Elacestrant vs Everolimus + Exemestane in Patients with ER+/HER2- Advanced/Metastatic Breast Cancer (a/mBC) and *ESR1*-mutated Tumors with ≥12 Months Prior Endocrine Therapy + CDK4/6 inhibitor: Combining Real-World and Clinical Trial Data

Presented at ISPOR EU 2024

Acceptance Code: RWD130

Felizzi F,[1] Fenu E,[1] Kloss S,[1] Laizet V,[2] Le Nouveau P,[2] Moreno S,[1]

[1]Menarini Group, Florence, Italy; [2]Amaris Consulting, Geneva, Switzerland

BACKGROUND

- Patients with ER+/HER2- a/mBC harboring *ESR1* mutations are associated with poorer survival outcomes.[1-5]
- *ESR1* mutations represent a type of acquired resistance that usually emerges in up to 40-50% of patients with ER+/HER2- a/mBC after endocrine therapy (ET) in the metastatic setting.[5-14]
- Elacestrant is the first oral selective estrogen receptor degrader (SERD) approved in ER+/HER2- a/mBC that targets *ESR1*-mutated tumors.[15,16]
- In the randomized phase 3 EMERALD trial, elacestrant significantly prolonged progression-free survival (PFS) with manageable safety versus standard-of-care (SOC) ET in patients with ER+/ HER2-, *ESR1*-mutated tumors, following ET plus a cyclin-dependent kinase 4/6 inhibitor (ET+CDK4/6i).[17,18]
- Patients with *ESR1*-mutated tumors had a 45% reduction in risk of progression or death with elacestrant versus SOC ET (HR = 0.55; 95% CI, 0.39-0.77; p = 0.0005).[17,18]
- In those patients with *ESR1*-mutated tumors who received prior ET+CDK4/6i ≥12 months, the median PFS for elacestrant compared to SOC ET was 8.6 versus 1.9 months (HR = 0.41; 95% CI, 0.26-0.63).[17,18]
- Longer exposure to prior ET+CDK4/6i may help identifying patients with *ESR1*-mutated tumors who remain endocrine-sensitive to elacestrant, enabling ET sequencing in the second line before other targeted therapies and drug combinations, and may delay chemotherapy-based regimens, including antibody-drug conjugates.
- This analysis was performed to compare the effectiveness of elacestrant vs everolimus + exemestane in patients with ER+/HER2- a/mBC and *ESR1*-mutated tumors who received prior ET+CDK4/6i ≥12 months using clinical trial data and real-world data (RWD).

METHODS

- In the absence of head-to-head clinical trials, an unanchored matching-adjusted indirect comparison (MAIC) was performed leveraging data from the phase 3 EMERALD trial with elacestrant and RWD with everolimus + exemestane, while adjusting for heterogeneity in population and study types
- Data on median PFS (mPFS), median overall survival (mOS), and baseline characteristics were collected from the EMERALD trial for elacestrant and US Flatiron clinico-genomic database (CGDB) for everolimus + exemestane.
- The prognostic factors (PFs) and treatment effect modifiers (TEMs), deemed relevant by medical experts, included factors such as age, prior ET lines, and prior chemotherapy administered in the advanced or metastatic setting.
- The matching was performed following a two-step approach:
  - First, patients from Flatiron real-world data (RWD) were selected to match as much as possible the inclusion/exclusion criteria as per EMERALD trial protocol.[17]
  - Second, populations were matched using the following retrievable PFs and TEMs: age, lines of prior ET and prior chemotherapy received in an advanced or metastatic setting.
- Data collection at specific visit times in EMERALD resulted in an initial drop in the mPFS Kaplan-Meier curves, highlighting possible endocrine resistance for some patients in the second- or third-line setting. This initial drop in the mPFS curves is a pattern not observed in RWD, suggesting a difference in the frequency of visits in the real-world setting.
- The proportional hazard assumption was thus not met in the early months, but held thereafter, thereby making the interpretation of MAIC results and their potential biases more difficult.

METHODS, Cont.

- The reweighted distribution of the estimated weights did not highlight outliers or high weights, and the effective sample size covered was 85.3% of the initial sample size (66.5 of the 78 initial elacestrant patients analyzed), indicating good matching quality (**Table 1**).

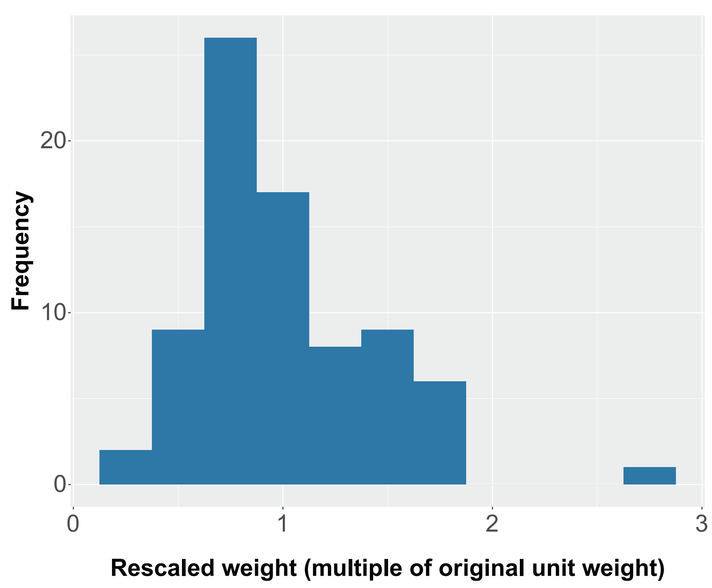
Table 1. Pre- and post-matching populations characteristics

	Elacestrant– Pre-weighting	Elacestrant– Post-weighting	EVE+EXE
Sample size/effective sample size (ESS)			
N/ESS (% initial population)	78	66.5 (85.3%)	32
Age*			
Mean (SD)	64.7 (10.8)	66.0 (9.2)	66.0 (9.2)
Lines of prior ET, n (%)*			
1	49 (62.8)	56.3	18 (56.3)
2	29 (37.2)	43.8	14 (43.8)
Prior CT in adv/metastatic setting*			
N (%) Yes	8 (10.3)	18.8	6 (18.8)

*Variables adjusted for in the MAIC

- Original elacestrant population had a higher percentage of patients with only 1 prior line of ET (63% vs 56%) and lower proportion of patients with previous chemotherapy in the a/mBC setting (10% vs 19%) respectively. After matching, the population characteristics were balanced.
- Weights were estimated for elacestrant patients through logistic regression and method of moments (**Figure 1**)[19] and were used to generate adjusted population characteristics and outcomes. Weighted HR and 95% confidence interval (CI) of the comparison of elacestrant vs everolimus + exemestane were generated for both mPFS and mOS.

Figure 1. Distribution of weights from the matching



RESULTS

- High-quality population matching was achieved, leading to balanced populations in PFs and TEMs for the comparison and high coverage of the original elacestrant cohort.
- The MAIC results showed a significant reduction in the hazard of progression.
- The analysis included 78 elacestrant EMERALD patients and 32 EVE+EXE RWD patients who received prior ET+CDK4/6i ≥12 months (**Table 1**).

Table 2. Pre-and post-matching survival data

	Elacestrant	Elacestrant post-matching	EVE+EXE
mPFS, months	8.61	7.39	4.57
mOS, months	27.73	27.73	17.97

- Matched estimated mPFS and OS Kaplan-Meier curves are shown in **Figures 2** and **3**.
- The matched mPFS showed a HR of 0.59, 95% CI [0.36, 0.96], and OS HR=0.64 [0.35, 1.16] for elacestrant versus everolimus + exemestane.

Figure 2. PFS in patients with ER+/HER2- a/mBC and *ESR1*-mutated tumors who received prior ET+CDK4/6i ≥12 months and treated with elacestrant or everolimus + exemestane

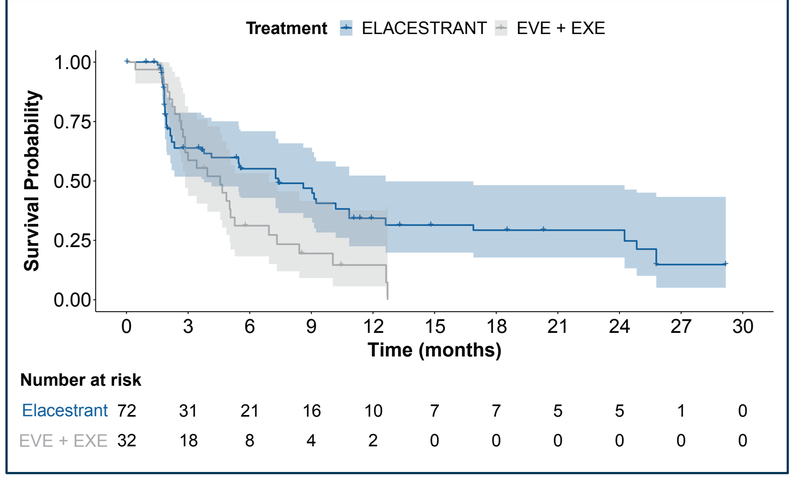
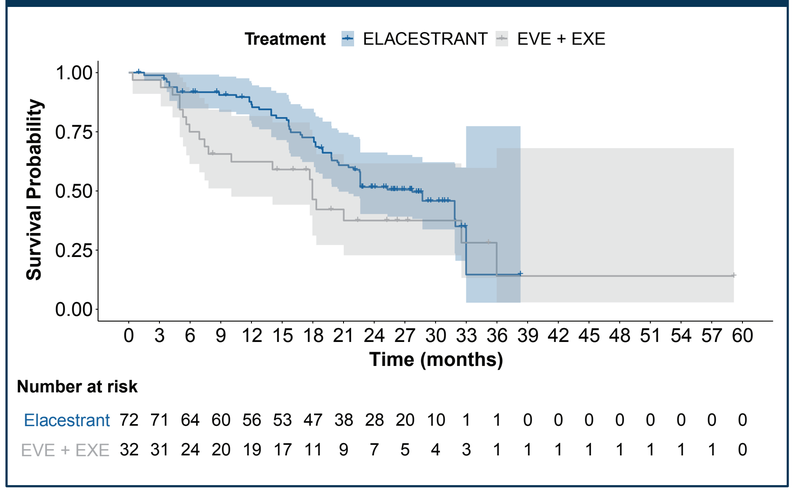


Figure 3. OS in patients with ER+/HER2- a/mBC and *ESR1*-mutated tumors who received prior ET+CDK4/6i ≥12 months and treated with elacestrant or everolimus + exemestane



CONCLUSIONS

These findings indicate that **elacestrant is associated with a significant 41% reduction in the risk of progression or death compared to everolimus + exemestane** in patients with ER+/HER2- a/mBC and *ESR1*-mutated tumors who received prior ET+CDK4/6i ≥12 months

- This analysis enabled an indirect comparison between elacestrant and everolimus + exemestane in the absence of head-to-head comparisons, while adjusting for population heterogeneity.
- A high quality of matching was successfully achieved, ensuring robust comparability between the populations. This was accomplished despite the absence of certain factors, such as the number of metastatic sites, bone/ visceral metastases, and time since the original diagnosis.
- This indirect treatment comparison provides valuable insight into the relative efficacy in patients treated with elacestrant versus everolimus + exemestane in ER+/HER2- a/mBC and *ESR1*-mutated tumors who received prior ET+CDK4/6i ≥12 months, in the absence of head-to-head clinical trials.

ABBREVIATIONS

a/mBC, advanced/metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CGDB, clinico-genomic database; CI, confidence interval; ER, estrogen receptor; ESS, effective sample size; *ESR1*, estrogen receptor 1; ET, endocrine therapy; EVE, Everolimus; EXE, exemestane; HER2, human epidermal growth factor 2; MAIC, matching-adjusted indirect comparison; OS, overall survival; PF, prognostic factor; PFS, progression-free survival; RWD, real-world data; SERD, selective estrogen receptor degrader; SOC, standard of care; TEM, treatment effect modifier; US, United States.

REFERENCES

1. Bardia A, et al. *N Engl J Med*. 2018;379:1946-53. **2.** Williams MM, et al. *Cancer Res*. 2021 81:732-746. **3.** Jeselsohn R, et al. *Nat Rev Clin Oncol*. 2015;12:573-583. **4.** Jeselsohn R, et al. *Cancer Cell*. 2018;33:173-186. **5.** Brett JO. *Breast Cancer Res*. 2021;23:85. **6.** Bidard FC, et al. *Lancet Oncol*. 2022;23(11):1367-1377. **7.** Santiago Novello RG, et al. ESMO Open. 2023;8(suppl 4):104409(abstr 220P). **8.** Jhaveri K, et al. *Ann Oncol*. 2023;34(suppl_2):S334-S390. **9.** Lin N, et al. *Ann Oncol*. 2023;34 (suppl_2):S334-S390. **10.** Bhave MA, et al. *Breast Cancer Res Treat*. 2024. doi:10.1007/s10549-024-07376-w. **11.** Clatot F, et al. *Breast Cancer Res*. 2020;22(1):56. **12.** Chandarlapaty S, et al. *JAMA Oncol*. 2016;2(10):1310-1315. **13.** Turner NC, et al. *Clin Cancer Res*. 2020;26(19):5172-5177. **14.** Zundelevich A, et al. *Breast Cancer Res*. 2020;22(1):16. **15.** Orserdu (elacestrant). US Package Insert. Stemline Therapeutics. 2023. **16.** Orserdu (elacestrant). SmPC 2024. **17.** Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-3256. **18.** Bardia A, et al. *Clin Cancer Res*. 2024;30(19):4299-4309. **19.** Signorovitch JE, et al. *PharmacoEconomics*. 2010;28(10):935-45.