CDK 4/6 inhibitor Ph3 trials

Trial	Population/Design	mPFS/ (Δ)	HR/ p value	mOS/ (Δ)	HR/ p value
PALOMA-2[1]	N = 666 Post-meno Letrozole +/- palbo (2:1)	24.8 mo/10mo	0.58/ <0.001	53.9 mo/ 3 mo	0.956/ 0.338
MONALEESA-2[2]	N = 668 Post-meno Letrozole +/- ribo (1:1)	25.3 mo/9 mo	0.57/ <0.001	63.9 mo/ 12.5 mo	0.76/ = 0.008
MONALEESA-3[3]	N = 365 (1L) Post-meno Fulvestrant +/- ribo (2:1)	33.6 mo/19.2 mo	0.55/ significant	67.6 mo/ 16mo	0.67/ Significant *expl longer f/up*
MONALEESA-7[4]	N = 672 Pre/peri-meno OFS+ tam or AI +/- ribo (1:1)	23.8mo/11 mo	0.55/ <0.001	58.7 mo/ 11mo	0.76/ Significant *expl longer f/up*
MONARCH-3[5]	N = 493 Post-meno AI +/- abema (2:1)	28.2 mo/13mo	0.54/ 0.00002	SABCS23	

Finn RS, et al. N Engl J Med. 2016, ASCO 2022
Hortobagyi GN, et al. NEJM 2022
Neven et al Breast Cancer Research 2023
Im et al NEJM 2019 and Lu et al CCR 2022
Goetz MP, t al. J Clin Oncol. 2017;35:3638-3646

*Expl= Exploratory

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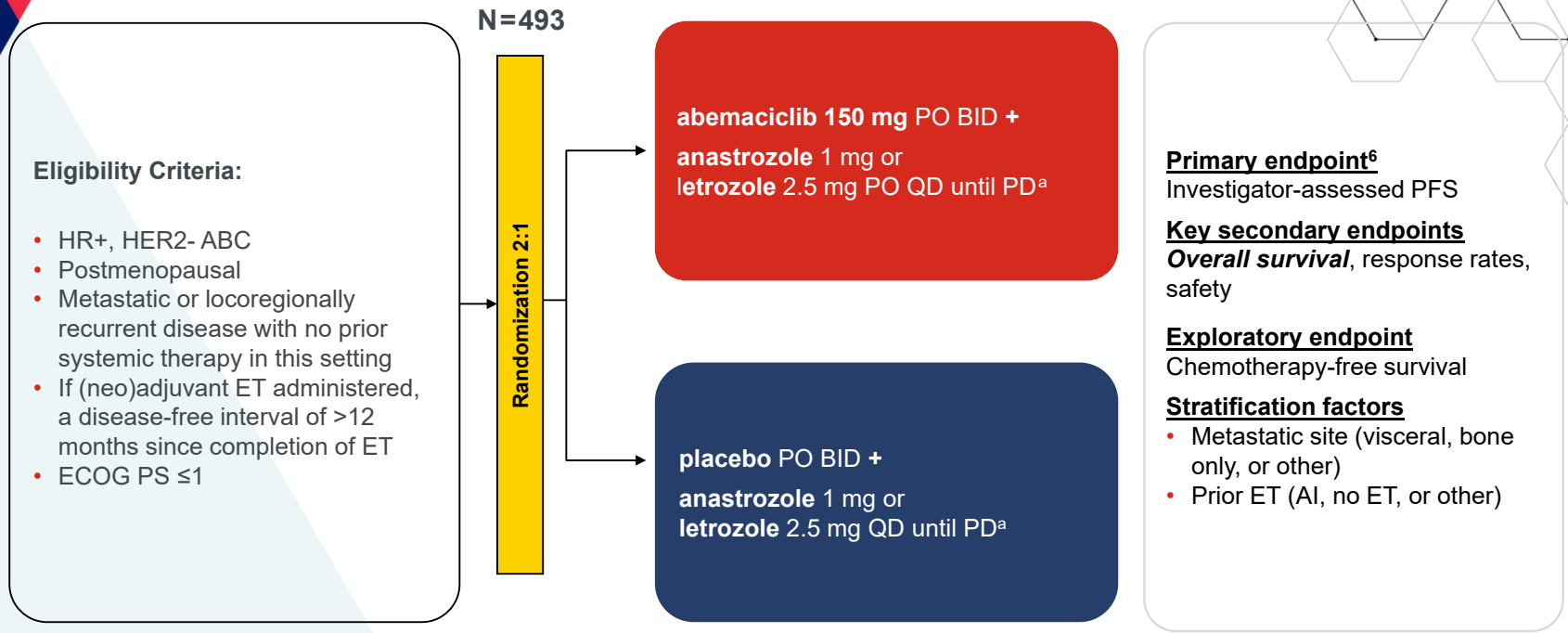
SABCS 2023 Update: MONARCH 3

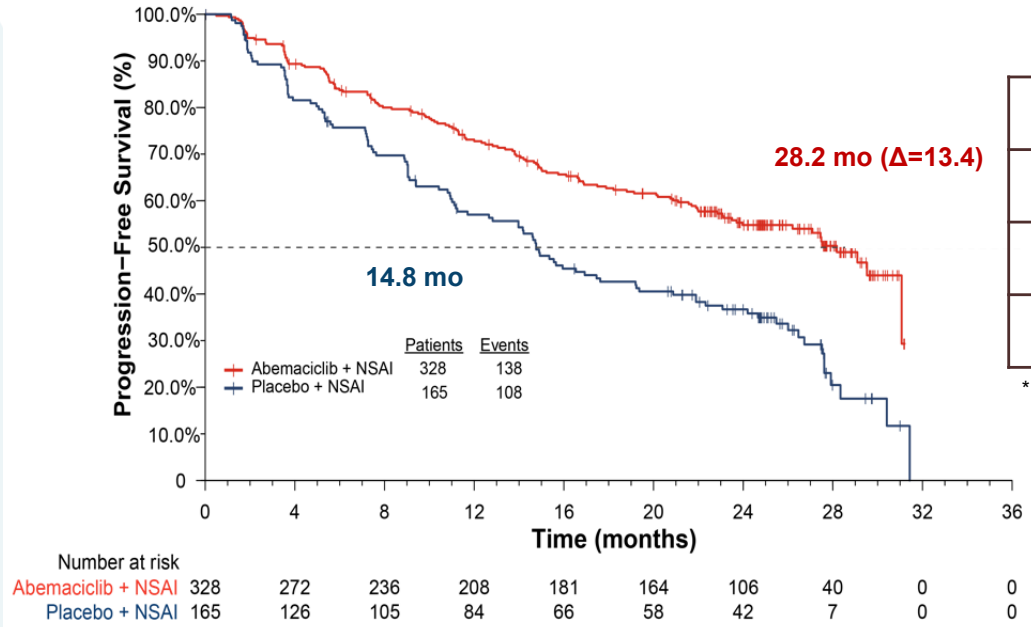


[a]per physician's choice: 79.1% received letrozole, 19.9% received anastrozole

MONARCH 3 enrolled from November 2014 to November 2015 in 158 centers from 22 countries

[6]Goetz MP, et al. *J Clin Oncol.* 2017;35(32):3638-3646

PFS Benefit in MONARCH 3 Led to Global Approvals



	abemaciclib + NSAI	placebo + NSAI
Median PFS (months)	28.2	14.8
HR (95% CI) 2-sided *P* value	0.540 (0.418-0.698) nominal p=0.000002*	
Pre-planned Final PFS Analysis[5] Data cut: 03 Nov 2017		

*Statistical significance was reached at the interim PFS analysis[6]

At the final PFS data cut with a median follow-up of 26.7 months, PFS was prolonged by a median 13.4 months in patients receiving abemaciclib. At that time, OS was immature with 29.5% events observed across both arms.

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[5]Johnston S, et al. *NPJ Breast Cancer.* 2019;5:5
[6]Goetz M, et al. *J Clin Oncol.* 2017;35(32):3638-3646

Statistical Analysis Plan for OS

Preplanned Analysis Points	Planned Number of Events	Information Fraction	Data Cut	Median Follow-up	% Patients on Treatment by Arm
OS Interim 1 (IA1)	~189 events in the ITT	0.6	03 Feb 2020	4.5 years	• 18.6% abemaciclib arm • 8.5% placebo arm
OS Interim 2 (IA2)	~252 events in the ITT	0.8	02 Jul 2021	5.8 years	• 12.5% abemaciclib arm • 3.0% placebo arm
Final OS	~315 events in the ITT	1	29 Sep 2023	8.1 years	• 7.0% abemaciclib arm • 3.0% placebo arm

- The family-wise type I error was controlled at 0.05 (2-sided), with a gate-keeping strategy between PFS and OS. OS only tested inferentially for significance if PFS significant.
- The pre-specified OS analyses were performed using a stratified log-rank test.
- Alpha was split according to graphical testing procedure between the ITT population and the subgroup with visceral disease (sVD) to enable testing in both populations.
- For OS, the cumulative 2-sided type I error of 0.05 was maintained using the Lan-Demets method with the O'Brien-Fleming type α-spending function to account for multiplicity of interim and final analyses.

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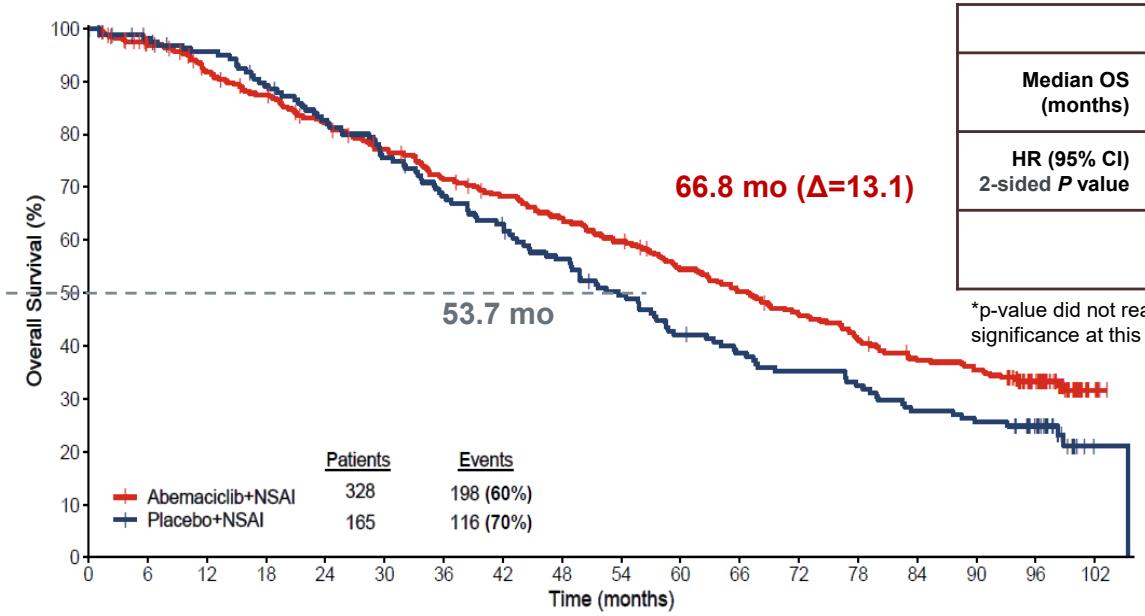
Goetz M, et al SABCS 2023

OS in the ITT Population



Number at Risk

Abemaciclib+NSAI	328	304	281	266	247	229	211	199	187	174	156	144	131	117	104	99	66	6
Placebo+NSAI	165	155	149	138	127	116	104	95	84	73	62	56	51	47	40	37	28	1

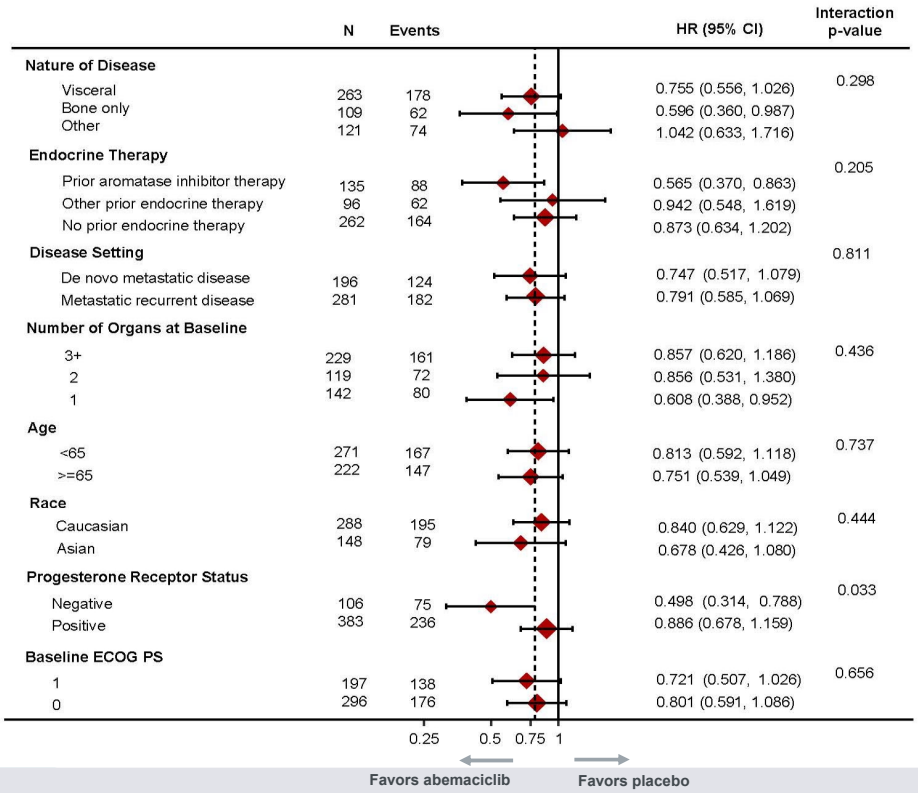
	abemaciclib + NSAI	placebo + NSAI
Median OS (months)	66.8	53.7
HR (95% CI) 2-sided *P* value	0.804 (0.637-1.015) p=0.0664*	
Final OS Analysis Data cut: 29 Sep 2023		

*p-value did not reach threshold (0.034) for statistical significance at this final analysis

Abemaciclib in combination with a NSAI resulted in longer OS compared to NSAI alone; however, statistical significance was not reached. The observed improvement in median OS was 13.1 months.

Goetz M, et al SABCS 2023

OS Subgroup Analysis



Consistent OS effect size observed across subgroups

Goetz M, et al SABCS 2023

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MONARCH-3[5]	N = 493 Post-meno AI +/- abema (2:1)	28.2 mo/13mo	0.54/ 0.00002	66.8 mo/ 13mo	0.80/ p=0.0664

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Differences in the CDK4/6 Inhibitors

Characteristic	Palbociclib[1-3]	Ribociclib[4,5]	Abemaciclib[5,6]
Target (IC_{50}, nM)	CDK4 (11); CDK6 (15)	CDK4 (10); CDK6 (39)	CDK4 (2); CDK6 (10)
Route	PO	PO	PO
Dose, mg	125 QD	600 QD	Monotx: 200 BID Combo w/ET: 150 BID
Schedule	3 wks on/1 wk off	3 wks on/1 wk off	Continuous
Half-life, hr	27	32.6	17-38
Adverse events - All Pneumonitis (class)	Neutropenia, GI	Neutropenia, GI, QTc, LFTs	GI, Neutropenia, VTE, elevated Cr

1. DeMichele A, et al. Clin Cancer Res. 2015;21:995-1001. 2. Hamilton E, et al. Cancer Treatment Rev. 2016;45:129-138. 3. Costa R, et al. Ann Oncol. 2017;28:44-56. 4. Infante JR, et al. Clin Cancer Res. 2016;22:5696-5705. 5. Barroso-Sousa R, et al. Breast Care. 2016;11:167-173. 6. Dickler MN, et al. ASCO 2016. Abstract 510.

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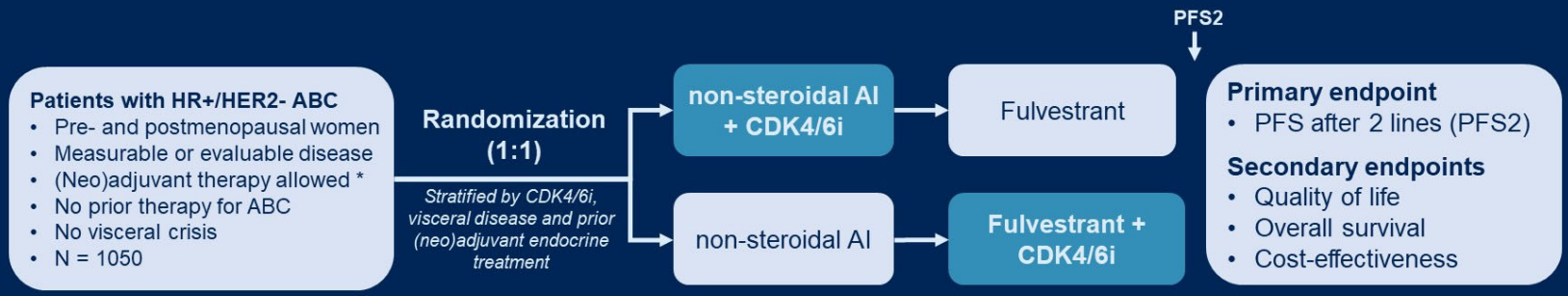
SONIA trial design

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

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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)

Trial overview

SONIA

Inclusion period: November 23, 2017 - September 1, 2021

Data cut-off date: December 1, 2022

Median follow-up: 37.3 months

		First-line CDK4/6i N=524	Second-line CDK4/6i N=526
Patient status, n	First-line treatment ongoing	207	122
	Second-line treatment ongoing	16	82
	Follow-up	117	134
Number of events, n	PFS1	310	407
	PFS2	281	310
	OS	184	188
Median duration on CDK4/6i, months		24.6	8.1

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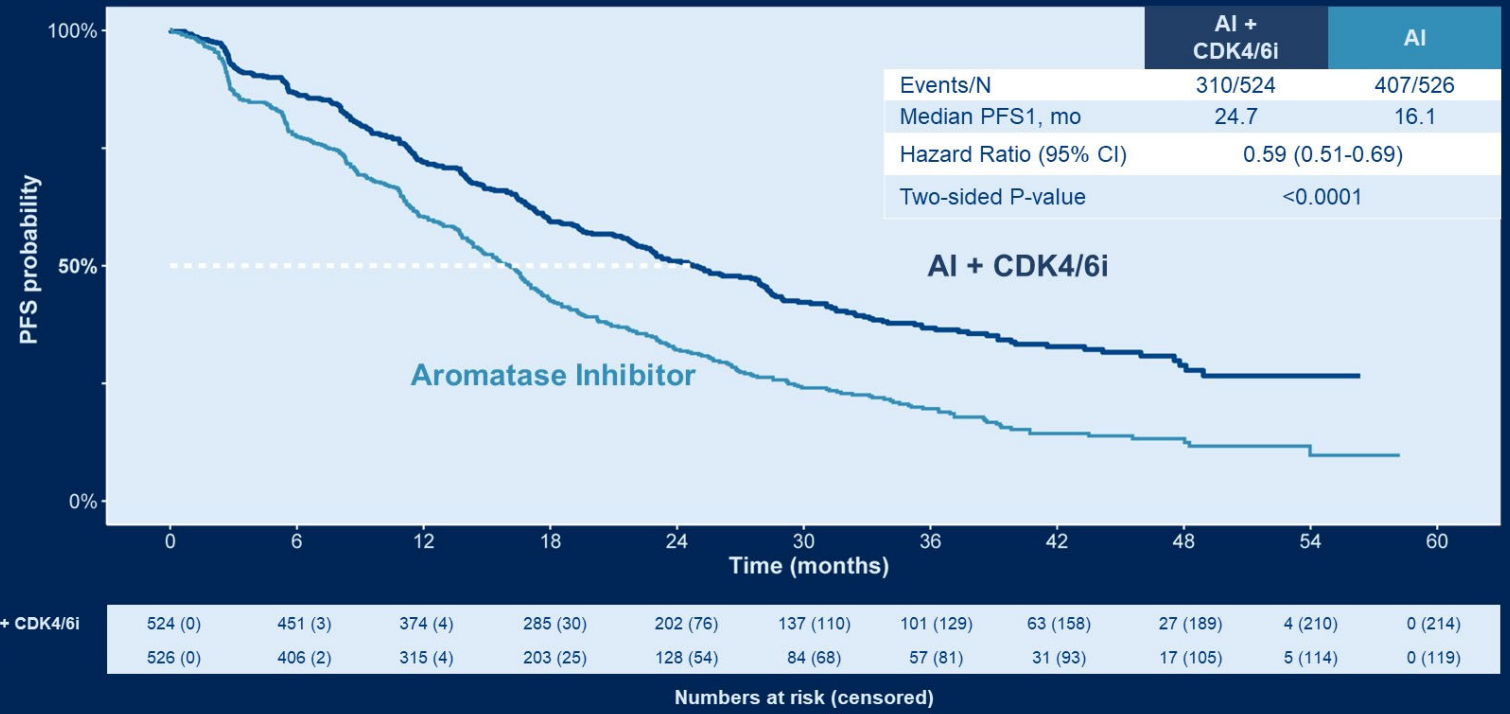
Progression-free survival in first line

SONIA



	AI + CDK4/6i	AI
Events/N	310/524	407/526
Median PFS1, mo	24.7	16.1
Hazard Ratio (95% CI)	0.59 (0.51-0.69)	
Two-sided P-value	<0.0001	

Numbers at risk (censored)											
AI + CDK4/6i	524 (0)	451 (3)	374 (4)	285 (30)	202 (76)	137 (110)	101 (129)	63 (158)	27 (189)	4 (210)	0 (214)
AI	526 (0)	406 (2)	315 (4)	203 (25)	128 (54)	84 (68)	57 (81)	31 (93)	17 (105)	5 (114)	0 (119)

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Primary endpoint: PFS2

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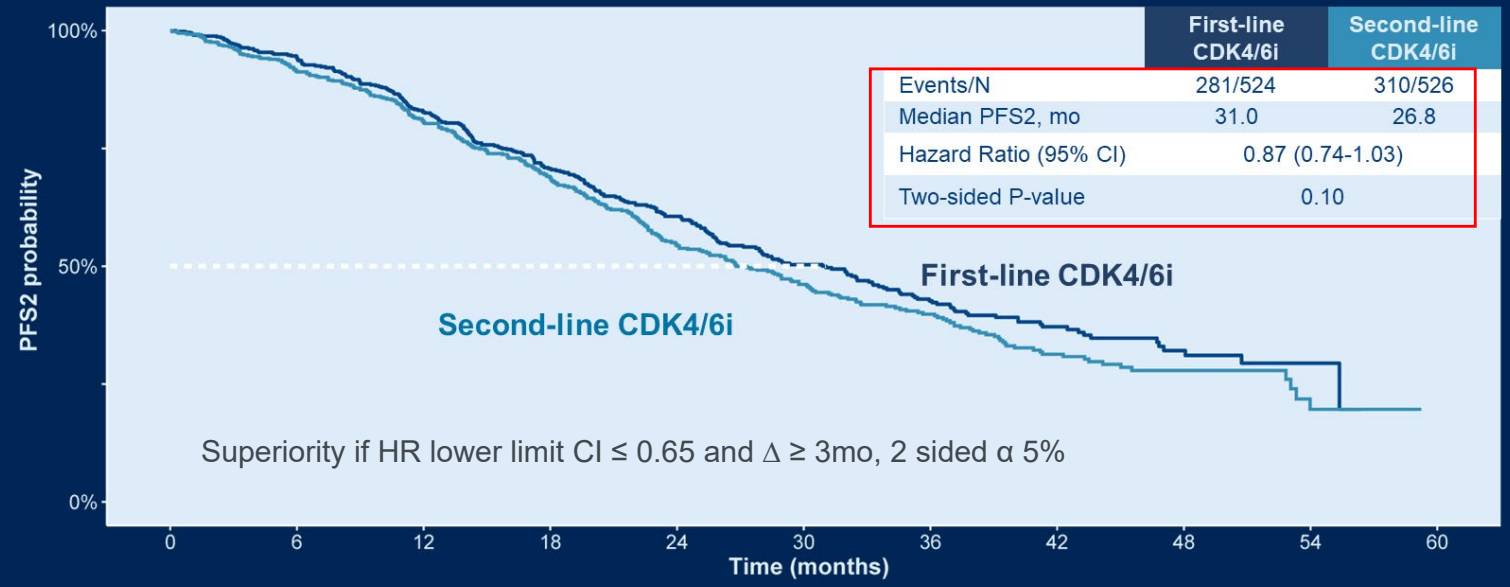

	First-line CDK4/6i	Second-line CDK4/6i
Events/N	281/524	310/526
Median PFS2, mo	31.0	26.8
Hazard Ratio (95% CI)	0.87 (0.74-1.03)	
Two-sided P-value	0.10	

Numbers at risk (censored)											
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)

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Safety summary

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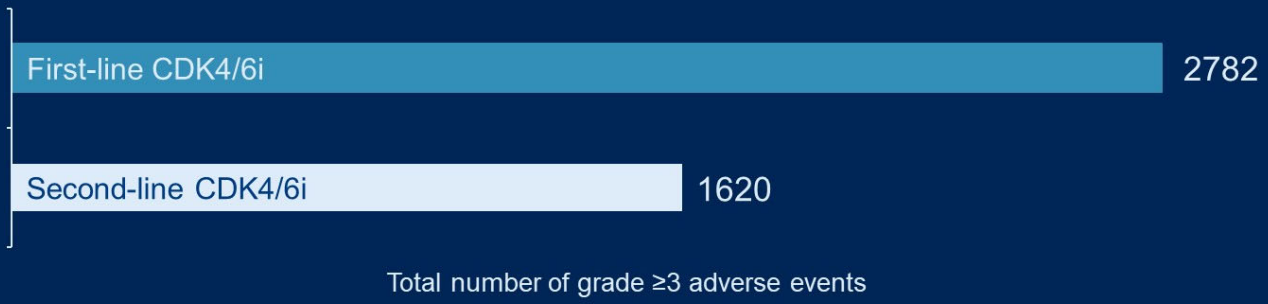
- The safety profile was characteristic for CDK4/6i
  - neutropenia, liver function abnormalities, anemia, thrombocytopenia
- 42% more grade ≥3 adverse events when CDK4/6i was used in first-line



First Line CDK4/6i Discussion

- **Ribociclib may be preferred as OS not met in PALOMA-2/MONARCH-3**
  - Studies with similar PFS benefit (HR and absolute)
  - Possibly underpowered/statistical design decisions (2:1, alpha spending)
  - Inclusion criteria (e.g. disease-free interval) may also impact outcomes
  - No direct comparison trials of CDK4/6i (Harmonia- ribo vs palbo for HER2- enriched)
  - Adjuvant data mixed- abemaciclib/ribociclib positive; palbociclib negative

- **SONIA questions if 1L CDK4/6i better than sequencing in 2nd line**
  - Study population likely had very endocrine sensitive disease
  - Majority received palbociclib (OS in PALOMA-2 not met)
  - Supports endocrine monotherapy in 1L for some patients, if aligned with preference
    - I.e. cost, extra visits/testing, side effects
- **Lack of a biomarker for CDK4/6i and direct comparison trials remain key challenges**

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NCCN Guidelines for First Line

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens

First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor[b]
  - Aromatase inhibitor + ribociclib (category 1)[c]
  - Aromatase inhibitor + abemaciclib
  - Aromatase inhibitor + palbociclib
- Fulvestrant[d] + CDK4/6 inhibitor[b]
  - Fulvestrant + ribociclib (category 1)[e]
  - Fulvestrant + abemaciclib (category 1)[e]
  - Fulvestrant + palbociclib

Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g]
- For *PIK3CA* or *AKT1* activating mutations or PTEN alterations, see targeted therapy options, see BINV-Q (6)[h]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[I,J]

Other Recommended Regimens

First- and/or Subsequent-Line Therapy

- Selective ER down-regulator
  - Fulvestrant[k]
  - For *ESR1* mutated tumors, see BINV-Q (6)
- Selective ER down-regulator (fulvestrant) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[k]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective ER modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances

Subsequent-Line Therapy

- Megestrol acetate
- Estradiol
- Abemaciclib[l]
- Targeted therapy options, see BINV-Q (6)

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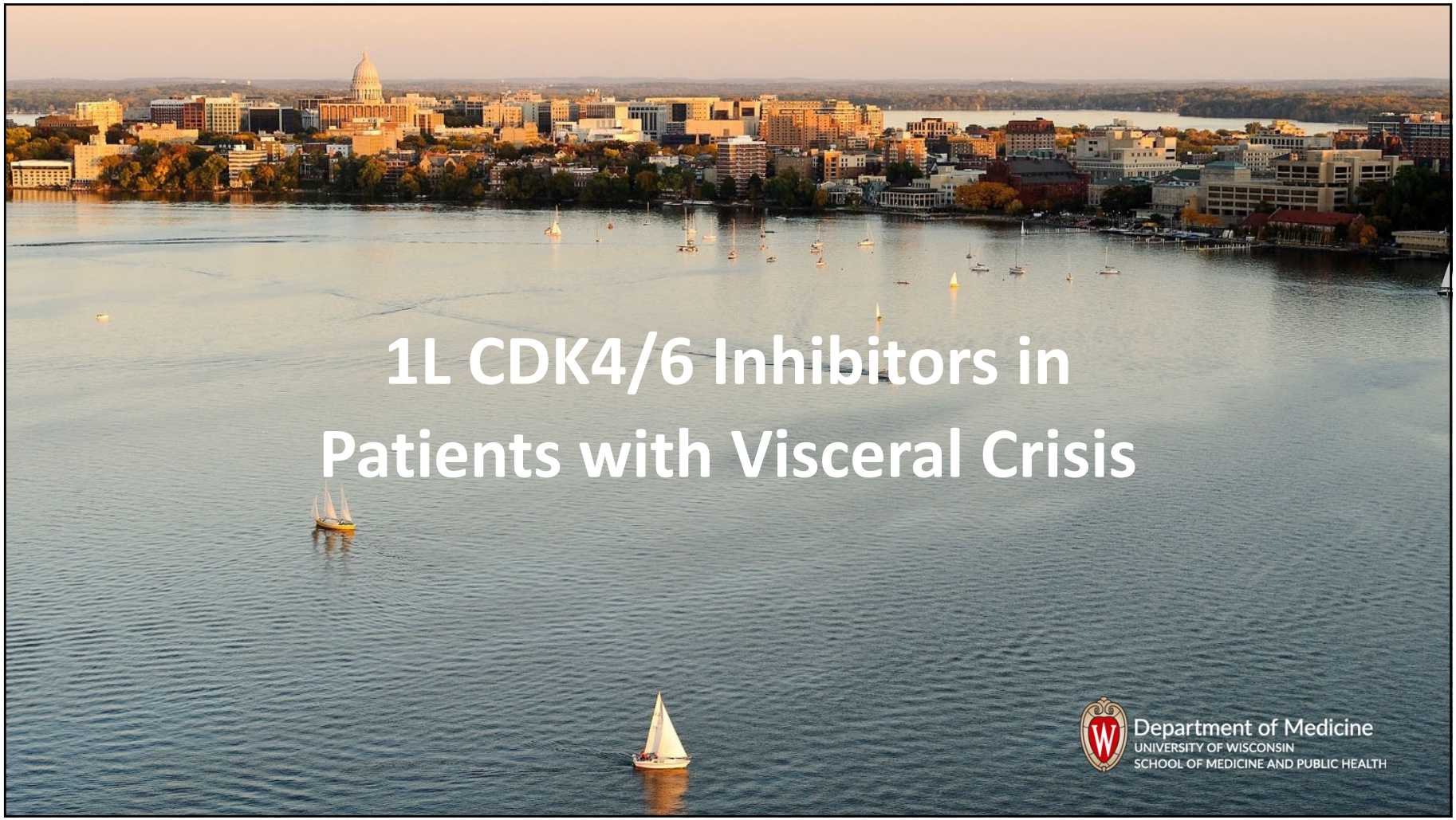
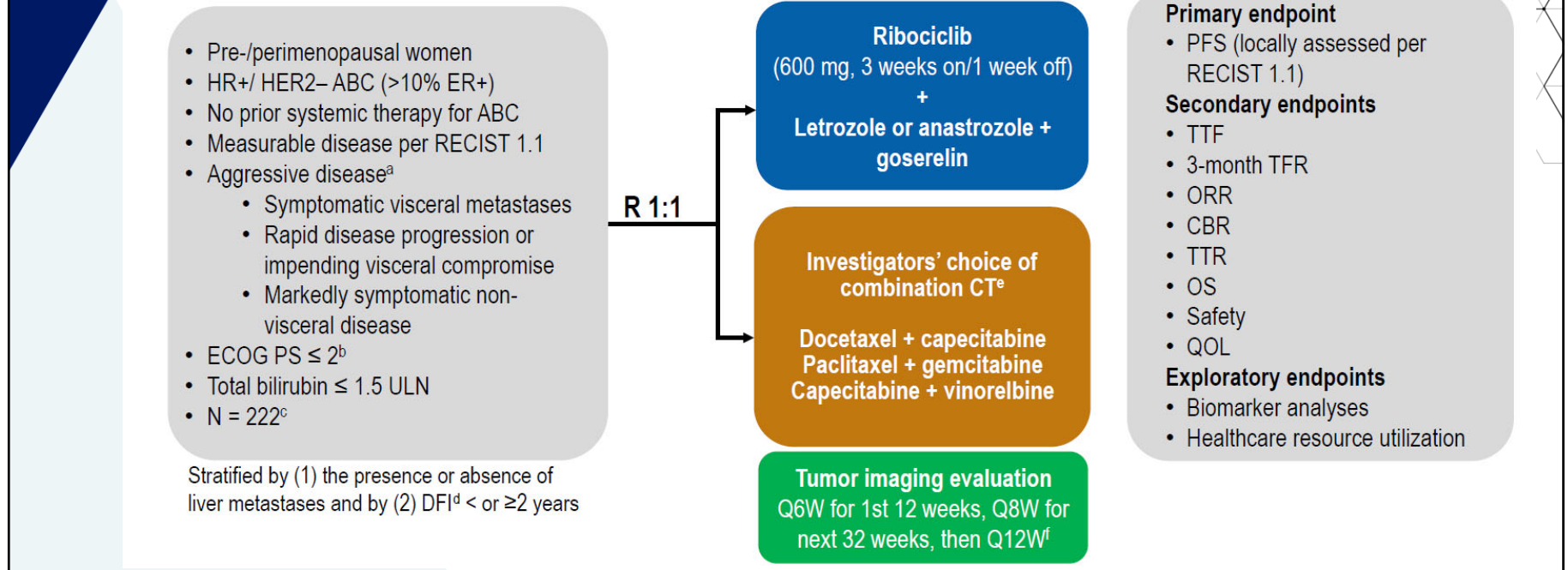


RIGHT Choice Study Design



Lu, Y et al. SABCS 2022, GS1-10

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Baseline Patient Population

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Median age, years	44.0	43.0
≥40 years	80 (71.4)	72 (65.5)
Race[a]		
Asian	60 (53.6)	58 (52.7)
White	51 (45.5)	52 (47.3)
Histological grade		
Grade 1	10 (8.9)	16 (14.5)
Grade 2	66 (58.9)	61 (55.5)
Grade 3	35 (31.3)	29 (26.4)
≥50% ER+	95 (84.8)	95 (86.4)
PR+	99 (88.4)	102 (92.7)

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Disease status		
De novo	71 (63.4)	73 (66.4)
Visceral metastatic sites[b]		
Liver	56 (50.0)	57 (51.8)
Lung	63 (56.3)	58 (52.7)
Liver or lung	89 (79.5)	85 (77.3)
Aggressive disease characteristic		
Rapid progression	23 (20.5)	18 (16.4)
Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis[c]	61 (54.5)	55 (50.0)

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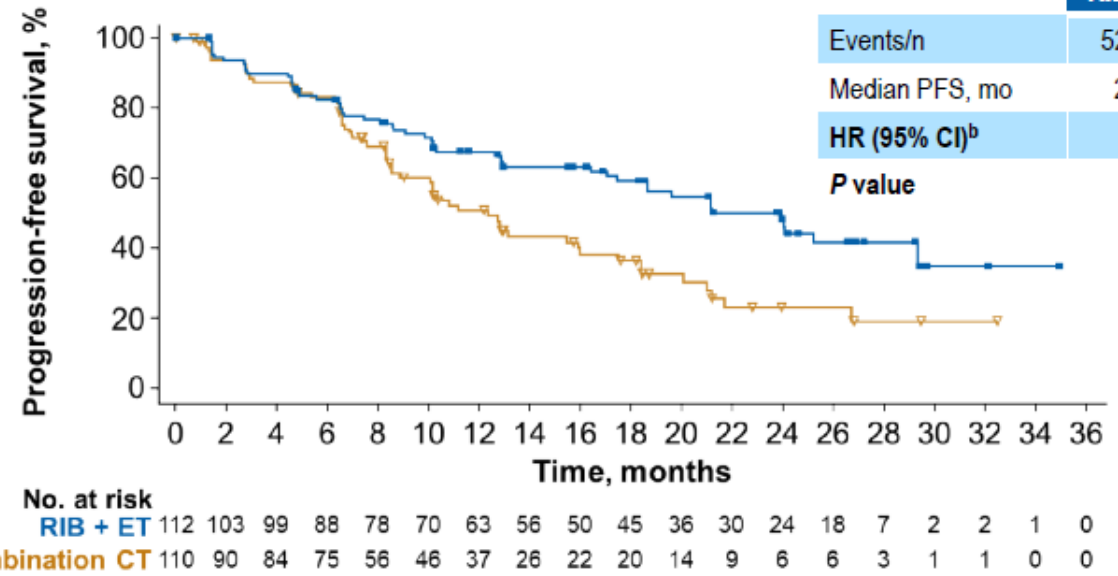
Lu, Y et al. SABCS 2022, GS1-10

Primary Endpoint: PFS

First-line RIB + ET achieved a statistically significant PFS benefit of ≈ 1 year over combination CT in aggressive HR+/HER2− ABC



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

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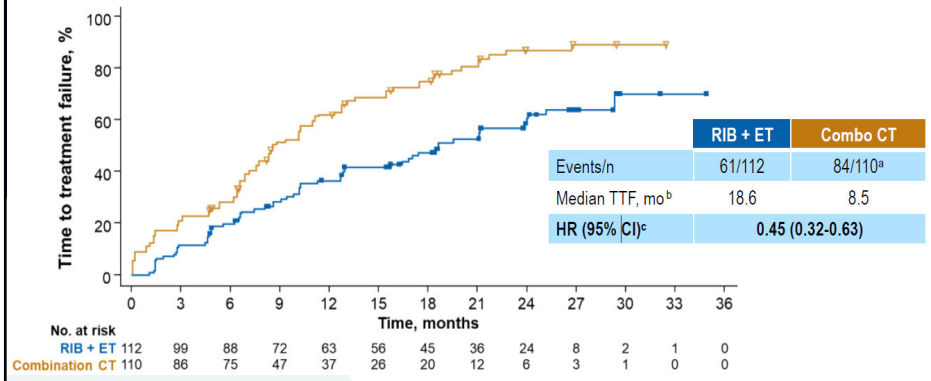
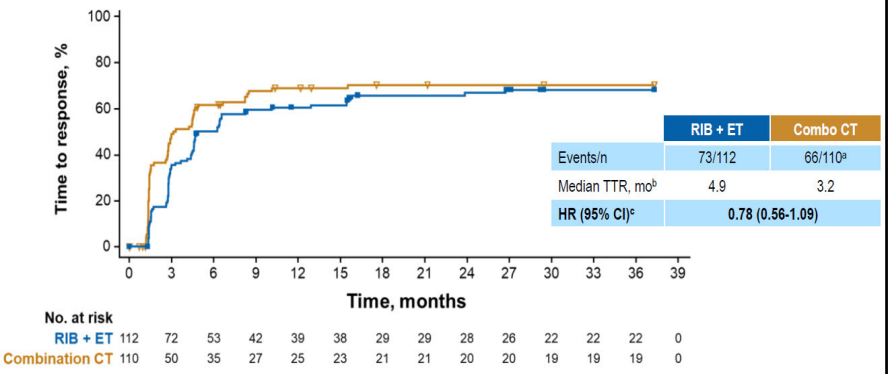
Lu, Y et al. SABCS 2022, GS1-10

Secondary Endpoints



	RIB + ET	Combo CT
Events/n	61/112	84/110[a]
Median TTF, mo[b]	18.6	8.5
HR (95% CI)[c]	0.45 (0.32-0.63)	



	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	0.78 (0.56-1.09)	

	Ribo + ET (n = 112)	Combo CT (n = 100)
ORR	65.2%	60.0%
CBR	80.4%	72.7%
Serious TRAE	1.8%	8.0%
TRAE leading to dc	7.1%	23.0%

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Lu, Y et al. SABCS 2022, GS1-10

RIGHT Choice Discussion

- **Ribociblib + endocrine therapy a 1L option for ER+ MBC in those with visceral crisis or aggressive disease in peri/pre-menopausal patients**

- Less toxic regimen, longer PFS, longer duration of treatment response, similar onset to treatment repsonse time

- Questions:
  - Not convinced this should be used for those with ER/PR low tumors (1-20%?), as may be biologically more similar to TNBC.
  - Does this apply to other CDK 4/6 inhibitors?

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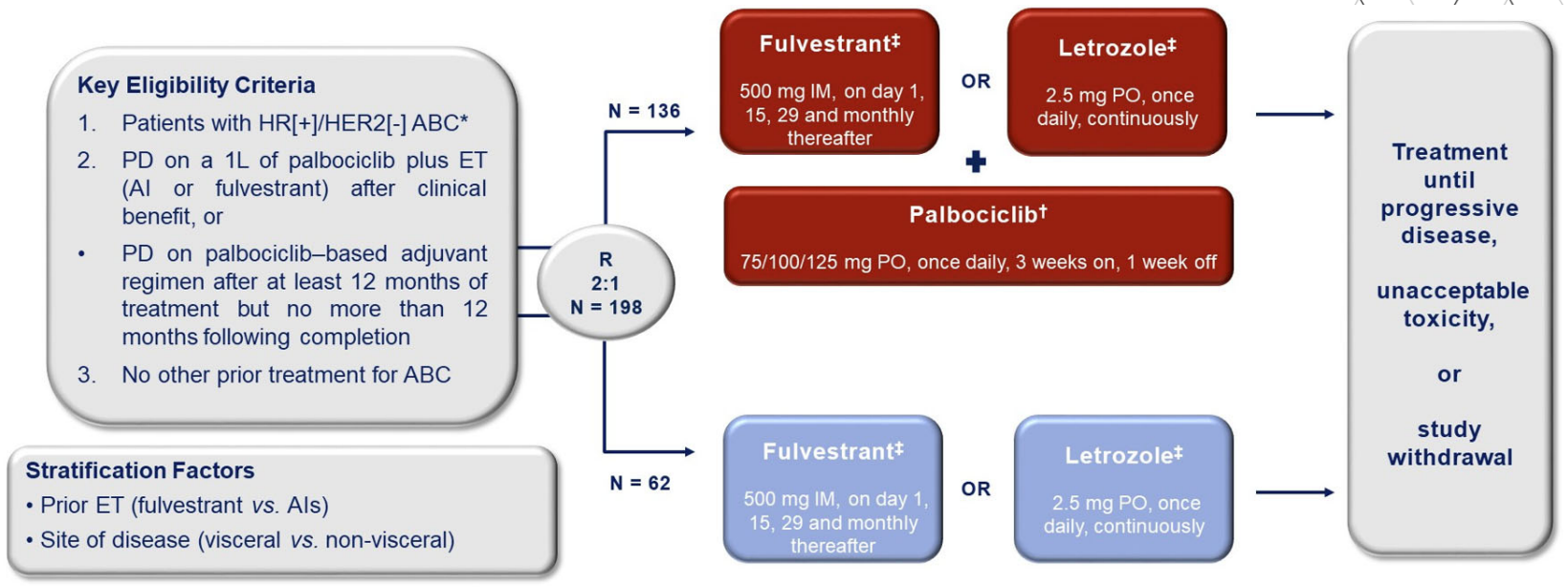
PALMIRA



1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; ET: Endocrine therapy; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; IM: Intramuscular injection; PO: oral administration; PD: Progressive disease; R: Randomization.
*If pre-menopausal, ovarian function suppression method required.
†Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.
‡Administration of endocrine therapy was chosen depending on the prior administered agent.

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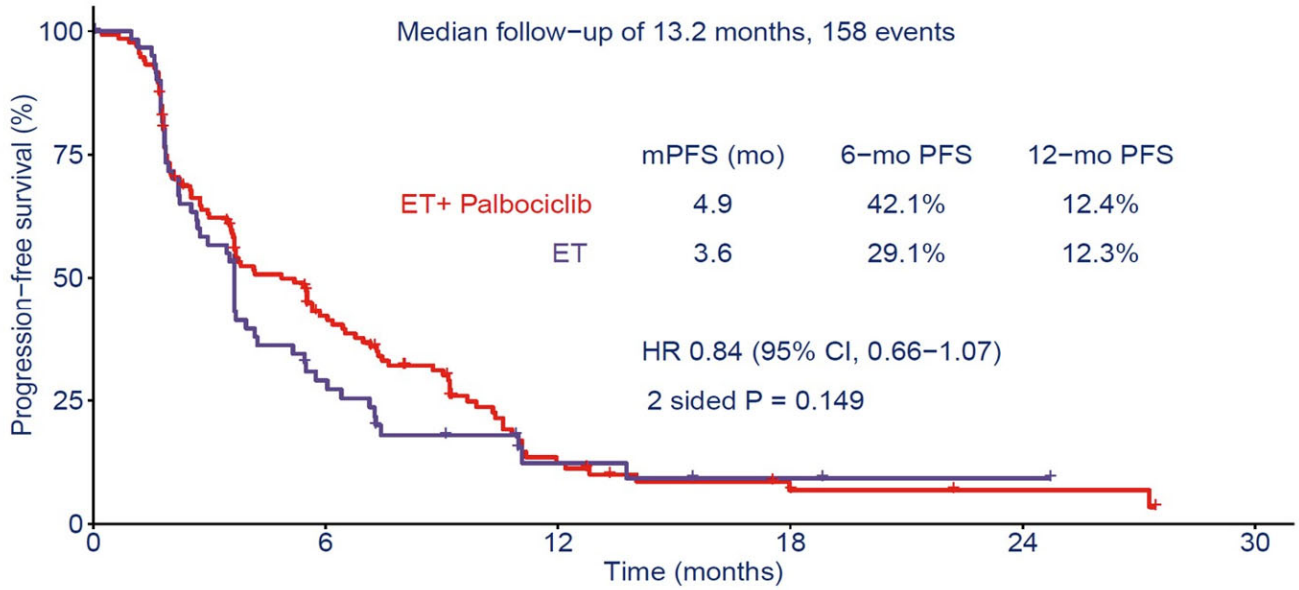
Llombart-Cussac, A et al ASCO 2023

Primary Objective: Investigator-assessed PFS (ITT Population)



Patients at risk, n (%)

ET+Palbociclib	136 (100)	47 (35)	11 (8)	4 (3)	2 (1)	0 (0)
ET	62 (100)	16 (26)	4 (6)	2 (3)	1 (2)	0 (0)

CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

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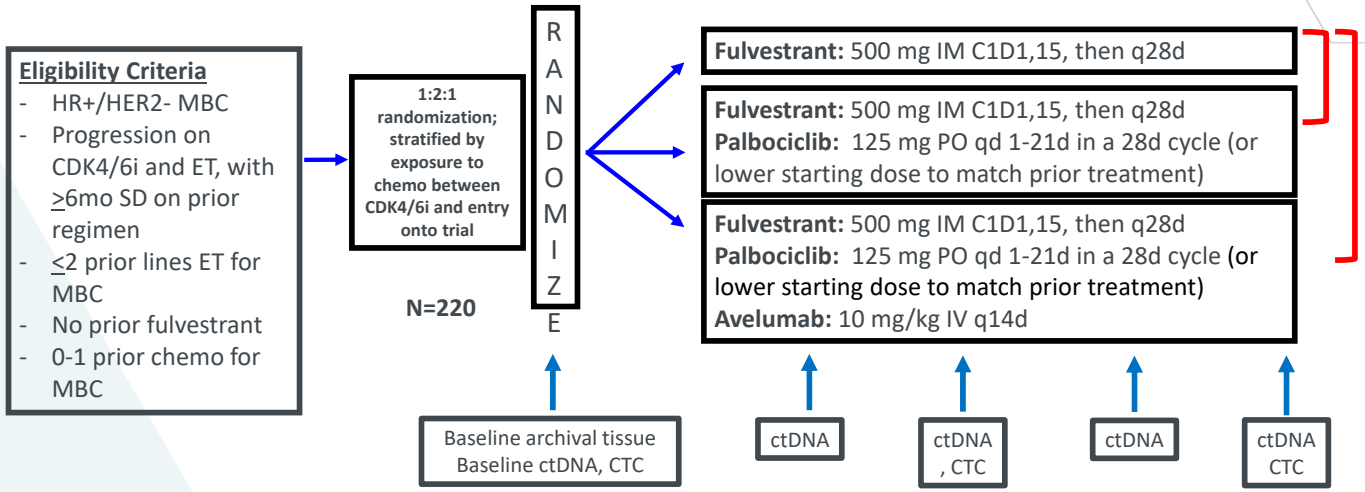
Llombart-Cussac, A et al ASCO 2023

PACE Trial: ET +/- palbociclib after prior CDK 4/6i



Primary objective: To compare PFS (RECIST-confirmed) for fulvestrant+palbociclib vs. fulvestrant alone

Secondary objectives: To compare PFS for fulvestrant+palbociclib+avelumab vs fulvestrant alone, response endpoints, safety, outcomes in predefined molecular subgroups including ESR1, PIK3CA, and Rb.

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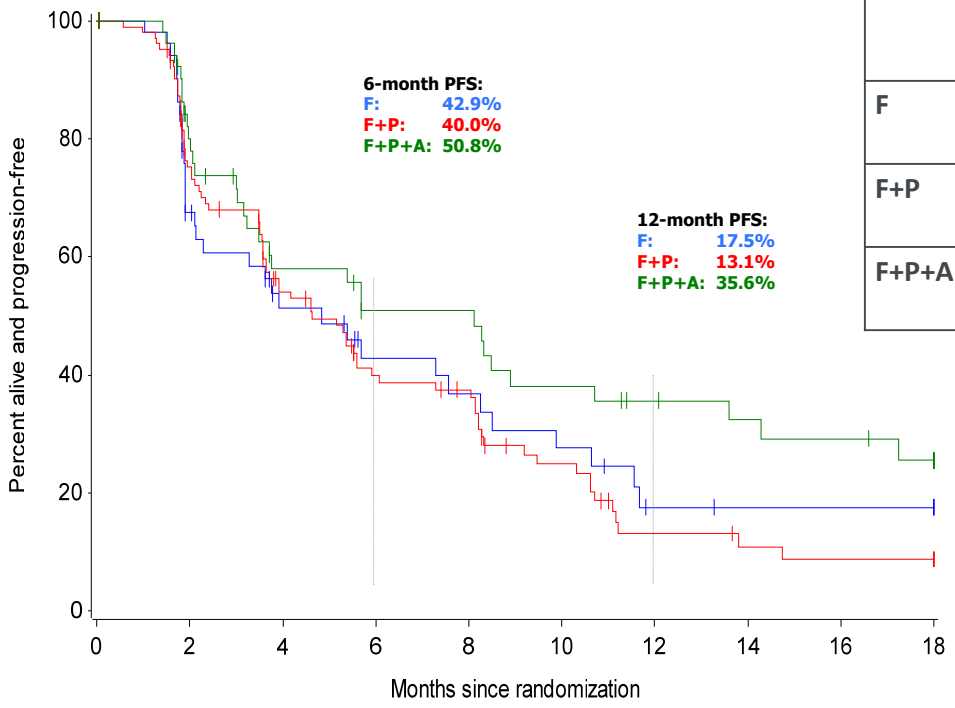
Mayer et al SABCS 2022

PACE: Progression Free Survival ITT



	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

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Mayer et al SABCS 2022

MAINTAIN TRIAL: ET +/- ribociclib after prior CDK 4/6 inhibitor

Schema

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

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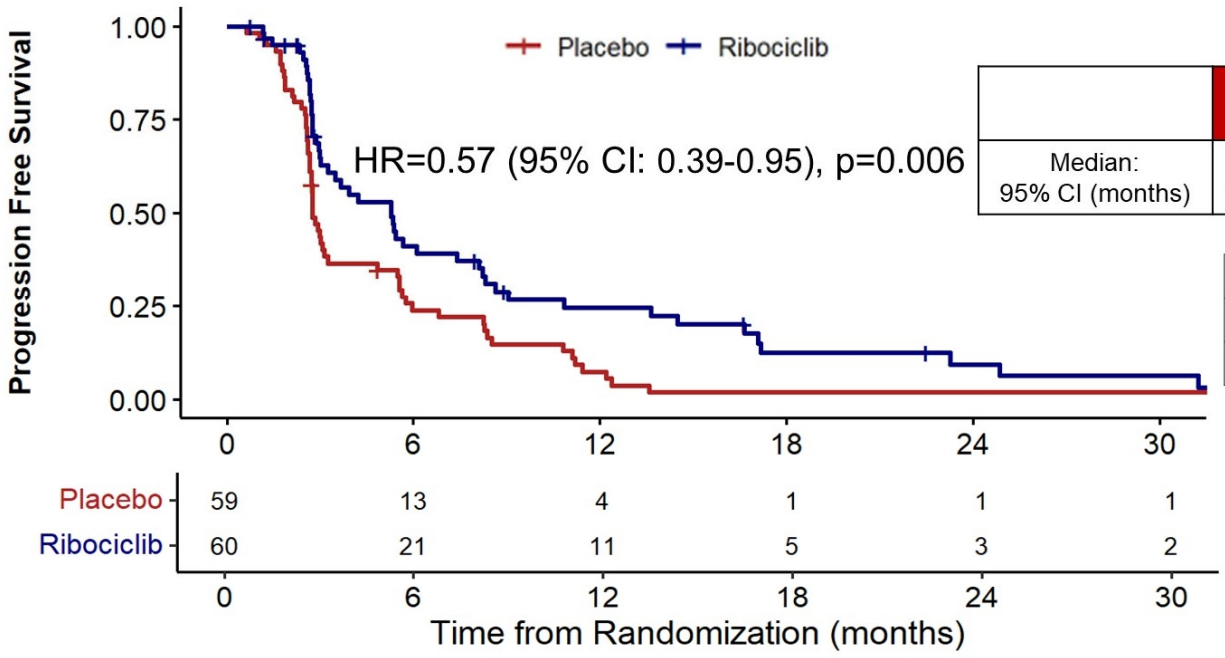
Kalinsky et al. ASCO 2022

Primary Endpoint: Progression Free Survival



	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%)

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Kalinsky et al. ASCO 2022

CDK4/6i Continuation Discussion

- **No clear data to support continuing CDK4/6i at progression**
  - MAINTAIN was a phase II study with PFS benefit
  - PACE and PALMIRA without benefit (same CDK4/6i= palbociclib)
  - Ongoing studies include EMBER-3 and postMONARCH (abemaciclib)

- Key questions that remain
  - Does the CDK4/6 inhibitor matter?
  - Who potentially benefits? Are there clinical characteristics or biomarkers that predict benefit to continued CDK4/6i?
  - Is the impact similar after progression on adjuvant CDK 4/6 inhibitor?

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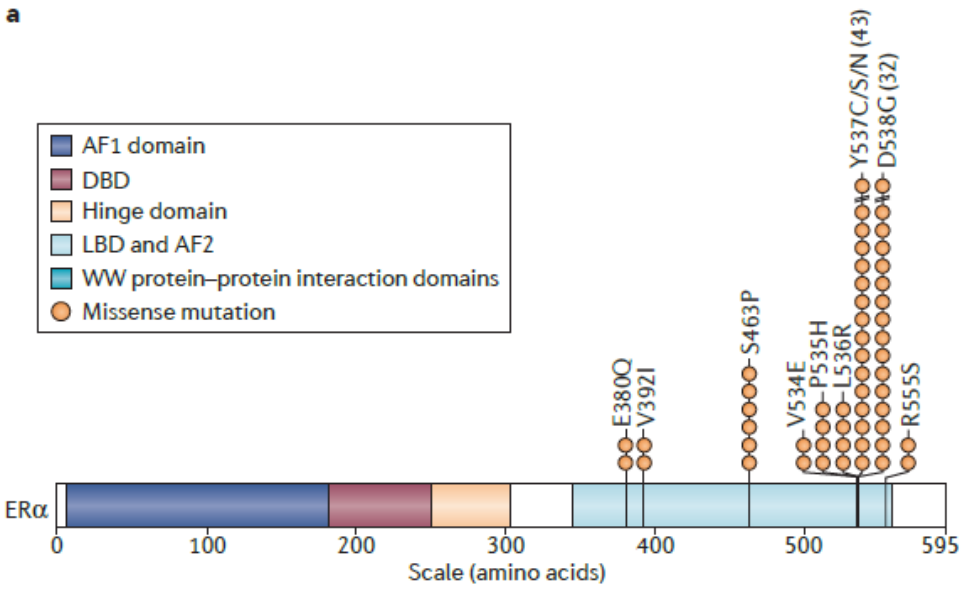
ESR1 Gain of Function Mutations

- 30-40% of metastatic ER+ breast cancer after prior endocrine therapy
- Resistance to aromatase inhibitors and standard dose tamoxifen
- High concordance between tumor & ctDNA; high detection in ctDNA



Fribbens C et al J Clin Oncol 2016
Ma C et al Nature Reviews 2015
Takeshita et al Transl Oncology 2017
Davis et al eBioMedicine 2020

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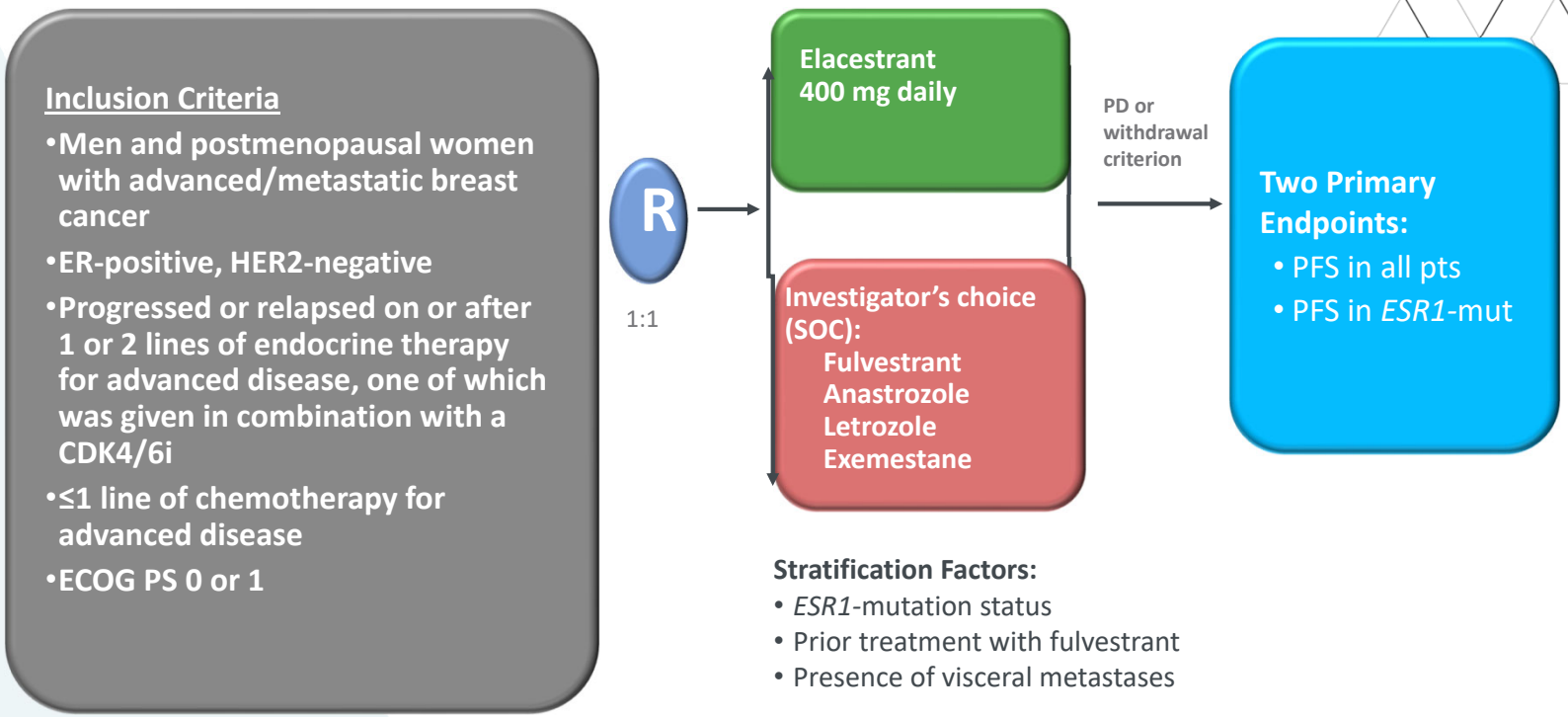
EMERALD Phase 3: Elacestrant



Bidard et al JCO 2022
Kaklamani et al SABCS 2022

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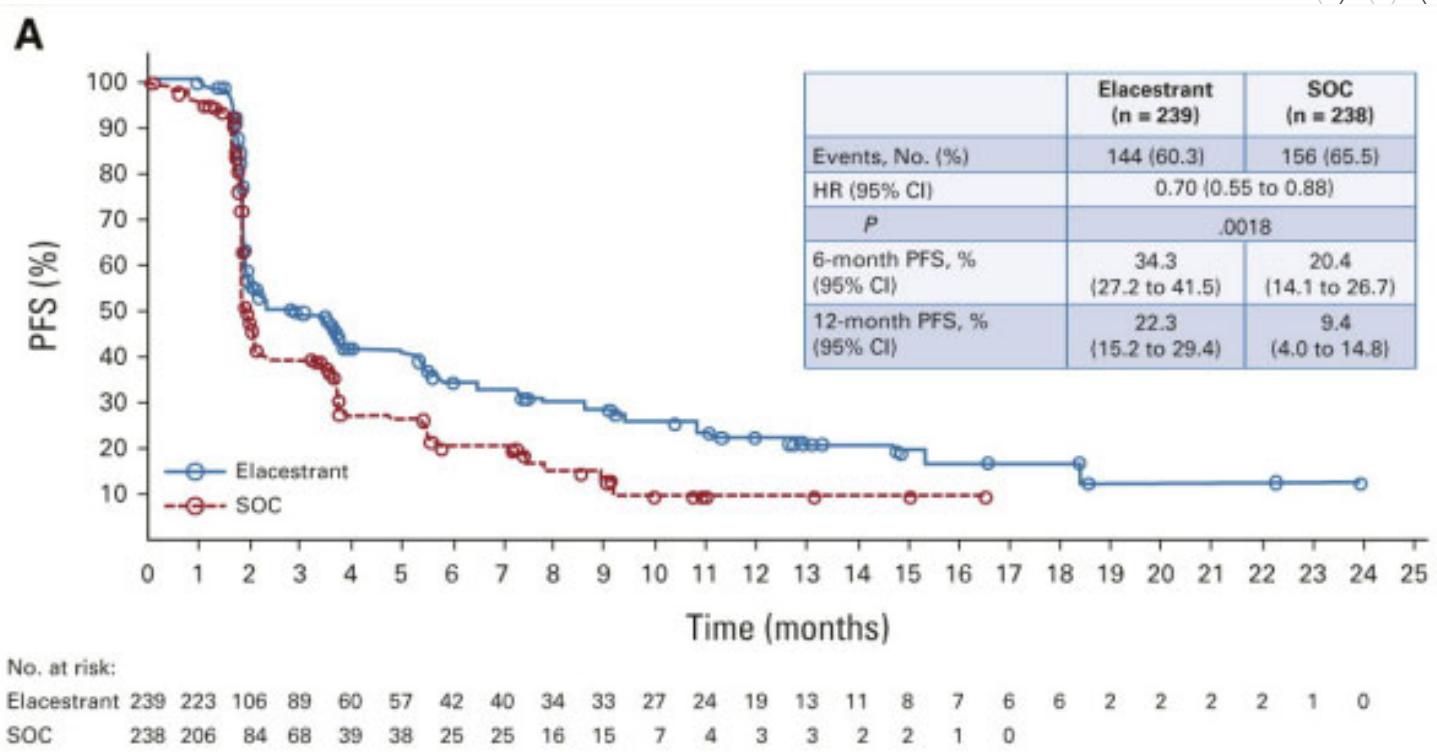
Baseline Characteristics

Parameter	Elacestrant		Total		Fulvestrant		AI	
	All (n = 239)	*ESR1* Mutation (n = 115)	All (n = 238)	*ESR1* Mutation (n = 113)	All (n = 165)	*ESR1* Mutation (n = 83)	All (n = 73)	*ESR1* Mutation (n = 30)
Median age, years (range)	63 (24-89)	64 (28-89)	64 (32-83)	63 (32-83)	63 (32-83)	62 (32-83)	67 (44-83)	68 (44-83)
Female, n (%)	233 (97.5)	115 (100)	237 (99.6)	113 (100)	164 (99.4)	83 (100)	73 (100)	30 (100)
Race or ethnicity, n (%)								
White	168 (88.4)	84 (89.4)	170 (87.6)	80 (87.0)	113 (86.9)	56 (84.8)	57 (89.1)	24 (92.3)
Asian	16 (8.4)	5 (5.3)	16 (8.2)	8 (8.7)	14 (10.8)	8 (12.1)	2 (3.1)	0
Black or African American	5 (2.6)	4 (4.3)	7 (3.6)	4 (4.3)	3 (2.3)	2 (3.0)	4 (6.3)	2 (7.7)
Other race	1 (0.5)	1 (1.1)	1 (0.5)	0	0	0	1 (1.6)	0
Hispanic	19 (7.9)	10 (8.7)	18 (7.6)	10 (8.8)	10 (6.1)	7 (8.4)	8 (11.0)	3 (10.0)
ECOG performance status 0, n (%)	143 (59.8)	67 (58.3)	135 (56.7)	62 (54.9)	91 (55.2)	46 (55.4)	44 (60.3)	16 (53.3)
Visceral metastasis[a], n (%)	163 (68.2)	81 (70.4)	169 (71)	84 (74.3)	117 (70.9)	60 (72.3)	52 (71.2)	24 (80.0)
Prior adjuvant therapy, n (%)	158 (66.1)	62 (53.9)	141 (59.2)	65 (57.5)	90 (54.5)	43 (51.8)	51 (69.9)	22 (73.3)
Prior CDK4/6 inhibitor, n (%)	239 (100)	115 (100)	238 (100)	113 (100)	165 (100)	83 (100)	73 (100)	30 (100)
No. of prior lines of endocrine therapy in the advanced or metastatic setting, n (%)								
1	129 (54.0)	73 (63.5)	141 (59.2)	69 (61.1)	120 (72.7)	64 (77.1)	21 (28.8)	5 (16.7)
2	110 (46.0)	42 (36.5)	97 (40.8)	44 (38.9)	45 (27.3)	19 (22.9)	52 (71.2)	25 (83.3)
No. of prior lines of chemotherapy in the advanced or metastatic setting, n (%)								
0	191 (79.9)	89 (77.4)	180 (75.6)	81 (71.7)	132 (80.0)	64 (77.1)	48 (65.8)	17 (56.7)
1	48 (20.1)	26 (22.6)	58 (24.4)	32 (28.3)	33 (20.0)	19 (22.9)	25 (34.2)	13 (43.3)

30% prior fulvestrant

Kaklamani et al SABCS 2022

EMERALD: Primary Endpoint: PFS by IRC



	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)

Kaklamani et al SABCS 2022

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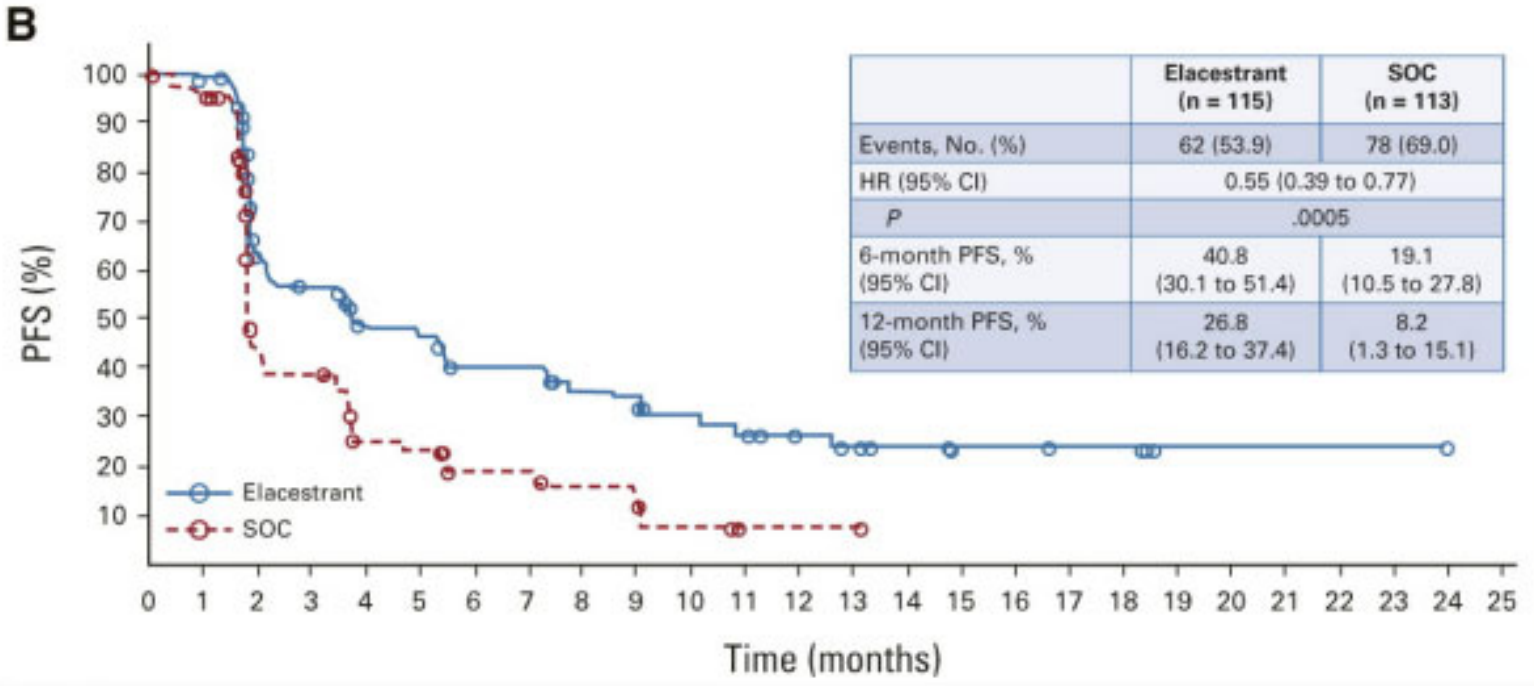
Patients With Tumors Harboring *mESR1*



	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)

Kaklamani et al SABCS 2022

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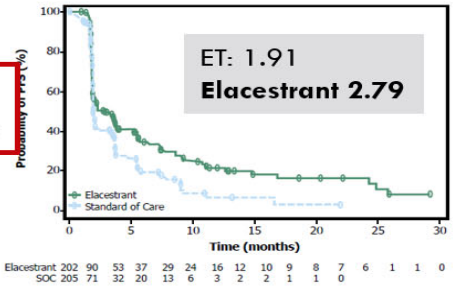
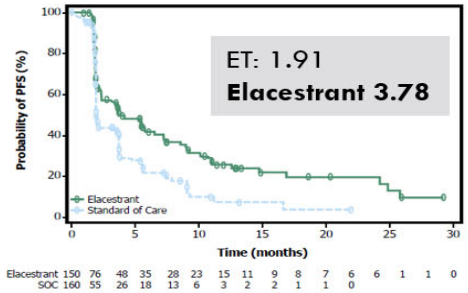
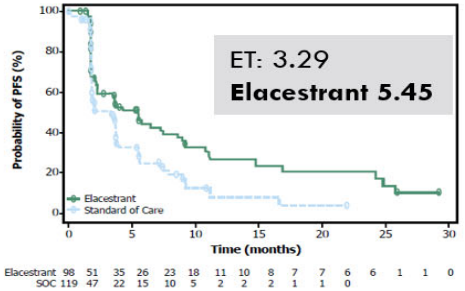
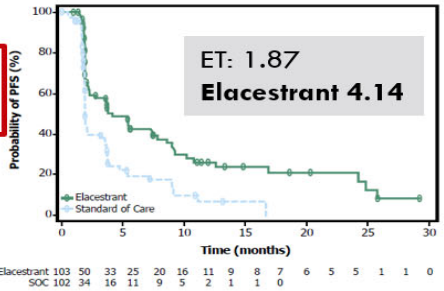
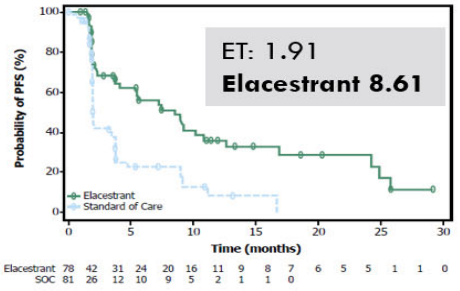
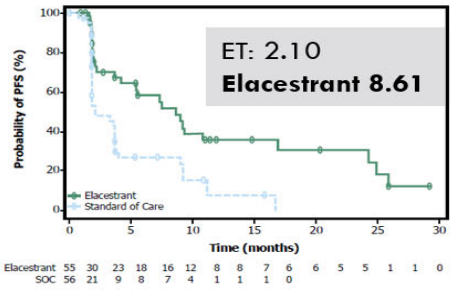
PFS by prior CDK 4/6 inhibitor duration and mESR1

	At least 6 mo CDK4/6i	At least 12 mo CDK4/6i	At least 18 mo CDK4/6i
All Patients			
ESR1 Mutant			

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Bardia A et al, SABCS December 2022, GS3-01

Adverse Events

	Elacestrant		Fulvestrant/AI	
	All grades	G3/4	All grades	G3/4
Nausea	35%	2.5%	19%	1%
Fatigue	19%	0.8%	16%	1%
Vomiting	19%	0.8%	8.8%	0
Anorexia	14.8%	0.8%	10.3%	<1%
Constipation	12.2%	0	6.5%	0
Back pain	13.9%	2.5%	9.6%	1%
Hot flush	11.4%	0	8.6%	0

More GI symptoms with elacestrant
Lipids/triglyceride monitoring also recommended

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Bardia A et al, SABCS December 2022, GS3-01

Elacestrant in ESR1 mut ER+/HER2- MBC

TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[w]	*PIK3CA* activating mutation	NGS, PCR (Blood or tumor tissue if blood negative)	Alpelisib + fulvestrant[x]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[y]	*PIK3CA or AKT1* activating mutations or *PTEN* alterations	NGS, (Blood or tumor tissue if blood negative)	Capivasertib + fulvestrant[y]	Category 1	Preferred second- or subsequent-line therapy in select patients[y]
HR-positive/ HER2-negative[z]	*ESR1* mutation	NGS, PCR (Tumor tissue or blood)	Elacestrant[z]	Category 2A	Other recommended regimen
Any	Germline *BRCA1* or *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (Tumor tissue or blood)	Larotrectinib[aa] Entrectinib[aa]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR, (Tumor tissue)	Pembrolizumab[bb,cc] Dostarlimab-gxly[dd]	Category 2A	
Any	TMB-H (≥10 mut/Mb)	NGS (Tumor tissue or blood)	Pembrolizumab[bb,cc]	Category 2A	
Any	*RET*-fusion	NGS (Tumor tissue or blood)	Selpercatinib[ee]	Category 2A	

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Oral SERDS: Mixed Results to Date

2 doses explored

Trial	EMERALD		AcelERA		AMEERA-3		SERENA	
Treatment	ELAC	FULV	GIRE	SAET	AMCE	SAET	CAM	FULV
n ITT	239	238	143	147	151	152	74/73	73
ESR1 mutation	115	113	65	55	44	34	30/36%	48%
Prior CDKi	100%	100%	80%	78%	43%	41%	51/51	51
PFS (mos.)	2.79	1.91	3.6	3.7	5.6	5.4	7.2/7.7	3.7
PFS in mESR1 (mos.)	3.78	1.87	3.7	2.0	5.3	3.5	6.3/9.2	2.2

ELAC = Elacestrant; GIRE = Giredestant; AMCE = Amcenestrant; CAM: Camizestrant; FULV = fulvestrant; SAET= Standard anti-estrogen therapy

ELAINE 1: PFS not met: with oral SERM (lasofoxifene) vs fulv in m*ESR1+* prior AI/CDK4/6 inhibitors
- HR 0.699; 95% CI 0.445–1.125; p=0.138

Jimenez et al ESMO 2022
Goetz et al ESMO 2022
Oliveira et al SABCS 2022
Tolaney et al ESMO 2022
Bidard et al J Clin Oncol 2022

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SERD Discussion

- **Elacestrant is the first oral SERD approved**
  - Use in ER+/HER2- MBC with ESR1 mutation
  - Most impact in those with > 1yr of prior CDK 4/6 inhibitor

- Questions/Future Directions:
  - Do outcomes differ based on different ESR1 mutations?
    - ESR1 mutations have variable affinity for different SERDs[1]
  - What about other novel anti-estrogens (PROTACs, novel SERMS, etc)
  - Will combinations with CDK4/6i or other targeted agents be safe and more efficacious?

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[1]Gerratana L et al, SABCS 2022, PD10-01

PI3K/AKT/mTOR Pathway in Breast Cancer

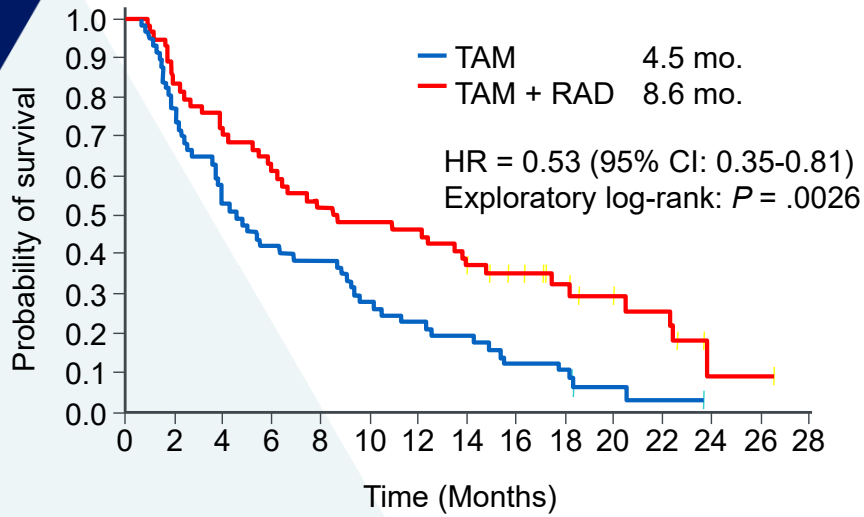
- Stimulator of cell survival and growth through glucose transporter expression, protein synthesis, and the protection of mitochondria
- Commonly altered in breast cancer
  - 30-35% of TNBCs harbor *PIK3CA/AKT1/ PTEN* alterations
  - **40% HR+/HER2- with *PIK3CA* activating mutations**

Pan-class I PI3K	Class I alpha isoform specific	Dual PI3K/mTOR
Buparlisib (BMN120)	**Alpelisib (BYL719)**	Gedatolisib (PF-05212384)
Pictilisib (GDC-0941)	Taselisib (GDC-0032) β-sparing	Omipalisib (GSK2126458)
Copanlisib (BAY 90-6946)	**Inavolisib (GDC-0077)**	Apitolisib (GDC-0980)
Pan AKT inhibitors		
Ipatasertib	**Capivasertib**	

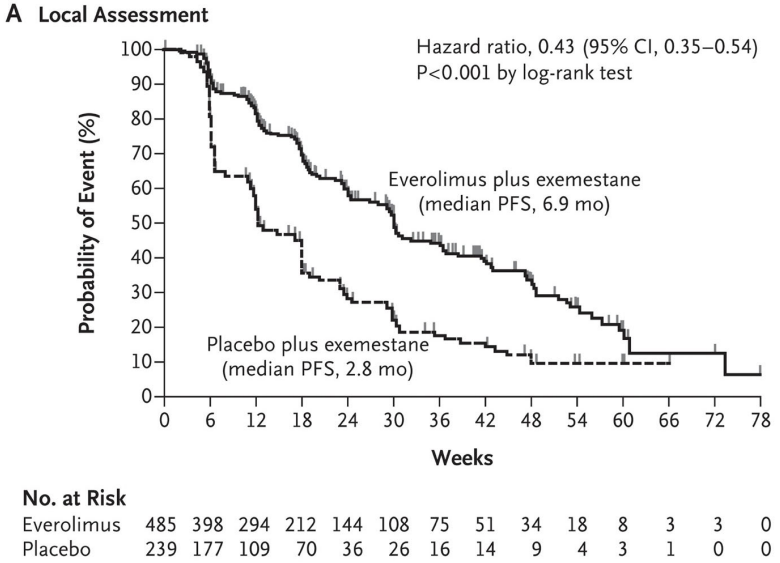
TCGA Network Koboldt et al Nature 2012
Hu et al Ca Res 2002
Wallin et al Ca Res 2012
Yan et al CCR 2013

Everolimus: mTOR Inhibitor

TamRad: phase 2



BOLERO-2: phase 3



No. at Risk

Everolimus	485	398	294	212	144	108	75	51	34	18	8	3	3	0
Placebo	239	177	109	70	36	26	16	14	9	4	3	1	0	0

Median OS not met: 31 vs 26.6 mo (HR = 0.89; 95% CI 0.73–1.10; stratified log-rank *P* = 0.1426).

Bachelot et al JCO 2012
Baselga et al NEJM 2012
Piccart et al Ann Oncology 2014

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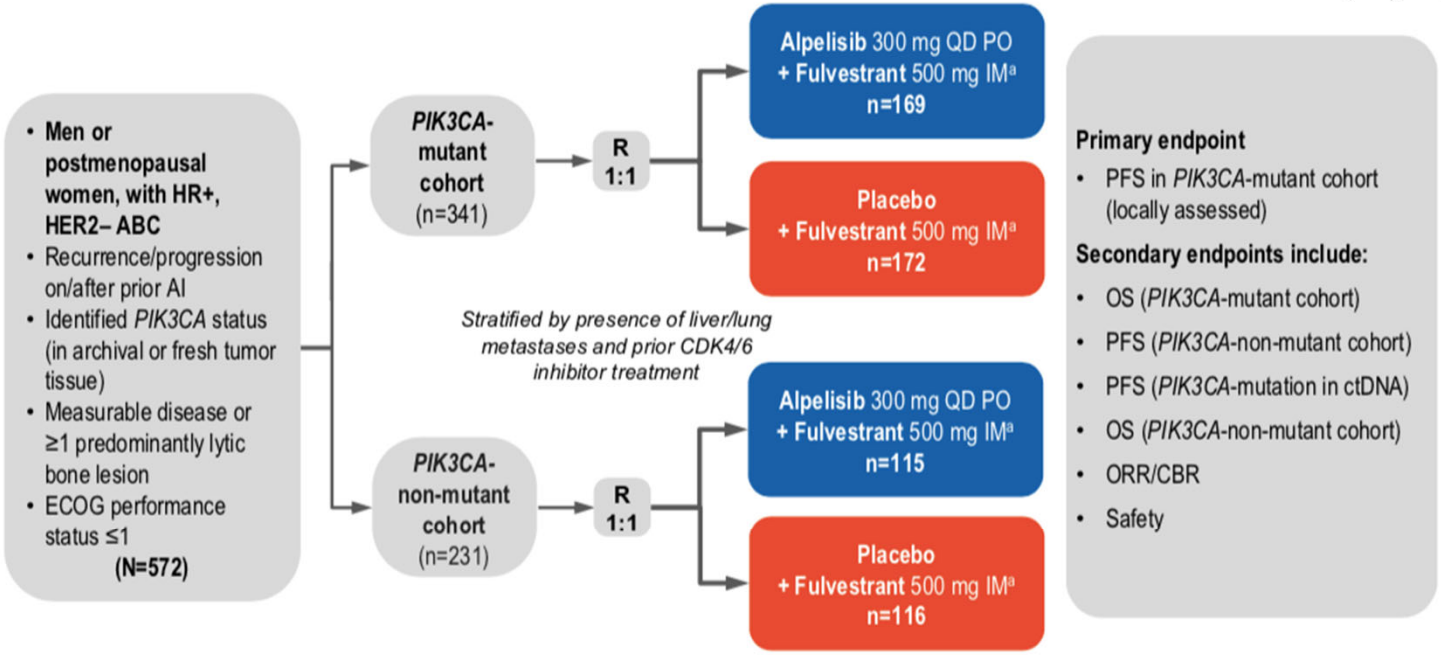
SOLAR-1: PI3K Inhibition with Fulvestrant



[a] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.
ABC, advanced breast caner; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinases 4 and 6; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor positive; IM, intramuscular; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PO, orally; QD, daily; R, randomization.

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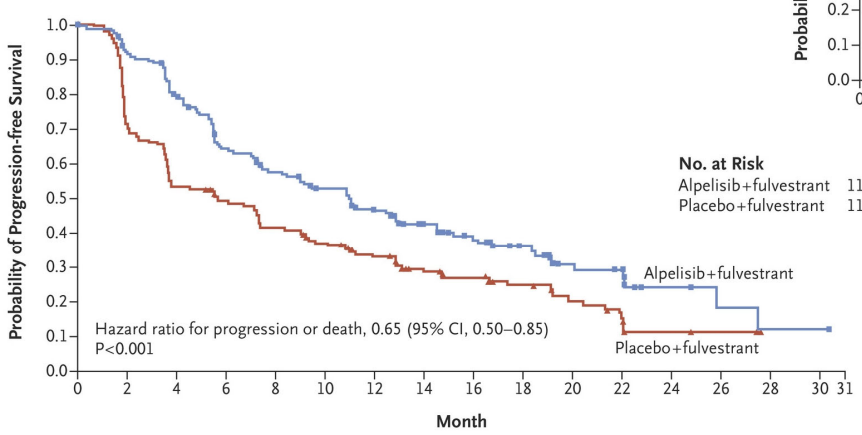
Andre et al ESMO 2018; NEJM 2019

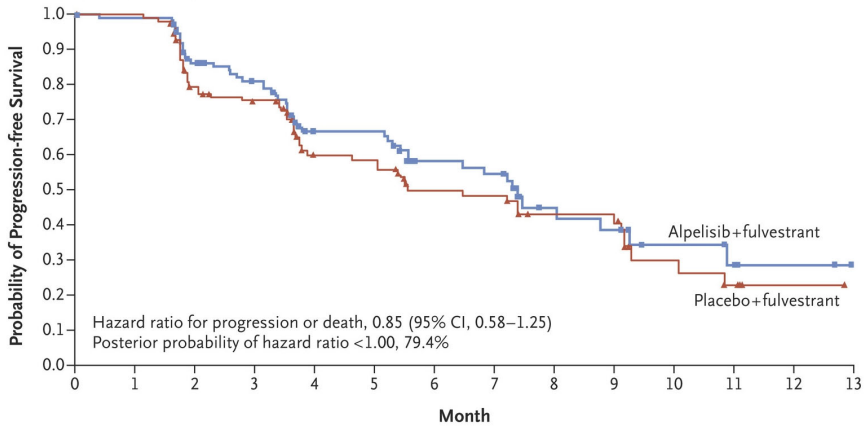
PFS improved in PI3K mutant cohort

A Cohort with *PIK3CA*-Mutated Cancer



No. at Risk															
Alpelisib+fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo+fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

B Cohort without *PIK3CA*-Mutated Cancer



No. at Risk														
Alpelisib+fulvestrant	115	110	86	76	48	48	31	29	14	12	7	5	3	0
Placebo+fulvestrant	116	110	79	72	43	42	31	30	20	20	8	5	1	0

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Andre et al NEJM 2019

BYLieve: PI3K inhibition after CDK4/6i

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated HR+, HER2– ABC

Men or pre-/postmenopausal[a] women with HR+, HER2– ABC with a *PIK3CA* mutation

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

Patients who received CDKi + AI as immediate prior treatment (N=112)[b]
(Cohort A)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Patients who received CDKi + fulvestrant as immediate prior treatment (N=112)
(Cohort B)
Alpelisib 300 mg oral QD + letrozole 2.5 mg[d]

Patients who progressed on/after AI and received chemotherapy or ET as immediate prior treatment (N=112)
(Cohort C)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Primary endpoint

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort
- **Secondary endpoints include**

(assessed in each cohort)

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

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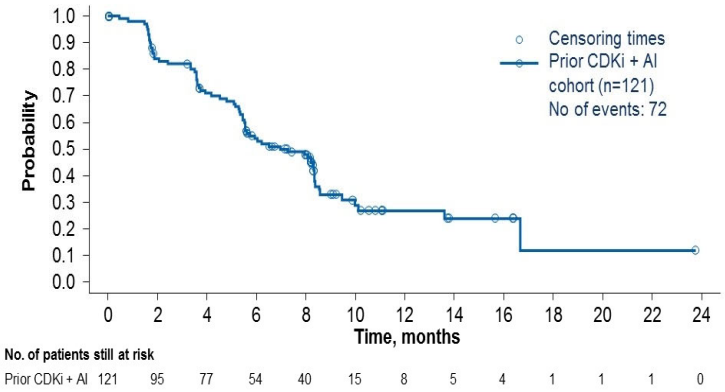
Rugo et al ASCO 2020

Primary Endpoint and PFS Results

Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)



The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

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Rugo et al ASCO 2020

CAPItello-291: Ph 3 of Fulvestrant +/- Capivasertib

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence 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

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Patient and Tumor Characteristics

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Median age; years (range)		59 (26–84)	58 (26–90)	58 (36–84)	60 (34–90)
Female; n (%)		352 (99.2)	349 (98.9)	153 (98.7)	134 (100)
Post menopausal; n (%)		287 (80.8)	260 (73.7)	130 (83.9)	105 (78.4)
Race; n (%)	White Asian Black or African American Other	201 (56.6) 95 (26.8) 4 (1.1) 55 (15.5)	206 (58.4) 94 (26.6) 4 (1.1) 49 (13.9)	75 (48.4) 48 (31.0) 2 (1.3) 30 (19.4)	76 (56.7) 35 (26.1) 1 (0.7) 22 (16.4)
Region*; n (%)	1 2 3	197 (55.5) 68 (19.2) 90 (25.4)	198 (56.1) 68 (19.3) 87 (24.6)	80 (51.6) 29 (18.7) 46 (29.7)	76 (56.7) 24 (17.9) 34 (25.4)
Metastatic sites; n (%)	Bone only Liver* Visceral	51 (14.4) 156 (43.9) 237 (66.8)	52 (14.7) 150 (42.5) 241 (68.3)	25 (16.1) 70 (45.2) 103 (66.5)	16 (11.9) 53 (39.6) 98 (73.1)
Hormone receptor status; n (%)†	ER+/PR+ ER+/PR- ER+/PR unknown	255 (71.8) 94 (26.5) 5 (1.4)	246 (69.7) 103 (29.2) 4 (1.1)	116 (74.8) 35 (22.6) 4 (2.6)	101 (75.4) 31 (23.1) 2 (1.5)
Endocrine resistance; n (%)	Primary Secondary	127 (35.8) 228 (64.2)	135 (38.2) 218 (61.8)	60 (38.7) 95 (61.3)	55 (41.0) 79 (59.0)
Prior endocrine therapy for ABC; n (%)	0 1 2	40 (11.3) 286 (80.6) 29 (8.2)	54 (15.3) 252 (71.4) 47 (13.3)	14 (9.0) 130 (83.9) 11 (7.1)	20 (14.9) 96 (71.6) 18 (13.4)
Previous CDK4/6 inhibitor for ABC; n (%)		245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy; n (%)	Adjuvant/neoadjuvant ABC	180 (50.7) 65 (18.3)	170 (48.2) 64 (18.1)	79 (51.0) 30 (19.4)	67 (50.0) 23 (17.2)

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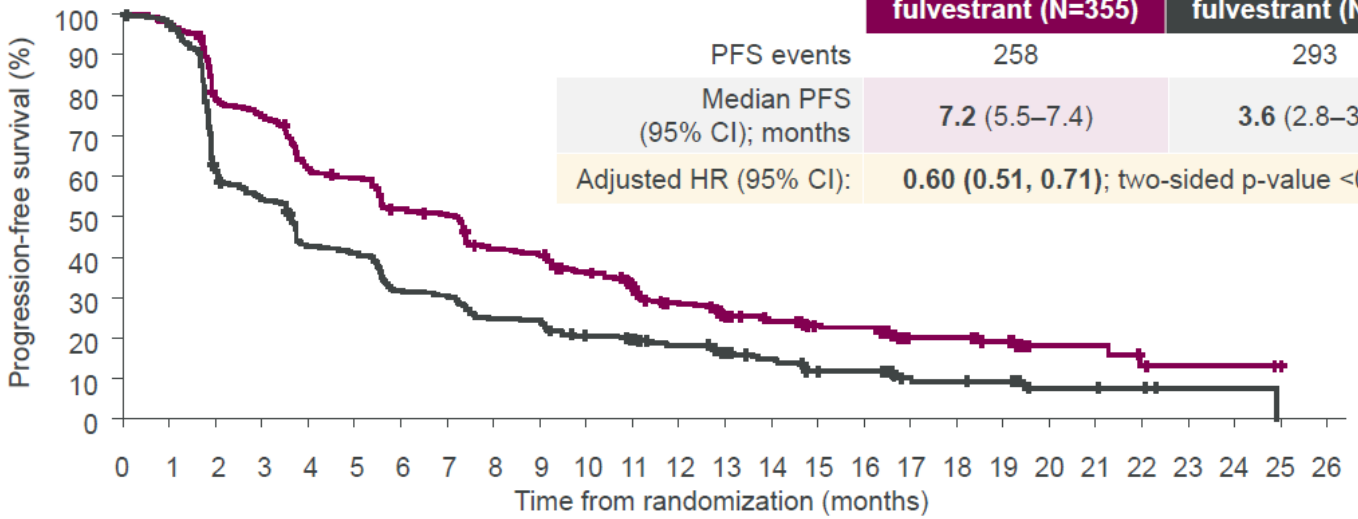
Dual-primary endpoint: Investigator-assessed PFS in the overall population

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	



Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

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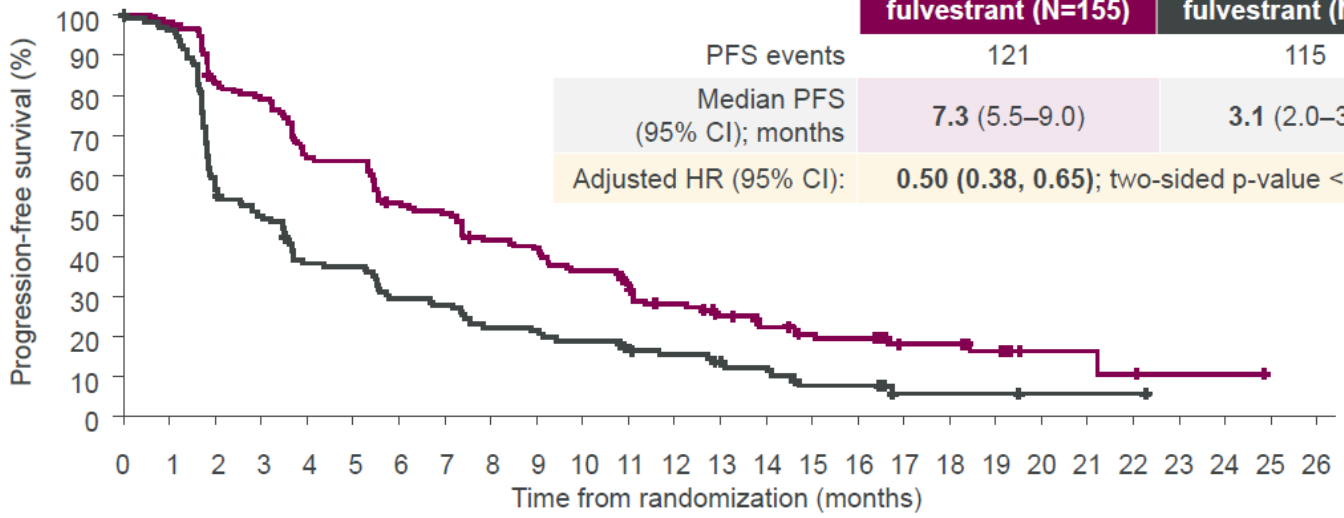
Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population

	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	



Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

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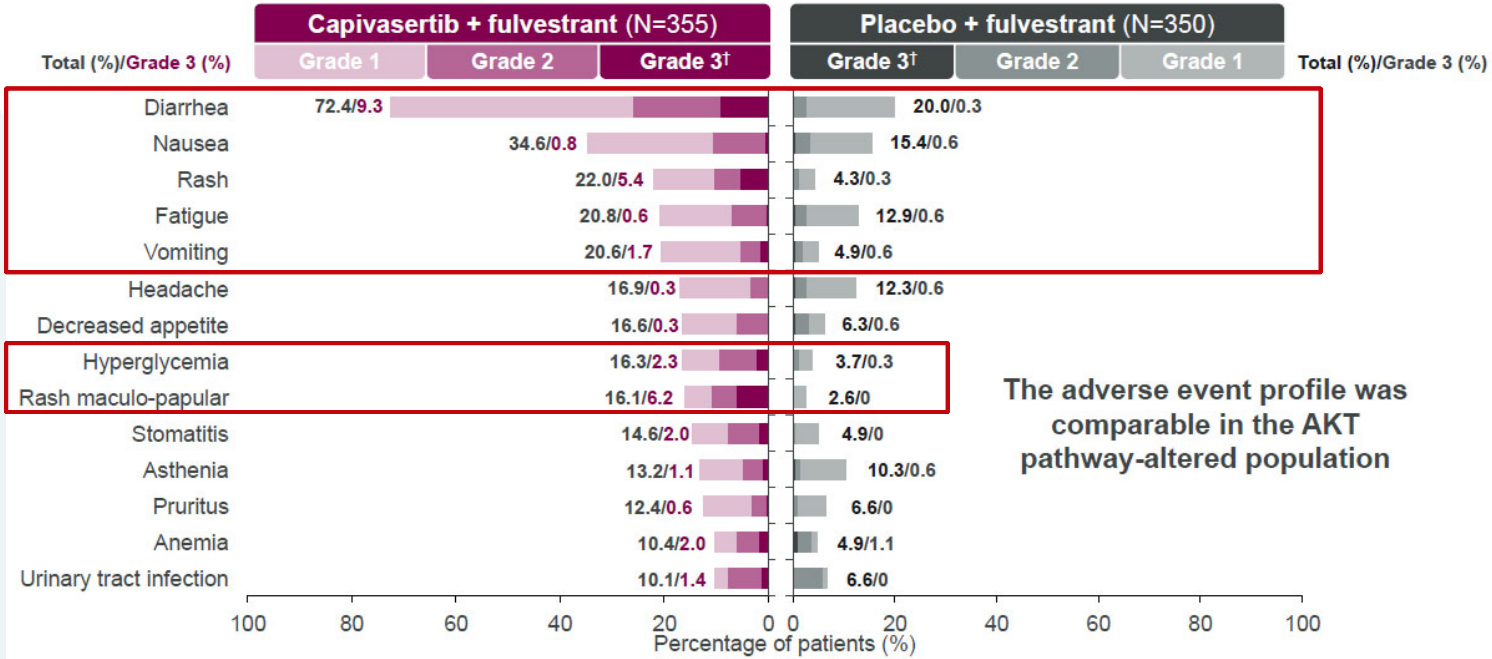
Adverse events (>10% of patients) – overall population



The adverse event profile was comparable in the AKT pathway-altered population

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

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Alpelisib and Capivasertib in ER+/HER2- MBC

TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[w]	*PIK3CA* activating mutation	NGS, PCR (Blood or tumor tissue if blood negative)	Alpelisib + fulvestrant[x]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[y]	*PIK3CA or AKT1* activating mutations or *PTEN* alterations	NGS, (Blood or tumor tissue if blood negative)	Capivasertib + fulvestrant[y]	Category 1	Preferred second- or subsequent-line therapy in select patients[y]
HR-positive/ HER2-negative[z]	*ESR1* mutation	NGS, PCR (Tumor tissue or blood)	Elacestrant[z]	Category 2A	Other recommended regimen
Any	Germline *BRCA1* or *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (Tumor tissue or blood)	Larotrectinib[aa] Entrectinib[aa]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR, (Tumor tissue)	Pembrolizumab[bb,cc] Dostarlimab-gxly[dd]	Category 2A	
Any	TMB-H (≥10 mut/Mb)	NGS (Tumor tissue or blood)	Pembrolizumab[bb,cc]	Category 2A	
Any	*RET*-fusion	NGS (Tumor tissue or blood)	Selpercatinib[ee]	Category 2A	

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INAVO120 study design

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019 to September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

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.

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Demographics and baseline disease characteristics

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Age (year)		
Median	53.0	54.5
Min–Max	27–77	29–79
Sex, n (%)		
Female	156 (96.9)	163 (99.4)
Race, n (%)		
Asian	61 (37.9)	63 (38.4)
Black or African American	1 (0.6)	1 (0.6)
White	94 (58.4)	97 (59.1)
ECOG PS, n (%)		
0	100 (62.1)	106 (64.6)
1	60 (37.3)	58 (35.4)
Menopausal status at randomization, n (%)		
Premenopausal	65 (40.4)	59 (36.0)
Postmenopausal	91 (56.5)	104 (63.4)

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Number of organ sites, n (%)		
1	21 (13.0)	32 (19.5)
2	59 (36.6)	46 (28.0)
≥3	81 (50.3)	86 (52.4)
Visceral disease, n (%)*	132 (82.0)	128 (78.0)
Liver	77 (47.8)	91 (55.5)
Lung	66 (41.0)	66 (40.2)
Bone only†	5 (3.1)	6 (3.7)
ER‡ and PgR status, n (%)		
ER+/PgR+	113 (70.2)	113 (68.9)
ER+/PgR-	45 (28.0)	45 (27.4)
Endocrine resistance, n (%)**		
Primary	53 (32.9)	58 (35.4)
Secondary	108 (67.1)	105 (64.0)

301 (92.6%) pts were enrolled per ctDNA testing (284 [94.4%] central, 17 [5.6%] local) and 24 (7.4%) were enrolled per local tissue testing

* "Visceral" (yes/no) refers to lung, liver, brain, pleural, and peritoneal involvement; † Patients with evaluable bone-only disease were not eligible; patients with disease limited to the bone but with lytic or mixed lytic/blastic lesions, and at least one measurable soft-tissue component per RECIST 1.1, may be eligible. ‡ Defined as 10% per ASCO-CAP guidelines. ** Endocrine resistance was defined per 4th ESO–[ESMO] International Consensus Guidelines for Advanced Breast Cancer. Primary resistance: Relapse while on the first 2 years of adjuvant endocrine therapy. Secondary resistance: Relapse while on adjuvant endocrine therapy after at least 2 years or relapse within 12 months of completing adjuvant endocrine therapy. ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor, Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo; PgR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumors.

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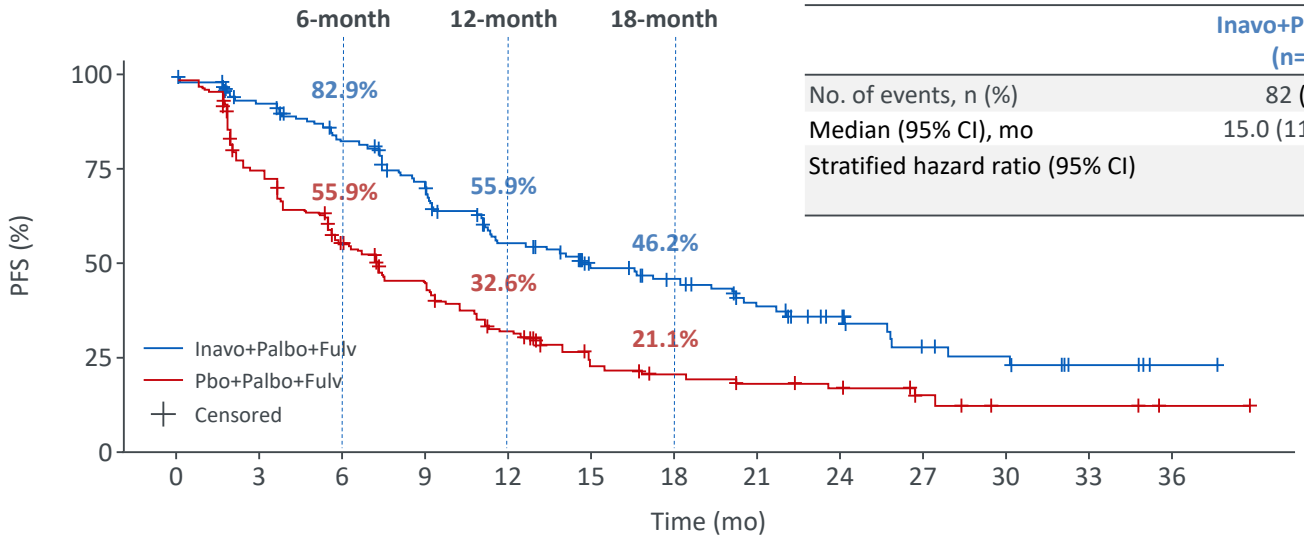
Prior therapy

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	132 (82.0)	137 (83.5)
Prior (neo)adjuvant endocrine therapy, n (%)		
Yes	160 (99.4)	163 (99.4)
Aromatase inhibitor only	60 (37.3)	71 (43.3)
Tamoxifen only	82 (50.9)	73 (44.5)
Aromatase inhibitor and tamoxifen	18 (11.2)	19 (11.6)
Prior adjuvant CDK4/6 inhibitor, n (%)		
Yes	3 (1.9)	1 (0.6)

CDK4/6, cyclin-dependent kinase 4 and 6; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

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**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

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.

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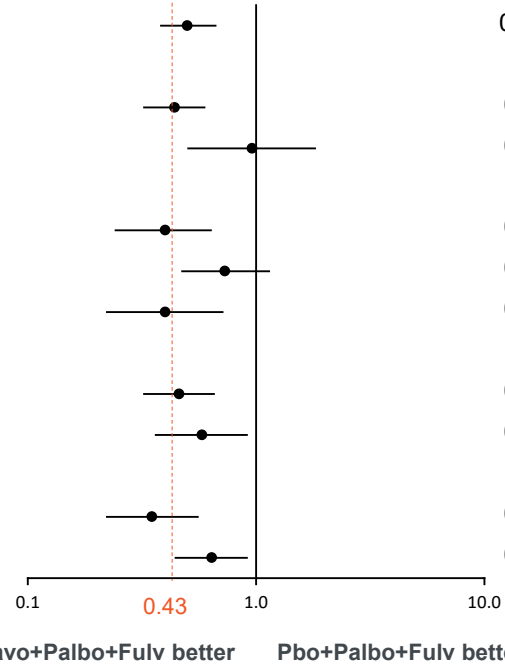
PFS (investigator-assessed) in key subgroups 1/2

	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv		Hazard ratio (95% CI)
	n	Median (mo)	n	Median (mo)	
All patients	161	15.0	164	7.3	0.50* (0.38, 0.67)
Age, years					
<65	136	16.6	130	7.2	0.44 (0.32, 0.60)
≥65	25	9.3	34	10.7	0.96 (0.50, 1.83)
Region					
Asia	56	14.6	58	5.8	0.40 (0.24, 0.64)
North America/Western Europe	63	13.8	64	9.3	0.73 (0.47, 1.15)
Other	42	21.0	42	5.6	0.40 (0.22, 0.72)
ECOG PS at baseline					
0	100	16.6	106	7.4	0.46 (0.32, 0.66)
1	60	11.4	58	5.6	0.58 (0.36, 0.92)
Menopausal status at randomization					
Premenopausal	65	20.1	59	6.5	0.35 (0.22, 0.56)
Post-menopausal	91	13.4	104	7.5	0.64 (0.44, 0.92)



* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Fulv, fulvestrant; Inavo, inavolisib; mo, months, Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

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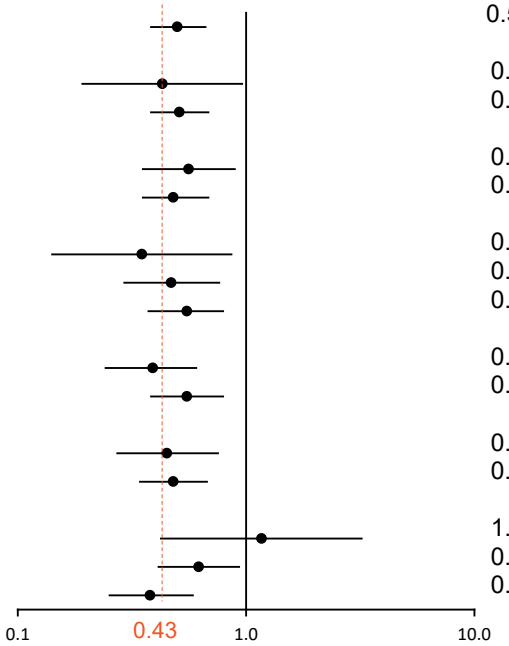
PFS (investigator-assessed) in key subgroups 2/2

	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv		Hazard ratio (95% CI)
	n	Median (mo)	n	Median (mo)	
All patients	161	15.0	164	7.3	0.50* (0.38, 0.67)
Visceral disease					
No	29	25.8	36	7.4	0.43 (0.19, 0.97)
Yes	132	13.8	128	7.2	0.51 (0.38, 0.69)
Liver metastasis at enrollment					
No	84	24.2	73	11.3	0.56 (0.35, 0.90)
Yes	77	11.0	91	5.6	0.48 (0.33, 0.69)
Number of metastatic organs at enrollment					
1	21	20.2	32	7.4	0.35 (0.14, 0.87)
2	59	18.2	46	7.4	0.47 (0.29, 0.77)
≥3	81	14.1	86	7.3	0.55 (0.37, 0.80)
Endocrine resistance					
Primary	53	11.4	58	3.7	0.39 (0.24, 0.61)
Secondary	108	18.2	105	9.7	0.55 (0.38, 0.80)
HR status					
ER+/PgR-	45	11.1	45	5.6	0.45 (0.27, 0.76)
ER+/PgR+	113	18.2	113	7.4	0.48 (0.34, 0.68)
Prior (neo)adjuvant endocrine therapy					
Aromatase inhibitor and tamoxifen	18	11.0	19	12.9	1.17 (0.42, 3.24)
Aromatase inhibitor only	60	10.9	71	5.8	0.62 (0.41, 0.94)
Tamoxifen only	82	21.0	73	7.4	0.38 (0.25, 0.59)



* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

CI, confidence interval; ER, estrogen receptor; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival; PgR, progesterone receptor.

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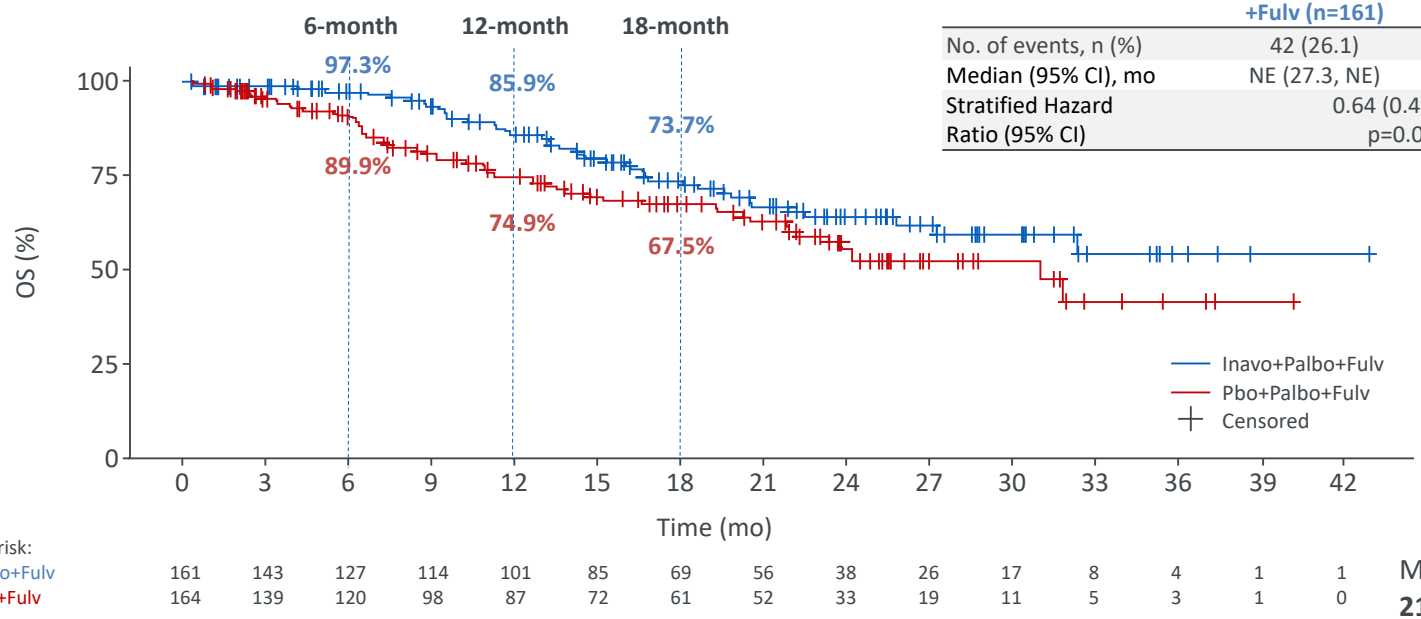
Key secondary endpoint: Overall survival (interim analysis)



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Patients at risk:

Inavo+Palbo+Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo+Palbo+Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

Median follow-up: **21.3 months**

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.

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Adverse events with any grade AEs ≥20% incidence in either treatment group

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Key AEs are shown in **bold.** AES were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

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Overview of adverse events

Patients with ≥1 AE, n (%)	Inavo+Palbo+Fulv (n=162)	Pbo+Palbo+Fulv (n=162)
All, n (%)	160 (98.8%)	162 (100%)
Grade 3–4 AE	143 (88.3%)	133 (82.1%)
Grade 5 AE*	6 (3.7%)	2 (1.2%)
Serious AE	39 (24.1%)	17 (10.5%)
AEs leading to discontinuation of treatment	11 (6.8%)	1 (0.6%)
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)
Palbociclib	8 (4.9%)	0
Fulvestrant	5 (3.1%)	0
AEs leading to dose modification/interruption of treatment	134 (82.7%)	121 (74.7%)
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)
Palbociclib	125 (77.2%)	116 (71.6%)
Fulvestrant	52 (32.1%)	34 (21.0%)

AES were assessed per CTCAE V5

* None of the grade 5 AEs were reported as related to study treatment by investigators. The grade 5 AEs reported were cerebral hemorrhage; cerebrovascular accident, gastrointestinal hemorrhage, acute coronary syndrome, death and COVID-19 in the inavo+palbo+fulv arm and COVID-19 pneumonia and cardiac arrest in the pbo+palbo+fulv arm.

AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

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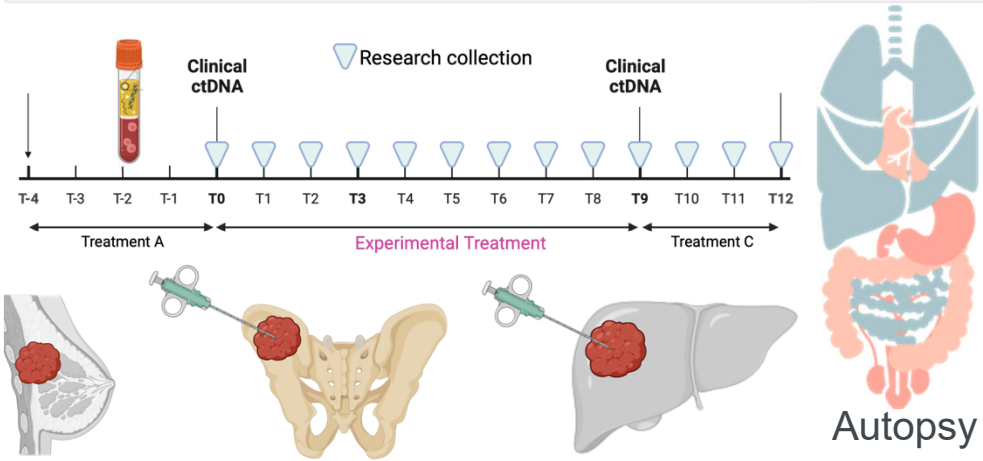
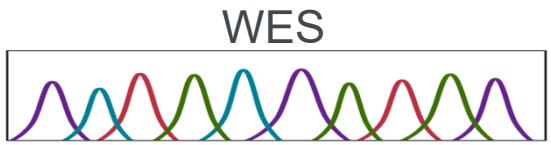
Varkaris et al SABCS 2023: PI3Ki resistance study

Hypothesis: H1: Acquired resistance to orthosteric PIK3CA inhibitors is mediated through frequent activating alterations within PI3K pathway. H2: These alterations may be amendable to specific therapeutic interventions with next generation PI3K/Akt inhibitors
Aim: Characterize the clinical landscape of resistance to orthosteric PIK3CA inhibitors.

Clinical Research samples

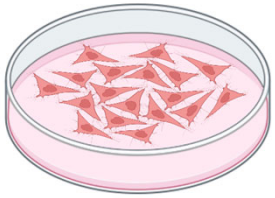


Methodology



Engineered Cell lines

Express genomic alterations found in clinical samples



Patients:

Serial ctDNA analysis

Autopsy samples analysis

Eligibility Criteria	
1	Histologically confirmed diagnosis of HR+/HER2- MBC
2	Documented baseline PIK3CA mutation(s) in blood or tumor per local assessment
3	Treatment with PI3K-alpha inhibitor (alpelisib and inavolisib) for >50 days.
4	Pretreatment and posttreatment evaluation with ctDNA analysis or autopsy

32 Patients

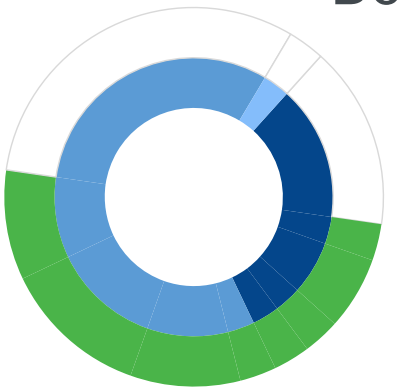
1 overlapping

8 Patients

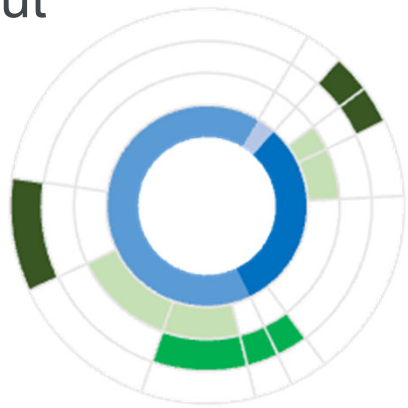
Within PI3K pathway alterations	
1	PIK3CA
2	PTEN
3	AKT
Other: MTOR, FGFR1/2, EGFR, HER2, RAS	

50% of patients acquired additional on-target and within pathway alterations beyond baseline PIK3CA mutations

Baseline PIK3CA Kinase/Helical Domain Mut



Total Acquired PI3K Pathway Alterations 50%

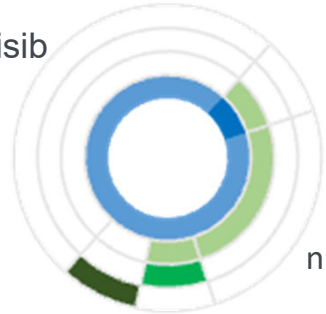


PIK3CA, PTEN, AKT1
28% 15% 15%

Inavolisib

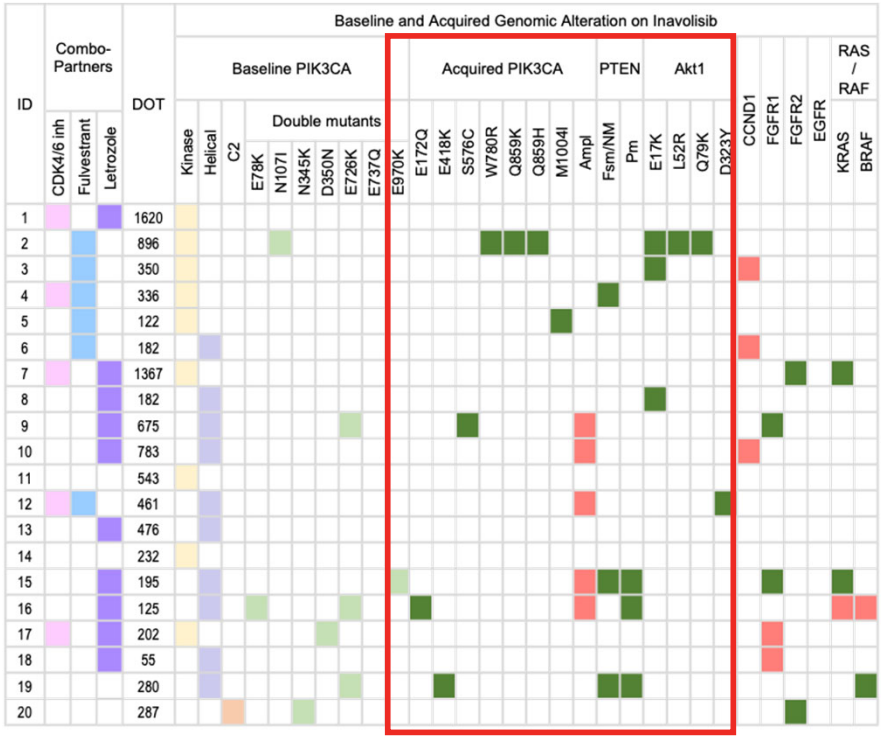
n:20

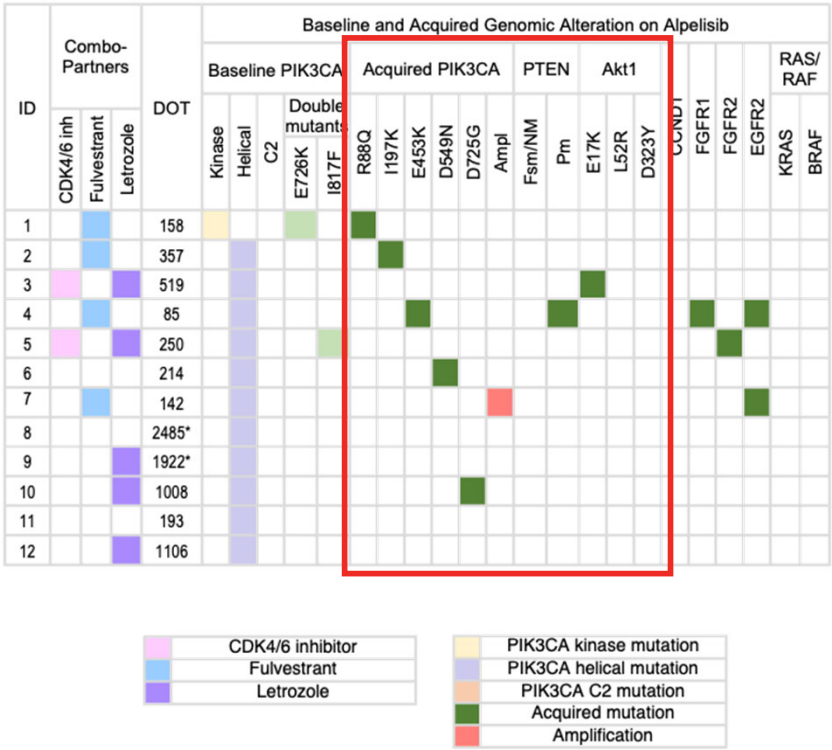
Alpelisib



n:12

ctDNA analysis reveals diverse landscape of polyclonal alterations in PIK3CA, AKT1 and PTEN





Analysis of rapid autopsy samples confirms presence of acquired PI3K pathway alterations in 38% of patients

Total population

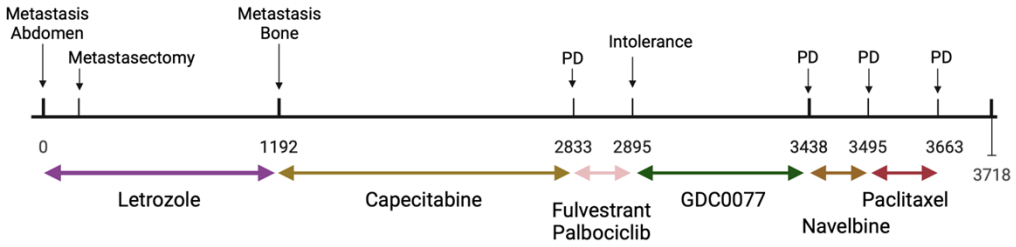
Baseline PIK3CA Kinase/Helical Domain Mutation

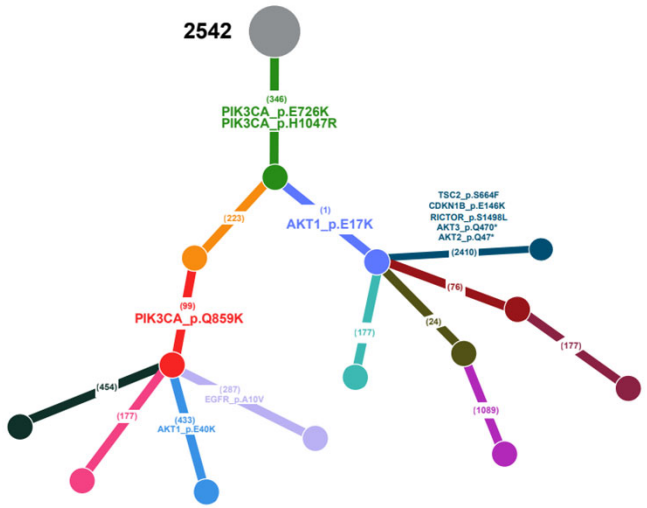
Total Acquired PI3K Pathway Alterations

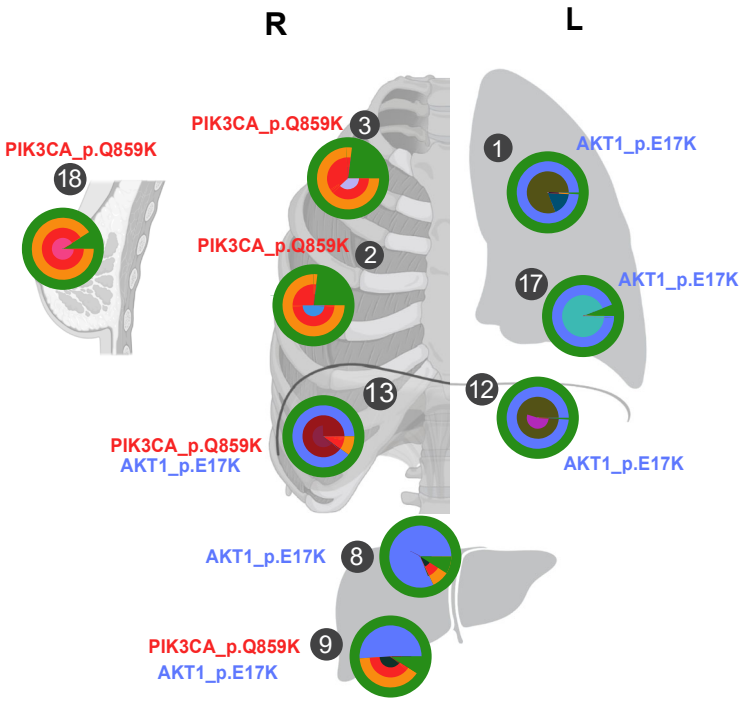
Mutation Breakdown

ID	PIK3CA inhibitor		Combo-partners			DOT	Baseline and Acquired Genomic Alterations in autopsy program													
							Baseline PIK3CA				Acquired PIK3CA				PTEN		Akt1			
	Alpelisib	Inavolisib	CDK4/6 inh	Fulvestrant	Letrozole		Kinase	Helical	I817F	E726K	E135Q	E726K	Q859K	M1004I	Fsm	Pm	E17K	E40K	CCND1	FGFR1	FGFR2	EGFR	RAS/RAF
MGH-1002	■				■	250			■		■	■				■					■	■	
MGH-2402		■				223		■															
MGH-2542		■				543				■			■				■	■					
MGH-1644		■			■	84																	
MGH-1326	■				■	65		■															
MGH-1558	■				■	56								■									
MGH-1045	■			■		1429		■													■	■	
Allp-1035	■				■	137		■													■	■	

Rapid autopsy reveals intra- and inter-lesional heterogeneity of secondary PIK3CA and AKT1 mutations

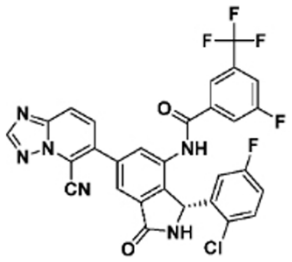


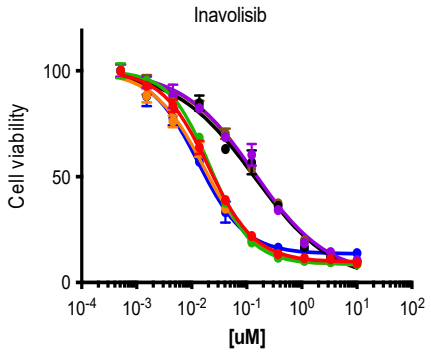


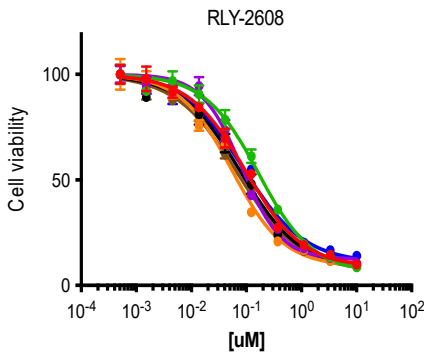


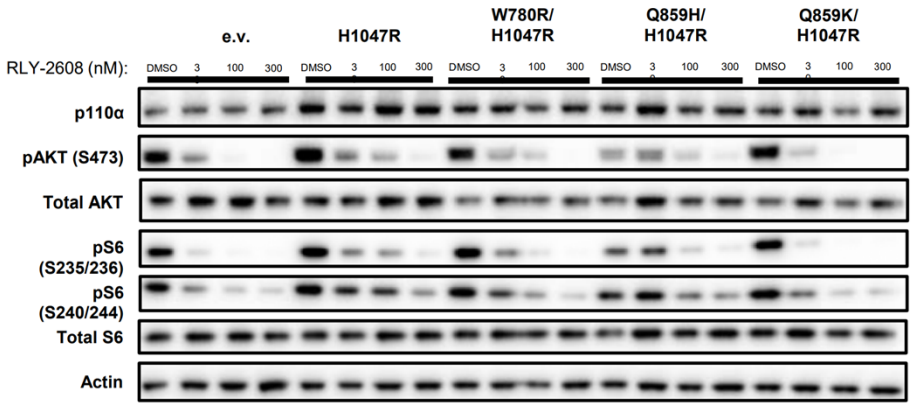
Allosteric mutant selective PIK3CA inhibitors overcome resistance due to acquired PIK3CA mutations

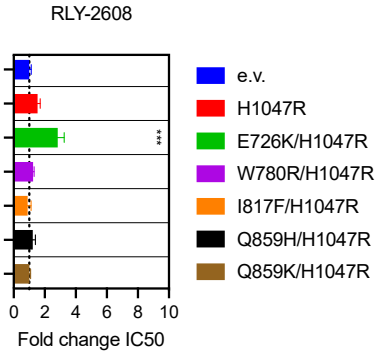
RLY-2608:
Pan-mutant selective allosteric PIK3CA inhibitor











PI3K/AKT/mTOR Pathway Discussion

- **Capivasertib approved for PIK3CA/AKT1/PTEN altered tumors after PD on 1L endocrine therapy (ET) or with recurrence within 12 mo of adjuvant ET**
  - Likely replaces alpelisib due to side effect profile appearing more favorable
  - Recognizing AKT and PTEN alterations will be important
- Everolimus remains an option for those without these identified alterations
- **Inavolisib with fulvestrant + palbociclib demonstrated impressive activity in 1L PIK3CA mutant MBC with early recurrence after adjuvant endocrine therapy**
- Future Directions/Questions:
  - Other combinations: Capi studies with oral SERDs; inavolisib with other CDK4/6i?
  - Is there a better biomarker of pathway activity and does the specific mutation matter?
  - Can allosteric mutant specific PI3K inhibitors improve outcomes?

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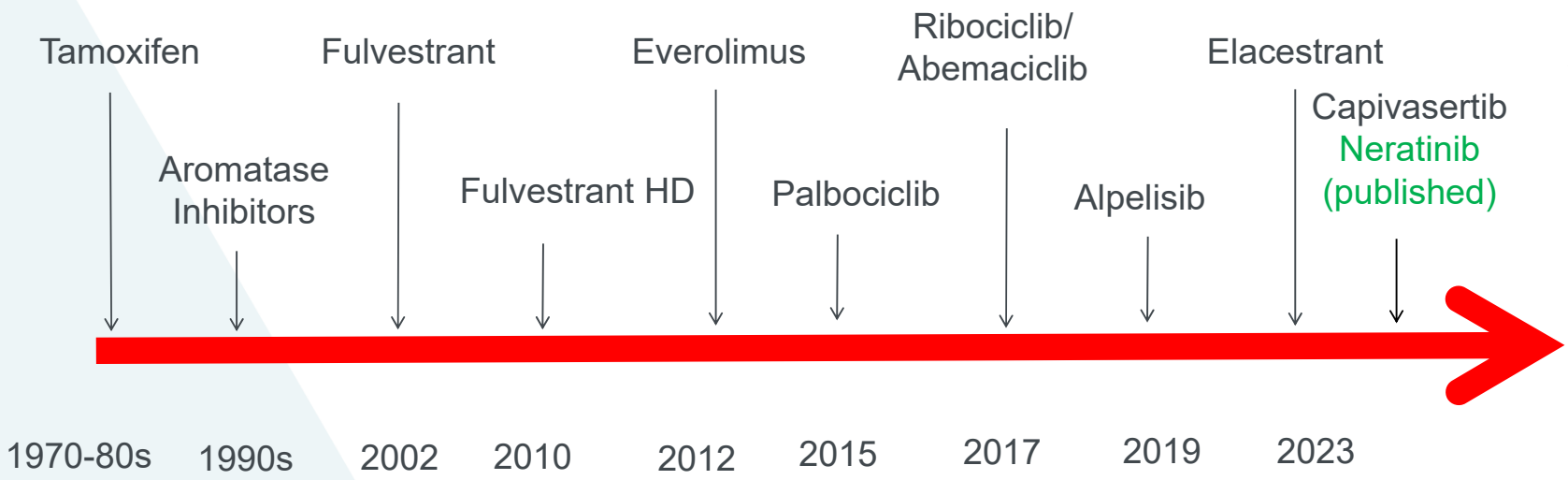
Expanding Treatment Options for HR-positive metastatic breast cancer



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Who We Are

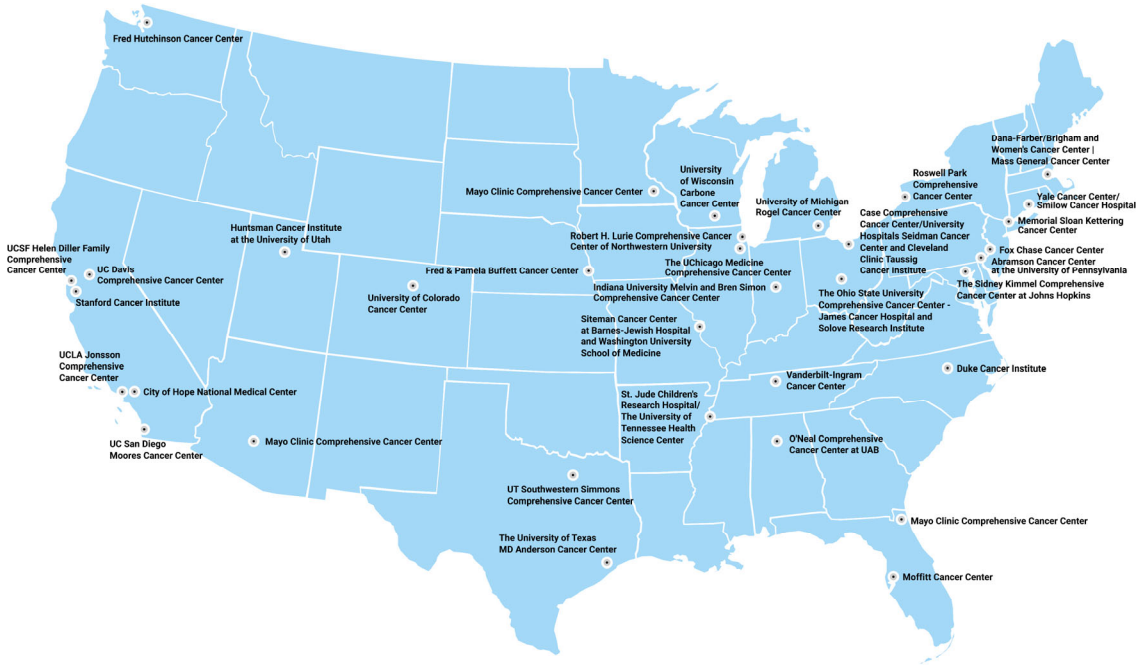
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



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