19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
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Capivasertib: una nueva opción para el cáncer de mama luminal metastásico

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Disclosure Information

- Consultative and advisory services for **Seagen, AstraZeneca, Daiichi Sankyo**, **Novartis, Gilead, Menarini, Jazz Pharmaceuticals**
- Consultancy/speaker fees from **Celgene**, **Eli Lilly**, **EISAI**, **MSD, Exact Sciences, Tecnofarma, Nolver (Adium), Asofarma, Roche**
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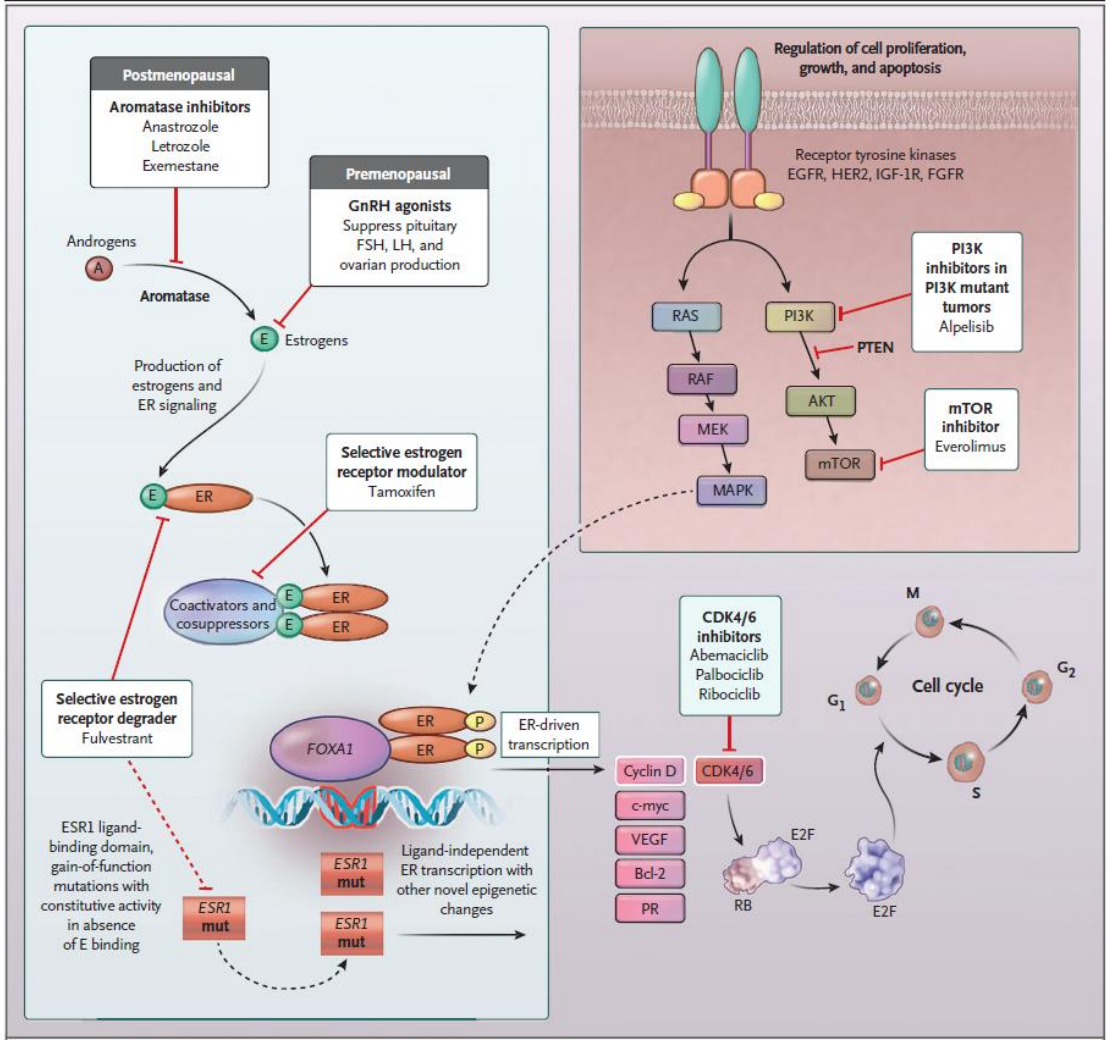


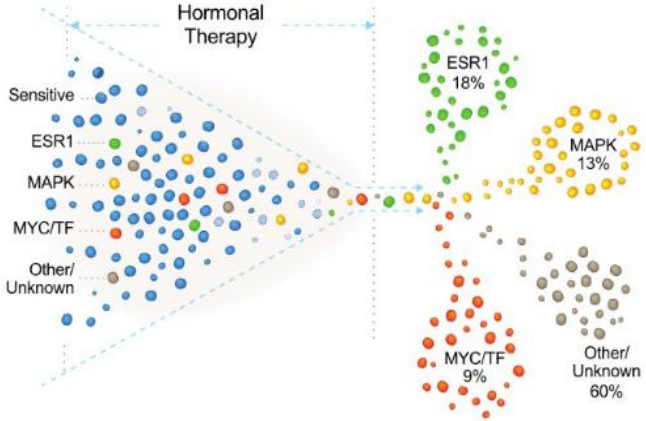
Burstein H. NEJM 2021

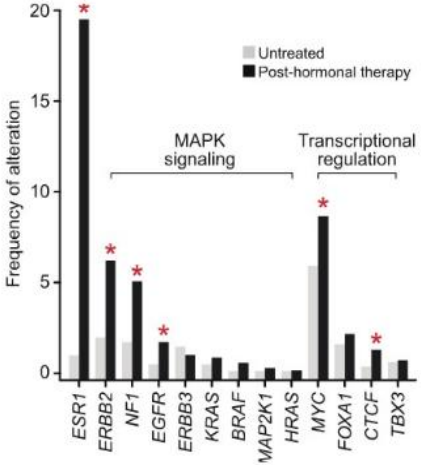
Randomized Phase III trials of CDK4/6-i in the 1st Line setting

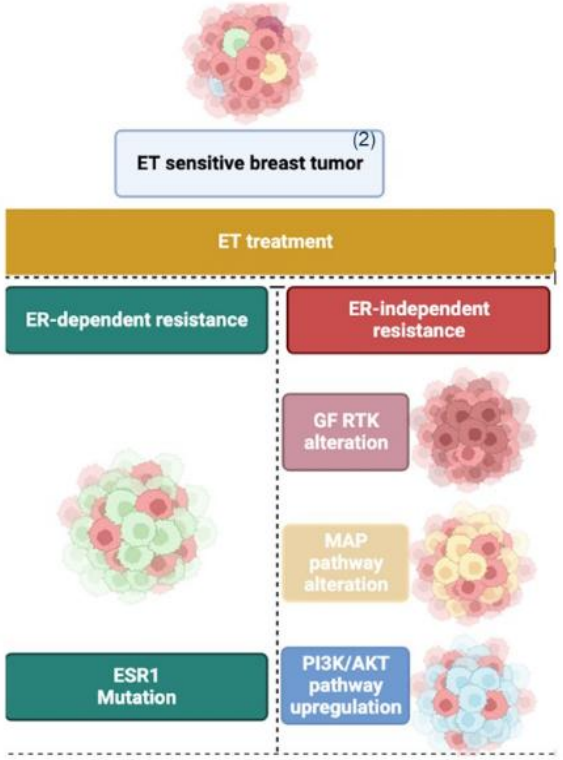
	PALOMA2	MONALEESA2	MONALEESA7	MONARCH3
Regimen	Letrozol +/- **Palbociclib** (2:1)	Letrozol +/- **Ribociclib** (1:1)	Goserelin + ET +/- **ribociclib** (1:1)	AI +/- **abemaciclib** (2:1)
Eligibility	Postmenopausal, untreated HR+/HER2- aBC	Postmenopausal, untreated HR+/HER2- aBC	Premenopausal, untreated HR+/HER2- aBC	Postmenopausal, untreated HR+/HER2- aBC
Sample size	666	668	572	493
De novo MBC	38%	34%	41%	20%
mPFS	27.6 vs 14.5 months (HR 0.56; 0.46-0.69)	25.3 vs 16 months (HR 0.57; 0.45-0.60)	23.8 vs 13 months (HR 0.55; 0.44-0.69)	29 vs 14.8 months (HR 0.53; 0.42-0.66)
mOS	**53.9 vs 51.2 months Δ 2.7** (HR 0.96; 0.77-1.17)	**53.9 vs 51.4 months Δ 12.4** (HR 0.76; 0.63-0.93)	**58.7 vs 48 months Δ 10.7** (HR 0.76; 0.69-0.95)	**53.7 vs 66.8 months Δ 13.1** (HR 0.76; 0.64-1.01)

Adapted from Chávez Mac Gregor SABCS 23

Endocrine Therapy Resistance







Ravazi P. Cancer Cell 2018

PFS with standard ET in CDK4/6i pre-treated patients

To interpret cautiously (different previous ET lines, ESR1m and CDK exposure)

Bidard F. JCO 2022; Turner N. ESMO Breast 2023; Llombart A, ASCO 2023; Olivera M SABCS 2022

Strategies in second line

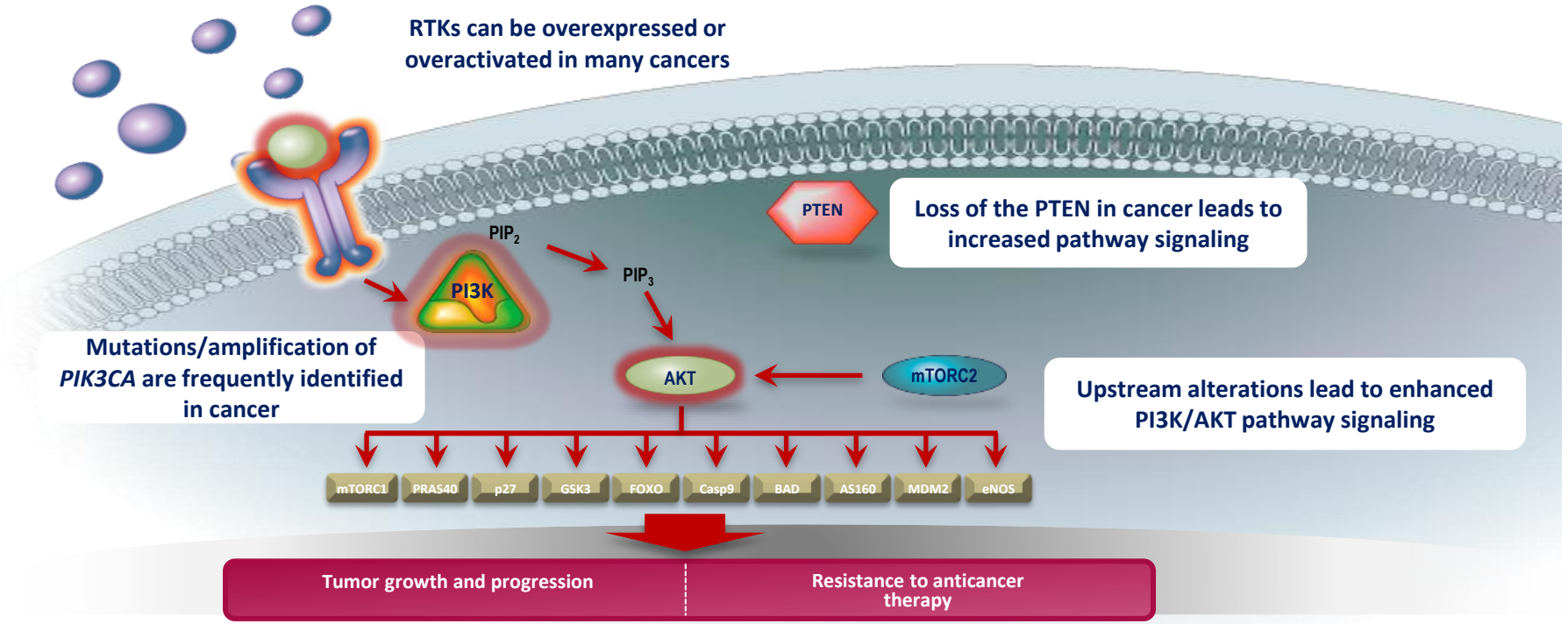
No actionable genomic alteration: endocrine therapy plus…

- **iCDK4/6 inhibition switch**
- **mTOR inhibition**

Actionable genomic mutation:

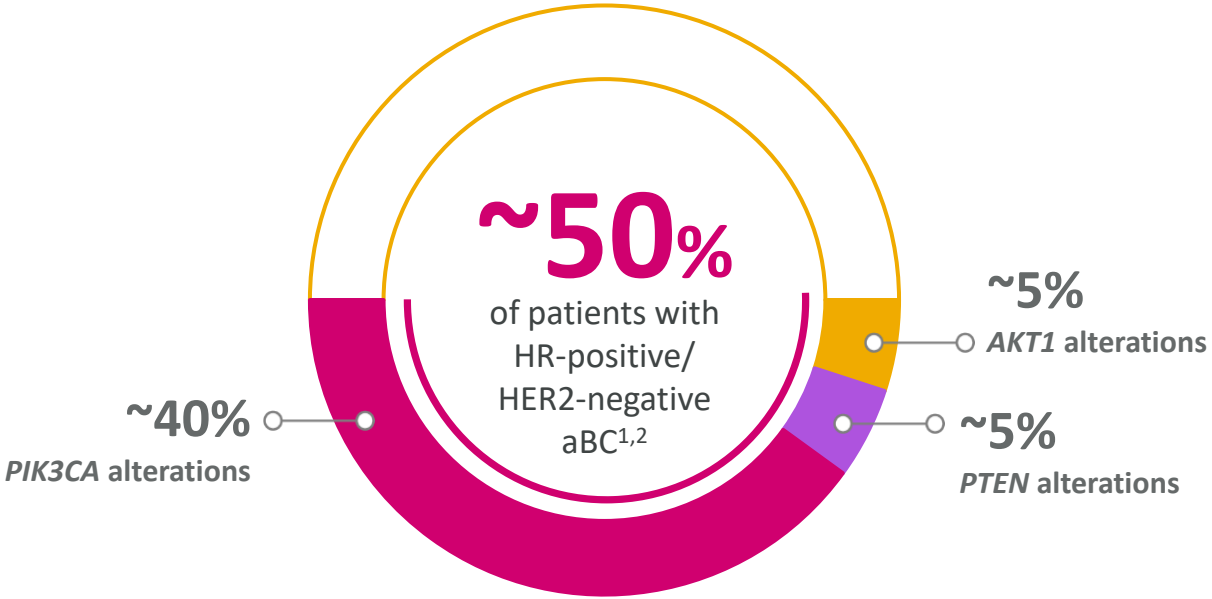
- **Ongoing trial with oral SERD.**
- **Endocrine therapy plus…**
  - pi3K-kinase or AKT inhibition
  - HER2 inhibition

PI3K/AKT/mTOR pathway is frequently disrupted in cancer



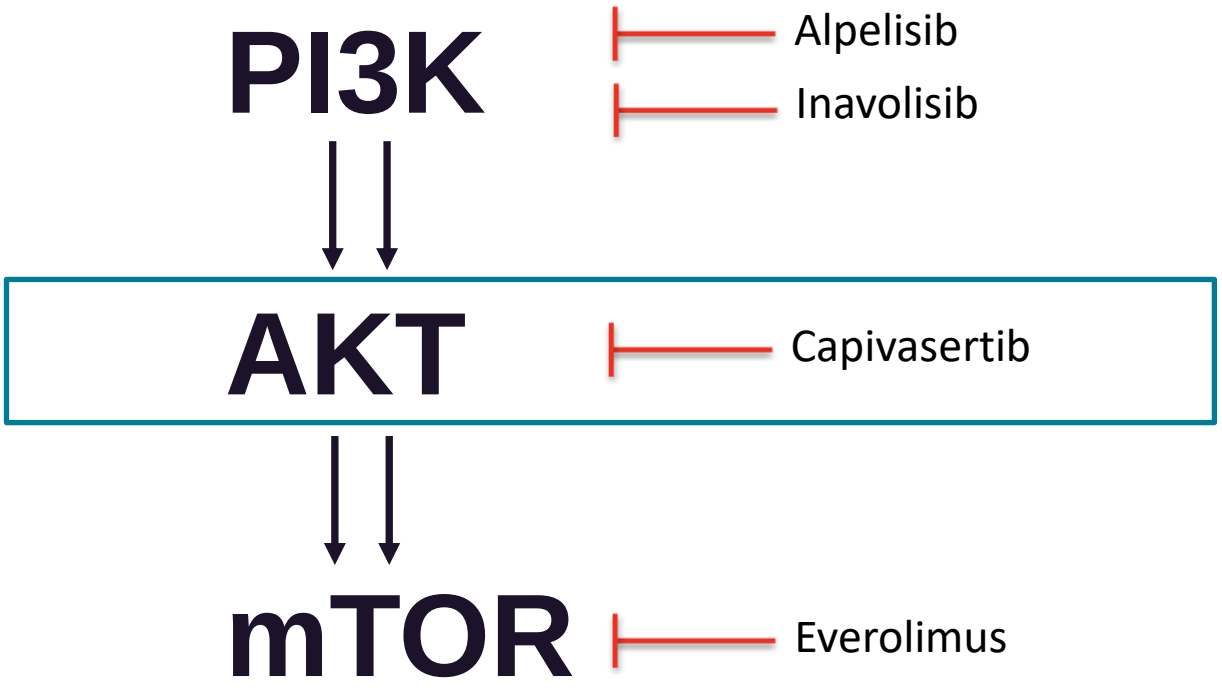
Samuels Y. 2010; Zoncu R. 2011

Genomic alterations within the PI3K/AKT pathway are present in 50% of patients with HR+/HER2- aBC



Cancer Genome Atlas Network. Nature. 2012; Martorana F. Front Pharmacol. 2021;1Miricescu D. Int J Mol Sci. 2020;Smyth LM. Cancer Discov. 2020

Targeting pi3K pathway

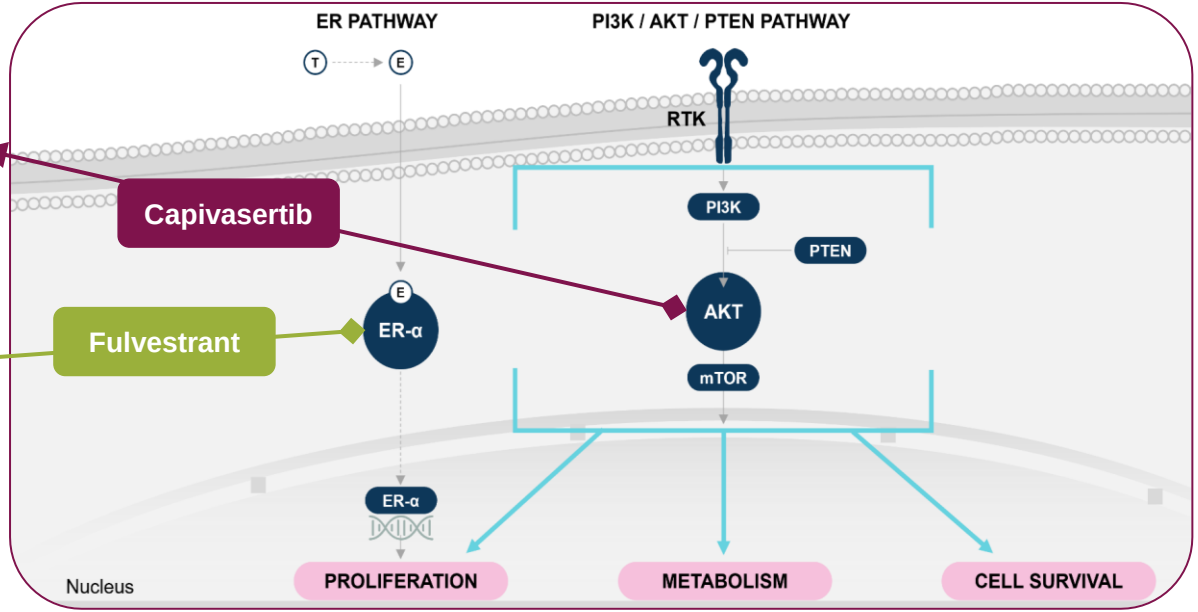


Capivasertib Mechanism of Action

Capivasertib (AZD5363) is an **ATP-competitive inhibitor** of **all three AKT isoforms (AKT1/2/3)**[1,2]

Fulvestrant is an ER degrader that can function synergistically with capivasertib to inhibit tumour growth and prevent treatment resistance[3,4]

Dual Approach with ER Downregulation and AKT Inhibition[3]



1. Turner N. NEJM 2023; 2. Martorana F. Front Pharmaco. 2021; 3. Alves C. Int J Mol Sci. 2023; 4. Ribas R et al. Mol Cancer Ther. 2015

CAPItello-291

Patients with HR+/HER2– ABC

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

R1:1 (N=708)

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

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

Dual primary endpoints

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

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

PIK3CA/AKT1/PTEN alteration status was determined centrally using NGS of tumour tissue with the **FoundationOne®CDx assay**

Turner N. SABCS 2022

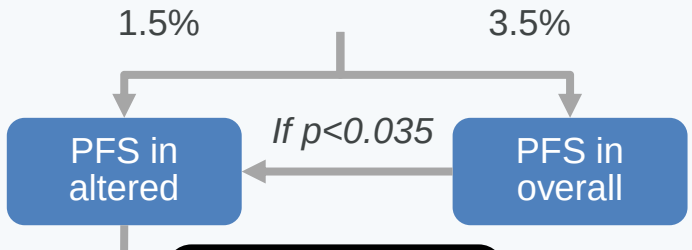
CAPItello-291: Statistical design

Multiple testing procedure

5% (2-sided)

Dual primary endpoints

PFS primary analysis (15 August 2022)



Two further formal OS analyses

Primary analysis for PFS by investigator assessment

With 542 PFS events in the overall population and 217 PFS events in the AKT pathway-altered population, the study had:

- >99% power to detect a difference in the overall population
- 91% power to detect a difference in the AKT pathway altered population

This assumed PFS HR=0.64 and 3.5% alpha is recycled to the AKT pathway altered population

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)
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)

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Prior treatments

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)

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AKT alteration

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)

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)

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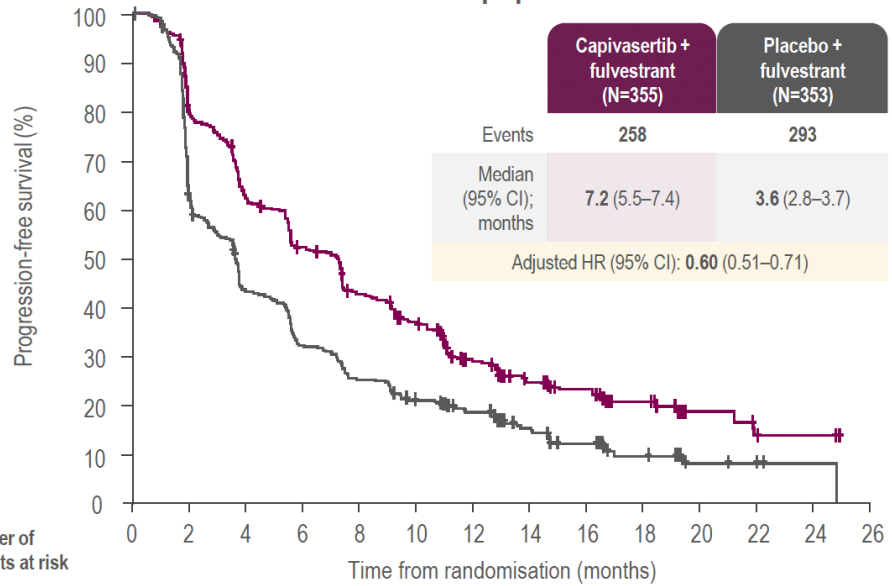
Dual-primary endpoint: PFS in the overall and AKT pathway population

Overall population

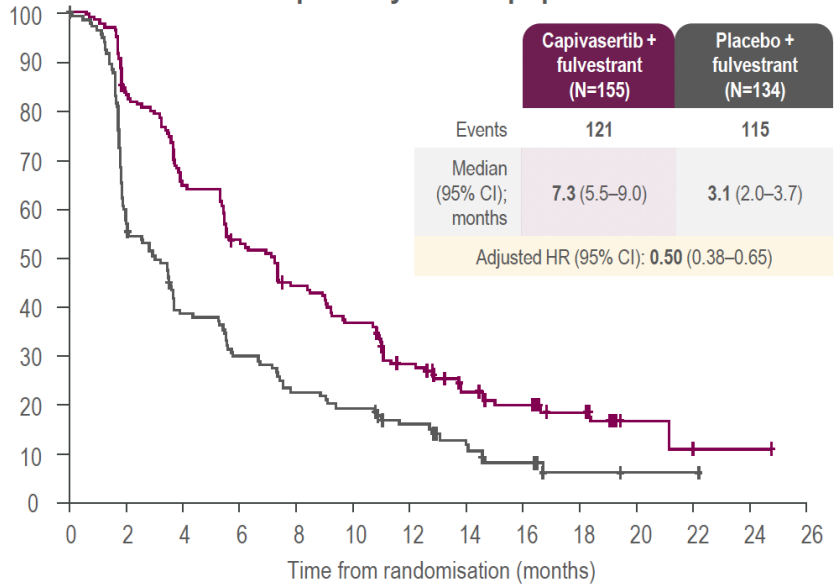


	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Events	258	293
Median (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI): **0.60** (0.51–0.71)		

Number of patients at risk

Capivasertib + fulvestrant	355	226	207	172	138	115	78	55	43	25	8	5	2	0
Placebo + fulvestrant	353	207	142	106	83	66	51	33	23	11	4	3	1	0

AKT pathway-altered population



	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Events	121	115
Median (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)		

Capivasertib + fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo + fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

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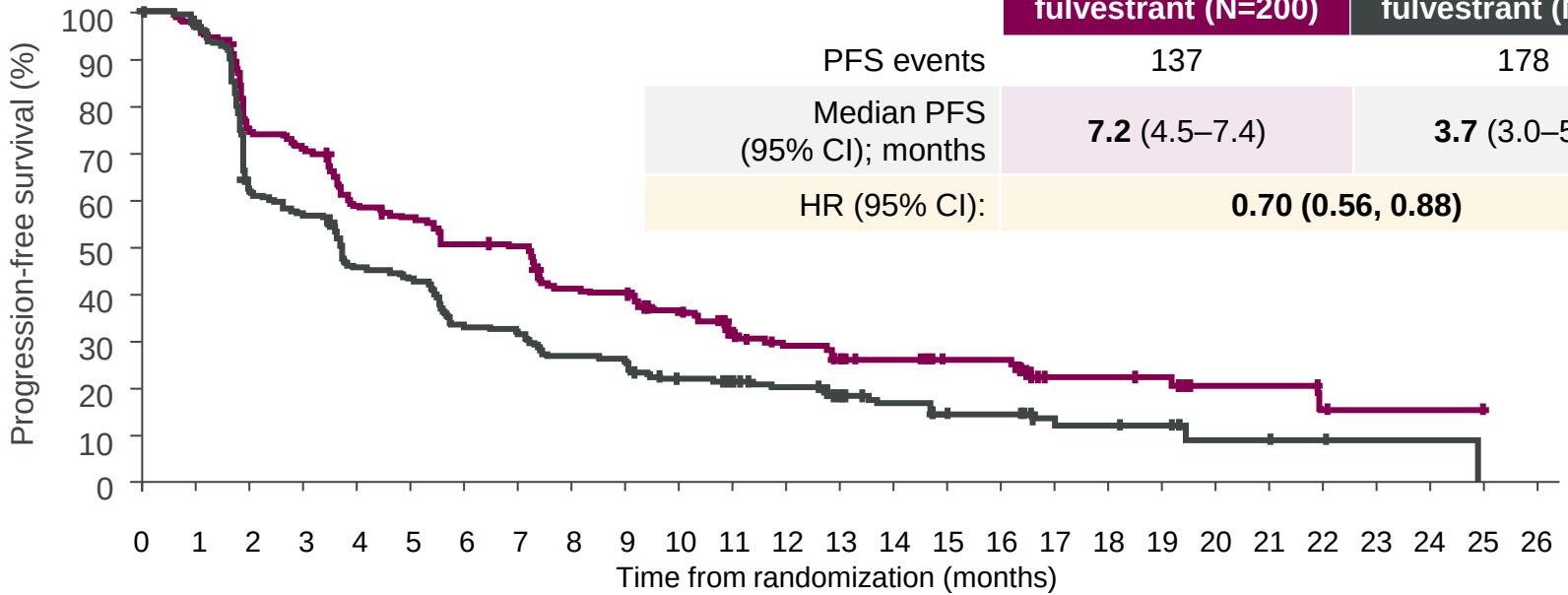
Exploratory analysis: Investigator-assessed PFS in the non-altered population

	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)**	



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

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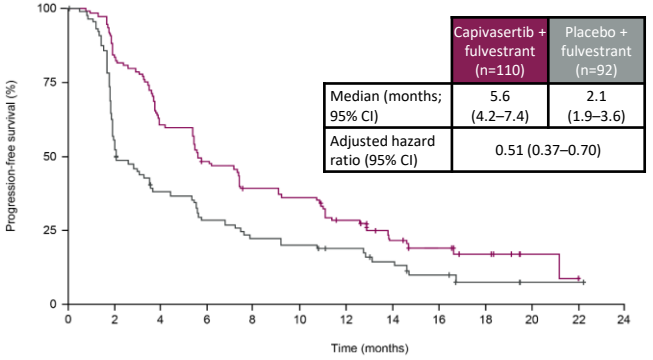
PFS according qualifying PIK3CA, AKT1, or PTEN alteration

PFS in Patients With *PIK3CA*-Altered Tumours Only

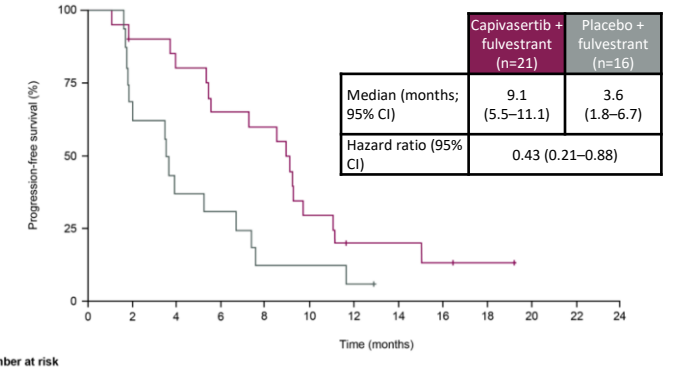


	Capivasertib + fulvestrant (n=110)	Placebo + fulvestrant (n=92)
Median (months; 95% CI)	5.6 (4.2–7.4)	2.1 (1.9–3.6)
Adjusted hazard ratio (95% CI)	0.51 (0.37–0.70)	

Number at risk

Capivasertib + fulvestrant	110	90	65	51	40	37	27	17	13	7	2	1	0
Placebo + fulvestrant	92	48	31	23	18	16	13	9	5	2	1	1	0

PFS in Patients With *PTEN*-Altered Tumours Only

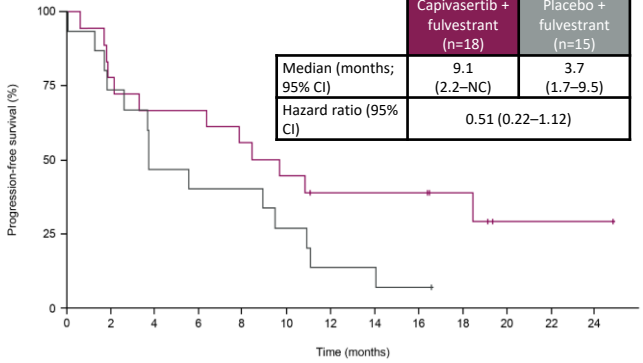


	Capivasertib + fulvestrant (n=21)	Placebo + fulvestrant (n=16)
Median (months; 95% CI)	9.1 (5.5–11.1)	3.6 (1.8–6.7)
Hazard ratio (95% CI)	0.43 (0.21–0.88)	

Number at risk

Capivasertib + fulvestrant	21	18	17	13	12	6	3	3	2	1	0	0	0
Placebo + fulvestrant	16	11	6	5	2	2	1	0	0	0	0	0	0

PFS in Patients With *AKT1*-Altered Tumours Only



	Capivasertib + fulvestrant (n=18)	Placebo + fulvestrant (n=15)
Median (months; 95% CI)	9.1 (2.2–NC)	3.7 (1.7–9.5)
Hazard ratio (95% CI)	0.51 (0.22–1.12)	

Number at risk

Capivasertib + fulvestrant	18	14	12	12	10	8	6	6	6	4	1	1	1
Placebo + fulvestrant	15	11	7	6	6	4	2	2	1	0	0	0	0

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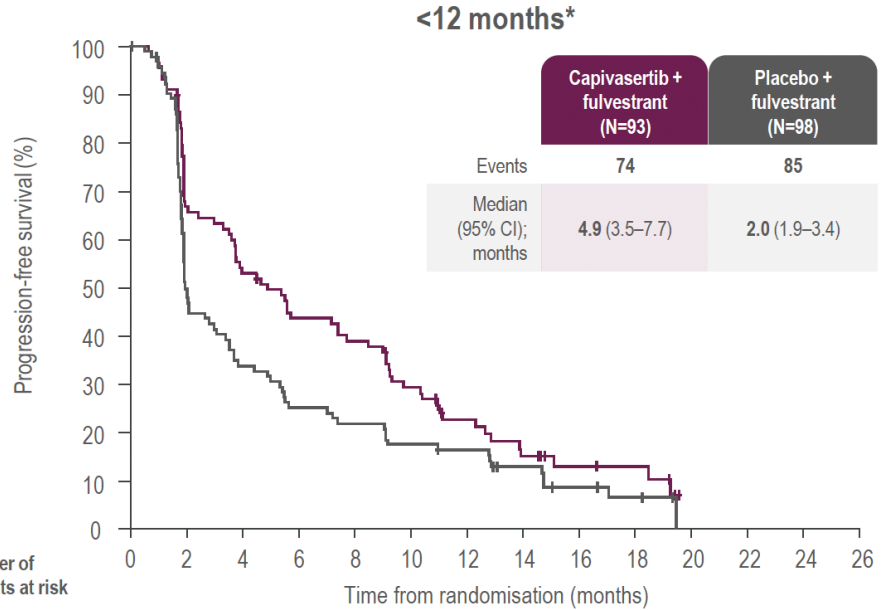
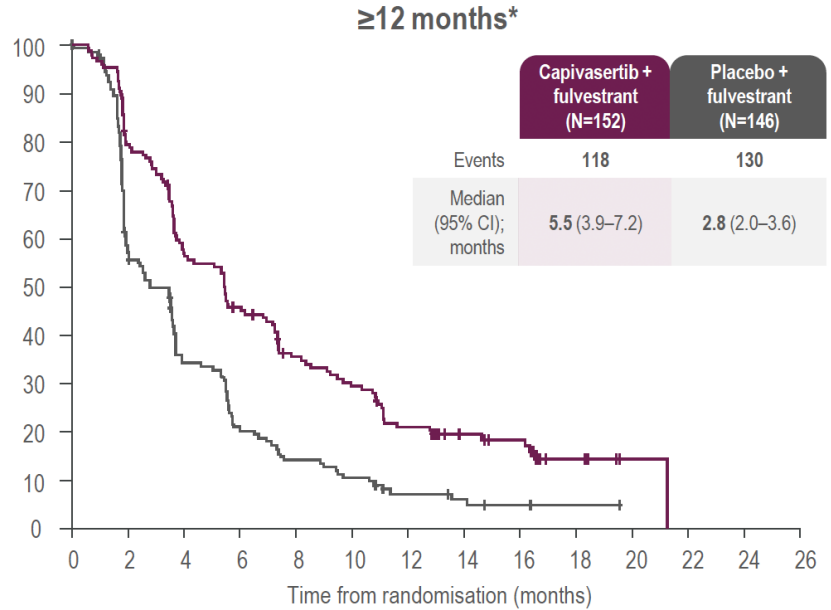
PFS by duration of prior CDK4/6 inhibitor (overall population; post-hoc exploratory analyses)





Number of patients at risk

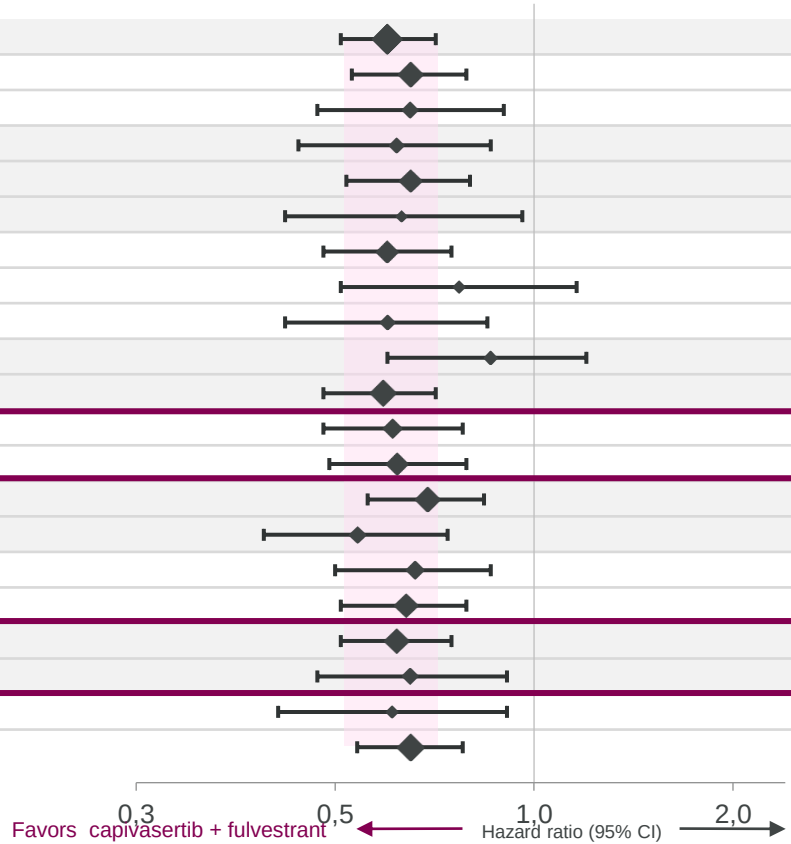
Capivasertib + fulvestrant	93	58	46	37	33	24	15	10	6	5	0	0	0	0
Placebo + fulvestrant	98	46	31	23	20	16	14	9	5	3	0	0	0	0

Capivasertib + fulvestrant	152	114	82	64	47	39	27	18	15	5	1	0	0	0
Placebo + fulvestrant	146	82	46	28	19	14	7	5	3	1	0	0	0	0

Oliveira M. ESMO B 2024

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)



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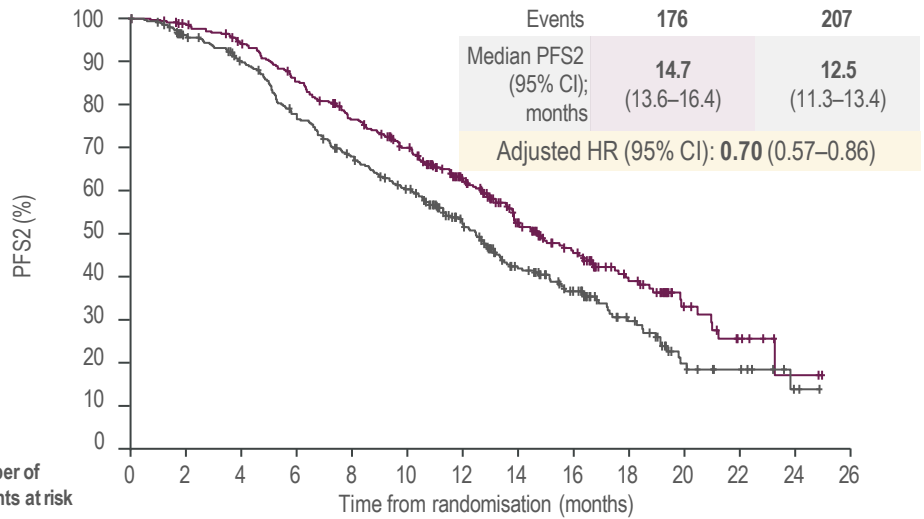
Progression-free survival 2 (PFS2)

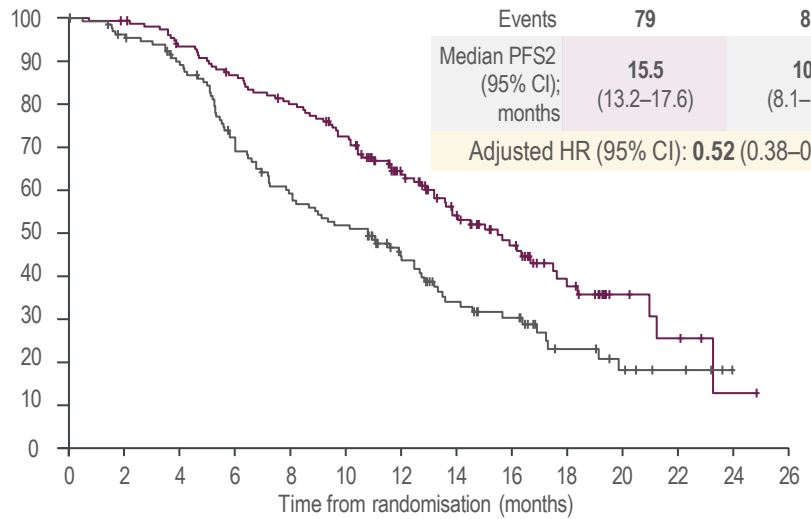
Extended treatment benefit with capivasertib-fulvestrant observed in the overall and the *PIK3CA*/*AKT1*/*PTEN*-altered populations



	Capivasertib-fulvestrant (N=355)	Placebo-fulvestrant (N=353)
Events	176	207
Median PFS2 (95% CI); months	14.7 (13.6–16.4)	12.5 (11.3–13.4)
Adjusted HR (95% CI): **0.70** (0.57–0.86)		

Number of patients at risk														
Capivasertib-fulvestrant	355	334	315	283	248	218	164	108	78	48	20	11	2	0
Placebo-fulvestrant	353	321	294	252	216	185	137	88	63	33	14	9	2	0

***PIK3CA*/*AKT1*/*PTEN*-altered population**



	Capivasertib-fulvestrant (N=155)	Placebo-fulvestrant (N=134)
Events	79	87
Median PFS2 (95% CI); months	15.5 (13.2–17.6)	10.8 (8.1–12.7)
Adjusted HR (95% CI): **0.52** (0.38–0.71)		

Capivasertib-fulvestrant	155	151	140	129	118	105	76	53	38	22	8	5	1	0
Placebo-fulvestrant	134	124	113	89	72	63	45	29	22	11	7	4	0	0

PFS2 defined as the time from randomisation to second progression (i.e. the earliest of either death or a progression event following treatment start after first progression).

Rugo H. ESMO B 2024

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)

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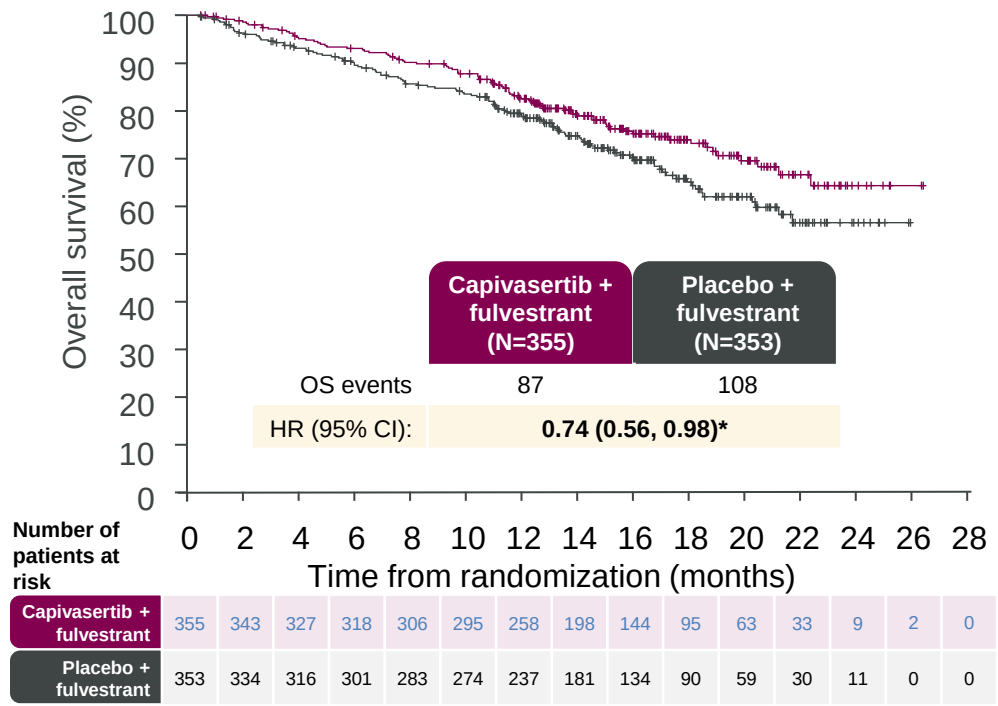
Overall survival at 28% maturity overall

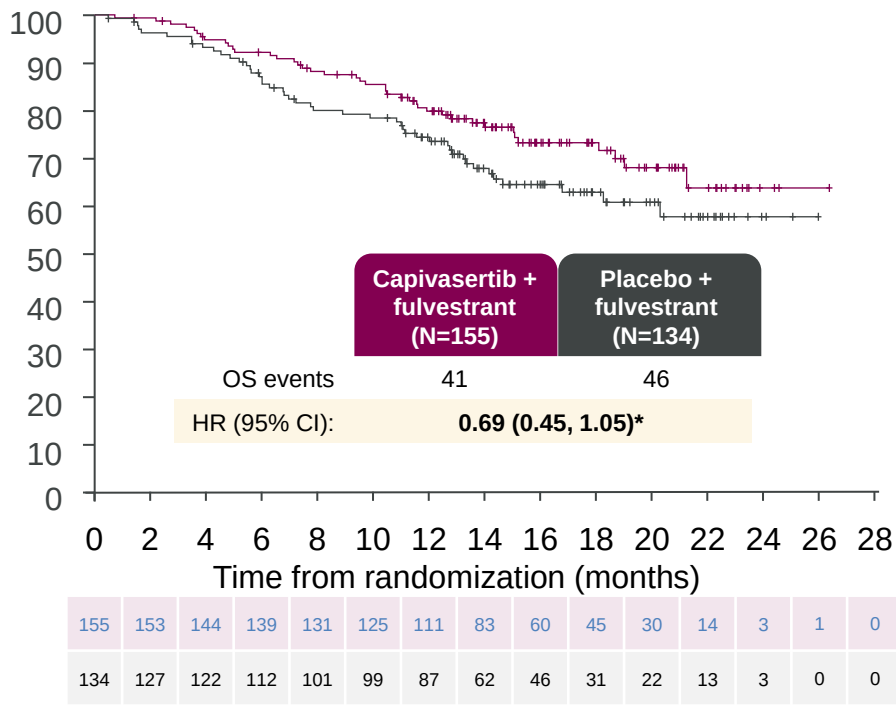
Overall population



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

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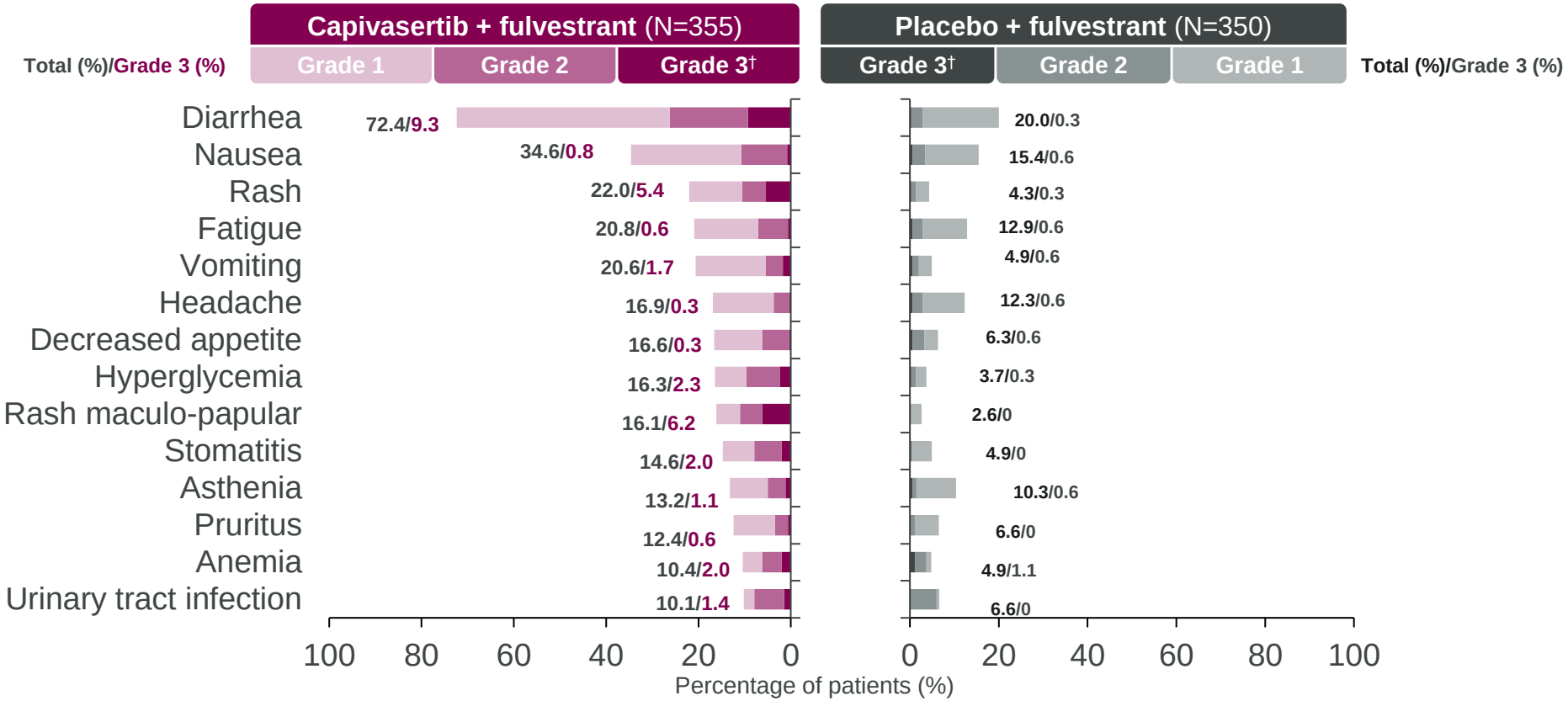
Adverse events (>10% of patients)



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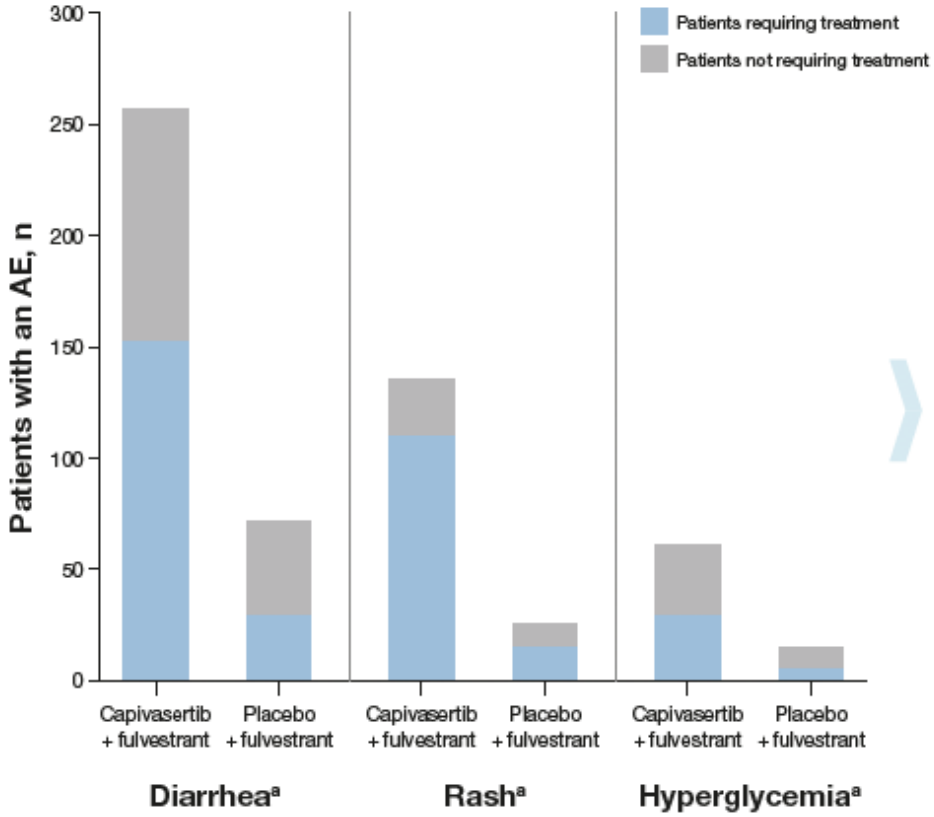
Most frequent AEs management



Most common treatments administered

	Capivasertib + fulvestrant (n=355)	Placebo + fulvestrant (n=350)
Diarrhea requiring treatment[a,b]	151 (42.5)	28 (8.0)
Loperamide	135 (38.0)	27 (7.7)
Rash requiring treatment[a,b]	109 (30.7)	14 (4.0)
Systemic corticosteroids	28 (7.9)	2 (0.6)
Topical corticosteroids	64 (18.0)	5 (1.4)
Antihistamines	75 (21.1)	7 (2.0)
Hyperglycemia requiring treatment[a,b]	28 (7.9)	4 (1.1)
Metformin	18 (5.1)	3 (0.9)
Insulin (and/or analogues)	10 (2.8)	2 (0.6)
Other blood glucose lowering drugs	10 (2.8)	1 (0.3)

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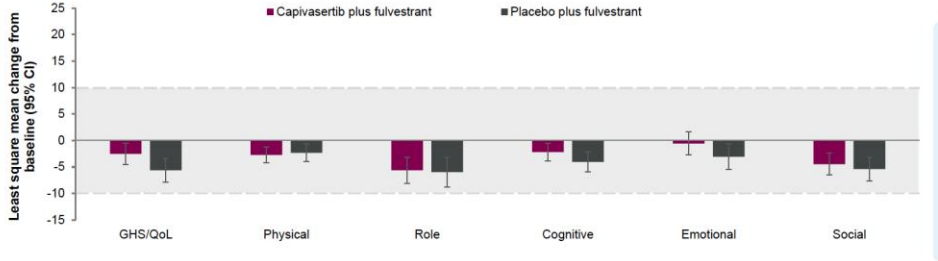
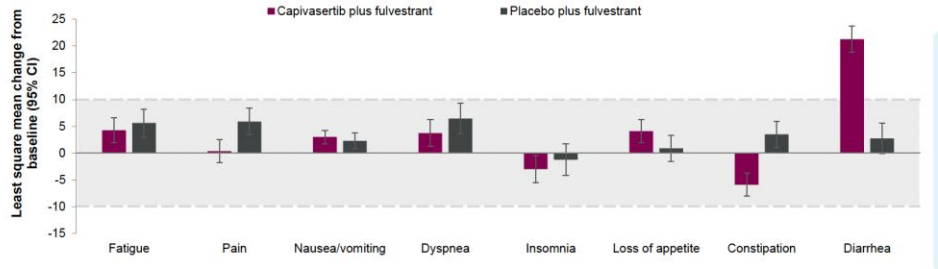
Overall change from baseline in EORTC QLQ-C30 GHS/QoL, functional domains and symptom scales



	GHS/QoL	Functional domains				
Treatment difference (95% CI)	3.1 (0.21, 5.98)	−0.42 (−2.53, 1.70)	0.35 (−3.22, 3.91)	1.87 (−0.48, 4.23)	2.49 (−0.67, 5.65)	0.94 (−1.93, 3.80)



	Symptom scales							
Treatment difference (95% CI)	-1.34 (-4.73, 2.04)	−5.51 (−8.65, −2.37)	0.73 (−1.04, 2.50)	−2.73 (−6.40, 0.94)	−1.78 (−5.48, 1.93)	3.21 (0.15, 6.27)	−9.38 (-12.50, −6.25)	18.49 (14.96, 22.01)

A clinically meaningful improvement or worsening from baseline in EORTC QLQ-C30 GHS/QoL and functional domains was defined as an increase or decrease of ≥10, respectively; a clinically meaningful improvement or worsening from baseline in EORTC QLQ-C30 symptom scales was defined as a decrease or increase of ≥10, respectively.

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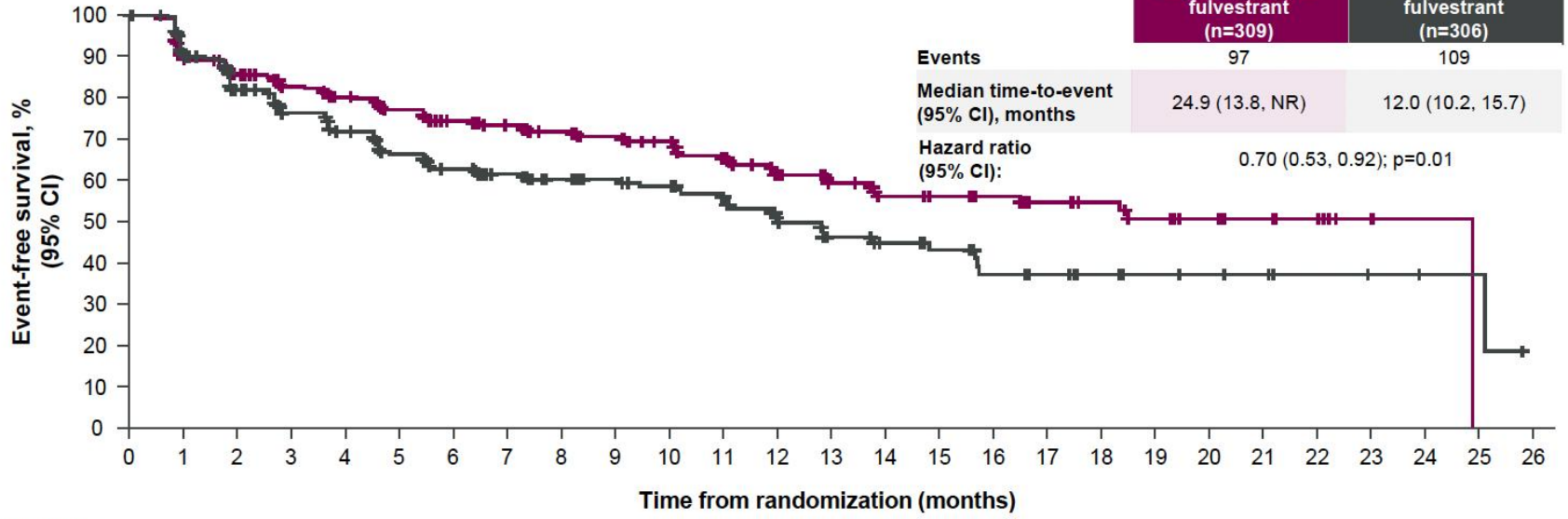
Time to deterioration EORTC QLQ-C30 GHS/QoL scores



Number of patients at risk

Capivasertib plus fulvestrant	309	261	225	202	184	169	151	143	129	119	109	90	68	58	50	47	40	33	28	24	17	12	10	3	1	0	0
Placebo plus fulvestrant	306	242	183	156	138	116	103	95	85	77	69	62	44	35	31	25	19	16	13	9	8	7	4	3	2	2	0

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CAPItello-291: Summary

Pretreatment: 69% CDK4/6i; 80% ET for ABC; 18% CTX for ABC

Cohorts	Treatment	PFS in mths (investigator-assessed)	Δ PFS in mths	; i	
Overall population	FUL+Cap	7.2 (5.5 - 7.4)	3.6	0.60 (0.51-0.71)	p<0.001
	FUL	3.6 (2.8 - 3.7)			
AKT pathway mutated (44%)*	FUL+Cap	7.3 (5.5 - 9.0)	4.2	0.50 (0.38-0.65)	p<0.001
	FUL	3.1 (2.0 - 3.7)			
Non-mutated / unknown (56%)	FUL+Cap	7.2 (4.5 – 7.4)	3.5	0.70 (0.56-0.88)	
	FUL	3.7 (3.0 – 5.0)			

*PIK3CA, AKT1 and / or PTEN alteration

Capivasertib plus fulvestrant has recently been FDA and EMA- approved for patients with HR+ ABC with PIK3CA/AKT1/PTEN who have progressed on an endocrine-based regimen

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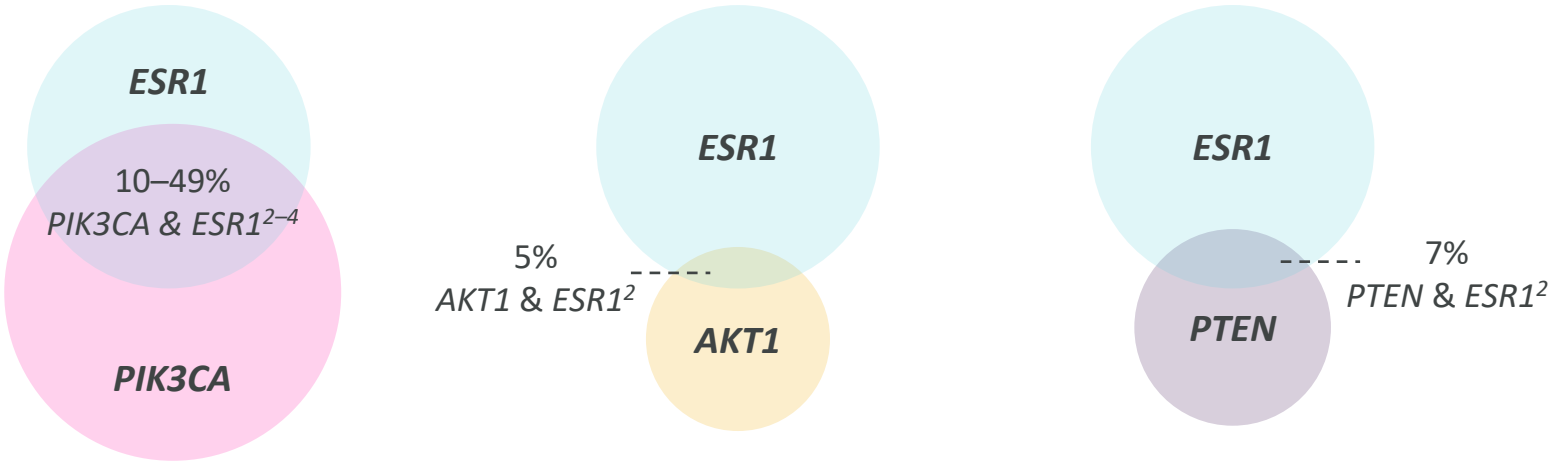
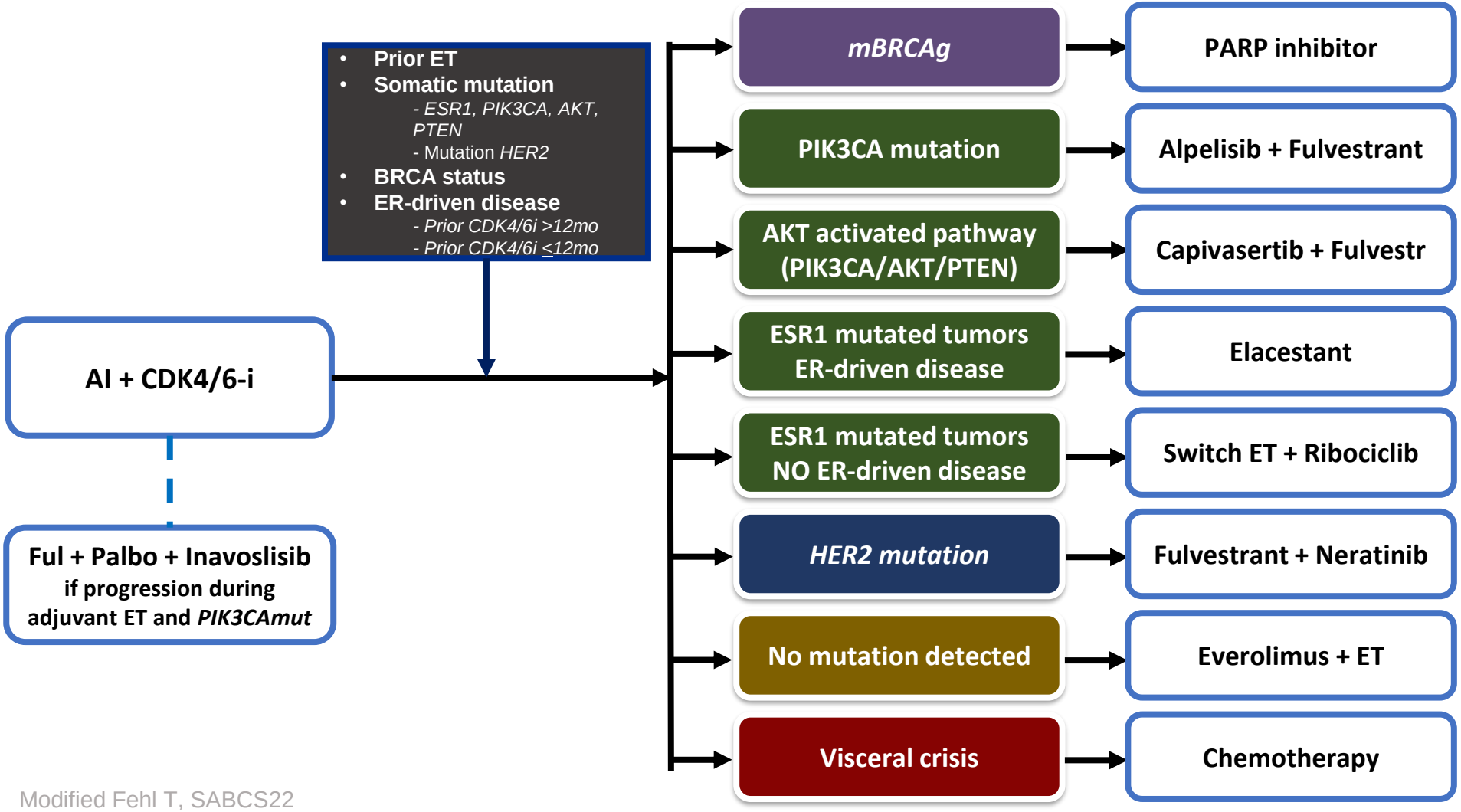
ESR1m co-occur with *PIK3CA*, *AKT1* or *PTEN* alterations HR+/HER2- aBC



The timing of ESR1m detection may impact prevalence data

Medford A. ASCO 2023; Tolaney SM..Clin Cancer Res. 2022; Dempsey N. ASCO 2023



Modified Fehl T, SABCS22

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