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Elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC) following progression on prior endocrine and CDK4/6 inhibitor therapy: Results of EMERALD phase 3 trial

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Disclosures

Presenter: Aditya Bardia

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Background

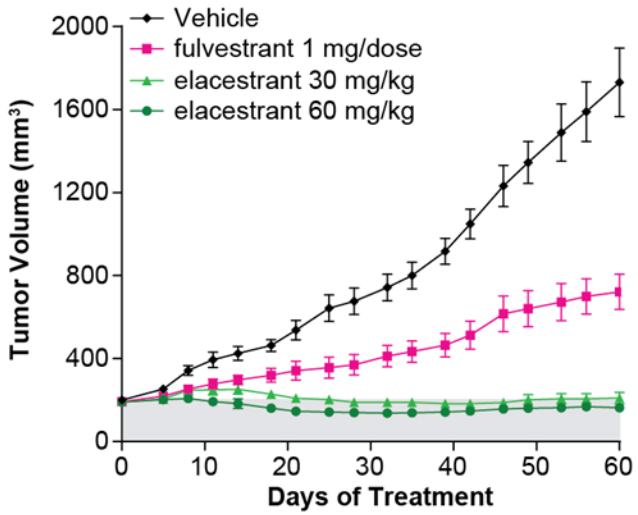
- Endocrine therapy plus CDK4/6i (inhibitor) is the mainstay for management of estrogen receptor-positive (ER+)/HER2- mBC as 1st-line therapy.[1]
- However, most patients with ER+ mBC eventually experience disease progression to 1st line therapy due to therapeutic resistance, including development of *ESR1* mutations (*mESR1*).[2]
- Treatment guidelines recommend use of sequential endocrine therapy before chemotherapy, in the absence of visceral crisis or until all endocrine therapy options have been exhausted.[1]
- Standard single-agent endocrine therapy (eg, fulvestrant) is associated with poor median progression-free survival (~2 months in 2nd/3rd line post-CDK 4/6i setting)[3-5], highlighting clinical need for better endocrine therapy for patients with ER+/HER2- mBC.

1. Moy B, et al. *J Clin Oncol*. 2021:JCO2101374; 2. Brett JO, et al. *Breast Cancer Res*. 2021;23:85; 3. Lindeman GJ, et al. *J Clin Oncol.* 2021;39:1004. 4. Turner NC, et al. *Lancet Oncol*. 2020;21:1296-1308.
5. Andre F, et al. *New Engl J Med*. 2019; 380(20):1929-1940.

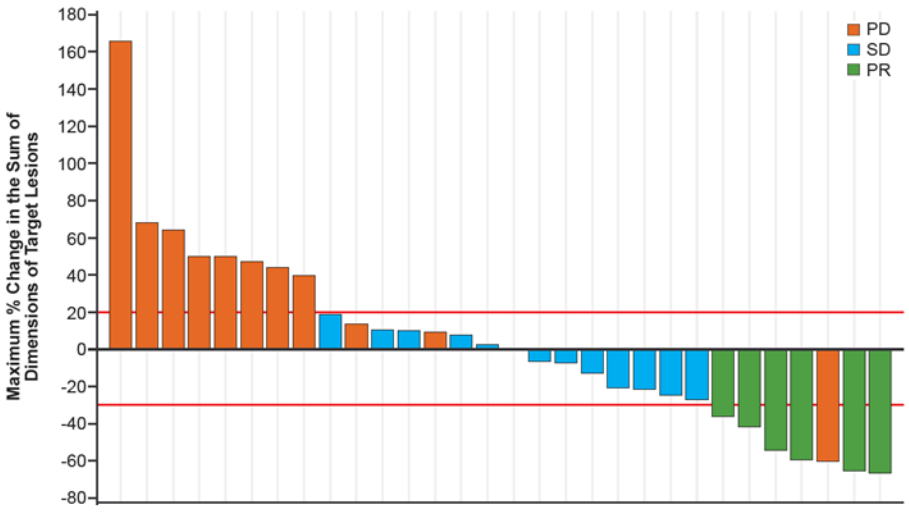
Background (cont.)

- Elacestrant (RAD1901) is an oral SERD that blocks ER and inhibits estradiol-dependent gene transcription induction and cell proliferation in ER+ BC cell lines with higher efficacy than fulvestrant.[1]
- In a phase 1 study of elacestrant in postmenopausal women with ER+/HER2- mBC:[2]
  - Single-agent activity was noted with confirmed partial responses in heavily pretreated patients, including those with prior CDK4/6i and prior fulvestrant, as well as those whose tumors harbored *mESR1.*

In vivo efficacy of elacestrant in tumors expressing *ESR1* mutations[1]

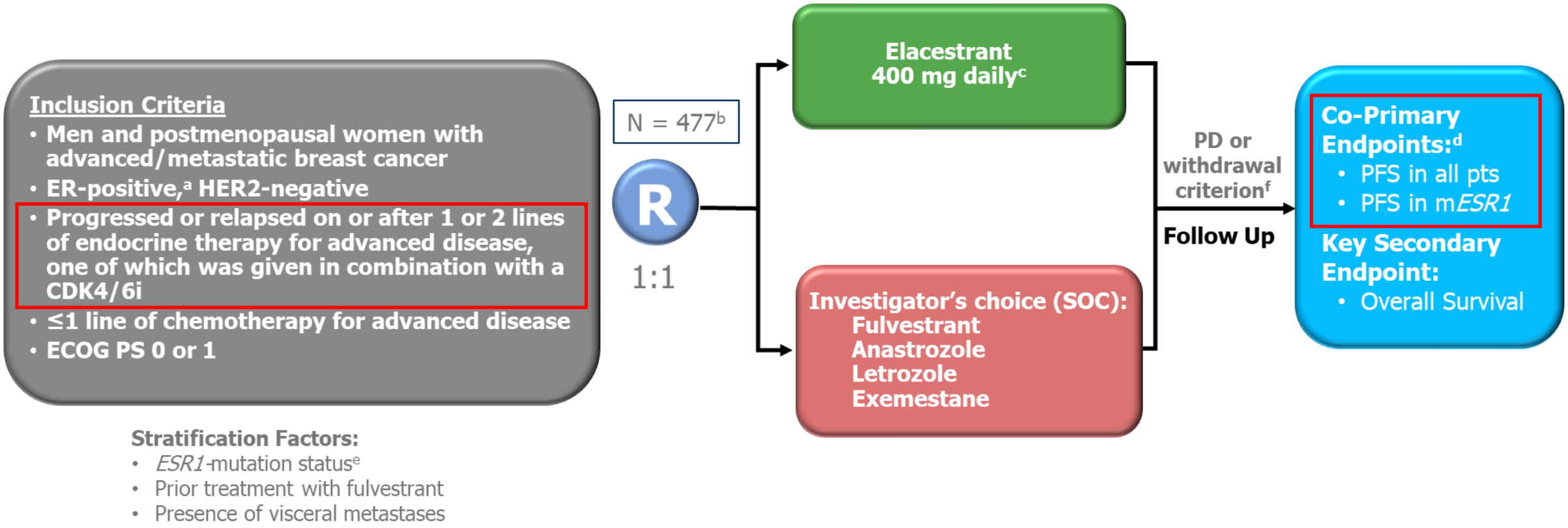


Maximum percent change in sum of diameters of all target lesions in patients treated with 400 mg of elacestrant[2]



1. Bihani T, et al. *Clin Cancer Res.* 2017;23:4793-4804; 2. Bardia A, et al. *J Clin Oncol.* 2021;39:1360-1370.

EMERALD Phase 3 Study Design



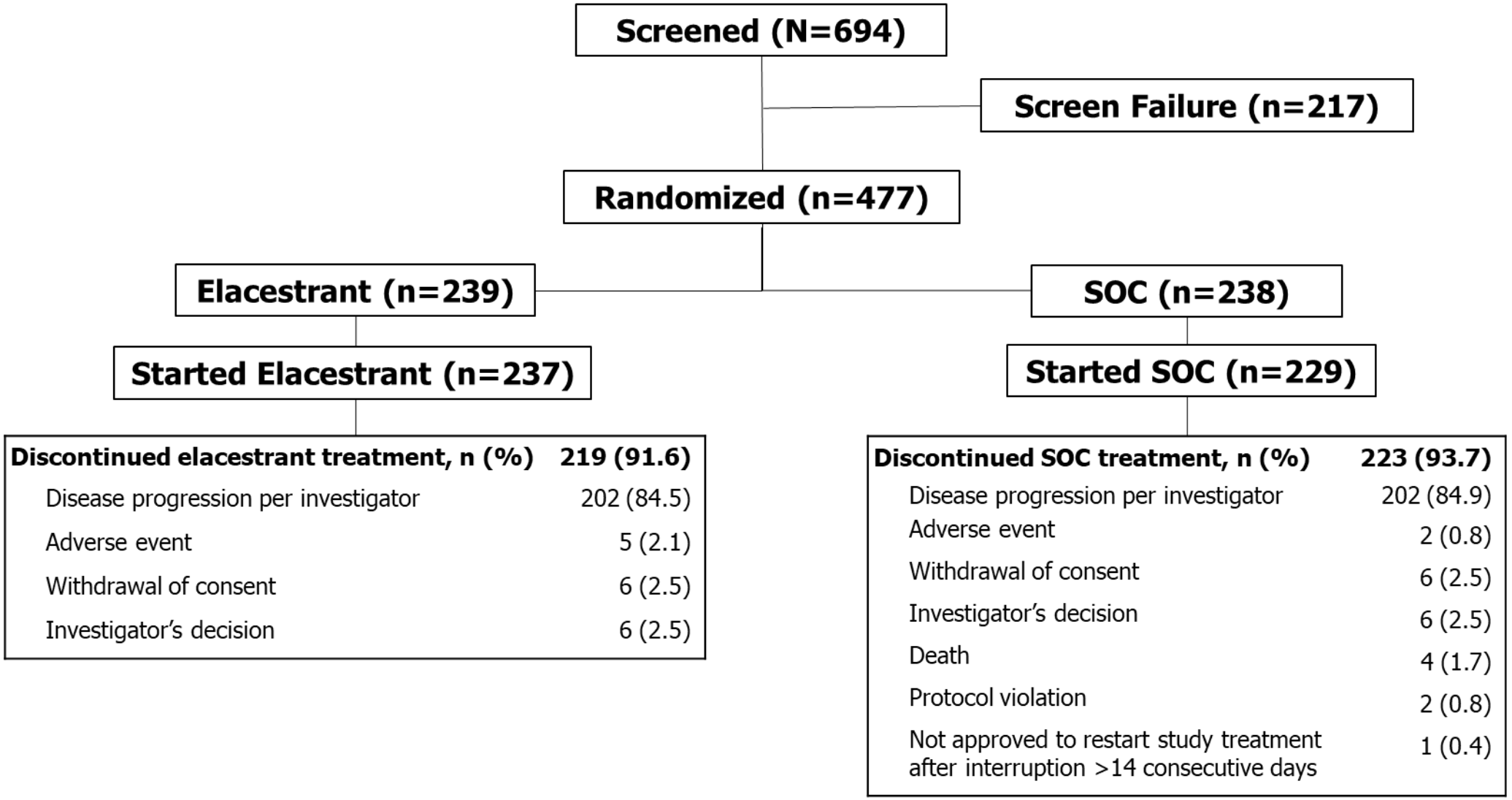
[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Blinded Independent Central Review. [e]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant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

CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival, PD, progressive disease; PFS: progression-free survival; Pts, patients; R, randomized. SOC, standard of care.

Statistical Considerations

- The study had two primary endpoints:
  - PFS among all patients (*mESR1* and *mESR1* non-detectable)
  - PFS among patients with *mESR1*
- The truncated Hochberg procedure was used to control the family-wise type I error rate at 5% (2-sided) and to allow alpha to pass along from the analyses of the primary endpoint of PFS to the analyses of the key secondary endpoint of OS.
- The study was designed with ≥90% power to evaluate a PFS hazard ratio (HR) of 0.667 in all patients and ≥80% power for a PFS HR of 0.610 in the *mESR1* subset
- Key secondary endpoints: OS in all patients and in patients with *mESR1* (tested only in case of statistically significant result of the PFS in the respective population) to be conducted at the time of the PFS analysis and when ~50% of the patients have died
- The OS analysis at the final PFS analysis allocated a 2-sided alpha level of 0.0001

Patient Disposition



Discontinued elacestrant treatment, n (%)	219 (91.6)
Disease progression per investigator	202 (84.5)
Adverse event	5 (2.1)
Withdrawal of consent	6 (2.5)
Investigator's decision	6 (2.5)

Discontinued SOC treatment, n (%)	223 (93.7)
Disease progression per investigator	202 (84.9)
Adverse event	2 (0.8)
Withdrawal of consent	6 (2.5)
Investigator's decision	6 (2.5)
Death	4 (1.7)
Protocol violation	2 (0.8)
Not approved to restart study treatment after interruption >14 consecutive days	1 (0.4)

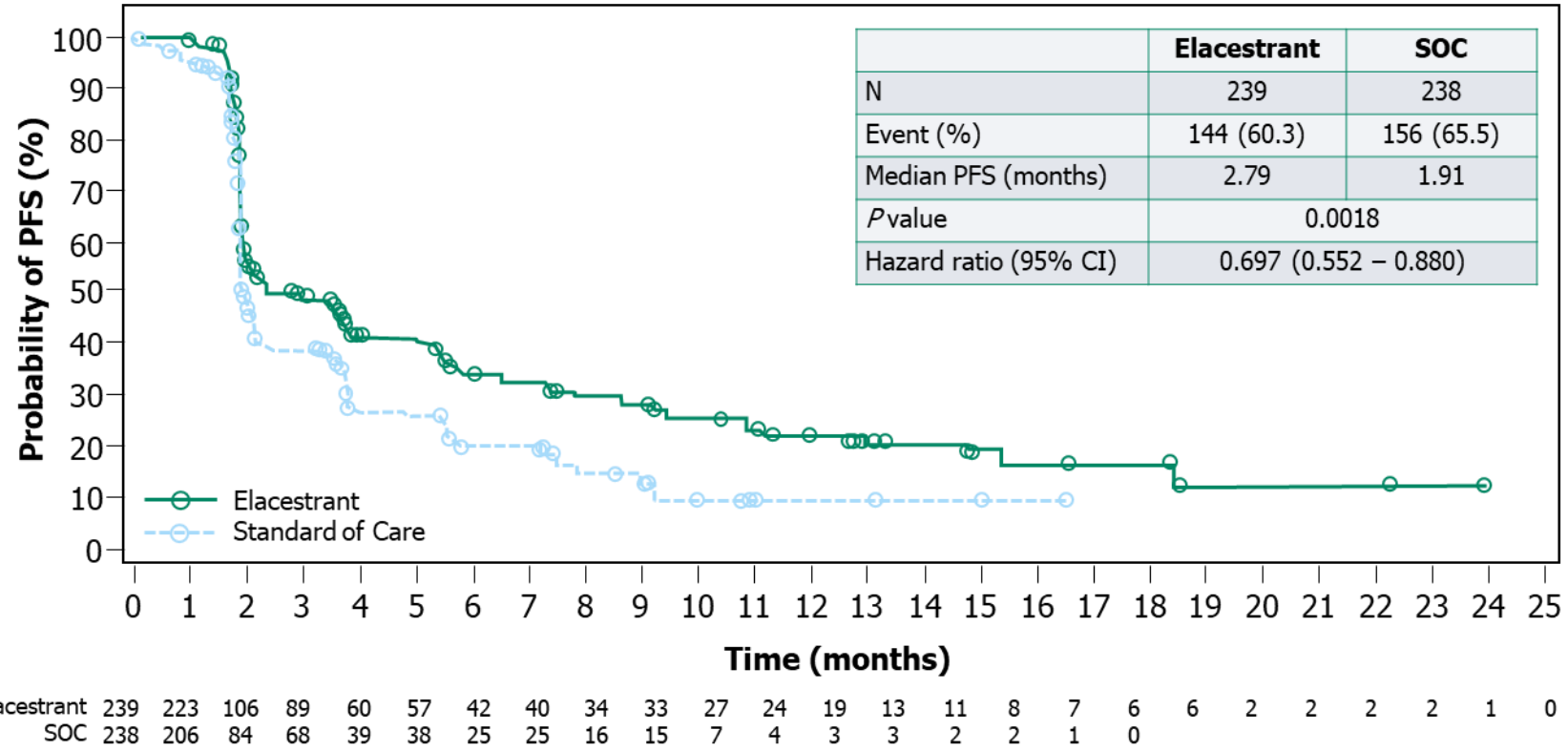
Baseline Demographic and Disease Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*mESR1* (N=115)	All (N=238)	*mESR1* (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.5 (32-83)	63.0 (32-83)
Gender, n % Female Male	233 (97.5) 6 (2.5)	115 (100) 0	237 (99.6) 1 (0.4)	113 (100) 0
ECOG PS, n (%) 0 1 >1	143 (59.8) 96 (40.2) 0	67 (58.3) 48 (41.7) 0	135 (56.7) 102 (42.9) 1 (0.4)	62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	168 (70.6)	83 (73.5)
Bone-only disease, n (%)	38 (15.9)	14 (12.2)	29 (12.2)	14 (12.4)
Prior adjuvant therapy, n (%)	158 (66.1)	62 (53.9)	141 (59.2)	65 (57.5)
Number of prior lines of endocrine therapy,** n (%) 1 2	129 (54.0) 110 (46.0)	73 (63.5) 42 (36.5)	141 (59.2) 97 (40.8)	69 (61.1) 44 (38.9)
Number of prior lines of chemotherapy,** n (%) 0 1	191 (79.9) 48 (20.1)	89 (77.4) 26 (22.6)	180 (75.6) 58 (24.4)	81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

Primary Endpoint: PFS by IRC

All Patients (ITT)



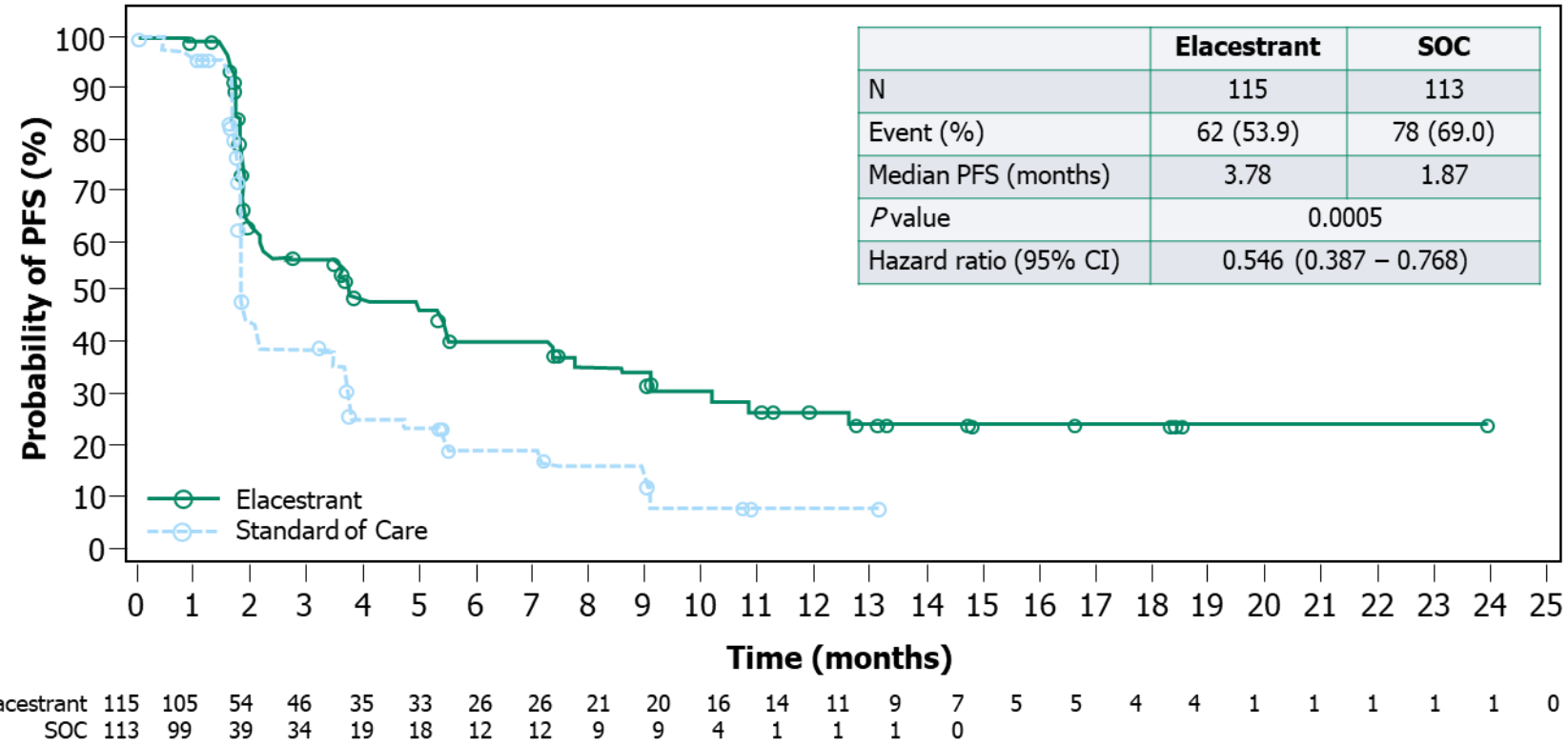
	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

Elacestrant is associated with a 30% reduction in the risk of progression or death in all patients with ER+/HER2- mBC

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

Primary Endpoint: PFS by IRC

Patients With Tumors Harboring *mESR1*



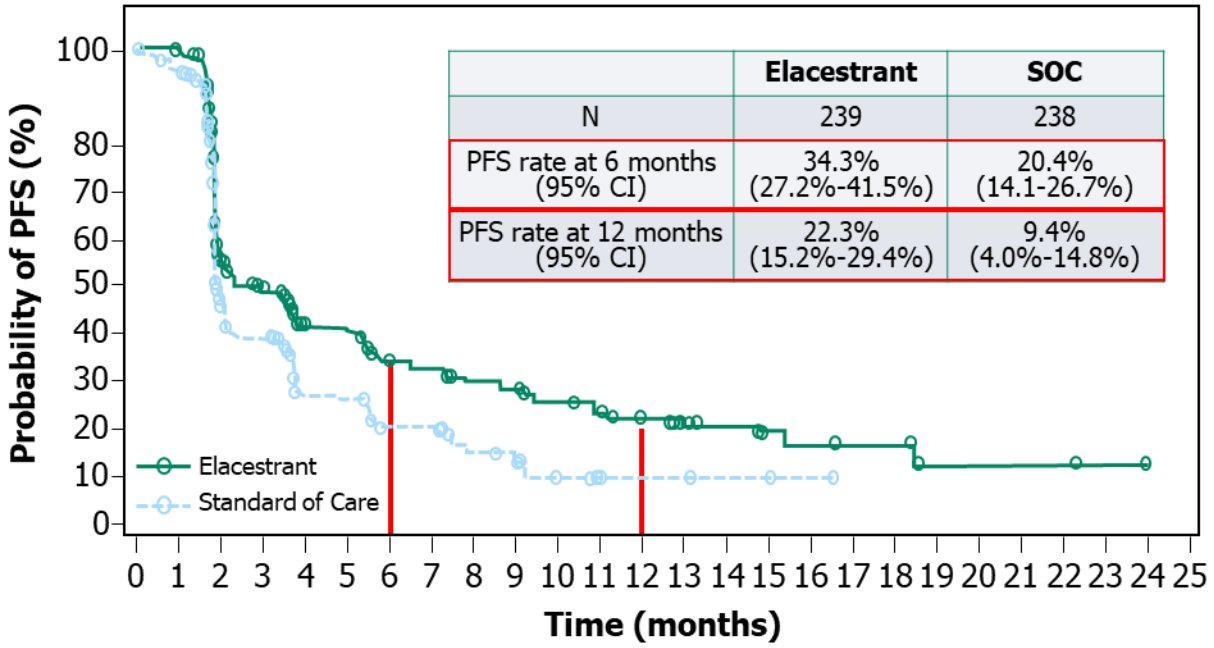
	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

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

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

PFS Rate at 6 and 12 Months: All Patients and *mESR1* Group

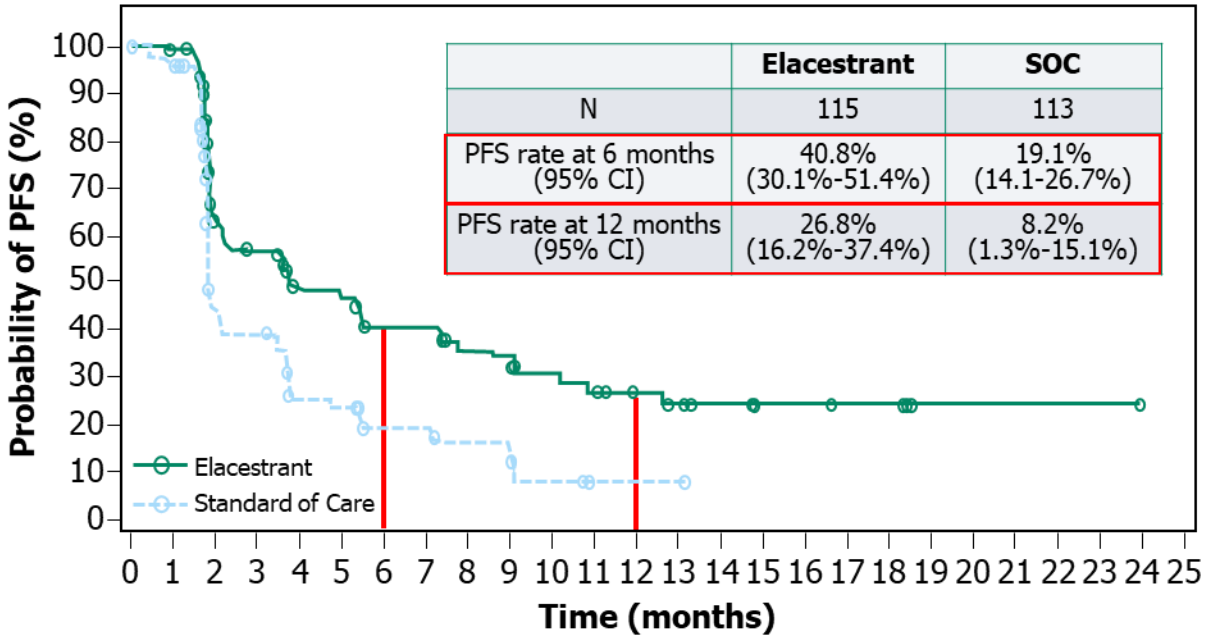
All Patients



	Elacestrant	SOC
N	239	238
PFS rate at 6 months (95% CI)	34.3% (27.2%-41.5%)	20.4% (14.1-26.7%)
PFS rate at 12 months (95% CI)	22.3% (15.2%-29.4%)	9.4% (4.0%-14.8%)

Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

Patients With Tumors Harboring *mESR1*



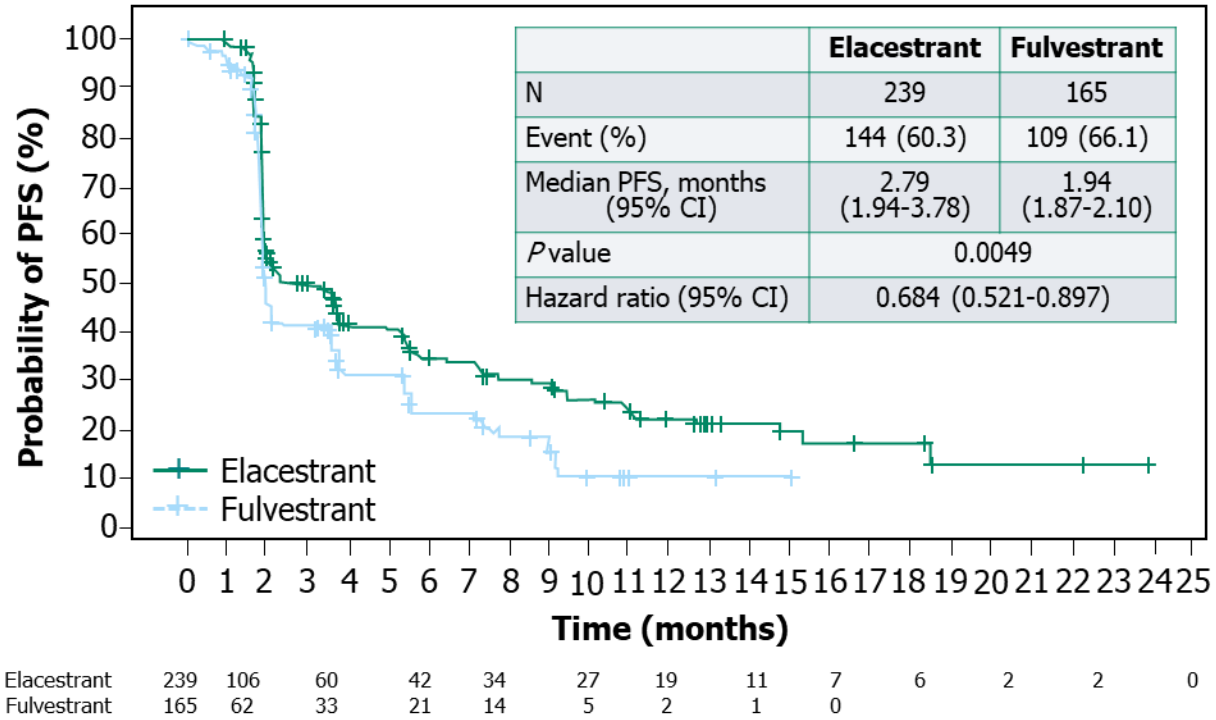
	Elacestrant	SOC
N	115	113
PFS rate at 6 months (95% CI)	40.8% (30.1%-51.4%)	19.1% (14.1-26.7%)
PFS rate at 12 months (95% CI)	26.8% (16.2%-37.4%)	8.2% (1.3%-15.1%)

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 demonstrated a higher PFS rate at 6 and 12 months versus SOC endocrine therapy in patients with ER+/HER2- advanced/metastatic breast cancer following prior CDK4/6i therapy

PFS: Elacestrant vs Fulvestrant (All Patients and *mESR1* Group)

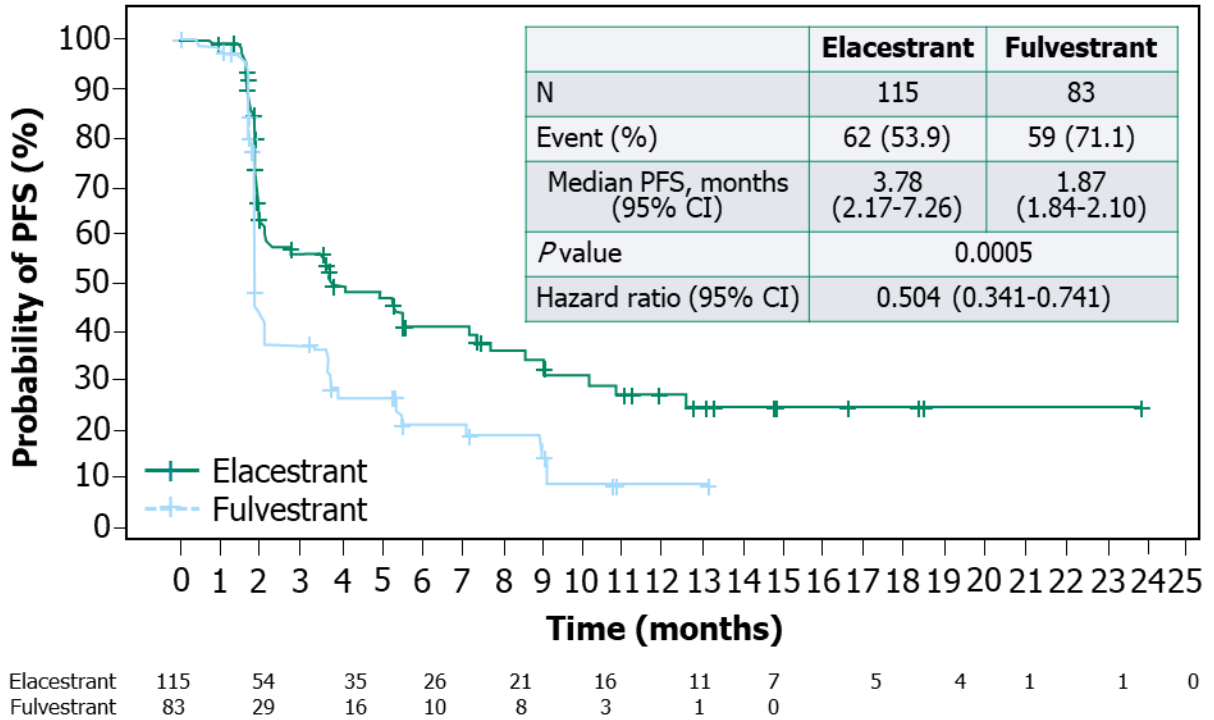
All Patients



	Elacestrant	Fulvestrant
N	239	165
Event (%)	144 (60.3)	109 (66.1)
Median PFS, months (95% CI)	2.79 (1.94-3.78)	1.94 (1.87-2.10)
P value	0.0049	
Hazard ratio (95% CI)	0.684 (0.521-0.897)	

Elacestrant	239	106	60	42	34	27	19	11	7	6	2	2	0	
Fulvestrant	165	62	33	21	14	5	2	1	0					

Patients With Tumors Harboring *mESR1*

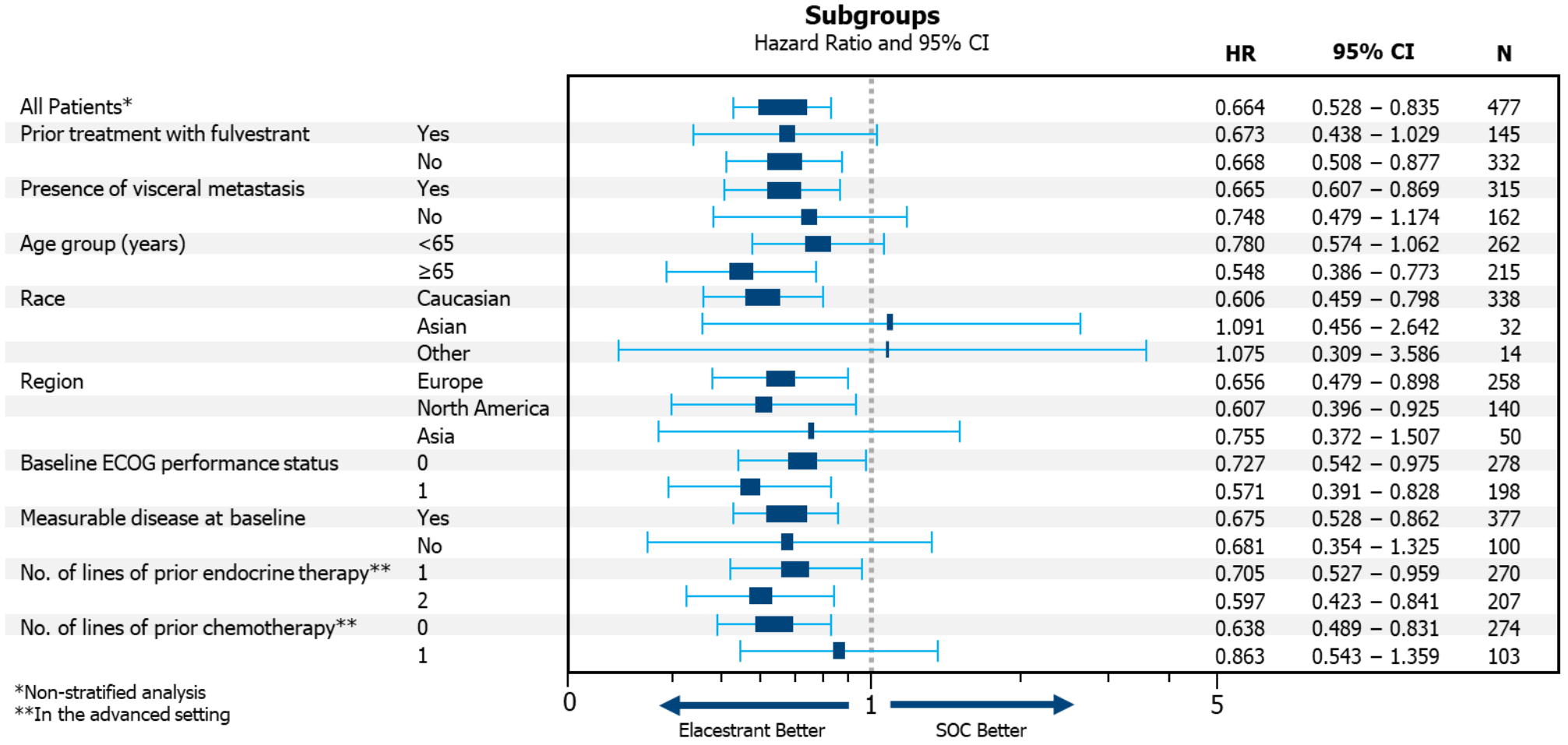


	Elacestrant	Fulvestrant
N	115	83
Event (%)	62 (53.9)	59 (71.1)
Median PFS, months (95% CI)	3.78 (2.17-7.26)	1.87 (1.84-2.10)
P value	0.0005	
Hazard ratio (95% CI)	0.504 (0.341-0.741)	

Elacestrant	115	54	35	26	21	16	11	7	5	4	1	1	0	
Fulvestrant	83	29	16	10	8	3	1	0						

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

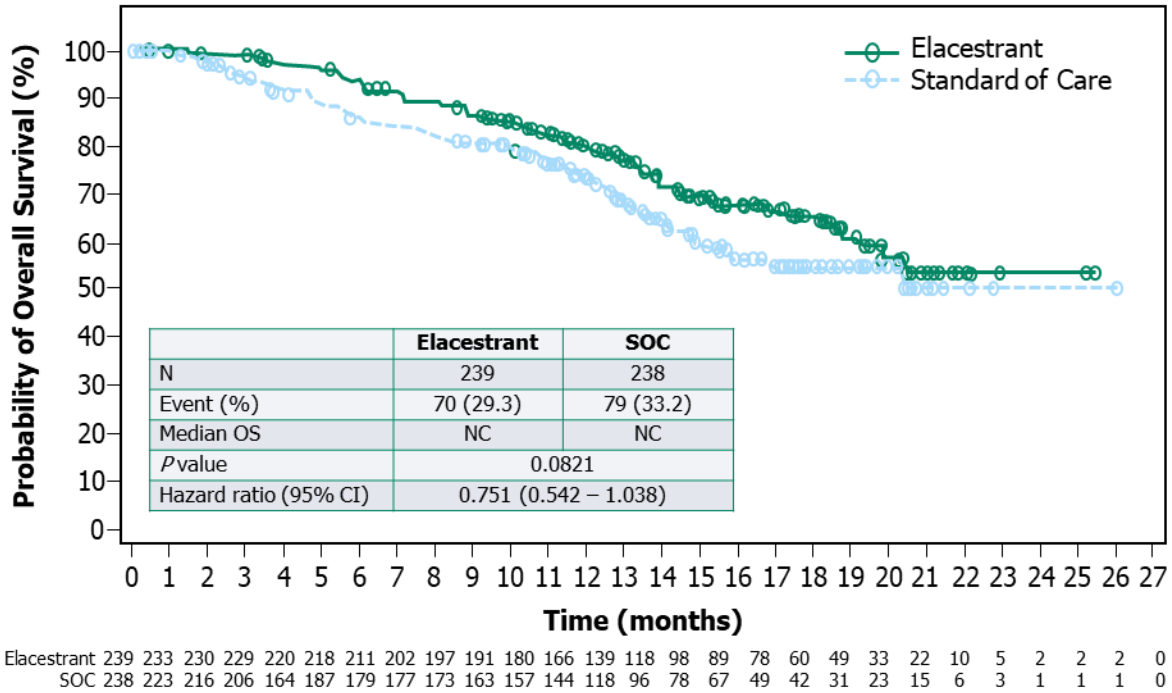
PFS in Clinically Relevant Subgroups (All Patients)



- Multiple pre-specified subpopulations showed a consistent trend for elacestrant versus SOC on PFS

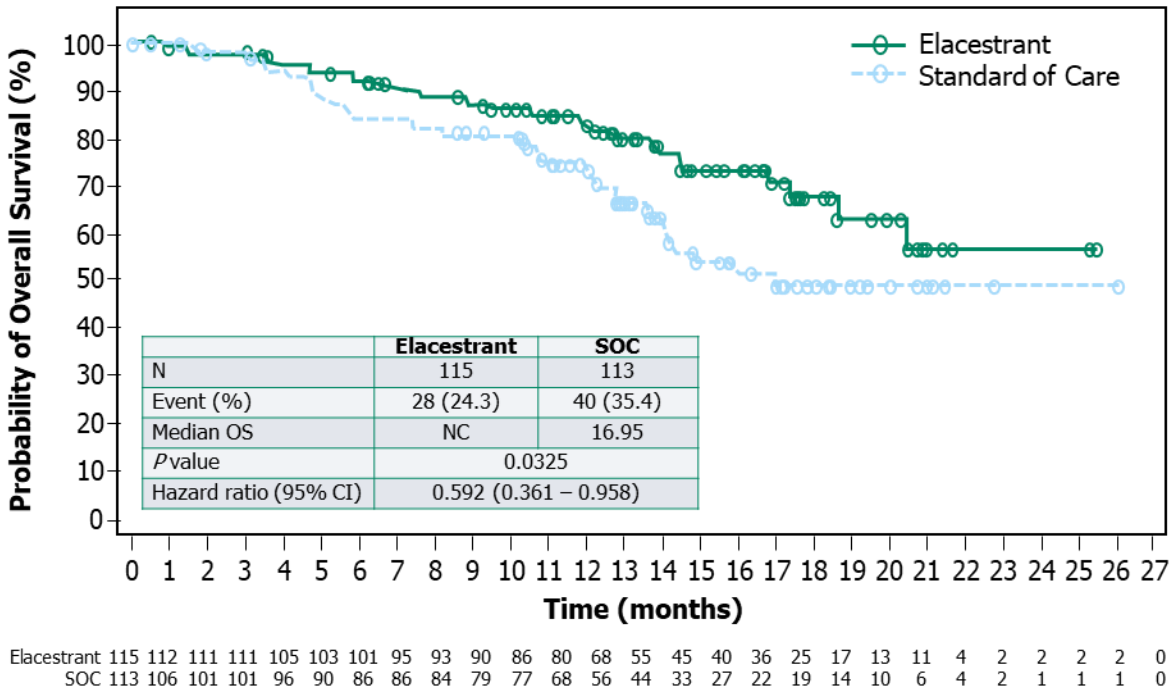
Overall Survival (Interim Analysis)

All Patients



	Elacestrant	SOC
N	239	238
Event (%)	70 (29.3)	79 (33.2)
Median OS	NC	NC
P value	0.0821	
Hazard ratio (95% CI)	0.751 (0.542 – 1.038)	

Patients with *mESR1*



	Elacestrant	SOC
N	115	113
Event (%)	28 (24.3)	40 (35.4)
Median OS	NC	16.95
P value	0.0325	
Hazard ratio (95% CI)	0.592 (0.361 – 0.958)	

- While no statistically significant differences were noted at the α=0.0001 level in OS, an evident trend favoring elacestrant over SOC was noted in both groups. Final analysis with mature data is expected to take place in late 2022/early 2023.

Safety Summary

	Elacestrant N = 237, n (%)	SOC		
		Total N = 229, n (%)	Fulvestrant N = 161, n (%)	AI N = 68, n (%)
Number of patients with at least 1 treatment-emergent adverse event (TEAE)	218 (92.0)	197 (86.0)	144 (89.4)	53 (77.9)
Any treatment-related TEAE (TRAE)	150 (63.3)	100 (43.7)	72 (44.7)	28 (41.2)
Any Grade 3 and Grade 4 TRAE	17 (7.2)	7 (3.1)	5 (3.1)	2 (2.9)
Any fatal TRAE (Grade 5)	0	0	0	0
Any serious TRAE	3 (1.3)	0	0	0
Any TRAE leading to dose reduction	6 (2.5)	0	0	0
Any TRAE leading to discontinuation of study drug	8 (3.4)	2 (0.9)	1 (0.6)	1 (1.5)

- TEAEs leading to discontinuation of elacestrant or SOC were infrequent in both arms (6.3% and 4.4%).
- There were no treatment-related deaths in either of the groups.

Treatment-Emergent Adverse Events (≥10% in Either Arm)

	Elacestrant N = 237, n (%)		SOC					
			Total N = 229, n (%)		Fulvestrant N = 161, n (%)		AI N = 68, n (%)	
Preferred Term	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	-	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)	2 (0.8)	19 (8.3)	-	12 (7.5)	-	7 (10.3)	-
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	-	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	-	28 (17.4)	-	9 (13.2)	-
Diarrhea	33 (13.9)	-	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	-
Aspartate aminotransferase increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	-
Headache	29 (12.2)	4 (1.7)	26 (11.4)	-	18 (11.2)	-	8 (11.8)	-
Constipation	29 (12.2)	-	15 (6.6)	-	10 (6.2)	-	5 (7.4)	-
Hot flush	27 (11.4)	-	19 (8.3)	-	15 (9.3)	-	4 (5.9)	-
Dyspepsia	24 (10.1)	-	6 (2.6)	-	4 (2.5)	-	2 (2.9)	-
Alanine aminotransferase increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	-	6 (8.8)	1 (1.5)

Conclusions

	Elacestrant N = 237, n (%)		SOC					
			Total N = 229, n (%)		Fulvestrant N = 161, n (%)		AI N = 68, n (%)	
Preferred Term	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	-	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)	2 (0.8)	19 (8.3)	-	12 (7.5)	-	7 (10.3)	-
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	-	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	-	28 (17.4)	-	9 (13.2)	-
Diarrhea	33 (13.9)	-	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	-
Aspartate aminotransferase increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	-
Headache	29 (12.2)	4 (1.7)	26 (11.4)	-	18 (11.2)	-	8 (11.8)	-
Constipation	29 (12.2)	-	15 (6.6)	-	10 (6.2)	-	5 (7.4)	-
Hot flush	27 (11.4)	-	19 (8.3)	-	15 (9.3)	-	4 (5.9)	-
Dyspepsia	24 (10.1)	-	6 (2.6)	-	4 (2.5)	-	2 (2.9)	-
Alanine aminotransferase increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	-	6 (8.8)	1 (1.5)

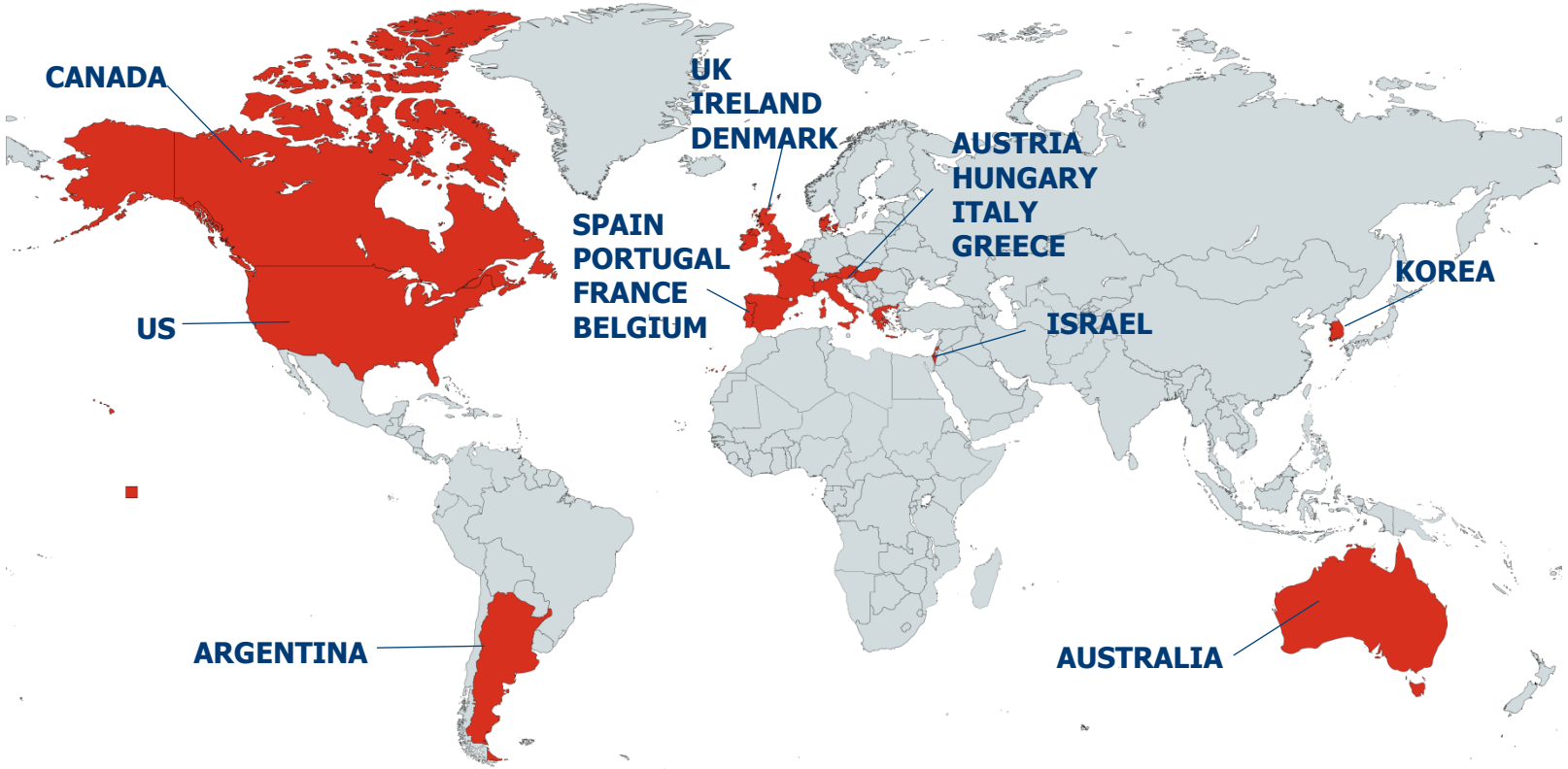
Conclusions

- Elacestrant is the first oral SERD that demonstrated a statistically significant and clinically meaningful improvement in PFS vs SOC endocrine therapy in a randomized global phase 3 study in men and postmenopausal women with ER+/HER2- mBC in the 2nd/3rd-line post-CDK4/6i setting:
  - 30% reduction in the risk of progression or death with elacestrant vs SOC in all patients (HR=0.697 [95% CI: 0.552 – 0.880]; *P*=0.0018)
  - 45% reduction in the risk of progression or death with elacestrant vs SOC in patients with *mESR1* (HR=0.546 [95% CI: 0.387 – 0.768]; *P*=0.0005)
  - Higher PFS rate at 6 and 12 months with elacestrant vs SOC endocrine therapy
  - Results with elacestrant vs fulvestrant were also consistent
- Elacestrant was well tolerated with a predictable and manageable safety profile consistent with other endocrine therapies.

Conclusions

- Final Overall Survival analysis of elacestrant vs SOC endocrine therapy expected next year.
- Clinically, elacestrant has the potential to become the new treatment option in the studied patient population.
- Further elacestrant combinations in earlier lines and with other targeted therapies, including CDK4/6 and mTOR inhibitors, are ongoing/planned for patients with ER+/HER2- breast cancer.

Acknowledgements



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