Phase I Study of Elacestrant (RAD1901), a Novel Selective Estrogen Receptor Degrader, in ER-Positive, HER2-Negative Advanced Breast Cancer

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PURPOSE This phase I study (RAD1901-005; NCT02338349) evaluated elacestrant, an investigational oral selective estrogen receptor degrader (SERD), in heavily pretreated women with estrogen receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer, including those with estrogen receptor gene alpha (ESR1) mutation. The primary objective was to determine the maximum tolerated dose and/or recommended phase II dose (RP2D).

METHODS The study consisted of a 3+3 design (elacestrant capsules) followed by expansion at RP2D (400-mg capsules, then 400-mg tablets) for the evaluation of safety and antitumor activity. Elacestrant was taken once daily until progression or intolerability.

RESULTS Of 57 postmenopausal women enrolled, 50 received RP2D (400 mg once daily): median age, 63 years; median three prior anticancer therapies, including cyclin-dependent kinase 4,6 inhibitors (CDK4/6i; 52%), SERD (52%), and ESR1 mutation (circulating tumor DNA; 50%). No dose-limiting toxicities occurred; the most common adverse events at RP2D (400-mg tablet; n = 24) were nausea (33.3%) and increased blood triglycerides and decreased blood phosphorus (25.0% each). Most adverse events were grade 1-2 in severity. The objective response rate was 19.4% (n = 31 evaluable patients receiving RP2D), 15.0% in patients with prior SERD, 16.7% in patients with prior CDK4/6i, and 33.3% in patients with ESR1 mutation (n = 5/15). The clinical benefit rate (24-week) was 42.6% overall (n = 47 patients receiving RP2D), 56.5% (n = 23, ESR1 mutation), and 30.4% (n = 23, prior CDK4/6i). Elacestrant clinical benefit was associated with decline in ESR1 mutant allele fraction.

CONCLUSION Elacestrant 400 mg orally once daily has an acceptable safety profile and demonstrated single-agent activity with confirmed partial responses in heavily pretreated patients with estrogen receptor–positive metastatic breast cancer. Notably, responses were observed in patients with ESR1 mutation as well as those with prior CDK4/6i and prior SERD. A phase III trial investigating elacestrant versus standard endocrine therapy is ongoing.

J Clin Oncol 39:1360-1370. © 2021 by American Society of Clinical Oncology

INTRODUCTION Endocrine therapy (ET) is the mainstay treatment for patients with estrogen receptor–positive (ER+) metastatic breast cancer (mBC). However, the majority of patients with ER+ mBC experience disease progression, likely related to the development of resistance to ET. Notably, estrogen receptor gene alpha (ESR1) mutations are associated with acquired ET resistance and shorter progression-free survival (PFS) in patients receiving aromatase inhibitors (AIs), whereas PFS in patients treated with the selective estrogen receptor degrader (SERD) fulvestrant remains similar regardless of ESR1 mutation status. However, acquired ESR1 mutations also occur following fulvestrant treatment, possibly because of poor bioavailability and incomplete ER blockade by the required route of intramuscular administration. Fulvestrant is the only SERD approved for the treatment of postmenopausal women with hormone receptor–positive mBC. Thus, there is an unmet need for an SERD with activity in tumors harboring ESR1 mutations and improved bioavailability allowing oral administration, and therefore possibly improved activity.

Elacestrant is an investigational, nonsteroidal, oral SERD that degrades the ER in a dose-dependent
**CONTEXT**

**Key Objective**
What is the recommended phase II dose of the novel oral selective estrogen receptor degrader elacestrant, and what is the preliminary efficacy and safety in postmenopausal women with advanced breast cancer with and without estrogen receptor gene alpha (ESR1) mutation?

**Knowledge Generated**
The recommended phase II dose of 400 mg once daily was safe and well-tolerated; adverse events were predominately grade 1-2 GI events.

In patients with a median of three prior lines of therapy for advanced breast cancer, 50% of whom had ≥ 1 ESR1 mutation, elacestrant 400 mg once daily demonstrated an objective response rate of 19.4%, including responses in patients with ESR1 mutation and overall clinical benefit rate (24 weeks) of 42.6%.

**Relevance**
These data demonstrated safety and preliminary antitumor activity of elacestrant, providing rationale for the phase III study comparing the efficacy and safety of elacestrant versus standard-of-care endocrine therapy (fulvestrant or aromatase inhibitor) in patients with estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer (EMERALD; ClinicalTrials.gov identifier: NCT03778931).

**METHODS**

**Study Design**
RAD1901-005 was a multicenter, open-label, four-part, dose-escalation study conducted at 11 centers in the United States between April 2015 and October 2019. The study was originally designed as a two-part study evaluating safety, tolerability, and preliminary antitumor efficacy of elacestrant in a 3 + 3 dose-escalation phase (part A), followed by a safety expansion phase at the RP2D (part B)—both using a capsule formulation. Following the development of a tablet formulation, the design was amended to add two sequential cohorts: part C to evaluate the tablet administered at RP2D and part D to evaluate the tablet at RP2D in a more heavily pretreated patient population, including patients with prior CDK4/6i and fulvestrant and ≥ 2 lines of prior endocrine therapies for mBC (Data Supplement, online only).

The primary end point was the frequency of dose-limiting toxicities (DLTs) during the first 28 days of treatment (part A). Secondary end points included safety, PK, and investigator-assessed tumor response using RECIST v 1.1. Exploratory end points included correlation of tumor response with baseline ESR1 mutation status measured in ctDNA.

The study Protocol (online only) and supporting documents were approved by the institutional review board at each site. Written informed consent was obtained from all participants. The study was performed in accordance with ethical principles consistent with the Declaration of Helsinki and International Council of Harmonisation/Good Clinical Practice and applicable regulatory requirements.

**Patients**
For all study parts, eligible patients were women of age ≥ 18 years and postmenopausal (defined in the Data Supplement) with ER+ (≥ 1% staining by immunohistochemistry) and HER2—locally advanced, inoperable, and/or metastatic breast adenocarcinoma and Eastern Cooperative Oncology Group performance status 0-1. Exclusion criteria included treatment with strong cytochrome 3A4 inducers or inhibitors; any ET within 14 days; chemotherapy within 28 days; luteinizing hormone-releasing hormone analogue within 12 months; and endometrial disorders, clinically significant cardiac disease, or history of thrombotic coagulopathy within prior 6 months. Prior anticancer therapy requirements differed between parts A-C and part D (Data Supplement). Briefly, parts A-C required ≤ 2 prior lines of chemotherapy for advanced or metastatic breast cancer and ≥ 6 months of prior ET in any...
TABLE 1. Demographics and Baseline Characteristics in Patients Receiving Elacestrant 400 mg Once Daily

| Parameter                                      | All Patients Receiving 400 mg N = 50 |
|------------------------------------------------|--------------------------------------|
| Median age, years (range)                      | 63.0 (43-81)                         |
| Race, n (%)                                    |                                      |
| White                                          | 45 (90.0)                            |
| Black or African American                      | 4 (8.0)                              |
| ECOG PS, n (%)                                 |                                      |
| 0                                              | 26 (52.0)                            |
| 1                                              | 24 (48.0)                            |
| mBC, n (%)                                     | 50 (100)                             |
| Visceral disease,* n (%)                       | 35 (70.0)                            |
| Bone-only disease, n (%)                       | 10 (20)                              |
| ESR1 mutation status; n (%)                    |                                      |
| ESR1 mutation detected                        | 25 (50.0)                            |
| No ESR1 mutation detected                     | 25 (50.0)                            |
| Number of lines of prior therapies (any setting), median (range) | 3.0 (1-7) |
| Prior treatment (advanced or mBC setting)      |                                      |
| Number of lines of prior therapies, median (range) | 3.0 (1-7) |
| Prior CDK4/6i, n (%)                           | 26 (52.0)                            |
| Prior mTORi, n (%)                             | 14 (28.0)                            |
| Prior chemotherapy, n (%)                      | 21 (42.0)                            |
| ≥ 2 prior chemotherapy regimens, n (%)         | 4 (8.0)                              |
| Prior ET, n (%)                                | 50 (100)                             |
| Number of prior lines of ET, median (range)    | 2.5 (1-7)                            |
| ≥ 2 prior lines of ET, n (%)                   | 38 (76.0)                            |
| Prior SERD, n (%)                              | 26 (52.0)                            |

Abbreviations: CDK4/6i, cyclin-dependent kinase 4,6 inhibitors; ECOG PS, Eastern Cooperative Oncology Group performance status; ESR1, estrogen receptor gene alpha; ET, endocrine therapy; mBC, metastatic breast cancer; mTORi, mammalian target of rapamycin inhibitor; SERD, selective estrogen receptor degrader.

*Visceral disease included CNS, liver, lung, peritoneum, and pleura.

Baseline ESR1 mutation status was based on Guardant360 assay. When Guardant results were unavailable, ESR1 status was based on the OncoBEAM assay.

setting with no limit on the number of lines of prior ET; part D required ≤ 1 prior line of chemotherapy for advanced or metastatic breast cancer, ≥ 2 prior lines of ET for advanced or metastatic breast cancer (as single agent or in combination, including one prior line of treatment with fulvestrant required with documented progression), and prior CDK4/6i. Full eligibility criteria are described in the Data Supplement.

Study Procedures

Patients were instructed to take elacestrant orally once daily approximately 30 minutes after a light meal. Elacestrant was provided as either multiple 100-mg capsules or a single 400-mg tablet. Elacestrant was continued until disease progression, intolerability, or withdrawn consent. Dosing interruptions < 7 days, but no dose reductions, were permitted for adverse events (AEs).

In part A, up to 18 patients were planned to be assigned sequentially to escalating doses of elacestrant with capsule formulation using a standard 3 + 3 design (200 mg-1,000 mg once daily in 200-mg dose increments), with a minimum of three to six evaluable patients at each dose. Dose escalation continued until the maximum tolerated dose (defined in the Data Supplement) was identified or an RP2D was selected based on safety and preliminary efficacy evaluations. In part B and part C, up to an additional 20 and 12 patients, respectively, were to be enrolled to evaluate the safety, tolerability, and preliminary efficacy of the RP2D of the capsule formulation (part B) and tablet formulation (part C). In part D, 36 patients with more specified prior anticancer therapies were to be enrolled to inform the planned phase II study design; change in corporate strategy led to early termination of enrollment after 10 patients in this cohort.

Assessments

Study visits occurred weekly for 1 month, then monthly, with a follow-up for 30 days after discontinuation of treatment or until resolution/stabilization of treatment-related AEs to grade ≤ 2. Physical examination, vital signs, hematology, chemistry and coagulation laboratory investigations, Eastern Cooperative Oncology Group assessment, and 12-lead ECG were performed monthly and at the end of treatment (EOT).

Tumor assessments (RECIST v1.1) were performed at baseline and then every 8 weeks. Responses were confirmed ≥4 weeks after the first documented response. Blood samples for ctDNA analysis were collected at screening, during treatment, and at the EOT. ESR1 mutations in ctDNA samples in parts A-C were analyzed using the OncoBEAM platform (Sysmex Inostics, Hamburg, Germany); samples in part D were analyzed using the Guardant360 assay (Guardant Health, Redwood City, CA); when residual samples were available, part A-C samples were retested using the Guardant assay (assay details in the Data Supplement). Blood samples for PK were collected pre- and postdose on day 8 and predose on day 28 and monthly (details in the Data Supplement). AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs v4.03 and coded using Medical Dictionary for Regulatory Activities, v17.1.

Statistical Methods

Data were summarized descriptively by dose cohort and the overall population treated at the RP2D. Safety data are presented separately for patients treated with capsule and tablet formulations. Efficacy data are presented for all parts combined, as well as for parts A-C and part D separately.
and patients with ESRI mutation, prior SERD, and prior CDK4/6i. Analysis populations are defined in the Data Supplement.

Response analyses were performed on the response-evaluable (RE) population. Analyses of clinical benefit rate (CBR; defined as partial response plus stable disease for ≥ 24 weeks) were performed on the clinical benefit-evaluable (CBE) population. Analyses of PFS using the Kaplan-Meier method were performed on the intent-to-treat population.

RESULTS

A total of 57 postmenopausal women with ER⁺, HER2− mBC were enrolled (Data Supplement), 50 at the RP2D of 400 mg once daily (26 with capsule and 24 with tablet). Baseline characteristics are presented for patients who received the RP2D (all patients, Table 1; by study part, Data Supplement) and for all dose cohorts (Data Supplement). In patients who received the RP2D, median age was 63 years; median number of prior lines of anticancer therapies in all settings and in the advanced setting was three; 52.0% of patients had prior CDK4/6i; and 52.0% had a prior SERD. ESRI mutations were detected at baseline in 50% of patients treated at RP2D. The most common ESRI mutations were D538G and Y537S; 44.0% of patients had ESRI mutation (Fig 1A and Data Supplement). The frequency of ESRI mutations increased with increasing lines of prior ET and was highest among patients with prior AI therapy (Fig 1B).

Safety

Dose escalation proceeded to 600 mg once daily. No DLTs were reported; however, upper GI events (grade 1-2 nausea, vomiting, dyspepsia, esophageal pain, gastroesophageal
reflux disease, and eructation) were concerning for long-term tolerability at 600 mg. Therefore, 400 mg once daily was selected as the RP2D. Expansion cohorts in parts B, C, and D confirmed acceptability of the safety profile.

For all patients receiving elacestrant 400 mg (parts A-D), the most common treatment-emergent AEs (TEAEs) were nausea (50.0%), dyspepsia (32.0%), vomiting (30.0%), and fatigue (28.0%; Table 2). These TEAEs all occurred with lower frequency among the 24 patients receiving one 400-mg tablet compared with the 26 patients receiving four 100-mg capsules: nausea (33.3% vs 65.4%, respectively), dyspepsia (20.8% vs 42.3%), vomiting (16.7% vs 42.3%), and fatigue (20.8% vs 34.6%). The majority of these events were of grade 1-2 severity. At the 400-mg dose level, grade 3-4 TEAEs occurred in 10 patients (41.7%) receiving the tablet and 12 patients (46.2%) receiving capsules. The most common grade 3-4 TEAEs in patients receiving the tablet were syncope (clinical event detailed in the Data Supplement) and decreased blood phosphorus, occurring in two patients each (8.3%). TEAEs leading to dose interruption and discontinuation and serious TEAEs are summarized in Table 2 and the Data Supplement. Dose interruptions for any reason occurred in 23 patients (46.0%).

### Pharmacokinetics

Limited PK data were collected. The elacestrant plasma concentrations were similar between the tablet and capsule formulations at the two observation time points (predose and 4-hour postdose) (Data Supplement). Although this comparison does not reach the level of a bioequivalence assessment, these plasma concentration data supported the use of the tablet formulation in part D.

### TABLE 2. TEAEs in Patients Receiving Elacestrant 400-mg Tablets or Capsules

| Preferred Term* | Elacestrant 400-mg Tablet (n = 24) | Elacestrant 400-mg Capsule (n = 26) | All Elacestrant 400-mg (N = 50) |
|------------------|-----------------------------------|------------------------------------|---------------------------------|
|                  | All Grades, n (%) Grade 3-4, n (%) | All Grades, n (%) Grade 3-4, n (%) | All Grades, n (%) Grade 3-4, n (%) |
| Any TEAE         | 22 (91.7) 10 (41.7)               | 26 (100) 12 (46.2)                | 48 (96.0) 22 (44.0)             |
| TEAE leading to treatment discontinuation | 1 (4.2) 1 (4.2) | 5 (19.2) 3 (11.5) | 6 (12.0) 4 (10.0) |
| Serious TEAE     | 8 (33.3) 8 (33.3)a                | 5 (19.2) 5 (19.2)a                | 13 (26.0) 13 (26.0)             |

Most common TEAEs occurring in ≥ 15% of all patients receiving 400 mg

| Preferred Term* | All Grades, n (%) | Grade 3-4, n (%) |
|------------------|------------------|------------------|
| Nausea           | 8 (33.3) 0       | 17 (66.4) 2 (7.7) |
| Dyspepsia        | 5 (20.8) 0       | 11 (42.3) 0 |
| Vomiting         | 4 (16.7) 0       | 11 (42.3) 2 (7.7) |
| Fatigue          | 5 (20.8) 0       | 9 (34.6) 0 |
| AST increased    | 3 (12.5) 0       | 9 (34.6) 4 (15.4) |
| Diarrhea         | 3 (12.5) 0       | 9 (34.6) 0 |
| Blood triglycerides increased | 6 (25.0) 0 | 6 (23.1) 1 (3.8) |
| Blood glucose increased | 4 (16.7) 1 (4.2) | 7 (26.9) 0 |
| Constipation     | 5 (20.8) 0       | 5 (19.2) 0 |
| Blood phosphorus decreased | 6 (25.0) 2 (8.3) | 4 (15.4) 1 (3.8) |
| Gastroesophageal reflux disease | 2 (8.3) 0 | 7 (26.9) 0 |
| ALT increased    | 3 (12.5) 0       | 6 (23.1) 2 (7.7) |
| Back pain        | 4 (16.7) 0       | 5 (19.2) 0 |
| Anemia           | 3 (12.5) 0       | 5 (19.2) 1 (3.8) |
| Blood cholesterol increased | 4 (16.7) 0 | 4 (15.4) 1 (3.8) |
| Arthralgia       | 4 (16.7) 0       | 4 (15.4) 0 |
| Cough            | 4 (16.7) 0       | 4 (15.4) 0 |

NOTE. Each patient was counted once under the highest severity.

Abbreviations: ALT, alanine aminotransferase; TEAEs, treatment-emergent adverse events.

aTEAEs are presented by Preferred Term in order of descending frequency based on all patients treated with 400 mg elacestrant.

bSerious TEAEs occurring with the elacestrant 400-mg tablet were syncope (n = 2) and disease progression, acute hepatic failure, anxiety, aorto-esophageal fistula, aphasia, encephalopathy, facial bone fracture, failure to thrive, gastroenteritis, viral gastroenteritis, hypoxia, laryngeal hemorrhage, noncardiac chest pain, pneumonia, and pulmonary embolism (n = 1 each). Serious TEAEs occurring with the elacestrant 400-mg capsule were disease progression, blood triglycerides increased, periorbital cellulitis, orbital cellulitis, depression, dyspnea, pneumothorax, and small-intestinal obstruction (n = 1 each).

cOne patient receiving 400-mg tablet and one patient receiving 400-mg capsule had a grade 5 event of disease progression.
FIG 2. Duration of treatment in patients treated with 400 mg of elacestrant in parts A-D (A) and maximum percent change in sum of diameters of all target lesions (B) in response-evaluable patients treated with 400 mg of elacestrant in parts A-D. Baseline ESR1 mutation status is based on Guardant360 assay. When Guardant results were unavailable, ESR1 status was based on Sysmex OncoBEAM assay. *Other includes Y537C, E542D, L536_Y537del, S463P, and V534L. CBE, clinical benefit–evaluable; CDK4/6i, cyclin-dependent kinase 4,6 inhibitors; ESR1, estrogen receptor gene alpha; PD, progressive disease; PR, partial response; RE, response-evaluable; SD, stable disease; SERD, selective estrogen receptor degrader.
**TABLE 3. Antitumor Activity in Patients Receiving Elacestrant 400 mg Once Daily**

| Parameter                                      | All Patients Receiving 400 mg N = 50 |
|------------------------------------------------|--------------------------------------|
| RE population, n                               | 31                                   |
| ORR, n (%)                                      | 6 (19.4)                             |
| Complete response                              | 0                                    |
| Partial response                               | 6 (19.4)                             |
| Stable disease                                 | 12 (38.7)                            |
| Progressive disease                            | 13 (41.9)                            |
| ORR by ESR1 mutation status, % (n/N)            |                                      |
| ESR1 mutation detected                         | 33.3 (5/15)                          |
| No ESR1 mutation detected                      | 6.3 (1/16)                           |
| ORR by prior SERD, % (n/N)                      |                                      |
| Prior SERD                                     | 15.0 (3/20)                          |
| No prior SERD                                  | 27.3 (3/11)                          |
| ORR by prior CDK4/6i, % (n/N)                   |                                      |
| Prior CDK4/6i                                   | 16.7 (3/18)                          |
| No prior CDK4/6i                                | 23.1 (3/13)                          |
| Median DoR, weeks (range)                       | 24.9 (13.4-44.3)                     |
| Median TRR, weeks (range)                       | 8.2 (7.9-40.0)                       |
| CBE population, n                              | 47                                   |
| CBR, n (%)                                     | 20 (42.6)                            |
| CBR by ESR1 mutation status, % (n/N)            |                                      |
| ESR1 mutation detected                         | 56.5 (13/23)                         |
| No ESR1 mutation detected                      | 29.2 (7/24)                          |
| CBR by prior SERD, % (n/N)                      |                                      |
| Prior SERD                                     | 33.3 (8/24)                          |
| No prior SERD                                  | 52.2 (12/23)                         |
| CBR by prior CDK4/6i, % (n/N)                   |                                      |
| Prior CDK4/6i                                   | 30.4 (7/23)                          |
| No prior CDK4/6i                                | 54.2 (13/24)                         |
| ITT population, n                              | 50                                   |
| Median PFS, months (95% CI)                     | 4.5 (1.9 to 7.4)                     |
| Median PFS by ESR1 mutation status, months (95% CI) | 7.4 (3.7 to 13.0)                 |
| ESR1 mutation detected                         | 2.8 (1.9 to 5.4)                     |
| Median PFS by prior SERD, months (95% CI)       |                                      |
| Prior SERD                                     | 3.7 (1.8 to 5.9)                     |
| No prior SERD                                  | 7.4 (3.7 to 13.0)                    |
| Median PFS by prior CDK4/6i, months (95% CI)    |                                      |
| Prior CDK4/6i                                   | 3.8 (1.9 to 5.4)                     |
| No prior CDK4/6i                                | 7.4 (1.9 to 16.8)                    |

Abbreviations: CBE, clinical benefit–evaluable; CBR, clinical benefit rate (defined as partial response plus stable disease ≥ 24 weeks); CDK4/6i, cyclin-dependent kinase 4,6 inhibitors; DoR, duration of response in RE patients who had confirmed responses; ESR1, estrogen receptor gene alpha; ITT, intent-to-treat; ORR, objective response rate; PFS, progression-free survival; RE, response–evaluable; SERD, selective estrogen receptor degrader; TTR, time to response in RE patients who had confirmed responses.

**Antitumor Activity**

Among the 50 patients receiving 400 mg once daily, 31 patients were in the RE population and 47 patients were in the CBE population. Eleven patients (22.0%) remained on treatment for ≥ 12 months; the longest treatment duration was 43 months (Fig 2A).

A partial response was observed in six patients for an objective response rate (ORR) of 19.4% among all 31 patients receiving 400 mg once daily (Table 3, Fig 2B). Responses were observed in patients with prior SERD (15.0%) and prior CDK4/6i (16.7%). Median time to response was 1.9 months (range, 1.8-9.3); median duration of response was 5.8 months (range, 3.1-10.3). The CBR was 42.6% among the 47 patients who received 400 mg once daily. The overall median PFS was 4.5 months (Data Supplement). Data for parts A-C, part D, and the intent-to-treat population (all doses studied) are presented in the Data Supplement.

**Relationship Between ESR1 Mutation and Response**

Responses were observed in patients whose tumors harbored ESR1 mutation, including those commonly associated with ET resistance, that is, Y537S and D538G (Data Supplement). The ORR was 33.3% in patients with ESR1 mutation (n = 5/15) and 6.3% in patients with no ESR1 mutation (n = 1/16; Table 3). The CBR was 56.5% in patients with ESR1 mutation (n = 13/23) and 29.2% in patients with no ESR1 mutation (n = 7/24). Median PFS was 7.4 months in patients with ESR1 mutation and 2.8 months in patients with no ESR1 mutation.

Among the 25 patients with any baseline ESR1 mutation, 16 had at least one paired baseline and postbaseline sample, tested with the same assay, to assess the change in ESR1 mutant allele fraction (MAF). Among the 16 patients with any ESR1 mutation at baseline and at least one postbaseline sample (28 specific ESR1 mutations), reduction in MAF at cycle (C) 1 day (D) 28, C2D28, C3D28, and EOT occurred in 81.8%, 81.8%, 100%, and 73.1% of mutations, respectively (Fig 3A and Data Supplement). Among the eight patients with the most frequent ESR1 mutation, D538G, reduction in MAF at C1D28, C2D28, C3D28, and EOT occurred in 100%, 100%, 100%, and 75.0% of patients, respectively (Fig 3B). Patients with partial response tended to have decline in MAF on treatment, with rise in MAF at EOT (ie, disease progression) (Figs 3A and 3C).

**DISCUSSION**

This phase I study of elacestrant demonstrated no DLTs at doses ranging from 200 mg to 600 mg once daily, a tolerable safety profile with the RP2D of 400 mg once daily, and reduced GI toxicity with the tablet formulation. At the 400-mg once-daily dose, antitumor activity was observed in patients with ER+, HER2− mBC, including those with prior
fulvestrant and/or prior CDK4/6i and those patients whose tumors harbored *ESR1* mutations.

Patients were heavily pretreated with a median of three prior lines of therapy in the advanced or metastatic breast cancer setting, 76% having received ≥ 2 prior ET, 52% having received a prior SERD (ie, fulvestrant), and 52% having received a CDK4/6i. Additionally, 50% of patients had ≥ 1 *ESR1* mutation, consistent with extensive prior ET.²,¹² In this poor prognostic setting, elacestrant demonstrated an ORR of 19.4%, CBR of 42.6%, and median PFS of 4.5 months. Only nine RE patients were enrolled in part D, and they had received more prior ET (median, three lines v two lines in parts A–C), which may explain the lack of responses in part D.

Responses were observed with elacestrant in patients whose tumors harbored *ESR1* mutations that confer endocrine resistance, including Y537S and D538G. These data are consistent with results from a pharmacodynamic study (RAD1901-106) where elacestrant demonstrated an ORR and CBR of 11.1% and 30.8% among nine RE

**FIG 3.** Change in *ESR1* MAF for patients who received elacestrant 400 mg. Change in *ESR1* MAF for all mutations in all patients with any baseline (screen) *ESR1* mutation and at least one baseline and postbaseline sample tested with the same assay (A). Change in *ESR1* D538G MAF for all patients with baseline D538G mutation and at least one baseline and postbaseline sample tested with the same assay (B). Change in *ESR1* MAF for all *ESR1* mutations in four patients with PR who had paired *ESR1* data (C). C, cycle; CB, clinical benefit; EOT, end of treatment; *ESR1*, estrogen receptor gene alpha; MAF, mutant allele fraction; ND, mutation not detected; PR, partial response.
and 13 CBE patients, respectively, and a PFS of 5.3 months in a heavily pretreated population, of which 56% had ESR1 mutations. Study RAD1901-106 also demonstrated that elacestrant greatly reduced ER availability, as measured by 16α-18F-fluoro-17β-estradiol positron emission tomography with low-dose computed tomography imaging, showing a median reduction of 88% in tumor 16α-18F-fluoro-17β-estradiol uptake from baseline to day 14 that was consistent regardless of ESR1 mutation status. The decline in MAF of different ESR1 mutations with elacestrant in the present study also provides pharmacodynamic proof of principle of the RP2D and highlights broad activity across different ESR1 mutations. Additionally, it suggests the potential to use ESR1 MAF using ctDNA to monitor response to elacestrant therapy.

Elacestrant efficacy in ESR1-mutated tumors may indicate that ESR1 mutation identifies an ER-dependent tumor that is more likely to respond to an ER antagonist in the endocrine-refractory setting. Endocrine resistance is conferred by various genetic mutations in addition to and mutually exclusive from ESR1 mutation, including genes involved in mitogen-activated protein kinase signaling that may confer ER independence and therapeutic refractoriness to ER inhibition.

An unmet need exists for an oral SERD with improved activity, including tumors harboring ESR1 mutations. In trials evaluating fulvestrant monotherapy in predominantly second or later lines of therapy, response rates are approximately 10% or less. In BELLE-3, patients with AI pretreatment and endocrine/mTOR inhibitor combination therapy resistance demonstrated a 3% ORR to fulvestrant. Although elacestrant is the most advanced in clinical development, several investigational oral SERDs and an oral selective estrogen receptor covalent antagonist are in early development, including SAR439859, AZD9833, LSZ102, GDC-9545, G-1T48, and H3B-6545. Response rates for studies performed in a population of patients similar to the population used in this study have ranged from 1.3% for LSZ102 to 16% for AZD9833, with activity noted in patients with ESR1 mutations for most agents.

GI side effects of elacestrant were improved with the tablet formulation compared with the capsule formulation, possibly due to reduced number of pills required with the tablet formulation and/or dissolution of the tablet lower in the GI tract. All GI events were approximately halved in frequency with the tablet compared with the capsule: nausea, 33.3% versus 65.4%; dyspepsia, 20.8% versus 42.3%; vomiting, 16.7% versus 42.3%; and diarrhea, 12.5% versus 34.6%.
As such, all subsequent studies of elacestrant are performed with the tablet formulation.

Preliminary reports of safety data for other investigational SERDs and selective estrogen receptor covalent antagonist have reported diarrhea rates as high as 27% to > 50% with some SERDs, and other AEs including bradycardia, ranging from 8% to 45%, and visual disturbances in 53% of patients.

In conclusion, elacestrant at the RP2D of 400 mg orally once daily has an acceptable safety profile, suitability for administration as monotherapy or in combination with other targeted agents, and improved tolerability with the tablet formulation as compared with the initial capsule formulation with a safety profile characterized predominately by grade 1-2 GI events. Elacestrant demonstrated single-agent activity with confirmed partial responses in heavily pretreated postmenopausal women with advanced ER+ breast cancer, including those with prior CDK4/6i and prior fulvestrant as well as those whose tumors harbored ESR1 mutations that confer resistance to ET. These data provided the rationale for the phase III study comparing the efficacy and safety of elacestrant versus standard-of-care endocrine treatment (fulvestrant or AI) in patients with ER+, HER2− advanced breast cancer (EMERALD; NCT03778931), with the primary end point of PFS, assessed in both the overall population and the population of patients with ESR1 mutation. Elacestrant is the first oral SERD to be studied in a phase III clinical trial (activated in 2018), and this phase I study provides preliminary evidence of clinical activity as a potential new therapeutic class in breast cancer.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Phase I Study of Elacestrant (RAD1901), a Novel Selective Estrogen Receptor Degrader, in ER-Positive, HER2-Negative Advanced Breast Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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No other potential conflicts of interest were reported.