Secuencia de tratamiento guiada por diagnóstico molecular en el cáncer de mama luminal avanzado

Dr. José Angel García_Sáenz

jgsaenz@salud.madrid.org

Hospital Clínico San Carlos
SaludMadrid
Comunidad de Madrid
IdISSC
Ruber Internacional | Hospital
GEICAM spanish breast cancer group

Disclosure Information

- Consultative and advisory services for **Seagen, AstraZeneca, Daiichi Sankyo**, **Novartis, Gilead, Menarini, Jazz Pharmaceuticals**

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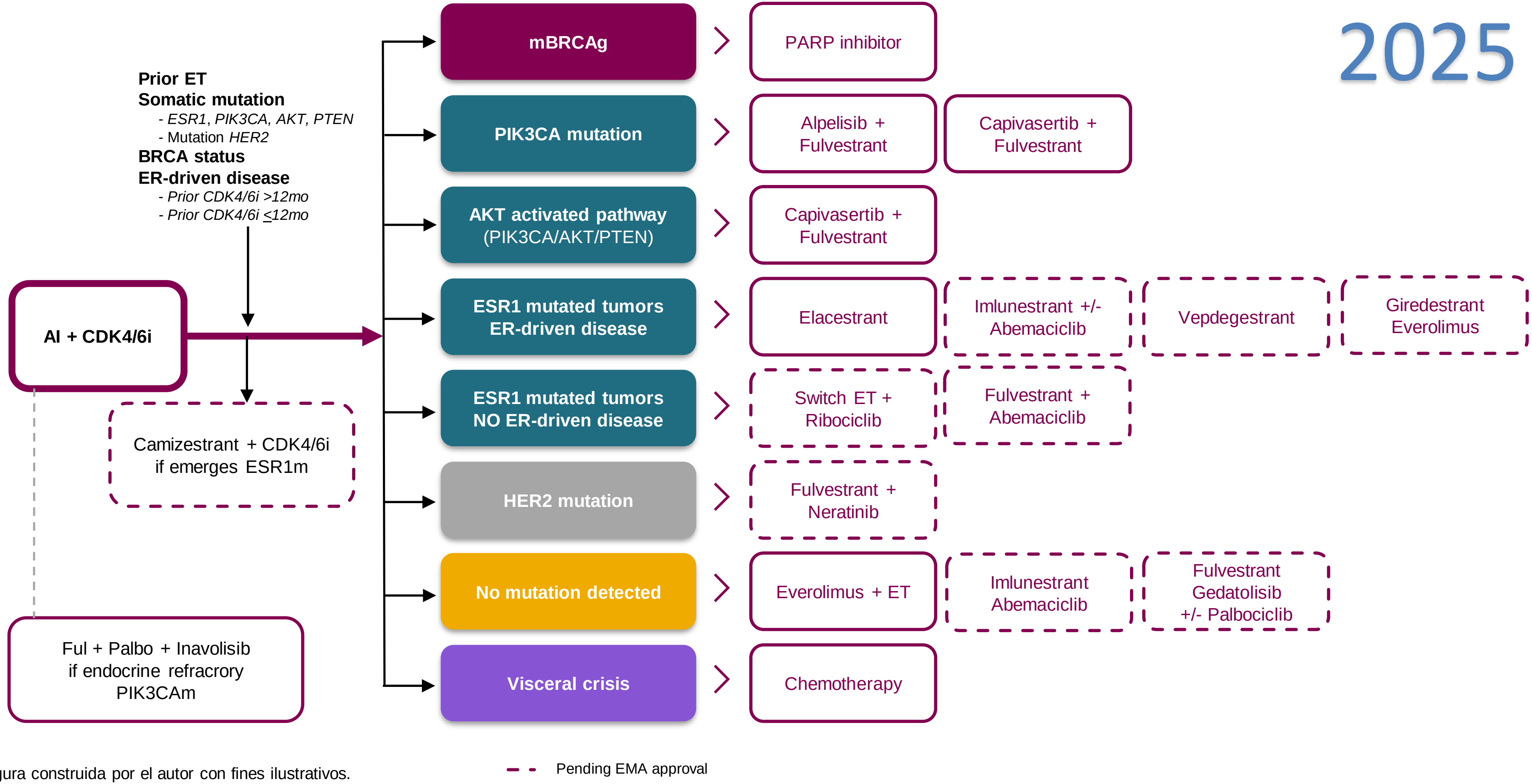

Figura construida por el autor con fines ilustrativos.

Despite advances in ER(+)/HER2(–) ABC, outcomes remain suboptimal and treatment efficacy declines across lines of therapy.

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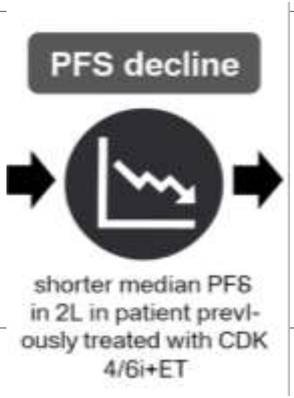
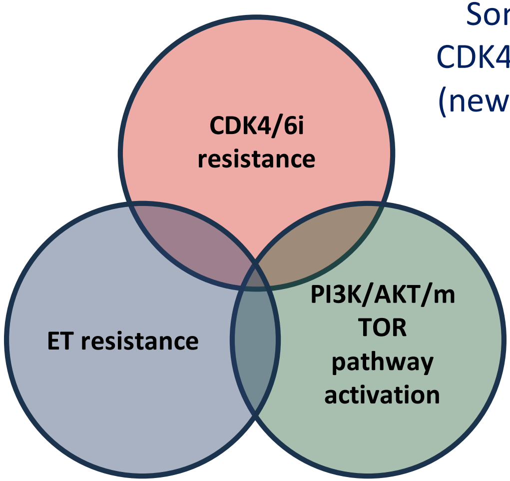


Piezzo et al. Int J Mol Sci 2020; Astore S et al. Crit Rev Oncol Hematol 2024

Mechanism of resistance and prospective therapeutic strategies



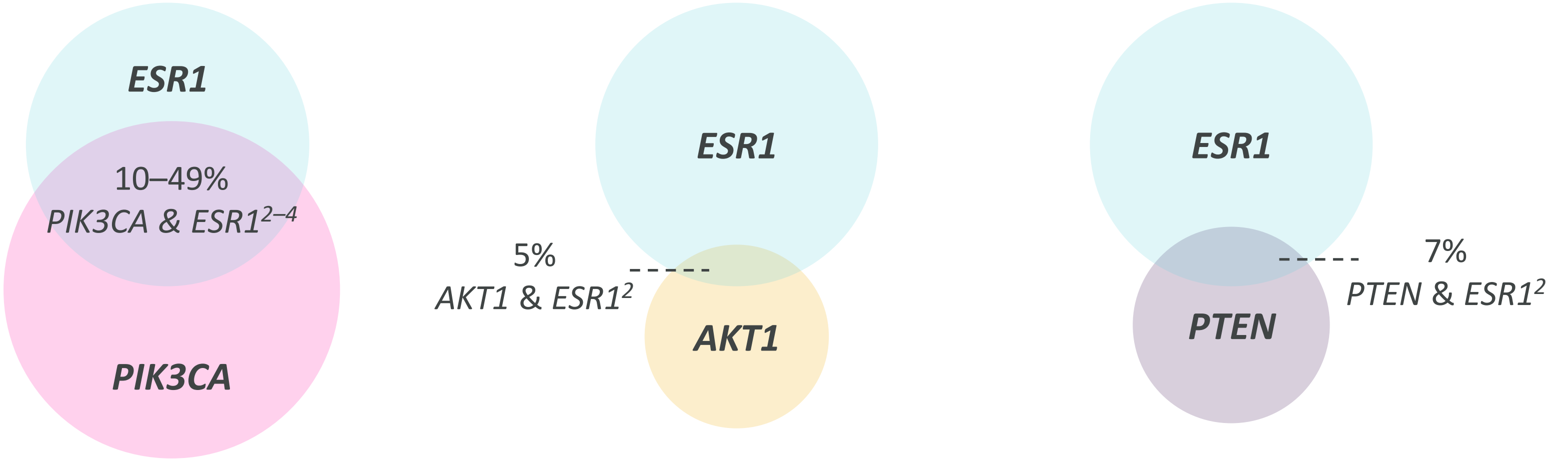
Some remain
CDK4/6i sensitive
(new generation)

Some remain
“estrogen receptor-
dependent resistant”
anti-estrogen
pressure m*ESR1*

ER-independent resistance:
The PI3K/AKT signaling pathway
plays a key role in cell growth,
protein translation, autophagy,
metabolism, and cell survival

Hartkopf AD, et al. Breast Care (Basel). 2020.

ESR1m co-occur with PIK3CA-AKT1-PTEN alterations in 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

Strategies in second line

No actionable genomic alteration: endocrine therapy plus…

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

Actionable genomic mutation:

- **Oral SERDs**
- **Endocrine therapy plus…**
  - pi3K-kinase or AKT inhibition
  - HER2 inhibition

Switch experience with CDK4/6-i

	MAINTAIN	PACE	PALMIRA	PostMONARCH
Phase	II	II	II	III
Sample size	120	220	198	350
HR+ aBC progression on iCDK + ET	ET +/- ribociclib	Fuvestrant F+ Palbociclib F + P +Avelumab	ET +/- Palbociclib	Ful +/-Abemaciclib
Continuation iCDK	Ribociclib	Palbociclib	Palbociclib	Abemaciclib
Inicial iCDK	Palbociclib 84%	Palbociclib 90%	Palbociclib 100%	Palbociclib 59%
iCDK >12mo	67%	75%	86%	77%
PFS: ET +iCDK Vs. ET	5.3 vs 2.8 mo (HR 0.56)	4.6 vs 4.8 mo (HR 1.11)	4.9 vs 3.6 mo (HR 0.84)	6.0 vs 5.3 mo (HR 0.73)

Kalinsky K. ASCO 2022; Mayer E SABCS2022. Llombart A, ASCO 2023; Kalinsky K, ASCO 2024

Strategies in second line

No actionable genomic alteration: endocrine therapy plus...

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- **mTOR inhibition**

Actionable genomic mutation:

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- **Endocrine therapy plus...**
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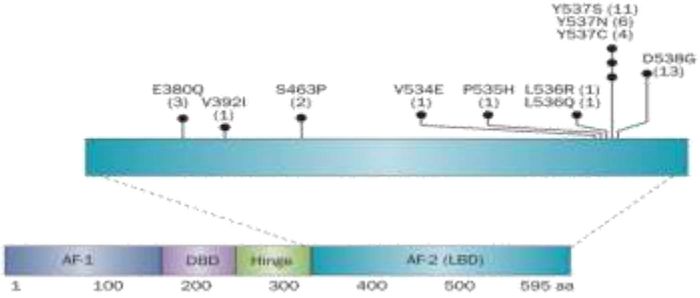
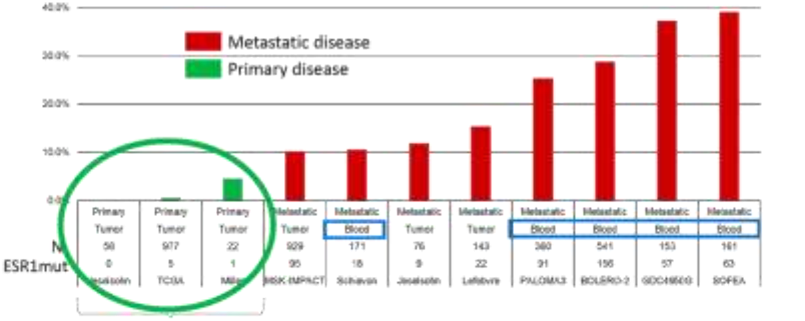
  - HER2 inhibition

ESR1 mutations



Jeselsohn R. Nat Rev Clin Oncol. 2015

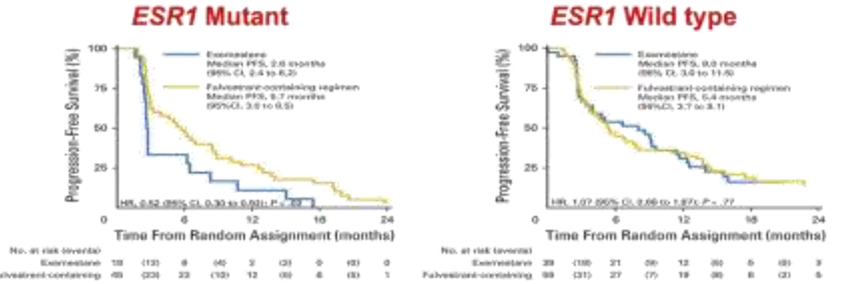
Frequency of ESR1 somatic mutation in breast cancer



Schiavon, Sci Transl Med 2015; Jeselsohn, Clin Cancer Res 2014; Lefebvre, PlosMedicine 2016; Miller Nat Comm 2016
Toy, Cancer Discovery 2016; Fribbens, JCO 2016; Chandarlapaty, Jama 2016

ESR1 mutations mutations might predict Fulvestrant vs AI survival benefit in ER+ MBC

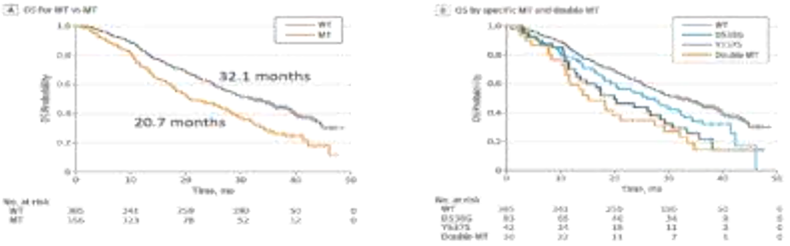
Retrospective Analyses from SoFEA Phase III trial



Fribbens et al. JCO 2016

ESR1 mutations predict overall survival in ER+ metastatic breast cancer

Retrospective Analyses from BOLERO-2 Phase III trial (n=541/724)
Exemestane +/- Everolimus



Chandarlapaty et al. JAMA 2017

Limitations of Fulvestrant

Fulvestrant	Oral SERDS
IM Injection	Oral Formulation
Poor PK	Enhaced PK profile
Efficacy is dose dependent	High potency
Activity limited post CDK4/6-i	Activity in ER-driven ESRm aBC
Activity limited in *ESR1* Y537S	Activity against *ESR1* Y537S

McDonell et al. JCO 2021

EMERALD Study Design

Inclusion Criteria

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1

N = 477

R

1:1

Elacestrant 400 mg daily[c]

Investigator's choice (SOC):
Fulvestrant
Anastrozole
Letrozole
Exemestane

PD or withdrawal criterion

Follow Up

Co-Primary Endpoints:[d]

- PFS in all pts
- PFS in m*ESR1*

Key Secondary Endpoint:

- Overall Survival

Stratification Factors:

- *ESR1*-mutation status[e]
- Prior treatment with fulvestrant
- Presence of visceral metastases

Bardia et al. JCO 2022

All Patients: PFS by Duration of CDK4/6i

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)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

Patients with ESR1-mut Tumors: PFS by Duration of CDK4/6i

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)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

Bardia et al. JCO 2022

EMBER-3 Study Design

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Jhaveri K. SABCS 2024

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Jhaveri K. SABCS 2024

Primary Endpoint: Imlunestrant + Abemaciclib vs Imlunestrant Investigator-assessed PFS in All Patients

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Imlunestrant + abemaciclib led to a 43% reduction in the risk of progression or death over imlunestrant alone in all patients

CI, confidence interval; HR, hazard ratio. [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm. The median follow-up was 13.5 months in the imlunestrant + abemaciclib arm and 13.7 months in the imlunestrant arm.

VERITAC-2: Vepdegestrant vs fulvestrant in ER+/HER2- ABC

Key inclusion criteria

- ER+, HER2- ABC
- Prior therapy:
  - 1 line of CDK4/6i + ET
  - ≤1 additional ET
  - Most recent ET for ≥6 mo
  - No prior SERD
  - No prior chemotherapy for advanced/metastatic disease

(N=624)

R 1:1

Vepdegestrant
200 mg/day PO
(n=313)

Stratification

- ESR1m (yes vs no)
- Visceral disease (yes vs no)

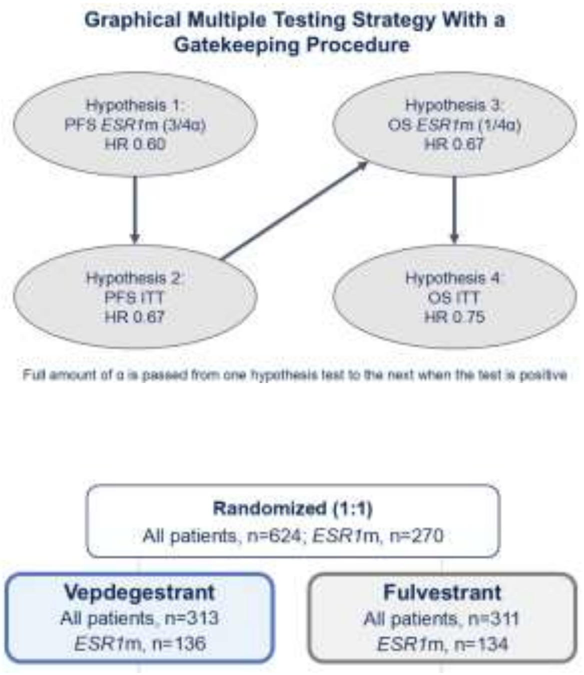
Fulvestrant
500 mg D1 IM
(n=311)

Primary endpoint

- PFS (BICR) ESR1m and all patients

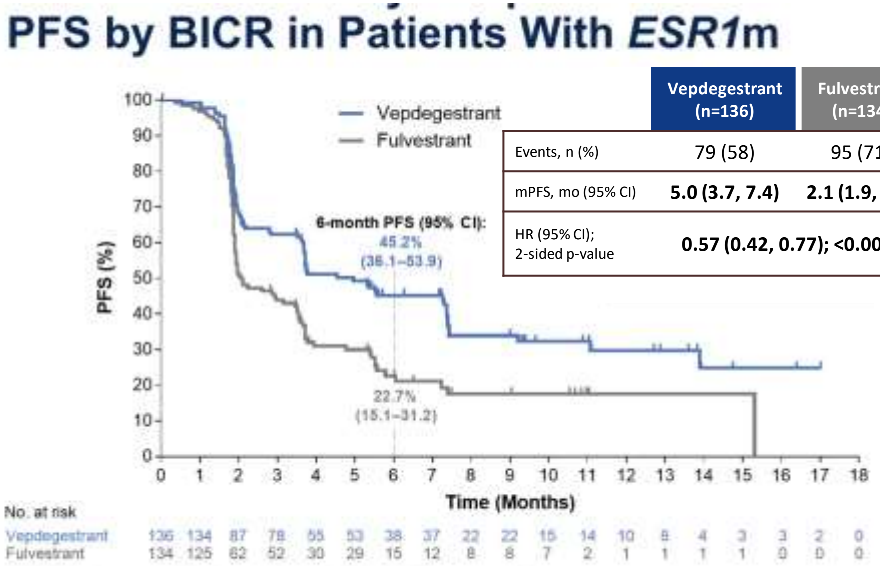
Secondary endpoints

- OS, CBR, ORR, safety



Hamilton EP. ASCO 2025

VERITAC-2 Primary Endpoint: PFS by BICR



	Vepdegestrant (n=136)	Fulvestrant (n=134)
Events, n (%)	79 (58)	95 (71)
mPFS, mo (95% CI)	**5.0 (3.7, 7.4)**	**2.1 (1.9, 3.5)**
HR (95% CI); 2-sided p-value	**0.57 (0.42, 0.77); <0.001**	

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	Vepdegestrant (n=313)	Fulvestrant (n=311)
Events, n (%)	186 (59)	198 (64)
mPFS, mo (95% CI)	**3.7 (3.6, 5.3)**	**3.6 (2.2, 3.8)**
HR (95% CI); 2-sided p-value	**0.83 (0.68, 1.02); <0.07**	

Hamilton EP. ASCO 2025

evERA: Giredestrant + EVE vs SOC + EVE in ER+/HER2- ABC

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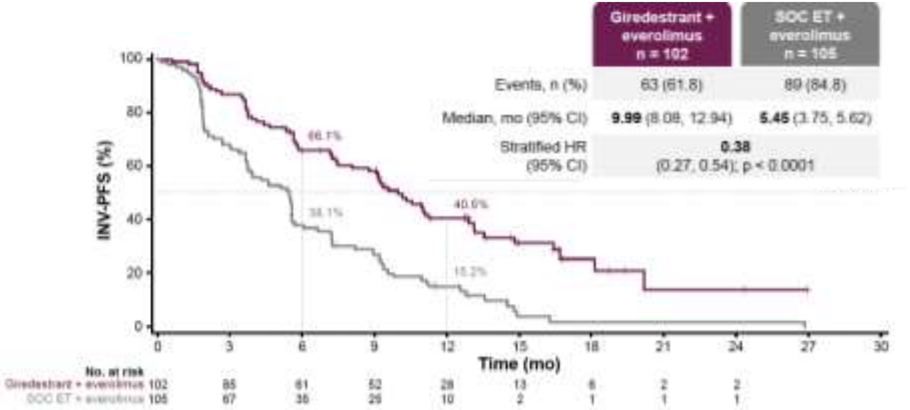
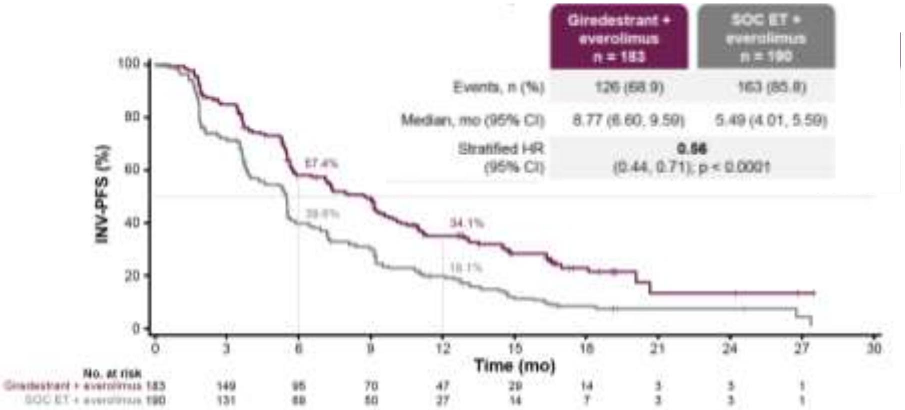
Mayer E. ESMO 2025

Co-primary endpoints: INV-PFS in *ESR1m* and ITT

INV-PFS in the *ESR1m* population



INV-PFS in the ITT population



Mayer E. ESMO 2025

SEREN A6 trial: ctDNA-guided of Camizestrant + CDK4/6i in emergent ESR1m during 1st line ET in HR+/HER2– ABC

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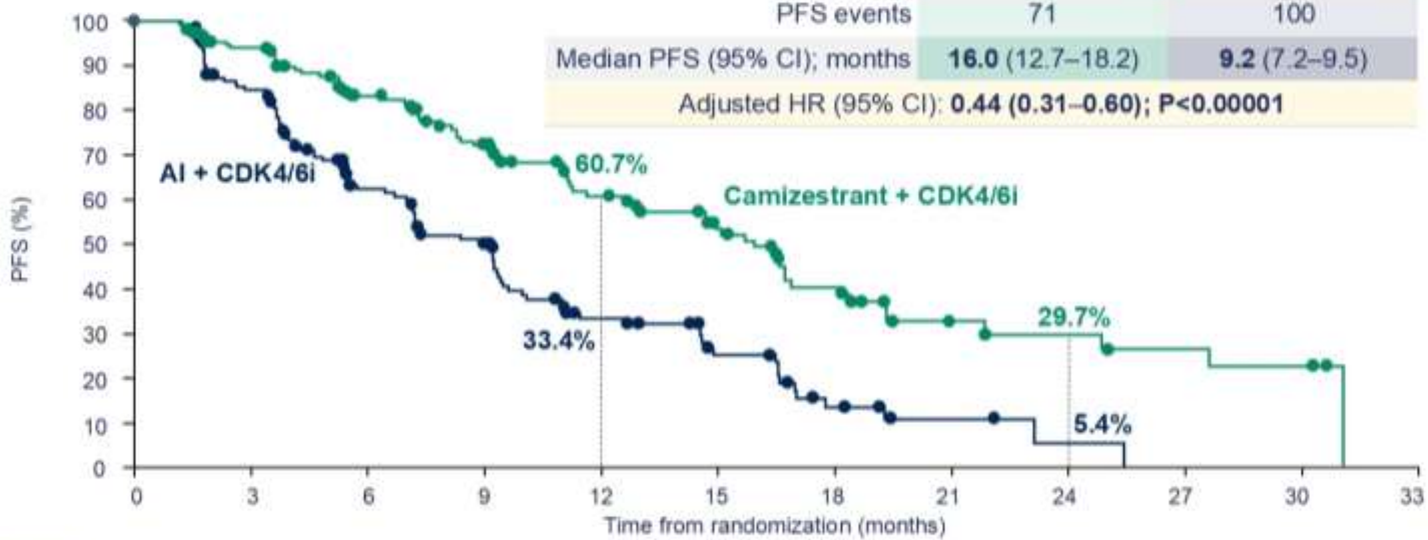
Turner N. ASCO 2025

Primary Endpoint: Investigator-assessed PFS

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS events	71	100
Median PFS (95% CI); months	**16.0** (12.7–18.2)	**9.2** (7.2–9.5)
Adjusted HR (95% CI): **0.44 (0.31–0.60); P<0.00001**		



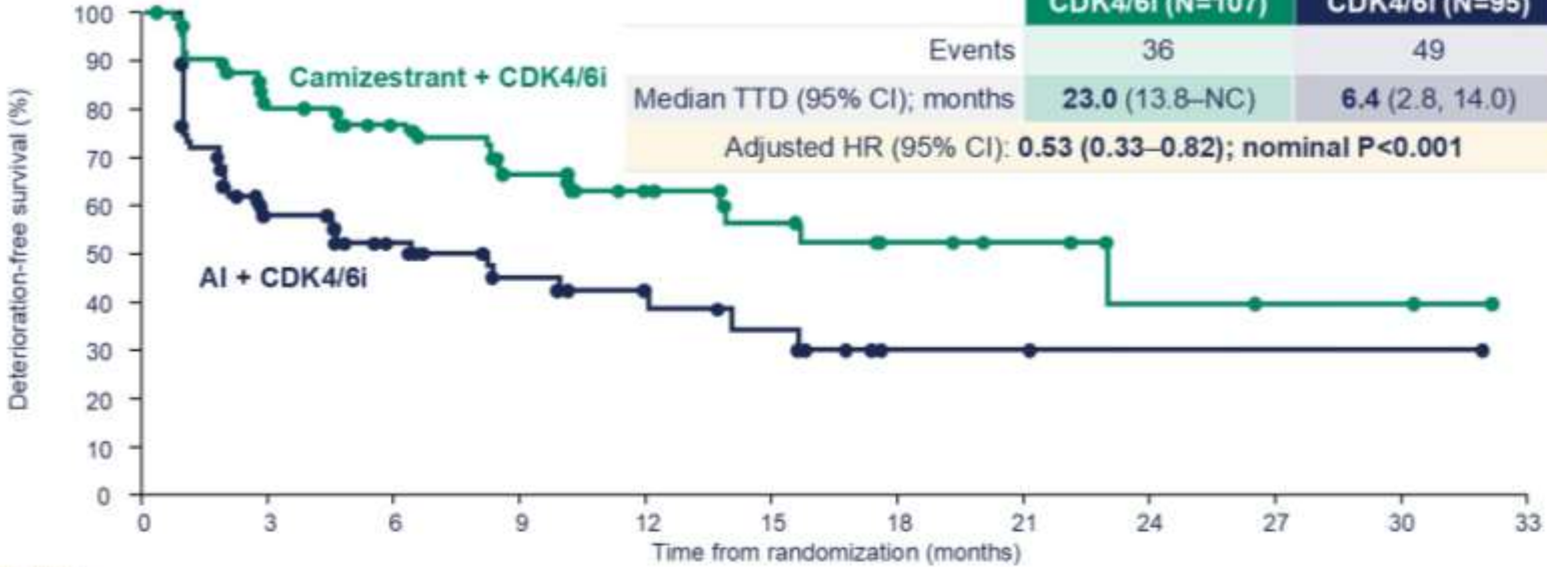
Number of patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33
Camizestrant + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

Turner N. ASCO 2025

Time to deterioration in global health status/QoL

EORTC QLQ-C30



	Camizestrant + CDK4/6i (N=107)	AI + CDK4/6i (N=95)
Events	36	49
Median TTD (95% CI); months	**23.0** (13.8–NC)	**6.4** (2.8, 14.0)
Adjusted HR (95% CI): **0.53 (0.33–0.82); nominal P<0.001**		

Number of patients at risk

Camizestrant + CDK4/6i	107	72	59	40	24	16	9	6	3	2	2	0
AI + CDK4/6i	95	42	26	16	11	8	2	2	1	1	1	0

Turner N. ASCO 2025

Second progression-free survival (PFS2)

The picture ca

Turner N. ASCO 2025

Strengths and caveats (1/2)

- First registrational trial to demostrate the utility of ctDNA monitoring to treat emerging resisntance in BC
- Switiching AI to camizestrant continuing CDK4/6i, guided by emergence of ESR1m during 1L significally improved PFS in HR+/HER2- ABC

Strengths and caveats (2/2)

- **mPFS delta similar as PADA-1**
- **9mo response in control arm. Worth giving up?**
- **OS might be awaited before to consider a SOC.**
- **What ET backbone might be used for 2nd line targeted therapy?**
- **Burden of ctDNA testing on Healthcare Systems.**

Strategies in second line

No actionable genomic alteration: endocrine therapy plus…

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

Actionable genomic mutation:

- **Oral SERDs**
- **Endocrine therapy plus…**
  - pi3K-kinase or AKT inhibition
  - HER2 inhibition

Targeting Pi3K pathway

The picture can't be displayed.

The picture can't be displayed. Inavolisib

The picture can't be displayed. Gedatolisib

The picture can't be displayed.

The picture can't be displayed. Gedatolisib

Everolimus + exemestane increases PFS irrespective PI3K-pathway activation

n=724

- **Postmenopausal HR+/HER2– mBC**
- **Progressing during/after NSAIs**

Everolimus plus exemestane

Placebo plus exemestane

Arms	Events/N	PFS (mo)	HR (95% CI)
EVE + EXE	310/485	10.6	0.36 (0.27–0.47)
PBO + EXE	200/239	4.1	

Baselga J. NEJM 2012

Why target PI3K signaling?

Checklist:

- ☑ Mutation frequency
- ☑ Prognostic impact of mutation
- ☐ Mutation(s) predict response to therapy

PFS in patients with *PIK3CA*-mutated HR+, HER2– ABC in SOLAR-1[1,*,†]

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HR 0.65; 95% CI, 0.50–0.85; p<0.001

Andre F. NEJM 2019

Inavolisib or placebo plus palbociclib and fulvestrant in pts with PIK3CA-mut HR(+)/HER2(-) ABC: INAVO120

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:

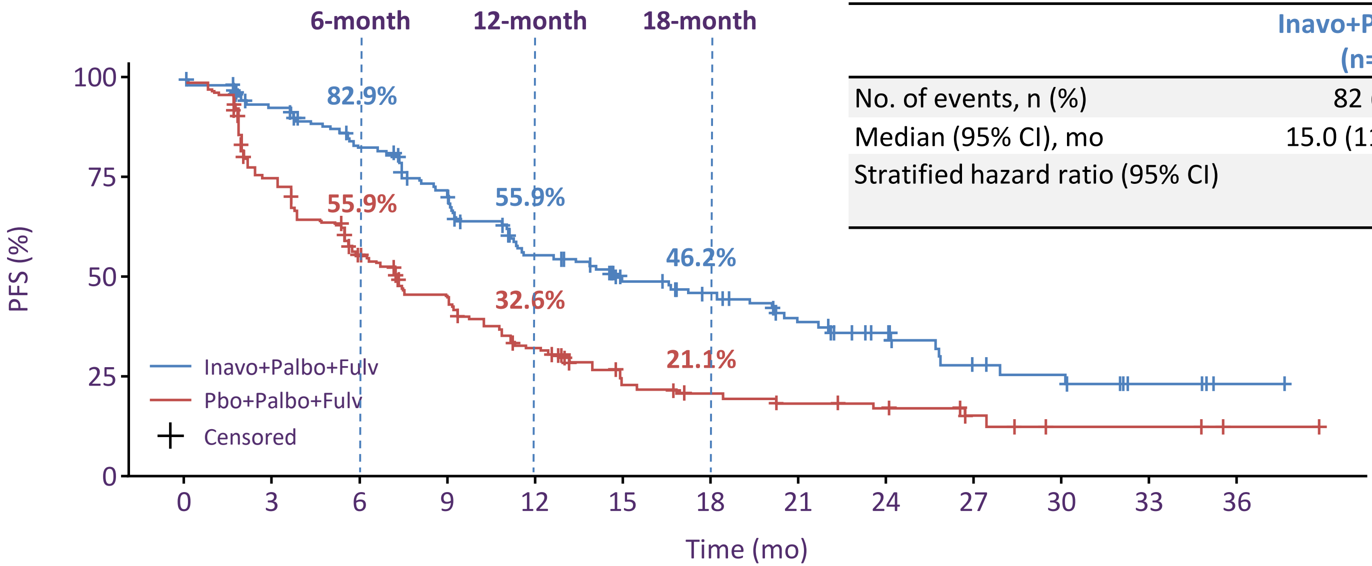
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

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

Jhaveri K, SABCS 2023

Primary endpoint: PFS



	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:

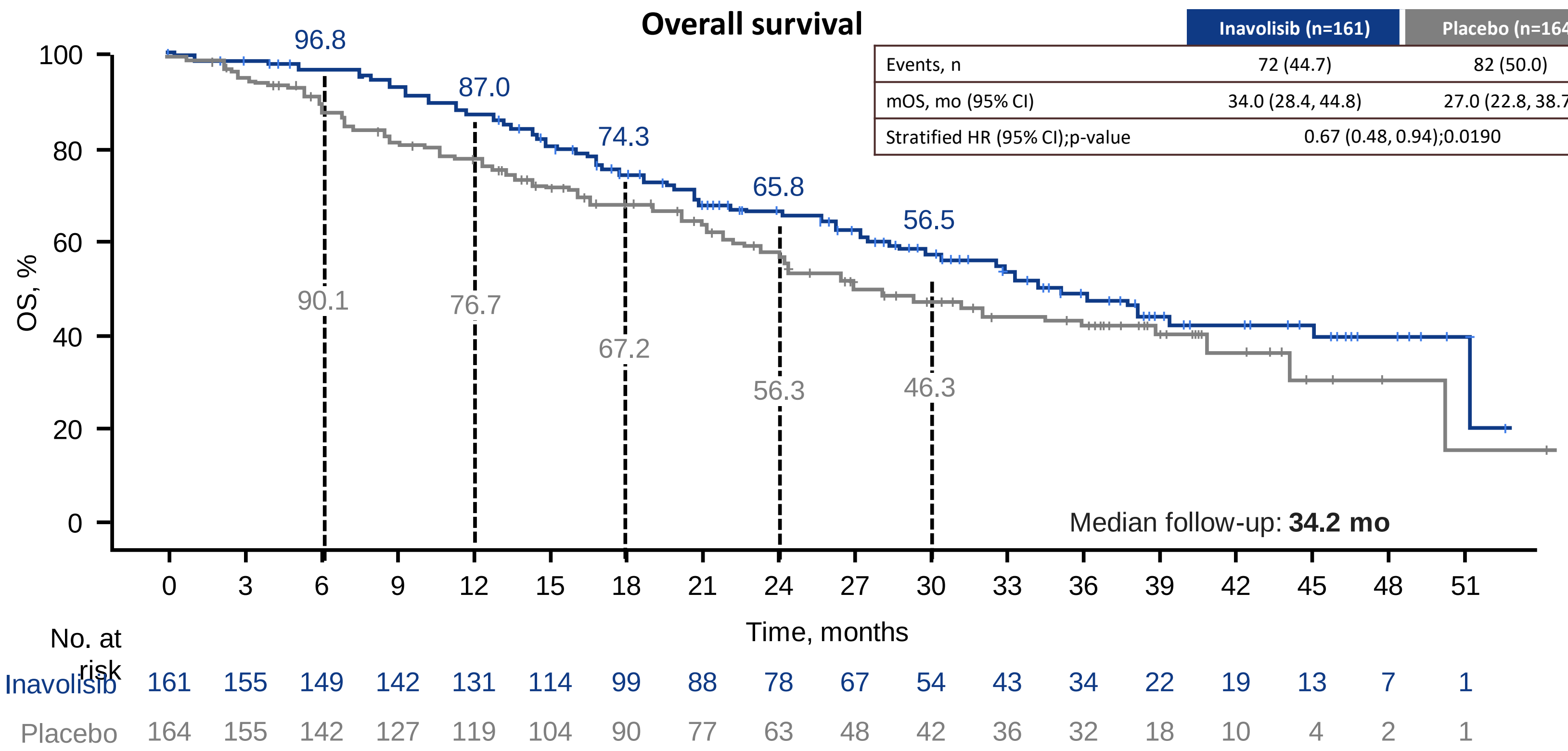
Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up: **21.3 months**

Jhaveri K, SABCS 2023

Key secondary endpoint: Overall survival

	Inavolisib (n=161)	Placebo (n=164)
Events, n	72 (44.7)	82 (50.0)
mOS, mo (95% CI)	34.0 (28.4, 44.8)	27.0 (22.8, 38.7)
Stratified HR (95% CI);p-value	0.67 (0.48, 0.94);0.0190	



Turner N. J ASCO 2025

CAPItello-291: Capivasertib + Fulvestrant vs Fulvestrant in HR(+) resistant ABC

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

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

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

Dual primary endpoints

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

Key secondary endpoints

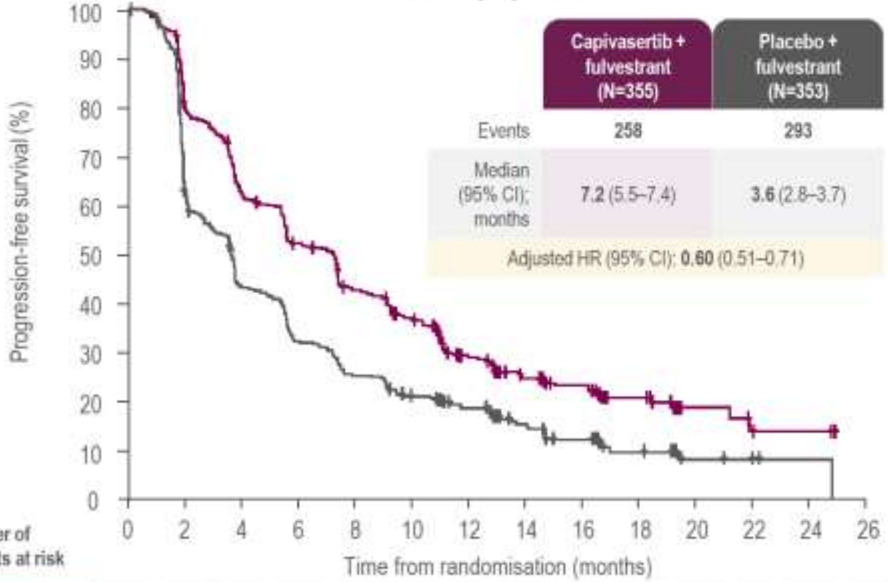
Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Turner N. SABCS 2022

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

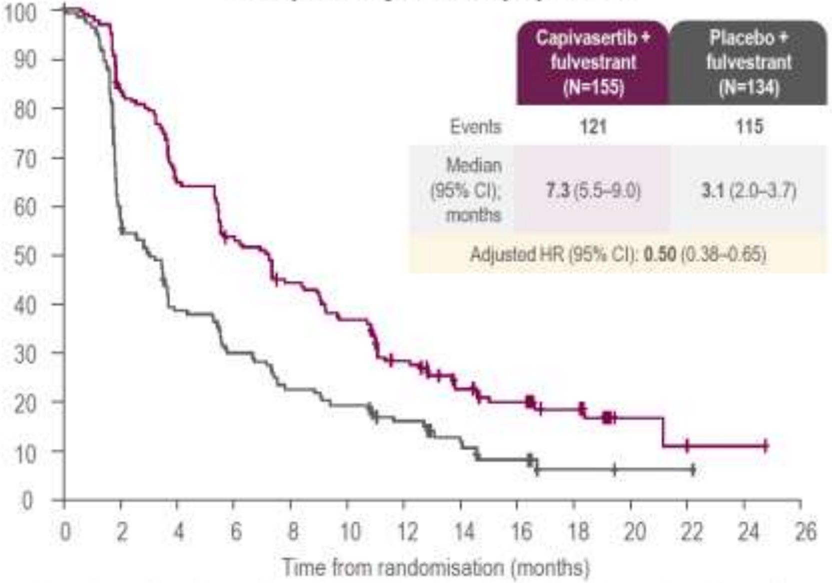
Overall population



Number of patients at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26
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

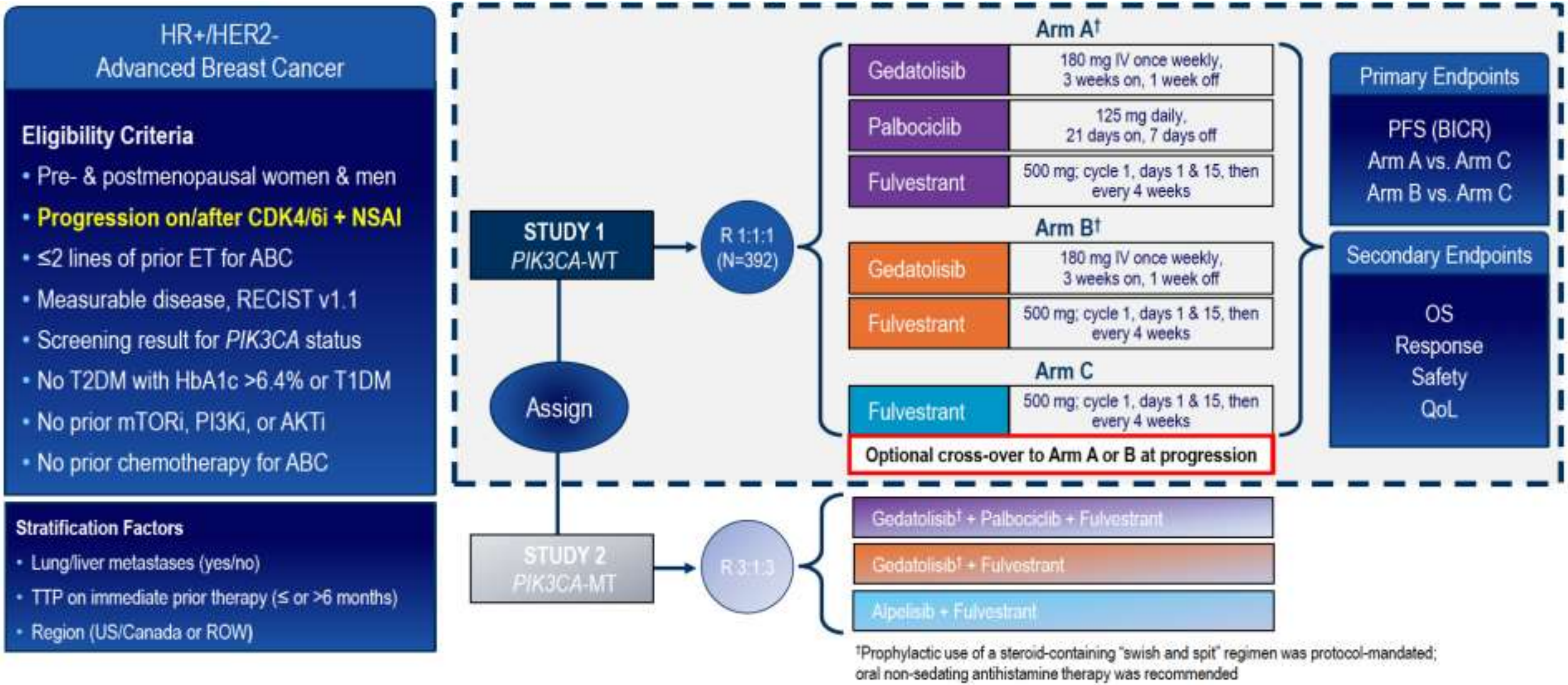
AKT pathway-altered population



	0	2	4	6	8	10	12	14	16	18	20	22	24	26
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

Turner N. SABCS 2022

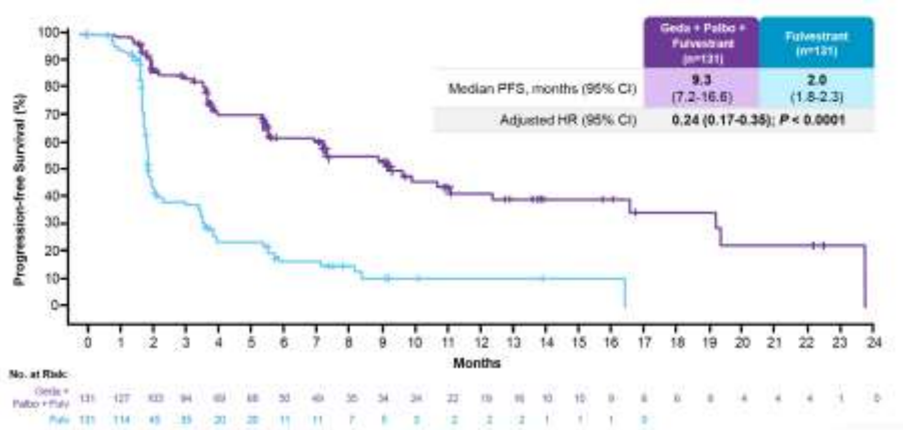
VIKTORIA-1: Gedatolisib + Fulvestrant w/wo Palbociclib in HR(+)/HER2(-)/PIK3CA-wt ABC



Hurvitz S. ESMO 2025

Co-primary endpoints: PFS doublet and triplet vs Fulvestrant

PFS Gedatolisib Triplet vs Fulvestrant



PFS Gedatolisib Doublet vs Fulvestrant

Hurvitz S. ESMO 2025

Strategies in second line

No actionable genomic alteration: endocrine therapy plus…

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- **mTOR inhibition**

Actionable genomic mutation:

- **Oral SERDS**
- **Endocrine therapy plus…**
  - pi3K-kinase or AKT inhibition
  - HER2 inhibition

SUMMIT: Neratinib Trastuzumab Fulvestrant in HER-mutant/HR+ ABC

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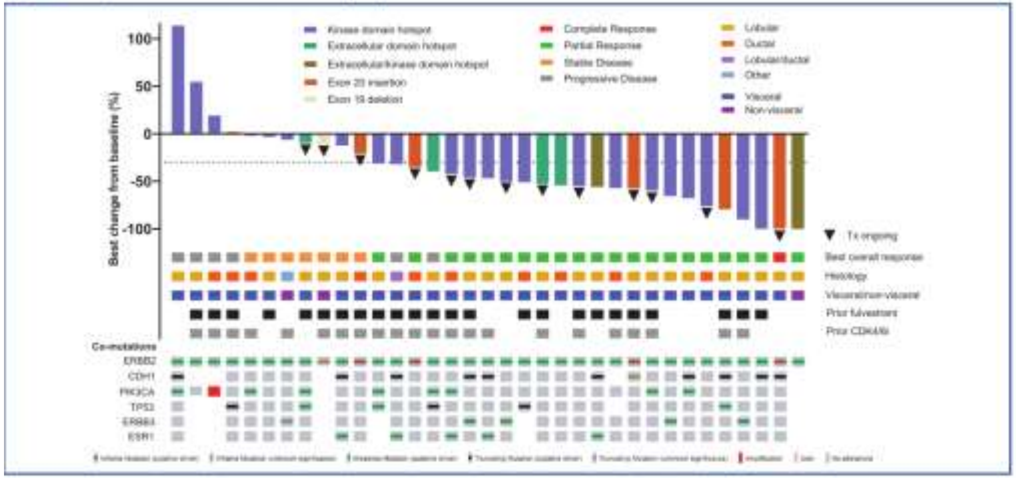
Figure 3. Change in tumor size and characteristics (n=35)[a]



Jhaveri K. SABCS2020

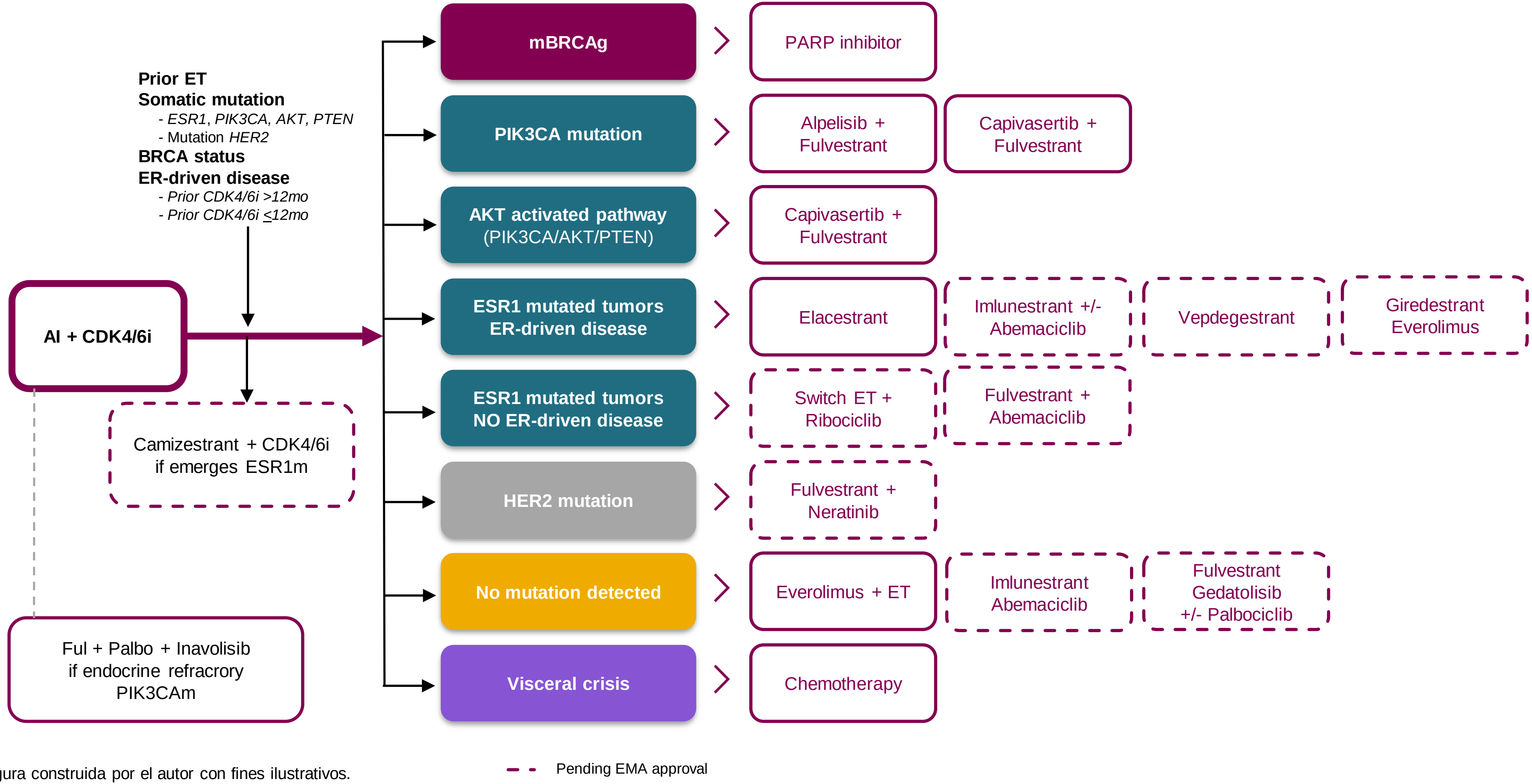


Figura construida por el autor con fines ilustrativos.

Should molecular testing guide successive targeted therapies in luminal ABC?

✓**SERDs** show meaningful benefit in *ESR1m* HR+/HER2– aBC post CDK-i

✓**SERD combinations** further **enhance clinical efficacy**

✓***PI3K–AKT–mTOR* targeting** helps **reverse endocrine resistance**

✓**Molecular testing** is key to **Precision Medicine** and sequencing **luminal ABC**