Markey Cancer Center

An NCI Comprehensive Cancer Center

Rapid Hot Topics
Breast Cancer

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DISCLOSURES

I have nothing to disclose

Objective

- Analyze recent clinical updates in breast cancer, focusing on targeted therapies for metastatic hormone receptor positive (HR+) disease

Treatment Algorithm for HR+ MBC

Hormone sensitive*	
First line	AI + CDK4/6i Fulvestrant + CDK4/6i Fulvestrant + CDK4/6i + **inavolisib**
Second line and beyond	Fulvestrant + CDK4/6i **Alpelisib** + fulvestrant, **capivasertib** + fulvestrant Fulvestrant, **elacestrant**, **imlunestrant** Everolimus + ET

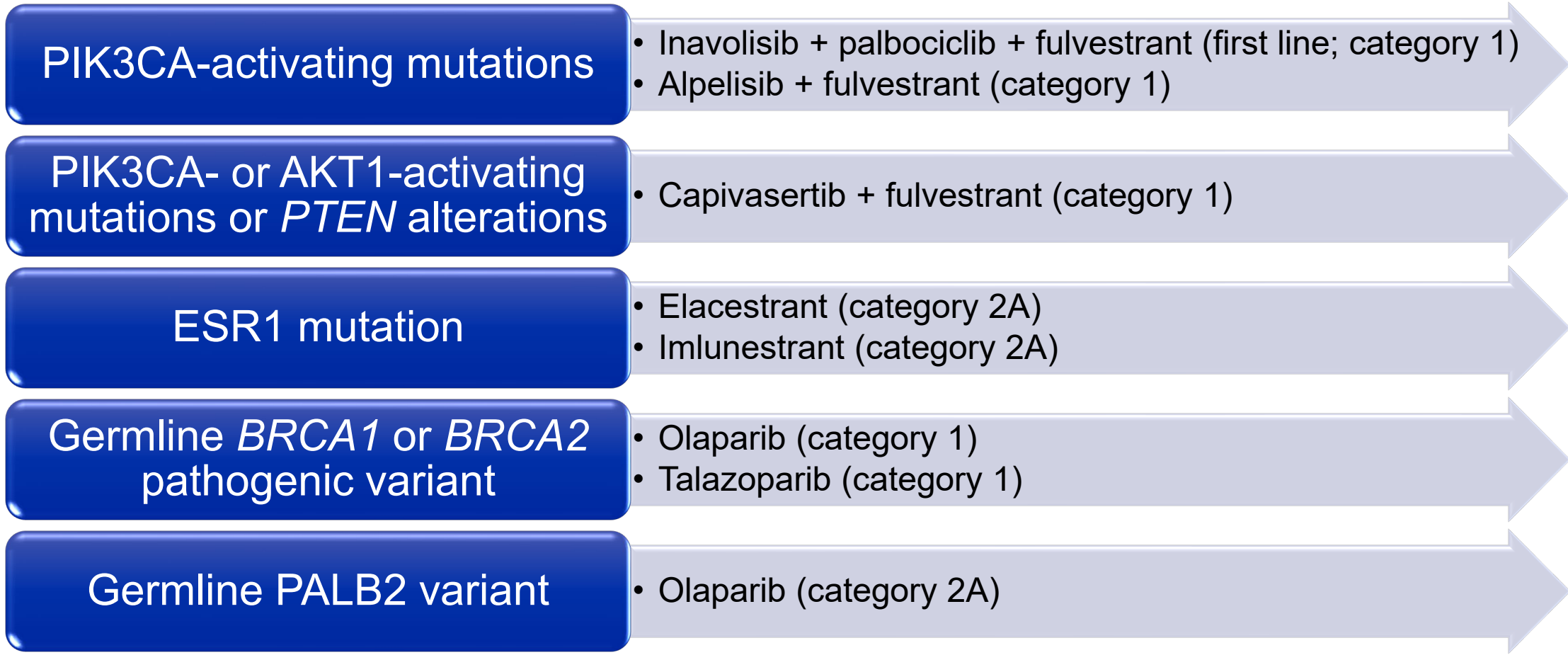
Hormone refractory or visceral crisis	
First line	Systemic chemotherapy PARPi
Second line and beyond	Fam-trastuzumab deruxtecan-nxki Sacituzumab govitecan, datopotamab deruxtecan Systemic chemotherapy

**ETs applicable to postmenopausal women or premenopausal women/men with suppressed gonadal function.*

AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; ET, endocrine therapy; MBC, metastatic breast cancer; PARPi, PARP inhibitor.

NCCN. Clinical Practice Guidelines in Oncology. Breast cancer, version 5.2025. Accessed January 2, 2026. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Mutation Testing in HR+ MBC



Regimens are approved for use in second line and beyond unless otherwise indicated.

NCCN. Clinical Practice Guidelines in Oncology. Breast cancer, version 5.2025. Accessed January 2, 2026. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

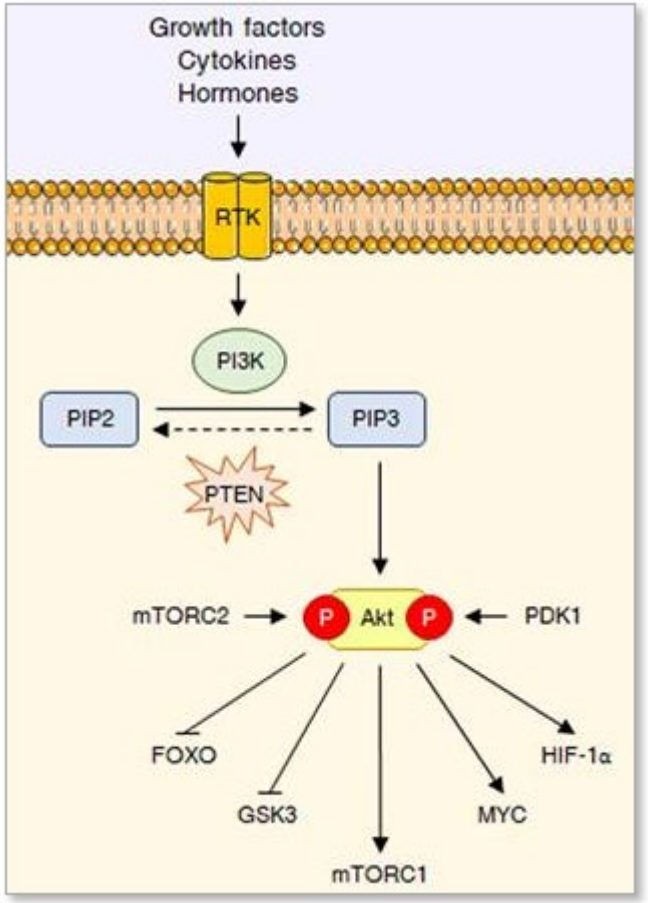
PIK3CA Mutations

Oncogenic mutation that leads to uncontrolled signaling via the PI3K-AKT pathway

Present in 35-40% of HR+ breast cancers

Prognostic and predictive biomarker

PI3K pathway is interconnected with both the ER and CDK4/6 pathways, and is believed to play a role in acquired resistance to endocrine therapies



Turner NC et al. *N Engl J Med*. 2024;391(17):1584-1596; Fonana F et al. *Int J Biol Sci*. 2024;20(8):3113-3125.

Previously FDA-Approved PI3K-AKT Pathway Inhibitors

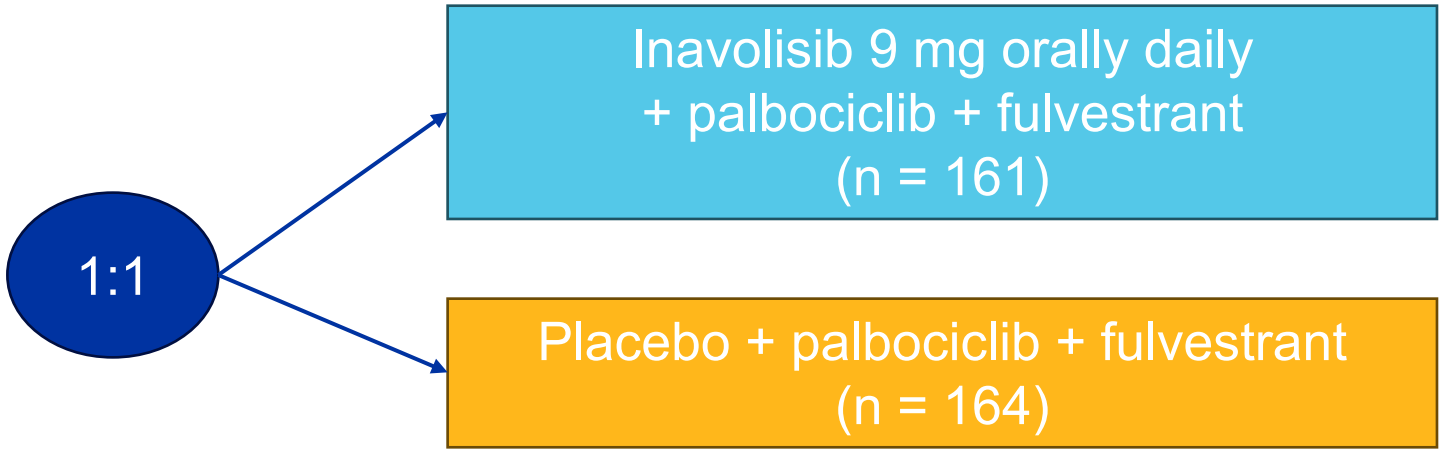
Alpelisib (SOLAR-1) Approved 5/2019	**Capivasertib (CAPItello-291)** Approved 11/2023
Post-menopausal women or men with HR+ MBC and progression on prior endocrine therapy	Pre, peri, or post-menopausal women or men with HR+ MBC and progression on prior endocrine therapy
Alpelisib + fulvestrant (n = 169) vs. **Placebo** + fulvestrant (n = 172)	**Capivasertib** + fulvestrant (n = 155) vs. **Placebo** + fulvestrant (n = 134)
Significant improvement in median PFS in the **PIK3CA mutated** cohort HR, 0.65 (95% CI, 0.50-0.85); *P<0.001*	Significant improvement in median PFS in the **AKT pathway-altered** cohort HR, 0.50 (95% CI, 0.38-0.65); *P<0.001*

Andre F et al. *N Engl J Med*. 2019;380(20):1929-1940; Andre F et al. *Ann Oncol*. 2021;32(2):208-217; Turner NC et al. *N Engl J Med*. 2023;388(22):2058-2070.

INAVO120

Inavolisib + Palbociclib + Fulvestrant

- Pre, peri, or postmenopausal women or men
- *PIK3CA*-mutated HR+/HER2– MBC
- **Recurrence or progression during or within 12 months of completion of adjuvant ET**
- FPG <126 mg/dL and HbA_{1c} <6%



- Pre and perimenopausal women and men received a GnRH agonist for hormone suppression.
- Palbociclib and fulvestrant were given at standard FDA-approved doses.

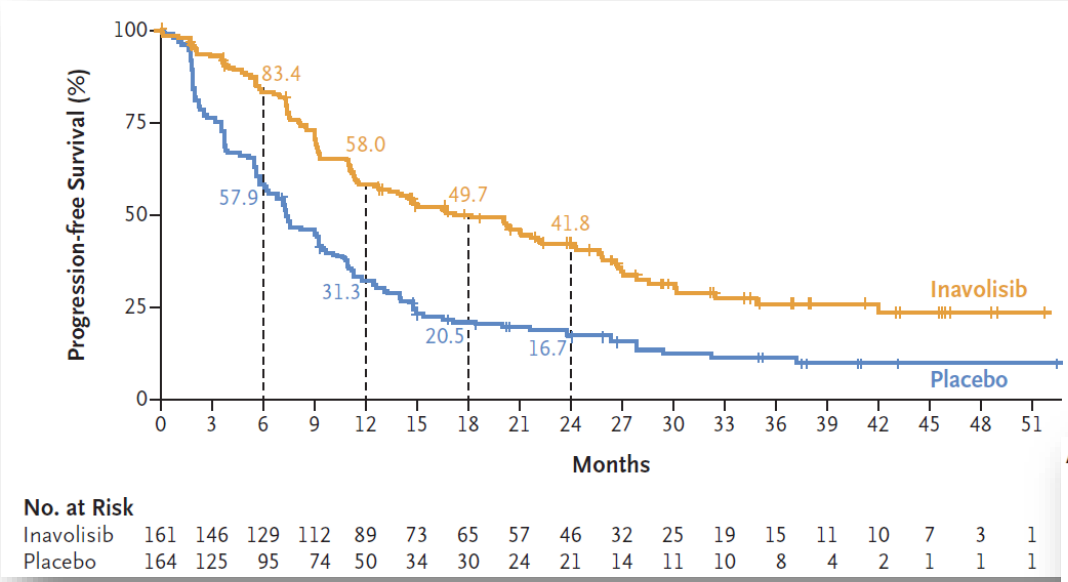
FPG, fasting plasma glucose; GnRH, gonadotropin-releasing hormone; Hb, hemoglobin.

Turner NC et al. *N Engl J Med*. 2024;391(17):1584-1596.

INAVO120 Results

Inavolisib + Palbociclib + Fulvestrant

Regimen FDA approved 10/2024

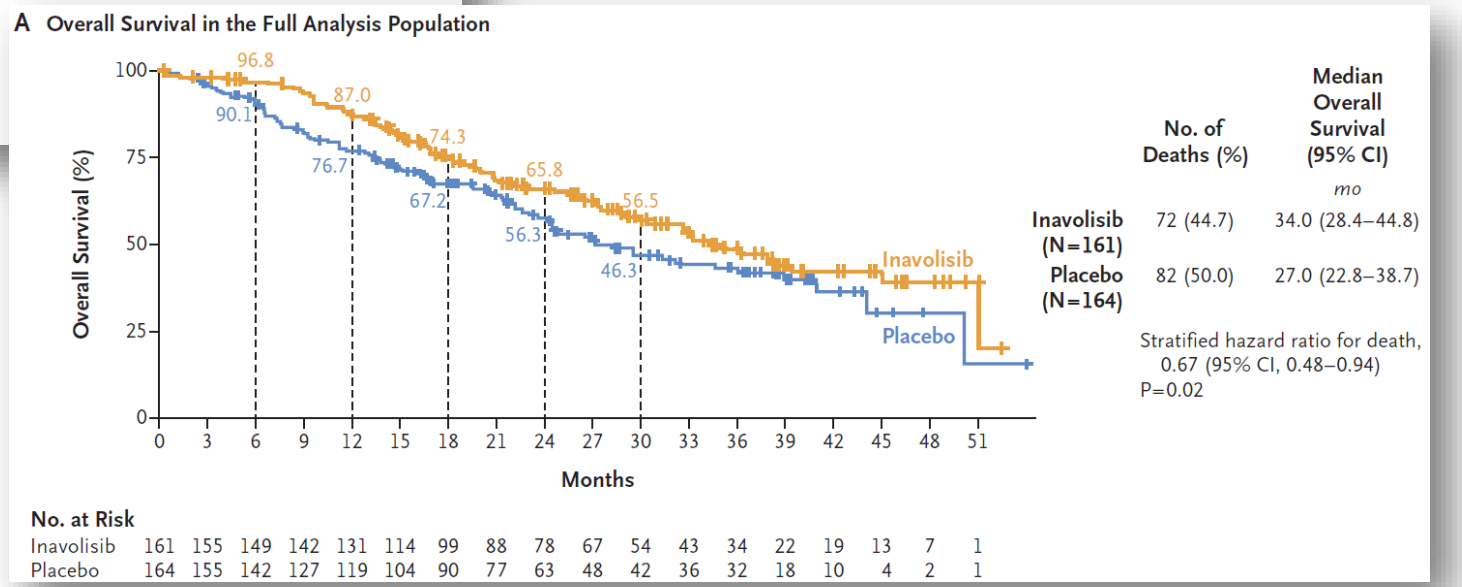


	No. of Patients with Event (%)	Median Progression-free Survival (95% CI)
		mo
Inavolisib (N=161)	103 (64.0)	17.2 (11.6–22.2)
Placebo (N=164)	141 (86.0)	7.3 (5.9–9.2)

Stratified hazard ratio for disease progression or death, 0.42 (95% CI, 0.32–0.55)

Significant improvement in median PFS

Significant improvement in median OS



	No. of Deaths (%)	Median Overall Survival (95% CI)
		mo
Inavolisib (N=161)	72 (44.7)	34.0 (28.4–44.8)
Placebo (N=164)	82 (50.0)	27.0 (22.8–38.7)

Stratified hazard ratio for death, 0.67 (95% CI, 0.48–0.94)
P=0.02

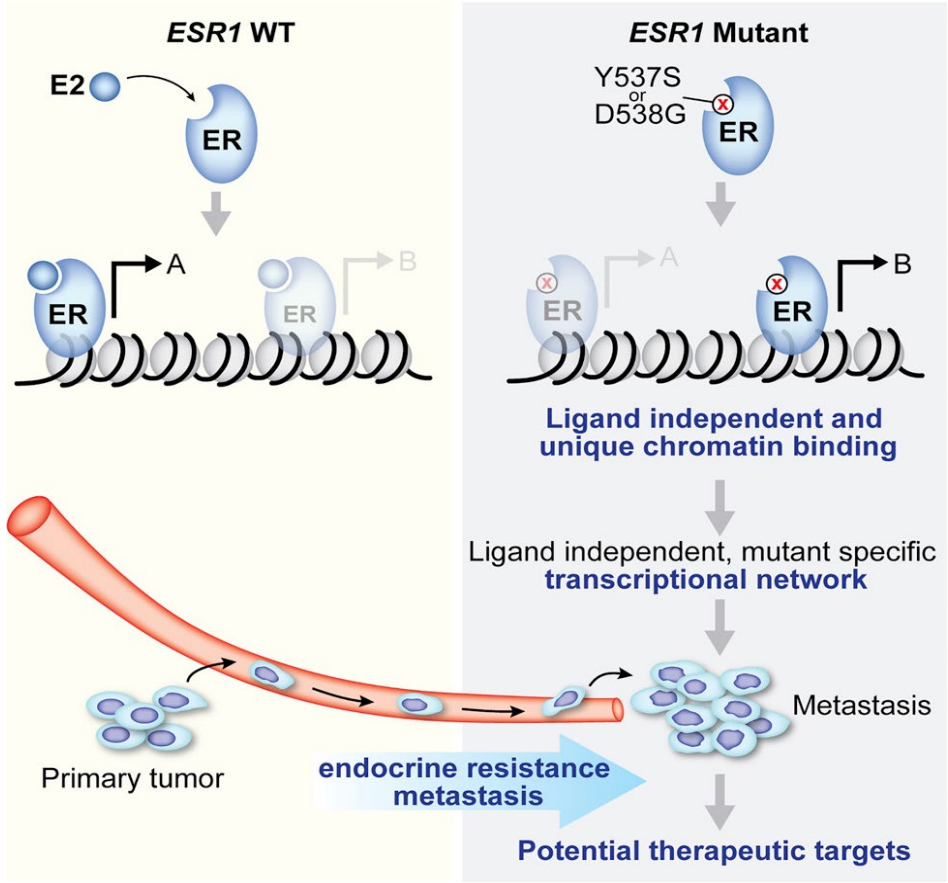
Turner NC et al. *N Engl J Med*. 2024;391(17):1584-1596; Jhaveri K et al. *N Engl J Med*. 2025;393(2): 151-161.

Barriers to implementation

- Patient selection
- Toxicity
- Implications on downstream treatment options
- CDK4/6i preference (ongoing studies)
- Impact of prior adjuvant CDK4/6i exposure to results

ESR1 Mutations

- Acquired resistance mutation in the ER ligand-binding domain
- Results in constitutively active, estrogen-independent signaling
- 25-40% of HR+ metastatic patients receiving endocrine therapy; <5% frequency in de novo disease
- Prognostic and predictive of reduced response/resistance to other anti-estrogen therapies



Jeselsohn R et al. *Curr Oncol Rep*. 2017;19(35):35; Jesselsohn R et al. *Cancer Cell*. 2018;33(2):173-186.

Previously FDA-Approved Oral SERD

Elacestrant (EMERALD)
1/2023

Post-menopausal women or men with HR+ MBC and progression on prior endocrine therapy, including a CDK4/6i

Elacestrant (n = 239) vs.
Investigator's choice aromatase inhibitor + fulvestrant (n = 238)

Significant improvement in median PFS in the **ESR1 mutated** cohort

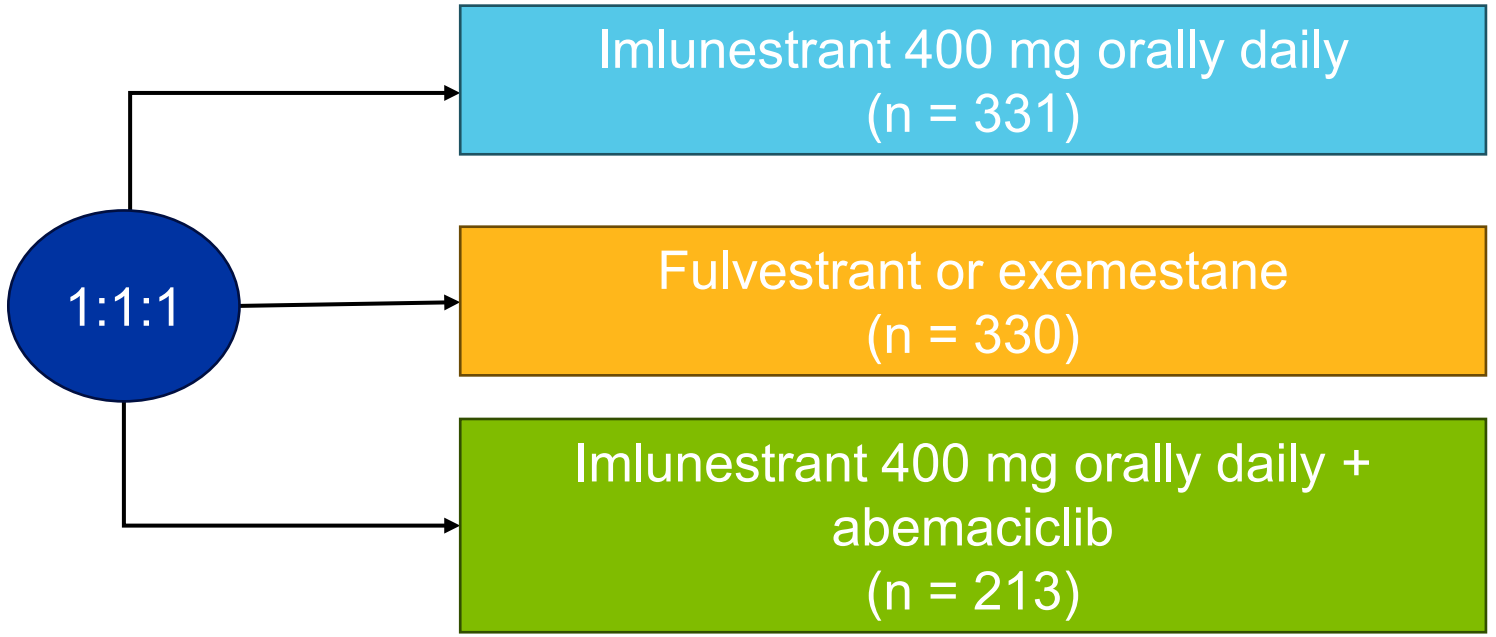
HR, 0.55 (95% CI, 0.39-0.77); *P=0.0005*

SERD, selective estrogen receptor degrader.

Bidard FC et al. *J Clin Oncol*. 2022;40(28):3246-3256.

EMBER-3
Imlunestrant

- Pre or postmenopausal women or men
- HR+/HER2- MBC
- **Recurrence on or within 12 months of completion of adjuvant AI ± CDK4/6i, or progression on first-line AI ± CDK4/6i in the metastatic setting**
- No additional therapy for advanced BC



- Premenopausal women and men received a GnRH agonist for hormone suppression.
- Abemaciclib was given at standard FDA-approved dose.

Jhaveri KL et al. *J Clin Oncol*. 2024;42(35):4173-4186; Jhaveri KL et al. *N Engl J Med.* 2024.

Primary PFS Endpoints of EMBER-3

Imlunestrant

SOC, standard of care.

*Imlunestrant + abemaciclib endpoint was tested if an imlunestrant monotherapy arm demonstrated benefit.

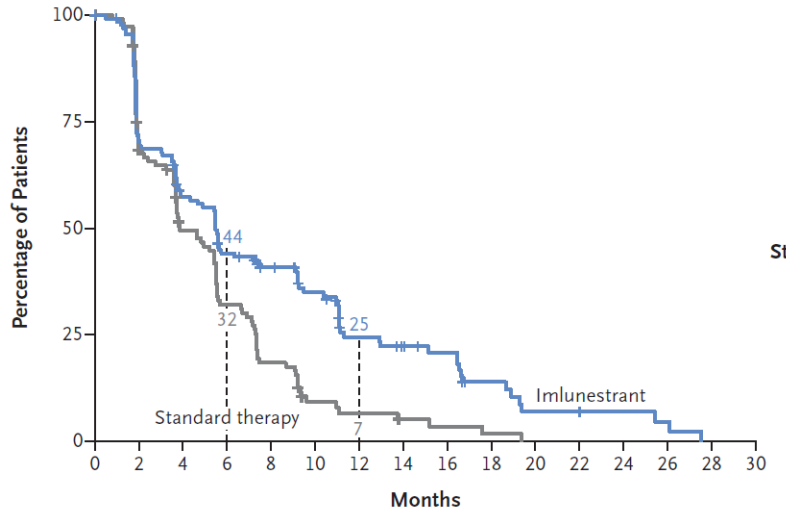
Jhaveri K et al. SABCS. Abstract SESS-3617; Jhaveri KL et al. *J Clin Oncol*. 2024;42(35):4173-4186; Jhaveri KL et al. *N Engl J Med.* 2024.

EMBER-3 PFS Results

Imlunestrant

Imlunestrant monotherapy FDA approved 9/2025 (ESR1m)

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



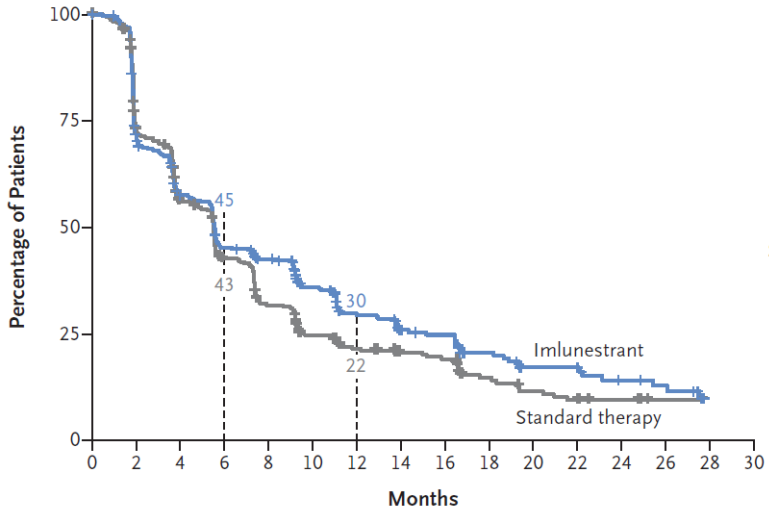
	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant	138	109	5.5 (3.9–7.4)
Standard Therapy	118	102	3.8 (3.7–5.5)

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

Significant improvement in median PFS in the **ESR1m cohort** (imlunestrant monotherapy)

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

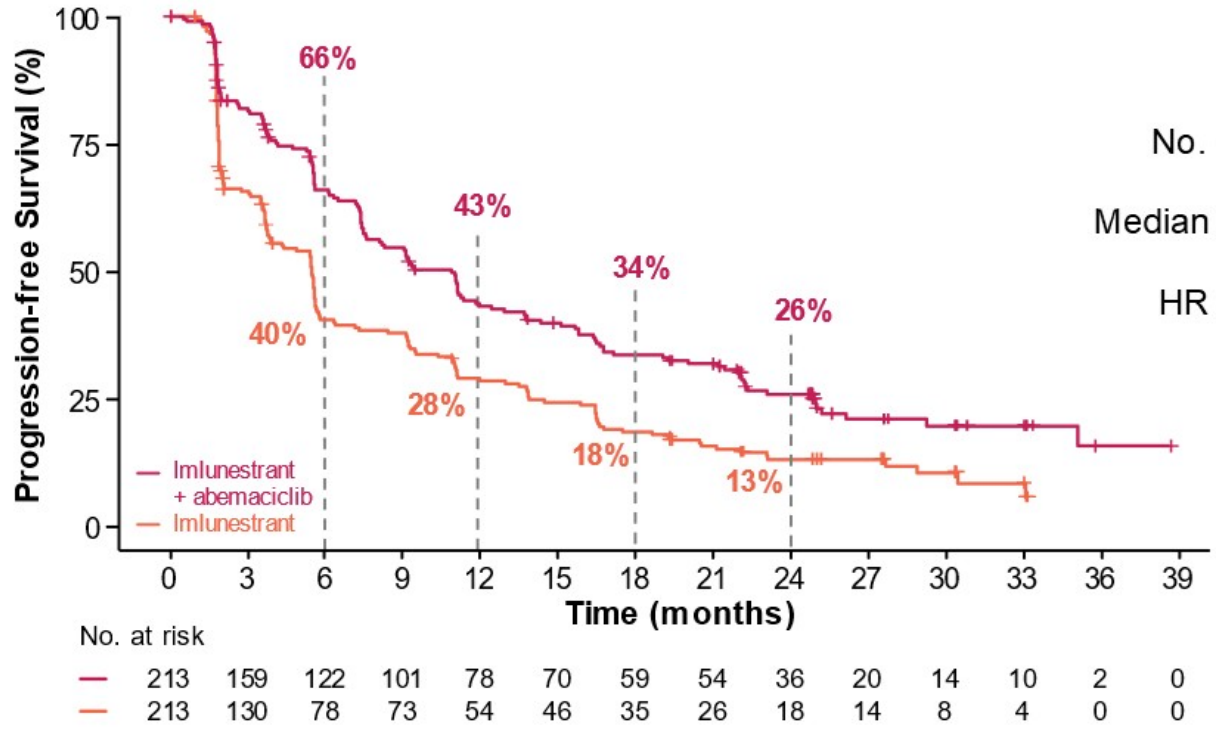
No. at Risk																
Imlunestrant	331	225	173	135	118	89	62	47	43	30	20	19	13	10	0	0
Standard therapy	330	221	165	122	89	63	51	41	38	23	17	14	10	2	0	0

No PFS benefit in the **full population** (imlunestrant monotherapy)

Jhaveri KL et al. *J Clin Oncol*. 2024;42(35):4173-4186; Jhaveri KL et al. *N Engl J Med.* 2024.; Jhaveri K et al. *Ann Oncol*. 2025; S0923-7534(25)06289-1; Jhaveri K et al. SABCS. 2025. GS3-08

EMBER-3 PFS Results

Imlunestrant



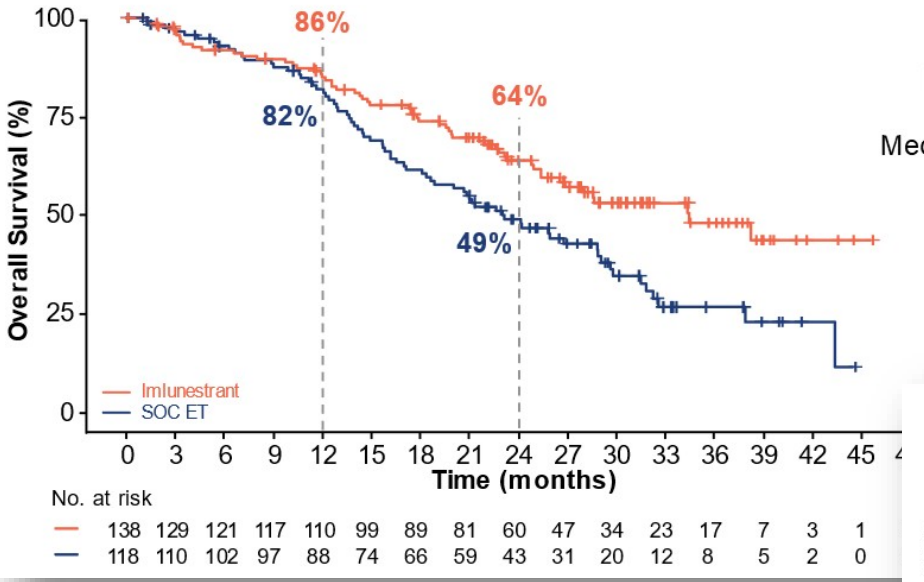
	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of events	144	174
Median (95% CI)	**10.9** (7.5-12.5)	**5.5** (3.8-5.6)
HR (95% CI)	**0.59 (0.47-0.74)**	
	Nominal *p*-value[a] < 0.0001	

Significant benefit of imlunestrant + abemaciclib combination therapy in the full study population, regardless of ESR1 mutation status, PIK3CA mutation status, or prior CDK4/6i use.

Jhaveri KL et al. *J Clin Oncol*. 2024;42(35):4173-4186; Jhaveri KL et al. *N Engl J Med.* 2024.; Jhaveri K et al. *Ann Oncol*. 2025; S0923-7534(25)06289-1; Jhaveri K et al. SABCS. 2025. GS3-08

EMBER-3 OS Results

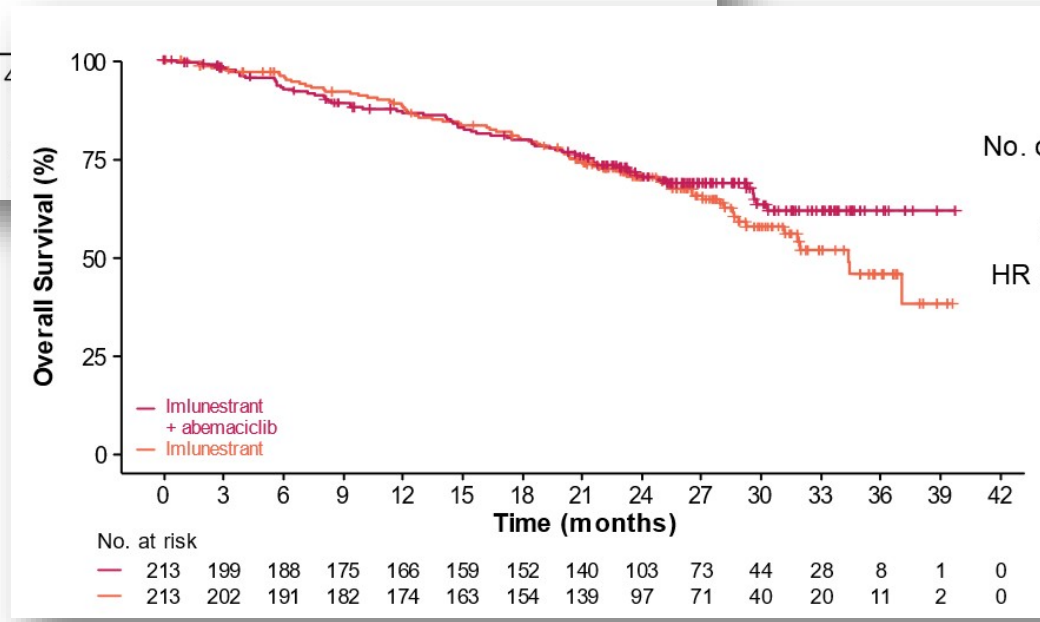
Imlunestrant



	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)

Median OS did not reach statistical significance in the **ESR1m cohort**, but result is clinically significant



	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of deaths	64	76
Median (95% CI)	**NR**	**34.4** (29.3-NR)
HR (95% CI)	**0.82 (0.59-1.16)**	
	p-value = 0.2622*	

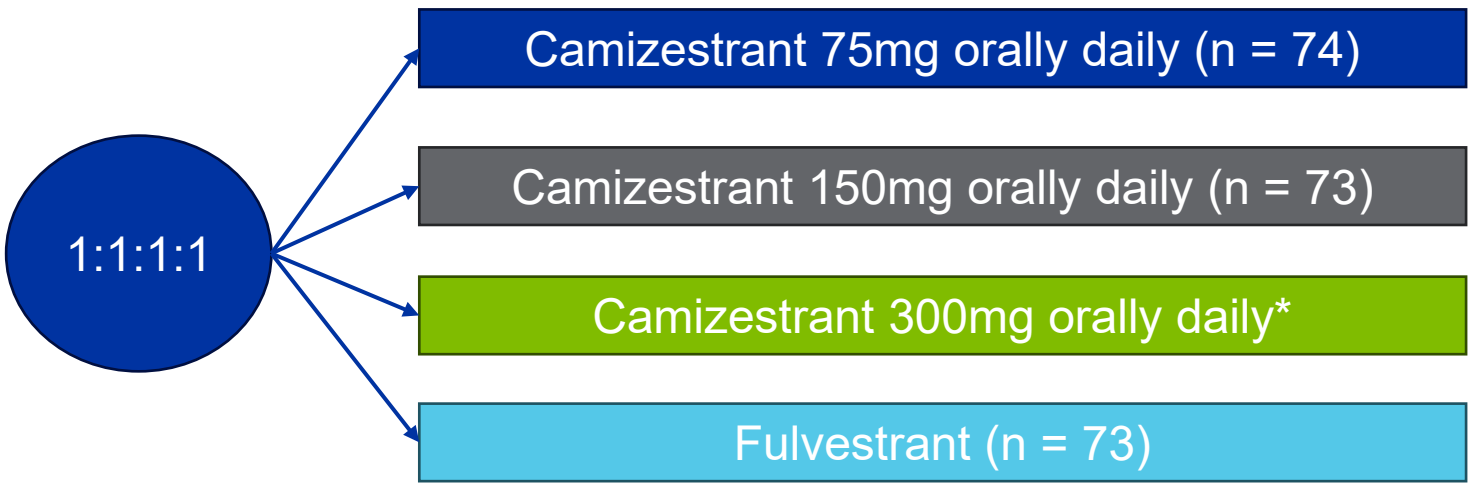
*p-value did not achieve prespecified threshold for significance (*p* < 0.0000001 at IA2)

No survival benefit shown in the combination arm; numerically the combination arm had more deaths upon initial analysis… Longer follow-up needed.

Jhaveri K et al. SABCS. 2025. GS3-08; Jhaveri K et al. *Ann Oncol*. 2025; S0923-7534(25)06289-1

SERENA-2
Camizestrant

- Postmenopausal women
- HR+/HER2– inoperable or MBC
- **Progression on one line of prior ET**
- No prior fulvestrant or other SERD



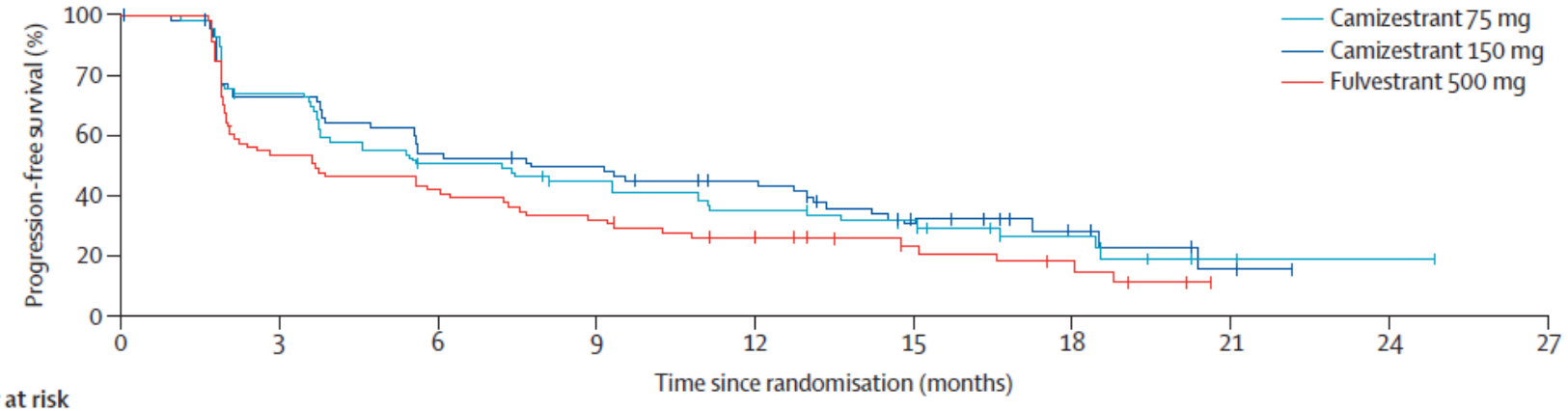
*300mg arm was closed early and not included in the efficacy analysis

Oliveira M et al. *Lancet Oncol.* 2024;25(11):1424-1439

SERENA-2 Results

Camizestrant

	Camizestrant 75 mg (n=74)	Camizestrant 150 mg (n=73)	Fulvestrant 500 mg (n=73)
Patients with events (%)	50 (68%)	48 (66%)	57 (78%)
Median progression-free survival (90% CI), months	7·2 (3·7–10·9)	7·7 (5·5–12·9)	3·7 (2·0–6·0)
HR (90% CI)*	0·59 (0·42–0·82)	0·64 (0·46–0·89)	..
Stratified log-rank p value*	0·017	0·0090	..
6-month progression-free survival rate (90% CI)	50·3% (40·0–59·7)	53·6% (43·3–62·9)	40·0% (30·4–49·4)
12-month progression-free survival rate (90% CI)	34·3% (24·9–44·0)	44·5% (34·4–54·1)	25·3% (17·1–34·2)
Median follow-up (IQR), months	16·6 (12·9–19·4)	16·3 (12·9–18·3)	14·7 (12·7–20·1)



Number at risk (number censored)										
Camizestrant 75 mg	74 (0)	50 (6)	33 (7)	27 (9)	21 (9)	14 (13)	7 (19)	2 (22)	1 (23)	0 (24)
Camizestrant 150 mg	73 (0)	50 (4)	37 (4)	32 (6)	25 (10)	13 (15)	6 (21)	2 (23)	0 (25)	..
Fulvestrant 500 mg	73 (0)	37 (3)	28 (3)	22 (3)	14 (7)	8 (12)	5 (13)	0 (16)	..	..

Significant improvement in median PFS

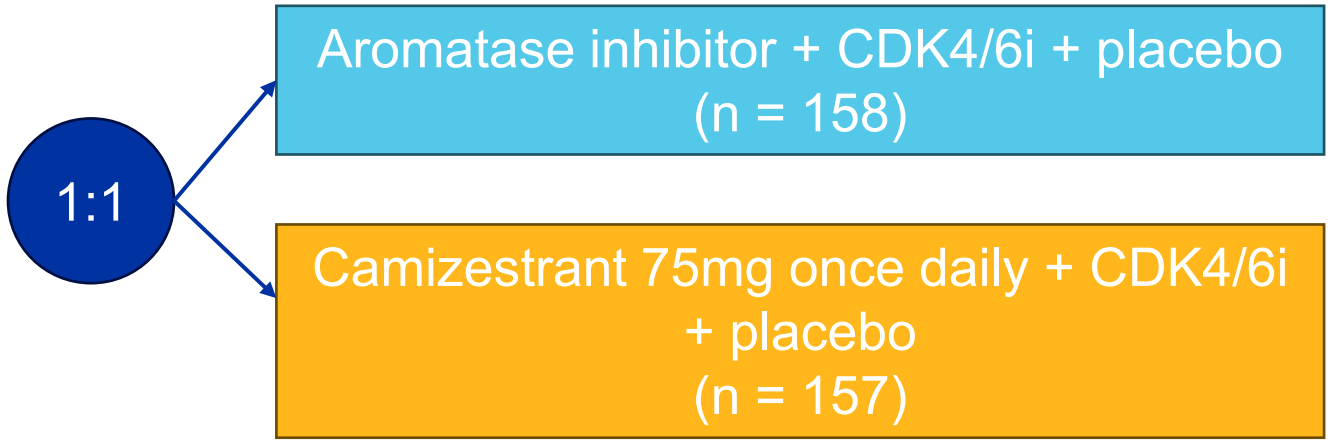
Oliveira M et al. *Lancet Oncol.* 2024;25(11):1424-1439

SERENA-6
Camizestrant

- Pre, peri, or postmenopausal women or men
- HR+/HER2– recurrent or MBC
- **≥6 months of an aromatase inhibitor + CDK4/6i as initial endocrine therapy for metastatic disease**

Surveillance for ESR1m in ctDNA Q2-3M

- If ESR1m detected without evidence of disease progression, patient eligible for randomization

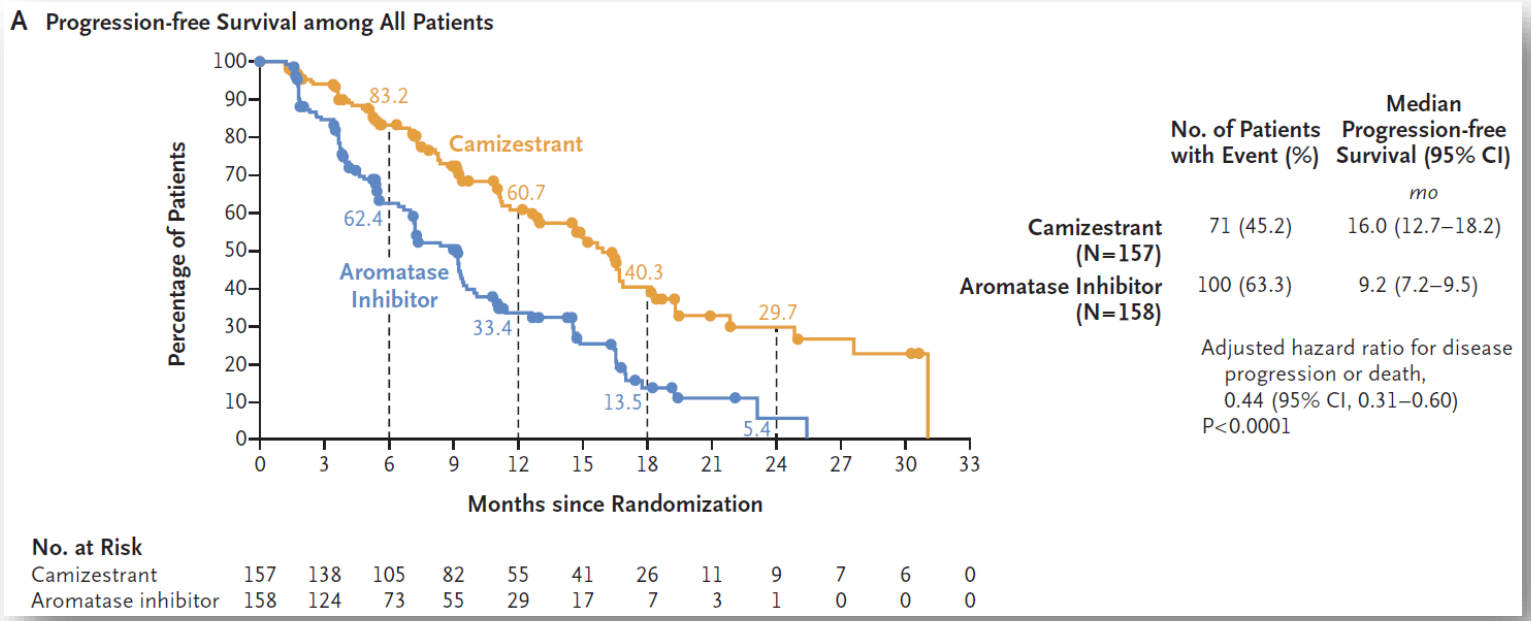


- Pre and perimenopausal women and men received a GnRH agonist for hormone suppression.
- Aromatase inhibitors and CDK4/6i continued at standard FDA-approved doses.

Bidard FC et al. *N Engl J Med*. 2025;393:569-580

SERENA-6 Results
Camizestrant

Characteristic		Camizestrant (n = 157)	Aromatase inhibitor (n = 158)
Median time from initiation of 1st-line therapy to randomization, months (range)		23 (7-96)	23 (6-96)
CDK4/6i maintained, %			
	Palbociclib	75.8	75.3
	Ribociclib	15.3	14.6
	Abemaciclib	8.9	10.1



Significant improvement in median PFS

Bidard FC et al. *N Engl J Med*. 2025;393:569-580

Barriers to implementation

Development of an ESR1m in the absence of radiologic progression has not been prospectively validated as an event necessitating a change in therapy.

In this study, patients who remained on standard therapy still had a median PFS of >9 months after ESR1m detected. What if we waited and started camizestrant after radiologic progression?

Cost of serial testing vs. benefit

(10 patients tested for every 1 ESR1m detected)

Additional Roles for Oral SERDS

Combination with mTOR inhibitor

- **ELEVATE:** Elacestrant + everolimus after progression on 1st-line treatment for HR+ MBC
- **ADELA:** Elacestrant + everolimus in patients with ESR1m tumors after progression 1st-line treatment for HR+ MBC
- **evERA:** Giredestrant + everolimus after progression on CDK4/6i + endocrine thearpy

Combination with CDK4/6 inhibitor

- **ELEVATE:** Elacestrant + abemaciclib/ribociclib/palbociclib after progression on 1st-line treatment for HR+ MBC
- **ELECTRA:** Elacestrant + abemaciclib with HR+ brain metastases

Combination with PIK3CA inhibitor

- **ELEVATE:** Elacestrant + capivasertib/alpelisib after progression on 1st-line treatment for HR+ MBC

Adjuvant setting

- **lidERA:** Giredestrant as ajuvant therapy
- **EMBER-4:** Imlunestrant following 2-5 years of standard adjuvant endocrine therapy ± CDK4/6i
- **ELEGANT:** Elacestrant following 2-5 years of standard adjuvant endocrine therapy ± CDK4/6i

Conclusions

- PI3K-AKT pathway mutations and ESR1 mutations represent a significant faction of breast cancer research
- Novel agents have been approved in the past year, with several more approvals on the horizon
- ctDNA monitoring is an additional growing area of interest amongst breast cancer researchers and practitioners (but additional data is needed overall)

Markey Cancer Center

An NCI Comprehensive Cancer Center

Rapid Hot Topics
Breast Cancer

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