Elacestrant in combination with abemaciclib in patients (pts) with brain metastasis (mets) from estrogen receptor-positive (ER+), HER2-negative (HER2-) breast cancer: Preliminary data from ELECTRA, an open-label, multicenter, phase 1b/2 study

Presented at ESMO 2024
September 13-17, 2024
Poster # 364P

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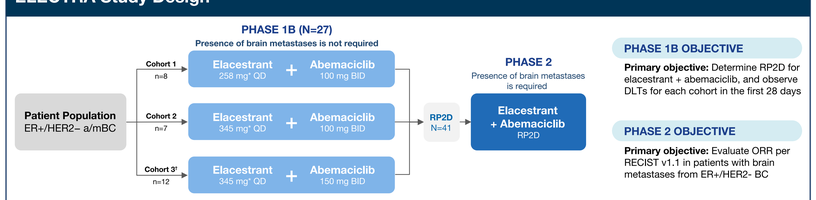
BACKGROUND

- Endocrine therapy (ET) + CDK4/6 inhibitors (CDK4/6i) is the mainstay as first-line therapy for the management of ER+/HER2- metastatic breast cancer (mBC).[1-3] However, tumors eventually develop resistance to ET, leading to disease progression.[4]
- *ESR1* mutations represent a type of acquired resistance in up to 50% of patients after initial ET in the metastatic setting.[5-7]
- Based on the phase 3 EMERALD trial, elacestrant is the first oral selective estrogen receptor degrader (SERD) approved in ER+/HER2- mBC that targets *ESR1*-mutated tumors.[8]
  - Patients with *ESR1*-mutated tumors had a 45% reduction in risk of progression or death with elacestrant vs standard-of-care ET (SOC) (HR = 0.55; 95% CI, 0.39-0.77; p = 0.0005).[9]
  - In those 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 (HR = 0.41; 95% CI, 0.26-0.63).[10]
  - Elacestrant was well tolerated with a manageable safety profile. Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs were reported.[9,10]
- The rationale for ELECTRA is to combine elacestrant with abemaciclib to overcome different endocrine resistance mechanisms.
- The phase 1b portion of ELECTRA evaluates the combination of elacestrant with abemaciclib in patients with ER+/HER2- mBC regardless of metastatic site and *ESR1* status. The phase 2 portion of ELECTRA is ongoing to further characterize efficacy and safety of this combination in patients with brain metastases from ER+/HER2- breast cancer, as both compounds cross the blood-brain barrier.[11,12]
- The recommended phase 2 dose (RP2D) of the combination was determined to be elacestrant 345 mg QD with abemaciclib 150 mg BID.[13]
- At the RP2D, no pharmacokinetic drug-drug interactions were observed between elacestrant and abemaciclib.[13]
- This analysis reports updated safety and efficacy with all 3 dose cohorts in patients who received prior ET + CDK4/6i.

METHODS

ELECTRA Study Design



*Elacestrant 258 mg is equivalent to 300 mg elacestrant dihydrochloride; 345 mg is equivalent to 400 mg elacestrant dihydrochloride. †Includes confirmatory cohort 3 expansion.

a/mBC, advanced or metastatic breast cancer; BC, breast cancer; BID, twice daily; DLT, dose-limiting toxicity; ECOG PS, ER, estrogen receptor; 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; v, version.

Clinical Trial: NCT05386108

Key Phase 1b Eligibility Criteria

Inclusion Criteria

- Women or men age ≥18 years with confirmed ER+/HER2- tumor status
- **In phase 1b, the presence of brain metastases is not required**
- Prior therapy in the metastatic setting including ≥1 ET, ≤2 chemotherapy regimens, and ≤2 CDK4/6i, not including abemaciclib
- Documented intra- and/or extra-cranial radiological progression while on or after most recent therapy
- Eastern Cooperative Oncology Group performance status ≤2

Exclusion Criteria

- Immediate central nervous system (CNS)-specific treatment is needed
- Leptomeningeal metastases
- Breast cancer treatment-naïve in the metastatic setting (recurrence while on or within 12 months of adjuvant therapy allowed)
- Imminent organ failure and/or visceral crisis
- Prior abemaciclib in the metastatic setting
- Prior elacestrant or other investigational SERDs or alike agents
- Prior anti-cancer therapies within certain time windows of starting trial therapy: fulvestrant (<42 days), ET (<14 days), chemotherapy (<14 days), radiotherapy other than CNS-directed (<14 days), any investigational anti-cancer drug therapy (<28 days or <5 half-lives)

REFERENCES: **1.** Zhao M, et al. *Target Oncol*. 2023;18(3):327-358; **2.** Burstein HJ, et al. *J Clin Oncol*. 2021;39(35):3959-3977; **3.** Burstein HJ, et al. *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.** Bhave MA, et al. Presented at SABCS 2023. December 5-9, 2023. PO2-16-05; **7.** Jhaveri KL, et al. Presented at SABCS 2023. December 5-9, 2023. PS15-09; **8.** Orserdu. Prescribing information. Stemline Therapeutics; 2023; **9.** Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-3256; **10.** Bardia A, et al. *Clin Cancer Res*. 2024; doi: 10.1158/1078-0432.CCR-24-1073; **11.** Conlan MG, et al. *Eur J Drug Metab Pharmacokinet*. 2020;45(5):675-689; **12.** Tolaney SM, et al. *Clin Cancer Res*. 2020;26(20):5310-5319. **13.** Ibrahim N, et al. *J Clin Oncol*. 2024;40 (suppl 16): abstr 1064; **14.** Cardoso F, et al. *Ann Oncol*. 2020;31(12):1623-1649.

RESULTS: In Patients Who Received Prior ET + CDK4/6i

Baseline Characteristics for Phase 1b

	Cohort 1 Elacestrant 258 mg QD + Abemaciclib 100 mg BID (n=5)[a]	Cohort 2 Elacestrant 345 mg QD + Abemaciclib 100 mg BID (n=7)	Cohort 3[b] (RP2D) Elacestrant 345 mg QD + Abemaciclib 150 mg BID (n=12)
Median age, years (range)	44 (32 – 67)	51 (41 – 71)	54 (48 – 74)
Female, n (%)	5 (100)	7 (100)	12 (100)
ECOG PS, n (%			
0	4 (80)	4 (57)	7 (58)
1	1 (20)	3 (43)	5 (42)
Visceral metastasis,[c] n (%)	4 (80)	6 (86)	9 (75)
Brain metastases, n (%)	0	0	0
Primary endocrine resistance,[d] n (%)	2 (40)	1 (14)	3 (25)
Median number of prior therapies for adv/mBC, n (range)	2 (1 – 3)	2 (1 – 4)	2 (1 – 6)
Prior CDK4/6i for adv/mBC, n (%)	5 (100)	7 (100)	12 (100)
Number of prior lines of endocrine therapy for adv/mBC, n (%)			
1	3 (60)	3 (43)	5 (42)
2	2 (40)	3 (43)	6 (50)
3	0	1 (14)	1 (8)
Type of prior endocrine therapy, n (%)			
Fulvestrant	4 (80)	5 (71)	9 (75)
AI	2 (40)	5 (71)	9 (75)
Tamoxifen	1 (20)	2 (29)	2 (17)
Tamoxifen/AI	0	1 (14)	1 (8)
Number of prior lines of chemotherapy, n (%)			
1	3 (60)	4 (57)	6 (50)
2	0	0	1 (8)

[a]Cohort 1 enrolled a total of 8 patients, of whom 3 did not receive prior CDK4/6i per the original protocol; [b]Includes confirmatory cohort 3 expansion; [c]Includes lung, liver, brain, pleural, and peritoneal involvement; [d]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[14]

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.

Data cut-off: 26 July 2024

Treatment-Emergent Adverse Events Across Cohorts (≥20% in RP2D Cohort)

	Cohort 1 Elacestrant 258 mg QD + Abemaciclib 100 mg BID (n=5)[a]		Cohort 2 Elacestrant 345 mg QD + Abemaciclib 100 mg BID (n=7)		Cohort 3[c] (RP2D) Elacestrant 345 mg QD + Abemaciclib 150 mg BID (n=12)	
Preferred Term, n	**All Grades**	**Grade 3[b]**	**All Grades**	**Grade 3**	**All Grades**	**Grade 3**
Diarrhea	3 (60)	0	6 (86)	0	11 (92)	0
Nausea	5 (100)	0	5 (71)	0	8 (67)	0
Neutropenia / Neutrophil count decreased	1 (20)	1 (20)	3 (43)	2 (29)	8 (67)	7 (58)
Asthenia	1 (20)	0	3 (43)	0	5 (42)	1 (8)
Upper abdominal pain	0	0	0	0	5 (42)	0
Anemia	0	0	2 (29)	0	4 (33)	1 (8)
Vomiting	1 (20)	0	3 (43)	0	4 (33)	1 (8)
Gamma-glutamyltransferase increased	1 (20)	0	1 (14)	0	3 (25)	1 (8)
Rash	0	0	0	0	3 (25)	0

[a]Cohort 1 enrolled a total of 8 patients, of whom 3 did not receive prior CDK4/6i per the original protocol; [b]No grade 4 AEs were reported during the elacestrant + abemaciclib treatment period; [c]Includes confirmatory cohort 3 expansion

Data cut-off: 26 July 2024

Safety Summary

- Most treatment-emergent adverse events (TEAEs) were grade 1 and 2.
- Most common grade 3 TEAEs (≥ 2 patients) were neutropenia and neutrophil count decreased.
  - **No grade 3 diarrhea was observed.**
  - Neutropenia was associated mainly with abemaciclib only.

Preferred term, n (%)	RP2D Elacestrant 345 mg QD + abemaciclib 150 mg BID (n=12)[a]	
	All Grades	Grade 3
Neutropenia/neutrophil count decreased	8 (67)	7 (58)
Related to abemaciclib only	5 (42)	5 (42)
Related to elacestrant + abemaciclib	3 (25)	2 (17)

[a]Includes confirmatory cohort 3 expansion. BID, twice daily; QD, once daily; RP2D, recommended phase 2 dose.

Data cut-off: 26 July 2024

- **No grade 4 TEAEs were observed** during the entire treatment period for all three cohorts.

Response and Clinical Benefit With Elacestrant Plus Abemaciclib[a]

Efficacy Outcome[b]	Cohort 1 Elacestrant 258 mg QD + Abemaciclib 100 mg BID (n=4)[c]	Cohort 2 Elacestrant 345 mg QD + Abemaciclib 100 mg BID (n=7)	Cohort 3[a] (RP2D) Elacestrant 345 mg QD + Abemaciclib 150 mg BID (n=12)
ORR, n (%)	1 (25)	2 (29)	3 (25)
CR	0	0	1 (8)
PR	1 (25)	2 (29)	2 (17)
SD	1 (25)	3 (43)	7 (58)
CBR16, n (%)	2 (50)	5 (71)	9 (75)

[a]Confirmed responses only; [b]Includes patients who had measurable disease (ie, at least 1 target lesion) at baseline and at least 1 post-baseline RECIST assessment. [c]Cohort 1 enrolled a total of 8 patients, of whom 3 did not receive prior CDK4/6i per the original protocol; [d]Includes confirmatory cohort 3 expansion

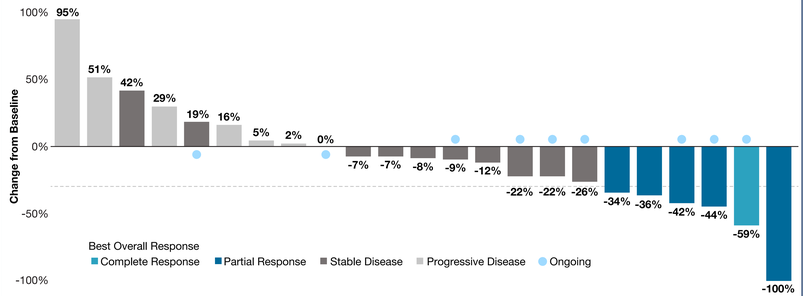
CBR, clinical benefit rate at weeks (CR + PR + SD ≥16 weeks); CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

Data cut-off: 26 July 2024

- CBR at 24 weeks (CR + PR + SD ≥24 weeks) was 57% in 23 evaluable patients.

Best Tumor Response

Efficacy-Evaluable Patients (n=23)



Data cut-off: 26 July 2024

CONCLUSIONS

In patients with NO brain metastases and prior therapy in the metastatic setting, including at least 1 line of ET + CDK4/6i (excluding abemaciclib), and ≤2 lines of chemotherapy:

- The combination was well tolerated and consistent with the known safety profile of abemaciclib + standard ET.
  - No grade 4 AEs or grade 3 diarrhea were observed during the treatment period.
  - Neutropenia was mainly associated with abemaciclib.
- Elacestrant in combination with abemaciclib demonstrated favorable efficacy in patients regardless of the metastasis site.
  - The ORR was 26% (1 CR and 5 PR).
  - The CBR at 16 weeks was 70% and the CBR at 24 weeks was 57% in 23 evaluable patients.
- The phase 2 portion of ELECTRA is ongoing at the RP2D of elacestrant 345 mg QD + abemaciclib 150 mg BID in patients with brain metastases from ER+/HER2- breast cancer.
- The phase 2 portion of ELEVATE (NCT05563220) for the combination of elacestrant with abemaciclib is ongoing to further characterize the efficacy and safety of this combination in patients with ER+/HER2- mBC to enable a convenient all-oral treatment option before use of fulvestrant-based combinations or chemotherapy-based regimens, including antibody-drug conjugates (ADCs).

DOI: **External Advisor: AstraZeneca; Daiichi Sankyo; Gilead; Lilly; MSD; Novartis; Pfizer; Reveal Genomics; Roche; Speaker for: AstraZeneca; Daiichi Sankyo; Gilead; Lilly; MSD; Novartis; Pfizer; Pierre Fabre; Reveal Genomics; Roche; Travel grants: AstraZeneca; Pfizer; Roche; Research grants: Seagen; Roche**
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