San Antonio Breast Cancer Symposium – December 10-14, 2019

PD7-07

Final analysis of phase 1 study of elacestrant (RAD1901), a novel selective estrogen receptor degrader (SERD), in estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer

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Background

- The majority of patients with advanced ER+ breast cancer (BC) will experience progression of disease after endocrine therapy (ET) due to acquired resistance, including development of *ESR1* mutations.[1]
- Response to conventional ET agents, including aromatase inhibitors (AIs) and fulvestrant, in late lines of therapy is poor with overall response rates (ORRs) ≤11%.[2-4]
- Fulvestrant is the only SERD marketed for the treatment of postmenopausal women with hormone receptor-positive advanced BC. Fulvestrant requires intramuscular administration; therefore, there is a need for an oral SERD with improved bioavailability.[5]
- Elacestrant is an investigational, nonsteroidal, oral SERD with marked antitumor activity documented in multiple *in vivo* patient-derived xenograft models of BC, including those derived from heavily pretreated patients and those with *ESR1* mutations.[5,6]
- Herein we present the updated results of RAD1901-005 (NCT02338349), a phase 1 trial of elacestrant in heavily pretreated postmenopausal women with ER+/HER2- metastatic breast cancer (mBC).

Objectives

PRIMARY OBJECTIVE:

- Determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D)

SECONDARY OBJECTIVES:

- Assess safety and tolerability
- Evaluate preliminary anti-tumor effect

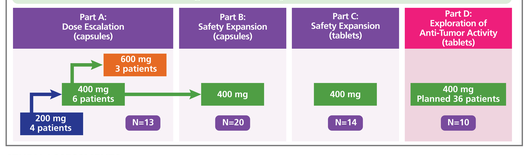
EXPLORATORY OBJECTIVE:

- Explore relationship between circulating tumor DNA (ctDNA) and clinical response (reported separately; Bihani P5-01-05)

Study Design and Methods

- Phase 1, multicenter, open-label, 4-part, dose-escalation safety and efficacy study (**Figure 1**). Study was originally designed as a 2-part study, with subsequent addition of Part C and Part D.
- Elacestrant dose administered orally (PO) daily (QD) until confirmed disease progression, intolerability, or withdrawn consent.
- Part A was a standard 3+3 design; decision to dose escalate determined by Study Committee (investigators, medical monitor, and sponsor).
- To reduce pill burden and improve tolerability, a tablet formulation was introduced in Part C to further evaluate safety and tolerability.
- Part D was added as a pilot sub-study to explore preliminary anti-tumor activity in a more heavily pretreated population with different eligibility criteria. However, based on a change in strategy to focus on an earlier line of therapy, patient accrual in Part D was terminated prior to completion of enrollment of the planned 36 patients (**Table 1**).

Figure 1. Study Schema



STUDY ASSESSMENTS

- Study visits weekly for 1 month, then monthly.
- Response assessed per RECIST v1.1 every 8 weeks.
- Blood samples for ctDNA analysis were collected at screening, during treatment, and at end of treatment. Baseline samples were analyzed using the OncoBEAM™ platform (Sysmex Inostics) for Parts A-C and the Guardant360® assay (Guardant Health) for Part D.

STATISTICS

- Analyses were based on a data cut of 04 Oct 2019.
- Data were summarized descriptively and are presented only for patients treated at RP2D. Safety data are presented separately for patients treated with capsule and tablet formulations. Anti-tumor activity data are presented separately for patients enrolled in Parts A-C and Part D, and for all 4 parts combined.
- Analyses of ORR and best response were performed on the response evaluable (RE) population, defined as all intent-to-treat (ITT) patients who had measurable disease (ie, at least 1 target lesion) at baseline and at least 1 post-baseline RECIST assessment and/or a new lesion.
- Analyses of clinical benefit rate (CBR) were performed on the clinical benefit evaluable (CBE) population, defined as all ITT patients who had measurable and/or evaluable disease (ie, target and/or non-target lesion[s]) at baseline and at least 1 post-baseline RECIST assessment and/or a new lesion.
- Analyses of PFS using Kaplan–Meier method were performed on the ITT population, defined as all patients who received at least 1 dose of study drug treatment.

Patient Population

Table 1. Key Eligibility Criteria

Parts A-C	Part D
Postmenopausal women with ER+ and HER2- locally advanced, inoperable, and/or metastatic adenocarcinoma of the breast	
Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1	
No tamoxifen within 14 days; no chemotherapy within 28 days	
Treated or asymptomatic central nervous system (CNS) metastases permitted	
• ≤2 prior lines of chemotherapy for advanced/mBC	• ≤1 prior line of chemotherapy for advanced/mBC
• ≥6 months of prior ET in either the advanced setting or for mBC – No fulvestrant within 90 days • Disease progression on prior ET • No limit on prior ET	• ≥2 or more lines of ET for advanced/mBC – As a single agent or in combination – 1 prior line fulvestrant required with documented progression occurring during treatment or ≤1 month from end of treatment – No fulvestrant within 42 days – Adjuvant ET <12 months before mBC diagnosis counted as a prior line
• Prior CDK4/6i allowed but not required	• Prior CDK4/6i required
• Measurable or evaluable disease: ≥1 lesion (measurable and/or non-measurable) accurately assessed by CT / MRI / X-ray	• Measurable disease per RECIST v1.1

Patient Disposition and Baseline Characteristics

- From April 2015 to March 2018, 57 postmenopausal women with ER+/HER2- mBC were enrolled (**Figure 2**).
- Baseline demographics and disease characteristics were generally well balanced across Parts A-D. The different eligibility criteria in Part D resulted in the accrual of patients with more advanced and more heavily pretreated disease than in Parts A-C (**Table 2**).
- A dose of 400 mg QD was determined to be the RP2D in Part A.

Figure 2. Patient Disposition

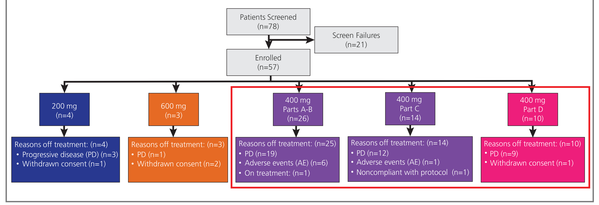


Table 2. Demographics and Baseline Characteristics*

Parameter	Parts A-C 400 mg N=40	Part D 400 mg N=10	All Parts 400 mg N=50
Median age, years (range)	61.5 (43.0-81.0)	64.5 (54.0-81.0)	63 (43.0-81.0)
ECOG PS, n (%)			
0	23 (57.5)	3 (30.0)	26 (52.0)
1	17 (42.5)	7 (70.0)	24 (48.0)
Visceral disease†, n (%)	28 (70.0)	7 (70.0)	35 (70.0)
Bone-only disease, n (%)	10 (25.0)	0 (0.0)	10 (20.0)
ctDNA status, n (%)			
ESR1 mut	20 (50.0)	5 (50.0)	25 (50.0)
ESR1 mut nd	20 (50.0)	5 (50.0)	25 (50.0)
Previous treatment (any setting)			
Number of prior therapies, median (range)	3.0 (1-7)	4.0 (2-5)	3.0 (1-7)
Prior CDK4/6i, n (%)	16 (40.0)	10 (100.0)	26 (52.0)
Prior mTORi, n (%)	10 (25.0)	4 (40.0)	14 (28.0)
Prior Chemotherapy, n (%)	26 (65.0)	7 (70.0)	33 (66.0)
≥2 prior lines of chemotherapy, n (%)	12 (30.0)	3 (30.0)	15 (30.0)
Prior Endocrine therapy, n (%)	40 (100.0)	10 (100.0)	50 (100.0)
≥2 prior lines of endocrine therapy, n (%)	32 (80.0)	10 (100.0)	42 (84.0)
Prior fulvestrant, n (%)	15 (37.5)	10 (100.0)	25 (50.0)

CDK4/6i, cyclin-dependent kinase 4,6 inhibitors; ECOG PS, Eastern Cooperative Oncology Group performance status; *ESR1*-mut, *ESR1* mutation detected; *ESR1* mut nd, *ESR1* mutation not detected; mTORi, mammalian target of rapamycin inhibitor.
*ITT population
†Visceral disease included CNS, liver, lung, peritoneum, and pleura.

Anti-tumor Activity

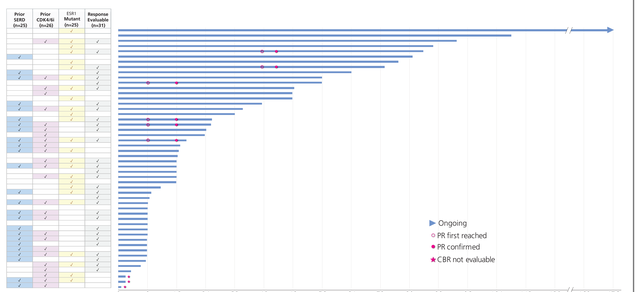
- Among the 50 patients dosed at the RP2D of 400 mg QD elacestrant, 22 and 38 patients in Parts A-C and 9 and 9 patients in Part D were response evaluable and clinical benefit evaluable, respectively. Fifty patients had baseline mutation data available. Anti-tumor activity is presented in **Table 3**. Eleven patients (22%) were on treatment for ≥12 months (**Figure 3**).
- Maximum percent change in sum of all target lesions from baseline is shown in **Figure 4.**

Table 3. Anti-tumor Activity

Parameter	Parts A-C 400 mg N=40	Part D 400 mg N=10	All Parts 400 mg N=50
RE population (n)	**22**	**9**	**31**
ORR (CR + PR), n (%)	6 (27.3)	0 (0)	6 (19.4)
Best response			
Complete response (CR)	0 (0)	0 (0)	0 (0)
Partial response (PR)	6 (27.3)	0 (0)	6 (19.4)
Stable disease (SD)	8 (36.4)	4 (44.4)	12 (38.7)
Progressive disease (PD)	8 (36.4)	5 (55.6)	13 (41.9)
ORR by *ESR1* status, % (n/N)			
ESR1-mut	45.5 (5/11)	0 (0/4)	33.3 (5/15)
ESR1-mut nd	9.1 (1/11)	0 (0/5)	6.3 (1/16)
Median DoR, wks (range)	24.9 (13.4-44.3)	0 (0)	24.9 (13.4-44.3)
Median TTR, wks (range)	8.2 (7.9-40.0)	0 (0)	8.2 (7.9-40.0)
CBE population (n)	**38**	**9**	**47**
CBR (PR + SD ≥ 24 wks), n (%)	18 (47.4)	2 (22.2)	20 (42.6)
mPFS, mo (95% CI)	5.4 (3.7-11.2)	1.9 (1.8-8.6)	4.5 (1.9-7.4)

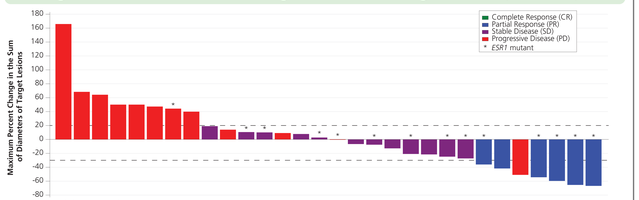
DoR, duration of response in RE patients who had confirmed responses; TTR, time to response in RE patients who had confirmed responses.

Figure 3. Duration of Treatment (Parts A-D)*



*Includes patients treated at 400 mg elacestrant

Figure 4. Maximum Percent Change in Sum of All Target Lesions (Parts A-D)†



†RE patient population; 400 mg dose
>20% increase in sum of diameters (progression per RECIST v1.1) (dashed line at y-axis = 20)
>30% decrease in sum of diameters (partial response per RECIST v1.1) (dashed line at y-axis = -30)

Safety

- The median treatment duration for all patients treated at 400 mg was 3.8 months (range: 0.2-40.1); 3.7 months (range: 0.2-40.1) and 4.7 months (range: 0.5-25.3) for the capsule and tablet formulations, respectively.
- Regardless of formulation, the most frequent all grade treatment-emergent AEs (TEAEs) were gastrointestinal (GI), fatigue, aspartate aminotransferase (AST) increased, and hypertriglyceridemia (**Table 4**).
- Regardless of formulation, the most frequent grade ≥3 TEAEs were AST and ALT increased, hypophosphatemia, vomiting, and nausea.
- GI events were generally less frequent and less severe with the tablet formulation.
- TEAEs leading to treatment discontinuation occurred in 6/26 (23%) patients receiving the 400 mg capsule (GI n=4, anemia n=1, and periorbital cellulitis n=1), and 1/24 (4%) patients receiving the 400 mg tablet (aortoesophageal fistula, n=1).
- Serious AEs (SAEs) occurred in 5/26 (19%) patients receiving the 400 mg capsule, and 8/24 (33%) patients receiving the 400 mg tablet.
  - Treatment-related SAEs with the capsule and tablet occurred in 0/26 (0%) and 1/24 (4.2%; acute hepatic failure) patients, respectively.
- No treatment-related deaths occurred.

Table 4. TEAEs Occurring in ≥15% of Patients*

Preferred Term†	400 mg Capsule (N=26) All Grades, n (%)	400 mg Capsule (N=26) Grade ≥3, n (%)	400 mg Tablet (N=24) All Grades, n (%)	400 mg Tablet (N=24) Grade ≥3, n (%)	All 400 mg (N=50) All Grades, n (%)	All 400 mg (N=50) Grade ≥3, n (%)
Gastrointestinal disorders	**24 (92.3)**	**5 (19.2)**	**19 (79.2)**	**2 (8.3)**	**43 (86.0)**	**7 (14.0)**
Nausea	17 (65.4)	2 (7.7)	8 (33.3)	0	25 (50.0)	2 (4.0)
Dyspepsia	11 (42.3)	0	5 (20.8)	0	16 (32.0)	0
Vomiting	11 (42.3)	2 (7.7)	4 (16.7)	0	15 (30.0)	2 (4.0)
Constipation	5 (19.2)	0	5 (20.8)	0	10 (20.0)	0
Diarrhea	9 (34.6)	0	3 (12.5)	0	12 (24.0)	0
GERD	7 (26.9)	0	2 (8.3)	0	9 (18.0)	0
General disorders and administration site conditions	**13 (50.0)**	**0**	**10 (41.7)**	**2 (8.3)**	**23 (46.0)**	**2 (4.0)**
Fatigue	9 (34.6)	0	5 (20.8)	0	14 (28.0)	0
Metabolism and nutrition disorders	**8 (30.8)**	**2 (7.7)**	**16 (66.7)**	**3 (12.5)**	**24 (48.0)**	**5 (10.0)**
Hypertriglyceridemia	6 (23.1)	1 (3.8)	6 (25.0)	0	12 (24.0)	1 (2.0)
Hyperglycemia	7 (26.9)	0	4 (16.7)	1 (4.2)	11 (22.0)	1 (2.0)
Hypophosphatemia	4 (15.4)	1 (3.8)	6 (25.0)	2 (8.3)	10 (20.0)	3 (6.0)
Musculoskeletal and connective tissue disorders	**12 (46.2)**	**0**	**12 (66.7)**	**1 (4.2)**	**24 (48.0)**	**1 (2.0)**
Back pain	5 (19.2)	0	4 (16.7)	0	9 (18.0)	0
Arthralgia	4 (15.4)	0	4 (16.7)	0	8 (16.0)	0
Nervous system disorders	**7 (26.9)**	**0**	**13 (54.2)**	**4 (16.7)**	**20 (40.0)**	**4 (8.0)**
Headache	3 (11.5)	0	5 (20.8)	0	8 (16.0)	0
Investigations	**12 (46.2)**	**5 (19.2)**	**9 (37.5)**	**1 (4.2)**	**21 (42.0)**	**6 (12.0)**
AST increased	9 (34.6)	4 (15.4)	3 (12.5)	0	12 (24.0)	4 (8.0)
ALT increased	6 (23.1)	2 (7.7)	3 (12.5)	0	9 (18.0)	2 (4.0)
Respiratory, thoracic, and mediastinal disorders	**9 (34.6)**	**2 (7.7)**	**8 (33.3)**	**2 (8.3)**	**17 (34.0)**	**4 (8.0)**
Cough	4 (15.4)	0	4 (16.7)	0	8 (16.0)	0
Blood and lymphatic system disorders	**6 (23.1)**	**2 (7.7)**	**4 (16.7)**	**0**	**10 (20.0)**	**2 (4.0)**
Anemia	5 (19.2)	1 (3.8)	3 (12.5)	0	8 (16.0)	1 (2.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GERD, gastroesophageal reflux disease
*TEAEs are presented in order of descending frequency grouped by system organ class based on all patients treated at 400 mg elacestrant in the ITT population.
†Each patient was counted once under the highest severity for each preferred term.

Conclusions

- Elacestrant at the RP2D of 400 mg orally QD has an acceptable safety profile. Tolerability was improved with the tablet formulation.
- Elacestrant 400 mg orally QD demonstrated single-agent activity with confirmed partial responses in heavily pre-treated patients with advanced ER+ breast cancer, including those with *ESR1* mutations, prior CDK4/6i and/or prior fulvestrant.
  - The ORR of 19.4% and mPFS of 4.5 months compare favorably with those reported for fulvestrant and AIs given in earlier treatment settings.
- These data provided the rationale for the phase 3 study of elacestrant ("EMERALD") comparing the efficacy and safety of elacestrant vs. standard-of-care endocrine treatment (fulvestrant or aromatase inhibitor) in patients with ER+/HER2- advanced BC (NCT03778931).[7]

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Author Disclosure: V. Kaklamani: Consulting Fees; Author; Amgen, Eisai, Puma, Celldex, AstraZeneca, Athenex. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents; Author; Pfizer, Celgene, Genentech, Genomic Health, Puma, Eisai, Novartis. Other; Author; Eisai. A. Bardia: Consulting Fees; Author; Novartis, Pfizer, Genentech/Roche, Radius, Merck, Spectrum Pharma, Immunomedics, Sanofi, Taho Pharma, Daiichi. Other, Author; Biotheranostics, Novartis, Pfizer, Genentech/Roche, Radius, Merck, Spectrum Pharma, Immunomedics, Sanofi, Mersana. S. Wilks: None. A. Weise: None. D. Richards: None. W. Harb: None. C. Osborne: None. R. Wesolowski: Consulting Fees; Author; Pfizer. M. Karuturi: None. P. Conkling: Other, Author; Roche, BMS, US Oncology Research. Radius authors are employees of and own company stock in Radius Health, Inc. PKabos: Contracted Research; Author; Radius Health, AstraZeneca, Pfizer, Eli Lilly, Sanofi, Genentech.This study was sponsored by Radius Health, Inc. on behalf of its wholly owned subsidiary, Radius Pharmaceuticals, Inc. and were funded by Radius Health, Inc. on behalf of its wholly owned subsidiary, Radius Pharmaceuticals, Inc.