Giredestrant for Estrogen Receptor–Positive, HER2-Negative, Previously Treated Advanced Breast Cancer: Results From the Randomized, Phase II acelERA Breast Cancer Study

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ABSTRACT

PURPOSE To compare giredestrant and physician's choice of endocrine monotherapy (PCET) for estrogen receptor–positive, HER2-negative, advanced breast cancer (BC) in the phase II acelERA BC study (ClinicalTrials.gov identifier: NCT04576455).

METHODS Post-/pre-/perimenopausal women, or men, age 18 years or older with measurable disease/evaluable bone lesions, whose disease progressed after 1-2 lines of systemic therapy (≤1 targeted, ≤1 chemotherapy regimen, prior fulvestrant allowed) were randomly assigned 1:1 to giredestrant (30 mg oral once daily) or fulvestrant/aromatase inhibitor per local guidelines (+luteinizing hormone–releasing hormone agonist in pre-/perimenopausal women, and men) until disease progression/unacceptable toxicity. Stratification was by visceral versus nonvisceral disease, prior cyclin-dependent kinase 4/6 inhibitor, and prior fulvestrant. The primary end point was investigator-assessed progression-free survival (INV-PFS).

RESULTS At clinical cutoff (February 18, 2022; median follow-up: 7.9 months; N = 303), the INV-PFS hazard ratio (HR) was 0.81 (95% CI, 0.60 to 1.10; P = .1757). In the prespecified secondary end point analysis of INV-PFS by $ESR1$ mutation (m) status in circulating tumor DNA–evaluable patients (n = 232), the HR in patients with a detectable $ESR1$m (n = 90) was 0.60 (95% CI, 0.35 to 1.03) versus 0.88 (95% CI, 0.54 to 1.42) in patients with no $ESR1$m detected (n = 142). Related grade 3-4 adverse events (AEs), serious AEs, and discontinuations due to AEs were balanced across arms.

CONCLUSION Although the acelERA BC study did not reach statistical significance for its primary INV-PFS end point, there was a consistent treatment effect with giredestrant across most key subgroups and a trend toward favorable benefit among patients with $ESR1$-mutated tumors. Giredestrant was well tolerated, with a safety profile comparable to PCET and consistent with known endocrine therapy risks. Overall, these data support the continued investigation of giredestrant in other studies.

INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer in women, with an estimated 2.3 million new cases and 700,000 deaths in 2020.[1] Sixty to seventy percent of BCs do not overexpress HER2 but express the estrogen receptor (ER),[2] and most are dependent on the ER for growth and progression. ER-expressing BCs are treated with endocrine therapies (ETs) that suppress ER signaling, either by blocking estradiol synthesis (eg, aromatase inhibitors [AIs]), antagonizing the effects of estradiol via competitive binding of ERs (eg, selective ER modulators), or by fully antagonizing and degrading ERs (ie, selective ER antagonists and degraders [SERDs]).[3,4] However, despite the effectiveness of

CONTEXT

Key objective

Can the oral, selective estrogen receptor antagonist and degrader (SERD) giredestrant improve outcomes compared with physician's choice of endocrine therapy (PCET) in patients with pretreated, estrogen receptor–positive (ER+), HER2-negative, advanced breast cancer?

Knowledge Generated

Giredestrant did not show statistically significant superiority to PCET with regards to investigator-assessed progression-free survival. In patients with *ESR1*-mutated tumors, there was a trend toward favorable benefit with giredestrant. Giredestrant was well tolerated, with a safety profile comparable to PCET and consistent with known endocrine therapy risks.

Relevance *(G. Fleming)*

Hopeful results continue to emerge from studies of novel ER-targeting drugs, with a number appearing to show more activity than historically available agents in the presence of a tumor *ESR1* mutation. However their significance in the treatment algorithm for women with ER+, HER2-negative breast cancer remains to be determined.*

*Relevance section written by *JCO* Associate Editor Gini Fleming, MD.

available ETs, alone or combined with targeted agents such as cyclin-dependent kinase 4/6 inhibitors (CDK4/6is), advanced BC (aBC) remains incurable, with significant unmet needs in terms of reducing impact on quality of life (QoL) and delaying chemotherapy for as long as possible. In most patients with aBC, the tumor will ultimately progress because of primary or secondary ET resistance[5]; the optimal ET sequence in subsequent lines remains uncertain, and may depend on which agents were used previously in the early or advanced settings. Further considerations regarding the choice of therapy in the second line and beyond are duration of response (DoR) to previous ET (particularly for second-line ET), disease burden, patient preference, treatment availability, and mechanisms of resistance that may have arisen during previous treatments.[6,7] Despite being refractory to prior ET, growth and survival of ER-positive (ER+) tumors may often remain dependent on ER signaling, and tumors can still respond to second- or third-line ET after prior progression.[8] Continuing ET with agents not previously used in the advanced setting, either as monotherapy or combined with targeted agents, represents an option to delay chemotherapy initiation.[9]

A common mechanism of acquired resistance to ET is the presence of an activating mutation (m) in the ligand binding domain of *ESR1* that results in ligand-independent ER signaling.[10] Although fulvestrant has some activity in *ESR1*m tumors, it has unfavorable bioavailability and pharmacokinetics requiring intramuscular injection; therefore, new oral SERDs with more potent activity against *ESR1*m tumors are needed.[11,12]

Giredestrant is a highly potent, nonsteroidal, oral SERD, with a similar mechanism of action to, but superior preclinical potency over, fulvestrant and other oral SERDs.[12] Giredestrant

is well tolerated, and has shown encouraging antitumor activity in aBC as a monotherapy and in combination with palbociclib, including in patients with *ESR1*m tumors and those who have received prior fulvestrant.[12-18]

The phase II acelERA BC study (ClinicalTrials.gov identifier: NCT04576455) compares the efficacy and safety of giredestrant with physician's choice of endocrine monotherapy (PCET) for ER+, HER2-negative (HER2−) aBC in the second or third line. We report the primary results.

METHODS

Study Design and Patients

Patients were postmenopausal or pre-/perimenopausal women, and men, age 18 years or older who had received one or two prior lines of systemic therapy for ER+, HER2− locally advanced or metastatic BC. One of the prior lines must have been ET for ≥6 months; ≤1 targeted agent (including, but not limited to, CDK4/6is) was allowed; and one of the lines may have included chemotherapy. Patients had measurable (per RECIST v1.1[19]) or bone-only disease, which must have had ≥1 predominantly lytic bone lesion. Key exclusion criteria included prior treatment with an investigational SERD (prior fulvestrant was allowed, as long as it was terminated ≥28 days before random assignment); advanced, symptomatic, visceral spread that risked life-threatening complications in the short term; known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease; and active cardiac disease or history of cardiac dysfunction.

Eligible patients were randomly assigned 1:1 using a permuted-block method to receive giredestrant or PCET.

Random assignment was stratified by disease site (visceral [lung and/or liver involvement] v nonvisceral), prior CDK4/6i (yes v no), and prior fulvestrant (yes v no; Data Supplement, Fig S1, online only).

Study Oversight

acelERA BC was designed by the senior academic authors and representatives of the sponsor (F. Hoffmann-La Roche Ltd, Basel, Switzerland). Data were collected by the sponsor and analyzed in collaboration with the senior academic authors, who vouched for the completeness and accuracy of the data and analyses, and for the fidelity of the study to the protocol. acelERA BC was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Protocol approval was obtained from an independent ethics committee for each participating site. Every patient gave written informed consent. An internal monitoring committee comprising employees of the sponsor reviewed cumulative safety data periodically throughout.

Study Procedures/Assessments

Patients received once daily oral giredestrant 30 mg (F. Hoffmann-La Roche Ltd/Genentech, Inc, South San Francisco, CA) as part of 28-day cycles until disease progression or unacceptable toxicity, or PCET (fulvestrant or an AI per local guidelines). No dose reductions were allowed for giredestrant. Dose reductions for comparator drugs were allowed according to local prescribing information. Pre-/perimenopausal women, and men, also received luteinizing hormone−releasing hormone agonist. ER and HER2 status were assessed locally. ESR1 testing was performed centrally using the FoundationOne Liquid CDx assay (Foundation Medicine, Inc, Cambridge, MA) or the PredicineCARE assay (Huidu Shanghai Medical Sciences Ltd, Shanghai, China) on baseline plasma circulating tumor (ct)DNA, and mutations were defined as short nucleotide variants with known or likely impact on ER protein function based on Catalogue Of Somatic Mutations In Cancer (COSMIC) status. Tumors were assessed by computed tomography or magnetic resonance imaging according to RECIST v1.1[19] within 28 days before random assignment (baseline), every 8 weeks (±7 days) from random assignment for the first 18 months, and then every 12 weeks (±7 days) thereafter until disease progression (except bone scans, which were performed every 24 weeks ±7 days, or as clinically indicated). All radiologic data (eg, computed tomography scan, magnetic resonance imaging, bone scan), photographs of skin lesions, and any additional clinical information required were sent to a blinded, independent, core imaging laboratory (contracted by the sponsor) to facilitate a retrospective evaluation of disease response and progression for the full population by a blinded independent review committee (BIRC). Patient-reported outcome (PRO) assessments are described in the Data Supplement. Adverse events (AEs) were recorded and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and were evaluated at every patient visit from baseline until 30 days after study treatment discontinuation.

Study End Points

The primary end point was progression-free survival (PFS), defined as the time from random assignment to the first occurrence of disease progression or death from any cause (whichever occurred first), as determined by the investigator (INV-PFS). PFS was also assessed by a BIRC as a sensitivity analysis. Secondary end points included overall survival (OS; time from random assignment to death from any cause), confirmed objective response rate (ORR; proportion of patients with a complete response [CR] or partial response [PR] on two consecutive occasions ≥4 weeks apart), DoR (time from first occurrence of a documented objective response to disease progression, or death from any cause [whichever occurred first]), clinical benefit rate (CBR; proportion of patients with stable disease for ≥24 weeks, or a CR or PR), INV-PFS in subgroups categorized by baseline ESR1m status, PROs, pharmacokinetics, and safety. Tumor assessments were done according to RECIST v1.1.

Statistical Analysis

The full analysis set comprised all patients assigned to treatment groups as randomly assigned; the safety population, all randomly assigned patients who received ≥1 dose of giredestrant or PCET; the ctDNA-evaluable population, all randomly assigned patients with evaluable plasma ctDNA at baseline (excluding 71 patients because of sample nonavailability or testing failure); and the PRO-evaluable population, all patients with a baseline and ≥1 postbaseline PRO assessment. Efficacy end points were assessed in the full analysis set (except PFS by ESR1m status, which was assessed in the ctDNA-evaluable population).

The planned sample size was 300 patients. The primary analysis was planned for when approximately 166 INV-PFS events from both arms had occurred; this enabled 80% power to detect a target INV-PFS hazard ratio (HR) of 0.647 (corresponding to an improvement in median INV-PFS from 5.5 to approximately 8.5 months) at a 5% (two-sided) level of significance. The largest HR determined to be statistically significant (minimal detectable difference) was approximately 0.738. Data for patients without disease progression or death at clinical cutoff were censored at the time of the last tumor assessment (or at the time of random assignment +1 day if no tumor assessment was performed after the baseline visit). INV-PFS was compared between arms using the stratified log-rank test, with the HR estimated using a stratified Cox proportional hazards model (stratified
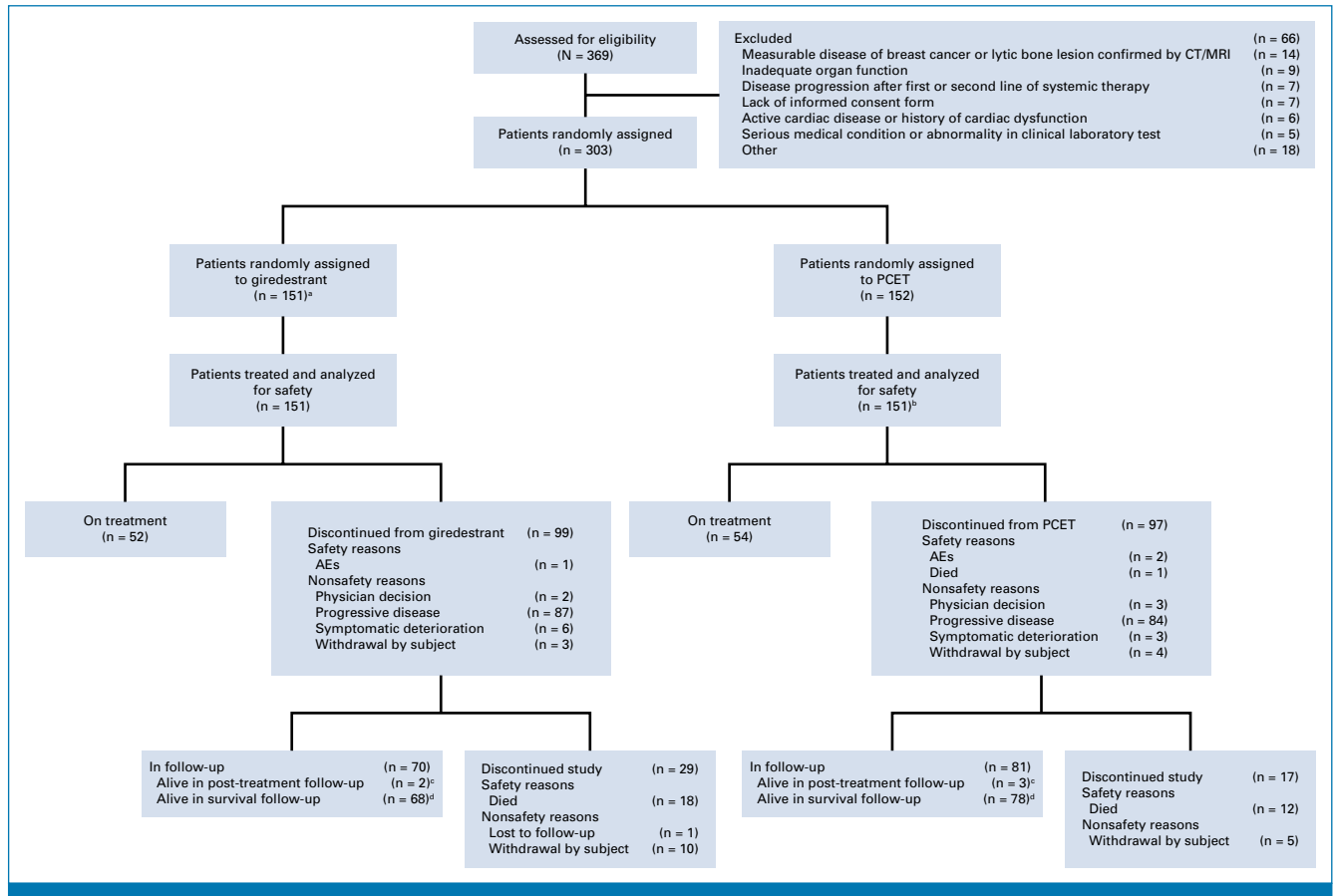
FIG 1. CONSORT diagram. [a]One patient was randomly assigned to the giredestrant arm but received fulvestrant. [b]Fulvestrant (n = 114), letrozole (n = 15), exemestane (n = 20), or anastrozole (n = 2). [c]Patients who discontinued treatment for reasons other than progressive disease. [d]Patients who discontinued treatment because of progressive disease. AE, adverse event; CT, computed tomography; MRI, magnetic resonance imaging; PCET, physician's choice of endocrine therapy.

by disease site, prior CDK4/6i, and prior fulvestrant). Un-stratified analyses were used for subgroups (excluding the secondary end point of INV-PFS in *ESR1*m tumors). For each treatment arm, Kaplan-Meier methodology was used to estimate median INV-PFS, and the Brookmeyer-Crowley method was used to construct the 95% CIs. OS was to be hierarchically tested using the same methodology if the primary end point was statistically significant at the primary analysis. For ORR analyses, patients without any postbaseline tumor assessment were considered nonresponders. An es-timate of ORR and its 95% CI were calculated using the Clopper-Pearson method for each treatment arm. ORRs were compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The difference in ORR be-tween treatment arms was calculated, and its 95% CI was calculated using the normal approximation to the binomial distribution. Analysis of DoR included only patients who had an objective response. The Kaplan-Meier approach was used to estimate the median DoR and the corresponding 95% CIs. CBR was analyzed using the same methods as those used for ORR. Safety analyses were descriptive.

RESULTS

Study Population

Between November 27, 2020, and October 27, 2021, 303 patients were enrolled (151 to giredestrant, 152 to PCET; Fig 1) across 85 sites in 17 countries. At clinical cutoff (February 18, 2022; median follow-up: 7.9 months), 106 patients (35.0%) were on treatment, 257 (84.8%) remained on study, and 46 (15.2%) had discontinued the study (Fig 1). In the PCET arm, 114 of 152 patients (75.0%) received ful-vestrant and 38 (25.0%) received an AI.

Baseline demographics and disease characteristics are shown in Table 1. All patients had metastatic disease, and most were from Asia or Europe, were postmenopausal, and had visceral disease. Prior treatments for aBC included a CDK4/6i, chemotherapy, and fulvestrant. In the ctDNA-evaluable population, an *ESR1*m was detected in 90 of 232 patients (38.8%), with higher prevalence in the giredestrant (51 of 117 [43.6%]) than the PCET arm (39 of 115 [33.9%]).

TABLE 1. Baseline Demographics, Disease Characteristics, and Prior Treatments in the FAS

Patient Demographic, Disease Characteristic, or Prior Treatment	Giredestrant (n = 151)	PCET (n = 152)	All (N = 303)
Age, years			
Median (range)	60.0 (28-85)	59.0 (32-93)	60.0 (28-93)
≥75, No. (%)	16 (10.6)	5 (3.3)	21 (6.9)
Female, No. (%)	151 (100)	151 (99.3)	302 (99.7)
Menopausal status, No. (%)			
Pre-/perimenopausal	23 (15.2)	27 (17.9)	50 (16.6)
Postmenopausal	128 (84.8)	124 (82.1)	252 (83.4)
Race, No. (%)			
American Indian or Alaska Native	1 (0.7)	0	1 (0.3)
Asian	58 (38.4)	66 (43.4)	124 (40.9)
Black or African American	2 (1.3)	2 (1.3)	4 (1.3)
White	89 (58.9)	81 (53.3)	170 (56.1)
Unknown	1 (0.7)	2 (1.3)	3 (1.0)
Multiple	0	1 (0.7)	1 (0.3)
Geographic region, No. (%)			
Asia	57 (37.7)	65 (42.8)	122 (40.3)
Europe	57 (37.7)	55 (36.2)	112 (37.0)
Australia	2 (1.3)	5 (3.3)	7 (2.3)
North America	4 (2.6)	1 (0.7)	5 (1.7)
Africa	3 (2.0)	5 (3.3)	8 (2.6)
South America	28 (18.5)	21 (13.8)	49 (16.2)
ECOG performance status, No. (%)			
0	75 (49.7)	82 (53.9)	157 (51.8)
1	76 (50.3)	70 (46.1)	146 (48.2)
Disease status, No. (%)			
Visceral[a]	104 (68.9)	103 (67.8)	207 (68.3)
Measurable	141 (93.4)	141 (92.8)	282 (93.1)
CNS involvement	3 (2.0)	3 (2.0)	6 (2.0)
Bone-only	14 (9.3)	14 (9.2)	28 (9.2)
PgR-negative	37 (24.5)	32 (21.1)	69 (22.8)
ESR1 status, No. (%)	n = 117	n = 115	n = 232[b]
Mutation detected	51 (43.6)	39 (33.9)	90 (38.8)
No mutation detected	66 (56.4)	76 (66.1)	142 (61.2)
Prior treatments for aBC, No. (%)			
Prior lines			
1	103 (68.2)	113 (74.3)	216 (71.3)
2	47 (31.1)	38 (25.0)	85 (28.1)
AI	123 (81.5)	111 (73.0)	234 (77.2)
Last prior line	102 (67.5)	94 (61.8)	196 (64.7)
Fulvestrant	30 (19.9)	28 (18.4)	58 (19.1)
Last prior line	24 (15.9)	25 (16.4)	49 (16.2)
Tamoxifen	20 (13.2)	32 (21.1)	52 (17.2)
Last prior line	15 (9.9)	24 (15.8)	39 (12.9)
Targeted	72 (47.7)	67 (44.1)	139 (45.9)
Last prior line	63 (41.7)	58 (38.2)	121 (39.9)
CDK4/6i	65 (43.0)	62 (40.8)	127 (41.9)
Last prior line	56 (37.1)	53 (34.9)	109 (36.0)
Chemotherapy	47 (31.1)	49 (32.2)	96 (31.7)
Last prior line	34 (22.5)	40 (26.3)	74 (24.4)

Abbreviations: aBC, advanced breast cancer; AI, aromatase inhibitor; BIRC, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Status; FAS, full analysis set; PCET, physician's choice of endocrine therapy; PgR, progesterone receptor.

[a]Visceral disease was defined as presence of liver and/or lung lesions. Looking specifically at liver involvement at baseline (by BIRC), there was a higher proportion of patients with at least one lesion in the liver in the giredestrant arm (37.1%) v the PCET arm (31.6%), which may have contributed to an observed imbalance in baseline AST (giredestrant: 9.3% v PCET: 0%) and ALT (giredestrant: 6.6% v PCET: 0.7%) levels, and might further be attributable to differences in tumor burden in the liver.

[b]Seventy-one patients were excluded because of nonavailability or testing failure of ctDNA sample.

Efficacy

The INV-PFS HR was 0.81 (95% CI, 0.60 to 1.10; P = .1757), with medians of 5.6 months in the giredestrant arm and 5.4 months in the PCET arm (patients with an event: 90 [59.6%] and 92 [60.5%]; Fig 2A). The INV-PFS rates at 6 months were 46.8% and 39.6% in the giredestrant and PCET arms, respectively. In the BIRC-PFS sensitivity analysis, the HR was 0.92 (95% CI, 0.64 to 1.33). In the prespecified secondary end point analysis of INV-PFS by *ESR1*m status in the ctDNA-evaluable population, the HR in patients with a detectable *ESR1*m was 0.60 (95% CI, 0.35 to 1.03; Fig 2B), versus 0.88 (95% CI, 0.54 to 1.42) in patients with no *ESR1*m detected (Data Supplement, Fig S2A). Further exploratory subgroup analyses for PFS are shown in Figure 2C-E and the Data Supplement (Figs S2B-S2G).

Secondary efficacy end points are shown in Table 2. Confirmed ORRs were all PRs, and OS data were immature. Most deaths were due to disease progression, with the imbalance between arms because of reasons classified as other, which were unrelated to study treatment and outside of the AE reporting period (COVID-19 [two patients], septic shock due to gastroenteritis, COVID-19 pneumonia, and septic shock in the giredestrant arm, and septicemia in the PCET arm [one patient each]; Table 2).

Safety

The mean dose intensity was 96.98% (standard deviation [SD], 9.60) for giredestrant and 99.57% (SD, 2.19) for PCET; treatment duration is shown in the Data Supplement (Table S1).

The safety profile is shown in Table 3. The most common AEs (in ≥10% of patients in either arm) were AST increased, arthralgia, ALT increased, anemia, and nausea. The most common grade 3-4 AEs (in ≥3 patients in either arm) were anemia, hypertension, AST increased, bone pain, and blood bilirubin increased. Selected AEs are also shown in Table 3; hepatotoxicity-related selected AEs and shift tables for liver function tests are shown in the Data Supplement (Tables S2 and S3, respectively).

In general, laboratory shifts from baseline for AST and ALT were consistent between the study arms, with a slightly higher number of patients in the giredestrant arm experiencing bilirubin shifts versus PCET.

Population	INV-PFS HR (95% CI)	mPFS, Months	CBR, %		ORR, %	
A) FAS						
Giredestrant (n = 151)	0.81 (0.60 to 1.10)	5.6	32		13	
PCET (n = 152)		5.4	21		7	
B) *ESR1*m						
Giredestrant (n = 51)	0.60 (0.35 to 1.03)	5.3	26		14	
PCET (n = 39)		3.5	3		NE	

No. at risk:

Giredestrant	151	109	81	50	27	8	2
PCET	152	105	70	40	19	6	2

Giredestrant	51	36	26	12	9	4	1
PCET	39	20	9	1			
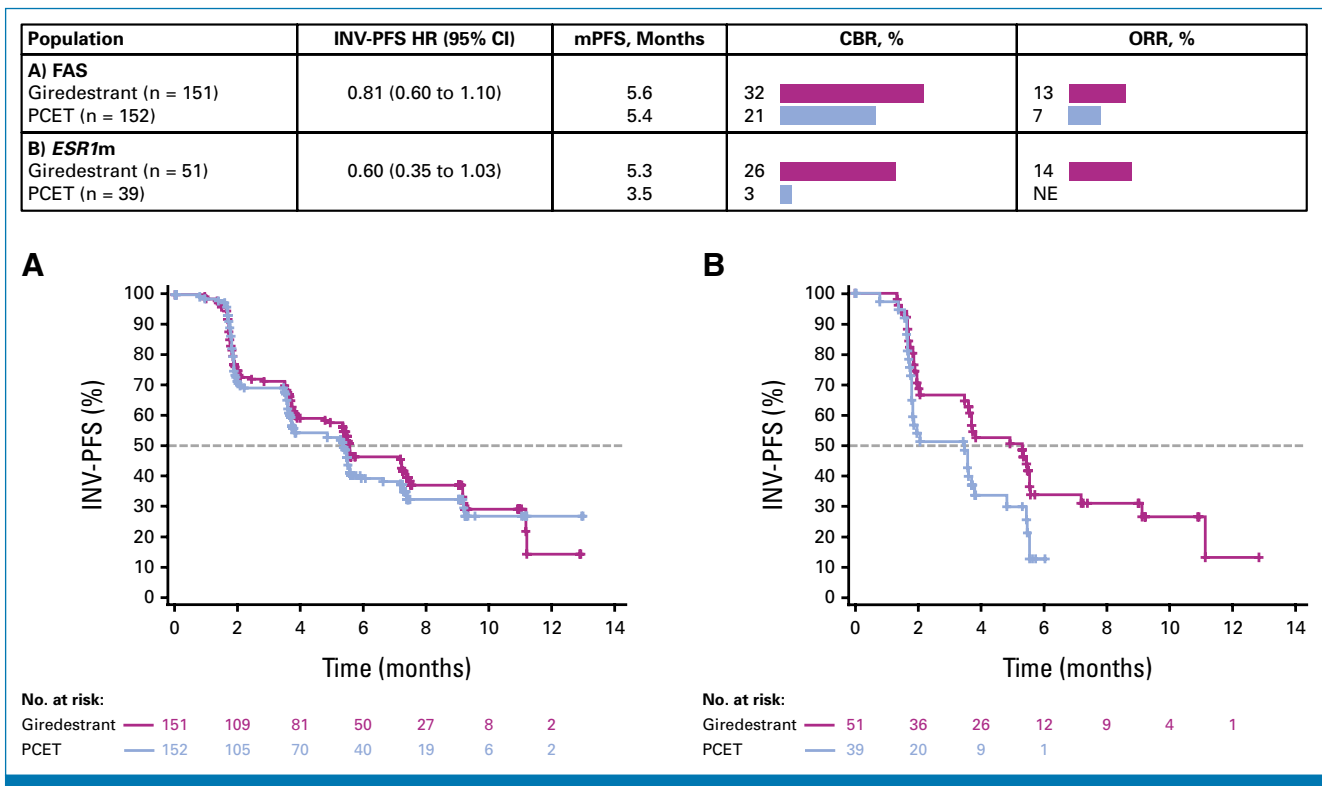
FIG 2. INV-PFS, CBR, and ORR in (A) the FAS (primary end point) and in (B) patients with *ESR1*m tumors; (C) INV-PFS in subgroups of the FAS. aBC, advanced breast cancer; CBR, clinical benefit rate (complete or partial response, or stable disease for ≥6 months, calculated in the FAS); CDK4/6, cyclin-dependent kinase 4/6; ECOG, Eastern Cooperative Oncology Group; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; FAS, full analysis set; HR, hazard ratio (stratified); INV-PFS, investigator-assessed progression-free survival; mPFS, median progression-free survival; mBC, metastatic breast cancer; NE, not evaluable; ORR, objective response rate (confirmed complete or partial response, calculated in the FAS); PCET, physician's choice of endocrine therapy; PgR, progesterone receptor. (continued on following page)

C

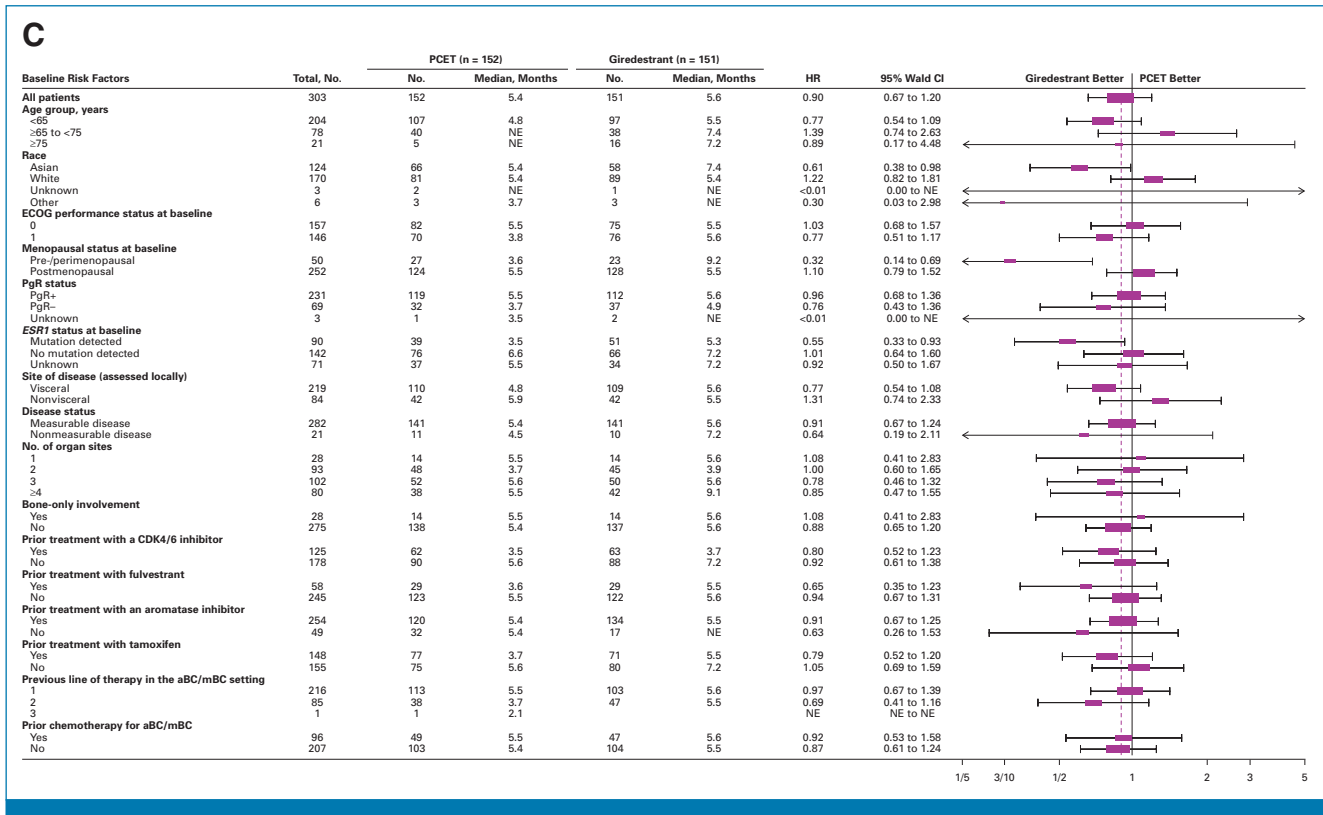| Baseline Risk Factors	Total, No.	PCET (n = 152)		Giredestrant (n = 151)		HR	95% Wald CI	Giredestrant Better | PCET Better
		No.	Median, Months	No.	Median, Months			
All patients	303	152	5.4	151	5.6	0.90	0.67 to 1.20	
Age group, years								
<65	204	107	4.8	97	5.5	0.77	0.54 to 1.09	
≥65 to <75	78	40	NE	38	7.4	1.39	0.74 to 2.63	
≥75	21	5	NE	16	7.2	0.89	0.17 to 4.48	
Race								
Asian	124	66	5.4	58	7.4	0.61	0.38 to 0.98	
White	170	81	5.4	89	5.4	1.22	0.82 to 1.81	
Unknown	3	2	NE	1	NE	<0.01	0.00 to NE	
Other	6	3	3.7	3	NE	0.30	0.03 to 2.98	
ECOG performance status at baseline								
0	157	82	5.5	75	5.5	1.03	0.68 to 1.57	
1	146	70	3.8	76	5.6	0.77	0.51 to 1.17	
Menopausal status at baseline								
Pre-/perimenopausal	50	27	3.6	23	9.2	0.32	0.14 to 0.69	
Postmenopausal	252	124	5.5	128	5.5	1.10	0.79 to 1.52	
PgR status								
PgR+	231	119	5.5	112	5.6	0.96	0.68 to 1.36	
PgR−	69	32	3.7	37	4.9	0.76	0.43 to 1.36	
Unknown	3	1	3.5	2	NE	<0.01	0.00 to NE	
$ESR1$ status at baseline								
Mutation detected	90	39	3.5	51	5.3	0.55	0.33 to 0.93	
No mutation detected	142	76	6.6	66	7.2	1.01	0.64 to 1.60	
Unknown	71	37	5.5	34	7.2	0.92	0.50 to 1.67	
Site of disease (assessed locally)								
Visceral	219	110	4.8	109	5.6	0.77	0.54 to 1.08	
Nonvisceral	84	42	5.9	42	5.5	1.31	0.74 to 2.33	
Disease status								
Measurable disease	282	141	5.4	141	5.6	0.91	0.67 to 1.24	
Nonmeasurable disease	21	11	4.5	10	7.2	0.64	0.19 to 2.11	
No. of organ sites								
1	28	14	5.5	14	5.6	1.08	0.41 to 2.83	
2	93	48	3.7	45	3.9	1.00	0.60 to 1.65	
3	102	52	5.6	50	5.6	0.78	0.46 to 1.32	
≥4	80	38	5.5	42	9.1	0.85	0.47 to 1.55	
Bone-only involvement								
Yes	28	14	5.5	14	5.6	1.08	0.41 to 2.83	
No	275	138	5.4	137	5.6	0.88	0.65 to 1.20	
Prior treatment with a CDK4/6 inhibitor								
Yes	125	62	3.5	63	3.7	0.80	0.52 to 1.23	
No	178	90	5.6	88	7.2	0.92	0.61 to 1.38	
Prior treatment with fulvestrant								
Yes	58	29	3.6	29	5.5	0.65	0.35 to 1.23	
No	245	123	5.5	122	5.6	0.94	0.67 to 1.31	
Prior treatment with an aromatase inhibitor								
Yes	254	120	5.4	134	5.5	0.91	0.67 to 1.25	
No	49	32	5.4	17	NE	0.63	0.26 to 1.53	
Prior treatment with tamoxifen								
Yes	148	77	3.7	71	5.5	0.79	0.52 to 1.20	
No	155	75	5.6	80	7.2	1.05	0.69 to 1.59	
Previous line of therapy in the aBC/mBC setting								
1	216	113	5.5	103	5.6	0.97	0.67 to 1.39	
2	85	38	3.7	47	5.5	0.69	0.41 to 1.16	
3	1	1	2.1			NE	NE to NE	
Prior chemotherapy for aBC/mBC								
Yes	96	49	5.5	47	5.6	0.92	0.53 to 1.58	
No	207	103	5.4	104	5.5	0.87	0.61 to 1.24	

Forest plot axis: 1/5 3/10 1/2 1 2 3 5

FIG 2. (Continued).

PROs

For key PROs, mean scores generally remained stable; however, differences between arms were observed for time to deterioration in pain presence and interference (HR, 0.55 [95% CI, 0.35 to 0.87]), pain severity (HR, 0.84 [95% CI, 0.51 to 1.38]), physical functioning (HR, 0.61 [95% CI, 0.36 to 1.05]), and global health status/QoL (HR, 0.67 [95% CI, 0.39 to 1.16]), though not in role functioning (HR, 0.96 [95% CI, 0.60 to 1.54]), and without medians being reached (Data Supplement, Fig S3).

A comparison of selected AEs via PRO-CTCAE versus clinician-reported AEs is shown in the Data Supplement (Table S4). Fatigue, nausea, diarrhea, and vomiting were mostly mild/moderate or occurred rarely/infrequently; similarly, AEs were reported as being mostly grade 1-2 by clinicians.

DISCUSSION

Although the phase II acelERA BC study did not reach statistical significance for its primary INV-PFS end point, giredestrant showed a numerical improvement versus PCET, with an approximately 20% relative reduction in the risk of progression or death in the overall population, and favorable results for the secondary efficacy end points CBR and ORR.

Other randomized studies of new oral SERDs versus single-agent ET in the pretreated aBC setting have shown conflicting efficacy results. Although the phase III EMERALD trial of elacestrant met its coprimary end points of PFS in the intention-to-treat and $ESR1$m populations (elacestrant was approved by the US Food and Drug Administration in 2023 in the $ESR1$m population only[20]),[21] and the phase II SERENA-2 multidose trial demonstrated a statistically significant (two-sided alpha 10%) benefit of camizestrant versus fulvestrant,[22] the phase II AMEERA-3 study of amcenestrant did not show superiority or numerical improvements in the intention-to-treat population.[23] Cross-trial comparisons are challenging because of marked differences in patient populations (eg, prior CDK4/6i, $ESR1$m prevalence), sample sizes, comparator choice, and end point assessment (BICR *v* INV).[23] Nevertheless, the limited efficacy gains over available single-agent ET observed with novel oral SERDs in later-line aBC questions the clinical usefulness as monotherapy in this setting. In particular, in an unselected population, combination treatment approaches might be warranted, as in the ongoing evERA BC study with giredestrant plus everolimus.[24]

In acelERA BC, giredestrant trended toward a favorable benefit among patients with $ESR1$m tumors, consistent with findings in EMERALD[21] and SERENA-2,[22] indicating that giredestrant, a potent antagonist of mutant ER-reversing progesterone hypersensitivity,[25] can target this mechanism of endocrine resistance more effectively than an AI or fulvestrant.

TABLE 2. Secondary Efficacy End Points

End Point	Giredestrant (n = 151)	PCET (n = 152)
Confirmed ORR, No. (%)	19 (12.6)	11 (7.2)
95% CI	7.75 to 18.95	3.67 to 12.58
OR (95% CI)	1.87 (0.86 to 4.07)	
DoR	n = 19	n = 11
Median, months (95% CI)	NR (5.55 to NE)	7.39 (7.39 to NE)
Range, months	2.0[a] to 8.9[a]	2.8[a] to 9.3[a]
CBR, No. (%)	48 (31.8)	32 (21.1)
95% CI	24.46 to 39.85	14.87 to 28.40
OR (95% CI)	1.79 (1.06 to 3.04)	
OS: deaths, No. (%)	18 (11.9)	11 (7.2)
PD, No.	12	9
Grade 5 AE, No.	1[b]	1[c]
Other (post-treatment)	5[d]	1[e]

Abbreviations: AE, adverse event; CBR, clinical benefit rate; DoR, duration of response; NE, nonestimable; NR, not reached; OR, odds ratio; ORR, objective response rate; OS, overall survival; PCET, physician's choice of endocrine therapy; PD, progressive disease.
[a]Censored value.
[b]Ischemic stroke.
[c]Pulmonary embolism.
[d]Unrelated—outside of AE reporting period (>30 days post-treatment discontinuation): three COVID-19–related, two septic shocks.
[e]Unrelated—outside of AE reporting period (>30 days post-treatment discontinuation): septicemia.

In later lines, particularly in patients without ESR1m tumors, additional mechanisms of resistance emerge that progressively decrease the dependence on the ER pathway,[26,27] as evidenced by the limited efficacy of single-agent ET in the aforementioned studies in patients without ESR1m tumors. However, the efficacy of giredestrant is not only linked to its activity in ESR1m tumors. In earlier lines or ET-naive settings, where ESR1m is infrequent and tumors are more dependent on ER signaling,[28] superiority over a standard-of-care AI (anastrozole) was demonstrated with giredestrant in the coopERA BC study in terms of reduction of Ki67.[29,30] Giredestrant thus has the potential to improve on AIs and fulvestrant given its mechanism of action, which targets both estrogen-dependent and -independent (eg, ESR1m) ER activity, with superior potency.

Other subgroups, such as Asian patients and those who were pre-/perimenopausal, appeared to show a benefit of giredestrant; however, there were important confounders (eg, imbalances in baseline characteristics, small numbers of patients), which mean results should be interpreted with caution.

Giredestrant exhibited manageable toxicities, the vast majority being grade 1 or 2, and its safety profile, including cardiac safety, appeared comparable overall to the PCET control and was consistent with known ET risks and previous experience.[17,31] Related grade 3-4 AEs, serious AEs, and discontinuations due to AEs were balanced across arms. Higher hepatotoxicity was reported with giredestrant (Table 3 and Data Supplement, Table S2); however, shifts in laboratory values of AST/ALT elevations were comparable across treatment arms (Data Supplement, Table S3), suggesting that liver abnormalities were similar across arms. Factors likely contributing to this were imbalances in proportions of patients with abnormal baseline AST/ALT levels (Table 1), as well as differential reporting between arms. GI toxicities occurred at a lower incidence and grades with giredestrant than reported with other oral SERDs.[21,23]

Patient-reported selected AEs showed, overall, no meaningful differences between arms compared with those reported by clinicians.

This phase II study has a number of limitations that may have impacted the results. The population was markedly heterogeneous, and, driven by the geographic footprint of the study (that included regions where CDK4/6is are not standard of care), included a majority of CDK4/6i-naive patients, with lower prevalence of ESR1m and higher use of first-line chemotherapy, and in whom efficacy versus PCET appeared worse than in those with prior CDK4/6i therapy. The relevance of endocrine monotherapy as a comparator for second-/third-line treatment in ER+, HER2– aBC, while commonly used, might be argued in some regions where combination therapy is preferred, such as the United States (especially with fit patients).[6,32]

Inherent to the open-label design, which was motivated by ethical concerns regarding intramuscular placebo administration, is the risk of investigator bias. For efficacy, there was a notable discordance between INV and BIRC assessments, and for safety, a trend toward underreporting of AEs in the PCET arm emerged in comparison with the expected rates from previous experience, likely related to the well-known safety profile of comparator ETs. The opposite trend was observed for the giredestrant arm, as evidenced by the comparison of selected common AEs reported by investigators versus by patients. With regard to the ESR1m assessment, of note were the approximately 25% sample attrition and imbalances in ESR1m prevalence between treatment arms (mutations were approximately 10% more frequent in the giredestrant arm), as baseline ESR1m status was not a random assignment stratification factor. ESR1m is a complex net effect, as it is negatively prognostic but positively predictive. However, the biologic plausibility and external replication with other agents of the oral SERD class[21,22] provides reassurance regarding the findings of a larger magnitude of benefit of giredestrant versus PCET, and specifically versus fulvestrant, in patients with ESR1m tumors.

Giredestrant is currently being investigated in two ongoing phase III trials in ER+, HER2– aBC: persevERA BC versus letrozole as an add-on to palbociclib in the first-line setting[33]; and evERA BC with everolimus in the

TABLE 3. Overall Safety Profile, AEs Occurring in ≥10% of Patients in Either Arm, Most Common Grade 3-4 AEs in ≥3 Patients, and Selected AEs

Safety Profile	Giredestrant (n = 150)	PCET (n = 152)
Overall Safety Profile		
All-grade AEs	127 (84.7)	108 (71.1)
Treatment-related	70 (46.7)	43 (28.3)
Grade 3-4 AEs	26 (17.3)	18 (11.8)
Treatment-related	6 (4.0)	4 (2.6)
Serious AEs	14 (9.3)	12 (7.9)
Treatment-related	3 (2.0)	1 (0.7)
Grade 5 AEs	1 (0.7)[a]	1 (0.7)[b]
AEs leading to treatment discontinuation	2 (1.3)	3 (2.0)
AEs Occurring in ≥10% of Patients in Either Arm		
AST increased	22 (14.7)	13 (8.6)
Arthralgia	18 (12.0)	12 (7.9)
ALT increased	17 (11.3)	11 (7.2)
Anemia	15 (10.0)	9 (5.9)
Nausea	15 (10.0)	11 (7.2)
Most Common Grade 3-4 AEs in ≥3 Patients		
Anemia	2 (1.3)	5 (3.3)
Hypertension	3 (2.0)	3 (2.0)
AST increased	4 (2.7)	1 (0.7)
Bone pain	3 (2.0)	1 (0.7)
Blood bilirubin increased	3 (2.0)	0
Selected AEs		
Hepatotoxicity		
Any grade	35 (23.3)	21 (13.8)
Grade 1-2	30 (20.0)	19 (12.5)
Grade 3-4	5 (3.3)	2 (1.3)
Musculoskeletal pain		
Any grade	22 (14.7)	22 (14.5)
Grade 1-2	18 (12.0)	21 (13.8)
Grade 3-4	4 (2.7)	1 (0.7)
Fatigue		
Any grade	21 (14.0)	12 (7.9)
Grade 1-2	20 (13.3)	12 (7.9)
Grade 3-4	1 (0.7)	0
Arthralgia		
Any grade	18 (12.0)	12 (7.9)
Grade 1-2	18 (12.0)	12 (7.9)
Nausea		
Any grade	15 (10.0)	11 (7.2)
Grade 1-2	15 (10.0)	10 (6.6)
Grade 3-4	0	1 (0.7)
Diarrhea		
Any grade	13 (8.7)	6 (3.9)
Grade 1-2	12 (8.0)	6 (3.9)
Grade 3-4	1 (0.7)	0
Dizziness		
Any grade	9 (6.0)	7 (4.6)
Grade 1-2	9 (6.0)	7 (4.6)

TABLE 3. Overall Safety Profile, AEs Occurring in ≥10% of Patients in Either Arm, Most Common Grade 3-4 AEs in ≥3 Patients, and Selected AEs (continued)

Safety Profile	Giredestrant (n = 150)	PCET (n = 152)
Vomiting		
Any grade	13 (8.7)	2 (1.3)
Grade 1-2	11 (7.3)	2 (1.3)
Grade 3-4	2 (1.3)	0
Hot flushes		
Any grade	6 (4.0)	7 (4.6)
Grade 1-2	6 (4.0)[c]	7 (4.6)[c]
Bradycardia		
Any grade	5 (3.3)	2 (1.3)
Grade 1-2	5 (3.3)[c]	2 (1.3)[c]
Renal toxicity		
Any grade	4 (2.7)	1 (0.7)
Grade 1-2	4 (2.7)	0
Grade 3-4	0	1 (0.7)
QT prolongation (preferred term: electrocardiogram QT prolonged)		
Any grade	1 (0.7)	2 (1.3)
Grade 1-2	1 (0.7)[c]	2 (1.3)[c]
VTE (preferred term: pulmonary embolism)		
Any grade	0	1 (0.7)
Grade 5	0	1 (0.7)

NOTE: Safety population. Data are No. of patients with ≥1 AE (%). Multiple occurrences of the same AE in one individual are counted only once. Missed doses were counted as an AE (without being graded) in the PCET arm. Preferred terms coded using MedDRA v24.1 and AE severity graded according to NCI-CTCAE v5.0. Selected AEs were defined based on the known potential and identified risks of giredestrant (fatigue, nausea, dizziness, hot flush, arthralgia, vomiting, musculoskeletal pain, bradycardia, diarrhea, hepatotoxicity, renal dysfunction, VTEs, and QT prolongation). Preferred terms (MedDRA v24.1) occurring in each category were hepatotoxicity: AST increased (14.7% v 8.6% at any grade; 2.7% v 0.7% at grade 3-4), ALT increased (11.3% v 7.2%; 1.3% v 0.7%), blood bilirubin increased (6.0% v 0.7%; 2.0% v 0), gamma-glutamyl transferase increased (2.7% v 2.0%; 0 v 1.3%), ascites (1.3% v 0.7%; 0 v 0), hyperbilirubinemia (1.3% v 0; 0 v 0), AST abnormal (0 v 0.7%; 0 v 0),[c] bilirubin conjugated increased (0.7% v 0; 0 v 0), hepatic failure (0 v 0.7%; 0 v 0),[c] hepatic pain (0.7% v 0; 0 v 0), or hepatic steatosis (0.7% v 0; 0 v 0);[c] musculoskeletal pain: bone pain (6.0% v 6.6%; 2.0% v 0.7%), back pain (5.3% v 2.6%; 0 v 0), pain in extremity (2.7% v 4.6%; 0 v 0.7%), myalgia (3.3% v 2.0%; 0.7% v 0), or musculoskeletal pain (0 v 2.0%; 0 v 0); fatigue: fatigue (7.3% v 3.9%; 0 v 0)[c] or asthenia (6.7% v 3.9%; 0.7% v 0); bradycardia: sinus bradycardia (3.3% v 0; 0 v 0)[c] or bradycardia (0 v 1.3%; 0 v 0);[c] renal toxicity: blood creatinine increased (2.7% v 0.7%; 0 v 0), azotemia (0.7% v 0; 0 v 0), blood urea increased (0.7% v 0; 0 v 0),[c] or renal failure (0 v 0; 0 v 0.7%).[d]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events; PCET, physician's choice of endocrine therapy; VTE, venous thromboembolism.
[a]Ischemic stroke.
[b]Pulmonary embolism.
[c]Grade 1 only.
[d]Grade 4 only.

postCDK4/6i setting.[24] In addition, lidERA BC[34] is a large, currently recruiting adjuvant study in medium-to-high risk ER+, HER2− early BC; the rationale for which is supported by the positive results of the randomized phase II neoadjuvant coopERA BC study.[29,30,35] The target populations in these studies include patients with tumors with expected high dependence on ER signaling and likelihood of benefit with giredestrant.

In conclusion, while the phase II acelERA BC study did not reach statistical significance for its primary INV-PFS end point, there was a consistent treatment effect with giredestrant across most key subgroups and a trend toward favorable benefit among patients with *ESR1*m tumors. Secondary efficacy end points numerically favored giredestrant in terms of CBR and ORR; while DoR and OS were still immature. Giredestrant was well tolerated, with a safety profile comparable to that of PCET and consistent with known ET risks. Grade 3-4 treatment-related AEs, serious AEs, and discontinuations due to AEs were balanced across arms. Overall, these data support the continued investigation of giredestrant in other studies.

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SUPPORT

CLINICAL TRIAL INFORMATION

NCT04576455 (acelERA Breast Cancer)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

DATA SHARING STATEMENT

For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli: https://vivli.org/ourmember/roche/. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient reidentification.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Giredestrant for Estrogen Receptor–Positive, HER2-Negative, Previously Treated Advanced Breast Cancer: Results From the Randomized, Phase II acelERA Breast Cancer Study

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Elgene Lim
Consulting or Advisory Role: Novartis (Inst), Lilly (Inst), Pfizer (Inst), AstraZeneca (Inst), Gilead Sciences (Inst), MSD Australia (Inst)
Speakers' Bureau: Limbic Australia
Research Funding: Novartis (Inst), Pfizer (Inst), Ellipses Pharma (Inst)
Patents, Royalties, Other Intellectual Property: Sensitization of BCL-2-expressing breast tumors to chemotherapy by the BH3 mimetic ABT-737
Travel, Accommodations, Expenses: Gilead Sciences, Novartis
Other Relationship: Roche/Genentech, Lilly, Novartis

Mariana Chavez-MacGregor
Employment: MD Anderson Physician's Network
Consulting or Advisory Role: Exact Sciences, AstraZeneca/Daiichi Sankyo, Pfizer, Abbott Laboratories, Exact Sciences, Pfizer, Lilly, AstraZeneca/Daiichi Sankyo, Exact Sciences, Roche/Genentech, Adium Pharma, Merck
Research Funding: Novartis (Inst), Genentech/Roche (Inst), Pfizer (Inst), Lilly
Expert Testimony: Lilly
Travel, Accommodations, Expenses: AstraZeneca, Exact Sciences, Zodiac Pharma
Uncompensated Relationships: Legacy Healthcare Services, The Hope Foundation

Aditya Bardia
Consulting or Advisory Role: Novartis, Genentech, Pfizer, Merck, Novartis (Inst), Genentech/Roche (Inst), Pfizer (Inst), Radius Health (Inst), Innocrin Pharma (Inst), Sanofi, Daiichi Sankyo/Astra Zeneca, Lilly, Lilly (Inst), Gilead Sciences, Gilead Sciences (Inst), Menarini, Menarini (Inst), Mersana
Research Funding: Genentech (Inst), Novartis (Inst), Pfizer (Inst), Merck (Inst), Sanofi (Inst), Radius Health (Inst), Immunomedics (Inst), AstraZeneca/Daiichi Sankyo (Inst)
Open Payments Link: https://openpaymentsdata.cms.gov/physician/523675

Jiong Wu
Leadership: Chinese Breast Cancer Society (Chairman), Breast Surgeon Committee (Vice Chairman), Chinese College of Surgeons
Honararia: Lilly, F. Hoffmann-La Roche Ltd, AstraZeneca, Pfizer
Research Funding: National Natural Science Foundation (Inst), F. Hoffmann-La Roche Ltd (Inst)
Patents, Royalties, Other Intellectual Property: Fudan University Shanghai Cancer Center (Microvascular anastomosis support dilator; degradable breast-conserving stent)

Qingyuan Zhang
Research Funding: F. Hoffmann-La Roche Ltd (Inst)

Zbigniew Nowecki
Travel, Accommodations, Expenses: F. Hoffmann-La Roche Ltd/Genentech, Inc
Research Funding: F. Hoffmann-La Roche Ltd (Inst)

Felipe Melo Cruz
Consulting or Advisory Role: Pfizer
Travel, Accommodations, Expenses: Janssen Oncology, Novartis

Rustem Safin
Speakers' Bureaus: F. Hoffmann-La Roche Ltd
Research Funding: F. Hoffmann-La Roche Ltd (Inst)

Sung-Bae Kim
Stock and Other Ownership Interests: Genopeaks
Honoraria: DAEHWA Pharmaceutical, LegoChem Biosciences, Kalbe Farma
Consulting or Advisory Role: Lilly (Inst), AstraZeneca, DAEHWA Pharmaceutical, ISU Abxis, BeiGene, Daiichi Sankyo/Astra Zeneca, OBI Pharma
Research Funding: Novartis (Inst), Dongkook Pharma (Inst), Genzyme (Inst)

Christian Schem
Honoraria: Roche, Lilly, AstraZeneca, MSD Oncology, Exact Sciences, Novartis
Consulting or Advisory Role: Novartis, AstraZeneca, Roche
Speakers' Bureau: Roche, AstraZeneca, Novartis
Research Funding: Roche (Inst), Daiichi Sankyo Europe GmbH (Inst), AstraZeneca (Inst), GlaxoSmithKline (Inst), Novartis (Inst), Lilly (Inst)
Travel, Accommodations, Expenses: Pfizer, Roche, AstraZeneca, Novartis, Gilead Sciences

Alberto J. Montero
Honoraria: Celgene, AstraZeneca, OncoSec
Consulting or Advisory Role: New Century Health, Welwaze, Paragon healthcare
Research Funding: F. Hoffmann-La Roche Ltd, Basel, Switzerland
Uncompensated Relationships: Roche
Open Payments Link: https://openpaymentsdata.cms.gov/physician/618396

Sarah Khan
Honoraria: Novartis Pharmaceuticals UK Ltd, Roche/Genentech
Consulting or Advisory Role: Lilly
Travel, Accommodations, Expenses: Novartis Pharmaceuticals UK Ltd

Reeti Bandyopadhyay
Employment: Genentech/Roche
Stock and Other Ownership Interests: Genentech/Roche

Heather M. Moore
Employment: Genentech, Pfizer (I)
Stock and Other Ownership Interests: Roche, Pfizer (I)

Mahesh Shivhare
Employment: Roche
Stock and Other Ownership Interests: Roche

Monika Patre
Employment: Roche
Stock and Other Ownership Interests: Roche
Patents, Royalties, Other Intellectual Property: US20190030181A1 Methods for treating HER2 breast cancer

Jorge Martinalbo
Employment: Roche, Novartis, Inhibrx
Stock and Other Ownership Interests: Roche

Laura Roncoroni
Employment: Roche, AstraZeneca
Stock and Other Ownership Interests: Roche

Pablo Diego Pérez-Moreno
Employment: Genentech
Stock and Other Ownership Interests: Roche/Genentech, Merck, Zymeworks, Johnson & Johnson/Janssen, Johnson & Johnson/Janssen

Joohyuk Sohn
Stock and Other Ownership Interests: Daiichi Sankyo
Research Funding: MSD (Inst), Roche (Inst), Novartis (Inst), Lilly (Inst), Pfizer (Inst), Daiichi Sankyo (Inst), AstraZeneca (Inst), GlaxoSmithKline (Inst), Sanofi (Inst), Boehringer Ingelheim (Inst), Seagan (Inst)

No other potential conflicts of interest were reported.

APPENDIX. LIST OF INVESTIGATORS

The following investigators participated in the acelERA Breast Cancer study:

Argentina—G. Aguil, M. Alfie, V. Caceres, G. Lerzo, S. Ostoich

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Germany—T.-O. Emde, G. Gaffunder, C. Hielscher, M. Lux, C. Schem, M. Welslau, C. Schumacher

Israel—I. Kuchuk, T. Peretz, L. Ryvo, R. Yerushalmi

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Singapore—A. Wong, Y.S. Yap

South Africa—M. Coccia-Portugal, N. Fourie, R. Khanyile, L. Schoeman

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Turkey—A. Alacacioglu, E. Algin, D. Cabuk, C. Demir, U. Demirci, D. Erdem, Ş. Gündüz, M.A. Kaplan, M.E. Yildirim

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USA—J.C. Andersen, M. Cairo, P. Cobb, V. Konala, S.L. McCune, A.J. Montero, D.A. Patt, I. Sanchez-Rivera, S. Strain, K. Wendell