Elacestrant plus abemaciclib (abema) combination in patients (pts) with estrogen receptor-positive (ER+), HER2-negative (HER2-) advanced or metastatic breast cancer (mBC)

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Hope S. Rugo,[1] Sara M. Tolaney,[2] Nancy Chan,[3] Erika Hamilton,[4] Eva Ciruelos,[5] Ji-Yeon Kim,[6] Elena López-Miranda,[7] Elia Seguí,[8] Neelima Vidula,[9] Joyce O'Shaughnessy,[10] Giuseppe Curigliano,[11] Javier Cortés,[12] Alessandro di Sanzo,[13] Paula Muñoz Romero,[13] Bartomeu Piza Vallespir,[13] Manuel Domínguez-Lizarbe,[13] Kathy Puyana Theall,[14] Alessandro Paoli,[13] Monica Binaschi,[13] Tomer Wasserman,[13] Virginia Kaklamani[15]

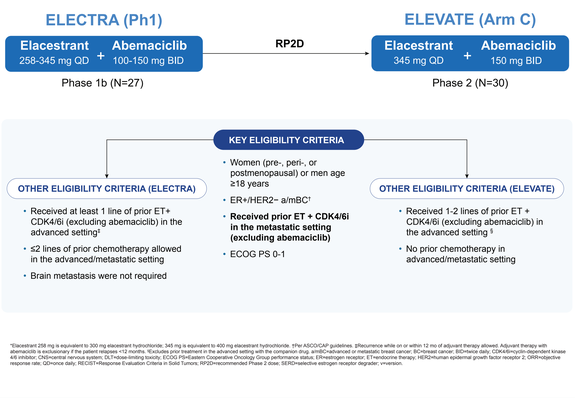
[1]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]NYU Langone Health, New York, NY, USA; [4]Sarah Cannon Research Institute, Nashville, TN, USA; [5]Hospital Universitario 12 de Octubre, Madrid, Spain; [6]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [7]Hospital Universitario Ramón y Cajal, Madrid, Spain; [8]Medical Oncology Department, Hospital Clínic-August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain; [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

- After first-line endocrine therapy (ET) + CDK4/6i in patients ER+/HER2− mBC, tumors eventually develop resistance to intrinsic alterations in the cell cycle or PI3K/AKT/mTOR pathways, or to acquired *ESR1*-mutations that emerge in up to 50% of patients, leading to disease progression.[1-18]
- In the phase 3 EMERALD trial, single-agent elacestrant significantly prolonged mPFS with a manageable safety profile vs. SOC ET, leading to the first oral SERD approved in ER+/HER2− mBC that targets *ESR1*-mutated tumors.[19,20]
  - Patients with *ESR1*-mutated tumors had a 45% reduction in risk of progression or death with elacestrant vs SOC (HR=0.55; 95% CI: 0.39–0.77; *P*=0.0005).[20]
  - In patients with ≥12 months of prior ET + CDK4/6i and *ESR1*-mutated tumors, mPFS with elacestrant was 8.6 months vs 1.9 months with SOC (HR=0.41; 95% CI: 0.26–0.63).[21]
- **The rationale for combining elacestrant + abemaciclib is to overcome different resistance mechanisms and enable an all-oral regimen.**
- In the ELECTRA phase 1b study (NCT05386108), the recommended phase 2 dose (RP2D) was determined:[22]
  - **Elacestrant 345 mg + abemaciclib 150 mg BID (RP2D)**
    - **ORR=25%; CBR at 16 weeks = 75%**
    - PK analyses showed no significant drug-drug interactions with a manageable safety profile
- **This pooled analysis reports updated safety and preliminary efficacy with the elacestrant + abemaciclib combination in patients with prior ET + CDK4/6i exposure** (excluding abemaciclib) from the ongoing ELECTRA (phase 1b portion) and ELEVATE (phase 2 [Arm C] NCT05563220) studies.

METHODS

Elacestrant + Abemaciclib Pooled Analysis



†Elacestrant 258 mg is equivalent to 300 mg elacestrant hydrochloride; 345 mg is equivalent to 400 mg elacestrant hydrochloride. ‡Per ASCO/CAP guidelines. §Recurrence while on or within 12 mo of adjuvant therapy allowed. Adjuvant therapy with abemaciclib is exclusionary if the patient relapses <12 months. ¶Excludes prior treatment in the advanced setting with the companion drug. a/mBC=advanced or metastatic breast cancer; BC=breast cancer; BID=twice daily; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; CNS=central nervous system; DLT=dose-limiting toxicity; ECOG PS=Eastern Cooperative Oncology Group performance status; ER=estrogen receptor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; ORR=objective response rate; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; SERD=selective estrogen receptor degrader; vs=versus.

RESULTS

Baseline Characteristics

Parameters	ELECTRA Cohort 1 (n=8) Elacestrant 258 mg QD + Abemaciclib 100 mg BID	ELECTRA Cohort 2 (n=7) Elacestrant 345 mg QD + Abemaciclib 100 mg BID	ELECTRA Cohort 3* RP2D (n=12) Elacestrant 345 mg QD + Abemaciclib 150 mg BID	ELEVATE Arm C (n=30) Elacestrant 345 mg QD + Abemaciclib 150 mg BID	POOLED ANALYSIS ELECTRA Cohort 3* + ELEVATE Arm C (n=42) Elacestrant 345 mg QD + Abemaciclib 150 mg BID
Median age, years (range)	43 (32–67)	51 (41–71)	54 (48–74)	61 (29–84)	**60 (29–84)**
Female, n (%)	8 (100)	7 (100)	12 (100)	30 (100)	**42 (100)**
ECOG PS, n (%)					
0	5 (63)	4 (57)	7 (58)	20 (67)	**27 (64)**
1	3 (38)	3 (43)	5 (42)	10 (33)	**15 (36)**
Metastatic site, n (%)					
Visceral	6 (75)	6 (86)	8 (67)	22 (73)	**30 (71)**
Brain	0	0	0	0	**0**
Liver	5 (63)	3 (43)	8 (67)	9 (30)	**17 (41)**
Lung	1 (13)	5 (71)	3 (25)	8 (27)	**11 (26)**
Bone	5 (63)	5 (71)	6 (50)	14 (47)	**20 (48)**
Mutations,† n (%)					
ESR1	2/5 (40)	2/7 (29)	7/12 (58)	14/28 (50)	**21/40 (53)**
PIK3CA	1/5 (20)	3/7 (43)	2/12 (17)	9/28 (32)	**11/40 (28)**
Primary endocrine resistance,‡ n (%)	3 (38)	1 (14)	3 (25)	2 (7)	**5 (12)**
Median number of prior therapies for adv/mBC, n (range)	2 (1–3)	2 (1–4)	2 (1–6)	1 (1–2)	**1 (1–6)**
Prior CDK4/6i for adv/mBC, n (%)	5 (63)	7 (100)	12 (100)	30 (100)	**42 (100)**
Palbociclib	3 (38)	5 (71)	5 (42)	18 (60)	**23 (55)**
Ribociclib	2 (25)	2 (29)	6 (50)	11 (37)	**17 (40)**
Palbociclib/Ribociclib	0	0	1 (8)	1 (3)	**2 (5)**
Number of prior lines of endocrine therapy for adv/mBC, n (%)					
1	3 (38)	3 (43)	5 (42)	25 (83)	**30 (71)**
2	3 (38)	3 (43)	6 (50)	5 (17)	**11 (26)**
3	0	1 (14)	1 (8)	0	**1 (2)**
Type of prior endocrine therapy, n (%)					
Fulvestrant	5 (63)	5 (71)	9 (75)	13 (43)	**22 (52)**
AI	3 (38)	5 (71)	9 (75)	21 (70)	**30 (71)**
Tamoxifen	1 (13)	2 (29)	2 (17)	1 (3)	**3 (7)**
Tamoxifen/AI	0	1 (14)	1 (8)	1 (3)	**2 (5)**
Number of prior lines of chemotherapy, n (%)					
0	5 (63)	3 (43)	5 (42)	30 (100)	**35 (83)**
1	3 (38)	4 (57)	6 (50)	0	**6 (14)**
2	0	0	1 (8)	0	**1 (2)**

Data cut-off: 15 OCT 2024 *Includes confirmatory cohort 3 expansion; †Mutation data not available for all patients at time of data analysis; ‡Relapse within the first two years while on adjuvant ET and/or progressive disease within the first six months of first-line ET for advanced/metastatic breast cancer[23]

adv/mBC=advanced or metastatic breast cancer; AI=aromatase inhibitor; BID=twice daily; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance status; ET=endocrine therapy; QD=once daily; RP2D=recommended phase 2 dose.

Treatment-Emergent Adverse Events (TEAEs) ≥20% at RP2D

Preferred Term, n (%)	ELECTRA Cohort 1 (n=8) Elacestrant 258 mg QD + Abemaciclib 100 mg BID		ELECTRA Cohort 2 (n=7) Elacestrant 345 mg QD + Abemaciclib 100 mg BID		ELECTRA Cohort 3* RP2D (n=12) Elacestrant 345 mg QD + Abemaciclib 150 mg BID		ELEVATE Arm C (n=30) Elacestrant 345 mg QD + Abemaciclib 150 mg BID		POOLED ANALYSIS ELECTRA Cohort 3* + ELEVATE Arm C (n=42) Elacestrant 345 mg QD + Abemaciclib 150 mg BID	
	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
Diarrhea	5 (63)	0	6 (86)	0	11 (92)	0	24 (80)	2 (7)	**35 (83)**	**2 (5)**
Nausea	6 (75)	0	5 (71)	0	8 (67)	0	19 (63)	2 (7)	**27 (64)**	**2 (5)**
Vomiting	1 (13)	0	3 (43)	0	4 (33)	1 (8)	13 (43)	0	**17 (41)**	**1 (2)**
Fatigue	1 (13)	0	1 (14)	0	2 (17)	0	13 (43)	2 (7)	**15 (36)**	**2 (5)**
Neutropenia/neutrophil decreased	2 (25)	2 (25)	3 (43)	2 (29)	9 (75)	7 (58)	5 (17)	4 (13)	**14 (33)**	**11 (26)**
Anemia	1 (13)	0	2 (29)	0	4 (33)	1 (8)	6 (20)	2 (7)	**10 (24)**	**3 (7)**
Constipation	0	0	3 (43)	0	0	0	9 (30)	0	**9 (21)**	**0**
Decreased appetite	2 (25)	0	3 (43)	0	2 (17)	0	7 (23)	0	**9 (21)**	**0**

No grade 4 AEs were reported during the elacestrant + abemaciclib treatment period

Data cut-off: 15 OCT 2024. *Includes confirmatory cohort 3 expansion. AE=adverse event; BID=twice daily; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; ET=endocrine therapy; QD=once daily; RP2D=Recommended Phase 2 dose.

Response and Clinical Benefit With Elacestrant + Abemaciclib in Efficacy-Evaluable Patients

Efficacy Outcome*†	ELECTRA Cohort 1 (n=7) Elacestrant 258 mg QD + Abemaciclib 100 mg BID	ELECTRA Cohort 2 (n=7) Elacestrant 345 mg QD + Abemaciclib 100 mg BID	ELECTRA Cohort 3‡ RP2D (n=12) Elacestrant 345 mg QD + Abemaciclib 150 mg BID	ELEVATE Arm C (n=26) Elacestrant 345 mg QD + Abemaciclib 150 mg BID	POOLED ANALYSIS ELECTRA Cohort 3‡ + ELEVATE Arm C (n=38) Elacestrant 345 mg QD + Abemaciclib 150 mg BID
ORR, n (%)	**2 (29)**	**2 (29)**	**3 (25)**	**4 (15)**	**7 (18)**
CR	-	-	1 (8)	1 (4)	**2 (5)**
PR	2 (29)	2 (29)	2 (17)	3 (12)	**5 (13)**
SD	2 (29)	3 (43)	7 (58)	18 (69)	**25 (66)**
PD	3 (43)	2 (29)	2 (17)	4 (15)	**6 (16)**
CBR, n (%)	**4 (57)**	**5 (71)**	**10 (83)**	**22 (85)**	**32 (84)**
CBR24wks, n (%)	**4 (57)**	**4 (57)**	**8 (67)**	In ELEVATE Arm C, average observation time has not reached 24 weeks	

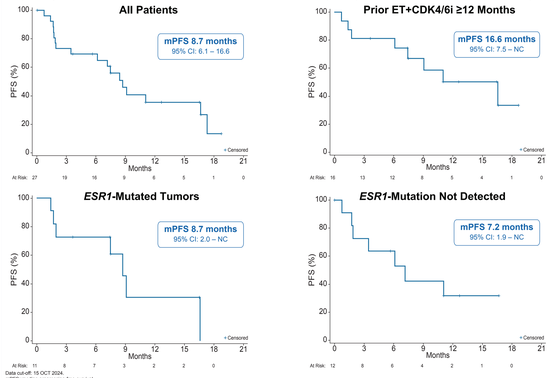
Data cut-off: 15 OCT 2024. *Confirmed responses only; †Includes patients who had measurable disease (ie, at least 1 target lesion) at baseline and at least 1 post-baseline RECIST assessment ‡Includes confirmatory cohort 3 expansion. CBR=clinical benefit rate (CR + PR + SD); CR=complete response; PR=partial response; SD=stable disease; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; ET=endocrine therapy; ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors

mPFS in Efficacy-Evaluable Patients from ELECTRA Phase 1b

Population	Elacestrant + Abemaciclib n	mPFS, mo	[95% CI]
All patients	27	**8.7**	[6.1 – 16.6]
Prior ET+CDK4/6i	24	**8.7**	[6.1 – 16.6]
ESR1-mutated tumors	11	**8.7**	[2.0 – NC]
ESR1-mutation not detected	12	**7.2**	[1.9 – NC]
Prior ET+CDK4/6i ≥12 months	16	**16.6**	[7.5 – NC]
Dose level			
Elacestrant 345 mg QD + Abemaciclib 150 mg BID (RP2D)	12	**8.7**	[7.2 – NC]
Elacestrant 345 mg QD + Abemaciclib 100 mg BID	7	**7.5**	[1.9 – NC]
Elacestrant 258 mg QD + Abemaciclib 100 mg BID	8	**8.4**	[1.7 – 17.3]

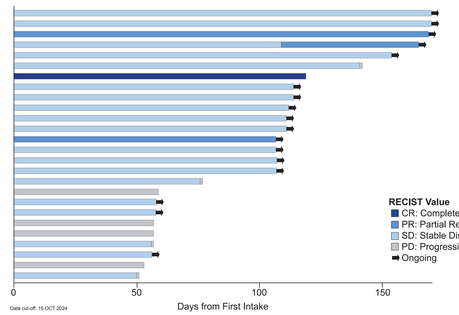
Patients in ELECTRA Phase 1b had a median observational time for PFS of 7.5 months at data cut-off

- Clinical characteristics: visceral metastases 74%, prior fulvestrant 70%, ≥2 prior lines of ET for adv/mBC 52%, primary endocrine resistance 26%, *ESR1*-mutated tumors 46% (11/24) and *PIK3CA*-mutated tumors 25% (6/24)



Data cut-off: 15 OCT 2024
mPFS=median progression-free survival.

ELEVATE Arm C: Best Tumor Response



Data cut-off: 15 OCT 2024

Evaluable patients (n=26/30) in ELEVATE Arm C had a median observational time for PFS of 4.6 months at data cut-off; therefore, mPFS cannot be evaluated

- Clinical characteristics for patients in ELEVATE Arm C: visceral metastases 73%, prior fulvestrant 43%, two prior lines of ET for adv/mBC 17%, primary endocrine resistance 7%, *ESR1*-mutated tumors 50% (14/28), and *PIK3CA*-mutated tumors 32% (9/28).

CONCLUSIONS

- In patients with prior ET + CDK4/6i, the safety of elacestrant + abemaciclib was consistent with the known profile of abemaciclib + standard ET, and no new signals were observed.
  - No grade 4 AEs were observed during the treatment period.
- **Elacestrant + abemaciclib showed clinically important efficacy regardless of *ESR1*-mutation status.**
  - **mPFS was 8.7 months in all patients.**
    - **mPFS was 8.7 months in patients with *ESR1*-mutated tumors and 7.2 months in tumors with *ESR1*-mutation not detected.**
  - **mPFS was 16.6 months in those patients who received prior ET + CDK4/6i ≥12 months.**
- The phase 2 portion of the combination of elacestrant 345 mg QD + abemaciclib 150 mg BID is currently ongoing.
- Elacestrant could become an ET backbone in combination with abemaciclib in patients with ER+/HER2-mBC due to its potential to extend PFS, enable an all-oral treatment option, and delay chemotherapy or ADC-based regimens.

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