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Updates in ER+ Breast Cancer:
Overcoming Endocrine Resistance

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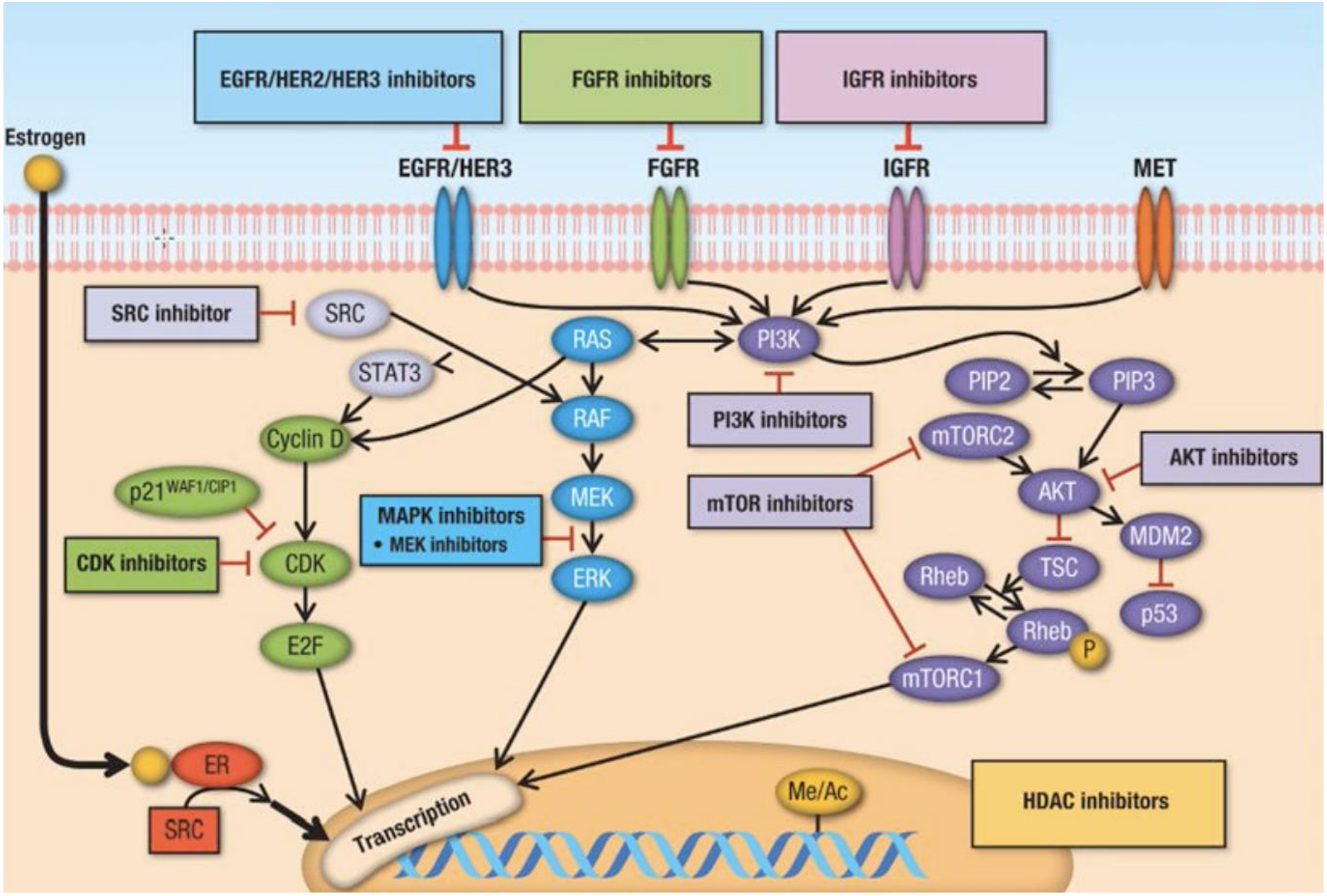
Overview: Overcoming Endocrine Resistance

- SONIA: 1st v. 2nd line CDK4/6 inhibitor
- EMERALD: Elacestrant (oral SERD)
- CAPItello: Capivasertib (AKT inhibitor)
- Active trials at UCSD



Zardavas D, Baselga J, Piccart M. Nat Rev Clin Oncol. 2013;10(35):191–210.

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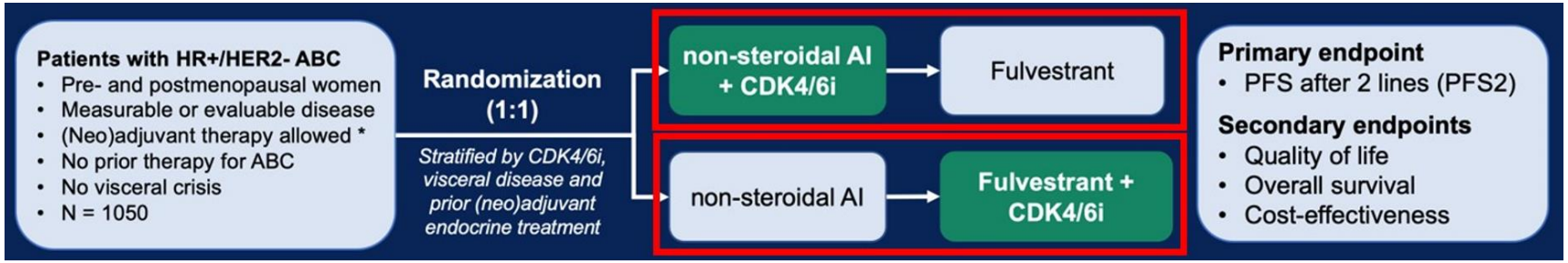
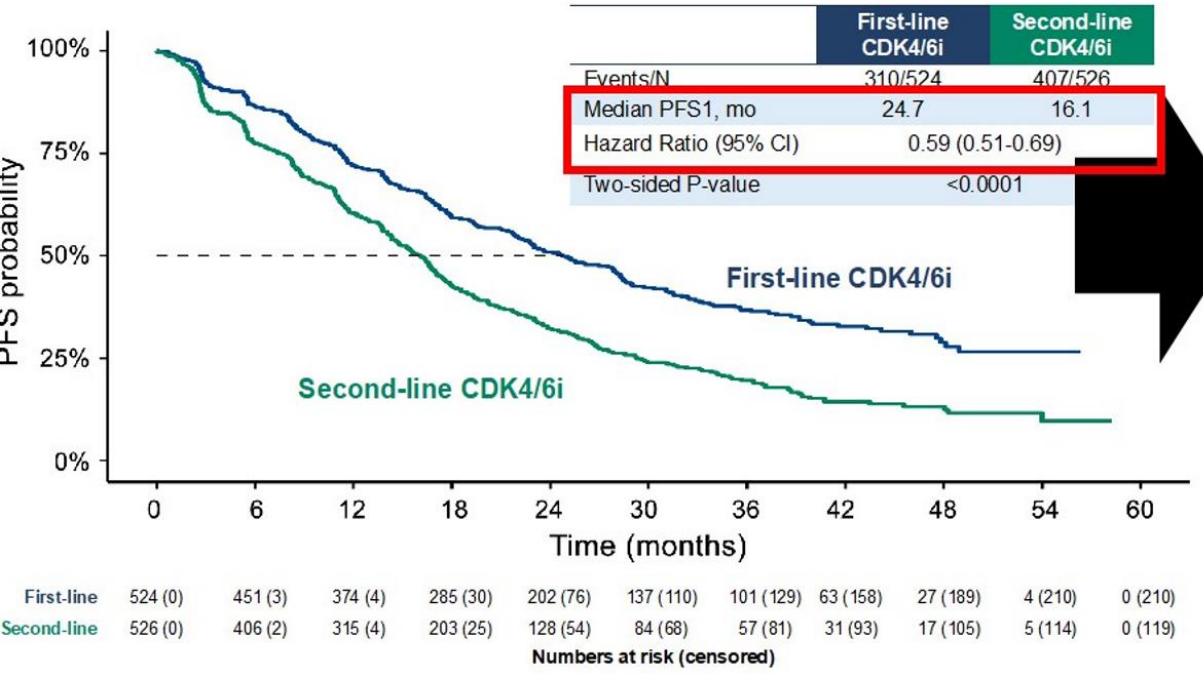
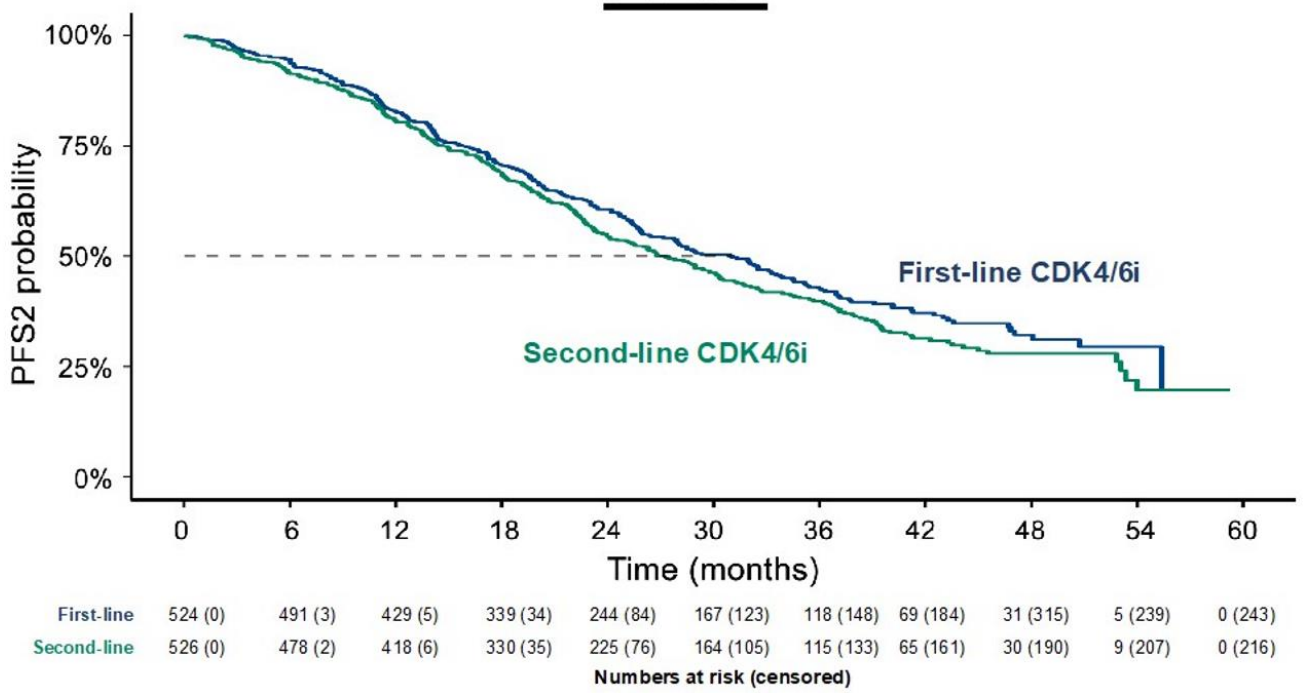
SONIA: Is there a difference between CDK4/6i in 1st vs 2nd line setting for HR+ HER2- MBC? Maybe not for some, but who?



PFS1

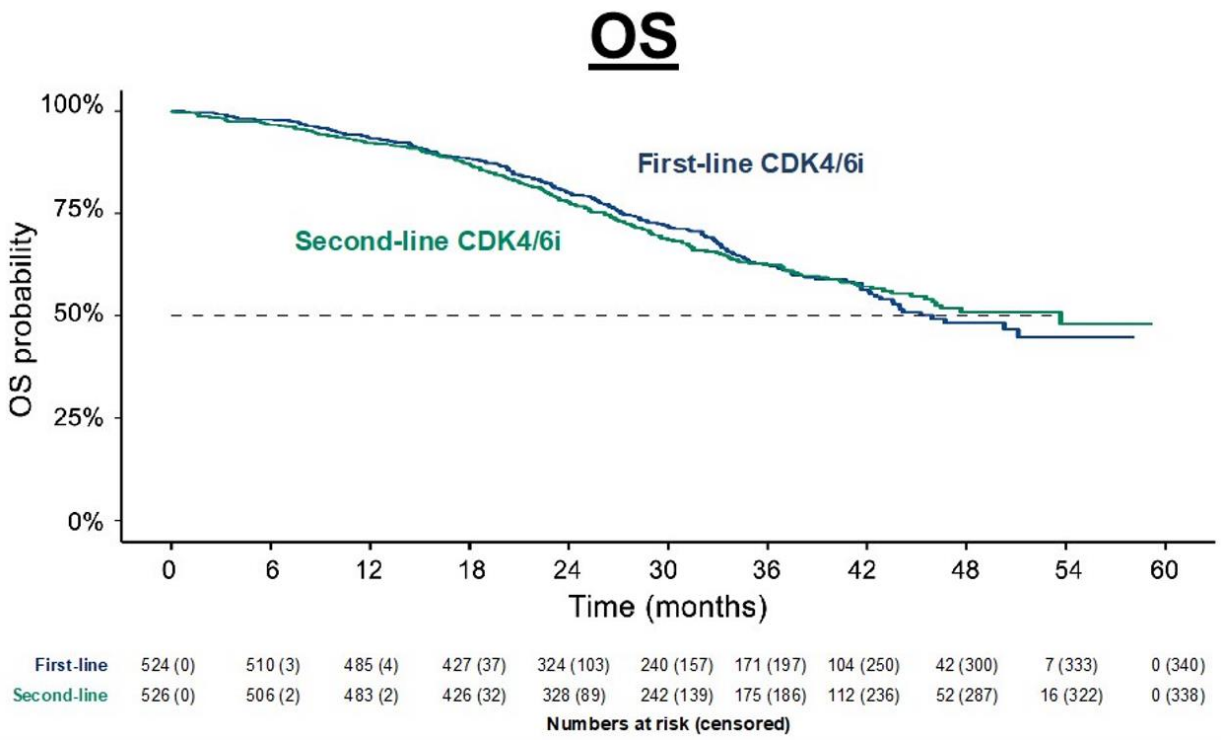


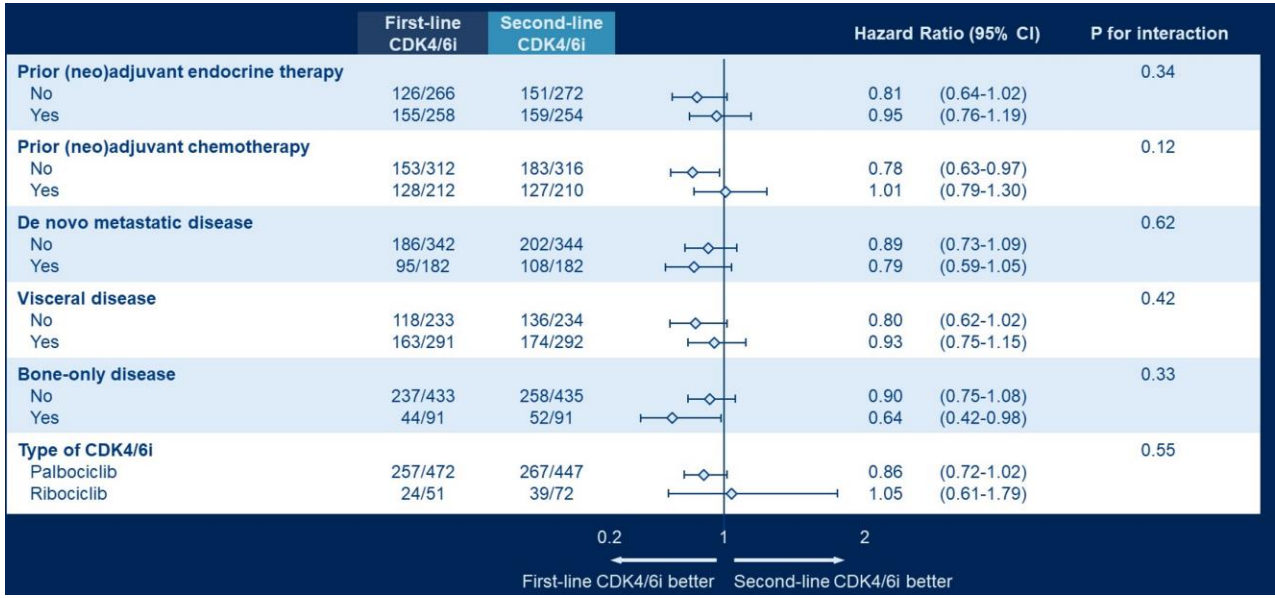
PFS2



Sonke et al, ASCO 2023

SONIA: Is there a difference between CDK4/6i in the 1st vs 2nd line setting for HR+ HER2- MBC? Maybe not for some, but who?





No difference in OS

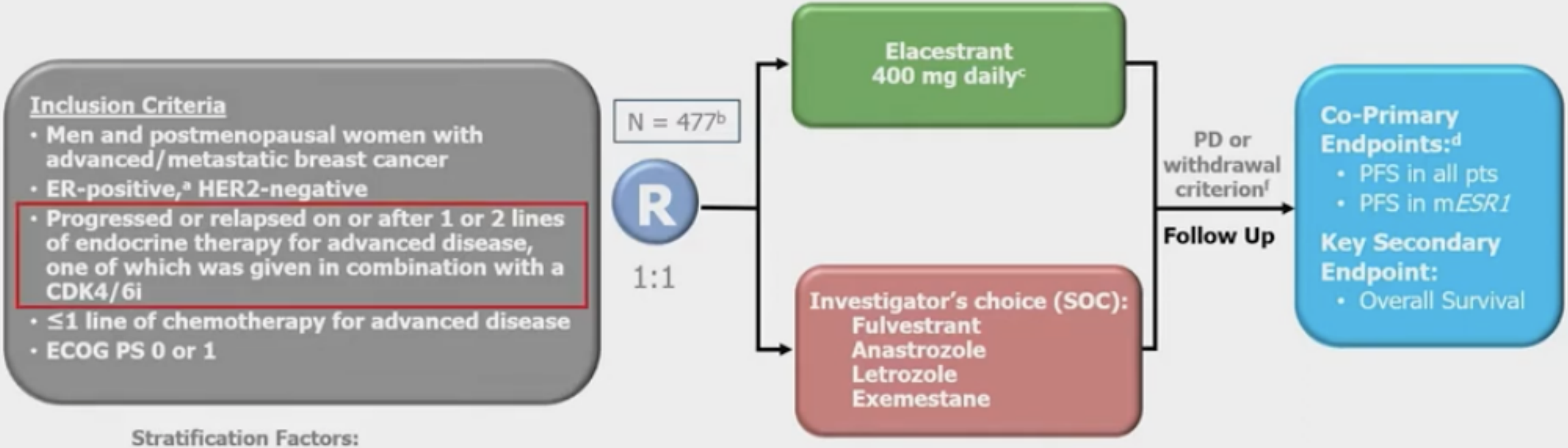
No clear differences by subgroups

Benefits of 2nd line CDK4/6: fewer AEs, shorter duration on CDK4/6i (24.6mos 1st line vs 8.4mos 2nd line), lower costs

Caveats:

1. Most patients received Palbociclib (>90%) which has no significant benefit in OS (PALOMA-2)
2. 2nd line therapy now is rapidly improving; Fulvestrant single agent may not be appropriate for 2nd line therapy anymore

EMERALD Phase 3 Study Design



[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Blinded Independent Central Review. [e]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant health, Redwood City, CA). [f]Restaging CT scans every 8 weeks.

CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival, PD, progressive disease; PFS: progression-free survival; Pts, patients; R, randomized. SOC, standard of care.

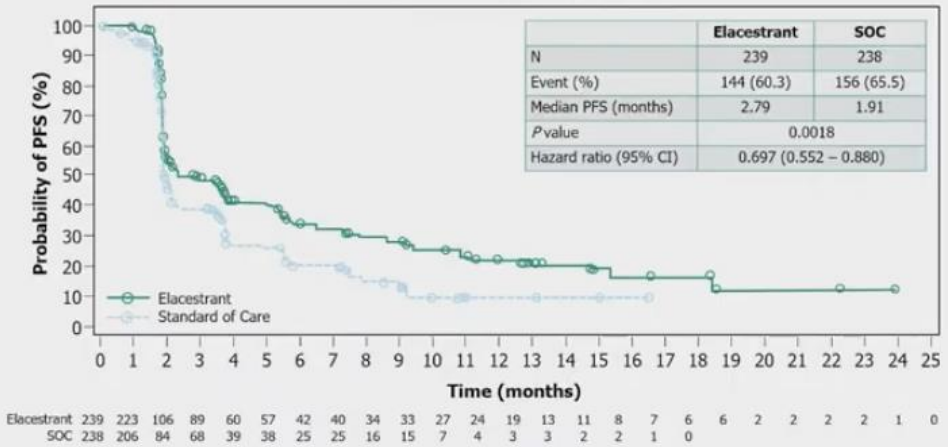
Baseline Demographic and Disease Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*mESR1* (N=115)	All (N=238)	*mESR1* (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.5 (32-83)	63.0 (32-83)
Gender, n % Female Male	233 (97.5) 6 (2.5)	115 (100) 0	237 (99.6) 1 (0.4)	113 (100) 0
ECOG PS, n (%) 0 1 >1	143 (59.8) 96 (40.2) 0	67 (58.3) 48 (41.7) 0	135 (56.7) 102 (42.9) 1 (0.4)	62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	168 (70.6)	83 (73.5)
Bone-only disease, n (%)	38 (15.9)	14 (12.2)	29 (12.2)	14 (12.4)
Prior adjuvant therapy, n (%)	158 (66.1)	62 (53.9)	141 (59.2)	65 (57.5)
Number of prior lines of endocrine therapy,** n (%) 1 2	129 (54.0) 110 (46.0)	73 (63.5) 42 (36.5)	141 (59.2) 97 (40.8)	69 (61.1) 44 (38.9)
Number of prior lines of chemotherapy,** n (%) 0 1	191 (79.9) 48 (20.1)	89 (77.4) 26 (22.6)	180 (75.6) 58 (24.4)	81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

Primary Endpoint: PFS by IRC

All Patients (ITT)



	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

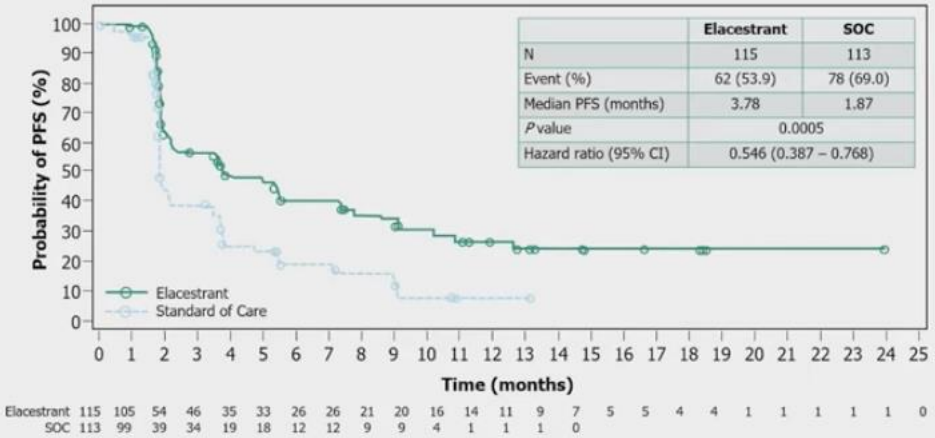
Elacestrant is associated with a 30% reduction in the risk of progression or death in all patients with ER+/HER2- mBC

Elacestrant demonstrated a significant improvement versus SOC in all patients with ER+/HER2- advanced/metastatic breast cancer following CDK4/6i therapy

San Antonio Breast Cancer Symposium®, December 7-10, 2021

Primary Endpoint: PFS by IRC

Patients With Tumors Harboring *mESR1*



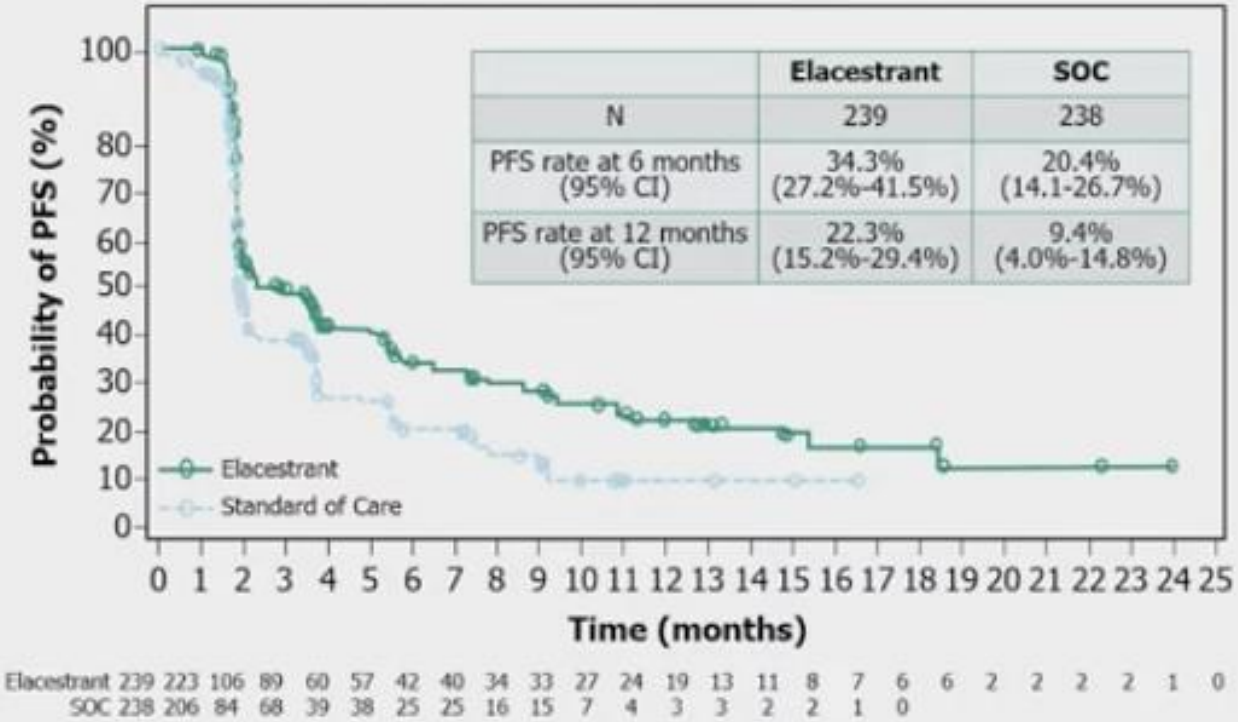
	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

Elacestrant is associated with a 45% reduction in the risk of progression or death in patients harboring *mESR1*

Elacestrant demonstrated a significant improvement versus SOC in patients with ER+/HER2- advanced/metastatic breast cancer and *mESR1* following CDK4/6i therapy

PFS Rate at 6 and 12 Months: All Patients and *mESR1* Group

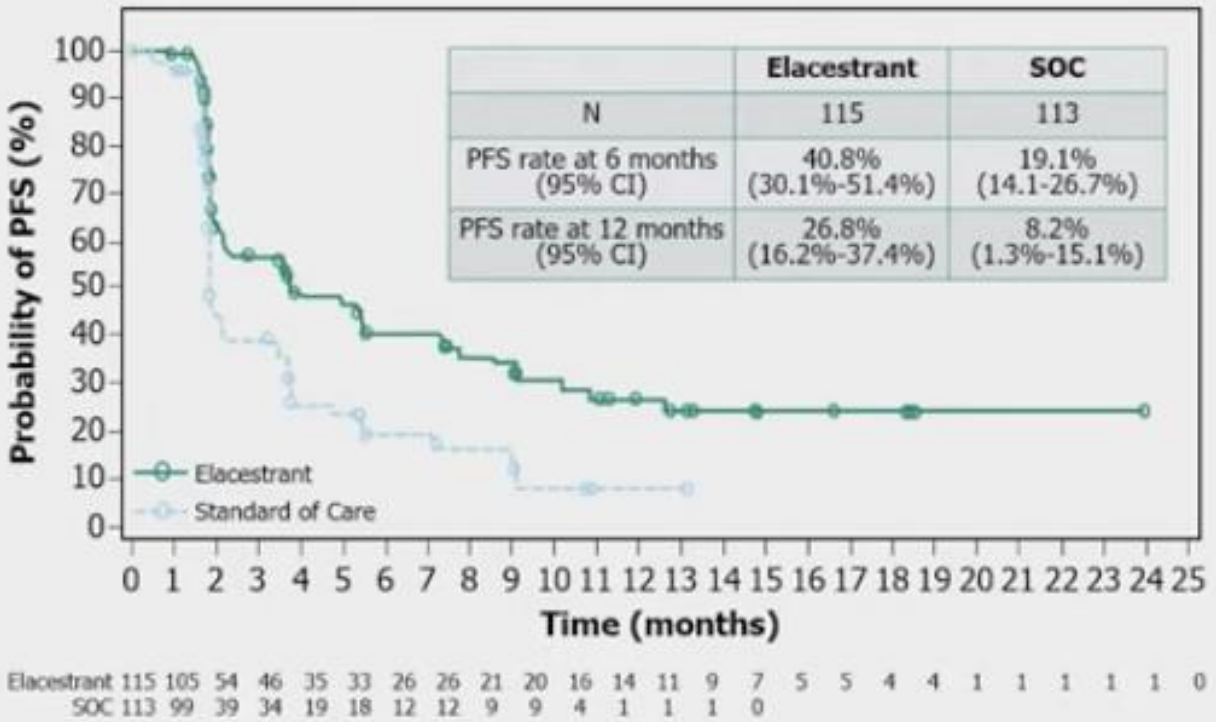
All Patients



	Elacestrant	SOC
N	239	238
PFS rate at 6 months (95% CI)	34.3% (27.2%-41.5%)	20.4% (14.1-26.7%)
PFS rate at 12 months (95% CI)	22.3% (15.2%-29.4%)	9.4% (4.0%-14.8%)

Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

Patients With Tumors Harboring *mESR1*



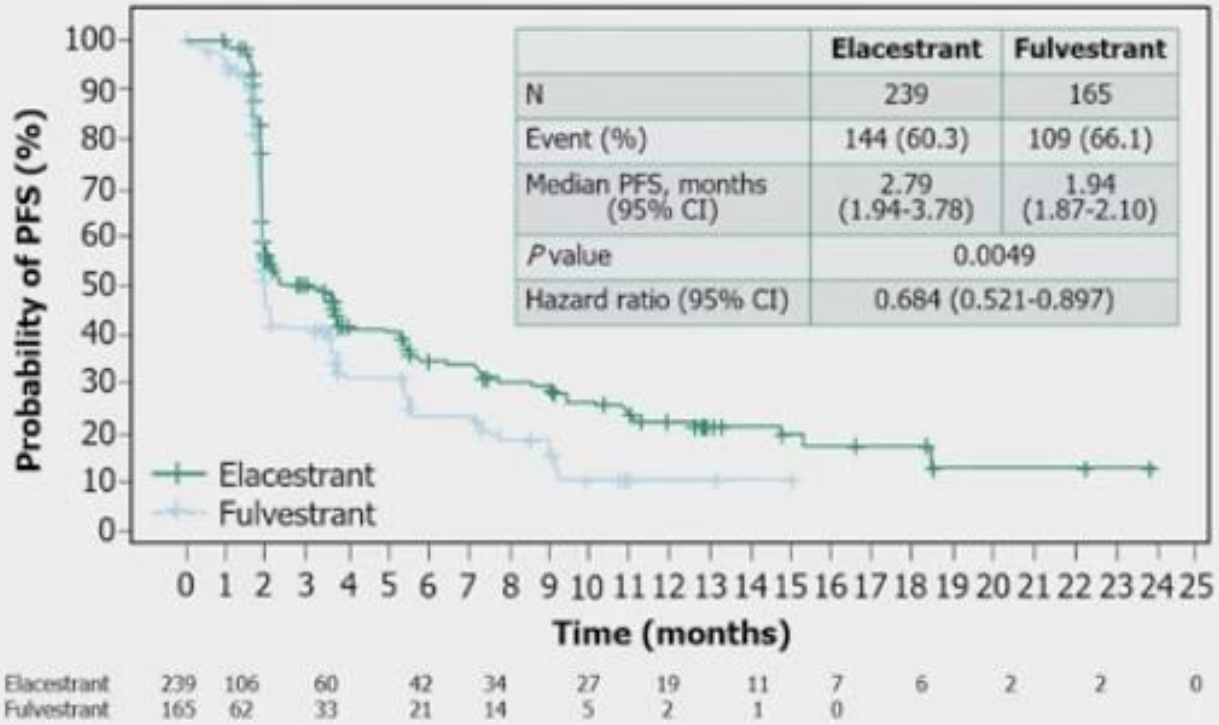
	Elacestrant	SOC
N	115	113
PFS rate at 6 months (95% CI)	40.8% (30.1%-51.4%)	19.1% (14.1-26.7%)
PFS rate at 12 months (95% CI)	26.8% (16.2%-37.4%)	8.2% (1.3%-15.1%)

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

Elacestrant demonstrated a higher PFS rate at 6 and 12 months versus SOC endocrine therapy in patients with ER+/HER2- advanced/metastatic breast cancer following prior CDK4/6i therapy

PFS: Elacestrant vs Fulvestrant (All Patients and *mESR1* Group)

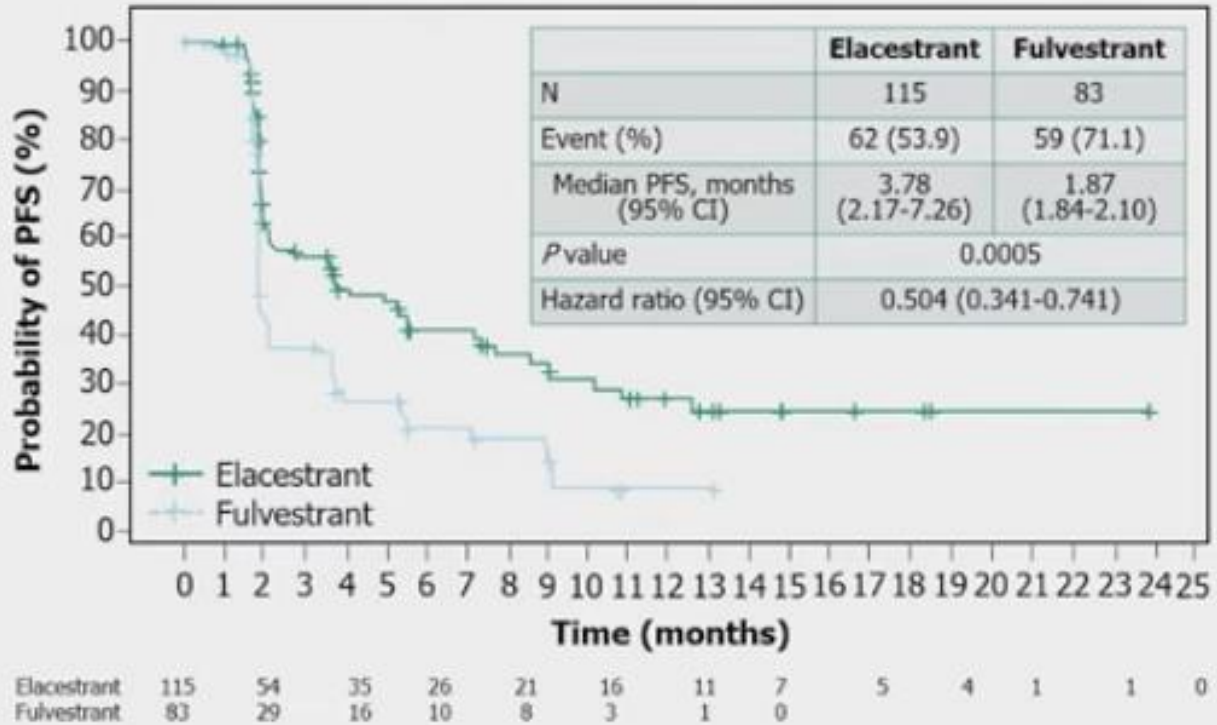
All Patients



	Elacestrant	Fulvestrant
N	239	165
Event (%)	144 (60.3)	109 (66.1)
Median PFS, months (95% CI)	2.79 (1.94-3.78)	1.94 (1.87-2.10)
P value	0.0049	
Hazard ratio (95% CI)	0.684 (0.521-0.897)	

Elacestrant	239	106	60	42	34	27	19	11	7	6	2	2	0	
Fulvestrant	165	62	33	21	14	5	2	1	0					

Patients With Tumors Harboring *mESR1*



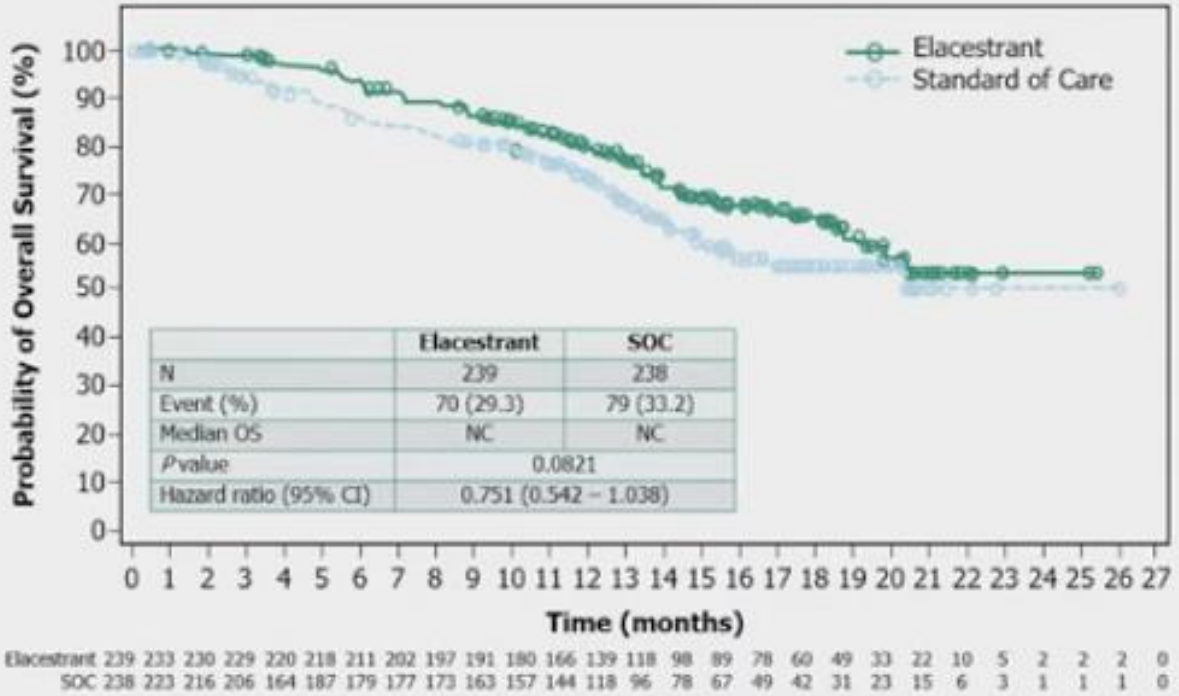
	Elacestrant	Fulvestrant
N	115	83
Event (%)	62 (53.9)	59 (71.1)
Median PFS, months (95% CI)	3.78 (2.17-7.26)	1.87 (1.84-2.10)
P value	0.0005	
Hazard ratio (95% CI)	0.504 (0.341-0.741)	

Elacestrant	115	54	35	26	21	16	11	7	5	4	1	1	0	
Fulvestrant	83	29	16	10	8	3	1	0						

Elacestrant demonstrated a significant improvement versus Fulvestrant as SOC in patients with ER+/HER2- advanced/metastatic breast cancer and *mESR1* following CDK4/6i therapy

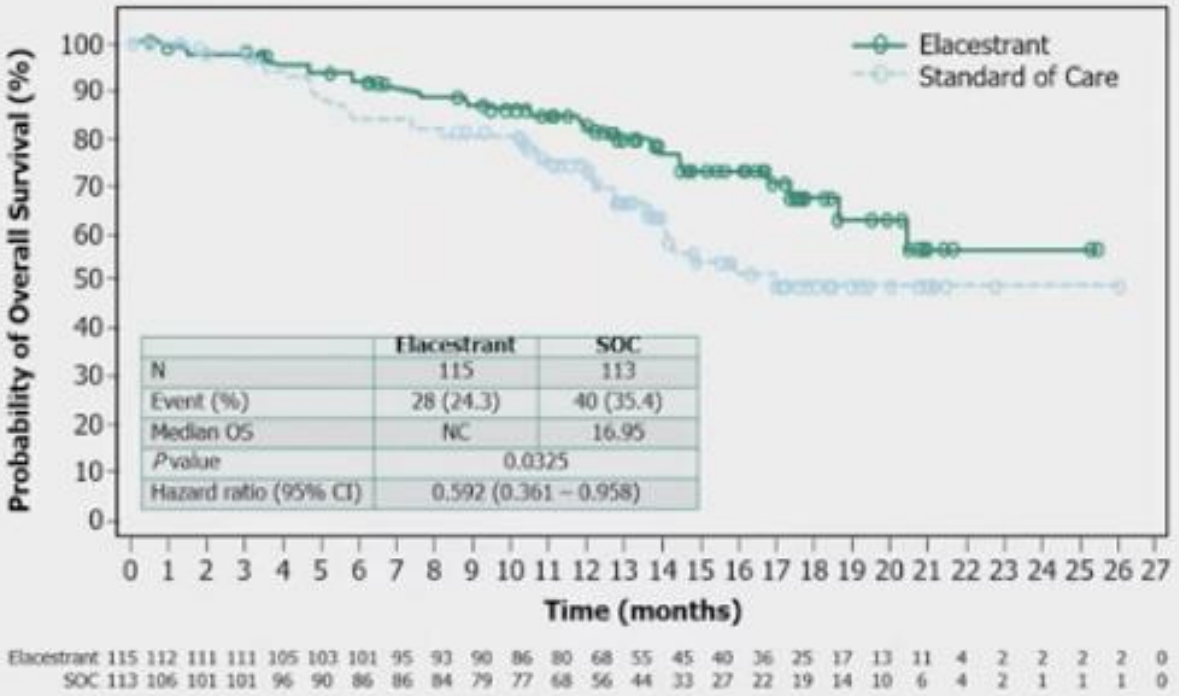
Overall Survival (Interim Analysis)

All Patients



	Elacestrant	SOC
N	239	238
Event (%)	70 (29.3)	79 (33.2)
Median OS	NC	NC
P value	0.0821	
Hazard ratio (95% CI)	0.751 (0.542 – 1.038)	

Patients with *mESR1*



	Elacestrant	SOC
N	115	113
Event (%)	28 (24.3)	40 (35.4)
Median OS	NC	16.95
P value	0.0325	
Hazard ratio (95% CI)	0.592 (0.361 – 0.958)	

- While no statistically significant differences were noted at the α=0.0001 level in OS, an evident trend favoring elacestrant over SOC was noted in both groups. Final analysis with mature data is expected to take place in late 2022/early 2023.

Treatment-Emergent Adverse Events (≥10% in Either Arm)

	Elacestrant N = 237, n (%)		SOC					
			Total N = 229, n (%)		Fulvestrant N = 161, n (%)		AI N = 68, n (%)	
Preferred Term	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	-	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)	2 (0.8)	19 (8.3)	-	12 (7.5)	-	7 (10.3)	-
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	-	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	-	28 (17.4)	-	9 (13.2)	-
Diarrhea	33 (13.9)	-	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	-
Aspartate aminotransferase increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	-
Headache	29 (12.2)	4 (1.7)	26 (11.4)	-	18 (11.2)	-	8 (11.8)	-
Constipation	29 (12.2)	-	15 (6.6)	-	10 (6.2)	-	5 (7.4)	-
Hot flush	27 (11.4)	-	19 (8.3)	-	15 (9.3)	-	4 (5.9)	-
Dyspepsia	24 (10.1)	-	6 (2.6)	-	4 (2.5)	-	2 (2.9)	-
Alanine aminotransferase increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	-	6 (8.8)	1 (1.5)

TEAE's leading to discontinuation of elacestrant or SOC were infrequent in both arms (6.3% and 4.4%)
No tx-related deaths in either group

Conclusions: EMERALD

- Elacestrant is the first oral SERD to demonstrate statistically significant improvement in PFS vs. SOC ET in 2nd/3rd line ER+/HER2- MBC
  - 30% reduction in risk of progression or death in all pts
  - 45% reduction in risk of progression or death in pts with mESR1
  - Higher PFS at 6 and 12 months with elacestrant vs. SOC ET
    - Most patients will not respond, but those who do can see durable benefit
- Elacestrant well tolerated with a predictable and manageable safety profile consistent with other endocrine therapies
- Elacestrant combinations (eg with mTOR inhibitors and CDK4/6 inhibitors) are ongoing or planned.

Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the Phase III CAPItello-291 trial

Nicholas C Turner,[1] Mafalda Oliveira,[2] Sacha Howell,[3] Florence Dalenc,[4] Javier Cortes,[5] Henry Gomez,[6] Xichun Hu,[7] Komal Jhaveri,[8] Sibylle Loibl,[9] Serafin Morales Murillo,[10] Zbigniew Nowecki,[11] Meena Okera,[12] Yeon Hee Park,[13] Masakazu Toi,[14] Lyudmila Zhukova,[15] Chris Yan,[16] Gaia Schiavon,[16] Andrew Foxley,[16] and Hope S Rugo[17]

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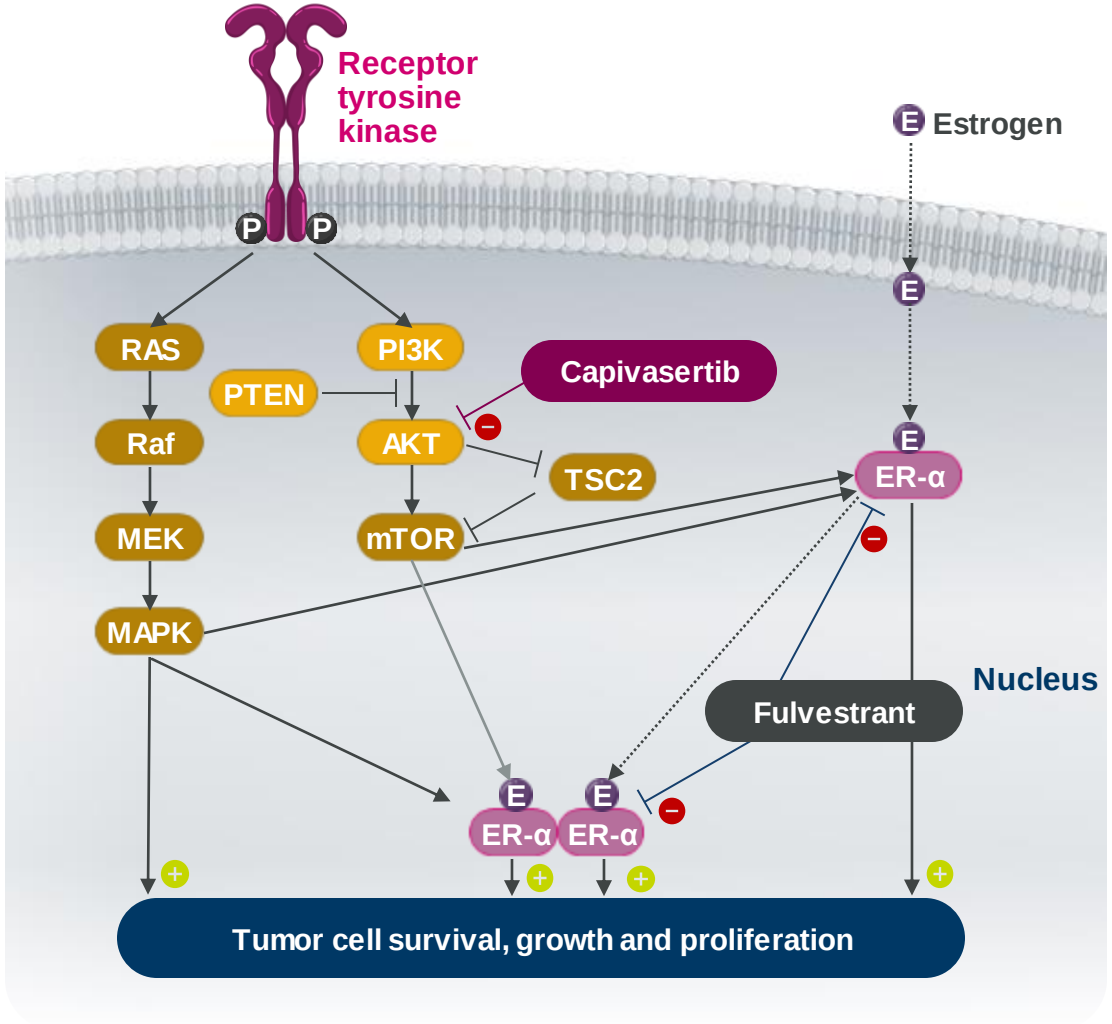
Background and overview of capivasertib

- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*, but may also occur in cancers without those genetic alterations.[1,2] AKT signalling is also implicated in the development of resistance to endocrine therapy[2]
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- In the Phase II, placebo-controlled FAKTION trial[3]:
  - The addition of capivasertib to fulvestrant significantly improved PFS and OS in postmenopausal women with AI-resistant HR+/HER2– ABC in the overall population, with a more pronounced benefit in pathway altered tumours
  - No patients had received prior CDK4/6 inhibitors



1. Millis et al. *JAMA Oncol* 2016;2:1565-1573; 2. Toss et al. *Oncotarget*. 2018;9:31606-31619; 3. How ell et al. *Lancet Oncol* 2022;23:851–64. ABC, advanced breast cancer.

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 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

Baseline 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	201 (56.6)	206 (58.4)	75 (48.4)	76 (56.7)
	Asian	95 (26.8)	94 (26.6)	48 (31.0)	35 (26.1)
	Black or African American	4 (1.1)	4 (1.1)	2 (1.3)	1 (0.7)
	Other	55 (15.5)	49 (13.9)	30 (19.4)	22 (16.4)
Region*; n (%)	1	197 (55.5)	198 (56.1)	80 (51.6)	76 (56.7)
	2	68 (19.2)	68 (19.3)	29 (18.7)	24 (17.9)
	3	90 (25.4)	87 (24.6)	46 (29.7)	34 (25.4)
Metastatic sites; n (%)	Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
	Liver*	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
Hormone receptor status; n (%)†	ER+/PR+	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
	ER+/PR-	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
	ER+/PR unknown	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
Endocrine resistance; n (%)	Primary	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
	Secondary	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)

*Baseline stratification factors. †One patient in the capivasertib + fulvestrant group was ER negative. Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia, Region 3: Asia. Primary and secondary resistance were defined using the 4th ESO-ESMO International Consensus Guidelines for ABC.

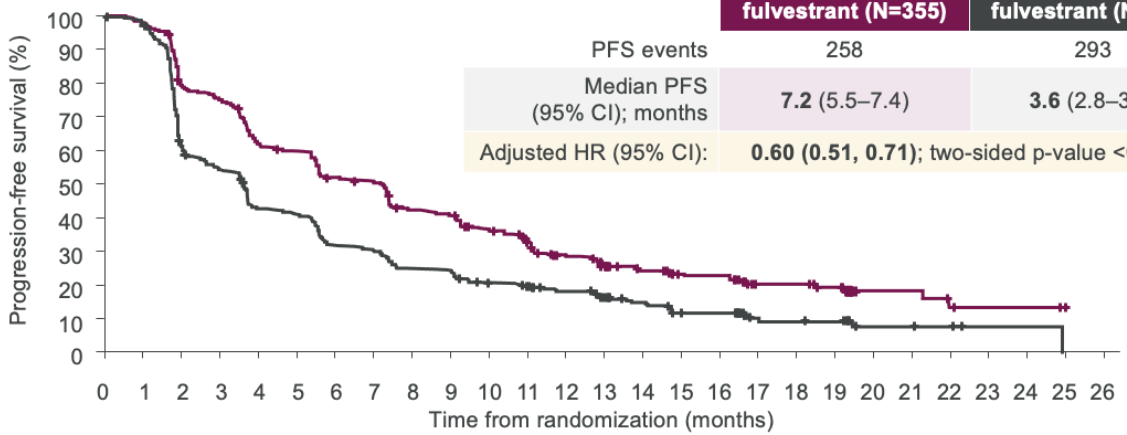
Prior treatments + AKT pathway alterations

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Prior endocrine therapy for ABC; n (%)	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	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	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)

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

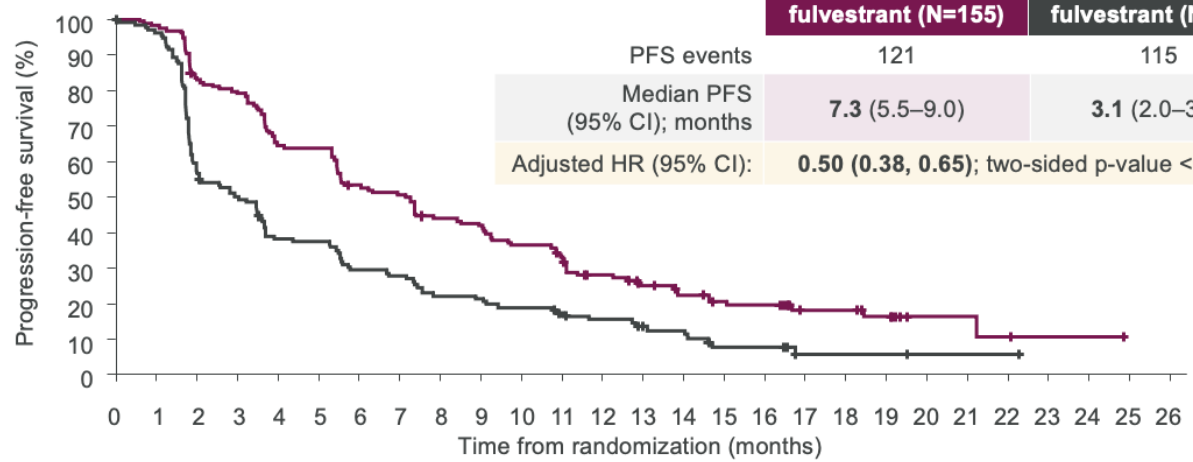
Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

San Antonio Breast Cancer Symposium®, December 6–10, 2022

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

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

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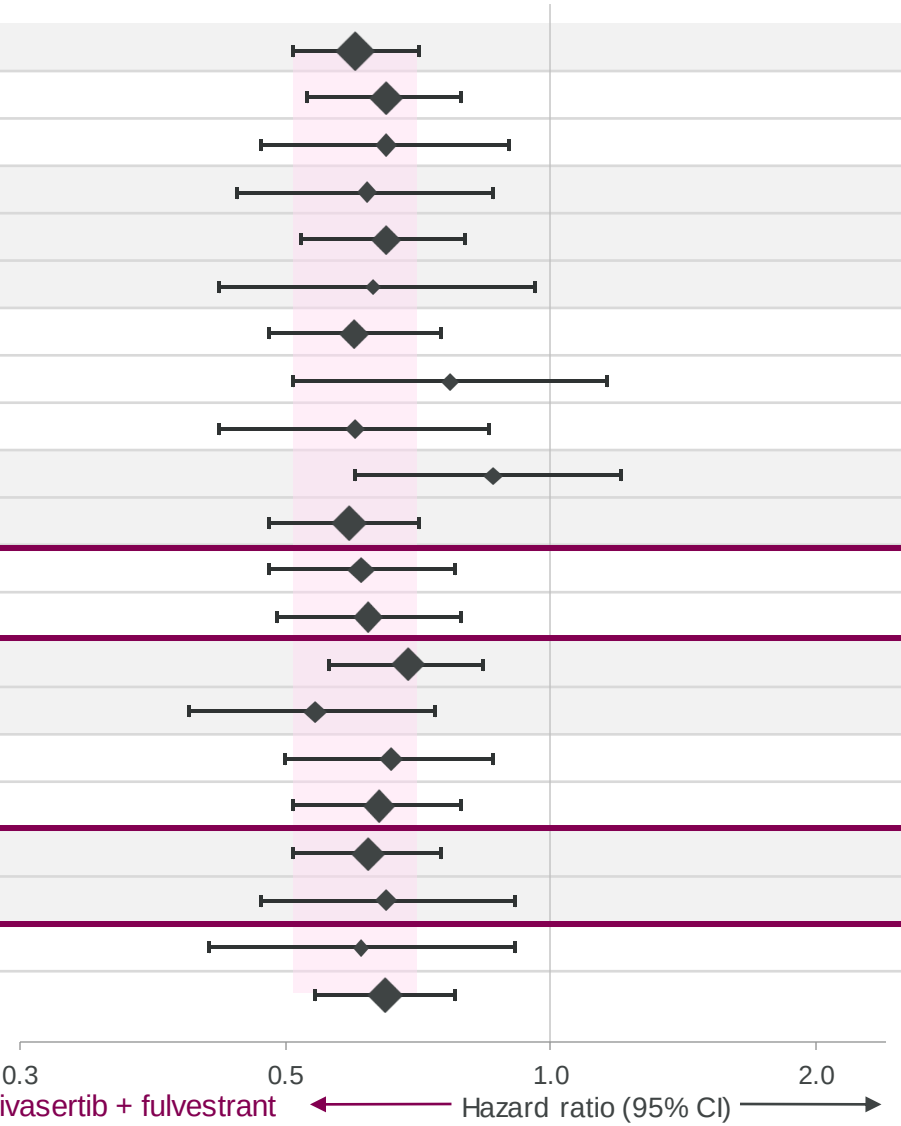
Investigator-assessed PFS by subgroup: Overall population

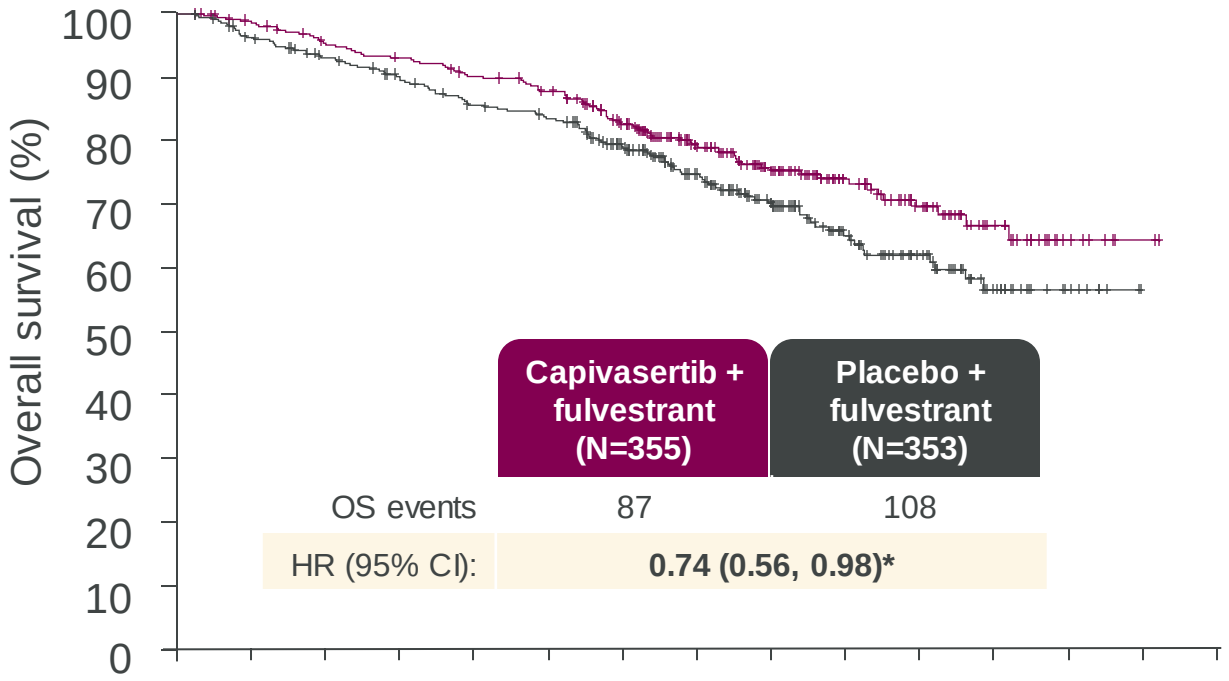
		Number of patients	HR (95%CI)
All patients		**708**	**0.60 (0.51, 0.71)**
Age	<65 years	491	0.65 (0.53, 0.79)
	≥65 years	217	0.65 (0.47, 0.90)
Race	Asian	189	0.62 (0.44, 0.86)
	White	407	0.65 (0.52, 0.80)
	Other	112	0.63 (0.42, 0.96)
Region	1	395	0.60 (0.48, 0.75)
	2	136	0.77 (0.51, 1.16)
	3	177	0.60 (0.42, 0.85)
Menopausal status (females only)	Pre/peri	154	0.86 (0.60, 1.20)
	Post	547	0.59 (0.48, 0.71)
Liver metastases	Yes	306	0.61 (0.48, 0.78)
	No	402	0.62 (0.49, 0.79)
Visceral metastases	Yes	478	0.69 (0.56, 0.84)
	No	230	0.54 (0.39, 0.74)
Endocrine resistance	Primary	262	0.66 (0.50, 0.86)
	Secondary	446	0.64 (0.51, 0.79)
Prior use of CDK4/6 inhibitors	Yes	496	0.62 (0.51, 0.75)
	No	212	0.65 (0.47, 0.91)
Prior chemotherapy for ABC	Yes	129	0.61 (0.41, 0.91)
	No	579	0.65 (0.54, 0.78)



Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia; Region 3: Asia. Primary and secondary resistance as per ESMO definition.

Overall survival at 28% maturity overall

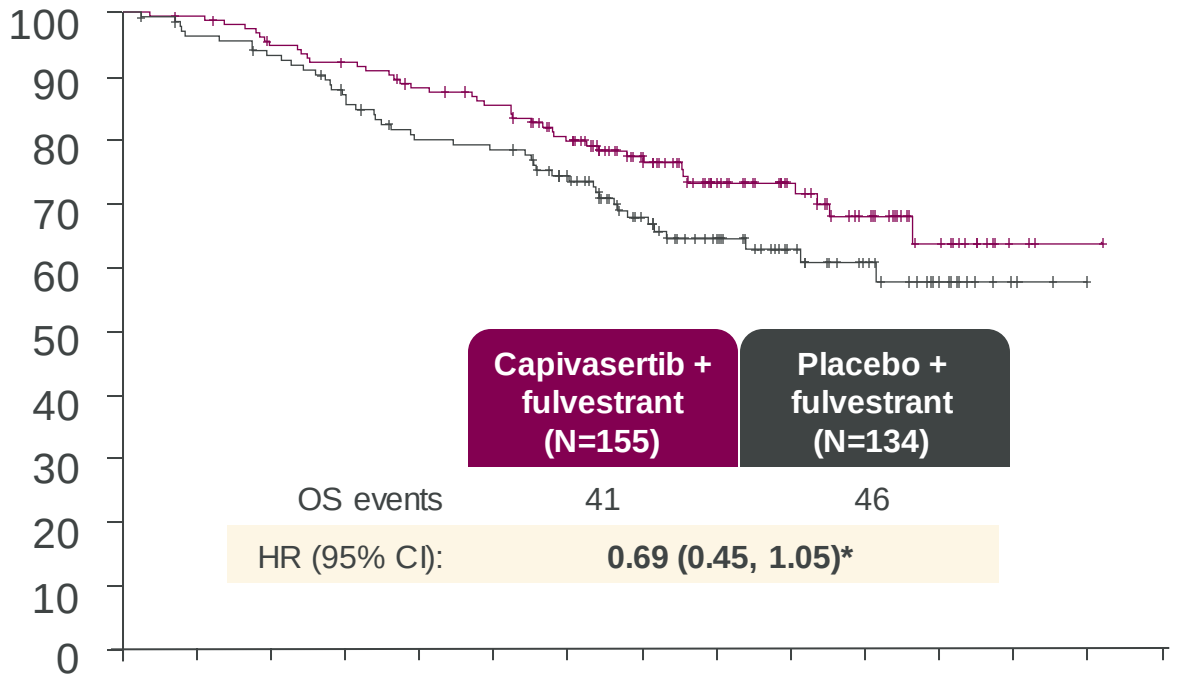
Overall population



Number of patients at risk

Capivasertib + fulvestrant	355	343	327	318	306	295	258	198	144	95	63	33	9	2	0
Placebo + fulvestrant	353	334	316	301	283	274	237	181	134	90	59	30	11	0	0

AKT pathway-altered population



Capivasertib + fulvestrant	155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
Placebo + fulvestrant	134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

*0.01% alpha penalty assigned to OS analyses of no detriment. Formal analysis not prespecified. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases (overall population only) and prior use of CDK4/6 inhibitor.

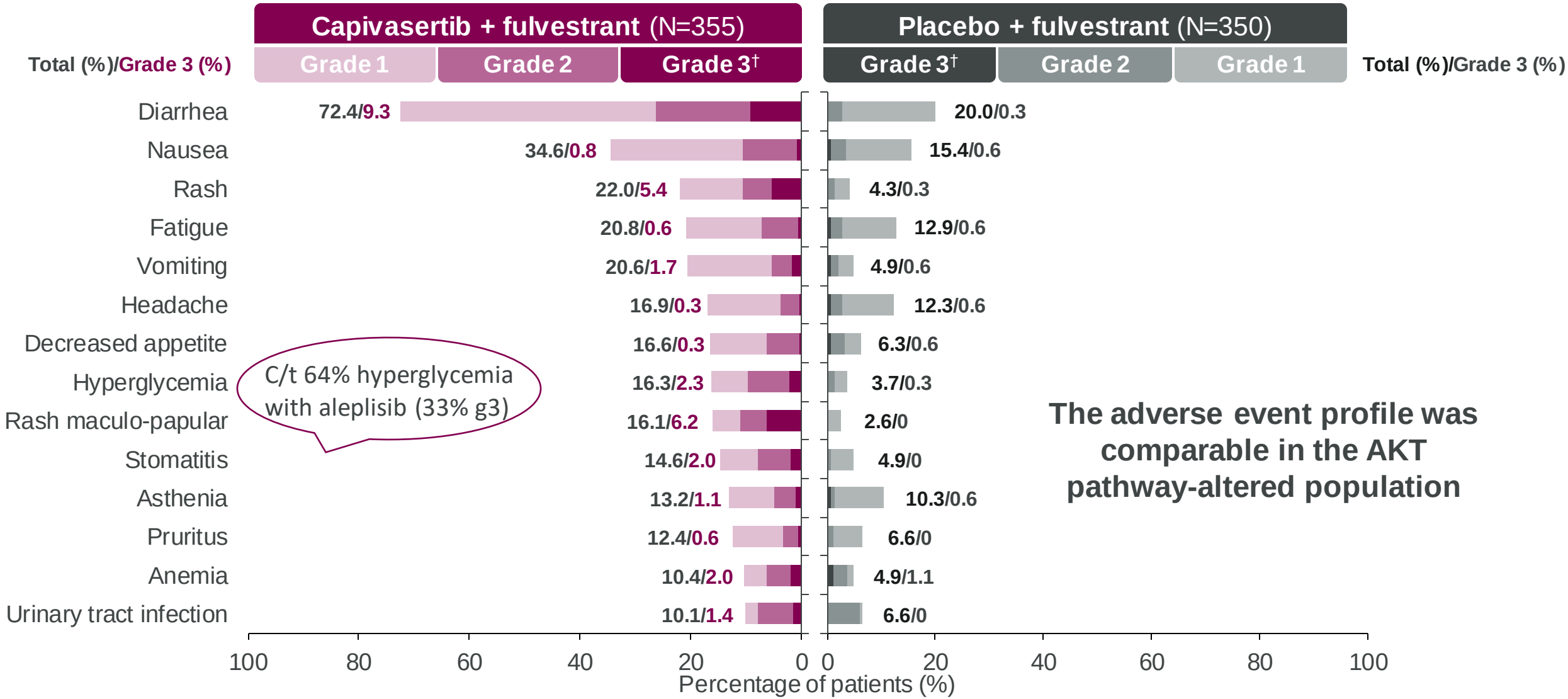
Safety summary: Overall population

n (%)	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=350)
Any adverse event	343 (96.6)	288 (82.3)
Any serious adverse event	57 (16.1)	28 (8.0)
Any adverse event leading to death*	4 (1.1)	1 (0.3)
Any adverse event leading to discontinuation	46 (13.0)	8 (2.3)
Discontinuation of capivasertib/placebo only	33 (9.3)	2 (0.6)
Discontinuation of both capivasertib/placebo and fulvestrant	13 (3.7)	6 (1.7)
Any adverse event leading to dose interruption of capivasertib/placebo only	124 (34.9)	36 (10.3)
Any adverse event leading to dose reduction of capivasertib/placebo only	70 (19.7)	6 (1.7)

The safety profile was comparable in the AKT pathway-altered population

*Grade 5 events included acute myocardial infarction, cerebral hemorrhage, pneumonia aspiration and sepsis (all n=1) in the capivasertib + fulvestrant group and COVID-19 (n=1) in the placebo + fulvestrant group. No grade 5 events were classified as related to capivasertib/placebo by local investigator. The safety analysis population included all patients who received at least one dose of the study drug.

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.

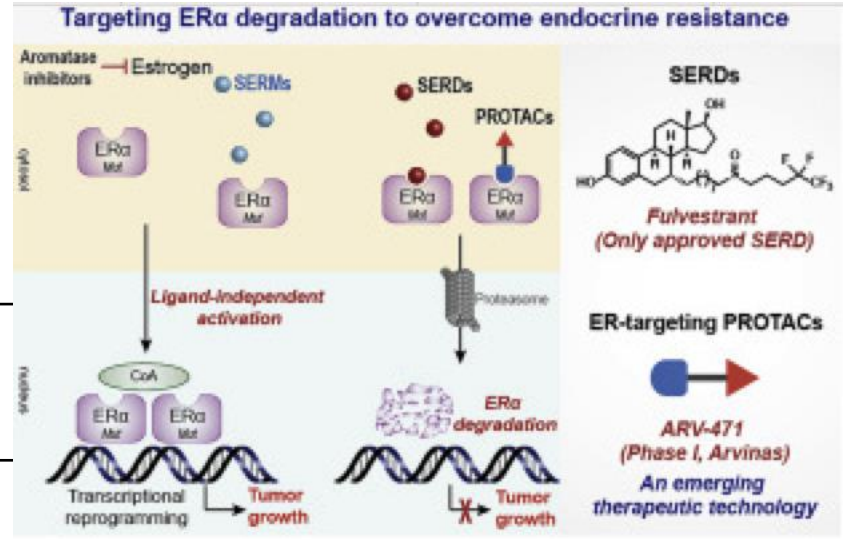
CAPItello-291: Conclusions

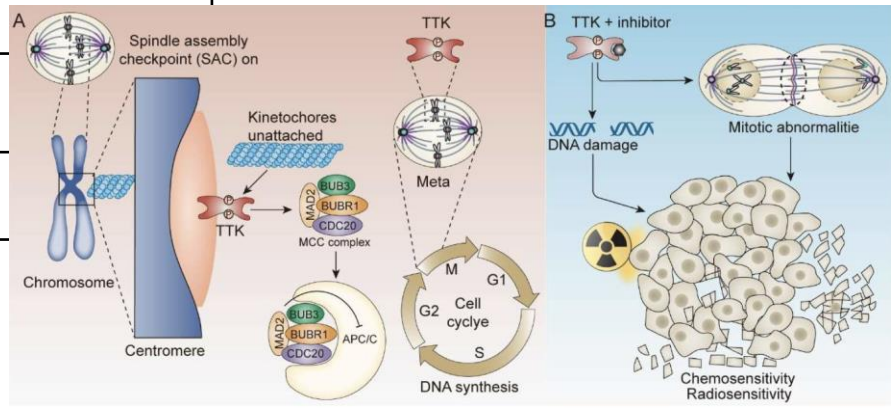
- Capivasertib plus fulvestrant provides a statistically significant and clinically meaningful improvement in PFS in the overall and the AKT pathway-altered population (dual primary)
- Benefit from capivasertib was consistent across clinically relevant subgroups, including in:
  - patients previously treated with a CDK4/6 inhibitor
  - patients with liver metastases
- Overall survival follow-up is ongoing
- Capivasertib plus fulvestrant safety profile appears consistent with that previously reported, with a relatively low discontinuation rate due to adverse events

Capivasertib plus fulvestrant has the potential to be a future treatment option for patients with HR+ ABC who have progressed on an endocrine-based regimen

Active HR+ HER2- MBC studies at UCSD

Study Name	ARVINAS study ARV-471-mBC-102 NCT04072952 Expansion Cohort	TREADWELL TWT-203 NCT05251714 Monotherapy Expansion
Drugs	ARV471 (ER PROTAC) + Everolimus 10mg daily	CFI-402257 (mitotic inhibitor)
Pt Cohort, # of pts	ER/PR+ HER2- MBC, 20 pts	ER and/or PR >10%, HER2- MBC, 10 pts
Nonmeasurable disease	Allowed	Not allowed
Post-CDK4/6i	•Required (mono or combo therapy) •Intolerant or PD •Has to be in the metastatic setting	•Required (mono or combo therapy) •requires PD •PD or recurrence within 2 mos of adjuvant CDK4/6i counts
Max line of chemo	1	1
Prior ET	Required at least 1 line in the metastatic setting	No limit
Max lines of therapy in the metastatic setting	3	Unlimited
Prohibited prior therapies	ARV471 or everolimus	none





Yao W et al; J Cell Signal 2021;
Lin X et al; Eur J Medicinal Chem 2020

Active TNBC studies at UCSD

Study Name	GS-US-592-6173 (ASCENT-04) Ph 3 Randomized Trial Sacituzumab Govitecan + Pembrolizumab v. TPC + Pembro in PD-L1+ mTNBC	GS-US-592-6238 (ASCENT-03) Ph 3 Randomized Trial Sacituzumab Govitecan + Pembrolizumab v. TPC + Pembro in PD-L1- mTNBC
Details	-1st line metastatic or locally advanced inoperable TNBC, PD-L1 positive at screening. -Measurable disease -No prior topoisomerase 1 inhibitors or antibody drug conjugates containing a topoisomerase inhibitor. -No IBD or GI perforation .	-1st line metastatic or locally advanced inoperable TNBC, PD-L1 negative at screening. -Measurable disease -No prior topoisomerase 1 inhibitors or antibody drug conjugates containing a topoisomerase inhibitor. -Pts whose tumors are PD-L1+ at screening will be eligible if they received an anti-programmed death (ligand) 1 (anti-PD-[L]1) inhibitor (ie, checkpoint inhibitor) in the adjuvant or neoadjuvant setting.

Active and Forthcoming Neoadjuvant/Adjuvant studies at UCSD

Study Name	ISPY-2: Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2	TROPION-Breast03: Ph 3 Open-label, Randomised Study of Datopotamab Deruxtecan (Dato-DXd) W/ or W/o Durvalumab Vs Investigator's Choice Therapy in Pts With Stage I-III TNBC w/ Residual Invasive Disease in Breast and/or ALN at Surgery Following Neoadjuvant Systemic Therapy
Details	-Breast tumor that is anatomic Stage II or III (per AJCC 8th edition). Metaplastic and inflammatory carcinomas are eligible. -Patients with extensive DCIS are also eligible if they have involved lymph nodes. -Pts with 2cm tumor (on imaging) with positive lymph nodes -Pts with at least 2.5 cm tumor (on imaging or clinical assessment). If patient LN positive, then tumor size must be at least 1.5cm -No Distant Mets -Willing to have serial MRIs and core biopsies	-Histologically confirmed invasive TNBC ·Residual invasive disease in breast and/or ALN following neoadjuvant therapy. ·Completed at least 6 cycles of neoadjuvant therapy containing an anthracycline and/or taxane with or without carboplatin, with or without pembrolizumab. ·Surgical removal of all clinically evident disease in the breast and lymph nodes ·No adjuvant systemic therapy. ·If post-operative radiation therapy is given, an interval of no more than 6 weeks between completion of XRT and date of randomization. ·No known germline BRCA1 or BRCA2 mutation.

th

Thank you!