

New endocrine therapies and combinations for the treatment of luminal metastatic breast cancer

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Disclosures

Gustavo Werutsky

Institutional financial interest

Research grants/ Local PI/ Steering Committee: AstraZeneca, Astellas, BeiGene, BMS, Roche, Ipsen, Janssen, Libbs, Lilly, MSD, Novartis, Roche, Pfizer and Takeda.

Personal financial interest

Honoraria/ Advisory: AstraZeneca, MSD, Novartis, Daiichi, Roche.

Non-financial interest

LACOG Executive Director, member of the Breast International Group (BIG) Executive Board and the EORTC Breast Cancer Group Steering Committee.

Overview of Clinical Trials with CDK 4/6 Inhibitors in Advanced Breast Cancer

ET Sensitive

MONARCH 3 ⁽¹⁾
Abemaciclib + AI

PALOMA-2 ⁽⁴⁾
Palbociclib + AI

MONALEESA-2 ⁽⁶⁾
Ribociclib + AI

MONALEESA-3 ⁽⁷⁾
Ribociclib + Fulvestrant

MONALEESA-7 ⁽⁸⁾
Ribociclib + Tamoxifen/AI (Premenopausal only)

DAWNA-2 ⁽⁹⁾
Dalpilisib + AI

PFS 23-33 months

ET Resistant

MONARCH 2 ⁽²⁾
Abemaciclib + Fulvestrant

PALOMA-3 ⁽⁵⁾
Palbociclib + Fulvestrant

DAWNA-1 ⁽¹⁰⁾
Dalpilisib + Fulvestrant

PFS 9-20 months

Prior Chemotherapy for MBC

MONARCH 1 ⁽³⁾
Abemaciclib

OS 53-67 months

1. Goetz PM, et al. J Clin Oncol. 2017;35:3638-3646; 2. Sledge GW Jr, et al. J Clin Oncol. 2017;35:2875-2884; 3. Dickler MN, et al. Clin Cancer Res. 2017;23:5218-5224; 4. Finn RS, et al. N Engl J Med. 2016;375:1925-1936; 5. Cristofanilli M, et al. Lancet Oncol. 2016;17:425-439; 6. Hortobagyi GN, et al. N Engl J Med. 2016;375:1738-1748; 7. Slamon DJ, et al. J Clin Oncol. 2018;36:2465-2472; 8. Tripathy D, et al. Lancet Oncol. 2018;19:904-915; 9. Xu B, et al. ESMO 2022 10. Xu B, et al. Nature Medicine volume 27, pages 1904–1909 (2021)

MAINTAIN: continuing CDK 4/6 inhibitors post progression

Key Entry Criteria

- Men or Women age \geq 18 yrs
- ER and/or PR \geq 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- \leq 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
 - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

1:1

N=120

Arm 1

Ribociclib + Switch Endocrine Therapy*

Arm 2

Placebo + Switch Endocrine Therapy*

Primary Endpoint

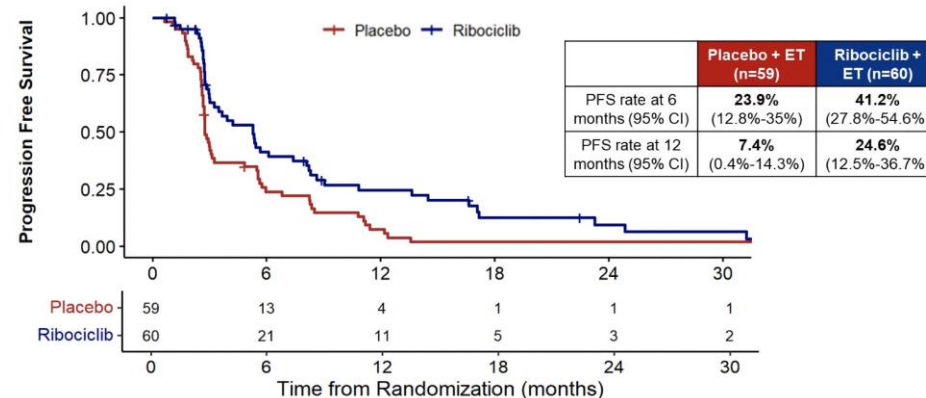
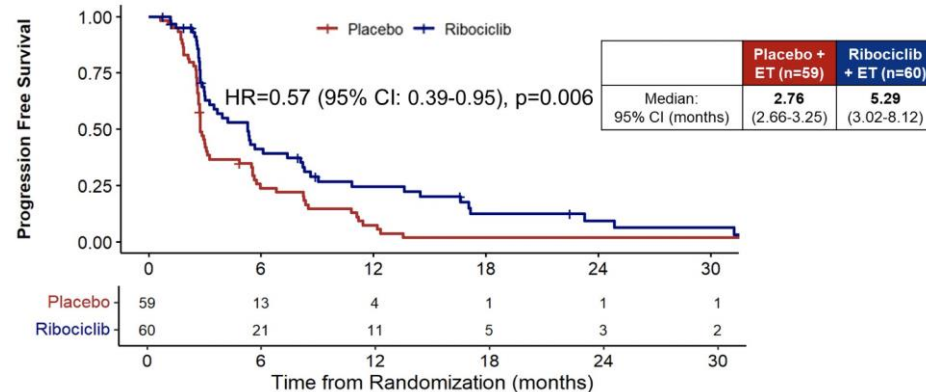
- Progression free survival
 - Locally assessed per RECIST 1.1

Secondary Endpoints

- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

- Prior CDK4/6 inhibitor: 87% Palbociclib
- Prior duration of CDK 4/6 inhibitor: 15.5 vs 17months
- 60% visceral metastasis



PACE: Palbociclib After CDK 4/6i and Endocrine Therapy

Luminal BC patients progressing to CDK 4/6i benefit from immunotherapy?

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

- 90% received prior Palbociclib

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

N=220

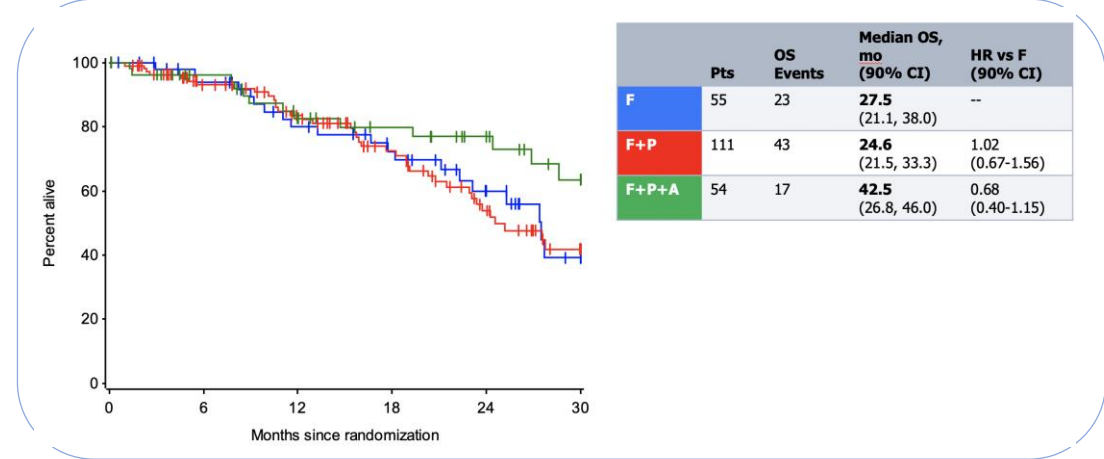
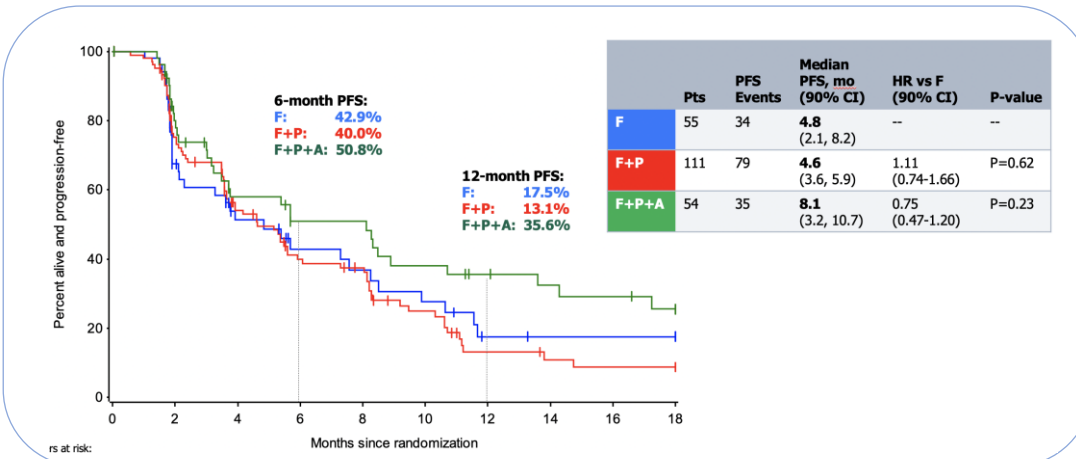
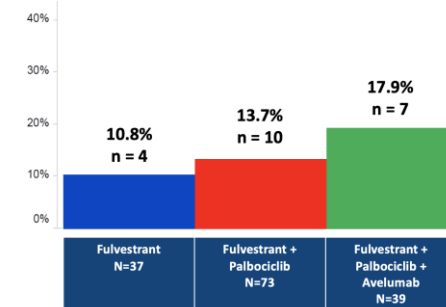
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Fulvestrant: 500 mg IM C1D1,15, then q28d

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)

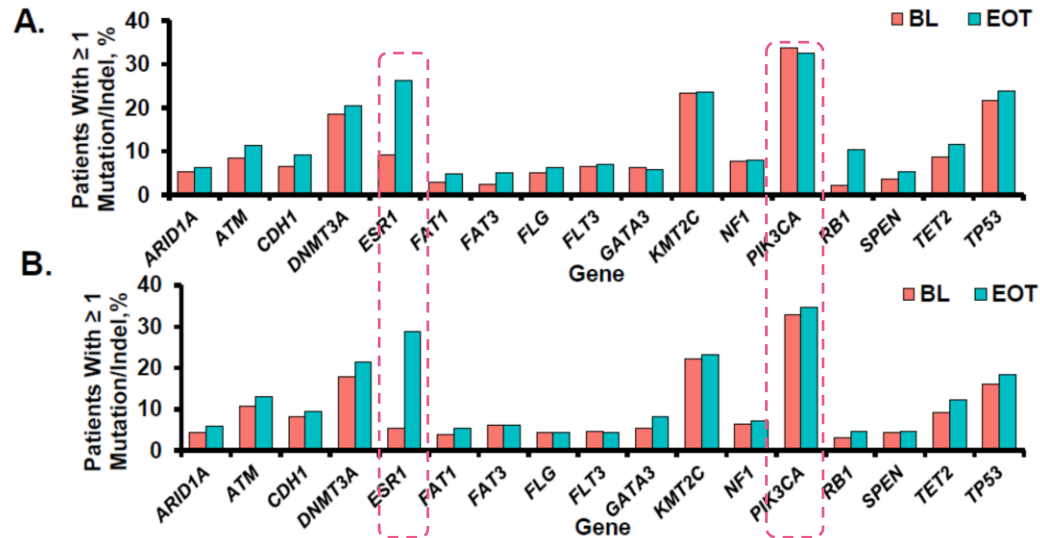
Fulvestrant: 500 mg IM C1D1,15, then q28d
Palbociclib: 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment)
Avelumab: 10 mg/kg IV q14d

ORR in measurable disease
population (n=149)



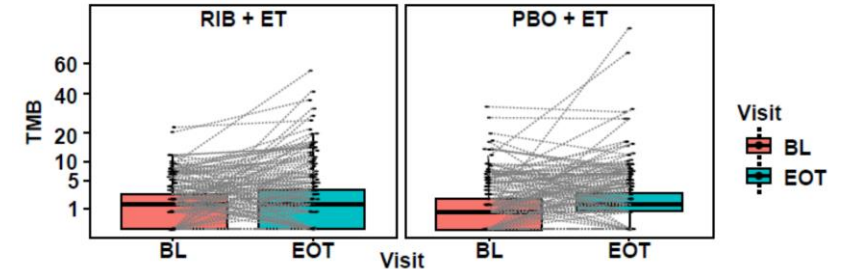
MONALESSA 2, 3, -7: Mechanisms of Acquired Resistance to Ribociclib Plus Endocrine Therapy

Frequency of Gene Alterations at BL and EOT for (A) RIB and (B) PBO Arms



- In the RIB arm, the frequency of alterations in RB1 (10.4% vs 2.0%), ATM (11.3% vs 8.4%), FAT1 (4.8% vs 3.0%), FAT3 (5.0% vs 2.5%), and TET2 (11.6% vs 8.6%) was higher at EOT vs BL (FDR-adj $P < .10$)
- GATA3 was higher at EOT vs BL in the ET alone arm but not with the combination of RIB + ET
- **In both arms, the frequency of alterations in ESR1 was also higher at EOT vs BL for RIB (26.3% vs 9.1%) and PBO (28.9% vs 5.4%) (FDR-adj $P < .0001$)**

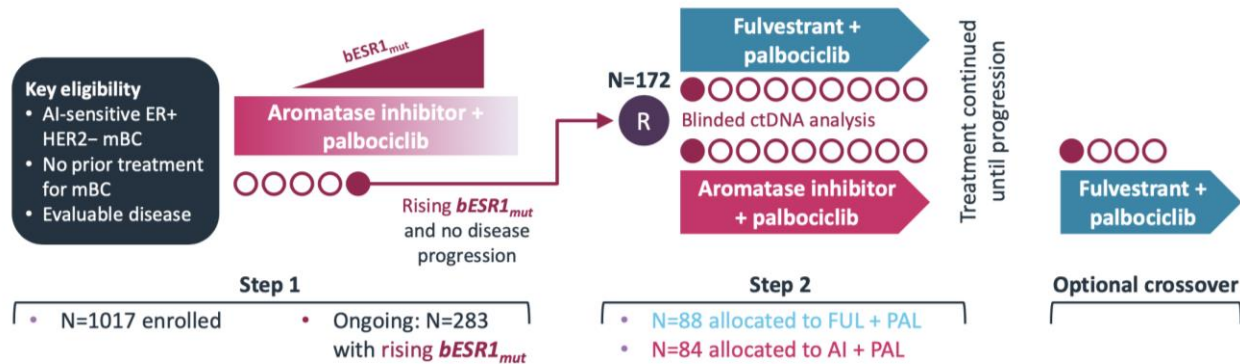
Figure 6. TMB at BL and EOT in RIB and PBO Arms



- An increase in TMB from BL to EOT was observed in both arms ($P < .0001$)
- **In the RIB arm, the percentage of patients with high TMB (> 10 mutations/Mb) increased from BL (1.1%) to EOT (5.7%) (McNemar $P = .0001$)**

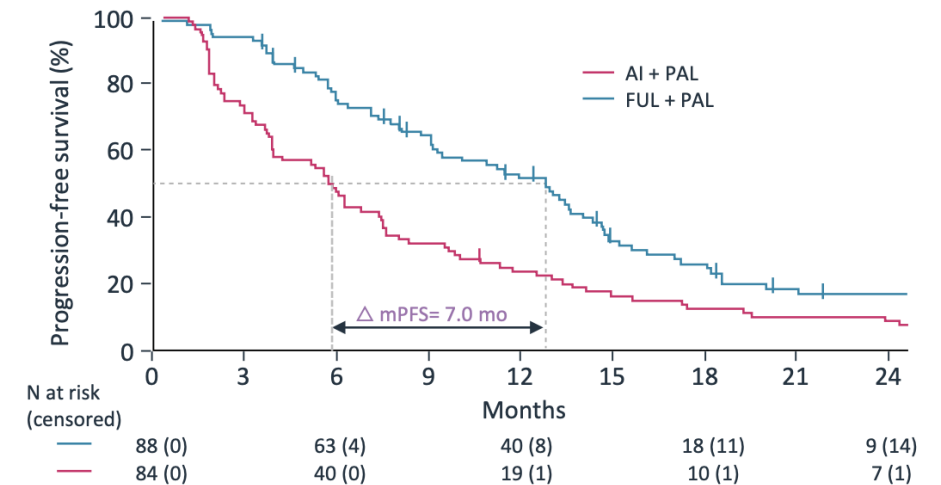
PADA-1: characterization of ESR1 mutations with aromatase inhibitor or fulvestrant + palbociclib therapy

PADA-1 strategy: Target rising *bESR1_{mut}* when they become detectable during first-line AI + palbociclib treatment



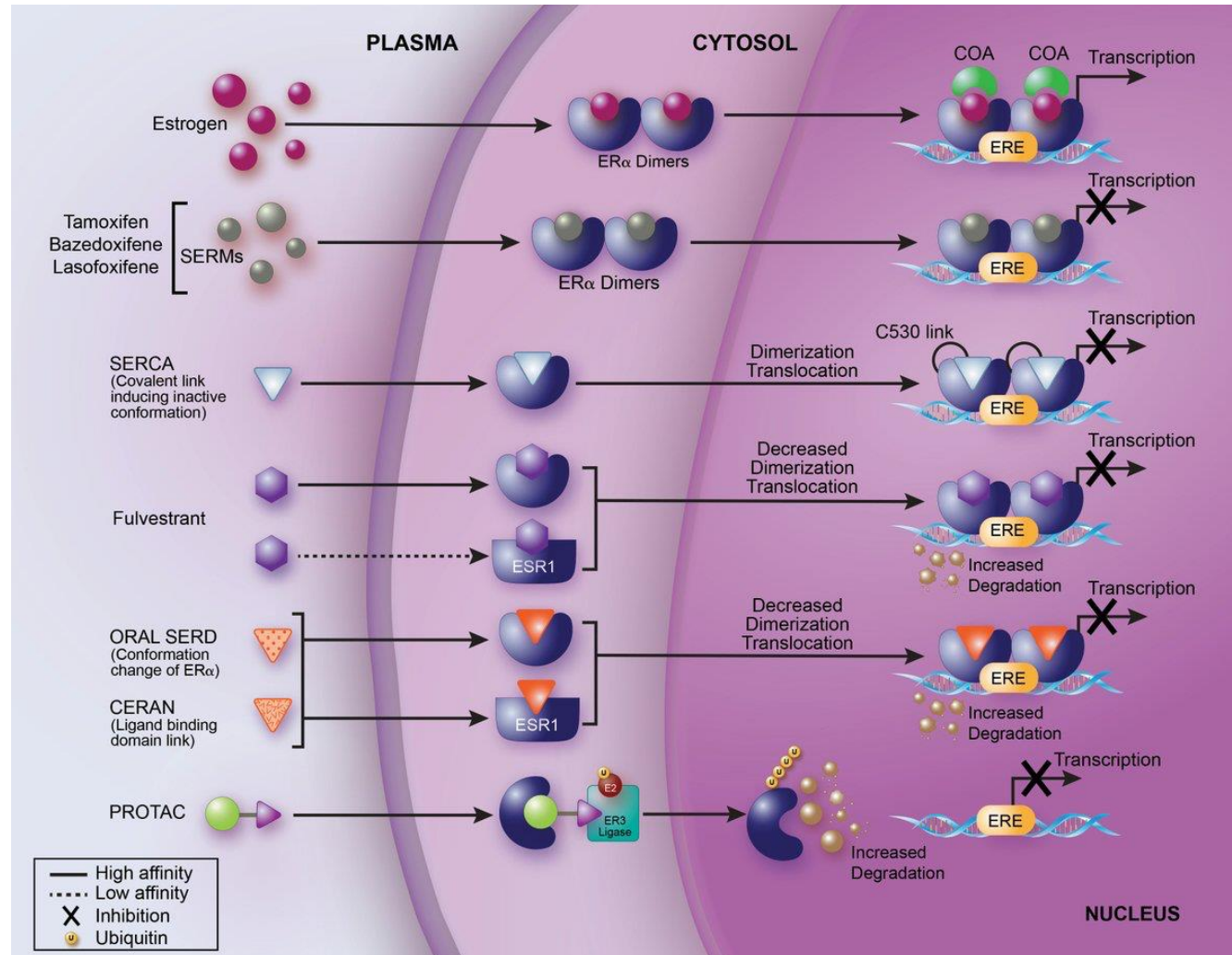
PADA-1: Updated PFS results

Updated PFS results (primary endpoint)
Data cutoff June 2022: Median F/U 28.2 mo; N=152 PFS events



	ASCO 2023 analysis		2021 analysis ¹	
	FUL + PAL	AI + PAL	FUL + PAL	AI + PAL
mPFS, mo (95% CI)	12.8 (9.3–14.7)	5.8 (3.9–7.5)	11.9	5.7
HR (95% CI)	0.54 (0.38–0.75)		0.61	
Optional crossover (n=49) mPFS (95% CI)	3.5 (2.4–5.4)			

New frontiers for ER inhibition



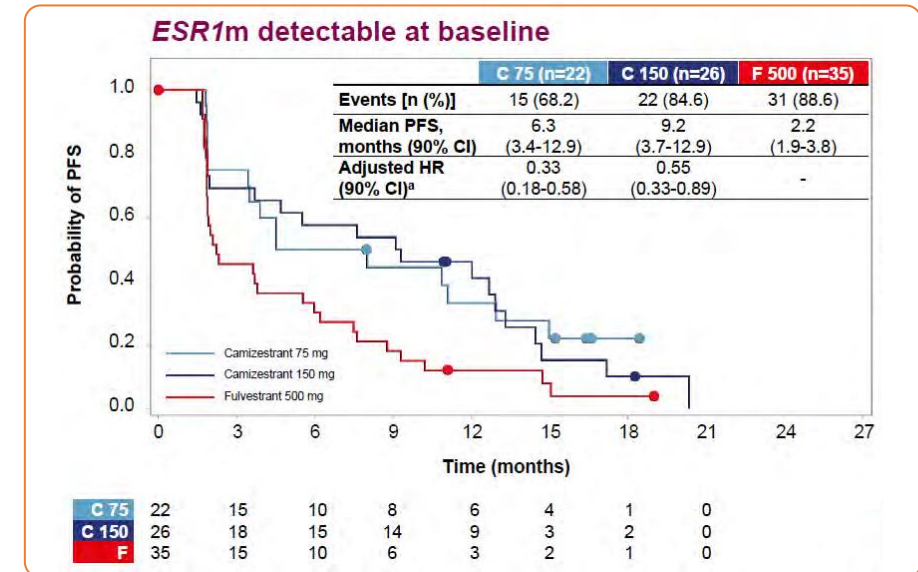
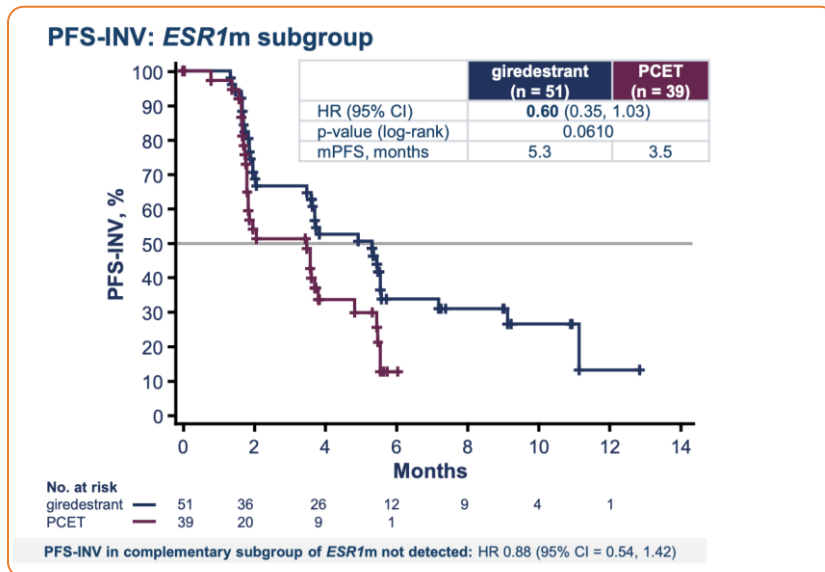
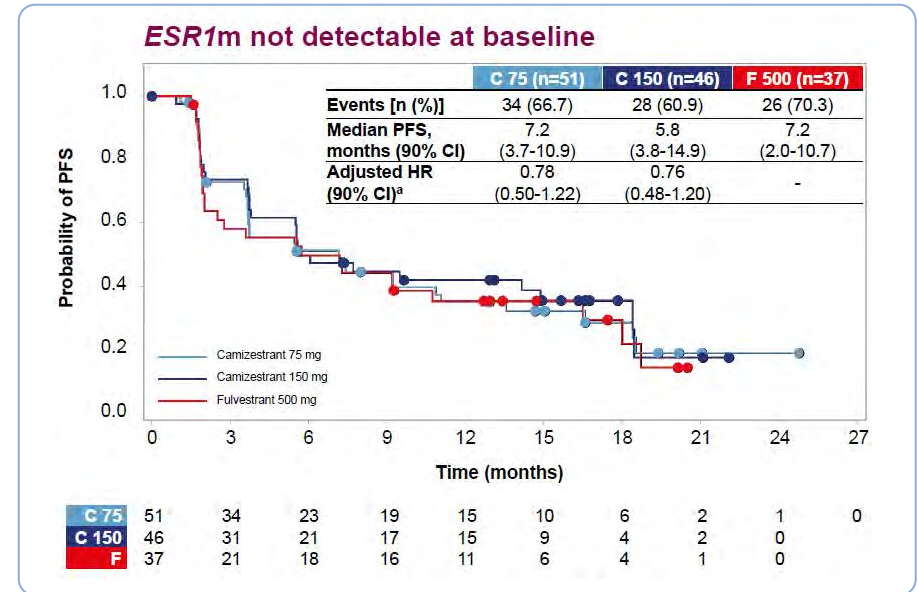
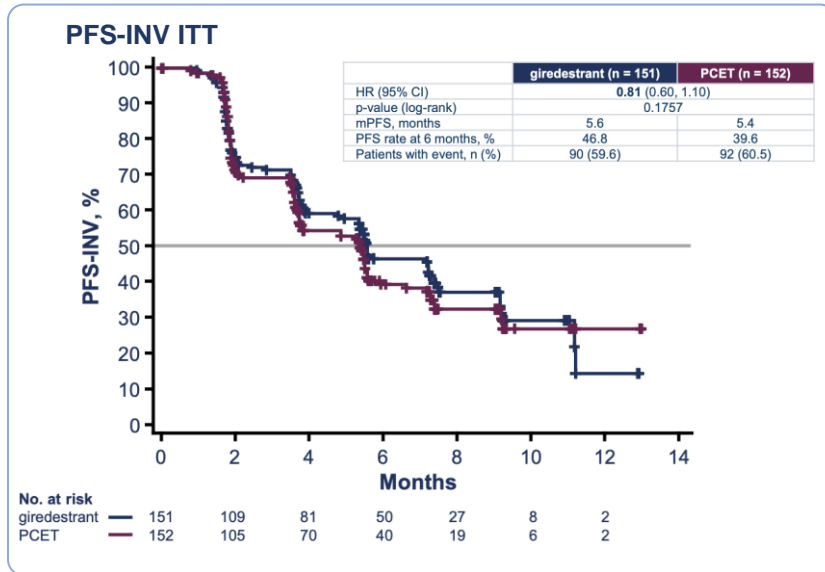
Oral SERD trial landscape in pretreated HR+/HER2- metastatic breast cancer

	EMERALD ¹	SERENA-2 ²	EMBER-3 ³	AMEERA-3 ⁴⁻⁶	aceIRA ⁶⁻⁹
Treatment	Elacestrant	Camizestrant	Imlunestrant +/- abemaciclib	Amceneztrant	Giredestrant
Control Arm	fulvestrant / Als	fulvestrant	fulvestrant / exemestane	fulvestrant / Als / tamoxifen	fulvestrant / Als
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	Required (100%)	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	YES	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	YES	YES	NO	YES	YES
Data readout	Positive (Registrational)	Positive (Non-Registrational)	Ongoing	Negative	Negative

1. Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, <https://clinicaltrials.gov/ct2/show/NCT04214288>; 3. EMBER-3. Clinical Trials.gov identifier: NCT04975308. Accessed November 18, 2022. <https://clinicaltrials.gov/ct2/show/NCT04975308>; 4. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. <https://clinicaltrials.gov/ct2/show/NCT04059484>; 5. Tolaney SM, et al. *Ann Oncol*. 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. <https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback>. Accessed July 20, 2022; 7. aceIRA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022. <https://clinicaltrials.gov/ct2/show/NCT04576455>; 8. Martin M, et al. *J Clin Oncol*. 2021;39(15):abstr TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol*. 2022;33(7):S88-S121 (abstr 211MO).

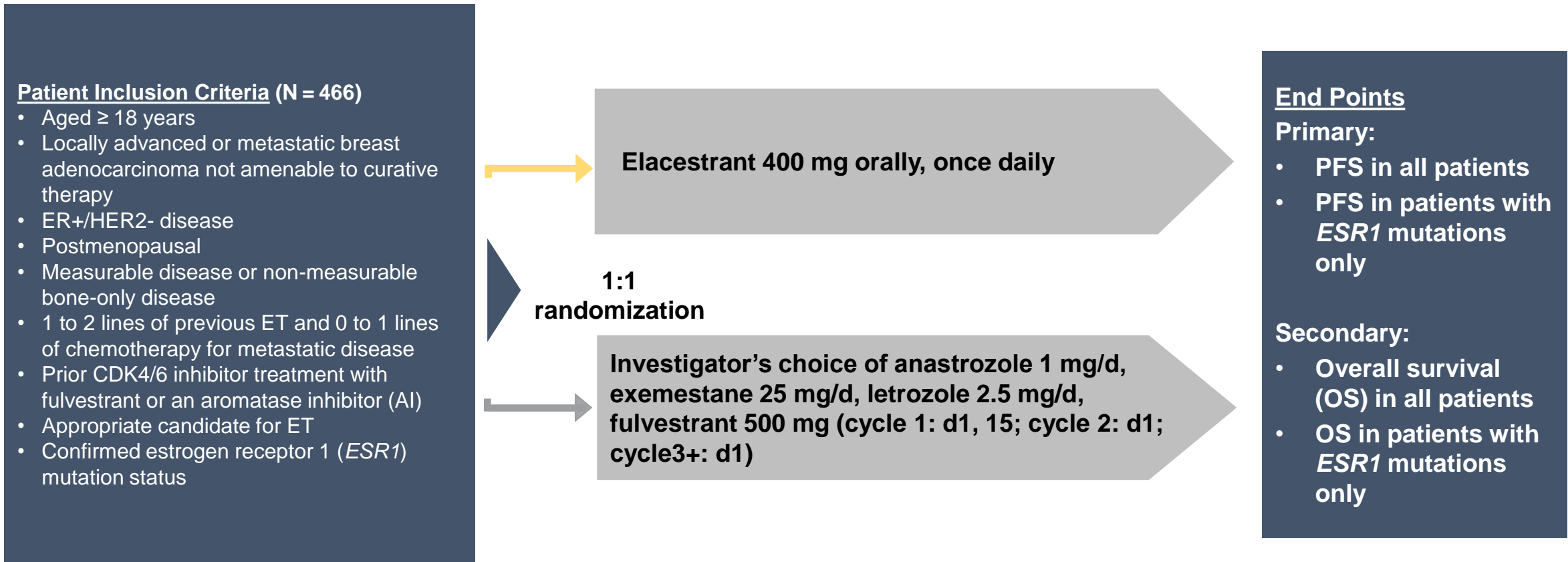
Study design: aceIRA BC (NCT04576455)

SERENA-2 study overview



EMERALD Phase 3 Study Design

International, multicenter, randomized, open-label, active-controlled, event-driven, phase III study

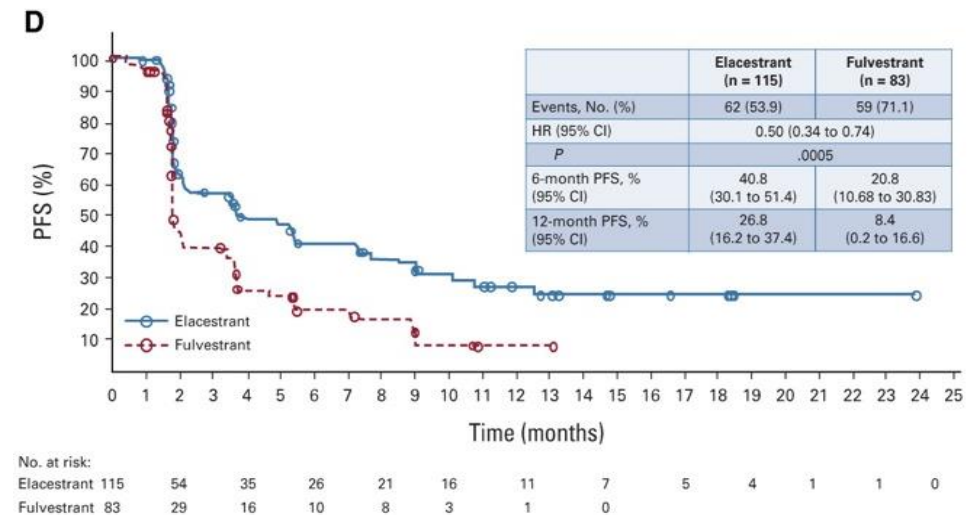
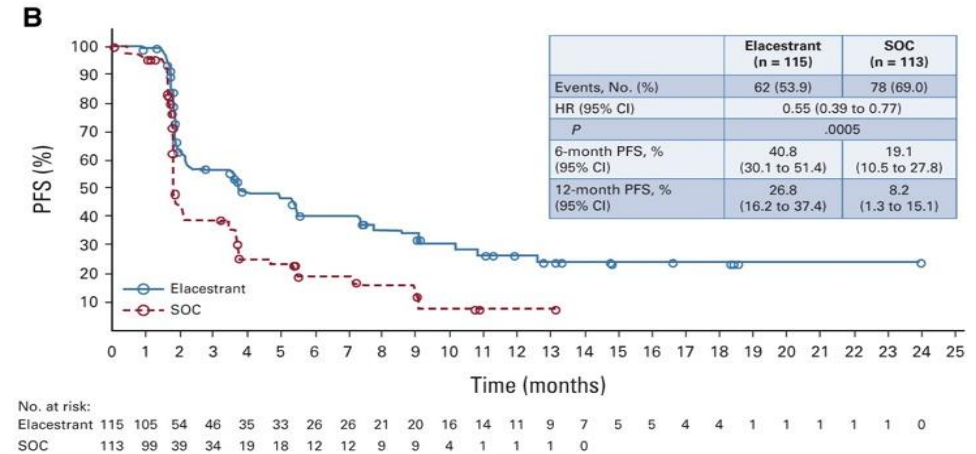
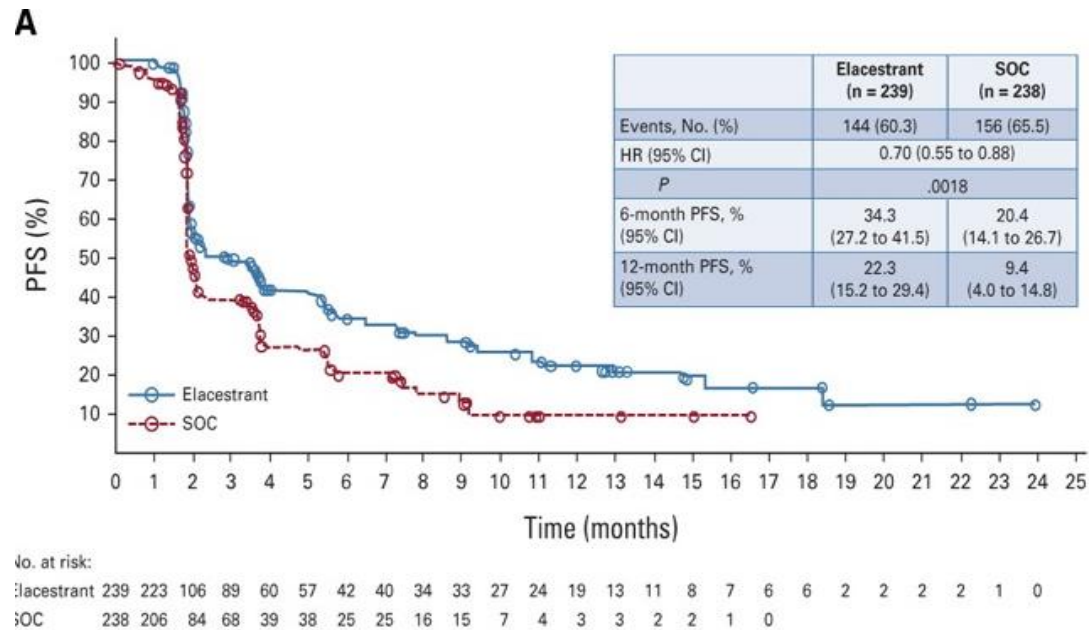


Stratification factors: *ESR1* mutation status, presence of visceral metastases, previous fulvestrant treatment

EMERALD: Primary endpoint PFS in all pts and ESR1 mut only

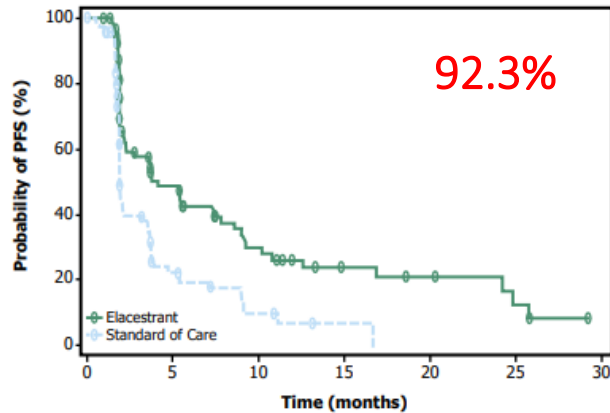
Patients with ESR1mut

All pts (ITT)



EMERALD: PFS by duration prior CDK4/6i (ESR1mut)

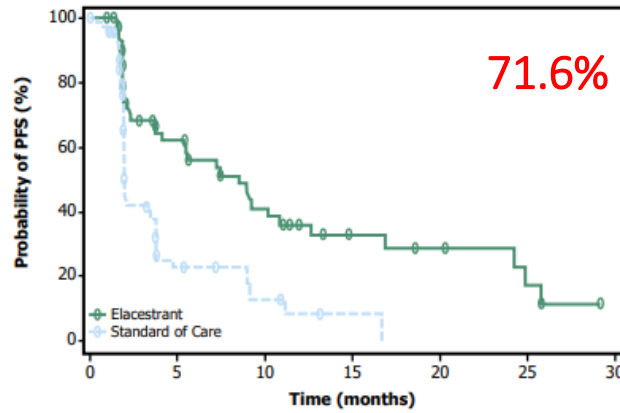
At least 6 mo CDK4/6i



Elacestrant 103 50 33 25 20 16 11 9 8 7 6 5 5 1 1 0
SOC 102 34 16 11 9 5 2 1 1 0

	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	4.14 (2.20 - 7.79)	1.87 (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	0.517 (0.361 - 0.738)	

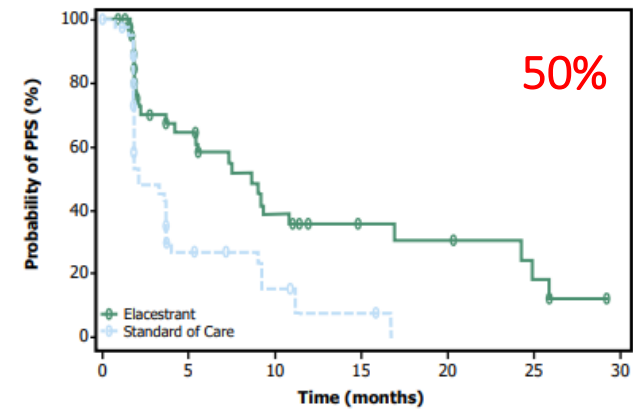
At least 12 mo CDK4/6i



Elacestrant 78 42 31 24 20 16 11 9 8 7 6 5 5 1 1 0
SOC 81 26 12 10 9 5 2 1 1 0

	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	8.61 (4.14 - 10.84)	1.91 (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	0.410 (0.262 - 0.634)	

At least 18 mo CDK4/6i



Elacestrant 55 30 23 18 16 12 8 8 7 6 6 5 5 1 1 0
SOC 56 21 9 8 7 4 1 1 1 0

	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	8.61 (5.45 - 16.89)	2.10 (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	0.466 (0.270 - 0.791)	

EMERALD Safety Summary

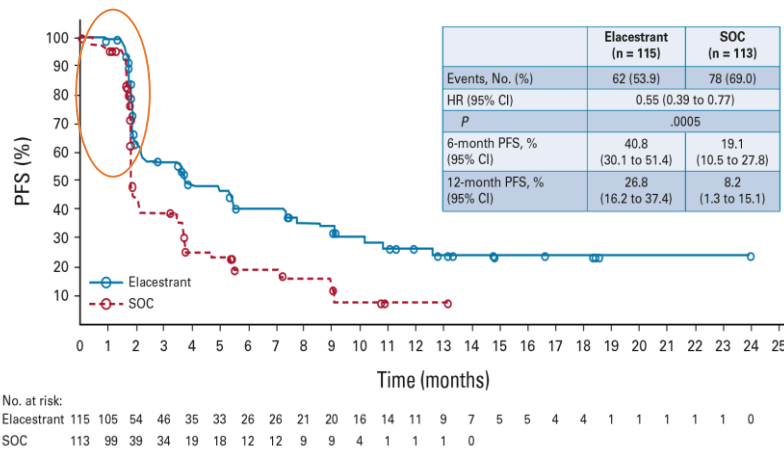
Updated safety data were consistent with previously reported results:

- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.

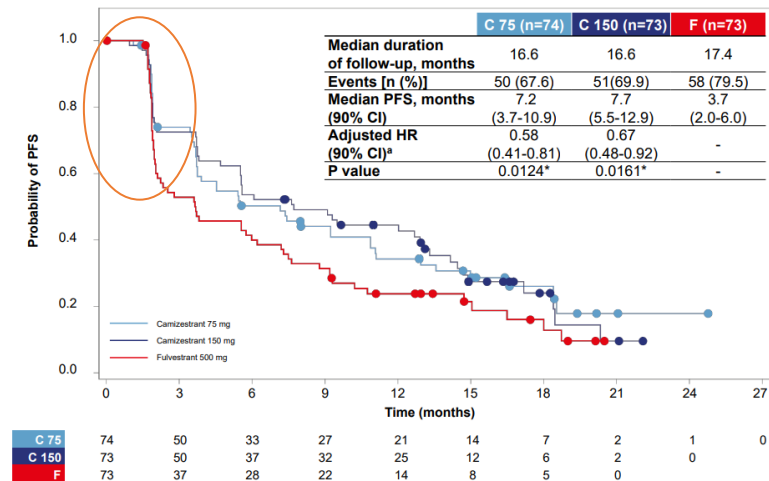
Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

ET resistance and impact on sequential use ET +/- combinations and new agents

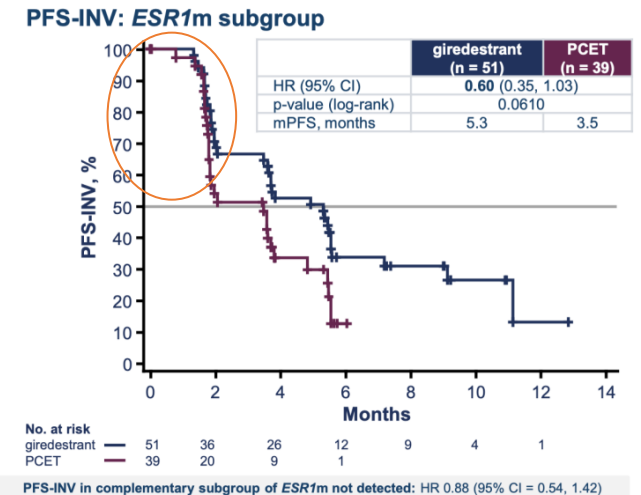
EMERALD



SERENA-2



aceIERA



Non-candidates to ET (monotherapy)



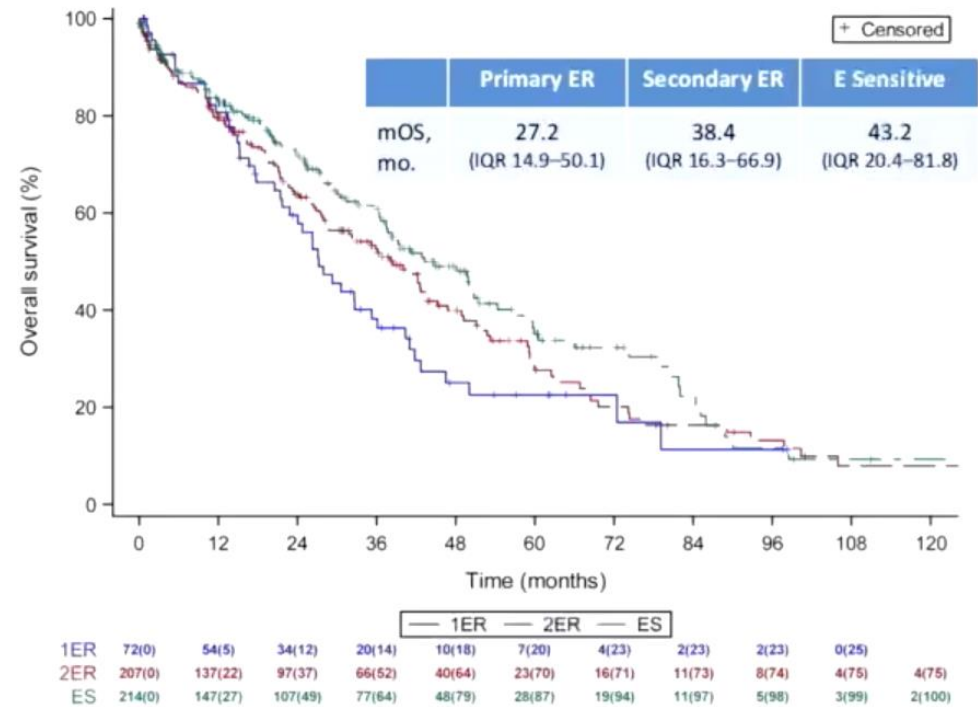
How do we select from our available treatments?

- Fulvestrant
- Rechallenge CDK4/6 inhibitors (+ ET)
- Fulvestrant + Capiwasertib
- Exemestane (Fulvestrant) + Everolimus
- Fulvestrant + Alpelisib (in PIK3CAmut)
- Elacestrant (in ESR1mut)
- Olaparib – Talazoparib in gBRCA1/2mut ADCs

Individual patient-level analysis from the Mammella Intergruppo (MIG) and Grupo Italiano Mammella (GIM) Studies (1992-2012)

- Using ESO/ESMO definitions, evaluated outcome in 6612 pts with HR+/HER2-ESBC enrolled in 4 ph III randomized trials evaluating chemo, ET and duration of ET
 - Median age 60, median FU 9 years; 9.7% with DR, primarily in bone
- 493 had DR as first DFS event
 - 14.6% primary endocrine resistant, 42% secondary endocrine resistant, 43.4% endocrine sensitive
 - Primary ER: more often young, and with higher incidence of visceral mets (particularly liver)

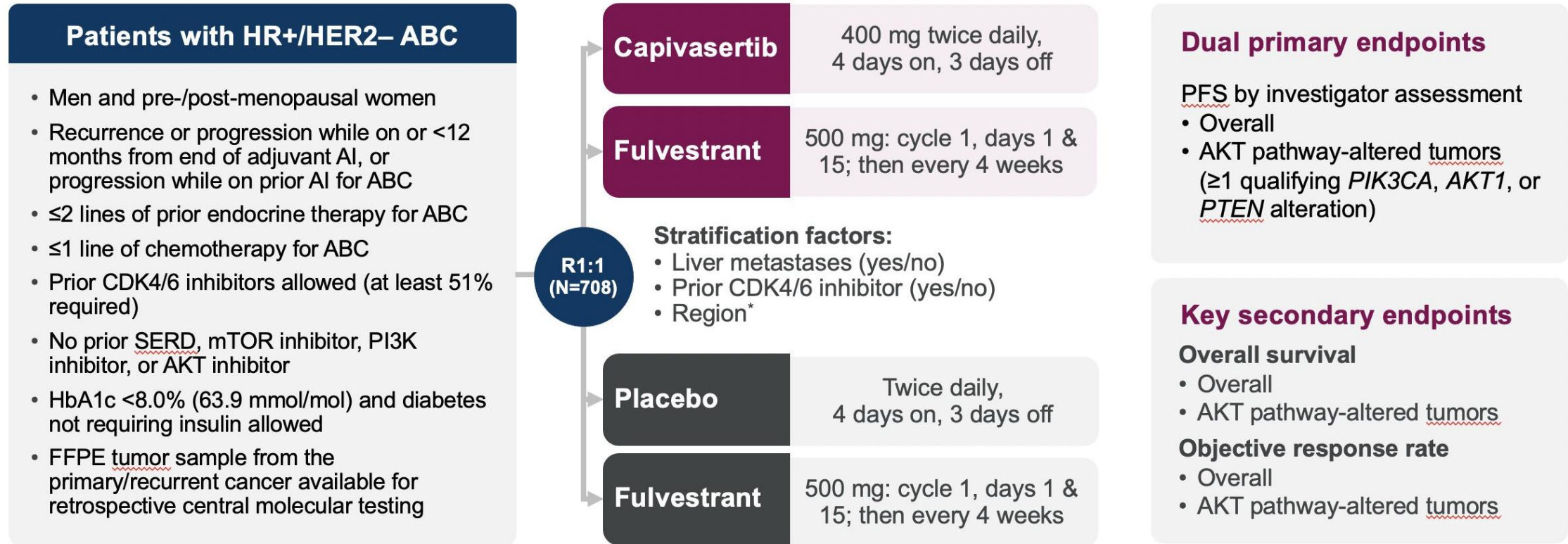
OS based on Endocrine Sensitivity



Lambertini et al, Lancet 2023;59: 101931

CAPitello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)



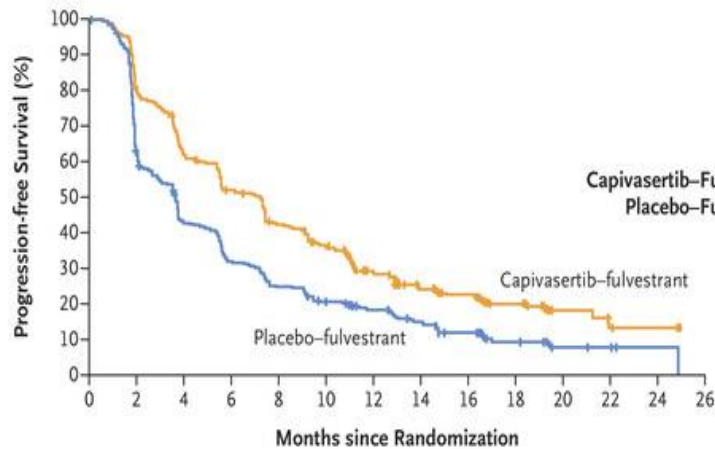
HER2- was defined as IHC 0 or 1+, or IHC 2+/ISH-. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.

ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.

Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

CAPItello-291: Primary endpoint PFS in ITT and AKT pathway alterations

A Overall Population



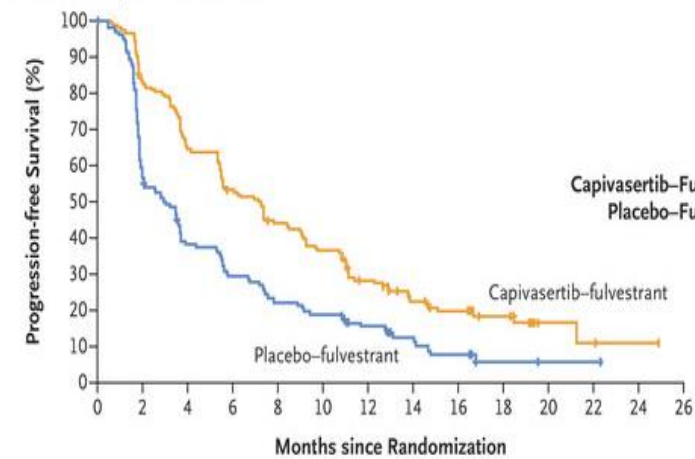
	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Capiasertib-Fulvestrant	355	258	7.2 (5.5–7.4)
Placebo-Fulvestrant	353	293	3.6 (2.8–3.7)

Adjusted hazard ratio for disease progression or death, 0.60 (95% CI, 0.51–0.71)
P<0.001

No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Capiasertib-fulvestrant	355	266	207	172	138	115	78	55	43	25	8	5	2	0
Placebo-fulvestrant	353	207	142	106	83	66	51	33	23	11	4	3	1	0

B Patients with AKT Pathway-Altered Tumors



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Capiasertib-Fulvestrant	155	121	7.3 (5.5–9.0)
Placebo-Fulvestrant	134	115	3.1 (2.0–3.7)

Adjusted hazard ratio for disease progression or death, 0.50 (95% CI, 0.38–0.65)
P<0.001

No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Capiasertib-fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo-fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

- **Visceral metastasis: 66% vs 73%**
- **Endocrine resistance: primary 38% vs 41% secondary 61% vs 59%**
- **Prior ET for ABC: ≥1 90% vs 85%**
- **Previous CDK 4/6i for ABC: 72% vs 67%**

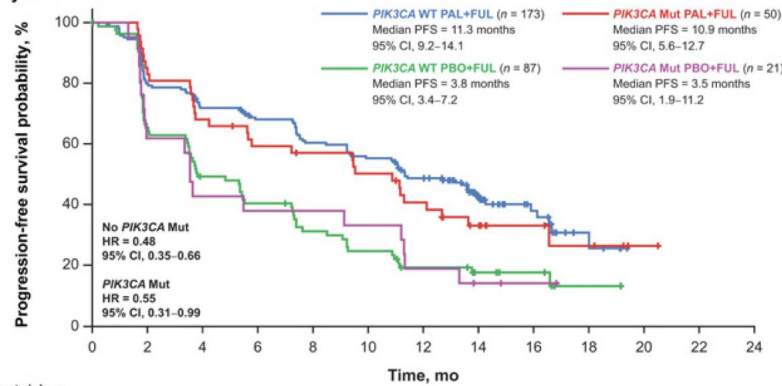
Any AKT pathway alterations 43.7% vs 38%

- **PIK3CA only 31% vs 26.1%**
- **PIK3CA and AKT1 0.6% vs 0.6%**
- **PIK3CA and PTEN 1.1% vs 1.5%**
- **AKT1 only 5.1% vs 4.2%**
- **PTEN only 5.9% vs 4.5%**

Exploratory analysis of CDK 4/6 inhibitor efficacy by PIK3CA mutation status

PALOMA 3

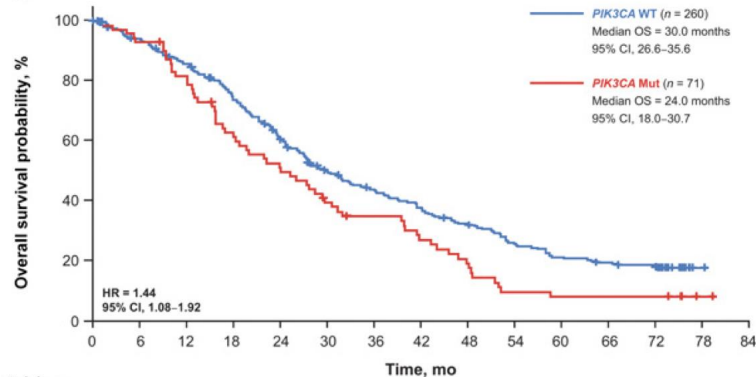
A PFS by treatment



Patients at risk, n

	0	2	4	6	8	10	12	14	16	18	20	22	24
PIK3CA Mut PAL+FUL	50	40	32	27	25	22	17	11	7	4	1	0	0
PIK3CA Mut PBO+FUL	21	13	9	8	8	7	4	2	1	0	0	0	0
PIK3CA Wt PAL+FUL	173	131	116	107	95	86	73	33	18	6	0	0	0
PIK3CA Wt PBO+FUL	87	53	39	32	24	19	13	8	6	1	0	0	0

B OS regardless of treatment

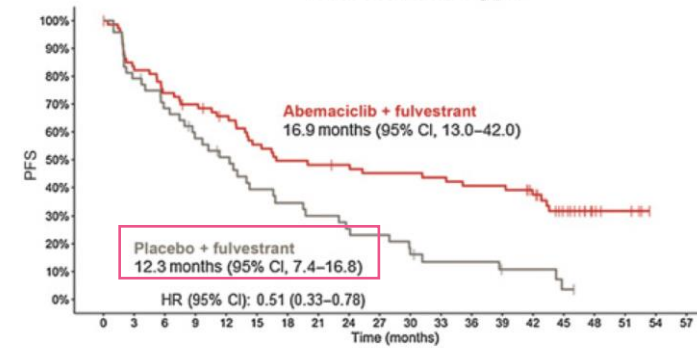


Patients at risk, n

	0	6	12	18	24	30	36	42	48	54	60	66	72	78
PIK3CA Mut	71	66	56	42	35	26	22	17	13	6	5	5	5	1
PIK3CA WT	260	238	215	184	149	116	100	86	73	58	47	42	39	1

MONARCH 2

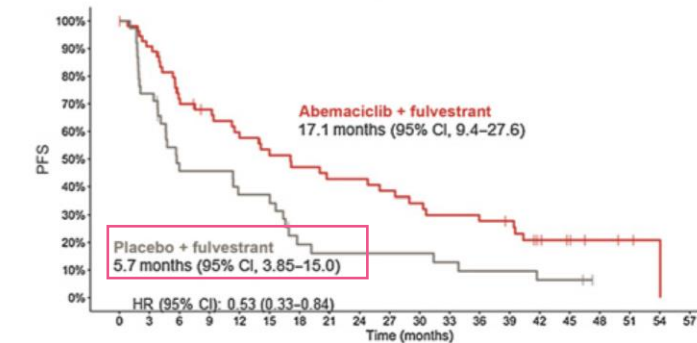
PIK3CA wild-type



Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Abemaciclib + fulvestrant	75	60	54	50	45	38	34	33	32	30	30	29	27	27	22	14	6	4	0
Placebo + fulvestrant	48	38	32	26	22	17	15	13	11	10	7	5	5	3	3	1	0	0	0

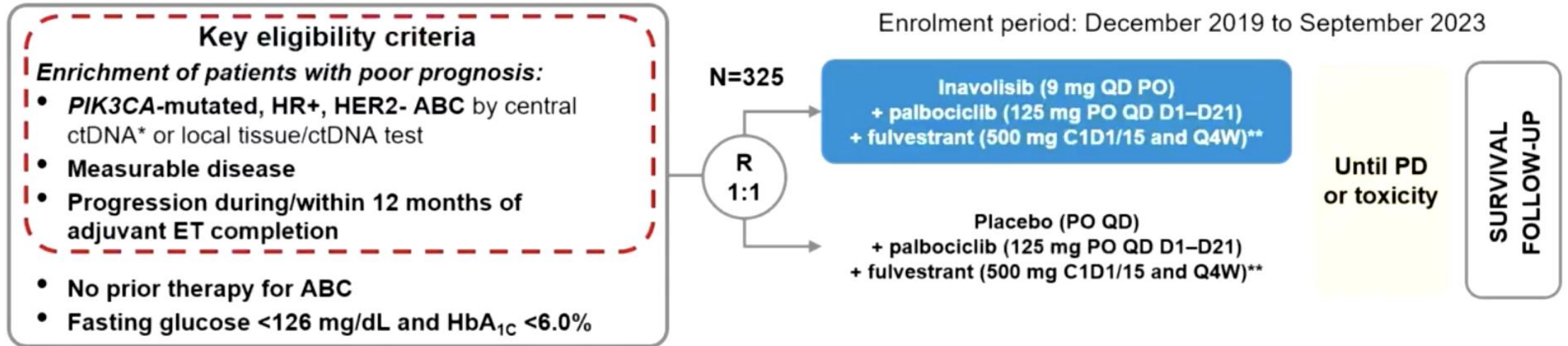
PIK3CA mutant



Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Abemaciclib + fulvestrant	58	49	37	33	29	24	22	20	20	18	16	14	13	12	7	5	3	2	1
Placebo + fulvestrant	38	28	16	16	13	13	6	5	5	5	5	4	3	3	2	2	0	0	0

INAVO120: Study Design



Stratification factors:

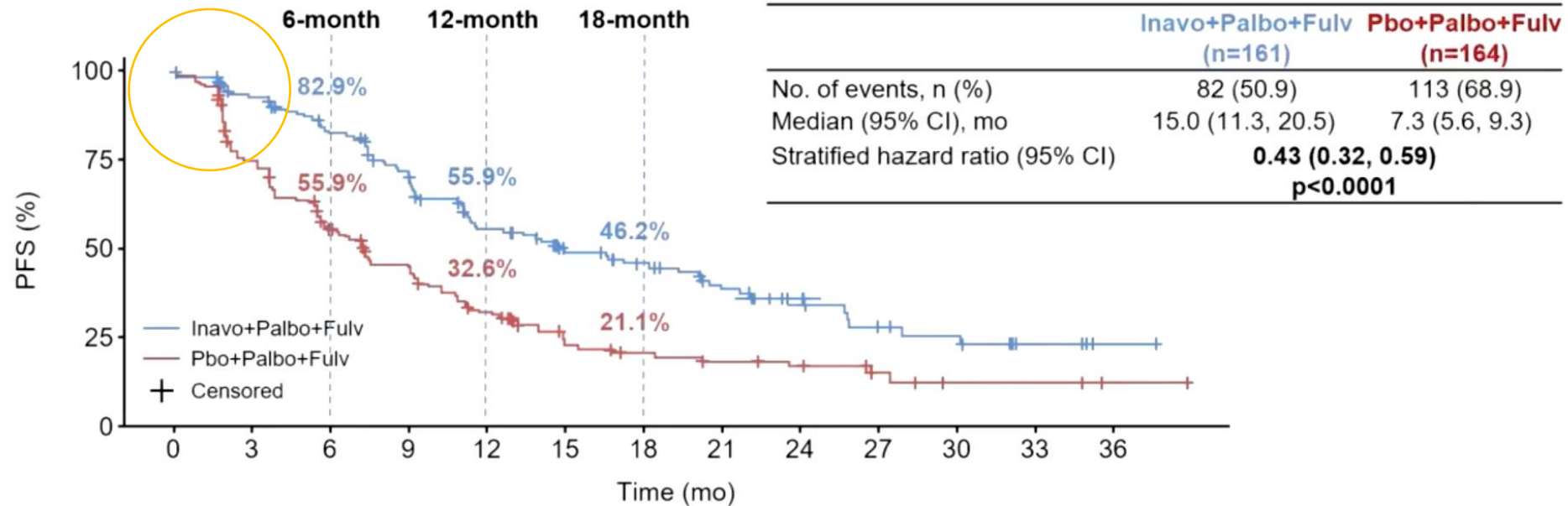
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)[†]
- Region (North America/Western Europe; Asia; Other)

Endpoints

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

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). [†] Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer. [‡] 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. [§] OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; ** Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29**:1634–1657.

INAVO120: Primary endpoint PFS (investigator-assessed)



Patients at risk:

Inavo+Palbo+Fulv
Pbo+Palbo+Fulv

161	134	111	92	66	48	41	31	22	13	11	5	1
164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Endocrine resistance:

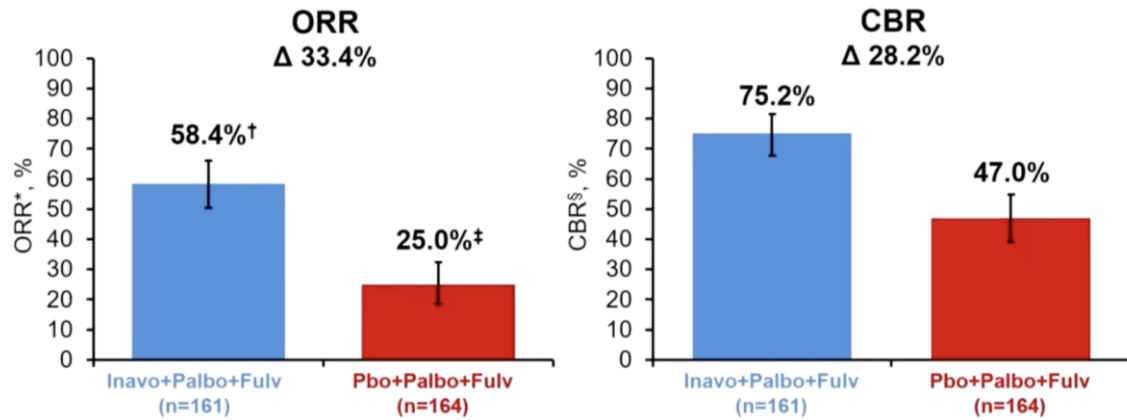
- 34% primary
- 66% secondary

High risk features:

- 48% premenopausal
- 80% visceral mets, 50% liver mets

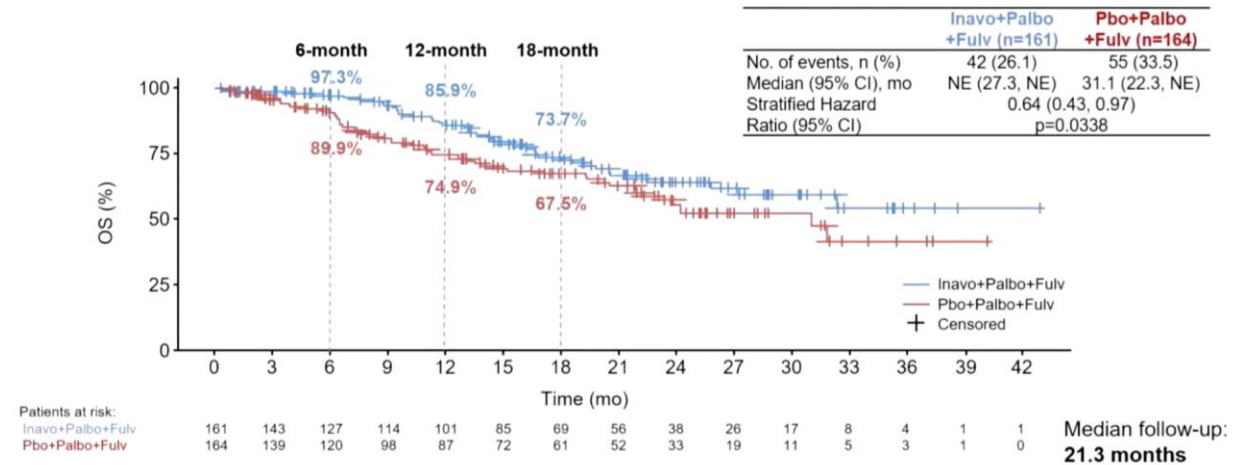
INAVO120: Key secondary endpoints

Secondary endpoints: ORR and CBR (investigator-assessed)



* Patients with a CR or PR on two consecutive occasions ≥4 weeks apart per RECIST v1.1. † Seven patients with CR, 87 patients with PR. ‡ One patient with CR, 40 patients with PR, 79 patients with SD, 34 patients with PD, and 10 with missing status. § Patients with a CR, PR, and/or SD for ≥24 weeks per RECIST v1.1. CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; Inavo, inavolisib; ORR, objective response rate; Palbo, palbociclib; Pbo, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Key secondary endpoint: Overall survival (interim analysis)



The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.

Adverse events from phase III trials: Inavolisib, Alpelisib and Capivasertib

Patients with key AEs, † %	INAVO120 ¹ Inavo + Palbociclib+ Fulvestrant (N=162)		INAVO120 ¹ Palbociclib + fulvestrant Control arm (n = 162)		SOLAR-1 ² Alpelisib + fulvestrant (n = 284)		CAPitello-291 ³ Capivasertib + fulvestrant (n = 355)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Hyperglycemia [#]	59	6	9	0	64	33	16	2
Diarrhea	48	4	16	0	58	7	72	9
Rash	25	0	17	0	54	20	38	12
Stomatitis*	51	6	27	0	25	3	15	2
Nausea	28	1	17	0	45	3	35	1
AEs leading to study treatment discontinuation	7	N/A	1	N/A	25	N/A	13	N/A

Cross-trial comparisons should be interpreted with caution due to differences in patient populations and AE reporting.

Notes:

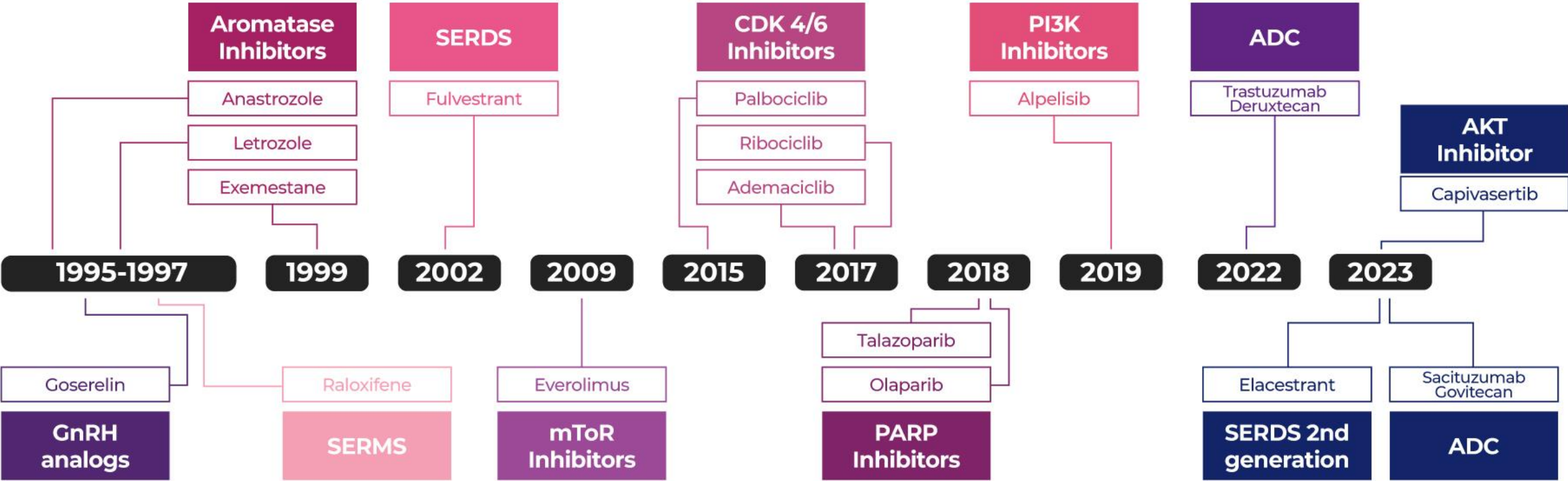
†For INAVO120, the key AEs were assessed as a medical concept (grouped terms),

[#]Eligibility varied widely between trials. For INAVO120, FBG <126 and HGBA1c <6%; For SOLAR-1, HGBA1c < 6.5%; For Capitello-291, HGBA1c <8%

*For INAVO120, stomatitis grouped term includes mucosal inflammation.

*For SOLAR-1 and CAPitello-291, stomatitis was reported as a single term; for Solar 1 mucosal inflammation was 18% for any Grade and 2% for Grade ≥3

Timeline of Targeted Therapies Approval for HR+ HER2- Metastatic Breast Cancer



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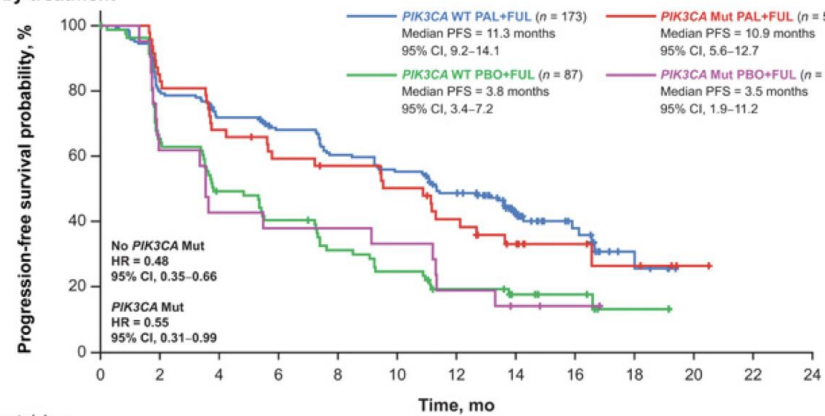


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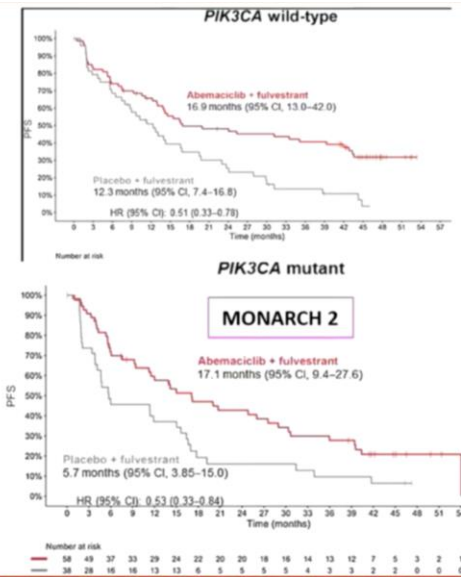
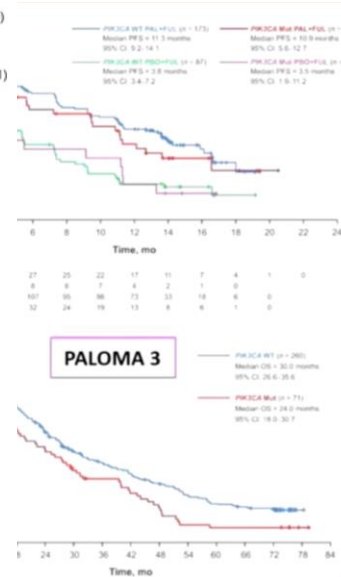
Exploratory analysis of CDK 4/6 inhibitor efficacy by PIK3CA mutation status

A PFS by treatment



Patients at risk, n

	0	2	4	6	8	10	12	14	16	18	20	22	24
PIK3CA Mut PAL+FUL	50	40	32	27	25	22	17	11	7	4	1	0	0
PIK3CA Mut PBO+FUL	21	13	9	8	8	7	4	2	1	0	0	0	0
PIK3CA WT PAL+FUL	173	131	116	107	95	86	73	33	18	6	0	0	0
PIK3CA WT PBO+FUL	87	53	39	32	24	19	13	8	6	1	0	0	0

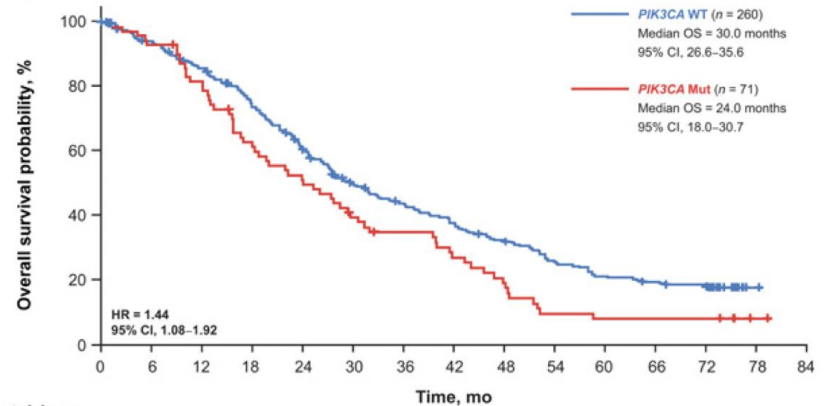


Monarch 2

- No prior chemo
- Primary ER: 22%
- Secondary ER: 78%

- PIK3CA mutations
- 96/219 (44%) available samples for ctDNA

B OS regardless of treatment



Patients at risk, n

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
PIK3CA Mut	71	66	56	42	35	26	22	17	13	6	5	5	5	1	0
PIK3CA WT	260	238	215	184	149	116	100	86	73	58	47	42	39	1	0

Cristofanilli et al. Clin Cancer Res. 2022;28:3433;
 Toloney et al. Clin Cancer Res 2022;28:1500

Adverse events with any grade AEs $\geq 20\%$ incidence in either treatment group

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Neutropenia	144 (88.9%)	130 (80.2%)	147 (90.7%)	127 (78.4%)
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	83 (51.2%)	9 (5.6%)	43 (26.5%)	0
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	95 (58.6%)	9 (5.6%)	14 (8.6%)	0
Diarrhea	78 (48.1%)	6 (3.7%)	26 (16.0%)	0
Nausea	45 (27.8%)	1 (0.6%)	27 (16.7%)	0
Rash	41 (25.3%)	0	28 (17.3%)	0
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Key AEs are shown in **bold**. AEs were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

Serious AE: 24.1% vs 10.5%

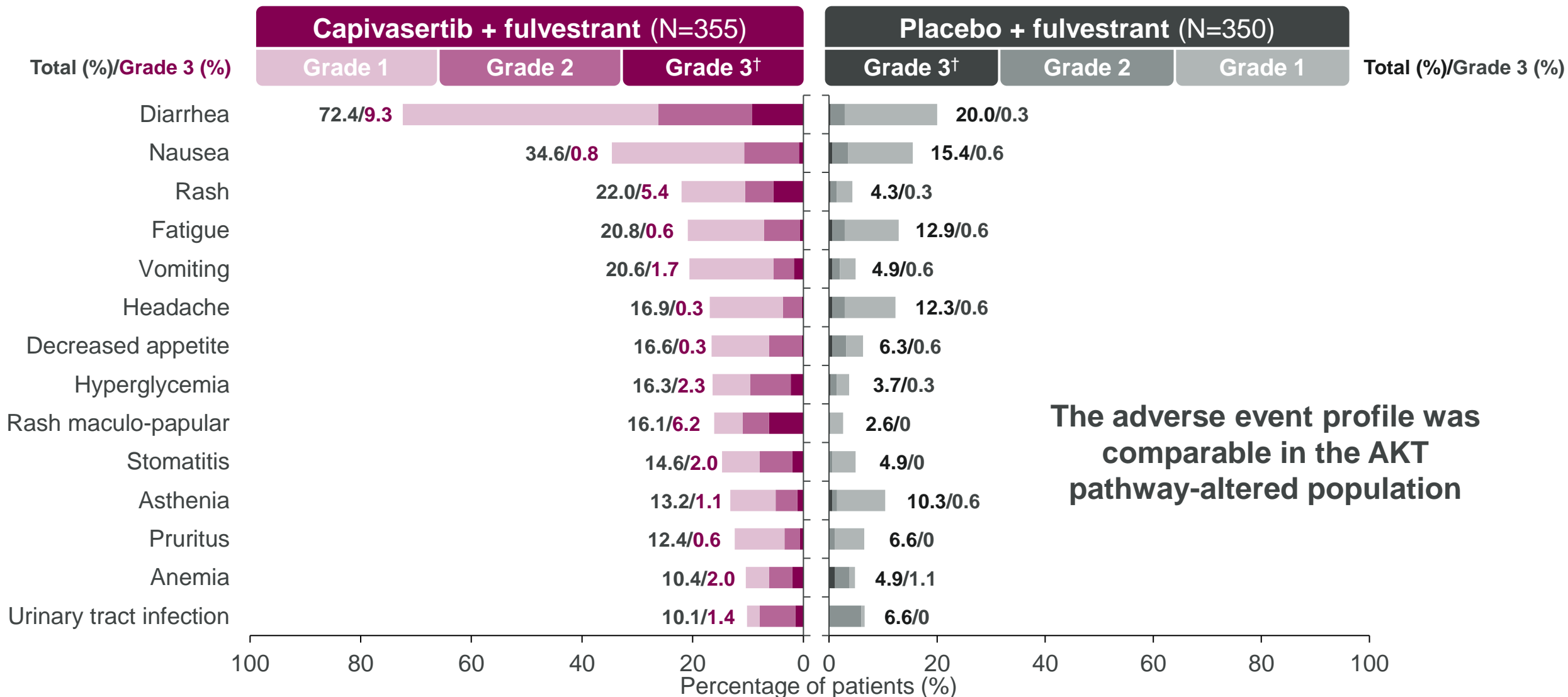
AE leading to discontinuation of treatment: 6.8% vs 0.6%

AE leading to dose modification/ interruption of treatment: 82.7% vs 74.7%

Prior treatments

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Prior endocrine therapy for ABC; n (%)	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor for ABC; n (%)		245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Alteration; n (%)		Capivasertib + fulvestrant (N=355)		Placebo + fulvestrant (N=353)	
Any AKT pathway alteration		155 (43.7)		134 (38.0)	
PIK3CA	Any	116 (32.7)		103 (29.2)	
	PIK3CA only	110 (31.0)		92 (26.1)	
	PIK3CA and AKT1	2 (0.6)		2 (0.6)	
	PIK3CA and PTEN	4 (1.1)		9 (2.5)	
AKT1 only		18 (5.1)		15 (4.2)	
PTEN only		21 (5.9)		16 (4.5)	

Adverse events (>10% of patients) – overall population



The adverse event profile was comparable in the AKT pathway-altered population

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

Targeted therapies and associated biomarker in HR+/HER2- MBC

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NCCN Guidelines Version 2.2023 Breast Cancer

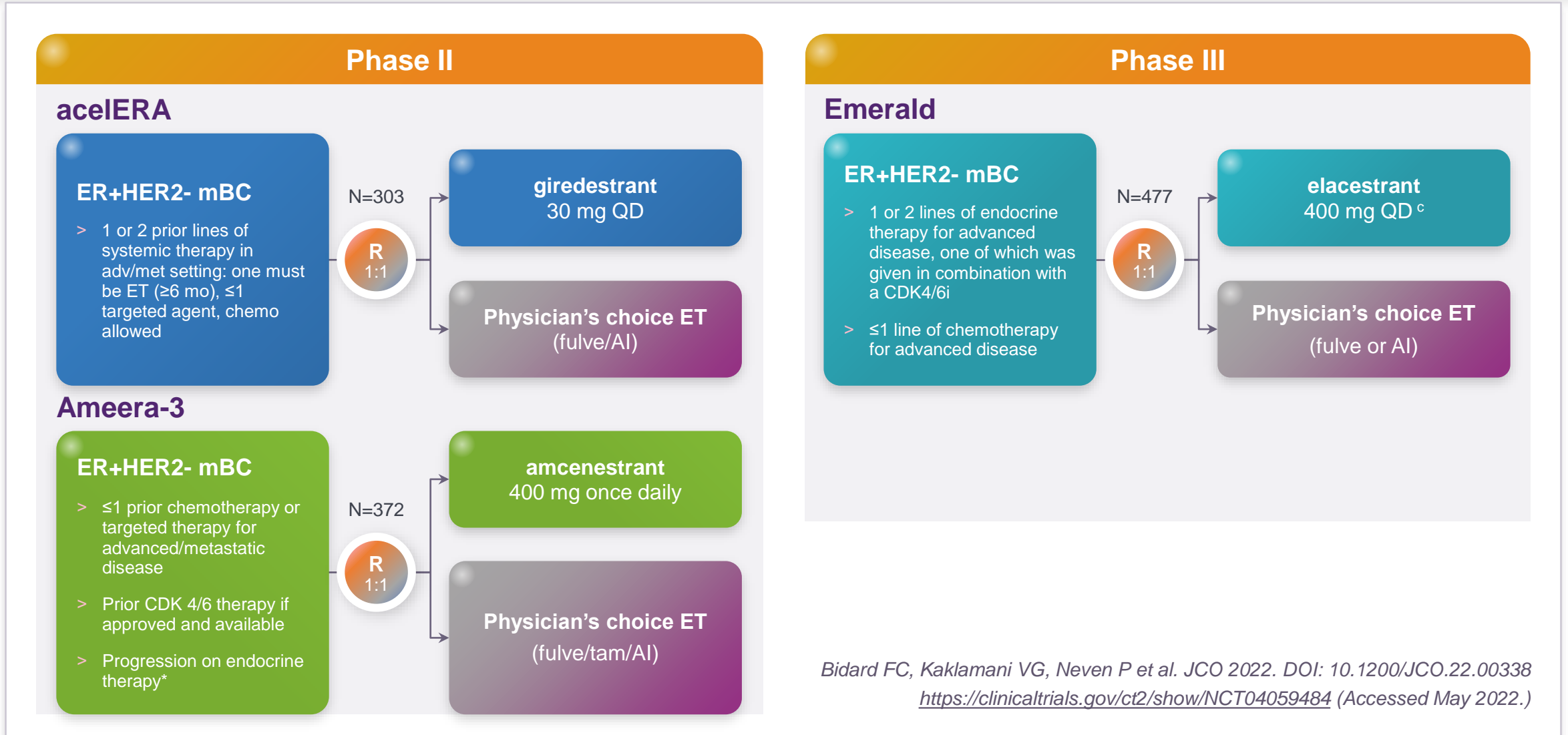
[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

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

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative ^v	<i>PIK3CA</i> activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant ^w	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative ^x	<i>ESR1</i> mutation	NGS, PCR (blood)	Elacestrant	Category 2A	Other recommended regimen
Any	<i>NTRK</i> fusion	FISH, NGS, PCR (tissue block)	Larotrectinib ^y Entrectinib ^y	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tissue block)	Pembrolizumab ^{z,aa} Dostarlimab-gxly ^{bb}	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab ^{z,aa}	Category 2A	
Any	<i>RET</i> -fusion	NGS	Selpercatinib ^{cc}	Category 2A	

Phase 3 oral SERDs clinical trials with available results

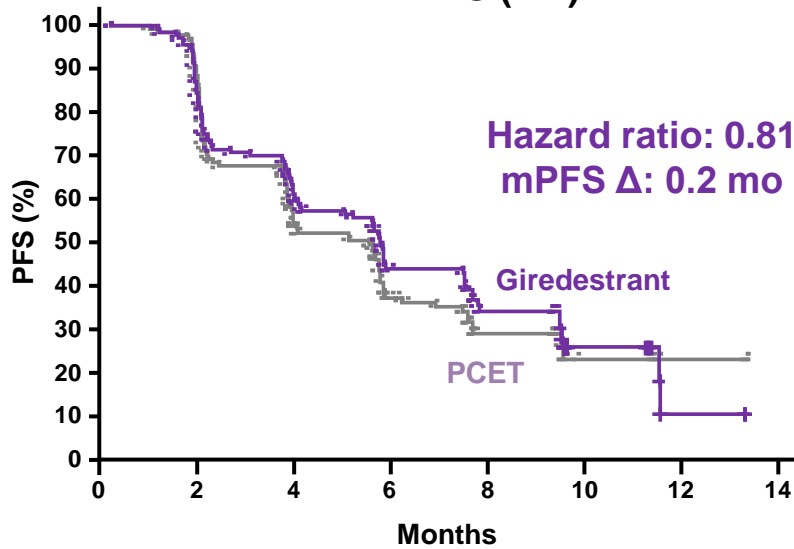


Overview of clinical trials with selected SERDs in development

SERD	Giredestrant	Elacestrant	Amcenestrant	Camizestrant	Imlunestrant
MBC					
1st line (combo with CDK4/6) Ph 3	PersevERA (Gire+palbo vs let+palbo)	--	AMEERA-5 (Amce+palbo vs letro+palbo)	SERENA-4 , (cami+Palbo vs ana+palbo) SERENA-6 (cami+Pablo, in ESR1)	EMBER 1 (imlune; imlune+ abema; imunle+abema+/-AI)
2nd line (single agent, Post CDK4/6)	AccelERA (gire vs Ful/AI) evERA (gire+everolimus)	EMERALD (Ela vs Ful/AI)	AMEERA-3 (amce vs Ful/AI/Tam)	SERENA-2 (cami vs fulv)	EMBER3 (Imlune vs Exe/Fulv vs Imlune+Abema)
EBC					
Neoadjuvant WoO phase 1, 2 studies	CoopERA (gire vs anastr)	ELIPSE (ph1; elace)	AMEERA-4 (amce vs retro) I-SPY EOP (amce+/-abema)	SERENA -3 (cami vs fulv)	EMBER-2 (ph1, imlune)
Adjuvant Phase 3	LidERA (gire vs AI/Tam)	--	AMEERA-6 (amce vs Tam)- In patients who discount AI	--	EMBER-4 (ph3, imlune vs PCE) In pts who have received ET for 3-5 years, based on rising ctDNA

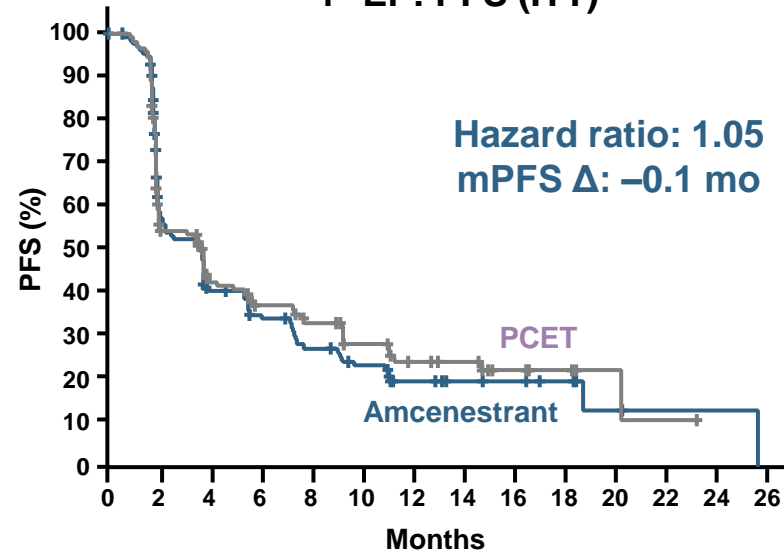
Overview of primary analysis results in ER+HER2- MBC with single agent oral SERDs

aceIERA BC¹
1° EP: PFS (ITT)



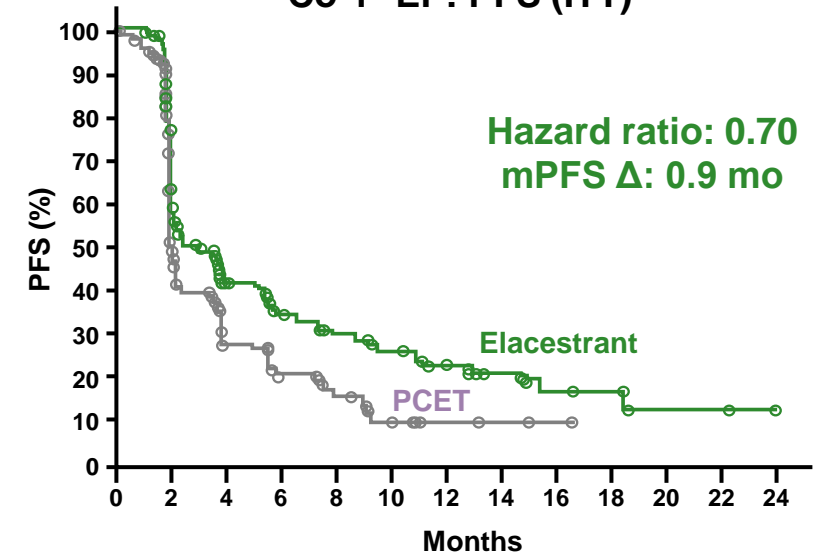
	Giredestrant (n = 151)	PCET (n = 152)
95% CI for hazard ratio	0.60, 1.10	
P value	0.176	
mPFS, mo	5.6	5.4

AMEERA-3^{*,2}
1° EP: PFS (ITT)



	Amcenestrant (n = 143)	PCET (n = 147)
95% CI for hazard ratio	0.79, 1.40	
P value	0.644	
mPFS, mo	3.6	3.7

EMERALD³
Co-1° EP: PFS (ITT)



	Elacestrant (n = 239)	PCET (n = 238)
95% CI for hazard ratio	0.55, 0.88	
P value	0.0018	
mPFS, mo	2.8	1.9

- mPFS was comparatively low in AMEERA-3 and EMERALD due to differences in patient populations; 79% of patients in AMEERA-3, and all patients in EMERALD, had received prior CDK4/6i (42% in aceIERA BC)
- PFS benefit in subgroups was generally consistent with the ITT population in all three studies

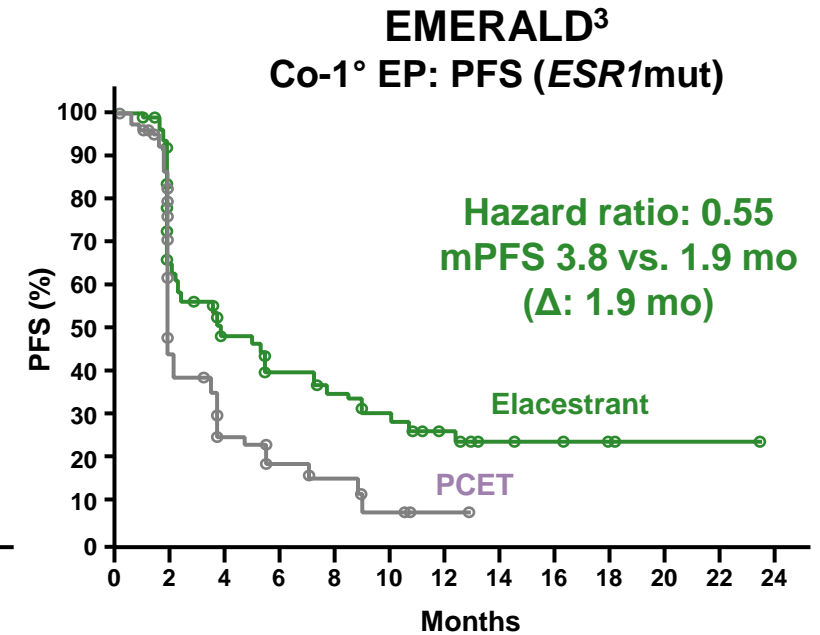
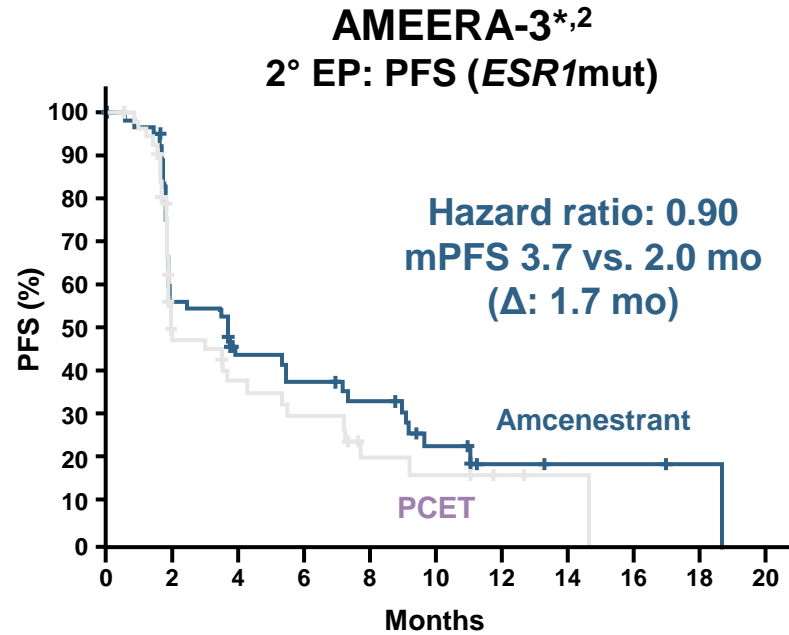
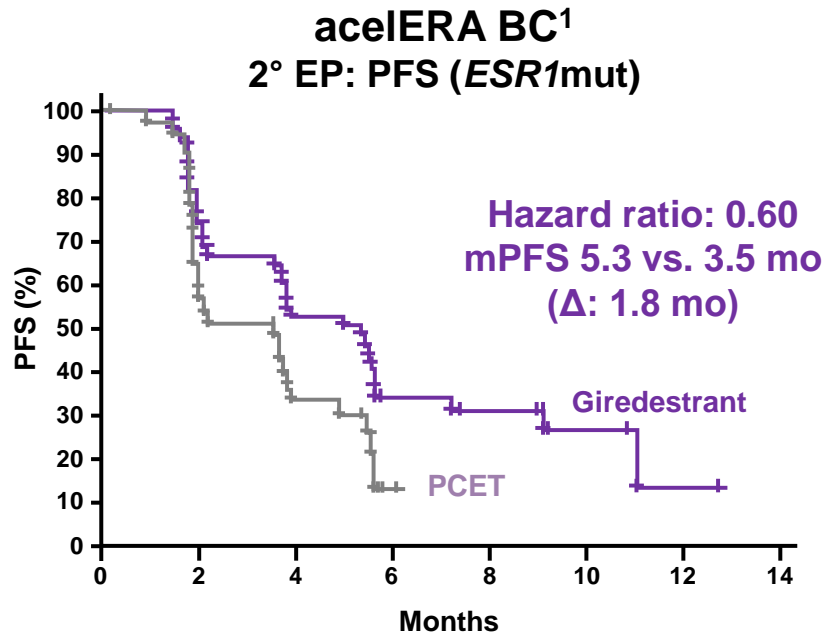
* Sanofi announced in August 2022 that the amcenestrant clinical development programme will be discontinued.⁴

1, primary; BC, breast cancer; CI, confidence interval; EP, endpoint; HR, hormone receptor; ITT, intention-to-treat; mBC, metastatic breast cancer; mo, months; mPFS, median progression-free survival; PCET, physician's choice of endocrine therapy; PFS, progression-free survival; SERD, selective oestrogen receptor degrader.

1. Martin M, *et al.* ESMO 2022 (Abstract 211MO; mini oral presentation); 2. Tolaney SM, *et al.* ESMO 2022 (Abstract 212MO; mini oral presentation); 3. Bidard F-C, *et al.* J Clin Oncol 2022; 4.

<https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668> (accessed August 2022).

A significant PFS benefit was seen in the *ESR1*-mutated population of EMERALD; a benefit trend was observed in aceIERA BC and AMEERA-3



- Giredestrant and elacestrant had comparable PFS hazard ratios vs. PCET in *ESR1*-mutated subpopulations; the hazard ratio for amcenestrant was notably higher
- Oral SERDs target both oestrogen-dependent and -independent activity,^{4,5} whereas AIs target oestrogen-dependent activity only⁶

* Sanofi announced in August 2022 that the amcenestrant clinical development programme will be discontinued.⁷

1° primary; 2°, secondary; BC, breast cancer; EP, endpoint; mo, months; mPFS, median progression-free survival; PCET, physician's choice of endocrine therapy; PFS, progression-free survival; SERD, selective oestrogen receptor degrader.
1. Martin M, *et al.* ESMO 2022 (Abstract 211MO; mini oral presentation); 2. Tolaney SM, *et al.* ESMO 2022 (Abstract 212MO; mini oral presentation); 3. Bidard F-C, *et al.* *J Clin Oncol* 2022; 4. Jhaveri KL, *et al.* ASCO 2021 (Abstract 1017; poster); 5. Turner N, *et al.* SABCS 2021 (Abstract PD-13-07; poster); 6. Miller WR & Larionov AA, *Breast Cancer Res* 2012; 7. <https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668> (accessed August 2022).