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

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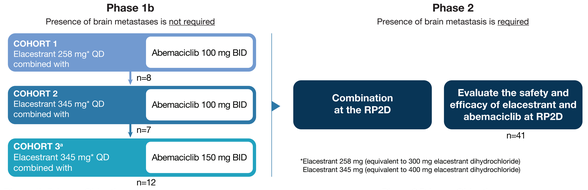
BACKGROUND

- Endocrine therapy (ET) plus 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 endocrine therapies, 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] Elacestrant is the first oral 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 (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, 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, 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 endocrine resistance and cell-cycle pathways associated resistance mechanisms. The phase 1b portion of the ELECTRA study (NCT05386108) evaluates the combination of elacestrant with abemaciclib in patients with ER+/HER2- mBC regardless of metastatic site and *ESR1* status, to enable a convenient all-oral treatment option before use of fulvestrant-based combinations or chemotherapy-based regimens, including antibody-drug conjugates (ADCs).
- The analysis reports updated safety, preliminary efficacy, PK, and recommended Phase 2 dose (RP2D).
- Phase 2 will evaluate the benefit of the combination in patients with ER+/HER2- advanced or metastatic breast cancer with brain metastases, as both compounds have demonstrated the ability to cross the blood-brain barrier.[11,12]

METHODS

ELECTRA Study Design



Phase 1b Primary Objective
- Determine the RP2D in patients with ER+/HER2- mBC
- DLT observation period is the first 28 days for each cohort

Phase 2 Primary Objective
- Evaluate ORR (RECIST v1.1) in patients with brain metastases from ER+/HER2- breast cancer

[a]Includes confirmatory cohort 3 expansion
DLT, dose-limiting toxicity; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose. 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
- ECOG PS ≤2

Exclusion Criteria
- Immediate CNS-specific treatment needed
- Leptomeningeal metastases
- Breast cancer treatment-naïve patients 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), RT other than CNS-directed (<14 days), any investigational anti-cancer drug therapy (<28 days or <5 half-lives)

RESULTS

Baseline Characteristics

	Cohort 1 Elacestrant 258 mg QD + Abemaciclib 100 mg BID (n=8)	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)
Median age, years (range)	43 (32 – 67)	51 (41 – 71)	54 (48 – 74)
Female, n (%)	8 (100)	7 (100)	12 (100)
ECOG PS, n (%)			
0	5 (63)	4 (57)	7 (58)
1	3 (38)	3 (43)	5 (42)
Visceral metastasis,[b] n (%)	6 (75)	6 (86)	9 (75)
Primary endocrine resistance,[c] n (%)	4 (50)	1 (14)	3 (25)
Median number of prior therapies for adv/mBC, n (range)	2 (1 – 3)	1 (1 – 4)	2 (1 – 6)
Prior CDK4/6i for adv/mBC, n (%)	5 (63)	7 (100)	12 (100)
Number of prior lines of ET for adv/mBC, n (%)			
1	3 (38)	3 (43)	5 (42)
2	3 (38)	3 (43)	6 (50)
3	0	1 (14)	1 (8)
Type of prior ET, n (%)			
Fulvestrant	5 (63)	5 (71)	9 (75)
AI	3 (38)	5 (71)	9 (75)
Tamoxifen	1 (13)	2 (29)	2 (17)
Tamoxifen/AI	0	1 (14)	1 (8)
Number of prior lines of chemotherapy, n (%)			
1	3 (38)	4 (57)	6 (50)
2	0	0	1 (8)

[a]Includes confirmatory cohort 3 expansion; [b]Includes lung, liver, brain, pleural, and peritoneal involvement; [c]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;[13]
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

Data Cut-off: 29 January 2024

Treatment-Emergent Adverse Events Across Cohorts (≥2 Patients)

	Cohort 1 Elacestrant 258 mg QD + Abemaciclib 100 mg BID (n=8)		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)	
Preferred Term, n (%)	**All Grades**	**Grade 3[a]**	**All Grades**	**Grade 3**	**All Grades**	**Grade 3**
Diarrhea	5 (63)	0	6 (86)	0	10 (83)	0
Nausea	6 (75)	0	5 (71)	0	8 (67)	0
Neutropenia	0	0	2 (29)	1 (14)	5 (42)	4 (33)
Neutrophil count decreased	3 (38)	2 (25)	1 (14)	1 (14)	3 (25)	3 (25)
Anemia	0	0	3 (43)	0	5 (42)	1 (8)
Asthenia	0	0	3 (43)	0	4 (33)	0
Decreased appetite	2 (25)	0	3 (43)	0	1 (8)	0
Vomiting	1 (13)	0	2 (29)	0	4 (33)	1 (8)
Abdominal pain / abdominal pain upper	0	0	3 (43)	0	3 (25)	0
Constipation	0	0	3 (43)	0	0	0
Peripheral edema	1 (13)	0	0	0	2 (17)	0
Pruritus	3 (38)	0	0	0	1 (8)	0
Rash	2 (25)	0	0	0	3 (25)	0
Arthralgia	0	0	2 (29)	0	0	0
Back pain	0	0	2 (29)	0	1 (8)	0
Cough	0	0	0	0	2 (17)	0
Dyspepsia	0	0	0	0	2 (17)	0
Lacrimation increased	2 (25)	0	0	0	0	0
Blood creatinine increased	0	0	2 (29)	0	2 (17)	0
Gamma-glutamyltransferase increased	1 (13)	0	1 (14)	0	2 (17)	1 (8)
Blood alkaline phosphatase increased	0	0	0	0	2 (17)	1 (8)
Blood lactate dehydrogenase increased	0	0	0	0	2 (17)	0
Glomerular filtration rate decreased	0	0	2 (29)	0	0	0
Platelet count decreased	0	0	0	0	2 (17)	0

[a]No grade 4 AEs were reported during the elacestrant + abemaciclib treatment period; [b]Includes confirmatory cohort 3 expansion

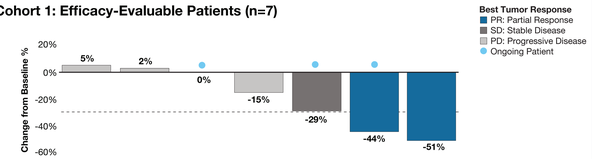
Data Cut-off: 29 January 2024

Safety Summary

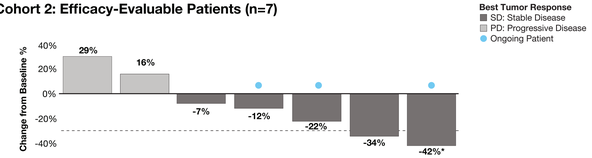
- **RP2D of the combination was determined to be elacestrant 345 mg QD with abemaciclib 150 mg BID.**
- Most treatment-emergent adverse events (TEAEs) were grade 1 and 2.
- Most common grade 3 TEAEs (≥ 2 patients) were neutropenia and neutrophil count decreased.
  - **No grade 3 diarrhea was observed.**
- **No grade 4 TEAEs were observed** during the entire treatment period for all three cohorts.

Best Tumor Response

Cohort 1: Efficacy-Evaluable Patients (n=7)

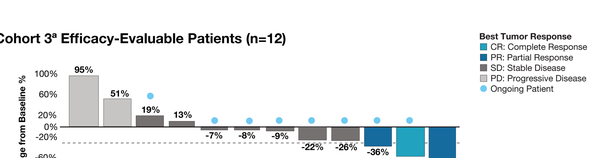


Cohort 2: Efficacy-Evaluable Patients (n=7)



*Partial response not confirmed at data cut-off date

Cohort 3[a] Efficacy-Evaluable Patients (n=12)



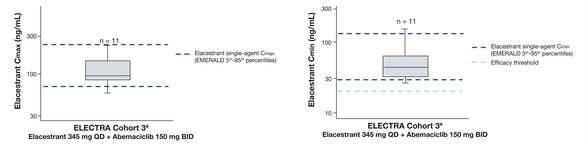
[a]Includes confirmatory cohort 3 expansion

Data Cut-off: 05 April 2024

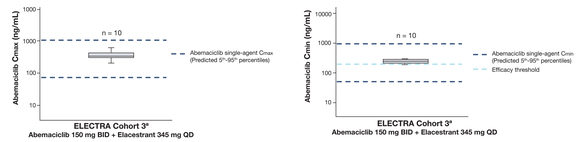
Pharmacokinetics Assessment at the RP2D of Elacestrant 345 mg QD + Abemaciclib 150 mg BID

- PK analyses showed no drug-drug interaction between elacestrant and abemaciclib
- Overall, all patients treated at the RP2D reached the efficacy thresholds

Elacestrant Steady State Maximum (C_{max}) and Trough Plasma Concentrations (C_{min})



Abemaciclib Steady State Maximum (C_{max}) and Trough Plasma Concentrations (C_{min})



[a]Includes confirmatory cohort 3 expansion

CONCLUSIONS

- Elacestrant in combination with abemaciclib demonstrated favorable efficacy in patients regardless of the metastases site.
  - The clinical benefit rate (CBR) was 73% in 26 evaluable patients (1 had CR, 4 had PR, and 14 had SD).
- The RP2D of the combination was determined to be elacestrant 345 mg QD with abemaciclib 150 mg BID.
- 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.
- At the RP2D, no PK drug-drug interactions were observed between elacestrant and abemaciclib.
- Phase 2 portion of ELECTRA started and is ongoing at the RP2D to further characterize efficacy and safety in patients with brain metastases from ER+/HER2- breast cancer, as both compounds cross the blood-brain barrier.[11,12]
- Phase 2 portion of ELEVATE study (NCT05563220) started and is ongoing at the RP2D to further characterize efficacy and safety in patients with ER+/HER2- mBC.

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