

Advancing Precision Care in HR+/HER2-Metastatic Breast Cancer: ESR1 Testing and the Expanding Role of Oral SERDs

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Disclosures

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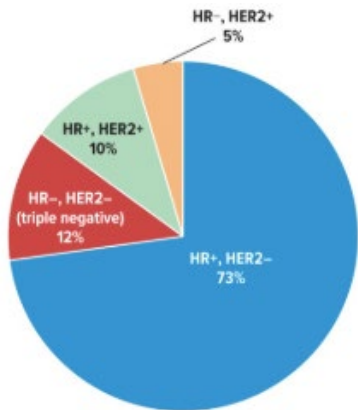
Learning Objectives

- Assess the clinical relevance of plasma-based testing for ESR1 mutations in HR+/HER2- mBC and the role of these mutations in ET resistance
- Summarize key evidence from recent and ongoing trials evaluating oral SERDs in the management of HR+/HER2- mBC, including outcomes by ESR1 mutation status
- Apply patient-centered approaches for incorporating oral SERDs into the management of HR+/HER2- BC to address treatment resistance and optimize care delivery

mBC = metastatic breast cancer; ET = endocrine therapy; SERD = selective estrogen receptor degrader.

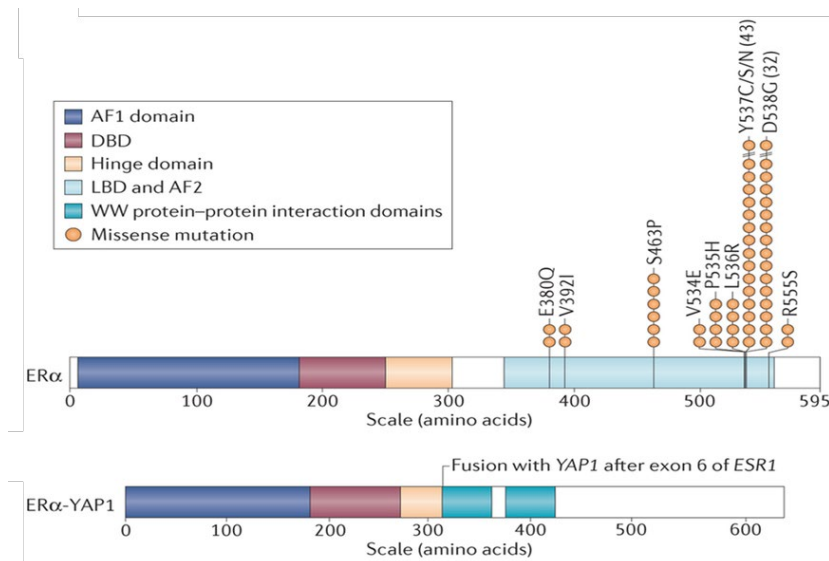
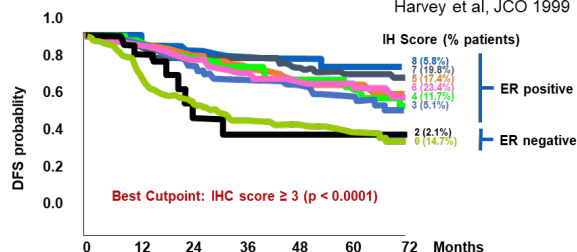
HR+/HER2- Breast Cancer and *ESR1* Mutations

ESR1 Mutations in HR+ mBC



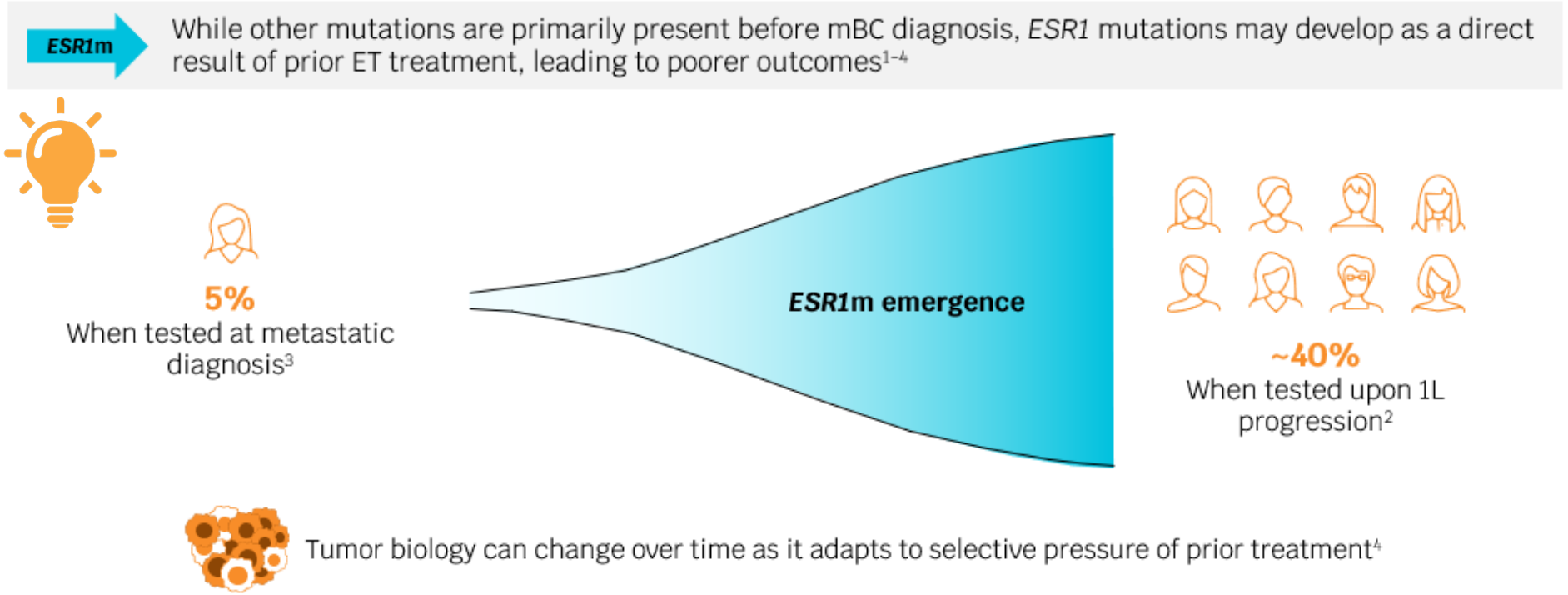
ER/PR: predictive of endocrine therapy benefit

Harvey et al, JCO 1999



ESR1 mutants favor formation of agonist conformation of ERα, enabling ligand-independent ER signaling → endocrine therapy resistance

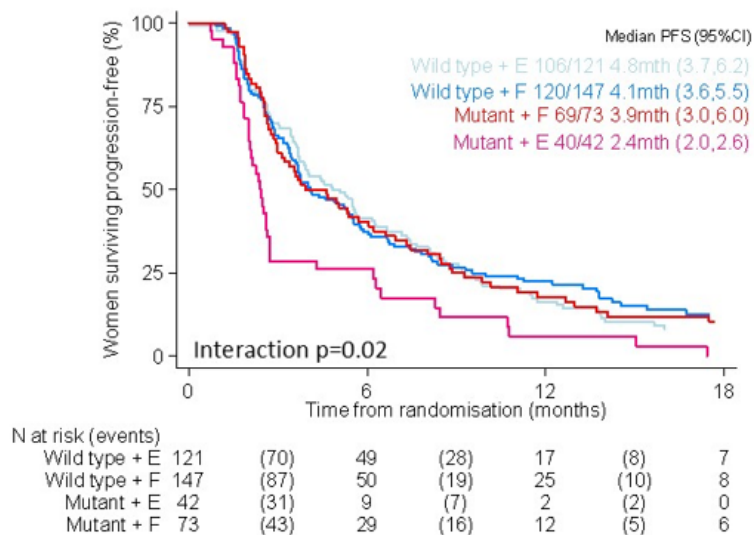
ESR1 Mutations Can Emerge during 1L Treatment with Endocrine Therapy



1. Zhang K, et al. *Cancer Manag Res*. 2018;10:2573-2580 2. Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85. 3. Mankoo PK, et al. *Proteins*. 2009;75(2):499-508. 4. Turner NC, et al. *Clin Cancer Res*. 2022;82(4 Suppl):PD13-07.

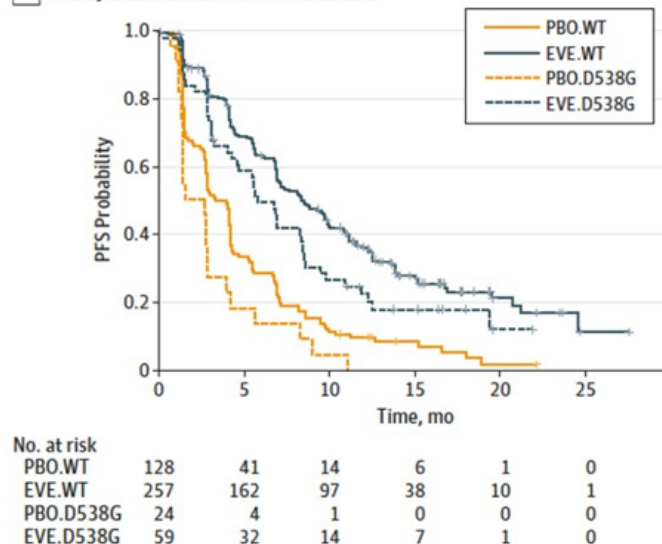
ESR1 Mutations Are Resistant to Standard Endocrine Therapy and Associated with Poorer Prognosis

Exemestane vs fulvestrant
combined analysis of SoFEA and EFACT



ESR1 mutations in BOLERO2

A PFS by treatment arm for WT vs D538G

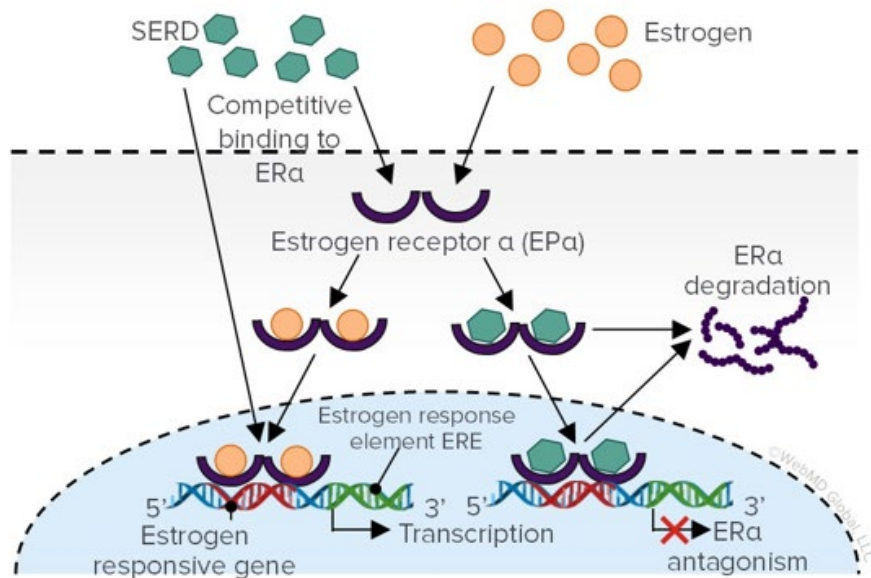


PFS = progression-free survival; WT = wild-type; PBO = placebo.

Turner NC, et al. *Clin Cancer Res*. 2020;26(19):5172-5177. Chandarlapaty S, et al. *JAMA Oncol*. 2016;2(10):1310-1315.

Development of Oral SERDs

SERD: Mechanism of action



- Fulvestrant is first-generation SERD but suboptimal therapy for *ESR1* mutant breast cancers
- IM administration limits exposure and causes discomfort for patients
- Next-generation SERDs have oral formulations, higher potency, and activity in *ESR1* mutant breast cancer



Key Learning Points

- *ESR1* mutations allow ligand-independent ER signaling and lead to endocrine therapy resistance
- *ESR1* mutations are acquired mutations that can develop in up to 40% of breast cancers after exposure to first-line endocrine therapy
- Important to test for these mutations with liquid biopsy over tissue to detect emergence of this mutation; the ability to detect tumor heterogeneity and emerging resistance in real time is a key advantage of plasma-based ctDNA testing for *ESR1* mutations compared with tissue biopsy in HR+/HER2- mBC
- Novel SERDs have been developed to fully inhibit and degrade both mutant and wild-type estrogen receptors

SERDs: Current Therapeutic Landscape

National Comprehensive Cancer Network® (NCCN®) Guidelines Version 6.2026

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}	Category 2A	Other recommended
			Vepdegestrant ^{bb}	Category 2A	Other recommended

NGS = next-generation sequencing; PCR = polymerase chain reaction; FDA = US Food and Drug Administration.
Reproduced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.6.2026. © 2026 National Comprehensive Cancer Network, Inc. All rights reserved. To view the most recent and complete version of the NCCN Guidelines, go online to [NCCN.org](https://www.nccn.org). The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.

NCCN Guidelines Version 6.2026

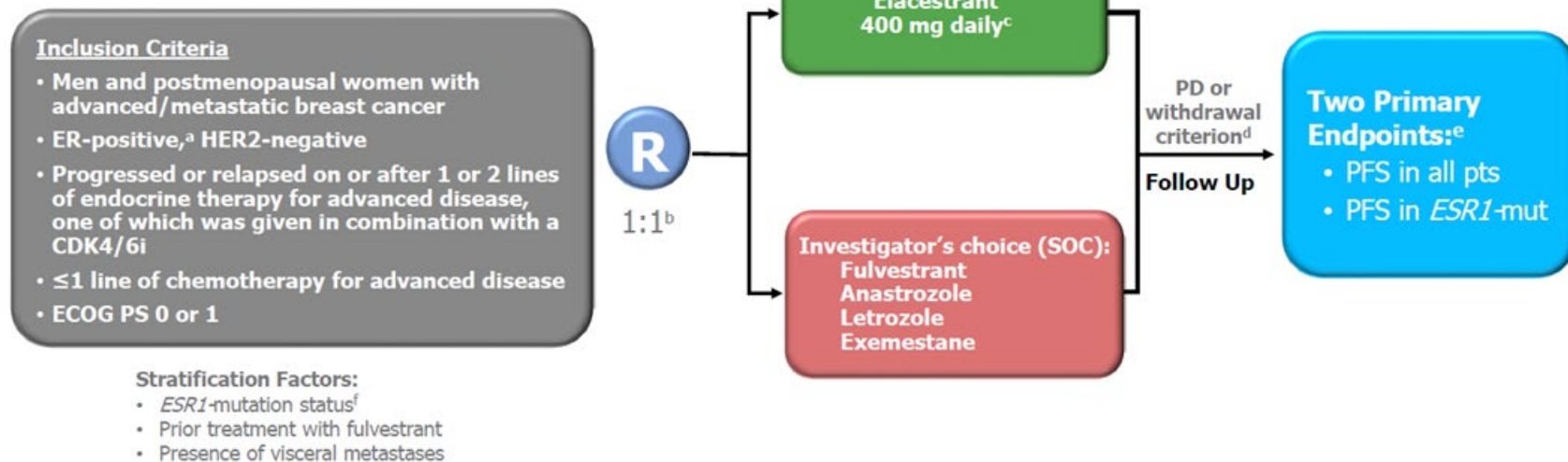
SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE^a

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression	
See BINV-P 1 of 3 for general considerations for therapy selection for HR-positive, HER2-negative disease.	
First-Line Therapy	Second- and/or Subsequent-Line Therapy
Preferred First-Line Therapy • Aromatase inhibitor + CDK4/6 inhibitor^b ▶ Aromatase inhibitor + Ribociclib (category 1)^c ▶ Aromatase inhibitor + Abemaciclib ▶ Aromatase inhibitor + Palbociclib If disease progression on adjuvant endocrine therapy or relapse within 12 months of adjuvant endocrine therapy completion consider: • For tumors with <i>PIK3CA</i> activating mutations: ▶ Fulvestrant/Inavolisib/Palbociclib, see BINV-Q 6 of 15 • Fulvestrant^d + CDK4/6 inhibitor^b ▶ Fulvestrant + Ribociclib (category 1)^e ▶ Fulvestrant + Abemaciclib (category 1)^e ▶ Fulvestrant + Palbociclib	Preferred Second- and/or Subsequent-Line Therapy • Fulvestrant + CDK4/6 inhibitor (Abemaciclib, Palbociclib, or Ribociclib) if CDK4/6 inhibitor not previously used (category 1)^{f,g} • For tumors without a <i>PIK3CA</i> mutation following progression on or after treatment with at least one line of endocrine therapy: Fulvestrant/Gedatolisib ± Palbociclib (category 1) • For tumors with <i>PIK3CA</i> or <i>AKT1</i> activating mutations or <i>PTEN</i> inactivating mutations and genomic changes (eg, deletion), see BINV-Q 6 of 15^h • Everolimus + endocrine therapy (Exemestane, Fulvestrant, Tamoxifen)^{i,j} Useful in Certain Circumstances for Second- and/or Subsequent-Line Therapy • Megestrol acetate • Estradiol • Abemaciclib^l • Imlunestrant + Abemaciclib^m • Targeted therapy, see BINV-Q 7 of 15, and emerging biomarker options, see BINV-Q 8 of 15
Other Recommended for First- and/or Subsequent-Line Therapy • For <i>ESR1</i> mutated tumors after a prior line of endocrine therapy ± CDK 4/6 inhibitor therapy (in adjuvant or metastatic setting), see BINV-Q 6 of 15 for options. • Fulvestrant + aromatase inhibitor (Anastrozole, Letrozole) (category 1)^k • Fulvestrant • Anastrozole • Letrozole • Tamoxifen • Exemestane	
Footnotes on BINV-P 3 of 3	

^m The combination of imlunestrant + abemaciclib may be most effective in those with *ESR1* mutations and no prior CDK4/6 inhibitor. The EMBER-3 trial (Jhaveri KL, et al. N Engl J Med 2025;392:1189-1202) included patients with and without *ESR1* mutations and compared the combination of imlunestrant + abemaciclib to imlunestrant alone versus comparing with the standard treatment containing an endocrine therapy plus CDK4/6 inhibitor.

EMERALD: Randomized Phase 3 Trial

All patients had prior CDK4/6 inhibitor



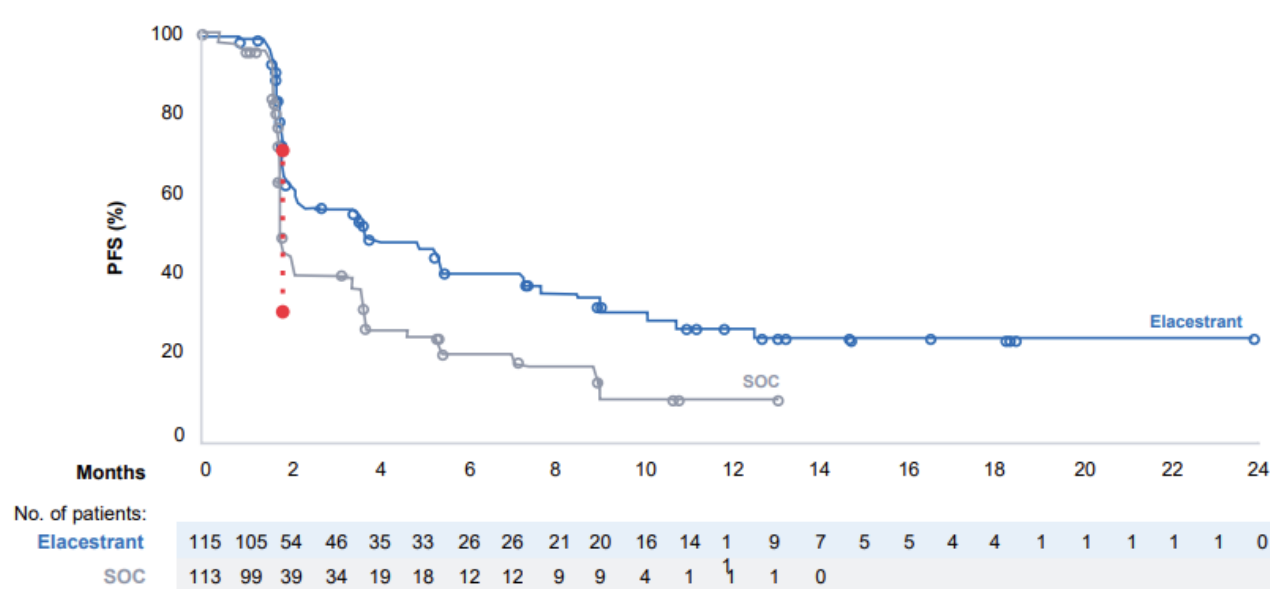
^aDocumentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; ^bRecruitment from February 2019 to October 2020; ^cProtocol-defined dose reductions permitted; ^dRestaging CT scans every 8 weeks;

^eBlinded Independent Central Review; ^f*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay

ECOG PS = Eastern Cooperative Oncology Group performance status; SOC = standard of care; PD = progressive disease; CT = computed tomography.

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

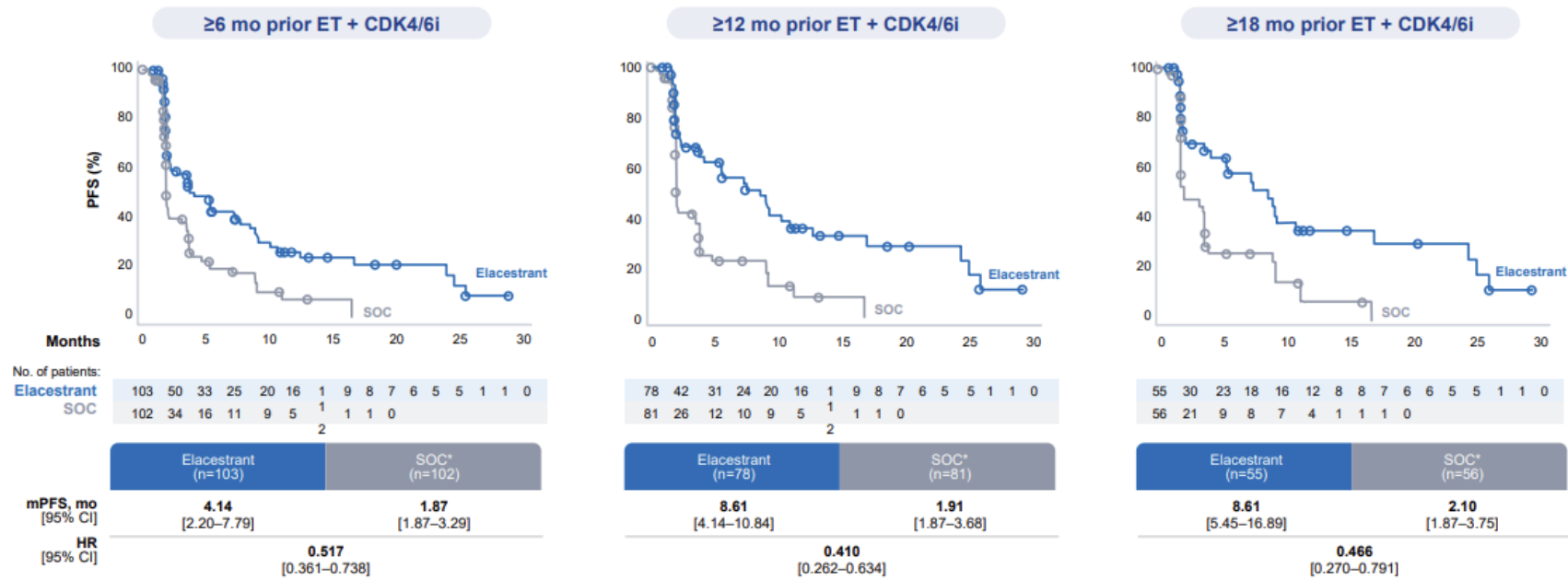
Progression-Free Survival in Patients with *ESR1m*



	Elacestrant (n=115)	SOC (n=113)
Events, n (%)	62 (53.9)	78 (69.0)
mPFS, mo	3.8	1.9
12-mo PFS, % [95% CI]	26.8 [16.2–37.4]	8.2 [1.3–15.1]
HR [95% CI]	0.55 [0.39–0.77]	

45%
reduction in risk of
progression or death
when compared to SOC

PFS by Duration of ET + CDK4/6i in Patients with *ESR1m*

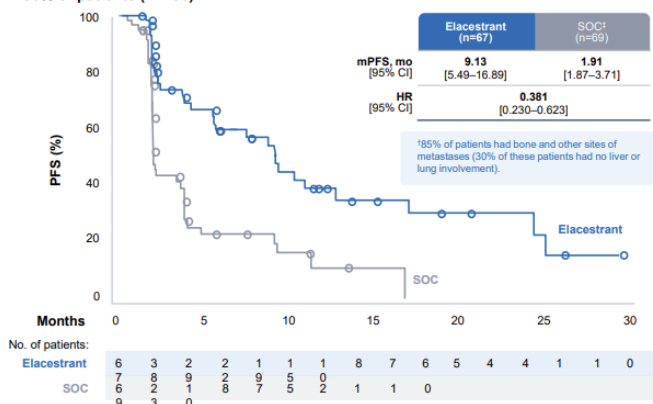


mPFS = median PFS.

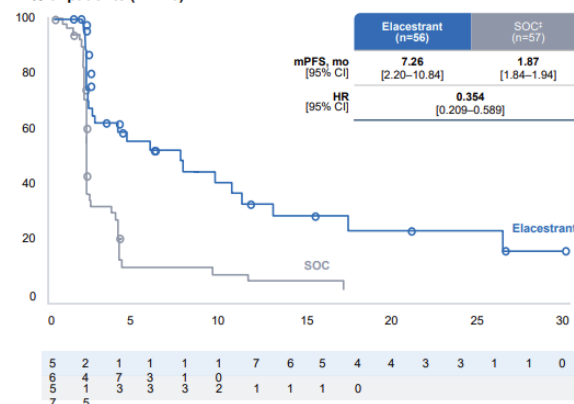
Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256.

PFS in Patients Who Received ET + CDK4/6i ≥ 12 months and *ESR1*m tumors

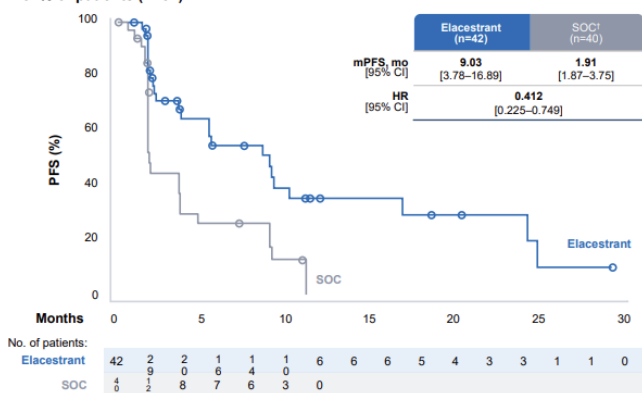
Bone metastases*
86% of patients (n=136)



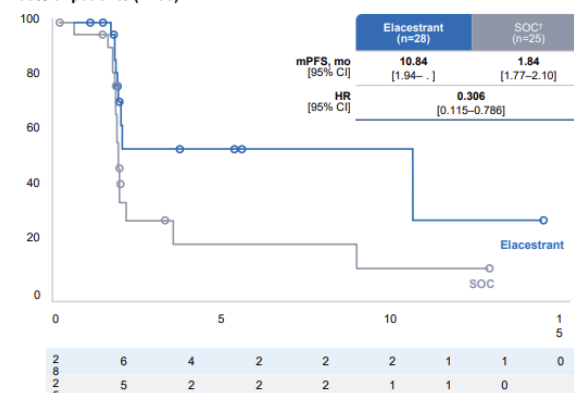
Liver and/or lung metastases*
71% of patients (n=113)



<3 metastatic sites*
52% of patients (n=82)



≥ 3 metastatic sites*
33% of patients (n=53)



m = mutated.

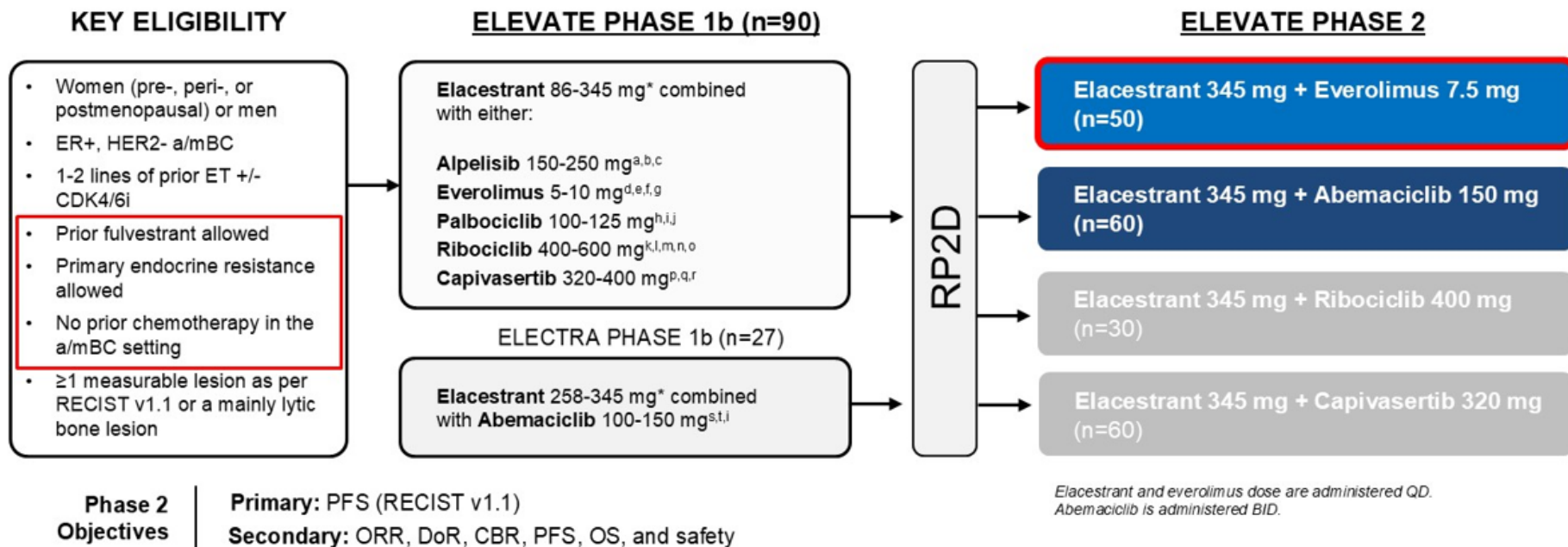
Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256.

Real-World Data Shows Consistent PFS Benefit

	Bardia et al, EMERALD CCR (n=78) ¹	Lloyd et al, Guardant Inform (n=742) ²	Swallow et al, Komodo Claims (n=276) ³
Baseline characteristics			
Prior CDK4/6i in mBC	100%	83%	90%
Prior CDK4/6i for >12 months	100%	–	88%
Prior fulvestrant in mBC	17%	53%	61%
Prior chemo in mBC	20%	41%	33%
Efficacy	<i>mPFS (months)</i>	<i>mTTNT (months)</i>	<i>rwPFS (months)</i>
2L	–	8.8 ^a	–
2–3L	8.6	–	8.0 ^b

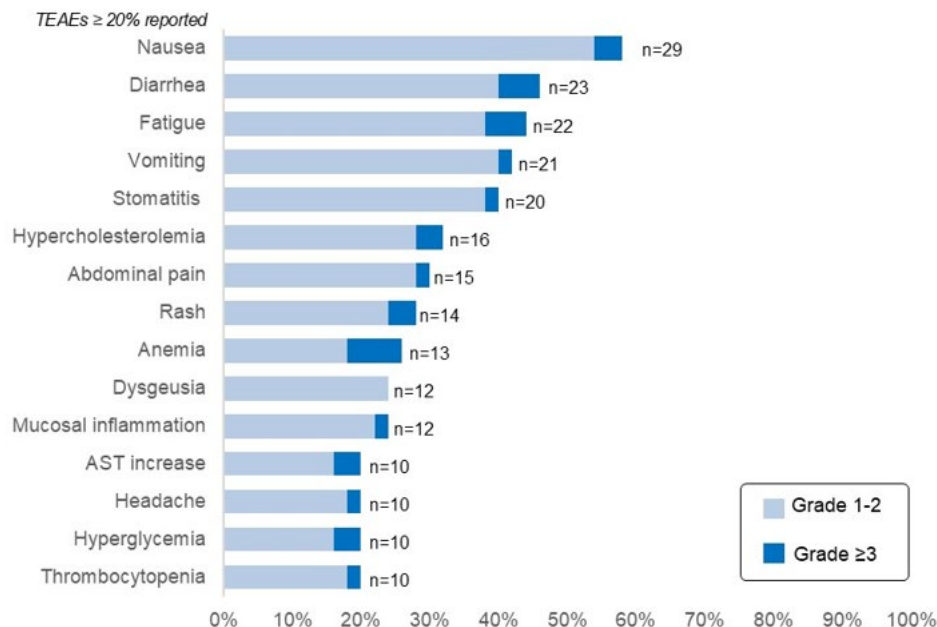
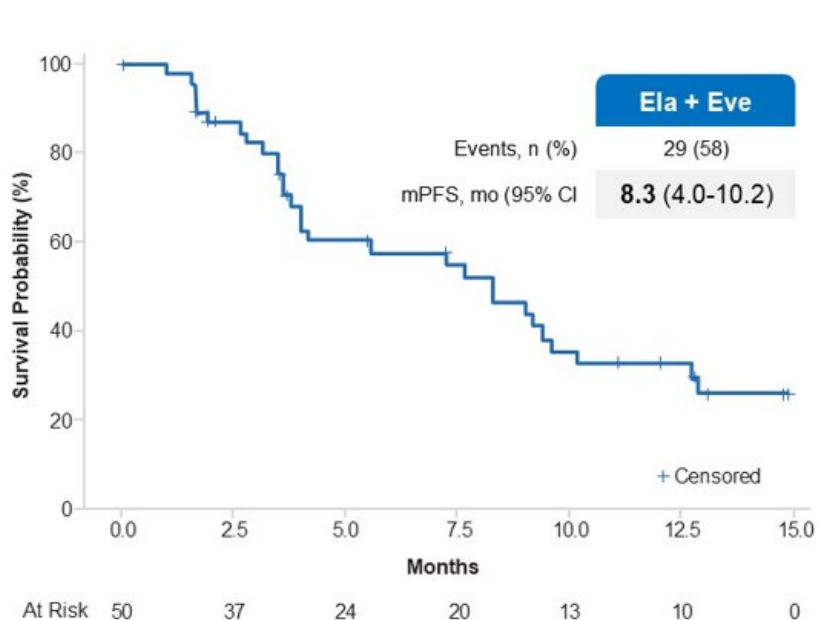
CDK4/6i = CDK4/6 inhibitor; 2L = second line; 3L = third line; TTNT = time to next treatment; rwPFS = real-world PFS.
 Bardia A, et al. *Clin Cancer Res.* 2024;30(19):4299-4309. Lloyd MR, et al. Presented at: SABCS; 2024. Abstract PS7-05. Swallow E, et al. Presented at: SABCS; 2024. Abstract P3 10-08.

ELEVATE Trial Design



a/mBC = advanced/metastatic breast cancer; RECIST = response evaluation criteria in solid tumors; RP2D = recommended phase 2 dose; ORR = objective response rate; DoR = duration of response; CBR = clinical benefit rate; OS = overall survival.
 Rugo HS, et al. Presented at: SABCS; 2025.

Elacestrant + Everolimus: PFS and Safety



Elacestrant + everolimus showed a consistent PFS benefit across all subgroups

TEAE = treatment-emergent adverse event; AST = aspartate transaminase.

Rugo HS, et al. Presented at: SABCS; 2025. Rugo HS, et al. *Clin Cancer Res*. 2026 Aug 24 [Epub ahead of print].



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

Phase 2 Objectives

Primary: PFS (RECIST v1.1)

Secondary: ORR, DoR, CBR, PFS, OS, and safety

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,l}**

RP2D

Elacestrant 345 mg + Everolimus 7.5 mg (n=50)

Elacestrant 345 mg + Abemaciclib 150 mg (n=60)

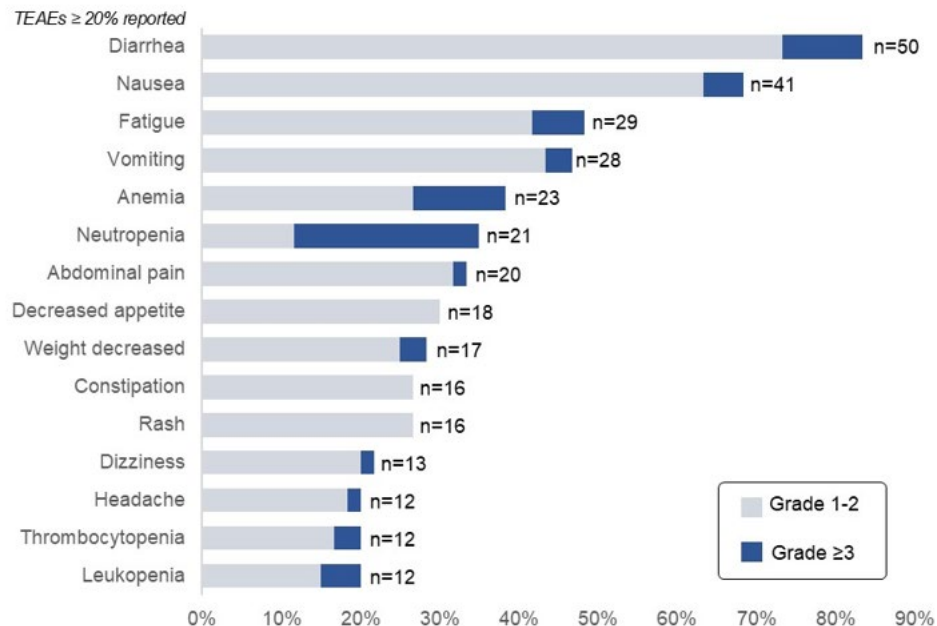
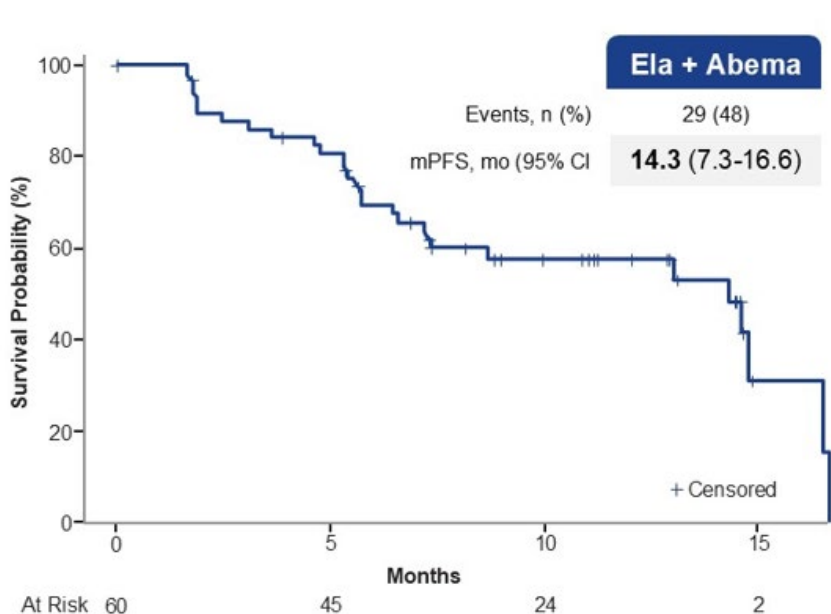
Elacestrant 345 mg + Ribociclib 400 mg (n=30)

Elacestrant 345 mg + Capivasertib 320 mg (n=60)

*Elacestrant and everolimus dose are administered QD.
Abemaciclib is administered BID.*



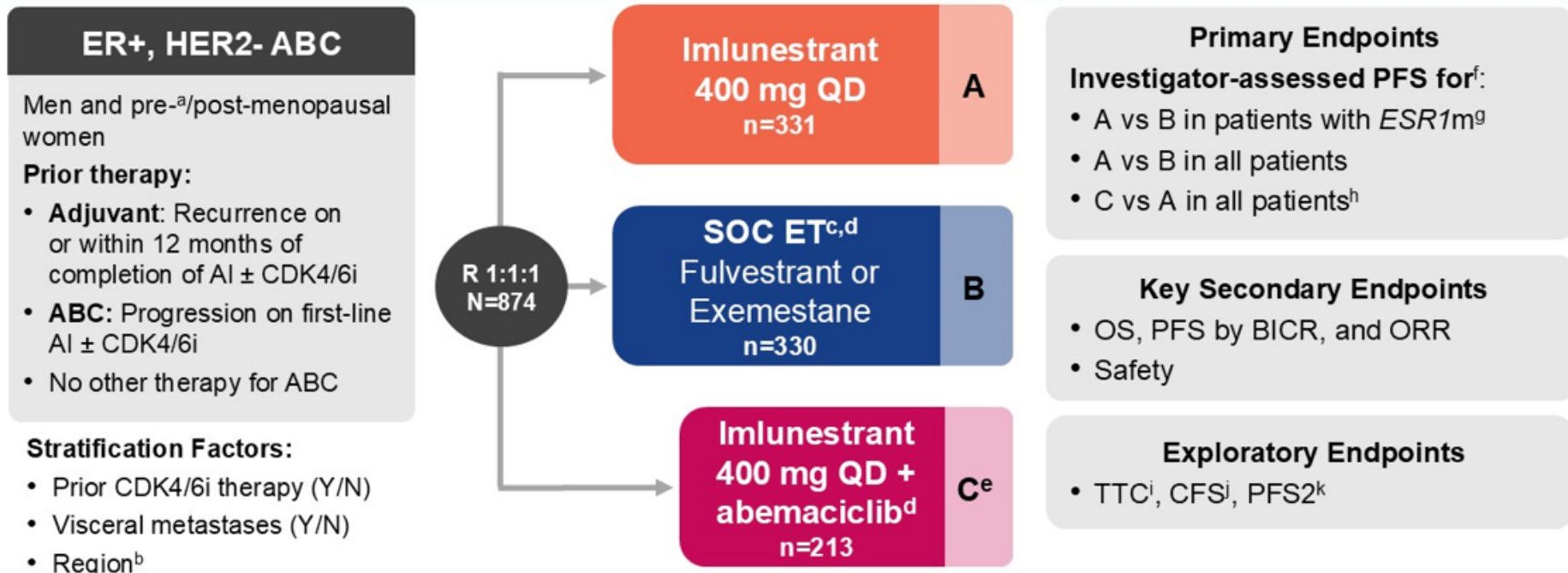
Elacestrant + Abemaciclib: PFS and Safety



Elacestrant + abemaciclib showed a consistent PFS benefit across key subgroups

Rugo HS, et al. Presented at: SABCS; 2025.

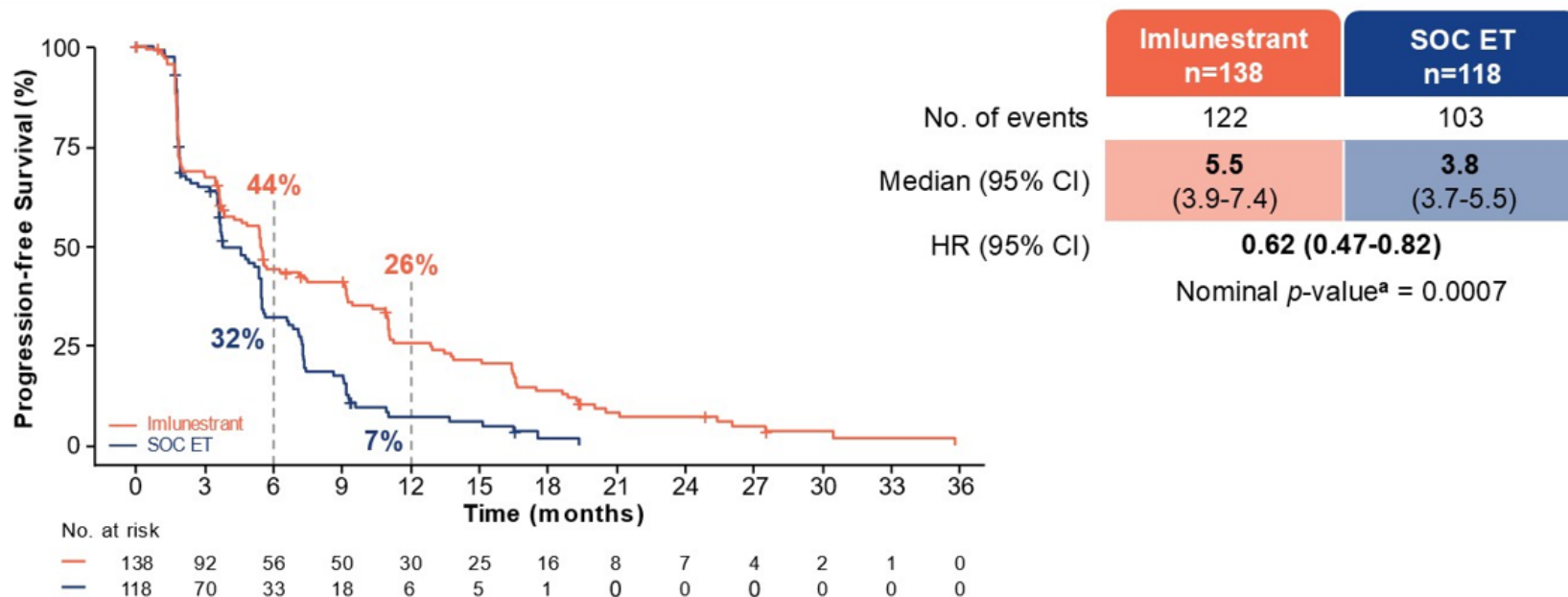
EMBER-3 Study Design



Did not require prior CDK4/6i

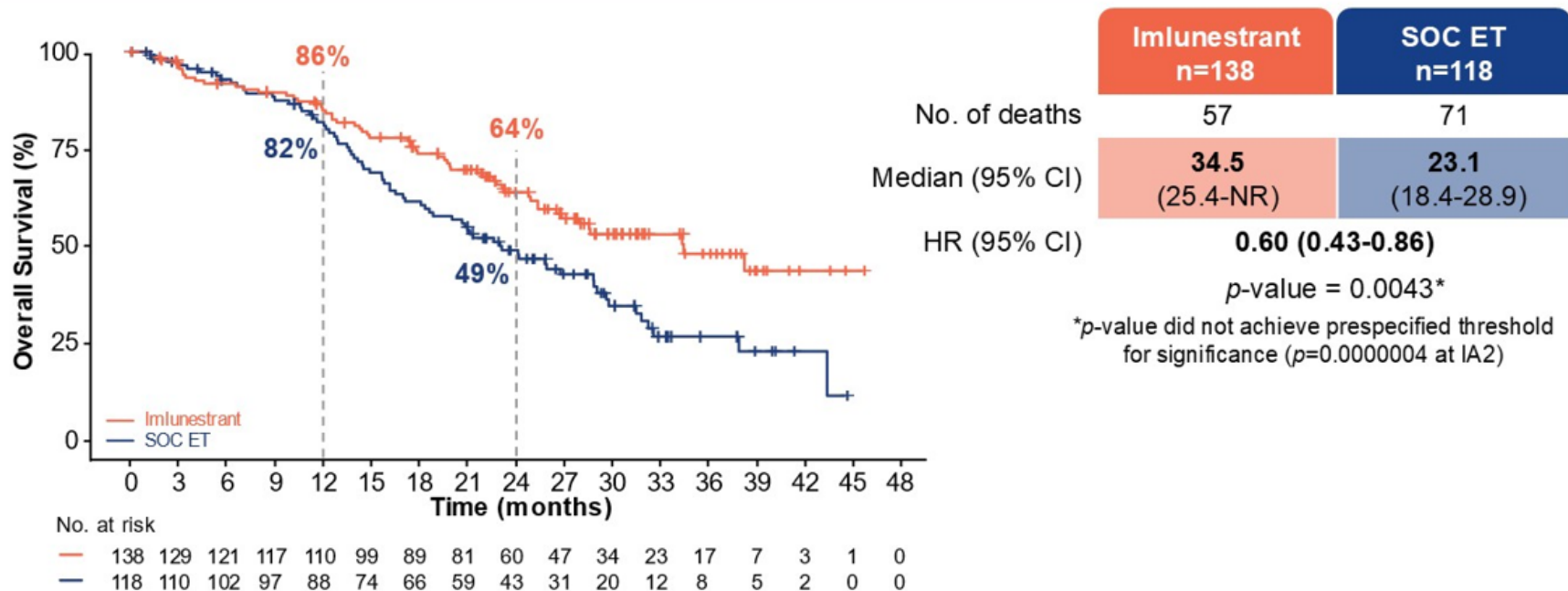
BICR = blinded independent central review; TTC = time to chemotherapy; CFS = chemotherapy-free survival; PFS2 = PFS on second-line treatment.
Jhaveri KL, et al. Presented at: SABCS; 2025.

Primary Endpoint: PFS of Imlunestrant vs SOC ET in Patients with *ESR1m*



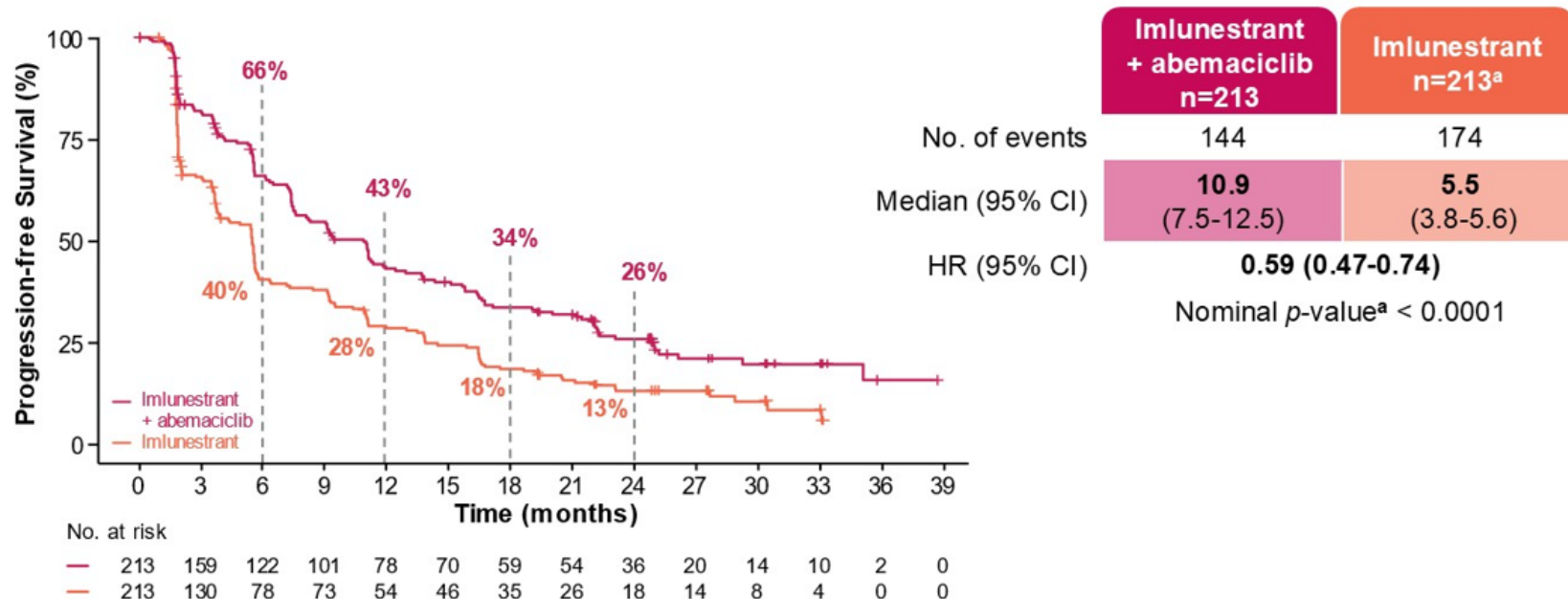
PFS benefit of imlunestrant was sustained in patients with *ESR1m*

Secondary Endpoint: Interim OS of Imlunestrant vs SOC ET at 50% Maturity in Patients with ESR1m



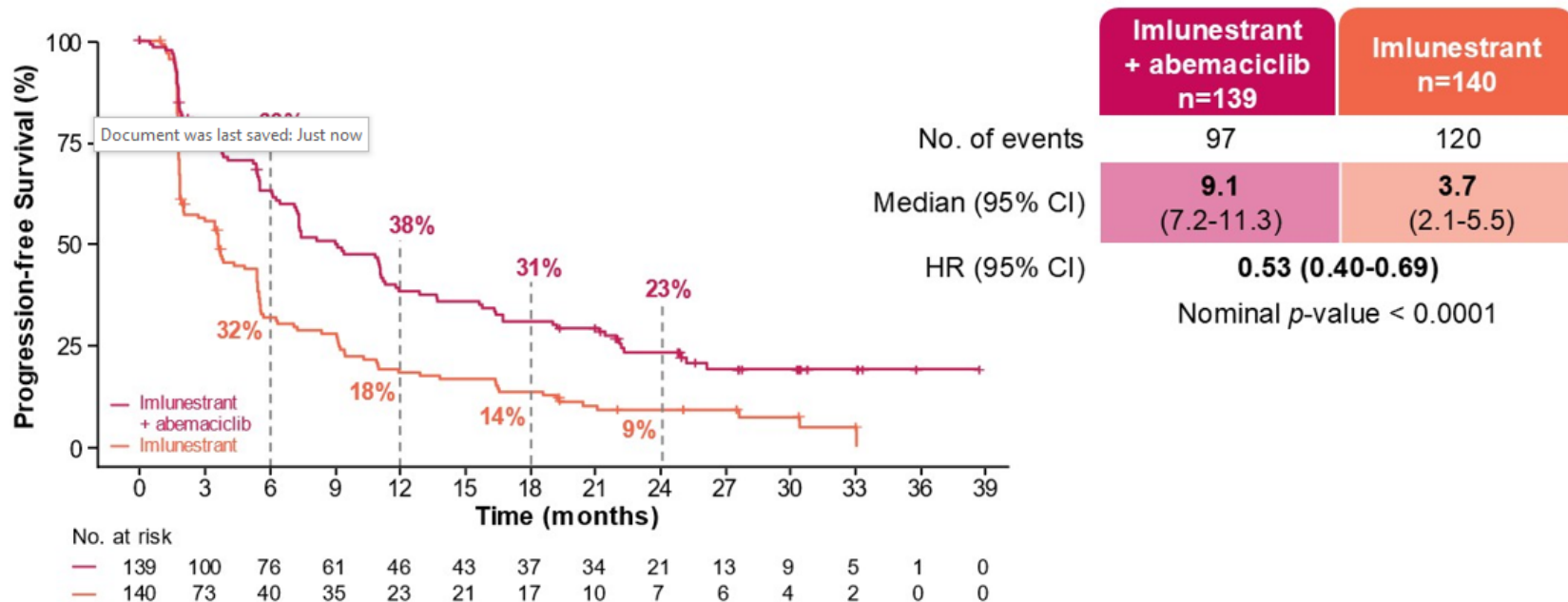
Imlunestrant led to an ~11 month numerical improvement in median OS in patients with *ESR1m*

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



PFS benefit of imlunestrant + abemaciclib was maintained in all patients

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



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

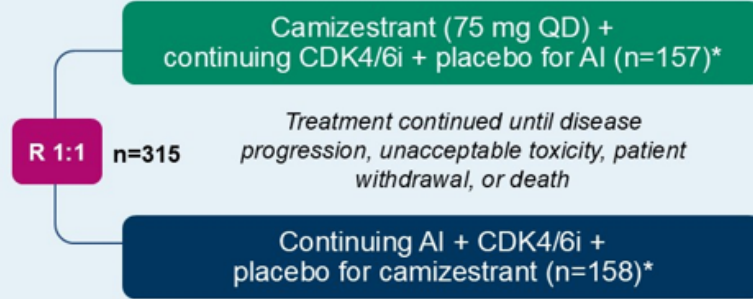
EMBER-3: Safety

TEAEs in ≥ 25% of Patients, %	Imlunestrant + abemaciclib n=208		Imlunestrant n=327		SOC ET n=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 TEAE	98	54	85	20	85	22
Diarrhea	86	9	23	<1	12	0
Neutropenia	50	22	6	3	5	2
Nausea	50	2	18	<1	14	0
Anemia	46	10	11	2	13	3
Fatigue	41	5	24	<1	14	1
Vomiting	32	<1	9	1	5	<1
Leukopenia	29	4	6	1	5	0
Hypercreatininemia	25	1	4	<1	3	0
TEAEs leading to discontinuation	9		5		1	
Treatment-related	5		2		0	

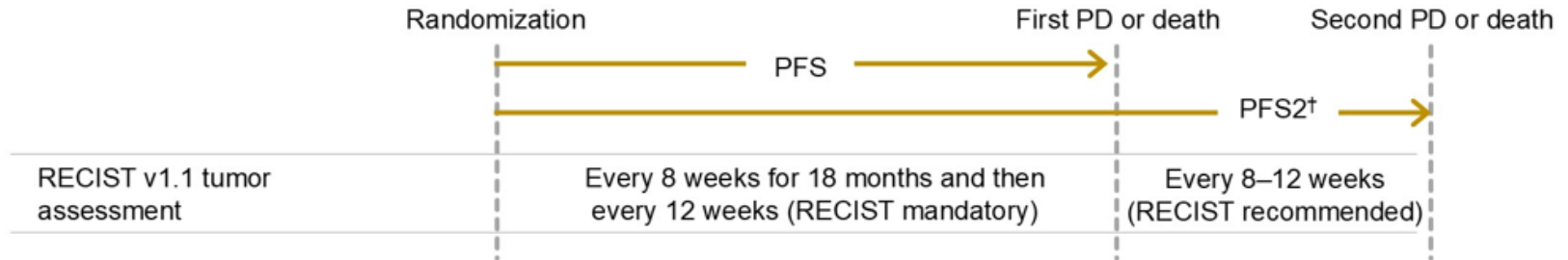
The safety profiles remained consistent with the known characteristics of imlunestrant and abemaciclib

SERENA-6: Study Design

- Adult patients with ER+/HER2– ABC
- All patients had received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1m* detected in ctDNA with no evidence of disease progression
- ≤1 prior line of chemotherapy for ABC



The study was powered for PFS (primary endpoint) and the key secondary endpoint of investigator-assessed PFS2



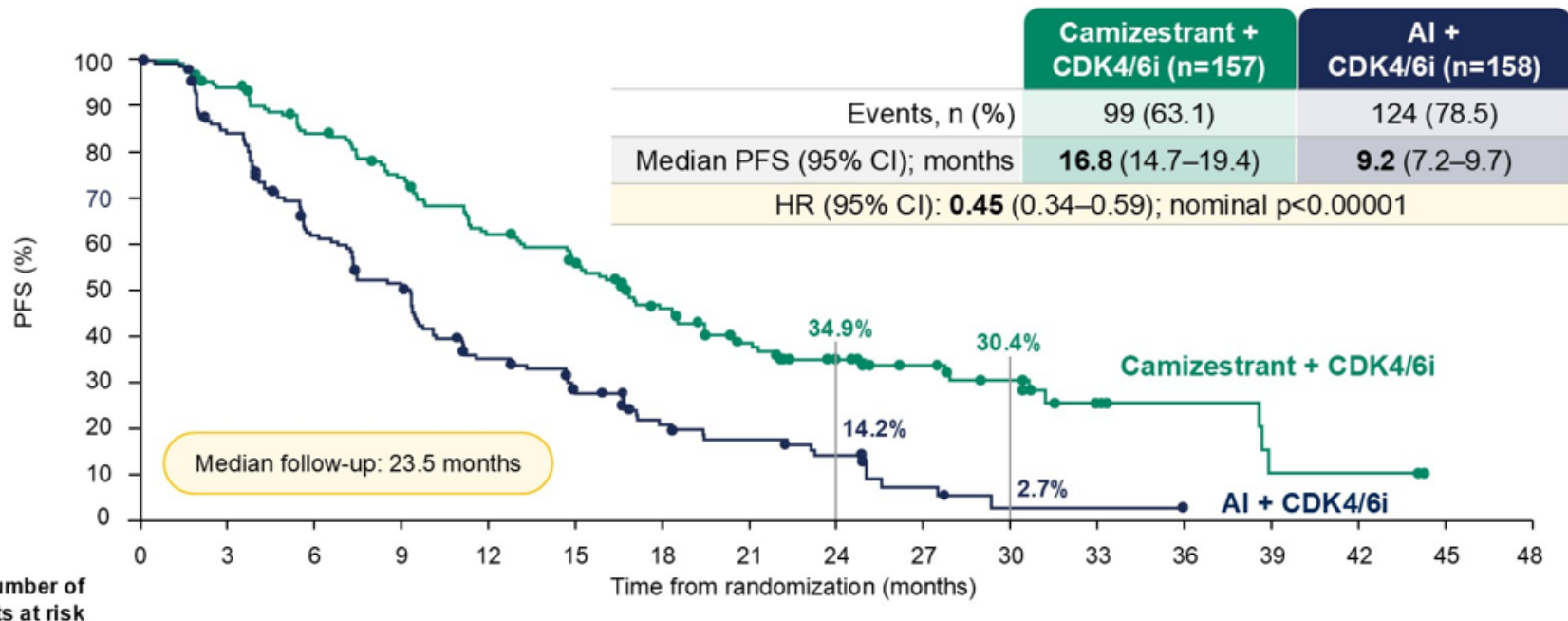
ABC, advanced breast cancer; ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; PD, progressive disease; QD, once daily; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors. *Pre- or perimenopausal women and men received a luteinizing hormone-releasing hormone agonist per clinical guidelines. [†]A new baseline was established at the start of subsequent therapy using imaging from PFS1 progression.

AI = aromatase inhibitor.

Bidard, F et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 2026.



Updated PFS (Primary Endpoint, Investigator-Assessed)

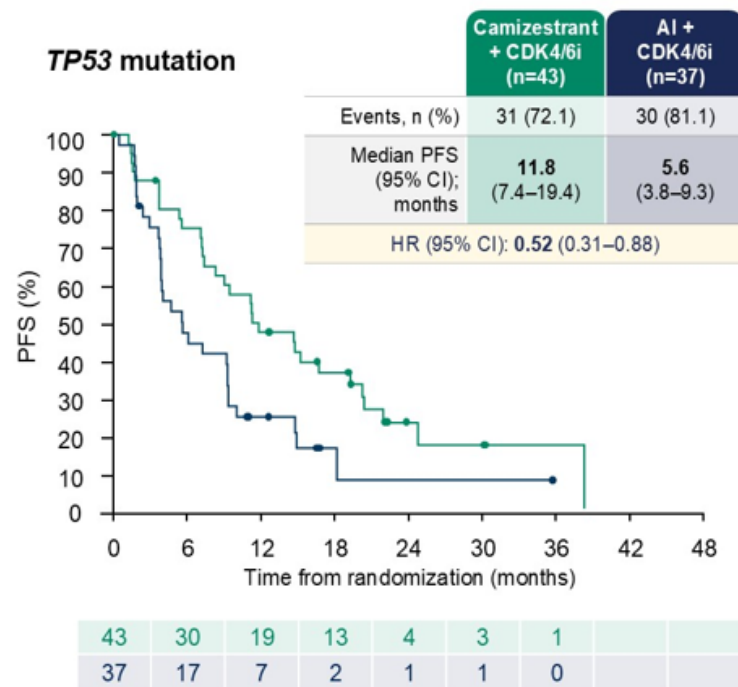
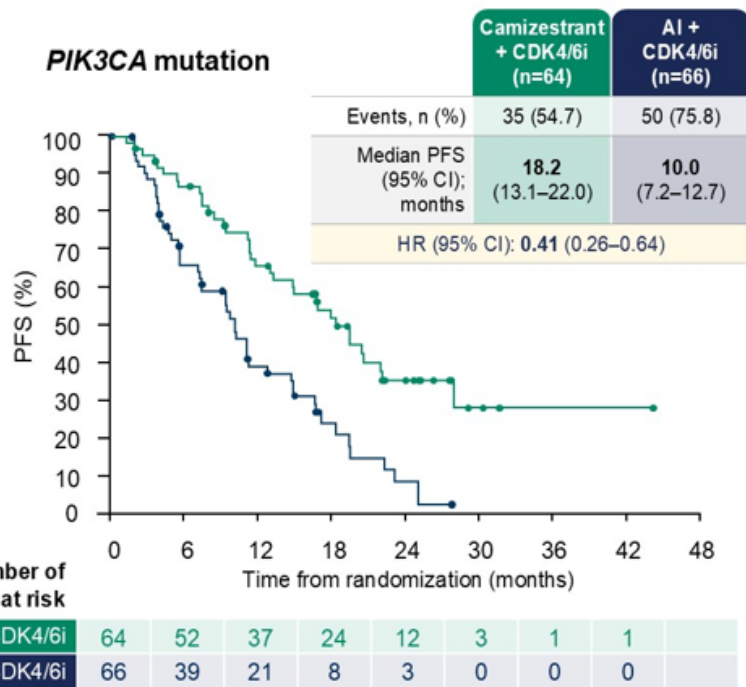


Camizestrant + CDK4/6i	157	143	125	109	90	78	57	42	31	23	17	7	5	2	2	0
AI + CDK4/6i	158	127	90	73	48	35	20	16	12	4	1	1	0	0	0	0

DCO3 (Jan 02, 2026). At DCO3, 45 patients in the camizestrant + CDK4/6i arm and 12 patients in the AI + CDK4/6i arm were still receiving study treatments. The p value is based on the stratified log-rank test, stratified by disease site (visceral vs non-visceral), timing of ESR1m detected (first vs subsequent test), and time from initiation of AI + CDK4/6i to randomization (<18 months vs ≥18 months).

DCO3 = third data cutoff.
Bidard F, et al. Presented at: ASCO Annual Meeting; 2026.

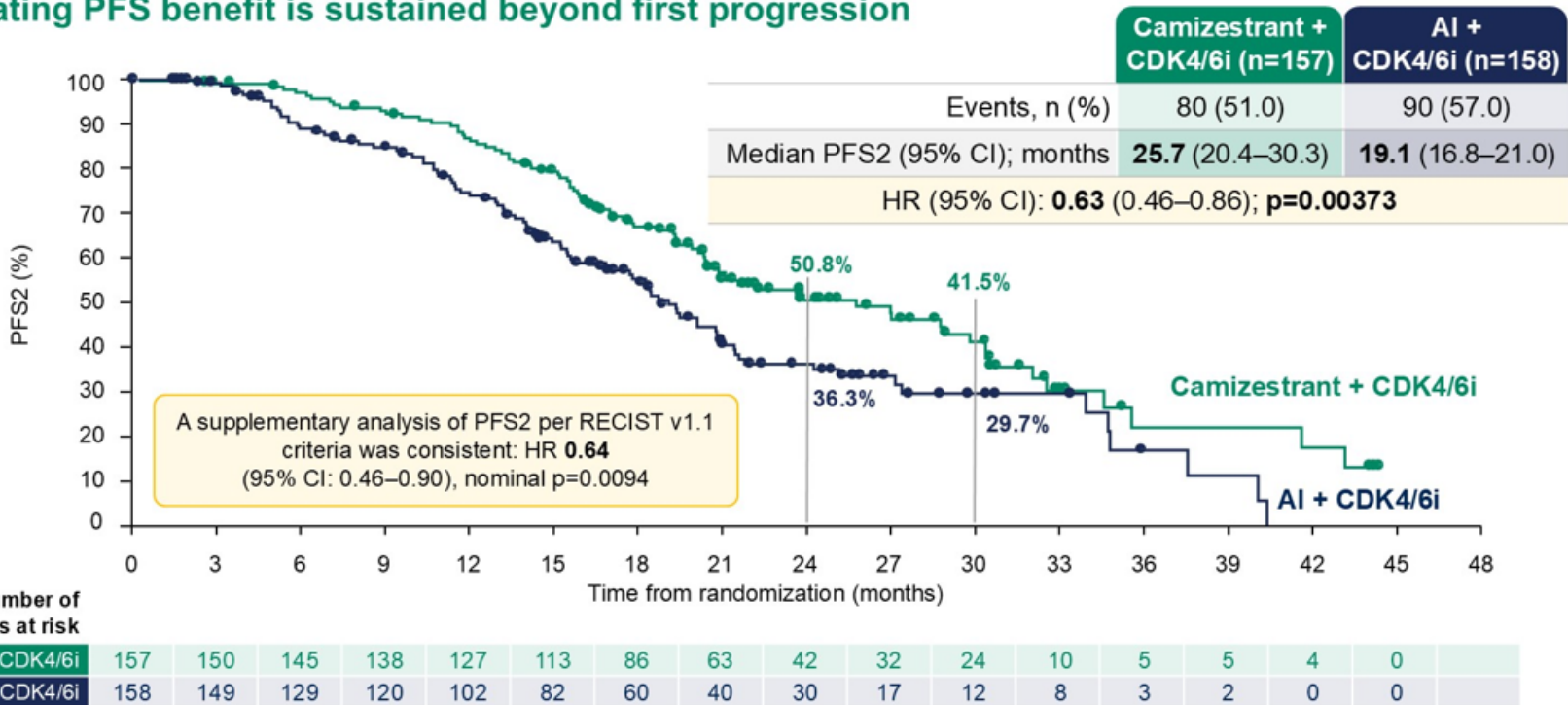
Updated PFS by Co-Mutations



DCO3 (Jan 02, 2026). PFS benefit was comparable in patients without a *PIK3CA* mutation (HR [95% CI]: **0.48** [95% CI: 0.34–0.68]) or a *TP53* mutation (**0.42** [0.30–0.58]).
PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase gene; *TP53*, tumor protein 53 gene.

Final Second Progression-Free Survival (PFS2)

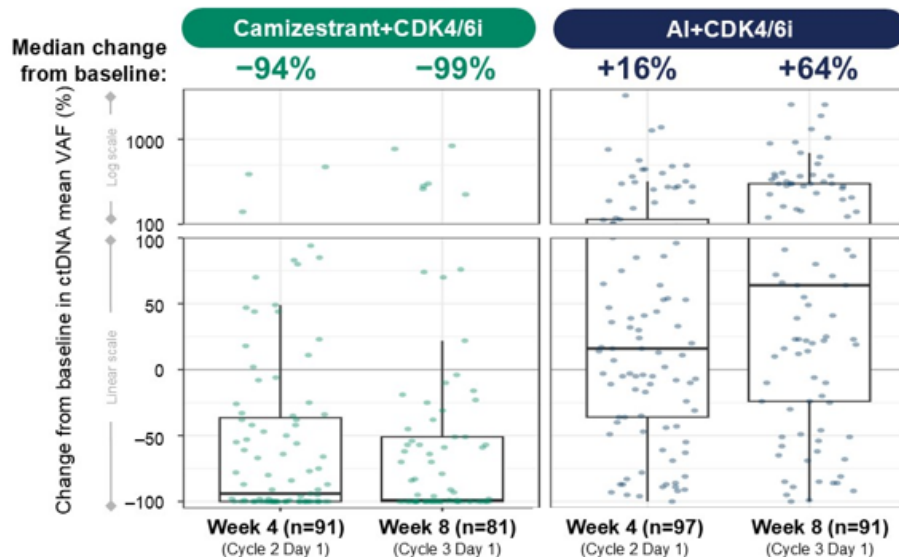
Camizestrant + CDK4/6i significantly extended time to second progression or death, demonstrating PFS2 benefit is sustained beyond first progression



DCO3 (Jan 02, 2026). PFS2, defined in a standard manner (assessed by the investigator according to local standard clinical practice) as the time from randomisation to the earliest of disease progression after first subsequent therapy or death in the primary analysis. The p value is based on the stratified log-rank test, stratified by disease site (visceral vs non-visceral), timing of ESRfm detected (first vs subsequent test), and time from initiation of AI+CDK4/6i to randomization (< 18 months vs > 18 months).

Total ctDNA Dynamics on Treatment

Change in total ctDNA



Total ctDNA was **profoundly reduced** in the camizestrant + CDK4/6i arm vs the AI + CDK4/6i arm (Wilcoxon nominal $P < 0.00001$) at Week 4 and 8

Total ctDNA clearance by Guardant360*

Camizestrant + CDK4/6i

51.0%

n=50/98

AI + CDK4/6i

1.9%

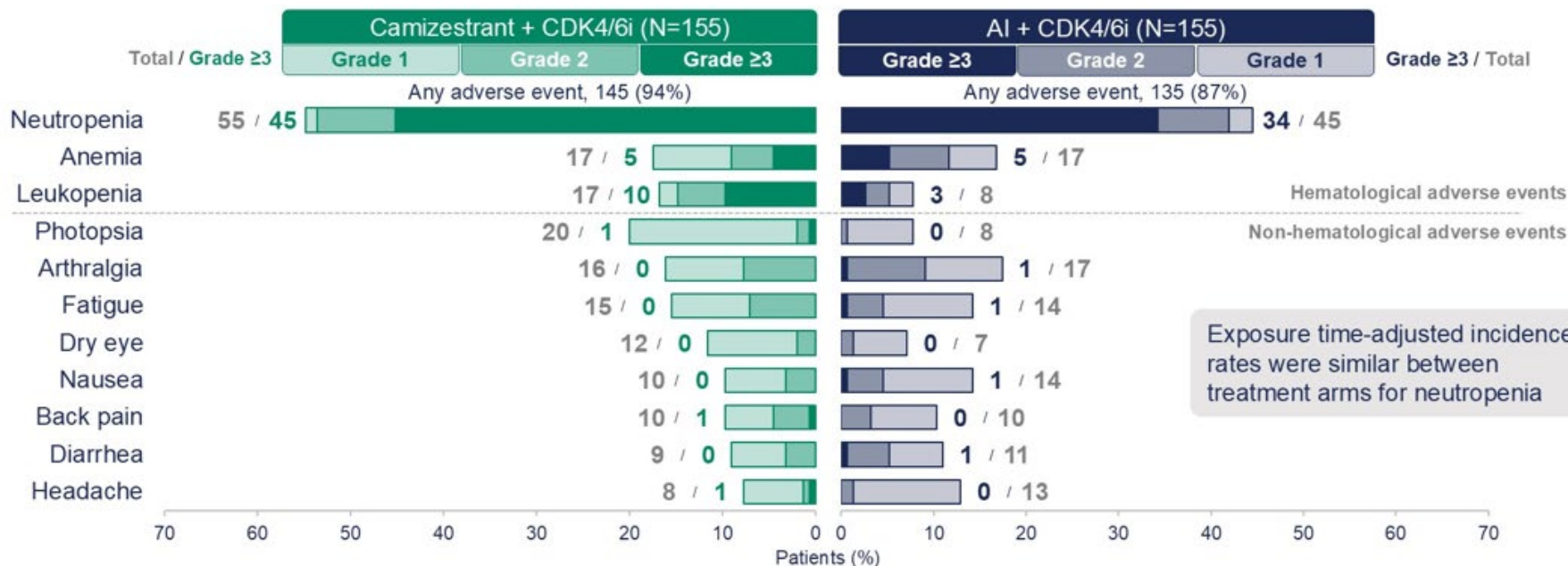
n=2/108

In an exploratory analysis pooled across arms, total ctDNA clearance is associated with OS benefit (HR 0.39; 95% CI 0.19–0.73); consistent with other studies

Total ctDNA = mean VAF of probable tumor-specific somatic mutations (Guardant360). *Total ctDNA clearance at Week 4 and/or Week 8 in clearance-evaluable patients.

VAF = variant allele frequency.
Bidard F, et al. Presented at: ASCO Annual Meeting; 2026.

Adverse Events ($\geq 10\%$ of Patients)



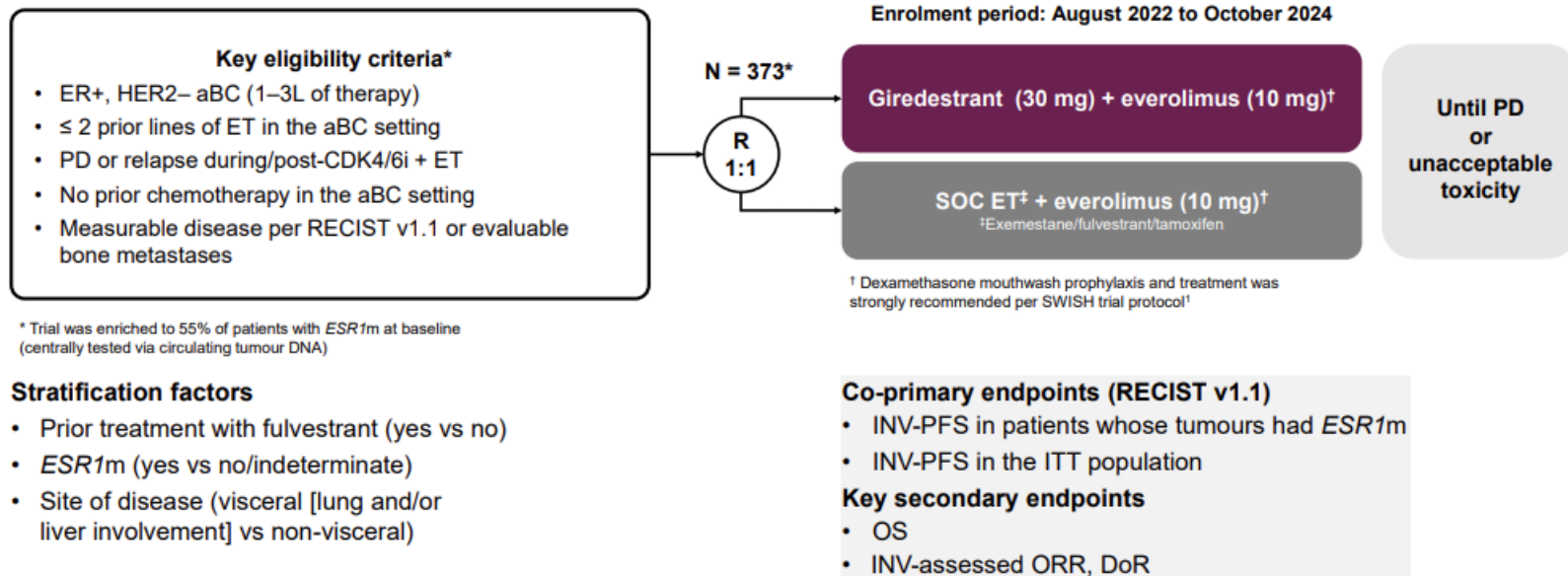
Photopsia (brief flashes of light in the peripheral vision) did not impact daily activities: If experienced, visual effects had no/minimal impact on daily activities, were typically ≤ 1 minute, ≤ 3 days/week, and reversible. There were no structural changes in the eye and no changes in visual acuity

evERA Phase III Trial

Study design

A global, randomised, open-label, Phase III trial

100% prior CDK4/6i



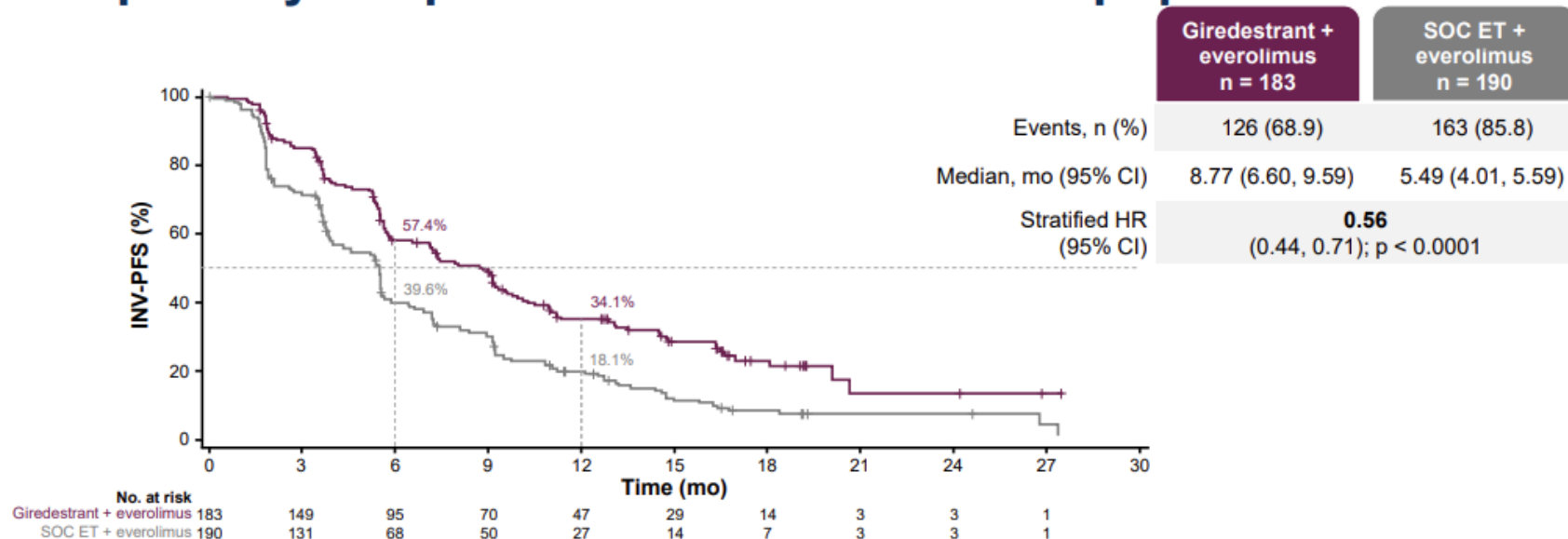
ClinicalTrials.gov number, NCT05306340. Adapted from Mayer EL, et al. SABCS 2022 (poster OT2-01-07) with permission.

1–3L, first to third line; aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, oestrogen receptor-positive; *ESR1m*, *ESR1* mutation; ET, endocrine therapy; HER2–, HER2-negative; INV, investigator-assessed; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SOC ET, standard of care endocrine therapy.

1. Ruqo HS, et al. *Lancet Oncology* 2017; 18:654–662.

evERA Phase III Trial

Co-primary endpoint – INV-PFS in the ITT population

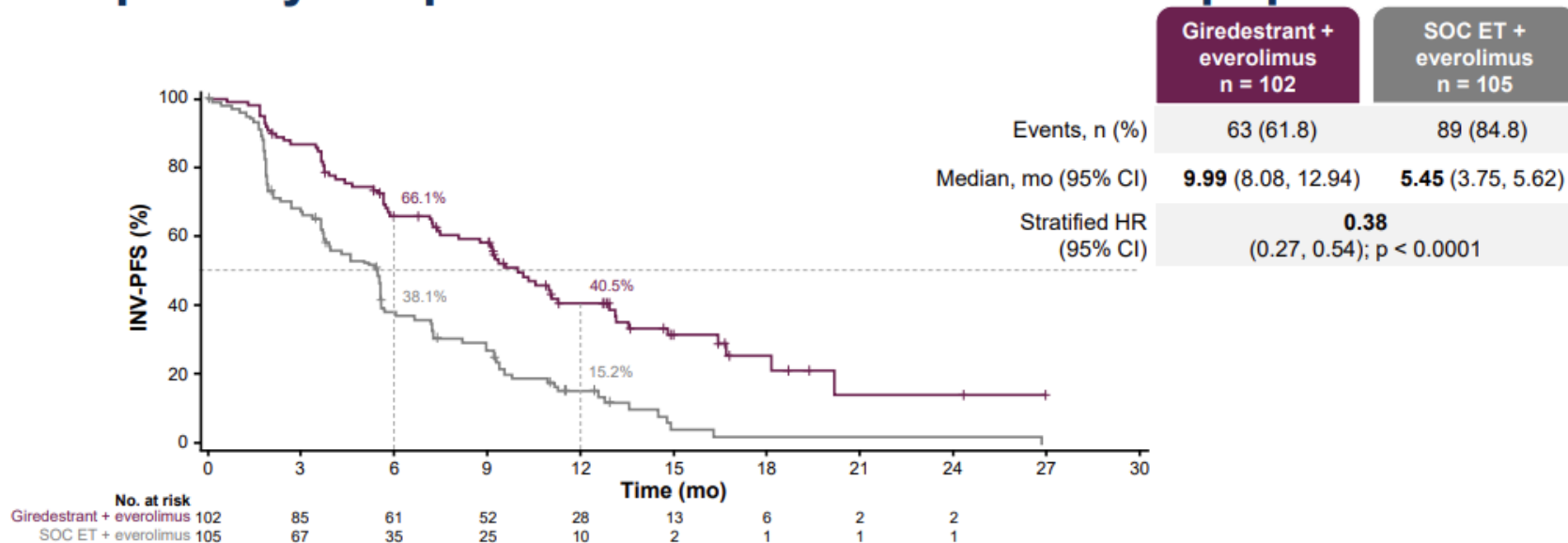


Combination therapy with giredestrant + everolimus led to a clinically meaningful 44% reduction in the risk of progression or death in patients in the ITT population

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 10.32 mo (giredestrant + everolimus) and 7.26 mo (SOC ET + everolimus); stratified HR, 0.66; 95% CI: 0.50, 0.87. CI, confidence interval; HR, hazard ratio; INV, investigator-assessed; ITT, intention to treat; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

evERA Phase III Trial

Co-primary endpoint – INV-PFS in the *ESR1m* population

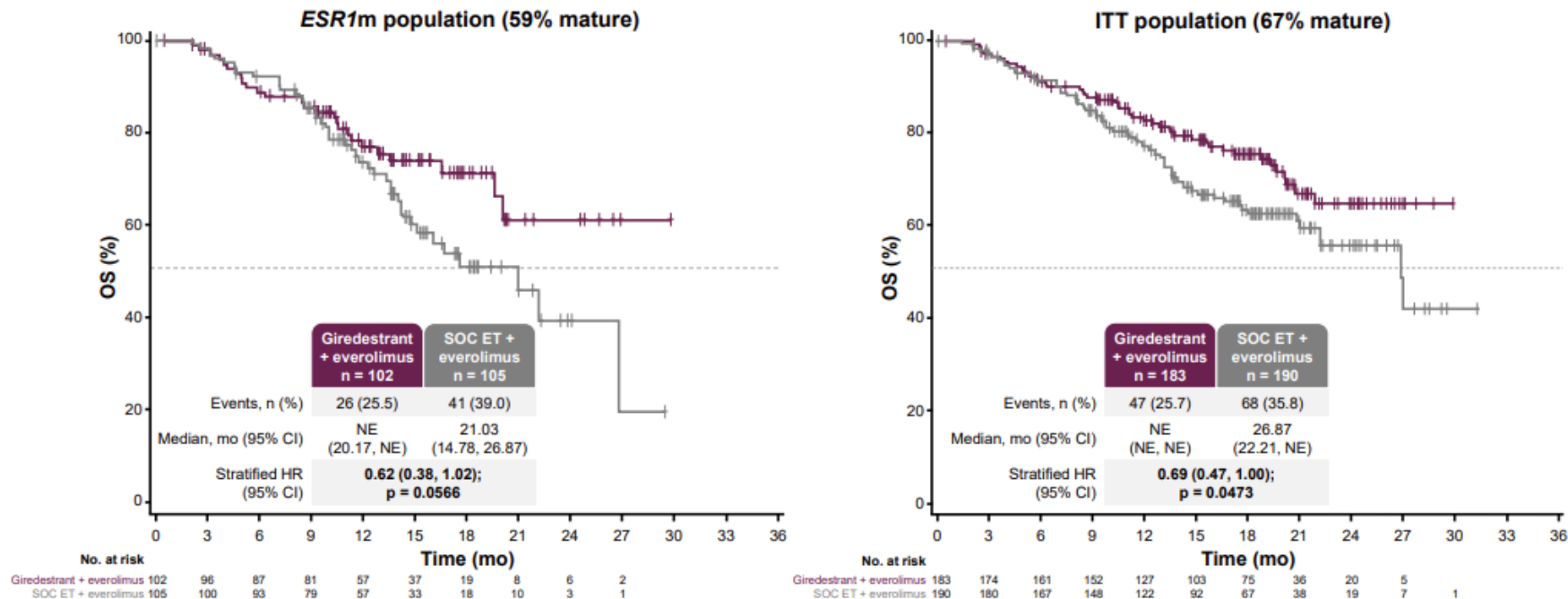


Combination therapy with giredestrant + everolimus led to a clinically meaningful 62% reduction in the risk of progression or death in patients with *ESR1m*

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 11.14 mo (giredestrant + everolimus) and 5.68 mo (SOC ET + everolimus); stratified HR, 0.49; 95% CI: 0.34, 0.71. CI, confidence interval; *ESR1m*, *ESR1* mutation; HR, hazard ratio; INV, investigator-assessed; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

evERA Phase III Trial

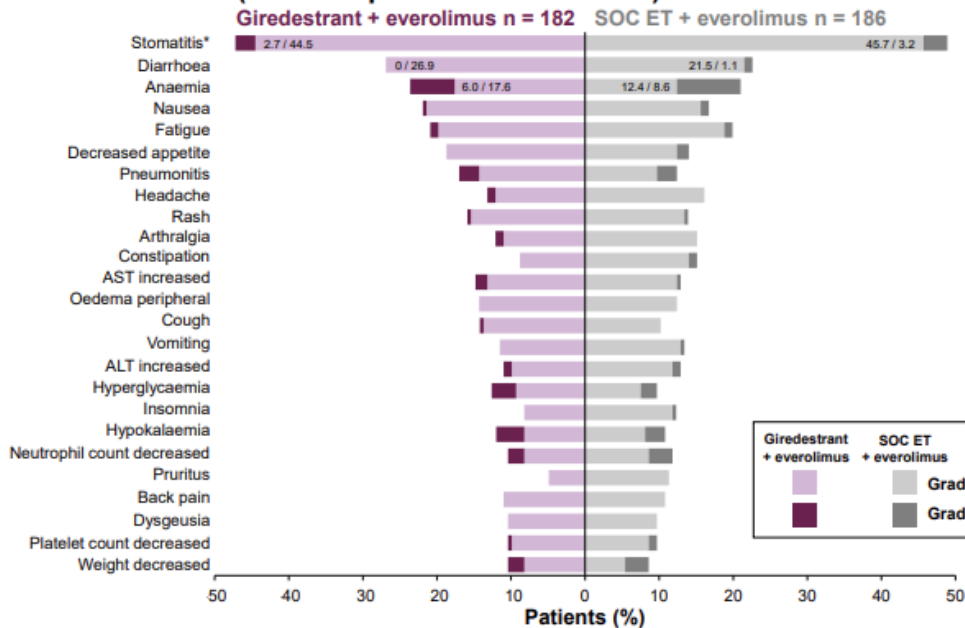
Interim OS in the *ESR1m* and ITT populations



evERA Phase III Trial

AEs overview

Common TEAEs (≥ 10% of patients in either arm)



Selected AEs

Patients with AE, n	Giredestrant + everolimus n = 182		SOC ET + everolimus n = 186	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Bradycardia†	7 (3.8)	0	1 (0.5)	0
Photopsia	0	0	0	0

Data cutoff: 16 July 2025. * Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol (Rugo HS, et al. *Lancet Oncology* 2017; 18:654-662).

† Assessed as a medical concept using grouped terms; all events were Grade 1, non-serious and no treatment interruptions/interventions were needed. All events had resolved by data cutoff.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC ET, standard of care endocrine therapy; TEAE, treatment-emergent adverse event.



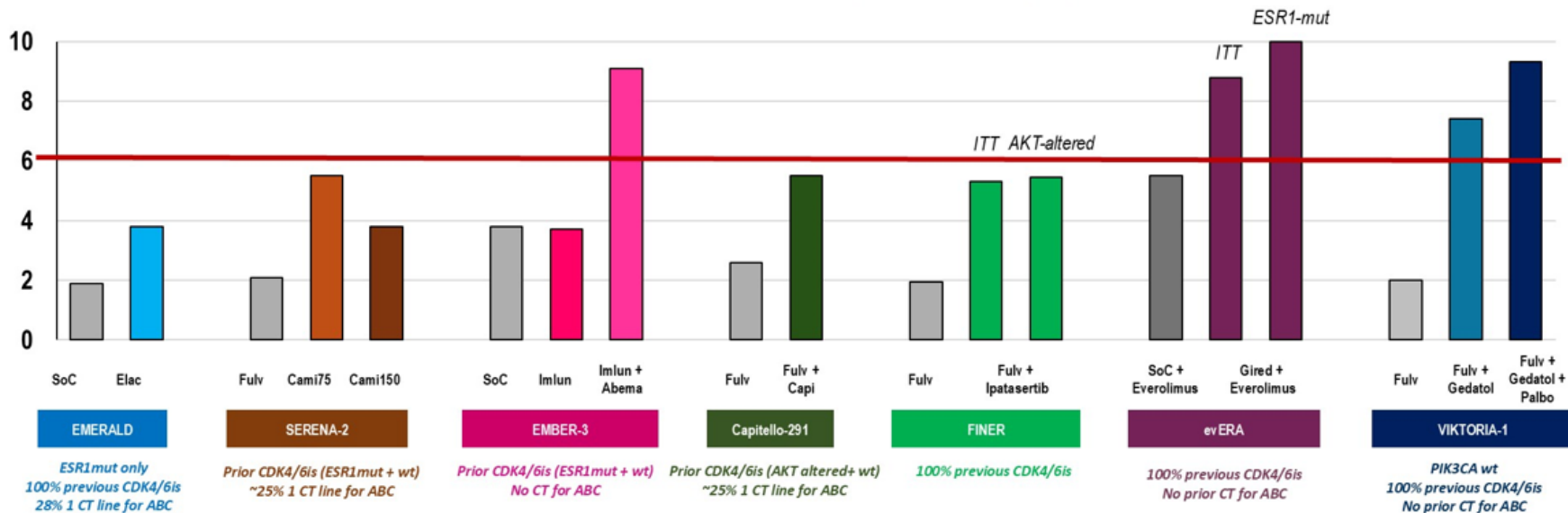
Key Learning Points (and Remaining Questions)

- Elacestrant monotherapy has sustained PFS benefit in heavily pretreated patients with *ESR1*m and potential to become an ET backbone for combination strategies
 - Will we need larger, phase 3 data to adopt?
- Imlunestrant monotherapy in patients with *ESR1*m demonstrated both PFS and OS benefit with a continued favorable safety profile.
 - Is patient population representative of our current patient population?
- Switching AI to camizestrant with continuation of CDK4/6i when emergence of *ESR1* mutation detected ahead of disease progression improved PFS
 - Does this improve overall survival?
- Giredestrant combined with everolimus showed meaningful improvement in PFS vs SOC ET + everolimus in ER+/HER2- aBC post-CDK4/6i
 - How will this drug get approved? *ESR1*m only?

Sequencing and Optimizing Patient Outcomes

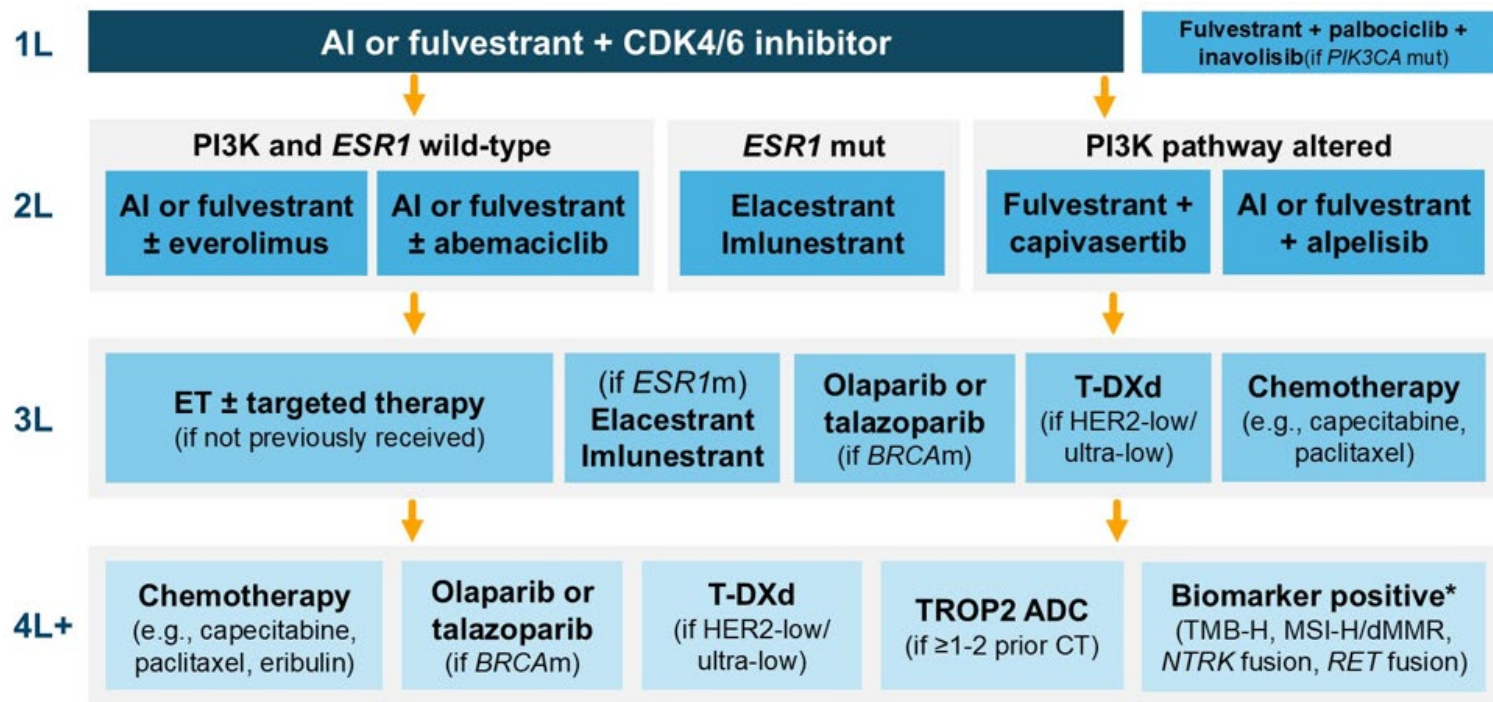
Pushing beyond the 6-Month PFS Ceiling after CDK4/6 Inhibitors

Novel endocrine agents combined with targeted therapies represents the future of ET-based treatment in CDK4/6i-pretreated population



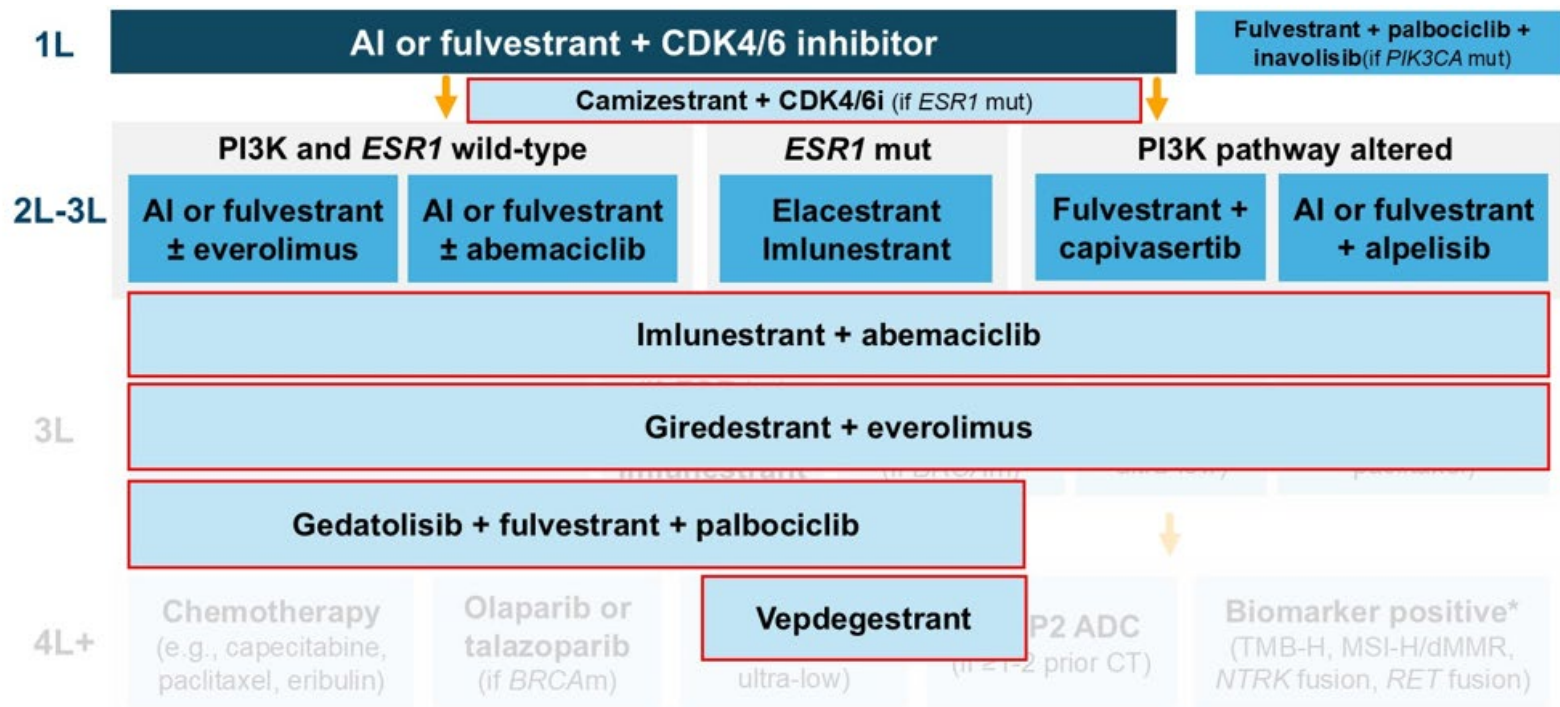
CT = chemotherapy.
Mayer EL. Presented at: SABCS; 2025.

Treatment Algorithm for HR+/HER2- MBC



T-DXd = trastuzumab deruxtecan-dlnk; TMB-H = high tumor mutational burden; dMMR = deficient mismatch repair.
Slide adapted from Garrido-Castro AC. Mayer EL. Presented at: SABCS; 2025.

Treatment Algorithm for HR+/HER2- MBC



Even More to Come...

Other endocrine therapies:

- CERAN (palazestrant), PROTAC (vepdegestrant), SERCA (H3B-6545)

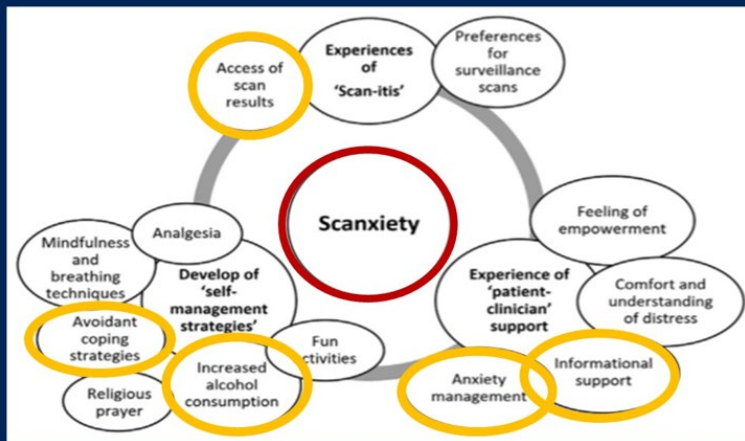
Moving oral SERD to first line?

- SERENA-4 and persevERA

Innovations on targeted partners:

- CDK2 inhibitors, CDK4 selective inhibitors, KAT6 inhibitors, Aurora kinase inhibitors, PI3K

What about Taking SERENA-6 Approach?

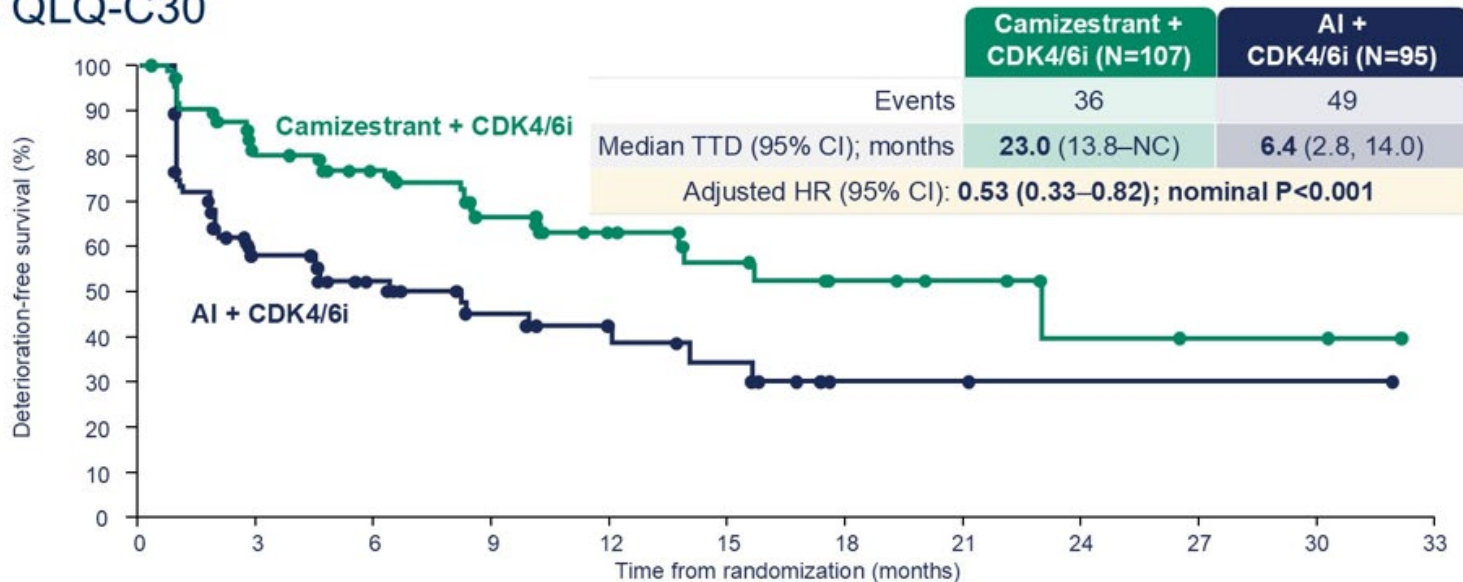


Will we add “test-xiety” to “scan-xiety”?

- Too early to determine OS benefit
- Burden of ctDNA testing on healthcare system and patients
→ costs and potential emotional distress
- Not FDA-approved yet

Time to Deterioration in Global Health Status/Quality of Life

EORTC QLQ-C30



Number of patients at risk

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

- Camizestrant + CDK4/6i also delayed the time to deterioration in pain compared with AI + CDK4/6i

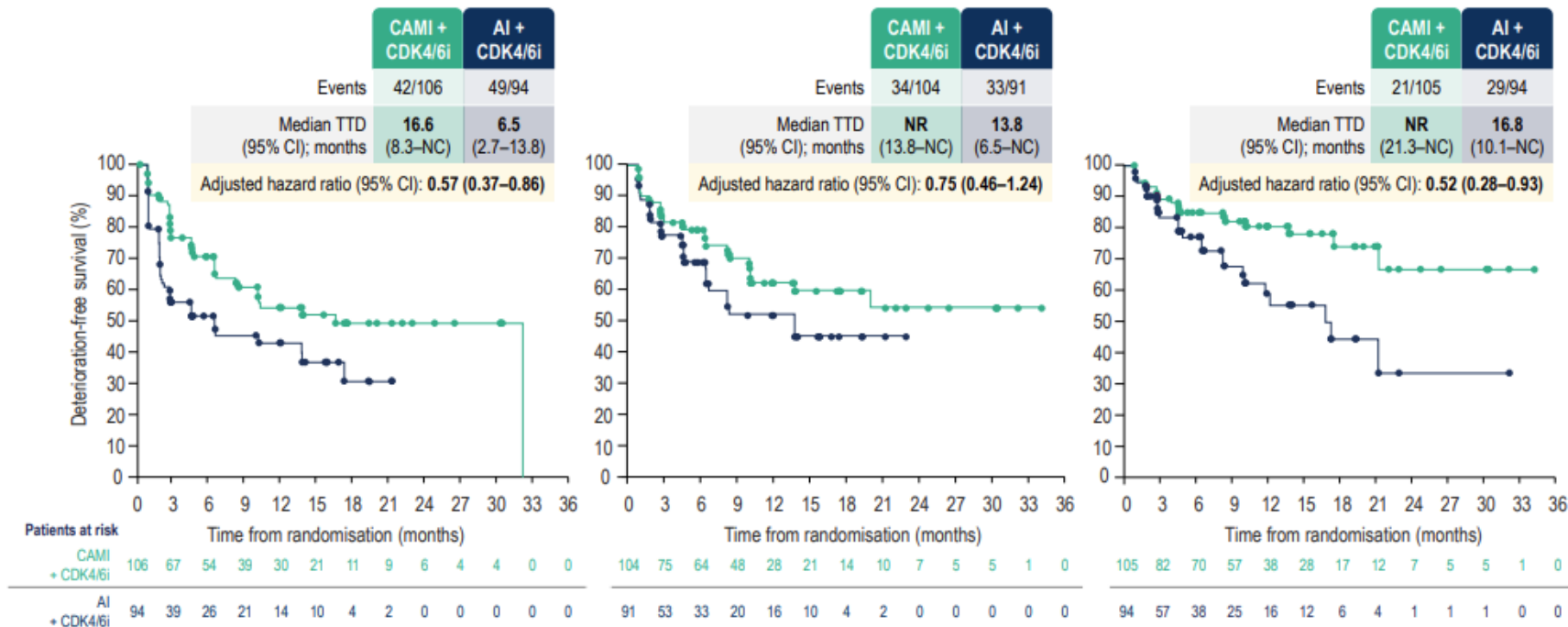
Assessments were conducted at baseline, weeks 4, 8 and 12 and then every 8 weeks until PFS2. Analysis conducted in patients with a baseline score and at least one post-baseline assessment. TTD in global health status/quality of life, an exploratory endpoint, was defined as the time from randomization to first deterioration that was confirmed at a subsequent timepoint measured using the European Organization for Research and Treatment of Cancer 30-item quality-of-life questionnaire (EORTC QLQ-C30). Deterioration was defined as a decrease from baseline ≥ 16.6 . HR was estimated using the Cox proportional hazard model stratified by time of ESR1m detection (one test vs more than one test), and time from initiation of AI + CDK4/6i to randomization (<18 months vs. ≥ 18 months). NC, not calculable; TTD, time to deterioration.

Camizestrant + CDK4/6i Delayed Time to Deterioration of Patient-Reported Cancer Symptoms Compared with AI + CDK4/6i

Pain (secondary endpoint)

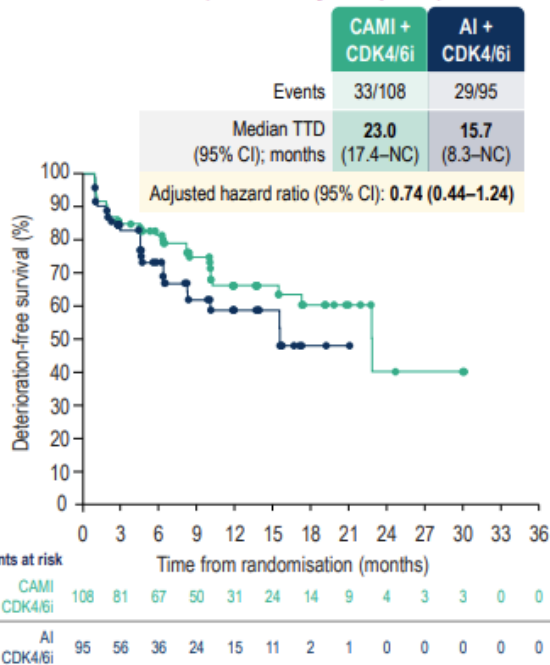
Fatigue

Shortness of breath/ dyspnoea

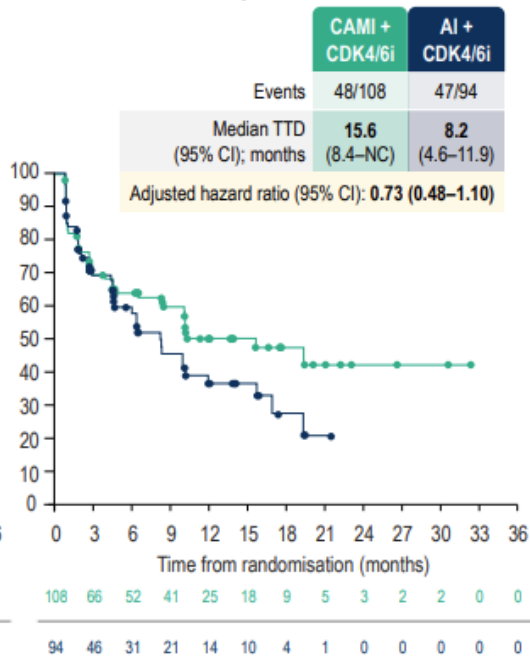


Camizestrant + CDK4/6i Delayed Time to Deterioration of Patient-Reported Functioning Compared with AI + CDK4/6i

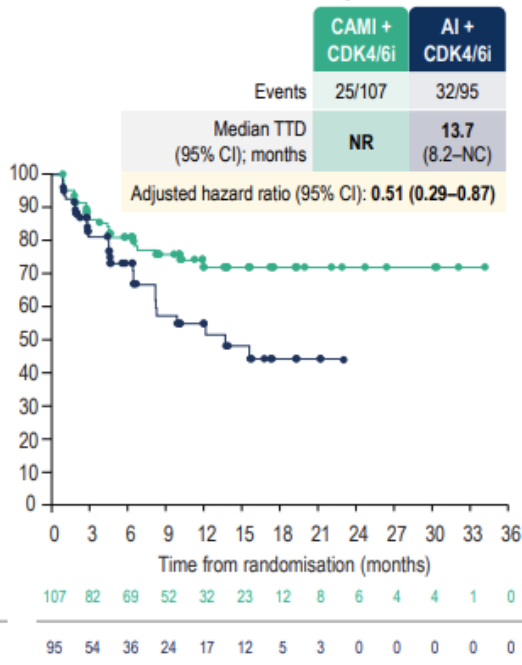
Physical: ability to perform everyday physical activities (secondary endpoint)



Role: impact of health on work and daily activities



Emotional: feelings of anxiety, depression and irritability



Pink title indicates secondary endpoint; blue title indicates exploratory endpoints.



Shared Decision-Making and Balancing Goals

- Can consider SERENA-6 approach for patients who are experiencing symptoms affecting QOL while on treatment
 - Or all patients? Will be a discussion with patient.
- Monotherapy vs doublet or triplet therapy
 - Less medication burden and fewer potential side effects
- Consider specific side effects that could affect patients
 - Photopsia
 - Bradycardia
 - Stomatitis

Will all of this become a moot point if SERDs move to first line?



Key Learning Points

- **Elacestrant** and **imlunestrant** monotherapy are FDA-approved options for second-line treatment of patients with HR+ mBC with *ESR1m*
- Camizestrant is not yet FDA-approved, but SERENA-6 approach leads to improved PFS2 and better quality of life for our patients based on PRO data presented
- SERD combination therapies in the second line are likely coming, but no FDA approvals yet
- Expect more discussions and shared decision-making with patients as we navigate a growing number of options

PRO = patient-reported outcome.