Novel Agents for ER+ Disease

Kevin Kalinsky, MD, MS, FASCO
Professor of Medicine
Director, Division of Medical Oncology
Director, Glenn Family Breast Center
Louisa and Rand Glenn Family Chair in Breast Cancer Research

Declaration of interests

Kevin Kalinsky, MD, MS, FASCO

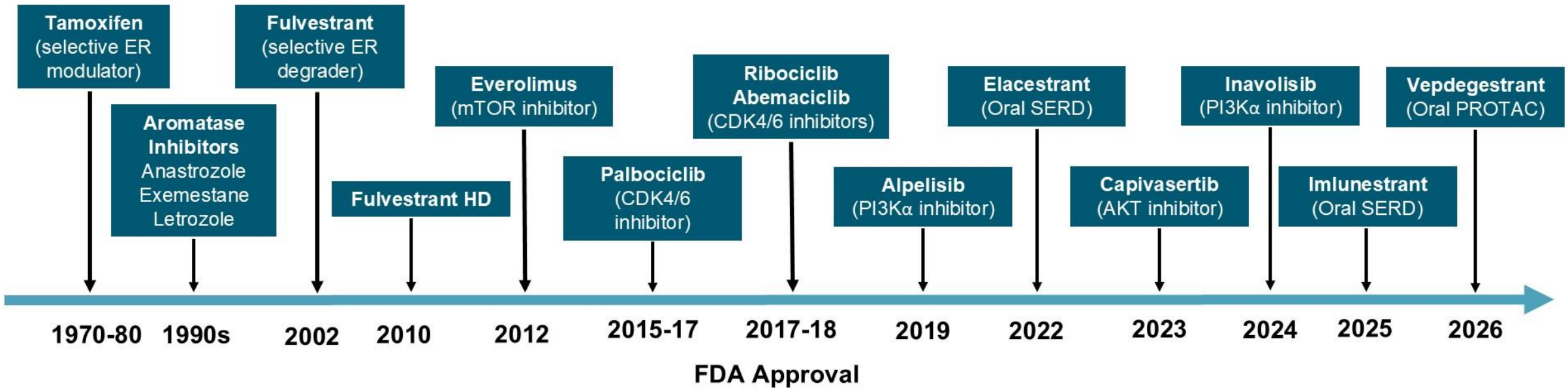
Consultant:

Genentech/Roche, Immunomedics, Seattle Genetics, AstraZeneca, Daiichi Sankyo, Puma Biotechnology, Mersana, Menarini Silicon Biosystems, Myovant Sciences, Takeda, Merck

Employee:

Spouse: EQRX (Prior Employee), ADC Therapeutics

Evolving *Hormonal* Treatment Landscape of HR+ Advanced MBC



CDK 4/6i: PFS and OS in First Line Metastatic Trials

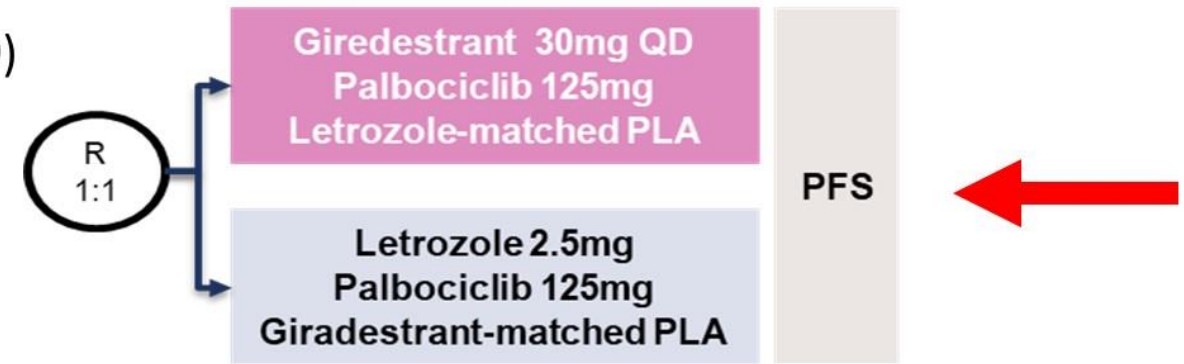
Trial	N=	CDK4/6i	Endocrine Therapy	Design	PFS - Median (Months)	OS – Median (Months)
PALOMA 1	**165**	**Palbociclib (P)**	Letrozole (L)	Phase II	**10.2 (L)** vs **20.2 (L+P)** HR 0.49; (95% CI 0.32–0.75)	**33.3 (L)** vs **37.5 (P+L)** HR 0.81 (95% CI 0.49-1.35)
PALOMA 2	**666**	**Palbociclib (P)**	Letrozole (L)	Phase III	**14.5 (L)** vs **24.8 (L+P)** HR 0.58; (95% CI, 0.46 to 0.72)	**51.2 (L)** vs **53.9 (P+L)** HR 0.96 (95% CI, 0.78 to 1.18)
MONARCH 3	**493**	**Abemaciclib (A)**	NSAI	Phase III	**14.7 (A)** vs **NR (ET+ A)** HR 0.54; (95% CI, 0.41 to 0.72)	**53.7 (AI)** vs **66.8 (AI + A)** HR 0.80; (95% CI 0.64-1.02)
MONALEESA 2	**668**	**Ribociclib (R)**	Letrozole (L)	Phase III	**16.0 (L)** vs **NR (L+R)** HR 0.56; (95% CI, 0.43 to 0.72)	**51.4 (L)** Vs **63.9 (R+L)** HR 0.76, (95% CI 0.63 to 0.93)
MONALEESA 7	**672**	**Ribociclib (R)**	ET (Tam or AI) + OFS	Phase III	**13.0 (ET)** vs **23.8 (R+ET)** HR 0.55; (95% CI 0.44-0.69)	**48.0 (ET) vs 58.7 (ET+Rib)** HR 0.71; (95% CI, 0.54 to 0.95)

Finn. *Lancet Oncol* 2014
Finn *NEJM* 2016 and Slamon *J Clin Oncol* 2024
Goetz *J Clin Oncol* 2017 and Goetz *Annals of Oncology* 2024
Hortobagyi *NEJM* 2016 and Hortobagyi *NEJM* 2022
Tripathy *Lancet Oncol* 2018 and Im *NEJM* 2019

Trials of Oral SERDs combined with CDK4/6i in the 1st-Line Endocrine Sensitive HR+/HER2- Metastatic Setting

persevERA (NCT04546009)

- ER+/HER2- LA/ABC
- No prior systemic tx for ABC
- N=992



SERENA-4 (NCT04711252)

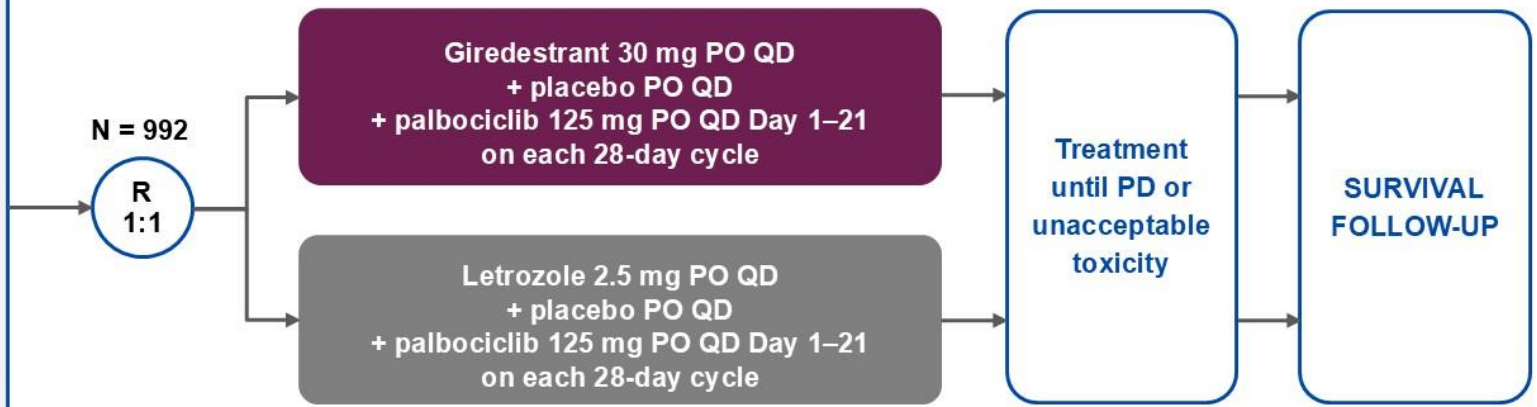
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC
- n=1342

persevERA BC study design

A Phase III, randomized, double-blind, placebo-controlled, multicenter trial in 1L LA/mBC

Key eligibility criteria:

- 1L ER+, HER2– LA/mBC*
- Locally confirmed histologic/cytologic diagnosis
- No prior treatment for advanced disease
- No prior treatment with a SERD
- Disease recurrence > 12 months from completing prior (neo)adjuvant tamoxifen/AI
- Disease recurrence ≤ 12 months for patients receiving (neo)adjuvant tamoxifen (protocol v1)
- No active cardiac disease or history of cardiac dysfunction



* Patients with *de novo* mBC were capped at 20%

Stratification factors:

- Site of disease: Visceral vs non-visceral
- Menopausal status: Post-menopausal vs pre-menopausal/male
- Region: North America vs Western Europe vs Asia–Pacific vs other
- TFI since the end of prior (neo)adjuvant therapy: *De novo* metastatic vs ≤ 12 months vs > 12 months

Primary endpoint:

- Investigator-assessed PFS (INV-PFS) per RECIST v1.1

Secondary endpoints:

- OS, ORR, CBR, DoR, safety, PROs (TTD of pain, physical functioning, role functioning, GHS/QoL)

Enrollment: October 9, 2020, to March 27, 2023. ER+ was defined as ≥ 1% positive cells by immunohistochemistry. Pre-menopausal women, and men, also received ovarian function suppression with an approved luteinizing hormone-releasing hormone agonist. 1L, first line; AI, aromatase inhibitor; CBR, clinical benefit rate; DoR, duration of response; ER+, estrogen receptor-positive; GHS/QoL, global health status/quality of life; HER2–, HER2-negative; (LA/m)BC, (locally advanced/metastatic) breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PO, orally; PRO, patient-reported outcome; QD, once daily; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumours; SERD, selective estrogen receptor antagonist and degrader; TFI, treatment-free interval; TTD, time to deterioration.
ClinicalTrials.gov number, NCT04546009. Adapted from Turner NC, *et al.* ASCO 2021 (TPS1103), with permission.

PRESENTED BY: Nicholas C. Turner, MD, PhD

Patient demographics and baseline characteristics

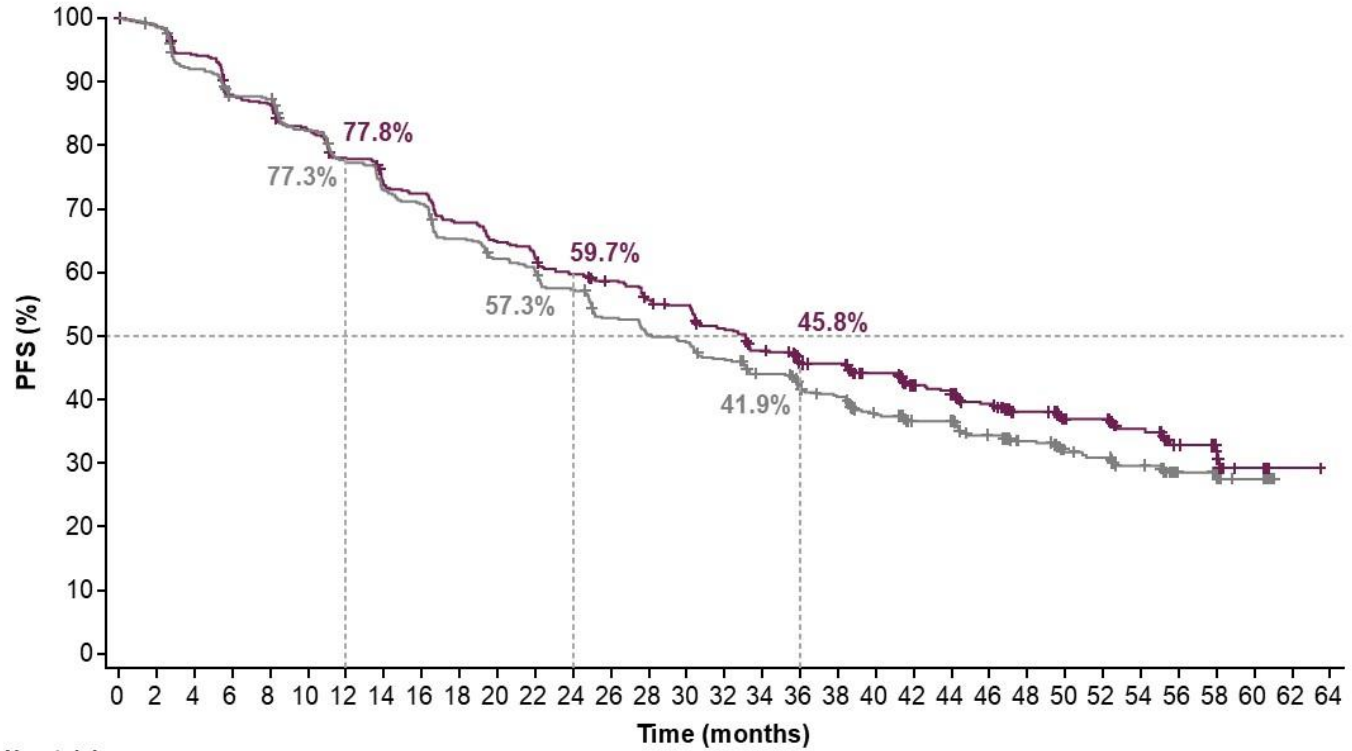
	Giredestrant + palbociclib n = 495	Letrozole + palbociclib n = 497
Median age, years (range)	63.0 (26–87)	63.0 (30–89)
Female sex, n (%)	491 (99.2)	493 (99.2)
Race, n (%)		
American Indian or Alaska Native	33 (6.7)	23 (4.6)
Asian	139 (28.1)	136 (27.4)
Black or African American	8 (1.6)	11 (2.2)
Other*	19 (3.8)	22 (4.4)
White	296 (59.8)	305 (61.4)
Region, n (%)†		
Asia–Pacific	137 (27.7)	135 (27.2)
North America	65 (13.1)	66 (13.3)
Western Europe	121 (24.4)	124 (24.9)
Other	172 (34.7)	172 (34.6)
Menopausal status, n (%)†		
Pre-/peri-menopausal	97 (19.6)	91 (18.3)
Post-menopausal	393 (79.4)	402 (80.9)
Male	4 (0.8)	4 (0.8)
Missing	1 (0.2)	0
ER status, n (%)		
Low-positive (1–10% of cells)	6 (1.2)	12 (2.4)
Positive (> 10% of cells)	487 (98.4)	485 (97.6)
Unknown	2 (0.4)	0

	Giredestrant + palbociclib n = 495	Letrozole + palbociclib n = 497
PgR status, n (%)		
Positive	412 (83.2)	390 (78.5)
Negative	81 (16.4)	104 (20.9)
Unknown	2 (0.4)	3 (0.6)
TFI since end of (neo)adjuvant therapy, n (%)†		
≤ 12 months‡	51 (10.3)	53 (10.7)
> 12 months	341 (68.9)	346 (69.6)
No prior therapy	103 (20.8)	98 (19.7)
Site of disease, n (%)†		
Visceral	301 (60.8)	298 (60.0)
Non-visceral	194 (39.2)	199 (40.0)
Bone only involvement, n (%)	42 (8.5)	47 (9.5)
Previous (neo)adjuvant treatment, n (%)	392 (79.2)	399 (80.3)
Previous (neo)adjuvant chemotherapy, n (%)	300 (60.6)	285 (57.3)
Previous (neo)adjuvant ET, n (%)		
AI only	173 (34.9)	162 (32.6)
Tamoxifen only	102 (20.6)	112 (22.5)
AI + tamoxifen	108 (21.8)	119 (23.9)

Baseline demographics and characteristics were balanced between arms

Data cutoff: January 30, 2026.
* "Other" refers to "Multiracial", "Native Hawaiian or Other Pacific Islander", or "unknown". † Per electronic case report form. ‡ Recurrence ≤ 12 months on prior adjuvant tamoxifen.
AI, aromatase inhibitor; ER, estrogen receptor; ET, endocrine therapy; PgR, progesterone receptor; TFI, treatment-free interval.

Primary endpoint: INV-PFS



No. at risk

Giredestrant + palbociclib	495	484	461	429	422	399	375	353	347	325	310	298	285	276	261	255	236	217	195	190	170	149	142	130	108	88	86	65	42	27	14	1
Letrozole + palbociclib	497	484	449	424	422	394	369	349	338	311	295	286	271	248	236	230	217	200	186	176	156	141	139	119	103	78	75	62	36	27	11	

	Giredestrant + palbociclib n = 495	Letrozole + palbociclib n = 497
Events, n (%)	300 (60.6)	323 (65.0)
Median, months (95% CI)	**33.1** (30.2, 38.3)	**28.2** (25.0, 33.1)
Stratified HR (95% CI)	**0.89** (0.76, 1.05); p = 0.1553	

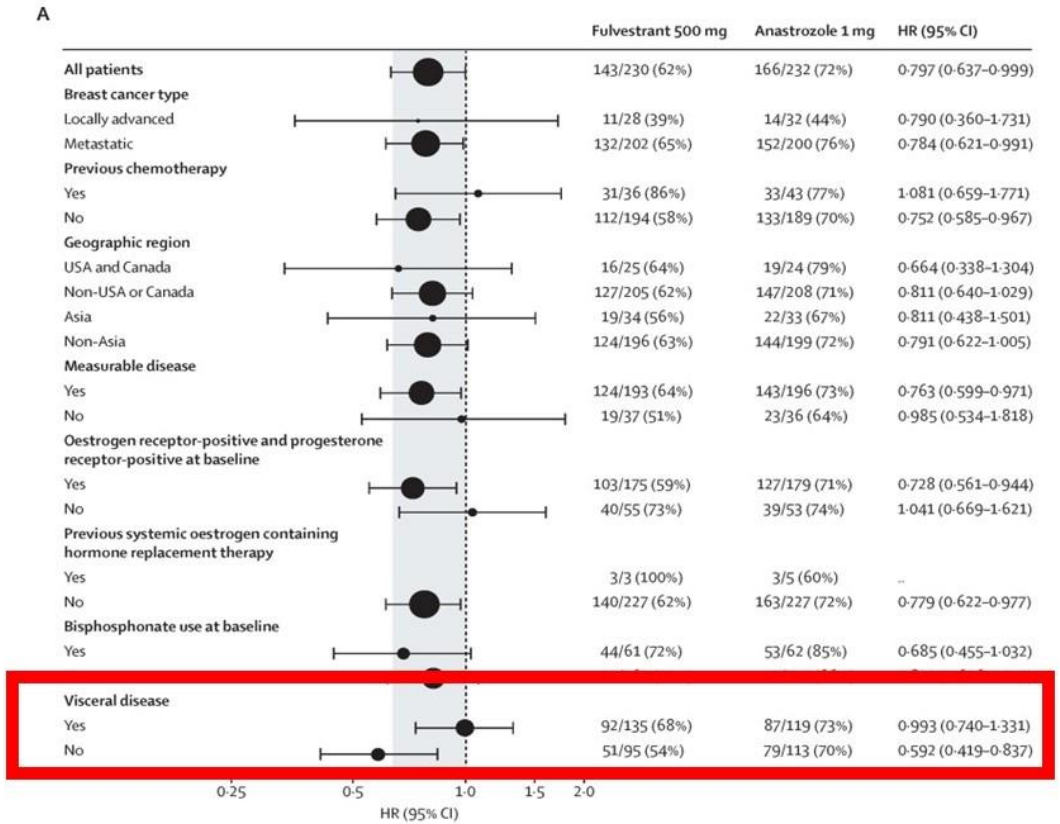
Median follow-up
Giredestrant arm: 52.2 months (range: 0.4–63.5)
Letrozole arm: 52.1 months (range: 0.3–62.6)

Giredestrant + palbociclib demonstrated a numerical improvement in INV-PFS vs letrozole + palbociclib, despite the lack of statistical significance

Data cutoff: January 30, 2026. The boundary for statistical significance was HR 0.85; 2-sided p < 0.0456.
CI, confidence interval; HR, hazard ratio; (INV-)PFS, (investigator-assessed) progression-free survival.

Outcomes in FALCON and PersevERA by Visceral/non-Visceral Status

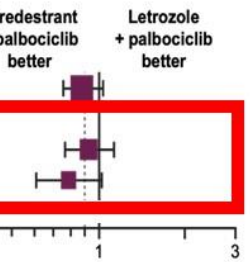
48% of FALCON patients had non-visceral mets



HR 0.59 (0-42-0.84) vs. 0.99 (0-74-1-33)

39% of PersevERA patients had non-visceral mets

Baseline risk factors	Total n	Giredestrant + palbociclib n = 495 n	Median (months)	Letrozole + palbociclib n = 497 n	Median (months)	HR	95% Wald CI
All patients	992	495	33.1	497	28.2	0.89	(0.76, 1.04)
Site of disease							
Visceral	599	301	27.9	298	25.2	0.94	(0.77, 1.15)
Non-Visceral	393	194	44.0	199	32.0	0.80	(0.62, 1.04)



HR 0.80 (0-62-1.04) vs. HR 0.94 (0-77-1.15)

Hypothesis: Patients with non-visceral disease (e.g. bone) may be:

1) More likely to derive benefit from SERDs vs AIs
2) More likely to develop *ESR1* mutations[1]

PADA-1 Cabel et al *Annals of Oncology* 2025

Prevalence of *ESR1* Mutations in Untreated vs Treated ER+/HER2- mBC

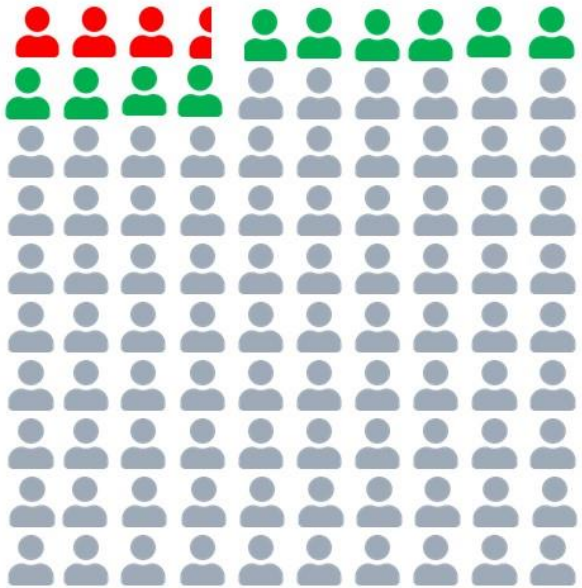
Treatment Setting	*ESR1* Mutation Prevalence[1-5]
At Initiation of First-Line ET	~5%
Second-Line	~33%
Third-Line	Up to 40%

1. Jeselsohn R et al. *Clin Cancer Res* 2014;20:1757-1767; **2.** Jeselsohn R et al. *Cancer Cell* 2018;33:173-186; **3.** Allouchery V et al. *Breast Cancer Res* 2018;20:40;
4. Schiavon G et al. Sci Transl Med 2015;7(313):313ra182; **5.** Brett JO et al. *Breast Cancer Res* 2021;23(1):85.

SERENA 6 Consort Diagram (Strategy)

SERENA-6
***ESR1* Mutation Screening every 2-3 months for years**

3256 Patients tested



548 with an *ESR1* Mutation
Cumulative incidence of *ESR1* mutations approx. 20% at 2 years[1]

117 had an *ESR1* mutation and radiographic progression. These patients went off study

315 had an *ESR1* mutation without radiographic progression and eligible for randomization

R

Switch to camizestrant and continue CDK 4/6

mPFS: 16.8 months

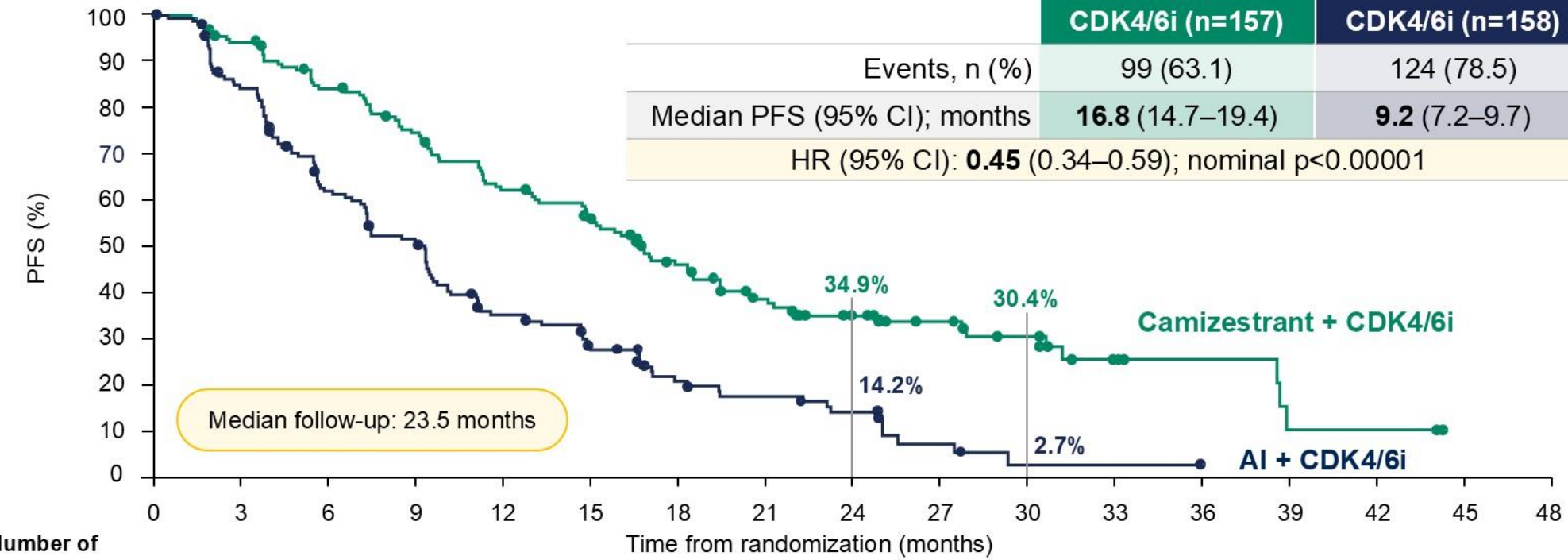
Continue SOC (AI plus CDK 4/6i)

mPFS: 9.2 months

Updated PFS (primary endpoint, investigator-assessed)

With longer follow-up, median PFS improvement with camizestrant + CDK4/6i is 7.6 months

	Camizestrant + CDK4/6i (n=157)	AI + CDK4/6i (n=158)
Events, n (%)	99 (63.1)	124 (78.5)
Median PFS (95% CI); months	**16.8** (14.7–19.4)	**9.2** (7.2–9.7)
HR (95% CI): **0.45** (0.34–0.59); nominal p<0.00001		



Number of patients at risk

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 *ESR1*m detected (first vs subsequent test), and time from initiation of AI + CDK4/6i to randomization (<18 months vs ≥18 months).

First subsequent therapy

	Patients who received a first subsequent therapy at DCO3	
	Camizestrant + CDK4/6i (n=87)	AI + CDK4/6i (n=117)
Endocrine-based therapy	**48 (55.2%)**	**78 (66.7%)**
SERD or novel ET* ± targeted therapy	24 (27.6%)	57 (48.7%)
Fulvestrant ± targeted therapy	22 (25.3%)	42 (35.9%)
Oral SERD or novel ET* ± targeted therapy	2 (2.3%)	15 (12.8%)
Other endocrine regimens† ± targeted therapy	24 (27.6%)	21 (17.9%)
Cytotoxic therapy	**38 (43.7%)**	**36 (30.8%)**
Oral chemotherapy	22 (25.3%)	12 (10.3%)
IV regimen	16 (18.4%)	24 (20.5%)
Chemotherapy	14 (16.1%)	14 (12.0%)
Antibody–drug conjugate	2 (2.3%)	10 (8.5%)
Other§	**1 (1.1%)**	**3 (2.6%)**

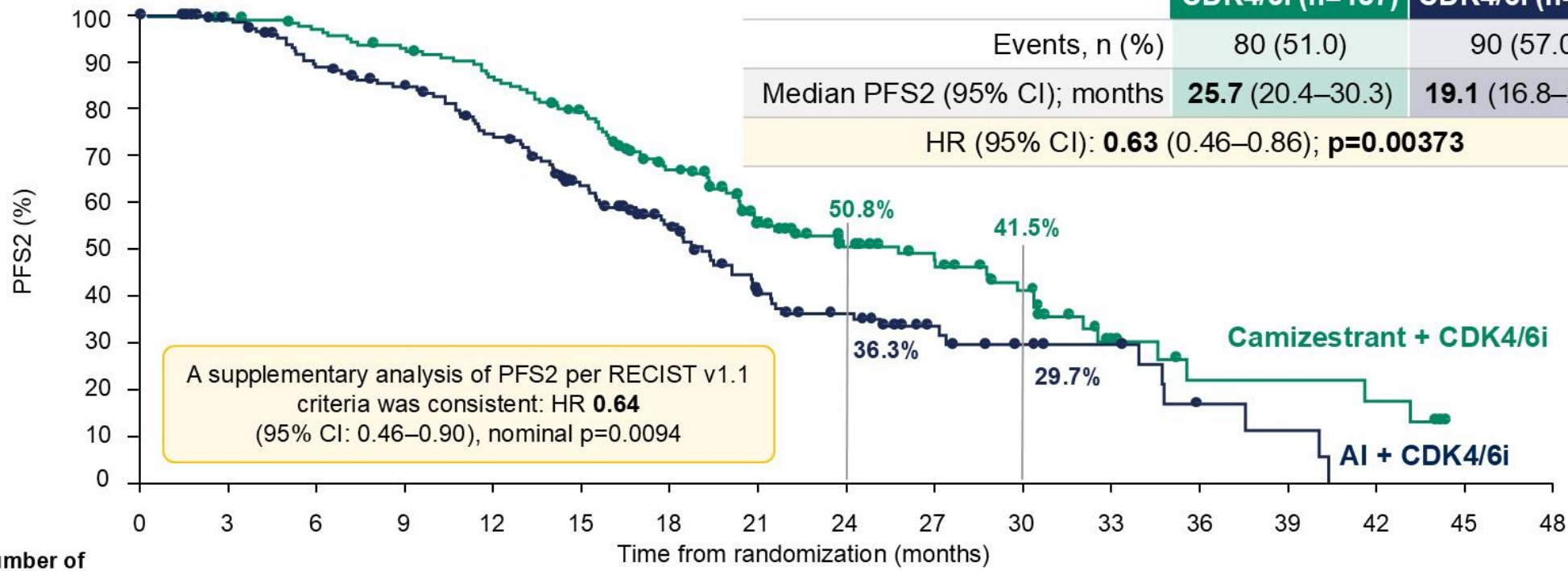
Rate of visceral disease at progression was balanced between arms (supplemental slides)
Approximately half of the patients in the control arm received SERD or novel ET ± targeted therapy

DCO3 (Jan 02, 2026). *"Novel ET" subgroup includes the following terms – elacestrant, imlunestrant, camizestrant, vepdegestrant, lasofoxifene, and palazestrant. Oral SERDs included elacestrant, imlunestrant, camizestrant, and palazestrant. †'Other' endocrine regimens include AI or tamoxifen. §"Other" included PARPi (olaparib, talazoparib) or androgen receptor modulator (enobosarm). Novel ET was used in any subsequent line of therapy in 2/87 (2.3%) patients in the camizestrant+CDK4/6i arm and 23/117 (19.7%) patients in the AI+CDK4/6i arm. ET, endocrine therapy; IV, intravenous; SERD, selective estrogen receptor degraders.

Final second progression-free survival (PFS2)

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

	Camizestrant + CDK4/6i (n=157)	AI + CDK4/6i (n=158)
Events, n (%)	80 (51.0)	90 (57.0)
Median PFS2 (95% CI); months	**25.7** (20.4–30.3)	**19.1** (16.8–21.0)
HR (95% CI): **0.63** (0.46–0.86); **p=0.00373**		



Number of patients at risk

Camizestrant + 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	

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 *ESR1*m detected (first vs subsequent test), and time from initiation of AI+CDK4/6i to randomization (<18 months vs ≥18 months).

Updated patient reported outcomes

Camizestrant + CDK4/6i reduced the risk of deterioration in patient-reported cancer symptoms and functioning

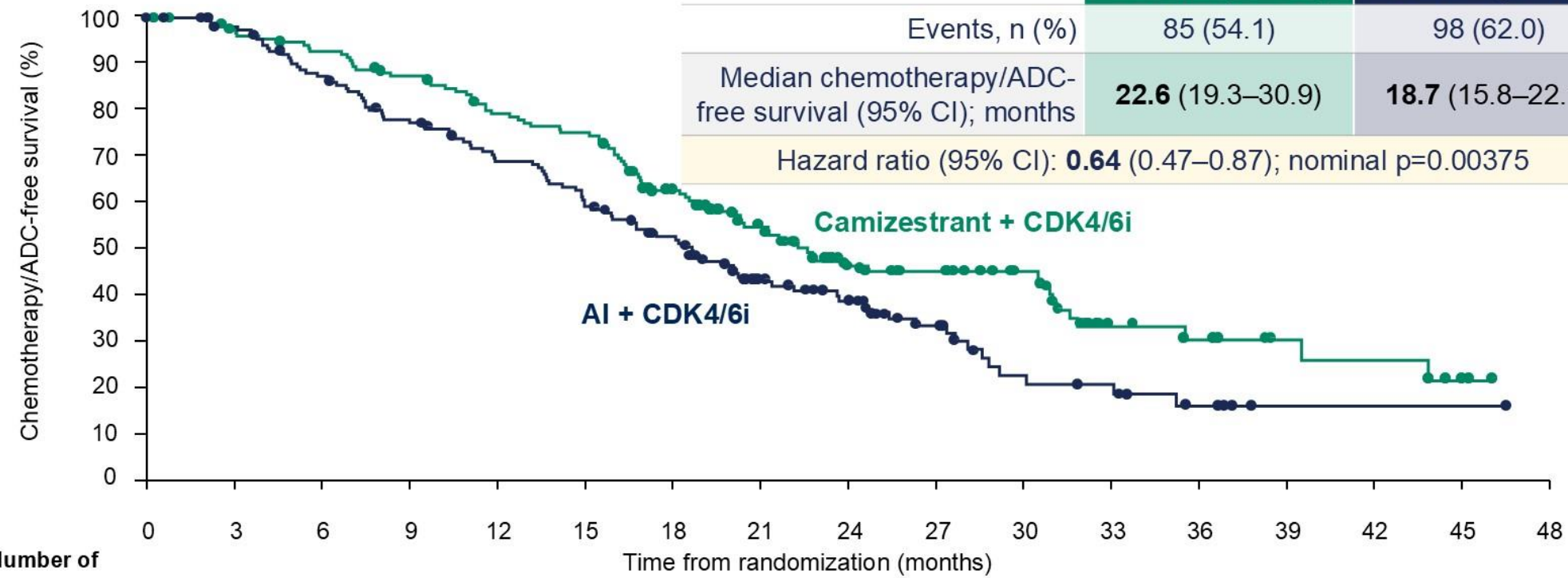
		Deterioration events, n/N		Hazard ratio (95% CI)
		Camizestrant + CDK4/6i	AI + CDK4/6i	
EORTC QLQ-C30	GHS/QOL	37/107	49/95	0.48 (0.31–0.76)
	Physical functioning*	38/108	36/95	0.68 (0.43–1.08)
	Role functioning	53/108	52/94	0.69 (0.47–1.03)
	Cognitive functioning	39/107	33/95	0.87 (0.55–1.40)
	Emotional functioning	29/107	33/95	0.55 (0.33–0.91)
	Social functioning	39/107	41/95	0.66 (0.42–1.03)
	Pain*	48/106	53/94	0.54 (0.36–0.81)
	Shortness of breath/ dyspnoea	25/105	36/94	0.41 (0.23–0.70)
	Fatigue	35/104	37/91	0.68 (0.42–1.10)
EORTC QLQ-BR23	Breast symptoms*	19/103	17/92	0.64 (0.32–1.28)
	Arm symptoms*	19/101	18/90	0.79 (0.41–1.55)

DCO3 (Jan 02, 2026). Time to deterioration defined as time from randomization to deterioration based on meaningful change thresholds (16.6 for GHS/QoL, role, emotional, cognitive, social functioning, pain and breast symptoms, 22.2 for fatigue and arm symptoms, 13.3 for physical functioning, and 10 for dyspnoea). *Time to deterioration in pain, physical functioning, breast symptoms, and arm symptoms were pre-defined secondary endpoints.
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; EORTC QLQ-BR23, EORTC QLQ breast cancer-specific supplement; GHS, global health status; QoL, quality of life.

Chemotherapy/ADC-free survival

Camizestrant + CDK4/6i extended chemotherapy/ADC-free survival

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Events, n (%)	85 (54.1)	98 (62.0)
Median chemotherapy/ADC-free survival (95% CI); months	**22.6** (19.3–30.9)	**18.7** (15.8–22.1)
Hazard ratio (95% CI): **0.64** (0.47–0.87); nominal p=0.00375		

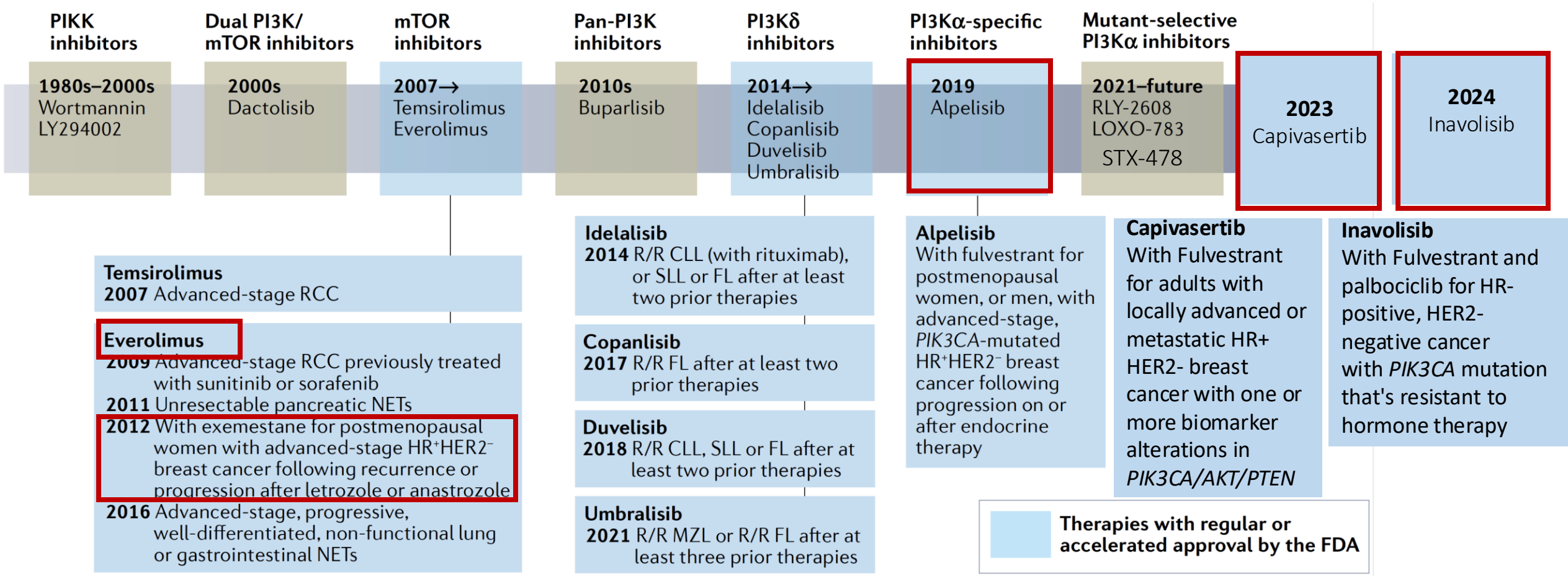


Number of patients at risk

Camizestrant + 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

DCO3 (Jan 02, 2026). 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).

Drugging the PI3K Pathway Through the Decades



CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MZL, marginal zone lymphoma; NET, neuroendocrine tumor; R/R, relapse/refractory; RCC, renal cell carcinoma; SLL, small lymphocytic lymphoma.

Adapted from Vasan N, et al. Nat Rev Clin Oncol. 2022;19:471-485

VIKTORIA-1 Study Design

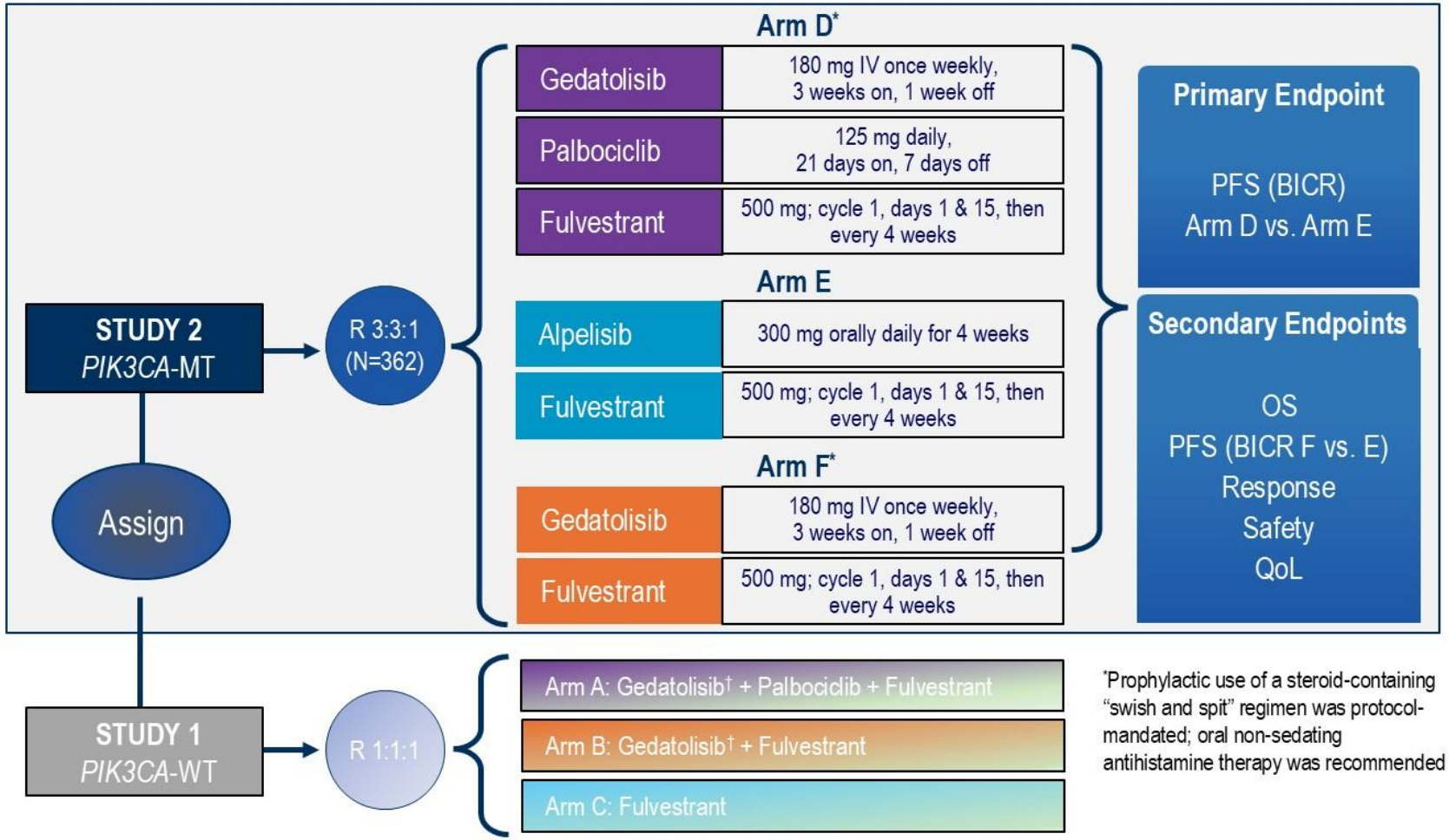
HR+/HER2- Advanced Breast Cancer

Eligibility Criteria

- Pre- & postmenopausal women & men
- Progression on/after CDK4/6i + NSAI
- ≤2 lines of prior ET for ABC
- Measurable disease, RECIST v1.1
- Screening result for *PIK3CA* status
- No T2DM with HbA1c >6.4% or T1DM
- No prior mTORi, PI3Ki, or AKTi
- No prior chemotherapy for ABC

Stratification Factors

- Lung/liver metastases (yes/no)
- TTP on immediate prior therapy (≤ or >6 months)
- Region (US/Canada or ROW)



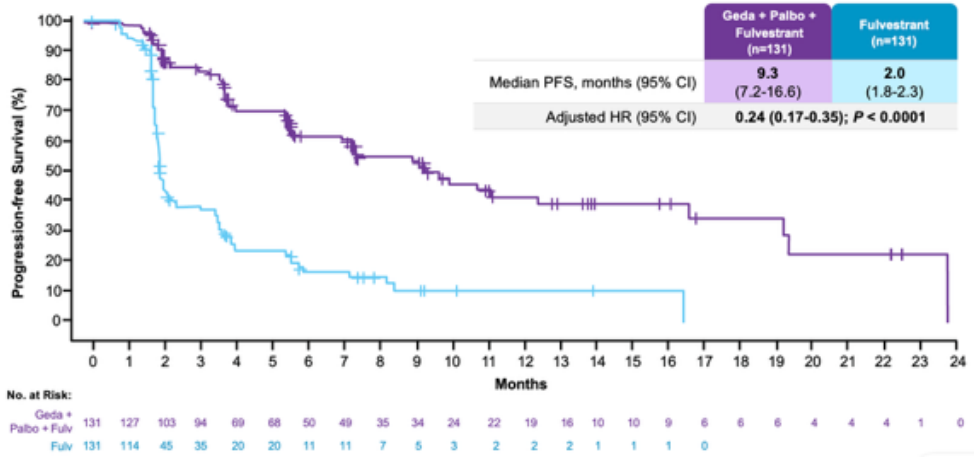
*Prophylactic use of a steroid-containing "swish and spit" regimen was protocol-mandated; oral non-sedating antihistamine therapy was recommended

Abbreviations: ABC, advanced breast cancer; AKTi, protein kinase B inhibitor; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; ET, endocrine therapy; HbA1c, hemoglobin A1c; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; IV, intravenous; MT, mutant; mTORi, mechanistic target of rapamycin inhibitor; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PFS, progression-free survival; PI3Ki, phosphatidylinositol 3-kinase inhibitor; QoL, quality of life; R, randomization; ROW, rest of world; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTP, time to progression; WT, wild-type

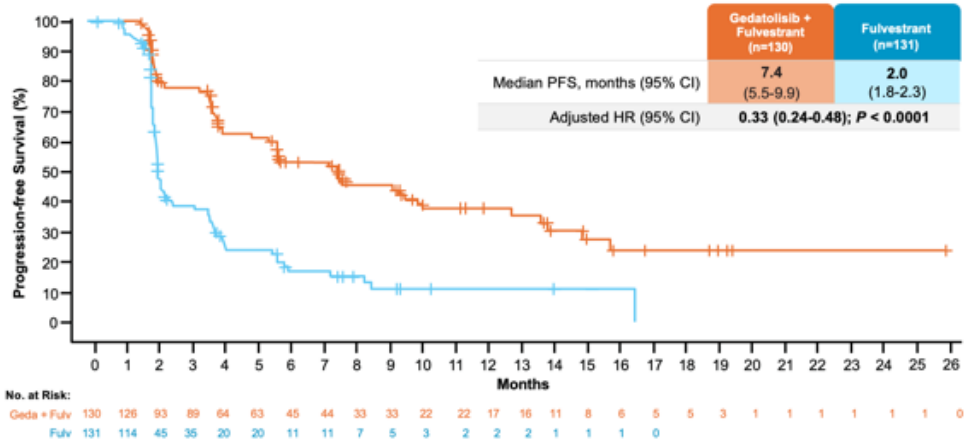
PRESENTED BY: Sara A. Hurvitz, MD, FACP

VIKTORIA-1 Study 1 results for PI3K WT

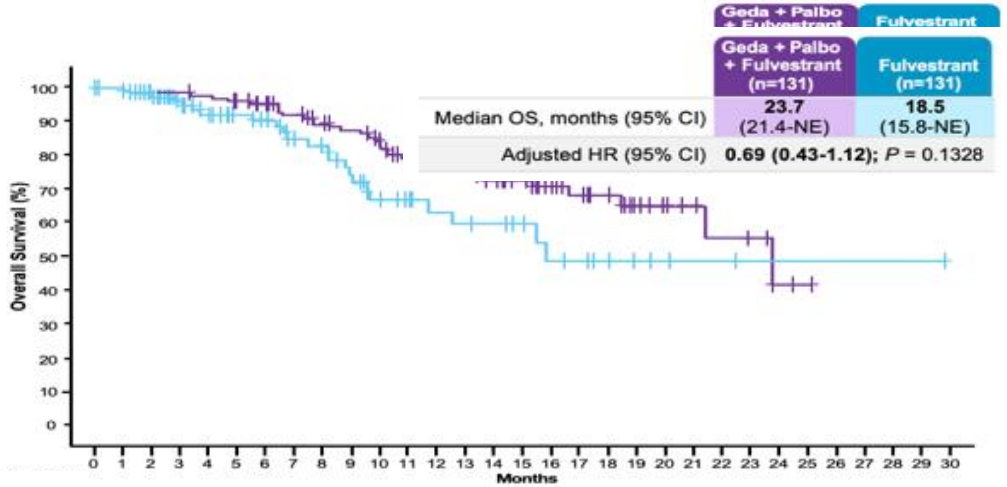
PFS Gedatolisib Triplet vs. Fulvestrant



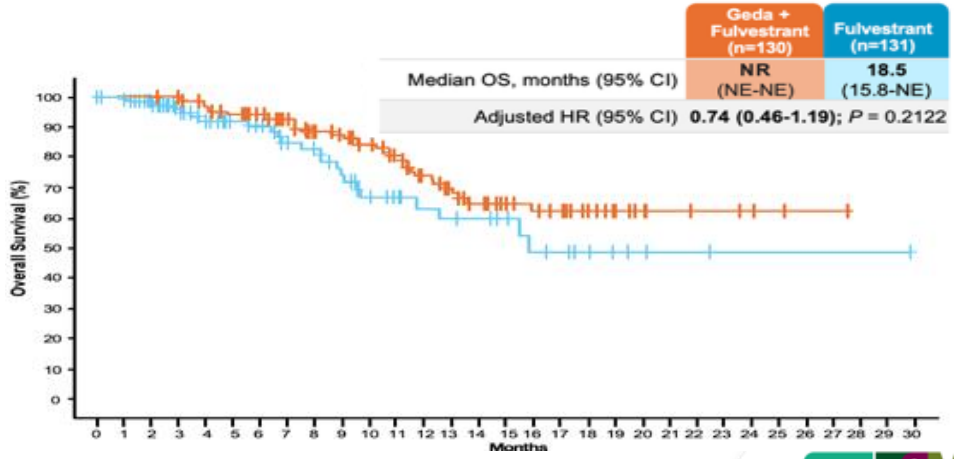
PFS Gedatolisib Doublet vs. Fulvestrant



Interim OS Censored at Cross-Over Gedatolisib Triplet vs. Fulvestrant



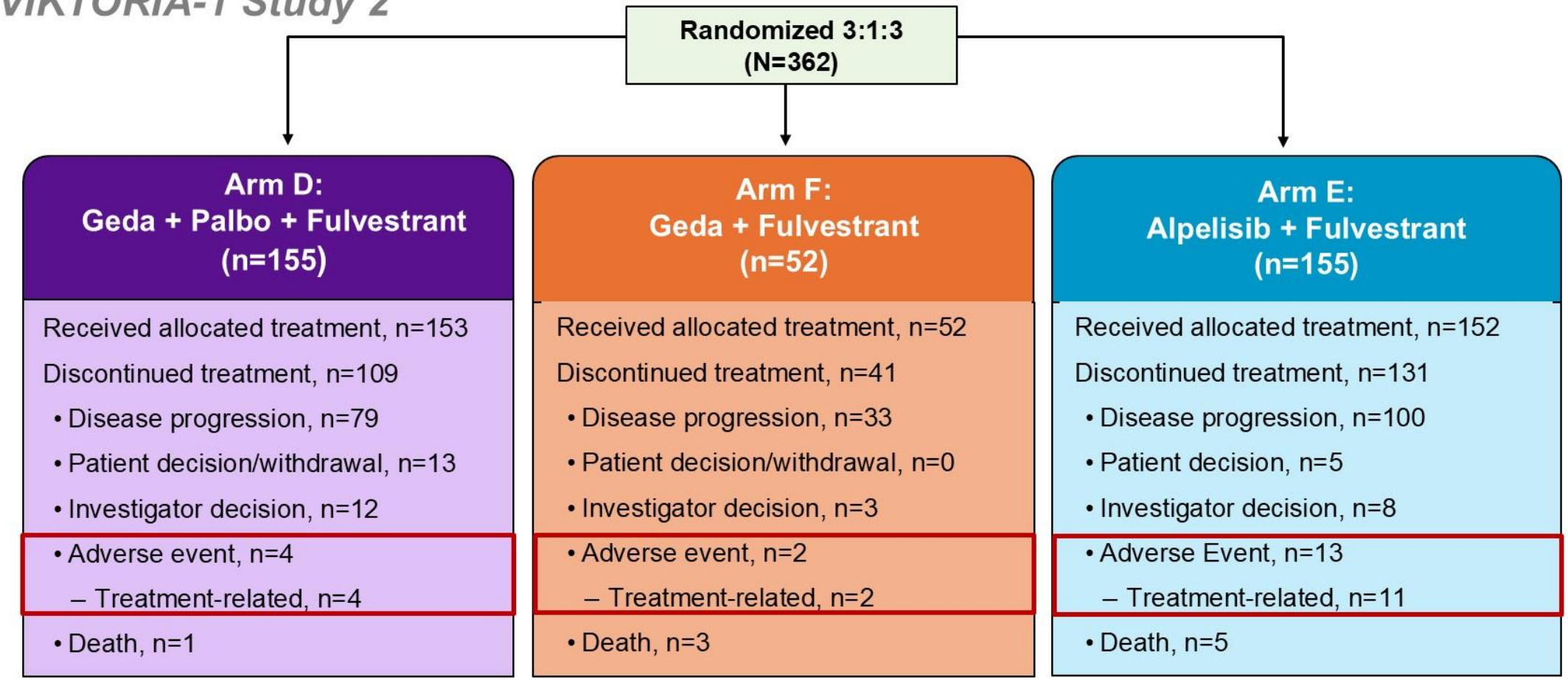
Interim OS Censored at Cross-Over Gedatolisib Doublet vs. Fulvestrant



Hurvitz SA et al, ESMO 2025.

Patient Disposition

VIKTORIA-1 Study 2

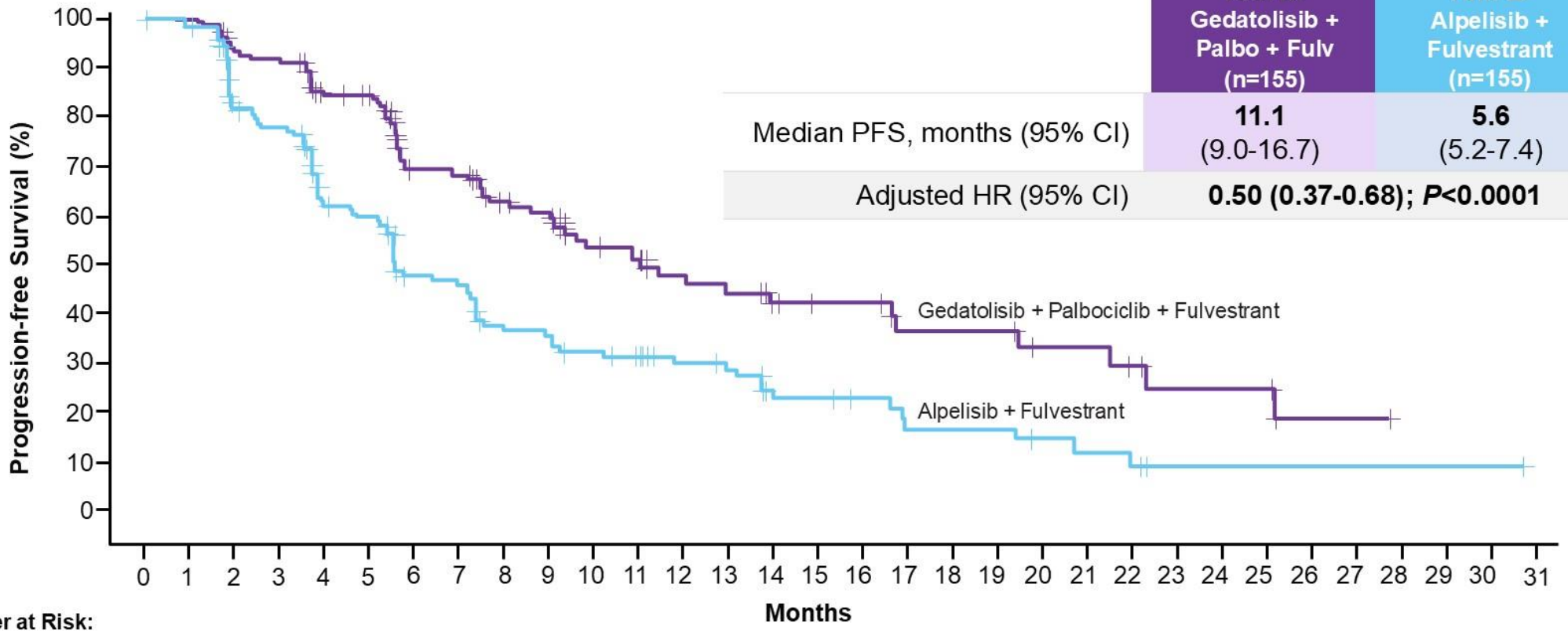


Abbreviations: Geda, gedatolisib; Palbo, palbociclib.

Data cut-off: March 9, 2026; median follow-up: 12.8 months (interquartile range: 7.5-19.9)

Primary Endpoint: Progression-Free Survival (BICR)

Gedatolisib Triplet vs. Alpelisib + Fulvestrant in VIKTORIA-1 Study 2



	Arm D: Gedatolisib + Palbo + Fulv (n=155)	Arm E: Alpelisib + Fulvestrant (n=155)
Median PFS, months (95% CI)	**11.1** (9.0-16.7)	**5.6** (5.2-7.4)
Adjusted HR (95% CI)	**0.50 (0.37-0.68); *P*<0.0001**	

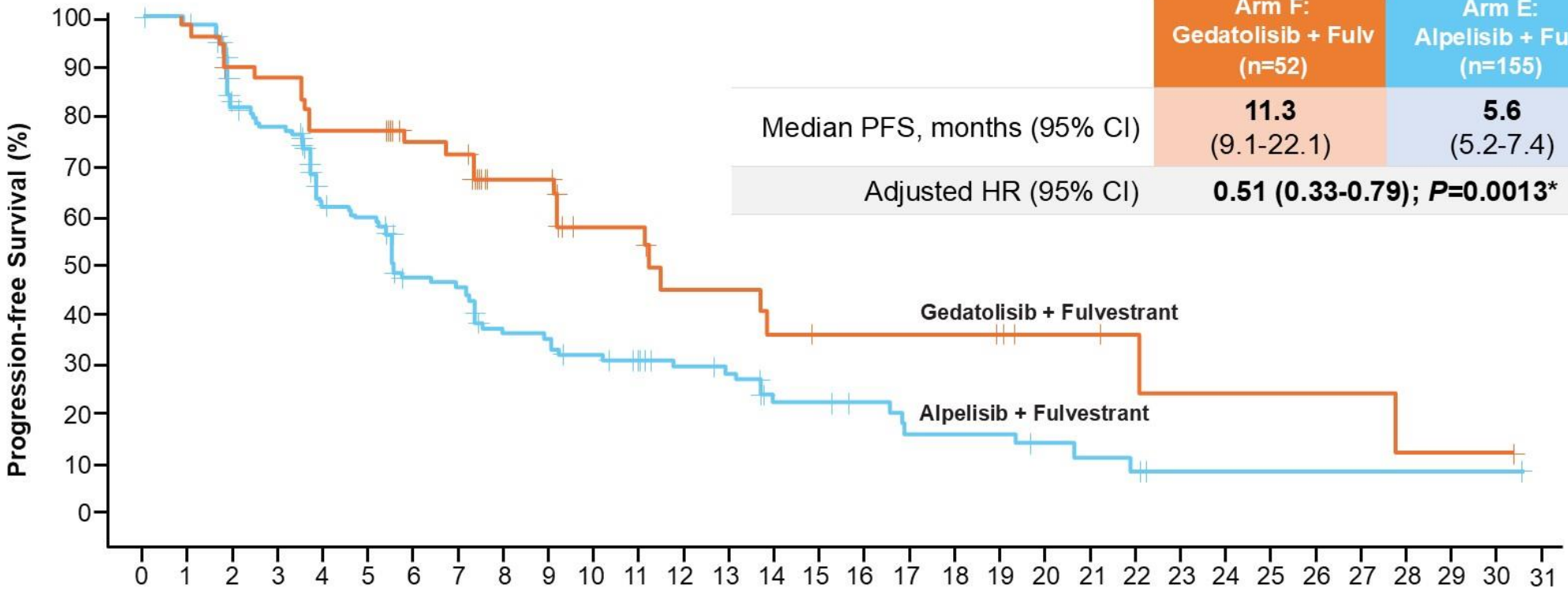
Number at Risk:

Geda + Palbo + Fulv	155	150	134	131	110	107	77	76	62	57	42	38	27	25	20	16	16	12	12	12	9	9	7	5	5	5	2	2	0
Alpelisib + Fulv	155	148	116	107	78	74	53	51	35	34	30	27	22	20	13	13	11	8	8	8	5	4	3	1	1	1	1	1	1	1	1	0

Secondary Endpoint: Progression-Free Survival (BICR)

Gedatolisib Doublet vs. Alpelisib + Fulvestrant in VIKTORIA-1 Study 2

	Arm F: Gedatolisib + Fulv (n=52)	Arm E: Alpelisib + Fulv (n=155)
Median PFS, months (95% CI)	**11.3** (9.1-22.1)	**5.6** (5.2-7.4)
Adjusted HR (95% CI)	**0.51 (0.33-0.79); *P*=0.0013***	



Number at Risk:

Gedatolisib + Fulv	52	48	42	41	36	36	31	30	23	23	15	15	10	10	8	7	7	7	7	6	4	4	3	2	2	2	2	2	1	1	1	0
Alpelisib + Fulv	155	148	116	107	78	74	53	51	35	34	30	27	22	20	13	13	11	8	8	8	5	4	3	1	1	1	1	1	1	1	1	0

*Arm F vs. E analysis was not part of the primary efficacy analysis in the hierarchical order.

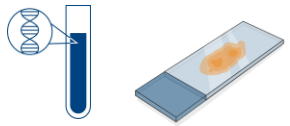
Safety and Tolerability

Safety Population in VIKTORIA-1 Study 2

Exposure	Arm D: Gedatolisib + Palbociclib + Fulvestrant (n=153)			Arm F: Gedatolisib + Fulvestrant (n=52)			Arm E: Alpelisib + Fulvestrant (n=152)		
Median RDI, Geda (IQR)	93.3 (80.6-100)			100 (97.8-100)			--		
Median RDI, Alpe (IQR)	--			--			81.7 (64.8-96.2)		
TRAE and TR-SAE, n (%)									
Pts with ≥1 TRAE	150 (98.0)			50 (96.2)			147 (96.7)		
Study tx D/C for TRAE	4 (2.6)			2 (3.8)			11 (7.1)		
Pts with ≥1 TR-SAE	16 (10.5)			2 (3.8)			20 (13.2)		
Deaths due to TR-SAE*	1 (0.7)			0			2 (1.3)		
TRAE, n (%)†	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Neutropenia‡	97 (63.4)	73 (47.7)	17 (11.1)	1 (1.9)	0	0	2 (1.3)	0	1 (0.7)
Stomatitis‡	94 (61.4)	25 (16.3)	0	32 (61.5)	3 (5.8)	0	52 (34.2)	8 (5.3)	0
Nausea	70 (45.8)	5 (3.3)	0	21 (40.4)	1 (1.9)	0	50 (32.9)	2 (1.3)	0
Rash‡	40 (26.1)	10 (6.5)	0	17 (32.7)	3 (5.8)	0	56 (36.8)	23 (15.1)	0
Vomiting	39 (25.5)	0	0	10 (19.2)	0	0	23 (15.1)	1 (0.7)	0
Fatigue	33 (21.6)	5 (3.3)	0	11 (21.2)	1 (1.9)	0	32 (21.1)	4 (2.6)	0
Diarrhea§	23 (15.0)	2 (1.3)	0	5 (9.6)	0	0	61 (40.1)	9 (5.9)	1 (0.7)
Hyperglycemia‡,§	23 (15.0)	4 (2.6)	0	6 (11.5)	0	0	88 (57.9)	21 (13.8)	1 (0.7)

*Grade 5 events include fatal cerebral hemorrhage (gedatolisib triplet), urosepsis (alpelisib + fulvestrant group), and general physical health decline (alpelisib + fulvestrant group)
†Shown are treatment-related adverse events of any grade that occurred in at least 20% of the patients in any trial group unless otherwise noted
‡For stomatitis, neutropenia, rash, and hyperglycemia, combined preferred terms are used in the table; if a patient experienced multiple terms, it was counted once for the highest grade.
§Additional events of clinical importance
Abbreviations: Alpe, alpelisib; D/C, discontinued; Geda, gedatolisib; IQR, interquartile range; Pts, patients; RDI, relative dose intensity; TRAE, treatment-related adverse event; TR-SAE, treatment-related serious adverse events; tx, treatment

Treatment Paradigm for HR+/HER2– MBC



- NGS – *PIK3CA*, AKT pathway, *ESR1*
- Germline
- ER/PR/HER2

1st LINE	2nd LINE	3rd LINE	4th LINE
ET + CDK4/6i	ET + AKTi	ET + AKTi	ET + mTORi
*ET + Inavolisib + palbociclib	ET + PI3Ki	ET + PI3Ki	
	ET + mTORi	ET + mTORi	
	ET + CDK4/6i	PARPi	PARPi
ET	ET SERD	ET SERD	ET SERD
Chemo	Chemo	Chemo	ADC/Chemo

*For *PIK3CA m* and those who recur on or within 12 mo of adj ET

Adapted from Komal Jhaveri

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