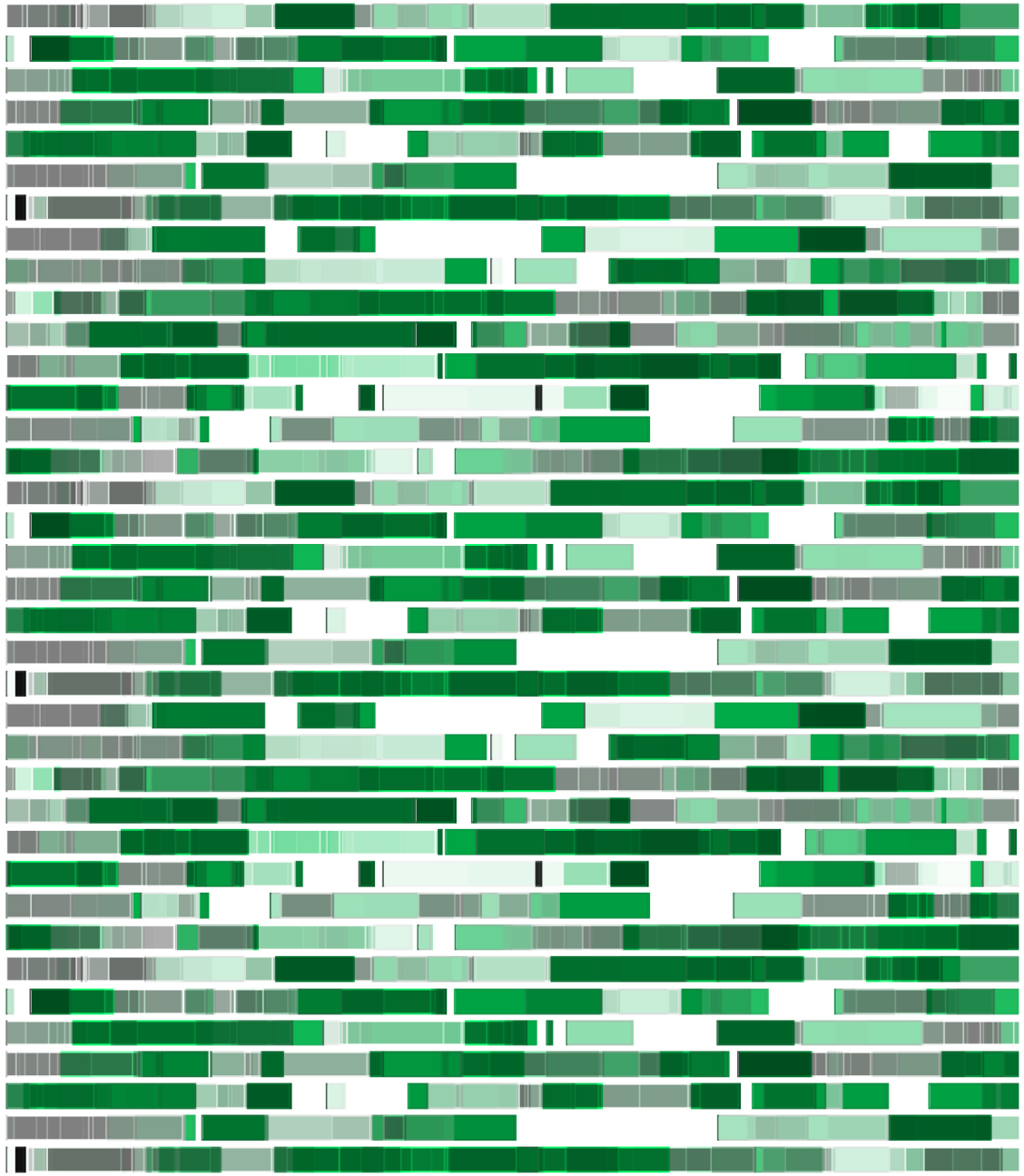
III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

INHIBIDORES DE CICLINAS CON LOS SERDS ¿HACIA DONDE VAMOS?



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Organizador por:
HENDERE HEALTHCARE

DISCLOSURE

- Consultoría o Advisory: Gilead Sicende, Daiichi-Sankyo, Astra Zeneca, Menarini/Stemline, Pfizer, Novartis, Pfizer, Eli Lilly.
- Fondos para Investigación: Pfizer.

AGENDA

Racional

Ensayos Clínicos relevantes:

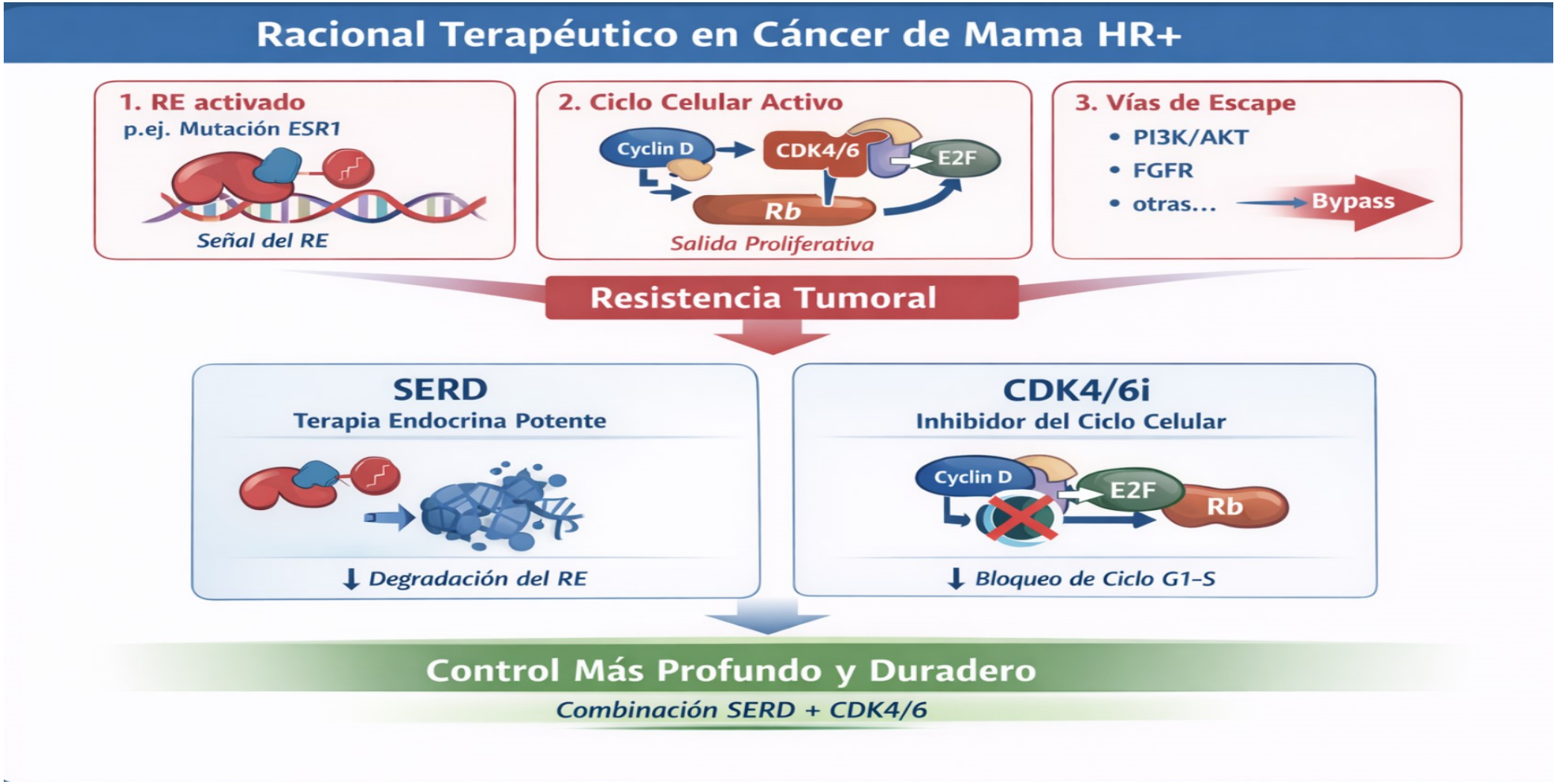
- EMBER
- ELEVATE
- SERENA-6

Como los posicionamos frente a otras alternativas

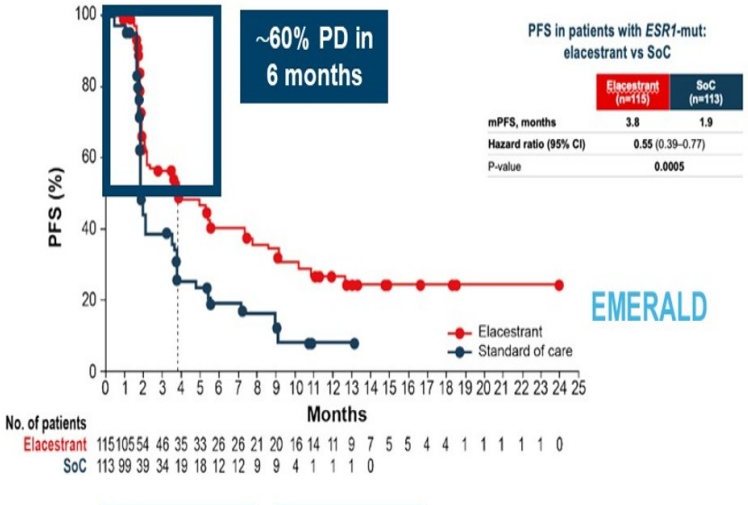
Dirección Futura

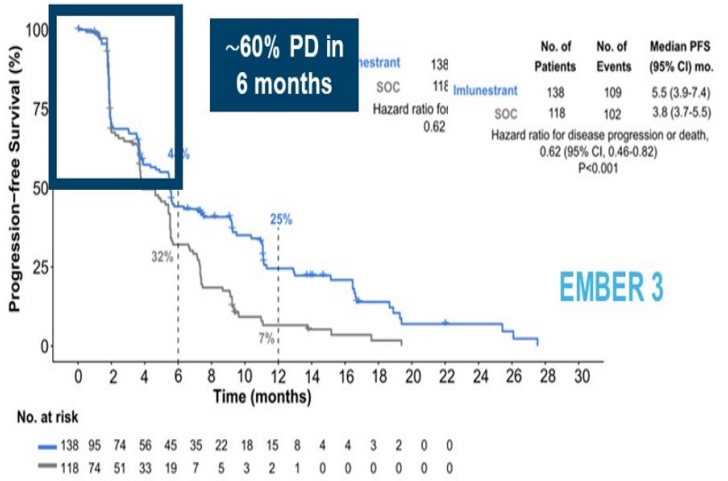
Conclusiones

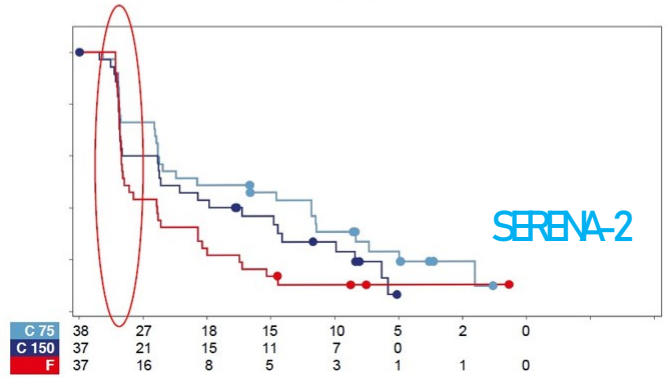
¿POR QUÉ COMBINAR LOS SERDS CON INH DE CICLINAS?



Giugliano F et al. Cancer Treat Rev 2025







APROXIMADAMENTE EL 60% DE LOS PACIENTES EN TTO CON SERDs ORAL EN MONOTERAPIA PROGRESAN EN LOS PRIMEROS 6 MESES

Bidart et al. JCO 2022. Jhaverti et al. NEJM 2025

ANN ONCOL

EMBER-3 Study Design

ER+, HER2- ABC

Men and pre-[a]/post-menopausal women

Prior therapy:

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification Factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[b]

R 1:1:1
N=874

- **A**: Imlunestrant 400 mg QD, n=331
- **B**: SOC ET[c,d] Fulvestrant or Exemestane, n=330
- **C[e]**: Imlunestrant 400 mg QD + abemaciclib[d], n=213

Primary Endpoints

Investigator-assessed PFS for[f]:

- A vs B in patients with *ESR1*m[g]
- A vs B in all patients
- C vs A in all patients[h]

Key Secondary Endpoints

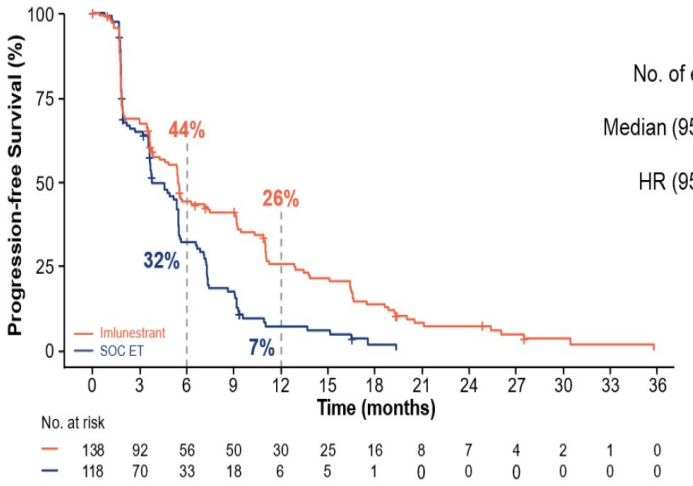
- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

- TTC[i], CFS[j], PFS2[k]

Jhavari. SABCS 2025

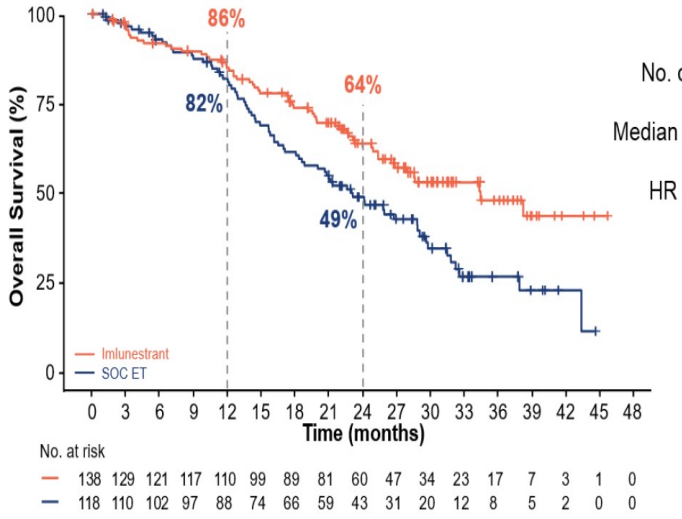
Primary Endpoint: PFS of Imlunestrant vs SOC ET in Patients With *ESR1*m



	Imlunestrant n=138	SOC ET n=118
No. of events	122	103
Median (95% CI)	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.47-0.82)**	
	Nominal *p*-value[a] = 0.0007	

PFS benefit of imlunestrant was sustained in patients with *ESR1*m

Secondary Endpoint: Interim OS of Imlunestrant vs SOC ET at 50% Maturity in Patients With *ESR1*m



	Imlunestrant n=138	SOC ET n=118
No. of deaths	57	71
Median (95% CI)	**34.5** (25.4-NR)	**23.1** (18.4-28.9)
HR (95% CI)	**0.60 (0.43-0.86)**	
	p-value = 0.0043*	

**p*-value did not achieve prespecified threshold for significance (*p*=0.0000004 at IA2)

Imlunestrant led to an ~11 month numerical improvement in median OS in patients with *ESR1*m

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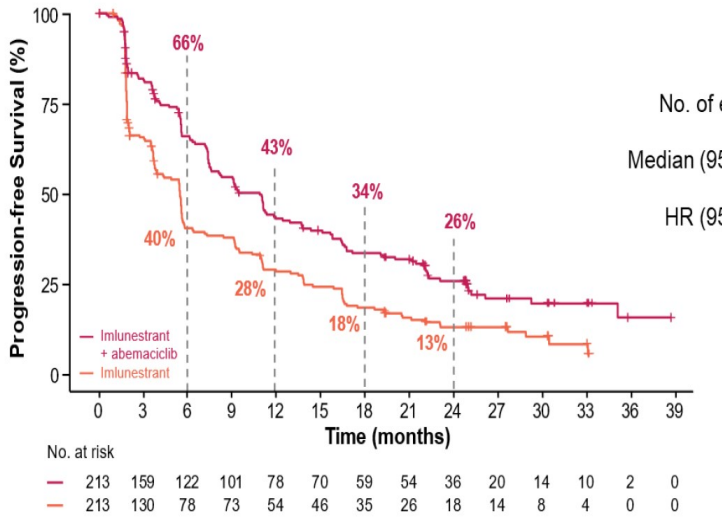
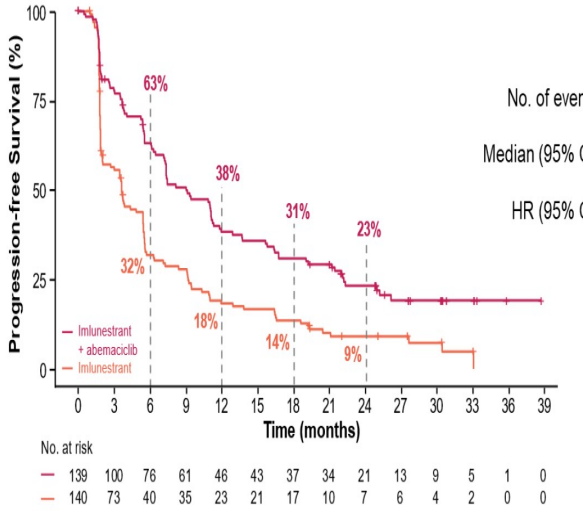
Primary Endpoint: PFS of Imlunestrant + Abemaciclib vs Imlunestrant in All Patients



	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of events	144	174
Median (95% CI)	**10.9** (7.5-12.5)	**5.5** (3.8-5.6)
HR (95% CI)	**0.59 (0.47-0.74)**	
Nominal *p*-value[a]	< 0.0001	

PFS benefit of imlunestrant + abemaciclib was maintained in all patients

Subgroup Analysis: PFS of Imlunestrant + Abemaciclib vs Imlunestrant in CDK4/6i Pretreated Patients



	Imlunestrant + abemaciclib n=139	Imlunestrant n=140
No. of events	97	120
Median (95% CI)	**9.1** (7.2-11.3)	**3.7** (2.1-5.5)
HR (95% CI)	**0.53 (0.40-0.69)**	
Nominal *p*-value	< 0.0001	

Consistent benefit of imlunestrant + abemaciclib maintained in patients previously treated with a CDK4/6i

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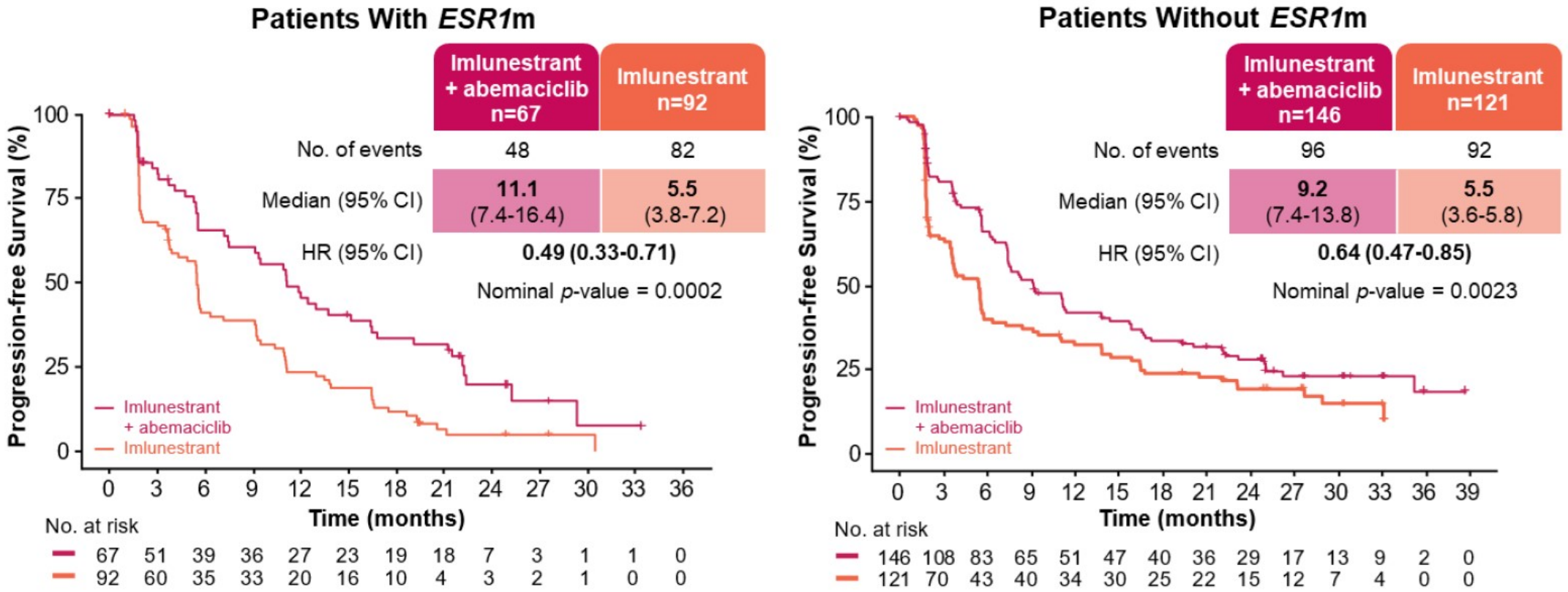
Subgroup Analysis: PFS of Imlunestrant + Abemaciclib vs Imlunestrant by *ESR1*m Status



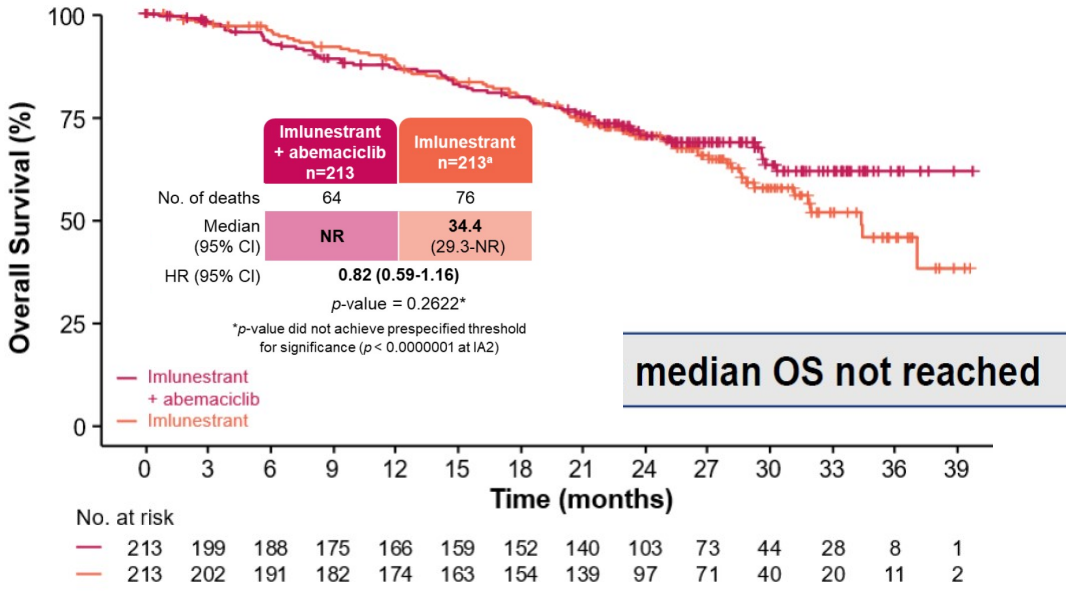
Consistent benefit of imlunestrant + abemaciclib maintained regardless of *ESR1*m status

Jhavari. SABCS 2025

PFS by Subgroup in CDK4/6i Pretreated Patients: Consistent Imlunestrant + Abemaciclib Benefit Across Subgroups

Subgroup		Imlunestrant + abemaciclib No. of Events/Total No.	Imlunestrant No. of Events/Total No.	Hazard Ratio (95% CI)	Interaction *p*-value
CDK4/6i pretreated patients		**97/139**	**120/140**	**0.53 (0.40, 0.69)**	
Age	< 65 years	57/77	78/92	0.62 (0.44, 0.88)	**0.192**
	≥ 65 years	40/62	42/48	0.43 (0.28, 0.67)	
No. of metastatic sites	1	24/46	27/35	0.48 (0.27, 0.83)	**0.884**
	2	24/34	40/49	0.56 (0.34, 0.93)	
	≥ 3	49/59	53/56	0.47 (0.32, 0.70)	
Liver metastasis	No	63/94	71/86	0.61 (0.43, 0.86)	**0.091**
	Yes	34/45	49/54	0.39 (0.24, 0.61)	
ESR1 mutation status	Detected	38/53	65/72	0.42 (0.28,0.64)	**0.629**
	Not detected	59/86	55/68	0.58 (0.40,0.84)	
Previous CDK4/6i indication	Adjuvant	6/7	9/11	0.51 (0.17, 1.58)	**0.931**
	Advanced	91/132	111/129	0.53 (0.40, 0.70)	
Choice of previous CDK4/6i in any setting	Abemaciclib	9/10	12/13	0.80 (0.34, 1.92)	**0.525**
	Palbociclib	59/90	73/86	0.48 (0.34, 0.68)	
	Ribociclib	28/37	34/39	0.54 (0.32, 0.90)	
Duration of previous CDK4/6i in advanced setting	< 12 months	24/40	26/32	0.32 (0.17, 0.57)	**0.014**
	≥ 12 months	67/92	85/97	0.61 (0.44, 0.84)	
	< 18 months	40/60	43/52	0.47 (0.30, 0.74)	**0.257**
	≥ 18 months	51/72	68/77	0.56 (0.39, 0.80)	
PI3K pathway mutation status	Detected	44/61	60/63	0.49 (0.33, 0.74)	**0.860**
	Not detected	51/75	56/69	0.50 (0.34, 0.73)	
Concurrent *ESR1* mutation and PI3K pathway mutation status	Detected	20/29	36/39	0.29 (0.15, 0.53)	**0.543**
	Not detected	75/107	80/93	0.53 (0.39, 0.73)	

Secondary Endpoint: Interim OS of Imlunestrant + Abemaciclib vs Imlunestrant at 33% Maturity in All Patients



median OS not reached

Jhavari. SABCS 2025

ELEVATE Trial Design

KEY ELIGIBILITY

- Women (pre-, peri-, or postmenopausal) or men
- ER+, HER2- a/mBC
- 1-2 lines of prior ET +/- CDK4/6i
- Prior fulvestrant allowed
- Primary endocrine resistance allowed
- No prior chemotherapy in the a/mBC setting
- ≥1 measurable lesion as per RECIST v1.1 or a mainly lytic bone lesion

ELEVATE PHASE 1b (n=90)

Elacestrant 86-345 mg* combined with either:

Alpelisib 150-250 mg[a,b,c]
Everolimus 5-10 mg[d,e,f,g]
Palbociclib 100-125 mg[h,i,j]
Ribociclib 400-600 mg[k,l,m,n,o]
Capivasertib 320-400 mg[p,q,r]

ELECTRA PHASE 1b (n=27)

Elacestrant 258-345 mg* combined with **Abemaciclib** 100-150 mg[s,t,i]

RP2D

ELEVATE PHASE 2

- **Elacestrant 345 mg + Everolimus 7.5 mg (n=50)**
- **Elacestrant 345 mg + Abemaciclib 150 mg (n=60)**
- **Elacestrant 345 mg + Ribociclib 400 mg** (n=30)
- **Elacestrant 345 mg + Capivasertib 320 mg** (n=60)

Phase 2 Objectives

Primary: PFS (RECIST v1.1)
Secondary: ORR, DoR, CBR, PFS, OS, and safety

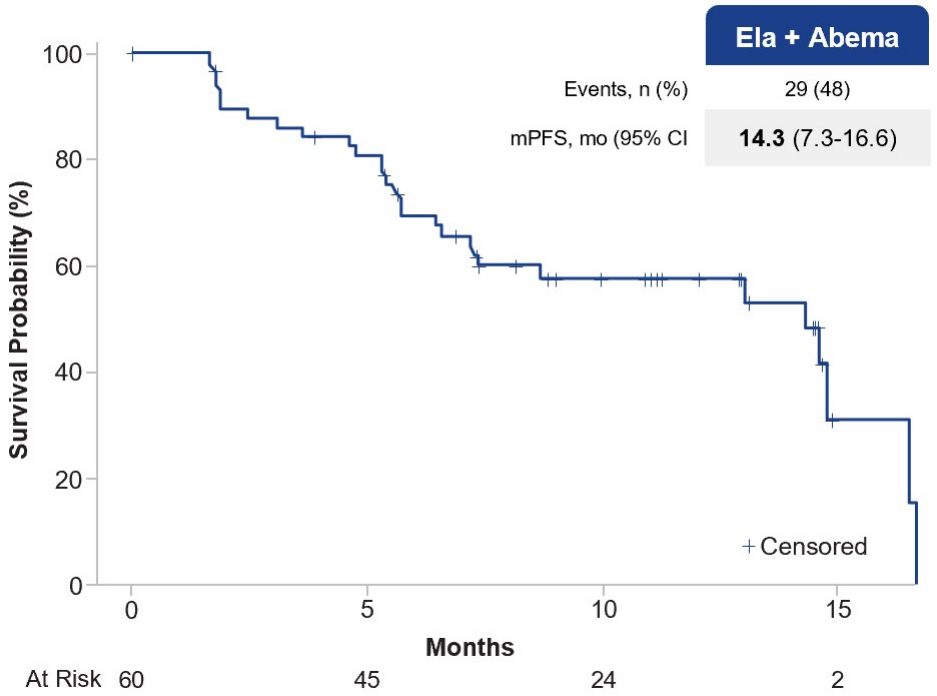
Rugo H. SABCS 2025

Baseline Characteristics: Elacestrant + Abemaciclib

	Elacestrant + abemaciclib, n=60
Median age, years (range)	61 (29-84)
Gender at birth, n (%)	
Female	57 (95)
Male	3 (5)
ECOG PS, n (%)	
0	46 (77)
1	14 (23)
Visceral metastasis,* n (%)	55 (92)
Mutations, n (%)	
ESR1m	20 (33)
PIK3CAm	16 (27)
Primary endocrine resistance,† n (%)	9 (15)
Median number of prior therapies for a/mBC, n (range)	1 (0-3)
Prior CDK4/6i for a/mBC, n (%)	30 (50)
Palbociclib	19 (32)
Ribociclib	12 (20)
Number of prior lines of ET for a/mBC, n (%)	
0	2 (3)
1	47 (78)
2	10 (17)
3+	1 (2)
Prior fulvestrant for a/mBC, n (%)	18 (30)

ORR (95%IC): **24.6% [14.1 – 37.8]**

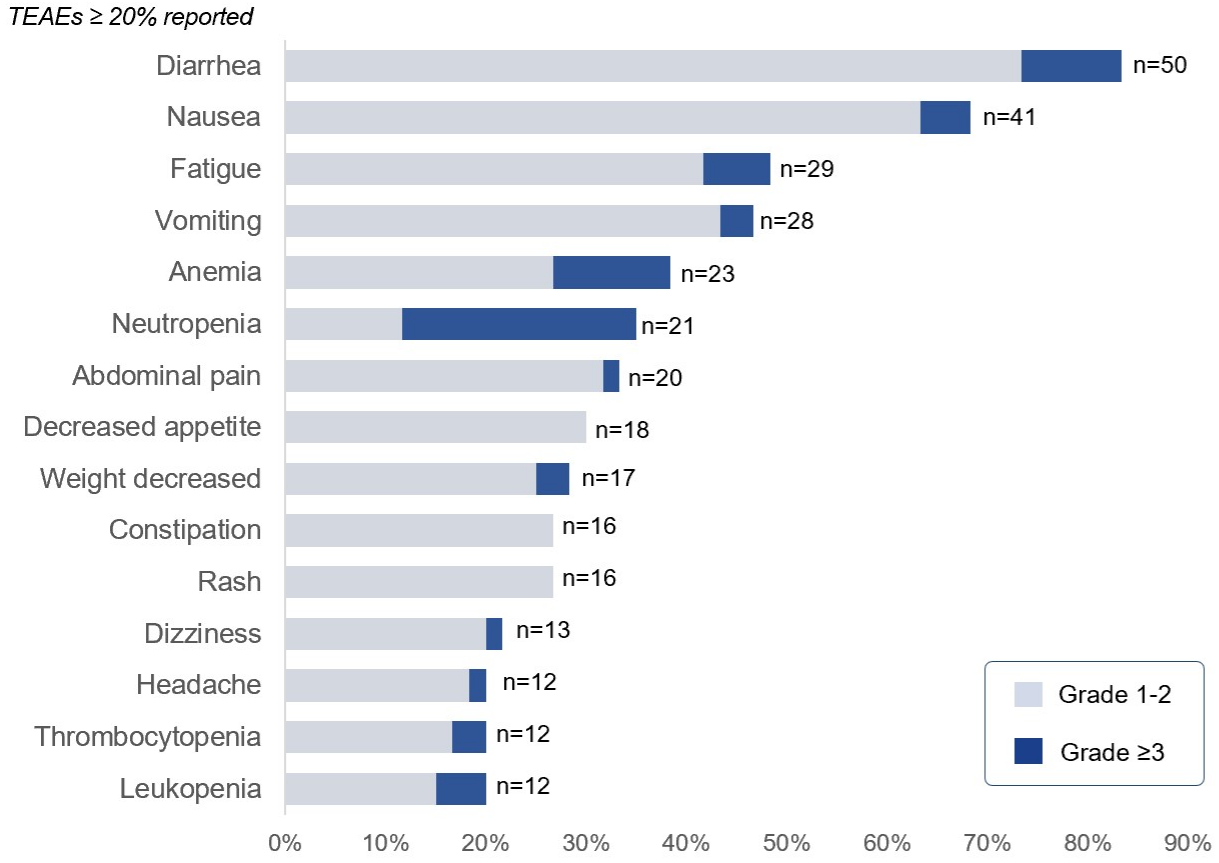
PFS RESULTS



Maturity not reached for PFS (95% CI) for genomic subgroups (*ESR1* / *PIK3CA*) or by prior CDK4/6i exposure

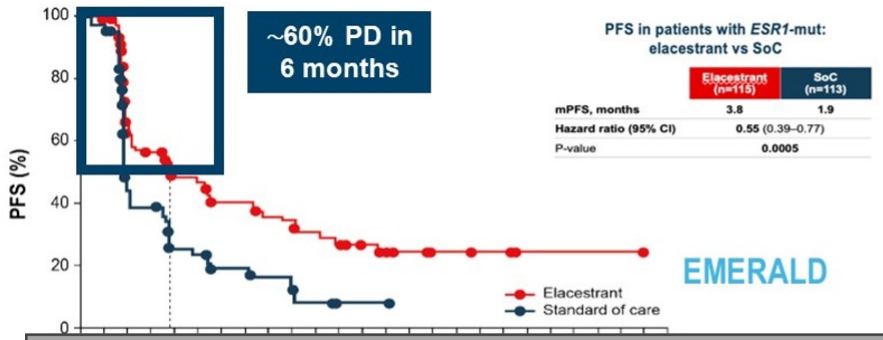
Rugo H. SABCS 2025

Adverse Events: Elacestrant + Abemaciclib



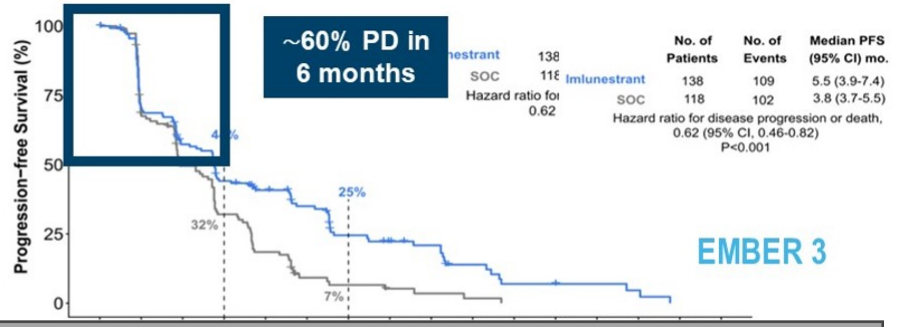
- **The safety profile is consistent with either abemaciclib plus standard ET or elacestrant**
- **No bradycardia or photopsia were reported, and no new safety signals were observed**
- **Any TEAE leading to elacestrant + abemaciclib drug withdrawal 0%**
- **Any TEAE leading to elacestrant + abemaciclib drug reduction 5%**

Rugo H. SABCS 2025



PFS in patients with *ESR1*-mut: elacestrant vs SoC

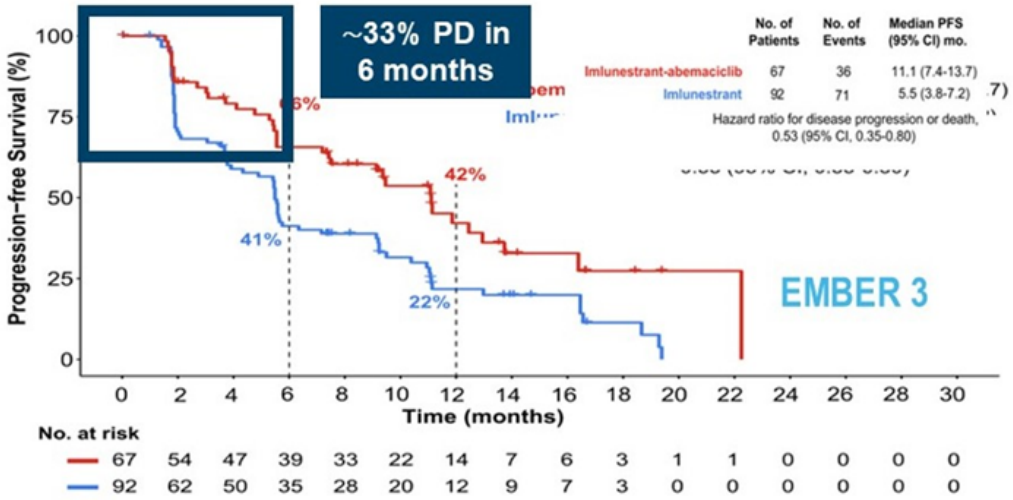
	Elacestrant (n=115)	SoC (n=113)
mPFS, months	3.8	1.9
Hazard ratio (95% CI)	0.55 (0.39–0.77)	
P-value	0.0005	



	No. of Patients	No. of Events	Median PFS (95% CI) mo.
Imlunestrant	138	109	5.5 (3.9-7.4)
SOC	118	102	3.8 (3.7-5.5)

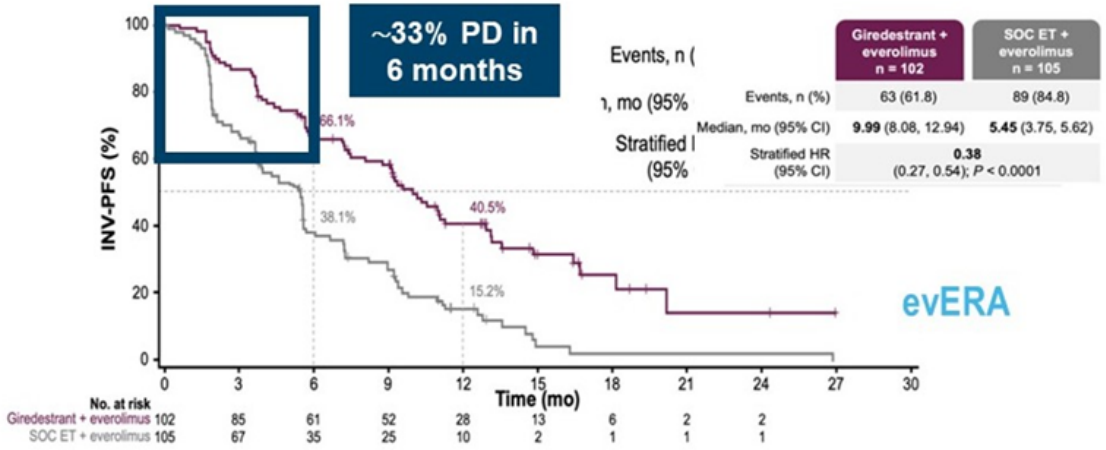
Hazard ratio for disease progression or death, 0.62 (95% CI, 0.46-0.82) P<0.001

APROXIMADAMENTE EL 60% DE LOS PACIENTES EN TTO CON SERDs ORAL EN MONOTERAPIA PROGRESAN EN LOS PRIMEROS 6 MESES



	No. of Patients	No. of Events	Median PFS (95% CI) mo.
Imlunestrant-abemaciclib	67	36	11.1 (7.4-13.7)
Imlunestrant	92	71	5.5 (3.8-7.2)

Hazard ratio for disease progression or death, 0.53 (95% CI, 0.35-0.80)



	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); *P* < 0.0001	

Mayer . ESMO 2025. Jhaveri et al NEJM 2025

2025 ASCO ANNUAL MEETING

Camizestrant + CDK4/6 inhibitor for the treatment of emergent *ESR1* mutations during first-line endocrine-based therapy and ahead of disease progression in patients with HR+/HER2– advanced breast cancer: Phase 3, double-blind ctDNA-guided SERENA-6 trial

ORIGINAL ARTICLE

First-Line Camizestrant for Emerging *ESR1*-Mutated Advanced Breast Cancer

F.-C. Bidard,[1] E.L. Mayer,[2] Y.H. Park,[3] W. Janni,[4] C. Ma,[5] M. Cristofanilli,[6] G. Bianchini,[7] K. Kalinsky,[8] H. Iwata,[9] S. Chia,[10] P.A. Fasching,[11] A. Brufsky,[12] Z. Nowecki,[13] J. Pascual,[14] L. Moreau,[15] S.-C. Chen,[16] N. Karadurmus,[17] E.N. Gal-Yam,[18] K.H. Jung,[19] S. Pernas,[20] S. McClain,[21] W. He,[22] T. Klinowska,[23] C. Huang-Bartlett,[21] and N.C. Turner,[24] for the SERENA-6 Study Group*

*ESR1*m surveillance during first-line AI+CDK4/6i

Screened, N=3325

Patients on first-line AI + CDK4/6i for ≥6 months

***ESR1*m testing** (every 2–3 months)

***ESR1*m surveillance, n=3256**

Patients with *ESR1*m detected, n=548

Positive on first test: 51%*
Positive after 2-5 tests: 38%*
Positive after >5 tests 11%*

Randomized, n=315

Patients tested for *ESR1*m in ctDNA with Guardant360 CDx every 2–3 months at time of routine staging scans

Patients ongoing in surveillance when screening closed, n=1949

Discontinued (n=233) due to:
- Screen failure (n=200)
  - Concurrent disease progression (n=53)
  - Patient not meeting other eligibility criteria (n=48)
  - Reason not provided (n=99)
- Withdrew consent, lost to follow-up or unknown (n=33)

SERENA-6 study design

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

R 1:1

N=315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

Stratification factors

- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

Continuing AI (anastrozole/ letrozole) + CDK4/6i + placebo for camizestrant

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

Primary endpoint

PFS by investigator assessment (RECIST v1.1)

Secondary endpoints

- PFS2**
- OS**
- Safety
- Patient-reported outcomes

*Pre- or perimenopausal women, and men received a luteinizing hormone–releasing hormone agonist per clinical guidelines. **Key secondary endpoint.
OS, overall survival; PFS2, second progression-free survival; qd, once daily dose; R, randomized; RECIST, response evaluation criteria in solid tumors.

PRESENTED BY: Nicholas Turner, MD, PhD

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

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Baseline characteristics

SERENA-6

Characteristic		Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Median age (range) — years		61.0 (29–81)	60.5 (35–89)
Female — n (%)		157 (100)	155 (98)
Race — n (%)	White	97 (62)	102 (65)
	Asian/other	39 (25) / 21 (13)	34 (22) / 22 (14)
Postmenopausal status — n (%)		123 (78)	127 (80)
ECOG performance-status score — n (%)*	0/1	107 (68) / 48 (31)	98 (62) / 56 (35)
Visceral metastases — n (%)†		66 (42)	71 (45)
Time of *ESR1*m detection — n (%)†	At first test	84 (54)	84 (53)
	At a subsequent test‖	73 (47)	74 (47)
	Median (range) – months	22 (4–95)	22 (6–96)
Time from initiation of AI + CDK4/6i to randomization — n (%)†	≥18 months	97 (62)	100 (63)
	<18 months	60 (38)	58 (37)
	Median (range) – months	23 (7–96)	23 (6–96)
CDK4/6i continued at randomization — n (%)†	Palbociclib	119 (76)	119 (75)
	Ribociclib	24 (15)	23 (15)
	Abemaciclib	14 (9)	16 (10)
Most common *ESR1*m at baseline — n (%)‡	D538G	70 (45)	82 (52)
	Y537S	61 (39)	60 (38)
	Y537N	29 (19)	25 (16)

*Data was missing for 2 patients in the camizestrant + CDK4/6i arm and 3 patients in the AI + CDK4/6i. One patient in the AI+CDK4/6i group had a score of 2, which was a protocol deviation. †Stratification factors. ‖Subsequent tests were performed every 2-3 months after the initial test. ‡Three most prevalent *ESR1*m detected of the 11 qualifying mutations. Patients may have had more than one *ESR1*m. ECOG, Eastern Cooperative Oncology Group.

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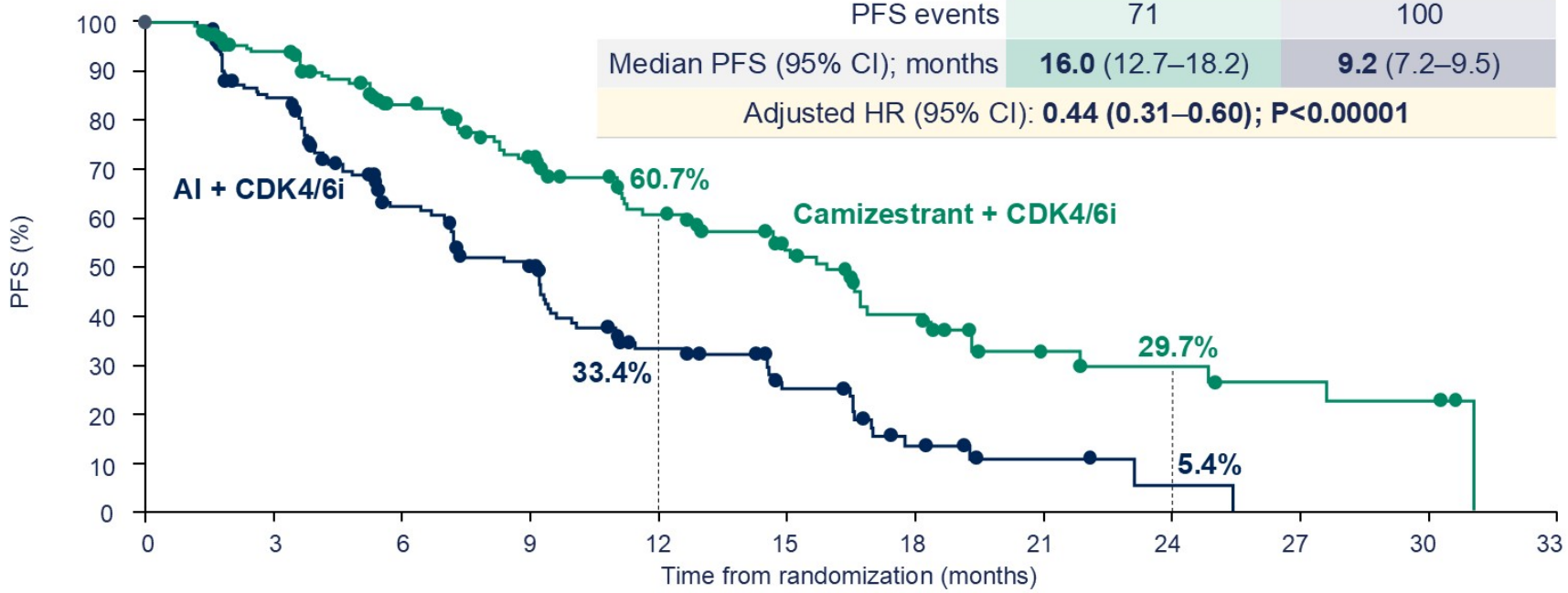
Primary endpoint: Investigator-assessed PFS

SERENA-6

	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

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

P-value crossed the threshold for significance (P=0.0001). PFS was defined per RECIST v1.1. HR was estimated using the Cox proportional hazard model adjusted for stratification factors.
CI, confidence interval; HR, hazard ratio.

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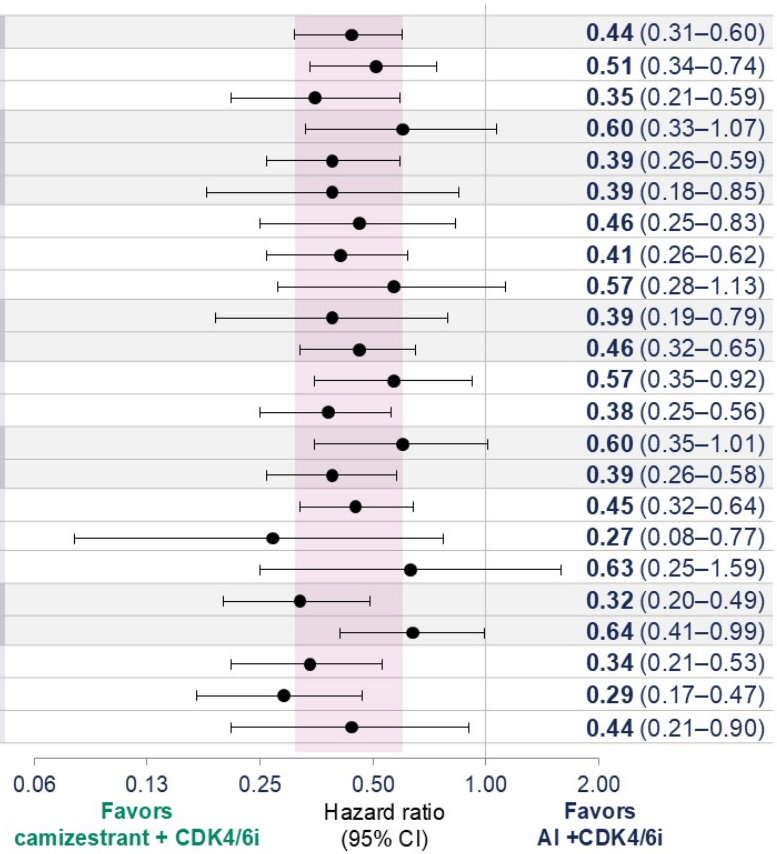
SERENA-6

Investigator-assessed PFS by subgroup

	Subgroup	Camizestrant + CDK4/6i	AI + CDK4/6i	Hazard ratio (95% CI)
		no. of events/total no.		
	All patients	71/157	100/158	**0.44** (0.31–0.60)
Age	<65 years	44/95	67/104	**0.51** (0.34–0.74)
	≥65 years	27/62	33/54	**0.35** (0.21–0.59)
Race	Asian	22/39	25/34	**0.60** (0.33–1.07)
	White	37/97	61/102	**0.39** (0.26–0.59)
	Other	12/21	14/21	**0.39** (0.18–0.85)
Region	Asia	19/40	28/39	**0.46** (0.25–0.83)
	Europe	37/89	54/91	**0.41** (0.26–0.62)
	North America	15/28	18/28	**0.57** (0.28–1.13)
Menopausal status	Pre-/perimenopausal women, and men	14/34	18/31	**0.39** (0.19–0.79)
	Postmenopausal	57/123	82/127	**0.46** (0.32–0.65)
Disease site*	Visceral	32/65	37/64	**0.57** (0.35–0.92)
	Non-visceral	39/92	63/92	**0.38** (0.25–0.56)
Time from initiation of AI + CDK4/6i to randomization*	<18 months	28/50	29/46	**0.60** (0.35–1.01)
	>18 months	43/105	69/110	**0.39** (0.26–0.58)
CDK4/6i*	Palbociclib	57/117	78/118	**0.45** (0.32–0.64)
	Ribociclib	4/23	13/23	**0.27** (0.08–0.77)
	Abemaciclib	10/15	9/15	**0.63** (0.25–1.59)
Time of *ESR1*m detection*	First test	36/82	56/79	**0.32** (0.20–0.49)
	A subsequent test‖	35/75	44/79	**0.64** (0.41–0.99)
Type of *ESR1*m	D538G	29/70	52/82	**0.34** (0.21–0.53)
	Y537S	24/61	46/60	**0.29** (0.17–0.47)
	Y537N	13/29	18/25	**0.44** (0.21–0.90)



*Stratification factors at randomization. ‖Subsequent tests were performed every 2-3 months after the initial test. HRs and 95% CIs were not calculated for subgroups with <20 events, except for the CDK4/6i subgroup. HRs and 95% CIs were calculated from a Cox proportional hazards model with treatment, factor and treatment-by-factor as covariates.

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Second progression-free survival (PFS2)

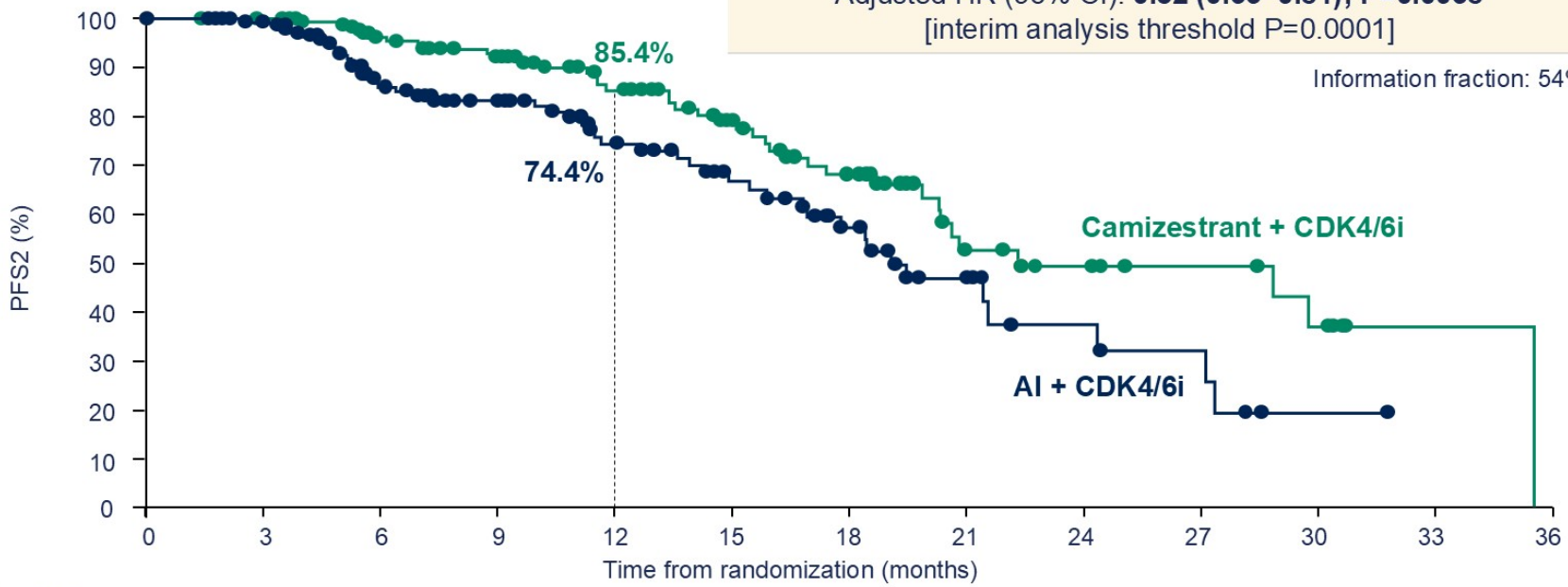
Key secondary endpoint

SERENA-6

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS2 events	38	47

Adjusted HR (95% CI): **0.52 (0.33–0.81); P=0.0038**
[interim analysis threshold P=0.0001]

Information fraction: 54%



Number of patients at risk

Camizestrant + CDK4/6i	157	146	120	103	74	55	39	17	12	9	6	1	0
AI + CDK4/6i	158	144	98	78	55	38	25	12	7	5	1	0	0

HR was estimated using the Cox proportional hazard model adjusted for stratification factors. Final PFS2 analysis will occur at 158 PFS2 events.

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COMO POSICIONAMOS ESTOS DATOS EN LA ACTUALIDAD EN PACIENTES CON ICDK PREVIOS

Estudio	Régimen (SERD + Socio)	N	% iCDK previo	mPFS (Meses)	HR	Población / Contexto
EMBER-3	**Imlunestrant** + Abemaciclib	874 213 (I+A)	**~82%**	**9.1 vs 3.7 (pre-ICDK)** **11.1 vs 5.5 (ESR1m)**	0.53	2ª línea (post-ET). 33% ESR1m
ELEVATE (FASE II)	**Elacestrant** + Abemaciclib	60	**50%**	**14.3**	--	Pacientes pretratados con ICDK 50%. 33% ESR1m
VIKTORIA 3 ramas	**Gedatolisib** + F + P	392 131 triplete	**100%**	**9.3 vs 2 (triplete vs HT)**	0.24	Triplete (ER + PI3K/mTOR + CDK4/6). Post- icdk pi3KCA wt
evERA	**Giredestrant** + Everolimus	373	**100%**	**9.99 vs 5.55 (ESR1m)** **8,77 vs 5.49 (ITT)**	0.38	55% ESR1m
ELEVATE (FASE II)	Elacestrant + everolimus	50	100%	**8.3**	--	*ESR1m* 42%,
CAPItello-291	Capivasertib + Fulvestrant	708	**100%**	**7.2 vs 3.6 (ITT)** **7.3 vs 3.1 (pik3CA/AKT/PTEN)**	0.60	Beneficio restringido a vía AKT/PI3K/PTEN alterada.

¿COMO INTEGRAMOS LA PRIMERA LINEA?

SERENA-6 study design

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

R 1:1, N=315

- Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI
- Continuing AI (anastrozole/letrozole) + CDK4/6i + placebo for camizestrant

Stratification factors
- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

Primary endpoint

PFS by investigator assessment (RECIST v1.1)

Secondary endpoints
- PFS2**
- OS**
- Safety
- Patient-reported outcomes

*Pre- or perimenopausal women, and men received a luteinizing hormone–releasing hormone agonist per clinical guidelines. **Key secondary endpoint.
OS, overall survival; PFS2, second progression-free survival; qd, once daily dose; R, randomized; RECIST, response evaluation criteria in solid tumors.

2025 ASCO ANNUAL MEETING #ASCO25 PRESENTED BY: Nicholas Turner, MD, PhD

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

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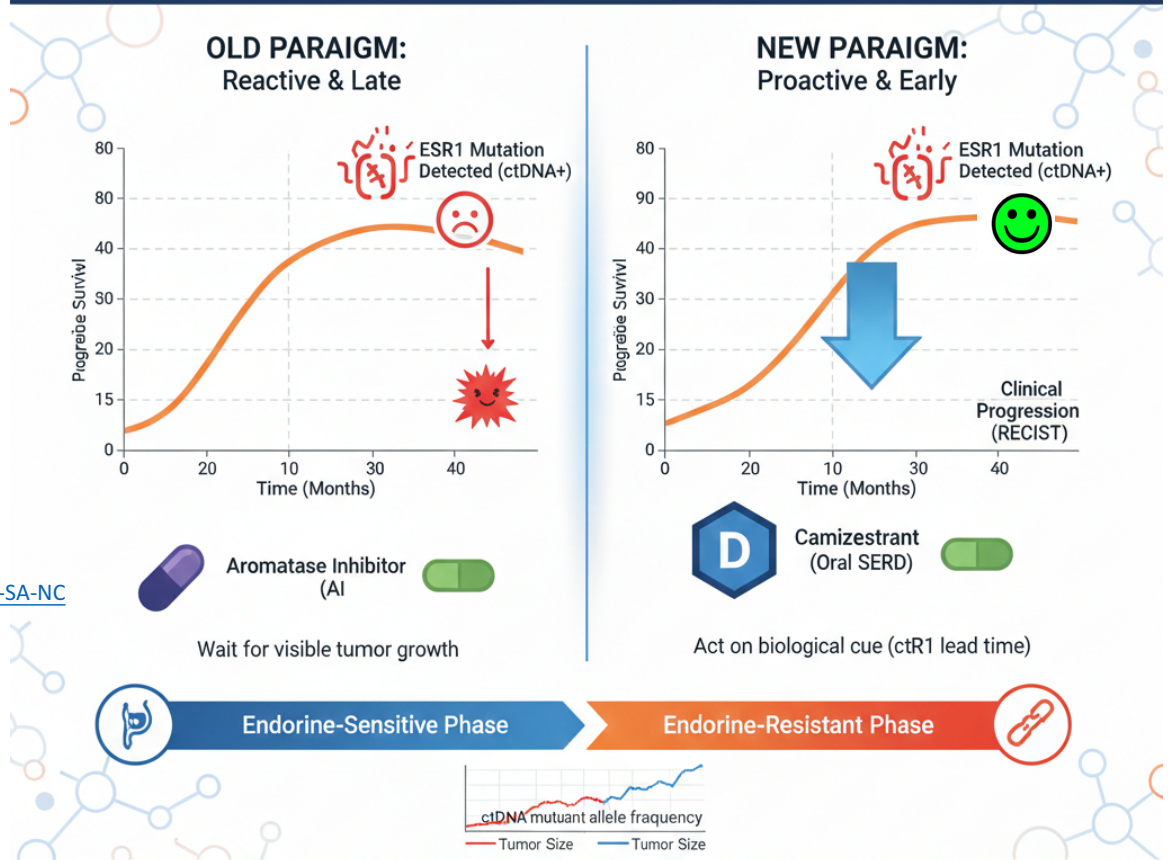
SERENA-6: Intervening on Biological Progression (ctDNA)

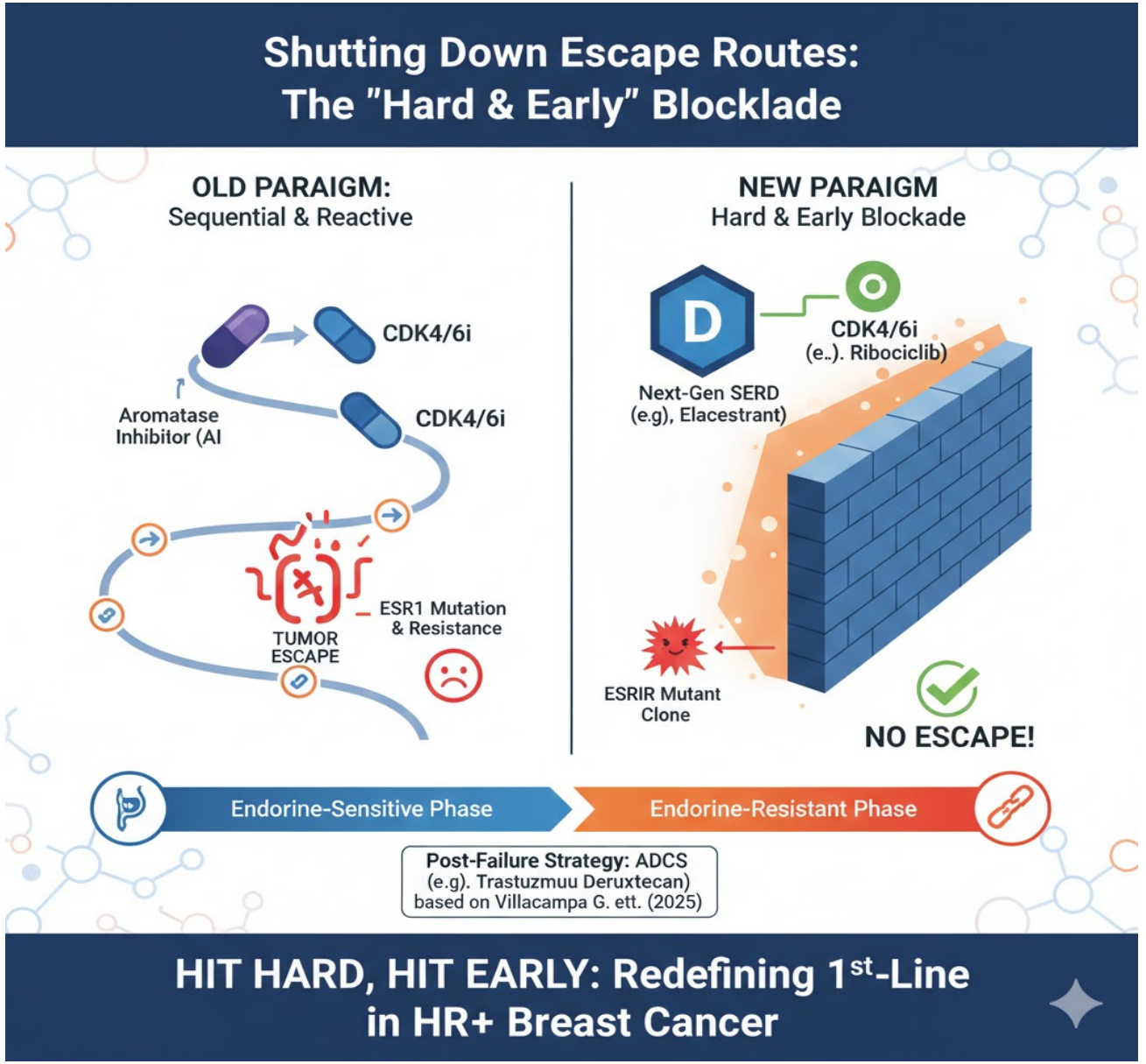
Switching AI to Camizatrant at ESR1 Mutation Emergence



IMPACT: Personalized Thereapy Before Inrervreable Resistance

Del tratamiento reactivo a la interceptación biológica

DIRECCION FUTURA



PRIMERAS LINEAS

persevERA

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

R 1:1

- Giredestrant 30mg QD + Palbociclib 125mg + Letrozole-matched PLA
- Letrozole 2.5mg + Palbociclib 125mg + Giradestrant-matched PLA

PFS

SERENA-4

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

R 1:1

- Camizestrant 75mg QD + Palbociclib 125mg + Anastrozole-matched PLA
- Anastrozole 1mg + Palbociclib 125mg + Camizestrant-matched PLA

PFS

SERAFA-1

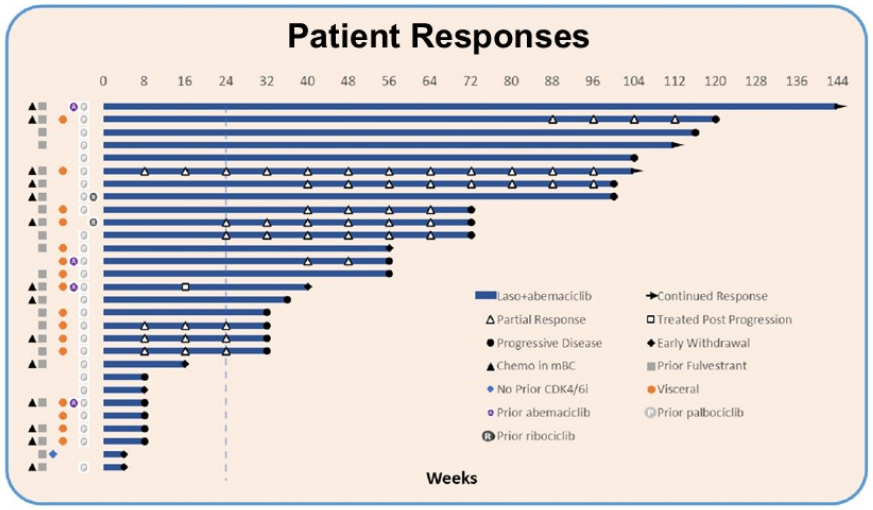
Fase IIIb

No prior systemic tx for ABC

→ Camizestrant 75 mg + Ribociclib 600 mg

ELAINE Program: Lasofoxifene Combined With Abemaciclib

ELAINE 2: Phase 2 Trial of Lasofoxifene + Abemaciclib in ER+/HER2- MBC With an ESR1 Mutation



ORR: 50% (95% CI, 29.0–71.0)
Median TTR: 169 days
Median DoR: 164 days
Median PFS: 55.7 weeks (13 months) (95% CI 32.0–NE)

ELAINE 3 (NCT05696626): Open-label, phase 3, multicenter, randomized-controlled study in 18 countries

Participants
- Women and men
- ER+/HER2-, locally advanced or metastatic breast cancer
- Progressed on AI plus palbociclib or ribociclib
- ≥1 *ESR1* mutation
- ***Enrollment goal:*** 400 patients (200 per group)

Lasofoxifene (oral; 5 mg/day) **plus** **abemaciclib** (oral; 150 mg BID)

Randomized 1:1

Fulvestrant (IM; 500 mg on days 1, 15, and 29, then monthly) **plus** **abemaciclib** (oral; 150 mg BID)

Taken until disease progression, death, unacceptable toxicity, or study withdrawal

Endpoints
- **Primary**
  - Progression-free survival
- **Secondary**
  - Objective response rate
  - Overall survival
  - Clinical benefit rate
- **Other**
  - *ESR1* MAF changes
  - Time to chemo-therapy
  - Quality of life
  - Safety

Statistical Analysis
- Target sample size is 400 based on progression-free survival
- Outcomes between treatments will be compared using a stratified, Cox proportional hazards model and stratified logrank test

Damodaran S et al. *Ann Oncol*. 2023;34:1131-1140.;Goetz MP et al. ASCO 2024. Abstract TPS1127.

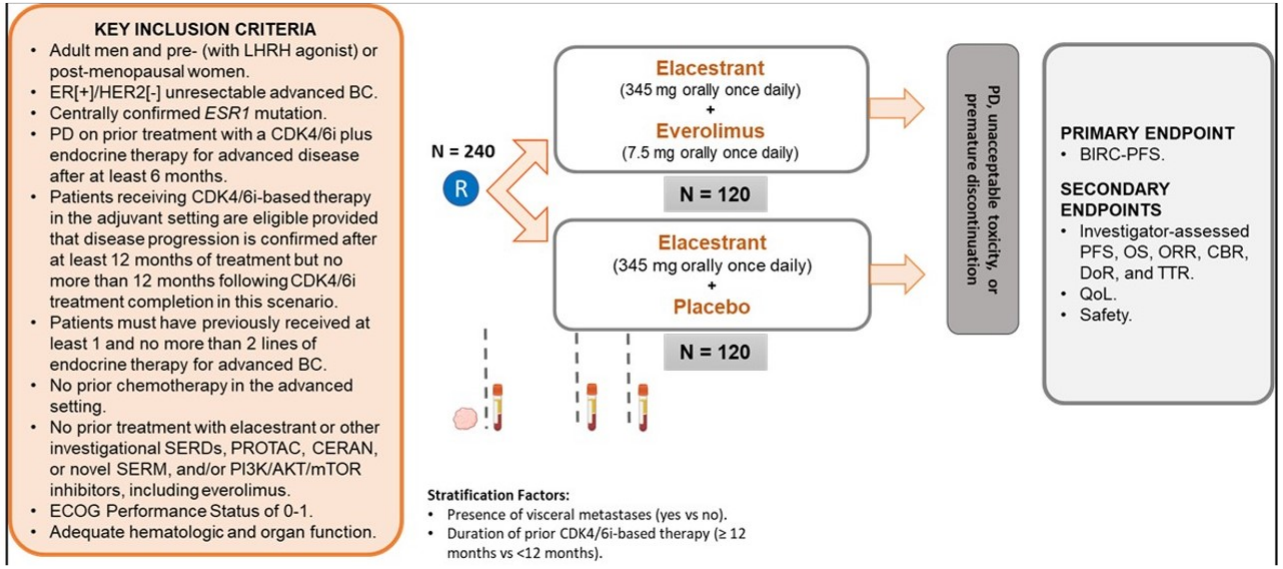
SEGUNDAS LINEAS

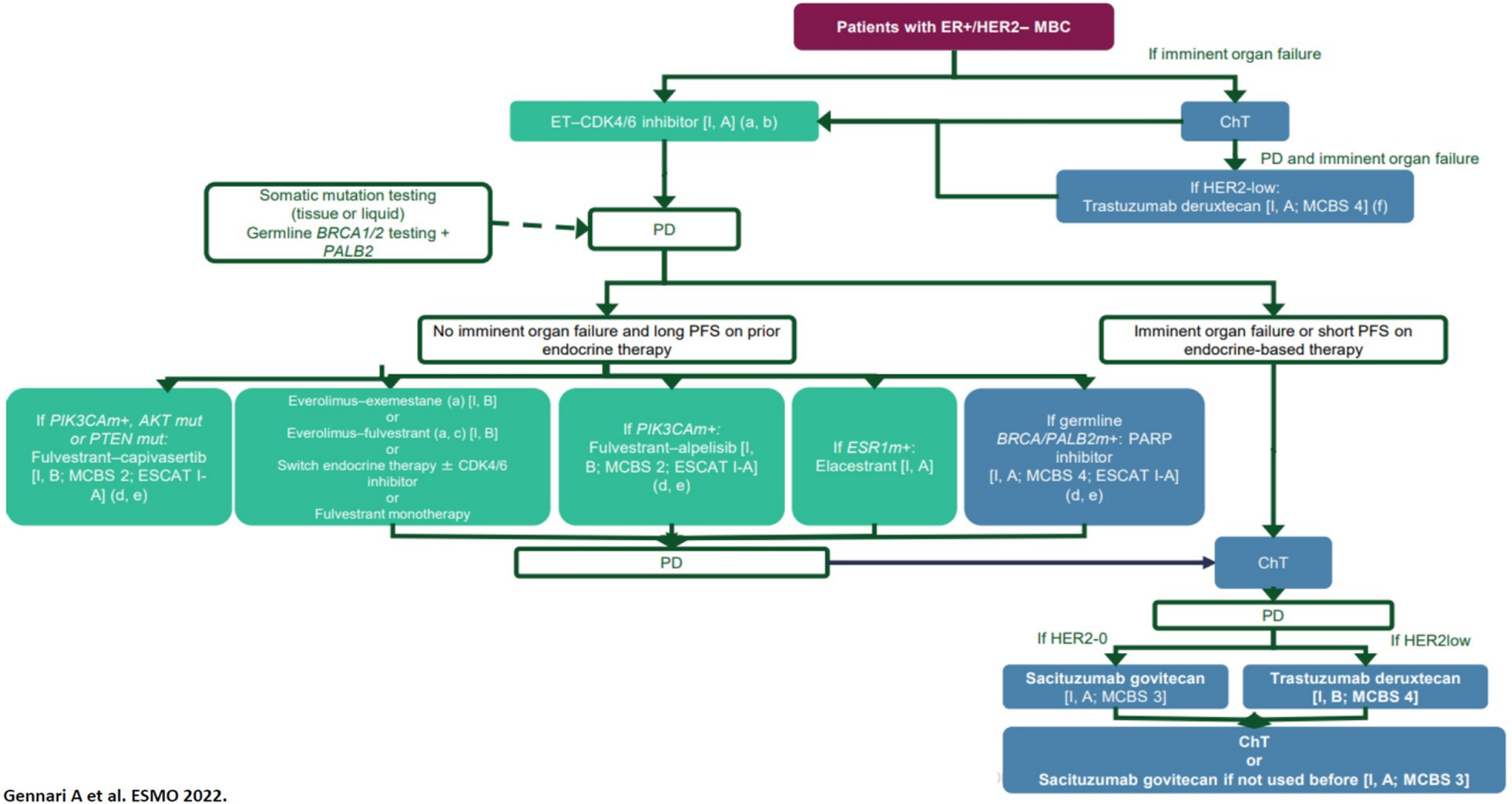
ADELA

NCT06382948

KEY INCLUSION CRITERIA

- Adult men and pre- (with LHRH agonist) or post-menopausal women.
- ER[+]/HER2[-] unresectable advanced BC.
- Centrally confirmed *ESR1* mutation.
- PD on prior treatment with a CDK4/6i plus endocrine therapy for advanced disease after at least 6 months.
- Patients receiving CDK4/6i-based therapy in the adjuvant setting are eligible provided that disease progression is confirmed after at least 12 months of treatment but no more than 12 months following CDK4/6i treatment completion in this scenario.
- Patients must have previously received at least 1 and no more than 2 lines of endocrine therapy for advanced BC.
- No prior chemotherapy in the advanced setting.
- No prior treatment with elacestrant or other investigational SERDs, PROTAC, CERAN, or novel SERM, and/or PI3K/AKT/mTOR inhibitors, including everolimus.
- ECOG Performance Status of 0-1.
- Adequate hematologic and organ function.





Gennari A et al. ESMO 2022.

ENFERMEDAD HORMONOSENSIBLE

Camizestrant + ICDK

ESRIR Mutant Clone

ET–CDK4/6 inhibitor [I, A] (a, b)

SERDs oral + ICDK

Somatic mutation testing (tissue or liquid)
Germline *BRCA1/2* testing + *PALB2*

PD

No imminent organ failure and long PFS on prior endocrine therapy

PFS **EMBER-3**
Imlunestrant + Abemaciclib

evERA
Giredestrant + Everolimus (ESRI mut)

If *PIK3CAm+, AKT mut or PTEN mut:* Fulvestrant–capivasertib [I, B; MCBS 2; ESCAT I-A] (d, e)

Everolimus–exemestane (a) [I, B]
or
Everolimus–fulvestrant (a, c) [I, B]
or
Switch endocrine therapy ± CDK4/6 inhibitor
or
Fulvestrant monotherapy

If *PIK3CAm+:* Fulvestrant–alpelisib [I, B; MCBS 2; ESCAT I-A] (d, e)

If *ESR1m+:* Elacestrant [I, A]

If germline *BRCA/PALB2m+*: PARP inhibitor [I, A; MCBS 4; ESCAT I-A] (d, e)

PFS **VIKTORIA**
Gedatolisib Triplete (SERD+P+PI3K/mTOR)

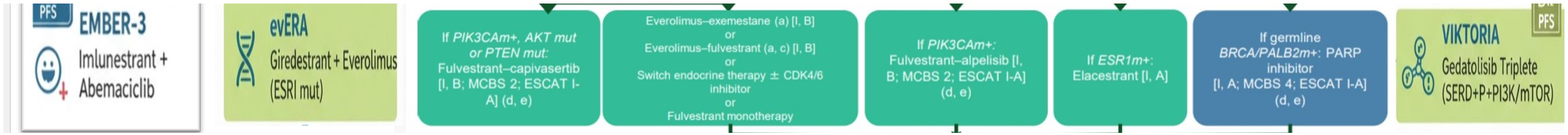
PD

Progressión Tardía: ADCS
T-DXd, Sacituzumab

CONCLUSIONES

- Los Serds se posicionan con el eje central del tratamiento hormonal en CMM
- ESR1 ya no es una barrera insuperable. Los SERDs orales han demostrado que pueden mantener el control hormonal del tumor bloqueando la vía de escape más común.
- Las combinaciones de SERDs + ICDK o SERDs+ Inh via pik3CA se posicionan como un alternativa atractiva en segunda línea de tratamiento hormonal
- Biospia líquida como brújula terapeútica. La oncología traslacional en el 2026, nos obliga la realización de pik3CA, AKT, PTEN y ESR1 de forma dinámica para seleccionar la terapia mas adecuada a cada paciente.
- Cambio de paradigma. Progresión radiológica vs progresión bioquímica

El tratamiento del cáncer de mama metastásico RH+/HER2– está entrando en una fase de **oncología de precisión real,** enfocándonos en la secuenciación basada en **biomarcadores (ESR1, AKT/PIK3CA/PTEN)** y en el uso prolongado de terapias endocrinas efectivas antes de quimioterapia.



GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025

blanca.cantos@salud.madrid.org