Elacestrant combinations in patients with estrogen receptor-positive (ER+), HER2-negative (HER2-) locally advanced or metastatic breast cancer (mBC): Update from ELEVATE, a phase 1b/2, open-label, umbrella study

Presented at SABCS® 2024
December 10-13, 2024
Poster # PS7-06

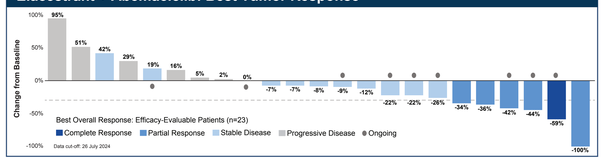
Hope S. Rugo,[1] Sara M. Tolaney,[2] Nancy Chan,[3] Erika Hamilton,[4] Marina N. Sharifi,[5] Kristine J. Rinn,[6] Wassim McHayleh,[7] Rinat Yerushalmi,[8] Neelima Vidula,[9] Joyce O'Shaughnessy,[10] Giuseppe Curigliano,[11] Javier Cortés,[12] Paula Muñoz Romero,[13] Bartomeu Piza Vallespir,[13] Kathy Puyana Theall,[14] Alessandro Paoli,[13] Monica Binaschi,[13] Tomer Wasserman,[13] Virginia Kaklamani[15]

[1]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]NYU Langone Health, New York, NY, USA; [4]Sarah Cannon Research Institute, Nashville, TN, USA; [5]University of Wisconsin, Madison, WI, USA; [6]Cancer Care Northwest, Spokane, WA, USA; [7]Adventhealth Cancer Institute, Orlando, FL, USA; [8]Rabin Medical Center, Petah Tikva, Israel; [9]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [10]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA; [11]Istituto Europeo di Oncologia, IRCCS, and University of Milano, Milano, Italy; [12]International Breast Cancer Center (IBCC), Quironsalud Group, Barcelona, Spain; [13]Menarini Group, Florence, Italy; [14]Menarini Group, New York, NY, USA; [15]University of Texas Health Sciences Center San Antonio, San Antonio, TX, USA

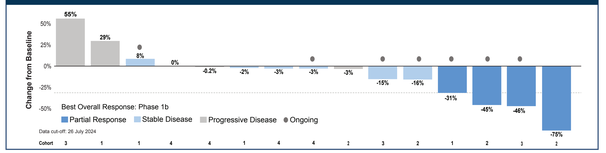
BACKGROUND

- Endocrine therapy (ET) + CDK4/6 inhibitor (CDK4/6i) is the mainstay for the management of ER+/HER2− mBC as first-line therapy.[1-3] However, tumors eventually become resistant to ET, leading to disease progression.[4] Resistance mechanisms include intrinsic alterations in the Cell Cycle or PI3K/AKT/mTOR pathway, or acquired *ESR1* mutations, which occur in up to 50% of patients after initial ET in the metastatic setting.[5-18]
- In the phase 3 EMERALD trial, single-agent elacestrant significantly prolonged median PFS with a manageable safety profile vs. SOC ET, leading to the first oral SERD approved in ER+/HER2− mBC that targets *ESR1*-mutated tumors.[19]
  - Patients with *ESR1*-mutated tumors had a 45% reduction in risk of progression or death with elacestrant vs SOC ET (HR=0.55; 95% CI: 0.39–0.77; *P*=0.0005).[19]
  - In patients with ≥12 months of prior ET + CDK4/6i and *ESR1*-mutated tumors, median PFS with elacestrant was 8.6 months vs 1.9 months with SOC ET (HR=0.41; 95% CI, 0.26-0.63).[20]
- **The rationale for combining elacestrant with PI3K/AKT/mTOR or CDK4/6 inhibitors is to overcome different resistance mechanisms and enable an all-oral regimen.**
- **Efficacy data with the following combinations demonstrated antitumor activity.**[21-23]
  - **Elacestrant + abemaciclib: mPFS 8.7 months, ORR 26%, and CBR 70%.**[23]
  - **Elacestrant + everolimus: ORR 22% and CBR 72%.**[22]

Elacestrant + Abemaciclib: Best Tumor Response[22]



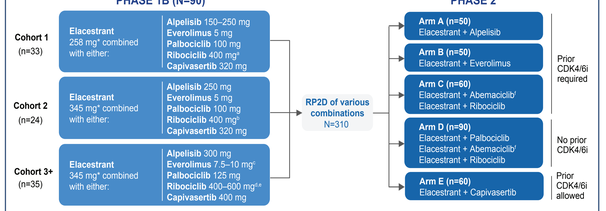
Elacestrant + Everolimus: Best Tumor Reduction in Patients With Prior ET+CDK4/6i[23]



- **This analysis reports updated safety data for the various elacestrant combinations: abemaciclib, everolimus, palbociclib, ribociclib, capivasertib, and alpelisib from the ongoing ELEVATE study.**

METHODS

ELEVATE Study Design



PHASE 1B OBJECTIVE

Primary: Determine RP2D of elacestrant in combination with each of the other study drugs

PHASE 2 OBJECTIVES

Primary: Evaluate the PFS of elacestrant in combination with each of the other study drugs

Secondary: Evaluate efficacy and safety of elacestrant in combination with each of the other study drugs

NCT05563220

Elacestrant 86 mg is equivalent to 100 mg elacestrant hydrochloride; elacestrant 172 mg is equivalent to 200 mg elacestrant hydrochloride; elacestrant 258 mg is equivalent to 300 mg elacestrant hydrochloride; and elacestrant 345 mg is equivalent to 400 mg elacestrant hydrochloride; †Elacestrant 86 mg + ribociclib (cohort 1); ‡Elacestrant 172 mg* + ribociclib (cohort 2); ‡Elacestrant 345 mg* + everolimus 7.5 mg (cohort 4); ‡Elacestrant 258 mg* + ribociclib 400 mg (cohort 3); ‡Elacestrant 172 mg* + ribociclib 600 mg (cohort 4); +The RP2D for the combination of elacestrant and abemaciclib is being evaluated in the ongoing ELECTRA trial (NCT05386108). +, additional Cohort 4; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; PFS, progression-free survival; RP2D, recommended phase 2 dose.

Eligibility Criteria

Key Inclusion Criteria

- Women or men age ≥18 years
- Female patients may be post-, pre-*, or perimenopausal*
- Histopathologic or cytologic confirmation of ER+, HER2-breast cancer as per the ASCO/CAP guidelines
- ≥1 measurable lesion as per RECIST v1.1 or a mainly lytic bone lesion
- ECOG PS 0–1
- **1-2 Prior lines of ET, one with CDK4/6i (alpelisib,† everolimus, palbociclib, ribociclib, and abemaciclib):‡**
  - **Alpelisib combination:** *PIK3CA*-mut by local lab
  - **Capivasertib combination:§** *PIK3CA/AKT1/PTEN*-alteration as detected by an approved test (local result)
    - 1-2 prior hormonal therapies in the advanced or metastatic setting, or radiological evidence of BC recurrence or progression ≤12 months from the end of adjuvant treatment with ET. Prior CDK4/6i is allowed
- Phase 2 is the same as Phase 1b, except no prior CDK4/6i is allowed for Arm D

Key Exclusion Criteria

- Active or newly diagnosed central nervous system (CNS) metastases, including meningeal carcinomatosis
- Advanced, symptomatic visceral spread with risk of life-threatening complications in the short-term
- Prior chemotherapy in the advanced or metastatic setting
- Prior therapy with elacestrant or other investigational compounds in the advanced or metastatic setting
  - Prior treatment with fulvestrant is allowed
- **Alpelisib combination:** Type 1 diabetes or uncontrolled type 2 diabetes¶
- **Ribociclib combination:** QTcF values ≥450 msec; patients who are at significant risk of developing QTc prolongation;† currently receiving or received drugs known to prolong QT interval ≤14 days or 5 half-lives, whichever is shorter, before the first dose of trial therapy
- **Capivasertib combination:** Clinically significant abnormalities of glucose metabolism¶

*Must be concurrently receiving a LHRH agonist at least 4 weeks before the start of trial therapy and are planning to continue LHRH agonist treatment during the study treatment. †Excludes prior therapy with alpelisib or any other PI3Ki. ‡Excludes prior treatment in the advanced setting with the companion drug. §Excludes prior therapy with AKTi, PI3Ki and mTORi. ¶Fasting plasma glucose level of >140 mg/dL [7.7 mmol/L] or HbA1c level >6.4%. ¶Patients with long QT syndrome; patients with uncontrolled or significant cardiac disease including recent (6 mo) myocardial infarction, congestive heart failure, unstable angina, and brady arrhythmias; patients with electrolyte abnormalities. ¶Defined by any of the following: patients with diabetes mellitus type 1, patients with diabetes mellitus type 2 requiring insulin treatment, or patients with HbA1c level of >8.0%

RESULTS

Baseline Characteristics

	Elacestrant + Everolimus n=73	Elacestrant + Alpelisib n=9	Elacestrant + Capivasertib n=7	Elacestrant + Palbociclib n=19	Elacestrant + Ribociclib n=24	Elacestrant + Abemaciclib n=30
Median age, years (range)	58 (30-83)	56 (49-85)	66 (43-78)	62 (32-73)	67 (45-85)	61 (29-84)
Gender at birth, n (%)						
Female	73 (100)	9 (100)	7 (100)	18 (95)	24 (100)	30 (100)
Male	0	0	0	1 (5)	0	0
ECOG PS, n (%)						
0	41 (56)	6 (67)	4 (57)	14 (74)	16 (67)	20 (67)
1	31 (43)	3 (33)	3 (43)	5 (26)	8 (33)	10 (33)
Visceral metastasis,* n (%)	67 (92)	7 (78)	6 (86)	18 (95)	23 (96)	22 (73)
Mutations,† n (%)						
ESR1	30/67 (45)	3/9 (33)	2/4 (50)	5/14 (36)	11/22 (50)	14/28 (50)
PIK3CA	29/67 (43)	9/9 (100)‡	7/7 (100)§	2/14 (14)	6/22 (27)	9/28 (32)
Primary endocrine resistance,¶ n (%)	13 (18)	3 (33)	2 (29)	4 (21)	1 (4)	2 (7)
Median number of prior therapies for adv/mBC, n (range)	1 (1-4)	2 (1–3)	1 (1-2)	1 (1-3)	1 (1-3)	1 (1-2)
Prior CDK4/6i for adv/mBC, n (%)	73 (100)	9 (100)	6 (86)	15 (79)	24 (100)	30 (100)
Number of prior lines of ET for adv/mBC, n (%)						
1	49 (67)	6 (67)	6 (86)	14 (74)	18 (75)	25 (83)
2+	23 (31)	3 (33)	0	4 (21)	6 (25)	5 (17)
Type of prior ET, n (%)						
Fulvestrant	36 (49)	3 (33)	2 (29)	9 (47)	13 (54)	13 (43)
AI	54 (74)	7 (78)	4 (57)	12 (63)	18 (75)	21 (70)
Tamoxifen	6 (8)	2 (22)	0	1 (5)	1 (4)	1 (3)
Tamoxifen/AI	5 (7)	2 (22)	0	1 (5)	0	1 (3)

Includes lung, liver, brain, pleural, and peritoneal involvement; †Mutation data not available for all patients at time of data analysis; ‡PIK3CA mutation per local assessment; §PI3K/AKT1/PTEN alteration per local assessment. ¶Relapse within the first two years of adjuvant on ET or progressive disease within the first six months of first-line ET for advanced breast cancer

AI, aromatase inhibitor; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; adv/mBC, advanced or metastatic breast cancer.

Data cut-off: 15 OCT 2024

Most Common TEAEs with Elacestrant + Abemaciclib (RP2D)*

	Arm C – RP2D (n=30) Elacestrant 345 mg + Abemaciclib 150 mg (BID)	
Preferred Term, n (%)	**All Grades**	**Grade 3/4**
Diarrhea	24 (80)	2 (7)
Nausea	19 (63)	2 (7)
Fatigue	13 (43)	2 (7)
Vomiting	13 (43)	0
Constipation	9 (30)	0
Abdominal pain	7 (23)	0
Decreased appetite	7 (23)	0
Anemia	6 (20)	2 (7)
Dizziness	5 (17)	1 (3)
Neutropenia	5 (17)	4 (13)
Rash	5 (17)	0
Weight decreased	5 (17)	1 (3)

Phase 2 for elacestrant 345 mg QD + abemaciclib 150 mg BID combination is ongoing.
Median observational time for PFS was 4.6 months at data cut-off; therefore, mPFS cannot be evaluated.

*TEAE ≥15% at RP2D.
RP2D=Recommended phase 2 dose; TEAEs=Treatment-emergent adverse events.

Data cut-off: 15 OCT 2024

Most Common TEAEs with Elacestrant + Everolimus (RP2D)*

	Cohort 1 (n=6) Elacestrant 258 mg + Everolimus 5 mg		Cohort 2 (n=6) Elacestrant 345 mg + Everolimus 5 mg		Cohort 3 (n=4) Elacestrant 345 mg + Everolimus 10 mg		Cohort 4 + Arm B – RP2D (n=57) Elacestrant 345mg + Everolimus 7.5 mg	
Preferred Term, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Nausea	4 (67)	0	2 (33)	1 (17)	3 (75)	0	29 (51)	1 (2)
Diarrhea	4 (67)	0	3 (50)	1 (17)	1 (25)	1 (25)	23 (40)	3 (5)
Stomatitis	3 (50)	0	2 (33)	0	1 (25)	0	19 (33)	2 (4)
Dysgeusia	1 (17)	0	1 (17)	0	1 (25)	0	14 (25)	0
Fatigue	3 (50)	1 (17)	3 (50)	1 (17)	1 (25)	0	13 (23)	1 (2)
Vomiting	2 (33)	1 (17)	1 (17)	0	1 (25)	0	12 (21)	0
Rash	1 (17)	0	2 (33)	0	1 (25)	0	11 (19)	0
Mucosal inflammation	1 (17)	0	0	0	1 (25)	1 (25)	11 (19)	0
Neutropenia	2 (33)	2 (33)	0	0	1 (25)	1 (25)	10 (18)	4 (7)
Decreased appetite	2 (33)	0	1 (17)	1 (17)	1 (25)	0	9 (16)	0
Blood cholesterol increased	1 (17)	0	1 (17)	0	1 (25)	0	9 (16)	1 (2)
Hyperglycemia	0	0	1 (17)	0	0	0	9 (16)	1 (2)

Phase 2 for elacestrant 345 mg QD + everolimus 7.5 mg QD combination is ongoing.
Median observational time for PFS for phase 2 was 2.8 months at data cut-off; therefore, mPFS cannot be evaluated.

*TEAE ≥15% at RP2D.
RP2D=Recommended phase 2 dose; TEAEs=Treatment-emergent adverse events.

Data cut-off: 15 OCT 2024

Most Common TEAEs with Elacestrant + Palbociclib (RP2D)*

	Cohort 1 (n=6) Elacestrant 258 mg + Palbociclib 100 mg		Cohort 2 (n=6) Elacestrant 345 mg + Palbociclib 100 mg		Cohort 3 – RP2D (n=7) Elacestrant 345 mg + Palbociclib 125 mg	
Preferred Term, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Neutropenia	2 (33)	2 (33)	4 (67)	1 (17)	4 (57)	3 (43)
Related to palbociclib	2 (33)	2 (33)	3 (50)	0	3 (43)	2 (29)
Related to elacestrant + palbociclib	0	0	1 (17)	1 (17)	1 (14)	1 (14)
Platelet count decreased	1 (17)	0	1 (17)	0	2 (29)	0
White blood cell count decreased	0	0	1 (17)	0	2 (29)	1 (14)
Insomnia	0	0	0	0	2 (29)	0

*TEAE ≥15% at RP2D.
RP2D=Recommended phase 2 dose; TEAEs=Treatment-emergent adverse events.

Data cut-off: 15 OCT 2024

Most Common TEAEs with Elacestrant + Ribociclib*

	Cohort 1 (n=6) Elacestrant 86 mg + Ribociclib 400 mg		Cohort 2 (n=6) Elacestrant 172 mg + Ribociclib 400 mg		Cohort 3 (n=6) Elacestrant 258 mg + Ribociclib 400 mg		Cohort 4 (n=6) Elacestrant 172 mg + Ribociclib 600 mg	
Preferred Term, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Neutropenia	3 (50)	2 (33)	4 (67)	2 (33)	1 (17)	1 (17)	3 (50)	2 (33)
Related to ribociclib	3 (50)	2 (33)	4 (67)	2 (33)	1 (17)	1 (17)	1 (17)	1 (17)
Related to elacestrant + ribociclib	0	0	0	0	0	0	2 (33)	1 (17)
Nausea	1 (17)	0	3 (50)	0	1 (17)	0	3 (50)	0
Vomiting	1 (17)	0	2 (33)	0	2 (33)	0	3 (50)	0
Fatigue	2 (33)	0	2 (33)	0	1 (17)	0	3 (50)	0
Anemia	1 (17)	0	3 (50)	0	1 (17)	0	1 (17)	0
AST increased	0	0	3 (50)	0	1 (17)	1 (17)	1 (17)	0
Blood creatinine increased	0	0	3 (50)	0	0	0	1 (17)	0

*Treatment-emergent adverse events (TEAEs) in ≥35% in any cohort
AST, aspartate aminotransferase

Data cut-off: 15 OCT 2024

Most Common TEAEs with Elacestrant + Capivasertib*

	Cohort 1 (n=7) Elacestrant 258 mg + Capivasertib 320 mg	
Preferred Term, n (%)	**All Grades**	**Grade 3/4**
Fatigue	4 (57)	0
Nausea	4 (57)	0
Vomiting	3 (43)	0
Diarrhea	3 (43)	0

*Treatment-emergent adverse events (TEAEs) in ≥35%.

Data cut-off: 15 OCT 2024

Most Common TEAEs with Elacestrant + Alpelisib*

	Cohort 1 (n=3) Elacestrant 258 mg + Alpelisib 250 mg		Cohort -1 (n=6) Elacestrant 258 mg + Alpelisib 200 mg	
Preferred Term, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Nausea	3 (100)	1 (33)	5 (83)	0
Maculopapular rash	1 (33)	1 (33)	3 (50)	1 (17)
Vomiting	2 (67)	0	2 (33)	0
Blurred vision	0	0	3 (50)	0
Stomatitis	0	0	3 (50)	0
Hyperglycemia	0	0	3 (50)	1 (17)
Dizziness	0	0	3 (50)	0
Fatigue	2 (67)	0	1 (17)	0

*Treatment-emergent adverse events (TEAEs) in ≥35% in any cohort.

Data cut-off: 15 OCT 2024

CONCLUSIONS

- The evaluated elacestrant combinations continue to demonstrate a known safety profile that is consistent with abemaciclib, everolimus, palbociclib, ribociclib, capivasertib, or alpelisib with SOC endocrine therapy.
- At current tested doses, the exposure-safety data support the selection of elacestrant as a potential endocrine therapy backbone due to the absence of drug-drug interactions. The safety profiles support the combinability of elacestrant with abemaciclib, ribociclib, palbociclib, everolimus, alpelisib, and capivasertib given that the co-administration of elacestrant does not increase the risk of associated adverse events:

Combination	TEAEs Adverse Events Summary
Elacestrant 345 mg + abemaciclib 150 mg BID (RP2D)	Diarrhea was mainly grade 1/2, neutropenia was associated mainly with abemaciclib 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.

- Phase 1b combinations for alpelisib, capivasertib, and ribociclib are currently ongoing.
- Elacestrant has the potential to become the ET partner for multiple targeted agents, providing an all-oral treatment option in patients with ER+/HER2- mBC, delaying chemotherapy or ADC-based regimens.

REFERENCES:
1. Zhao M, et al. *Target Oncol.* 2023;18(3):327-358; **2.** Burstein HJ, et al. *J Clin Oncol.* 2021;39(35):3999-3977; **3.** Burstein HJ. *N Engl J Med.* 2020;383(26):2557-2570; **4.** Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247; **5.** Brett JO, et al. *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; **8.** Giavalisco A, et al. *Mol Cancer.* 2023;22(1):138; **9.** Cancer Genome Atlas Network. *Nature.* 2012;490(7418):61-70; **10.** Hartkopf AD, et al. *Breast Care (Basel).* 2020;15:347-54; **11.** Lei JT, et al. *Breast.* 2019;48:S28–S30; **12.** Jeselsohn R, et al. *Clin Cancer Res.* 2014;20(7):1757-1767; **13.** Toy W, et al. *Nat Genet.* 2013;45(12):1439-1445; **14.** Oesterreich S, et al. *Nat Genet.* 2013;45(12):1415-1416; **15.** Lloyd MR, et al. *Ther Adv Med Oncol.* 2022;14:17588359221136904; **16.** Robinson DR, et al. *Nat Genet.* 2013;45:1446-51; **17.** Jhaveri K, et al. *Ann Oncol.* 2023;34(suppl_2):S334-S390; **18.** Bhave MA, et al. SABCS 2023. PO2-16-05; **19.** Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-3256; **20.** Bardia A, et al. Clin Cancer Res. 2024;30:4299-4309; **21.** Rugo HS, et al. ASCO 2024; **22.** Ciruelos EM, et al. *Ann Oncol.* 2024;35(suppl 2):S357-S405; **23.** Rugo HS, et al. *Ann Oncol.* 2024;35(suppl 2):S357-S405; **24.** Cardoso F, et al. *Ann Oncol.* 2020;31(12):1623-1649.