UPDATES IN TARGETED THERAPIES FOR HR+ HER- ADVANCED BREAST CANCER: BEYOND CDK4/6 INHIBITTION

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Disclosure of interest

Consulting/Advisor: Roche , Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp&Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics.

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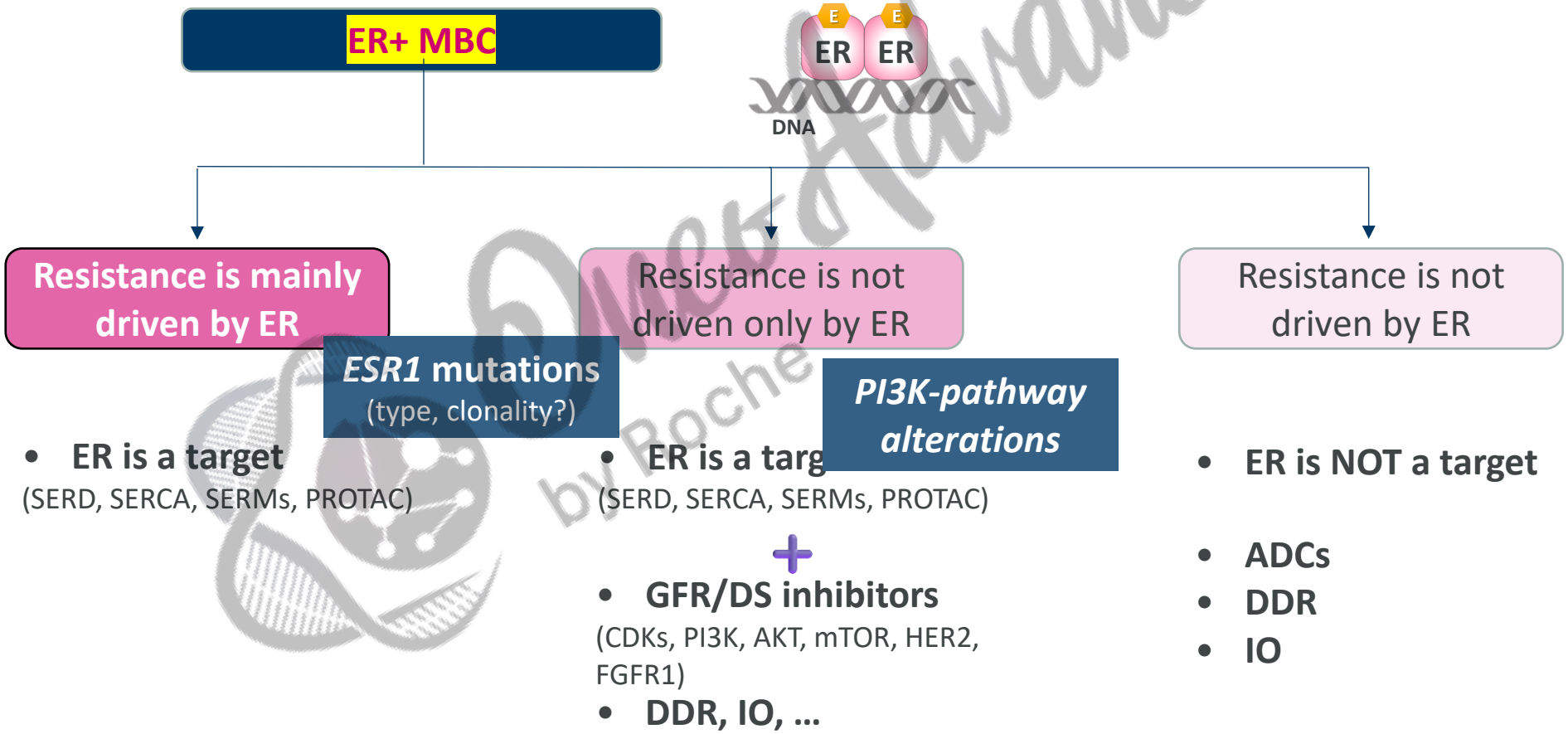
Patents: Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A.

Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés.US 2019/ 0338368 A1.

THE EVOLVING LANDSCAPE OF **HR+ MBC:** INTEGRATING NEW THERAPIES

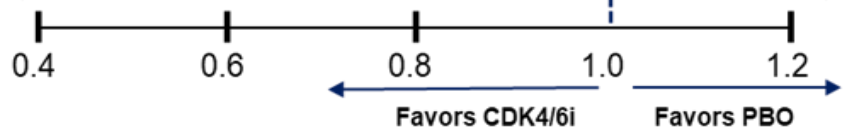
How to deal with endocrine resistance



Courtesy of Carmen Criscitiello (modified).

CDK4/6 inhibitors – Phase III Registration Studies
OS Efficacy Results

		Treatment arm: OS, median, mo	Placebo arm: OS, median, mo	Hazard ratio	Hazard ratio (95% CI)	*P* value	Significance reached vs placebo[a]
PAL	PALOMA-2[1] Palbociclib + letrozole	53.9	51.2		0.956 (0.777-1.177)	0.3378	✗
PAL	PALOMA-3[2] Palbociclib + fulvestrant	34.9	28.0		0.81 (0.64-1.03)	.09	✗ ✓
ABE	MONARCH 2[3] Abemaciclib + fulvestrant	46.7	37.3		0.76 (0.61-0.95)	.01	✓
ABE	MONARCH 3[4] Abemaciclib + NSAI	67.1	54.5		0.754 (0.584-0.974)	.0301*	✗ ✓
RIBO	MONALEESA-2[5,6] Ribociclib + letrozole	63.9	51.4		0.76 (0.63-0.93)	.004	✓
RIBO	MONALEESA-7[7] Ribociclib + goserelin + tamoxifen/NSAI	NR	40.9		0.71 (0.54-0.95)	.00973	✓
RIBO	MONALEESA-3[8] Ribociclilb + fulvestrant	NR	40.0		0.72 (0.57-0.92)	.00455	✓



*Interim OS

Inavolisib is a PI3Kα-selective inhibitor and mutated PI3Kα degrader

Inavolisib is a potent, selective inhibitor of p110α, the catalytic subunit of PI3Kα, and promotes the degradation of mutated p110α[1]

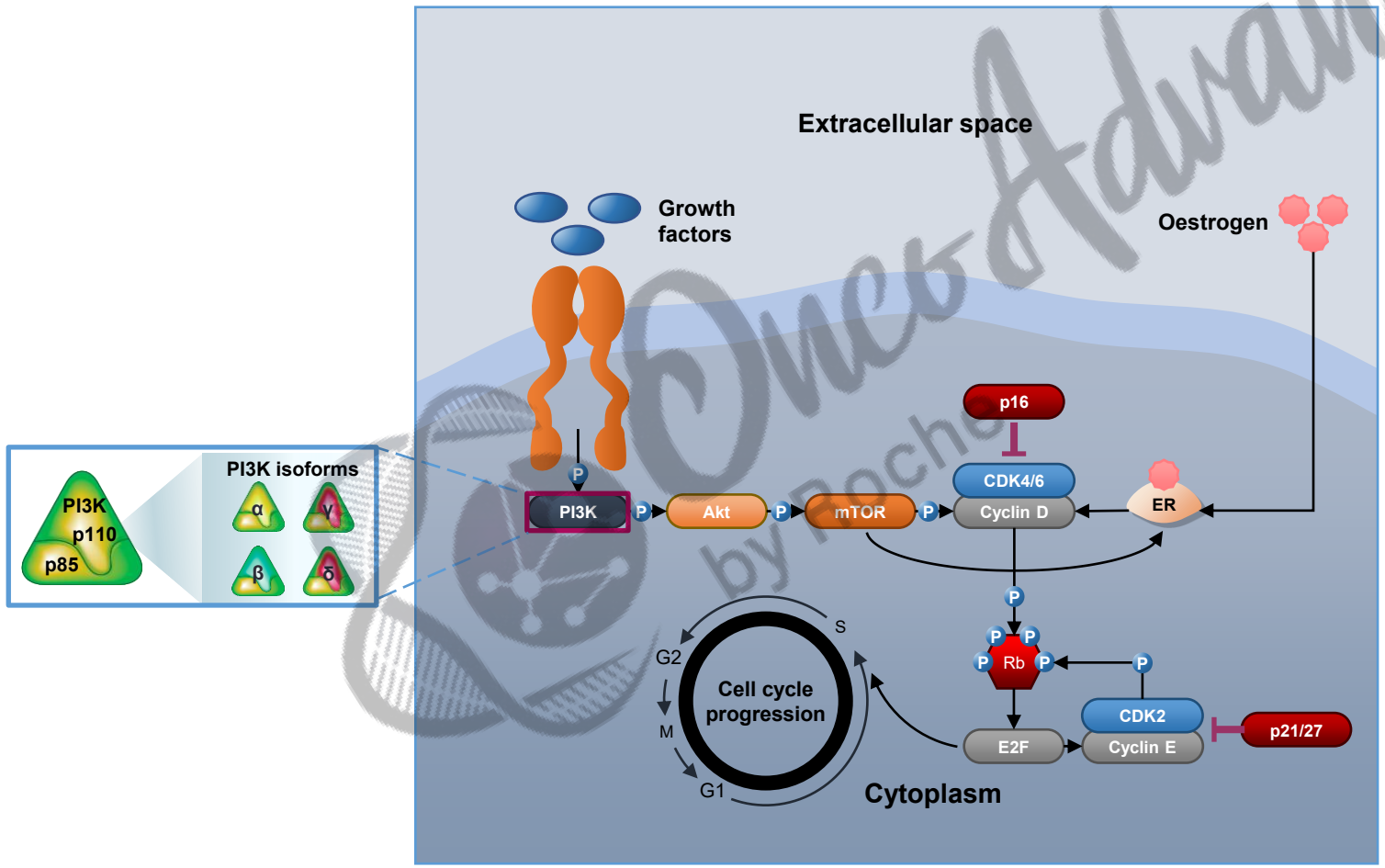


Image adapted from: Brufsky AM & Dickler MN. Oncologist. 2018; **23:**528.

1. Dey *et al*. SABCS 2019 (Poster P3-11-23);
2. Juric D, *et a*l. SABCs 2019 (Abstract OT1-08-04; oral presentation);
3. Jhaveri K, *et al*. SABCS 2019 (Abstract P1-19-46; poster presentation).

INAVO-120-OS data: Turner N, ASCO 2025

Trial Design

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019-September 2023

N=325

R 1:1

- Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**
- Placebo (PO QD) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

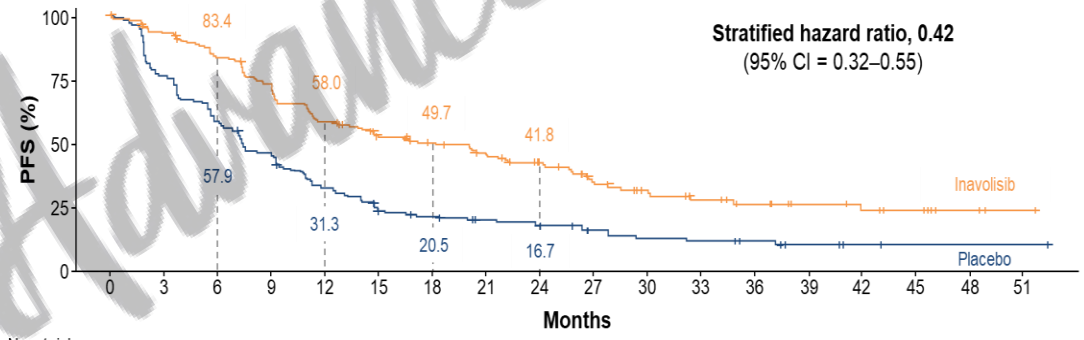
Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

Updated PFS

	Events, n (%)	Median, months (95% CI)
Inavolisib (n = 161)	103 (64.0)	17.2 (11.6–22.2)
Placebo (n = 164)	141 (86.0)	7.3 (5.9–9.2)

Stratified hazard ratio, 0.42
(95% CI = 0.32–0.55)



Median follow-up: **34.2 months**

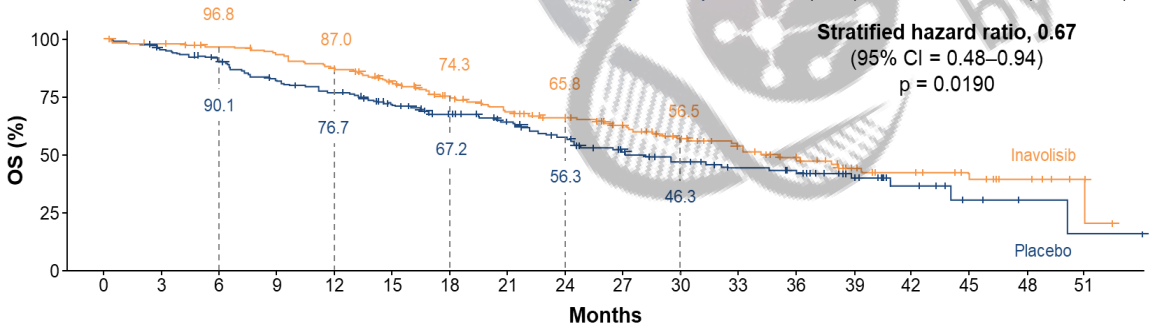
No. at risk

Inavolisib	161	146	129	112	89	73	65	57	46	32	25	19	15	11	10	7	3	1
Placebo	164	125	95	74	50	34	30	24	21	14	11	10	8	4	2	1	1	1

OS

	Deaths, n (%)	Median, months (95% CI)
Inavolisib (n = 161)	72 (44.7)	34.0 (28.4–44.8)
Placebo (n = 164)	82 (50.0)	27.0 (22.8–38.7)

Stratified hazard ratio, 0.67
(95% CI = 0.48–0.94)
p = 0.0190



Median follow-up: **34.2 months**

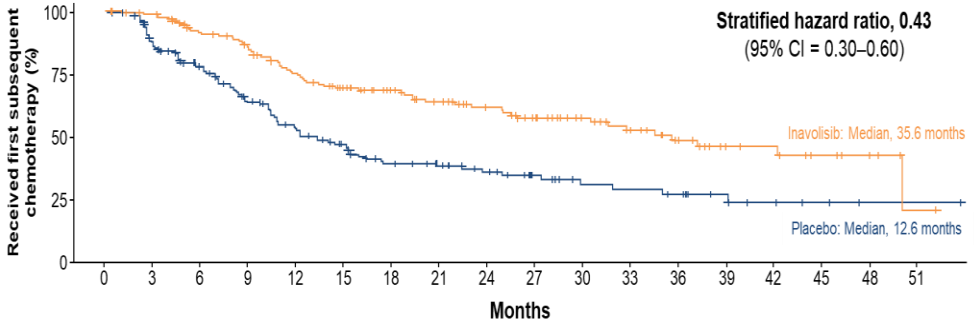
No. at risk

Inavolisib	161	155	149	142	131	114	99	88	78	67	54	43	34	22	19	13	7	1
Placebo	164	155	142	127	119	104	90	77	63	48	42	36	32	18	10	4	2	1

Time to first subsequent chemotherapy

	Events n, (%)	Median, months (95% CI)
Inavolisib (n = 161)	64 (39.8)	35.6 (25.4–NR)
Placebo (n = 164)	94 (57.3)	12.6 (10.4–16.1)

Stratified hazard ratio, 0.43
(95% CI = 0.30–0.60)



Median follow-up: **34.2 months**

No. at risk

Inavolisib	161	153	136	122	104	89	77	67	57	47	39	31	23	14	13	9	5	1
Placebo	164	134	111	89	68	58	45	40	31	22	16	15	13	9	5	3	1	1

The NCCN Guidelines recommend NGS testing for detection of actionable biomarkers, such as *PIK3CA*, *AKT1*, and *PTEN*, in HR+/HER2- aBC†[1]

Why to test

– PIK3CA, AKT1,PTEN are recognized as actionable biomarkers in metastatic HR+/HER2- breast cancer

Whom to test

– Patients with HR+/HER2- locally advanced or metastatic breast cancer

When to test

– NCCN Guidelines® recommend ordering an NGS panel test during the initial patient work-up for metastatic disease

NGS panel tests can also be ordered after progression on first line treatment

How to test

– Utilize NGS

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

AKT1, serine/threonine protein kinase 1; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; NCCN, National Comprehensive Cancer Network; NGS, next- generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.2.2024.

Targeted treatment options beyond progression on CDK 4/6 inhibitors

CDKs after CDKs

Mantain

Key inclusion criteria
- Men or women ≥18 years
- ER and/or PR ≥1%, HER2- MBC
- Progression on ET + CDK4/6 inhibitor
- ≤1L chemotherapy
- PS 0–1

(n=119)

R 1:1

Placebo + ET* (n=59)

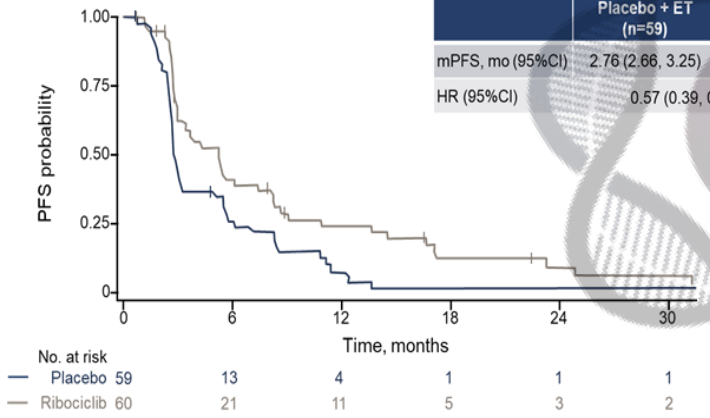
Ribociclib 600 mg 3 weeks on/1 week off + **ET*** (n=60)

Primary endpoint
- PFS (locally assessed)

Secondary endpoints
- ORR, CBR, tumor and blood markers, safety

PFS

	Placebo + ET (n=59)	Ribociclib + ET (n=60)
mPFS, mo (95%CI)	2.76 (2.66, 3.25)	5.29 (3.02, 8.12)
HR (95%CI)	0.57 (0.39, 0.95); p=0.006	



PACE

Eligibility Criteria
- HR+/HER2- MBC
- Progression on CDK4/6i and ET, with ≥6mo SD on prior regimen
- ≤2 prior lines ET for MBC
- No prior fulvestrant
- 0-1 prior chemo for MBC

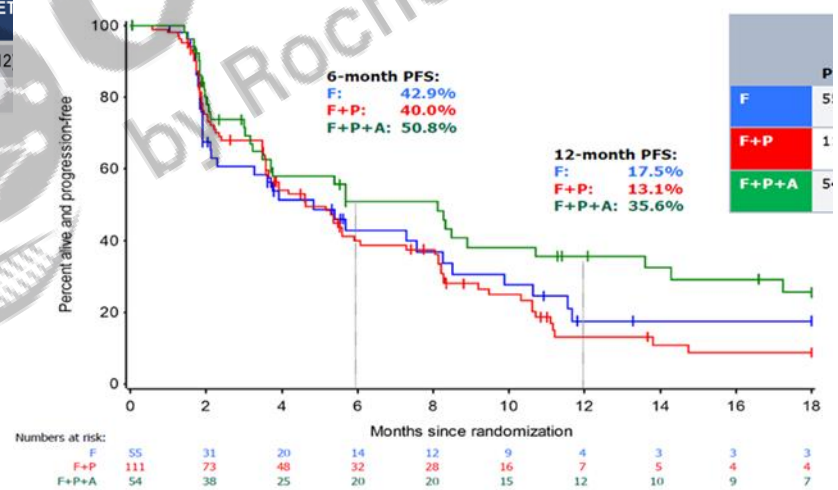
1:2:1 randomization; stratified by exposure to chemo between CDK4/6i and entry onto trial

N=220

RANDOMIZE

- **Fulvestrant:** 500 mg IM C1D1,15, then q28d
- **Fulvestrant:** 500 mg IM C1D1,15, then q28d; **Palbociclib:** 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment)
- **Fulvestrant:** 500 mg IM C1D1,15, then q28d; **Palbociclib:** 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment); **Avelumab:** 10 mg/kg IV q14d

Baseline archival tissue; Baseline ctDNA, CTC; ctDNA; ctDNA, CTC; ctDNA; ctDNA CTC



PALMIRA

N = 136

Fulvestrant‡ 500 mg IM, on day 1, 15, 29 and monthly thereafter

OR

Letrozole‡ 2.5 mg PO, once daily, continuously

+

Palbociclib† 75/100/125 mg PO, once daily, 3 weeks on, 1 week off

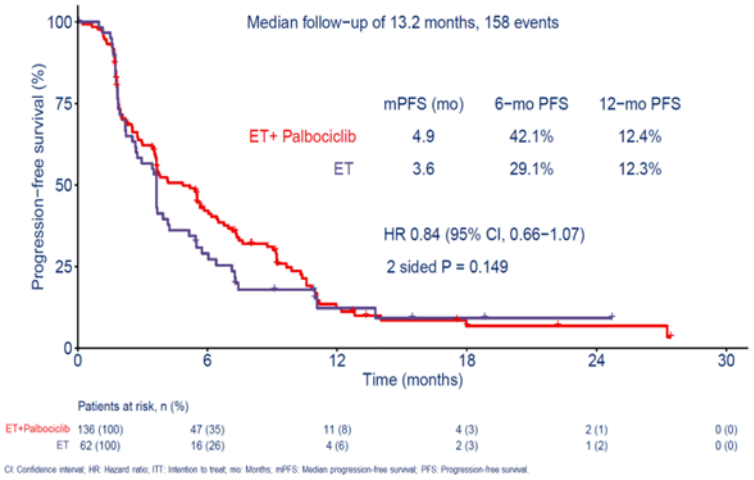
R 2:1 N = 198

N = 62

Fulvestrant‡ 500 mg IM, on day 1, 15, 29 and monthly thereafter

OR

Letrozole‡ 2.5 mg PO, once daily, continuously



Kalinsky K, et al. ASCO 2022; Mayer EL, et al. SABCS 2022; Llombart A, et al. ASCO 2023

postMONARCH (Phase 3): Abemaciclib + fulvestrant vs fulvestrant alone for HR+/HER2– MBC following CDK4/6 inhibitor + ET progression

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

Prior Therapy:

- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC

Randomization 1:1

N = 368

Abemaciclib + Fulvestrant

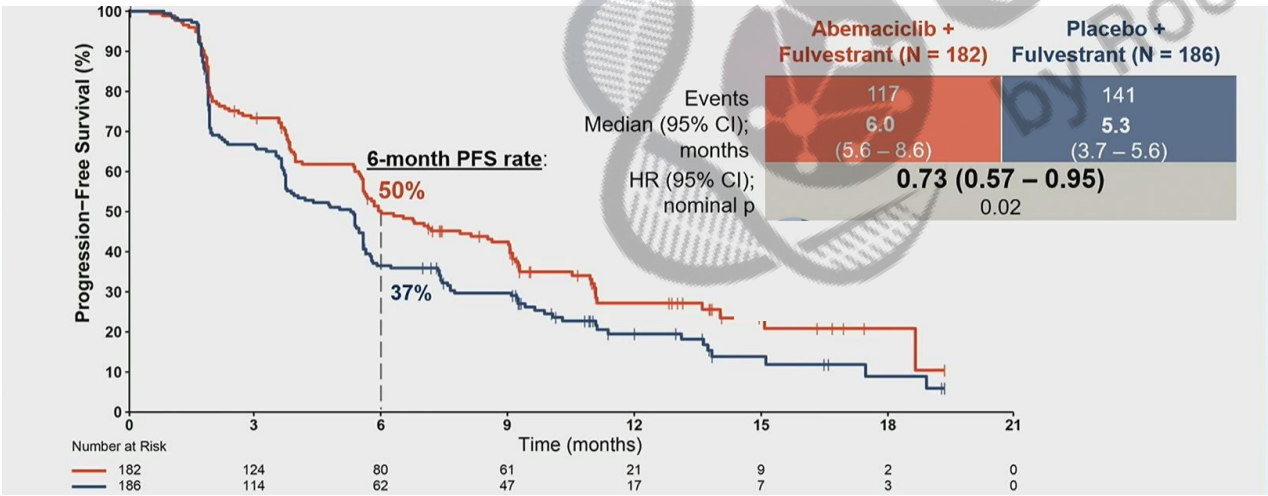
Placebo + Fulvestrant

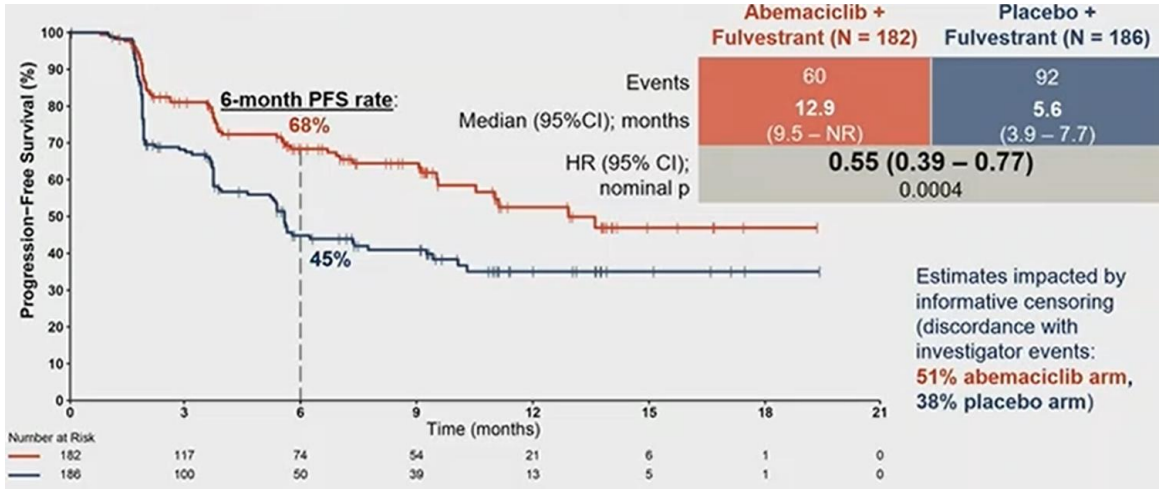
Primary Endpoint:
Investigator-Assessed PFS

Secondary Endpoints:
OS, PFS by BICR, ORR, CBR, DCR, DoR, Safety, PK & PRO

Stratification Factors:

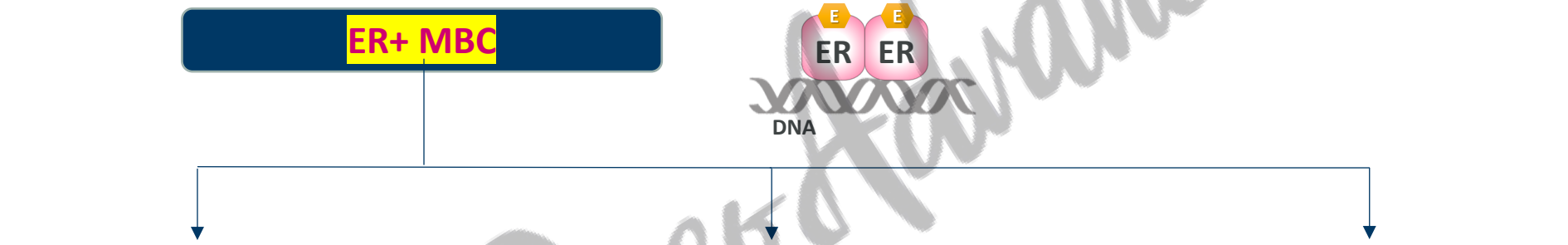
- Duration of prior CDK4/6i
- Visceral metastases
- Geographic region





Kalinsky K, et al. ASCO 2024

How to deal with endocrine resistance



***ESR1* mutations**
(type, clonality?)

PI3K-pathway alterations

- **ER is a target**

(SERD, SERCA, SERMs, PROTAC)

- **ER is a targ**

(SERD, SERCA, SERMs, PROTAC)

+

- **GFR/DS inhibitors**

(CDKs, PI3K, AKT, mTOR, HER2, FGFR1)

- **DDR, IO, …**

- **ER is NOT a target**

- **ADCs**
- **DDR**
- **IO**

Courtesy of Carmen Criscitiello (modified).

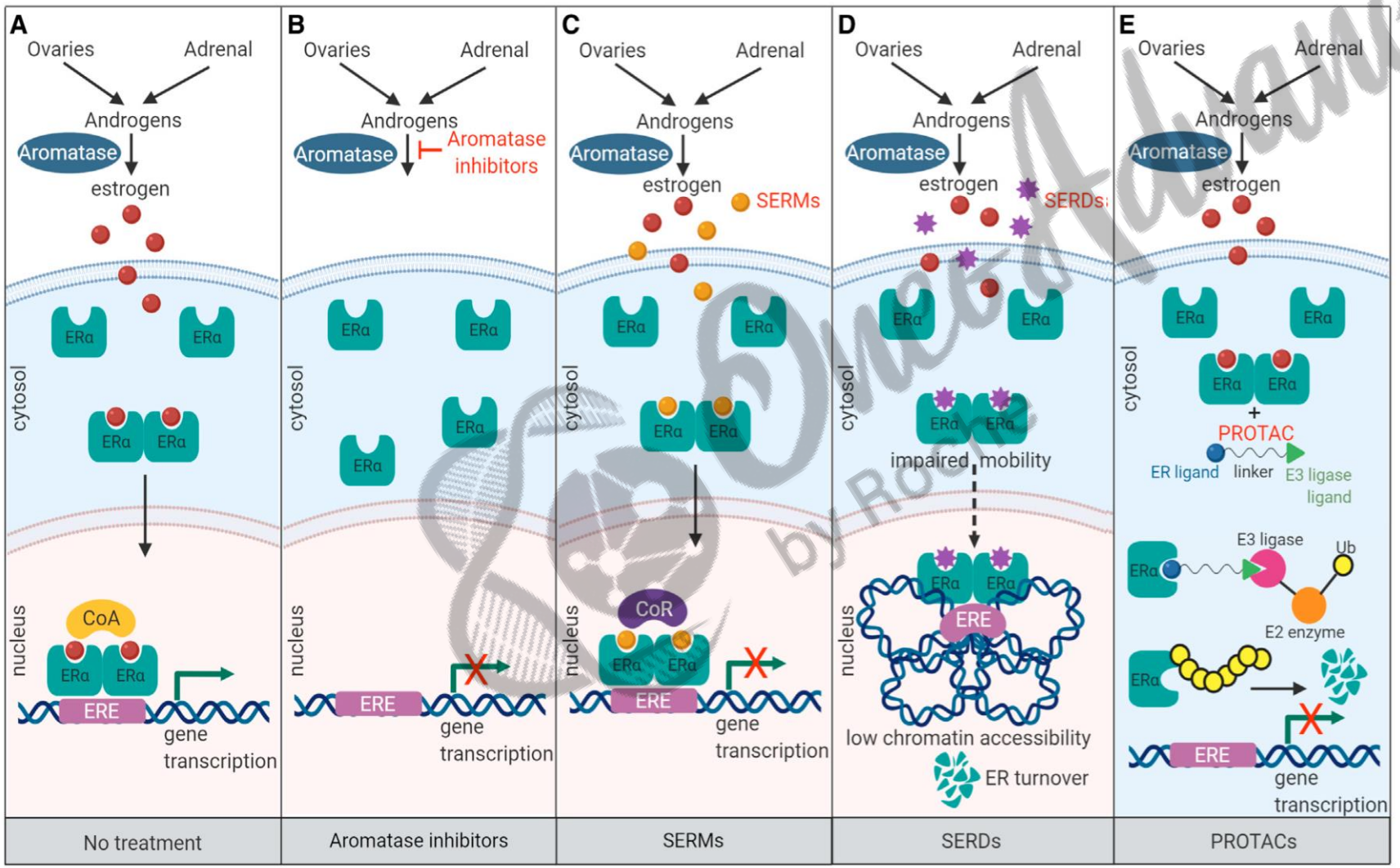
Prevalence of *ESR1* Mutations in Untreated vs Treated ER+/HER2- mBC

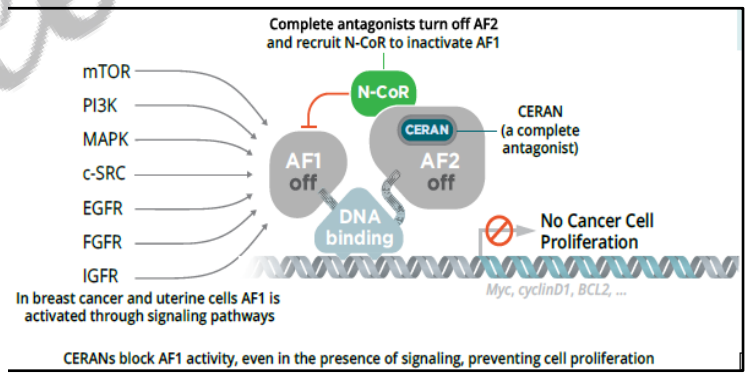
Treatment Setting	*ESR1* Mutation Prevalence[1-5]
At Initiation of First-Line ET	~5%
Second-Line	~33%
Third-Line	Up to 40%

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.

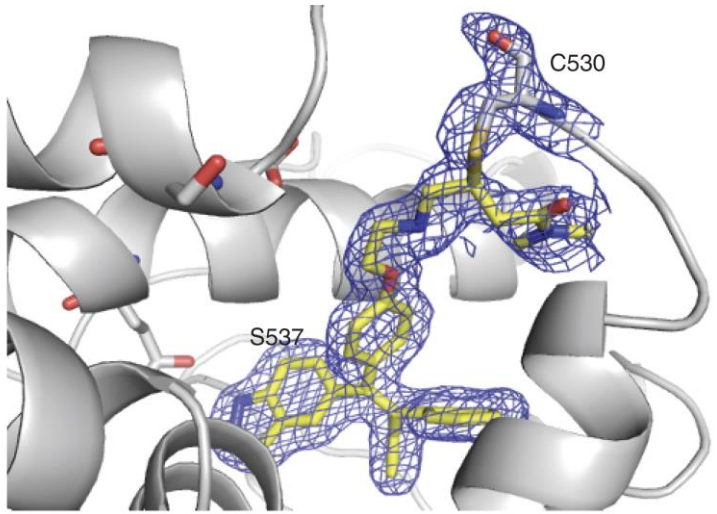
Mechanism of Action of New Endocrine Agents Targeting the ER Domain

SERM | SERD | PROTAC | CERAN





SERCAs



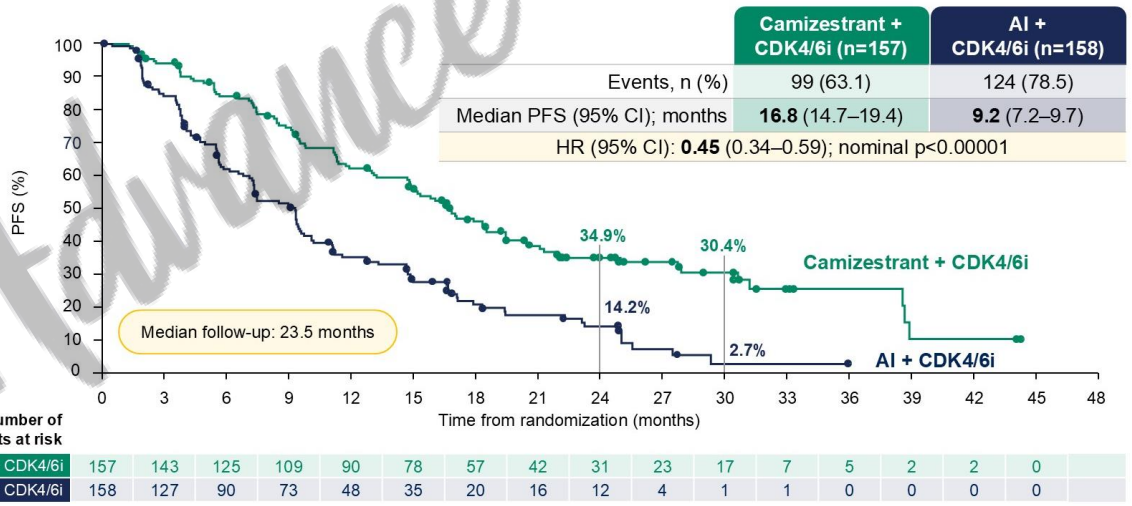
Hanker AB et al. *Cancer Cell*. 2020;37:496-513; Jhaveri SABCS 2021

SERENA-6 Study (Turner N, ASCO 2025; Bidard FC, NEJM 2025 ; Bidard FC ASCO 2026)

Baseline characteristics

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/other	39 (25) / 21 (13)	34 (22) / 22 (14)
Postmenopausal status — n (%)		123 (78)	127 (80)
ECOG performance-status score — n (%)*	0/1	107 (68) / 48 (31)	98 (62) / 56 (35)
Visceral metastases — n (%)†		66 (42)	71 (45)
Time of *ESR1*m detection — n (%)†	At first test	84 (54)	84 (53)
	At a subsequent test‖	73 (47)	74 (47)
	Median (range) – months	22 (4–95)	22 (6–96)
Time from initiation of AI + CDK4/6i to randomization — n (%)†	≥18 months	97 (62)	100 (63)
	<18 months	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)
Most common *ESR1*m at baseline — n (%)‡	D538G	70 (45)	82 (52)
	Y537S	61 (39)	60 (38)
	Y537N	29 (19)	25 (16)

Updated Investigator-assessed PFS

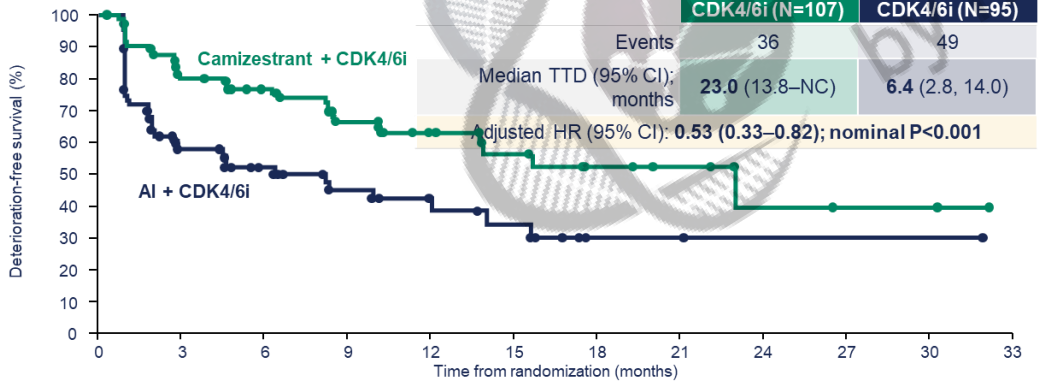


	Camizestrant + CDK4/6i (n=157)	AI + CDK4/6i (n=158)
Events, n (%)	99 (63.1)	124 (78.5)
Median PFS (95% CI); months	**16.8** (14.7–19.4)	**9.2** (7.2–9.7)
HR (95% CI): **0.45** (0.34–0.59); nominal p<0.00001		

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	

Time to deterioration in global health status/quality of life

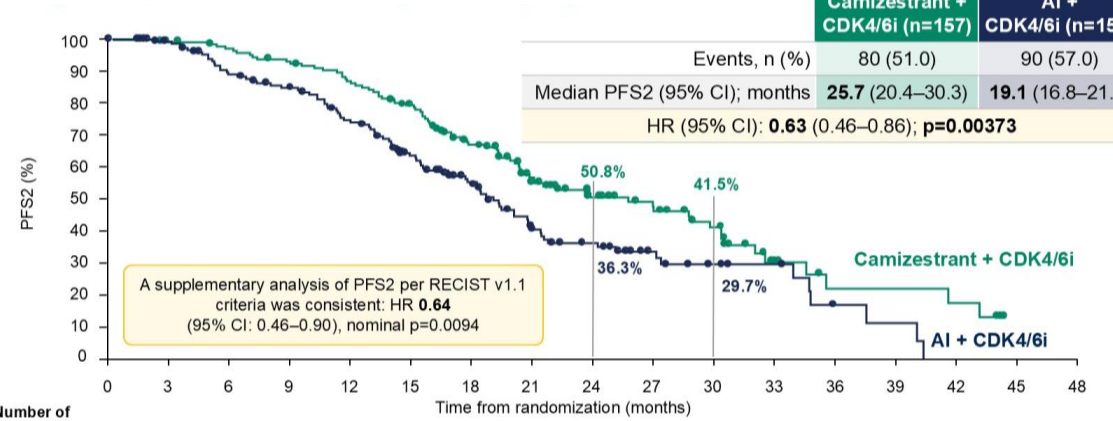


	Camizestrant + CDK4/6i (N=107)	AI + CDK4/6i (N=95)
Events	36	49
Median TTD (95% CI); months	**23.0** (13.8–NC)	**6.4** (2.8, 14.0)
Adjusted HR (95% CI): **0.53 (0.33–0.82); nominal P<0.001**		

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

Final PFS2



	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	

EMERALD Phase 3 Study Design & Primary Endpoint (PFS by IRC)

Inclusion Criteria

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed on 1 or 2 lines of endocrine therapy, including 1 line containing a CDK4/6i
- ≤1 line of chemotherapy in the advanced or metastatic setting
- ECOG PS 0 or 1

R
1:1[b]

Elacestrant
400 mg once daily[c]
(n=239)

Investigator's choice (n=239)
Fulvestrant (n=166)
Aromatase Inhibitor (n=73)
- Anastrozole
- Letrozole
- Exemestane

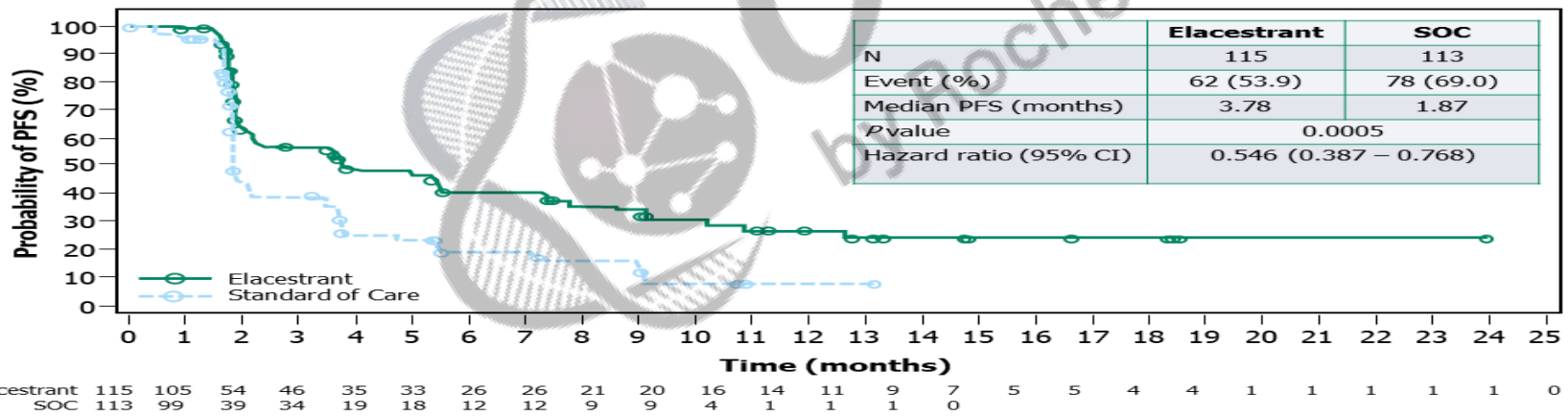
Disease progression or unacceptable toxicity[d]

Follow Up

Two Primary Endpoints:
- PFS by BIRC in all patients
- PFS by BIRC in *ESR1*-mut

Other Secondary Endpoints included:
- PROs
- HRQoL

Patients With Tumors Harboring *mESR1*



	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

Elacestrant is associated with a 45% reduction in the risk of progression or death in patients harboring *mESR1*

- Elacestrant demonstrated a statistically significant and clinically meaningful PFS improvement versus SOC in patients with ER+/HER2- advanced/metastatic breast cancer and *mESR1* following CDK4/6i therapy

Bardia A, et al. SABCS 2021

PFS by Duration of Prior CDK4/6i in 1st Line mBC

Duration on CDK4/6i in the metastatic setting

	At least 6 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=103)	**SOC (n=102)**	**Elacestrant (n=78)**	**SOC (n=81)**	**Elacestrant (n=55)**	**SOC (n=56)**
Median PFS Months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

Kaklamani V, et al. SABCS 2022

VERITAC-2 Study (Hamilton E, ASCO 2025; Campone M, NEJM 2025)

Trial Design

Key Eligibility Criteria

- Age ≥18 years old
- ER+/HER2- advanced or metastatic breast cancer
- Prior therapy:
  - 1 line of CDK4/6i + ET
  - ≤1 additional ET
  - Most recent ET for ≥6 months
  - No prior SERD (eg, fulvestrant, elacestrant)
  - No prior chemotherapy for advanced or metastatic disease
- Radiological progression during or after the last line of therapy

Randomization (1:1)

28-day Treatment Cycles

- **Vepdegestrant (n=313)**: 200 mg orally (once daily)
- **Fulvestrant (n=311)**: 500 mg IM (days 1 and 15 of cycle 1; day 1 of subsequent cycles)

Stratification Factors:

- *ESR1* mutation[a] (yes vs no)
- Visceral disease (yes vs no)

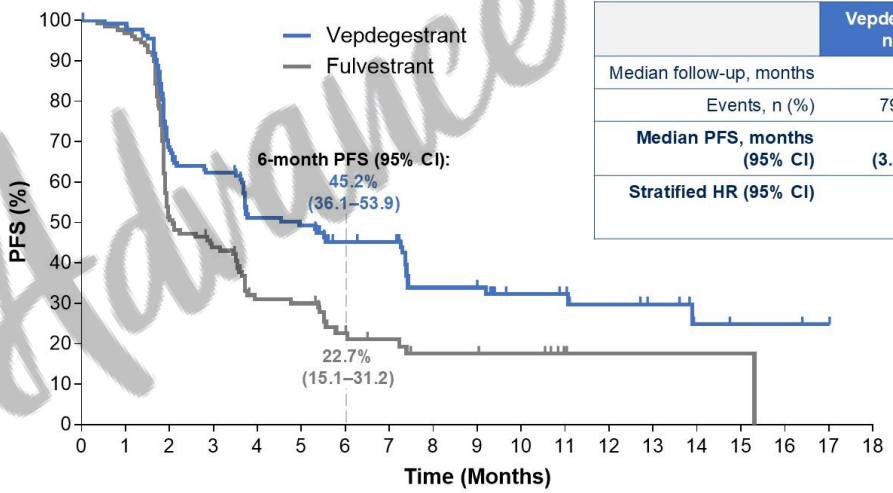
Primary Endpoint:

- PFS by BICR in
  - *ESR1*m population
  - All patients

Secondary Endpoints:

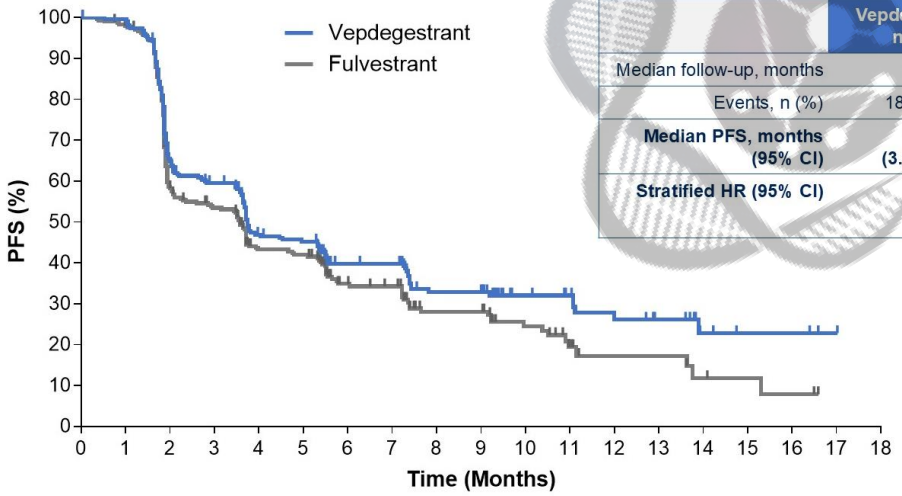
- OS (key secondary)
- CBR and ORR by BIC
- AEs

PFS by BICR in pts with ESR1m



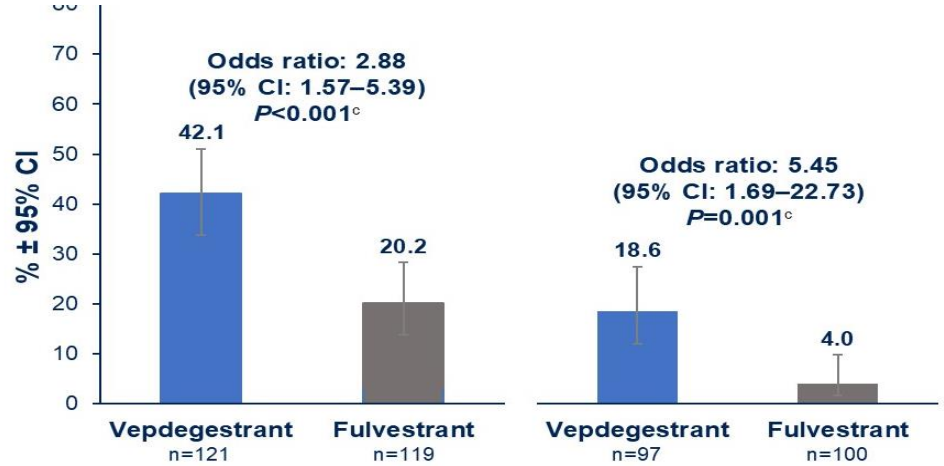
	Vepdegestrant n=136	Fulvestrant n=134
Median follow-up, months	7.4	6.0
Events, n (%)	79 (58)	95 (71)
Median PFS, months (95% CI)	**5.0 (3.7–7.4)**	**2.1 (1.9–3.5)**
Stratified HR (95% CI)	**0.57 (0.42–0.77)**	
	2-sided *P*<0.001	

PFS by BICR in All pts



	Vepdegestrant n=313	Fulvestrant n=311
Median follow-up, months	7.4	7.2
Events, n (%)	186 (59)	198 (64)
Median PFS, months (95% CI)	**3.7 (3.6–5.3)**	**3.6 (2.2–3.8)**
Stratified HR (95% CI)	**0.83 (0.68–1.02)**	
	2-sided *P*=0.07	

CBR[a] and ORR[b] in pts with ESR1m



[a]CBR was defined as the rate of confirmed CR or PR at any time, or SD, non-CR, or non-progressive disease for ≥24 weeks
[b]ORR was defined as the rate of confirmed CR or PR and was estimated in patients with measurable disease at baseline.

EMBER-3 trial: Design and Key outcomes

Trial Design

ER+, HER2- ABC

Men and Pre-[a]/Post-menopausal women

Prior therapy:

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification Factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]

R 1:1:1[b] N=874

- Imlunestrant 400 mg QD — A
- SOC ET[d,e] Fulvestrant or Exemestane — B
- Imlunestrant 400 mg QD + abemaciclib[e] — C[b]

Primary Endpoints

Investigator-assessed PFS f

- A vs B in patients with *ESR1*
- A vs B in all patients
- C vs A in all[h] patients

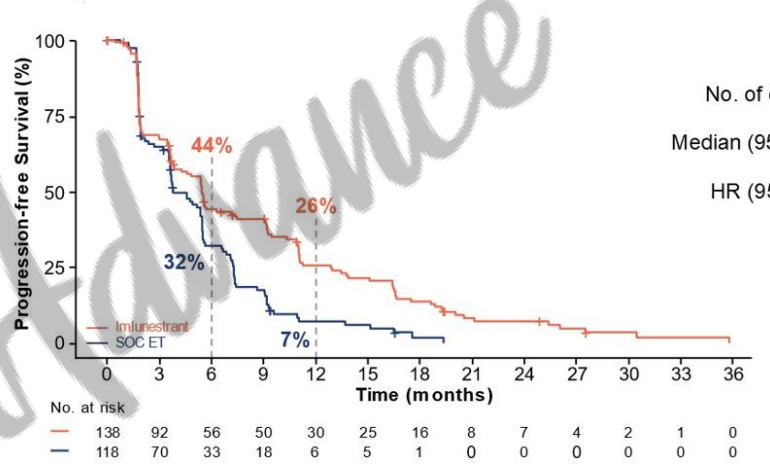
Key Secondary Endpoints

- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

- PFS and OS for C vs B in all[h] patients

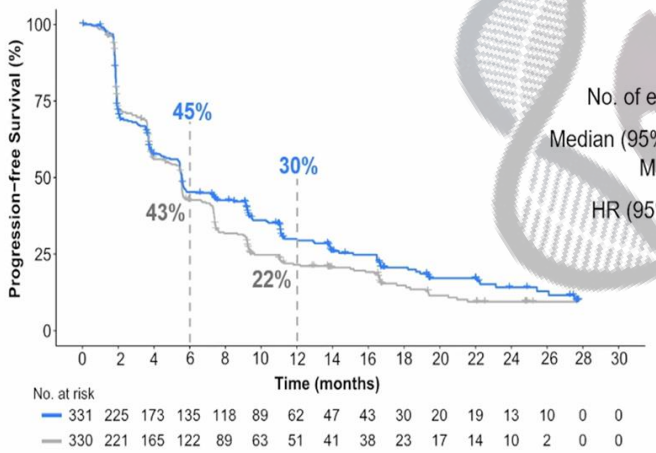
PFS in pts with ESR1m



	Imlunestrant n=138	SOC ET n=118
No. of events	122	103
Median (95% CI)	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.47-0.82)**	
	Nominal *p*-value[a] = 0.0007	

PFS benefit of imlunestrant was sustained in patients with *ESR1*m

PFS by BICR in All pts

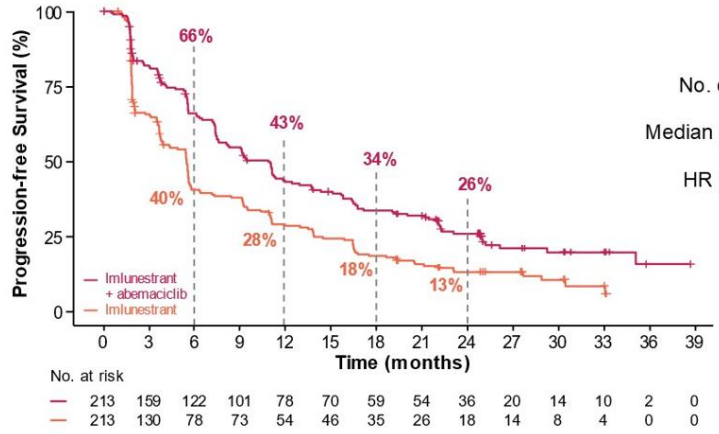


	Imlunestrant n=331	SOC ET n=330
No. of events	237	253
Median (95% CI); Months	**5.6** (5.3-7.3)	**5.5** (4.6-5.6)
HR (95% CI)	**0.87 (0.72-1.04)**	
	p-value 0.12	

Prespecified Critical HR < 0.84[a]

PFS difference of imlunestrant vs SOC ET in all patients did not reach significance

Imlunestrant + Abema vs Imlunestrant in All pts



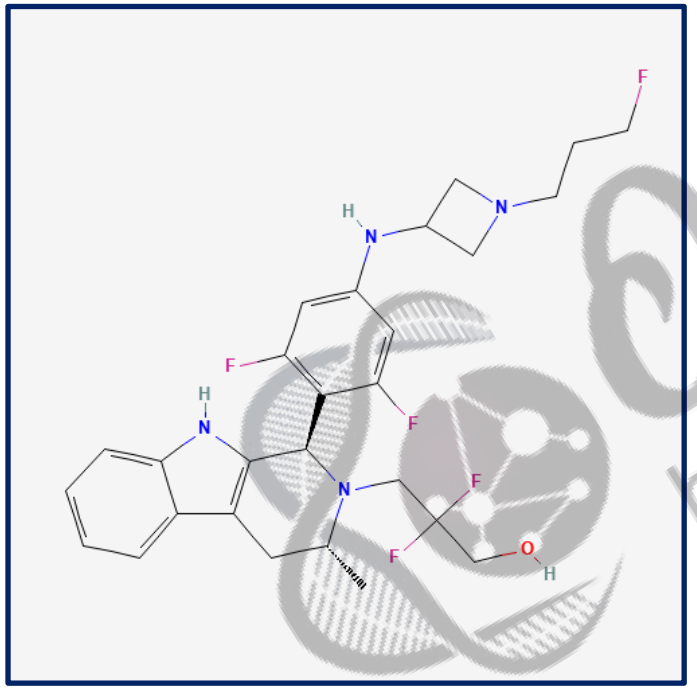
	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of events	144	174
Median (95% CI)	**10.9** (7.5-12.5)	**5.5** (3.8-5.6)
HR (95% CI)	**0.59 (0.47-0.74)**	
	Nominal *p*-value[a] < 0.0001	

PFS benefit of imlunestrant + abemaciclib was maintained in all patients

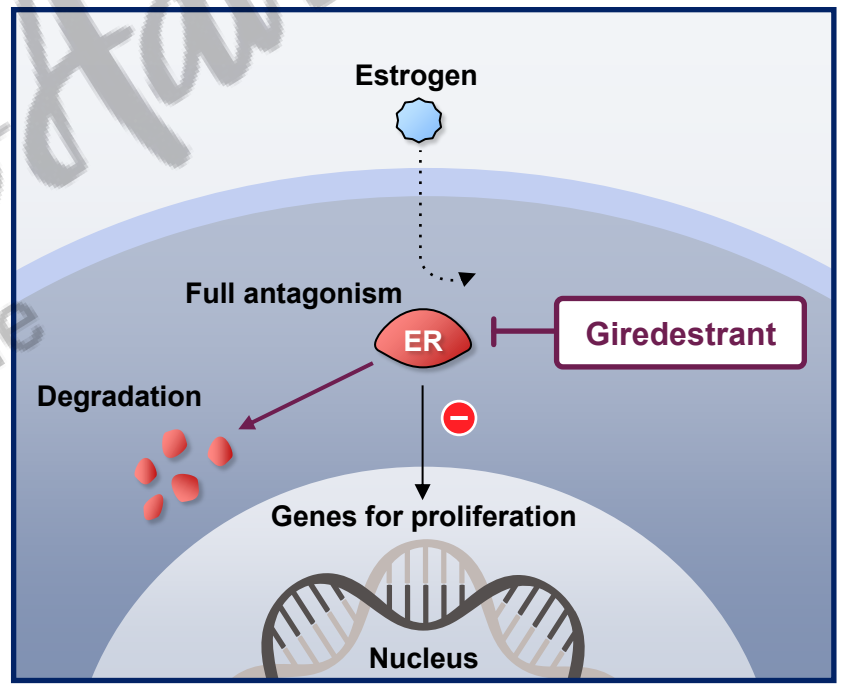
Jhavery K, et al. SABCS 2024; Jhavery K, et al SABCS 2025

Background – giredestrant

Giredestrant (GDC-9545) is a potent next-generation oral SERD and full ER antagonist, designed to drive deep and sustained inhibition of ER signaling, both ligand-dependent and ligand-independent.[1]



Giredestrant chemical structure (basic amine side chain)[2]



Giredestrant mechanism of action (selective estrogen receptor antagonist and degrader)

ER, estrogen receptor; SERD, selective estrogen receptor antagonist and degrader. 1. Liang J, *et al*. *J Med Chem* 2021; **64:**11841–11856;
2. National Center for Biotechnology Information. PubChem Compound Summary for CID 121410806, Giredestrant. https://pubchem.ncbi.nlm.nih.gov/compound/Giredestrant. Accessed December 9, 2025.

evERA: Design and Key outcomes

Trial Design

Key eligibility criteria*
- ER+, HER2– aBC (1–3L of therapy)
- ≤ 2 prior lines of ET in the aBC setting
- PD or relapse during/post-CDK4/6i + ET
- No prior chemotherapy in the aBC setting
- Measurable disease per RECIST v1.1 or evaluable bone metastases

Enrolment period: August 2022 to October 2024

N = 373* → R 1:1

- Giredestrant (30 mg) + everolimus (10 mg)†
- SOC ET‡ + everolimus (10 mg)†
  ‡Exemestane/fulvestrant/tamoxifen

Until PD or unacceptable toxicity

† Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol[1]

* Trial was enriched to 55% of patients with *ESR1*m at baseline (centrally tested via circulating tumour DNA)

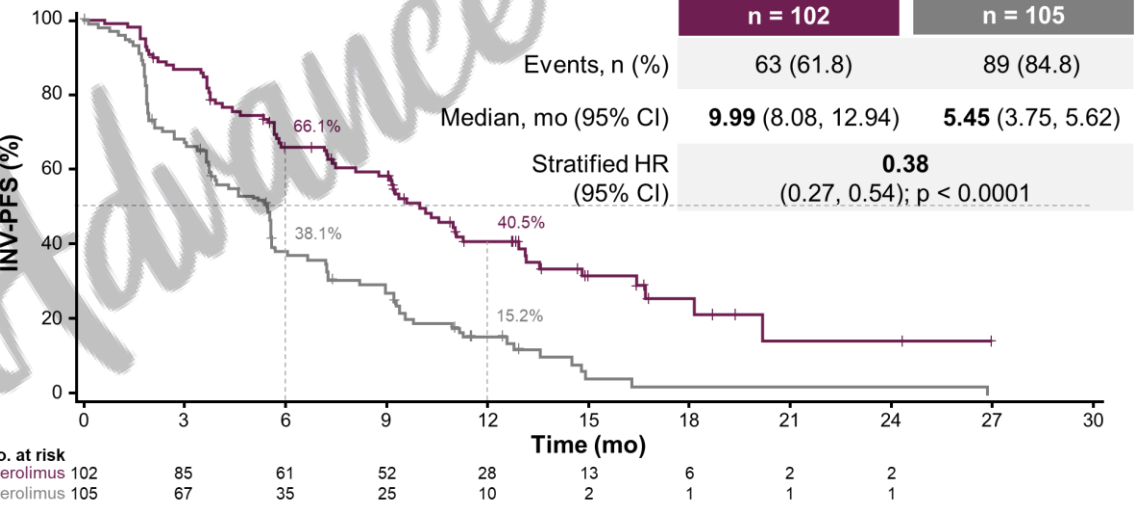
Stratification factors
- Prior treatment with fulvestrant (yes vs no)
- *ESR1*m (yes vs no/indeterminate)
- Site of disease (visceral [lung and/or liver involvement] vs non-visceral)

Co-primary endpoints (RECIST v1.1)
- INV-PFS in patients whose tumours had *ESR1*m
- INV-PFS in the ITT population

Key secondary endpoints
- OS
- INV-assessed ORR, DoR

PFS in ESR1m

	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < 0.0001	

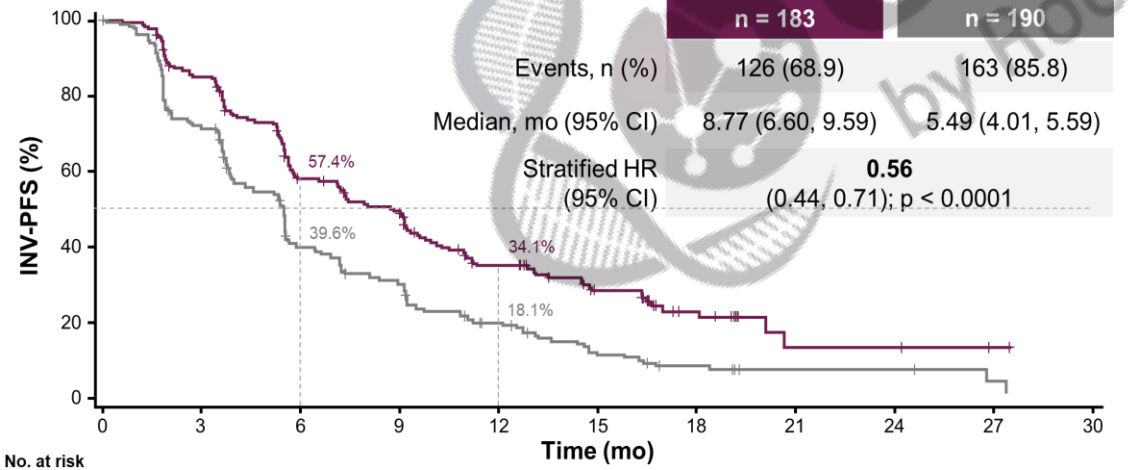


No. at risk

Giredestrant + everolimus	102	85	61	52	28	13	6	2	2
SOC ET + everolimus	105	67	35	25	10	2	1	1	1

PFS in ITT

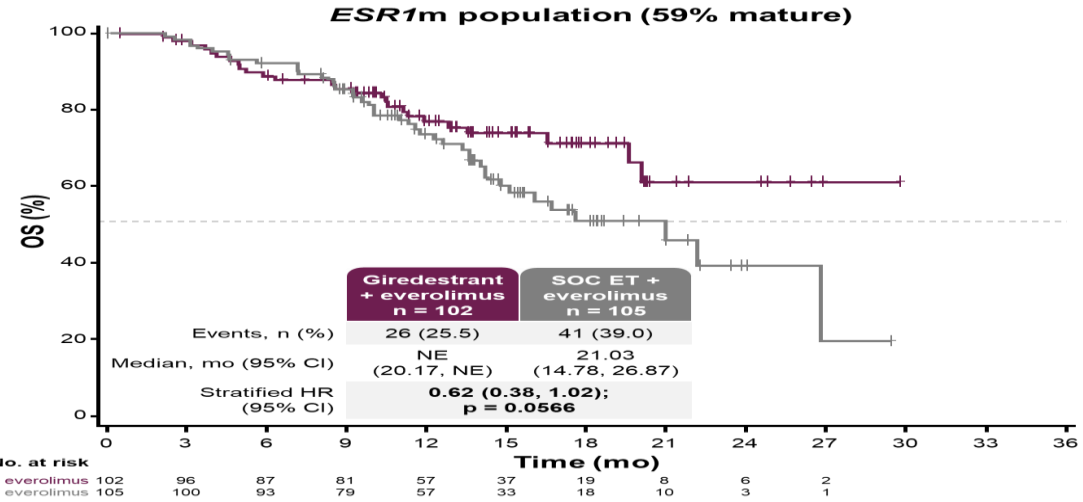
	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
Events, n (%)	126 (68.9)	163 (85.8)
Median, mo (95% CI)	8.77 (6.60, 9.59)	5.49 (4.01, 5.59)
Stratified HR (95% CI)	**0.56** (0.44, 0.71); p < 0.0001	



No. at risk

Giredestrant + everolimus	183	149	95	70	47	29	14	3	3	1
SOC ET + everolimus	190	131	68	50	27	14	7	3	3	1

OS in ESR1m (immature)



	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	26 (25.5)	41 (39.0)
Median, mo (95% CI)	NE (20.17, NE)	21.03 (14.78, 26.87)
Stratified HR (95% CI)	**0.62 (0.38, 1.02); p = 0.0566**	

No. at risk

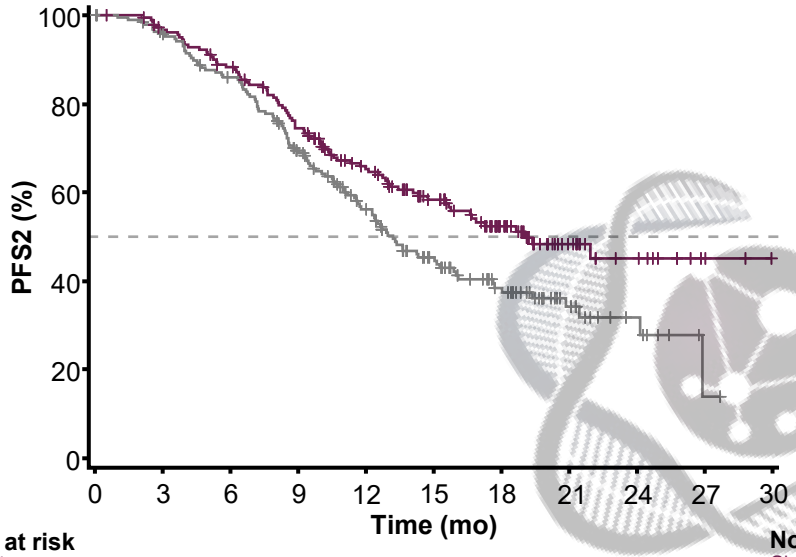
Giredestrant + everolimus	102	96	87	81	57	37	19	8	6	2
SOC ET + everolimus	105	100	93	79	57	33	18	10	3	1

Mayer E, et al. ESMO 2025

PFS2 in the overall study, *ESR1*m, and *ESR1*m not detected populations

Overall study

	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
Events, n (%)	81 (44.3)	108 (56.8)
Median, mo (95% CI)	**19.02** (15.51, NE)	**13.17** (11.70, 15.87)
HR (95% CI)	**0.69** (0.51, 0.92)	

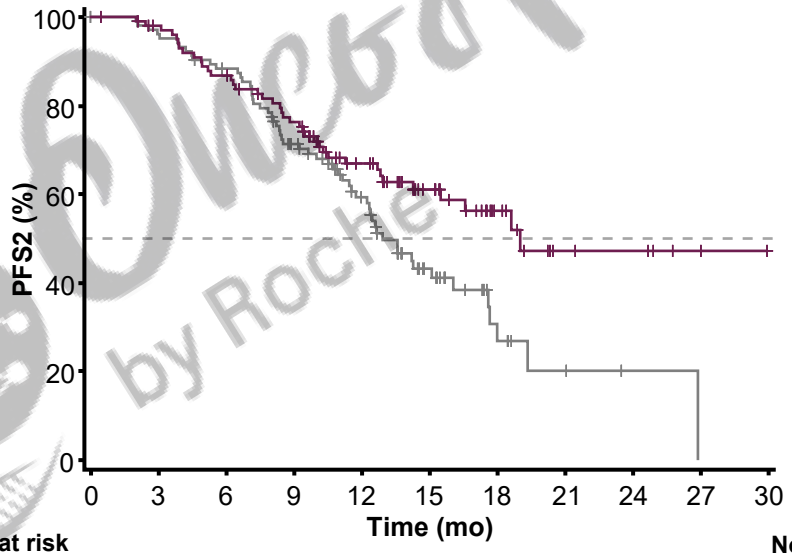


No. at risk

Giredestrant + everolimus	183	173	156	129	100	74	48	21	11	3
SOC ET + everolimus	190	177	157	121	87	58	38	18	8	1

*ESR1*m

	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	39 (38.2)	57 (54.3)
Median, mo (95% CI)	**19.02** (15.51, NE)	**12.94** (11.76, 17.61)
HR (95% CI)	**0.61** (0.40, 0.93)	

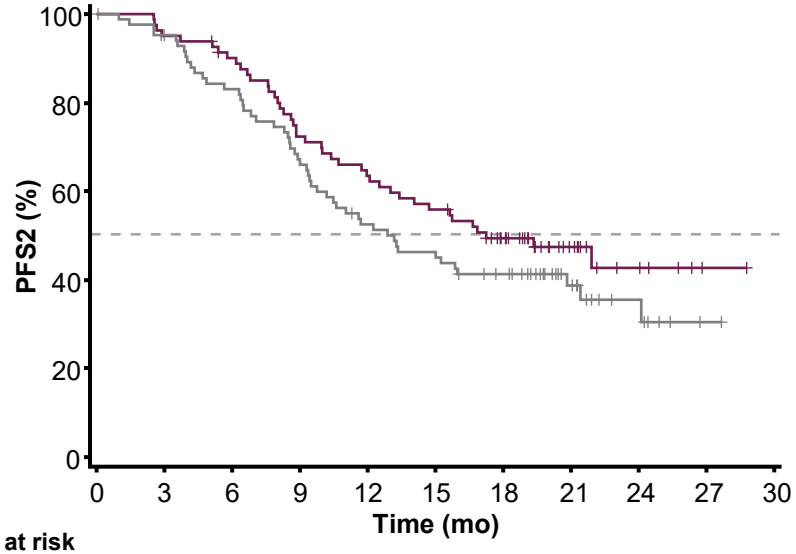


No. at risk

Giredestrant + everolimus	102	96	85	72	50	30	15	6	5	2
SOC ET + everolimus	105	99	89	66	45	21	8	3	1	

*ESR1*m not detected

	Giredestrant + everolimus n = 81	SOC ET + everolimus n = 85
Events, n (%)	42 (51.9)	51 (60.0)
Median, mo (95% CI)	**17.25** (13.01, NE)	**12.88** (9.76, 20.83)
HR (95% CI)	**0.77** (0.51, 1.17)	



No. at risk

Giredestrant + everolimus	81	77	71	57	50	44	33	15	6	1
SOC ET + everolimus	85	78	68	55	42	37	30	15	7	1

Data cutoff: July 16, 2025. Median follow-up: 18.4 mo (giredestrant + everolimus); 18.7 mo (SOC ET + everolimus). HR estimates are stratified. PFS2 was defined as the time from randomization to first progression on next-line therapy or death.
CI, confidence interval; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; HR, hazard ratio; mo, months; NE, not evaluable; PFS2, progression-free survival 2; SOC, standard-of-care.

Key follow-up anti-cancer therapies

Patients, n (%)	Overall study		*ESR1*m		*ESR1*m not detected	
	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105	Giredestrant + everolimus n = 81	SOC ET + everolimus n = 85
Discontinued all study treatment	**142 (77.6)**	**176 (92.6)**	**72 (70.6)**	**98 (93.3)**	**70 (86.4)**	**78 (91.8)**
Received follow-up therapy*,†	**110 (60.1)**	**137 (72.1)**	**49 (48.0)**	**75 (71.4)**	**61 (75.3)**	**62 (72.9)**
Chemotherapies	**76 (69.1)**	**98 (71.5)**	**31 (63.3)**	**49 (65.3)**	**45 (73.8)**	**49 (79.0)**
Capecitabine	49 (44.5)	66 (48.2)	18 (36.7)	33 (44.0)	31 (50.8)	33 (53.2)
Paclitaxel	31 (28.2)	43 (31.4)	13 (26.5)	21 (28.0)	18 (29.5)	22 (35.5)
ETs	**42 (38.2)**	**42 (30.7)**	**22 (44.9)**	**26 (34.7)**	**20 (32.8)**	**16 (25.8)**
Fulvestrant	22 (20.0)	21 (15.3)	9 (18.4)	10 (13.3)	13 (21.3)	11 (17.7)
Elacestrant	5 (4.5)	12 (8.8)	4 (8.2)	9 (12.0)	1 (1.6)	3 (4.8)
Exemestane	9 (8.2)	7 (5.1)	6 (12.2)	6 (8.0)	3 (4.9)	1 (1.6)
Tamoxifen	3 (2.7)	2 (1.5)	1 (2.0)	1 (1.3)	2 (3.3)	1 (1.6)
ADCs	**27 (24.5)**	**43 (31.4)**	**9 (18.4)**	**19 (25.3)**	**18 (29.5)**	**24 (38.7)**
Trastuzumab deruxtecan	20 (18.2)	31 (22.6)	4 (8.2)	15 (20.0)	16 (26.2)	16 (25.8)
Sacituzumab govitecan	5 (4.5)	18 (13.1)	4 (8.2)	5 (6.7)	1 (1.6)	13 (21.0)
Targeted therapies	**29 (26.4)**	**19 (13.9)**	**13 (26.5)**	**12 (16.0)**	**16 (26.2)**	**7 (11.3)**
Capivasertib	10 (9.1)	5 (3.6)	2 (4.1)	2 (2.7)	8 (13.1)	3 (4.8)
Biologics‖	**17 (15.5)**	**22 (16.1)**	**4 (8.2)**	**11 (14.7)**	**13 (21.3)**	**11 (17.7)**
CDKis‡	**8 (7.3)**	**13 (9.5)**	**4 (8.2)**	**6 (8.0)**	**4 (6.6)**	**7 (11.3)**

Key follow-up cancer therapies reflect the expected follow-up therapies for this patient population

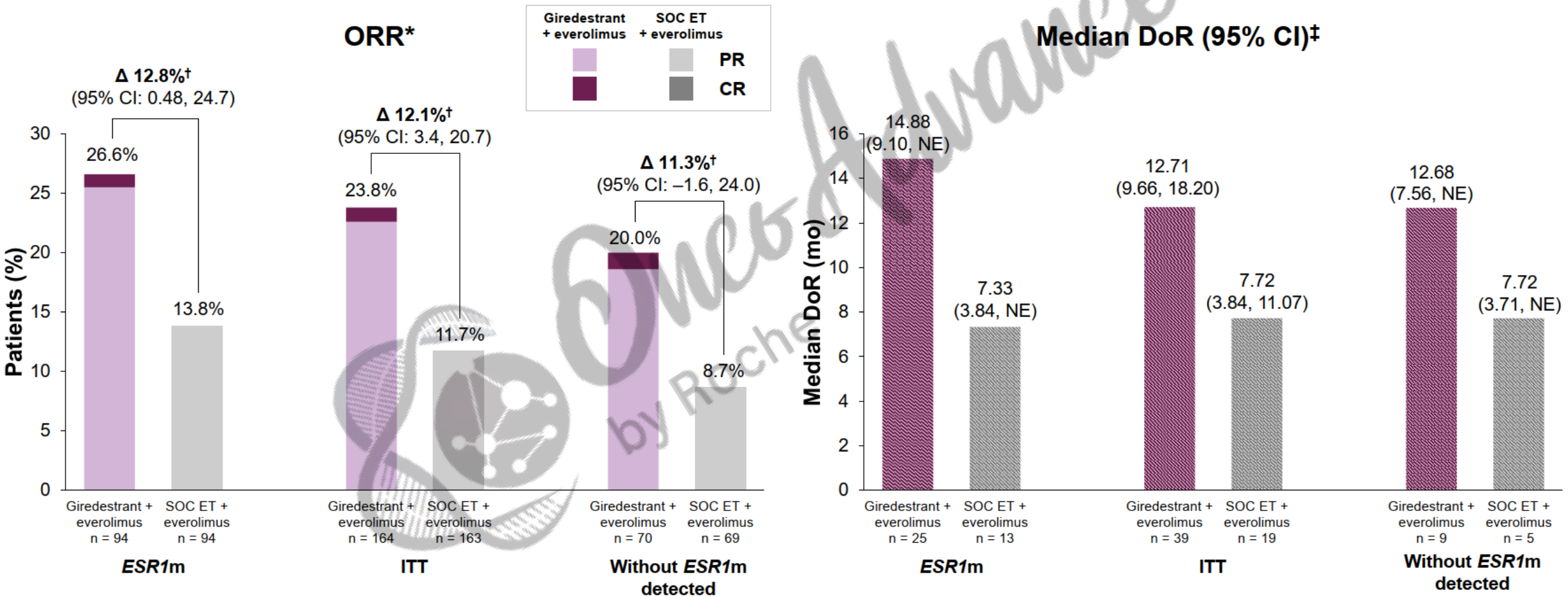
Data cutoff: July 16, 2025.

* Includes patients who received ≥ 1 follow-up cancer therapy, excluding radiotherapy and surgery, regardless of the line of treatment. † Percentages for therapies listed were calculated using the number of patients who received follow-up therapy as the denominator. ‡ Includes patients who received an approved CDK4/6i and those who received an investigational CDK2i or CDK4i. ‖ Includes bevacizumab, immunotherapy, and HER2-targeted antibodies.

ADC, antibody–drug conjugate; CDK(2/4/6)i, cyclin-dependent kinase (2/4/6) inhibitor; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; SOC, standard-of-care.

PRESENTED BY: Komal L. Jhaveri, MD, FACP, FASCO

ORR and DoR in the *ESR1*m and ITT populations, and in patients without *ESR1*m detected

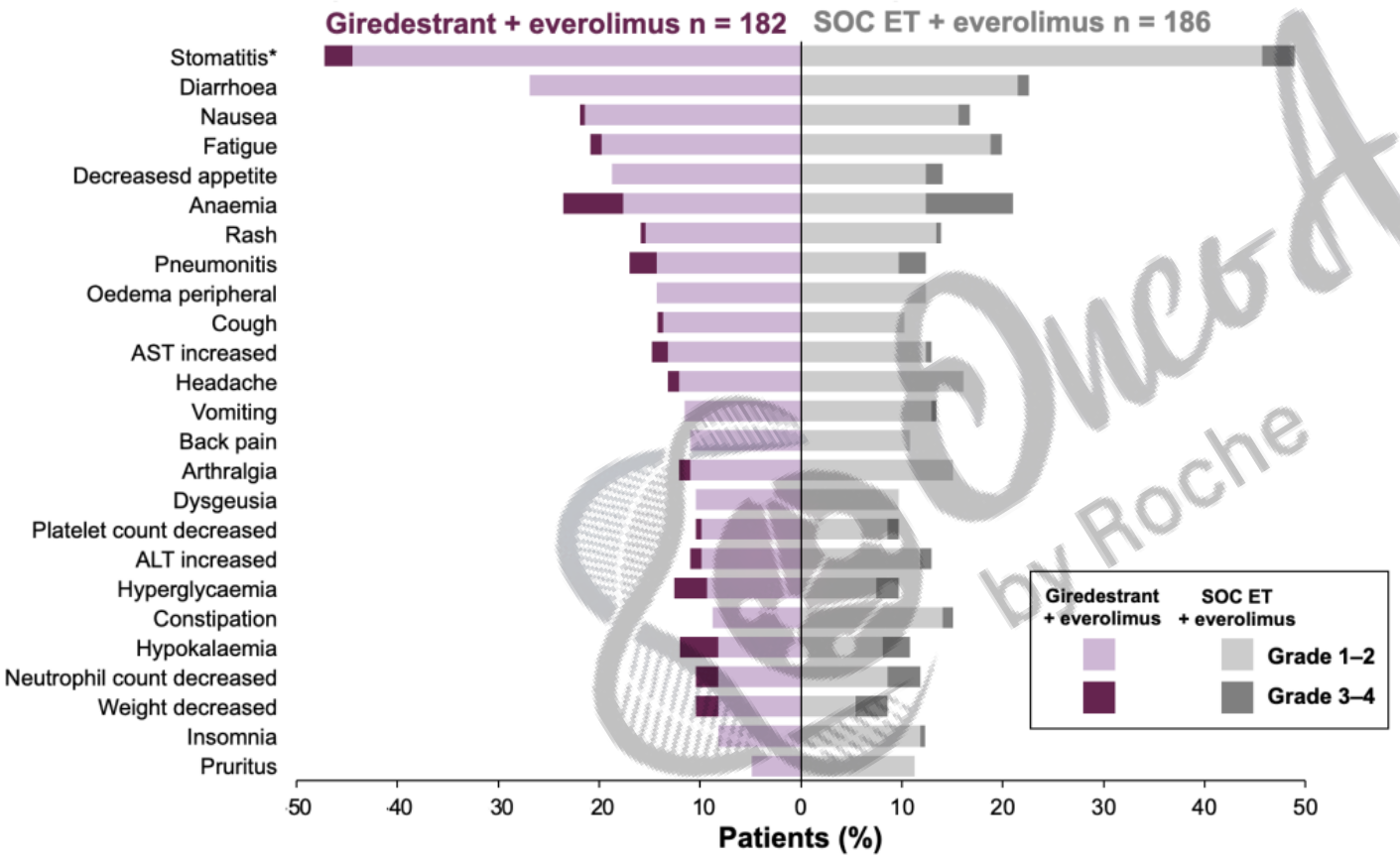


Data cutoff: 16 July 2025. * Patients who had measurable disease at baseline; all responses were confirmed on two consecutive occasions ≥ 4 weeks apart. † Stratified analysis. ‡ Patients who had measurable disease at baseline and an objective response.
CI, confidence interval; CR, complete response; DoR, duration of response; *ESR1*m, *ESR1* mutation; ITT, intention to treat; mo, months; NE, not evaluable; ORR, objective response rate; PR, partial response; SOC ET, standard of care endocrine therapy.

Presented by: Erica L. Mayer, MD, MPH.

Safety profile

No signal of cumulative tox



	Giredestrant + everolimus n = 182	SOC ET + everolimus n = 186
Treatment-related AEs		
Giredestrant or SOC ET	118 (64.8)	106 (57.0)
Everolimus	168 (92.3)	160 (86.0)
Any	171 (94.0)	163 (87.6)
AEs leading to discontinuation from treatment		
Giredestrant or SOC ET	15 (8.2)	12 (6.5)
Everolimus	31 (17.0)	22 (11.8)
Any	31 (17.0)	22 (11.8)

BOLERO2 toxicity profile

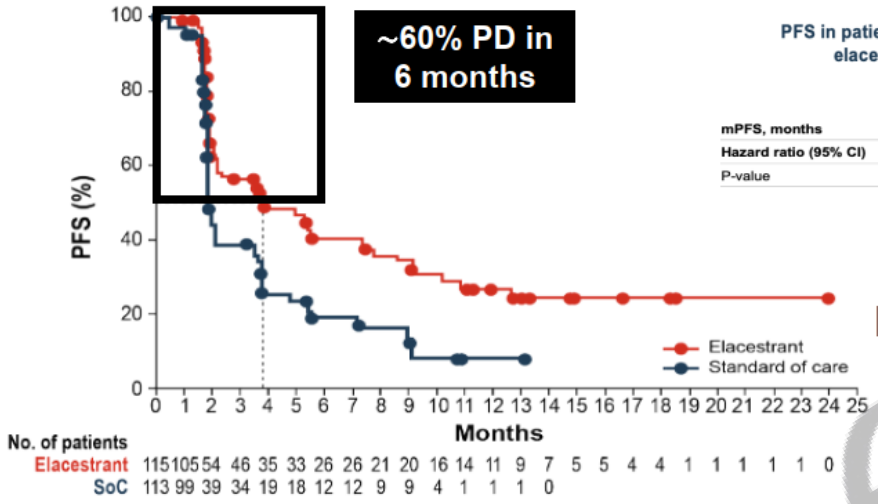
Table 2. Adverse Events Irrespective of Relationship to Study Treatment (with at Least 10% Incidence in the Everolimus–Exemestane Group).

Adverse Event	Everolimus and Exemestane (N=482)			Placebo and Exemestane (N=238)		
	Any Event	Grade 3 Event	Grade 4 Event	Any Event	Grade 3 Event	Grade 4 Event
	percent					
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Decreased appetite	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Cough	22	1	0	11	0	0
Dysgeusia	21	<1	0	5	0	0
Headache	19	<1	0	13	0	0
Decreased weight	19	1	0	5	0	0
Dyspnea	18	4	0	9	1	<1

A Gennari

Mayer EL et al, ESMO 2025.
Baselga J et al. N Engl J Med. 2012

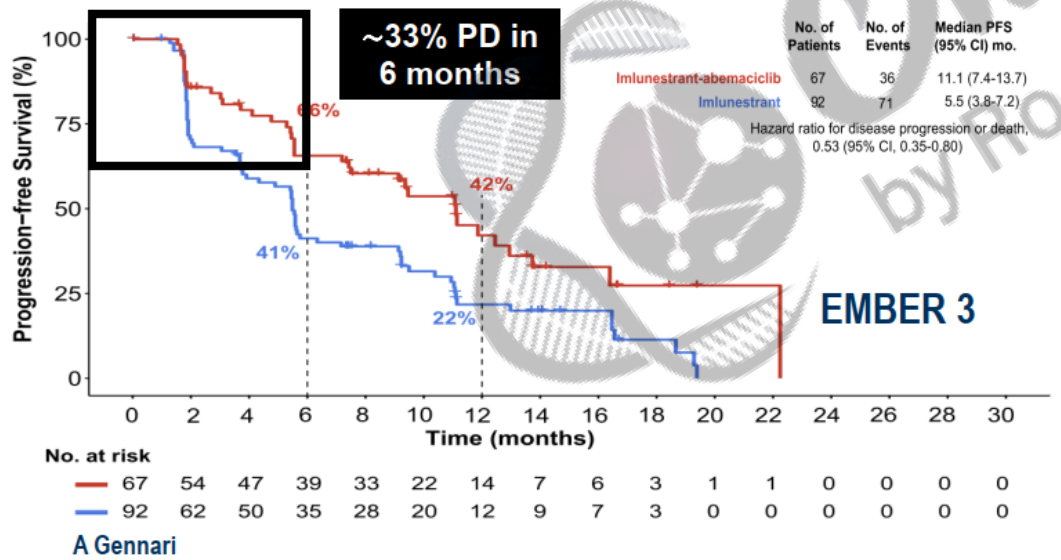
Early progression in ESR1 mut: single agent SERD vs SERD + targeted therapy



PFS in patients with *ESR1*-mut: elacestrant vs SoC

	Elacestrant (n=115)	SoC (n=113)
mPFS, months	3.8	1.9
Hazard ratio (95% CI)	0.55 (0.39–0.77)	
P-value	0.0005	

EMERALD

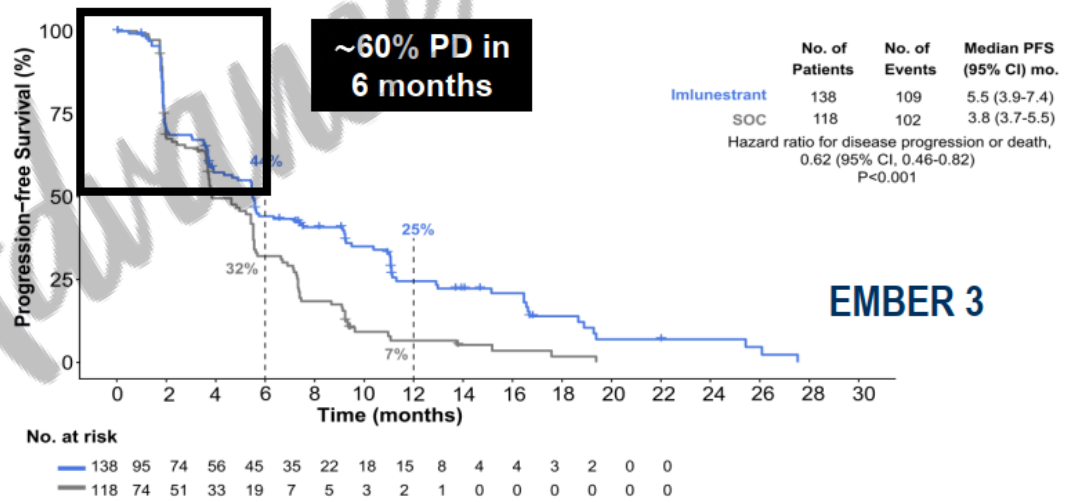


	No. of Patients	No. of Events	Median PFS (95% CI) mo.
Imlunestrant-abemaciclib	67	36	11.1 (7.4-13.7)
Imlunestrant	92	71	5.5 (3.8-7.2)

Hazard ratio for disease progression or death, 0.53 (95% CI, 0.35-0.80)

EMBER 3

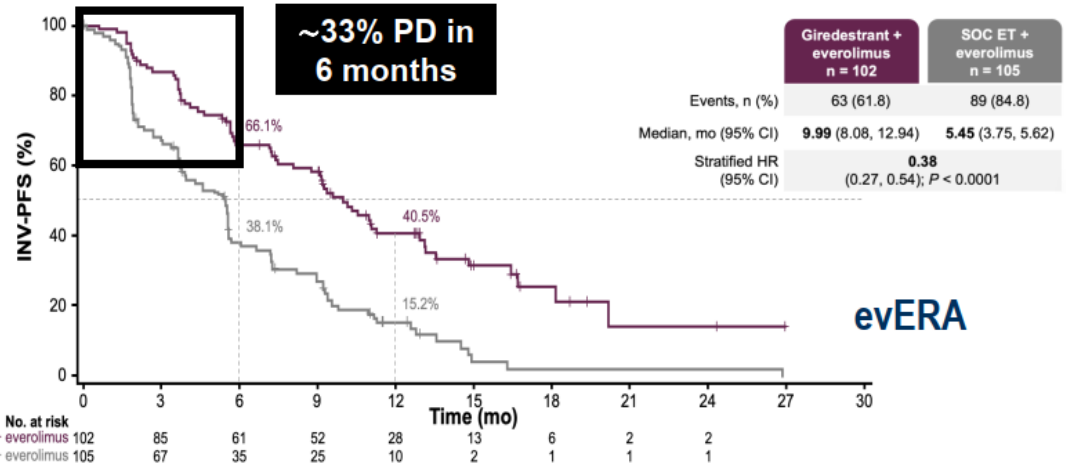
A Gennari



	No. of Patients	No. of Events	Median PFS (95% CI) mo.
Imlunestrant	138	109	5.5 (3.9-7.4)
SOC	118	102	3.8 (3.7-5.5)

Hazard ratio for disease progression or death, 0.62 (95% CI, 0.46-0.82) P<0.001

EMBER 3



	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); *P* < 0.0001	

evERA

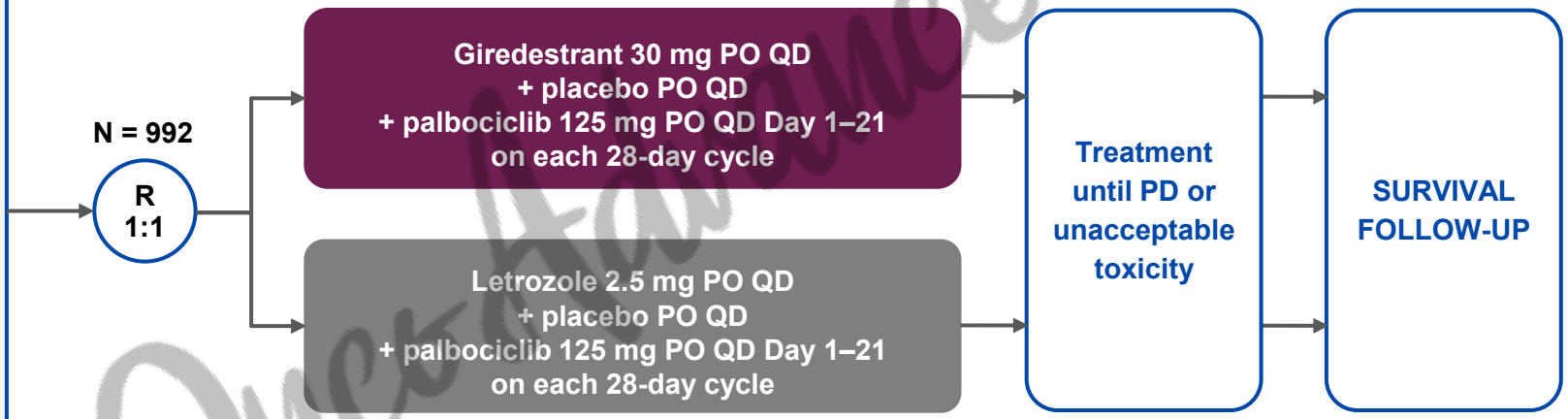
Mayer EL et al, ESMO 2025. Bidard FC et al. J Clin Oncol. 2022. Jhaveri KL et al. N Engl J Med. 2025.

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

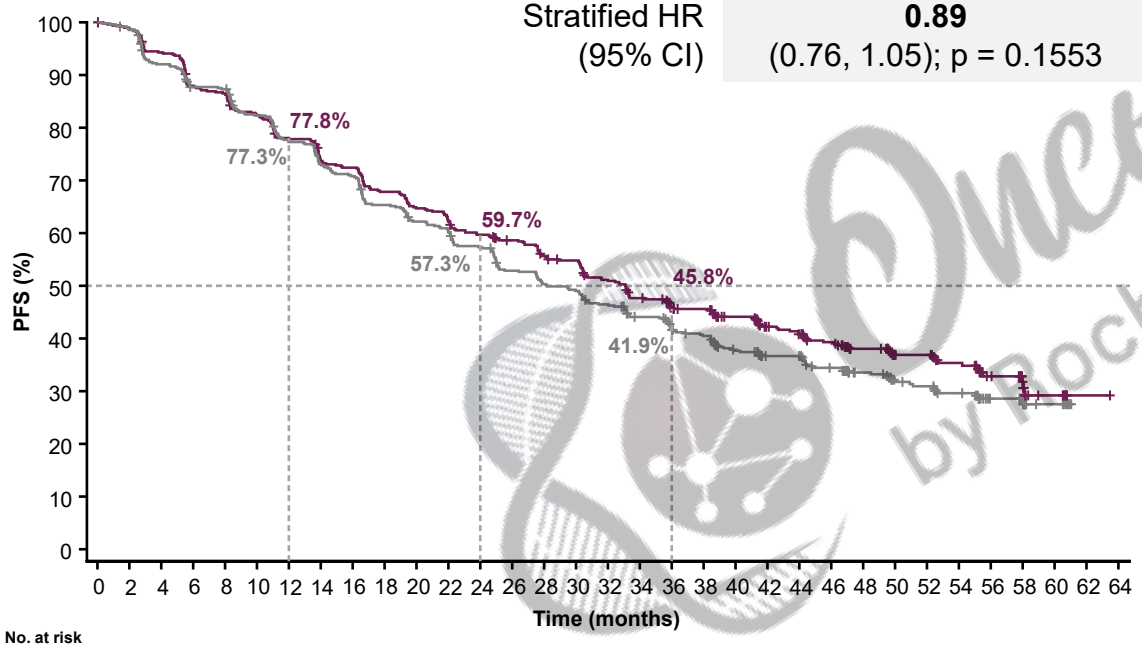
Secondary endpoints:

- 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.

Primary endpoint: INV-PFS

	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	

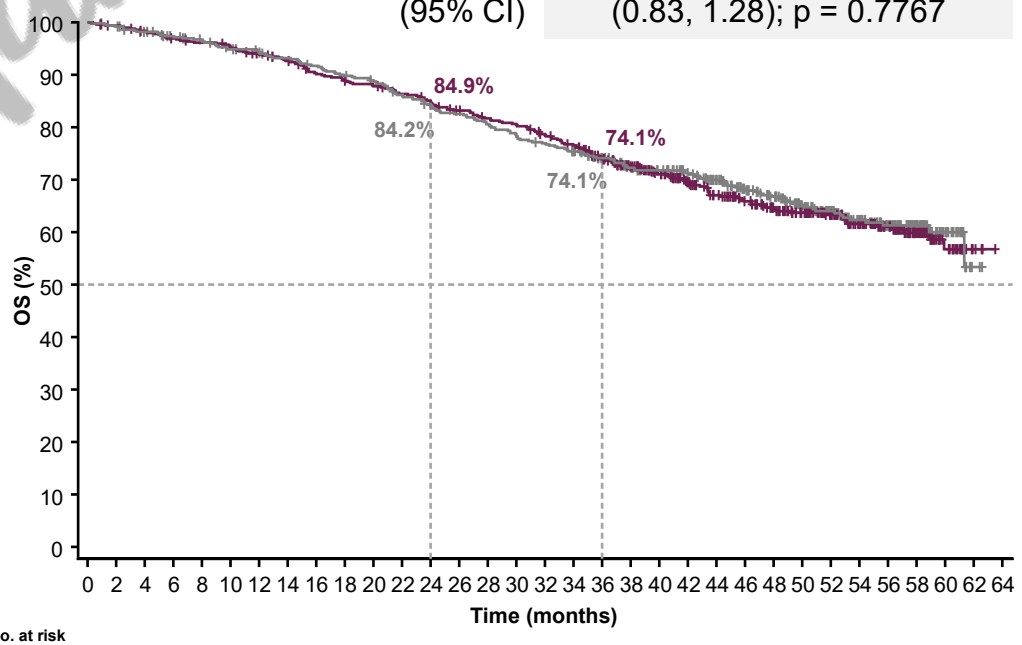


No. at risk

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	

Secondary endpoint: OS

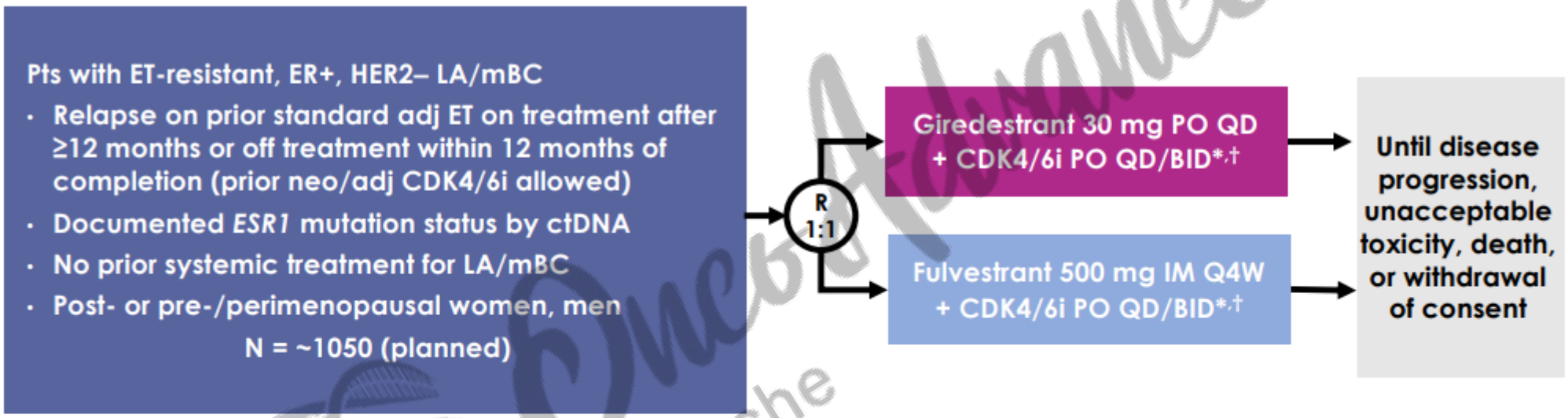
	Giredestrant + palbociclib n = 495	Letrozole + palbociclib n = 497
Events, n (%)	172 (34.7)	166 (33.4)
Median, months (95% CI)	**NE** (NE, NE)	**NE** (61.3, NE)
Stratified HR (95% CI)	**1.03** (0.83, 1.28); p = 0.7767	



No. at risk

Giredestrant + palbociclib	495	489	482	474	469	463	454	446	432	425	419	410	402	391	382	376	365	353	331	308	286	263	239	222	199	182	159	132	112	71	31	6
Letrozole + palbociclib	497	492	482	472	464	454	448	440	432	423	416	403	392	384	375	364	357	348	328	305	291	275	257	232	214	185	162	134	111	69	27	2

pionERA Breast Cancer: Phase III study of 1L giredestrant vs. fulvestrant, both combined with a CDK4/6i, in pts with ER+, HER2– LA/mBC with resistance to prior adjuvant ET



Stratification factors

- Disease site (visceral vs. non-visceral)
- *ESR1* mutation status (*ESR1*mut vs. *ESR1*nmd)
- Choice of CDK4/6i
- Prior adj CDK4/6i (yes vs. no)

Co-primary endpoints

- Investigator-assessed PFS in the *ESR1*mut population and in the full analysis set (per RECIST v1.1)

Secondary endpoints

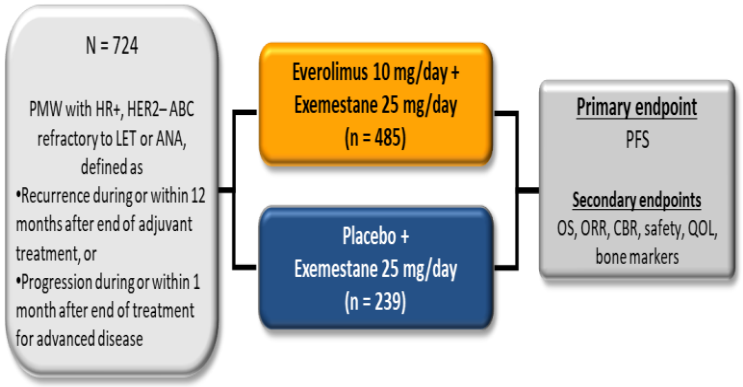
- PFS (*ESR1*nmd population)
- OS‡
- Investigator-assessed confirmed ORR‡, DoR‡, and CBR‡ (per RECIST v1.1)
- Time to chemotherapy‡
- PROs‡ (time to confirmed deterioration in pain, physical and role functioning, GHS/QoL)
- Safety

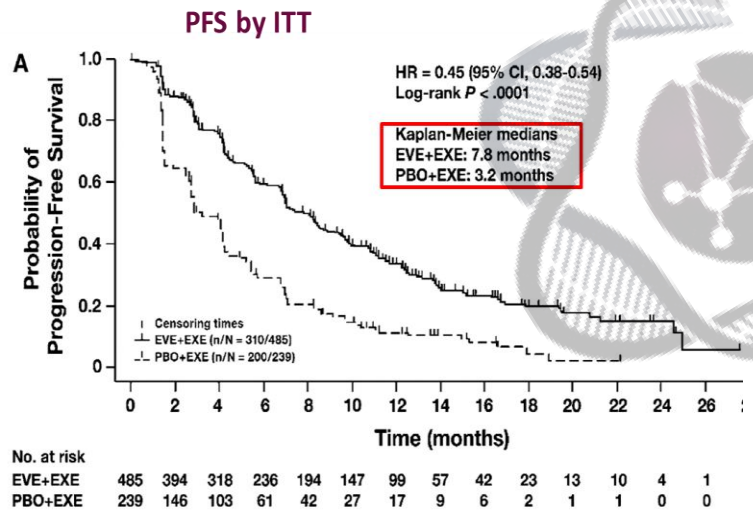
Kevin Kalinsky, TPS1130, ASCO 2024

Targeting the PI3K/AKT/mTOR pathway

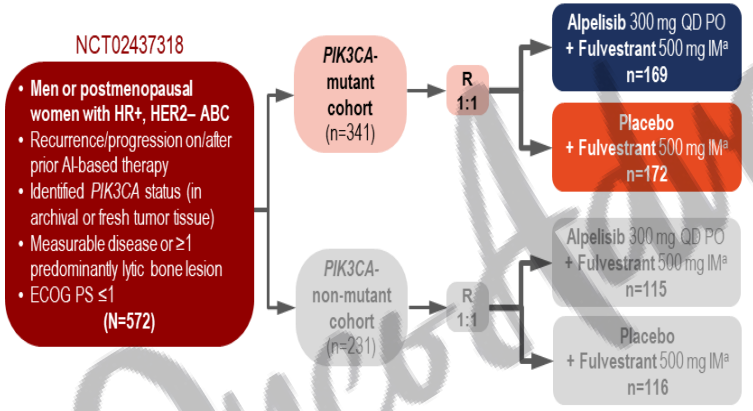
PI3K/AKT/mTOR inh in ET resistant tumors

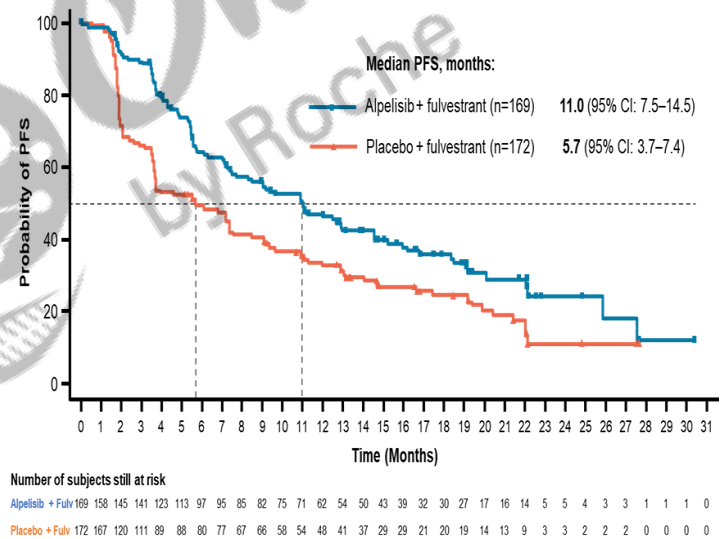
BOLERO



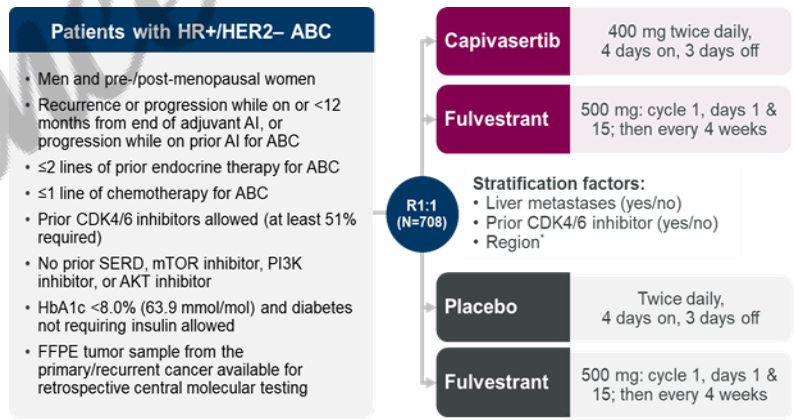


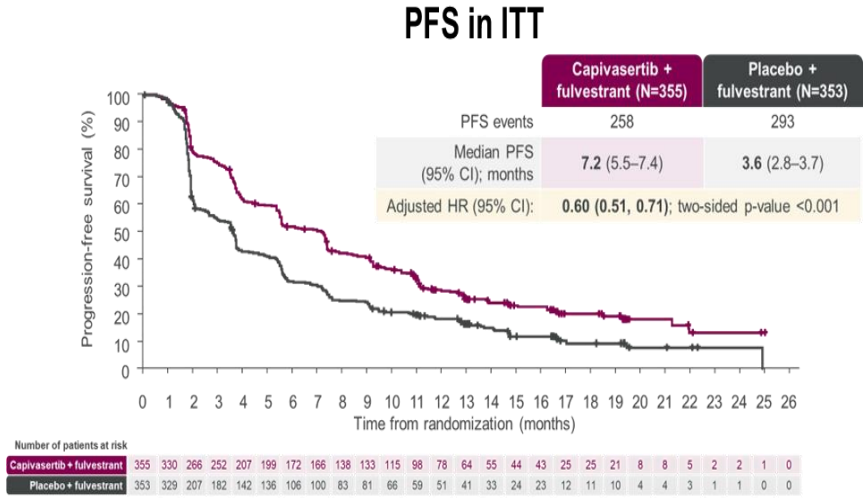
SOLAR-1





CAPITello 291

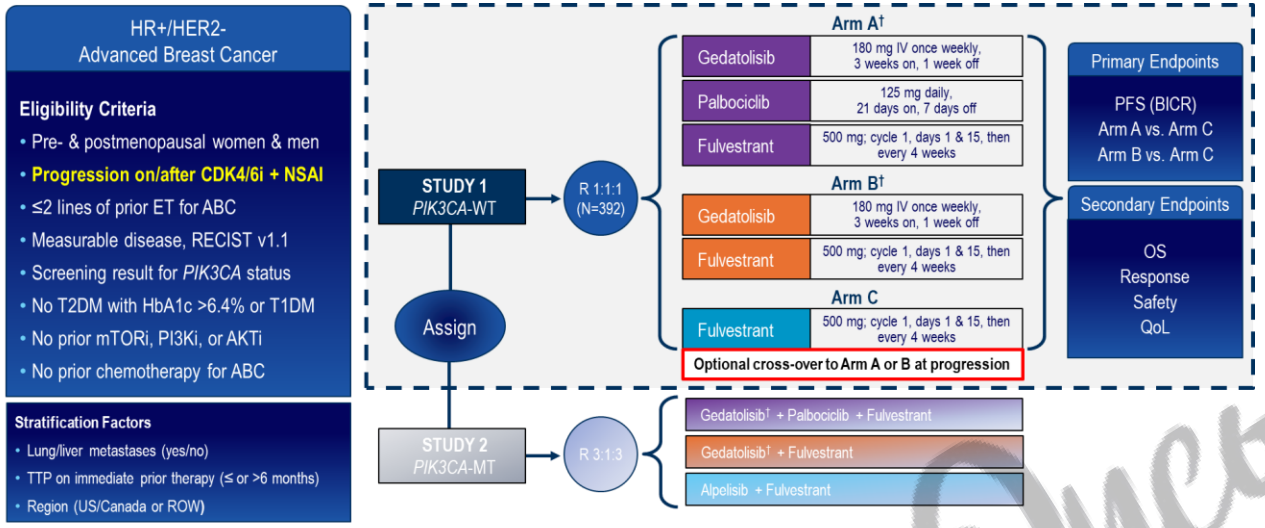




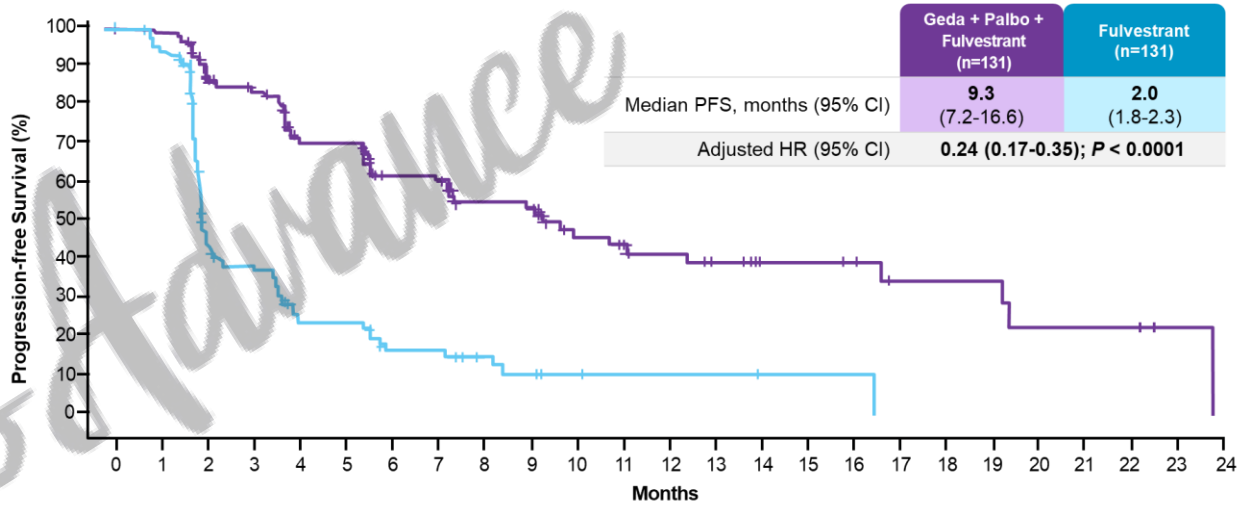
Baselga K, et al. NEJM 2012; Andre F, et al. NEJM 2019; Turner N, et al. NEJM 2023

Viktoria 1 Study 1: Design and Key outcomes (PI3K wt)

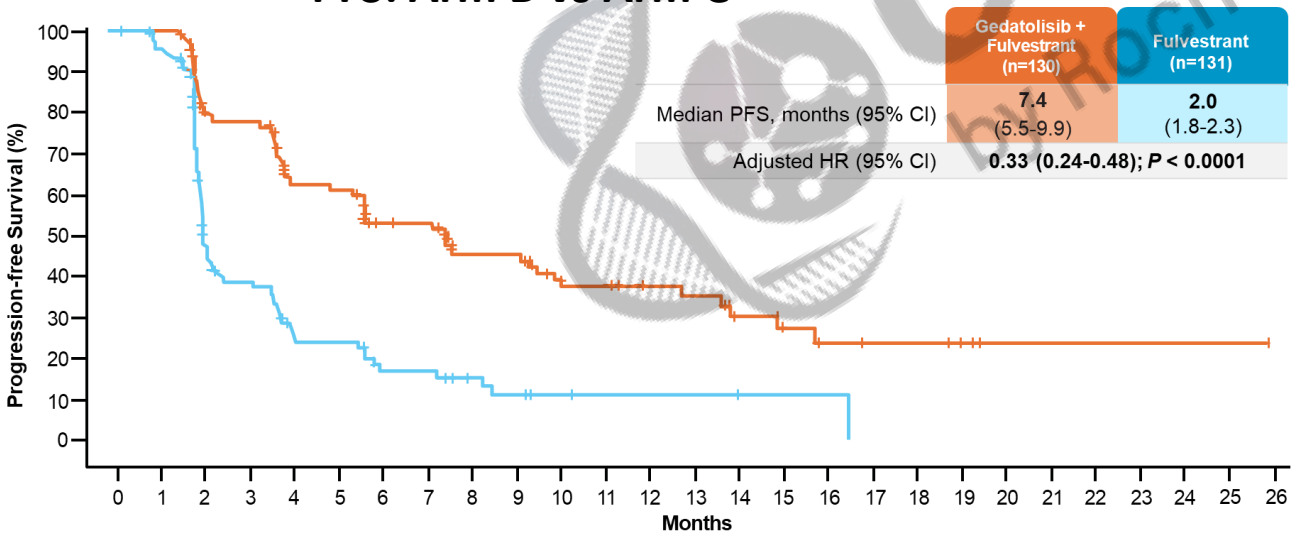
Trial Design



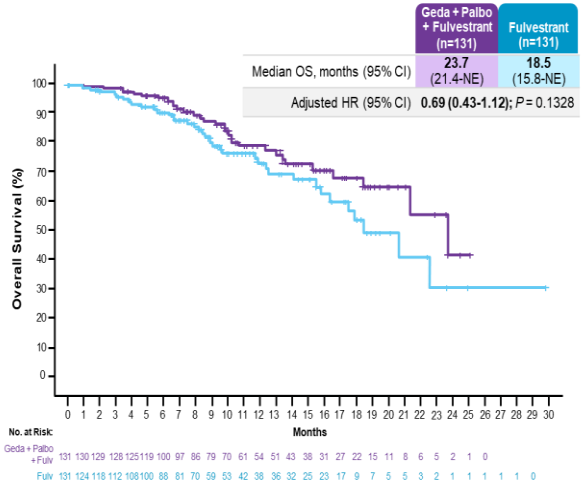
PFS: Arm A vs Arm C

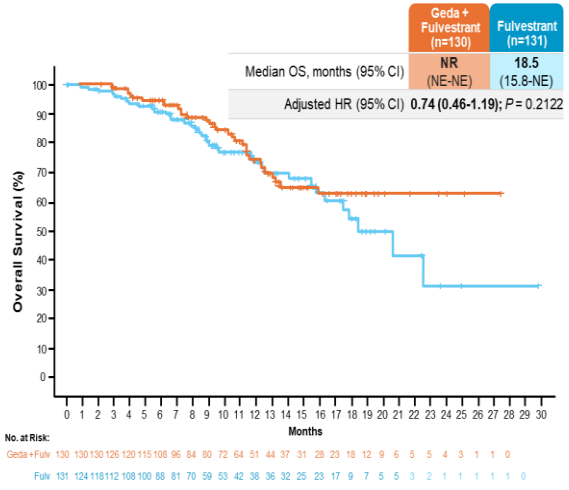


PFS: Arm B vs Arm C



OS (immature)





Hurvitz S, et al. ESMO 2025

Viktoria 1 Study 2: Design and Key outcomes (PI3K mut)

Trial 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)

STUDY 2 *PIK3CA*-MT → R 3:3:1 (N=362) → Assign

Arm D*	Gedatolisib	180 mg IV once weekly, 3 weeks on, 1 week off
	Palbociclib	125 mg daily, 21 days on, 7 days off
	Fulvestrant	500 mg; cycle 1, days 1 & 15, then every 4 weeks
Arm E	Alpelisib	300 mg orally daily for 4 weeks
	Fulvestrant	500 mg; cycle 1, days 1 & 15, then every 4 weeks
Arm F*	Gedatolisib	180 mg IV once weekly, 3 weeks on, 1 week off
	Fulvestrant	500 mg; cycle 1, days 1 & 15, then every 4 weeks

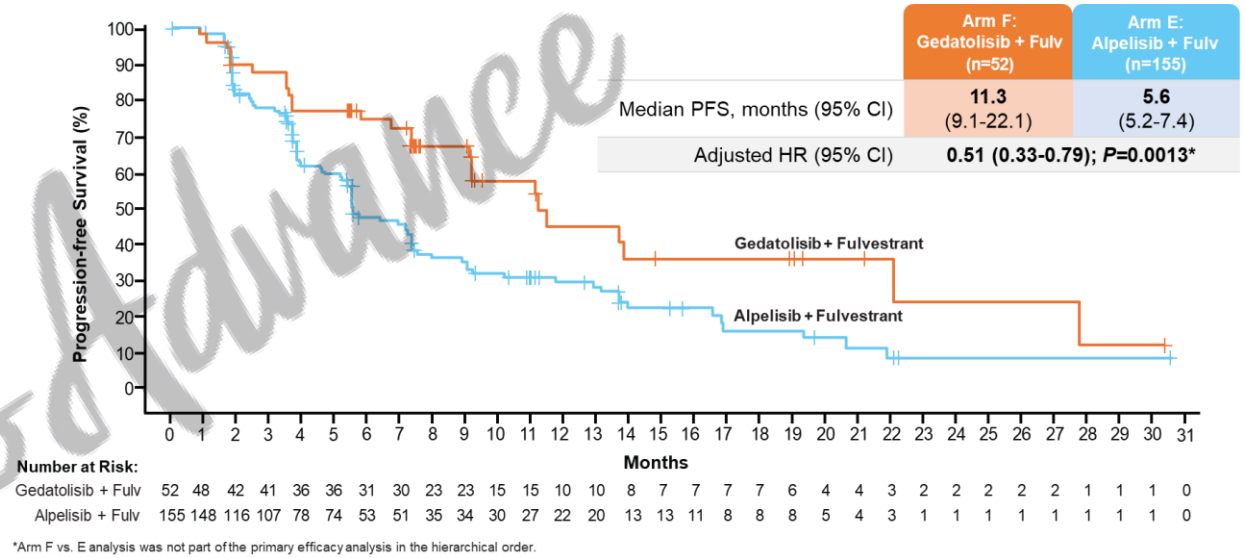
Primary Endpoint: PFS (BICR) Arm D vs. Arm E

Secondary Endpoints: OS; PFS (BICR F vs. E); Response; Safety; QoL

STUDY 1 *PIK3CA*-WT → R 1:1:1
- Arm A: Gedatolisib† + Palbociclib + Fulvestrant
- Arm B: Gedatolisib† + Fulvestrant
- Arm C: Fulvestrant

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

PFS: Arm E vs Arm F



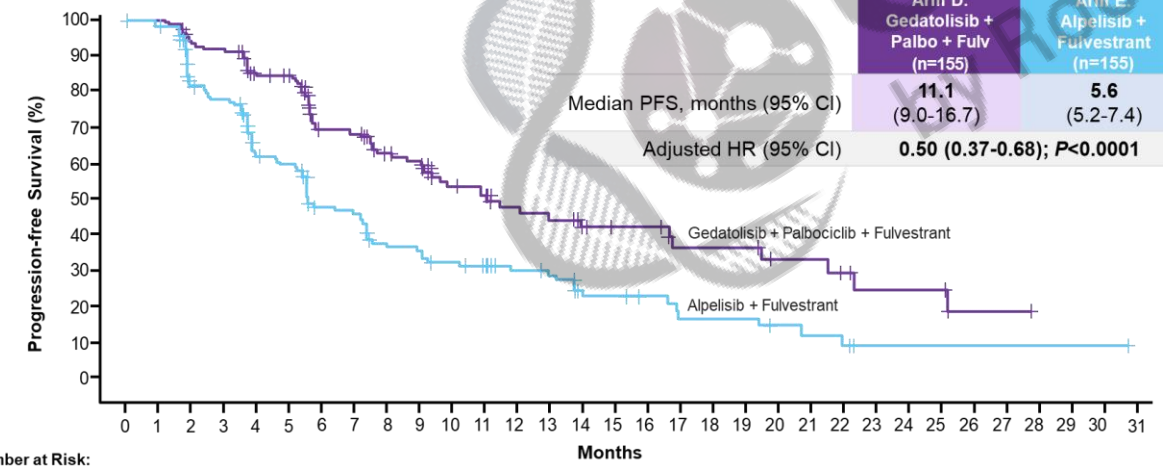
	Arm F: Gedatolisib + Fulv (n=52)	Arm E: Alpelisib + Fulv (n=155)
Median PFS, months (95% CI)	**11.3** (9.1-22.1)	**5.6** (5.2-7.4)
Adjusted HR (95% CI)	**0.51 (0.33-0.79); *P*=0.0013***	

Number at Risk:

Gedatolisib + Fulv	52	48	42	41	36	36	31	30	23	23	15	15	10	10	8	7	7	7	6	4	4	3	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	0

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

PFS: Arm D vs Arm E

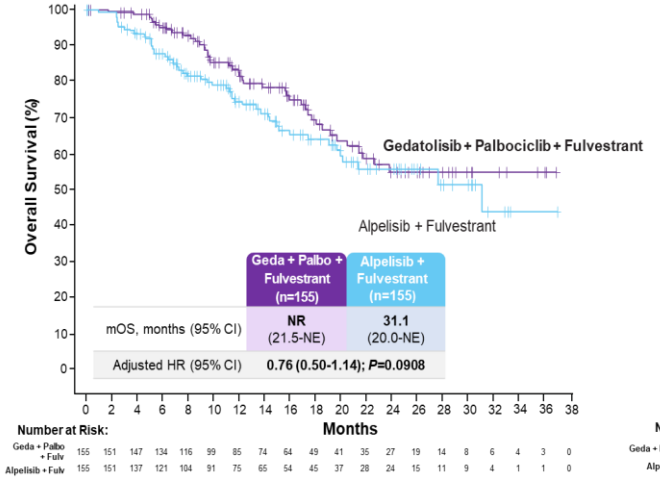


	Arm D: Gedatolisib + Palbo + Fulv (n=155)	Arm E: Alpelisib + Fulvestrant (n=155)
Median PFS, months (95% CI)	**11.1** (9.0-16.7)	**5.6** (5.2-7.4)
Adjusted HR (95% CI)	**0.50 (0.37-0.68); *P*<0.0001**	

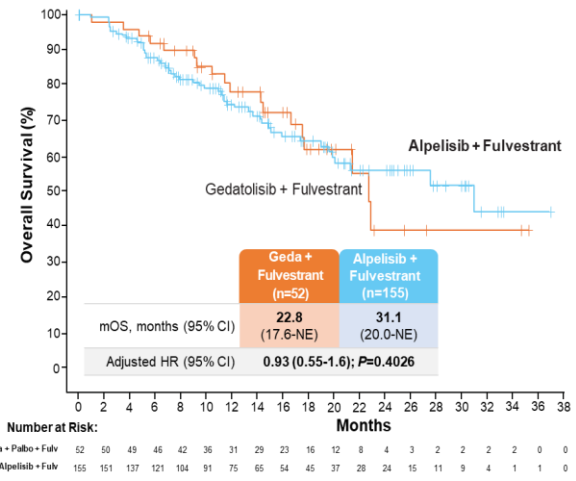
Number at Risk:

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	0	

OS (immature)



	Geda + Palbo + Fulvestrant (n=155)	Alpelisib + Fulvestrant (n=155)
mOS, months (95% CI)	NR (21.5-NE)	31.1 (20.0-NE)
Adjusted HR (95% CI)	0.76 (0.50-1.14); *P*=0.0908	



	Geda + Fulvestrant (n=52)	Alpelisib + Fulvestrant (n=155)
mOS, months (95% CI)	22.8 (17.6-NE)	31.1 (20.0-NE)
Adjusted HR (95% CI)	0.93 (0.55-1.6); *P*=0.4026	

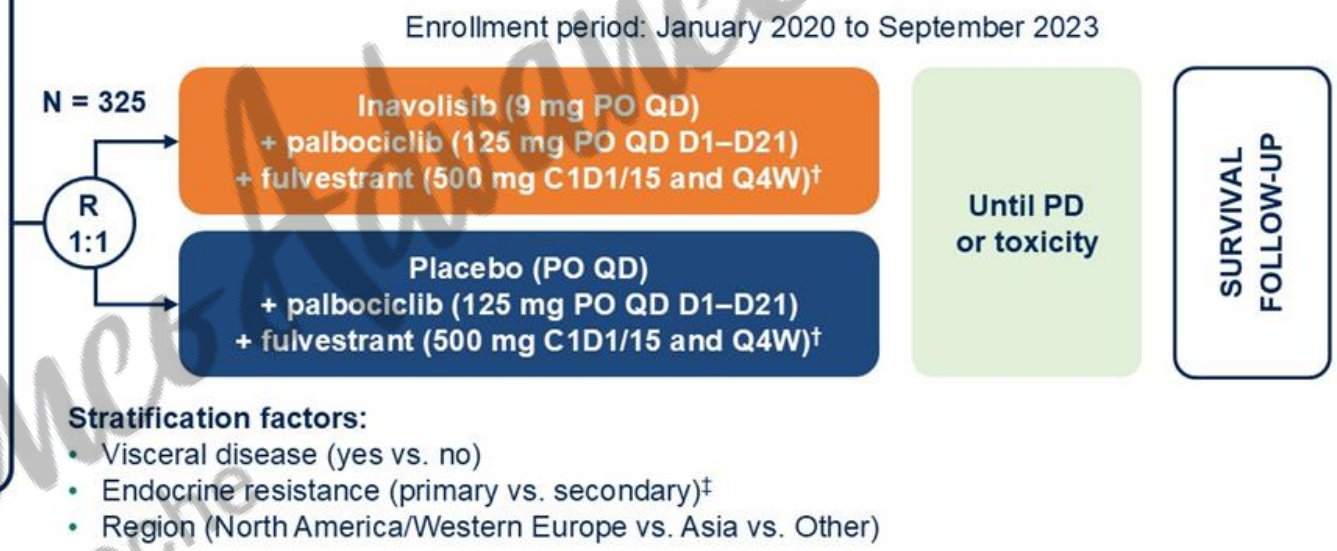
Hurvitz S, et al. ASCO 2026

INAVO120: A Phase III, randomized, double-blind, placebo-controlled study[1,2]

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2– aBC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **No prior therapy for aBC**
- **Fasting glucose <126 mg/dL and HbA_{1c} <6.0%**



Stratification factors:

- Visceral disease (yes vs. no)
- Endocrine resistance (primary vs. secondary)‡
- Region (North America/Western Europe vs. Asia vs. Other)

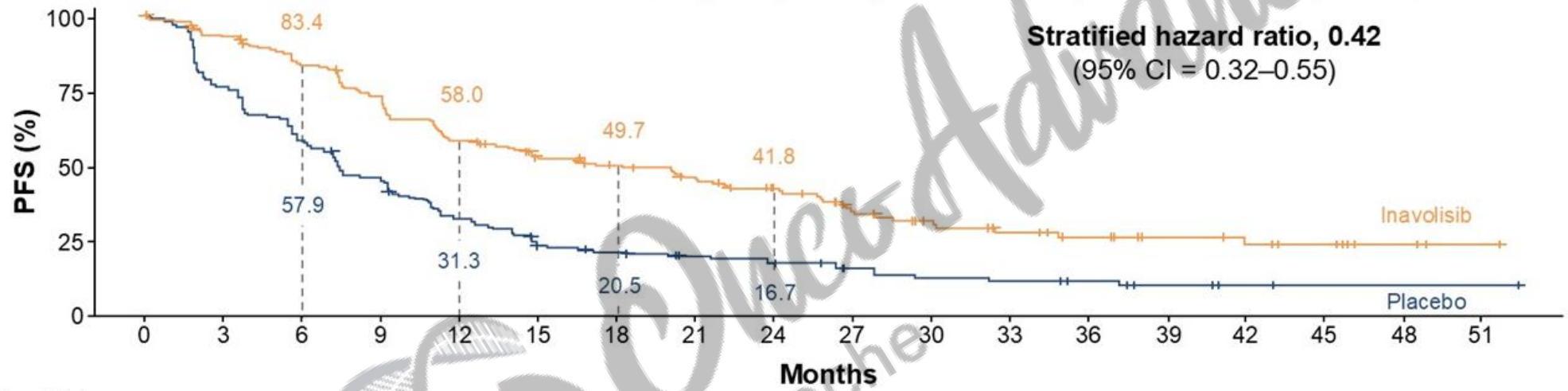
- Primary endpoint: Investigator-assessed PFS
- Secondary endpoints included: OS; investigator-assessed ORR, BOR, CBR, and DoR; PROs

ClinicalTrials.gov number, NCT04191499.
Adapted from Jhaveri KJ, *et al.* SABCS 2023 (Abstract GS03-13). * Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine, Inc.). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu); † Pre-menopausal women received ovarian suppression; ‡ Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[3]
Primary: Relapse while on the first 2 years of adjuvant ET; secondary: Relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.
aBC, advanced breast cancer; BOR, best overall response; C, cycle; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; D, day; DoR, duration of response; ET, endocrine therapy; HbA_{1c}, glycated hemoglobin; HER2–, HER2-negative; HR+, hormone receptor-positive; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, by mouth; PRO, patient-reported outcome; Q4W, every 4 weeks; QD, daily; R, randomization.
1. Turner NC, *et al. N Engl J Med* 2024; **391:**1584–1596; 2. Jhaveri KJ, *et al.* SABCS 2023 (Abstract GS03-13); 3. Cardoso F, *et al. Ann Oncol* 2018; **29:**1634–1657.

INAVO120 updated PFS

	Events, n (%)	Median, months (95% CI)
Inavolisib (n = 161)	103 (64.0)	17.2 (11.6–22.2)
Placebo (n = 164)	141 (86.0)	7.3 (5.9–9.2)

Stratified hazard ratio, 0.42
(95% CI = 0.32–0.55)



Median follow-up:
34.2 months

No. at risk																		
Inavolisib	161	146	129	112	89	73	65	57	46	32	25	19	15	11	10	7	3	1
Placebo	164	125	95	74	50	34	30	24	21	14	11	10	8	4	2	1	1	1

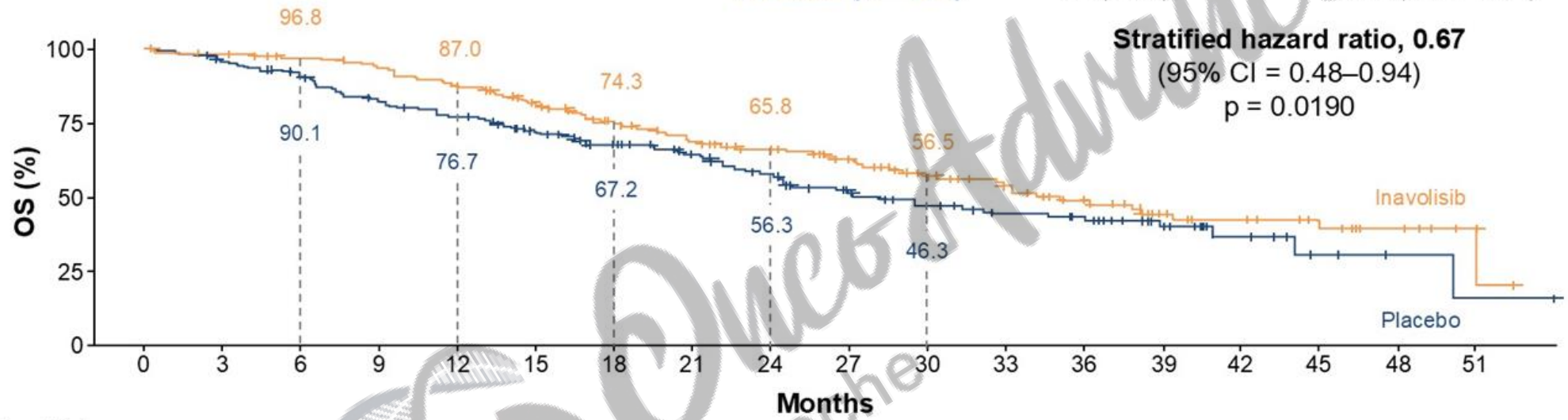
The improvement in PFS was maintained during longer follow-up

Data cutoff: November 15, 2024.
CI, confidence interval; PFS, progression-free survival.

INAVO120 key secondary endpoint: OS

	Deaths, n (%)	Median, months (95% CI)
Inavolisib (n = 161)	72 (44.7)	34.0 (28.4–44.8)
Placebo (n = 164)	82 (50.0)	27.0 (22.8–38.7)

Stratified hazard ratio, 0.67
(95% CI = 0.48–0.94)
p = 0.0190



Median follow-up:
34.2 months

No. at risk

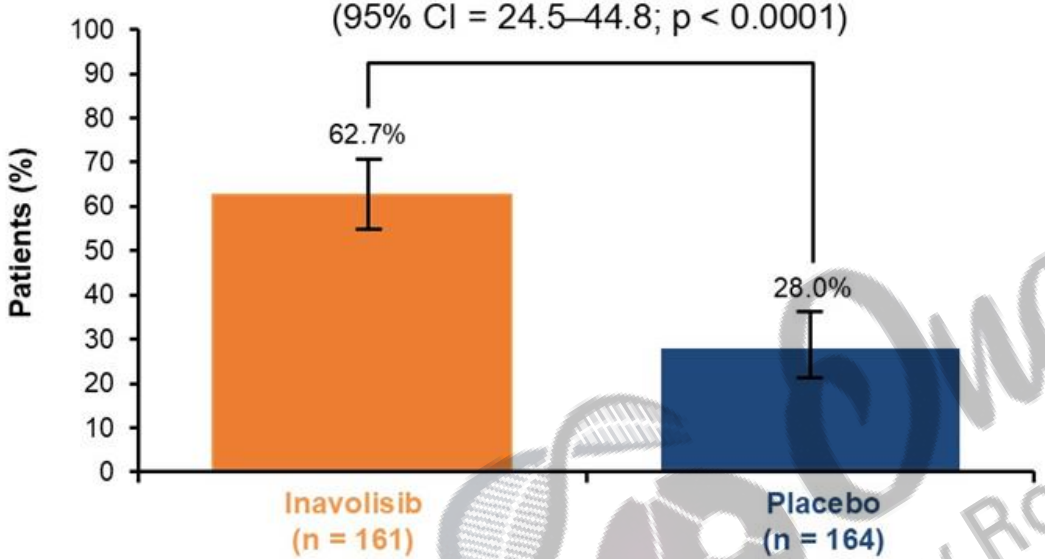
Inavolisib	161	155	149	142	131	114	99	88	78	67	54	43	34	22	19	13	7	1
Placebo	164	155	142	127	119	104	90	77	63	48	42	36	32	18	10	4	2	1

Improvement in median OS: 7 months. The prespecified boundary for statistical significance (p < 0.0469) was crossed

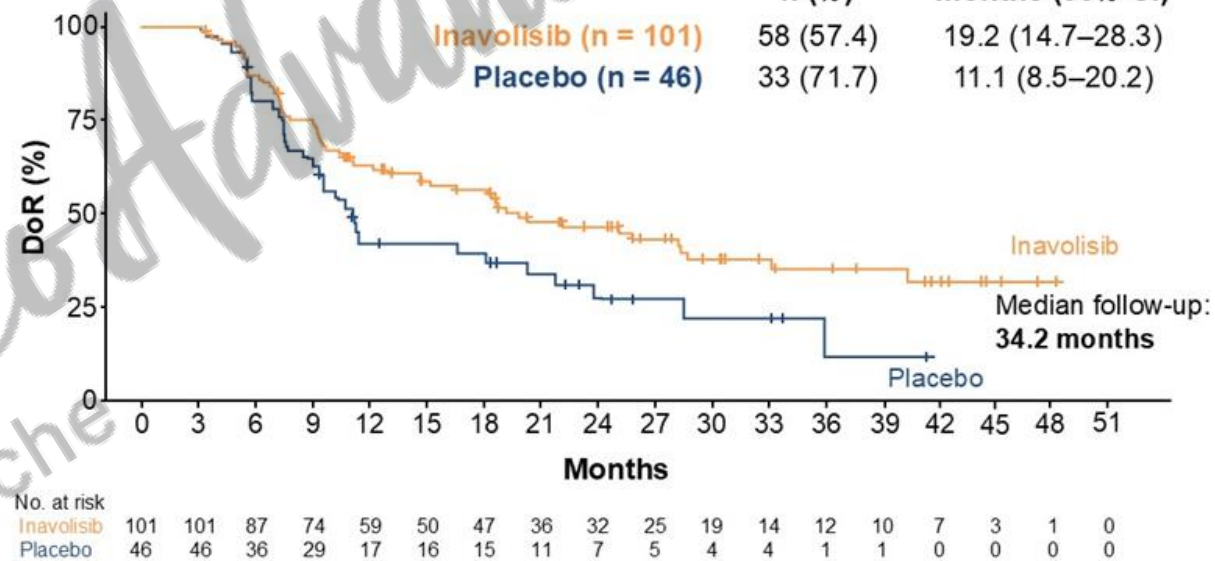
Data cutoff: November 15, 2024.
CI, confidence interval; OS, overall survival.

INAVO120 other key secondary endpoints

ORR*



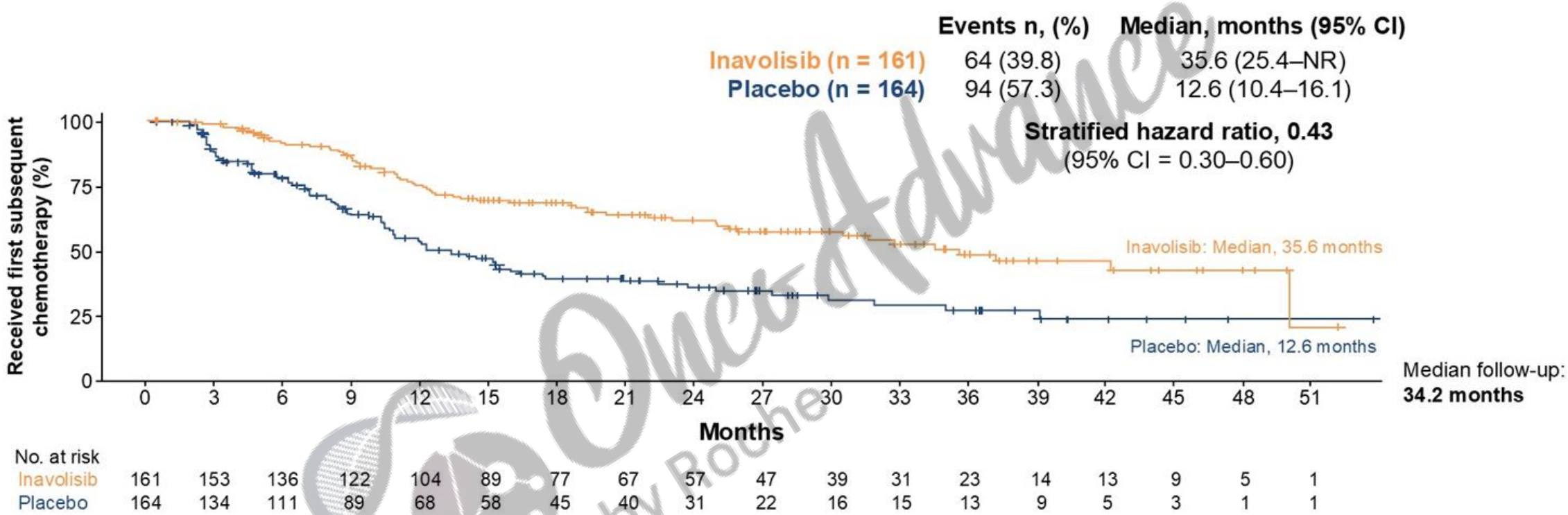
DoR



Substantially higher rates of objective response with an 8 month median improvement in duration of response

Data cutoff: November 15, 2024.
* Patients with a compete or partial response on two consecutive occasions ≥4 weeks apart per RECIST v1.1.
CI, confidence interval; DoR, duration of response; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours.

INAVO120 time to first subsequent chemotherapy



Median time to first subsequent chemotherapy was substantially delayed by almost 2 years (23 months)

Data cutoff: November 15, 2024.
CI, confidence interval; NR, not reached.

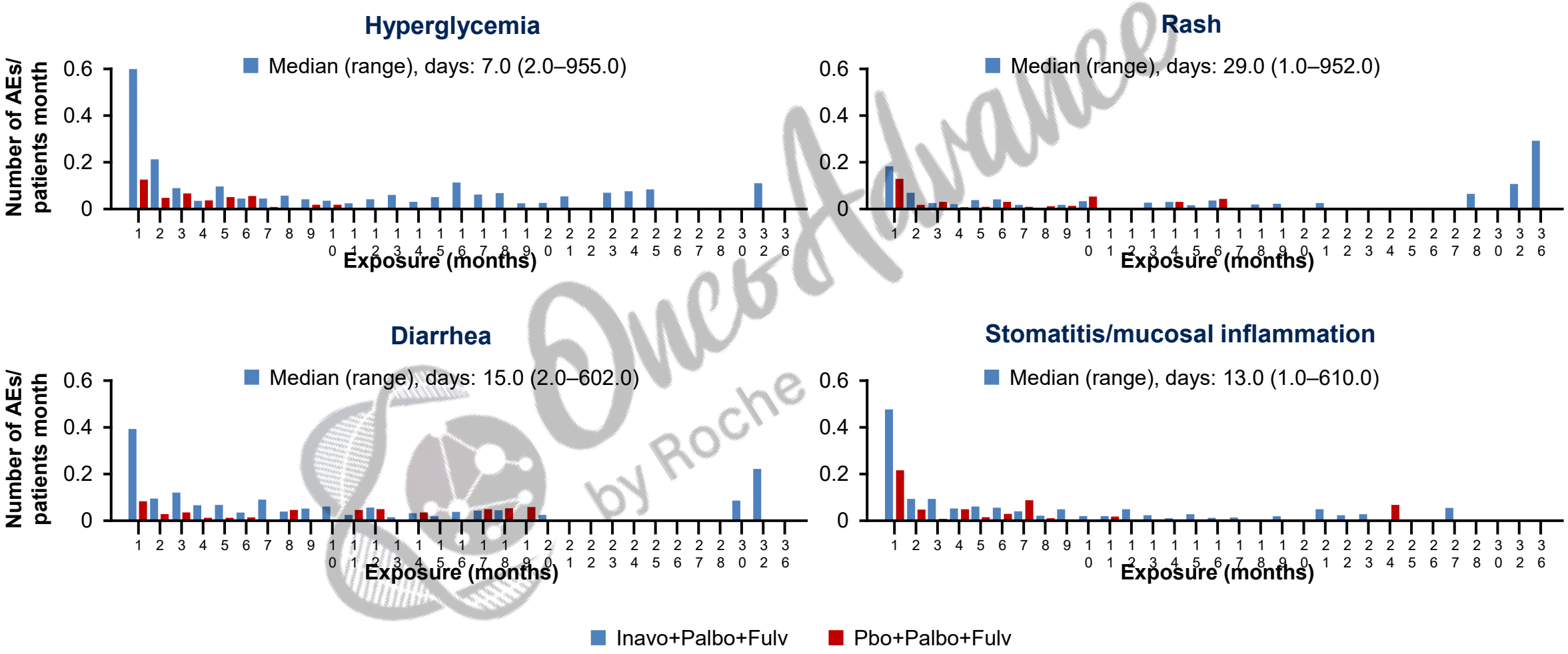
INAVO120 overview of AEs

Patients, n (%) with at least one:	Inavolisib (n = 161)	Placebo (n = 163)
Any-grade AE	161 (100)	163 (100)
Grade 3–4 AE	146 (90.7)	138 (84.7)
Grade 5 AE*	6 (3.7)	2 (1.2)
Serious AE	44 (27.3)	22 (13.5)
AE leading to discontinuation of treatment		
Inavolisib/placebo	11 (6.8)	1 (0.6)
Palbociclib	10 (6.2)	0
Fulvestrant	6 (3.7)	0
AE leading to dose reduction of treatment		
Inavolisib/placebo	24 (14.9)	6 (3.7)
Palbociclib	65 (40.4)	56 (34.4)

There was a low discontinuation rate due to AEs

Data cutoff: November 15, 2024. AE severity was graded per National Cancer Institute Common Terminology Criteria for AEs v5.0. * None of the grade 5 AEs were reported as related to study treatment by investigators.
The grade 5 AEs reported were cerebral hemorrhage, cerebrovascular accident, gastrointestinal hemorrhage, acute coronary syndrome, death, and COVID-19 in the inavolisib group, and COVID-19 pneumonia, and cardiac arrest in the placebo group.[1]
AE, adverse event. 1. Turner NC, *et al. N Engl J Med* 2024; **391:**1584–1596.

Time to onset of key selected AEs*



* Median time to onset of first occurrence of the AE, i.e. if an AE was resolved and recurred in the same patient it is not included a second time in this dataset.
AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

NCCN Guidelines Version 3.2026
Invasive Breast Cancer

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

Inavolisib + Palbociclib + Fulvestrant for PIK3CA-mutated, HR-positive HER2-negative breast cancer, following disease progression on adjuvant endocrine therapy or relapse within 12 months of adjuvant endocrine therapy completion **(Category 1)**

The NCCN Guidelines recommend NGS testing for detection of actionable biomarkers, such as *PIK3CA*, *AKT1*, and *PTEN*, in HR+/HER2- aBC†[1]

Why to test

– PIK3CA, AKT1,PTEN are recognized as actionable biomarkers in metastatic HR+/HER2- breast cancer

Whom to test

– Patients with HR+/HER2- locally advanced or metastatic breast cancer

When to test

– NCCN Guidelines® recommend ordering an NGS panel test during the initial patient work-up for metastatic disease

NGS panel tests can also be ordered after progression on first line treatment

How to test

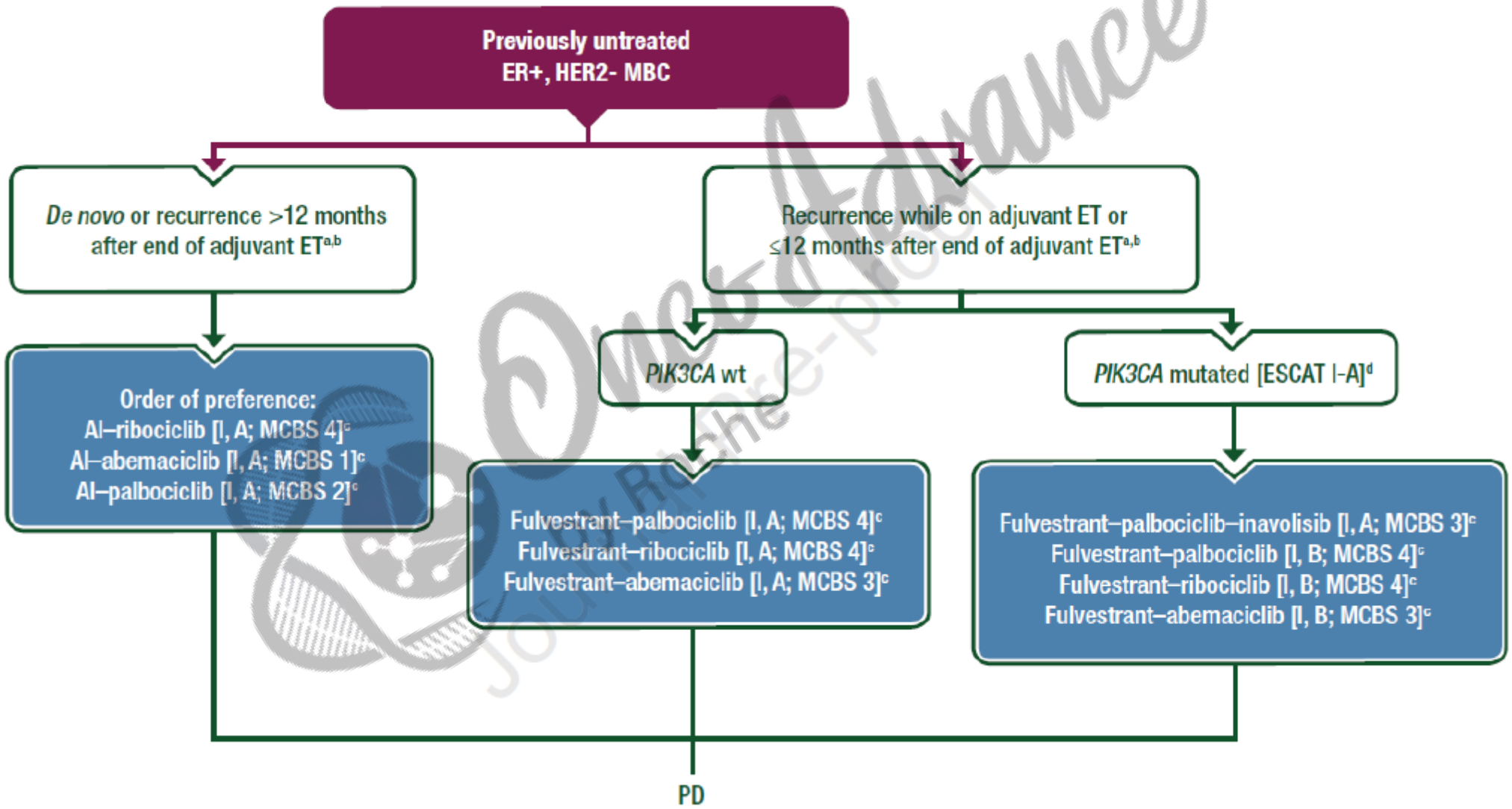
– Utilize NGS

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

AKT1, serine/threonine protein kinase 1; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; NCCN, National Comprehensive Cancer Network; NGS, next- generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights

ESMO Guidelines 2026



Azambuja E, et al. Ann Oncol 2026