Elacestrant nel carcinoma mammario metastatico HR+/HER2-negativo/mESR1

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Disclosure Information

Luisa Carbognin, MD PhD

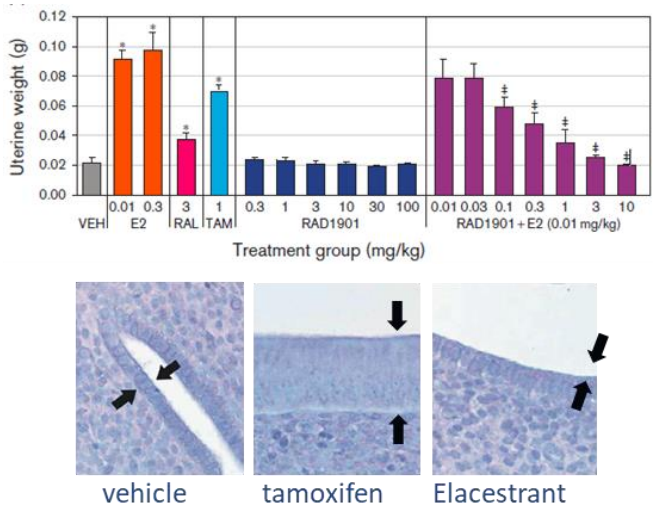
Relevant financial relationships to disclose:

- Honoraria from: Novartis, Astrazeneca, Gilead, Menarini
- Grant/Research support from: AIRC

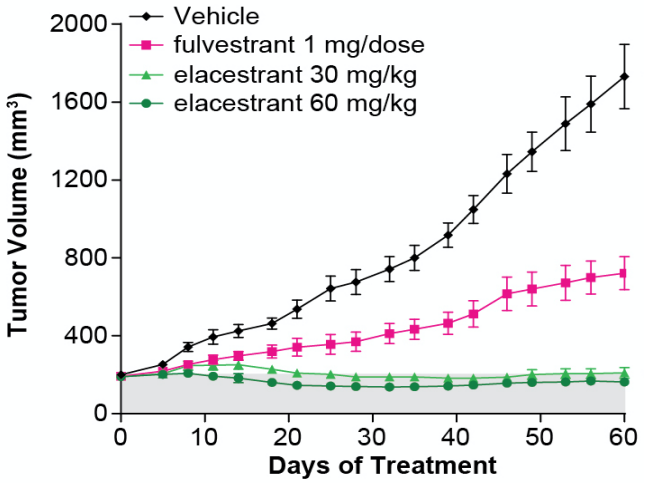
Elacestrant - Mechanism of action

- Elacestrant is a novel, nonsteroidal, **oral SERD and ER antagonist.**
- In preclinical studies Elacestrant:
  1) induced the **degradation of ER alpha in a dose-dependent manner and disrupted ER signaling**, significantly inhibiting cell proliferation *in vitro* and *in vivo* BC models, including those harboring *mESR1*[1,2,3,4]
  2) prevented bone loss in osteopenic rat model with negligible SERM-like activity detected at uterine level.[1,2,3]
- Elacestrant demonstrated antitumor activity and tolerability in a phase I trial of heavily pretreated patients with advanced ER+/HER2- BC, including patients with *mESR1*[5]

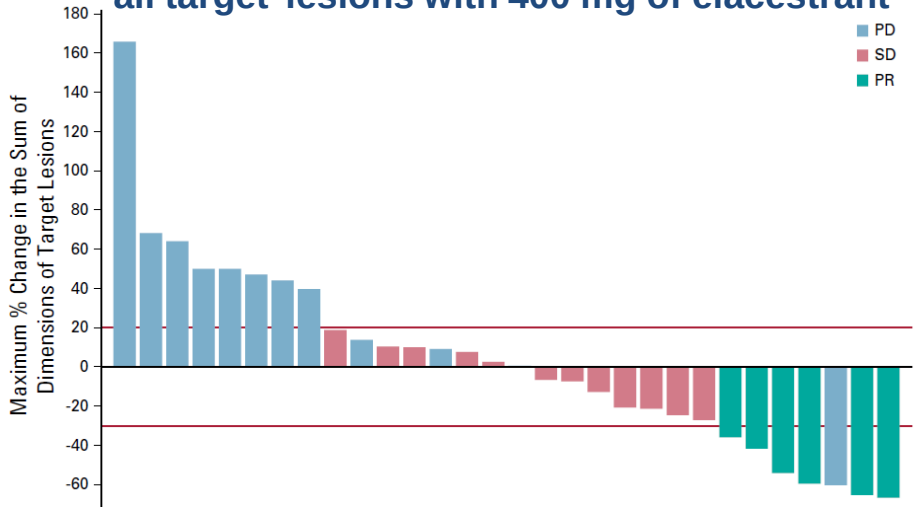
No stimulation in the immature rat model[2]



***In vivo* efficacy of elacestrant in tumors expressing *ESR1* mutations[1]**



Maximum percent change in sum of diameters of all target lesions with 400 mg of elacestrant[5]



1. Bihani T, et al. Clin Cancer Res. 2017; 2. Wardell SE, et al. Endocr Relat Cancer. 2015; 3. Patel HK, et al. Pharmacol Ther. 2018; 4. Garner F, et al. Anticancer Drugs. 2015; 5. Patel HK, et al. Breast Cancer Res. 2019;. 5. Bardia A, et al. J Clin Oncol. 2021

Elacestrant - Pharmacokinetics

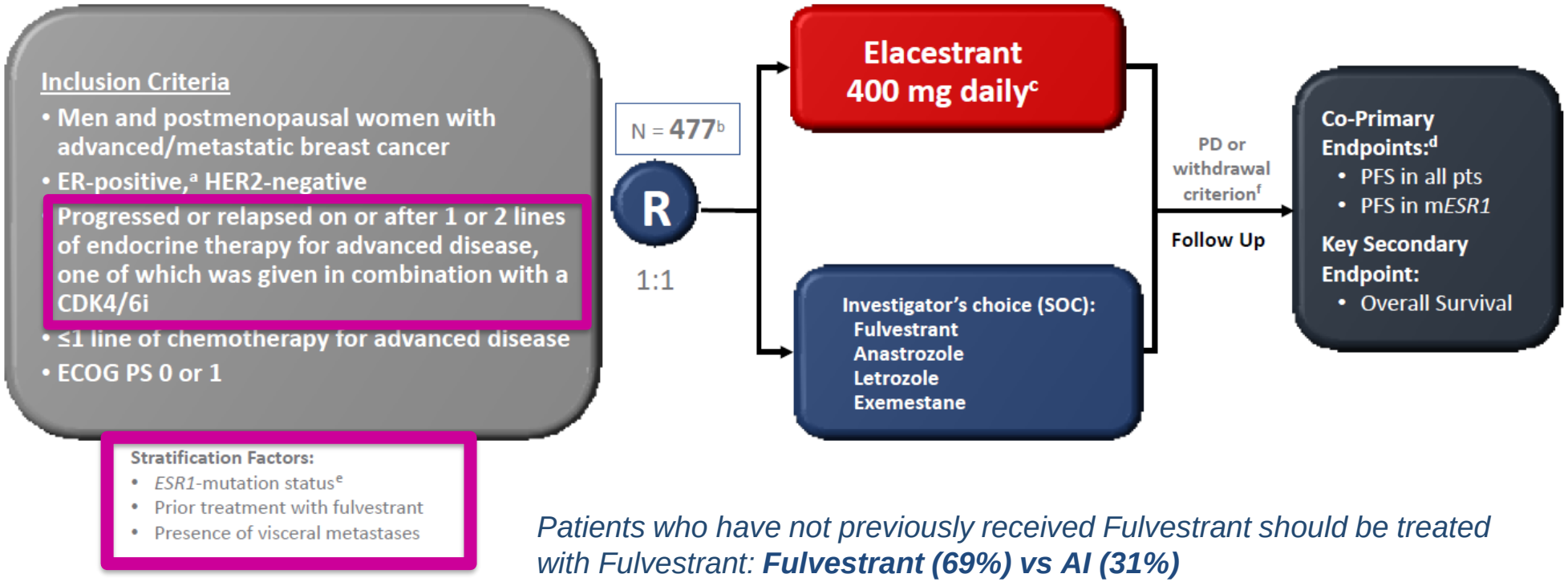
- **Elacestrant is predominately metabolized by CYP3A4.**
- As Elacestrant is a CYP3A4 substrate, its coadministration with a moderate/strong CYP3A4 inhibitor increases exposure (which may increase the risk of AEs) while the concomitant use with a moderate or strong CYP3A4 inducer decreases exposure (potentially reducing the effectiveness).
- **Administration: with food once daily**.
- Standard Dose: **345 mg** (equivalent to 400 mg Elacestrant hydrochloride); Dose Reduction: **258 mg** (3 tablets 86 mg, equivalent to 300 mg)
- Pharmacokinetics: not affected by age, sex and body weight.
- No relevant differences in Elacestrant Cmax/AUC values in mild hepatic impairment (Child-Pugh A). No studies in severe hepatic impairment.

CYP3A4/5 Moderate or Strong Inducers	CYP3A4/5 Moderate or Strong inhibitors
Apalutamide	Aprepitant
Bosentan	Boceprevir
Carbamazepine	Ciprofloxacin
Enzalutamide	Cobicistat
Etravirine	Conivaptan
Mitotane	Crizotinib
Phenobarbital	Cyclosporine
Phenytoin	Diltiazim
Primidone	Dronedarone
Rifampin	Eruthromycin
St. John's Wort	Fluconazole
	Fluvoxamine
	Grapefruit[a]
	Imatinib
	Itraconazole
	Ketoconazole
	Pomelo[a]
	Posaconazole
	Ritonavir (alone or with danoprevir, dasabuvir, elvitegravir, indinavir, lopinavir, paritaprevir, ombitsavir, saquinavir, tipranavir)
	Seville Orange[a]
	Star Fruit[a]
	Telaprevir
	Telithromycin
	Tofisopam
	Troleandomycin
	Verapimil
	Voriconazole

[a]Note: Subjects should avoid consumption of the following fruits, and juices and products derived from them: grapefruit, pomelo, Seville orange and Star Fruit
Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Guglielmi G, et al., Eur J of Pharmacol 2024; Sheridan M. Hoy, Drugs 2023

EMERALD Trial



	All Patient Population	*mESR1* Population
PFS events needed	~340	~ 160
Power	92%	80%
Hazard ratio (HR)	0.667	0.610
2-sided alpha level	0.025	0.025
Planned sample size	466	220

Patients who have not previously received Fulvestrant should be treated with Fulvestrant: ***Fulvestrant (69%) vs AI (31%)***

Median Age: 63 years (24-89)

Visceral metastasis: ~ 70%

Prior Adjuvant Therapy: ~ 65%

Prior CT for ABC: ~ 20%

2 prior lines of ET in ABC: ~ 45%

Prior Target Therapy for ABC: ~ 4% mTOR inhibitor; ~ 1% PI3K inhibitor

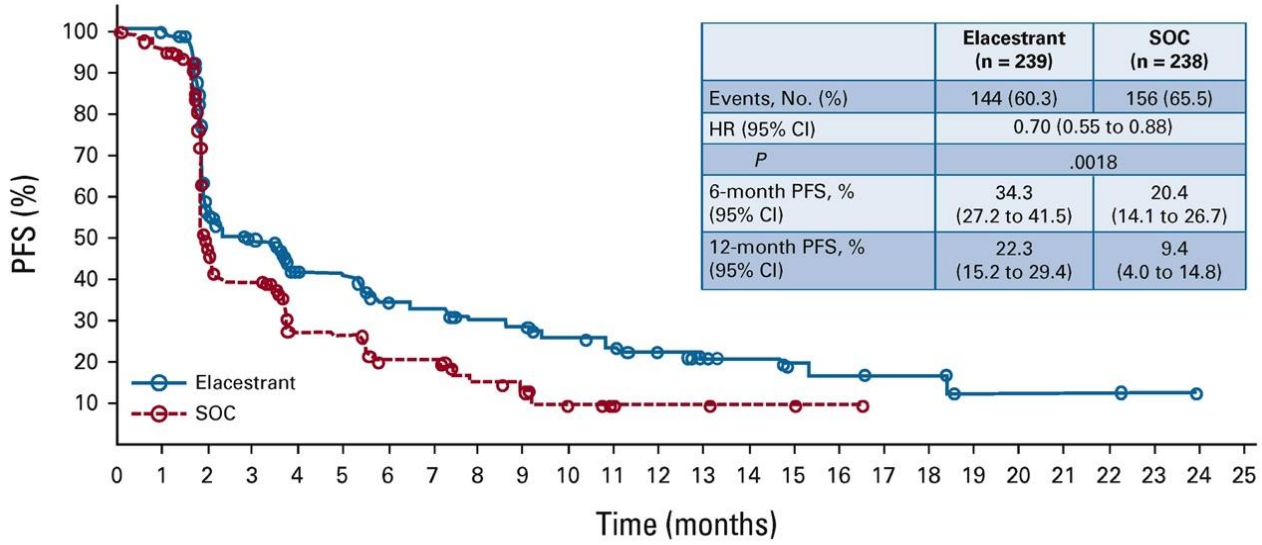
Prior Fulvestrant: ~ 30%

***ESR1m*: ~ 48%**

Bidard, et al., J Clin Oncol 2022

Primary End-points: PFS by BCIR

All Patients (ITT)

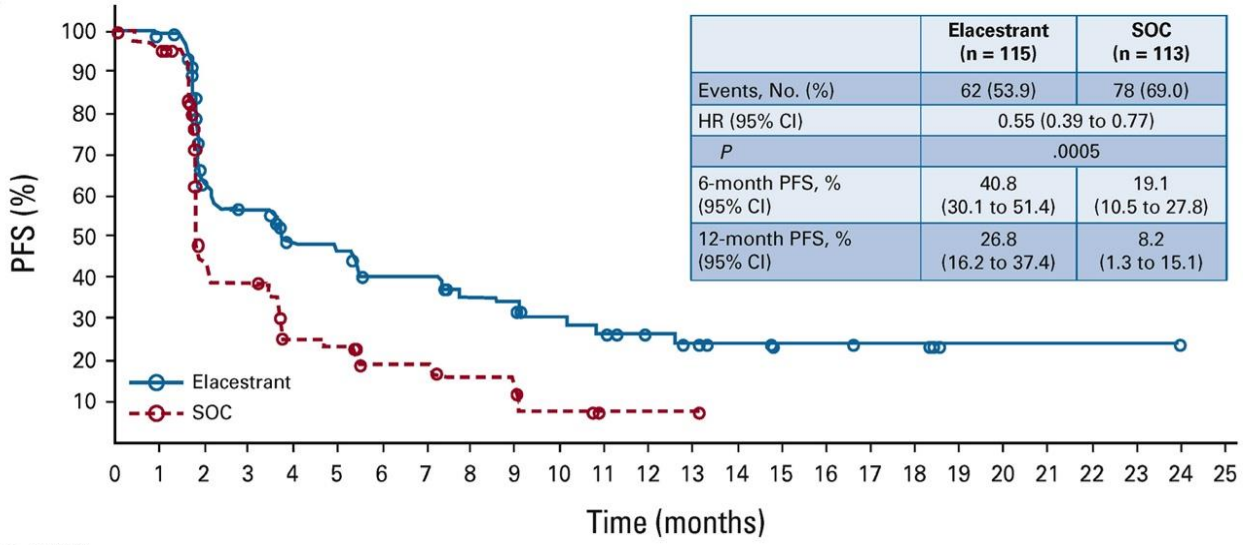


	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

No. at risk:

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

Patients with Tumors Harboring m*ESR1*



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

No. at risk:

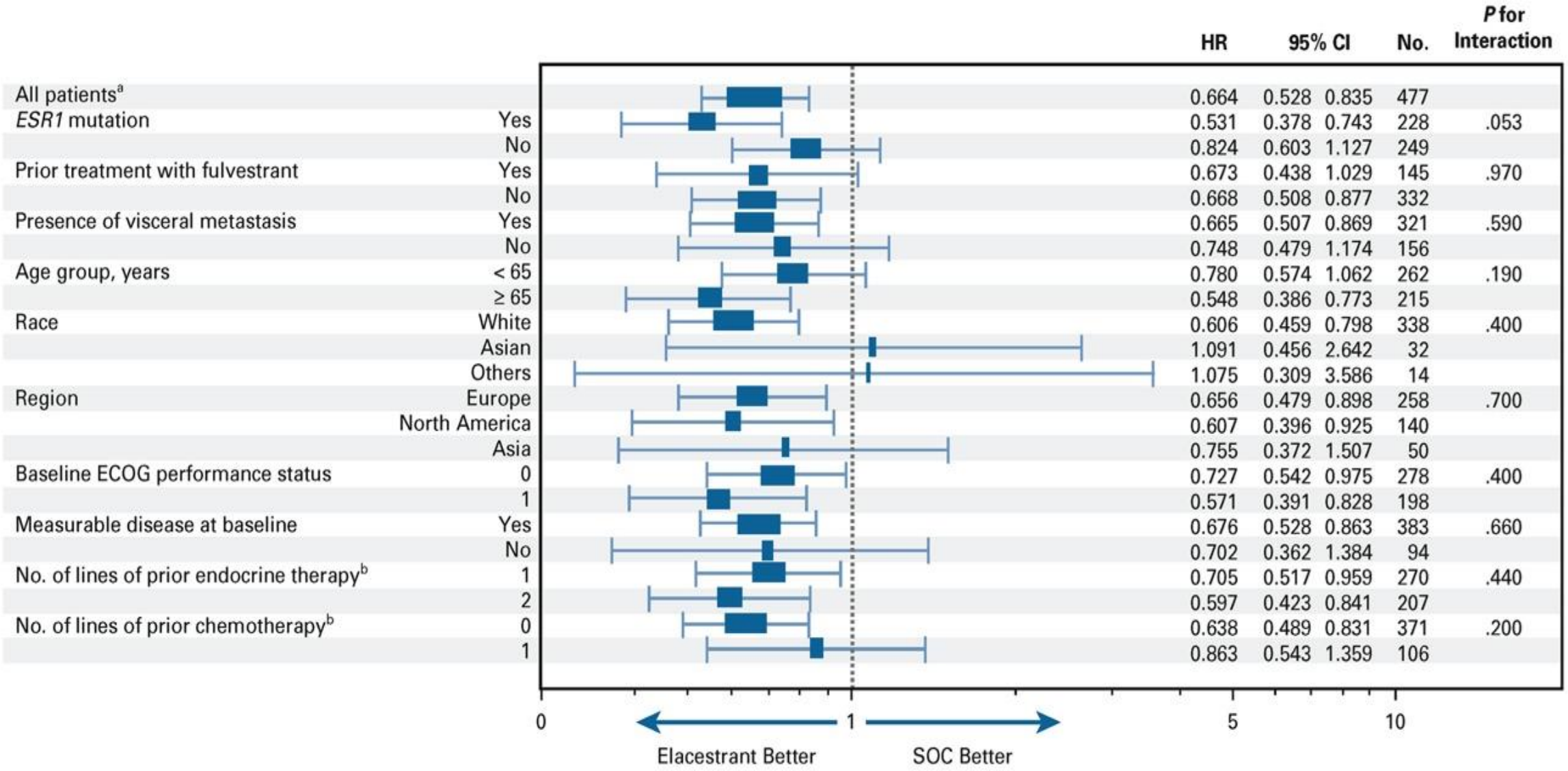
Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

- **Median PFS (2.8 months vs 1.9 months)**
- **Median PFS (3.8 months vs 1.9 months)**
- Kaplan Meier curves show an initial drop in both arms, highlighting possible endocrine resistance in the 2nd/3rd-line setting, but then clear separation of the curves in the endocrine sensitive setting.

Elacestrant improved PFS compared with fulvestrant or AI in both the overall population and patients with *ESR1-mut*

Bidard, et al., J Clin Oncol 2022

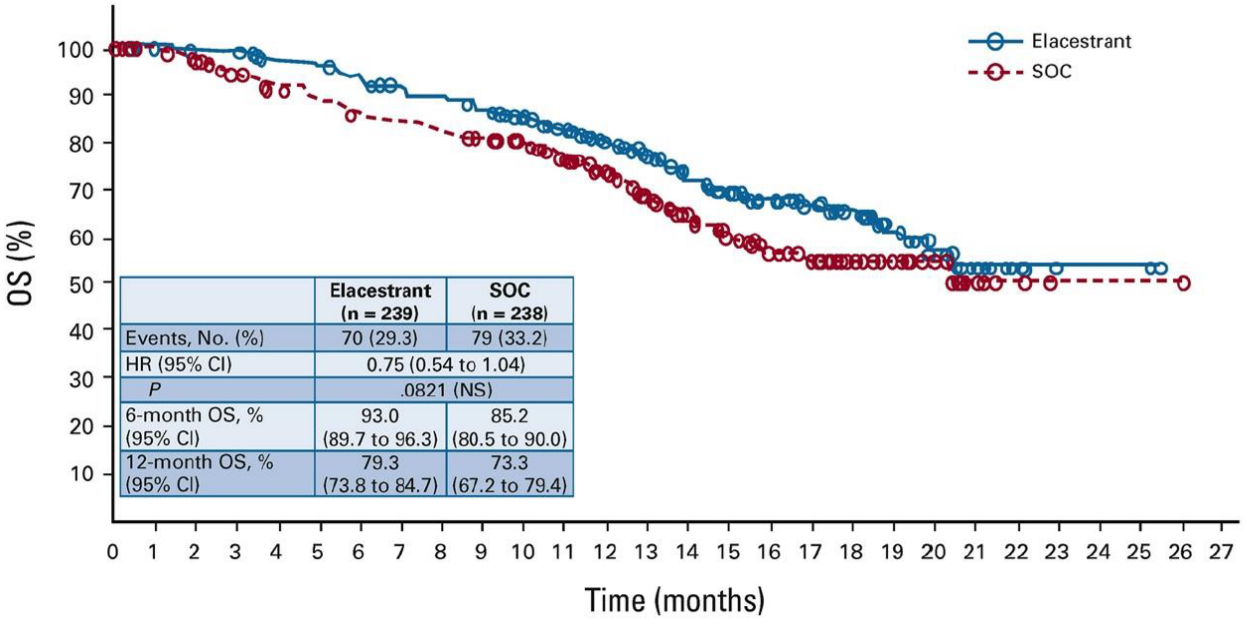
Subgroup Analysis of PFS (all patients)



Bidard, et al., J Clin Oncol 2022

OS (Interim Analysis)

All Patients

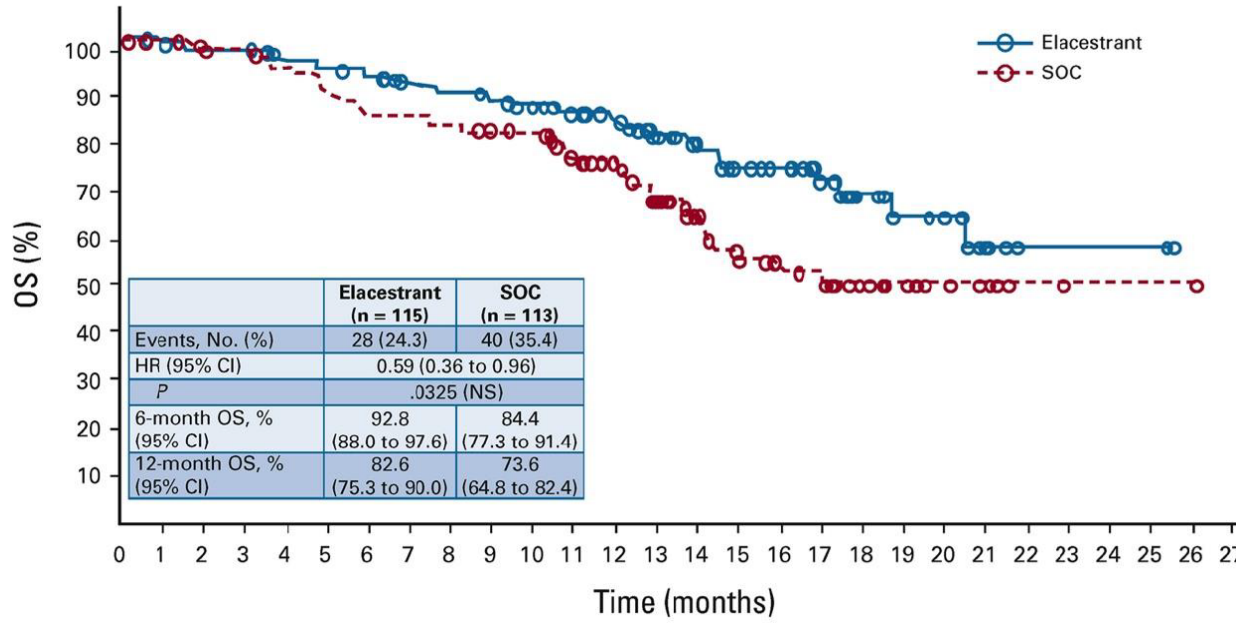


	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	70 (29.3)	79 (33.2)
HR (95% CI)	0.75 (0.54 to 1.04)	
P	.0821 (NS)	
6-month OS, % (95% CI)	93.0 (89.7 to 96.3)	85.2 (80.5 to 90.0)
12-month OS, % (95% CI)	79.3 (73.8 to 84.7)	73.3 (67.2 to 79.4)

No. at risk:

Elacestrant	239	233	230	229	220	218	211	202	197	191	180	166	139	118	98	89	78	60	49	33	22	10	5	2	2	2	0
SOC	238	223	216	206	164	187	179	177	173	163	157	144	118	96	78	67	49	42	31	23	15	6	3	1	1	1	0

Patients with ESR1mut



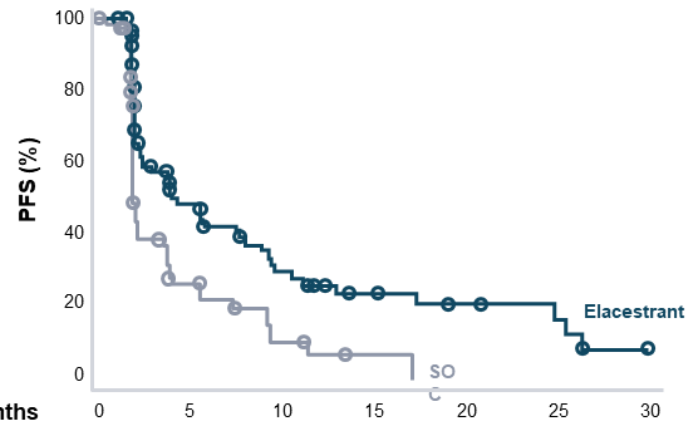
	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	28 (24.3)	40 (35.4)
HR (95% CI)	0.59 (0.36 to 0.96)	
P	.0325 (NS)	
6-month OS, % (95% CI)	92.8 (88.0 to 97.6)	84.4 (77.3 to 91.4)
12-month OS, % (95% CI)	82.6 (75.3 to 90.0)	73.6 (64.8 to 82.4)

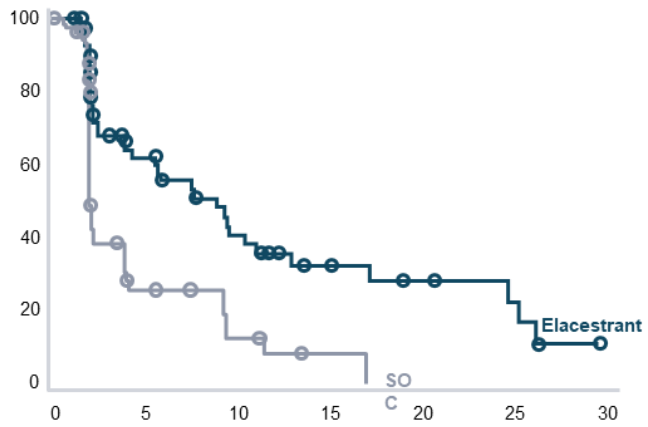
No. at risk:

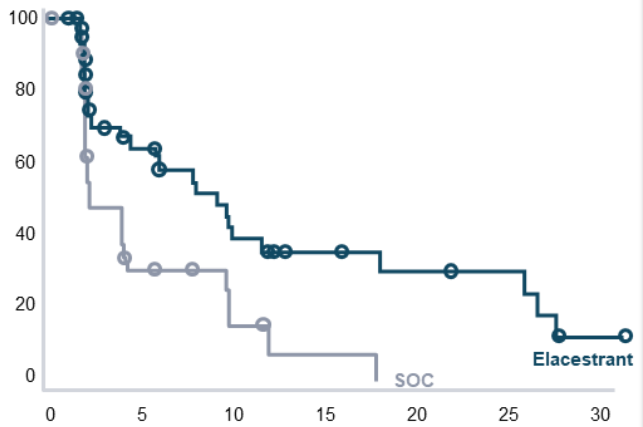
Elacestrant	115	112	111	111	105	103	101	95	93	90	86	80	68	55	45	40	36	25	17	13	11	4	2	2	2	2	0
SOC	113	106	101	101	96	90	86	86	84	79	77	68	56	44	33	27	22	19	14	10	6	4	2	1	1	1	0

Bidard, et al., J Clin Oncol 2022

PFS by Duration of CDK4/6i: Patients with *ESR1m*







No. of patients:

Elacestrant	103	50	33	25	20	16	11	9	8	7	6	5	5	1	1	0
SOC	76	26	14	10	8	4	2	1	1	0						

	78	42	31	24	20	16	11	9	8	7	6	5	5			
	58	19	10	9	8	4	2	1	1	0						

	55	30	23	18	16	12	8	8	7	6	6	5	5			
	39	16	8	7	6	3	1	1	1	0						

	Elacestrant (n=103)	Fulvestrant (n=76)
mPFS, mo [95% CI]	4.14 [2.20–7.79]	1.87 [1.84–3.45]
HR [95% CI]	0.472 [0.316–0.703]	

	Elacestrant (n=78)	Fulvestrant (n=58)
mPFS, mo [95% CI]	8.61 [4.14–10.84]	1.87 [1.84–3.68]
HR [95% CI]	0.406 [0.251–0.651]	

	Elacestrant (n=55)	Fulvestrant (n=39)
mPFS, mo [95% CI]	8.61 [5.45–16.89]	2.10 [1.87–3.94]
HR [95% CI]	0.453 [0.252–0.804]	

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error

SUPPLEMENTAL FIGURE 3. CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HR=hazard ratio; mo=months; mPFS=median progression-free survival; mut=mutation; no=number; PFS=progression-free survival; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

Bardia A et al, Clin Cancer Res 2024

PFS in Subgroups with *ESR1m* Tumors & Prior CDK4/6i ≥12 Mo

Patient Subgroup	n (%)	mPFS, mo		HR [95% CI]
		Elacestrant	SOC*	
All patients with *ESR1*-mut tumors	159 (100)	8.6	1.9	0.41 [0.26–0.63]
Bone metastases[†]	136 (86)	9.1	1.9	0.38 [0.23–0.62]
Liver and/or lung metastases	113 (71)	7.3	1.9	0.35 [0.21–0.59]
<3 metastatic sites[§]	82 (52)	9.0	1.9	0.41 [0.23–0.75]
≥3 metastatic sites[§]	53 (33)	10.8	1.8	0.31 [0.12–0.79]
PIK3CA-mut[¶]	62 (39)	5.5	1.9	0.42 [0.18–0.94]
TP53-mut	61 (38)	8.6	1.9	0.30 [0.13–0.64]
HER2-low expression[#]	77 (48)	9.0	1.9	0.30 [0.14–0.60]
ESR1 D538G-mut	97 (61)	9.0	1.9	0.38 [0.21–0.67]
ESR1 Y537S/N-mut	92 (58)	9.0	1.9	0.25 [0.13–0.47]

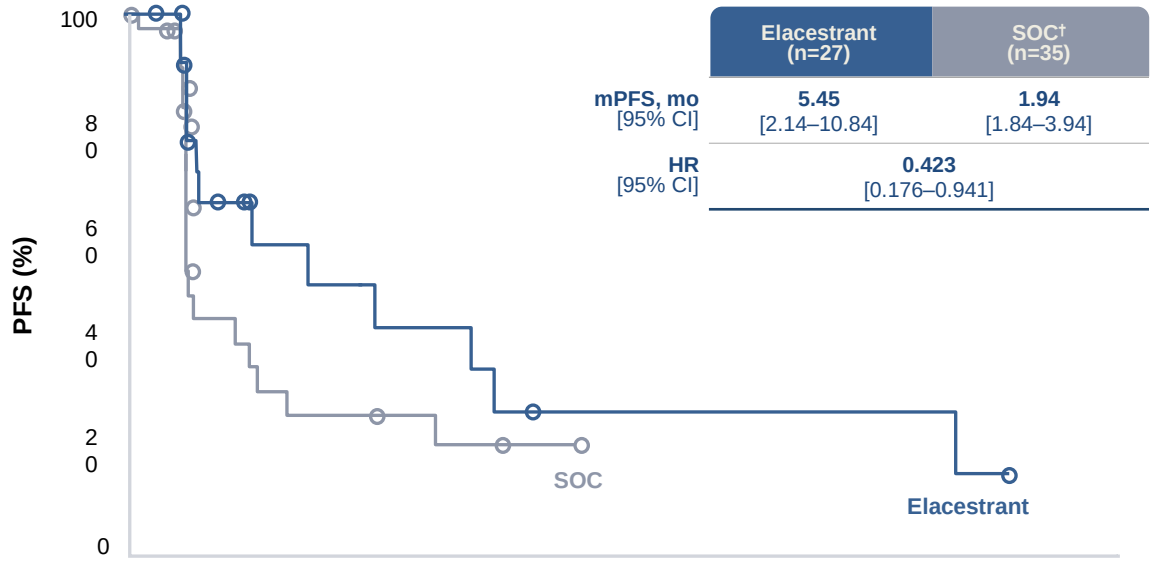
The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error.

Bardia A et al, Clin Cancer Res 2024

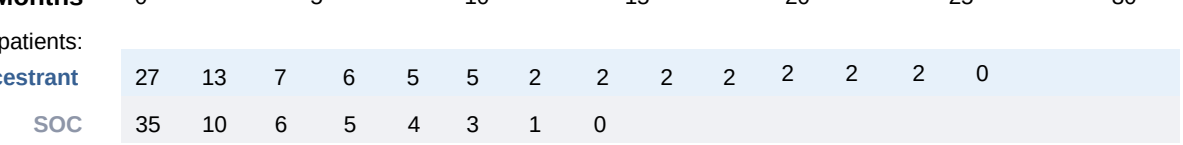
PFS in Prior CDK4/6i≥12 Mo & *ESR1m* Tumors according to PIK3CA

PIK3CA-mut*

39% of patients (n=62)



	Elacestrant (n=27)	SOC† (n=35)
mPFS, mo [95% CI]	5.45 [2.14–10.84]	1.94 [1.84–3.94]
HR [95% CI]	0.423 [0.176–0.941]	

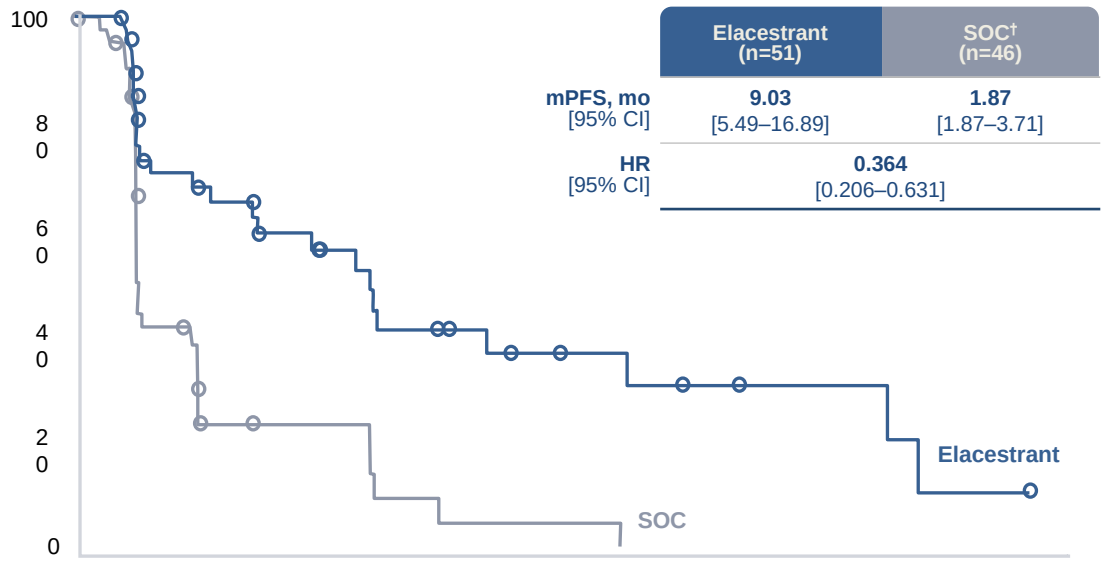


No. of patients:

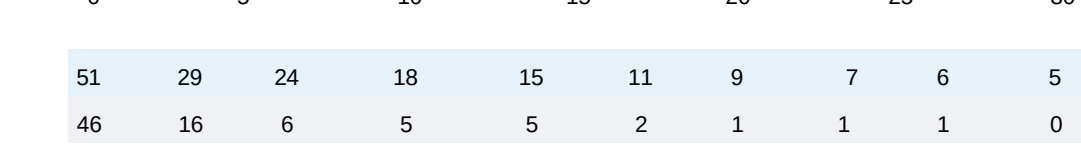
Elacestrant	27	13	7	6	5	5	2	2	2	2	2	2	2	0
SOC	35	10	6	5	4	3	1	0						

PIK3CA WT

61% of patients (n=97)



	Elacestrant (n=51)	SOC† (n=46)
mPFS, mo [95% CI]	9.03 [5.49–16.89]	1.87 [1.87–3.71]
HR [95% CI]	0.364 [0.206–0.631]	



51	29	24	18	15	11	9	7	6	5
46	16	6	5	5	2	1	1	1	0

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error.

Bardia A et al, Clin Cancer Res 2024

EMERALD - Most common AEs (≥10%) (*Updated*)

Adverse Reaction,† %	Elacestrant (n=237)		SOC* (n=230)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Musculoskeletal/Connective tissue disorders				
Musculoskeletal pain‡	41	7	39	1
Gastrointestinal disorders				
Nausea	35	2.5	19	0.9
Vomiting‡	19	0.8	9	0
Diarrhea	13	0	10	1
Constipation	12	0	6	0
Abdominal pain‡	11	1	10	0.9
Dyspepsia	10	0	2.6	0
General disorders				
Fatigue‡	26	2	27	1
Metabolism and nutritional disorders				
Decreased appetite	15	0.8	10	0.4
Nervous system disorders				
Headache	12	2	12	0
Vascular disorders				
Hot flush	11	0	8	0

Nausea summary	Elacestrant (n=237) n (%)	SOC* (n=230) n (%)
Dose-reduction rate due to nausea	3 (1.3)	NA
Discontinuation rate due to nausea	3 (1.3)	0 (0.0)
Antiemetic use	19 (8.0)	AI: 7 (10.3) Fulvestrant: 6 (3.7)

- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.

Bardia A et al, Clin Cancer Res 2024

Safety profile of different SERD as monotherapy

	Elascestrant[1]	Camizestrant[2,3]	Amcenestrant[4,5]	Giredestrant[6-9]	Imlunestrant[11]
Stage	Phase 3 completed; APPROVED	Phase 2 completed; POSITIVE (non registrational)	Phase 2 completed NEGATIVE	Phase 2 completed NEGATIVE	Phase 3 (EMBER-3)
Study	EMERALD (N=477)	SERENA-2 (N=240)	AMEERA-3 (N=367)	acelERA (N=303)	EMBER (N=114)
Frequent AEs All Grade/Gr3-4 (%)	Nausea 35/3 Fatigue 19/1 Vomiting 19/1 Hot flushes 11/0	Visual dist. 18/0 Anemia 11/0 Bradycardia 5/0 Hypertension 3/1	Nausea 20/2 Vomiting 20/0 Fatigue 11/1 Back pain 13/1	Hepatotoxicity 23/3 Fatigue 14/1 Nausea 10/0 Diarrhea 9/1	Nausea 41/1 Fatigue 33/2 Diarrhea 31/2 Vomiting 11/0

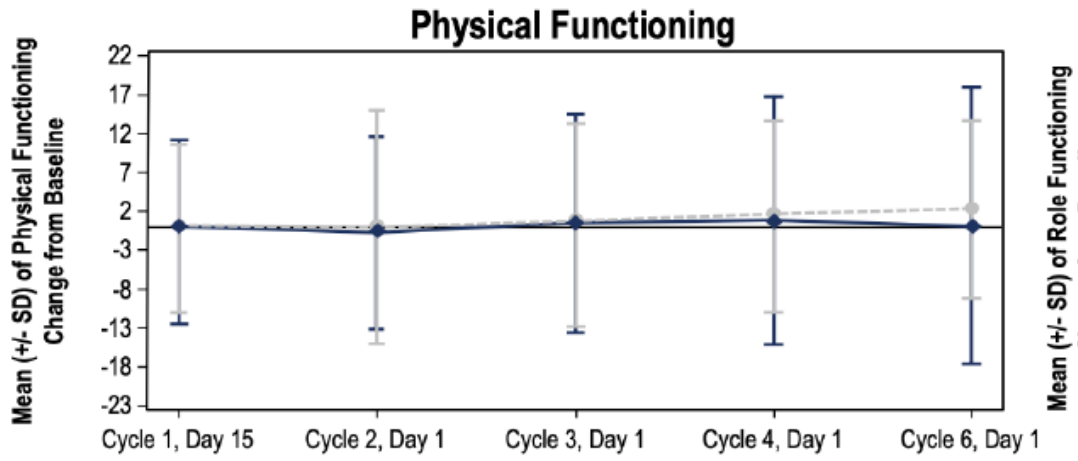
Elacestrant – Monitoring & Management

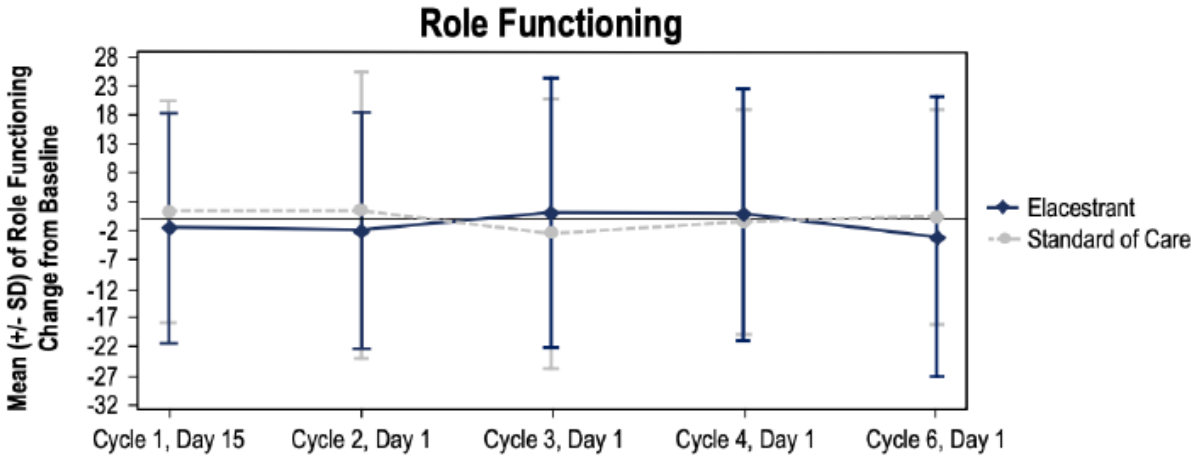
- Eye examination is not necessary
- ECG monitoring is not necessary
- Clinical laboratory data (ie, hematology, chemistry, and coagulation) according to clinical practice

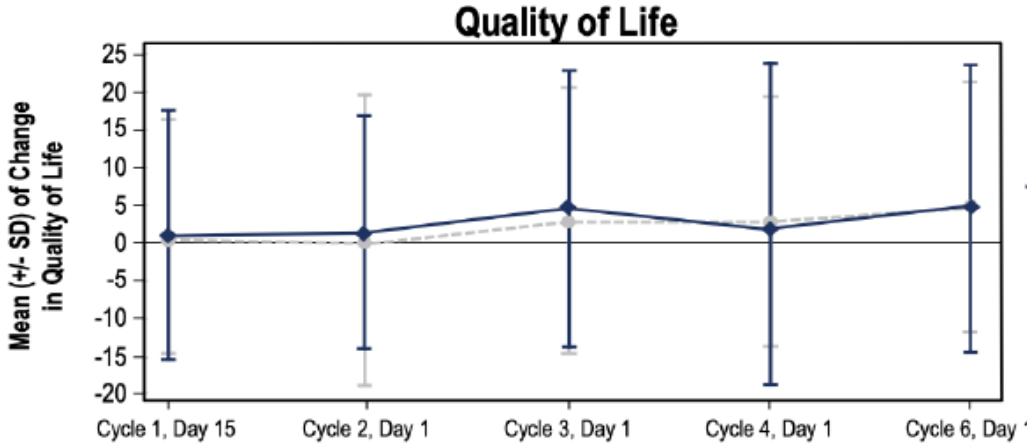
EMERALD – EORTC QLQ-C30 & EQ-5D-5L

EORTC QLQ-C30 scores were similar for **elacestrant and SoC**, with no differences across all time points for functional, symptom, and global health status/QoL domains

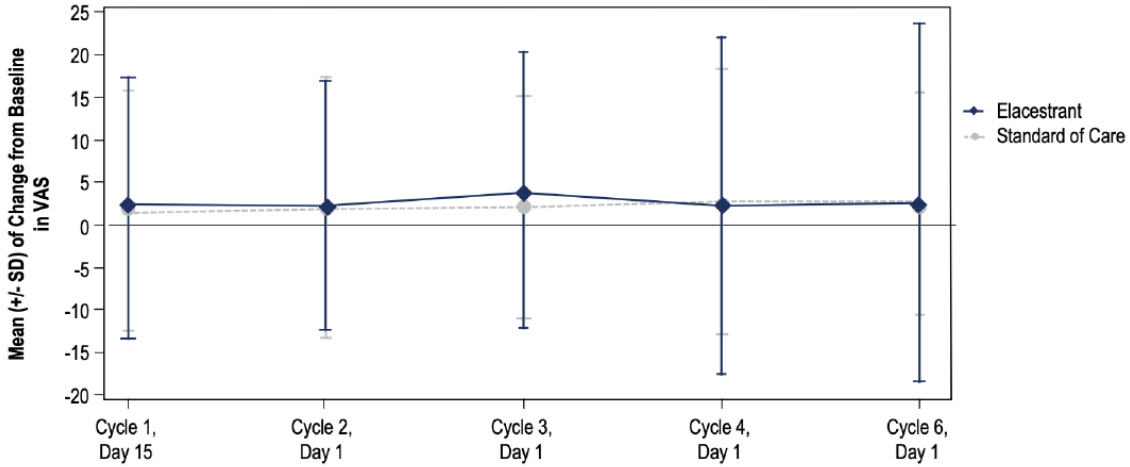
There were no differences between subgroups (*ESR1*-mut and all patients)





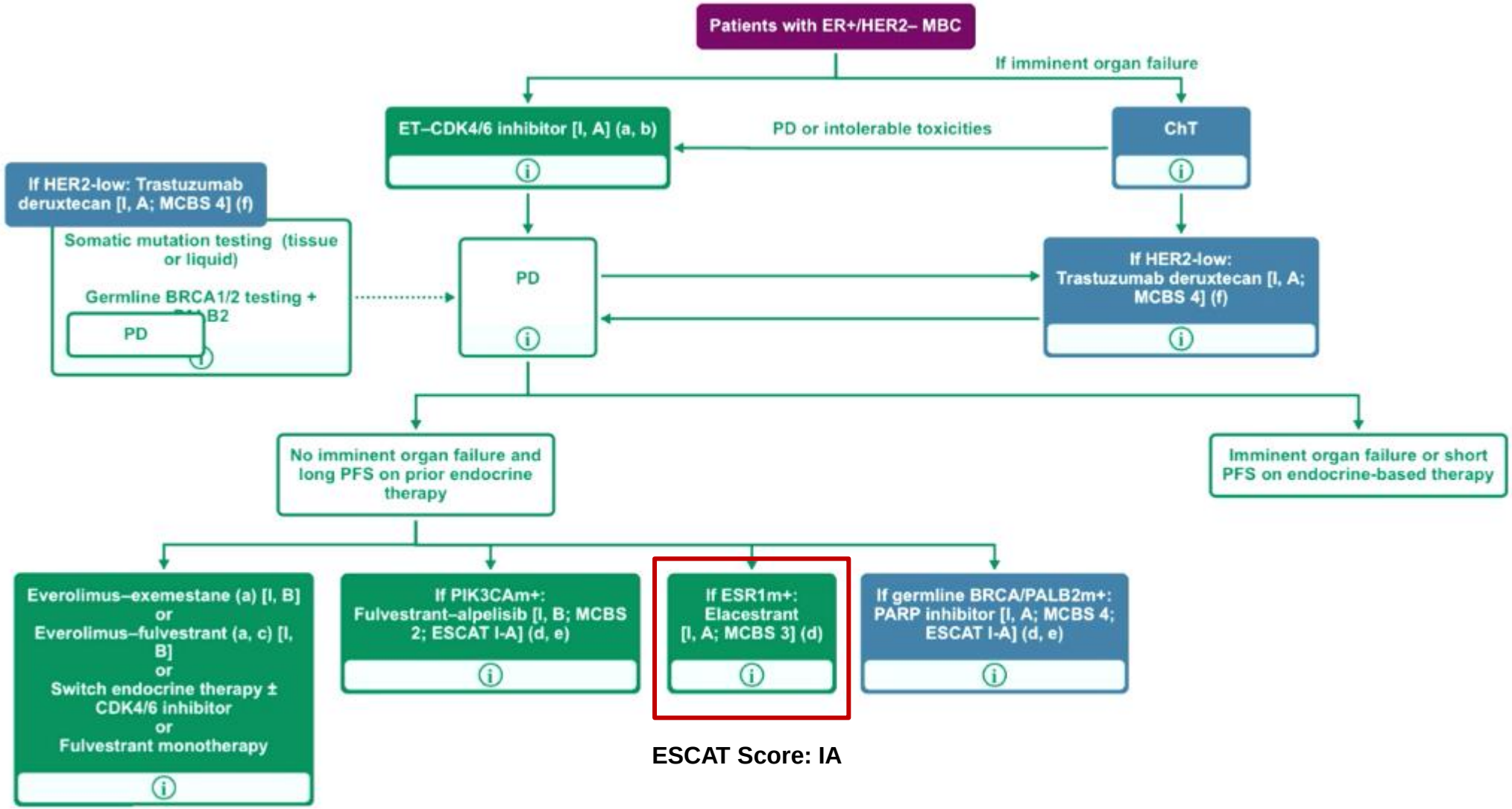


EQ-5D-5L scores were generally comparable in all patients (**elacestrant vs SoC**) for mobility, self-care, and usual activities



Cortes J et al, SABCS 2023

ESMO MBC Living Guideline (ER+/HER2-)



ESCAT Score: IA

ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023 | Gennari A et al, Ann Oncol. 2021

Elacestrant Approval

- On January 2023, **FDA** approved Elacestrant for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.
- FDA also approved the Guardant360 CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with Elacestrant.

- On September 2023, **EMA** Commission approved Elacestrant for the treatment of postmenopausal women and men with ER–positive, HER2-negative, locally advanced, or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor.

- On December 2023, **AIFA** approved Elacestrant with the same indication of EMA.

European EAP (closed) – Elacestrant

Inclusion Criteria

Subject must have a histologically- or cytologically proven diagnosis of adenocarcinoma of ER+ and HER2- ABC and must be appropriate candidates for endocrine monotherapy.
Post-menopausal women or man ≥ 18 years of age.
Disease progression following at least one but no more than two lines of endocrine therapy, including CDK4/6 inhibitors.
Activating mutations of the estrogen receptor 1 (ESR1) gene
Adequate organ function and ECOG 0-1

Countries:

Exclusion Criteria

Prior treatment with elacestrant or other SERD or ER antagonist (e.g. in clinical trials)
Fulvestrant treatment (last injection) < 28 days before first dose of drug.
Any other endocrine therapy < 14 days before first dose of drug.
Radiation therapy within 14 days before the first dose of elacestrant
Chemotherapy-based regimens (including ADCs) in metastatic or advanced setting.
Any investigational anti-cancer drug therapy < 28 days or 5 half-lives (whichever is shorter) before first dose of drug.
Major surgery < 28 days before the first dose of elacestrant
Presence of symptomatic metastatic visceral disease, including but not limited to, extensive hepatic involvement, untreated or progressive central nervous system (CNS) metastases, or symptomatic pulmonary lymphangitic spread.
Intact uterus with a history of endometrial intraepithelial neoplasia (atypical endometrial hyperplasia or higher-grade lesion).
Major Cardiovascular conditions/events
Child-Pugh Score greater than Class A (ie, score >6).
Coagulopathy or any history of coagulopathy within the past 6 months, including history of deep vein thrombosis or pulmonary embolism.

RWE Data Collection

Voluntary Participation

Art. 6 DM 7/9/2017 "I dati relativi all'uso del medicinale, di cui al presente decreto, non sostituiscono i dati necessari per la procedura di autorizzazione all'immissione in commercio, ai sensi del decreto legislativo 24 aprile 2006, n. 219 e della normativa comunitaria, ma possono essere utilizzati come dati a supporto della suddetta procedura. "

bjective	Variables that will be collected
escribe *elacestrant tolerability in the Real World*	- Dose modifications (dose reductions, skipped administrations, treatment discontinuation) of elacestrant. - Reason for dose modifications of elacestrant.
escribe *baseline* patient characteristics, *disease characteristics* f patients with mBC treated with elacestrant in the compassionate se programme	- Age, Gender - ECOG performance status - BC Surgery date (if applicable) - Breast cancer diagnosis date - Metastatic BC diagnosis date - Date of start of previous treatment line(s) - Type of previous treatments - Visceral met (yes or not) - Date of last treatment line interruption - ER, HER2, ESR1 status
escribe *ESR1m testing practices of patients with mBC treated* ith elacestrant in the compassionate use programme	- Date of test - Type of biopsy (Liquid vs tissue) - Date of ESR1m test results - Mutation type
escribe *effectiveness of elacestrant in patients with mBC treated* the compassionate use programme	- Date of elacestrant treatment start - Date of elacestrant treatment discontinuation

MODULO CONSENSO (AD HOC) + CRF

CNN Italia (ongoing) - Elacestrant

Indicazione terapeutica: ORSERDU (elacestrant) in monoterapia è indicato per il trattamento di donne in postmenopausa, e di uomini, **con carcinoma mammario localmente avanzato o metastatico positivo per i recettori degli estrogeni (ER) e negativo per HER2, con una mutazione attivante di ESR1**, che mostrano progressione della malattia in seguito ad almeno una linea di terapia endocrina comprendente un inibitore di CDK 4/6

	Il paziente è in indicazione?		SI	☐
			Altrimenti blocca la richiesta	
	Durata della precedente terapia con inibitore CDK4/6		0-5 mesi	☐
			6-11 mesi	☐
			≥12 mesi	☐
	Numero di precedenti linee ormonali in fase metastatica		1	☐
			2	☐
			2+ blocco	
	Numero precedenti linee di chemioterapia in fase metastatica		0	☐
			1	☐
			1+ blocco	

Elacestrant: Real-Word Analysis (>700 Pts)

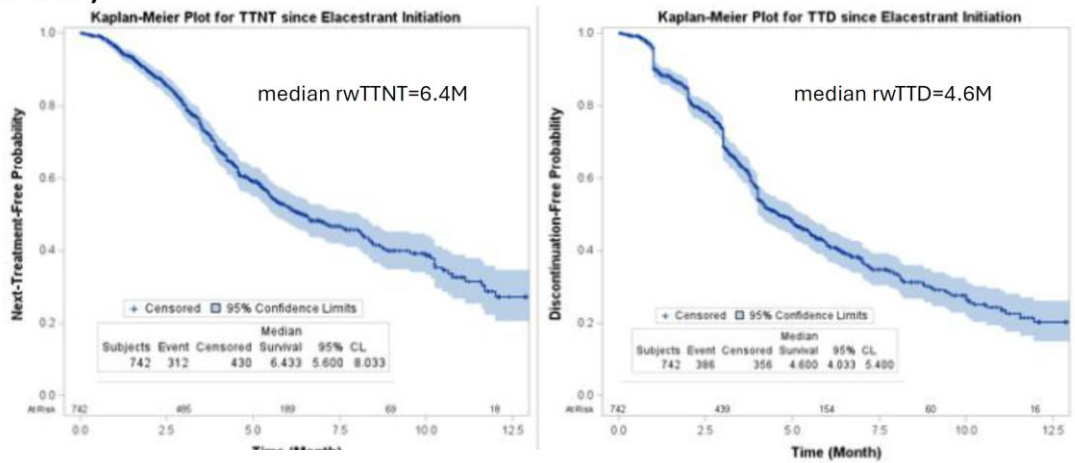
Results: Patient Characteristics

Demographics	N/Mean	%/SD
Total N	756	
Age (years)		
18-49	100	13%
50-64	322	43%
65+	334	44%
Mean (SD)	63	11.8
Sex		
Female	749	99%
Most frequent metastasis sites		
Bone	554	73%
Brain	71	9%
Liver	237	31%
Lung	115	15%

Therapy exposure prior to elacestrant

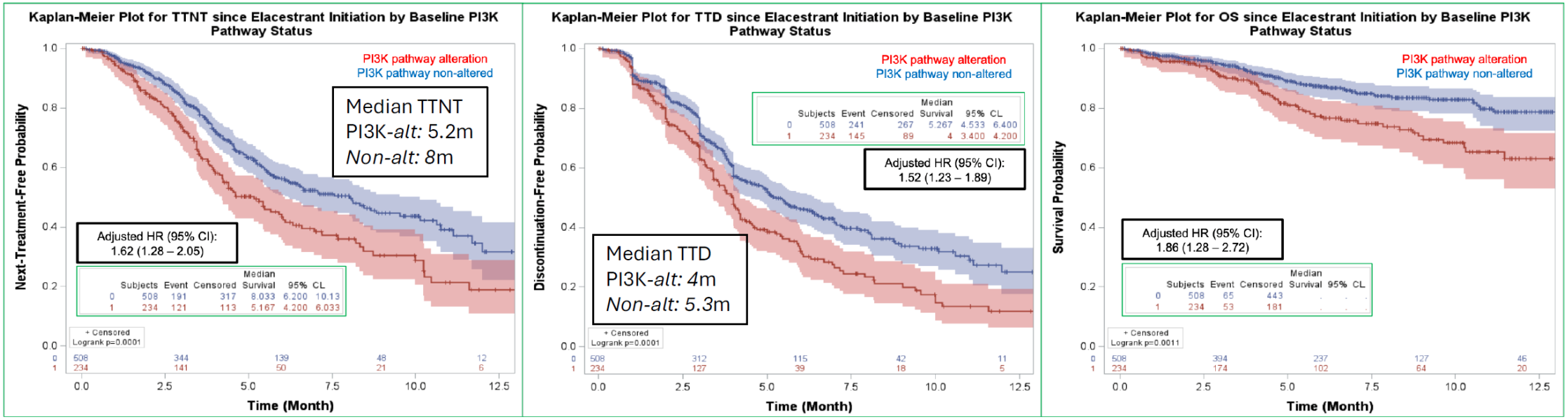
Therapy category	N	%
Total N	756	
Aromatase inhibitor	683	90%
Fulvestrant	402	53%
CDK4/6 inhibitor	624	83%
Chemotherapy	312	41%
Alpelisib	79	10%
Trastuzumab deruxtecan	58	8%
Sacituzumab govitecan	28	4%

Results: Time To Next Tx and Time To Tx Discontinuation in all patients (N=742)



PIK3CA pathway alterations were associated with worse outcomes

PIK3CA (n=197), *AKT1* (n=30), and/or *PTEN* (n=15)



Lloyd MR et al, SABCS 2024

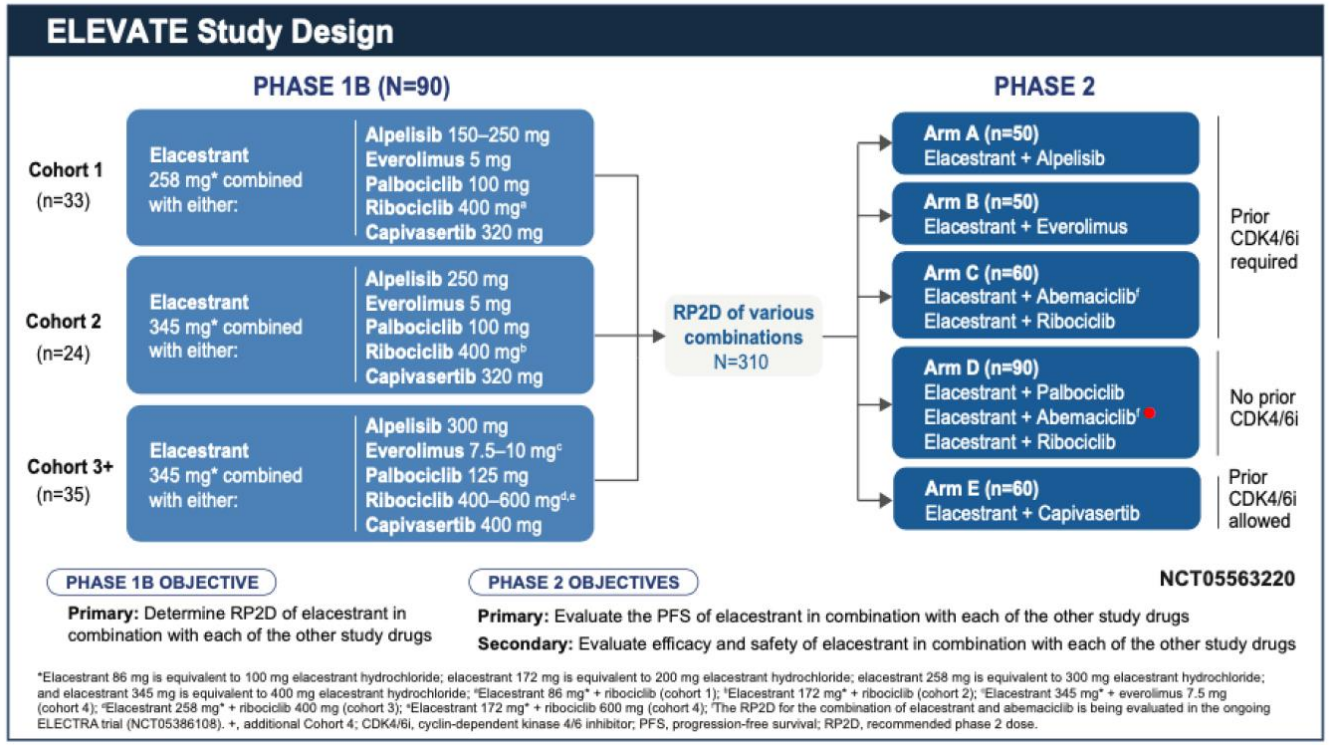
ELEVATE: a phase 1b/2, open-label, umbrella study

Main eligibility:

-1-2 Prior lines of ET, **one with CDK4/6i (**no prior treatment with everolimus, alpelisib, capivasertib, and the companion CDK4/6i**):**

– **Alpelisib combination:** *PIK3CA*-mut by local lab

– **Capivasertib combination:§** *PIK3CA/AKT1/PTEN*-alteration as detected by an approved test (local result)

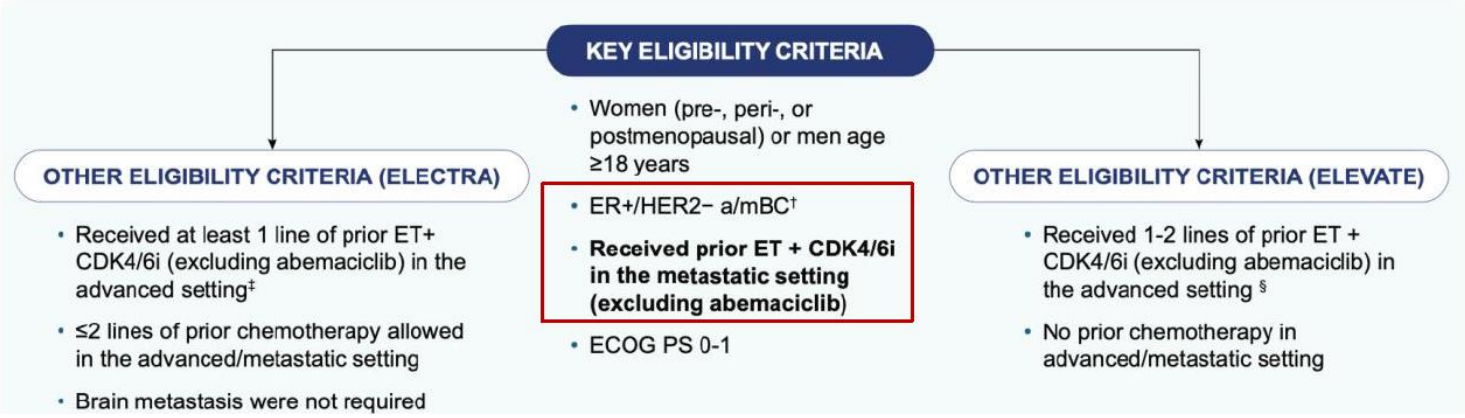


Combination	TEAEs Adverse Events Summary
Elacestrant 345 mg + abemaciclib 150 mg BID (RP2D)	Diarrhea was mainly grade 1/2, neutropenia was associated mainly with abemacicib only.
Elacestrant 345 mg + everolimus 7.5 mg (RP2D)	Stomatitis, rash and diarrhea were mainly grade 1/2.
Elacestrant 345 mg + palbociclib 125 mg (RP2D)	Neutropenia was associated mainly with palbociclib only.
Elacestrant 172 mg + ribociclib 600 mg	Neutropenia was associated mainly with ribociclib only. No grade 3/4 QTc prolongation observed.
Elacestrant 258 mg + capivasertib 320 mg	No grade 3/4 diarrhea, hyperglycemia or rash were observed.
Elacestrant 258 mg + alpelisib 200 mg	Rash and hyperglycemia were mainly grade 1/2. No grade 3/4 diarrhea was observed.

- RP2Ds are established for elacestrant in combination with abemaciclib, everolimus and palbocicilib.
- The safety profiles of the combination are consistent with the combination of these drugs with SOC ET and there is no evidence of drug-drug interactions.

Rugo HS et al, SABCS 2024

Elacestrant plus Abemaciclib combination: ELEVATE & ELECTRA



Response and Clinical Benefit With Elacestrant + Abemaciclib in Efficacy-Evaluable Patients

	ELECTRA Cohort 1 (n=7)	ELECTRA Cohort 2 (n=7)	ELECTRA Cohort 3‡ RP2D (n=12)	ELEVATE Arm C (n=26)	POOLED ANALYSIS ELECTRA Cohort 3‡ + ELEVATE Arm C (n=38)
Efficacy Outcome*†	Elacestrant 258 mg QD + Abemaciclib 100 mg BID	Elacestrant 345 mg QD + Abemaciclib 100 mg BID	Elacestrant 345 mg QD + Abemaciclib 150 mg BID	Elacestrant 345 mg QD + Abemaciclib 150 mg BID	**Elacestrant 345 mg QD + Abemaciclib 150 mg BID**
ORR, n (%)	**2 (29)**	**2 (29)**	**3 (25)**	**4 (15)**	**7 (18)**
CR	-	-	1 (8)	1 (4)	**2 (5)**
PR	2 (29)	2 (29)	2 (17)	3 (12)	**5 (13)**
SD	2 (29)	3 (43)	7 (58)	18 (69)	**25 (66)**
PD	3 (43)	2 (29)	2 (17)	4 (15)	**6 (16)**
CBR, n (%)	**4 (57)**	**5 (71)**	**10 (83)**	**22 (85)**	**32 (84)**
CBR24wks, n (%)	**4 (57)**	**4 (57)**	**8 (67)**	In ELEVATE Arm C, average observation time has not reached 24 weeks	

Data cut-off: 15 OCT 2024. *Confirmed responses only; †Includes patients who had measurable disease (ie, at least 1 target lesion) at baseline and at least 1 post-baseline RECIST assessment ‡Includes confirmatory cohort 3 expansion.
CBR=clinical benefit rate (CR + PR + SD); CR=complete response; PR=partial response; SD=stable disease; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; ET=endocrine therapy; ORR=objective response rate;

- Early results from a relatively small number of patients (N=27) from the Phase Ib ELECTRA trial show a median PFS of 8.7 mo.
- *An Open-label Multicenter Phase 1b-2 Study of Elacestrant in Combination with Abemaciclib in Women and Men with Brain Metastasis from Estrogen Receptor Positive, HER-2 Negative Breast Cancer (ELECTRA) is ongoing*

Rugo HS et al, SABCS 2024

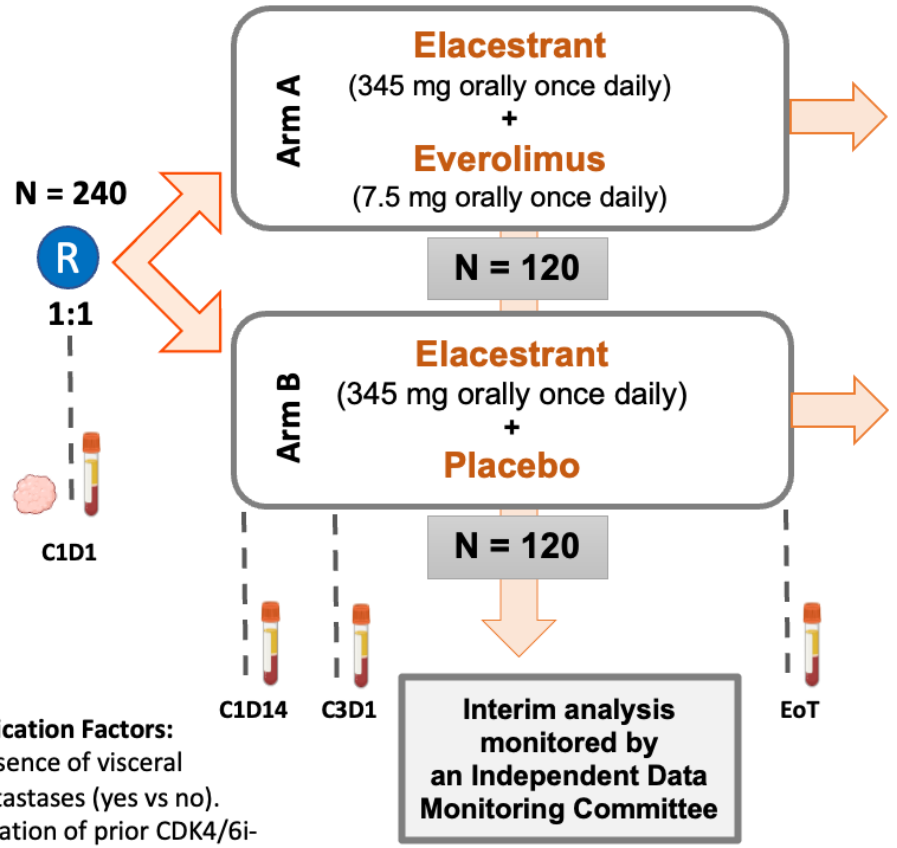
ADELA Trial: Elacestrant plus Everolimus vs Elacestrant in ESR1m

Randomized, double-blind, placebo-controlled, phase III trial

Screening → **Randomized phase** → **EoS**

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.



Stratification Factors:

- Presence of visceral metastases (yes vs no).
- Duration of prior CDK4/6i-based therapy (≥ 12 months vs <12 months).

PRIMARY ENDPOINT

- BICR-PFS.

SECONDARY ENDPOINTS

- OS, Investigator-assessed PFS, ORR, CBR, DoR, and TTR.
- QoL.
- Safety.

EXPLORATORY ENDPOINTS

- Biomarkers of sensitivity/resistance.
- PK parameters.

Oral SERD in pretreated MBC

	EMERALD[1]	SERENA-2[2]	EMBER-3[3]	AMEERA-3[4-6]	acelERA[6-9]
Treatment	**Elacestrant**	**Camizestrant**	**Imlunestrant** +/- abemaciclib	**Amcenestrant**	**Giredestrant**
Control Arm	fulvestrant / AIs	fulvestrant	fulvestrant / exemestane	fulvestrant / AIs / tamoxifen	fulvestrant / AIs
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	**Required (100%)**	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	**YES**	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	**YES**	YES	NO	YES	YES
Data readout	**Positive (Registrational)**	Positive (Non-Registrational)	Positive	Negative	Negative

1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, https://clinicaltrials.gov/ct2/show/NCT04214288; 3. EMBER-3. Clinical Trials.gov identifier: NCT04975308. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04975308; 4. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04059484; 5. Tolaney SM, et al. *Ann Oncol*. 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback. Accessed July 20, 2022; 7. acelERA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04576455; 8. Martin M, et al. *J Clin Oncol*. 2021;39(15):abstr TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol.* 2022;33(7):S88-S121 (abstr 211MO).

Modified from **Kaklamani V** et al., *GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting*. Abstract GS3-01; SABCS 2022

EMBER-3 Trial: Imlunestrant, as monotherapy and with Abemaciclib

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) **~60%**
- Visceral metastases (Y/N)
- Region[c]

R 1:1:1[b] N=874

- **Imlunestrant 400 mg QD** — A
- **SOC ET[d,e]** Fulvestrant or Exemestane — B
- **Imlunestrant 400 mg QD + abemaciclib[e]** — C[b]

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[h] patients

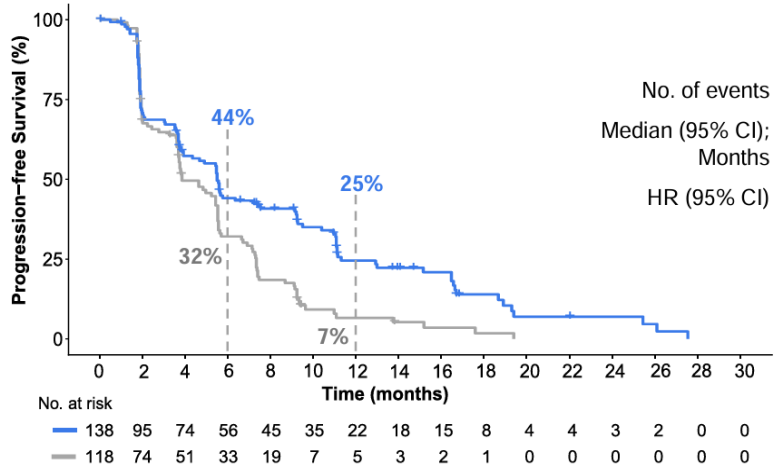
Key Secondary Endpoints

- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

- PFS and OS for C vs B in all[h] patients

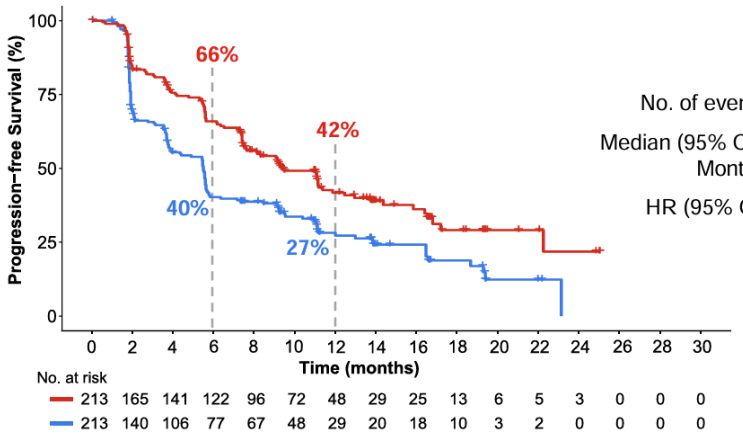
ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 to November 2023 across 195 sites in 22 countries. [a] A GnRH agonist was required in men and premenopausal women; [b] Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c] East Asia vs United States/European Union vs others; [d] Investigator's choice; [e] Labeled dose; [f] Scans every 8 weeks for the first 12 months, then every 12 weeks; [g] *ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h] Analysis conducted in all concurrently randomized patients.



	Imlunestrant n=138	SOC ET n=118
No. of events	109	102
Median (95% CI); Months	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.46-0.82)[a]** *p*-value<0.001	

Imlunestrant led to a 38% reduction in the risk of progression or death in patients with *ESR1*m

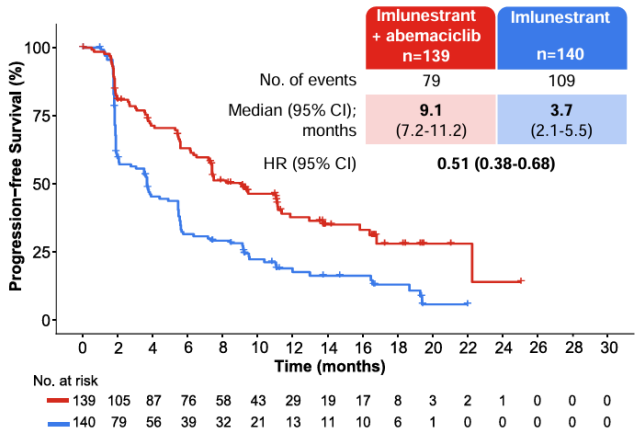
PFS difference of imlunestrant vs SOC ET in all patients did not reach significance(And ESR1WT)



	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of events	114	149
Median (95% CI); Months	**9.4** (7.5-11.9)	**5.5** (3.8-5.6)
HR (95% CI)	**0.57 (0.44-0.73)** *p*-value <0.001	

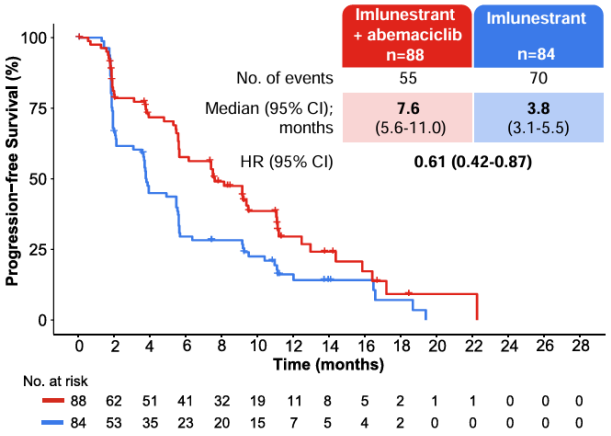
Imlunestrant + abemaciclib led to a 43% reduction in the risk of progression or death over imlunestrant alone in all patients

Patients with prior CDK4/6i treatment



	Imlunestrant + abemaciclib n=139	Imlunestrant n=140
No. of events	79	109
Median (95% CI); months	**9.1** (7.2-11.2)	**3.7** (2.1-5.5)
HR (95% CI)	**0.51 (0.38-0.68)**	

Patients with PI3K pathway mutation[a]



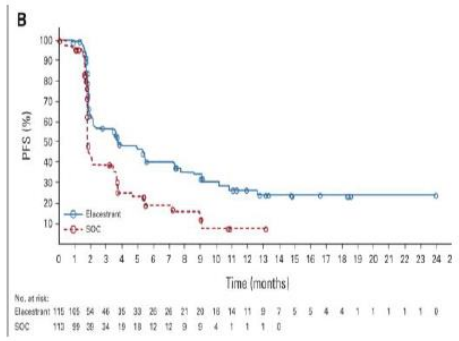
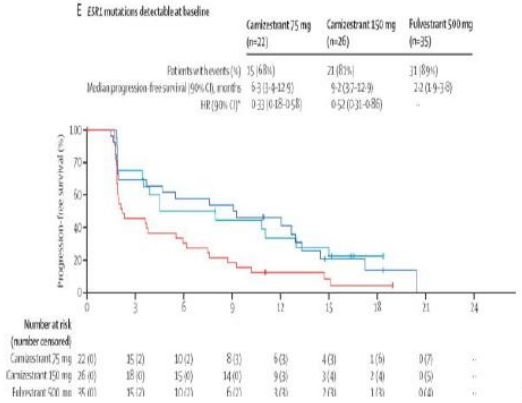
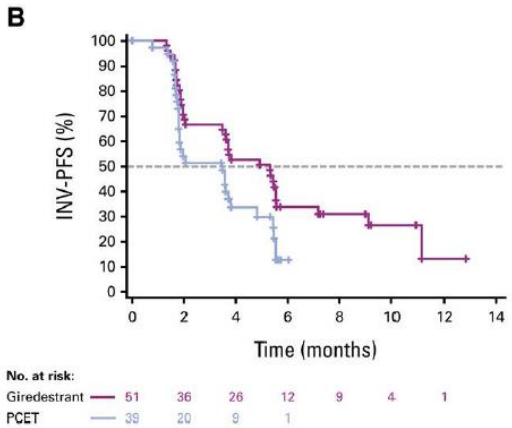
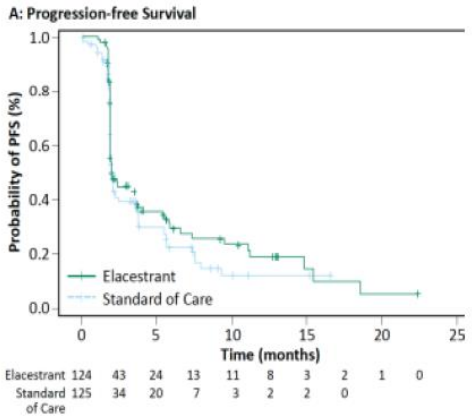
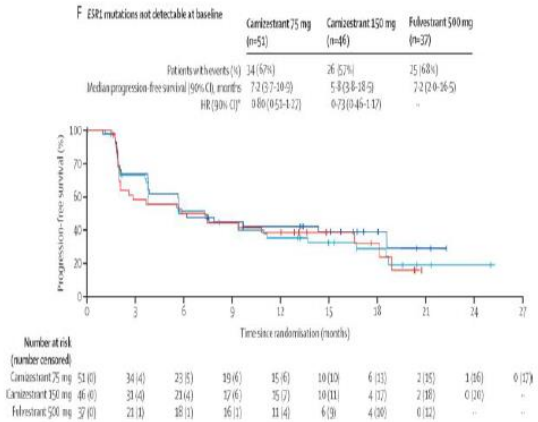
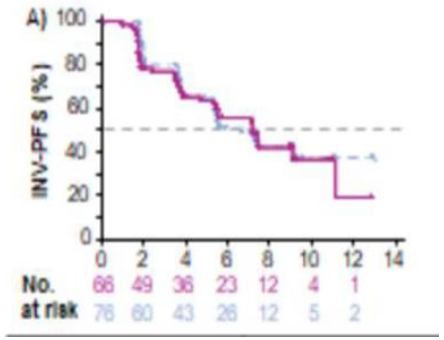
	Imlunestrant + abemaciclib n=88	Imlunestrant n=84
No. of events	55	70
Median (95% CI); months	**7.6** (5.6-11.0)	**3.8** (3.1-5.5)
HR (95% CI)	**0.61 (0.42-0.87)**	

Consistent benefit of imlunestrant + abemaciclib across key clinical subgroups

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

Jhaveri KL et al, SABCS 2024 & NEJM 2024

Better Efficacy of oral SERD in *ESR1m*

	EMERALD SOC vs Elacestrant	SERENA-2 Fulv vs Camizestrant	acelERA PCET vs Giredestrant
***ESR1* mut**			
***ESR1* wt**			
	Bidard, FC et al. J Clin Oncol 2022;40:3246	Oliveira M, et al. Lancet Oncol 2024;25:1424	Martin M, et al. J Clin Oncol 2024;42:2149

Summary

- Elacestrant is an oral SERD with better bioavalaibility and efficacy compared to Fulvestrant
- EMERAL is the only pivotal trial in 2nd/3rd line with 100% prior CDK4/6i progression
- **Once-daily oral Elacestrant is well-tolerated.** *Musculoskeletal pain and Gastrointestinal AEs (mainly Low-grade) are the most common side effects. No incidence of bradycardia, hematologic, and ocular symptoms.*
- **How to identify patients with potential benefit to ET after CDK4/6i?**
  - Duration of CDK4/6i & ESR1m were associated with better PFS
  - Need to perform a liquid biopsy for ESR1m at the time of disease progression
  - A subset of patients (i.e. PIK3CAm) have limited benefit to ET and should they be treated with modern cytotoxic agents or ET plus target therapy or ADC.
- Elacestrant represents an optimal partner for combination with target agents (i.e. ongoing trials with Abemaciclib, Everolimus, Alpelisib and Capivasertib).
- EMBER-3 suggest that Imlunestrant plus Abemaciclib can achieve substantial durations of tumor control irrespective of tumor ESR1 mutation status or PIK3CA status
- Additional data with other SERDs & more potent ER-inhibitors are coming (SERENA-4 or pre-treated ABC) also including other settings (early BC). Moreover, other genomic driven strategy are ongoing (positive high-level results from a planned interim analysis of the SERENA-6)

Thank you for your attention