# Phase Ia/b Study of Giredestrant ± Palbociclib and ± Luteinizing Hormone-Releasing Hormone Agonists in Estrogen Receptor–Positive, HER2-Negative, Locally Advanced/Metastatic Breast Cancer

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## ABSTRACT

**Purpose:** Giredestrant is an investigational next-generation, oral, selective estrogen receptor antagonist and degrader for the treatment of estrogen receptor–positive (ER+) breast cancer. We present the primary analysis results of the phase Ia/b GO39932 study (NCT03332797).

**Patients and Methods:** Patients with ER+, HER2-negative locally advanced/metastatic breast cancer previously treated with endocrine therapy received single-agent giredestrant (10, 30, 90, or 250 mg), or giredestrant (100 mg) ± palbociclib 125 mg ± luteinizing hormone-releasing hormone (LHRH) agonist. Detailed cardiovascular assessment was conducted with giredestrant 100 mg. Endpoints included safety (primary), pharmacokinetics, pharmacodynamics, and efficacy.

**Results:** As of January 28, 2021, with 175 patients enrolled, no dose-limiting toxicity was observed, and the MTD was not reached. Adverse events (AE) related to giredestrant occurred in 64.9% and 59.4% of patients in the single-agent ± LHRH agonist and giredestrant + palbociclib ± LHRH agonist cohorts, respectively (giredestrant-only–related grade 3/4 AEs were reported in 4.5% of patients across the single-agent cohorts and 3.1% of those with giredestrant + palbociclib). Dose-dependent asymptomatic bradycardia was observed, but no clinically significant changes in cardiac-related outcomes: heart rate, blood pressure, or exercise duration. Clinical benefit was observed in all cohorts (48.6% of patients in the single-agent cohort and 81.3% in the giredestrant + palbociclib ± LHRH agonist cohort), with no clear dose relationship, including in patients with *ESR1*-mutated tumors.

**Conclusions:** Giredestrant was well tolerated and clinically active in patients who progressed on prior endocrine therapy. Results warrant further evaluation of giredestrant in randomized trials in early- and late-stage ER+ breast cancer.

## Introduction

Breast cancer is the most common cancer type worldwide (1). Around 70%–80% of cases are estrogen receptor–positive (ER+; ref. 2, 3), most are driven by ER activity for tumor growth and progression, and endocrine therapy (ET) is a treatment mainstay. Standard-of-care ETs include aromatase inhibitors (AI), for example, anastrozole, which block estradiol synthesis; selective ER modulators (SERM), for example, tamoxifen, which antagonize estradiol effects via competitive binding to ERs; and selective ER antagonists and

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## Translational Relevance

Endocrine therapy (ET) is a mainstay of estrogen receptor–positive breast cancer (ER+ BC) treatment; however, resistance to current standard-of-care ETs remains a key limitation, with *ESR1* mutations being an important mechanism of resistance. Moreover, available ETs can be associated with adverse events (that reduce treatment adherence) and/or may lack a more convenient oral formulation. Therefore, new ETs with oral dosing, acceptable safety profiles, increased antitumor activity, and the ability to overcome resistance are needed to prolong survival of patients with ER+ BC. The primary analysis of the phase Ia/b GO39932 study demonstrated that giredestrant, a next-generation, oral, selective estrogen receptor antagonist and degrader, is well tolerated and potentially clinically active as a single agent and in combination with palbociclib for the treatment of patients who have disease progression on prior ETs, including in patients with *ESR1*-mutated tumors.

degraders (SERD), for example, the first-generation agent fulvestrant, which fully antagonize and degrade ERs (4). Combining fulvestrant with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), for example, palbociclib, ribociclib, or abemaciclib, improves outcomes, as shown in the phase III studies PALOMA-3, MONALEESA-3, and MONARCH-2, respectively (5–7). Currently approved ETs have limitations, including resistance development during/after treatment (8, 9). Resistance to AIs may result from acquisition of mutations in *ESR1* (10), the gene that encodes ER, which drives constitutive estrogen-independent transcription and proliferation (11, 12). The high prevalence of *ESR1*-mutated tumors among patients in the metastatic setting is associated with selective treatment pressure with AIs (13, 14). *ESR1* mutations, for example, Y537S, also drive resistance to fulvestrant and several SERMs, including tamoxifen (11). Furthermore, the widely used SERD fulvestrant is given as an intramuscular injection, which limits clinical acceptability (4, 15–17), and has poor efficacy in patients previously treated with CDK4/6is (18, 19). In addition, ET adherence may be decreased by associated adverse events (AE) and their subsequent impact on patients' quality of life (20, 21).

Despite becoming refractory to currently available ETs, most tumors remain ER signaling dependent, and patients with ER+ breast cancer may respond to second-/third-line ET after progression on previous therapies (22, 23). Therefore, there is an unmet need for new, orally available, ER-targeting therapies with acceptable safety profiles that delay disease progression (PD) and overcome resistance, which may thus prolong survival.

Giredestrant is a highly potent, nonsteroidal oral SERD that binds to the ER ligand binding domain, outcompeting estrogen and causing intranuclear ER immobilization before its degradation (24). Giredestrant achieves robust ER occupancy, is well tolerated alone and in combination with palbociclib, and shows encouraging activity regardless of *ESR1* mutation status (25–29).

We present the primary analysis of the phase Ia/b GO39932 study (NCT03332797), which evaluated giredestrant as a single agent or in combination with palbociclib in patients with ER+, HER2-negative (HER2−) locally advanced/metastatic breast cancer.

## Patients and Methods

### Study design

GO39932 is an ongoing (with some patients still receiving study treatment), phase Ia/Ib, multicenter, open-label study conducted at 23 sites in five countries: Australia, Spain, UK, US, and Republic of Korea. Patients were enrolled in two stages (**Fig. 1**). First, a single-agent dose-escalation stage was enrolled to determine the MTD or maximum-administered dose (MAD), which included multiple pharmacokinetic (PK) time point collections. Once the single-agent MTD/MAD was established, the following cohorts were included: backfill single-agent escalation cohorts (≤7 patients) to collect additional PK, pharmacodynamic, and response data, at dose levels that had been shown

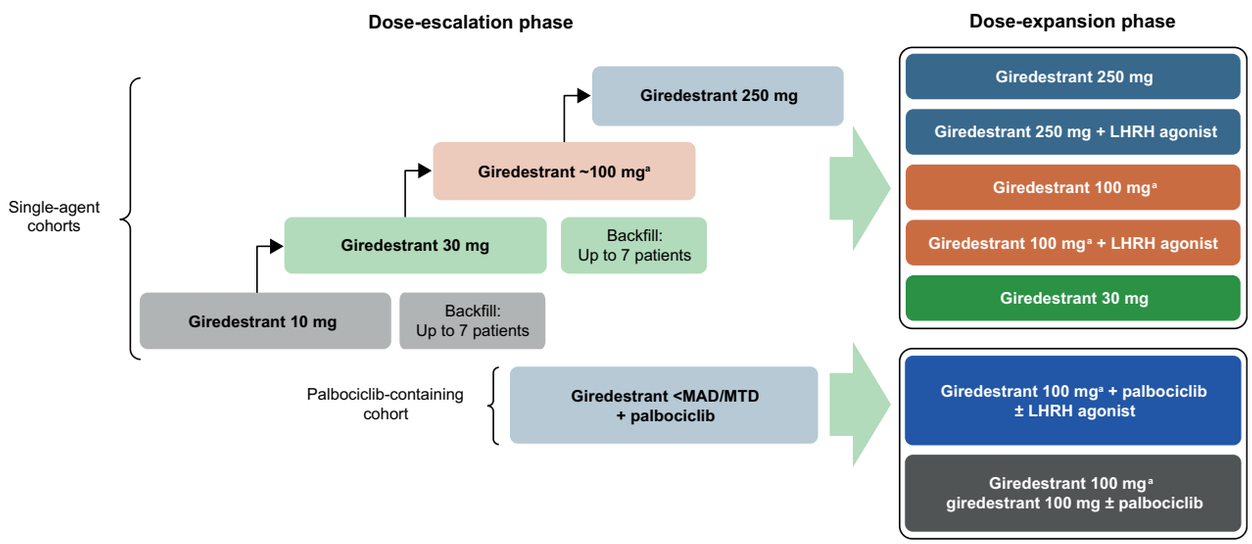


**Figure 1.**
Study design. Giredestrant (orally once daily) days 1–28 of each 28-day cycle; palbociclib (125 mg orally once daily); LHRH (every 4 weeks) at the label recommended dose (the schedule for goserelin acetate; the only LHRH used in this study despite leuprolide acetate and triptorelin pamoate being allowed). LHRH, luteinizing hormone–releasing hormone. [a]The 90-mg dose originally assigned in the escalation stage was adjusted to 100 mg to account for existing tablet strength and considered equivalent to the 90-mg dose.

not to exceed MTD; dose-expansion stage cohorts to acquire additional PK, pharmacodynamic, and safety data with giredestrant at or below MTD/MAD as a single agent [± luteinizing hormone-releasing hormone (LHRH) agonist] or in combination with palbociclib (± LHRH agonist).

GO39932 was conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, the International Council for Harmonization Good Clinical Practice guidelines, or applicable laws and regulations of each country where the research was conducted if they provided greater protection to the individual. All patients provided written informed consent. The protocol, protocol amendments, informed consent form, Investigator Brochure, and other relevant documents (for example, advertisements) were submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study was initiated. Any amendments to the protocol required IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

### Patient eligibility

The key eligibility criteria were: histologically/cytologically proven diagnosis of adenocarcinoma of the breast; evidence of either locally recurrent disease not amenable to resection or radiotherapy with curative intent or with metastatic disease; locally assessed ER positivity (staining in ≥1% cells by IHC) and HER2 negativity (per American Society of Clinical Oncology/College of American Pathologists; refs. 30, 31); locally advanced/metastatic breast cancer that had recurred/progressed while being treated with adjuvant ET for ≥24 months and/or ET in the incurable/locally advanced/metastatic setting and derived a clinical benefit from ET [tumor response/stable disease (SD) for ≥6 months]; ≤2 prior lines of treatment for locally advanced/metastatic breast cancer; ≥2 weeks elapsed from the use of any other ET/targeted therapy/chemotherapy; and postmenopausal women (pre-/perimenopausal women simultaneously received LHRH agonists with giredestrant 100 mg). The key exclusion criteria were: known brain metastases that were untreated/symptomatic/required therapy to control symptoms; serious medical conditions/clinically significant abnormalities detected in clinical laboratory tests that precluded the patient's safe participation in and completion of the study; abnormal electrocardiogram, including complete left bundle branch block/second-/third-degree heart block/evidence of prior myocardial infarction; ongoing treatment with medications that prolong the QT interval; and, in a cardiac evaluation cohort (detailed below), ongoing treatment with medications that decrease heart rate (HR), including beta blockers. In the giredestrant 100 mg + palbociclib 125 mg ± LHRH agonist cohorts, no prior treatment with a CDK4/6i was allowed; however, prior treatment with these drugs was allowed in the cardiac evaluation cohort.

### Procedures

In the single-agent dose-escalation stage, increasing doses of once-daily giredestrant were tested on days 1–28 of each 28-day cycle: 10, 30, 90, or 250 mg. Patients were sequentially assigned to the escalating doses using a standard 3+3 design (**Fig. 1**).

Safety and tolerability of giredestrant 100 mg (once daily, days 1–28) + palbociclib 125 mg (once daily, days 1–21, 21-day on/7-day off schedule) in 28-day cycles was explored in the combination dose-escalation stage. The 90-mg dose originally assigned in the escalation stage was adjusted to 100 mg to account for existing tablet strength. The 100-mg dose was considered equivalent to the 90-mg dose, since only around 10% exposure difference would be expected between the two dose levels.

In the expansion stage, patients received giredestrant once daily at 30, 100, and 250 mg, ± LHRH agonist and ± 125 mg palbociclib (**Fig. 1**). LHRH agonists (leuprolide acetate/goserelin acetate/triptorelin pamoate) were administered every 4 weeks from cycle 1, day 1 of 28-day cycles according to their prescribing information in premenopausal patients. Only one patient received giredestrant 250 mg + LHRH agonist.

A cohort was dedicated to close evaluation of potential cardiac effects; patients received giredestrant 100-mg monotherapy and underwent 24-hour Holter HR monitoring and exercise tolerance testing before starting study drug and again after 8 (+3) days of treatment. Once cardiac assessments were completed, patients continued on single-agent giredestrant 100 mg or giredestrant 100 mg + palbociclib 125 mg per physician's choice for the study duration. The giredestrant 100-mg dose was evaluated in the cardiac evaluation cohort to increase the likelihood of observing relevant cardiac effects, bradycardia being a dose-dependent AE (32). All patients were treated until PD, unacceptable toxicity, withdrawal of consent, or study termination. Enrollment for the 250-mg dose was halted based on a clinical development decision to explore lower dose levels. A second cohort dedicated to evaluating potential cardiac effects was not enrolled based upon review of the favorable safety data from the first cardiac cohort.

### Assessments

The primary objective was to evaluate the safety and tolerability of giredestrant when administered as a single agent or in combination with palbociclib, including estimation of the MTD (or MAD), assessed by the following endpoints: occurrence and severity of AEs, including dose-limiting toxicities (DLT), with severity determined according to National Cancer Institute Common Terminology Criteria for AEs v4.0 (33) and changes in targeted vital signs.

The PK objectives were to evaluate the PK of giredestrant as a single agent following single- and multiple-dose treatment, and to characterize the giredestrant, palbociclib, and LHRH agonist PK profiles when giredestrant was administered in combination with palbociclib and/or an LHRH agonist.

The activity objective was to make a preliminary assessment of giredestrant antitumor activity, assessed by objective response rate [ORR; complete/partial response (CR/PR) on two consecutive occasions ≥4 weeks apart], clinical benefit rate (CBR; percentage of patients achieving confirmed CR/PR/first occurrence of PD after 24 weeks of study treatment)], and duration of response (DOR; time from first occurrence of a documented objective response until first observation of PD/death from any cause). These were determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Tumor assessments were performed approximately every 8 weeks from cycle 1, day 1 and every 3 months after cycle 12 whenever PD was suspected, as well as at the end of treatment.

Additional objectives were to identify a recommended phase II dose for giredestrant, and to perform an exploratory evaluation of pharmacodynamic response with [$^{18}$F]-fluoroestradiol PET (FES-PET) in a subset of patients in single-agent dose-escalation cohorts. For these patients, recent prior use of tamoxifen (within 2 months) and fulvestrant (within 6 months) was not allowed. Change in FES uptake was assessed at cycle 2 (day 3; 18–24 hours after dosing) and quantified as the mean percentage of change from baseline in background-corrected maximum standardized uptake value measured in up to five FES-avid

lesions. Disease in the liver and some areas of the gastrointestinal tract was considered unevaluable in the FES analysis because of confounding normal physiologic uptake of the tracer.

*ESR1* mutation status in circulating tumor DNA (ctDNA) was centrally determined from plasma samples collected at baseline before any study treatment; at cycle 1, day 15; and at cycle 2, day 1 using the BEAMing digital PCR assay (Sysmex Inostics). *ESR1* mutations were defined as nucleotide substitutions that result in the following amino acid changes: E380Q, S463P, V534E, P535H, L536H/P/Q/R, Y537C/N/S, and D538G.

### Statistical analysis

Approximately 30 patients were planned to be enrolled in the single-agent dose-escalation stage, with an additional 3 receiving giredestrant 100 mg + palbociclib 125 mg. The exact number depended upon the observed safety and PK/pharmacodynamic profile according to the dose-escalation rules. Approximately 220 patients were planned to be enrolled in this study.

For safety analyses, the population included enrolled patients who received ≥1 dose of study medication. Safety data were analyzed on the basis of the patient's assigned dose level. All AEs reported during the AE reporting period were considered treatment emergent. Safety data for patients who received 90-mg single-agent giredestrant in the dose-escalation stage were combined with those for patients receiving 100-mg single-agent giredestrant in the dose-expansion stage, and the data are presented for single-agent giredestrant ± LHRH agonist, single-agent giredestrant 30 mg (the recommended phase II dose), and giredestrant 100 mg ± palbociclib 125 mg and ± LHRH agonist. Safety data for patients in the cardiac evaluation cohort are included within either the single-agent or combination cohorts, where appropriate.

For PK analyses, patients with an evaluable post-dose PK sample and estimable PK parameters in the giredestrant 100-mg monotherapy cohort and giredestrant 100 mg + palbociclib 125 mg combination cohorts were included. For activity analyses, ORRs and CBRs were summarized by dose level and cohort.

### Data availability

Phase I studies are not in scope of the Roche global policy on data sharing. Qualified researchers may submit an enquiry through the data request platform, Vivli, https://vivli.org/ourmember/roche/; however, this does not guarantee that the data can be shared. 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: 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 re-identification.

The datasets for this study can be shared via the Vivli platform; however, for phase I studies there will normally be a delay between receiving a request and the ability to fulfill the request to comply with approval of the product/indication.

## Results

### Patients

Between November 27, 2017, and January 28, 2021, 175 patients were enrolled. Data cutoff was September 17, 2021. Demographics and baseline characteristics are shown in **Table 1** (representativeness of study participants is shown in Supplementary Table S1). Across all single-agent cohorts, 111 patients were included at all dose levels. At data cutoff, 19 patients (17.1%) were still on study treatment. A total of 93 patients (83.8%) discontinued giredestrant, mostly due to PD [86 (77.5%)] and none due to an AE. Giredestrant-related AEs occurred in 72 patients (64.9%), leading to giredestrant dose modifications/interruptions in 5 (4.5%). Patients received a median of 6.0 giredestrant cycles (range, 1–39), remained on treatment for a median of 5.6 months (range, 1–36), and the mean dose intensity was 97.5% (standard deviation, 6.0).

Sixty-four patients were included in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort; 37 (57.8%) discontinued giredestrant: 34 due to PD (53.1%), one due to an AE (grade 3 QT prolongation), and one due to grade 5 breast cancer progression. Thirty-six patients (56.3%) discontinued palbociclib, primarily due to PD [32 (50.0%)]. Three (4.7%) discontinued palbociclib due to an AE (neutropenia, arthritis bacterial, QT prolongation). For giredestrant, patients received a median of 14.0 cycles (range, 1–38) and remained on treatment for a median of 12.8 months (range, 0–34); the mean dose intensity was 94.0% (standard deviation, 14.3). A total of 37 patients (57.8%) missed ≥1 dose. For palbociclib, patients received a median of 14.0 cycles (range, 1–38) and remained on treatment for a median of 12.6 months (range, 0–34); the mean dose intensity was 90.9% (standard deviation, 11.4).

In the cardiac evaluation cohort, 20 patients were included. The median age was 59 years (range, 45–72).

### Safety

A total of 111 patients in the single-agent cohorts were analyzed for safety; 41 were analyzed in the giredestrant 30-mg cohort; and 64 in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort.

No patients experienced DLTs and the MTD was not reached.

In the single-agent cohorts, 95 patients (85.6%) experienced ≥1 AE (Supplementary Table S2). Across all giredestrant single-agent cohorts, 17 (15.3%) patients had dose interruptions and 3 (2.7%) had dose reductions. Giredestrant-related AEs occurred in 72 patients (64.9%), leading to giredestrant dose interruption in 5 (4.5%), with 4 of these patients also having a dose reduction. No giredestrant-related AEs led to giredestrant withdrawal (Supplementary Table S2). The most frequently reported AEs assessed as related to giredestrant by the investigator (≥5% of patients) were fatigue [18 (16.2%)], arthralgia [13 (11.7%)], nausea [11 (9.9%)], bradycardia [9 (8.1%)], alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase [8 (7.2%)], diarrhea [7 (6.3%)], hot flush [7 (6.3%)], constipation [6 (5.4%)], dyspepsia [6 (5.4%)], and dry mouth [6 (5.4%)]. Most of the frequently reported AEs were grade 1 or 2 in maximum severity. Grade 3 or 4 AEs were reported in 5 patients: increase of ALT transaminases [1 (0.9%)], AST transaminases [1 (0.9%)], diarrhea [1 (0.9%)], fatigue [1 (0.9%)], and hypertension [1 (0.9%)]. Serious AEs (SAE), both related and unrelated, occurred in 11 patients (9.9%). The only SAE reported in ≥2 patients was pleural effusion [2 (1.8%)]. SAEs were considered unrelated to giredestrant, except grade 2 transient ischemic attack in one patient in the 30-mg cohort, and grade 3 fatigue in one patient in the 100-mg cohort. Fatal AEs occurred in 2 patients (1.8%) and were considered unrelated to giredestrant: 1 patient in the 30-mg cohort died from a malignant pleural effusion associated with PD from a new second primary malignancy (squamous cell carcinoma), and another in the 100-mg cohort died from duodenal ulcer perforation that occurred after discontinuation of giredestrant due to PD and start of a new line of treatment with paclitaxel (Supplementary Table S2).

In the giredestrant 30-mg single-agent cohort, 34 patients (82.9%) experienced ≥1 AE (Supplementary Table S2). Giredestrant-related AEs occurred in 28 (68.3%), leading to giredestrant dose

**Table 1.** Demographics and baseline characteristics of the intention-to-treat population.

| | Giredestrant 10 mg ($n = 6$) | Giredestrant 30 mg ($n = 41$) | Giredestrant 90/100 mg ± LHRH ($n = 55$) | Giredestrant 250 mg ± LHRH ($n = 9$) | All giredestrant doses ($n = 111$) | Giredestrant 100 mg + palbociclib 125 mg ± LHRH ($n = 64$) | All patients ($N = 175$) |
|---|---|---|---|---|---|---|---|
| Age, mean years (standard deviation) | 58.7 (10.6) | 60.1 (11.4) | 57.6 (10.8) | 57.4 (11.2) | 58.6 (11.0) | 56.9 (10.9) | 58.0 (10.9) |
| Ethnicity | | | | | | | |
| Hispanic/Latino | 0 | 2 (4.9%) | 2 (3.6%) | 0 | 4 (3.6%) | 1 (1.6%) | 5 (2.9%) |
| Not Hispanic/Latino | 5 (83.3%) | 37 (90.2%) | 49 (89.1%) | 8 (88.9%) | 99 (89.2%) | 62 (96.9%) | 161 (92.0%) |
| Not stated | 1 (16.7%) | 2 (4.9%) | 0 | 0 | 3 (2.7%) | 0 | 3 (1.7%) |
| Unknown | 0 | 0 | 4 (7.3%) | 1 (11.1%) | 5 (4.5%) | 1 (1.6%) | 6 (3.4%) |
| Race | | | | | | | |
| American Indian/ Alaska Native | 0 | 0 | 1 (1.8%) | 0 | 1 (0.9%) | 0 | 1 (0.6%) |
| Asian | 0 | 12 (29.3%) | 13 (23.6%) | 4 (44.4%) | 29 (26.1%) | 11 (17.2%) | 40 (22.9%) |
| White | 6 (100%) | 28 (68.3%) | 37 (67.3%) | 4 (44.4%) | 75 (67.6%) | 53 (82.8%) | 128 (73.1%) |
| Unknown | 0 | 1 (2.4%) | 4 (7.3%) | 1 (11.1%) | 6 (5.4%) | 0 | 6 (3.4%) |
| Mean weight at baseline (kg; standard deviation) | 62.87 (8.64) | 69.94 (16.79) | 65.37 (15.60) | 65.60 (18.57) | 66.99 (16.01) | 67.86 (14.43) | 67.31 (15.41) |
| ECOG performance status score at baseline | | | | | | | |
| 0 | 4 (66.7%) | 24 (58.5%) | 37 (67.3%) | 6 (66.7%) | 71 (64.0%) | 39 (60.9%) | 110 (62.9%) |
| 1 | 2 (33.3%) | 17 (41.5%) | 18 (32.7%) | 3 (33.3%) | 40 (36.0%) | 25 (39.1%) | 65 (37.1%) |
| Bone-only disease at baseline | | | | | | | |
| Yes | 1 (16.7%) | 6 (14.6%) | 12 (21.8%) | 1 (11.1%) | 20 (18.0%) | 11 (17.2%) | 31 (17.7%) |
| No | 5 (83.3%) | 35 (85.4%) | 43 (78.2%) | 8 (88.9%) | 91 (82.0%) | 53 (82.8%) | 144 (82.3%) |
| Visceral disease at baseline | | | | | | | |
| Yes | 3 (50.0%) | 30 (73.2%) | 35 (63.6%) | 4 (44.4%) | 72 (64.9%) | 45 (70.3%) | 117 (66.9%) |
| No | 3 (50.0%) | 11 (26.8%) | 20 (36.4%) | 5 (55.6%) | 39 (35.1%) | 19 (29.7%) | 58 (33.1%) |
| Measurable disease at baseline | | | | | | | |
| Yes | 4 (66.7%) | 30 (73.2%) | 41 (74.5%) | 6 (66.7%) | 81 (73.0%) | 56 (87.5%) | 137 (78.3%) |
| No | 2 (33.3%) | 11 (26.8%) | 14 (25.5%) | 3 (33.3%) | 30 (27.0%) | 8 (12.5%) | 38 (21.7%) |
| Number of lines of prior metastatic therapies, median (range) | 1.50 (0–3.0) | 1.00 (0–2.0) | 1.00 (0–2.0) | 1.00 (0–2.0) | 1.00 (0–3.0) | 1.00 (0–2.0) | 1.00 (0–3.0) |
| Prior use of fulvestrant | | | | | | | |
| Yes | 2 (33.3%) | 8 (19.5%) | 13 (23.6%) | 0 | 23 (20.7%) | 5 (7.8%) | 28 (16.0%) |
| No | 4 (66.7%) | 33 (80.5%) | 42 (76.4%) | 9 (100%) | 88 (79.3%) | 59 (92.2%) | 147 (84.0%) |
| Prior use of CDK4/6i | | | | | | | |
| Yes | 4 (66.7%) | 27 (66.9%) | 34 (61.8%) | 7 (77.8%) | 72 (64.9%) | 5 (7.8%)[a] | 77 (44.0%) |
| No | 2 (33.3%) | 14 (34.1%) | 21 (38.2%) | 2 (22.2%) | 39 (35.1%) | 59 (92.2%) | 98 (56.0%) |
| Baseline *ESR1* mutation status | | | | | | | |
| No mutation detected | 2 (33.3%) | 19 (46.3%) | 32 (58.2%) | 3 (33.3%) | 56 (50.5%) | 40 (62.5%) | 96 (54.9%) |
| Mutation detected | 4 (66.7%) | 21 (51.2%) | 21 (38.2%) | 6 (66.7%) | 52 (46.8%) | 18 (28.1%) | 70 (40.0%) |
| Unknown | 0 | 1 (2.4%) | 2 (3.6%) | 0 | 3 (2.7%) | 6 (9.4%) | 9 (5.1%) |
| Prior chemotherapy in the metastatic setting | | | | | | | |
| Yes | 2 (33.3%) | 8 (19.5%) | 8 (14.5%) | 1 (11.1%) | 19 (17.1%) | 13 (20.3%) | 32 (18.3%) |
| No | 4 (66.7%) | 33 (80.5%) | 47 (85.5%) | 8 (88.9%) | 92 (82.9%) | 51 (79.7%) | 143 (81.7%) |
| Prior use of chemotherapy[b] | | | | | | | |
| Yes | 5 (83.3%) | 20 (48.8%) | 36 (65.5%) | 7 (77.8%) | 68 (61.3%) | 53 (82.8%) | 121 (69.1%) |
| No | 1 (16.7%) | 21 (51.2%) | 19 (34.5%) | 2 (22.2%) | 43 (38.7%) | 11 (17.2%) | 54 (30.9%) |
| Histologic subtype | | | | | | | |
| Ductal | 4 (66.7%) | 31 (77.5%) | 42 (80.8%) | 7 (77.8%) | 84 (78.5%) | 56 (88.9%) | 140 (82.4%) |
| Lobular | 2 (33.3%) | 6 (15.0%) | 10 (19.2%) | 2 (22.2%) | 20 (18.7%) | 7 (11.1%) | 27 (15.9%) |
| NOS | 0 | 2 (5.0%) | 0 | 0 | 2 (1.9%) | 0 | 2 (1.2%) |
| Other | 0 | 1 (2.5%) | 0 | 0 | 1 (0.9%) | 0 | 1 (0.6%) |
| Nuclear grade (pleomorphism) | | | | | | | |
| Grade 1 | 0 | 3 (7.5%) | 5 (9.8%) | 0 | 8 (7.5%) | 2 (3.3%) | 10 (6.0%) |
| Grade 2 | 1 (16.7%) | 12 (30.0%) | 18 (35.3%) | 4 (44.4%) | 35 (33.0%) | 23 (37.7%) | 58 (34.7%) |
| Grade 3 | 2 (33.3%) | 10 (25.0%) | 9 (17.6%) | 2 (22.2%) | 23 (21.7%) | 20 (32.8%) | 43 (25.7%) |

*(Continued on the following page)*

**Table 1.** Demographics and baseline characteristics of the intention-to-treat population. (Cont'd)

| | Giredestrant 10 mg ($n = 6$) | Giredestrant 30 mg ($n = 41$) | Giredestrant 90/100 mg ± LHRH ($n = 55$) | Giredestrant 250 mg ± LHRH ($n = 9$) | All giredestrant doses ($n = 111$) | Giredestrant 100 mg + palbociclib 125 mg ± LHRH ($n = 64$) | All patients ($N = 175$) |
|---|---|---|---|---|---|---|---|
| Unknown | 3 (50.0%) | 15 (37.5%) | 19 (37.3%) | 3 (33.3%) | 40 (37.7%) | 16 (26.2%) | 56 (33.5%) |
| Classification of breast cancer, distant metastasis at initial diagnosis | | | | | | | |
| MX | 0 | 5 (12.2%) | 4 (7.5%) | 1 (11.1%) | 10 (9.3%) | 3 (4.8%) | 13 (7.6%) |
| M0 | 2 (50.0%) | 23 (56.1%) | 38 (71.7%) | 7 (77.8%) | 70 (65.4%) | 50 (79.4%) | 120 (70.6%) |
| M1 | 2 (50.0%) | 13 (31.7%) | 11 (20.8%) | 1 (11.1%) | 27 (25.2%) | 10 (15.9%) | 37 (21.8%) |

Note: Data are number of patients (%) unless specified.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

[a]Prior use of CDK4/6i was allowed in the cardiac evaluation cohort (5 patients within this cohort had received a prior CDK4/6i).

[b]Prior use of chemotherapy in any line of therapy.

modifications/interruptions in 3 (7.3%), and no giredestrant withdrawals (Supplementary Table S2). The most frequently reported AEs assessed as related to giredestrant by the investigator (≥5% of patients) were fatigue [6 (14.6%)], arthralgia [6 (14.6%)], nausea [6 (14.6%)], dyspepsia [5 (12.2%)], dry mouth [4 (9.8%)], diarrhea [3 (7.3%)], vomiting [3 (7.3%)], and myalgia [3 (7.3%)]. Most were grade 1, except in some patients who experienced grade 2 fatigue [4 (9.8%)], arthralgia [1 (2.4%)], dyspepsia [1 (2.4%)], and vomiting [1 (2.4%)]. SAEs occurred in 5 patients (12.2%) and were considered unrelated to giredestrant by the investigator, except the grade 2 transient ischemic attack in 1 patient (2.4%) that resolved within 24 hours.

In the giredestrant 100 mg + palbociclib ± LHRH agonist cohort, 63 patients (98.4%) experienced ≥1 AE (Supplementary Table S2). Giredestrant-related AEs occurred in 38 (59.4%), leading to giredestrant dose modification/interruption in 3 (4.7%), and giredestrant withdrawal in 1 (1.6%; Supplementary Table S2). The most frequently reported AEs assessed as related to giredestrant by the investigator (≥5% of patients) were bradycardia [15 (23.4%)], diarrhea [5 (7.8%)], photopsia [4 (6.3%)], blurred vision [4 (6.3%)], visual impairment [4 (6.3%)], nausea [4 (6.3%)], and neutropenia [4 (6.3%)]. Of these, most were grade 1, except grade 2 nausea in 1 patient (1.6%), grade 2 neutropenia in 3 patients (4.7%), and grade 3 neutropenia in 1 patient (1.6%).

All events of photopsia were reported as grade 1, non-serious, and described as "flashes'" or "flashes of light." All events were reported as either recovered or recovering without dosing changes. Two events were also reported as related to palbociclib.

All events of visual impairment were reported as grade 1 and non-serious. One event was specifically described as "visual auras" and one as "strobing both eyes." No other events were specifically described. One event was also reported as related to palbociclib.

SAEs occurred in 13 patients (20.3%). Neutropenia/neutrophil count decrease [4 patients (6.3%)] was the only SAE reported in ≥2 patients. SAEs were considered unrelated to giredestrant except grade 3 QT prolongation [1 (1.6%)]. A total of 5 patients (7.8%) experienced palbociclib-related SAEs: grade 4 neutropenia (3 patients); grade 4 thrombocytopenia (1 patient), and grade 3 febrile neutropenia (1 patient; Supplementary Table S2). One patient died due to breast cancer progression (mentioned above), which was considered unrelated to giredestrant (Supplementary Table S2).

In the single-agent cohorts (irrespective of study treatment attribution), blurred vision occurred in 6 patients (5.4%), photopsia in 2 (1.8%), and visual impairment in 2 (1.8%), whereas in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort, frequencies of blurred vision [5 (7.8%)], photopsia [6 (9.4%)], and visual impairment [6 (9.4%)] were higher, likely reflecting the known overlapping toxicity with palbociclib. Eye disorders were transient, and only led to dose modifications in 2 patients (3.1%) in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort.

Bradycardia frequency was higher in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort [18 (28.1%)] than in the single-agent cohorts [11 (9.9%), all single-agent cohorts], including the 90/100-mg single-agent cohort [6 (10.9%); **Table 2**]; however, mean changes in HR were similar between these two groups (Supplementary Table S3).

Twenty-six patients (14.9%) had grade 1 bradycardia events. Three grade 2 bradycardia events were reported: one in the giredestrant 250-mg cohort (related to giredestrant, which occurred after 22 months on treatment and lasted 7 months, resolving approximately 1 month after stopping giredestrant), one in the 30-mg cohort (unrelated to giredestrant, caused by treatment of an episode of atrial fibrillation with beta-blockers and digoxin), and one in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort that was considered related to giredestrant and required giredestrant interruption on day 28. Bradycardia resolved on day 41 and giredestrant was re-started on day 42 without incident. Overall, 34/37 bradycardia events (91.9%) were resolved/resolving at data cutoff; they were of low intensity, clinically manageable, and reversible.

### Cardiac evaluation cohort

No clinically significant changes in HR (**Fig. 2A**), blood pressure (**Fig. 2B**), or exercise duration were observed with treatment. Mean exercise duration was 7.16 minutes (standard deviation, 2.34) at baseline and 7.74 minutes (2.84) on treatment. Exercise intensity was similar before and after starting treatment [mean metabolic equivalent expenditures were 7.52 (standard deviation, 2.81) and 8.68 (2.78), respectively]. HR recovery time following exercise was similar before and during treatment, with one patient having an abnormal HR recovery on exercise testing at screening and again during treatment; all other patients had a normal HR recovery both at screening and during treatment. Twenty-four-hour Holter HR monitoring of patients showed a clinically non-significant reduction in HR, while patients were on study treatment compared with screening. A similar diurnal variation with a clinically non-significant reduction in HR, while patients were on treatment compared with screening was observed and normal sinus rhythm was maintained (**Fig. 2C**).

**Table 2.** Most common (≥10%) treatment-emergent adverse events of any grade in the safety-evaluable population.

| | Giredestrant 10 mg (*n* = 6) | Giredestrant 30 mg (*n* = 41) | Giredestrant 90/100 mg ± LHRH (*n* = 55) | Giredestrant 250 mg ± LHRH (*n* = 9) | All single-agent giredestrant doses (*n* = 111) | Giredestrant 100 mg + palbociclib 125 mg ± LHRH (*n* = 64) | All patients (*N* = 175) |
|---|---|---|---|---|---|---|---|
| Arthralgia | 2 (33.3%) | 10 (24.4%) | 11 (20.0%) | 2 (22.2%) | 25 (22.5%) | 14 (21.9%) | 39 (22.3%) |
| Fatigue | 2 (33.3%) | 7 (17.1%) | 12 (21.8%) | 3 (33.3%) | 24 (21.6%) | 21 (32.8%) | 45 (25.7%) |
| Back pain | 2 (33.3%) | 7 (17.1%) | 13 (23.6%) | 1 (11.1%) | 23 (20.7%) | 14 (21.9%) | 37 (21.1%) |
| Nausea | 2 (33.3%) | 9 (22.0%) | 10 (18.2%) | 0 | 21 (18.9%) | 13 (20.3%) | 34 (19.4%) |
| Diarrhea | 1 (16.7%) | 5 (12.2%) | 8 (14.5%) | 2 (22.2%) | 16 (14.4%) | 18 (28.1%) | 34 (19.4%) |
| Constipation | 2 (33.3%) | 6 (14.6%) | 6 (10.9%) | 0 | 14 (12.6%) | 15 (23.4%) | 29 (16.6%) |
| Cough | 1 (16.7%) | 3 (7.3%) | 9 (16.4%) | 1 (11.1%) | 14 (12.6%) | 14 (21.9%) | 28 (16.0%) |
| Pain in extremity | 0 | 3 (7.3%) | 8 (14.5%) | 1 (11.1%) | 12 (10.8%) | 7 (10.9%) | 19 (10.9%) |
| Anemia | 0 | 5 (12.2%) | 4 (7.3%) | 2 (22.2%) | 11 (9.9%) | 16 (25.0%) | 27 (15.4%) |
| Bradycardia | 0 | 3 (7.3%) | 6 (10.9%) | 2 (22.2%) | 11 (9.9%) | 18 (28.1%) | 29 (16.6%) |
| Dizziness | 3 (50.0%) | 4 (9.8%) | 3 (5.5%) | 1 (11.1%) | 11 (9.9%) | 9 (14.1%) | 20 (11.4%) |
| Vomiting | 0 | 7 (17.1%) | 4 (7.3%) | 0 | 11 (9.9%) | 7 (10.9%) | 18 (10.3%) |
| Headache | 2 (33.3%) | 4 (9.8%) | 4 (7.3%) | 0 | 10 (9.0%) | 8 (12.5%) | 18 (10.3%) |
| Asthenia | 0 | 4 (9.8%) | 4 (7.3%) | 0 | 8 (7.2%) | 13 (20.3%) | 21 (12.0%) |
| Alopecia | 0 | 2 (4.9%) | 3 (5.5%) | 0 | 5 (4.5%) | 15 (23.4%) | 20 (11.4%) |
| Neutropenia | 1 (16.7%) | 2 (4.9%) | 2 (3.6%) | 0 | 5 (4.5%) | 52 (81.3%) | 57 (32.6%) |
| Thrombocytopenia | 2 (33.3%) | 1 (2.4%) | 1 (1.8%) | 1 (11.1%) | 5 (4.5%) | 13 (20.3%) | 18 (10.3%) |

Note: Data are number of patients (%).

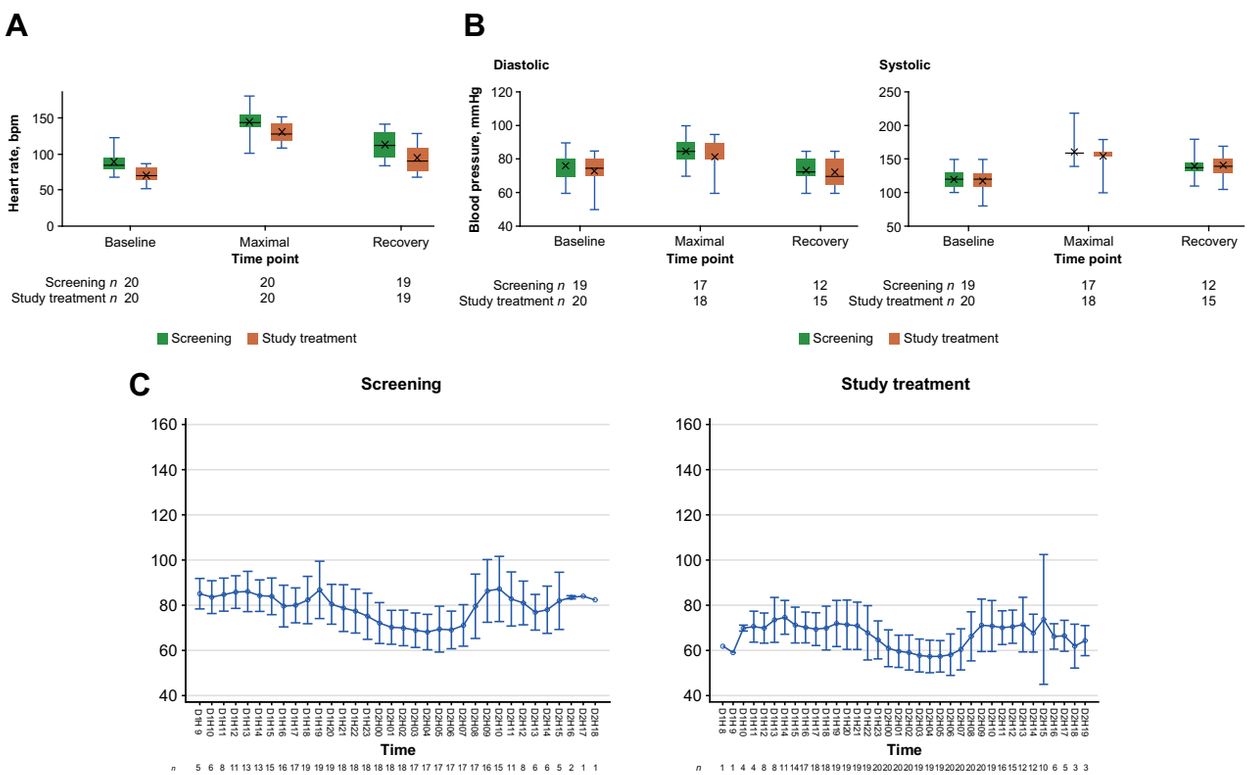


**Figure 2.**

Boxplots of exercise test results for heart rate (**A**), diastolic and systolic blood pressure (**B**), and mean plot of electrocardiogram results from Holter monitor by visit and real time (**C**). **A** and **B,** Raw assessment results are summarized at each time point. All measures at study treatment were collected after 7 days of single-agent dosing (giredestrant 100 mg). **C,** Average of the observations is taken if there are multiple observations per real time point. Plot starts with real time when 24-hour Holter HR monitoring started for screening or study treatment, respectively. For example, starting point of D1H9 on screening means Holter monitoring started at 9 am on the day of screening. All measures at study treatment were collected after 7 days of single-agent dosing (giredestrant, 100 mg). Abbreviations: bpm, beats per minute; CCOD, clinical cutoff date; CRF, case report form; D, day; H, hour.

### Activity

In the single-agent cohorts, ORR in patients with measurable disease at baseline was 19.8% (16/81 patients) and CBR was 48.6% (54/111; **Table 3**). Tumor responses are shown in **Fig. 3A**. Median DOR was 17.5 months [95% confidence interval (CI), 7.5 months–not evaluable (NE); **Table 3**]. Clinical benefit was observed in 6/23 patients (26.1%) previously treated with fulvestrant, 25/72 (34.7%) previously treated with a CDK4/6i, 32/68 (47.1%) previously treated with chemotherapy in the (neo)adjuvant and/or metastatic settings, and 26/52 (50.0%) with baseline *ESR1*-mutated tumors (Supplementary Table S4). Response by specific baseline *ESR1* mutation is shown in Supplementary Fig. S1. A total of 18 patients in the single-agent dose-escalation stage underwent FES-PET scans: 14 had FES-avid disease at baseline (3 each at 10 and 250 mg; 4 each at 30 and 90 mg), and 11 of the 14 (78.6%) showed complete or near-complete (>90%) suppression of FES uptake relative to background levels, including patients with *ESR1*-mutated tumors (Supplementary Fig. S2). One patient discontinued early from the study (no on-study scan), and 3 patients had no FES-avid disease at baseline discerinble from physiologic uptake; none of these patients achieved clinical benefit. The vast majority of patients (98%) with a detectable *ESR1* mutation at baseline demonstrated a decrease in *ESR1* variant allele frequency at cycle 1, day 15 and/or cycle 2, day 1 upon treatment with single-agent giredestrant (Supplementary Fig. S3). Of these, 65% overall had a reduced *ESR1* variant allele frequency below the limit of detection, with saturation observed at doses of 30 mg and greater (10 mg: 25%; 30 mg: 75%; 90 or 100 mg: 62%; 250 mg: 67%), and with a higher rate observed in patients who achieved clinical benefit regardless of dose (no clinical benefit, 54%; clinical benefit, 74%).

In the giredestrant 30-mg single-agent cohort, ORR in patients with measurable disease at baseline was 30.0% (9/30 patients), and CBR was 53.7% (22/41; **Table 3**). Median DOR was not reached (95% CI, 7.5 months–NE; **Table 3**). Clinical benefit was observed in 3/8 patients (37.5%) previously treated with fulvestrant, 11/27 (40.7%) previously treated with a CDK4/6i, 11/20 (55.0%) previously treated with chemotherapy in the (neo)adjuvant and/or metastatic settings, and 13/21 (61.9%) with baseline *ESR1*-mutated tumors (Supplementary Table S4).

In the giredestrant 100 mg + palbociclib ± LHRH agonist cohort, ORR in patients with measurable disease at baseline was 48.2% (27/56 patients) and CBR was 81.3% (52/64; **Table 3**). Tumor responses are shown in **Fig. 3B**. Median DOR was not reached (95% CI, 17.4 months–NE; **Table 3**). Clinical benefit was observed in 3/5 patients (60.0%) previously treated with

**Table 3.** Clinical benefit and confirmed best overall response rates in the safety-evaluable population and selected subgroup responders (objective response rate).

| | Giredestrant 10 mg (*n* = 6) | Giredestrant 30 mg (*n* = 41) | Giredestrant 90/100 mg ± LHRH (*n* = 55) | Giredestrant 250 mg ± LHRH (*n* = 9) | All giredestrant doses (*n* = 111) | Giredestrant 100 mg + palbociclib 125 mg ± LHRH (*n* = 64) | All patients (*N* = 175) |
|---|---|---|---|---|---|---|---|
| Clinical benefit by investigator in clinical benefit–evaluable[a] patients | 1 (16.7%) | 22 (53.7%) | 28 (50.9%) | 3 (33.3%) | 54 (48.6%) | 52 (81.3%) | 106 (60.6%) |
| ORR | 1 (16.7%) | 9 (22.0%) | 6 (10.9%) | 0 | 16 (14.4%) | 27 (42.2%) | 43 (24.6%) |
| (95% CI) | (0.42–64.12) | (10.56–37.61) | (4.11–22.25) | (0–33.63) | (8.47–22.35) | (29.94–55.18) | (18.39–31.64) |
| ORR in patients with measurable disease at baseline | 1 (25.0%) | 9 (30.0%) | 6 (14.6%) | 0 | 16 (19.8%) | 27 (48.2%) | 43 (31.4%) |
| Total *n* (95% CI) | 4 (0.63–80.59) | 30 (14.73–49.40) | 41 (5.57–29.17) | 6 (0–45.93) | 81 (11.73–30.09) | 56 (34.66–61.97) | 137 (23.73–39.87) |
| CR | 0 | 0 | 0 | 0 | 0 | 6 (9.4%) | 6 (3.4%) |
| PR | 1 (16.7%) | 9 (22.0%) | 6 (10.9%) | 0 | 16 (14.4%) | 21 (32.8%) | 37 (21.1%) |
| SD | 2 (33.3%) | 12 (29.3%) | 27 (49.1%) | 5 (55.6%) | 46 (41.4%) | 28 (43.8%) | 74 (42.3%) |
| Non-CR/non-PD | 0 | 6 (14.6%) | 5 (9.1%) | 0 | 11 (9.9%) | 2 (3.1%) | 13 (7.4%) |
| PD | 2 (33.3%) | 14 (34.1%) | 13 (23.6%) | 3 (33.3%) | 32 (28.8%) | 6 (9.4%) | 38 (21.7%) |
| NE | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Missing | 1 (16.7%) | 0 | 4 (7.3%) | 1 (11.1%) | 6 (5.4%) | 1 (1.6%) | 7 (4.0%) |
| Duration of response (months) | | | | | | | |
| Median | 12.0 | NE | 17.5 | NE | 17.5 | NE | 22.8 |
| 95% CI | NE | (7.5–NE) | (3.7–NE) | NE | (7.5–NE) | (17.4–NE) | (14.9–NE) |
| Range | 12–12 | 3[b]–14[b] | 3–34[b] | NE | 3–34[b] | 4[b]–32[b] | 3–34[b] |

Note: Data are number of patients (%) unless specified. Responders are patients with best confirmed response of CR or PR by RECIST v1.1. 95% CI for rates were constructed using the Clopper–Pearson method. Patients were classified as "SD" if assessment was at least 6 weeks from baseline/study entry. Patients were classified as "NE" if all post-baseline response assessments were reported as NE, or SD assessment occurred within 6 weeks from baseline/study entry. Patients were classified as "missing" if no post-baseline response assessments were available. Clinical benefit includes patients with confirmed CR, PR, or the first occurrence of disease progression observed on or after 24 weeks. Note that one patient from the giredestrant 100 mg ± LHRH agonist cohort is currently counted as one of the patients who had SD as the best overall response as well as having clinical benefit; however, this patient had the target lesion removed, and therefore became response non-evaluable per RECIST v1.1.

[a]Clinical benefit–evaluable population is defined as patients with confirmed CR, PR, or patients who discontinued from study, or patients staying on the treatment for at least 24 weeks since cycle 1, day 1 of giredestrant.

[b]Censored observation.

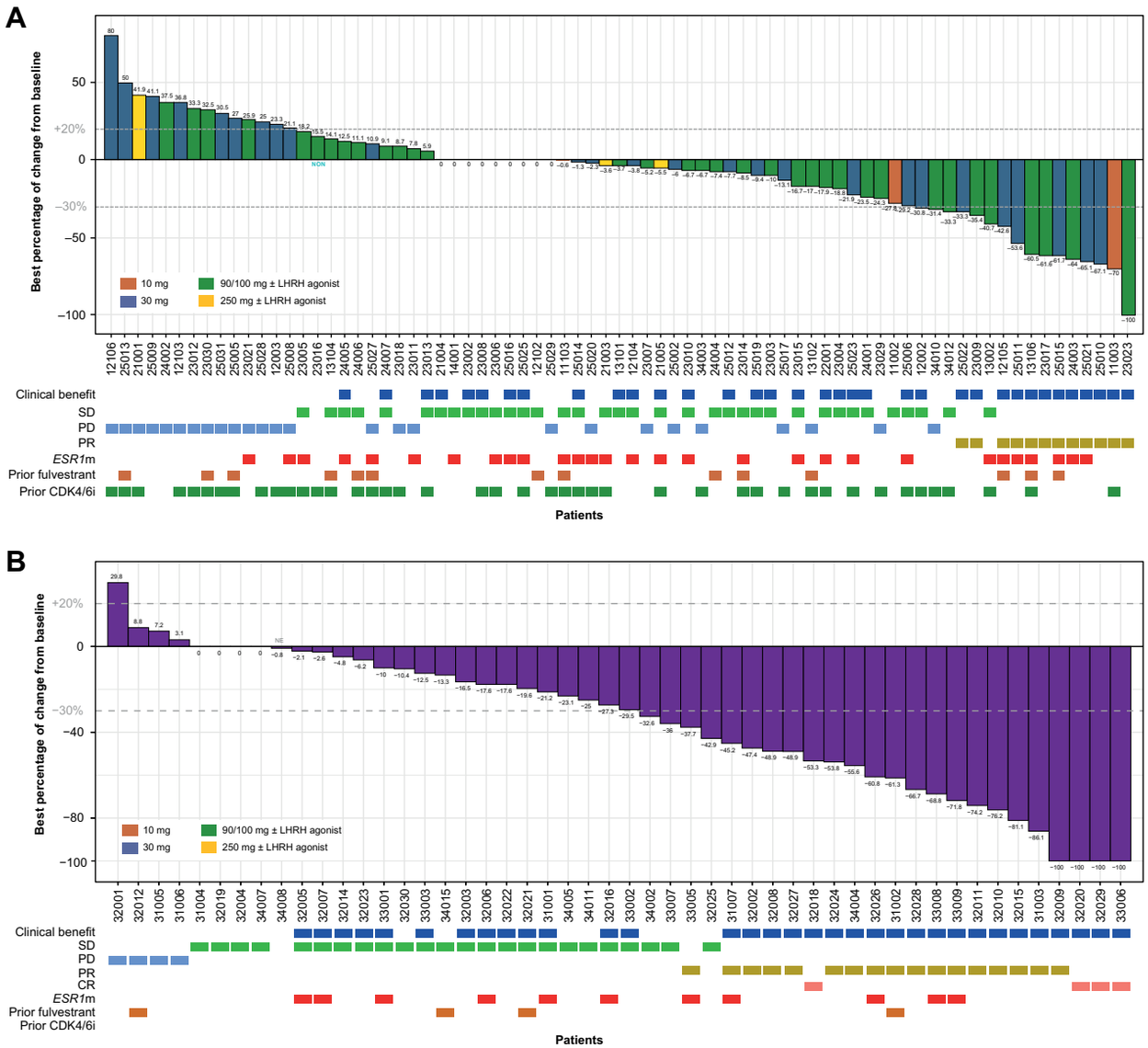


**Figure 3.**

Waterfall plot of best percentage of change from baseline in tumor sum of diameters in the safety-evaluable population: single-agent cohorts (**A**) and giredestrant 100 mg + palbociclib ± LHRH agonist cohorts (**B**). Cohorts of best confirmed overall response are shown on the plot. Abbreviations: *ESR1*m, *ESR1* mutant; NA, not assessed; NON, non-CR/non-PD.

fulvestrant, 4/5 (80.0%) previously treated with a CDK4/6i, 42/53 (79.2%) previously treated with chemotherapy in the (neo)adjuvant and/or metastatic settings, and 18/18 (100%) with baseline *ESR1*-mutated tumors (Supplementary Table S4). Decreases in *ESR1* variant allele frequencies were more pronounced in the combination cohort, with 83% of patients with a baseline *ESR1* mutation having no detectable levels of mutated *ESR1* at cycle 2, day 1 (Supplementary Fig. S3).

No clinically relevant drug–drug interaction was observed between palbociclib and giredestrant (Supplementary Table S5), and thus no dose adjustment was needed for giredestrant in combination with palbociclib.

## Discussion

In this phase Ia/b study of single-agent giredestrant in patients with ER+, HER2− locally advanced/metastatic breast cancer, giredestrant was well tolerated; the observed safety profile of the combination of giredestrant and palbociclib was consistent with the known safety profile of the individual drugs at all dose levels tested, including the 30-mg phase III dose. All-grade and grade 3/4 AEs, and SAEs, were more frequent in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort than in the single-agent cohorts, mainly due to hematologic toxicities of palbociclib. No DLTs were observed and the MTD was not reached. Bradycardia has been reported with other SERDs, including camizestrant (34), H3B-6545 (35), and amcenestrant (36); however, the

mechanism of bradycardia is unknown. Bradycardia is a dose-dependent adverse reaction of giredestrant. In the single-agent cohorts, the incidence of bradycardia was numerically higher at doses of 90/100 mg [6/55 (10.9%)] and 250 mg [2/9 (22.2%)] than that at 30 mg [3/41 (7.3%)]. All bradycardia events were low grade, with no SAEs reported at any dose level. Thus, the 30-mg dose was chosen for further evaluation. The frequency of bradycardia was higher in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort [18/64 (28.1%)] than in the corresponding 90/100-mg single-agent cohort [6/55 (10.9%)]. However, the mean changes in HR by time on study were similar in these two groups. The reasons for this are unclear, but there is not an obvious more pronounced effect on HR in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort. The bradycardia observed with giredestrant is generally asymptomatic, and the protocol did not mandate reporting changes in vital signs as AEs, unless they were accompanied by clinical symptoms, required intervention, resulted in change of study treatment, or were otherwise considered clinically significant. It is possible that the early discovery of the safety signal for bradycardia and resulting protocol amendment encompassing evaluation of cardiac effects led to greater awareness, and hence greater reporting of this asymptomatic event.

Once the safety signal of bradycardia at doses of 100 mg and above was observed, the protocol was amended to provide an in-depth evaluation of cardiac effects in a dedicated cohort with 24-hour Holter HR monitoring and exercise stress testing. Patients who received 100-mg giredestrant showed a clinically non-significant reduction in HR with maintenance of normal sinus rhythm; exercise stress testing demonstrated no effects on the ability to exercise or duration of exercise, and no effects on blood pressure. The clinical results are reassuring as the decrease in HR observed with the 100-mg dose was modest and not associated with impact on physical activity or clinical symptoms.

In addition to bradycardia, visual disturbances observed in this study have also been observed with camizestrant; in SERENA-1, these affected 53% of treated patients (34). This has not been reported with other oral SERDs, and the mechanism is unknown. In our study, small numbers of ocular AEs were reported among the single-agent cohorts that were not considered attributable to giredestrant. Larger numbers of ocular AEs were seen in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort, consistent with the palbociclib product labeling (which states that eye disorders are common; ref. 37). Similarly, when looking at ocular toxicity irrespective of causality, the incidence of ocular AEs in the single-agent cohorts was consistent with that seen at baseline but was increased relative to baseline in the palbociclib cohort. AEs of interest include blurred vision (5.4% across giredestrant cohorts vs. 7.8% in the palbociclib combination cohort), photopsia (1.8% vs. 9.4%), and visual impairment (1.8% vs. 9.4%). None of these AEs were reported in the 250-mg cohort; therefore, there was no obvious correlation between these AEs and dose. In addition, the phase I GO40987 study (27), phase II acelERA Breast Cancer study (38), and phase II coopERA Breast Cancer study (29, 39) have not reported eye disorders as SAEs and these were not classified as identified or potential risks associated with giredestrant. Eye disorders reported as related to giredestrant were grade 1/2 and non-serious. However, because eye disorders are listed as common on the palbociclib label, these increases are likely due to palbociclib.

Encouraging clinical activity was observed with single-agent giredestrant at all dose levels and patient subgroups, including across patients who received a range of prior treatment types such as chemotherapy, CDK4/6is, and fulvestrant. Activity in patients with *ESR1*-mutated tumors was notable, showing that an ET resistance mechanism commonly observed in the clinic was overcome. FES-PET data demonstrated target engagement and robust reduction in ER activity.

Given that maximal clinical benefit was observed at the 30-mg dose or higher, and that bradycardia was more frequent at doses greater than 30 mg, this dose was selected for further evaluation in phase II/III studies. Although ORR appeared greater at the 30-mg dose compared with higher doses, the CIs were overlapping, suggesting that this was a result of chance. In this disease setting, CBR may be a more informative efficacy endpoint given the biology of ER-positive breast cancer that typically has a slower disease course and high incidence of non-measurable disease due to bone involvement. Here, CBRs were comparable. Pharmacodynamic evaluations support the choice of the 30-mg dose, as evidenced by the FES-PET findings and change in *ESR1* ctDNA showing high target engagement at 30 mg, not further enhanced at higher doses. Additionally, in the phase I GO40987 study in the postmenopausal, neoadjuvant setting, giredestrant monotherapy showed pharmacodynamic activity consistent with a 30-mg dose achieving maximal ER inhibition (27).

Additional clinical benefit was achieved with giredestrant in combination with palbociclib 125 mg (± LHRH agonist) compared with giredestrant monotherapy, with more patients with confirmed complete or partial responses in the giredestrant 100 mg + palbociclib ± LHRH agonist cohort. In addition, the median DOR for the giredestrant 100 mg + palbociclib ± LHRH agonist cohort was longer than in the single-agent cohorts. Clinical benefit was observed across the clinically relevant subgroups.

Palbociclib steady-state maximum and minimum concentrations observed in this study were consistent with previous reports (40), indicating that giredestrant did not appear to have a clinically relevant impact on palbociclib exposures. Exposures for giredestrant in combination with palbociclib were generally comparable to those observed with single-agent giredestrant. In contrast with amcenestrant (41), no dose adjustment was needed when giredestrant was given in combination with palbociclib.

Strengths of this study include its large sample size for a phase Ia/b study (175 patients) and inclusion of both pre- and postmenopausal women. The study was conducted globally across the US, Europe, Asia, and Australia. In addition, it explored a wide range of dose levels, including a dose-expansion stage at three dose levels in the single-agent cohorts, and with palbociclib to determine the appropriate dose for further study, which was determined to be 30 mg given the more tolerable safety profile and similar activity.

A limitation of this study is that enrollment was limited to patients who had prior prolonged response to ET. Prior knowledge about the safety profile of giredestrant may have led to bias in the reporting of cardiac AEs such as bradycardia. Results obtained for the study endpoints may not be applicable to patients from other regions that were not studied.

Overall, results were consistent with the evaluation of giredestrant in the neoadjuvant early breast cancer setting (27, 39). In the phase I GO40987 study, giredestrant monotherapy showed a promising impact on tumor cell proliferation (Ki67) after 14 days of treatment and no discontinuations due to AEs (27). This was consistent with the results of the phase II coopERA Breast Cancer study, which evaluated activity of giredestrant ± palbociclib in the neoadjuvant setting, and demonstrated superior antiproliferative activity of giredestrant 30 mg compared with anastrozole after 2 weeks of treatment; this superiority was maintained following addition of palbociclib (29, 39). Although the phase II acelERA Breast Cancer study, which compared efficacy and safety of giredestrant versus physician's choice of endocrine monotherapy in the advanced setting, did not meet its primary

endpoint (investigator-assessed progression-free survival), giredestrant showed a numeric improvement, which was more pronounced in patients with *ESR1*-mutated tumors (38). The continued investigation of giredestrant as a single agent in the locally advanced setting is warranted as it is expected to have superior efficacy to currently available SERDs, for example, fulvestrant, based on preclinical data (25). Similarly, and as seen in coopERA Breast Cancer in the clinical setting (39), clinical data suggest that giredestrant combined with palbociclib may have superior efficacy to currently approved ET–palbociclib combinations (42–45).

Giredestrant is one of several oral SERDs that are being evaluated in clinical trials. Results from the phase Ia/b GO39932 study demonstrate that giredestrant has the potential to provide a well-tolerated, clinically active treatment in patients who have progressed on prior ET, for which there is a high unmet need. As a class, next-generation SERDs may offer a new therapeutic choice for patients with ER+ breast cancer (19, 46), both as monotherapy and in combination with standard-of-care treatment for ER+ breast cancer (elacestrant is now FDA-approved for patients with *ESR1*-mutant tumors based on the EMERALD trial; ref. 19). Giredestrant has shown superior potency compared with other SERDs, and displays nearly full ER occupancy, including in patients with *ESR1*-mutated tumors (25). There are other mechanisms of endocrine resistance beyond *ESR1* mutations, and combinations with novel SERDs may be an option for many patients. For example, the phase III evERA Breast Cancer study will assess giredestrant in combination with everolimus (47), whereas MORPHEUS Breast Cancer (NCT04802759) will investigate a range of therapies. Giredestrant continues to be assessed in ER+ breast cancer in an ongoing phase III, randomized study of single-agent giredestrant in the HER2-negative early breast cancer treatment setting (lidERA Breast Cancer; ref. 48), as well as in the HER2-negative metastatic setting in persevERA Breast Cancer (49). Finally, in the HER2-positive metastatic setting, giredestrant is being evaluated in heredERA Breast Cancer (50).

## Authors' Disclosures

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## Note

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