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AstraZeneca

Camizestrant + CDK4/6i for Treatment of HR-positive, HER2-negative Advanced Breast Cancer Upon Emergence of *ESR1* Mutation During First-Line Endocrine-Based Therapy

United States Food and Drug Administration
Oncologic Drugs Advisory Committee

April 30, 2026

AstraZeneca

Introduction

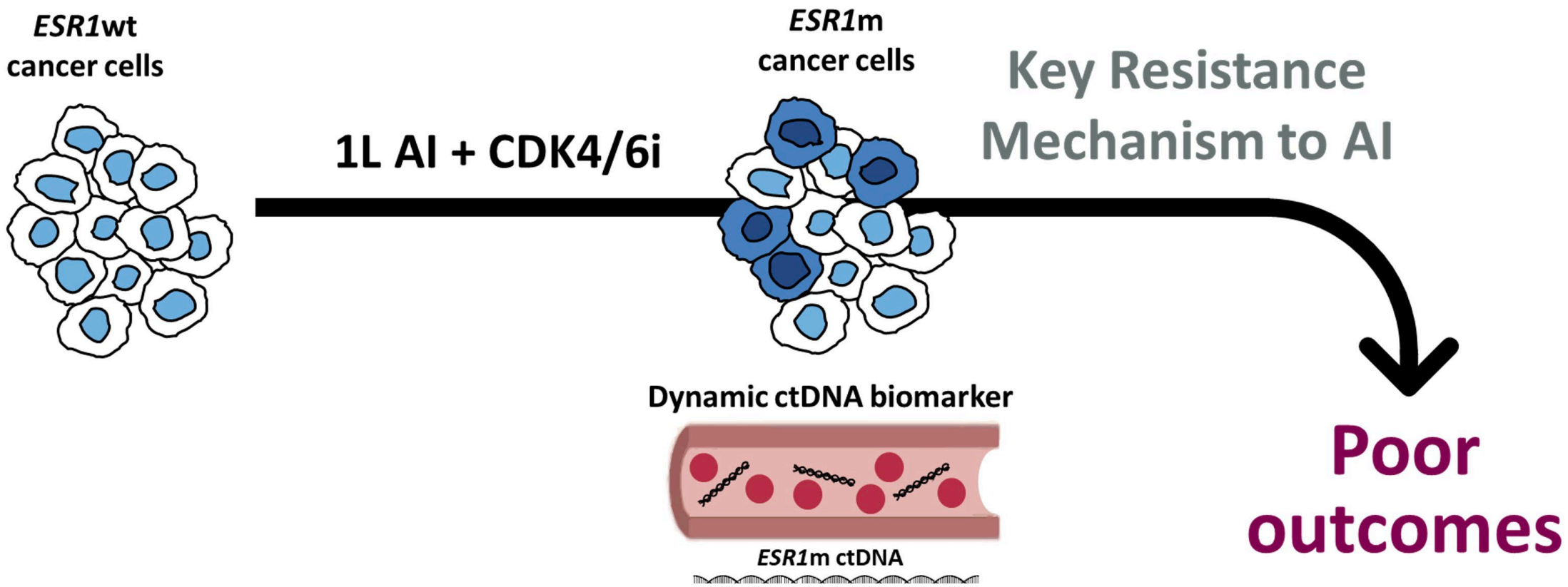
Ingrid Mayer, MD, MSCI

VP, Global Clinical Strategy Head, Breast/GYN Cancers

Late Development Oncology, Research & Development

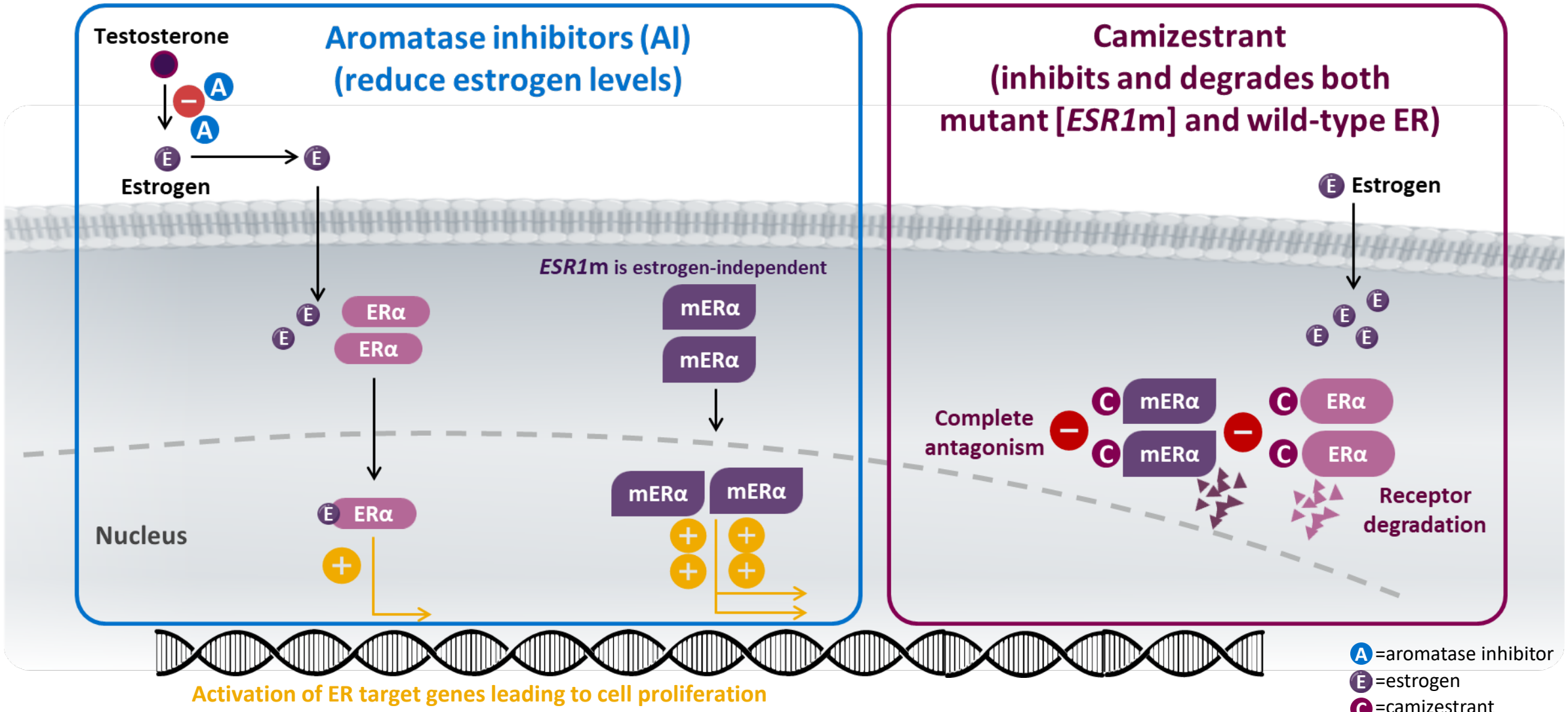
AstraZeneca

ESR1 Mutation Clonal Evolution Drives Clinical Progression During First-Line AI + CDK4/6i Therapy for HR+ aBC



1L=first-line; aBC=advanced breast cancer; AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ctDNA=circulating tumor DNA; HR+=hormone receptor-positive; *ESR1*m = mutation in the estrogen-receptor gene; *ESR1*wt=no mutation in the estrogen-receptor gene.

Camizestrant Is a Potent Oral SERD and Complete ER Antagonist

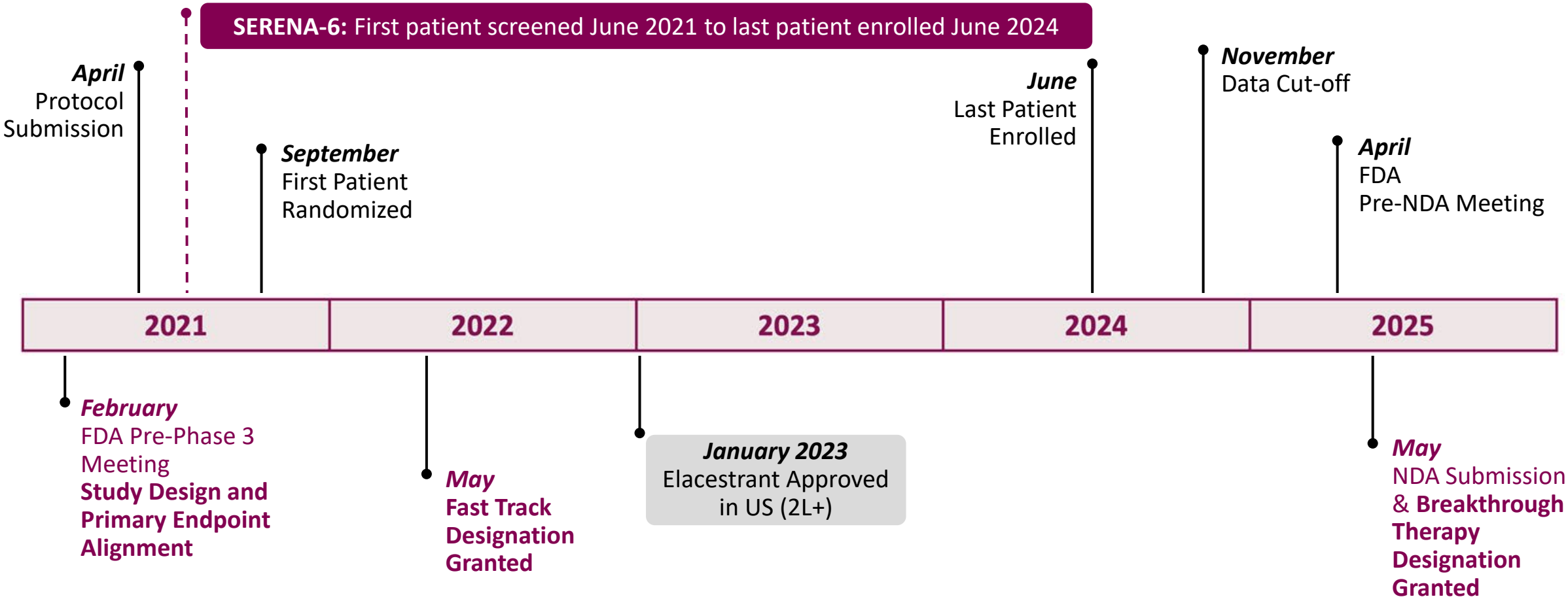


ERα=wild-type estrogen receptor alpha; mERα=mutant estrogen-receptor alpha; SERD=selective estrogen receptor degrader.

Proposed Indication

Camizestrant in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) for the treatment of adult patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer, **upon emergence of *ESR1* mutation during first-line endocrine-based therapy**, based on an FDA approved test.

SERENA-6 Key Regulatory Milestones: Breakthrough Therapy Designation in May 2025



Current Treatment Paradigm for *ESR1*m HR+ aBC

DELAY 1L PROGRESSION (2017+)

Approved 1L ET-Based Therapy	HR	Δ PFS (months)
ET Replacement[1] (AI → fulvestrant)	0.8	2-3
Add-On[2-5] (AI + CDK4/6i)	0.54-0.57	9-13

REACT AFTER 1L PROGRESSION (2023+)

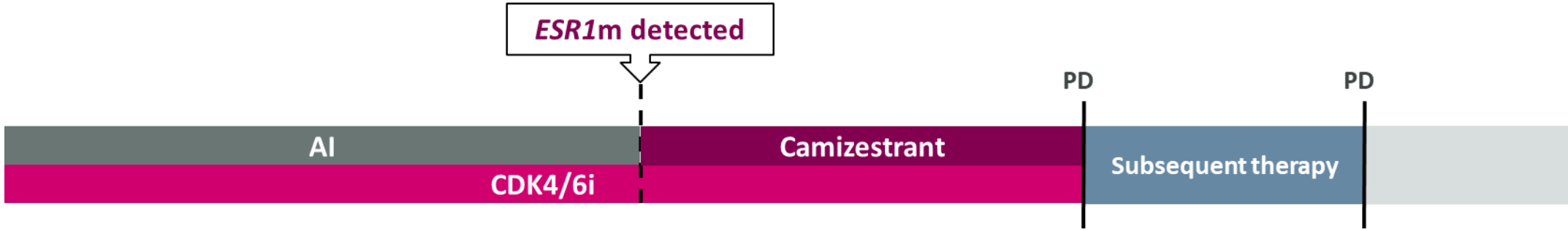
Approved 2L ET-Based Therapy	HR	Δ PFS (months)
ET Replacement[6-9] (elacestrant, imlunestrant)	0.55-0.72	<2
Add-On[10-12] (fulv/exe + targeted Tx)	0.43-0.62	3-5

PD=clinical/radiological disease progression.

1. Robertson JFR, et al. *Lancet*. 2016;388:2997-3005; 2. Finn RS, et al. *N Engl J Med*. 2016;375;1925-1936; 3. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541-1547; 4. Tripathy D, et al. *Lancet Oncol*. 2018;19(7):904-915; 5. Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5; 6. Bidard F-C, et al. *J Clin Oncol*. 2022;40(28):3246-3256; 7. Jhaveri KL, et al. *N Engl J Med*. 2025;392(12):1189-1202; 8. Jhaveri KL, et al. *Ann Oncol*. 2026;37(4):532-543; 9. Inluriyo EMA Summary of Product Characteristics; 10. Oliveira M, et al. *ESMO Open*. 2024; Abstract 1870; 11. De Laurentiis M, et al. *Clin Cancer Res*. 2026;32(4 suppl). Abstract RF7-02; 12. Baselga J, et al. *N Engl J Med*. 2012;366:520-529.

SERENA-6: A New Treatment Paradigm for *ESR1*m HR+ aBC

Hypothesis: Replacing AI with camizestrant at emergence of *ESR1*m suppresses resistant clones, maximizing the benefit of first-line ET + CDK4/6i by delaying disease progression



INTERCEPT 1L RESISTANCE

AI → Camizestrant	HR	Δ PFS (months)
ET Replacement[1] (*ESR1*m)	0.44	7

1. Bidard F-C, et al. *N Engl J Med*. 2025;393:569-580.

Camizestrant at *ESR1*m Emergence in 1L: Positive Benefit/Risk

	Benefit for Camizestrant + CDK4/6i Replacement Strategy
PFS[a]	Delays disease progression (HR=0.44; primary endpoint) Allows patients to get subsequent endocrine-based therapy
PFS2[b]	Positive benefit is preserved through subsequent line of therapy (HR=0.63)
OS[b]	No detriment (HR=0.87)
Chemotherapy/ADC-free survival[b]	Prolongs chemotherapy/ADC-free survival (HR=0.64) and time on ET
	Camizestrant + CDK4/6i Is Patient-Centric
PRO	Maintains QoL
	Risk for Camizestrant + CDK4/6i
Adverse event rate	Well-tolerated
Discontinuation rate	1%
Impact on activities of daily living	None or minimal impact

a. Data cut-off 1 (DCO1).
b. DCO3.

What You Will Hear Today

Disease Background & Unmet Need

Massimo Cristofanilli, MD, FACP
Scientific Director of the Englander Institute of Precision Medicine
Weill-Cornell Medicine and NY Presbyterian

SERENA-6 Efficacy and PROs

Cynthia Huang-Bartlett, MD
Global Clinical Head – Camizestrant
AstraZeneca

SERENA-6 Clinical Safety

Andrew Walding, MSc
Global Safety Head – Camizestrant
AstraZeneca

Clinical Perspective

Kevin Kalinsky, MD, MS, FASCO
Emory University School of Medicine
Director of the Glenn Family Breast Center at Winship Cancer Center

Concluding Remarks

Ingrid Mayer, MD, MSCI
VP, Global Clinical Strategy Head, Breast/GYN Cancers Late Development Oncology, Research & Development
AstraZeneca

External Experts Available to Address Your Questions

Patient-Reported Outcomes

David Cella, PhD
Associate Director for Cancer Prevention, Control, and Survivorship
Robert H. Lurie Comprehensive Cancer Center
Northwestern University

Ophthalmology

Ranya Habash, MD
Board Certified Ophthalmologist
Bascom Palmer Eye Institute
University of Miami

Cardiology

Anju Nohria, MD, MSc
Cardio-Oncology Site-Director
New York University Langone Medical Center

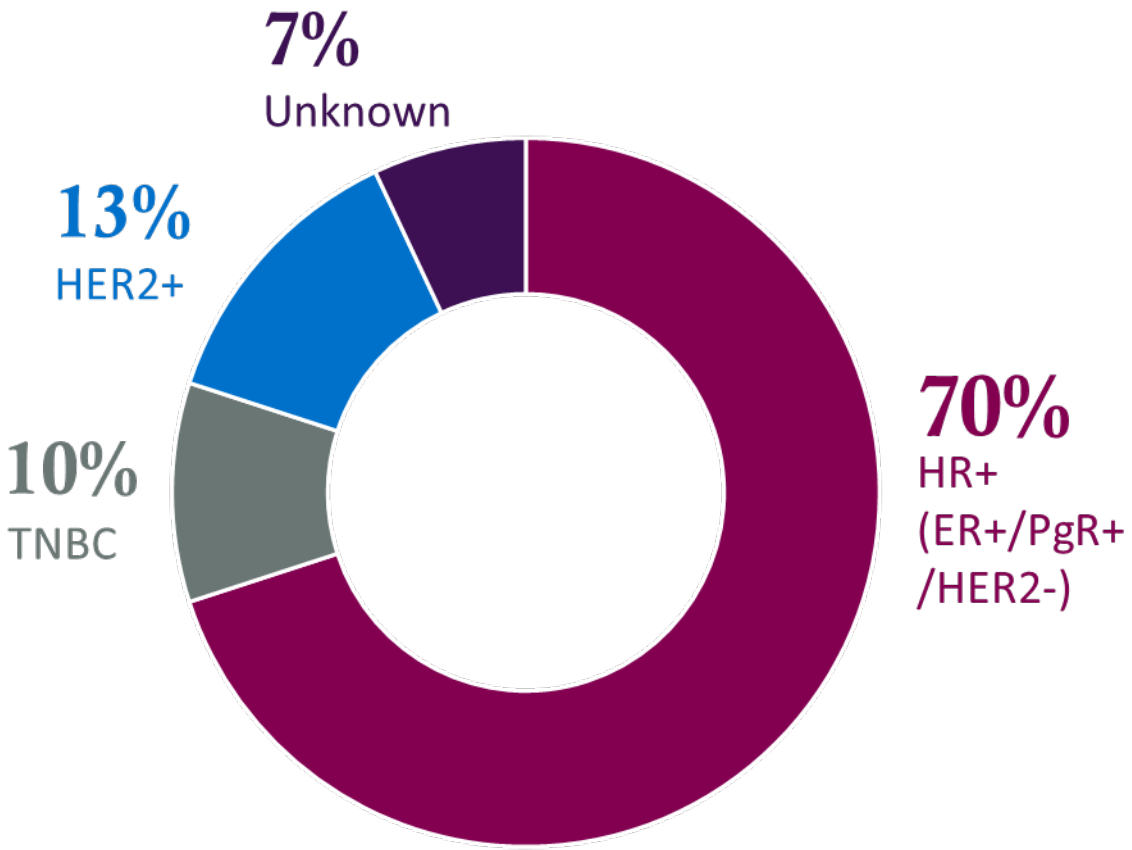
Disease Background & Unmet Need

Massimo Cristofanilli, MD, FACP

Scientific Director of the Englander Institute of Precision Medicine

Weill-Cornell Medicine and NY Presbyterian

Hormone-Receptor Positive Advanced Breast Cancer Is Incurable



In the US, >150,000 people living with metastatic breast cancer (mBC)[1]

- >105,000 living with HR+ mBC
- ~29,000 die from HR+ mBC annually[2]

Goal of systemic treatment:

- **Extend disease control**
- **Improve symptoms**
- **Maintain quality of life**

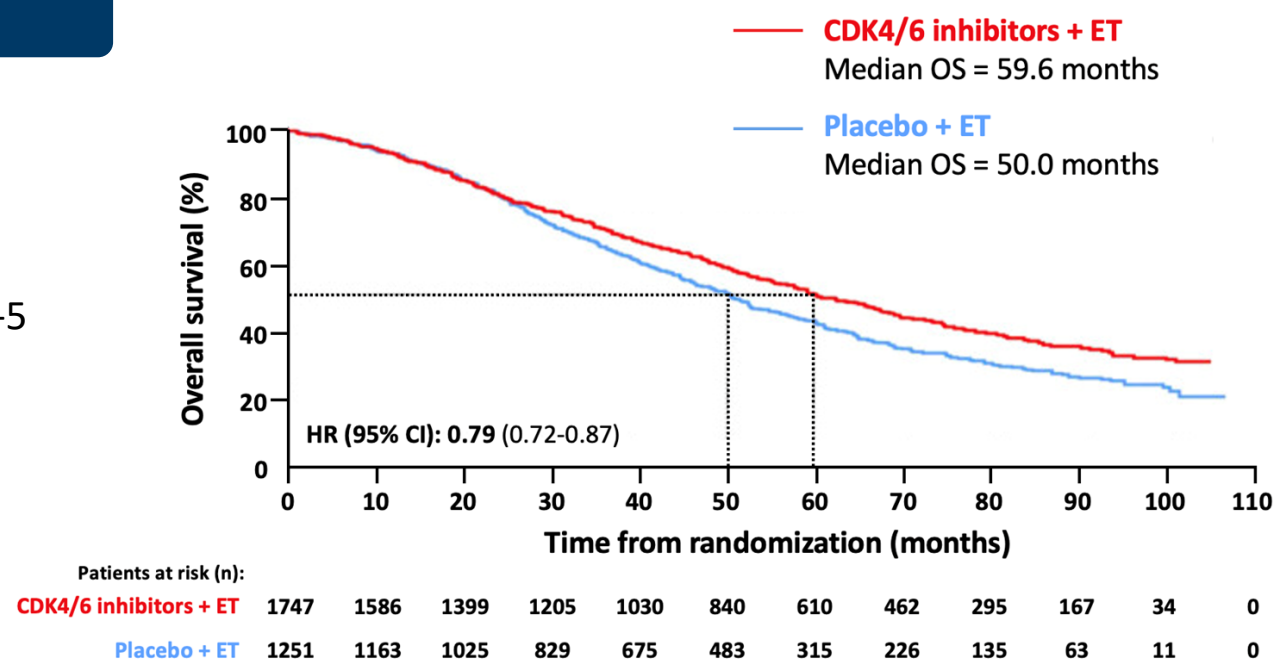
ER=estrogen receptor; HER2=human epidermal growth factor receptor-2; HR=hormone receptor; PgR=progesterone receptor; TNBC=triple-negative breast cancer.
Advanced breast cancer includes locally advanced breast cancer treated without curative intent and metastatic breast cancer.
American Cancer Society Cancer, Breast Cancer Facts & Figures 2024-2025. 1. Gallicchio L, et al. *J Natl Cancer Inst*. 2022;114(11):1476-1483. 2. National Cancer Institute SEER statistics.

First-line Treatment With ET + CDK4/6i Is Highly Effective for ER-Signaling–Dependent Disease and Is Well-Tolerated

1L SoC AI + CDK4/6i
mPFS: ~25-34 months

- Longest PFS in the HR+ aBC treatment journey[1-4]
- Prolonged QoL with good tolerability[1-5]
- Dependency on ER-signaling is greatest in this setting[6]

1L ET + CDK4/6i prolongs OS[7]



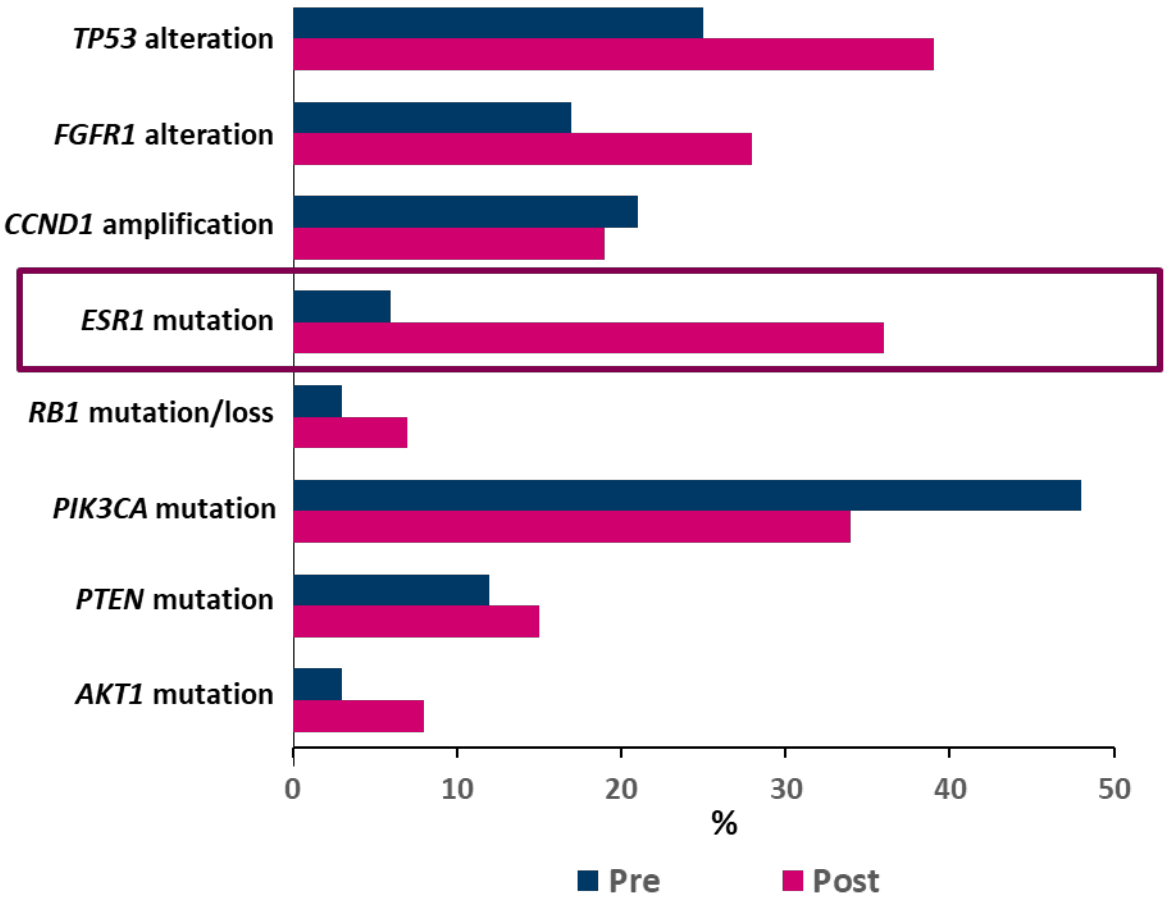
1. Finn RS, et al. *N Engl J Med*. 2016;375;1925-1936; 2. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541-1547; 3. Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5; 4. Slamon D, et al. *N Engl J Med.* 2020;382:514-524; 5. Di Lauro V, et al. *ESMO open* 2022;16;7(6):100629; 6. Pagliuca M, et al. *Crit Rev Oncol Hematol*. 2022;180:103861; 7. Reprinted with permission from Wang X, et al. *Front Pharmacol*. 2025;16:1600892.

After Progression on AI + CDK4/6i, Disease Becomes Harder to Treat Due to Endocrine Resistance

Progression is associated with

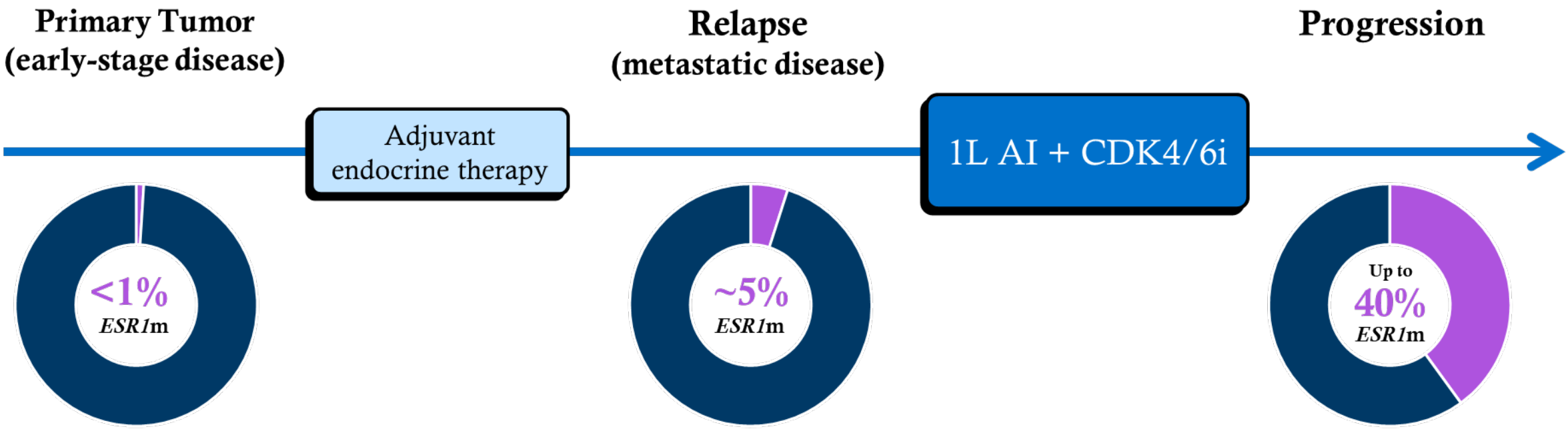
- Increased disease burden
- Worsening symptoms
- Deterioration in QoL
- Greater tumor heterogeneity

Prevalence (%) of genomic alterations pre- and post-treatment with 1L AI + CDK4/6i in a cohort of 508 patients[1]



1. Data from Chaudhary N. *NPJ Breast Cancer*. 2024;10:15. Supplemental Figure 3.

ESR1 Mutations Emerge Under Selective Pressure of Aromatase Inhibition

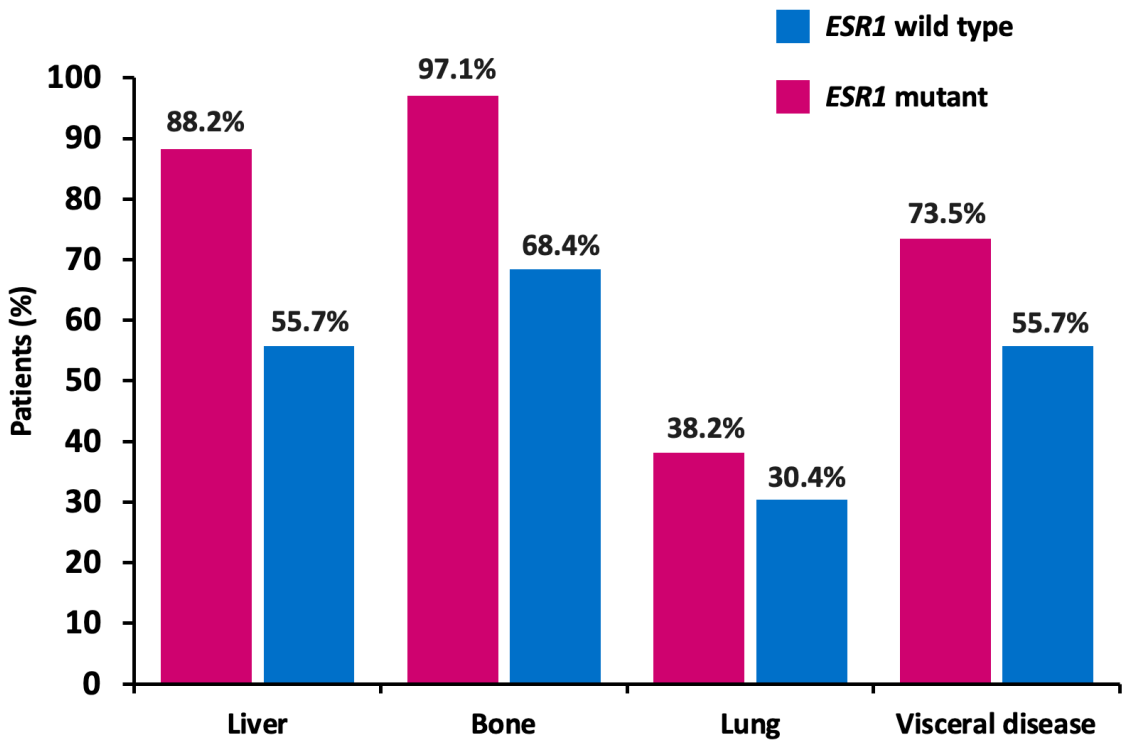


Adapted from Allouchery V, et al. *Breast Cancer Res*. 2018;20:40.
Cabel L, et al. *Ann Oncol*. 2026;37:329-340; Chaudhary N. *NPJ Breast Cancer*. 2024;10(1):15. Supplemental Figure 3; Razavi P, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract 1009.

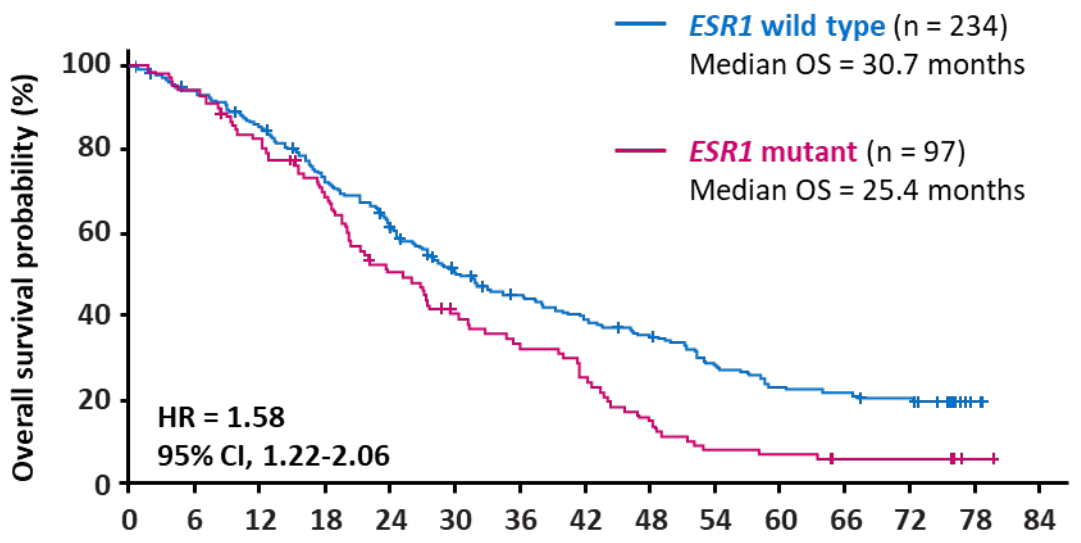
*ESR1*m Is a Key Mechanism of Resistance to Traditional Endocrine Therapy in HR+ aBC

_ESR1_m is associated with more aggressive disease biology and worse clinical outcomes

Sites of metastasis[1]



OS in patients with HR+ aBC that progressed on prior ET (PALOMA-3)[2]

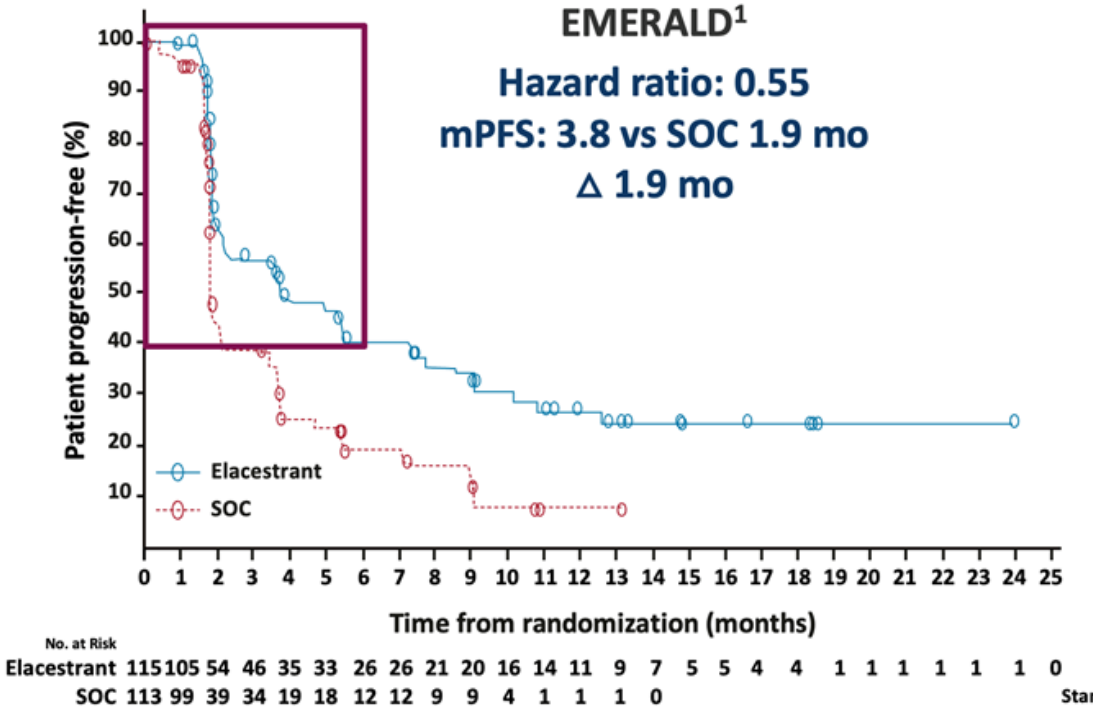


At risk, n	Time from randomization (months)														
ESR1 mut	97	91	79	64	46	35	29	22	14	7	6	4	4	1	0
ESR1 wt	234	213	192	162	138	107	93	81	72	57	46	43	40	1	0

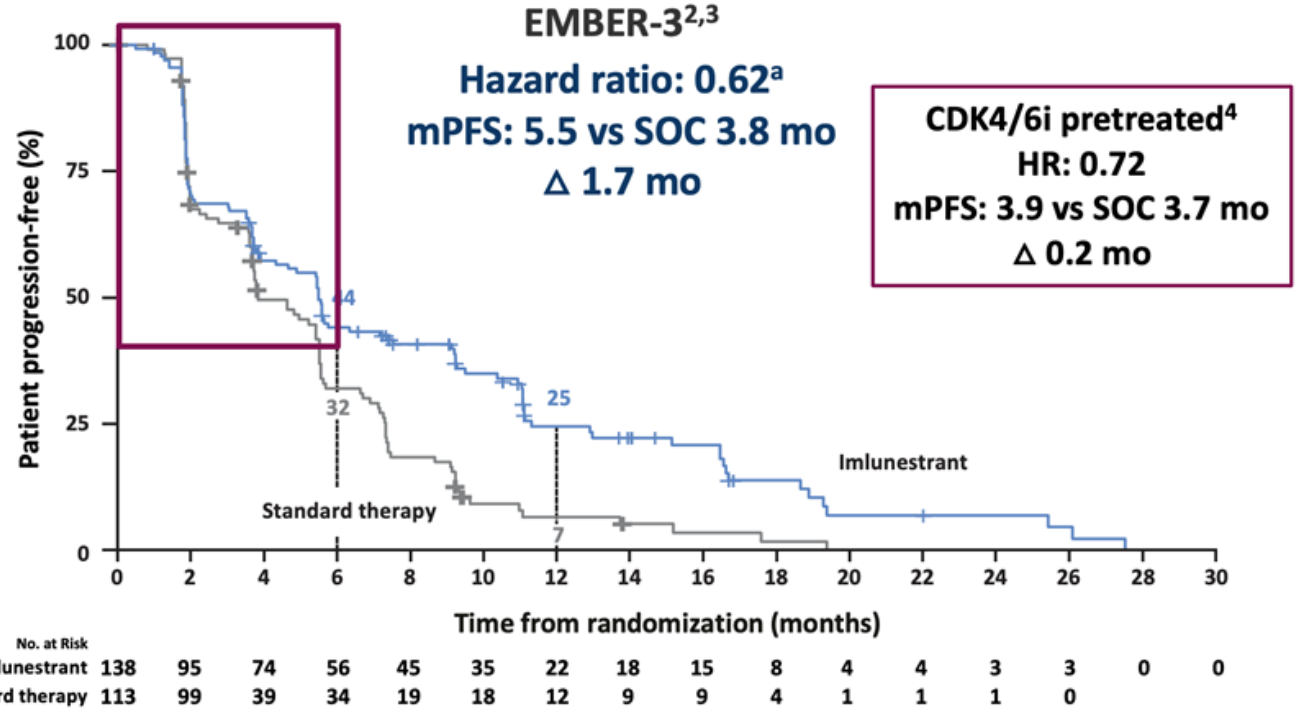
1. Kuang Y, et al. *NPJ Breast Cancer*. 2018;4:22; 2. Reprinted from *Clin Cancer Res*, 2022, 28(16), 3433-3442, Cristofanilli M, et al, Overall survival with palbociclib and fulvestrant in women with HR /HER2⁻ aBC: updated exploratory analyses of PALOMA-3, a double-blind, phase III randomized study, with permission from AACR.

Targeting *ESR1*m After Progression on AI + CDK4/6i Has Limited Benefit

Elacestrant FDA approved in 2023



Imlunestrant FDA approved in 2025



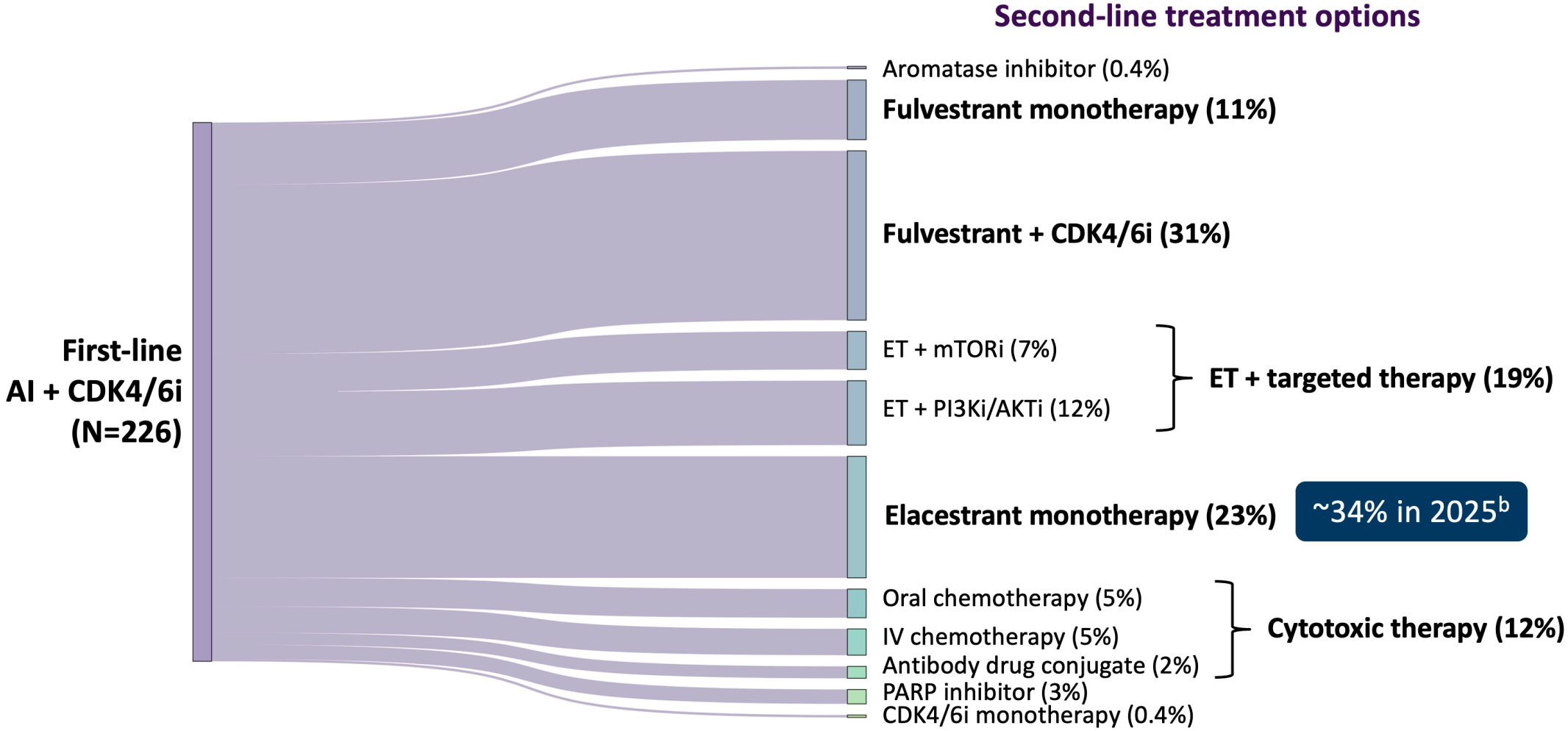
- **Despite activity against *ESR1*m, median PFS remains under 6 months after progression on ET + CDK4/6i**
- **~60% of patients with an *ESR1*m progress within 6 months**

a. 30% of patients in this cohort were CDK4/6i naive.

1. Bidard F-C, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol* (an American Society of Clinical Oncology journal). 2022;40(28):3246-3256, https://ascopubs.org/doi/10.1200/JCO.22.00338?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed; 2. Reprinted from *N Engl J Med*. Jhaveri KL, et al. Imlunestrant with or without abemaciclib in advanced breast cancer: updated efficacy results from the phase III EMBER-3 trial, 392(12), 1189-1202, Copyright 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; 3. Jhaveri KL, et al. *Ann Oncol*. 2026;37(4):532-543; 4. Inluriyo EMA Summary of Product Characteristics.

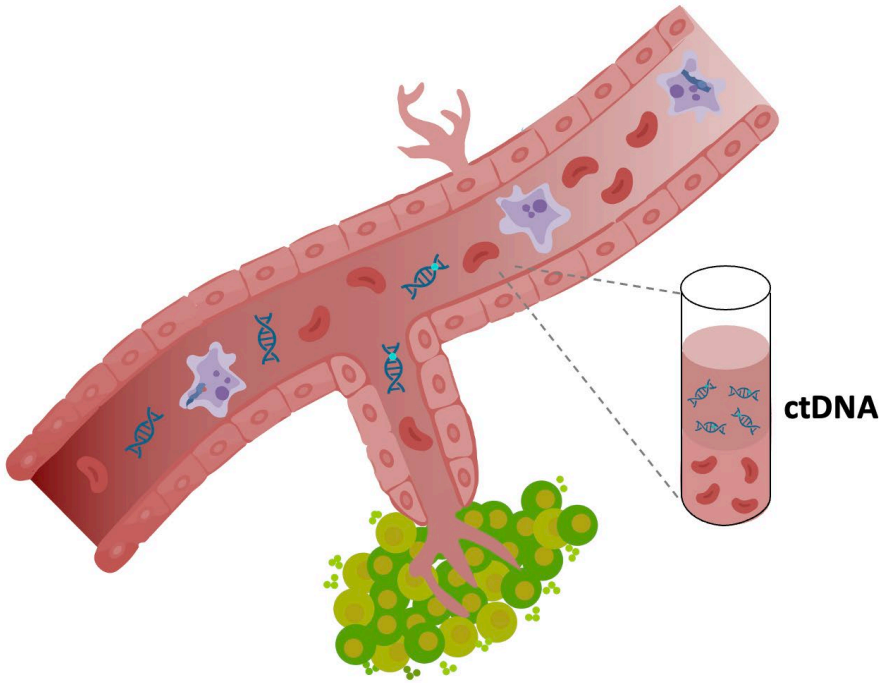
Complexity of 2L Treatment Options in Patients With *ESR1*m After AI + CDK4/6i

Real-World US Treatment Patterns[a]



a. Flatiron Health Research Database; patients diagnosed with HR+/HER2- *ESR1*m mBC from 2015 to 2025 with positive *ESR1*m test at initiation of second-line therapy.
b. As of 2025 RWE, elacestrant usage was ~34% (AstraZeneca data on file).

*ESR1*m Can Be Detected in ctDNA, Which Is Routinely Used in Clinical Practice

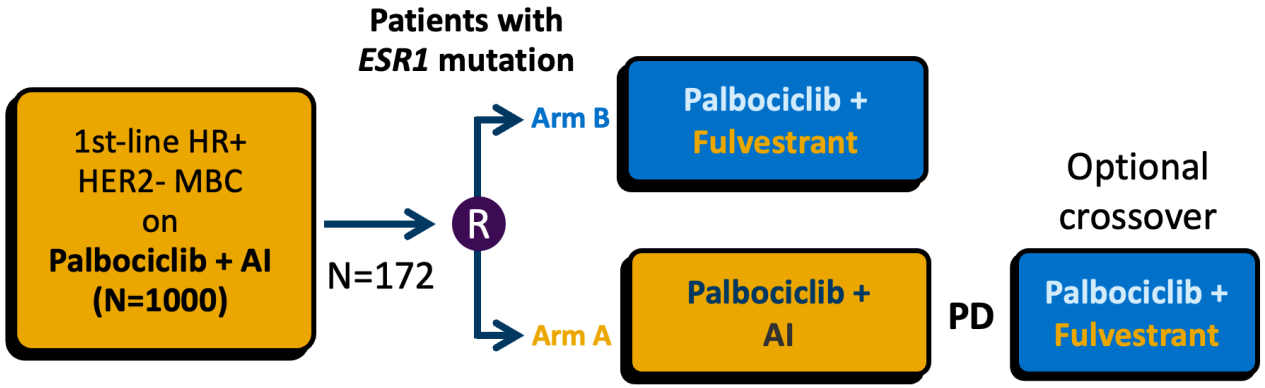


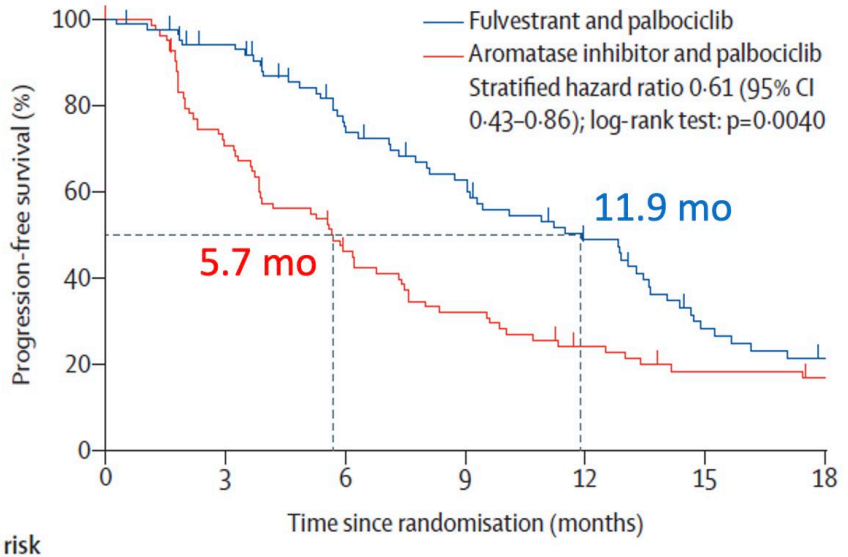
Blood-based ctDNA profiling

- Does not require invasive tissue biopsy
- Representative of predominant cancer clone(s)
- Assesses tumor clonal evolution → aids treatment decisions
- **Ideal test to detect *ESR1*m**[1]

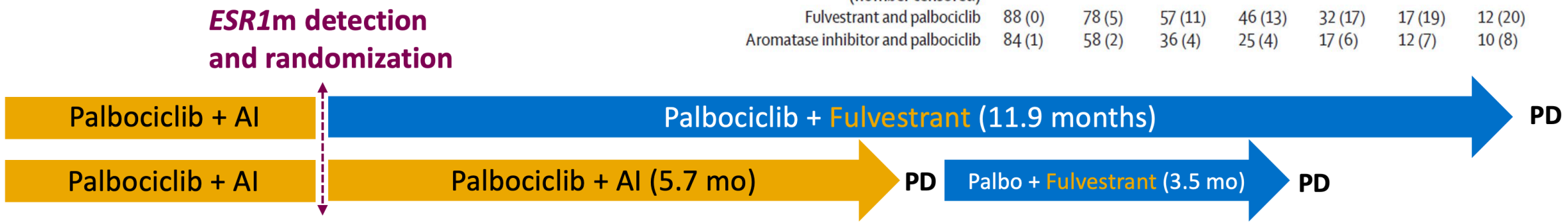
1. Bidard FC, et al. *Lancet Oncol*. 2022;23(11):1367-1377.

PADA-1 Demonstrated Significant Improvement in PFS





Number at risk (number censored)							
Fulvestrant and palbociclib	88 (0)	78 (5)	57 (11)	46 (13)	32 (17)	17 (19)	12 (20)
Aromatase inhibitor and palbociclib	84 (1)	58 (2)	36 (4)	25 (4)	17 (6)	12 (7)	10 (8)



Unmet Need Summary

Target Resistance and Keep Patients on 1L ET + CDK4/6i Longer

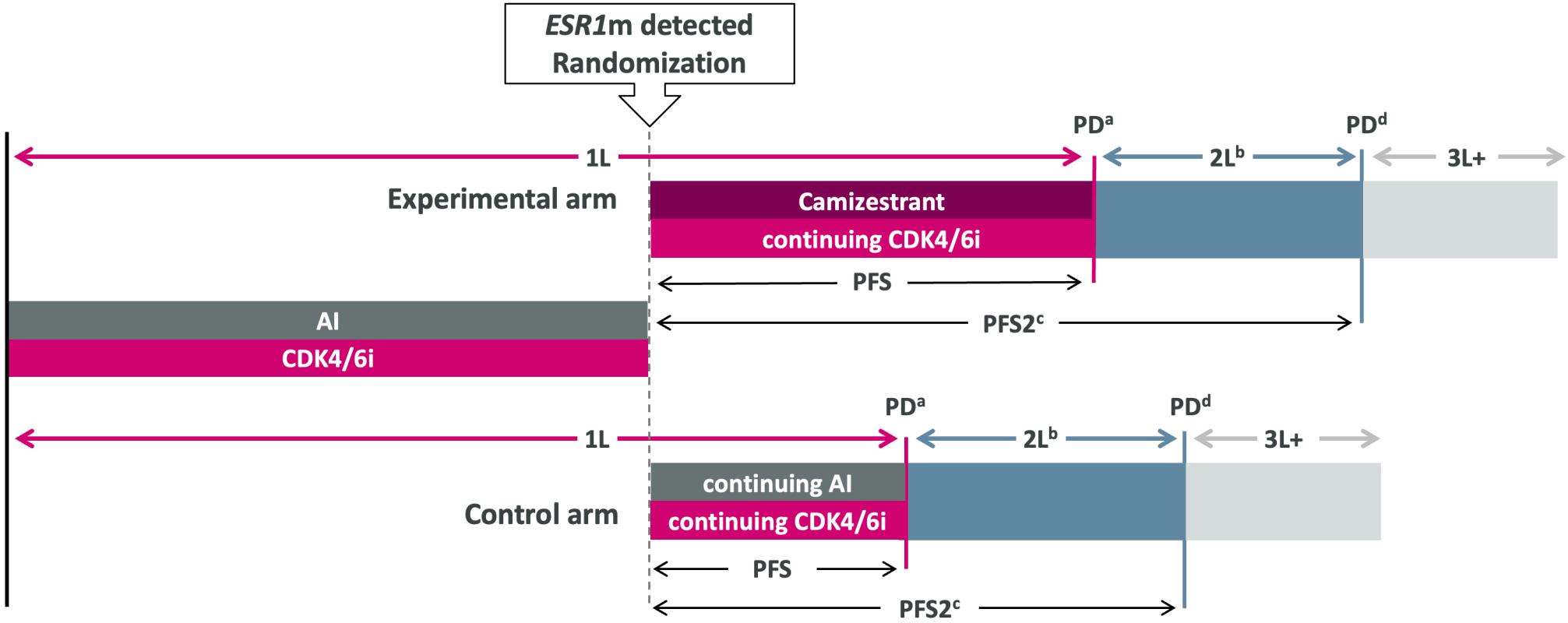
- **Resistance leading to disease progression in 1L invariably occurs, and disease becomes harder to treat**
  - Increased tumor burden and genomic complexity
  - Worsening symptoms and QoL
- ***ESR1*m is a key acquired mechanism of resistance to aromatase inhibitors**
  - Associated with poor outcomes
  - Endocrine sensitivity decreases and patients' needs are heterogeneous
  - Real-world choices of 2L therapy yield modest benefit
  - ~34% of US patient population with *ESR1*m HR+ aBC received an oral SERD in 2025
- ***ESR1*m ctDNA monitoring during AI + CDK4/6i therapy offers opportunity to replace the ineffective AI ahead of clinical/radiographic disease progression**
  - Allows patients to remain on well-tolerated 1L ET + CDK4/6i longer

SERENA-6
Efficacy and PROs

Cynthia Huang-Bartlett, MD
Global Clinical Head – Camizestrant
AstraZeneca

SERENA-6 Hypothesis

Replacing AI with camizestrant at emergence of *ESR1*m suppresses resistant clones, maximizing the benefit of first-line ET + CDK4/6i by delaying disease progression



a. PD per RECIST 1.1 by investigator assessment.
b. 2L treatment options per SoC and physician's preference (include endocrine mono- or combination with targeted therapy, or chemotherapy or ADCs).
c. PFS2 defined per EMA guideline on the evaluation of anticancer medicinal products in man.
d. Clinical or objective PD; 170 patients had a second progression event (PFS2) at DCO3.

SERENA-6: Two-Step Design

STEP 1: *ESR1*m detection phase

HR+ /HER2- aBC on 1L AI + CDK4/6i ≥6 months

ctDNA blood test every 2-3 months with routine tumor scans

*ESR1*m assessed at global central lab

*ESR1*m detected, no radiographic or clinical progression

STEP 2: Randomized treatment phase

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

315 Randomized 1:1

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

Primary Endpoint
PFS by investigator assessment
(RECIST v1.1)

Secondary Endpoints
- **PFS2**[a]
- **OS**[a]
- Safety
- Patient-reported outcomes

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

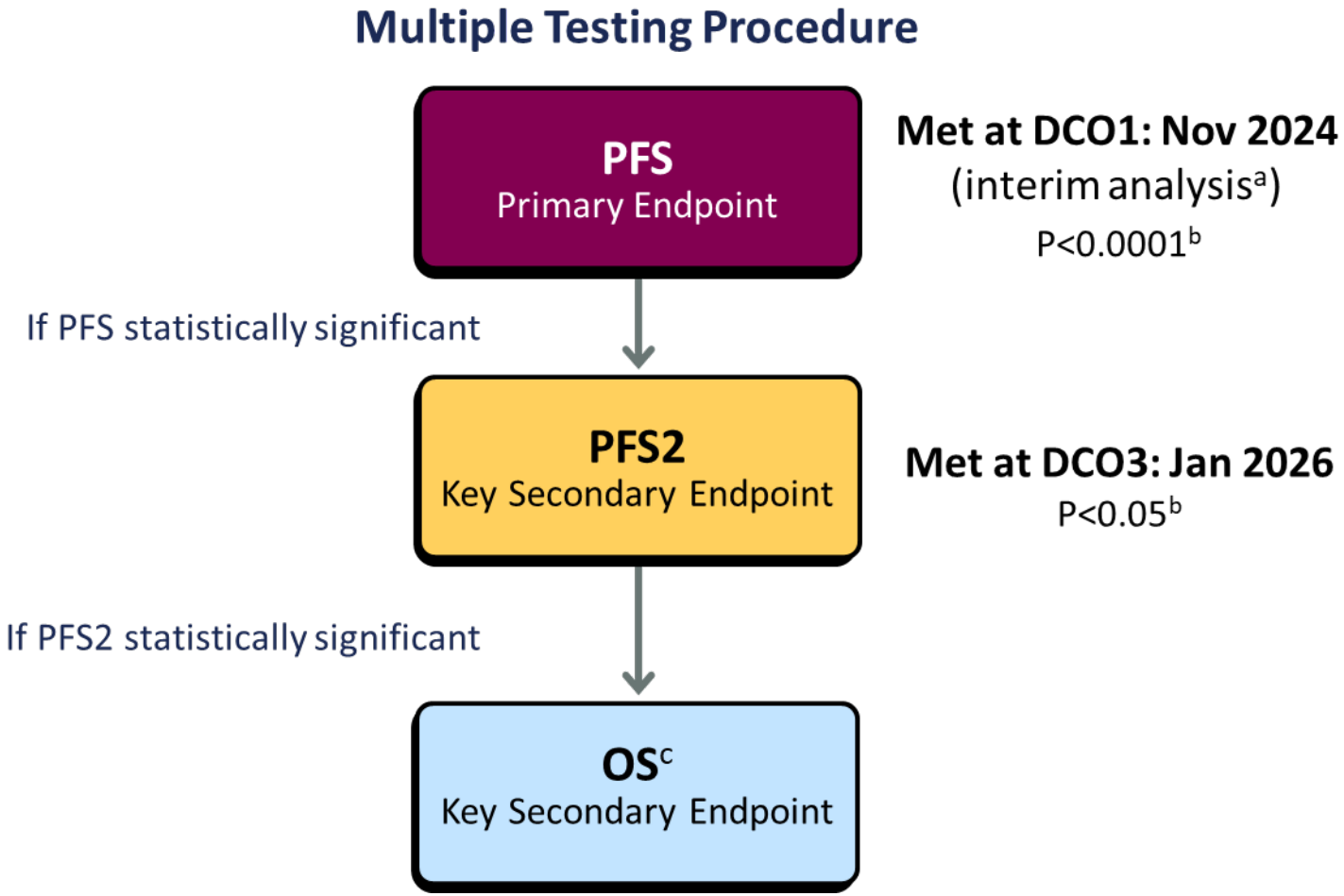
a. Key secondary endpoints.

SERENA-6 Statistical Considerations

Planned enrollment: 300 patients

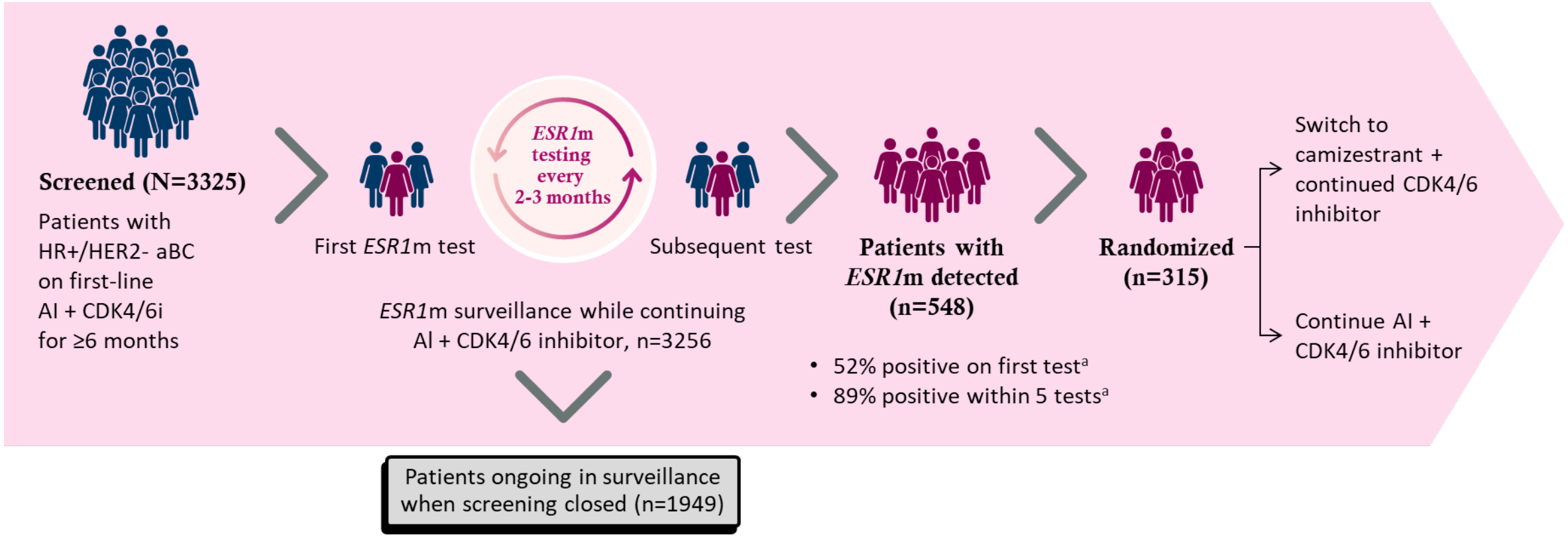
Power for PFS:
93%, assuming HR=0.61
at ~5% two-sided significance

Power for PFS2:
77%, assuming HR=0.65
at ~5% two-sided significance



DCO=data cutoff.
a. Interim analysis was triggered by 135 PFS events and all randomized patients had at least 1 tumor assessment (actual number of events is 171).
b. 2-sided alpha using Haybittle-Peto boundary.
c. Primary OS analysis planned at DCO4.

SERENA-6 Patient Flow



Crude rate of *ESR1*m positive = 548 positive for *ESR1*m/1949 who completed surveillance (42%).
a. Number of tests obtaining a positive *ESR1*m test result based on N=548 patients.

Baseline Demographics & Disease Characteristics Well Balanced

SERENA-6

Characteristic		Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Median age (range), years		61.0 (29-81)	60.5 (35-89)
Female, n (%)		157 (100)	155 (98)
Race, n (%)	White	97 (62)	102 (65)
	Asian	39 (25)	34 (22)
	Other/Not reported	21 (13)	22 (14)
Postmenopausal status, n (%)		123 (78)	127 (80)
ECOG performance-status score, n (%)[a]	0	107 (68)	98 (62)
	1	48 (31)	56 (35)
Most common *ESR1*m at baseline, n (%)[b]	D538G	70 (45)	82 (52)
	Y537S	61 (39)	60 (38)
	Y537N	29 (19)	25 (16)
Region, n (%)	Asia	40 (25)	39 (25)
	Europe	89 (57)	91 (57)
	North America [US/Canada]	22 (14)/6 (4)	23 (15)/5 (3)

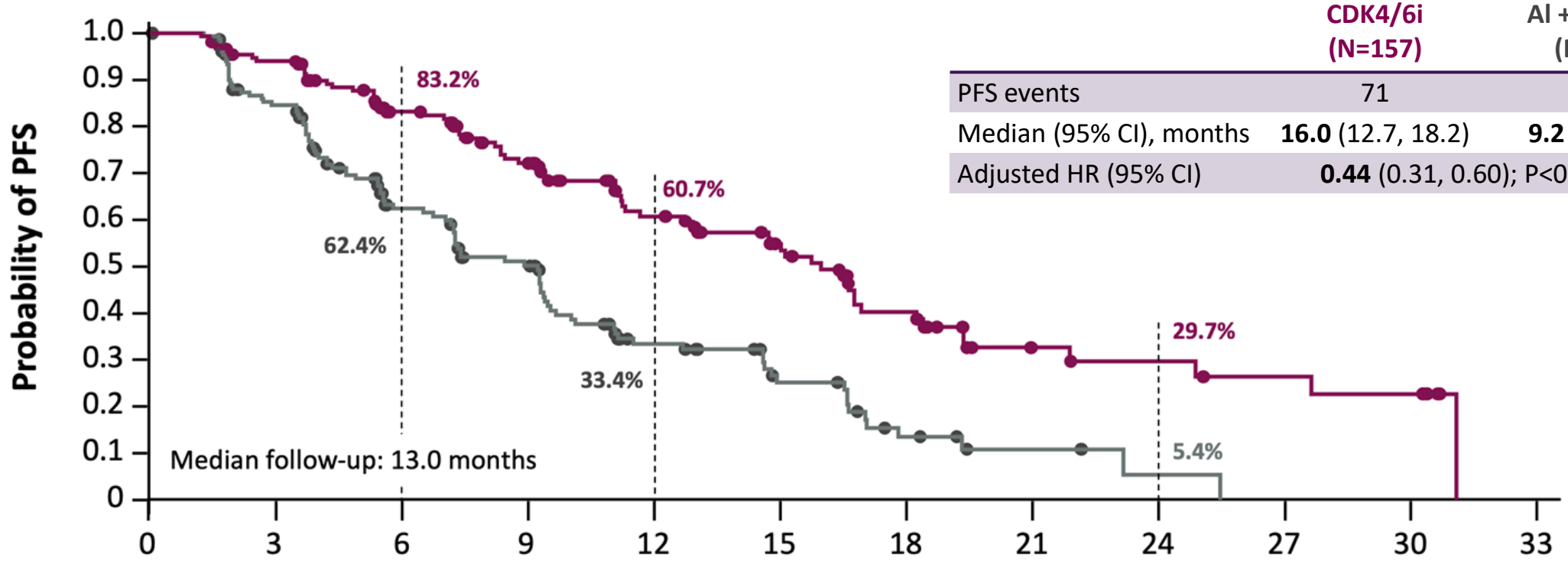
a. Data missing for 2 patients in the camizestrant + CDK4/6i arm and 3 patients in the AI + CDK4/6i arm. One patient in the AI + CDK4/6i arm had an ECOG performance status score of 2, which was a protocol deviation.
b. The 3 most prevalent *ESR1*m detected of the 11 qualifying mutations. Patients may have had more than 1 *ESR1*m.

Stratification Factors
SERENA-6

Stratification Factor		Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Sites of metastases, n (%)	Visceral	66 (42)	71 (45)
	Non-visceral	91 (58)	87 (55)
Time of *ESR1*m detection, n (%)	At first test	84 (54)	84 (53)
	At a subsequent test	73 (47)	74 (47)
Time from initiation of AI + CDK4/6i to randomization	≥18 months, n (%)	97 (62)	100 (63)
	<18 months, n (%)	60 (38)	58 (37)
	Median (range), months	23 (7-96)	23 (6-96)
CDK4/6i continued at randomization, n (%)	Palbociclib	119 (76)	119 (75)
	Ribociclib	24 (15)	23 (15)
	Abemaciclib	14 (9)	16 (10)

SERENA-6 Met Primary Endpoint (DCO1): Statistically Significant and Clinically Meaningful PFS Benefit

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS events	71	100
Median (95% CI), months	**16.0** (12.7, 18.2)	**9.2** (7.2, 9.5)
Adjusted HR (95% CI)	**0.44** (0.31, 0.60); P<0.00001	



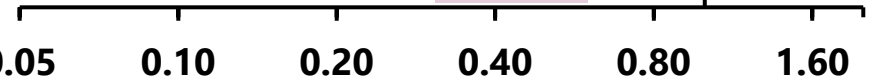
At risk, n											
Cami + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

DCO1: 28 November 2024.

Consistent PFS Benefit Across All Key Subgroups

SERENA-6 (DCO1)

	Subgroup	Camizestrant + CDK4/6i	AI + CDK4/6i	Hazard ratio (95% CI)
	All patients	71/157	100/158	**0.44** (0.31, 0.60)
Age	<65 years	44/95	67/104	**0.51** (0.34, 0.74)
	≥65 years	27/62	33/54	**0.35** (0.21, 0.59)
Race	Asian	22/39	25/34	**0.60** (0.33, 1.07)
	White	37/97	61/102	**0.39** (0.26, 0.59)
	Other	12/21	14/21	**0.39** (0.18, 0.85)
Region	Asia	19/40	28/39	**0.46** (0.25, 0.83)
	Europe	37/89	54/91	**0.41** (0.26, 0.62)
	North America	15/28	18/28	**0.57** (0.28, 1.13)
Menopausal status	Pre-/perimenopausal women, and men	14/34	18/31	**0.39** (0.19, 0.79)
	Postmenopausal	57/123	82/127	**0.46** (0.32, 0.65)
Disease site[a]	Visceral	32/65	37/64	**0.57** (0.35, 0.92)
	Non-visceral	39/92	63/92	**0.38** (0.25, 0.56)
Time from initiation of AI + CDK4/6i to randomization[a]	<18 months	28/50	29/46	**0.60** (0.35, 1.01)
	≥18 months	43/105	69/110	**0.39** (0.26, 0.58)
CDK4/6i[a]	Palbociclib	57/117	78/118	**0.45** (0.32, 0.64)
	Ribociclib	4/23	13/23	**0.27** (0.08, 0.77)
	Abemaciclib	10/15	9/15	**0.63** (0.25, 1.59)
Time of *ESR1*m detection[a]	First test	36/82	56/79	**0.32** (0.20, 0.49)
	Subsequent test	35/75	44/79	**0.64** (0.41, 0.99)
Type of *ESR1*m	D538G	29/70	52/82	**0.34** (0.21, 0.53)
	Y537S	24/61	46/60	**0.29** (0.17, 0.47)
	Y537N	13/29	18/25	**0.44** (0.21, 0.90)



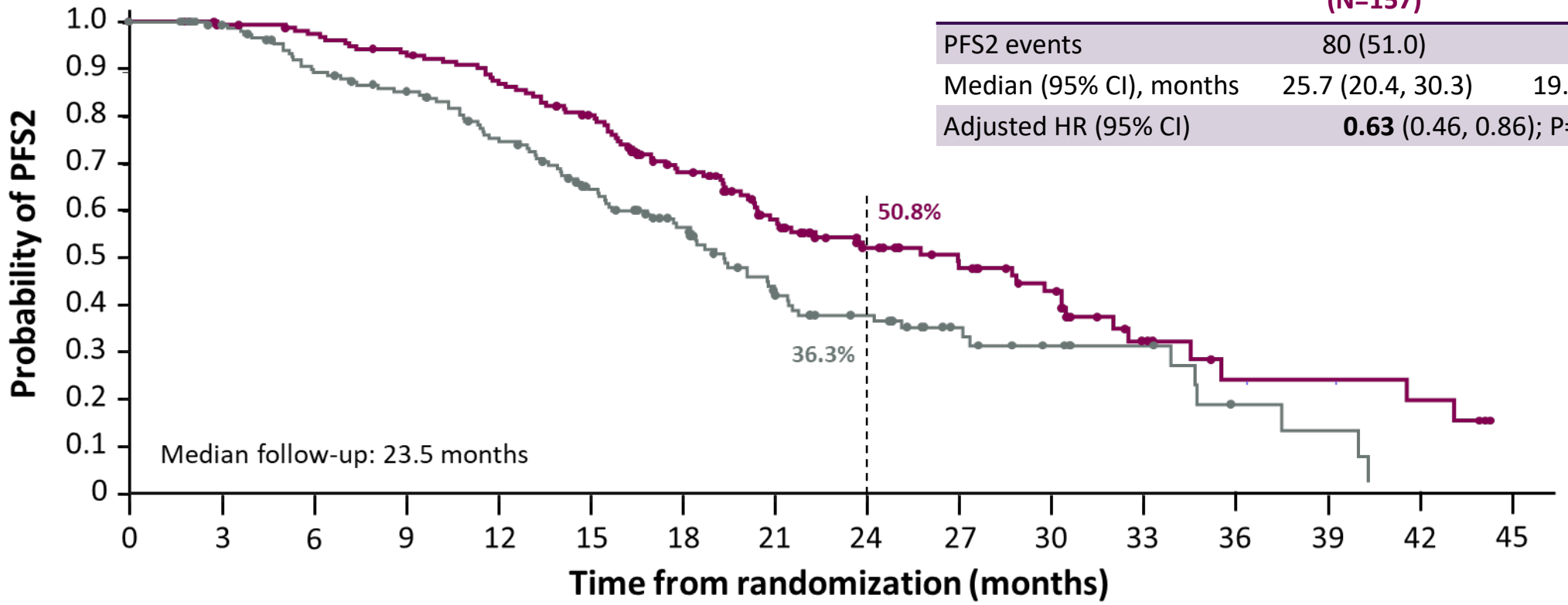
← Favors Camizestrant + CDK4/6i Favors AI + CDK4/6i →

a. Stratification factor.

Statistically Significant and Clinically Meaningful PFS2 Demonstrating Sustained Benefit

SERENA-6 (DCO3[a])

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS2 events	80 (51.0)	90 (57.0)
Median (95% CI), months	25.7 (20.4, 30.3)	19.1 (16.8, 21.0)
Adjusted HR (95% CI)	**0.63** (0.46, 0.86); P=0.0037	



At risk, n																
Cami + CDK4/6i	157	150	145	138	127	113	86	63	42	32	24	10	5	5	4	0
AI + CDK4/6i	158	149	129	120	102	82	60	40	30	17	12	8	3	2	0	0

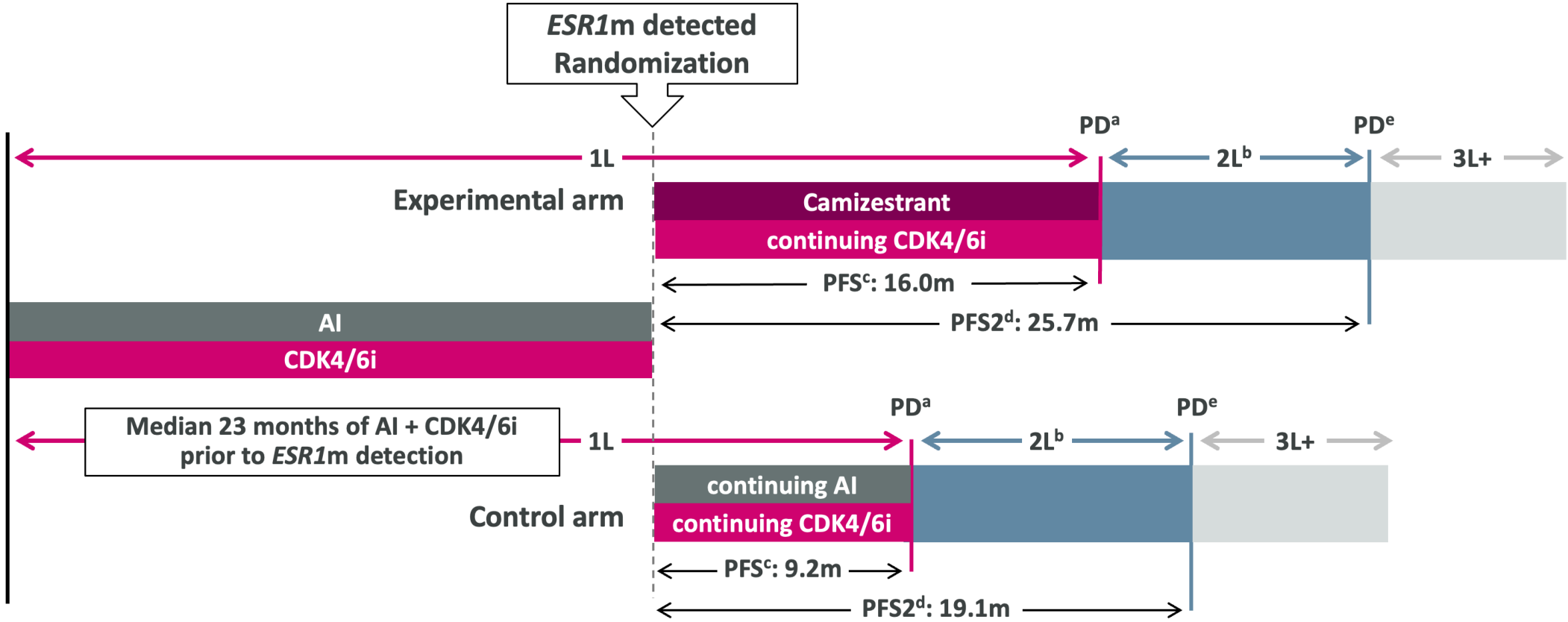
a. DCO3 is the data cutoff for the prespecified primary analysis of PFS2, per protocol.

Prespecified Analysis of PFS2 by RECIST Criteria Is Consistent With Primary PFS2 Analysis

SERENA-6 (DCO3)

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS2 events per RECIST 1.1, n	69	78
Median (95% CI), months	27.7 (22.3, 30.5)	20.8 (17.7, 25.1)
Adjusted HR (95% CI)	**0.64** (0.46, 0.90)	
Nominal P value	0.00939	

PFS Benefit Is Sustained Through PFS2

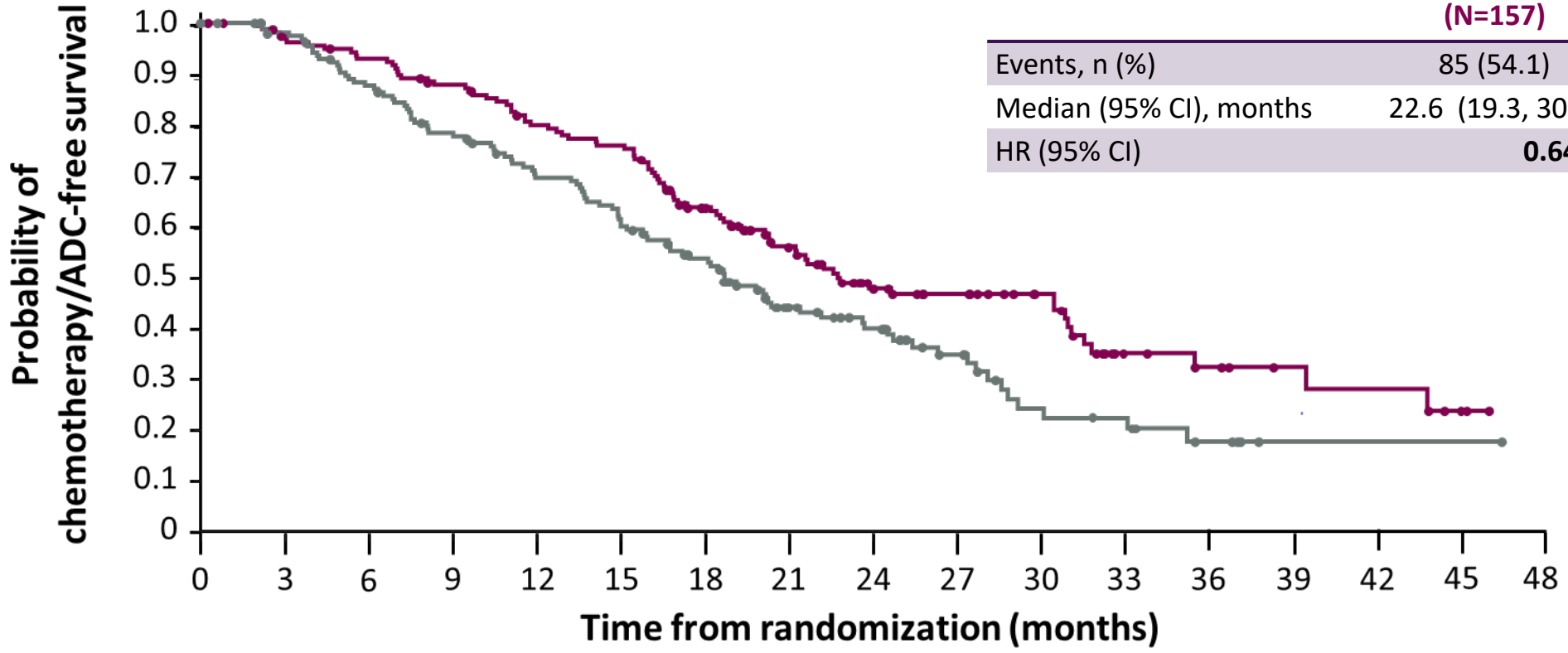


a. First progression per RECIST 1.1 by investigator assessment.
b. 2L treatment options per SoC and physician's preference (include endocrine mono- or combination with targeted therapy, or chemotherapy or ADCs).
c. Primary analysis at DCO1.
d. PFS2 defined per EMA guideline on the evaluation of anticancer medicinal products in man, primary analysis at DCO3.
e. Clinical or objective PD; 170 patients had a second progression event (PFS2) at DCO3.

Chemotherapy/ADC-Free Survival Is Prolonged

SERENA-6 (DCO3)

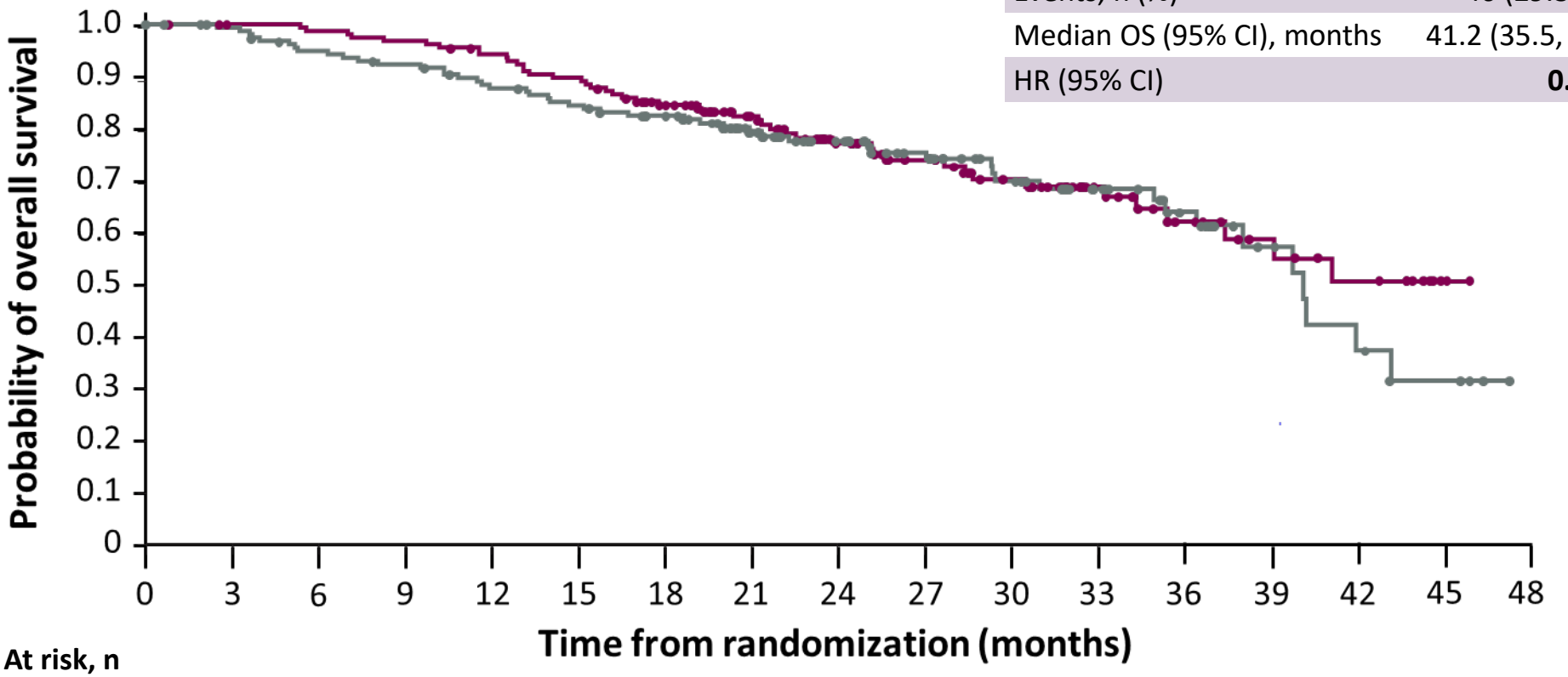
	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Events, n (%)	85 (54.1)	98 (62.0)
Median (95% CI), months	22.6 (19.3, 30.9)	18.7 (15.8, 22.1)
HR (95% CI)	**0.64** (0.47, 0.87)	



At risk, n																	
Cami + CDK4/6i	157	149	141	131	117	111	85	65	43	36	28	13	10	7	6	3	0
AI + CDK4/6i	158	149	131	115	99	85	69	45	35	22	12	10	5	1	1	1	0

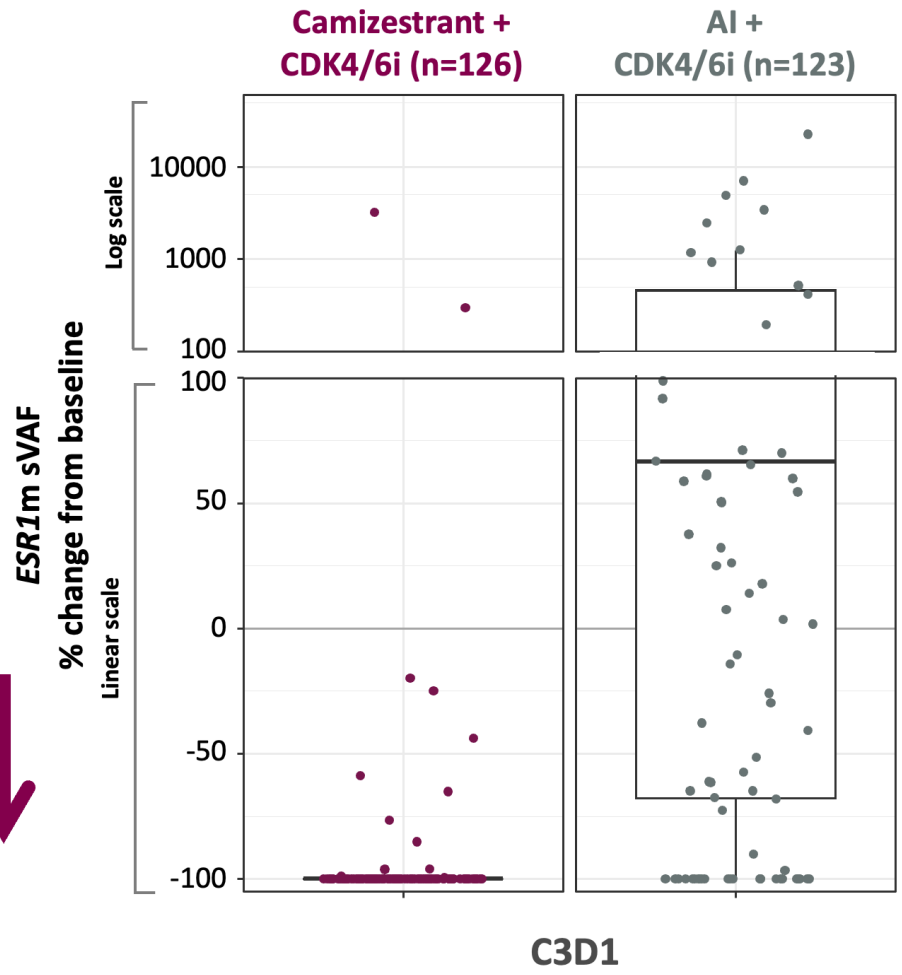
Overall Survival
SERENA-6 (DCO3)

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Events, n (%)	46 (29.3)	49 (31.0)
Median OS (95% CI), months	41.2 (35.5, NC)	40.2 (36.5, 43.3)
HR (95% CI)	**0.87** (0.57, 1.30)	



At risk, n																	
Cami + CDK4/6i	157	154	152	149	143	136	121	101	75	62	50	34	21	15	11	4	0
AI + CDK4/6i	158	153	144	139	130	124	115	92	74	61	48	35	24	12	8	4	0

Camizestrant + CDK4/6i Profoundly Reduces *ESR1*m ctDNA



Median change from baseline at C3D1 (8 weeks):

−100% (IQR: −100 to −100)

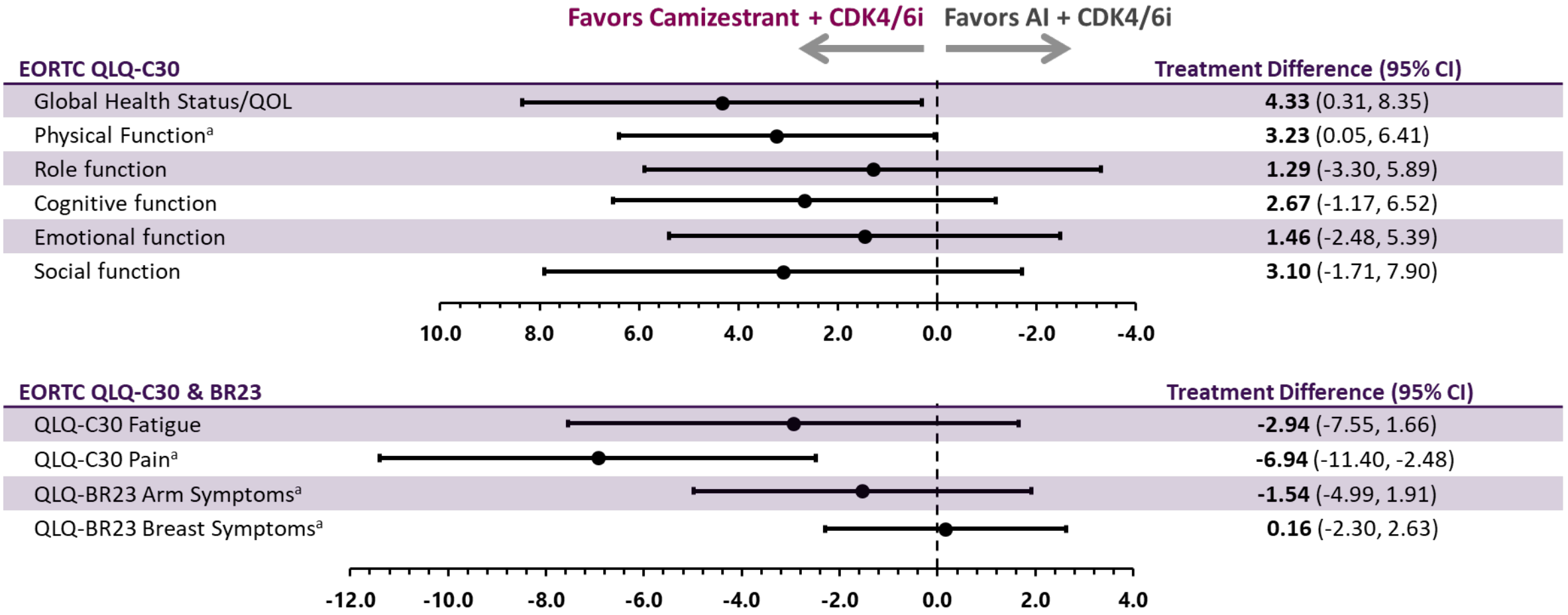
Median change from baseline at C3D1 (8 weeks):

+66.7% (IQR: −67.9 to +465.0)

C3D1=Cycle 3, Day 1; IQR=interquartile range; sVAF=summed variant allele fraction.

Patient-Reported Outcomes Favor Camizestrant

Model-Adjusted Mean Change From Baseline Over First 28 Weeks



a. Prespecified secondary endpoints.

Estimates were obtained using a mixed model repeated measures (MMRM) analysis, including treatment, visit, and treatment-by-visit interaction as exploratory variables and the baseline score and the baseline score by visit interaction as covariates. Reprinted from *Ann Oncol*, 37(2), Mayer EL, et al. Patient-reported outcomes in the SERENA-6 trial of camizestrant plus CDK4/6 inhibitor in patients with advanced breast cancer and emergent ESR1 mutations during first-line endocrine-based therapy, 180-193, Copyright 2026, with permission from Elsevier.

Summary

- SERENA-6 is an innovative study using cutting-edge technology
  - Design was aligned with the FDA and global health authorities
- Switching to camizestrant with continued CDK4/6i upon *ESR1*m detection demonstrated
  - Statistically significant and clinically meaningful 56% reduction in the risk of progression or death compared with AI + CDK4/6i (HR=0.44, P<0.00001)
    - Consistent PFS benefit across subgroups
  - Statistically significant and clinically meaningful PFS2 results (HR=0.63, P=0.0037)
  - No OS detriment (HR=0.87)
- PRO data further support the positive benefit/risk assessment

AstraZeneca

SERENA-6 Clinical Safety

Andrew Walding, MSc

Global Safety Head – Camizestrant

AstraZeneca

Safety Profile of Camizestrant 75 mg Is Well-Characterized

Completed studies provide a robust supportive safety pool (N=380)

	Camizestrant + CDK4/6i combination	Camizestrant monotherapy
Total	**263**	**117**
SERENA-1	108[a]	24[b]
SERENA-2		74
SERENA-6	155	
Japan Phase I		7
China Phase I		12

- >6000 patients exposed to camizestrant across early and advanced breast cancer
- Over 3000 patients with >1 yr exposure to camizestrant, including some with >4 yrs

SERENA-6 safety pool is of sufficient size to enable characterization of AEs

a. SERENA-1 parts C, D, G, H, K, and L.
b. SERENA-1 parts A and B.

Exposure and Dose Intensity
SERENA-6

	Camizestrant + CDK4/6i (N=155)	AI + CDK4/6i (N=155)
Median treatment exposure, months		
Camizestrant/AI	10.1	6.3
CDK4/6i	9.8	6.1
Median relative dose intensity,[a] %		
Camizestrant/AI	99.6	99.7
CDK4/6i	98.8	99.5

60% longer median exposure in camizestrant arm; no impact on the CDK4/6i dose intensity

a. Relative dose intensity is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation.

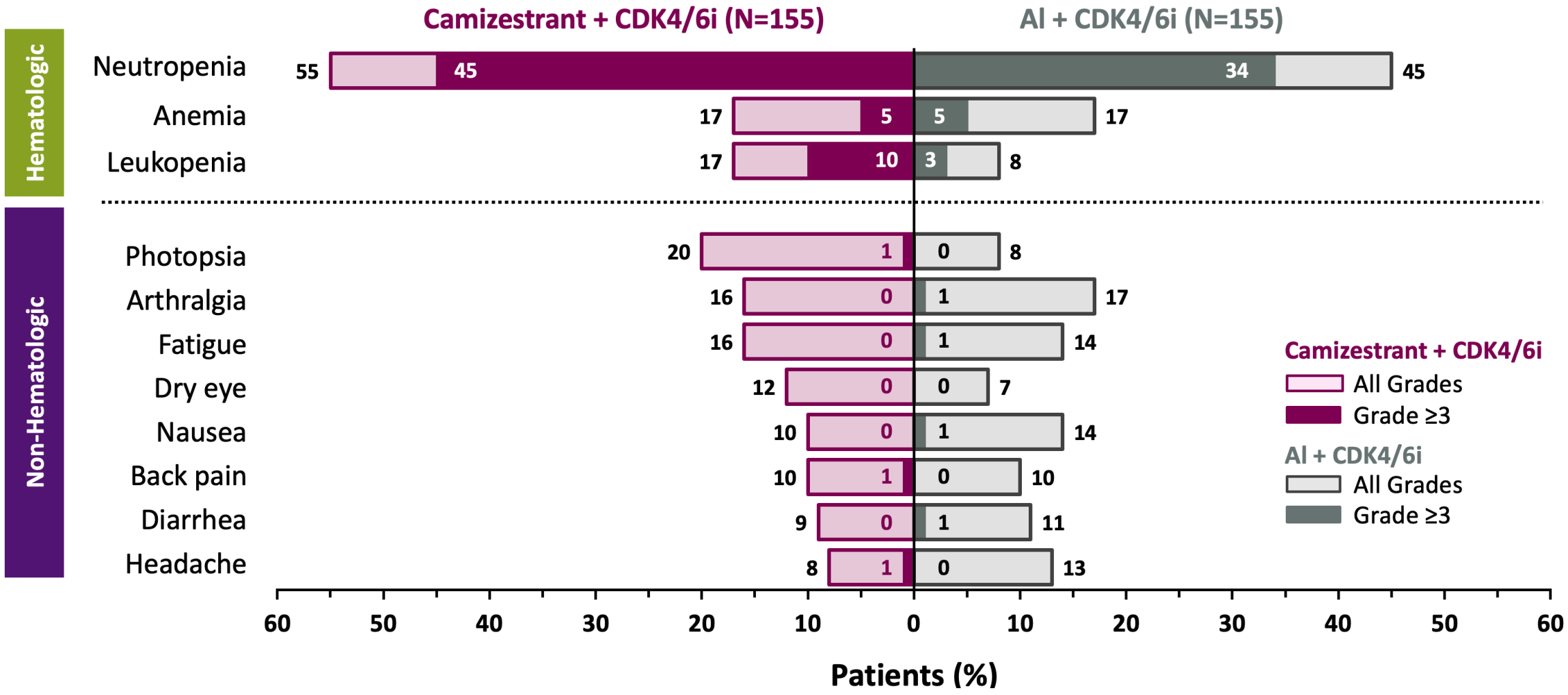
Overview of Safety Profile
SERENA-6

	Patients, n (%)	
	Camizestrant + CDK4/6i (N=155)	AI + CDK4/6i (N=155)
Any adverse event (AE)	145 (94)	135 (87)
AEs of CTCAE Grade ≥3	93 (60)	71 (46)
Serious AEs	16 (10)	19 (12)
AEs leading to death	2 (1)	1 (1)
AEs leading to discontinuation		
Camizestrant/AI	2 (1)	3 (2)
CDK4/6i	2 (1)	2 (1)
AEs leading to dose reduction		
Camizestrant/AI[a]	9 (6)	2 (1)
CDK4/6i	18 (12)	17 (11)
AEs leading to dose interruption		
Camizestrant/AI	34 (22)	22 (14)
CDK4/6i	75 (48)	53 (34)

a. Dose reductions in the AI arm apply to camizestrant placebo.

Most Common Adverse Events (≥10% of Patients) by Grade

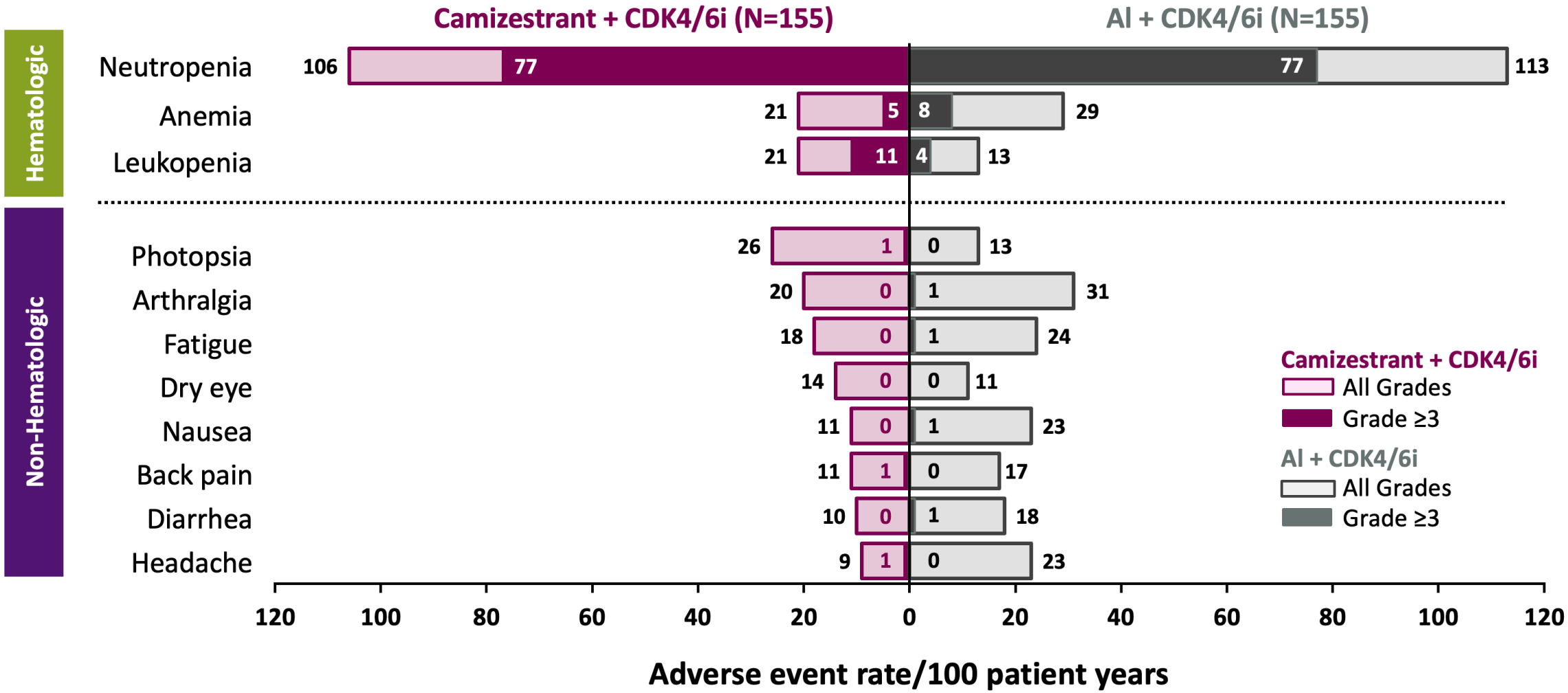
SERENA-6



Data from Bidard F-C, et al. *N Engl J Med*. 2025;393:569-580.

Exposure-Adjusted Incidence of AEs by Grade

SERENA-6



Exposure-adjusted incidence rates were calculated as the total number of patients who had an AE reported, divided by the total number of days at risk for AEs across all subjects in each arm, multiplied by 365.25 and then by 100.

ADR: Reversible, Sinus Rhythm Bradycardia

Grouped term/preferred term[a]	Patients, n (%)	
	Camizestrant + CDK4/6i (N=155)	AI + CDK4/6i (N=155)
Bradycardia[b]	**12 (7.7)**	**0**
Bradycardia	8 (5.2)	0
Sinus bradycardia	4 (2.6)	0

- Camizestrant lowers heart rate through HCN4 “pacemaker channel” in the sinoatrial node
- Median decrease in heart rate of 14 bpm from baseline to Day 15, reaching a stable nadir at that time
  - Magnitude of effect is dependent on baseline heart rate (ie, small effect for those with low baseline heart rate)
  - Heart rate recovered to baseline at the safety follow-up

a. MedDRA preferred term coded from investigator verbatim reported term.
b. Adverse Drug Reaction grouping.

Camizestrant + Ribociclib Combination

- Camizestrant monotherapy has no independent effect on QT interval at clinically relevant doses
  - High-quality clinical QTc study using 24-hr Holter monitoring, in line with international guidelines
- Mechanisms of camizestrant-mediated bradycardia and ribociclib-mediated QTc prolongation are distinct
- Camizestrant + ribociclib studied in 83 patients in SERENA-1 and SERENA-6
  - No significant QTc prolongation or arrhythmias in SERENA-6
  - 1 Grade 4 QT prolongation AE in SERENA-1
    - Event heavily confounded; ribociclib not interrupted when QTcF >550 ms, contrary to ribociclib dose-modification requirements

ADR: Reversible, Transient Peripheral Visual Effects

Grouped term/preferred term	Patients, n (%)	
	Camizestrant + CDK4/6i (N=155)	AI + CDK4/6i (N=155)
Visual effects[a]	**49 (31.6)**	**25 (16.1)**
Photopsia	31 (20.0)	12 (7.7)
Vision blurred	11 (7.1)	11 (7.1)
Visual impairment	6 (3.9)	3 (1.9)
Diplopia	3 (1.9)	2 (1.3)
Photophobia	3 (1.9)	0
Visual perseveration	2 (1.3)	0

- Mostly (~90%) Grade 1 with few (2.6%) dose interruptions
- Early onset, reversible, non-structural effect
- Comprehensive ocular exams[b] showed
  - No evidence of structural effects on the eye
  - No change in visual acuity or visual fields attributed to camizestrant

a. Adverse Drug Reaction grouping.
b. Comprehensive visual exams included assessment of visual field, best corrected distance visual acuity, intraocular pressure, optical coherence tomography (OCT), and fundoscopy.

Summary of Safety

- Camizestrant + CDK4/6 inhibitor demonstrated a favorable safety profile
- Well-tolerated, with a low treatment discontinuation rate due to AEs
- Safety profile of camizestrant + CDK4/6 inhibitor combination is consistent with clinical experience of camizestrant and each CDK4/6 inhibitor
- Despite longer exposure on the camizestrant arm, patients report that AEs were not bothersome, with no or minimal impact of AEs on activities of daily living

Clinical Perspective

Kevin Kalinsky, MD, MS, FASCO

Emory University School of Medicine

Director of the Glenn Family Breast Center at Winship Cancer Center

Patient Case

45-year-old female diagnosed with *de novo* metastatic breast cancer to bone only

June 2021

Bone biopsy:
ER 99% PgR 79%
HER2-negative

ctDNA at baseline:
no actionable mutation

Lupron + letrozole + ribociclib + denosumab

June 2024

Clinical progression:
New back pain with T4 lesion, received xRT for 5 fractions

ctDNA at progression:
ESR1 mutation

Several options discussed:
- Single-agent oral SERD
- Fulvestrant + everolimus
- Fulvestrant + abemaciclib

She opted for fulvestrant + abemaciclib

Patient Concerns and Treatment Goals

> I have been checking monthly tumor markers (CEA, CA15-3, CA27-29), but these always remained normal for me.

> I was doing scans every 3-4 months.

> What other tests could I have done to detect a change before I developed back pain?

Treatment goals important to my patients

- Delay disease progression
- Palliate disease symptoms
- Delay need for chemotherapy
- Prolong survival
- Maintain good quality of life

Why I Would Incorporate the SERENA-6 Approach

SERENA-6 is a positive study, demonstrating a favorable benefit/risk

Disease Biology

- *ESR1*m is a key driver of AI resistance and is actionable
- Tumors are most sensitive to endocrine therapy before clinical progression

Extend Benefit of 1L Therapy

- 56% reduction in risk of progression/death
- Extended benefit of 1L ET + CDK4/6i
- Maximizes time on well-tolerated endocrine therapy

Delay IV Treatment

- Chemotherapy and ADC often more toxic
- Time in the infusion center can be burdensome

Maintain QoL

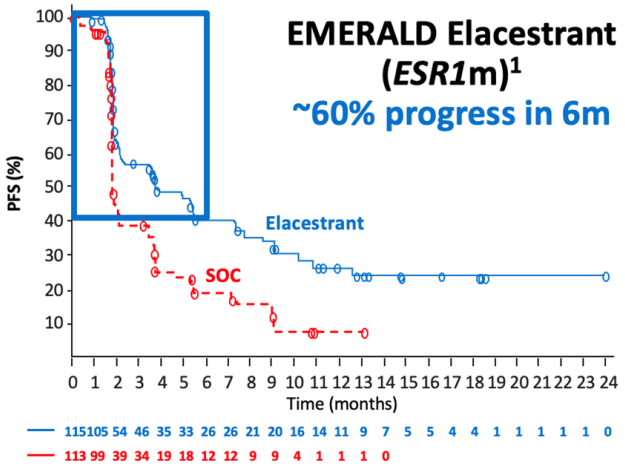
- Delayed onset of disease-related symptoms (eg, pain) and decline in physical function and emotional well-being

Disease Biology: Tumors Most Sensitive to ET Before Clinical Progression

Approved 2L Novel SERD MonoTx

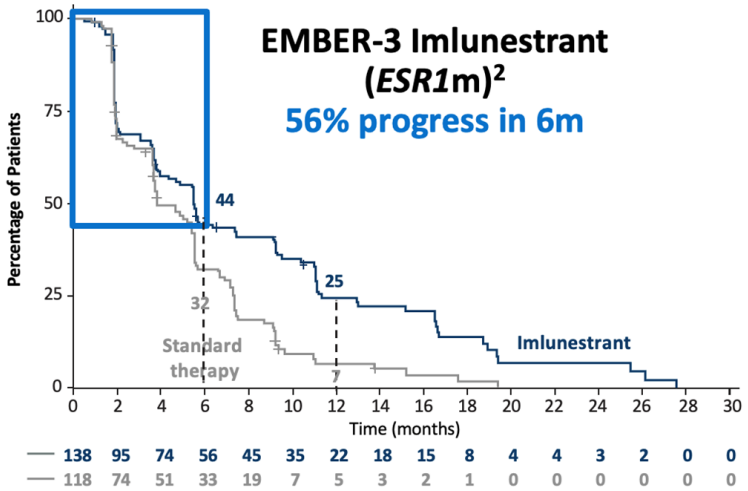
EMERALD Elacestrant (*ESR1*m)[1]

~60% progress in 6m



EMBER-3 Imlunestrant (*ESR1*m)[2]

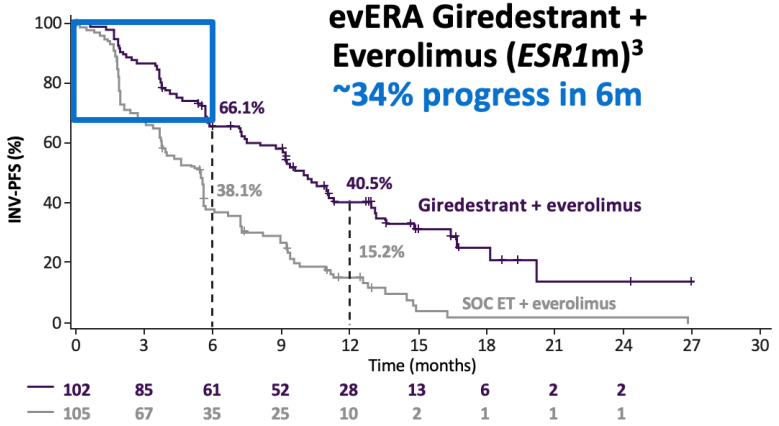
56% progress in 6m



Data from 2L Novel SERD Combos (Unapproved)

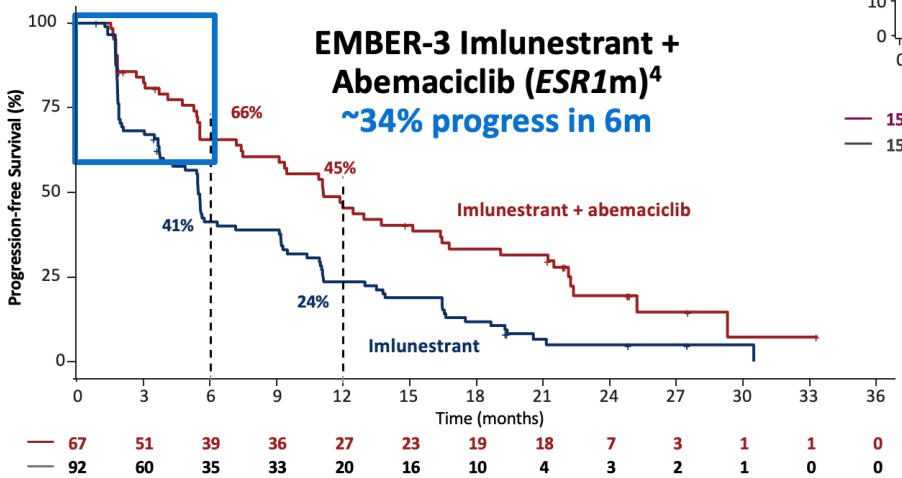
evERA Giredestrant + Everolimus (*ESR1*m)[3]

~34% progress in 6m



EMBER-3 Imlunestrant + Abemaciclib (*ESR1*m)[4]

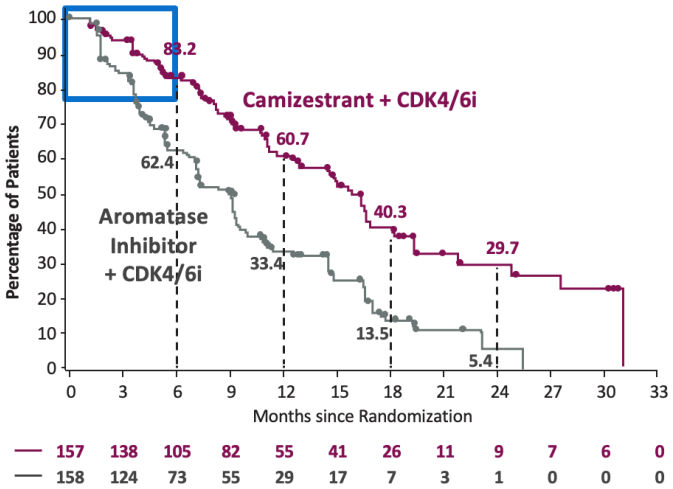
~34% progress in 6m



1L ET-Switch to camizestrant

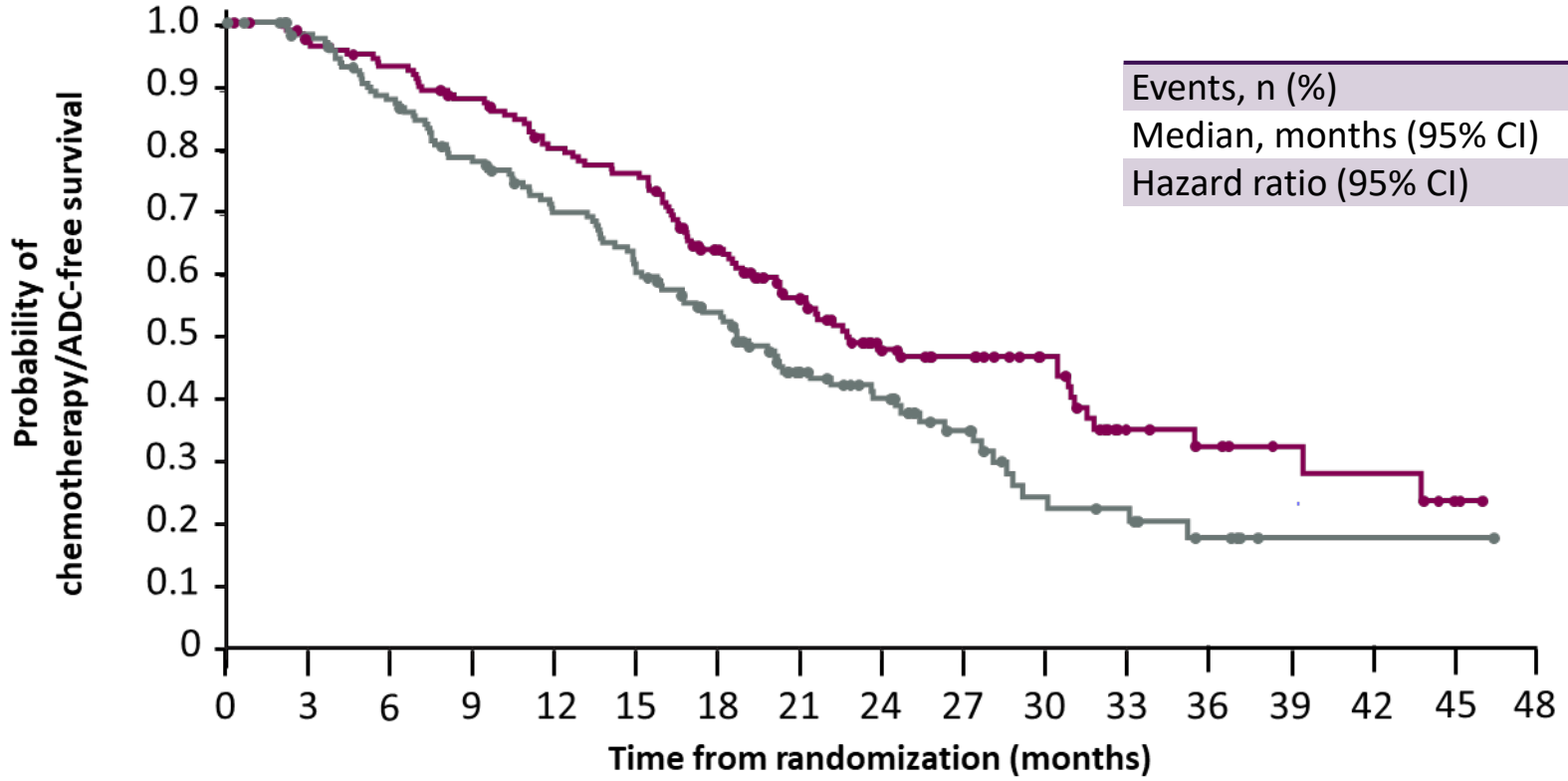
SERENA-6 Camizestrant + CDK4/6i (*ESR1*m)[5]

17% progress in 6m



1. Bidard F-C, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol* (an American Society of Clinical Oncology journal). 2022;40(28):3246-3256, https://ascopubs.org/doi/10.1200/JCO.22.00338?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed; 2. Reprinted from *N Engl J Med*. Jhaveri KL, et al. Imlunestrant with or without abemaciclib in advanced breast cancer: updated efficacy results from the phase III EMBER-3 trial, 392(12), 1189-1202, Copyright 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; 3. Reprinted with permission from Mayer E, et al. ESMO 2025. Abstract LBA16; 4. Reprinted from *Ann Oncol*, 37(4), Jhaveri KL, et al. Imlunestrant with or without abemaciclib in advanced breast cancer: updated efficacy results from the phase III EMBER-3 trial, 532-543, Copyright 2026, with permission from Elsevier; 5. Reprinted from *N Engl J Med*, Bidard F-C, et al. First-line camizestrant for emerging ESR1-mutated advanced breast cancer, 393, 569-580, Copyright 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Prolonging Chemotherapy/ADC-Free Survival



	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Events, n (%)	85 (54.1)	98 (62.0)
Median, months (95% CI)	22.6 (19.3, 30.9)	18.7 (15.8, 22.1)
Hazard ratio (95% CI)	**0.64** (0.47, 0.87)	

IV Chemotherapy/ADC-Free Survival

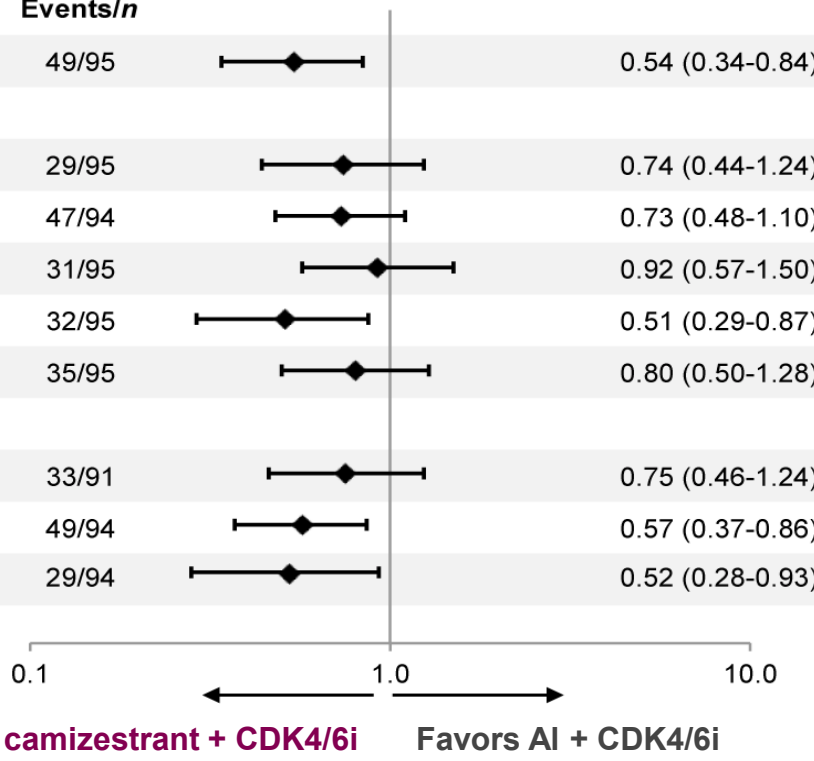
HR 0.71 (95% CI: 0.51, 0.99)

At risk, n																	
Cami + CDK4/6i	157	149	141	131	117	111	85	65	43	36	28	13	10	7	6	3	0
AI + CDK4/6i	158	149	131	115	99	85	69	45	35	22	12	10	5	1	1	1	0

Delaying Time to Deterioration in Patient-Reported EORTC QLQ-C30 Symptoms, Function, and QoL

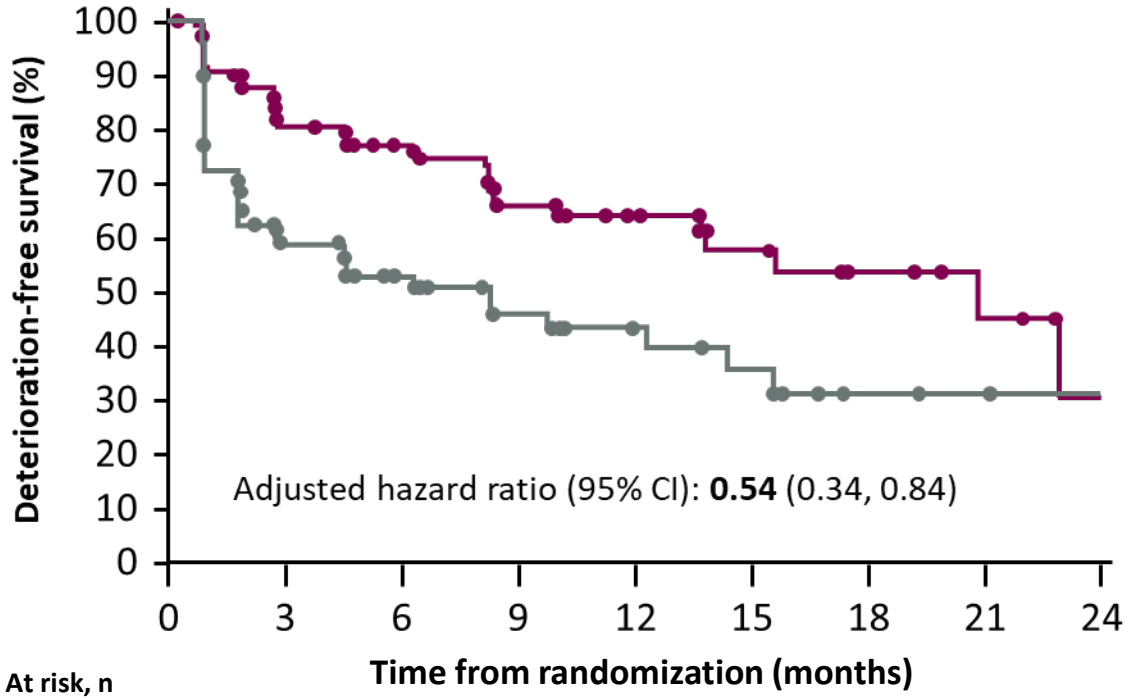
Pre-specified meaningful change thresholds

	Camizestrant-CDK4/6 inhibitor Events/*n*	AI-CDK4/6 inhibitor Events/*n*	Hazard ratio (95% CI)
GHS/QoL	37/107	49/95	0.54 (0.34-0.84)
Functional domains			
Physical	33/108	29/95	0.74 (0.44-1.24)
Role	48/108	47/94	0.73 (0.48-1.10)
Cognitive	38/107	31/95	0.92 (0.57-1.50)
Emotional	25/107	32/95	0.51 (0.29-0.87)
Social	39/107	35/95	0.80 (0.50-1.28)
Symptom domains			
Fatigue	34/104	33/91	0.75 (0.46-1.24)
Pain	42/106	49/94	0.57 (0.37-0.86)
Shortness of breath/dyspnoea	21/105	29/94	0.52 (0.28-0.93)



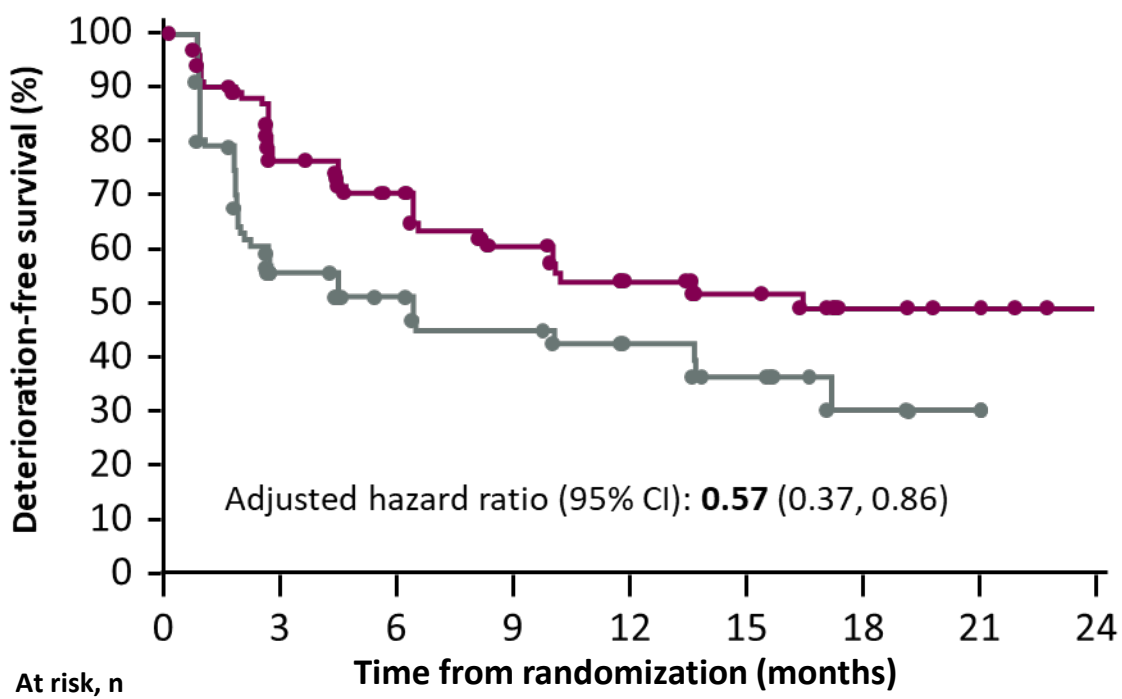
Delaying Time to Deterioration in Patient-Reported EORTC QLQ-C30 Global Health Status/QoL and Pain

Global Health Status/QoL



At risk, n									
Cami + CDK4/6i	107	72	59	40	24	16	9	5	2
AI + CDK4/6i	95	42	27	17	11	8	3	2	1

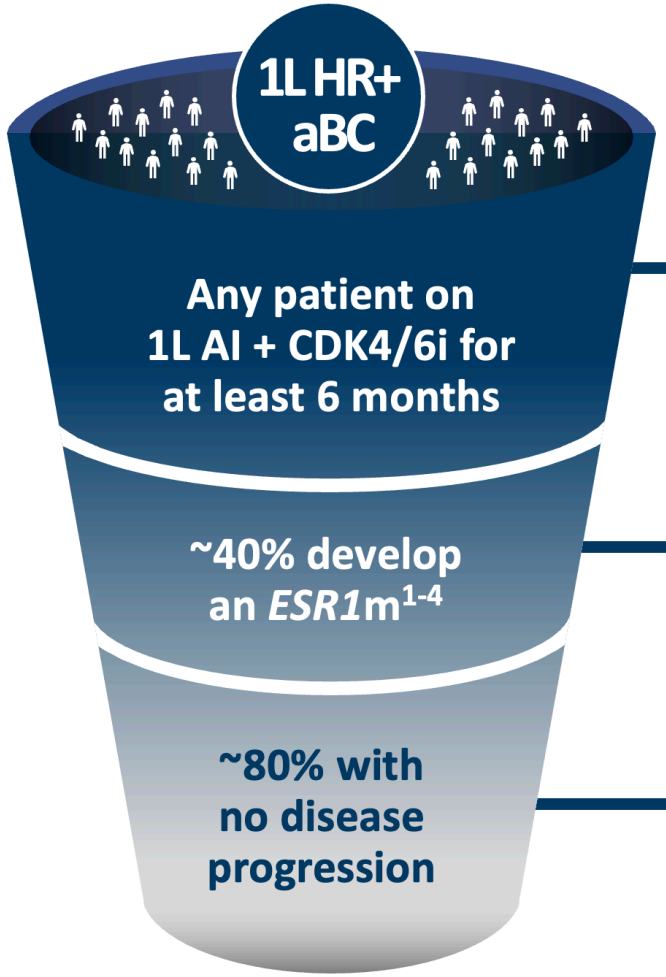
Pain



At risk, n									
Cami + CDK4/6i	106	67	54	39	30	21	11	9	6
AI + CDK4/6i	94	39	26	21	14	10	4	2	0

The analysis population is a subset of the full analysis set and includes all randomized patients with a baseline score that would allow deterioration, plus at least 1 evaluable post-baseline assessment.

Taking Action to Stay Ahead of Progression in Patients Suitable for the SERENA-6 Approach



Test for *ESR1*m as part of routine blood work

***ESR1*m detected: check for disease progression**

Benefit from switch to camizestrant while maintaining CDK4/6i in first-line

1. Bidard F-C, et al. *N Engl J Med*. 2025;393:569-580; 2. Bidard F-C, et al. *J Clin Oncol*. 2022;40(28):3246-3256; 3. Bhave MA. *Breast Cancer Res Treat*. 2024;207(3):599-609; 4. Chaudhary N. *NPJ Breast Cancer*. 2024;10(1):15.

I Would Recommend the SERENA-6 Approach to My Patients

SERENA-6 trial demonstrated a positive benefit/risk, and this paradigm shift addresses patients' treatment goals

Switching to camizestrant + CDK4/6i at emergence of *ESR1*m

- ☑ Prolongs 1L ET+CDK4/6i by 7 months
- ☑ 1/3 pts progression-free at 2 years
- ☑ Extends overall time on endocrine therapies
- ☑ Delays need for chemotherapy/ADCs
- ☑ Delays deterioration in QoL
- ☑ Well-tolerated

Encourages more active patient engagement

- Easy to implement
- Empowers patients to adjust treatment before disease progression or worsening symptoms

AstraZeneca

Concluding Remarks

Ingrid Mayer, MD, MSCI

VP, Global Clinical Strategy Head, Breast/GYN Cancers

Late Development Oncology, Research & Development

AstraZeneca

SERENA-6: A New Treatment Paradigm for *ESR1*m HR+ HER2- Advanced Breast Cancer

Positive Benefit/Risk for Patients