UCSF Helen Diller Family Comprehensive Cancer Center

Novel Strategies Under Investigation for Patients with HR-Positive Metastatic Breast Cancer

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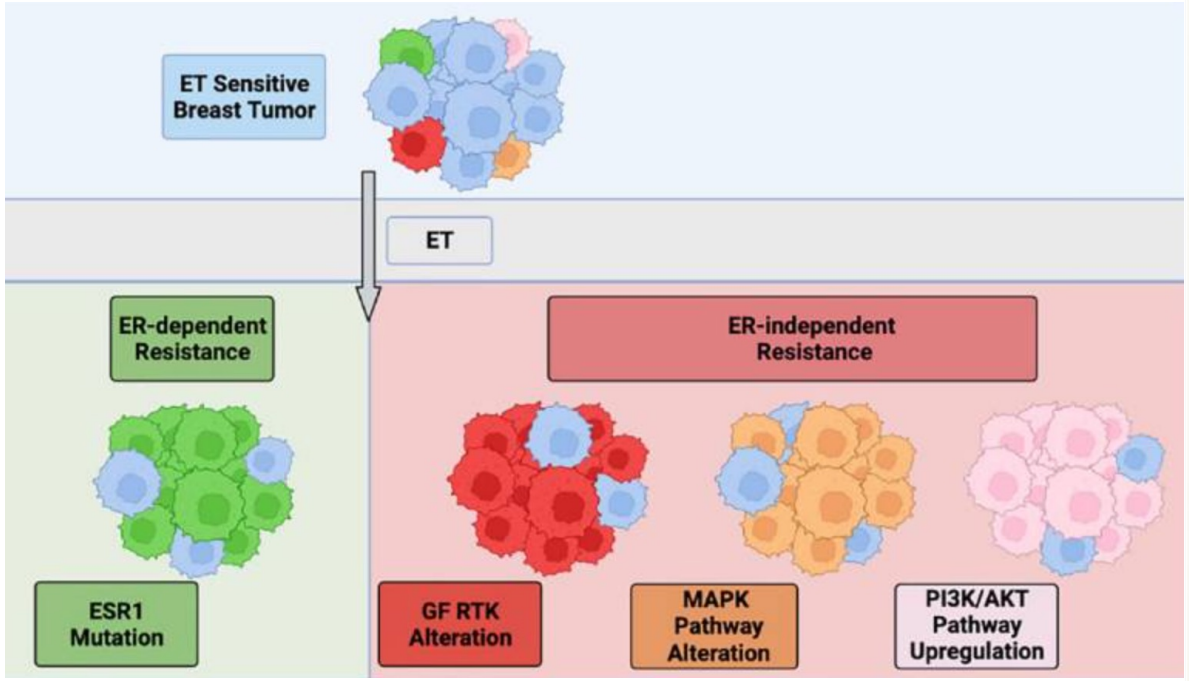
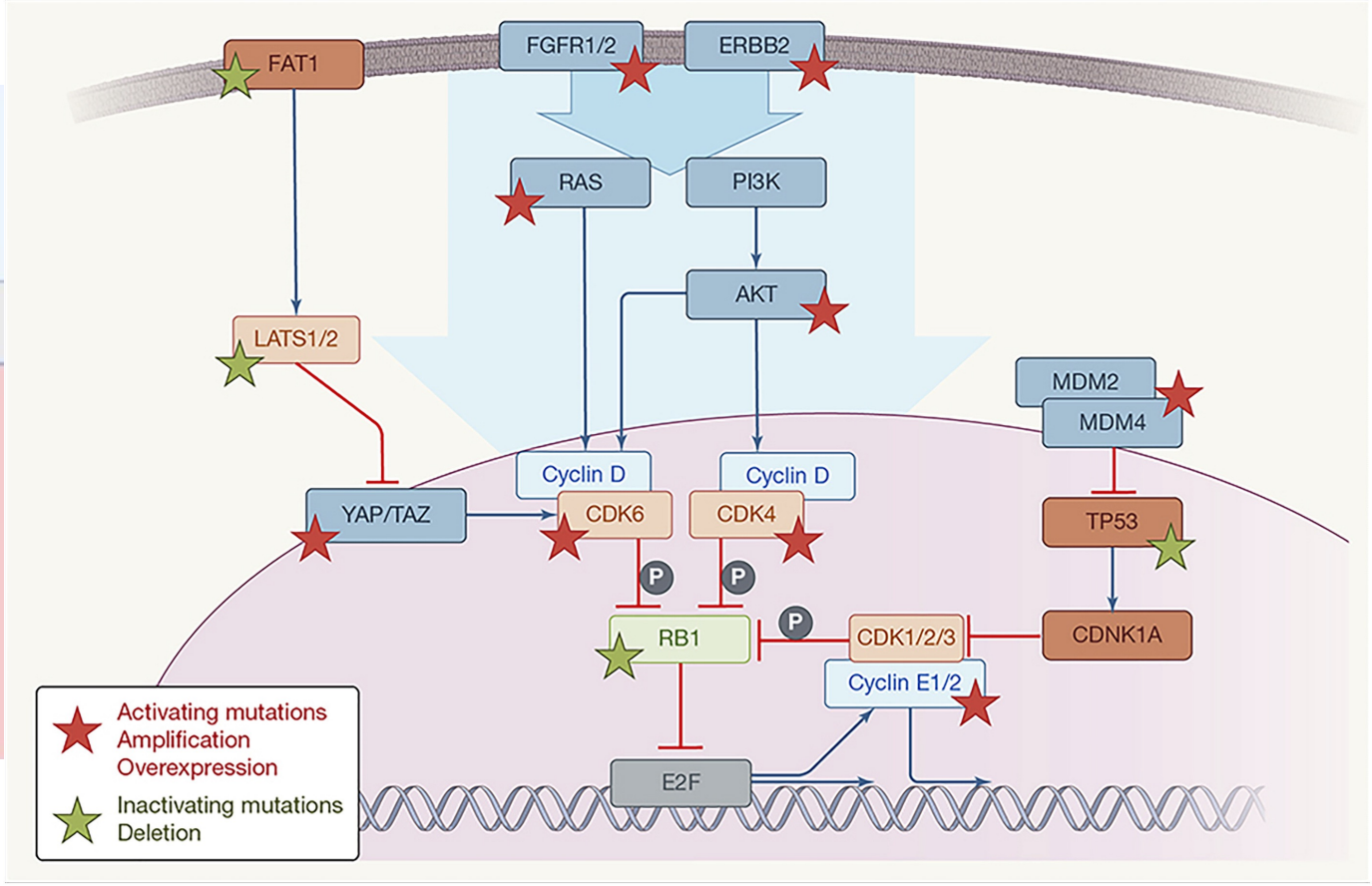
Resistance to ET + CDK4/6i: Now a High Unmet Need



ER dependent and independent mechanism of resistance



Major Mechanisms of Resistance to CDK4/6 Inhibitors

Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25
Álvarez-Fernández M, Malumbres M. *Cancer Cell*. 2020;37:514-529.

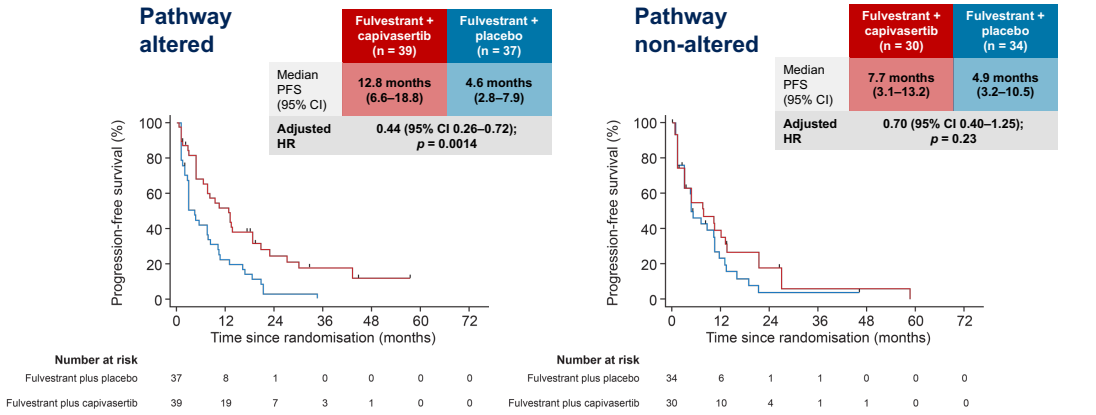
Inhibiting AKT

- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*
  - May also occur in cancers without these genetic alterations
  - AKT signalling implicated in development of ET resistance
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)

Turner et al, SABCS 2022; Jones RH, et al. Lancet Oncol 2020; Howell et al, Lancet Oncology 2022

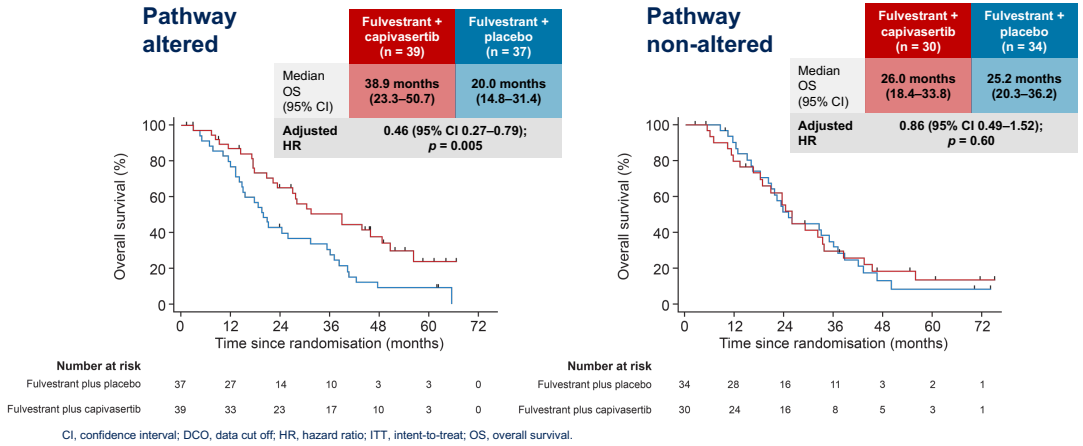
Phase II FAKTION Trial

- Adding Capi to Fulv in PM women with AI resistant HR+ MBC (no prior CDKi) improved PFS and OS, with most benefit in altered population



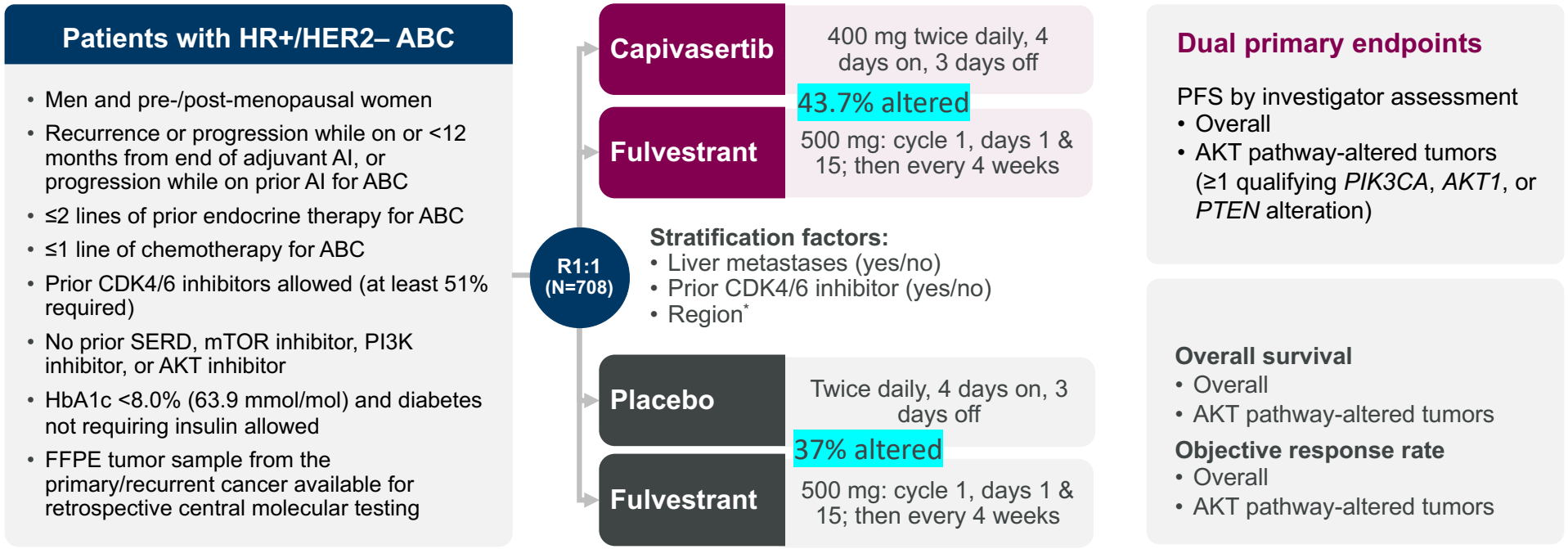
CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

DCO Nov 2021



CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

CAPItello-291: Phase III, randomized, double-blind, placebo-controlled study



Summary of Demographics

- Median age ~59
- Asian 26%, Black 1%
- Primary ET resistance ~38%
- Visceral mets ~68%
- One line of prior ET for MBC ~75%
- Prior CDK4/6i for MBC ~70%
- Chemotherapy for ABC ~18%

Turner et al, SABCS 2022

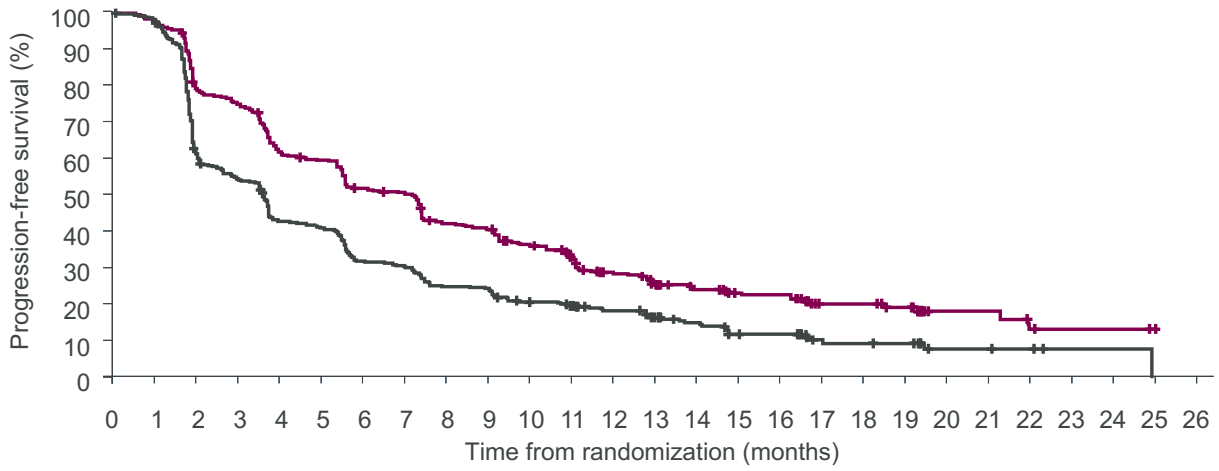
AKT Pathway Alterations

Alteration; n (%)			
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)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
	No sample available	10 (2.8)	4 (1.1)
	Preanalytical failure	39 (11.0)	34 (9.6)
	Post analytical failure	9 (2.5)	10 (2.8)

AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

Turner et al, SABCS 2022

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

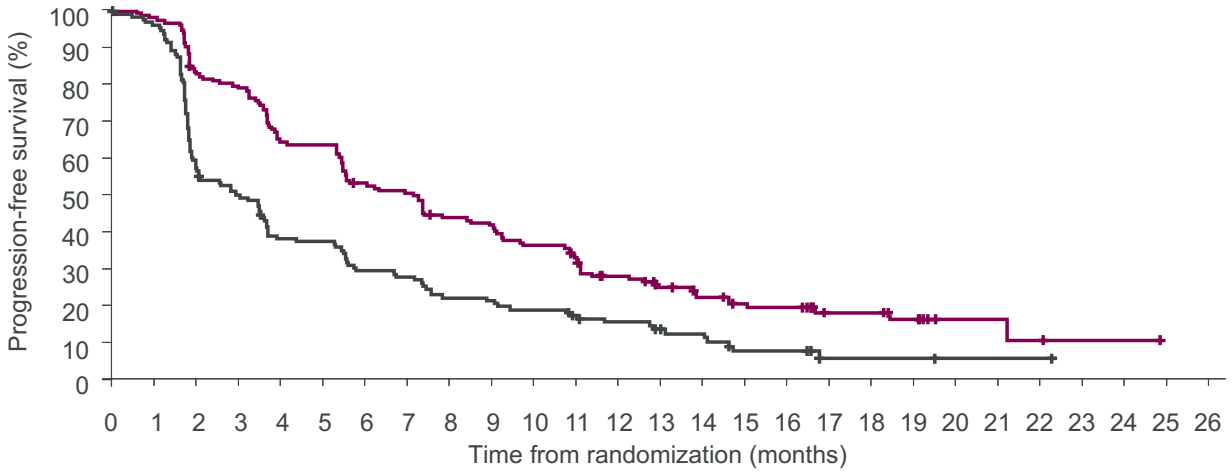


Number of patients at risk

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

	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	

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



Number of patients at risk

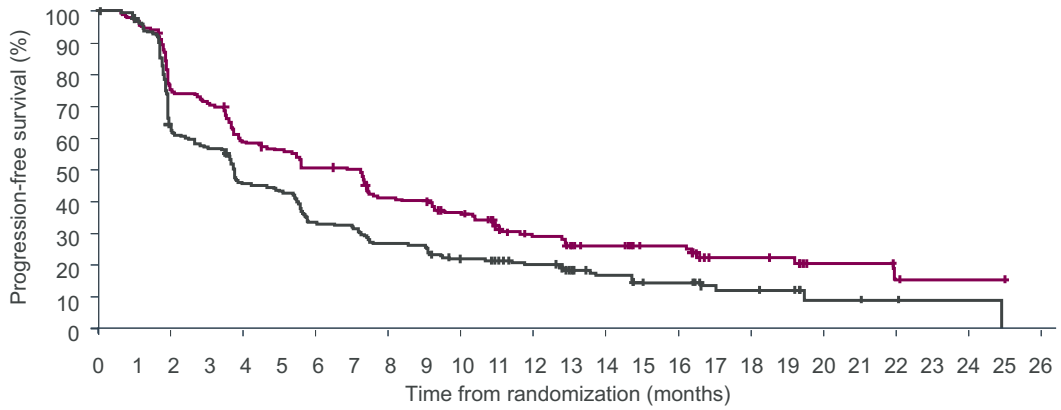
Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

	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	

Turner et al, SABCS 2022

Additional Analyses

Exploratory analysis: Investigator-assessed PFS in the non-altered population (including unknown†)



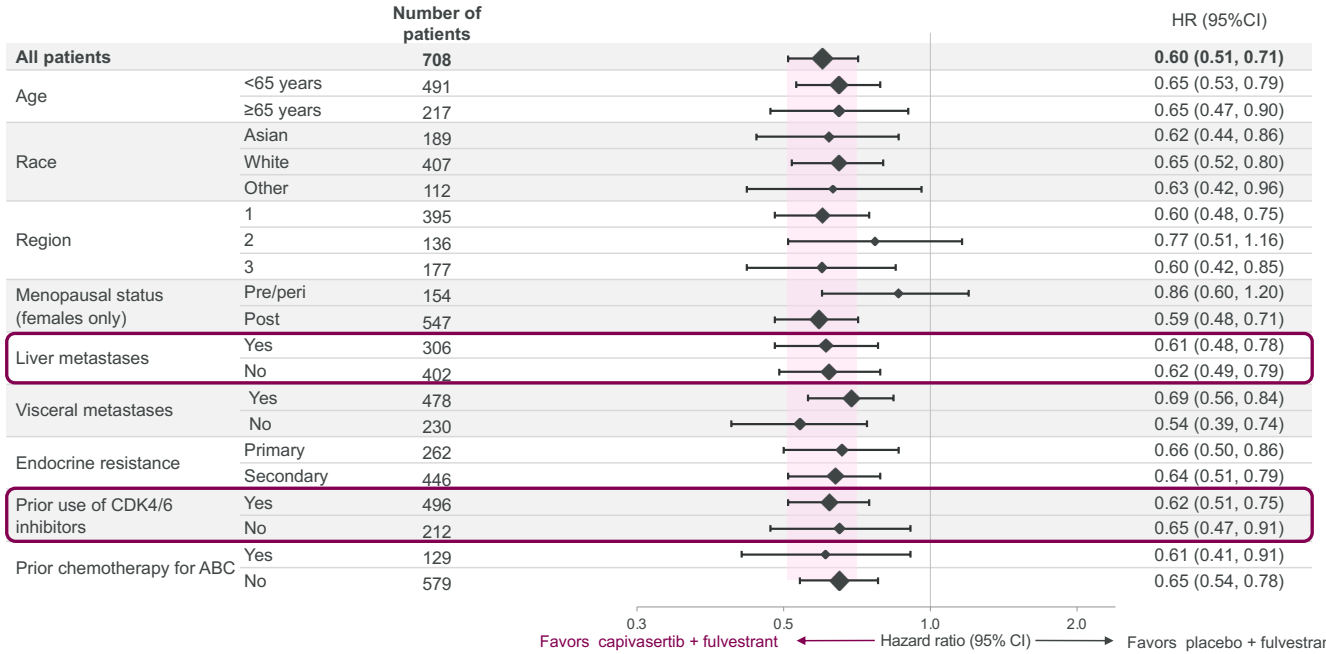
Number of patients at risk

Capivasertib + fulvestrant	200	180	139	131	108	102	92	90	73	71	61	49	40	33	29	22	22	13	13	12	5	5	3	1	1	1	0
Placebo + fulvestrant	219	205	130	118	94	89	69	65	55	54	42	39	34	27	22	18	17	10	9	8	3	3	2	1	1	0	0

	Capivasertib + fulvestrant (N=200)	Placebo + fulvestrant (N=219)
PFS events	137	178
Median PFS (95% CI); months	**7.2** (4.5–7.4)	**3.7** (3.0–5.0)
HR (95% CI):	**0.70 (0.56, 0.88)**	

Excluding unknowns (58 v 48): HR 0.79 (95% CI 0.61, 1.02)

Investigator-assessed PFS by subgroup: Overall population



Response per investigator assessment

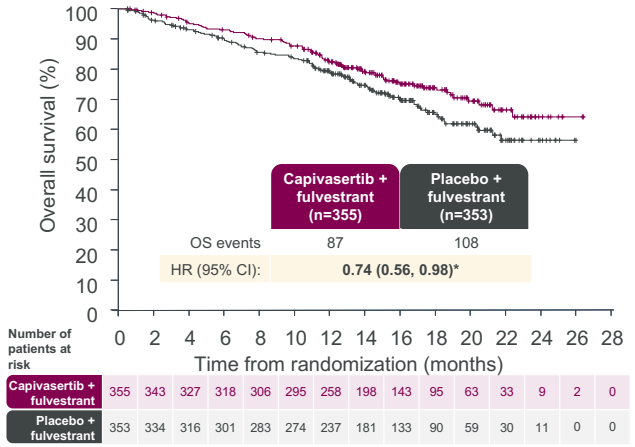
	Overall population		AKT pathway-altered population	
	Capivasertib + fulvestrant	Placebo + fulvestrant	Capivasertib + fulvestrant	Placebo + fulvestrant
Patients with measurable disease at baseline	310	320	132	124
Objective response rate; n (%)	71 (22.9)	39 (12.2)	38 (28.8)	12 (9.7)
Odds ratio (95% CI)*	2.19 (1.42, 3.36)		3.93 (1.93, 8.04)	

Turner et al, SABCS 2022

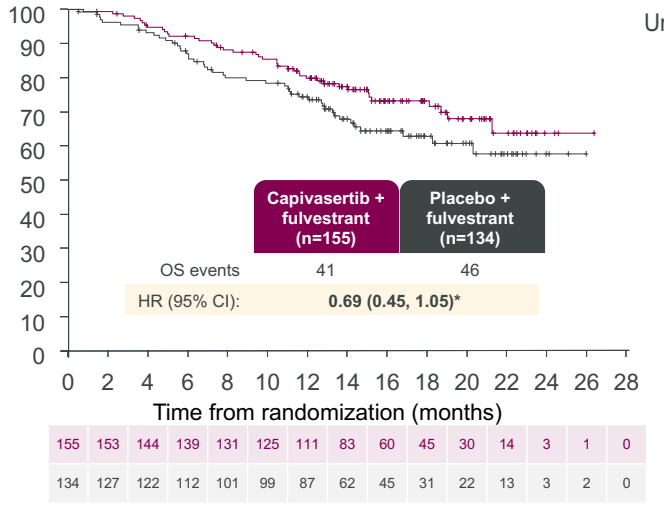
Overall Survival

- Overall survival immature at just 28% maturity
  - Less events in the Capi arm

Overall population

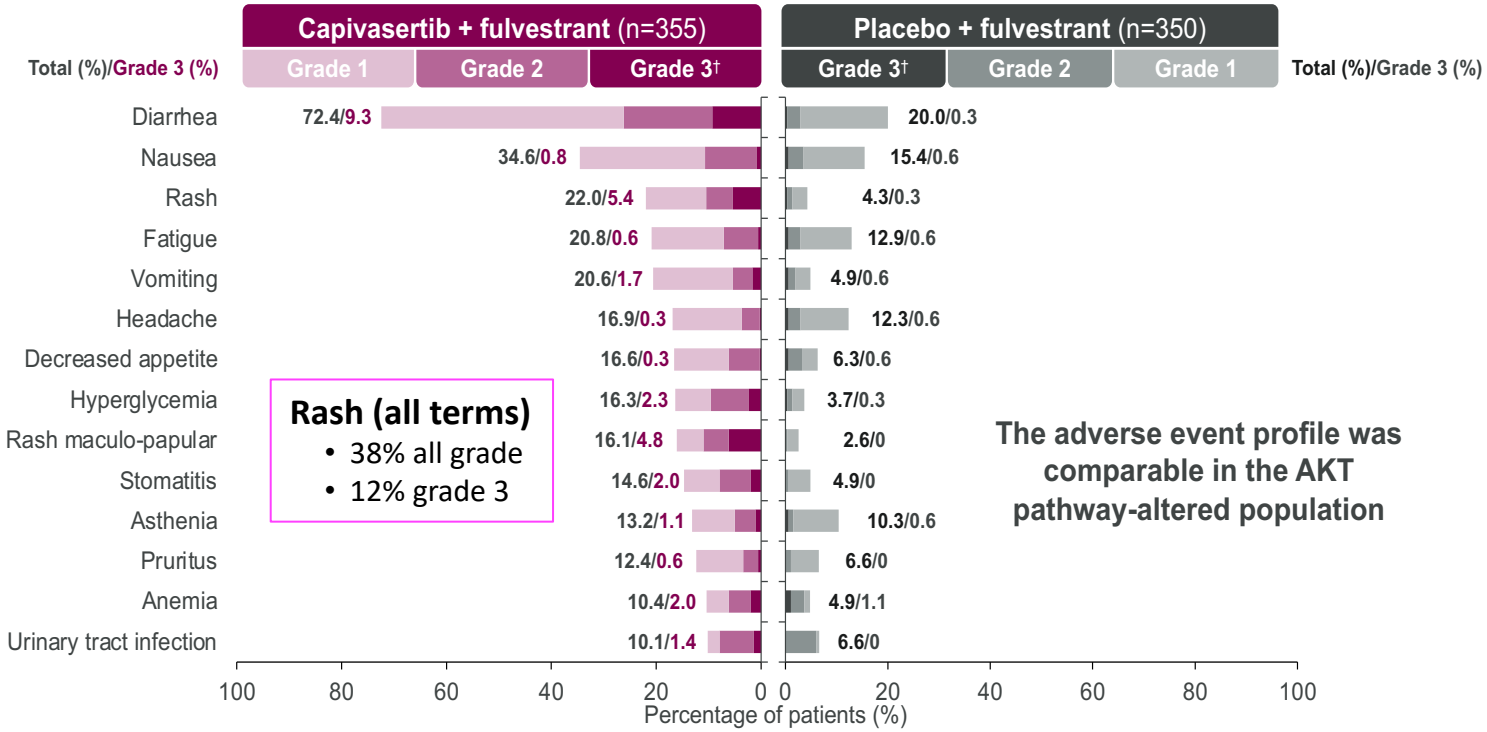


AKT pathway-altered population



Safety

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



Rash (all terms)
- 38% all grade
- 12% grade 3

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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AEs leading to:

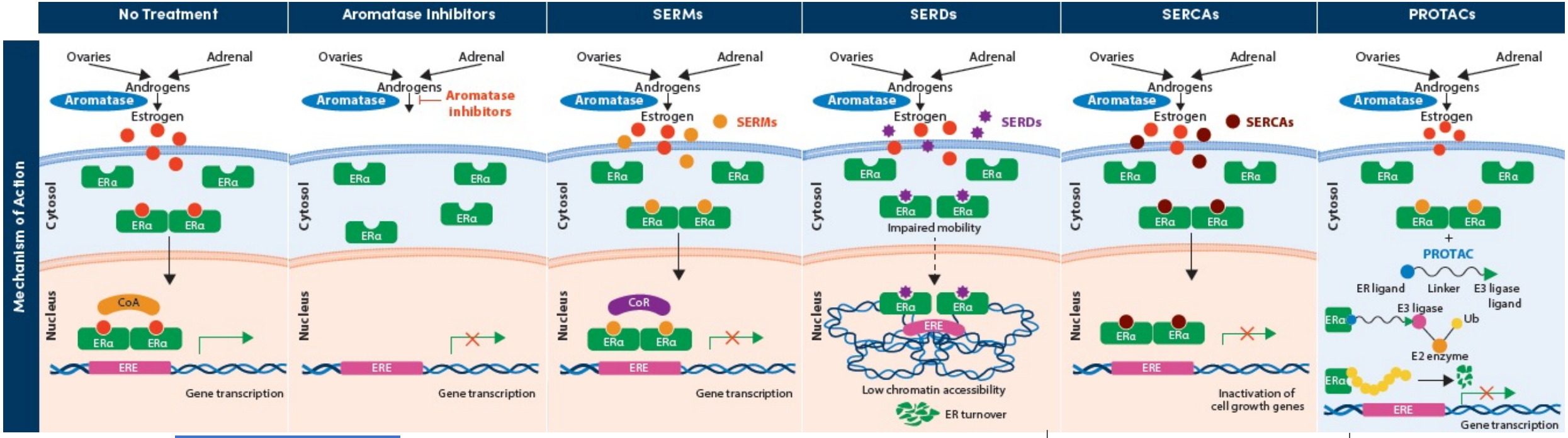
- Discontinuation capi/pla: 9.3 vs 0.6%
- Interruption capi/pla: 34.9 vs 10.3%
- Dose reduction capi/pla: 19.7 vs 1.7%

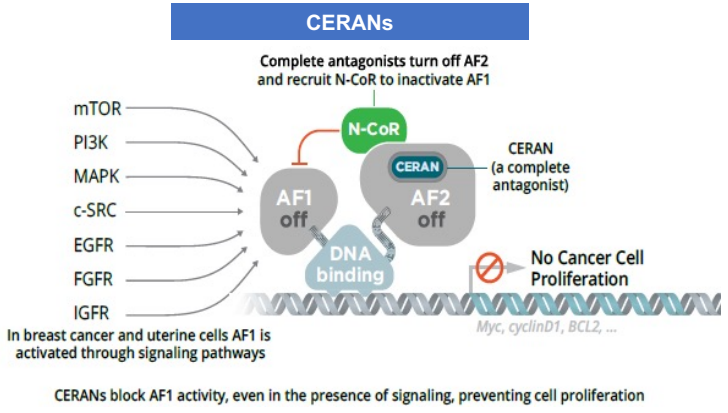
Turner et al, SABCS 2022

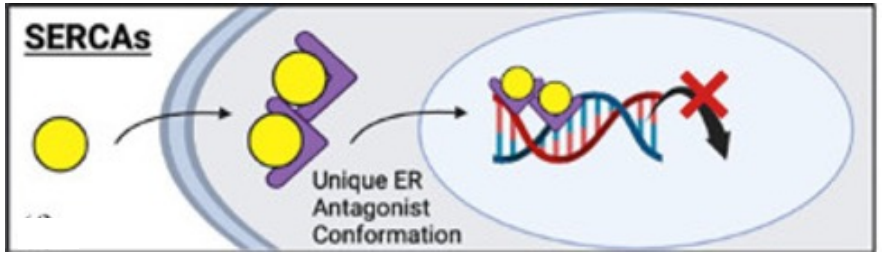
Conclusions and Next Steps

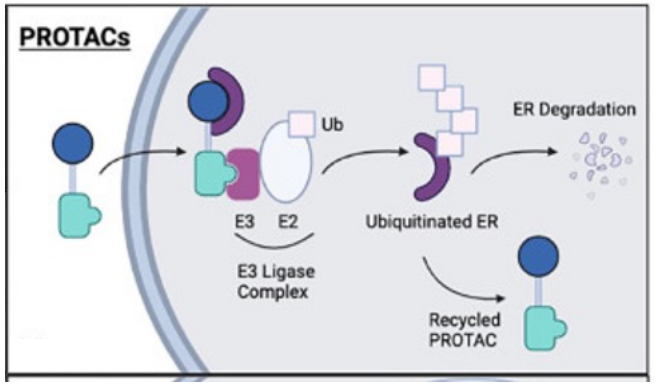
- Capivasertib/fulvestrant vs Pla/fulvestrant improved PFS in the overall population and in patients with tumor PIK3CA altered population; overall survival immature
- Efficacy in the subset of patients with non-altered tumors uncertain
  - Trial was not powered to look at this subgroup; small group with unknown mutation profile hard to take into account
- Benefit seen across subgroups including those with prior CDK4/6i and with visceral metastases
- Safety: GI toxicity, primarily lower grade resulted in modestly more discontinuations, dose holds and dose reductions of capivasertib
  - All/Grade 3 diarrhea 72/9%, rash 38/12%, hyperglycemia 16/2.3%, nausea 35/0.8%
- Data to be considered for regulatory approval
- Additional studies
  - **CAPItello-292** (NCT04862663): Fulvestrant/Palbociclib +/- Capi
  - Additional studies with ipatasertib with similar designs
  - New PIK3CA inhibitors: Inavolisib, LOX783 and more!

Mechanism of Action of New Endocrine Agents Targeting the ER Domain







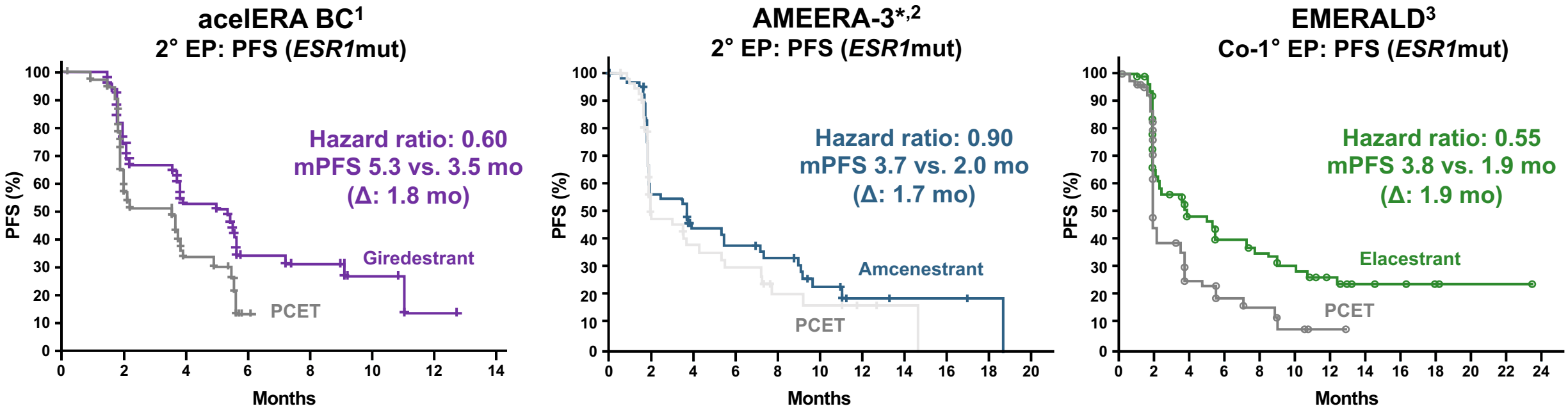


1. Hanker AB et al. *Cancer Cell.* 2020;37:496-513 2. Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25

Oral SERDS: Randomized Trials in the Post-CDK4/6 Inhibitor Setting

	EMERALD (NCT03778931)	AMEERA-3 (NCT04059484)	acelERA (NCT04576455)	SERENA-2 (NCT04214288)	EMBER-3 (NCT04975348)
N	477	282	303	288	830
Patient Population	ER+/HER2- ABC	ER+/HER2- ABC (ET sensitivity required)	ER+/HER2- ABC Measurable disease	ER+/HER2- MBC	ER+/HER2- MBC
Number of Prior Therapies	1-2	0-2	0-2	0-2	1 (AI + CDK4/6i)
Prior Chemotherapy	20% had 1 line	Allowed (≤1) or CDK	Allowed (≤1)	Allowed (≤1)	Not allowed
Prior Fulvestrant	30%	Allowed	Allowed	Not allowed	Not allowed
Prior CDK 4/6i	100%	80%	Allowed	Allowed	Allowed
Treatment Arms	Elacestrant vs ET (AI or Fulvestrant)	Amcenestrant vs ET (AI, Tamoxifen or Fulvestrant)	Giredestrant vs ET (AI or Fulvestrant)	Camizestrant (various doses) vs Fulvestrant	Imlunestrant (N~370) vs ET (AI or Fulv) (N=280) vs Imlunestrant + Abemaciclib (N= 180)
Primary Endpoint	PFS in ITT and *ESR1* mutant	PFS	PFS	PFS	PFS
Results	**Positive** **IIT: 2.79 vs 1.891** **HR 0.7** ***ESR1*m: 3.78 vs 1.87** **HR 0.55**	**Did not meet primary EP**	**Did not meet primary EP**	**Positive (SABCS 2022)** **3.7 vs 7.2 (75mg)** **HR 0.58** **3.7 vs 7.7(150mg)** **HR 0.67**	Not yet reported Modified from Jhaveri

A significant PFS benefit was seen in the *ESR1*-mutated population of EMERALD; a benefit trend was observed in acelERA BC and AMEERA-3



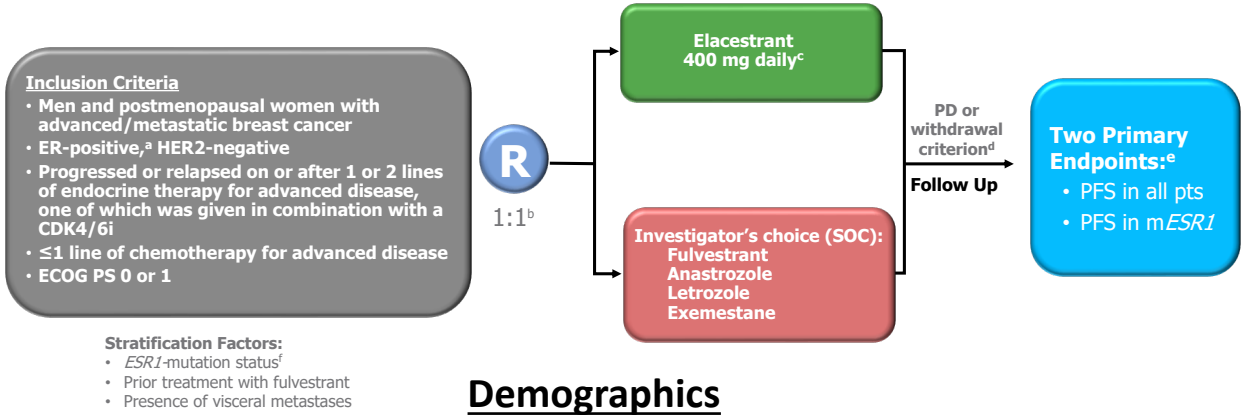
Giredestrant and elacestrant had comparable PFS hazard ratios vs. PCET in *ESR1*-mutated subpopulations; the HR for amcenestrant was notably higher

- It was announced in August 2022 that the amcenestrant clinical development programme will be discontinued.[4]

1° primary; 2°, secondary; BC, breast cancer; EP, endpoint; mo, months; mPFS, median progression-free survival; PCET, physician's choice of endocrine therapy; PFS, progression-free survival; SERD, selective oestrogen receptor degrader.

1. Martin M, *et al*. ESMO 2022 (Abstract 211MO; mini oral presentation); 2. Tolaney SM, *et al*. ESMO 2022 (Abstract 212MO; mini oral presentation); 3. Bidard F-C, *et al. J Clin Oncol* 2022; 4. https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668 (accessed August 2022).

EMERALD Phase 3 Trial: Elacestrant vs SOC ET



Demographics

- ~70% visceral mets
- ~40% 2 lines prior ET for MBC
- ~24% one line of chemotherapy
- 100% prior CDK4/6i

Conclusions

- Hazard ratios are relatively similar in pts who received >6 months prior CDK4/6i or longer
- Pts with endocrine sensitive disease had remarkable PFS with elacestrant alone
- Benefit was more marked in the ESR1 mutant population
- Next steps: combinations with targeted agents (ELEVATE)

Bardia, Bidard …… and **Kaklamani;** SABCS 2022

PFS by Duration of CDK4/6i: All Patients

Duration on CDK4/6i in the metastatic setting

	At least 6 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=202)	SOC (n=205)	Elacestrant (n=150)	SOC (n=160)	Elacestrant (n=98)	SOC (n=119)
Median PFS Months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 6 months (95% CI)	34.40 (26.70 - 42.10)	19.88 (12.99 - 26.76)	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)
PFS rate at 12 months (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months (95% CI)	16.24 (8.75 - 23.74)	3.21 (0.00 - 8.48)	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

PFS by Duration of CDK4/6i: ESR1 mutant

Duration on CDK4/6i in the metastatic setting

	At least 6 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=103)	SOC (n=102)	Elacestrant (n=78)	SOC (n=81)	Elacestrant (n=55)	SOC (n=56)
Median PFS Months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

SERENA-2 Phase 2 Trial: Camizestrant plus Fulvestrant

Primary endpt: Inv assessed PFS of each C arm to F

Post-menopausal ER+/HER2- ABC candidates to receive fulvestrant monotherapy in the ABC setting

Stratification: Prior CDK4/6i Lung/liver mets

R

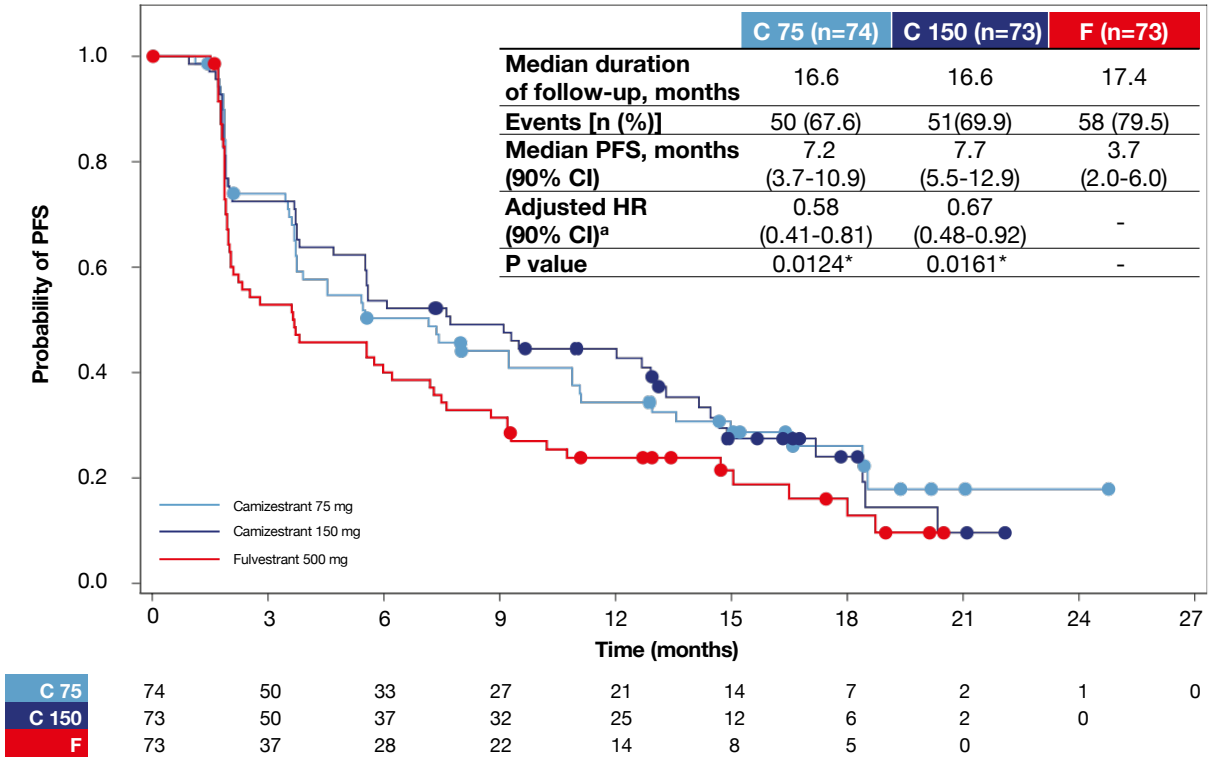
1:1:1:1
N=240

- camizestrant 300 mg (n=20) (CSP v5 amendment: 16Dec20)
- camizestrant 75 mg (n=74)
- camizestrant 150 mg (n=73)
- fulvestrant (n=73)

Demographics

- 90-95% white
- Imbalance in liver (not visceral) mets: 31 v 41 vs 48%
- Imbalance in ESR1m: 30 v 36 v 48%
- 77% one line ET, 63% prior AI; 50% prior CDK4/6i
- Prior chemo for MBC: 22 v 12 v 26%

Primary endpoint: PFS by investigator assessment



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

C 75	74	50	33	27	21	14	7	2	1	0
C 150	73	50	37	32	25	12	6	2	0	
F	73	37	28	22	14	8	5	0		

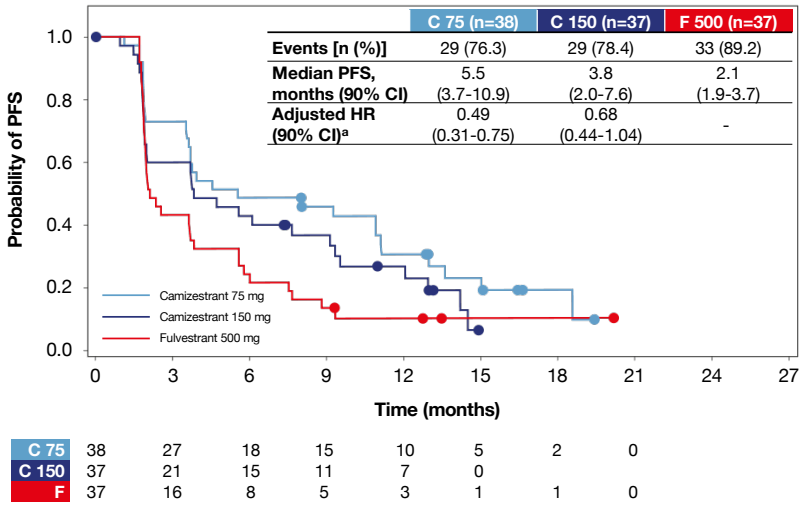
*Statistically significant; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

PFS by BICR: Significant discordance with inv PFS for 150 mg

	C 75 (n=74)	C 150 (n=73)	F (n=73)
Events [n (%)]	39 (52.7)	33 (45.2)	53 (72.6)
Median PFS, months (90% CI)	7.4 (4.5-10.9)	12.7 (9.3-18.4)	3.7 (2.0-3.8)
Adjusted HR (90% CI)[a]	0.56 (0.39-0.80)	0.47 (0.33-0.68)	-
P value	0.0079*	0.0004*	-

Oliveira et al, SABCS 2022

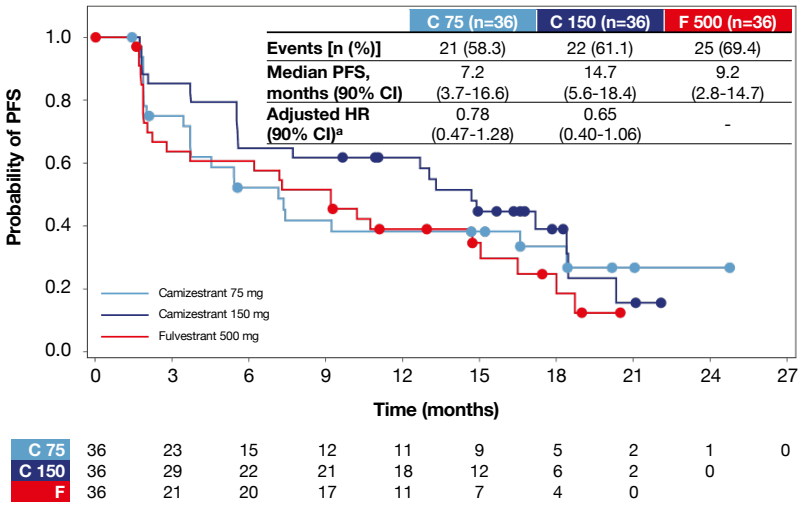
Prior CDK4/6i



	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-

C 75	38	27	18	15	10	5	2	0	
C 150	37	21	15	11	7	0			
F	37	16	8	5	3	1	1	0	

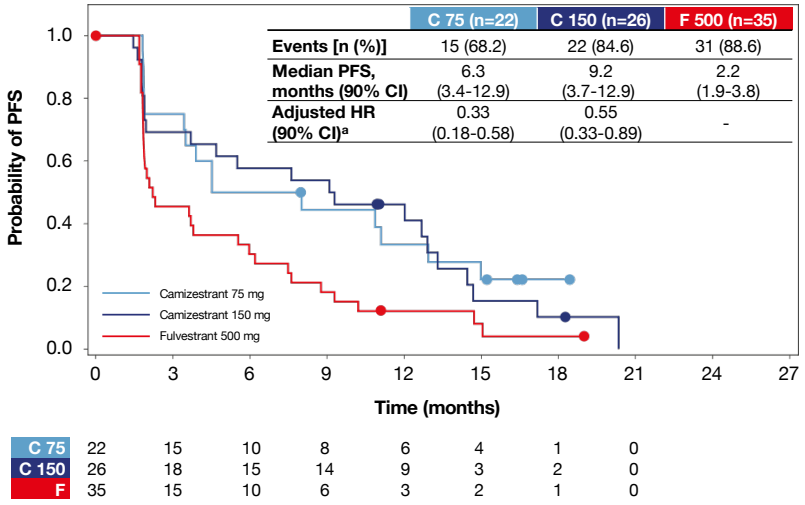
No prior CDK4/6i



	C 75 (n=36)	C 150 (n=36)	F 500 (n=36)
Events [n (%)]	21 (58.3)	22 (61.1)	25 (69.4)
Median PFS, months (90% CI)	7.2 (3.7-16.6)	14.7 (5.6-18.4)	9.2 (2.8-14.7)
Adjusted HR (90% CI)[a]	0.78 (0.47-1.28)	0.65 (0.40-1.06)	-

C 75	36	23	15	12	11	9	5	2	1	0
C 150	36	29	22	21	18	12	6	2	0	
F	36	21	20	17	11	7	4	0		

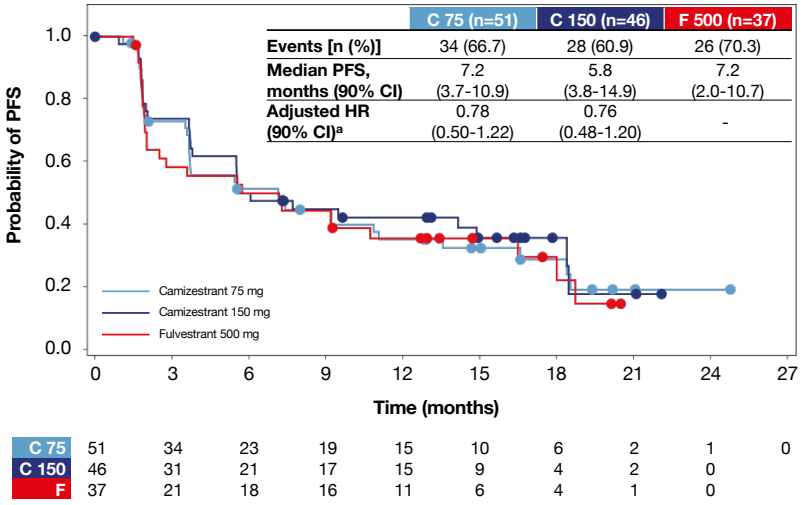
*ESR1*m detectable at baseline



	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

C 75	22	15	10	8	6	4	1	0
C 150	26	18	15	14	9	3	2	0
F	35	15	10	6	3	2	1	0

*ESR1*m not detectable at baseline



	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

Liver and/or lung mets

YES	C 75 (n=43)	C 150 (n=43)	F 500 (n=43)
Events [n (%)]	31 (72.1)	32 (74.4)	39 (90.7)
Median PFS, months (90% CI)	7.2 (3.6-11.1)	5.6 (3.7-9.1)	2.0 (1.9-3.6)
Adjusted HR (90% CI)[a]	0.43	0.55	-

NO	C 75 (n=31)	C 150 (n=30)	F 500 (n=30)
Events [n (%)]	19 (61.3)	19 (63.3)	19 (63.3)
Median PFS, months (90% CI)	5.5 (3.7-15.0)	14.5 (5.6-17.2)	9.2 (3.7-18.7)
Adjusted HR (90% CI)[a]	0.99 (0.57-1.69)	0.91 (0.53-1.56)	-

Biomarkers

- Camizestrant reduced ESR1 ctDNA to near zero by C2D1

Safety

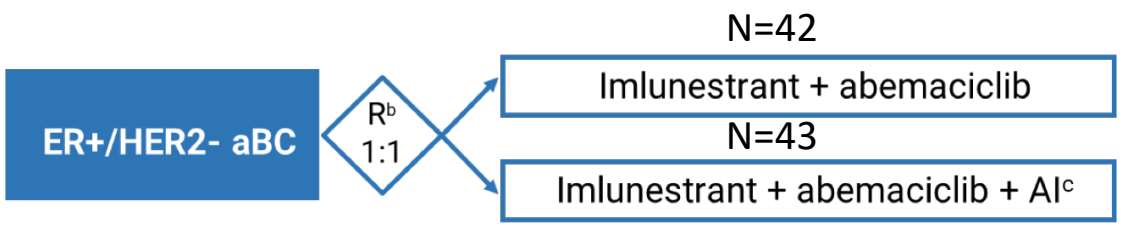
- Very low rate discontinuation
- Interruption TRAEs ~med 7 days: ~10%
- Very low rate of grade 3 AEs
- All grade AEs (low-high dose):
  - Photopsia: 12-25%
  - Sinus bradycardia: 5-26%
  - More fatigue, arthralgia, AST/ALT elevation at higher dose

Conclusion

- Met its primary endpoint
- No comment about dosing or imbalance in specific factors
  - Ph 3 trials ongoing
  - Dose: 75 mg

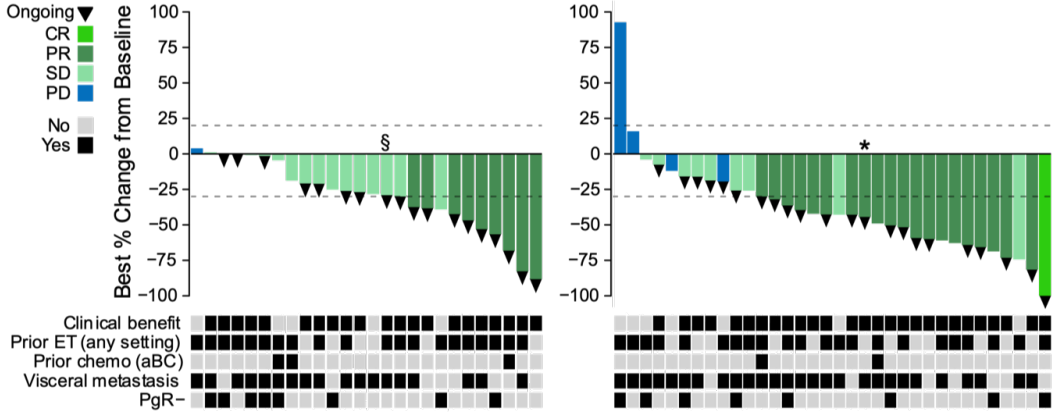
Oliveira et al, SABCS 2022

Imlunestrant: Phase Ia/b Trial



≤1 prior therapy for MBC, no prior CDK4/6i
ET sensitive disease (≥24 weeks on ET)

	Imlunestrant + abemaciclib N=42	Imlunestrant + abemaciclib + AI N=43	Total N=85
ORR, n/N (%)	9/28 (32)	20/34 (59)	29/62 (47)
Median TTR, months (min-max)	3.7 (1.6-10.9)	3.7 (1.7-7.1)	3.7 (1.6-10.9)
CBR, n/N (%)	30/42 (71)	34/43 (79)	64/85 (75)
12-month PFS, %	80	80	80



Demographics

- ESR1m: 7 v 10%
- Visceral mets: 50 v 65%
- De novo: 19 v 33%
- Measurable dse: 67 v 79%
- 70% Rxd in first line; 10% prior chemo
- Recurrence <12 mo adj Rx: 67 v 44%

RP2D Imlunestrant combined with abemaciclib

- 150 mg BID

Safety (all/gr3, averaged)

- Diarrhea: 92/10%
- Nausea: 59/0%
- Neutropenia: 41/14%

D/C for TRAE: 1%

Dose reduction for AE:

- Both: 6%
- Abema: 29%

- PFS: small number of events; 80% prog free at 12 mos
- ctDNA: ORR/PFS assoc with decline
- No PK drug interaction with abemaciclib
- Phase III trials ongoing in metastatic and adjuvant settings

Jhaveri et al, SABCS 2022

Additional Phase III SERD Trials for MBC: Examples

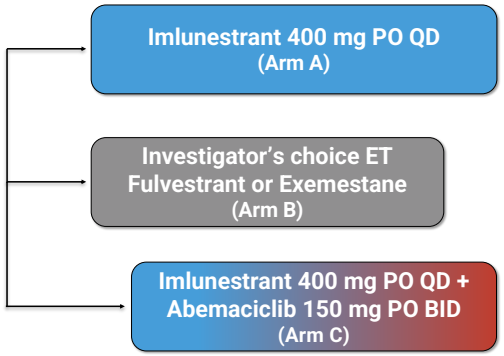
EMBER-3

1:1:1 Randomization
N = ~860

ER+, HER2-, Advanced Breast Cancer

- Relapsed on (neo) adjuvant/within 1 year of adjuvant AI, alone or in combination with a CDK4/6 inhibitor
  OR
- Progressed on 1L AI, alone or in combination with a CDK4/6 inhibitor
- Prior CDK4/6i treatment is expected if approved and reimbursed

Stratified for:
- Prior CDK4 & 6 inhibitor therapy
- Presence of visceral metastases
- Region

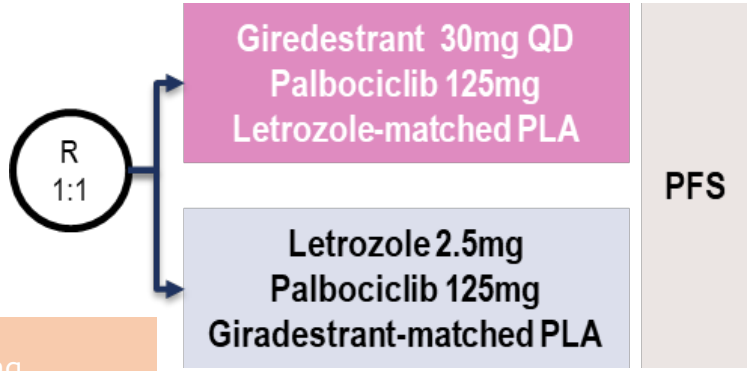


Primary Objective:
- Investigator-assessed PFS for A vs B
- Investigator-assessed PFS for A vs B in the *ESR1*-mutation detected population
- Investigator-assessed PFS for C vs A (gated, i.e. only tested if A vs B is stat sig)

Secondary Objectives:
- OS (gated), PFS by BICR, ORR, CBR, DoR, PRO's

persevERA

N=978
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

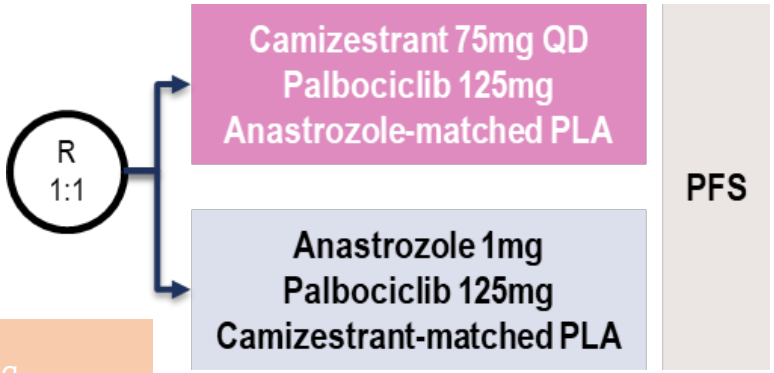


Recruiting

NCT04546009

SERENA-4

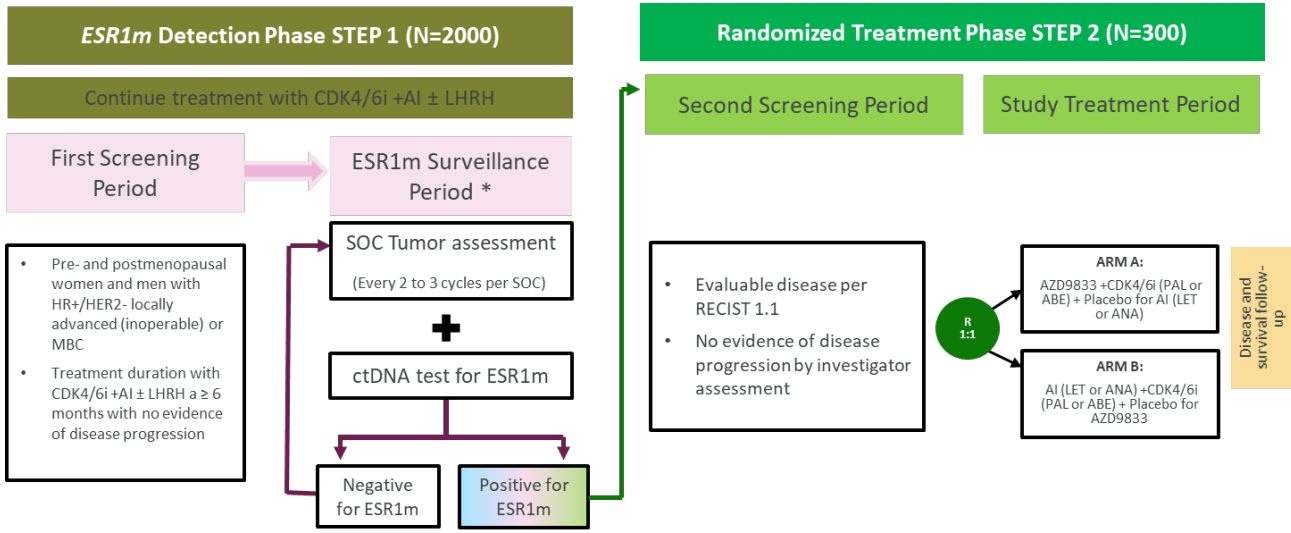
N=1342
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



Recruiting

NCT04711252

SERENA-6



ARV-471 (PROTAC ER Degrader): VERITAC Phase II Expansion Trial

- ARV-471 directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER then proteasomal degradation
- ≥1 ET for MBC, a CDK4/6i
  - 35 pts at 200mg/d; 36 pts at 500 mg/d
  - 58% ESR1 mutations; 79% prior fulvestrant, 45% liver mets

- Primary toxicities: fatigue, nausea, but ≤grade 2
- PFS

	All Patients	
	200 mg QD (n=35)	Total (N=71)
Events, n (%)	24 (68.6)	41 (57.7)
mPFS, mo (95% CI)	3.5 (1.8–7.8)	3.7 (1.9–8.3)

	Mutant *ESR1*	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)
Patients with mutant *ESR1*	(n=19)	(n=22)	(n=41)
CBR, % (95% CI)	47.4 (24.4–71.1)	54.5 (32.2–75.6)	51.2 (35.1–67.1)

Median ER degradation was 69% (range: 28%–95%)

Phase 3 VERITAC-2 Trial
- Fulvestrant vs ARV471 200 mg/d

Hurvitz, **Schott** et al, SABCS 2022

Newer ER Targeted Agents

- Other agents
  - **SERCA**: serum ER covalent antagonist, H3B-6546 (n=94)
    - ORR 16%, CVR 40%, mPFS 3.8 mo but 7.3 mo with ESR1Y537S in phase I
    - Phase 1 trial of H3B6545 with Palbociclib is ongoing (NCT04288089)
  - **CERAN**: complete ER antagonist, OP-1250 (n=40)
    - ORR 18%, CBR 38%
    - Phase I trial OP-1250 + Palbociclib (NCT05266105)

Hamilton et al, SABCS 2021; Patel MR et al. SABCS 2021; Burke et al, Front Cell Dev Biol; 2022

And more……

- More oral SERDS in development
- SARM: selective androgen receptor modulator
  - Enobosarm: ORR 48%, CBR 80%, and median PFS 5.5 months in AR+++ (n=24); Phase III ARTEST trial in 3rd line metastatic setting
  - Fast track designation by FDA
- SERM: Lasofoxifene
  - Elaine 2: n=29 with abemaciclib: CBR 69% at 24 wks (ORR 50%), PFS 13 months
    - DVT 6.9% (n=2), one with risks (knee surgery etc)
  - Elaine 1: Phase II in ESR1 mut v fulvestrant

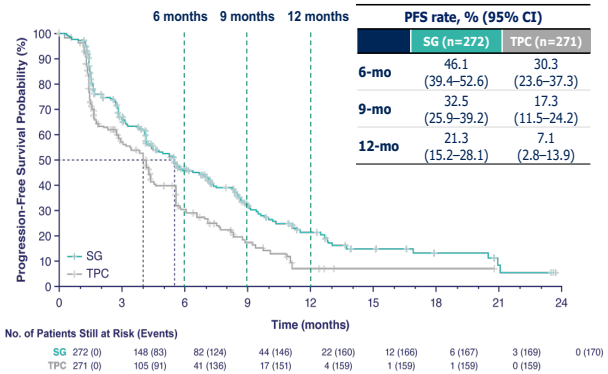
Palmieri ASCO 2021; Barroso-Sousa et al, SABCS 2021; Jhaveri et al, SABCS 2021; Damodaran et al, ASCO 2022

ADCs in HR+ MBC (not including HER2 low)

Phase III TROPiCS: Sacituzumab govitecan in HR+/HER2neg MBC

PFS[1]

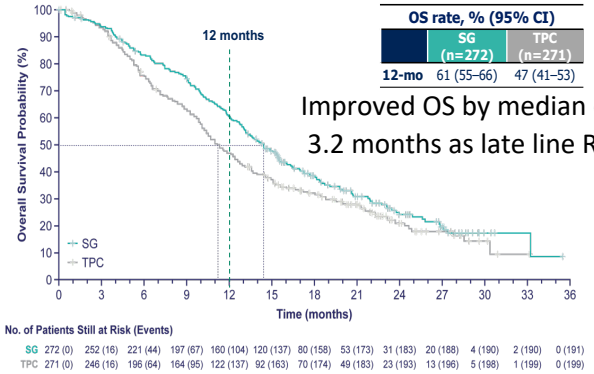
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

OS[2]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	



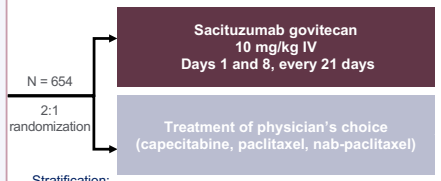
OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

Improved OS by median of 3.2 months as late line Rx

No Impact of TROP2 expression on efficacy

Key eligibility criteria:
- HR+/HER2* negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced mBC
- Progressed after 1 or more ET for mBC, or relapsed within 12 months of completing adjuvant ET or while receiving adjuvant ET
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Prior CDK 4/6i not required (no prior CDK 4/6i capped at 30%)

Ascent-07



Stratification:
- Duration of prior CDK 4/6i in metastatic setting (none/≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/EU vs. ROW)

Primary Endpoint
- PFS by BICR

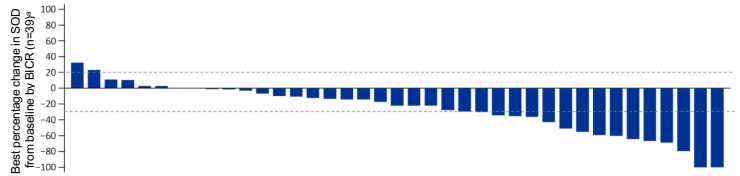
Key Secondary Endpoints
- OS
- ORR by BICR
- TTDD to Physical functioning

Secondary Endpoints
- PFS by investigator
- ORR by investigator
- DOR
- Safety

Rugo et al, JCO 2022, ESMO 2022, SABCS 2022

Phase 1 TROPION-PanTumor01: Datopotomab deruxtecan in HR+/HER2neg MBC

- N=40
- Median 2 prior chemo for MBC (1-6)
- Efficacy: ORR (all PR): 27%; CBR: 44%; med PFS 8.3 mo.
- Safety: stomatitis (Gr 3 10%); ILD Gr 2 and 3 (2 pts)



TROPION-Breast01

Key Eligibility Criteria
- HR-positive, HER2-negative inoperable/ metastatic breast cancer with disease progression following 1 or 2 lines of chemotherapy (& progressed on, or not suitable for, endocrine therapy)
- Targeted agents (i.e., inhibitors of mTOR, PD-1/PD-L1, CDK4/6, PARP) and endocrine therapies do not count as prior lines of chemotherapy
- At least 1 measurable lesion
- FFPE tumor sample
- Adequate organ function

Stratification factors:
- 1 vs. 2 previous lines of chemotherapy in the inoperable/metastatic setting
- Geographic location (US/Canada/EU vs rest of world)
- Previous CDK 4/6 inhibitor use

1:1

Dato-DXd
6mg/kg IV Q3W
N=350

Investigator's Choice of Chemotherapy
(Eribulin, Vinorelbine, Capecitabine or Gemcitabine)
N=350

Dual primary endpoints
PFS (BICR), OS

Secondary endpoints
PFS (inv), ORR, DoR, DCR, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints
TROP2 IHC

Statistical Considerations:
To strongly control the familywise type I error rate at the 5.0% level (2-sided), an alpha level of 1.0% will be allocated to the PFS dual primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses

Response assessment: Scan Q6W for 48 weeks, then Q9W until RECIST1.1 disease progression (as assessed by Investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional follow-up scan should be performed as per Imaging schedule.

Targeting HER3: Patritumab deruxtecan; ORR 30%
Krop et al, ASCO 2022

Meric-Bernstam et al, SABCS 2022

Summary and Conclusions

- Exciting new data with novel approaches to the treatment of HR+ MBC
- Capivasertib
  - Improved PFS added to fulvestrant with better safety profile than existing PIK3CA inhibitors
  - Benefit in pathway non-altered population still unclear
  - Next step in combination with CDK4/6i, early stage?
- Oral SERDs
  - We are finally making progress!
  - Benefit clearer in ESR1m population
  - Multiple phase III trials in metastatic and early stage disease ongoing
- ADCs
  - Very encouraging efficacy in HR+/HER2 negative (and HER2 low disease)
  - Sequencing is the most important next question along with efficacy in earlier lines