EMERALD Subgroup Analysis

External Literature Review

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Disclaimer

- The information contained within this slide deck is provided for informational purposes pursuant to scientific exchange
- Elacestrant is indicated for the treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy
- Please see the Full Prescribing Information here

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Highlights of Prescribing Information

These highlights do not include all the information needed to use elacestrant safely and effectively. See full prescribing information for elacestrant.

Indications and Usage

Elacestrant is an estrogen receptor antagonist indicated for treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy

Warnings and Precautions

Dyslipidemia

Elacestrant may cause hypercholesterolemia and hypertriglyceridemia. Monitor lipid profile prior to starting treatment and periodically thereafter

Embryo-Fetal Toxicity

Elacestrant can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception

Adverse Reactions

The most common (>10%) adverse reactions, including laboratory abnormalities, of elacestrant were musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia

Drug Interactions

Strong and Moderate CYP3A4 Inducers

Avoid concomitant use with elacestrant

Strong and Moderate CYP3A4 Inhibitors

Avoid concomitant use with elacestrant

Use in Specific Populations

Lactation

Advise not to breastfeed

Hepatic Impairment

Avoid use in patients with severe hepatic impairment (Child-Pugh C)

Reduce the dosage for patients with moderate hepatic impairment (Child-Pugh B)

Elacestrant in ER+, HER2– mBC with *ESR1*-mutated Tumors: Subgroup Analyses From the Phase III EMERALD Trial by Prior Duration of Endocrine Therapy Plus CDK4/6 Inhibitor and in Clinical Subgroups

Bardia A,[1] Cortés J,[2] Bidard FC,[3] Neven P,[4] Garcia-Sáenz J,[5] Aftimos P,[6] O'Shaughnessy J,[7] Lu J,[8] Tonini G,[9] Scartoni S,[9] Paoli A,[9] Binaschi M,[9] Wasserman T,[9] Kaklamani V[10]

Bardia A, et al. *Clin Cancer Res*. 2024. doi: 10.1158/1078-0432.CCR-24-1073.

1. University of California Los Angeles (UCLA) Health Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, CA, USA. 2. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, and IOB Madrid, Hospital Beata Maria Ana, and Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain. 3. Institut Curie, Paris and Saint Cloud, France. 4. Universitaire Ziekenhuizen (UZ) - Leuven Cancer Institute, Leuven, Belgium. 5. Instituto de Investigación Sanitaria Hospital Clinico San Carlos (IdISSC), Madrid, Spain. 6. Institut Jules Bordet – Université Libre de Bruxelles, Brussels, Belgium. 7. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA. 8. Northwestern University Robert H. Lurie Comprehensive CancerCenter, Chicago, IL, USA. 9. Menarini Group, Florence, Italy. 10. University of TexasHealth Sciences Center, San Antonio, TX, USA.

CDK4/6=cyclin-dependent kinase 4/6; ER=estrogen receptor; ESR1=estrogen receptor 1; HER2=human epidermal growth factor receptor 2; mBC=metastatic breast cancer.

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01 BACKGROUND

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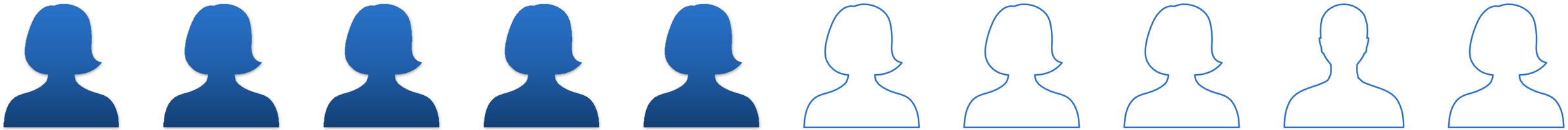
BACKGROUND

Current Treatment Options For ER+/HER2– mBC Patients

Management of ER+/HER2– mBC involves ET + CDK4/6i as the 1L SOC regimen.[1-3]

- A challenge of treatment after 1L therapy is to overcome endocrine resistance[4]
- Molecular resistance patterns include[5-7]:
  - Intrinsic alterations of the PI3K/AKT/mTOR pathways, among others
  - Acquired resistance mechanisms

A common type of acquire resistance mechanism consists of alterations in the *ESR1* gene.[5,6]



***ESR1*-mut may occur in up to 50% of patients and predominantly emerge in the metastatic setting during 1L ET, particularly with AIs[8-10]**

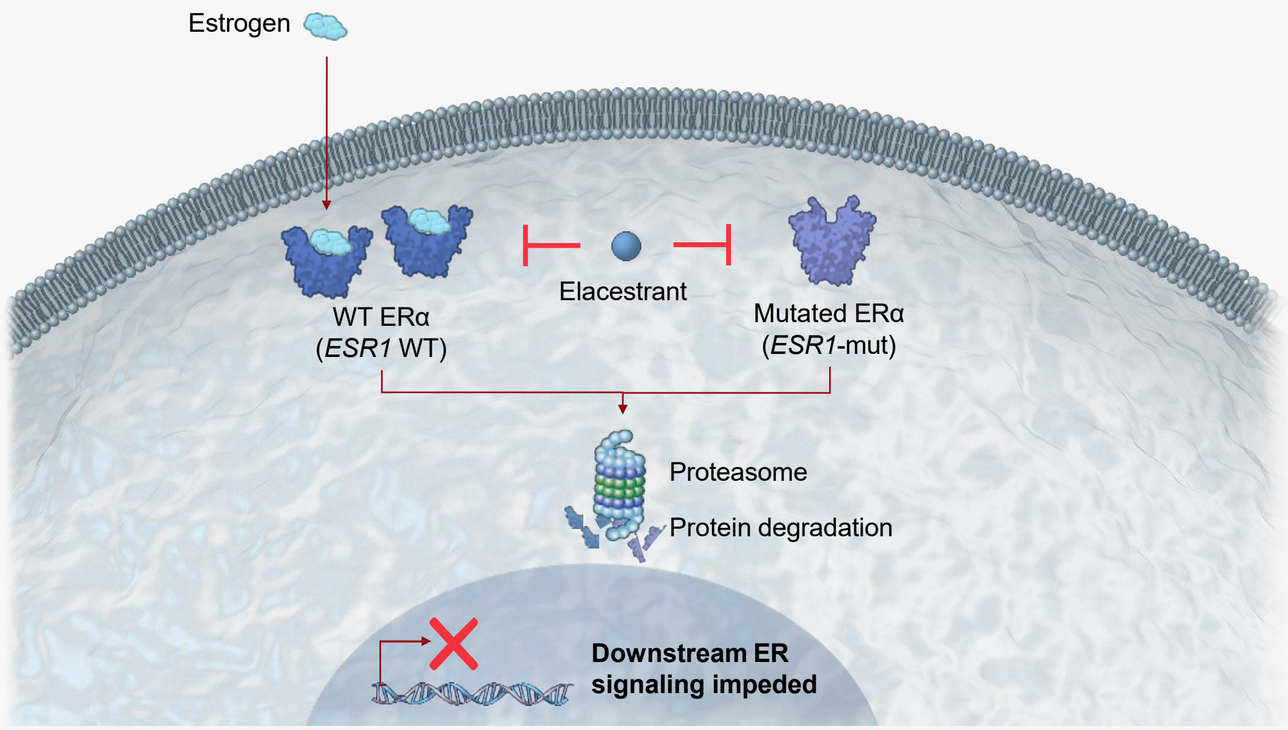
1L=first line; AI=aromatase inhibitor; AKT=protein kinase B; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; mBC=metastatic breast cancer; mTOR=mammalian target of rapamycin; PI3K=phosphoinositide 3-kinase; SOC=standard of care.
1. Bardia A, et al. *Clin Cancer Res*. 2024. **2.** Burstein HJ, et al. *J Clin Oncol*. 2021;39:3959-3977. **3.** Gennari A, et al. *Ann Oncol*. 2021;32:1475-95. **4.** Burstein HJ. *N Eng J Med*. 2020;383:2557-70. **5.** Rani A, et al. *Front Endocrinol (Lausanne)*. 2019;10:245. **6.** Belachew EB, et al. *Front Endocrinol (Lausanne)*. 2021;12:599586. **7.** Xu X-Q, et al. *Acta Pharmacol Sin*. 2021;42:171-8. **8.** Jhaveri KL, et al. *Ann Oncol*. 2023;34(Suppl 2):S338-9. **9.** Lin NU, et al. *Ann Oncol*. 2023;34(Suppl 1):S338. **10.** Bhave MA, et al. *Breast Cancer Res Treat*. 2024.

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BACKGROUND

Elacestrant Indication Overview

Elacestrant is the first oral SERD to demonstrate increased efficacy compared with SOC endocrine monotherapy in the randomized Phase III EMERALD trial, particularly in tumors harboring *ESR1*-mut, leading to regulatory approval in the United States for the treatment of postmenopausal women or adult men with ER+, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy.[1-4]



ER=estrogen receptor; ERα=estrogen receptor alpha; ESR1=estrogen receptor 1; HER2=human epidermal growth factor receptor 2; mut=mutation; SERD=selective estrogen receptor degrader; SOC=standard of care; WT=wild type. **1.** Bardia A, et al. *Clin Cancer Res*. 2024. **2.** Orserdu. Prescribing Information. Stemline Therapeutics, Inc.; 2026. **3.** Orserdu (elacestrant). SmPC. Stemline Therapeutics B.V; 2023. **4.** Bidard FC, et al. *J Clin Oncol*. 2022;40:3246.

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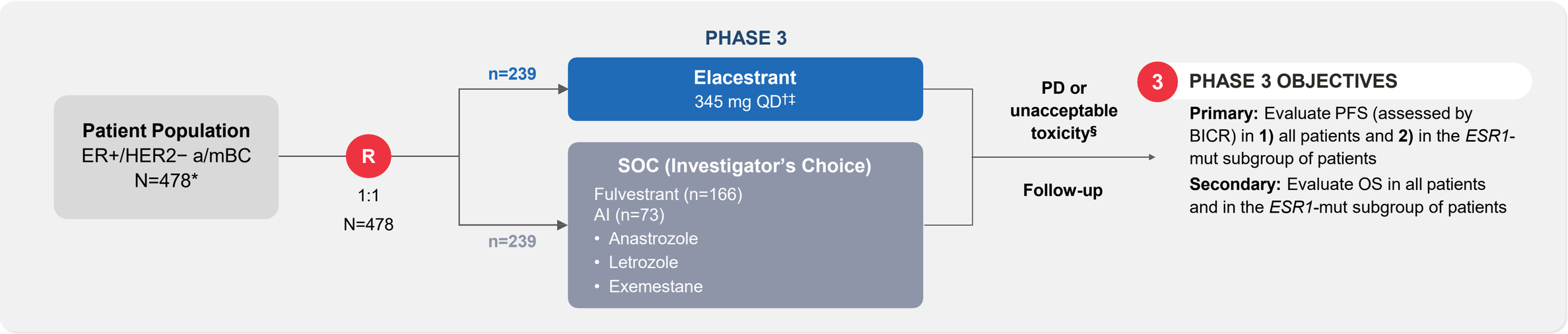
02 METHODS

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METHODS

EMERALD: Study Design

The efficacy of elacestrant was evaluated in EMERALD (NCT03778931), a randomized, open-label, active-controlled, multicenter trial that enrolled 478 postmenopausal women and men with ER+/HER2− advanced or metastatic breast cancer, of which 228 patients had tumors with *ESR1* mutations.



STRATIFICATION FACTORS

- *ESR1*-mut status#
- Presence of visceral metastases
- Prior treatment with fulvestrant

KEY INCLUSION CRITERIA

- Men and postmenopausal women with a/mBC
- ER+‖/HER2− disease
- ≤1 line of chemotherapy in the advanced or metastatic setting
- Progressed or relapsed on or after 1–2 lines of ET for advanced disease, one of which was given in combination with a CDK4/6i
- ECOG PS 0–1

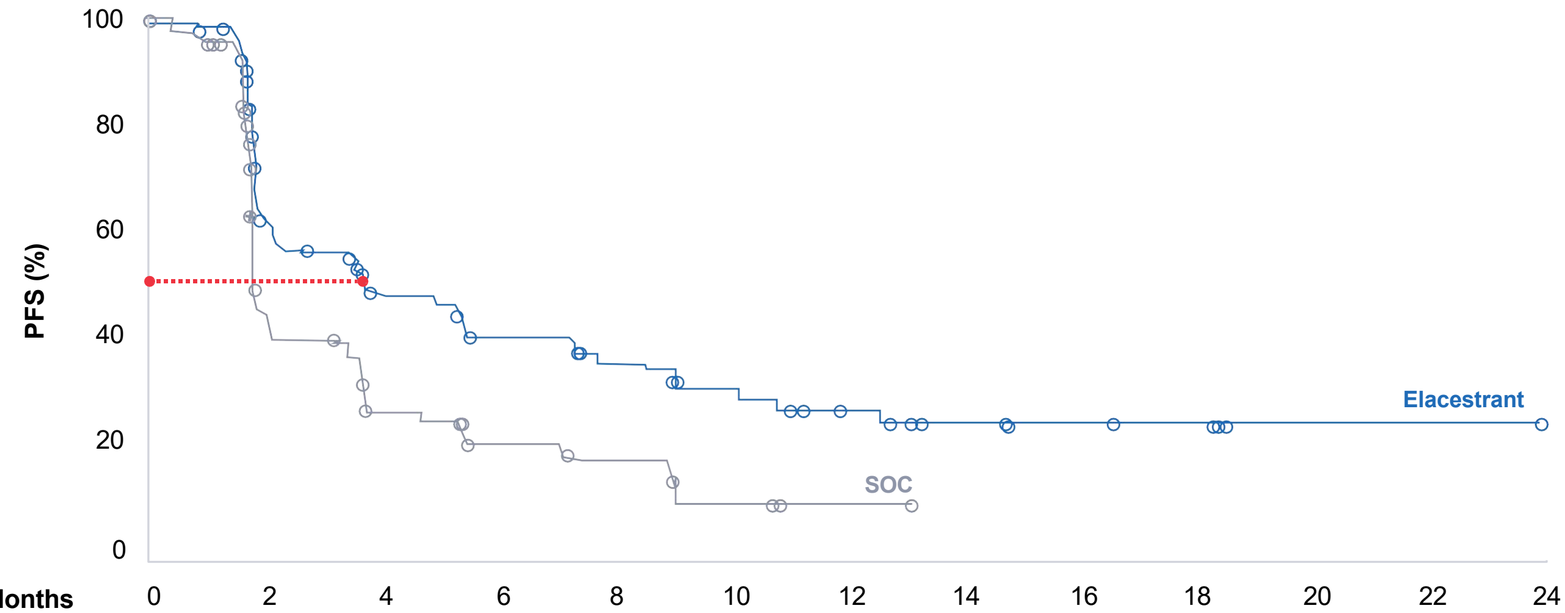
*Recruitment from February 2019 to October 2020. †Protocol-defined dose reductions permitted. ‡345 mg elacestrant QD is equivalent to 400 mg elacestrant hydrochloride. §Restaging CT scans every 8 weeks. ¶Blinded Independent Central Review. #*ESR1*-mut status was determined by cell-free circulating DNA analysis using Guardant360® CDx (Guardant Health, Redwood City, CA). ‖Documentation of ER+ tumor with ≥1% staining by IHC. a/mBC=advanced or metastatic breast cancer; AI=aromatase inhibitor; BICR=blinded independent central review; CDx=companion diagnostic; ECOG PS=Eastern Cooperative Oncology Group performance status; ER=estrogen receptor; ESR1=estrogen receptor 1. ET=endocrine therapy; HER2=human epidermal growth factor receptor **2.** IHC=immunohistochemistry; mut=mutated/mutation; OS=overall survival; PD=progressive disease; PFS=progression-free survival; QD=once daily; R=randomized; SOC=standard of care. **1.** Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-3256.

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METHODS

EMERALD: Primary Analysis Efficacy Results

Single-agent elacestrant significantly prolonged mPFS and reduced the risk of progression or death by 45% in patients with ER+/HER2– mBC previously treated with ET + CDK4/6i and who had tumors with *ESR1* mutations.



No. of patients:

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

	Elacestrant (n=115)	SOC (n=113)
Events, n (%)	**62 (53.9)**	**78 (69.0)**
mPFS, mo [95% CI]	**3.8** [2.2–7.3]	**1.9** [1.9–2.1]
HR [95% CI]	**0.55** [0.39–0.77]	
p-value	0.0005	

These data suggest a treatment benefit for elacestrant in patients who have ER-driven disease

CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ER=estrogen receptor; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; mBC=metastatic breast cancer; mo=months; mPFS=median progression-free survival; mut=mutated; No=number; PFS=progression-free survival; SOC=standard of care. **1.** Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-3256.

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METHODS

EMERALD: Subgroup Analysis Rationale

The effects of treatment duration, tumor metastasis sites, and the coexistence of common genomic alterations or other molecular expressions on the efficacy of elacestrant are of continued interest to better define treatment selection.[1]

Treatment Duration[2]

- Longer exposure to ET during the treatment of metastatic disease is related to increased risk of developing an *ESR1*-mut

Tumor Metastasis Sites and Number[1,3]

- *ESR1*-mut are associated with visceral metastases and endocrine resistance

Molecular Expression[1,4,5]

- HER2-low expression occurs in up to 65% of HR+ BC
- Understanding of the prognostic value between HER2-low vs HER2-zero expression in mBC is limited
- Evidence indicates that HER2-low disease biology is primarily driven by HR expression

Coexisting Mutations[1,6-11]

- *PIK3CA*- and *TP53*-mut occur in ~30–40% of ER+ BC and confer poor prognosis and treatment resistance
- Coexisting *PIK3CA*- and *ESR1*-mut can be found in ~15–30% of patients with ER+/HER2– mBC
- Coexisting *TP53*- and *ESR1*-mut occur in 8–15% of tumors in patients with HR+/HER2– mBC previously treated with ET

***Post-hoc* exploratory subgroup analyses were conducted according to prior ET + CDK4/6i duration, metastatic site, and presence of common coexisting mutations or molecular expression with *ESR1* to identify tumors that remain endocrine sensitive despite acquired resistance to previous ET[1]**

BC=breast cancer; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; mut=mutation; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; TP53=tumor protein 53.

1. Bardia A, et al. *Clin Cancer Res*. 2024. **2.** Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85. **3.** Kuang Y, et al. *NPJ Breast Cancer*. 2018;4:22. **4.** Miglietta F, et al. *NPJ Breast Cancer*. 2022;8:66. **5.** Molinelli C, et al. *ESMO Open*. 2023;8(4):101592. **6.** Sobhani N, et al. *J Cell Biochem*. 2018;119:4287-92. **7.** Fillbrunn M, et al. *BMC Cancer*. 2022;22:1002. **8.** Meric-Bernstam F, et al. *JCO Precis Oncol*. 2018;PO.17.00245. **9.** Ungerleider NA. *Breast Cancer Res*. 2018;20:115. **10.** Silwal-Pandit L, et al. *Clin Cancer Res*. 2014;20:3569-80. **11.** Tolaney SM, et al. *Clin Cancer Res*. 2022;28:1500-06.

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03 BASELINE CHARACTERISTICS

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BASELINE CHARACTERISTICS

Baseline Characteristics of Patients With *ESR1*-mutated Tumors and Prior ET + CDK4/6i ≥12 Mo

	Elacestrant (n=78)	SOC* (n=81)
Median age, years (range)	65.5 (40–89)	63 (32–82)
Female, n (%)	78 (100)	81 (100)
Race or ethnicity, n (%)		
Asian	3 (3.9)	3 (3.7)
Black or African American	3 (3.9)	4 (4.9)
Other	1 (1.3)	0
White	59 (75.6)	59 (72.8)
Hispanic or Latino	6 (7.7)	7 (8.6)
ECOG PS 0, n (%)	42 (53.9)	49 (60.5)
Metastatic site, n (%)		
Bone†	67 (85.9)	69 (85.2)
Visceral	58 (74.4)	57 (70.4)
Liver and/or lung‡	56 (71.8)	57 (70.3)
Number of metastatic sites§, n (%)		
<3	42 (53.8)	40 (49.4)
≥3	28 (35.9)	25 (30.9)
Mutations, n (%)		
ESR1¶	78 (100)	81 (100)
D583G	48 (61.5)	49 (60.5)
Y537S/N	49 (62.8)	43 (53.1)

TABLE 1. *SOC therapies include fulvestrant and AIs. †85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement). ‡55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had lung and other sites of metastases (2% of these patients had no liver or bone involvement). §The number of metastatic sites was available for 135 of 159 patients with *ESR1*-mut tumors and prior ET + CDK4/6i ≥12 mo. ¶90% of patients had one or more *ESR1*-mut detected in the three hot spots presented (D538G; Y537S and/or Y537N). AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance score; ESR1=estrogen receptor 1; ET=endocrine therapy; mo=months; mut=mutated; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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BASELINE CHARACTERISTICS

Baseline Characteristics of Patients With *ESR1*-mutated Tumors and Prior ET + CDK4/6i ≥12 Mo

	Elacestrant (n=78)	SOC* (n=81)
Mutations, n (%)		
***PIK3CA*†**	27 (34.6)	35 (43.2)
H1041X	10 (12.8)	16 (19.8)
E542X, E545X	12 (15.4)	15 (18.5)
TP53	32 (41.0)	29 (35.8)
BRCA1/2	16 (20.5)	16 (19.8)
HER2-low expression‡, n (%)	37 (47.4)	40 (49.4)
Prior adjuvant therapy, n (%)	44 (56.4)	47 (58.0)
No. of prior lines of ET in the advanced/metastatic setting, n (%)		
1	49 (62.8)	55 (67.9)
2	29 (37.2)	26 (32.1)
No. of prior lines of chemotherapy in the advanced/metastatic setting, n (%)		
0	62 (79.5)	63 (77.8)
1	16 (20.5)	18 (22.2)
Prior CDK4/6i, n (%)		
Abemaciclib	3 (3.8)	3 (3.7)
Palbociclib	70 (89.7)	77 (95.1)
Ribociclib	14 (17.9)	11 (13.6)
Any prior ET, n (%)	78 (100)	80 (98.8)
Fulvestrant	13 (16.7)	22 (27.2)
AI	72 (92.3)	71 (87.7)
Tamoxifen	7 (9.0)	7 (8.6)
PI3Ki, n (%)	0	0
mTORi, n (%)	5 (6.4)	1 (1.2)

TABLE 1. *SOC therapies include fulvestrant and AIs. †Includes E545K, H1047R, E542K, and others. ‡Locally assessed HER2 IHC 1+, and 2+ with no ISH amplification. Data not available for all patients. AI=aromatase inhibitor; BRCA=breast cancer gene 1/2; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization; mo=months; mut=mutated; no=number; mTORi=mammalian target of rapamycin inhibitor; PI3Ki=phosphoinositide 3-kinases inhibitor; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC=standard of care; TP53=tumor protein 53. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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BASELINE CHARACTERISTICS

Baseline Characteristics of Patients With *ESR1*-mutated Tumors by Prior ET + CDK4/6i Duration*

	≥6 Mo (92.3%)		≥12 Mo (71.6%)		≥18 Mo (50.0%)	
	Elacestrant (n=103)	SOC† (n=102)	Elacestrant (n=78)	SOC† (n=81)	Elacestrant (n=55)	SOC† (n=56)
Median age, years (range)	64 (28–89)	62.5 (32–83)	65.5 (40–89)	63 (32–82)	67 (40–88)	63 (32–82)
Female, n (%)	103 (100)	102 (100)	78 (100)	81 (100)	55 (100)	56 (100)
Race or ethnicity, n (%)						
Asian	5 (4.9)	7 (6.9)	3 (3.9)	3 (3.7)	3 (5.5)	3 (5.4)
Black or African American	3 (2.9)	4 (3.9)	3 (3.9)	4 (4.9)	2 (3.6)	4 (7.1)
Other	1 (1.0)	0	1 (1.3)	0	1 (1.8)	0
White	77 (74.8)	74 (72.6)	59 (75.6)	59 (72.8)	39 (70.9)	40 (71.4)
Hispanic or Latino	8 (7.8)	8 (7.8)	6 (7.7)	7 (8.6)	4 (7.3)	6 (10.7)
ECOG PS 0, n (%)	60 (58.3)	58 (56.9)	42 (53.9)	49 (60.5)	28 (50.9)	34 (60.7)
Visceral metastases, n (%)	71 (68.9)	72 (70.6)	58 (74.4)	57 (70.4)	42 (76.4)	41 (73.2)
Prior adjuvant therapy, n (%)	53 (51.5)	57 (55.9)	44 (56.4)	47 (58.0)	35 (63.6)	30 (53.6)
No. of prior lines of ET in the advanced/metastatic setting, n (%)						
1	65 (63.1)	64 (62.8)	49 (62.8)	55 (67.9)	35 (63.6)	41 (73.2)
2	38 (36.9)	38 (37.3)	29 (37.2)	26 (32.1)	20 (36.4)	15 (26.8)
No. of prior lines of chemotherapy in the advanced/metastatic setting, n (%)						
0	81 (78.6)	74 (72.6)	62 (79.5)	63 (77.8)	43 (78.2)	43 (76.8)
1	22 (21.4)	28 (27.5)	16 (20.5)	18 (22.2)	12 (21.8)	13 (23.2)

SUPPLEMENTAL TABLE 2. *n=222. †SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance status; ESR1=estrogen receptor 1; ET=endocrine therapy; mo=months; mut=mutated; no=number; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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BASELINE CHARACTERISTICS

Baseline Characteristics of Patients With *ESR1*-mutated Tumors by Prior ET + CDK4/6i Duration*

	≥6 Mo (92.3%)		≥12 Mo (71.6%)		≥18 Mo (50.0%)	
	Elacestrant (n=103)	SOC† (n=102)	Elacestrant (n=78)	SOC† (n=81)	Elacestrant (n=55)	SOC† (n=56)
Prior CDK4/6i, n (%)						
Abemaciclib	4 (3.9)	4 (3.9)	3 (3.8)	3 (3.7)	2 (3.6)	1 (1.8)
Palbociclib	92 (89.3)	93 (91.2)	70 (89.7)	77 (95.1)	50 (90.9)	54 (96.4)
Ribociclib	17 (16.5)	17 (16.7)	14 (17.9)	11 (13.6)	8 (14.5)	8 (14.3)
Any prior ET, n (%)	103 (100)	100 (98.0)	78 (100)	80 (98.8)	55 (100)	55 (98.2)
Fulvestrant	22 (21.4)	25 (24.5)	13 (16.7)	22 (27.2)	9 (16.4)	16 (28.6)
AI	96 (93.2)	90 (88.2)	72 (92.3)	71 (87.7)	49 (89.1)	48 (85.7)
Tamoxifen	9 (8.7)	9 (8.8)	7 (9.0)	7 (8.6)	5 (9.1)	6 (10.7)
PI3Ki, n (%)	1 (1.0)	0	0	0	0	0
mTORi, n (%)	7 (6.8)	3 (2.9)	5 (6.4)	1 (1.2)	5 (9.1)	1 (1.8)

SUPPLEMENTAL TABLE 2. *n=222. †SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ESR1=estrogen receptor 1; ET=endocrine therapy; mo=months; mTORi=mammalian target of rapamycin inhibitor; mut=mutated; PI3Ki=phosphoinositide 3-kinase inhibitor; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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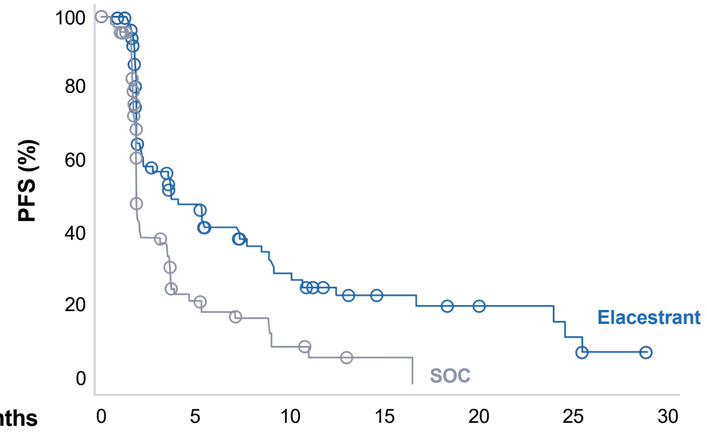
04 KEY EFFICACY RESULTS

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KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS by Duration of ET + CDK4/6i in Patients With *ESR1*-mutated Tumors Receiving Elacestrant or SOC

≥6 mo prior ET + CDK4/6i

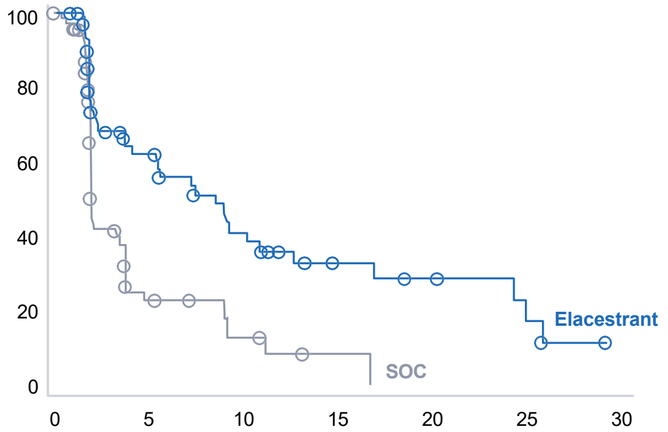


No. of patients:

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 (n=103)	SOC* (n=102)
mPFS, mo [95% CI]	**4.14** [2.20–7.79]	**1.87** [1.87–3.29]
HR [95% CI]	**0.517** [0.361–0.738]	

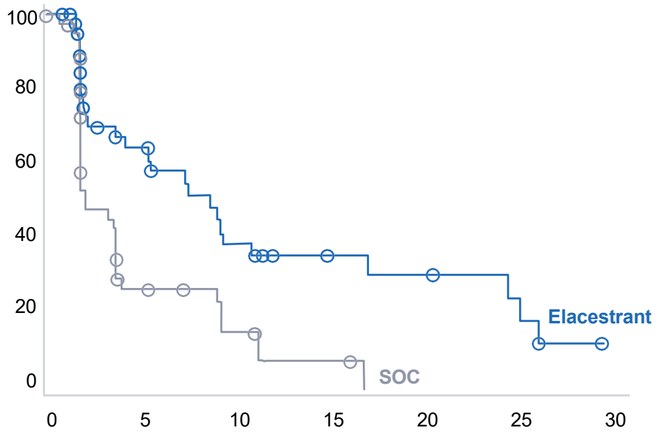
≥12 mo prior ET + CDK4/6i



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 (n=78)	SOC* (n=81)
mPFS, mo [95% CI]	**8.61** [4.14–10.84]	**1.91** [1.87–3.68]
HR [95% CI]	**0.410** [0.262–0.634]	

≥18 mo prior ET + 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 (n=55)	SOC* (n=56)
mPFS, mo [95% CI]	**8.61** [5.45–16.89]	**2.10** [1.87–3.75]
HR [95% CI]	**0.466** [0.270–0.791]	

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error

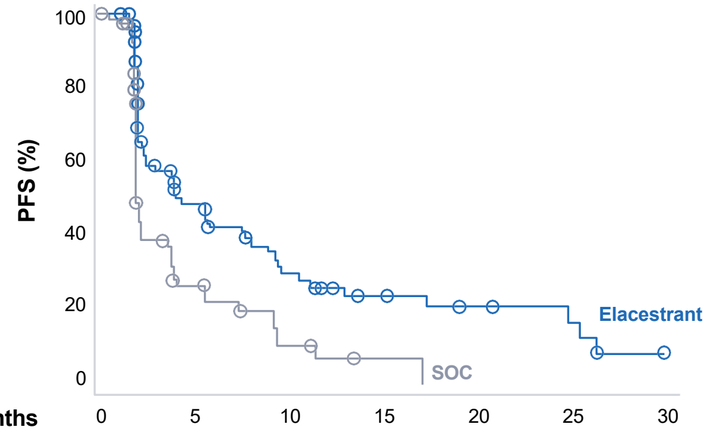
SUPPLEMENTAL FIGURE 2. *SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HR=hazard ratio; mo=months; mPFS=median progression-free survival; mut=mutated; No=number; PFS=progression-free survival; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS by Duration of ET + CDK4/6i in Patients With *ESR1*-mutated Tumors Receiving Elacestrant or Fulvestrant

≥6 mo prior ET + CDK4/6i

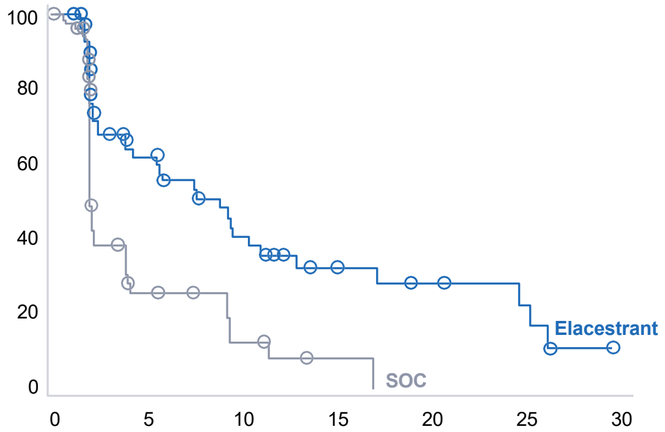


No. of patients:

Elacestrant	103	50	33	25	20	16	11	9	8	7	6	5	5	1	1	0
SOC	76	26	14	10	8	4	2	1	1	0						

	Elacestrant (n=103)	Fulvestrant (n=76)
mPFS, mo [95% CI]	**4.14** [2.20–7.79]	**1.87** [1.84–3.45]
HR [95% CI]	**0.472** [0.316–0.703]	

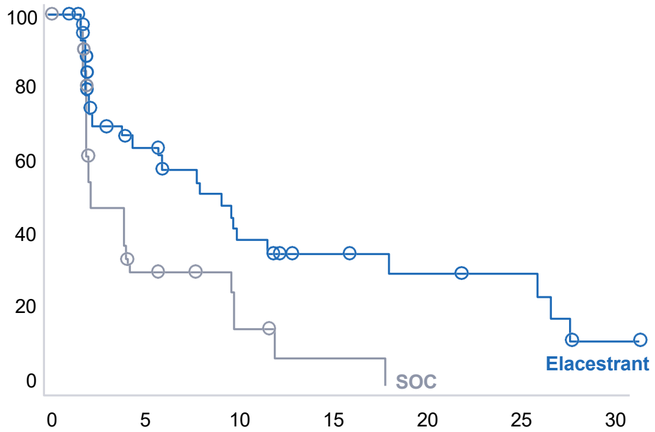
≥12 mo prior ET + CDK4/6i



Elacestrant	78	42	31	24	20	16	11	9	8	7	6	5	5
SOC	58	19	10	9	8	4	2	1	1	0			

	Elacestrant (n=78)	Fulvestrant (n=58)
mPFS, mo [95% CI]	**8.61** [4.14–10.84]	**1.87** [1.84–3.68]
HR [95% CI]	**0.406** [0.251–0.651]	

≥18 mo prior ET + CDK4/6i



Elacestrant	55	30	23	18	16	12	8	8	7	6	6	5	5
SOC	39	16	8	7	6	3	1	1	1	0			

	Elacestrant (n=55)	Fulvestrant (n=39)
mPFS, mo [95% CI]	**8.61** [5.45–16.89]	**2.10** [1.87–3.94]
HR [95% CI]	**0.453** [0.252–0.804]	

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error

SUPPLEMENTAL FIGURE 3. CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HR=hazard ratio; mo=months; mPFS=median progression-free survival; mut=mutation; no=number; PFS=progression-free survival; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS in Patient Subgroups with *ESR1*-mutated Tumors and Prior ET + CDK4/6i ≥12 Mo

Patient Subgroup	n (%)	mPFS, mo		HR [95% CI]
		Elacestrant	SOC*	
All patients with *ESR1*-mut tumors	159 (100)	8.6	1.9	0.41 [0.26–0.63]
Bone metastases†	136 (86)	9.1	1.9	0.38 [0.23–0.62]
Liver and/or lung metastases‡	113 (71)	7.3	1.9	0.35 [0.21–0.59]
<3 metastatic sites§	82 (52)	9.0	1.9	0.41 [0.23–0.75]
≥3 metastatic sites§	53 (33)	10.8	1.8	0.31 [0.12–0.79]
***PIK3CA*-mut¶**	62 (39)	5.5	1.9	0.42 [0.18–0.94]
***TP53*-mut**	61 (38)	8.6	1.9	0.30 [0.13–0.64]
HER2-low expression#	77 (48)	9.0	1.9	0.30 [0.14–0.60]
***ESR1* D538G-mut**	97 (61)	9.0	1.9	0.38 [0.21–0.67]
***ESR1* Y537S/N-mut**	92 (58)	9.0	1.9	0.25 [0.13–0.47]

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error. Elacestrant is NOT indicated to target *PIK3CA*- or *TP53*-mut

TABLE 2. *SOC therapies include fulvestrant and AIs. †85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement). ‡55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had lung and other sites of metastases (2% of these patients had no liver or bone involvement). §The number of metastatic sites was available for 135 of 159 patients with *ESR1*-mut tumors and prior ET + CDK4/6i ≥12 mo. ¶Includes E545K, H1047R, E542K, and others. #Locally assessed HER2 IHC 1+, and 2+ with no ISH amplification. Data not available for all patients. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; IHC=immunohistochemistry; ISH=*in situ* hybridization; mo=months; mPFS=median progression-free survival; mut=mutated; PFS=progression-free survival; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC=standard of care; TP53=tumor protein p53. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

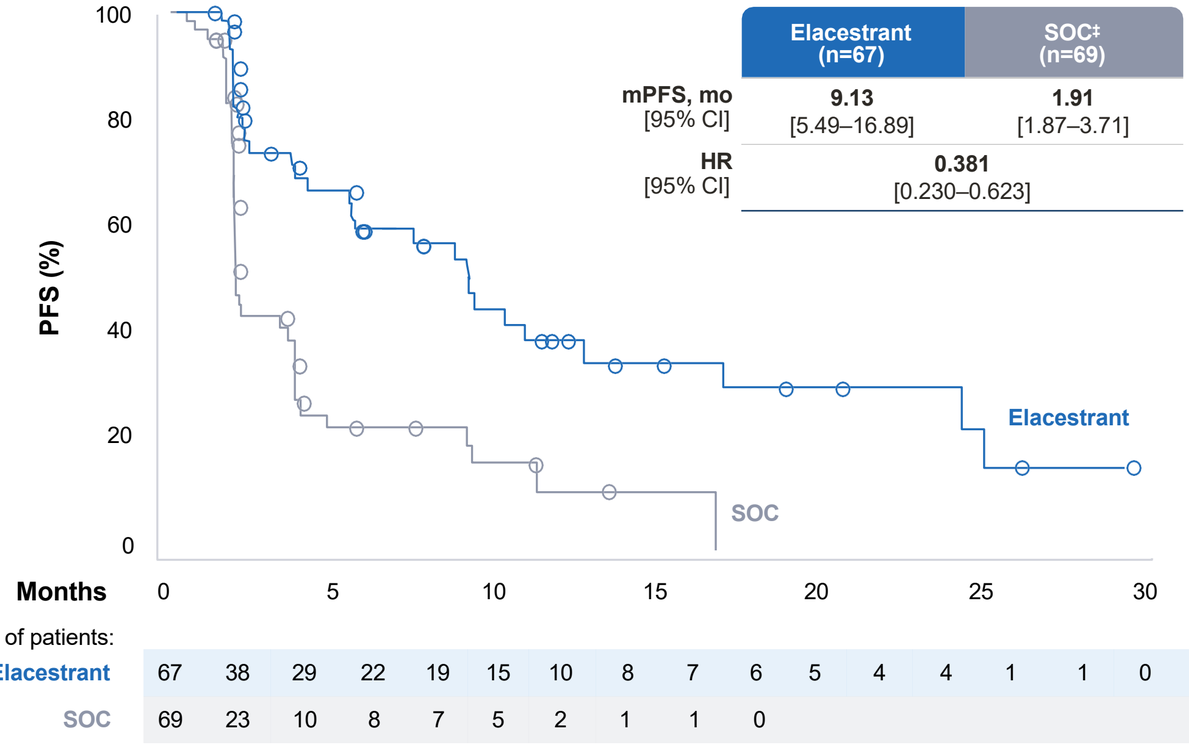
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KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS in Patients Who Received Prior ET + CDK4/6i ≥12 Mo and Harbor *ESR1*-mutated Tumors Regardless of Metastatic Site

Bone metastases*

86% of patients (n=136)



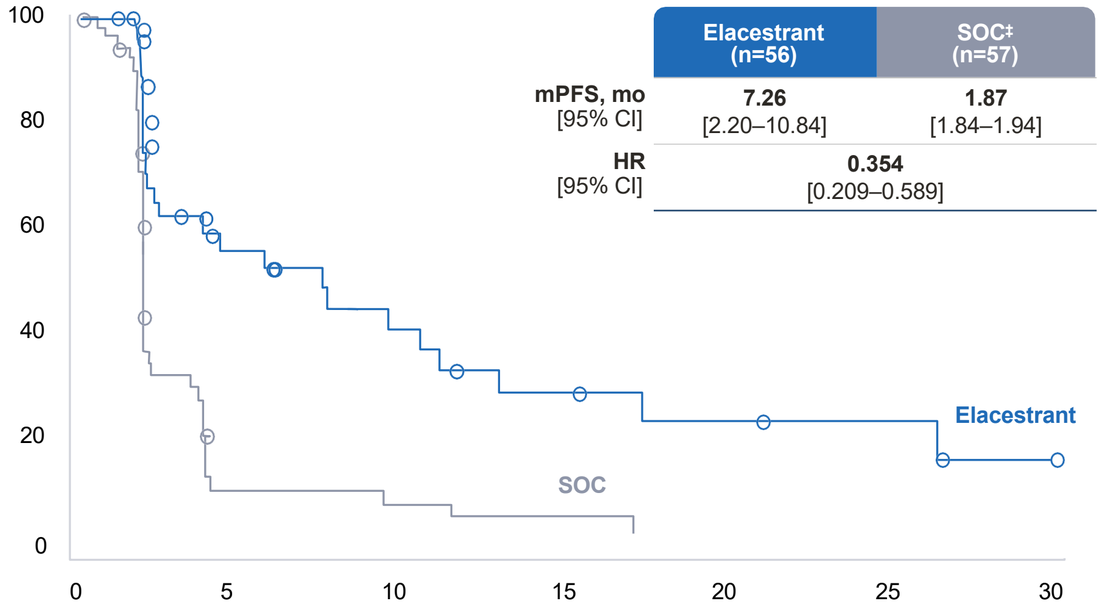
	Elacestrant (n=67)	SOC‡ (n=69)
mPFS, mo [95% CI]	**9.13** [5.49–16.89]	**1.91** [1.87–3.71]
HR [95% CI]	**0.381** [0.230–0.623]	

No. of patients:

Elacestrant	67	38	29	22	19	15	10	8	7	6	5	4	4	1	1	0
SOC	69	23	10	8	7	5	2	1	1	0						

Liver and/or lung metastases†

71% of patients (n=113)



	Elacestrant (n=56)	SOC‡ (n=57)
mPFS, mo [95% CI]	**7.26** [2.20–10.84]	**1.87** [1.84–1.94]
HR [95% CI]	**0.354** [0.209–0.589]	

Elacestrant	56	24	17	13	11	10	7	6	5	4	4	3	3	1	1	0
SOC	57	15	3	3	3	2	1	1	1	0						

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error

FIGURES 2A, 2B. *85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement). †55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had lung and other sites of metastases (2% of these patients had no liver or bone involvement). ‡SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HR=hazard ratio; mo=months; mPFS=median progression-free survival; mut=mutated; No=number; PFS=progression-free survival; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

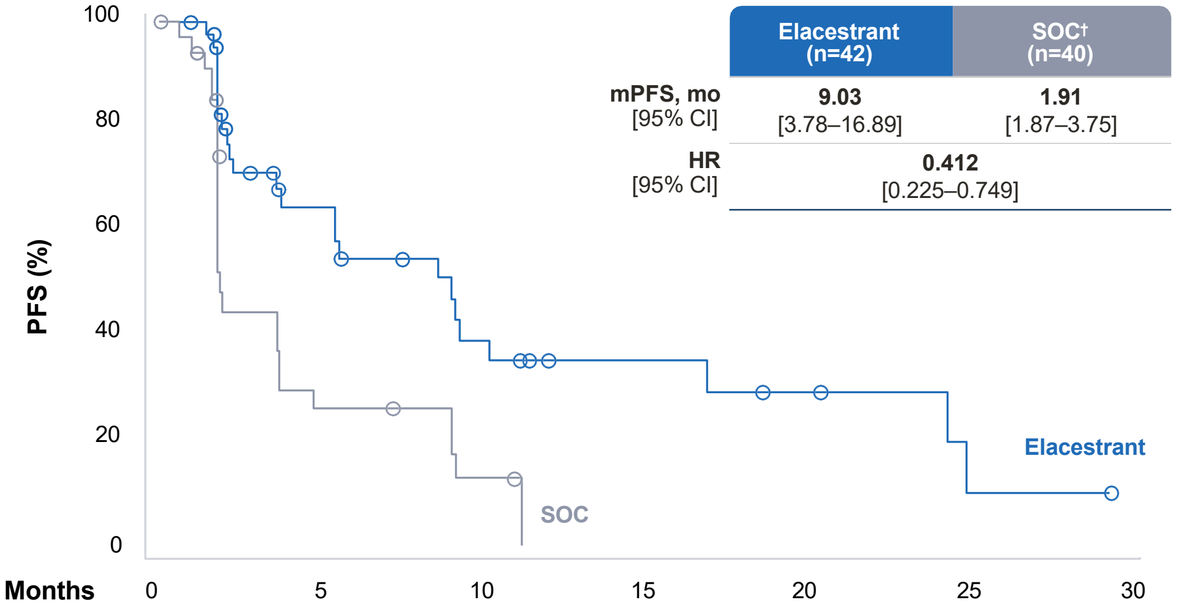
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KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS in Patients Who Received Prior ET + CDK4/6i ≥12 Mo and Harbor *ESR1*-mutated Tumors Based on Number of Metastatic Sites

<3 metastatic sites*

52% of patients (n=82)



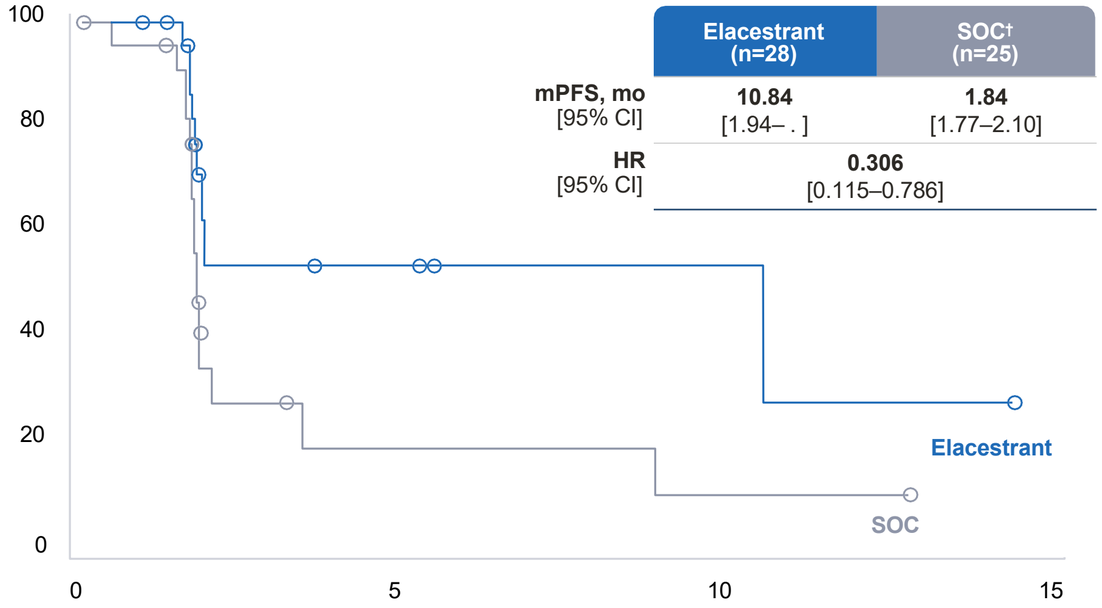
	Elacestrant (n=42)	SOC† (n=40)
mPFS, mo [95% CI]	9.03 [3.78–16.89]	1.91 [1.87–3.75]
HR [95% CI]	0.412 [0.225–0.749]	

No. of patients:

Elacestrant	42	29	20	16	14	10	6	6	6	5	4	3	3	1	1	0
SOC	40	12	8	7	6	3	0									

≥3 metastatic sites*

33% of patients (n=53)



	Elacestrant (n=28)	SOC† (n=25)
mPFS, mo [95% CI]	10.84 [1.94– .]	1.84 [1.77–2.10]
HR [95% CI]	0.306 [0.115–0.786]	

28	6	4	2	2	2	1	1	0
25	5	2	2	2	1	1	0	

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error

FIGURES 2C, 2D. *The number of metastatic sites was available for 135 of 159 patients with *ESR1*-mut tumors and prior ET + CDK4/6i ≥12 mo. †SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HR=hazard ratio; mo=months; mPFS=median progression-free survival; mut=mutated; No=number; PFS=progression-free survival; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

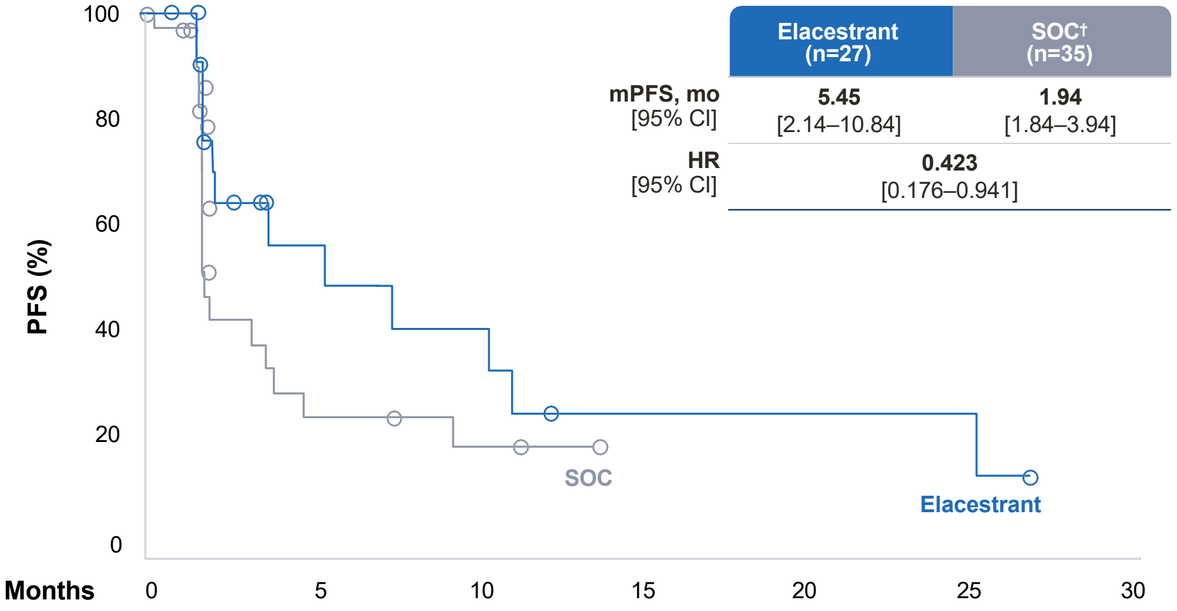
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KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS in Patients Who Received Prior ET + CDK4/6i ≥12 Mo and Harbor *ESR1*-mutated Tumors With or Without the Coexistence of *PIK3CA*-mut

PIK3CA-mut*

39% of patients (n=62)

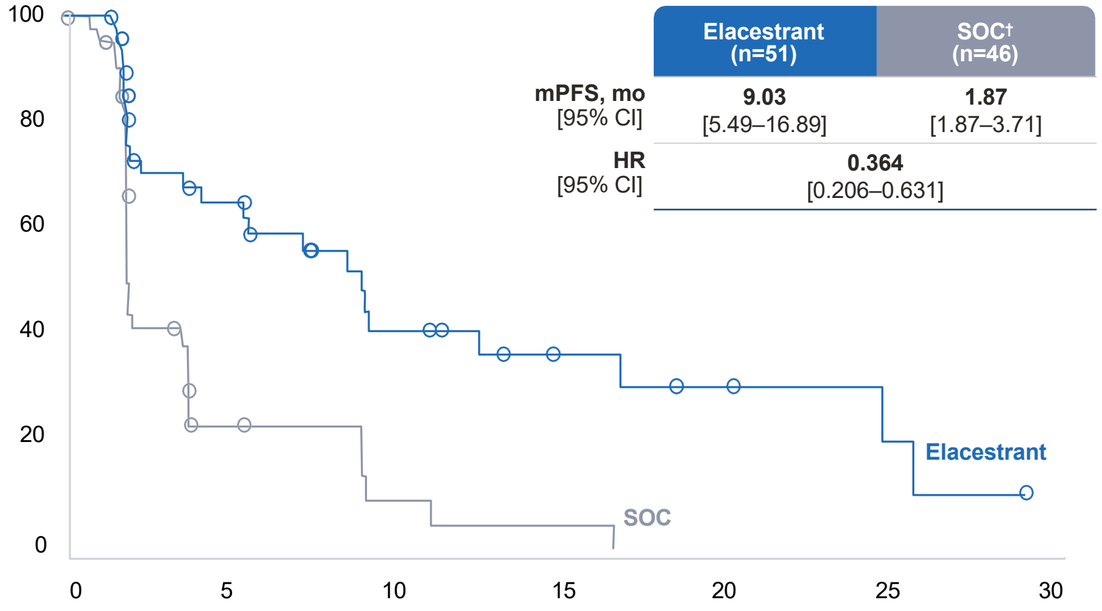


	Elacestrant (n=27)	SOC† (n=35)
mPFS, mo [95% CI]	5.45 [2.14–10.84]	1.94 [1.84–3.94]
HR [95% CI]	0.423 [0.176–0.941]	

Months	0	5	10	15	20	25	30
No. of patients:							
Elacestrant	27	13	7	6	5	5	2	2	2	2	2	2	2	0
SOC	35	10	6	5	4	3	1	0						

PIK3CA WT

61% of patients (n=97)



	Elacestrant (n=51)	SOC† (n=46)
mPFS, mo [95% CI]	9.03 [5.49–16.89]	1.87 [1.87–3.71]
HR [95% CI]	0.364 [0.206–0.631]	

Months	0	5	10	15	20	25	30
Elacestrant	51	29	24	18	15	11	9	7	6	5
SOC	46	16	6	5	5	2	1	1	1	0

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error. Elacestrant is NOT indicated to target *PIK3CA*-mut

FIGURES 3A, 3B. *E545K, H1047R, and E542K amongst others. †SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HR=hazard ratio; mo=months; mPFS=median progression-free survival; mut=mutated; No=number; PFS=progression-free survival; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC=standard of care; WT=wild type. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS in Subgroups of Patients With *ESR1*-mutated Tumors and Prior ET + CDK4/6i ≥12 Mo by *PIK3CA*-mut Location, and *BRCA1/2*-mut Status

		mPFS, mo		
Patient Subgroup	**n (%)**	**Elacestrant**	**SOC***	**HR [95% CI]**
***ESR1*- and *PIK3CA* H1041X-mut tumors, and ET + CDK4/6i ≥12 mo**	26	4.6	3.3	0.77 [0.27–2.15]
***ESR1*- and *PIK3CA* E542X/E545X-mut tumors, and ET + CDK4/6i ≥12 mo**	27	5.5	1.9	0.80 [0.26–2.48]
***ESR1*- and *BRCA1/2*-mut tumors, and ET + CDK4/6i ≥12 mo**	32	5.5	2.1	0.44 [0.15–1.29]

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error. Elacestrant is NOT indicated to target *PIK3CA*-mut and *BRCA1/2*-mut

SUPPLEMENTAL TABLE 3. *SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; BRCA1/2=breast cancer genes 1 and/or 2; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HR=hazard ratio; mo=months; mPFS=median progression-free survival; mut=mutated; PFS=progression-free survival; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC=standard-of-care.

1. Bardia A, et al. *Clin Cancer Res*. 2024.

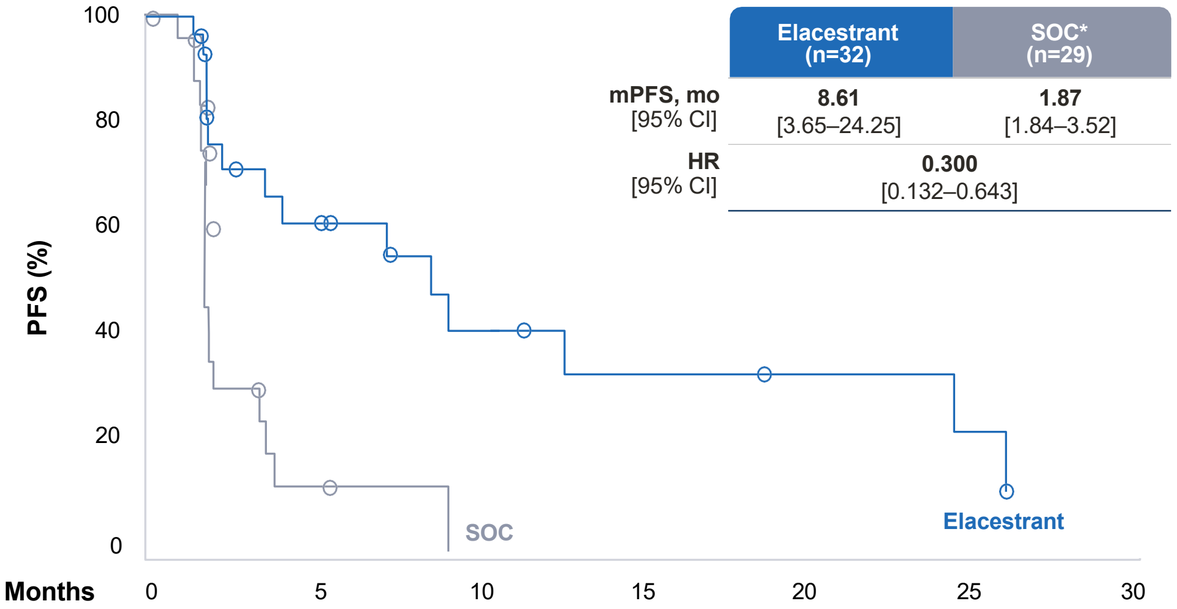
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KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS in Patients Who Received Prior ET + CDK4/6i ≥12 Mo and Harbor *ESR1*-mutated Tumors With or Without the Coexistence of *TP53*-mut

TP53-mut*

38% of patients (n=61)

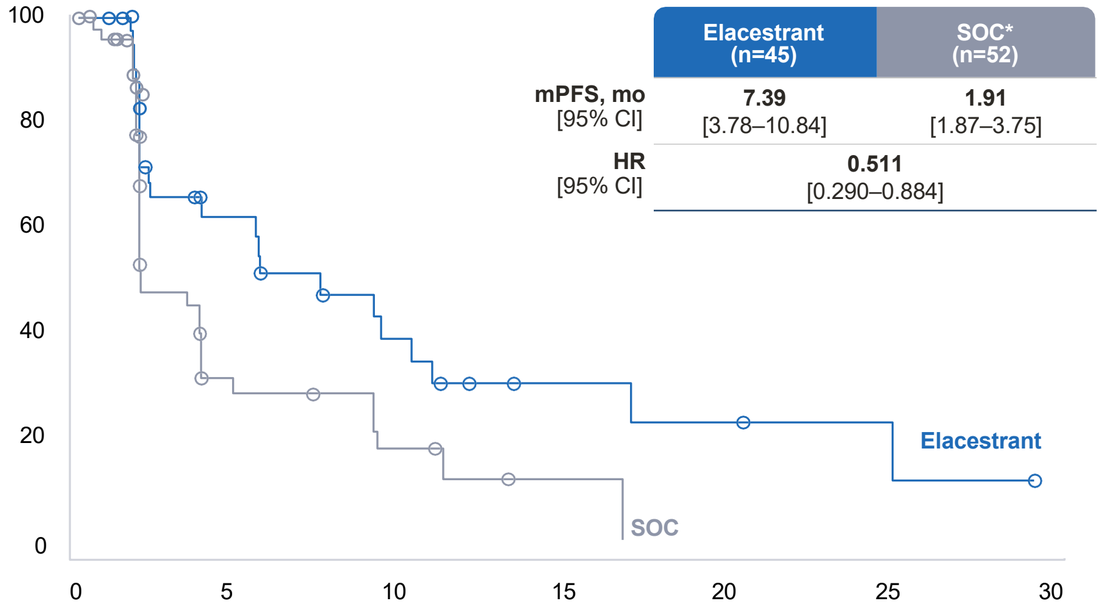


	Elacestrant (n=32)	SOC* (n=29)
mPFS, mo [95% CI]	8.61 [3.65–24.25]	1.87 [1.84–3.52]
HR [95% CI]	0.300 [0.132–0.643]	

Months	0	5	10	15	20	25	30
No. of patients:							
Elacestrant	32	16	13	10	8	6	5	4	4	4	3	3	3	0
SOC	29	8	2	1	1	0								

TP53 WT*

61% of patients (n=97)



	Elacestrant (n=45)	SOC* (n=52)
mPFS, mo [95% CI]	7.39 [3.78–10.84]	1.91 [1.87–3.75]
HR [95% CI]	0.511 [0.290–0.884]	

	0	5	10	15	20	25	30
Elacestrant	45	25	17	13	11	9	5	4	4	3	3	2	2	1	1	0
SOC	52	18	10	9	8	5	2	1	1	0						

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error. Elacestrant is NOT indicated to target *TP53*-mut

FIGURES 3C, 3D. *SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HR=hazard ratio; mo=months; mPFS=median progression-free survival; mut=mutated; No=number; PFS=progression-free survival; SOC=standard of care; TP53=tumor protein p53; WT=wild type. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

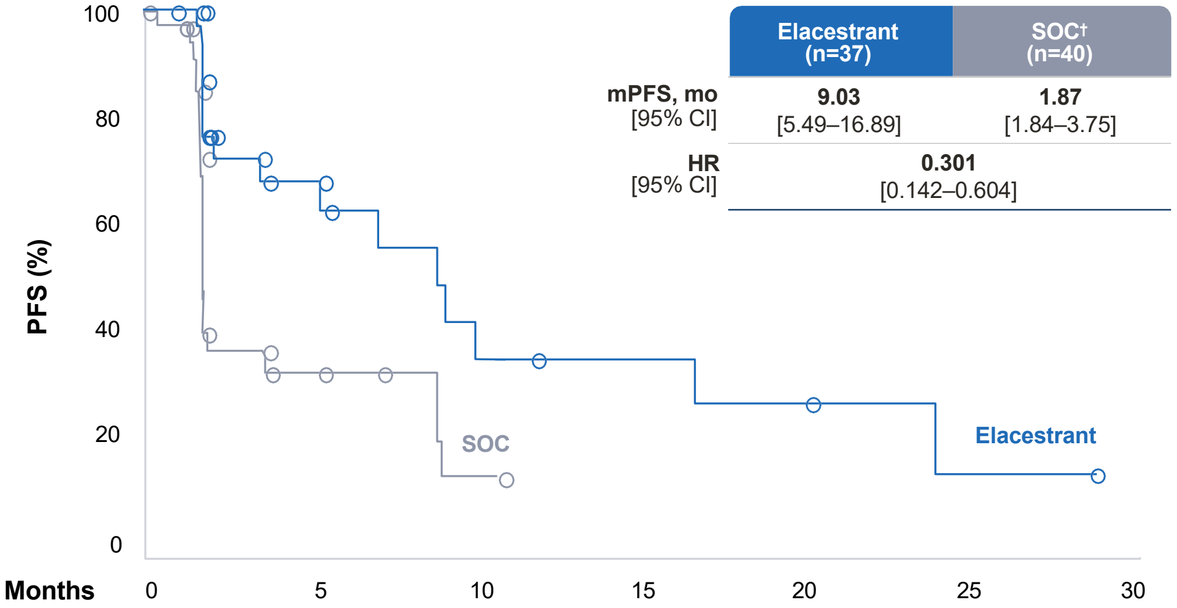
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KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS in Patients Who Received Prior ET + CDK4/6i ≥12 Mo and Harbor *ESR1*-mutated Tumors With or Without the Coexistence of HER2-low Expression

HER2-low expression*

48% of patients (n=77)

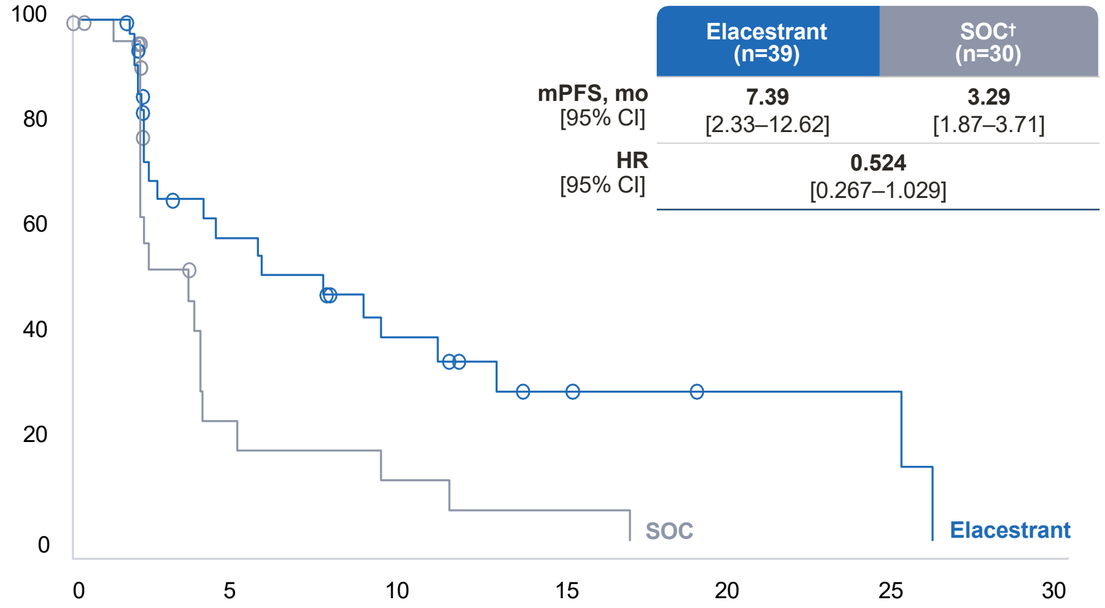


	Elacestrant (n=37)	SOC† (n=40)
mPFS, mo [95% CI]	9.03 [5.49–16.89]	1.87 [1.84–3.75]
HR [95% CI]	0.301 [0.142–0.604]	

Months	0	5	10	15	20	25	30
No. of patients:							
Elacestrant	37	20	13	9	8	6	4	4	4	3	3	2	2	1	1	0
SOC	40	11	7	6	5	2	0									

HER2-zero expression

43% of patients (n=69)



	Elacestrant (n=39)	SOC† (n=30)
mPFS, mo [95% CI]	7.39 [2.33–12.62]	3.29 [1.87–3.71]
HR [95% CI]	0.524 [0.267–1.029]	

	0	5	10	15	20	25	30
Elacestrant	39	21	17	14	11	9	6	4	3	3	2	2	2	0
SOC	30	11	4	3	3	2	1	1	1	0				

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error

FIGURES 3E, 3F. *Locally assessed HER2 IHC 1+, and 2+ with no ISH amplification. Data not available for all patients. †SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; IHC=immunohistochemistry; ISH=*in situ* hybridization; mo=months; mPFS=median progression-free survival; mut=mutated; No=number; PFS=progression-free survival; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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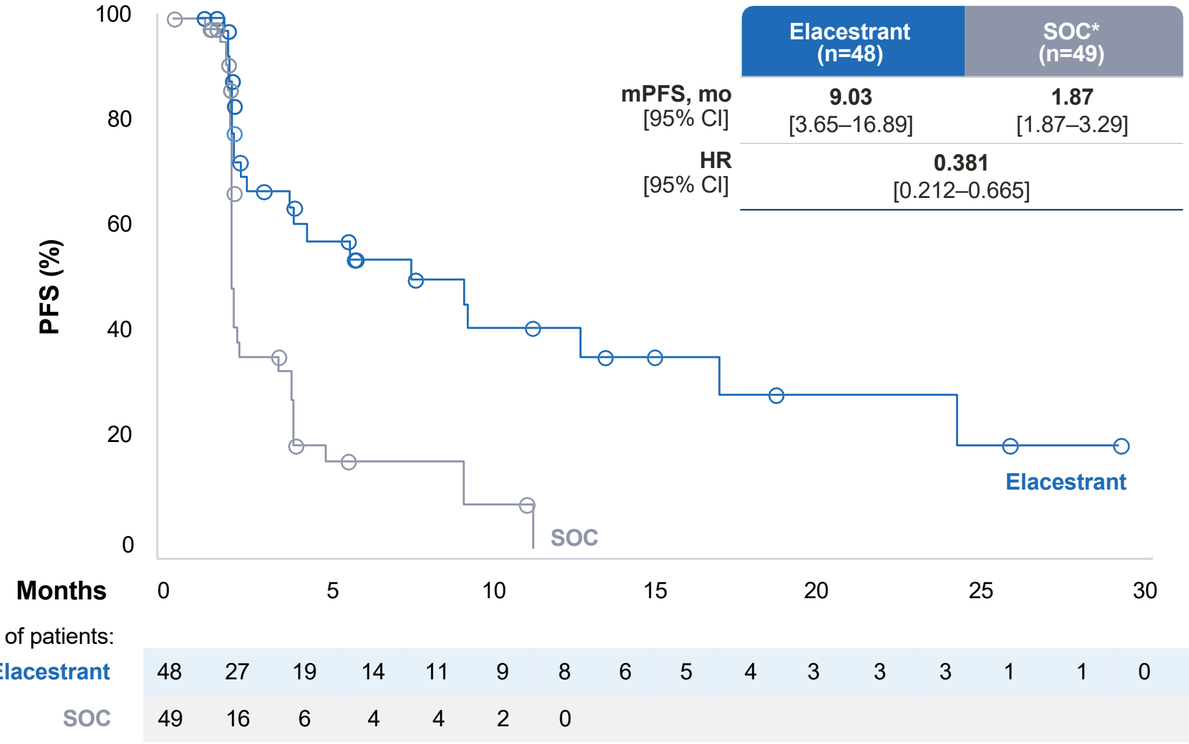
KEY EFFICACY RESULTS: *Exploratory Post Hoc Subgroup Analysis*

PFS in Patients Who Received Prior ET + CDK4/6i ≥12 Mo Based on *ESR1*-mut Tumor Variant

90% of patients had one or more *ESR1*-mut detected in the three hot spots presented (D538G; Y537S and/or Y537N).

ESR1-mut, D538G variant

61% of patients (n=97)



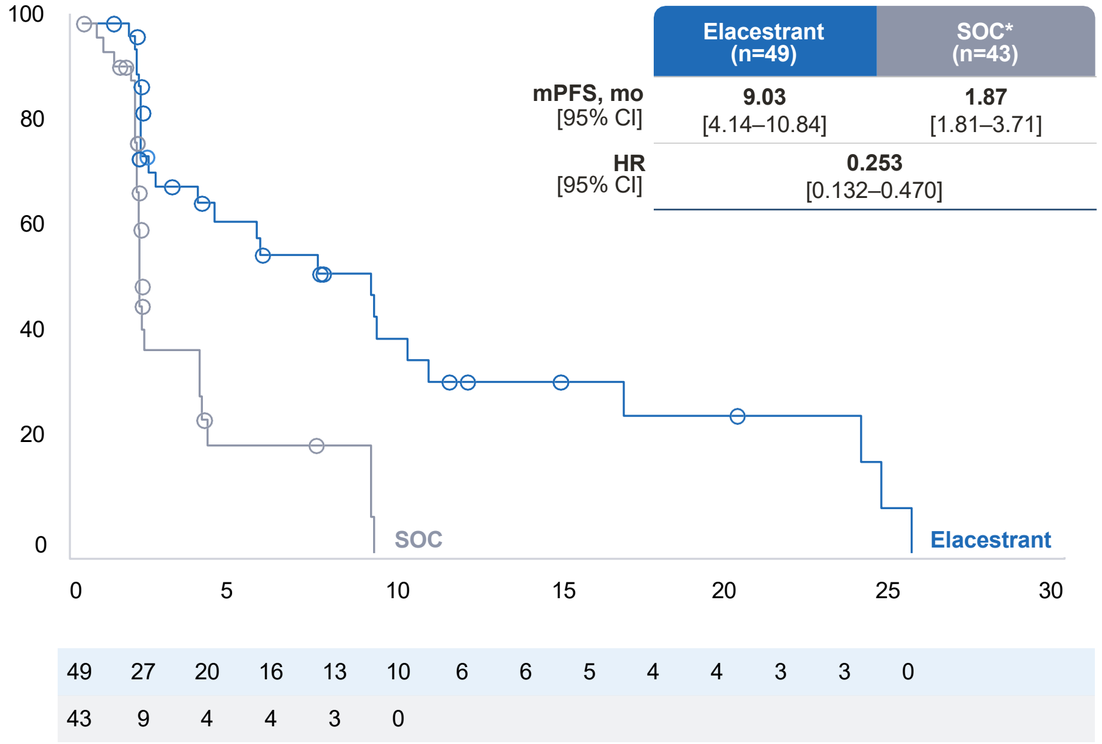
	Elacestrant (n=48)	SOC* (n=49)
mPFS, mo [95% CI]	9.03 [3.65–16.89]	1.87 [1.87–3.29]
HR [95% CI]	0.381 [0.212–0.665]	

No. of patients:

Elacestrant	48	27	19	14	11	9	8	6	5	4	3	3	3	1	1	0
SOC	49	16	6	4	4	2	0									

ESR1-mut, Y537S/N variants

58% of patients (n=92)



	Elacestrant (n=49)	SOC* (n=43)
mPFS, mo [95% CI]	9.03 [4.14–10.84]	1.87 [1.81–3.71]
HR [95% CI]	0.253 [0.132–0.470]	

	49	27	20	16	13	10	6	6	5	4	4	3	3	0		
	43	9	4	4	3	0										

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error

FIGURES 3G, 3H. *SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ESR1=estrogen receptor 1; ET=endocrine therapy; HR=hazard ratio; mo=months; mPFS=median progression-free survival; mut=mutated; No=number; PFS=progression-free survival; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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05 SAFETY

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SAFETY

The Most Common AEs (>10% in Either Arm) in the Overall Population

Adverse Reaction,† %	Elacestrant (n=237)		SOC* (n=230)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Musculoskeletal/Connective tissue disorders				
Musculoskeletal pain‡	41	7	39	1
Gastrointestinal disorders				
Nausea	35	2.5	19	0.9
Vomiting‡	19	0.8	9	0
Diarrhea	13	0	10	1
Constipation	12	0	6	0
Abdominal pain‡	11	1	10	0.9
Dyspepsia	10	0	2.6	0
General disorders				
Fatigue‡	26	2	27	1
Metabolism and nutritional disorders				
Decreased appetite	15	0.8	10	0.4
Nervous system disorders				
Headache	12	2	12	0
Vascular disorders				
Hot flush	11	0	8	0

Nausea summary	Elacestrant (n=237) n (%)	SOC* (n=230) n (%)
Dose-reduction rate due to nausea	3 (1.3)	NA
Discontinuation rate due to nausea	3 (1.3)	0 (0.0)
Antiemetic use	19 (8.0)	AI: 7 (10.3) Fulvestrant: 6 (3.7)

TABLE 3. *SOC therapies include fulvestrant and AIs. †ARs were graded using NCI CTCAE version 5.0. ‡Includes other related terms. AE=adverse event; AI=aromatase inhibitor; AR=adverse reaction; CTCAE=Common Terminology Criteria for Adverse Events; ESR1=estrogen receptor 1; NA=not applicable; NCI=National Cancer Institute; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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06 DISCUSSION

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DISCUSSION

Longer Duration of Prior ET + CDK4/6i In ER+/HER2– mBC Patients Who Had Tumors With *ESR1* Mutations

These subgroup analyses of EMERALD suggest that longer duration of prior ET + CDK4/6i was associated with clinically meaningful improvement in PFS for elacestrant compared to SOC* endocrine monotherapy in patients with *ESR1*-mutated, ER+/HER2– mBC.

In patients who had received prior ET + CDK4/6i ≥12 mo, elacestrant was associated with improved mPFS: 8.6 mo (95% CI: 4.14–10.84) with elacestrant vs 1.9 mo (95% CI: 1.87–3.68) with SOC* (HR=0.410 [95% CI: 0.262–0.634])

The statistically significant P value for the interaction between elacestrant treatment and prior CDK4/6i duration of <12 mo versus ≥12 mo suggests that longer exposure to CDK4/6i is associated with endocrine sensitivity to elacestrant in *ESR1*-mutated tumors

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error

*SOC therapies include fulvestrant and AIs. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; mBC=metastatic breast cancer; mo=months; mPFS=median progression-free survival; mut=mutated; PFS=progression-free survival; SOC=standard of care. **1.** Bardia A, et al. *Clin Cancer Res.* 2024.

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DISCUSSION

Subgroup Analysis In Patients Who Had Tumors With *ESR1* Mutations and Received Prior ET + CDK4/6i ≥12 Mo

Additional subgroup analyses suggest that, among patients with *ESR1*-mutated tumors who received prior ET + CDK4/6i ≥12 mo, single-agent elacestrant was associated with a prolonged PFS vs SOC* for patients in clinically relevant subgroups, including patients with:

- Bone metastases
- <3 or ≥3 metastatic sites
- Liver and/or lung metastases
- Tumors with *PIK3CA*-, *TP53*-, *ESR1*-mut variants†, HER2-low tumor expression

- P values for interaction between elacestrant treatment and *PIK3CA*-mut, *TP53*-mut, or HER2-low expression suggested that the benefit observed with elacestrant vs SOC* was not impacted by the presence of these common coexisting mutations or protein expression patterns

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error. Elacestrant is NOT indicated to target *PIK3CA*- or *TP53*-mut

*SOC therapies include fulvestrant and AIs. †D538G or Y537S/N. AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; mBC=metastatic breast cancer; mo=months; mPFS=median progression-free survival; mut=mutation; PFS=progression-free survival; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; SOC=standard of care; TP53=tumor protein p53 gene. **1.** Bardia A, et al. *Clin Cancer Res*. 2024.

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DISCUSSION

Current Treatment Options for Patients With ER+/HER2– *ESR1*-mutated mBC

For patients who had disease progression on prior ET + CDK4/6i, subsequent ET-based options include:

Endocrine monotherapy[1-5]

- A well-tolerated option; however, continuing AI monotherapy is limited by potential resistance in patients with *ESR1*-mutated tumors
- Fulvestrant has a mPFS of ~2–3 mo in the post-CDK4/6i and *ESR1*-mut setting

Continuation of ET + CDK4/6i[1,7-9]

- Current evidence does not support this practice in patients with *ESR1*-mutated tumors

PI3K/AKT/mTOR pathway-ET combination regimens[1]

- Data with PI3K/AKT/mTOR pathway inhibitors in patients with *ESR1*-mutated tumors, who have received prior ET + CDK4/6i ≥12 mo, are not available
- The findings of the EMERALD subgroup analysis suggest a clinical benefit with elacestrant in patients with tumor harboring coexisting *ESR1*- and *PIK3CA*-mut, indicating that disease progression post-ET + CDK4/6i in this subgroup may remain ER-driven

The presence of acquired resistance mechanisms to conventional ET requires treatment options that target *ESR1*-mut.
The exploratory *post hoc* EMERALD subgroup analysis suggests that elacestrant can be an option for patients with endocrine-sensitive tumors[1]

AI=aromatase inhibitor; AKT=protein kinase B; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; mBC=metastatic breast cancer; mo=months; mPFS=median progression-free survival; mut=mutation; mTOR=mammalian target of rapamycin; PI3K=phosphoinositide 3-kinase; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha.

1. Bardia A, et al. *Clin Cancer Res*. 2024. **2.** Jeselsohn R, et al. *Clin. Cancer Res*. 2014;20:1757-1767. **3.** Toy W, et al. *Nat Genet*. 2013;45(12):1439-1445. **4.** Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85. **5.** Oesterreich S, et al. *Nat Genet*. 2013;45:1415-6. **6.** Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004-13. **7.** Llombart-Cussac A, et al. *J Clin Oncol*. 2023;41(suppl 16; abstr 1001). **8.** Mayer EL, et al. *J Clin Oncol*. 2024:JCO2301940. **9.** Kalinsky K, et al. *J Clin Oncol*. 2024;42 (suppl 17; abstr LBA1001).

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DISCUSSION

Authors' Summary and Conclusions

The findings of the EMERALD subgroup analyses are hypothesis-generating due to their *post-hoc* exploratory nature and may be used to help identify signals in patients with tumors that remain endocrine sensitive. These analyses provide evidence that may help inform real-world clinical decision-making in the 2L, post-ET + CDK4/6i setting for patients with *ESR1*-mutated tumors in the metastatic setting.

Prior ET + CDK4/6i ≥12 mo

- Associated with a clinically meaningful improvement in PFS for elacestrant compared to SOC* endocrine monotherapy in patients with ER+/HER2– mBC and *ESR1*-mutated tumors

Clinically Relevant Subgroups

- PFS results were consistent in patients with:
  - Bone metastases
  - Liver and/or lung metastases
  - <3 or ≥3 metastatic sites
  - *TP53*-, *PIK3CA*-, *ESR1*-mut variant† tumors
  - HER2-low tumor expression

Elacestrant Safety Profile

- Subgroup safety analyses showed that elacestrant has a manageable safety profile that is consistent with the profile in the overall population

Elacestrant in the Treatment Landscape

- Although future studies are warranted, elacestrant may enable ET sequencing in the 2L before other targeted therapies and drug combinations, and may delay chemotherapy-based regimens, including ADCs

ESR1-mut Testing Recommendations

- Based on the high rate and availability of an effective *ESR1*-targeting therapeutic, testing for the emergence of *ESR1* mutations at each disease progression is recommended by clinical guidelines

The results of these exploratory *post hoc* analyses of mPFS by ET + CDK4/6i duration are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type 1 error. Elacestrant is NOT indicated to target *PIK3CA*- or *TP53*-mut

*SOC therapies include fulvestrant and AIs. †D538G or Y537S/N. 2L=second line; ADC=antibody-drug conjugate; AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; ESR1=estrogen receptor 1; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; mBC=metastatic breast cancer; mo=months; mPFS=median progression-free survival; mut=mutation; PFS=progression-free survival; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; SOC=standard of care; TP53=tumor protein p53 gene.

1. Bardia A, et al. *Clin Cancer Res*. 2024.

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