Novel Endocrine Therapies

The Year in Review

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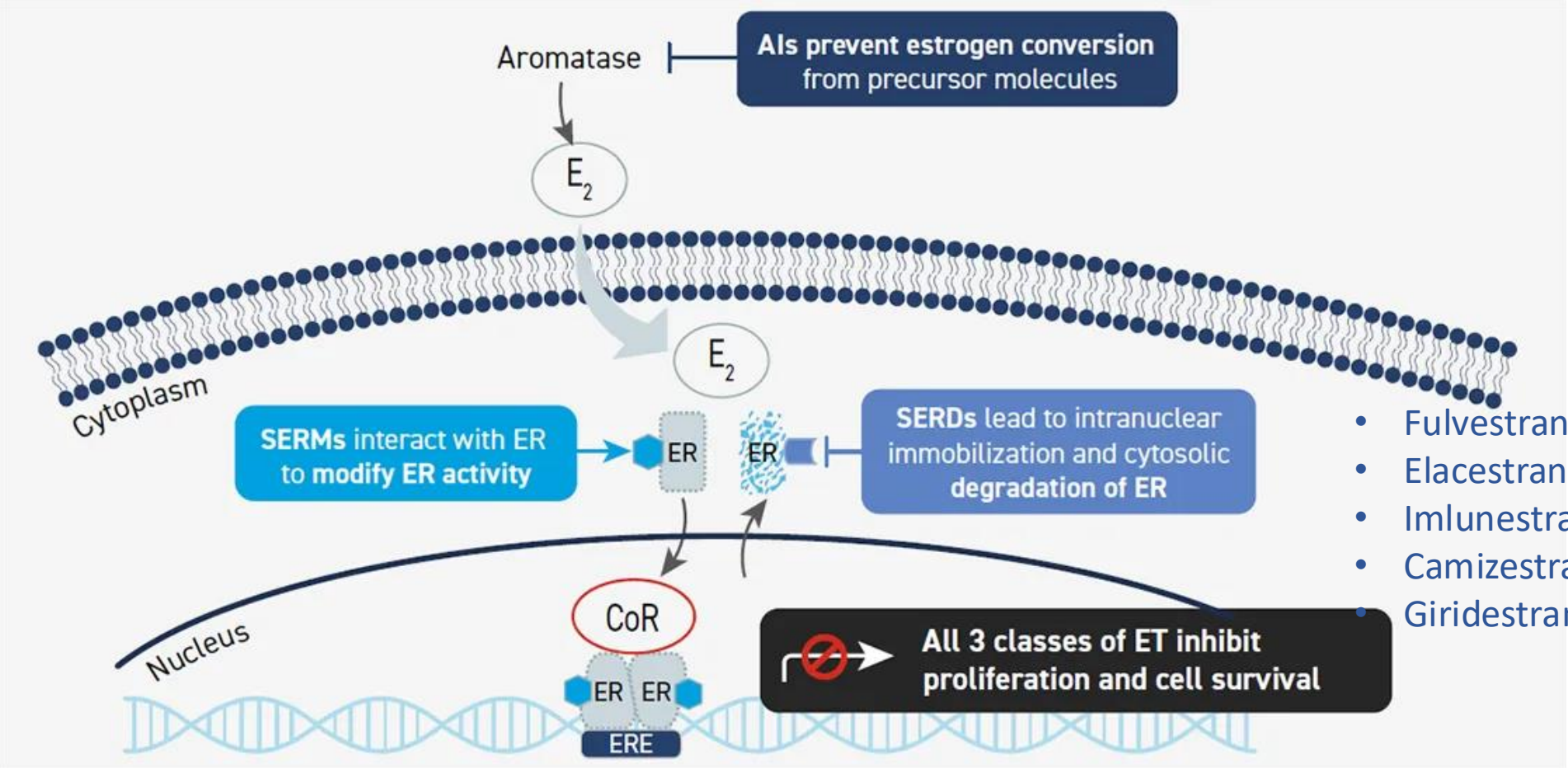
Novel Endocrine Therapies 2024-2025

- Oral SERDs
  - Elacestrant
  - Imlunestrant
- PROTAC
  - Vepdegestrant
- PI3K inhibitor
  - Inavolisib

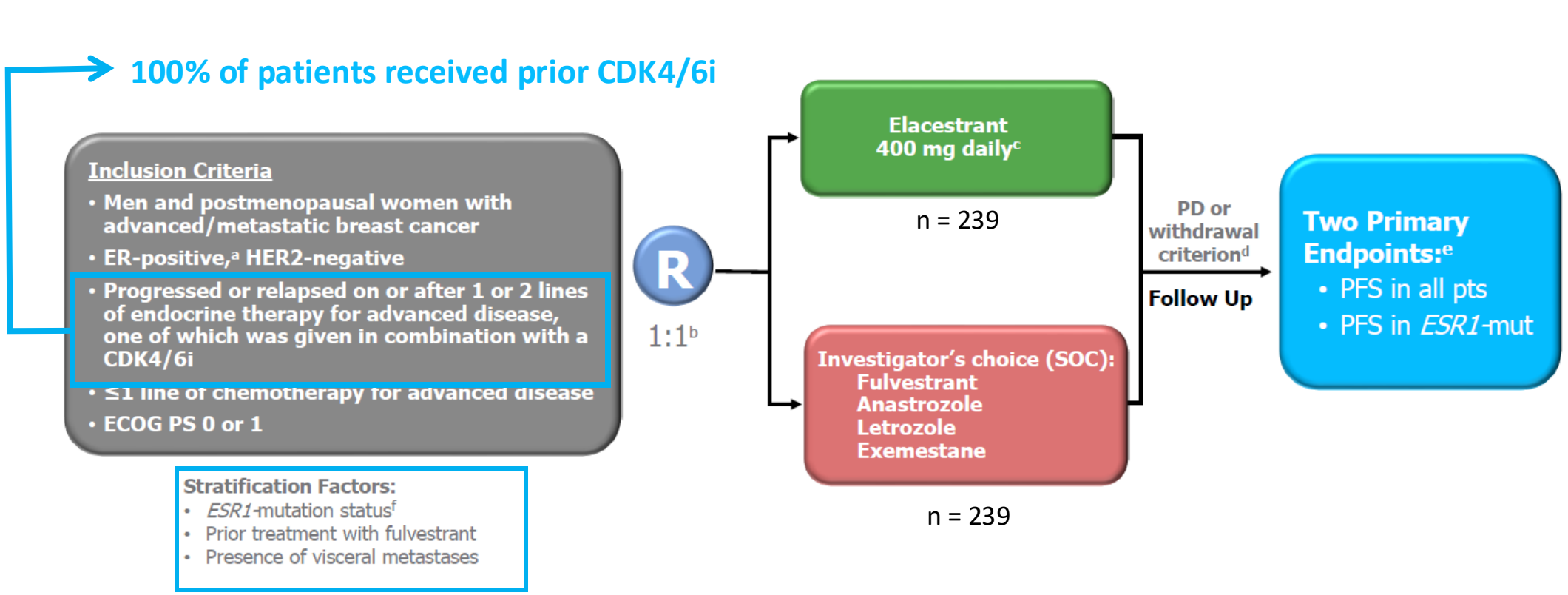
ER targeting and SERDs



- Fulvestrant
- Elacestrant
- Imlunestrant
- Camizestrant
- Giridestrant

References: 1. Le Romancer M et al. *Endocr Rev*. 2011;32(5):597-622. **2.** Misganaw M et al. *PLoS One*. 2023;18(1):e0279656. **3.** Shanle EK et al. *Adv Drug Deliv Rev*. 2010;62(13):1265-76. **4.** Williams MM et al. *Cell Death Dis*. 2018;9(2):21. **5.** Chen YC et al. *Expert Opin Investig Drugs*. 2022;31(6):515-529. **6.** Patel HK et al. *Pharmacol Ther.* 2018;186:1-24. **7.** Patel R et al. *npj Breast Cancer*. 2023;9(1):20. **8.** Gradishar WJ et al. *J Natl Compr Canc Netw*. 2023;21(6):594-608. **9.** Zhou FH et al. *Front Cell Dev Biol*. 2023;11:1148792.

EMERALD Phase 3 trial: Elacestrant and CDK4/6i and Endocrine Therapy



[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).

EMERALD: Key Baseline Characteristics

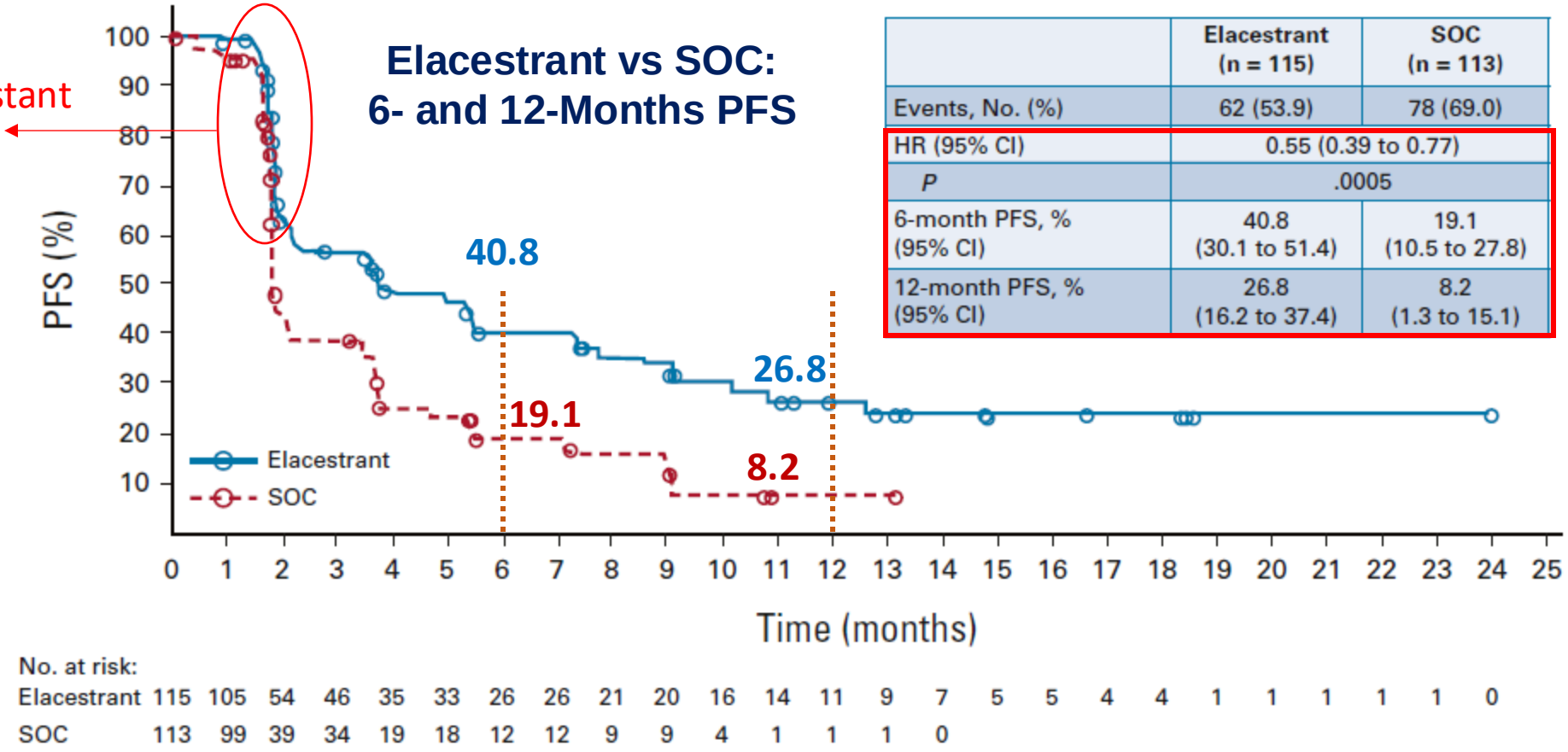
649 Patients Screened→ 477 Patients Randomized→ 228 (47.8%) Had Detectable *ESR1* Mutation

	Elacestrant		SOC Endocrine Therapy	
	All Patients (n = 239)	***ESR1m* (n = 115)**	**All Patients (n = 238)**	***ESR1m* (n = 113)**
Age, median (range), years	63 (24-89)	64 (28-89)	64 (32-83)	63 (32-83)
ECOG PS 0, %	59.8	58.3	56.7	54.9
Visceral Metastasis, %	68.2	70.4	71	74.3
Prior Adjuvant Therapy, %	66.1	53.9	59.2	57.5
No. Prior Lines of ET for MBC, %				
1 / 2	54.0 / 46.0	63.5 / 36.5	59.2 / 40.8	61.1 / 38.9
No. Prior Lines of CT for MBC, %				
0 / **1**	79.9 / **20.1**	77.4 / **22.6**	75.6 / **24.4**	71.7 / **28.3**
Prior ET, %				
Fulvestrant	29.3	23.5	31.5	24.8
AI	80.8	87.8	81.1	85.0
Tamoxifen	7.9	7.8	6.3	8.0
Prior mTORi / PI3Ki, %	4.2 / 1.3	5.2 / 0.9	2.5 / 0.4	2.7 / 0

Bidard F, et al. *J Clin Oncol*. 2022;40:3246-3256.

EMERALD: Landmark Analysis of PFS—Detectable *ESR1mut* Subgroup (Co-Primary Endpoint)

Endocrine-resistant disease



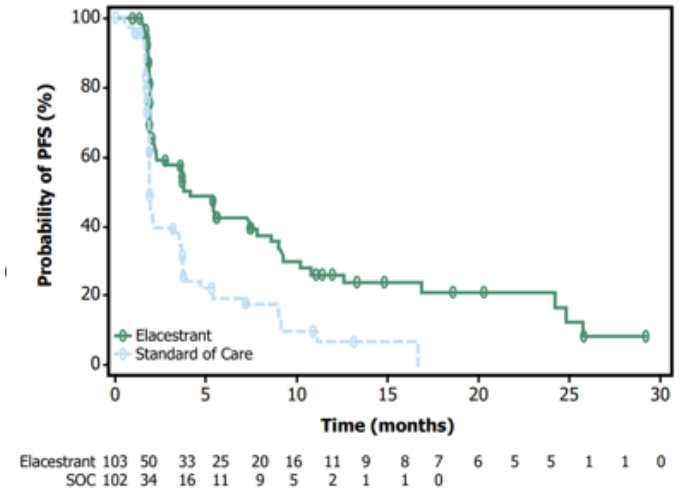
	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

Secondary Analysis ELA vs FUL in *ESR1*m	HR, 0.50 (0.34-0.74); P = .0005
	6-mo PFS, 40.8 vs 20.8 / 12-mo PFS, 26.8 vs 8.4

Bidard F, et al. *J Clin Oncol*. 2022;40:3246-3256.

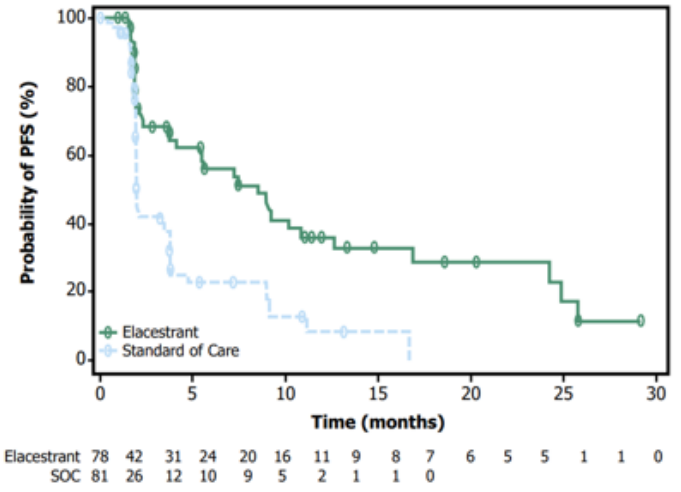
EMERALD: PFS by Duration of CDK4/6i—Detectable *ESR1*mut Subgroup

≥6 Months CDK4/6i



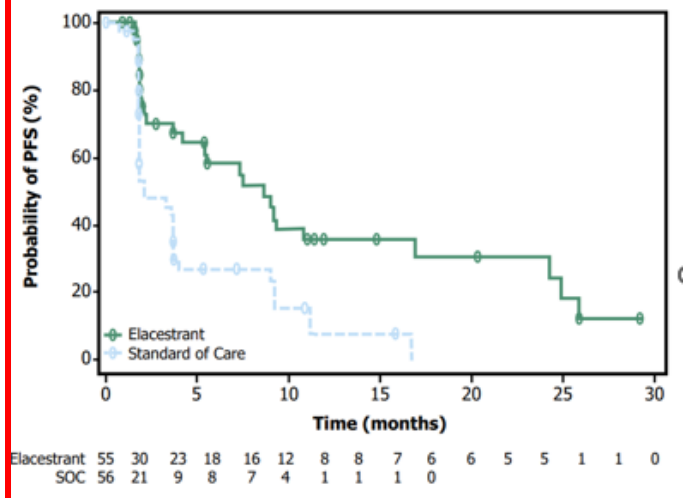
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

≥12 Months CDK4/6i



	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)	

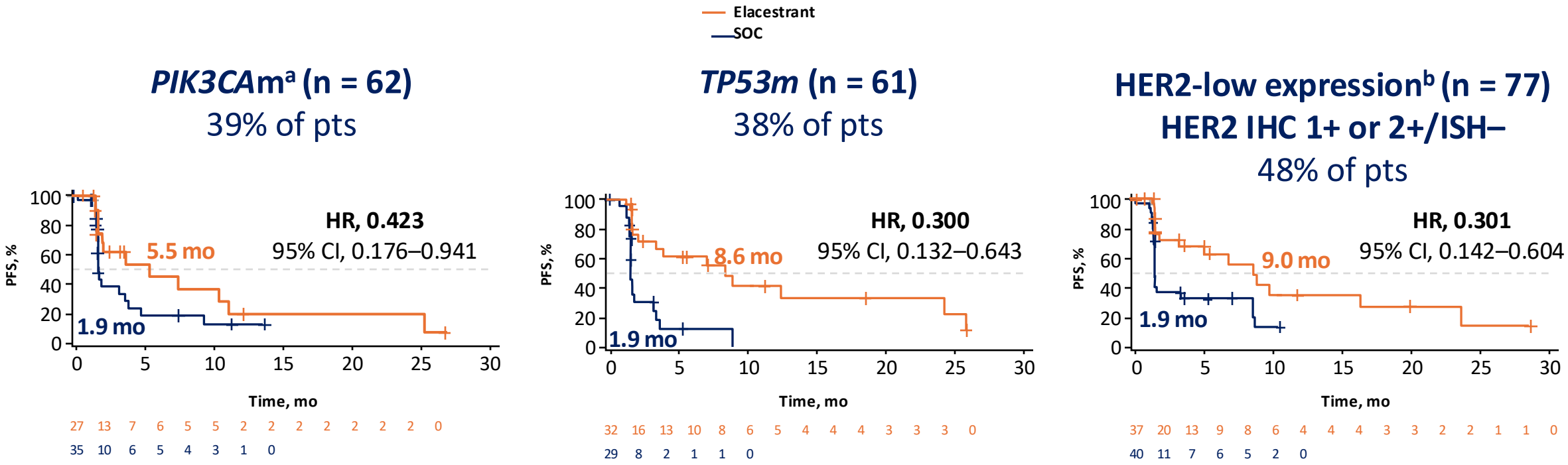
≥18 Months CDK4/6i



	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)	

Bardia, A, et al. SABCS 2022. Abstract GS3-01.

EMERALD: PFS in Patients With ≥12 Months of Prior ET + CDK4/6i and *ESR1*m—Subgroup Analyses of Co-occurring Biomarkers



- Post-hoc/exploratory analysis; no prespecified statistical procedure controlling for type 1 error.
- a Includes E545K, H1047R, E542K, and others; b Locally assessed HER2 IHC; Data not available for all patients.
- ELA, elacestrant; *ESR1*, estrogen receptor 1; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in situ hybridization; m, mutated; mo, month(s); PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase; pts, patients; SOC, standard of care; TP53, tumor protein p53; wt, wild type.
  Bardia A, et al. *Clin Cancer Res*. 2024;30:4299-4309.

Real world data with elacestrant

Lloyd et al. SABCS 2024 PS7-05

- 750 patients GuardantINFORM
- TTD and TTNT similar to PFS in EMERALD
- Line of treatment did not impact outcome
- PIK3CA pathway alterations had worse outcomes

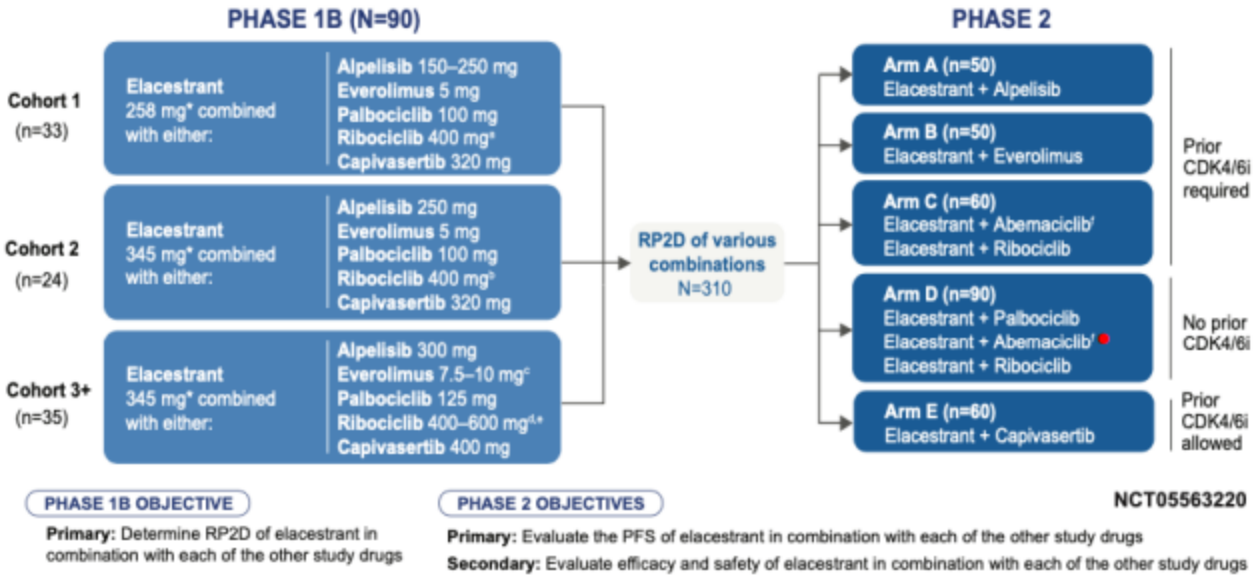
Swallow et al. SABCS 2024 P3-10-08

- 212 patients in Komodo Research Database (US insurance claims)
- rwPFS benefit consistent among all patients with ER+/HER2- MBC and across clinically relevant subgroups

Phase 1b/2 ELEVATE Umbrella Study of Elacestrant Combinations for ER+HER2- MBC: Update

Main eligibility

- 1-2 Prior lines of ET, one with CDK4/6i (no prior everolimus, alpelisib, capivasertib, and the companion CDK4/6i):
- 1-2 prior hormonal therapies in MBC setting, or radiological evidence of BC recurrence or progression ≤12 mo from end of adj ET
- Phase 2 is same as Phase 1b, except no prior CDK4/6i is allowed for Arm D and in arm E, prior CDK4/6i allowed but not required

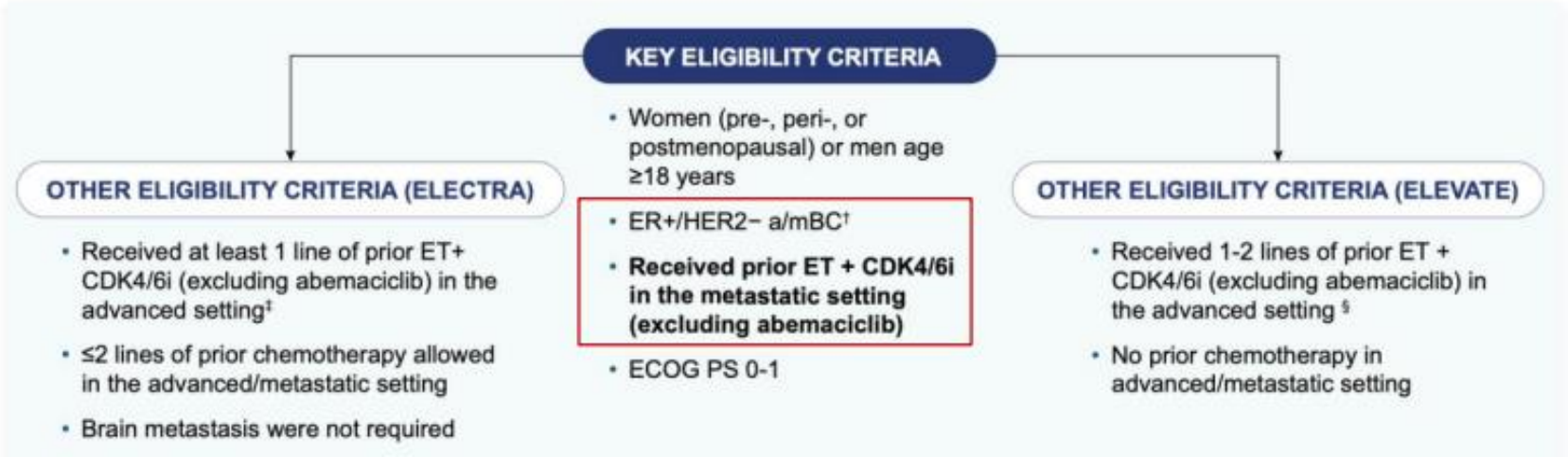


Combination	TEAEs Adverse Events Summary
Elacestrant 345 mg + abemaciclib 150 mg BID (RP2D)	Diarrhea was mainly grade 1/2, neutropenia was associated mainly with abemacicib only.
Elacestrant 345 mg + everolimus 7.5 mg (RP2D)	Stomatitis, rash and diarrhea were mainly grade 1/2.
Elacestrant 345 mg + palbociclib 125 mg (RP2D)	Neutropenia was associated mainly with palbociclib only.
Elacestrant 172 mg + ribociclib 600 mg	Neutropenia was associated mainly with ribociclib only. No grade 3/4 QTc prolongation observed.
Elacestrant 258 mg + capivasertib 320 mg	No grade 3/4 diarrhea, hyperglycemia or rash were observed.
Elacestrant 258 mg + alpelisib 200 mg	Rash and hyperglycemia were mainly grade 1/2. No grade 3/4 diarrhea was observed.

Data from ELEVATE alone is too early for efficacy data

Rugo HS, et al. SABCS 2024. Abstract PS7-06.

ELECTRA 1b and ELEVATE (Arm C) of Elacestrant + Abemaciclib for ER+/HER2- MBC: Pooled Analysis



**Safety profile of RP2D of elacestrant + abemaciclib consistent with that of abemaciclib + SOC ET

Rugo HS, et al. SABCS 2024. Abstract PS7-07.

Results: Patient Characteristics and TEAEs

Baseline Characteristics

Parameters	ELECTRA Cohort 1 (n=8) Elacestrant 258 mg QD + Abemaciclib 100 mg BID	ELECTRA Cohort 2 (n=7) Elacestrant 345 mg QD + Abemaciclib 100 mg BID	ELECTRA Cohort 3* RP2D (n=12) Elacestrant 345 mg QD + Abemaciclib 150 mg BID	ELEVATE Arm C (n=30) Elacestrant 345 mg QD + Abemaciclib 150 mg BID	POOLED ANALYSIS ELECTRA Cohort 3* + ELEVATE Arm C (n=42) Elacestrant 345 mg QD + Abemaciclib 150 mg BID
Median age, years (range)	43 (32–67)	51 (41–71)	54 (48–74)	61 (29–84)	**60 (29–84)**
Female, n (%)	8 (100)	7 (100)	12 (100)	30 (100)	**42 (100)**
ECOG PS, n (%)					
0	5 (63)	4 (57)	7 (58)	20 (67)	**27 (64)**
1	3 (38)	3 (43)	5 (42)	10 (33)	**15 (36)**
Metastatic site, n (%)					
Visceral	6 (75)	6 (86)	8 (67)	22 (73)	**30 (71)**
Brain	0	0	0	0	**0**
Liver	5 (63)	3 (43)	8 (67)	9 (30)	**17 (41)**
Lung	1 (13)	5 (71)	3 (25)	8 (27)	**11 (26)**
Bone	5 (63)	5 (71)	6 (50)	14 (47)	**20 (48)**
Mutations,[1] n (%)					
ESR1	2/5 (40)	2/7 (29)	7/12 (58)	14/28 (50)	**21/40 (53)**
PIK3CA	1/5 (20)	3/7 (43)	2/12 (17)	9/28 (32)	**11/40 (28)**
Primary endocrine resistance,[2] n (%)	3 (38)	1 (14)	3 (25)	2 (7)	**5 (12)**
Median number of prior therapies for adv/mBC, n (range)	2 (1–3)	2 (1–4)	2 (1–6)	1 (1–2)	**1 (1–6)**
Prior CDK4/6i for adv/mBC, n (%)	5 (63)	7 (100)	12 (100)	30 (100)	**42 (100)**
Palbociclib	3 (38)	5 (71)	5 (42)	18 (60)	**23 (55)**
Ribociclib	2 (25)	2 (29)	6 (50)	11 (37)	**17 (40)**
Palbociclib/Ribociclib	0	0	1 (8)	1 (3)	**2 (5)**
Number of prior lines of endocrine therapy for adv/mBC, n (%)					
1	3 (38)	3 (43)	5 (42)	25 (83)	**30 (71)**
2	3 (38)	3 (43)	6 (50)	5 (17)	**11 (26)**
3	0	1 (14)	1 (8)	0	**1 (2)**
Type of prior endocrine therapy, n (%)					
Fulvestrant	5 (63)	5 (71)	9 (75)	13 (43)	**22 (52)**
AI	3 (38)	5 (71)	9 (75)	21 (70)	**30 (71)**
Tamoxifen	1 (13)	2 (29)	2 (17)	1 (3)	**3 (7)**
Tamoxifen/AI	0	1 (14)	1 (8)	1 (3)	**2 (5)**
Number of prior lines of chemotherapy, n (%)					
0	5 (63)	3 (43)	5 (42)	30 (100)	**35 (83)**
1	3 (38)	4 (57)	6 (50)	0	**6 (14)**
2	0	0	1 (8)	0	**1 (2)**

Data cut-off: 15 OCT 2024. *Includes confirmatory cohort 3 expansion; [1]Mutation data not available for all patients at time of data analysis; [2]Relapse within the first two years while on adjuvant ET and/or progressive disease within the first six months of first-line ET for advanced/metastatic breast cancer[47]

adv/mBC=advanced or metastatic breast cancer; AI=aromatase inhibitor; BID=twice daily; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance status; ET=endocrine therapy; QD=once daily; RP2D=recommended phase 2 dose.

Treatment-Emergent Adverse Events (TEAEs) ≥20% at RP2D

Preferred Term, n (%)	ELECTRA Cohort 1 (n=8) Elacestrant 258 mg QD + Abemaciclib 100 mg BID		ELECTRA Cohort 2 (n=7) Elacestrant 345 mg QD + Abemaciclib 100 mg BID		ELECTRA Cohort 3* RP2D (n=12) Elacestrant 345 mg QD + Abemaciclib 150 mg BID		ELEVATE Arm C (n=30) Elacestrant 345 mg QD + Abemaciclib 150 mg BID		POOLED ANALYSIS ELECTRA Cohort 3* + ELEVATE Arm C (n=42) Elacestrant 345 mg QD + Abemaciclib 150 mg BID	
	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
Diarrhea	5 (63)	0	6 (86)	0	11 (92)	0	24 (80)	2 (7)	**35 (83)**	**2 (5)**
Nausea	6 (75)	0	5 (71)	0	8 (67)	0	19 (63)	2 (7)	**27 (64)**	**2 (5)**
Vomiting	1 (13)	0	3 (43)	0	4 (33)	1 (8)	13 (43)	0	**17 (41)**	**1 (2)**
Fatigue	1 (13)	0	1 (14)	0	2 (17)	0	13 (43)	2 (7)	**15 (36)**	**2 (5)**
Neutropenia/neutrophil decreased	2 (25)	2 (25)	3 (43)	2 (29)	9 (75)	7 (58)	5 (17)	4 (13)	**14 (33)**	**11 (26)**
Anemia	1 (13)	0	2 (29)	0	4 (33)	1 (8)	6 (20)	2 (7)	**10 (24)**	**3 (7)**
Constipation	0	0	3 (43)	0	0	0	9 (30)	0	**9 (21)**	**0**
Decreased appetite	2 (25)	0	3 (43)	0	2 (17)	0	7 (23)	0	**9 (21)**	**0**

No grade 4 AEs were reported during the elacestrant + abemaciclib treatment period

Data cut-off: 15 OCT 2024. *Includes confirmatory cohort 3 expansion. AE=adverse event; BID=twice daily; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; ET=endocrine therapy; QD=once daily; RP2D=Recommended Phase 2 dose.

Rugo HS, et al. SABCS 2024. Abstract PS7-07.

ELECTRA 1b and ELEVATE : Early efficacy results

Response and Clinical Benefit With Elacestrant + Abemaciclib in Efficacy-Evaluable Patients

	ELECTRA Cohort 1 (n=7)	ELECTRA Cohort 2 (n=7)	ELECTRA Cohort 3‡ RP2D (n=12)	ELEVATE Arm C (n=26)	POOLED ANALYSIS ELECTRA Cohort 3‡ + ELEVATE Arm C (n=38)
Efficacy Outcome*†	Elacestrant 258 mg QD + Abemaciclib 100 mg BID	Elacestrant 345 mg QD + Abemaciclib 100 mg BID	Elacestrant 345 mg QD + Abemaciclib 150 mg BID	Elacestrant 345 mg QD + Abemaciclib 150 mg BID	**Elacestrant 345 mg QD + Abemaciclib 150 mg BID**
ORR, n (%)	**2 (29)**	**2 (29)**	**3 (25)**	**4 (15)**	**7 (18)**
CR	-	-	1 (8)	1 (4)	**2 (5)**
PR	2 (29)	2 (29)	2 (17)	3 (12)	**5 (13)**
SD	2 (29)	3 (43)	7 (58)	18 (69)	**25 (66)**
PD	3 (43)	2 (29)	2 (17)	4 (15)	**6 (16)**
CBR, n (%)	**4 (57)**	**5 (71)**	**10 (83)**	**22 (85)**	**32 (84)**
CBR24wks, n (%)	**4 (57)**	**4 (57)**	**8 (67)**	In ELEVATE Arm C, average observation time has not reached 24 weeks	

Data cut-off: 15 OCT 2024. *Confirmed responses only; †Includes patients who had measurable disease (ie, at least 1 target lesion) at baseline and at least 1 post-baseline RECIST assessment ‡Includes confirmatory cohort 3 expansion.
CBR=clinical benefit rate (CR + PR + SD); CR=complete response; PR=partial response; SD=stable disease; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; ET=endocrine therapy; ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors

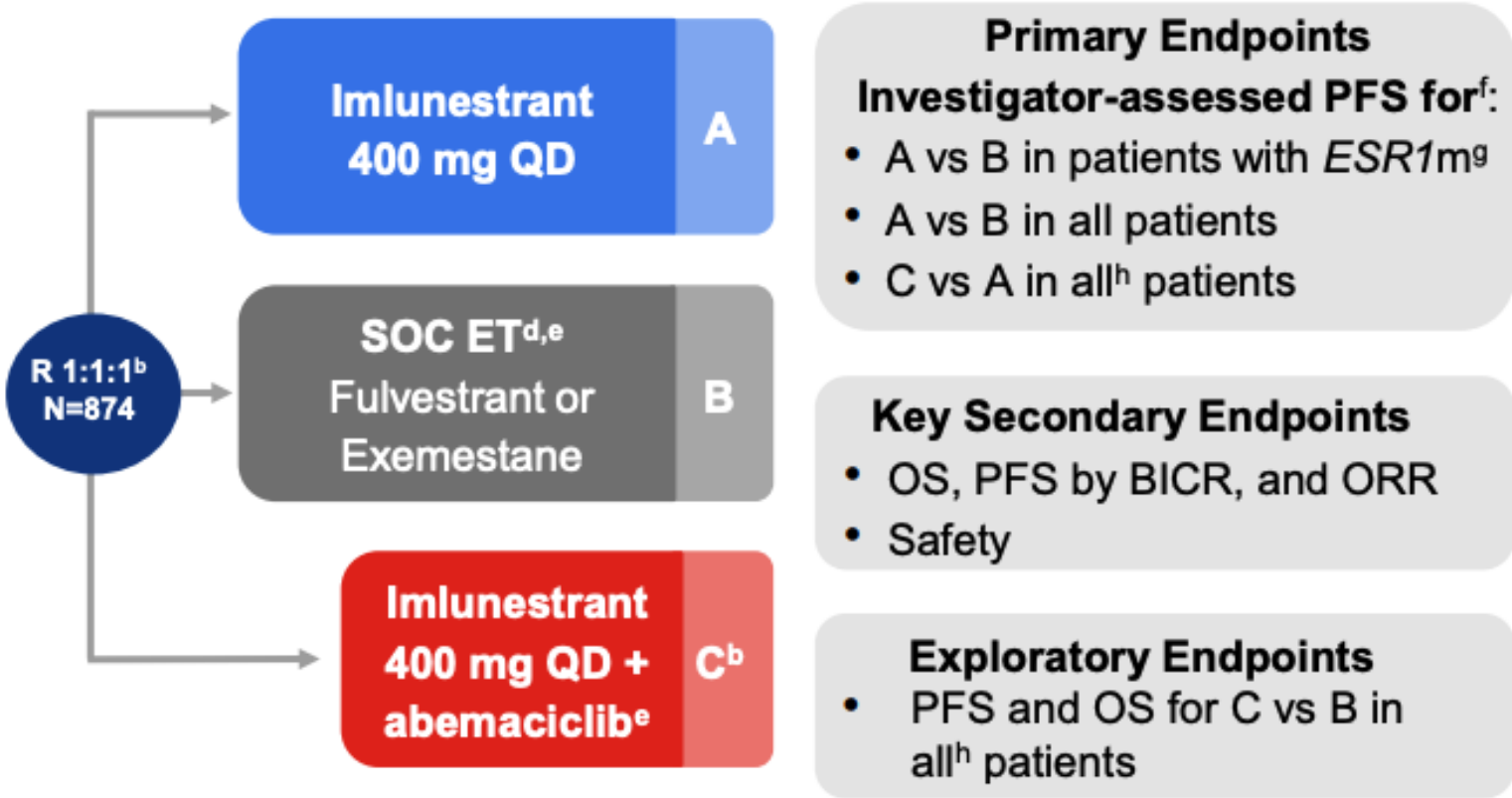
mPFS in Efficacy-Evaluable Patients from ELECTRA Phase 1b

	Elacestrant + Abemaciclib		
Population	**n**	**mPFS, mo**	**[95% CI]**
All patients	27	**8.7**	[6.1 – 16.6]
Prior ET+CDK4/6i	24	**8.7**	[6.1 – 16.6]
ESR1-mutated tumors	11	**8.7**	[2.0 – NC]
ESR1-mutation not detected	12	**7.2**	[1.9 – NC]
Prior ET+CDK4/6i ≥12 months	16	**16.6**	[7.5 – NC]
Dose level			
Elacestrant 345 mg QD + Abemaciclib 150 mg BID (RP2D)	12	**8.7**	[7.2 – NC]
Elacestrant 345 mg QD + Abemaciclib 100 mg BID	7	**7.5**	[1.9 – NC]
Elacestrant 258 mg QD + Abemaciclib 100 mg BID	8	**8.4**	[1.7 – 17.3]

Patients in ELECTRA Phase 1b had a median observational time for PFS of 7.5 months at data cut-off

Rugo HS, et al. SABCS 2024. Abstract PS7-07.

EMBER-3 Study Design



ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 to November 2023 across 195 sites in 22 countries. [a] A GnRH agonist was required in men and premenopausal women; [b] Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c] East Asia vs United States/European Union vs others; [d] Investigator's choice; [e] Labeled dose; [f] Scans every 8 weeks for the first 12 months, then every 12 weeks; [g] *ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h] Analysis conducted in all concurrently randomized patients.

EMBER-3 Baseline Characteristics

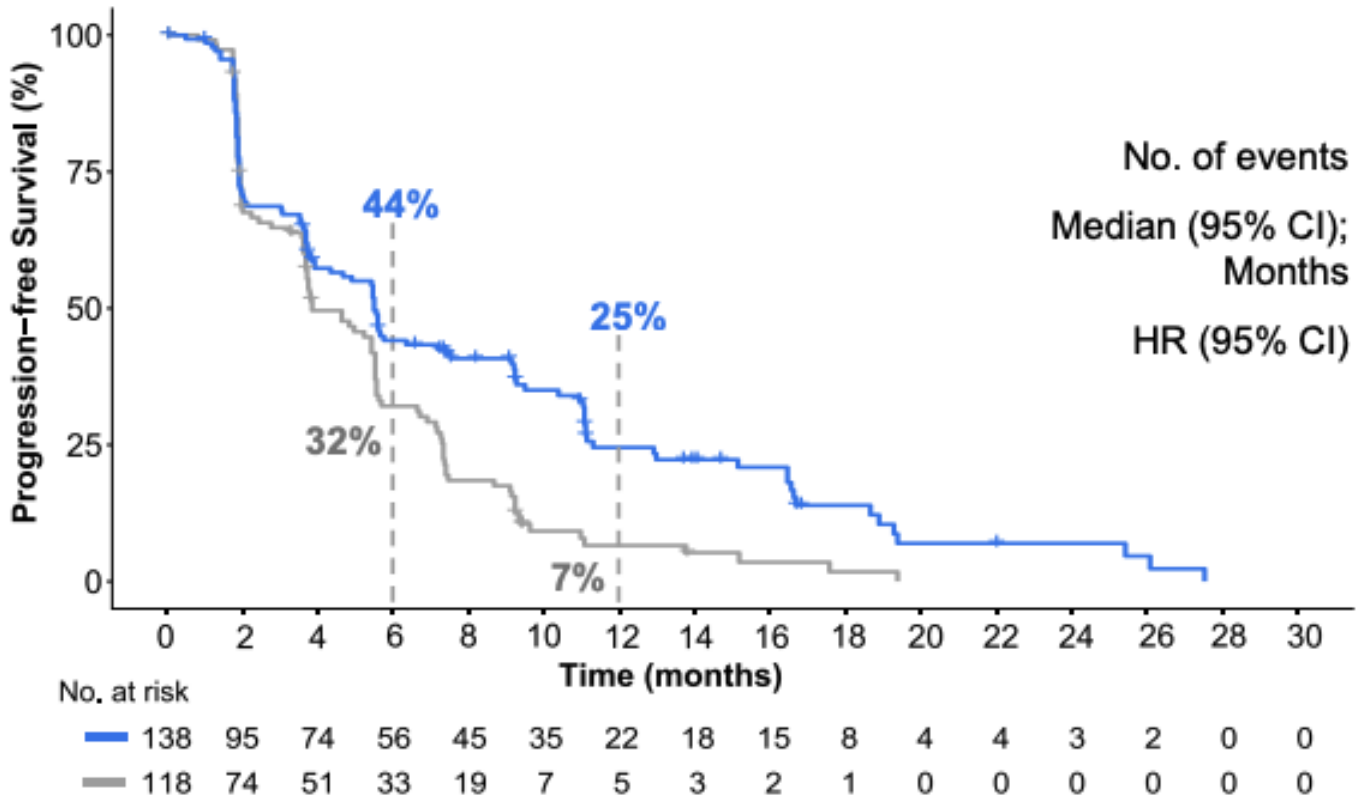
Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Median age, years (range)		61 (28-87)	62 (27-89)	62 (36-87)
Female, %		99	99	99
Post-menopausal, %		84	86	86
Race, %	White	56	58	52
	Asian	28	29	34
	Black or African American	3	2	4
Region, %	East Asia	25	26	31
	North America/ Western Europe	38	39	45
	Other	37	36	24
PR-positive, %		78	79	74
***ESR1* mutation, %[a]**		42	36	32
PI3K pathway mutations, %[b]		39	39	41

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Site of metastases, %	Visceral	57	54	56
	Liver	32	30	27
	Bone-only	22	26	24
Endocrine resistance, %[c]	Primary	8	11	8
	Secondary	92	89	93
Most recent ET, %[d]	Adjuvant	32	34	30
	ABC	63	63	68
Previous CDK4/6i, %	Overall	59	57	65
	Adjuvant	4	5	3
	ABC	55	53	62
Previous CDK4/6i therapy, %[e]	Palbociclib	61	69	65
	Ribociclib	29	27	27
	Abemaciclib	10	4	7

Baseline characteristics were generally well balanced including in patients with *ESR1*m[f]

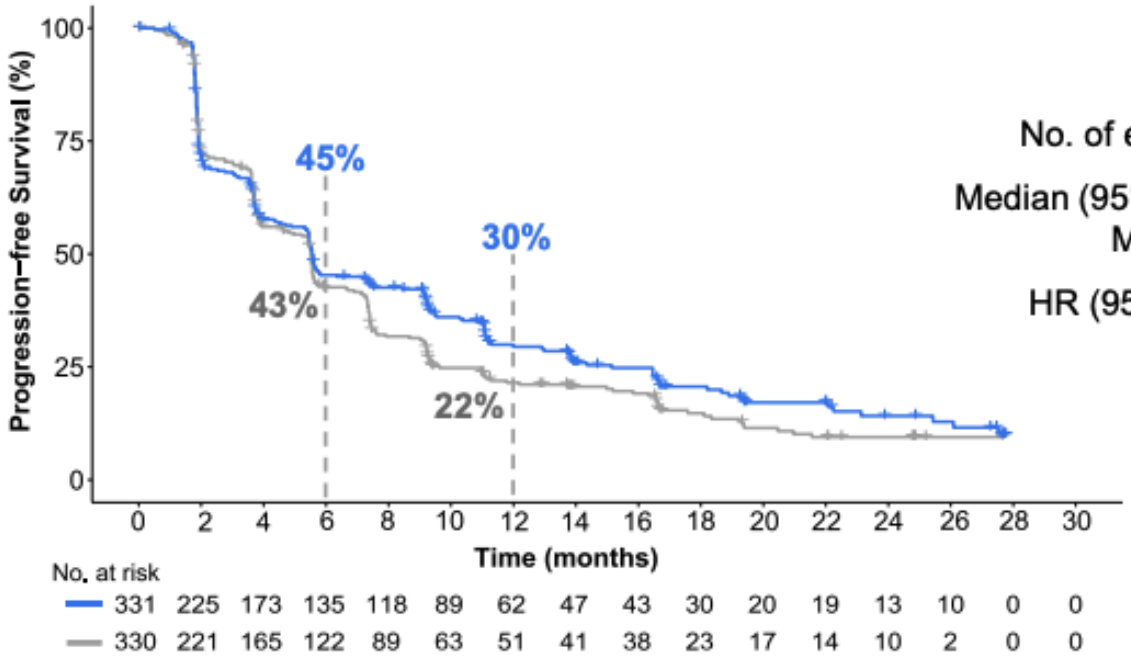
CDK4/6i, CDK4/6 inhibitor; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; PR, progesterone receptor; SOC ET, standard of care endocrine therapy. [a] Samples were analyzed by Guardant360 CDx, except for patients from China where samples were analyzed by OncoCompass Target assay, Burning Rock Biotech; [b] Includes single nucleotide variants and insertions/deletions of *PIK3CA*, *AKT1* or *PTEN* analyzed by Guardant 360 ctDNA assay. This analysis excludes patients from China or with unknown *ESR1*m status; [c] Per ESO-ESMO International Consensus Guidelines for ABC (ABC 6 and 7); [d] Adjuvant ET = First-line; ABC = Second-line; [e] Percentages calculated based on the numbers of patients who received prior CDK4/6i therapy (imlunestrant, n=195; SOC ET, n=189; imlunestrant + abemaciclib, n=139); [f] Data available in the online supplementary slides.

Imlunestrant vs SOC in *ESR1m: investigator-assessed PFS*



	Imlunestrant n=138	SOC ET n=118
No. of events	109	102
Median (95% CI); Months	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.46-0.82)[a]** *p*-value<0.001	

Imlunestrant vs SOC in all patients



	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	

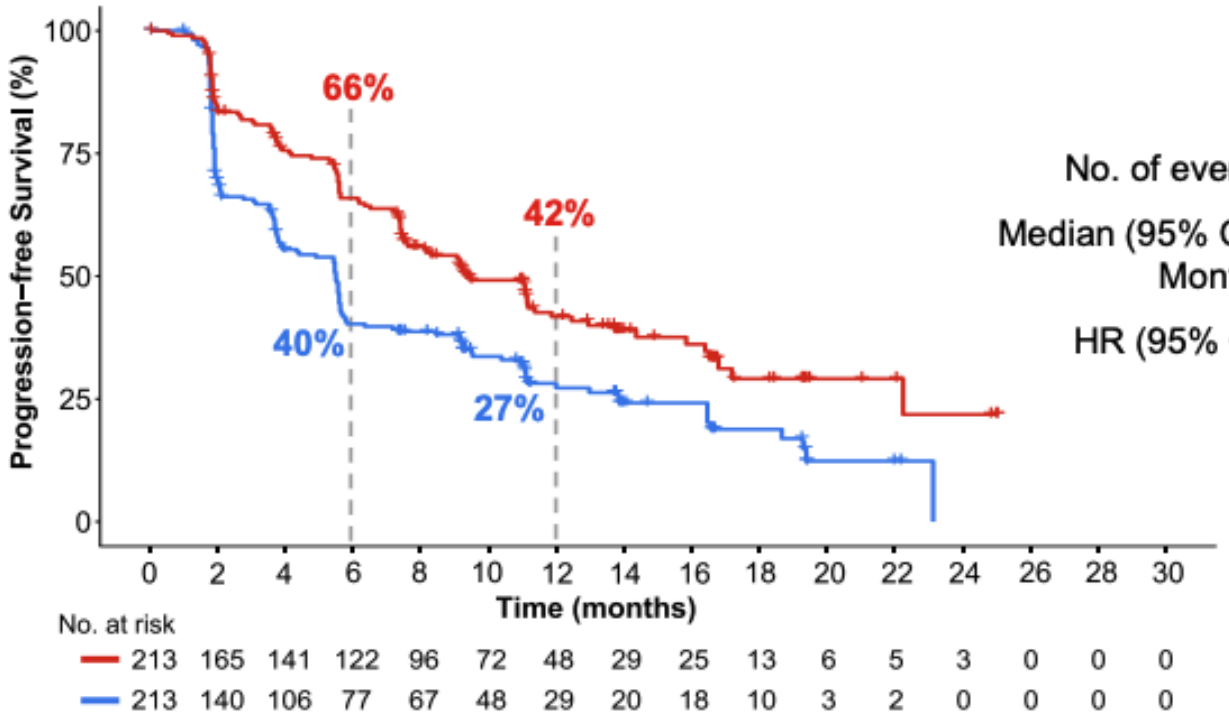
Prespecified Critical HR < 0.84[a]

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

- The majority subgroup of patients <u>without</u> *ESR1*m showed no difference in PFS (HR=1.00; 95% CI, 0.79-1.27)[b]

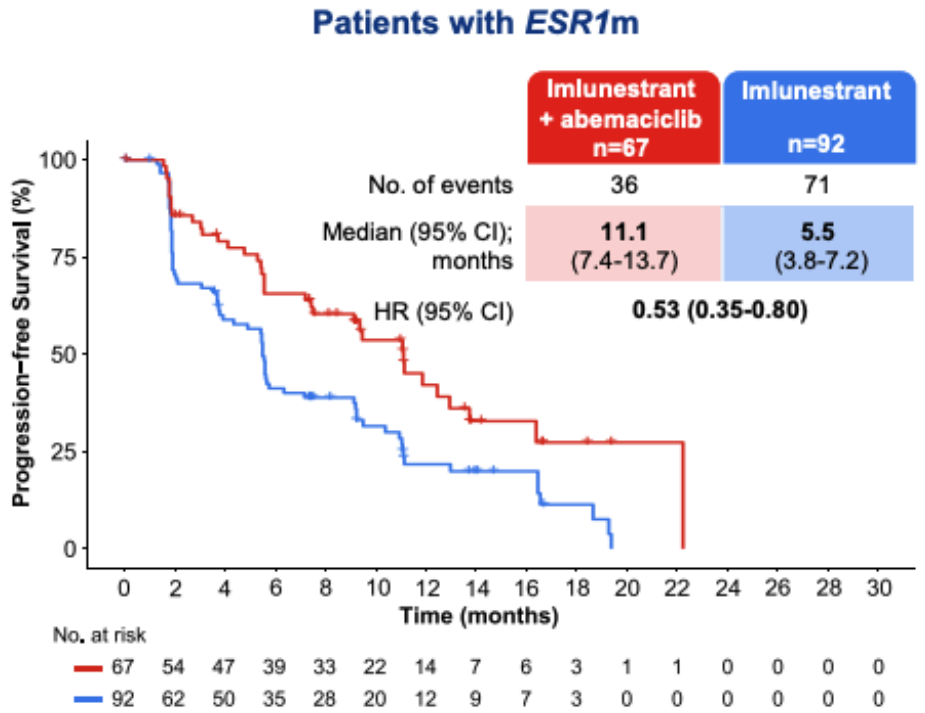
CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; PFS, progression-free survival; SOC ET, standard of care endocrine therapy. The median follow-up was 16.6 months in the imlunestrant arm and 16.8 months in the SOC ET arm.
[a] At full alpha; [b] Data available in the online supplementary slides.

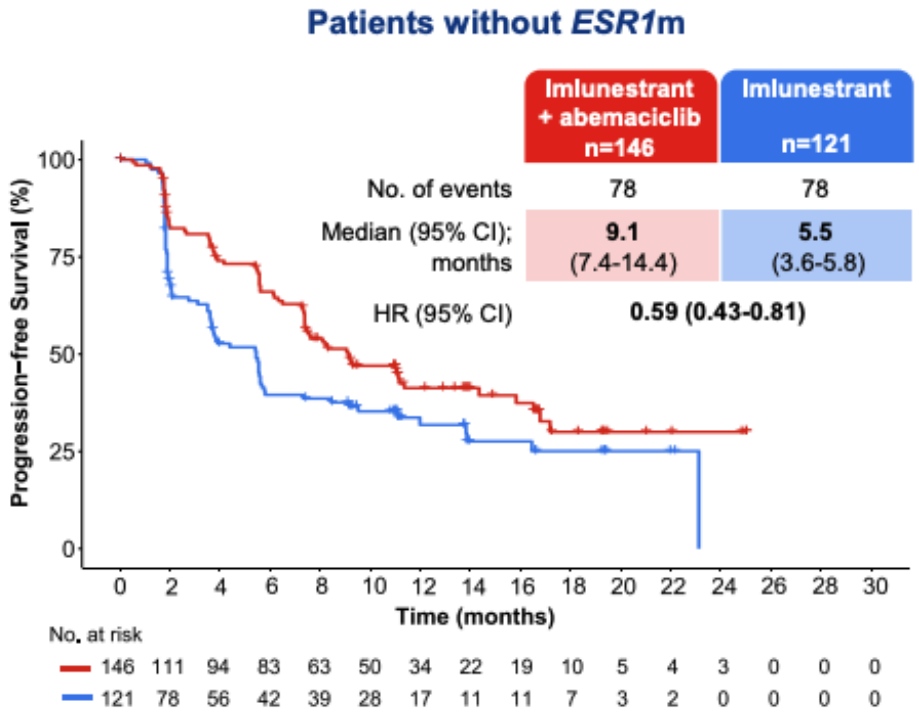
Imlunestrant vs Abemaciclib + imlunestrant in All Patients

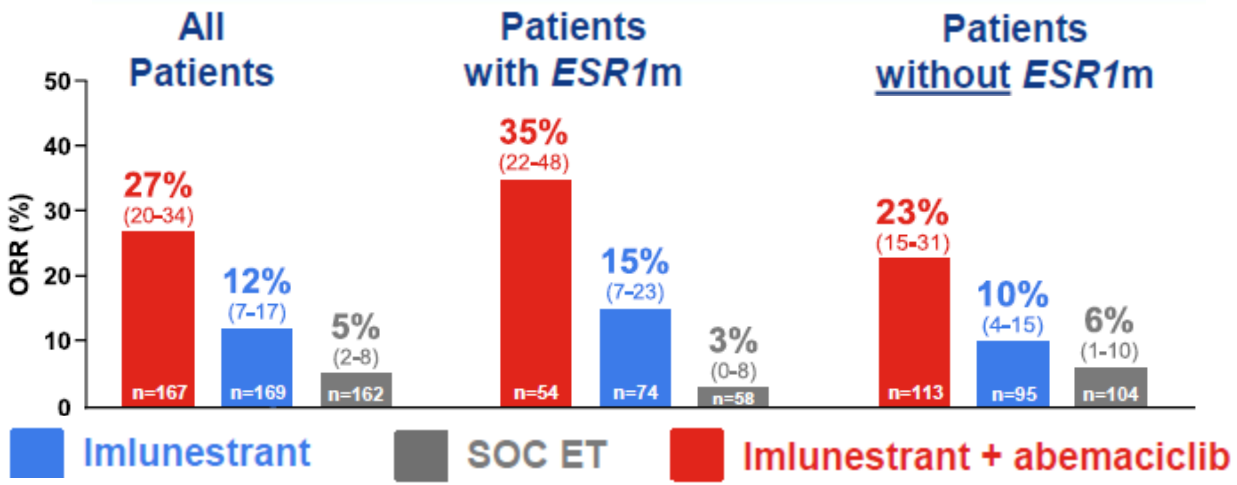


	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of events	114	149
Median (95% CI); Months	**9.4** (7.5-11.9)	**5.5** (3.8-5.6)
HR (95% CI)	**0.57 (0.44-0.73)** *p*-value <0.001	

EMBER-3: Imlunestrant + abemaciclib ESR1m and wt







Jhaveri K, et al. SABCS 2024. Abstract GS1-01. Jhaveri K, et al. *J Clin Oncol*. 2024 Dec 11. doi: 10.1056/NEJMoa2410858.

EMBER-3

TEAEs in ≥ 10% of Patients, %	Imlunestrant n=327		SOC ET n=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	83	17	84	21
Fatigue[a]	23	<1	13	1
Diarrhea	21	<1	12	0
Nausea	17	<1	13	0
Arthralgia	14	1	14	<1
AST increased	13	1	13	1
Back pain	11	1	7	<1
ALT increased	10	<1	10	1
Anemia[a]	10	2	13	3
Constipation	10	0	6	<1

Patients with ≥ 1 SAE, %		10	12
Dose reductions due to AE, %		2	0
Discontinuations due to AE, %		4	1
Deaths due to AE on study, %		2	1
Injection Site Reaction[a]	TEAE, n/N (%)[b]	NA	27/292 (9%)
	PRO-CTCAE, n/N (%)[c]	NA	201/278 (72%)

TEAEs in ≥ 20% of Patients, %	Imlunestrant + abemaciclib n=208	
	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	98	49
Diarrhea	86	8
Nausea	49	2
Neutropenia[a]	48	20
Anemia[a]	44	8
Fatigue[a]	39	5
Vomiting	31	1
Leukopenia[a]	26	4
Hypercreatinemia[a]	22	1
Abdominal pain[a]	20	2
Decreased appetite	20	1

Patients with ≥ 1 SAE, %	17
Dose reductions due to AE, %[d]	39
Discontinuations due to AE, %	6
Deaths due to AE on study, %	1

Jhaveri K, et al. SABCS 2024. Abstract GS1-01.
Jhaveri K, et al. *J Clin Oncol*. 2024 Dec 11.
doi: 10.1056/NEJMoa2410858.

EMBER-3 Takeaways

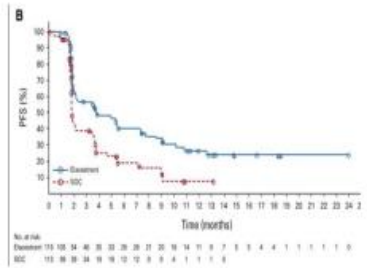
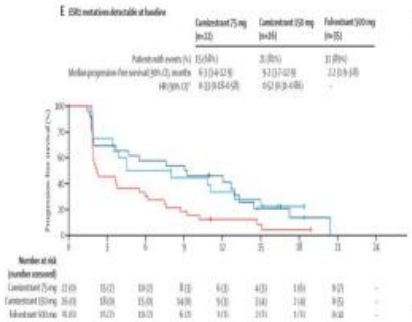
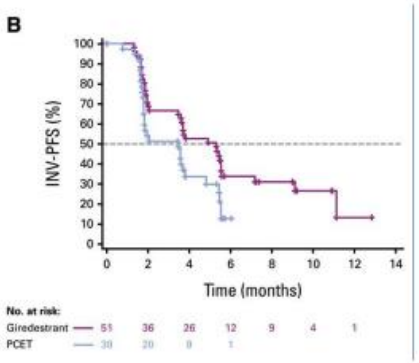
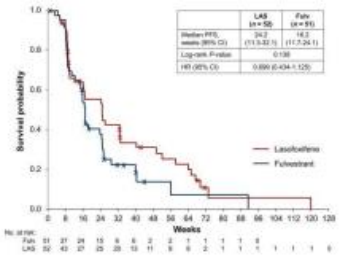
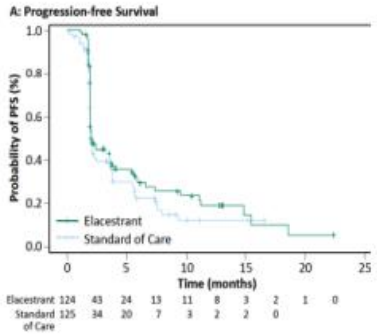
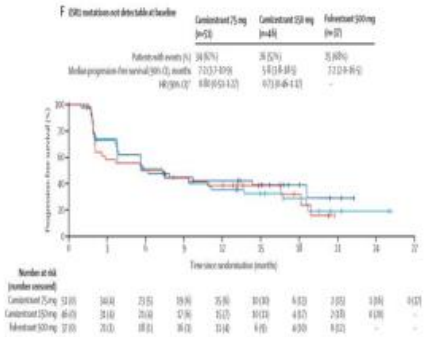
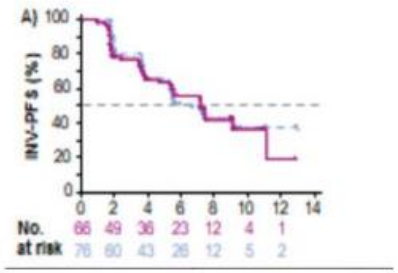
- Imlunestrant monotherapy
  - Significant PFS benefit vs SOC ET in *ESR1m* (HR=0.62; 95% CI 0.46-0.82)
  - Favorable safety
  - OS immature
- Imlunestrant + abemaciclib
  - Significant PFS benefit regardless of *ESR1m* status (HR = 0.57; 95% CI 0.44-0.73)
  - Consistent benefit across subgroups

Oral SERDs data

	EMERALD[1]	EMBER-3[2]	
	Elacestrant (n = 239)	**Imlunestrant (n = 331)**	**Imlunestrant + Abemaciclib (n = 213)**
Lines of ET for MBC (0 / 1 / 2), %	☒ / 54 / 46	32 / 63 / ☒	x / x / ☒
Prior MBC therapy			
CDK4/6i	100*	55	62
CT	20	☒	☒
FULV	30	☒	☒
Population, %			
Primary resistance	24	8	8
Visceral mets	68	57	56

1. Bidard F, et al. *J Clin Oncol*. 2022;40:3246-3256.
2. Jhaveri K, et al. SABCS 2024. Abstract GS1-01.

Oral SERDS and ESR1 mut

	EMERALD SOC vs Elacestrant	SERENA-2 Fulv vs Camizestrant	acelERA PCET vs Giredestrant	ELAINE 1 Fulv vs Lasofoxifene
***ESR1* mut**				
***ESR1* wt**				
	Bidard, FC et al. J Clin Oncol 2022;40:3246	Oliveira M, et al. Lancet Oncol 2024;25:1424	Martin M, et al. J Clin Oncol 2024;42:2149	Goetz MP, et al. Ann Oncol 2023;34:1141

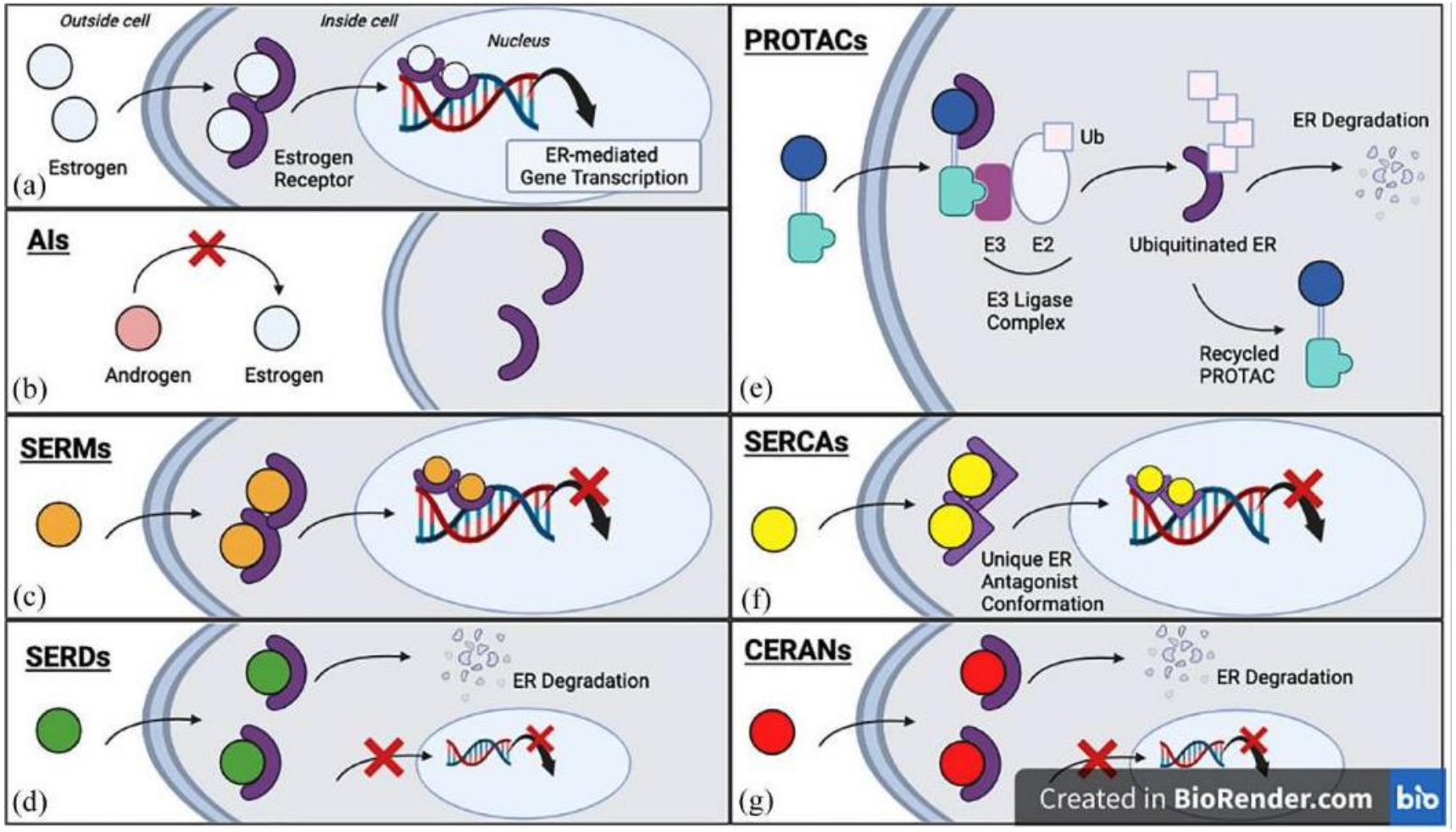
Burstein SABCS 2024

Oral SERD side effect profiles

Side Effect	Elacestrant	Imlunestrant	Giredestrant	Camizestrant
Fatigue		X		X
Nausea	X	X	X	X
Vomiting	X	X	X	
Constipation	X			
Diarrhea	X	X		
Bradycardia			X	X
Photopsia				X
Transaminitis			X	
Hypertriglyceridemia	X			

Burstein SABCS 2024

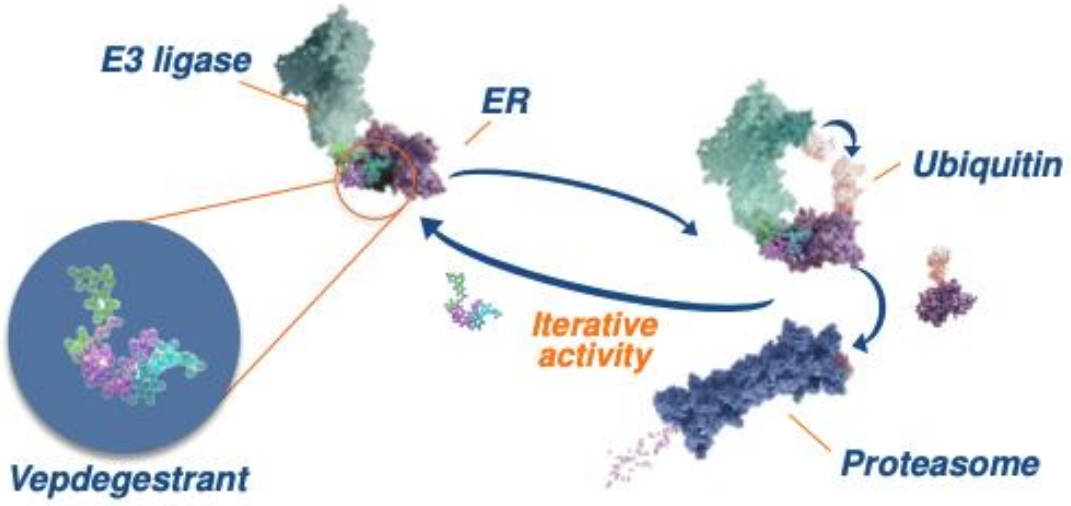
Current methods of ER Targeting



Lloyd et al. Ther Adv Med Onc 2022

PROTAC: a look to the future

- Vepdegestrant (ARV-471), an oral PROTAC ER degrader, directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER leading to its subsequent proteasomal degradation
- In contrast, SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER
- The SERD fulvestrant must be administered intramuscularly, 3 and at its optimal dose, ER protein degradation is limited to only 40%–50%



VERITAC Phase 1/2 Study

First-in-human, open-label, 3-part study of ARV-471 alone or in combination with palbociclib in patients with ER+/HER2- locally advanced/metastatic breast cancer

Phase 1 dose escalation (Part A)	Phase 2 cohort expansion (Part B; VERITAC)	Phase 1b combination (Part C)
Treatment • ARV-471 orally	**Treatment** • ARV-471 orally	**Treatment** • ARV-471 plus palbociclib orally
Primary objective • Evaluate the safety and tolerability of ARV-471 in order to estimate the MTD and select the RP2Ds	**Primary objective** • Assess the antitumor activity of ARV-471	**Primary objective** • Evaluate the safety and tolerability of ARV-471 plus palbociclib and select the RP2D of the combination

Schott SABCS 2022

Treatment-Emergent Adverse Event Summary (VERITAC)

n (%)	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
TEAEs			
Any grade	32 (91)	30 (83)	62 (87)
Grade 3/4	9 (26)	6 (17)	15 (21)
Grade 5[a]	1 (3)	0	1 (1)
Leading to discontinuation	1 (3)	2 (6)	3 (4)
Leading to dose reduction	0	3 (8)	3 (4)

- Dose reductions due to TEAEs
  - 500-mg QD cohort (to 400 mg QD)
    - ALT increased (n=1)
    - Neutropenia (n=1)
    - Fatigue (n=1)
- Discontinuations due to TEAEs
  - 200-mg QD cohort
    - QT prolongation (n=1)[b]
  - 500-mg QD cohort
    - ECG T-wave abnormality (n=1)[c]
    - Back pain/spinal cord compression (n=1)

[a]Acute respiratory failure in the setting of disease progression and unrelated to ARV-471 treatment
[b]Patient had QT prolongation at baseline, received a concomitant QT-prolonging drug during ARV-471 treatment, and had hypokalemia
[c]Patient had ECG T-wave abnormality at baseline
ALT=alanine aminotransferase; ECG=electrocardiogram; QD=once daily; TEAE=treatment-emergent adverse event

Primary Endpoint: Clinical Benefit Rate[a] (VERITAC)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)
Patients with mutant *ESR1*	(n=19)	(n=22)	(n=41)
CBR, % (95% CI)	47.4 (24.4–71.1)	54.5 (32.2–75.6)	51.2 (35.1–67.1)

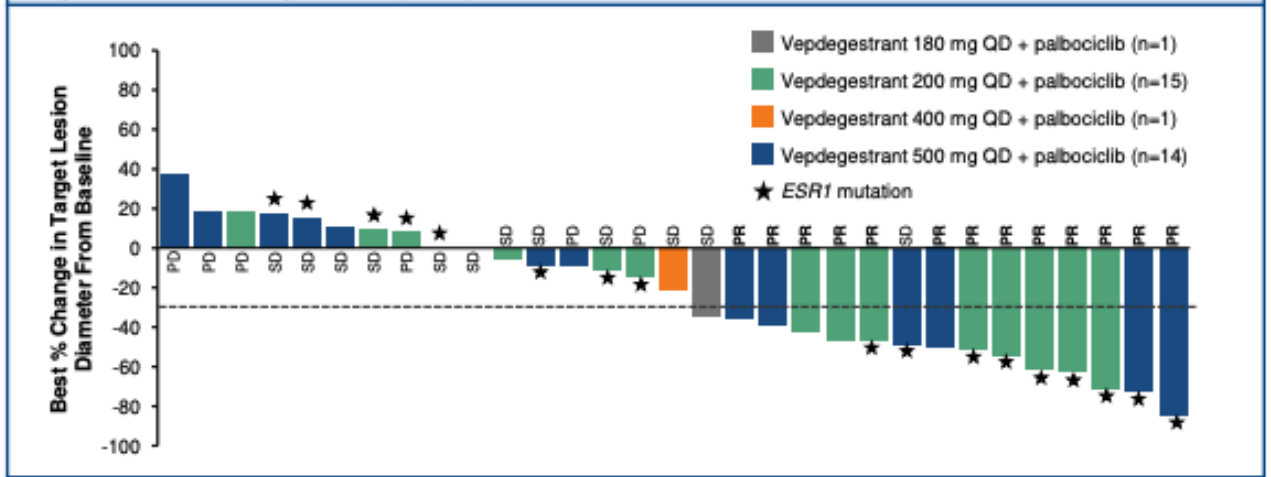
Phase 1b: Vepdegestrant plus Palbociclib

Table 2: TEAE summary

n (%)	Total (N=46)[a]	200 mg QD cohort (n=21)	500 mg QD cohort (n=20)
Any grade	46 (100)	21 (100)	20 (100)
Grade 3/4	42 (91)	19 (90)	18 (90)
Grade 5	0	0	0
Vepdegestrant dose reduction	5 (11)	2 (10)	3 (15)
Vepdegestrant discontinuation	4 (9)	3 (14)	1 (5)
Palbociclib dose reduction	34 (74)	15 (71)	15 (75)
Palbociclib discontinuation	8 (17)	5 (24)	3 (15)

[a]Includes 2 patients who received vepdegestrant 180 mg QD and 3 patients who received vepdegestrant 400 mg QD
QD=once daily; TEAE=treatment-emergent adverse event

Figure 1: Antitumor activity (best percentage change from baseline in sum of target lesions) in response-evaluable patients (n=31)

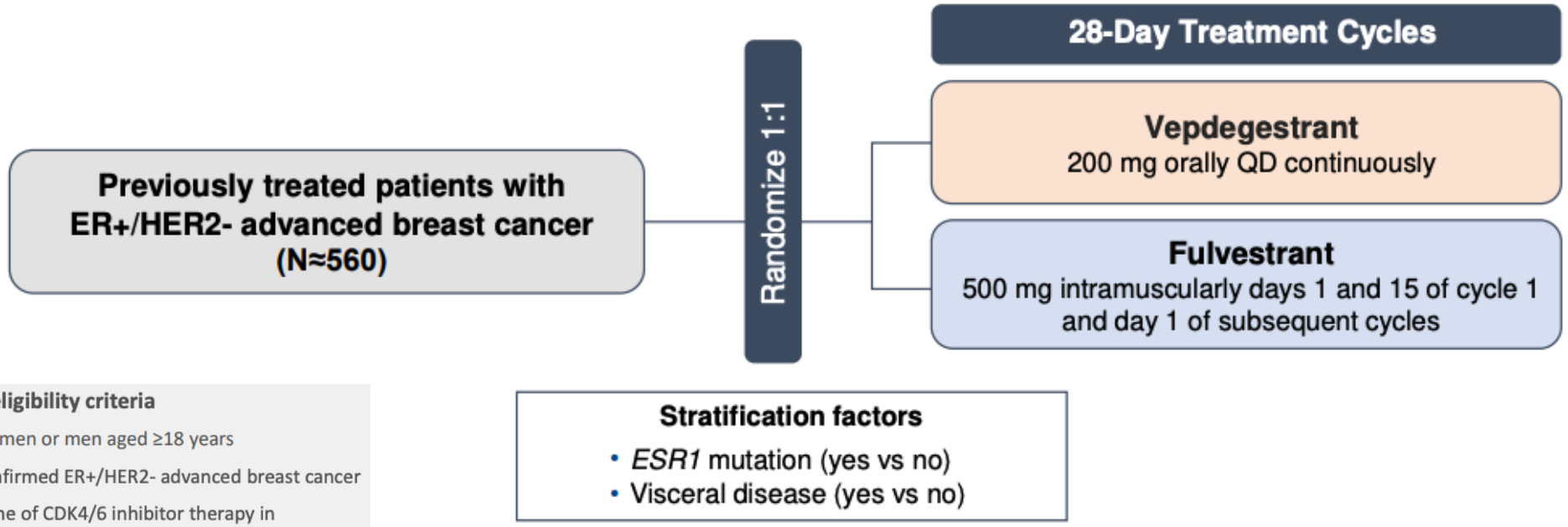


ESR1=estrogen receptor 1 gene; PD=progressive disease; PR=confirmed partial response; QD=once daily; SD=stable disease

VERITAC Conclusions

- Favorable safety profile
  - Combination with Palbociclib – more neutropenia
- Early signal for clinical activity
  - Monotherapy: CBR 37% (200mg dose)
  - Combination with palbo: CBR 67% (200mg dose)
- Vepdegestrant 200mg QD selected RP2D
- VERITAC-2: 2L setting vs Fulvestrant
- VERITAC-3: 1L setting with palbociclib vs Letrozole + palbo

VERITAC-2 Study Design



Primary endpoint:

- PFS by BICR in
  - ITT population
  - *ESR1* mutant population

Secondary endpoints:

- Overall survival
- ORR, DOR, and CBR
- Safety
- QoL measurements

Key eligibility criteria

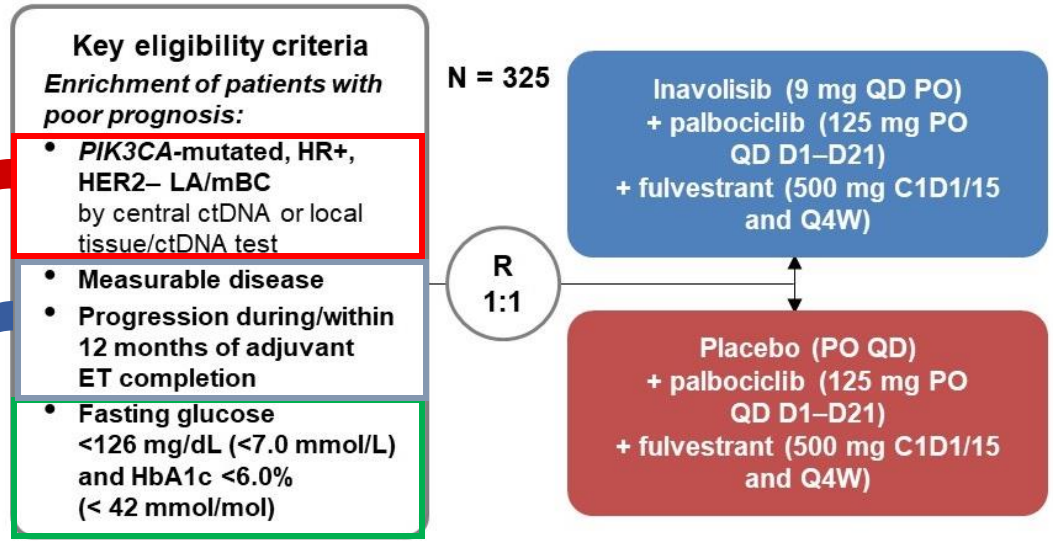
- Women or men aged ≥18 years
- Confirmed ER+/HER2- advanced breast cancer
- 1 line of CDK4/6 inhibitor therapy in combination with endocrine therapy
- ≤1 additional endocrine therapy
- Most recent endocrine treatment given for ≥6 months prior to disease progression
- No prior fulvestrant
- No prior chemotherapy for locally advanced/metastatic disease
- Radiological progression during or after the last line of therapy

Press release: Positive Topline Results March 11, 2025

Inavolisib: The new approval for HR+HER2- mBC in 2024

FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer

INAVO120 Study Design



ctDNA-based testing used to determine tumor *PIK3CA* mutation status in > 90% of pts

Efficacy endpoints
- PFS by investigator
- OS
- ORR, BOR, CBR, DOR
- **Time from randomization to end or discontinuation of next-line treatment, or death from any cause (proxy for PFS2)**
- **Time from randomization to first subsequent chemotherapy after treatment discontinuation**

Safety endpoints
Key selected AEs (hyperglycemia, diarrhea, rash, and stomatitis/mucosal inflammation)*

Patient-reported outcomes endpoints†
- **BPI-SF: TTCD in worse pain‡§**
- **EORTC QLQ-C30: mean change from baseline in HRQoL, physical functioning, and role functioning‖**
- **PRO-CTCAE: presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities**
- **An overall bother item: overall bother experienced due to side effects of treatment**

Resistance to ET defined as:*
- Primary resistance = relapse during first 2 years of adjuvant ET
- Secondary resistance = relapse after start of year 2 of adjuvant ET or relapse within 12 months after completion of adjuvant ET

*According to 4th European School of Oncology–European Society of Medical Oncology International Consensus Guidelines for Advanced Breast Cancer

Presented by Juric D, et al. ASCO 2024. Abstract 1003.

Turner NC, et al. *N Engl J Med.* 2024;391:1584-1596..

INAVO120

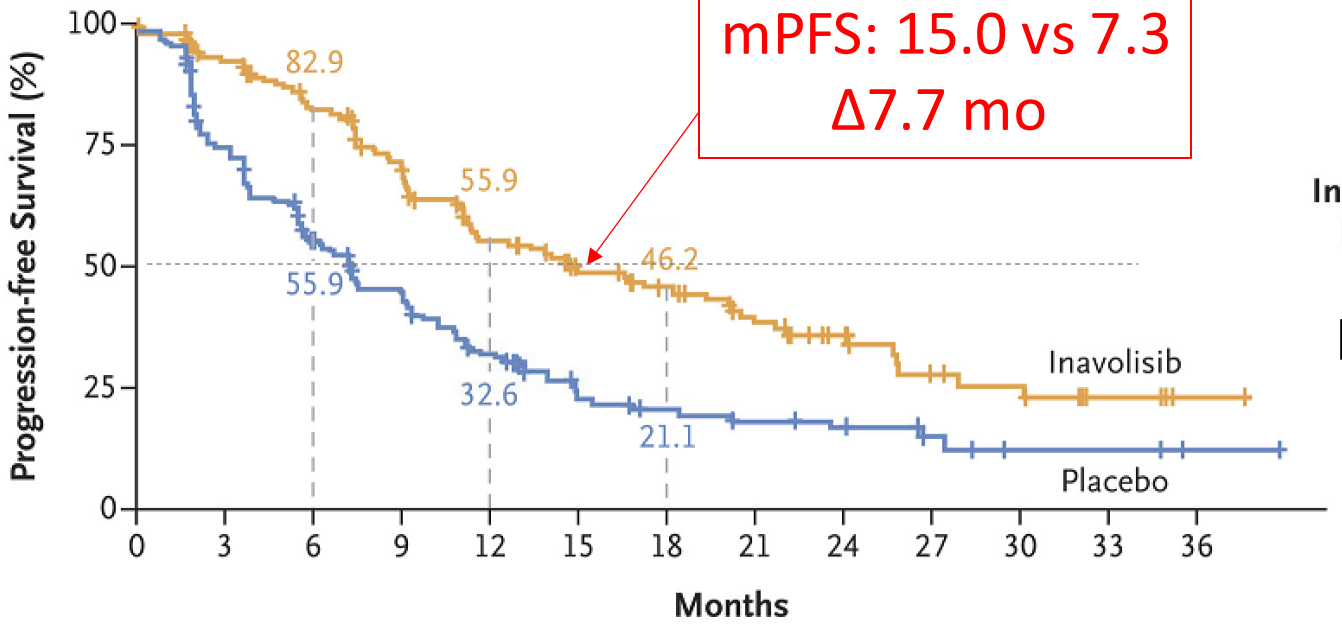
Baseline Characteristics

	Inavo + Palbo + Fulv N=161	Pbo + Palbo + Fulv N=164
Median Age, yrs (range)	**53 (27-77)**	**55 (29-79)**
Menopausal Status, Post, %	**58**	**64**
Visceral Disease, %	**79**	**77**
Endocrine Resistance, % (primary vs secondary)	**(35 vs 65)**	**(36 vs 64)**
Race/Ethnicity, %, White	**58**	**59**
Asian	**38**	**38**
Black	**1**	**1**
Hispanic/Latino	**6**	**6**
Region, N America*/W Europe %	**39**	**38**
Prior CDK 4/6 inh, Yes %	**2**	**1**
Prior Chemotherapy %	**82**	**84**

Inavo=inavolisib; Palbo=palbociclib; Fulv=fulvestrant; Pbo=placebo; inh=inhibitor
*Includes 16 pts enrolled from US and 14 pts from Canada

INAVO120 Primary Endpoint

A **Progression-free Survival in the Full Analysis Population**

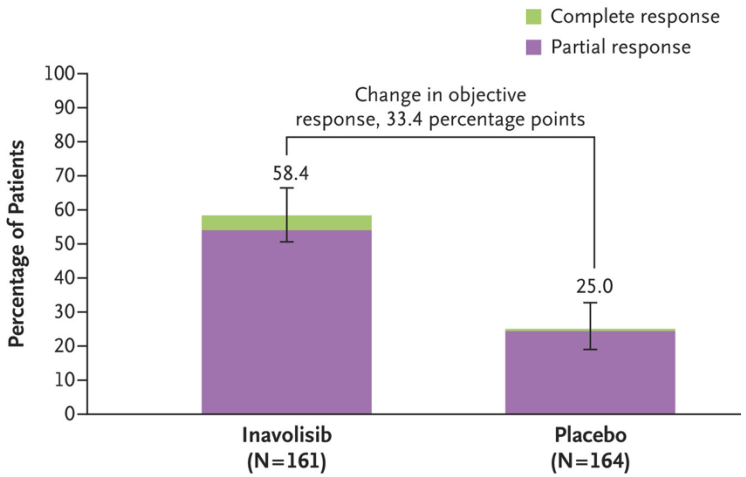


mPFS: 15.0 vs 7.3
Δ7.7 mo

No. at Risk													
Inavolisib	161	134	111	92	66	48	41	31	22	13	11	5	1
Placebo	164	113	77	59	40	23	19	16	12	6	3	3	1

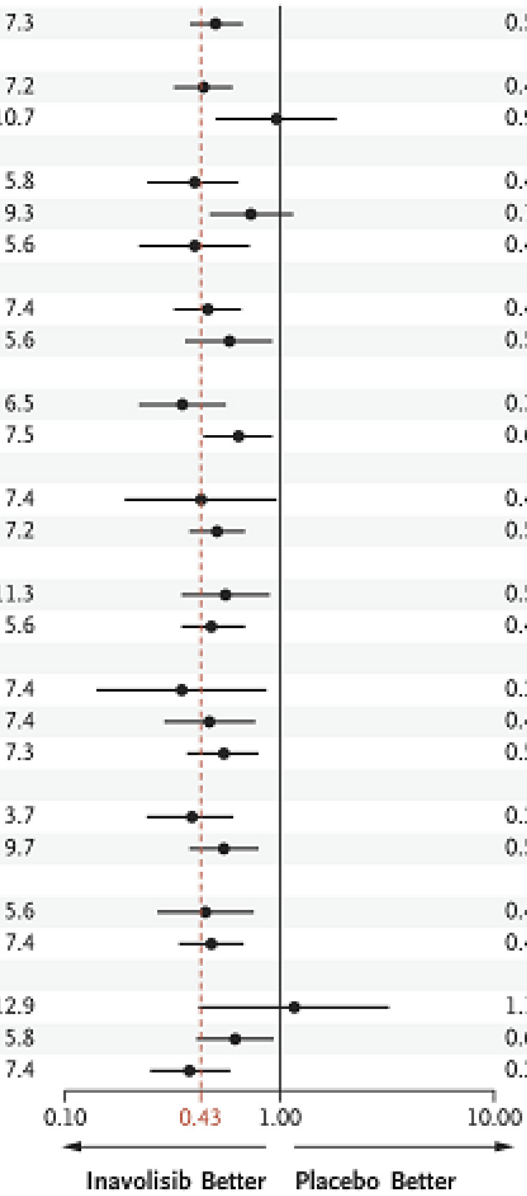
	No. of Events (%)	Median Progression-free Survival (95% CI)
		mo
Inavolisib (N=161)	82 (50.9)	15.0 (11.3–20.5)
Placebo (N=164)	113 (68.9)	7.3 (5.6–9.3)

HR, 0.43 (95% CI, 0.32-0.59)
P <.001



Data cutoff: September 29, 2023.
Turner NC, et al. *N Engl J Med.* 2024;391:1584-1596.

Subgroup	No. of Patients		Median Progression-free Survival		Hazard Ratio for Disease Progression or Death (95% CI)
	Inavolisib	Placebo	Inavolisib	Placebo	
			mo		
All patients	161	164	15.0	7.3	0.50 (0.38–0.67)
Age					
<65 yr	136	130	16.6	7.2	0.44 (0.32–0.60)
≥65 yr	25	34	9.3	10.7	0.96 (0.50–1.83)
Geographic region					
Asia	56	58	14.6	5.8	0.40 (0.24–0.64)
North America or Western Europe	63	64	13.8	9.3	0.73 (0.47–1.15)
Other	42	42	21.0	5.6	0.40 (0.22–0.72)
ECOG performance-status score at baseline					
0	100	106	16.6	7.4	0.46 (0.32–0.66)
1	60	58	11.4	5.6	0.58 (0.36–0.92)
Menopausal status at randomization					
Premenopausal	65	59	20.1	6.5	0.35 (0.22–0.56)
Postmenopausal	91	104	13.4	7.5	0.64 (0.44–0.92)
Visceral disease					
No	29	36	25.8	7.4	0.43 (0.19–0.97)
Yes	132	128	13.8	7.2	0.51 (0.38–0.69)
Liver metastasis at enrollment					
No	84	73	24.2	11.3	0.56 (0.35–0.90)
Yes	77	91	11.0	5.6	0.48 (0.33–0.69)
No. of organs with metastases at enrollment					
1	21	32	20.2	7.4	0.35 (0.14–0.87)
2	59	46	18.2	7.4	0.47 (0.29–0.77)
≥3	81	86	14.1	7.3	0.55 (0.37–0.80)
Resistance to endocrine therapy					
Primary	53	58	11.4	3.7	0.39 (0.24–0.61)
Secondary	108	105	18.2	9.7	0.55 (0.38–0.80)
Hormone receptor status					
ER-positive, PR-negative	45	45	11.1	5.6	0.45 (0.27–0.76)
ER-positive, PR-positive	113	113	18.2	7.4	0.48 (0.34–0.68)
Previous endocrine therapy					
Aromatase inhibitor and tamoxifen	18	19	11.0	12.9	1.17 (0.42–3.24)
Aromatase inhibitor only	60	71	10.9	5.8	0.62 (0.41–0.94)
Tamoxifen only	82	73	21.0	7.4	0.38 (0.25–0.59)



Turner NC, et al. *N Engl J Med.* 2024;391:1584-1596.

Adverse Events

Table 2. Adverse Events.*

Adverse Event	Inavolisib (N=162)		Placebo (N=162)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 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 and 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)	0	14 (8.6)	0
Fatigue	38 (23.5)	0	21 (13.0)	2 (1.2)
Covid-19	37 (22.8)	3 (1.9)	17 (10.5)	1 (0.6)
Headache	34 (21.0)	0	22 (13.6)	0
Leukopenia	28 (17.3)	11 (6.8)	40 (24.7)	17 (10.5)
Ocular toxic effects	36 (22.2)	0	21 (13.0)	0

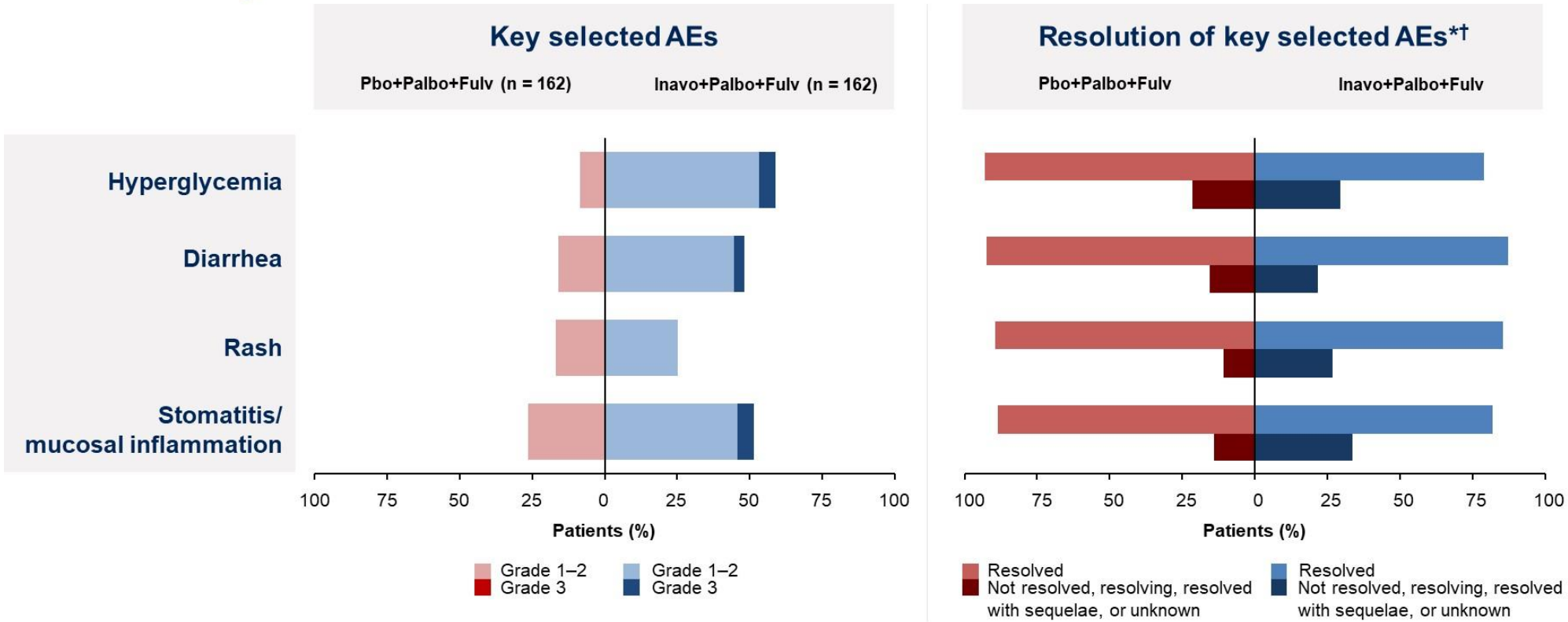
Turner NC, et al. *N Engl J Med.* 2024;391:1584-1596.

Select Adverse Events

	Inavo + Palbo + Fulv N=161		Pbo + Palbo + Fulv N=164	
	All grades %	Grades 3-4 %	All grades %	Grades 3-4 %
Neutrophils decreased*	95	82	97	79
Glucose (fasting) increased*	85	12	43	0
Platelets decreased*	84	16	71	4
Stomatitis/mucosal inflammation	51	6	27	0
Diarrhea	48	4	16	0
Rash	26	0	19	0
COVID-19 Infection	23	2	10	1

*Based on laboratory values; Inavo=inavolisib; Palbo=palbociclib; Fulv=fulvestrant; Pbo=placebo

Safety



*** Majority of key selected AEs had resolved ('resolution' was per investigator decision) by the CCOD; some patients were enrolled close to the CCOD and AE follow-up is ongoing for these patients.**

† Denominators are patients with at least one AE (hyperglycemia, Inavo+Palbo+Fulv: n = 95, Pbo+Palbo+Fulv: n = 14; diarrhea, Inavo+Palbo+Fulv: n = 78, Pbo+Palbo+Fulv: n = 26; rash, Inavo+Palbo+Fulv: n = 41, Pbo+Palbo+Fulv: n = 28; and stomatitis/mucosal inflammation, Inavo+Palbo+Fulv: n = 83, Pbo+Palbo+Fulv: n = 43).

AE, adverse event; CCOD, clinical cutoff date; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

Patient-Reported Symptoms Assessed by PRO-CTCAE in INAVO120

Symptom (attribute)	Any symptom before treatment (%)		Any worsening on treatment (%)		Worsening to Score 3 or 4 (%)	
	Inavo+P+F (N=148)	Pbo+P+F (N=152)	Inavo+P+F (N=148)	Pbo+P+F (N=152)	Inavo+P+F (N=148)	Pbo+P+F (N=152)
Diarrhea (frequency), %	23	15	78	49	32	8
Mouth Sores (severity), %	11	14	74	52	30	9

Inavo=inavolisib; P=palbociclib; F=fulvestrant; Pbo=placebo
The symptom attribute scoring is defined by amount/frequency/severity with a score of 0 = 'not at all'/'never'/'none'; 1 = 'a little bit'/'rarely'/'mild'; 2 = 'somewhat'/'occasionally'/'moderate'; 3 = 'quite a bit'/'frequently'/'severe'; 4 = 'very much'/'almost constantly'/'very severe'.

INAVO120 Takeaways

Improved PFS and numeric OS

More toxicity with triplet therapy

Who is the right population for triplet therapy?

- Recur on or shortly after adjuvant therapy
- PIK3CA mutation (poor prognosis in metastatic setting)
- High volume disease/visceral metastasis

Novel Endocrine Therapies Conclusions

- Oral SERDs
  - Elacestrant established monotherapy for *ESR1m*
  - SABCS 2024: Imlunestrant monotherapy for *ESR1m*
  - Combinations: Imlunestrant + abemaciclib improved PFS regardless of *ESR1* status
    - Others:
      - Elacestrant + abemaciclib and others
      - Camizestrant + Ribociclib
- Around the corner: PROTAC?
- Inavolisib + palbo + fulvestrant

Thank you!