

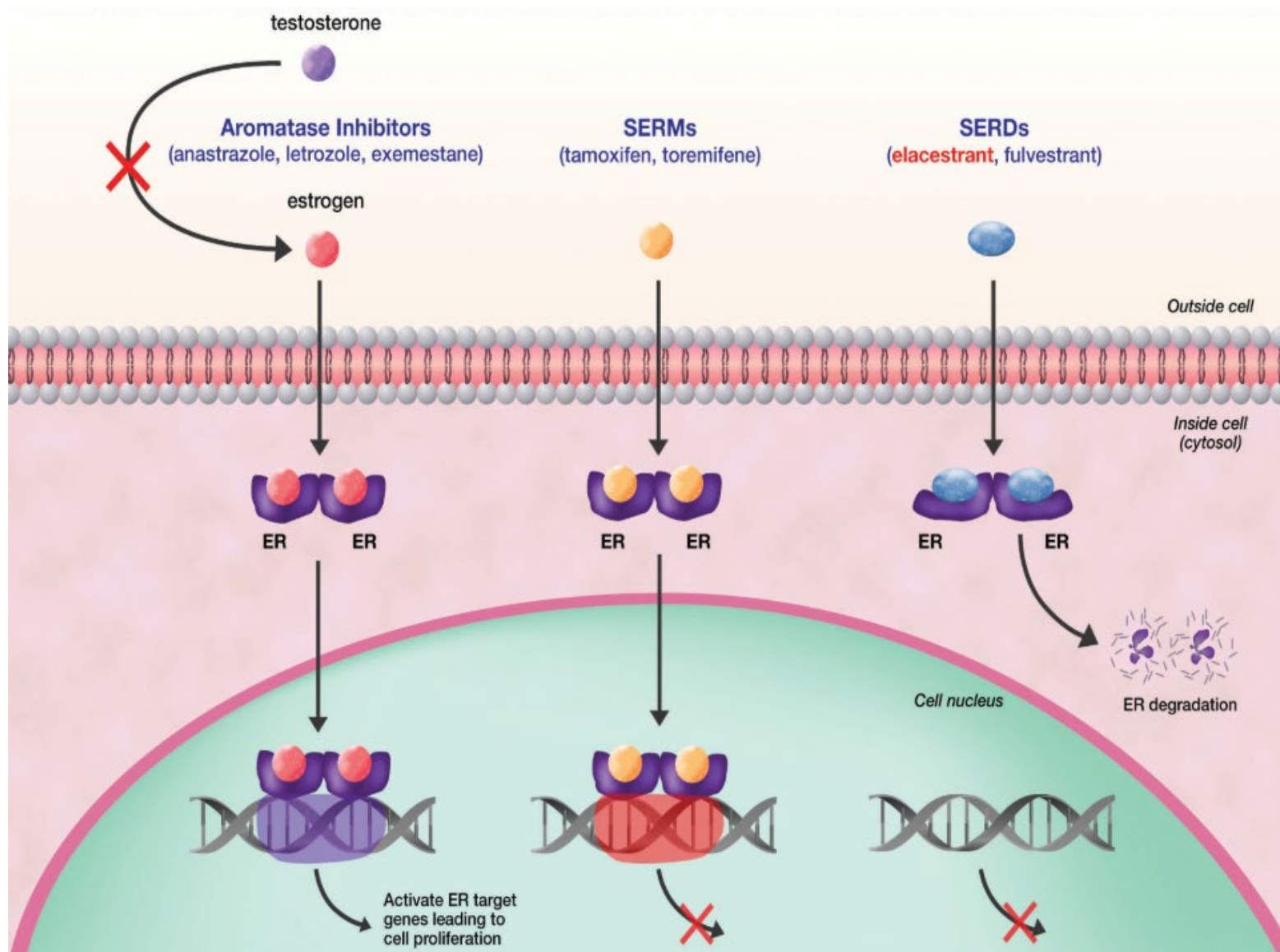
Emerging Landscape of Oral SERDs

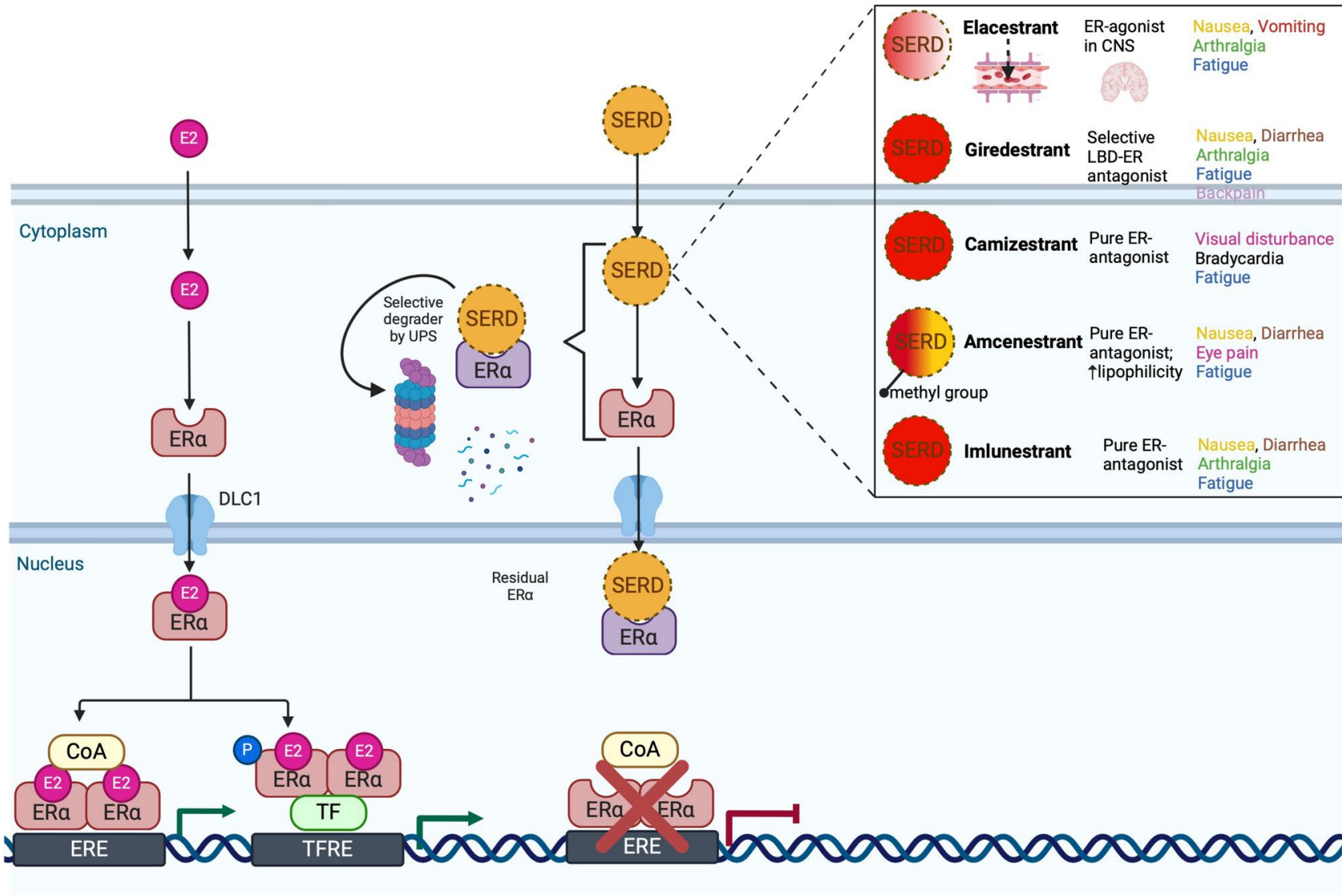
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Ochsner MD Anderson Cancer Center

Disclosures

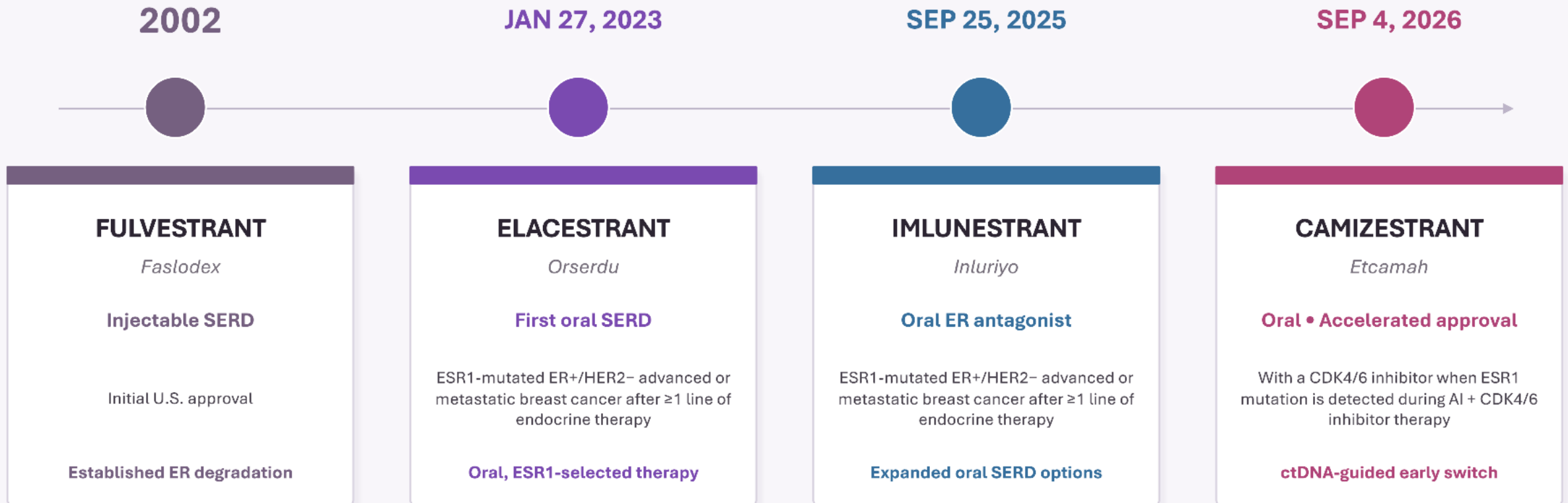
- ▶ Speakers Bureau: Astra-Zeneca, Daiichi-Sankyo
- ▶ Consultant: Astra-Zeneca
- ▶ Honoraria: MJH Lifesciences, OncLive





Approved Therapies

FDA Approvals of SERD



EMERALD Trial

A GLOBAL, PROSPECTIVE, RANDOMIZED, OPEN-LABEL PHASE 3 TRIAL^{1,2}

Select eligibility criteria (n=228)^{1*}

- Postmenopausal women and men
- ER+/HER2- advanced or metastatic breast cancer
- Progression on 1-2 lines of ET, at least one in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced or metastatic disease
- ECOG PS 0 or 1

Randomized 1:1

ORSERDU

345 mg (n=115)¹

Investigator's choice of fulvestrant or AI (n=113)¹

Fulvestrant, anastrozole, letrozole,
or exemestane

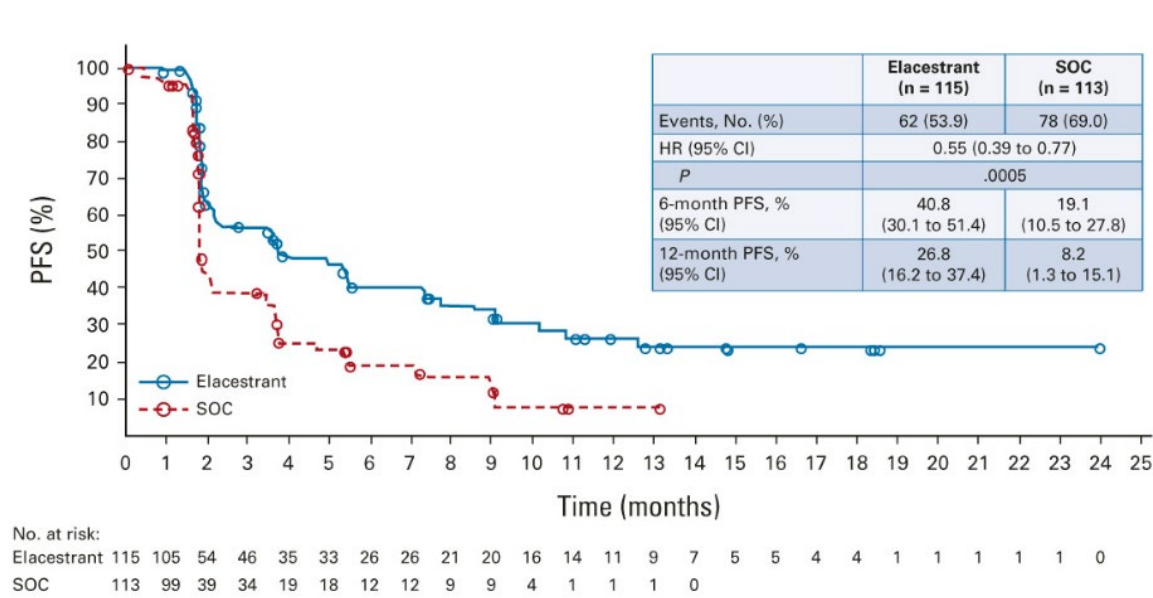
Progressive
disease or
unacceptable
toxicity

Primary endpoint

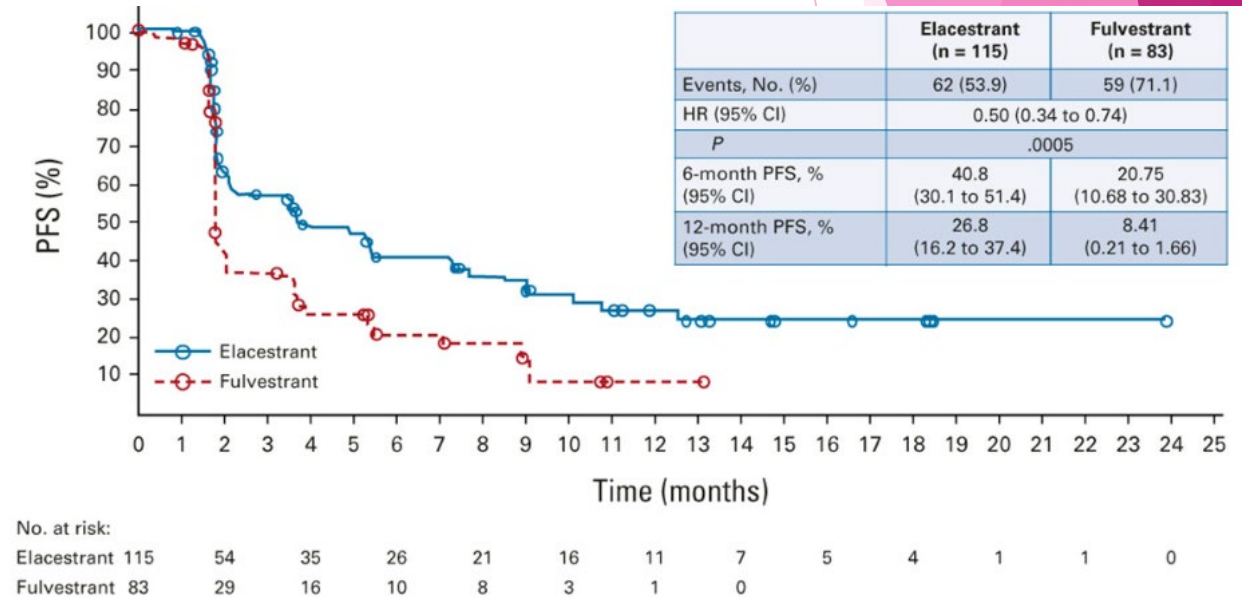
- PFS in the *ESR1*-mutated mBC population^{1†}
 - Median PFS

Every patient had prior ET + CDK4/6i²

EMERALD Trial



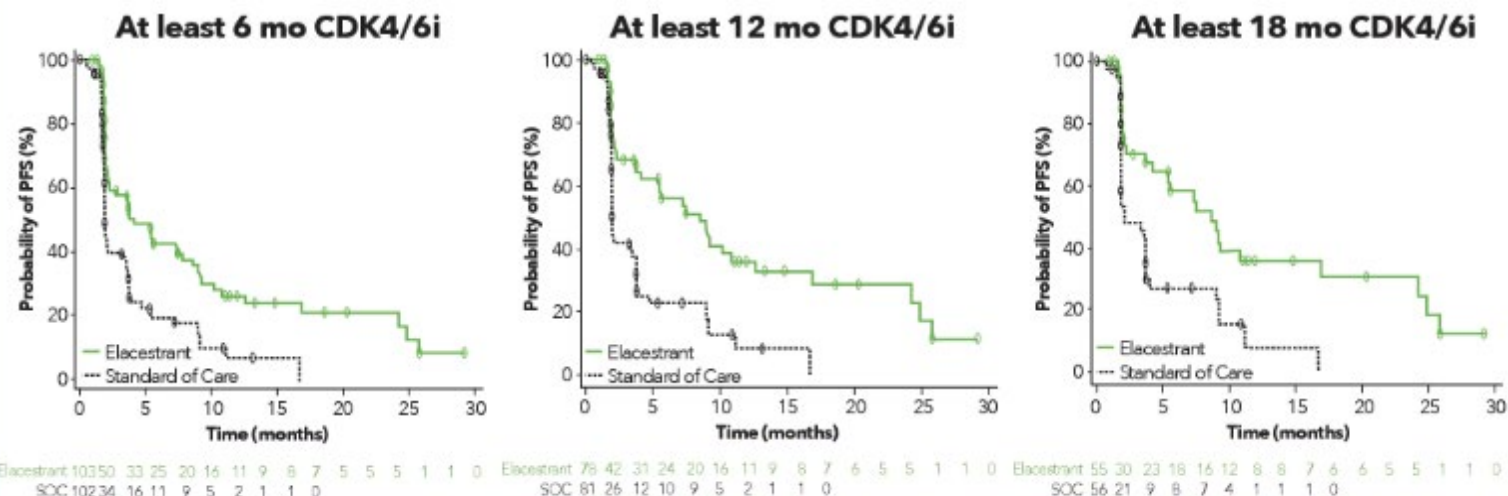
Elacestrant versus SOC in patients with detectable *ESR1* mutation



Elacestrant versus Fulvestrant in patients with detectable *ESR1* mutation

PRIOR CDK4/6i DATA

Patients with ESR1-mut Receiving ≥ 12 Months of Prior CDK4/6i Achieved 8.61 Months mPFS with Elacestrant vs 1.91 Months with SOC Endocrine Therapy (Absolute Difference = 6.7 Months)⁶

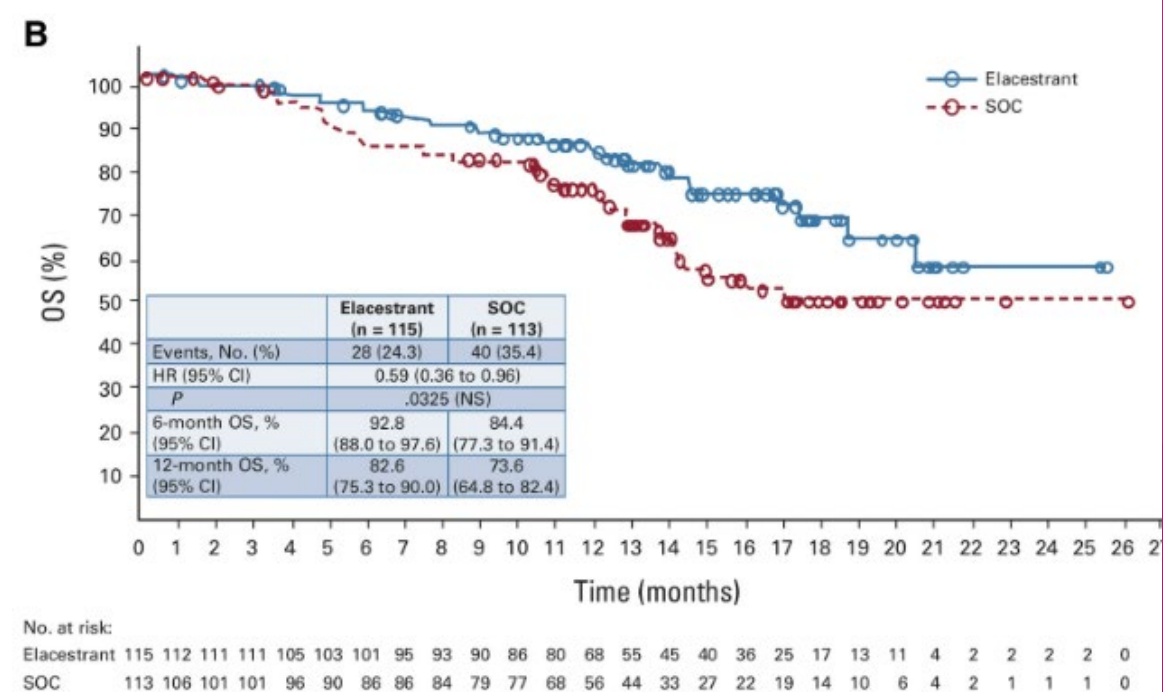
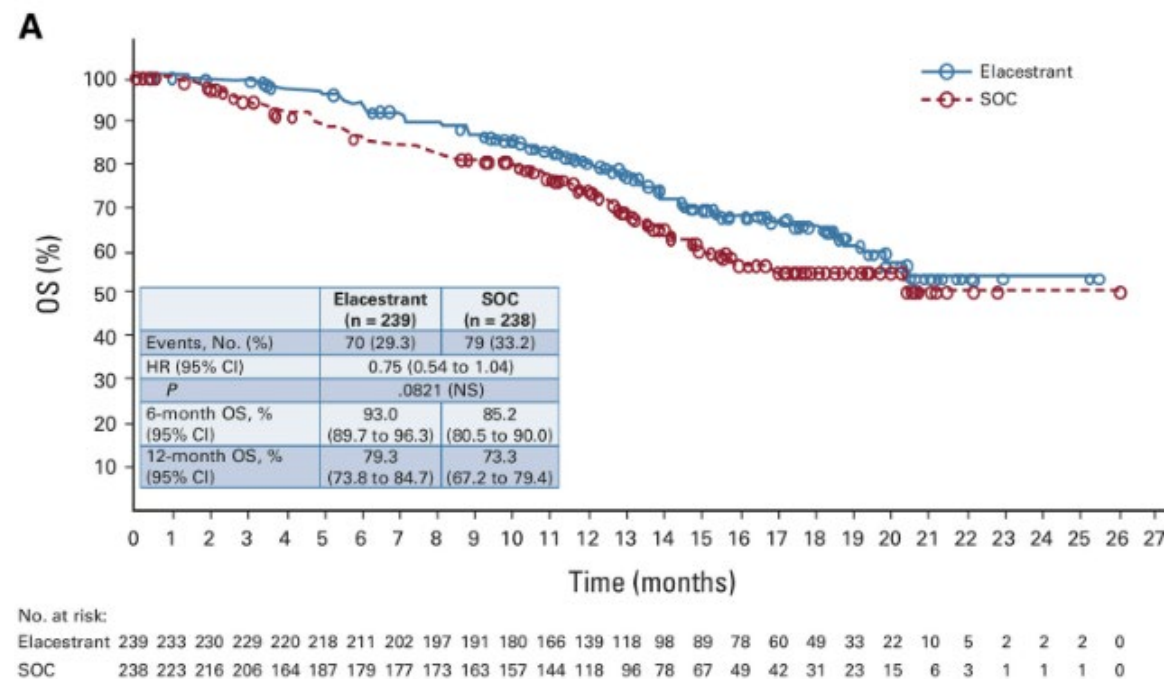


	Elacestrant (n=103)	Standard of Care (n=102)
Median PFS, months (95% CI)	4.14 (2.20-7.79)	1.87 (1.87-3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12-36.92)	6.45 (0.00-13.65)
Hazard ratio (95% CI)	0.517 (0.361-0.738)	

	Elacestrant (n=78)	Standard of Care (n=81)
Median PFS, months (95% CI)	8.61 (4.14-10.84)	1.91 (1.87-3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84-49.78)	8.39 (0.00-17.66)
Hazard ratio (95% CI)	0.410 (0.262-0.634)	

	Elacestrant (n=55)	Standard of Care (n=56)
Median PFS, months (95% CI)	8.61 (5.45-16.89)	2.10 (1.87-3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54-52.05)	7.73 (0.00-20.20)
Hazard ratio (95% CI)	0.466 (0.270-0.791)	

Interim OS Analysis



Interim analysis of OS. Kaplan-Meier estimates of overall survival at the interim analysis are (A) shown for all patients and (B) patients with detectable *ESR1* mutation. The differences in overall survival in this interim analysis were not statistically significant on the basis of the allocated two-sided alpha level of .0001

ELEVATE: Phase 1b/2 Umbrella Trial

Elacestrant + Everolimus

- ▶ 1-2 lines of ET+CDK4/6i
- ▶ No prior chemotherapy in advanced stage
- ▶ Elacestrant with either:
 - Everolimus
 - Alpelisib
 - Capivasertib
 - Ribociclib
 - Abemaciclib
 - Palbociclib

Subgroup	Median PFS (months)	95% CI
All patients	8.3	4.0-10.2
ESR1 mutated	8.3	3.5-12.9
ESR1 wild type	9	4.2-12.7
PIK3CA mutated	8.3	3.6-10.2
PIK3CA wild type	9.4	4.0-NR

ctDNA in ESR1 detection

- ▶ Indication and Timing:
 - <5% of ER+/HER2- have ESR1 mutation at initial metastatic diagnosis
 - Arise in ~40-50% of patients after AI-based therapy
 - Can be detected 6 months before radiologic progress
 - NCCN Guidelines: Testing at each progression on ET
- ctDNA > Tissue:
 - mutations are subclonal and dynamic
 - ctDNA allows for real-time testing
- Modalities: NGS or digital/droplet PCR
 - NGS: broad coverage of ESR1 mutation spectrum
 - dPCR: high analytic sensitivity for hotspots (Y537S, D538G)



TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	Biomarker	Detection ^u	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive, HER2-negative	<i>PIK3CA</i> activating mutation	NGS, PCR	Fulvestrant/Inavolisib/Palbociclib ^x	Category 1	Preferred
HR-positive/HER2-negative	<i>PIK3CA</i> activating mutation	NGS, PCR	Alpelisib/Fulvestrant	Category 1	Preferred
HR-positive/HER2-negative	<i>PIK3CA</i> or <i>AKT1</i> activating mutations or <i>PTEN</i> ^w inactivating mutations and genomic changes (eg, deletion)	NGS, PCR	Capivasertib/Fulvestrant ^y	Category 1	Preferred ^y
HR-positive/HER2-negative ^{u,v}	<i>ESR1</i> mutation ^v	NGS, PCR	Elacestrant ^z	Category 2A	Other recommended
			Imlunestrant ^{aa}		
			Vepdegestrant ^{bb}		
HR-positive/HER2-negative	<i>ESR1</i> mutation detected during AI + CDK4/6 inhibitor therapy ^{cc}	NGS, PCR ^{cc}	Camizestrant + continue the same CDK4/6 inhibitor ^{cc}	Category 2B	Useful in Certain Circumstances

^u Some plasma-based ctDNA assays include a measure of tumor fraction (TF), which can aid in identification of low ctDNA content. Samples with low TF, especially <1% or negative, should be interpreted with caution. Tests have varying sensitivities at low TF. Additional sampling from current tumor sample or future plasma can be considered.

^v Assess for *ESR1* mutations at progression following prior lines of endocrine therapy (ctDNA preferred). If *ESR1* negative and TF is low, consider reflex testing with tissue-based next-generation sequencing (NGS) assay.

^w Tissue biopsy is preferred to ctDNA at detecting homozygous copy loss of *PTEN* or TMB.

^x Consider for disease progression on adjuvant endocrine therapy or with early disease relapse within 12 months of adjuvant endocrine therapy completion.

^y In adult patients with *PIK3CA* or *AKT1* activating mutations, or for *PTEN* inactivating mutations and genomic changes (eg, deletion) after disease progression or recurrence after a prior line of endocrine therapy + CDK4/6 inhibitor.

^z For disease progression during or after prior line of aromatase inhibitor plus CDK 4/6 inhibitor therapy in the adjuvant or metastatic setting.

^{aa} For disease progression during or after a prior line of aromatase inhibitor with or without CDK 4/6 inhibitor therapy in the adjuvant or metastatic setting.

^{bb} For disease progression after at least one line of endocrine therapy + CDK 4/6 inhibitor in the metastatic setting.

^{cc} If *ESR1* mutation is detected (category 2B) in a patient on an AI + CDK4/6 inhibitor for at least 6 months, in the absence of radiologic progression, could consider switching to camizestrant and continue the same CDK 4/6 inhibitor (category 2B) (see [BINV-P 2 of 3](#)).

Note: All recommendations are category 2A unless otherwise indicated.

EMBER-3 Trial

Global, open-label, randomized phase III study • primary analysis

ELIGIBLE POPULATION

**ER-positive / HER2-negative
locally advanced or
metastatic breast
cancer**

- Progression during or after an aromatase inhibitor
- Prior CDK4/6 inhibitor permitted
- No prior chemotherapy for advanced disease

RANDOMIZE 1:1:1

N = 874

Stratified by prior CDK4/6i,
visceral metastases, and
region

Imlunestrant

400 mg orally once daily

n = 331

Standard endocrine therapy

Fulvestrant or exemestane

n = 330

Imlunestrant + abemaciclib

400 mg QD + 150 mg BID

n = 213

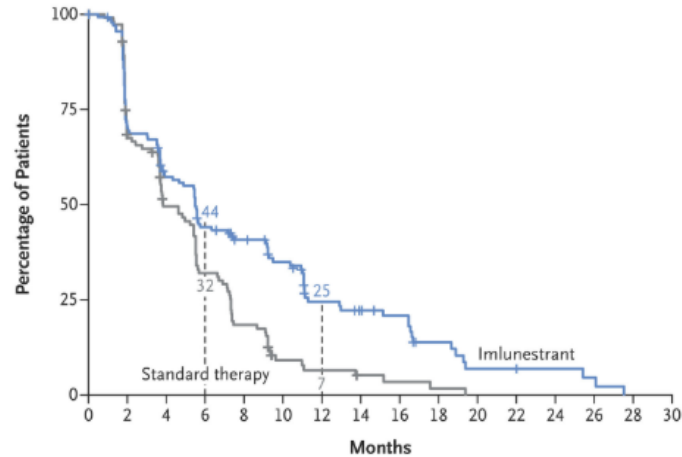
Primary endpoints Investigator-assessed PFS: imlunestrant vs SOC in ESR1-mutated and overall populations; combination vs imlunestrant in concurrently randomized patients.

EMBER-03

- ▶ Three primary end points
 - PFS with imlunestrant vs SOC with ESR1 mutation patients
 - PFS with imlunestrant as compared with SOC among all patients
 - PFS with imlunestrant-abemaciclib vs imlunestrant among all patients
- ▶ Secondary end points
 - OS of the above groups

Imlunestrant vs Fulvestrant / Exemestane

A Progression-free Survival among Patients with *ESR1* Mutations, Imlunestrant vs. Standard Therapy



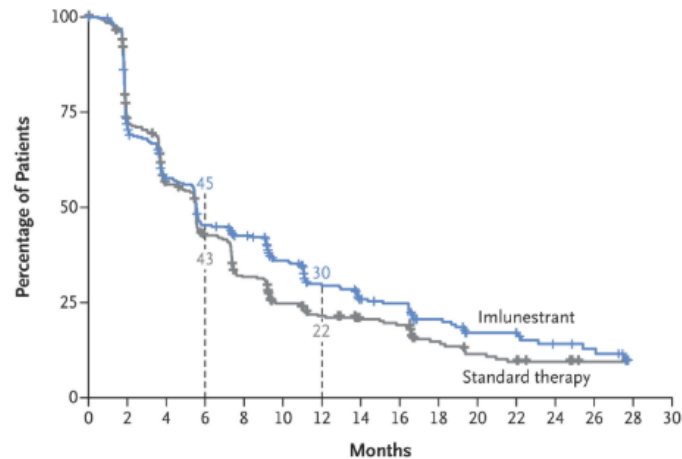
	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Imlunestrant	138	109	5.5 (3.9–7.4)
Standard Therapy	118	102	3.8 (3.7–5.5)

Difference in restricted mean survival time, 2.6 mo (95% CI, 1.2–3.9)
P<0.001

No. at Risk

Imlunestrant	138	95	74	56	45	35	22	18	15	8	4	4	3	2	0	0
Standard therapy	118	74	51	33	19	7	5	3	2	1	0	0	0	0	0	0

B Progression-free Survival among All Patients, Imlunestrant vs. Standard Therapy



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Imlunestrant	331	237	5.6 (5.3–7.3)
Standard Therapy	330	253	5.5 (4.6–5.6)

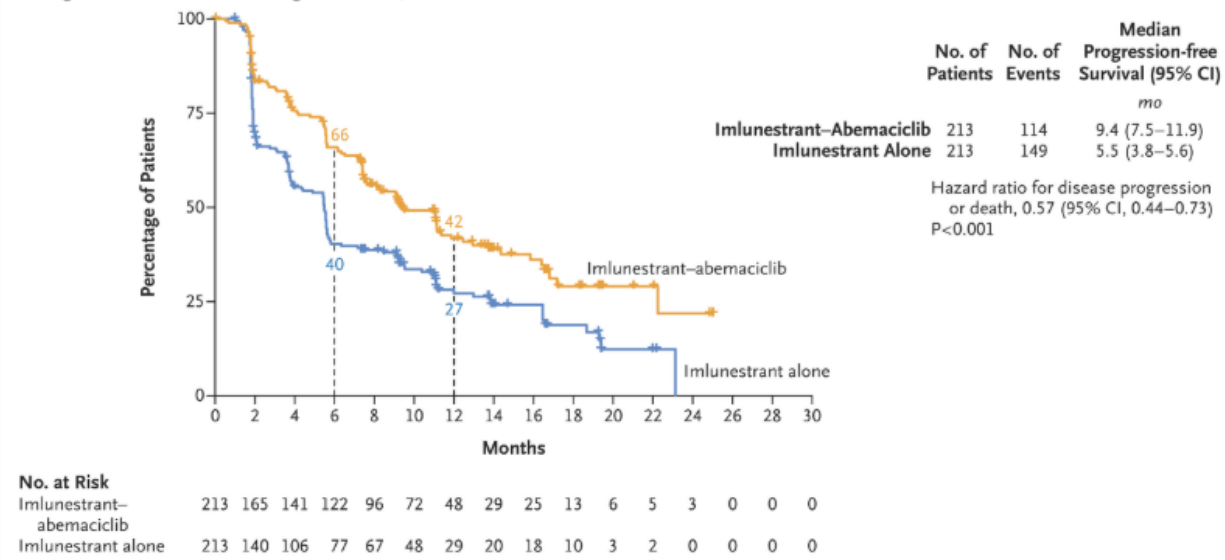
Hazard ratio for disease progression or death, 0.87 (95% CI, 0.72–1.04)
P=0.12

No. at Risk

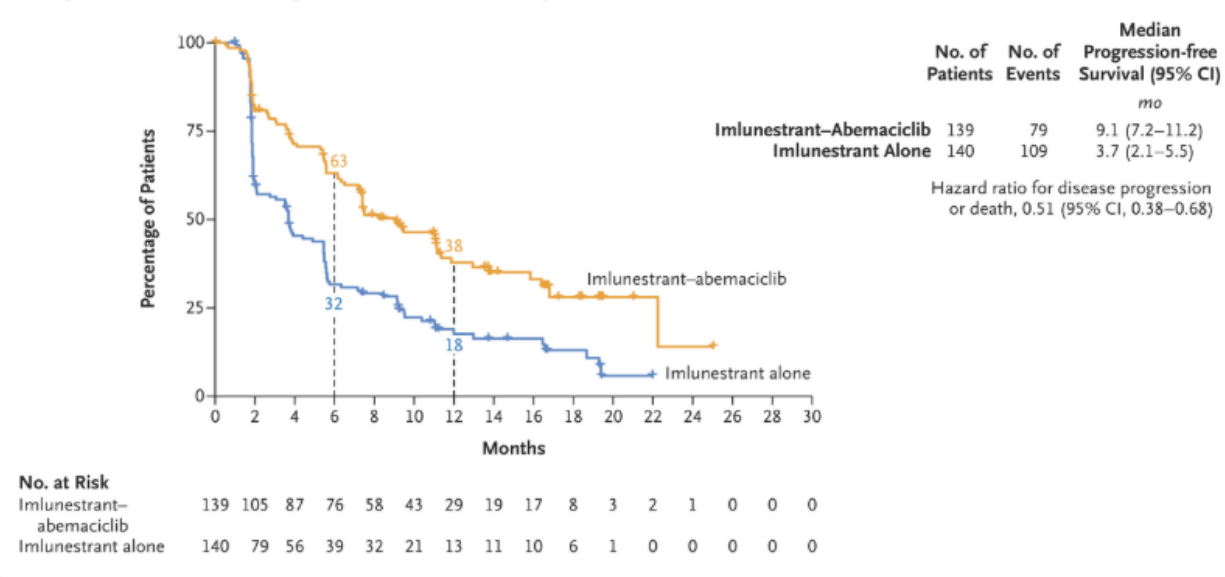
Imlunestrant	331	225	173	135	118	89	62	47	43	30	20	19	13	10	0	0
Standard therapy	330	221	165	122	89	63	51	41	38	23	17	14	10	2	0	0

Imlunestrant + Abemaciclib vs Imlunestrant

A Progression-free Survival among All Patients, Imlunestrant–Abemaciclib vs. Imlunestrant Alone



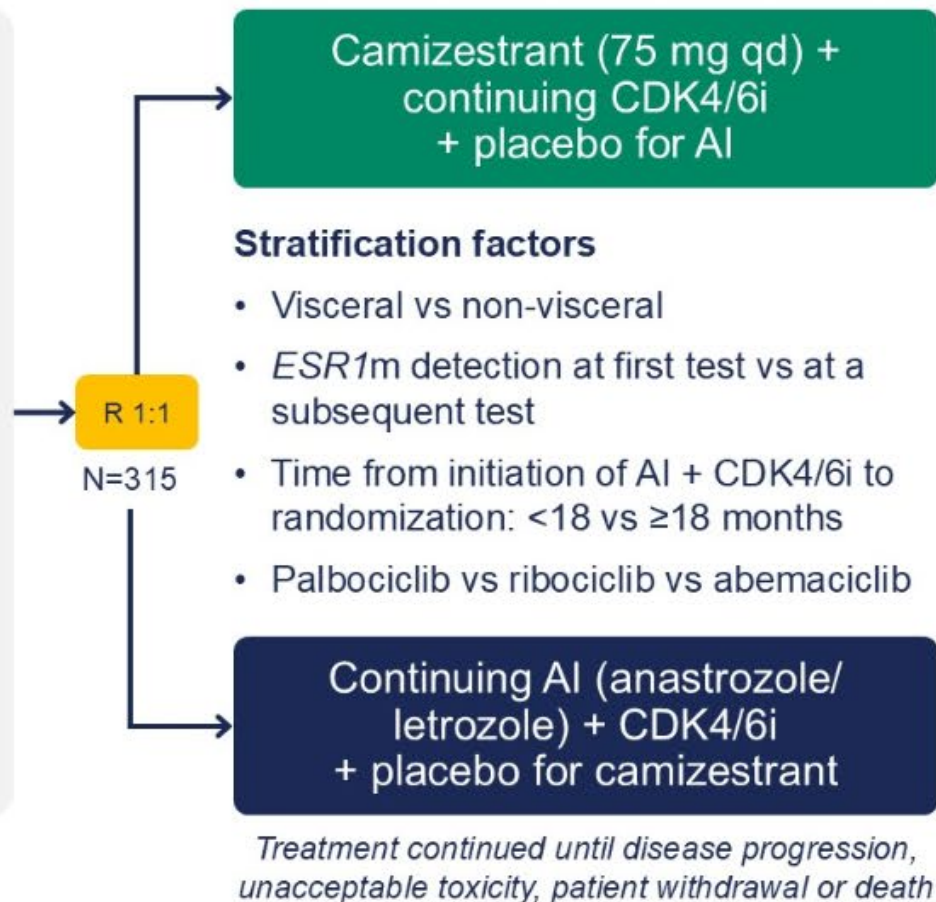
B Progression-free Survival among Patients with Previous CDK4/6 Inhibitor Treatment, Imlunestrant–Abemaciclib vs. Imlunestrant Alone



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



Primary endpoint

PFS by investigator assessment (RECIST v1.1)

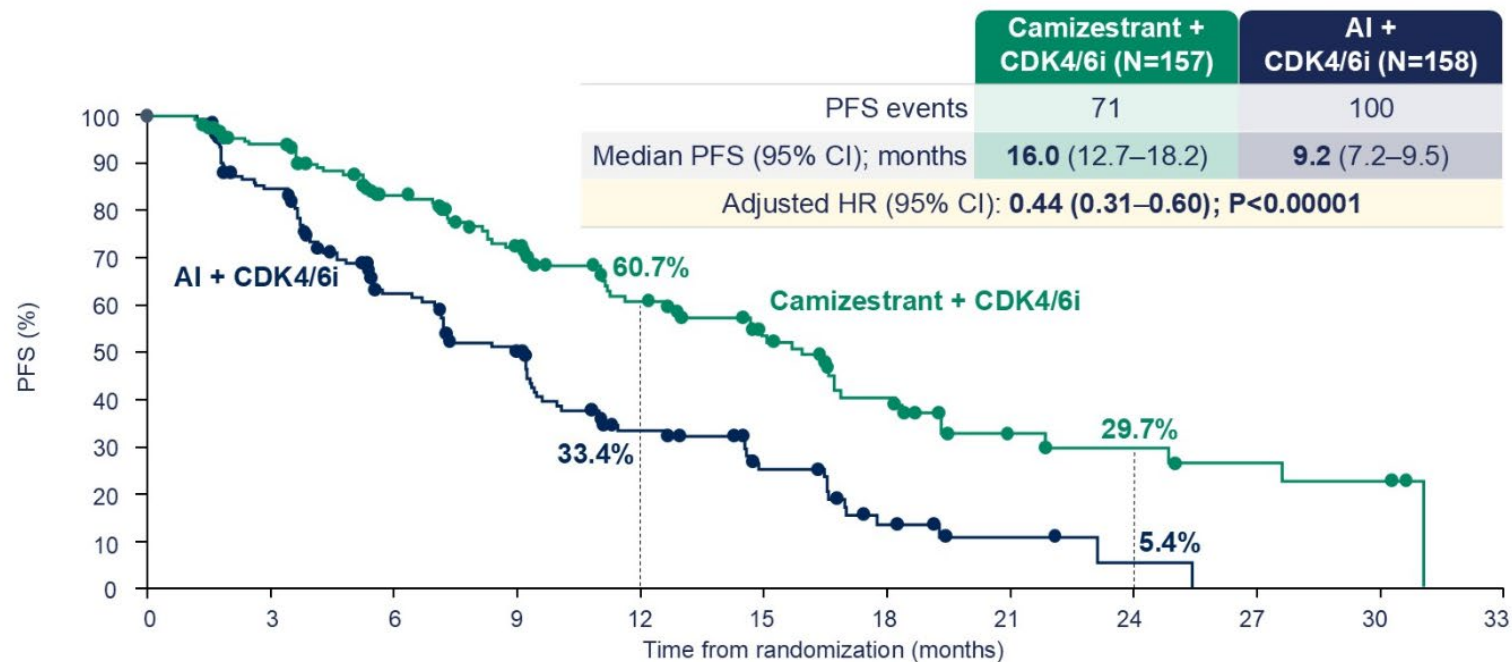
Secondary endpoints

- 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.

SERENA-6

Primary endpoint: Investigator-assessed PFS



Number of patients at risk

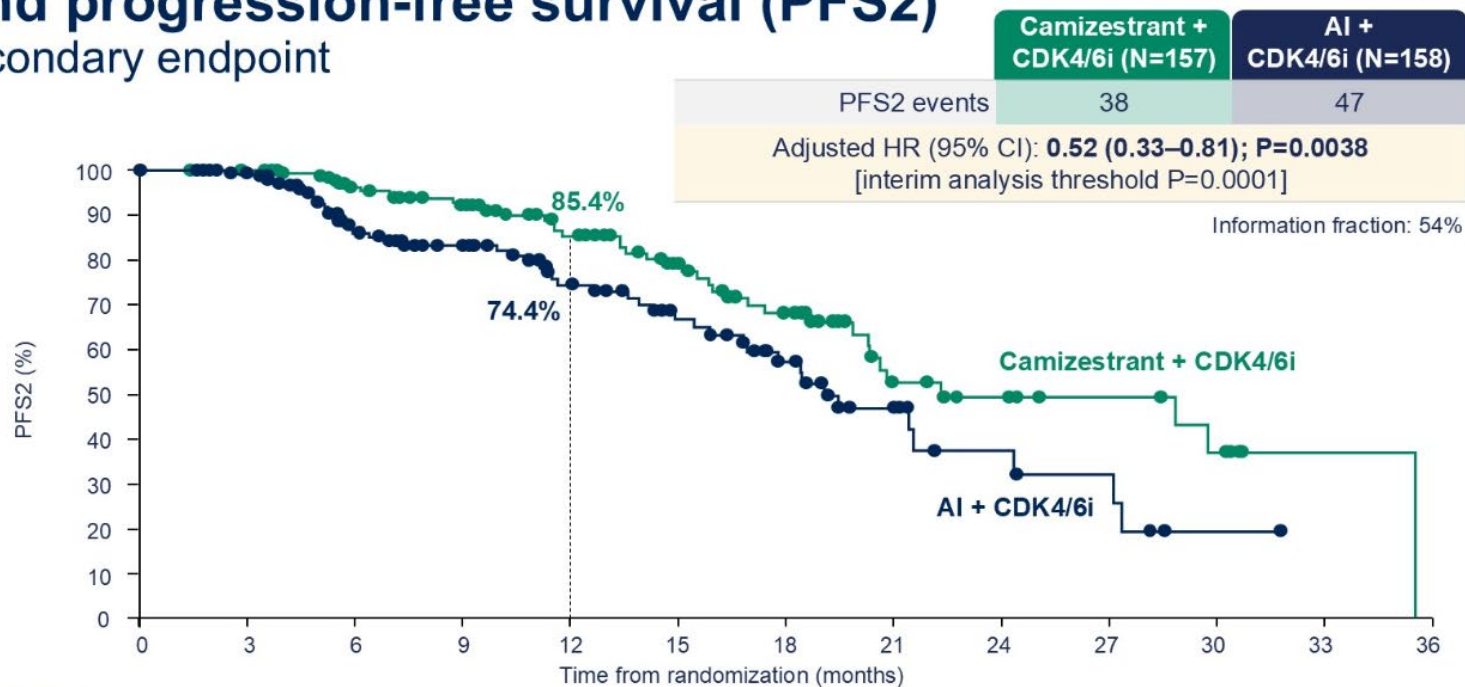
Camizestrant + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

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.

PFS2 - Progression after next line

Second progression-free survival (PFS2)

Key secondary endpoint

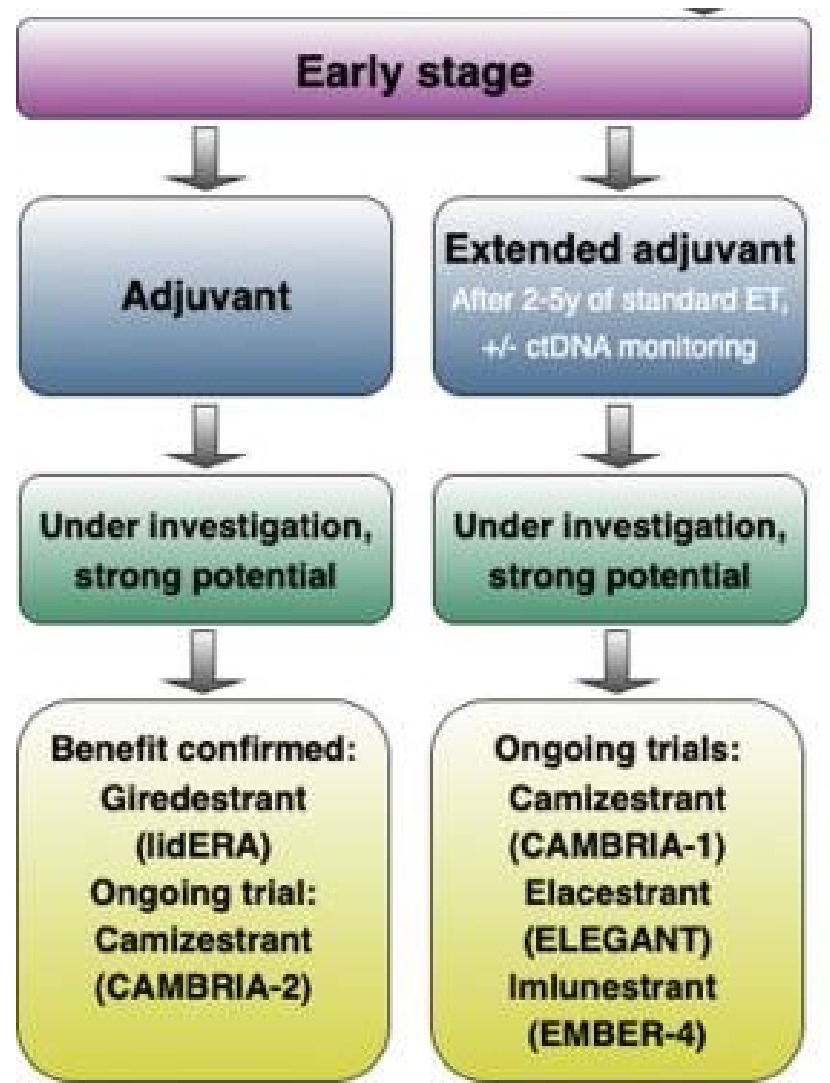


Number of patients at risk

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

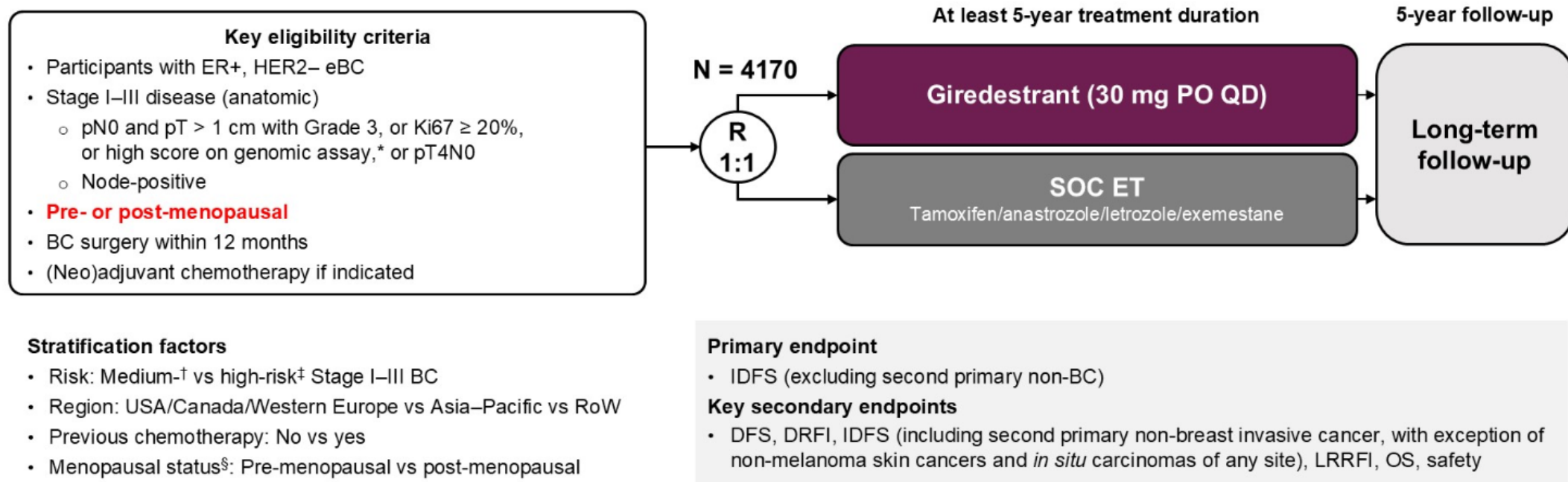
HR was estimated using the Cox proportional hazard model adjusted for stratification factors. Final PFS2 analysis will occur at 158 PFS2 events.

Future Directions



lidERA BC study design

A global, randomized, open-label, multicenter, Phase III trial

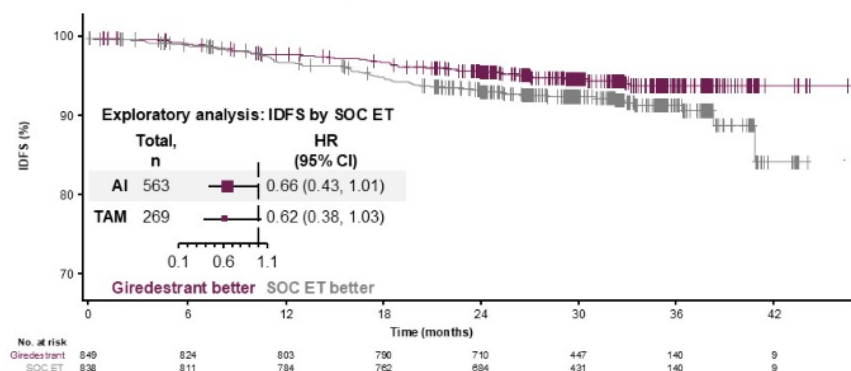


Ovarian function suppression with an approved LHRH agonist was required for all men and pre-menopausal women receiving AIs or giredestrant

IDFS by menopausal status

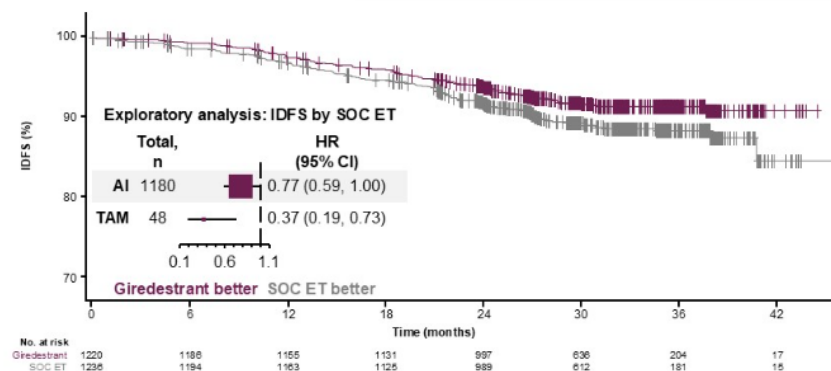
Pre-menopausal

	Giredestrant n = 849	SOC ET n = 838
Events, n (%)	44 (5.2)	66 (7.9)
3-year rate, %	94.0	91.5
HR (95% CI)	0.65 (0.44, 0.95)	



Post-menopausal

	Giredestrant n = 1220	SOC ET n = 1236
Events, n (%)	96 (7.9)	129 (10.4)
3-year rate, %	91.3	88.3
HR (95% CI)	0.74 (0.57, 0.96)	



Giredestrant showed IDFS benefit and higher 3-year rates in both pre-menopausal and post-menopausal subgroups

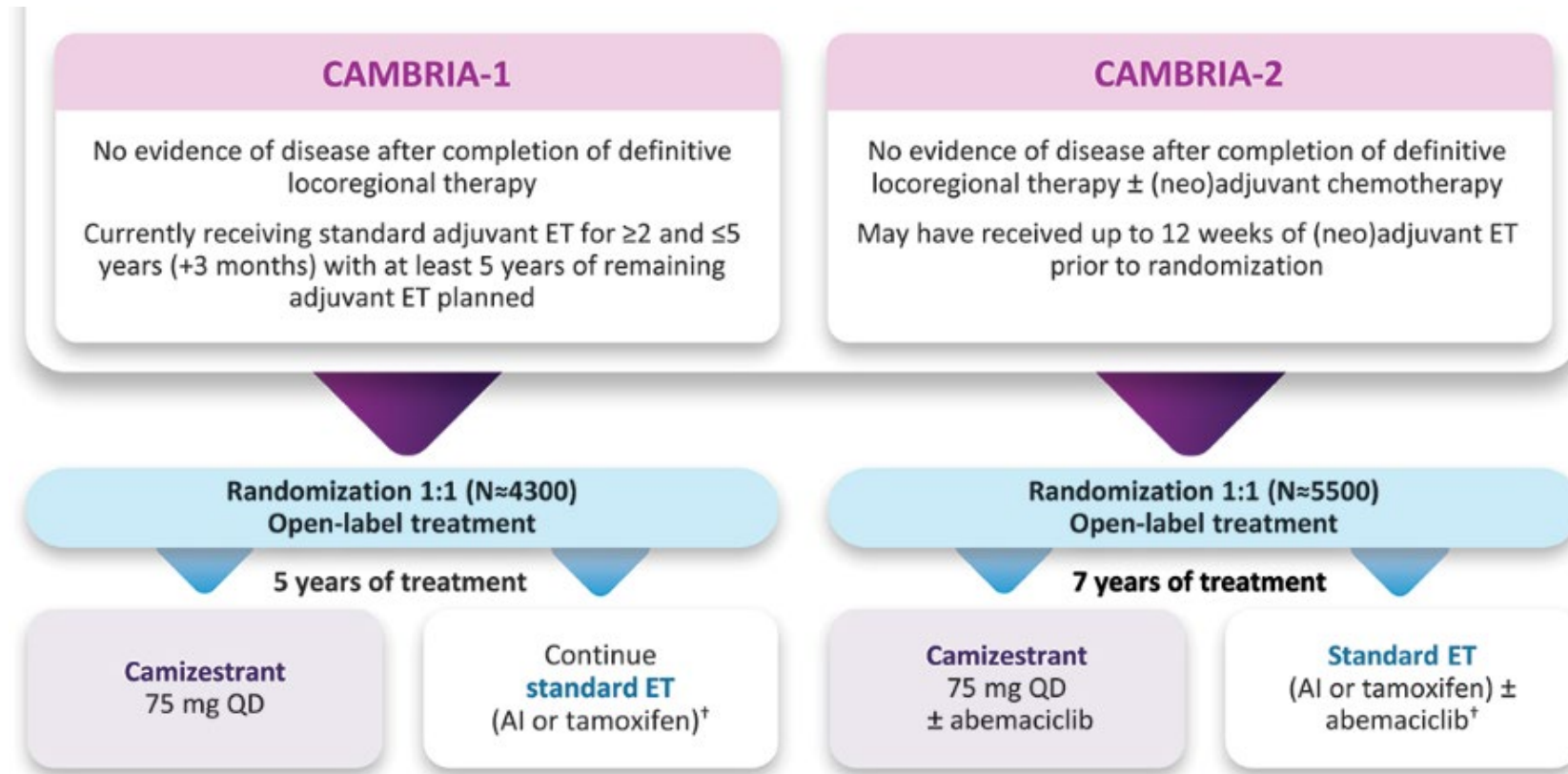
Fewer arthralgia discontinuations

Musculoskeletal pain*

	Pre-menopausal n = 1672				Post-menopausal n = 2440			
	Giredestrant n = 840	SOC ET n = 832	AI n = 563	TAM n = 269 + LHRH agonist n = 185 / - LHRH agonist n = 84	Giredestrant n = 1209	SOC ET n = 1231	AI n = 1183	TAM n = 48 (not on LHRH agonist)
Patients, n (%)								
All grade	488 (58.1)	445 (53.5)	336 (59.7)	109 (40.5) 71 (38.4) / 38 (45.2)	614 (50.8)	660 (53.6)	646 (54.6)	14 (29.2)
Grade 1	332 (39.5)	304 (36.5)	223 (39.6)	81 (30.1) 52 (28.1) / 29 (34.5)	419 (34.7)	423 (34.4)	411 (34.7)	12 (25.0)
Grade 2	141 (16.8)	126 (15.1)	99 (17.6)	27 (10.0) 19 (10.3) / 8 (9.5)	179 (14.8)	210 (17.1)	208 (17.6)	2 (4.2)
Grade 3	15 (1.8)	15 (1.8)	14 (2.5)	1 (0.4) 0 / 1 (1.2)	16 (1.3)	27 (2.2)	27 (2.3)	0
Leading to discontinuation	13 (1.5)	31 (3.7)	28 (5.0)	3 (1.1) 1 (0.5) / 2 (2.4)	20 (1.7)	51 (4.1)	51 (4.3)	0

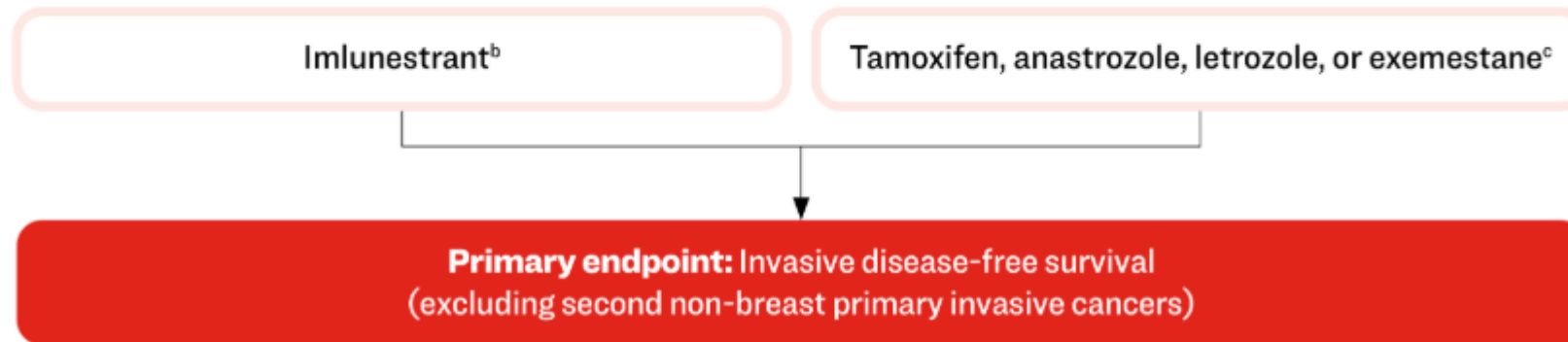
Fewer discontinuations with giredestrant compared with SOC ET, regardless of menopausal status

Adjuvant Camizestrant: In Trial



Adjuvant Imlunestrant: EMBER-4

A Randomized, Open-Label, Phase 3 Study of Adjuvant Imlunestrant vs Standard Adjuvant Endocrine Therapy in Patients Who Have Previously Received 2 to 5 Years of Adjuvant Endocrine Therapy for ER+, HER2- Early Breast Cancer With an Increased Risk of Recurrence^a



The future is bright... and full of SERDs