Subgroup analysis of patients with no prior chemotherapy in EMERALD: A phase 3 trial evaluating elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC)

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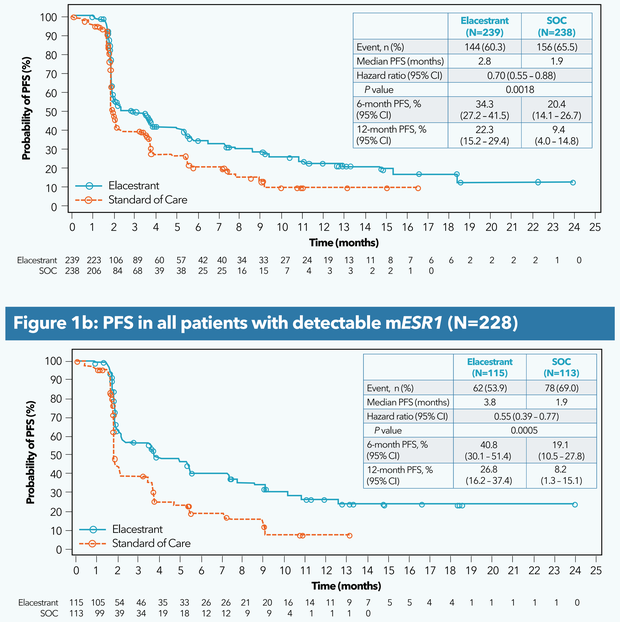
Kaklamani V,[1] Bardia A,[2] Aftimos P,[3] Cortes J,[4] Lu J,[5] Neven P,[6] Streich G,[7] Montero AJ,[8] Forget F,[9] Mouret-Reynier MA,[10] Sohn JH,[11] Taylor D,[12] Harnden KK,[13] Khong H,[14] Kocsis J,[15] Dalenc F,[16] Dillon P,[17] Tonini G,[18] Grzegorzewski KJ,[19] Bidard FC[20]

[1]University of Texas Health Sciences Center, Houston, TX; [2]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [3]Institut Jules Bordet – Université Libre de Bruxelles, Brussels, Belgium; [4]International Breast Cancer Center (IBCC), Quiron Group, Barcelona, Spain; [5]University Of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [6]Universitaire Ziekenhuizen (UZ) – Leuven Cancer Institute, Leuven, Belgium; [7]Centro Médico Austral, Buenos Aires, Argentina; [8]University Hospitals Seidman Cancer Center – Case Western Reserve University, Cleveland, OH, USA; [9]Centre Hospitalier de l'Ardenne – Site de Libramont, Libramont-Chevigny, Belgium; [10]Centre Jean Perrin, Clermont-Ferrand, France; [11]Yonsei Cancer Center, Yonsei University Health System – Medical Oncology, Seoul, Republic of Korea; [12]Université catholique de Louvain, CHU UCL Namur – Site Sainte-Elisabeth, Namur, Belgium; [13]Inova Schar Cancer Institute, Fairfax, Virginia; [14]Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [15]Bács-Kiskun Megyei Kórház, Kecskemét, Hungary; [16]Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France; [17]University of Virginia Cancer Center, Charlottesville, VA, USA; [18]Menarini Group, Florence, Italy; [19]Stemline Therapeutics/Menarini Group, New York, NY, USA; [20]Institut Curie, Paris and Saint Cloud, France

BACKGROUND

- Endocrine therapy, with aromatase inhibitor (AI) or fulvestrant, plus cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is the recommended first-line treatment of estrogen receptor-positive (ER+)/HER2- mBC.[1-3]
- Subsequent disease progression is associated with endocrine resistance, including the development of *ESR1* mutations (*mESR1*).[4]
- Treatment guidelines recommend use of sequential endocrine therapy before chemotherapy, in the absence of visceral crisis or until all endocrine therapy (ET) options have been exhausted.[1-3,5]
- Standard single-agent endocrine therapy (eg, fulvestrant) in patients who have received prior CDK4/6i or mTOR inhibitor is associated with poor median progression-free survival (~2 months),[6-9] highlighting a major unmet need for patients with ER+/HER2- mBC.
- 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.[10]
- In a phase 3 study of elacestrant in postmenopausal women with ER+/HER2- mBC (EMERALD), elacestrant significantly reduced the risk of disease progression or death by 30% in all patients and by 45% in patients with *ESR1* mutation (Figure 1a & b).[11]
- In this analysis, we compared PFS between elacestrant and SOC in patients without prior chemotherapy in the metastatic setting.

Figure 1a: PFS in all patients (ITT) (N=477)

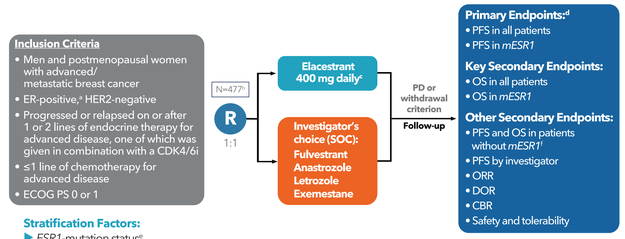


	Elacestrant (N=239)	SOC (N=238)
Event, n (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.8	1.9
Hazard ratio (95% CI)	0.70 (0.55 – 0.88)	
P value	0.0018	
6-month PFS, % (95% CI)	34.3 (27.2 – 41.5)	20.4 (14.1 – 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 – 29.4)	9.4 (4.0 – 14.8)

Figure 1b: PFS in all patients with detectable m*ESR1* (N=228)

	Elacestrant (N=115)	SOC (N=113)
Event, n (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.8	1.9
Hazard ratio (95% CI)	0.55 (0.39 – 0.77)	
P value	0.0005	
6-month PFS, % (95% CI)	40.8 (30.1 – 51.4)	19.1 (10.5 – 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 – 37.4)	8.2 (1.3 – 15.1)

EMERALD STUDY DESIGN[12]



Stratification Factors:
- *ESR1*-mutation status[e]
- Prior treatment with fulvestrant
- Presence of visceral metastases

SOC guidance recommended use of a different ET than previously received (ie, fulvestrant recommended for patients who had not previously received fulvestrant, and selection of AI was based on prior AI therapy)

[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry (local laboratory); [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 cell-free circulating DNA analysis using the Guardant360® CDx (Guardant Health, Redwood City, CA); [f]Restaging CT scans every 8 weeks.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; *mESR1*, *ESR1*-mutant breast cancer population); PFS, progression-free survival; R, randomized; SOC, standard of care.

RESULTS

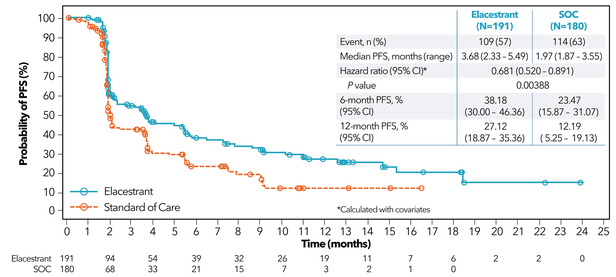
Baseline demographic and disease characteristics

Among the 477 patients enrolled in the trial, 77.8% (n=371) had not received prior chemo for mBC

Parameter	Elacestrant All (N=191)	Elacestrant *mESR1* (N=89)	SOC All (N=180)	SOC *mESR1* (N=81)
Median age, years (range)	64 (28-89)	64 (28-89)	64 (35-83)	63 (35-83)
Gender, n %				
Female	185 (96.9)	89 (100)	180 (100)	81 (100)
Male	6 (3.1)	0	0	0
ECOG PS, n (%)				
0	111 (58.1)	48 (53.9)	100 (55.6)	44 (54.3)
1	80 (41.9)	41 (46.1)	180 (44.4)	37 (45.7)
Visceral metastasis*, n (%)	127 (66.5)	62 (69.7)	125 (69.4)	61 (75.3)
Bone-only disease, n (%)	32 (16.8)	10 (11.2)	25 (13.9)	10 (12.3)
Prior adjuvant therapy, n (%)	129 (67.5)	50 (56.2)	114 (63.3)	51 (63.0)
Prior CDK4/6 inhibitor, n (%)	191 (100)	89 (100)	180 (100)	81 (100)
Number of prior lines of endocrine therapy,** n (%)				
1	103 (53.9)	56 (62.9)	115 (63.9)	56 (69.1)
2	88 (46.1)	33 (37.1)	65 (36.1)	25 (30.9)
Number of prior lines of chemotherapy,** n (%)				
0	191 (100)	89 (100)	180 (100)	81 (100)

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

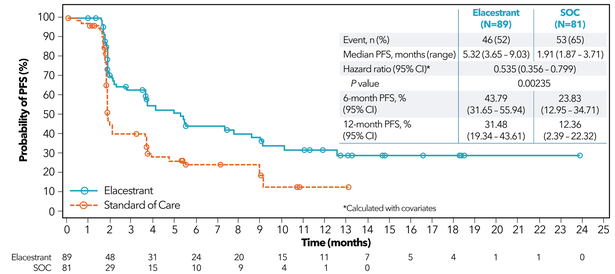
PFS: elacestrant vs SOC in all patients without prior chemotherapy (N=371)



	Elacestrant (N=191)	SOC (N=180)
Event, n (%)	109 (57)	114 (63)
Median PFS, months (range)	3.68 (2.33 - 5.49)	1.97 (1.87 – 3.55)
Hazard ratio (95% CI)*	0.681 (0.520 - 0.891)	
P value	0.00388	
6-month PFS, % (95% CI)	38.18 (30.00 – 46.36)	23.47 (15.87 – 31.07)
12-month PFS, % (95% CI)	27.12 (18.87 – 35.36)	12.19 (5.25 - 19.13)

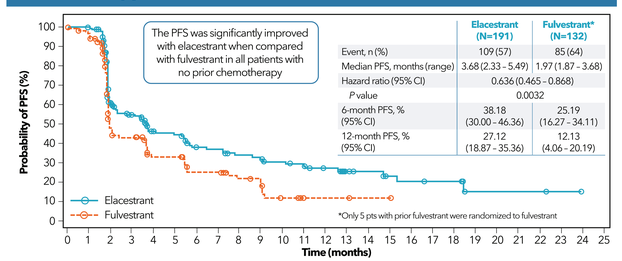
Among patients with ER+/HER2– mBC without prior chemotherapy, elacestrant significantly prolonged PFS compared to SOC

PFS: elacestrant vs SOC in patients with *mESR1* without prior chemotherapy (N=170)



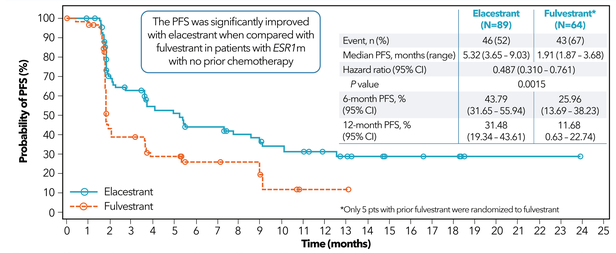
	Elacestrant (N=89)	SOC (N=81)
Event, n (%)	46 (52)	53 (65)
Median PFS, months (range)	5.32 (3.65 – 9.03)	1.91 (1.87 – 3.71)
Hazard ratio (95% CI)*	0.535 (0.356 – 0.799)	
P value	0.00235	
6-month PFS, % (95% CI)	43.79 (31.65 – 55.94)	23.83 (12.95 – 34.71)
12-month PFS, % (95% CI)	31.48 (19.34 – 43.61)	12.36 (2.39 – 22.32)

PFS: elacestrant vs fulvestrant in all patients without prior chemotherapy (N=323)



	Elacestrant (N=191)	Fulvestrant* (N=132)
Event, n (%)	109 (57)	85 (64)
Median PFS, months (range)	3.68 (2.33 - 5.49)	1.97 (1.87 - 3.68)
Hazard ratio (95% CI)	0.636 (0.465 – 0.868)	
P value	0.0032	
6-month PFS, % (95% CI)	38.18 (30.00 - 46.36)	25.19 (16.27 - 34.11)
12-month PFS, % (95% CI)	27.12 (18.87 - 35.36)	12.13 (4.06 - 20.19)

PFS: elacestrant vs fulvestrant in patients with *mESR1* without prior chemotherapy (N=153)



	Elacestrant (N=89)	Fulvestrant* (N=64)
Event, n (%)	46 (52)	43 (67)
Median PFS, months (range)	5.32 (3.65 - 9.03)	1.91 (1.87 - 3.68)
Hazard ratio (95% CI)	0.487 (0.310 - 0.761)	
P value	0.0015	
6-month PFS, % (95% CI)	43.79 (31.65 - 55.94)	25.96 (13.69 - 38.23)
12-month PFS, % (95% CI)	31.48 (19.34 - 43.61)	11.68 (0.63 - 22.74)

Treatment-emergent adverse events (≥10% in either arm)

	Elacestrant N=189, n (%)		SOC: Total N=175, n (%)		SOC: Fulvestrant N=129, n (%)		SOC: Aromatase inhibitor N=46, n (%)	
Preferred term	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	64 (33.9%)	2 (1.1)	34 (19.4%)	–	21 (16.3%)	–	13 (28.3%)	–
Fatigue	36 (19.0%)	–	28 (16%)	–	21 (16.3%)	–	7 (15.2%)	–
Vomiting	33 (17.5%)	1 (0.5)	12 (6.9%)	–	9 (7.0%)	–	3 (6.5%)	–
Arthralgia	28 (14.8%)	–	30 (17.1%)	–	23 (17.8%)	–	7 (15.2%)	–
Decreased appetite	25 (13.2%)	1 (0.5)	13 (7.4%)	–	9 (7.0%)	–	4 (8.7%)	–
Back pain	25 (13.2%)	1 (0.5)	14 (8.0%)	–	10 (7.8%)	–	4 (8.7%)	–
Diarrhea	24 (12.7%)	–	19 (10.9%)	–	13 (10.1%)	–	6 (13.0%)	–
Headache	24 (12.7%)	1 (0.5)	21 (12%)	–	15 (11.6%)	–	6 (13.0%)	–
Hot flush	24 (12.7%)	–	15 (8.6%)	–	11 (8.5%)	–	4 (8.7%)	–
AST increased	23 (12.2%)	–	21 (12%)	–	16 (12.4%)	–	5 (10.9%)	–
Constipation	22 (11.6%)	–	11 (6.3%)	–	7 (5.4%)	–	4 (8.7%)	–
Dyspepsia	19 (10.1%)	–	5 (2.9%)	–	4 (3.1%)	–	1 (2.2%)	–

- Key treatment-related adverse events (AEs) in the no prior chemotherapy elacestrant group were nausea (25.9%), fatigue (12.7%), and hot flush (11.1%). There were no treatment-related deaths in either group.

CONCLUSIONS

- Among patients with ER+/HER2– mBC without prior chemotherapy, elacestrant significantly prolonged PFS compared to SOC endocrine therapy and showed favorable outcomes in this subgroup.
  - 31% reduction in the risk of progression or death with elacestrant vs SOC in all patients (HR=0.681 [95% CI: 0.520 – 0.891]; P=0.00388) and prolonged median PFS (3.68 vs 1.97 months).
  - 46% reduction in the risk of progression or death with elacestrant vs SOC in patients with *mESR1* (HR=0.535 [95% CI: 0.356 – 0.799]; P=0.00235) and prolonged median PFS (5.32 vs 1.91 months).
- In exploratory subgroup analyses, elacestrant significantly reduced the risk of progression or death and prolonged median PFS vs fulvestrant in all patients (HR=0.636 [95% CI: 0.465-0.868]; mPFS 3.68 vs 1.97 months), and in patients with *mESR1* (HR=0.487 (95% CI: 0.310-0.761; mPFS 5.32 vs 1.91 months).
- Elacestrant had a manageable safety profile consistent with other endocrine therapies.
- Final overall survival analysis of elacestrant vs SOC endocrine therapy expected late 2022/early 2023.
- 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.

REFERENCES:
1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated December 20, 2021. Accessed March 24, 2022; **2.** Gennari A, et al. *Ann Oncol*. 2021;32:1475-1495; **3.** Burstein HJ, et al. *J Clin Oncol*. 2021;39:3959-3977; **4.** Jeselsohn R, et al. *Clin Cancer Res*. 2014;20:1757-1767; **5.** Moy B, et al. *J Clin Oncol*. 2021;39:3938-3958; **6.** Lindeman GJ, et al. *J Clin Oncol*. 2021;39 (suppl 15); abstr 1004; **7.** Turner NC, et al. *Lancet Oncol*. 2020;21:1296-1308; **8.** Di Leo A, et al. *Lancet Oncol*. 2018;19:87-100; **9.** André F, et al. *N Engl J Med*. 2019;380:20:1929-1940; **10.** Bihani T, et al. *Clin Cancer Res*. 2017;23:4793-4804; **11.** Bidard FC, et al. *J Clin Oncol*. 2022: In press.

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Contact Kaklamani@uthscsa.edu with questions.