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Lerociclib plus fulvestrant in patients with HR+/HER2− locally advanced or metastatic breast cancer who have progressed on prior endocrine therapy: LEONARDA-1 a phase III randomized trial

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Lerociclib (GB491), a highly selective oral CDK4/6 inhibitor, has displayed anti-tumor activity and differentiated safety and tolerability profile in previous ph1/2 clinical trials. The LEONARDA-1, a randomized, double-blind, phase III study, was conducted to evaluate the efficacy and safety of lerociclib in HR+/HER2− locally advanced or metastatic breast cancer patients, who had relapsed or progressed on prior endocrine therapy. A total of 275 patients were randomized at 1:1 ratio to receive lerociclib (137 patients, 150 mg twice daily) or placebo (138 patients) plus fulvestrant. Progression-free survival (PFS) assessed by investigators was significantly improved in lerociclib arm versus placebo arm (11.07 vs 5.49 months; hazard ratio, 0.451, 95% CI: 0.311-0.656, $P = 0.000016$), meeting the pre-specified primary endpoint. The secondary endpoints included PFS assessed by Blinded Independent Central Review (BICR), objective response rate (ORR), duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR), overall survival (OS), safety and tolerability and pharmacokinetic profile. DOR is not reported, and OS data was immature at the data cut-off but unplanned ad hoc analysis is reported. These findings support lerociclib plus fulvestrant as a treatment option for patients with HR+/HER2− endocrine-resistant advanced breast cancer (ABC). (Funded by Genor Biopharma; LEONARDA-1 ClinicalTrials.gov identifier, NCT05054751.)

Breast cancer ranks as the most frequently diagnosed cancer and stands as the foremost contributor to cancer-related fatalities among women globally[1]. In 2016, there were approximately 306,000 new cases diagnosed and more than 71,700 deaths from breast cancer in China[2]. Over 70% of patients diagnosed with ABC exhibit hormone receptor-positive (HR+) disease, rendering them eligible candidates for endocrine therapy (ET). However, the efficacy of this therapy decreases over time due to the development of drug resistance[3].

The mechanisms responsible for resistance to ET and the promotion of oncogenic growth intersect within the cell cycle[4]. Cyclin-dependent kinases 4 and 6 (CDK4/6) are enzymes that play a crucial role in cell cycle progression and are involved in regulating the transition from the G1 phase to the S phase of the cell cycle, where DNA

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synthesis occurs[5]. CDK4/6 inhibitors work by blocking the activity of CDK4 and CDK6, thus preventing the phosphorylation of the retinoblastoma protein (Rb). This, in turn, leads to the inhibition of cell cycle progression from the G1 to S phase[6]. Numerous phase 3 clinical trials have evaluated the efficacy of combining a CDK4/6 inhibitor with fulvestrant in HR+, HER2-negative (HER2−) endocrine-resistant ABC[7–15]. While CDK4/6 inhibitors are generally tolerated, they are commonly associated with adverse reactions such as hematologic toxicity, gastrointestinal toxicity, abnormal liver function, venous thromboembolism, and skin adverse reactions. Managing these side effects while maintaining therapeutic efficacy is an ongoing challenge and these side effects have limited the clinical application of CDK4/6 inhibitors in some breast cancer patients.

Lerociclib (GB491), a potent and selective oral CDK4/6 inhibitor, is highly potent for CDK4/cyclin D_1 and CDK6/cyclin D_3 (IC_{50} of 1 nM and 2 nM, respectively), but moderately potent for CDK9/cyclin T (IC_{50} of 28 nM). The in-vitro study showed that lerociclib produced a precise G1 arrest and inhibited the phosphorylation of Rb and cancer cell proliferation[16]. In xenograft models of breast cancer, non-small cell lung cancer, and prostate cancer, daily oral treatment with lerociclib caused significant, durable, and dose-dependent inhibition of tumor growth[16,17]. In a phase I/II study of patients with HR+/HER2− ABC, continuous lerociclib dosing with fulvestrant showed a differentiated safety profile with low rates of Grade 4 neutropenia, gastrointestinal toxicity, fatigue, stomatitis and alopecia[18]. Additionally, the efficacy data were consistent with that of fulvestrant combined with approved CDK4/6 inhibitors[18].

Here, we show the results from the LEONARDA-1 study (ClinicalTrials.gov identifier: NCT05054751), a phase III trial that evaluated the efficacy and safety of lerociclib plus fulvestrant versus placebo plus fulvestrant in HR+/HER2− endocrine-resistant ABC.

Results

Patients

From September 10, 2021 to July 28, 2022, a total of 357 participants were screened and 275 participants were randomly assigned to lerociclib plus fulvestrant ($n = 137$) or placebo plus fulvestrant ($n = 138$; Fig. 1) arms. The data cut-off date was December 2, 2022. Baseline characteristics were well balanced between the two arms (Table 1). At baseline, 174 patients (63.3%) exhibited visceral metastatic lesions including 104 patients (37.8%) with liver metastasis, while 41 patients (14.9%) showed bone-only metastatic lesions. All patients had previously shown resistance to ET, with 70 patients (25.5%) displaying primary ET resistance (defined as disease relapsed while receiving the first 2 years of (neo)adjuvant ET or progressed while receiving the first 6 months of ET for ABC[19,20]) and 205 patients (74.5%) displaying secondary drug resistance (defined as disease relapsed while on adjuvant ET but after the first 2 years, or relapsed within 12 months of completing adjuvant ET, or progressive disease (PD) > 6 months after initiating ET for ABC, while on ET[19,20]). The majority of patients (92.4%) had received prior chemotherapy, while during the relapsed/metastatic phase, and 80 patients (29.1%) received first-line chemotherapy. Nearly half of the patients (43.3%) were pre/perimenopausal women or men.

Treatment

At the data cut-off, a higher percentage of patients were continuing with the study treatment in the lerociclib arm (63.5%) compared to the

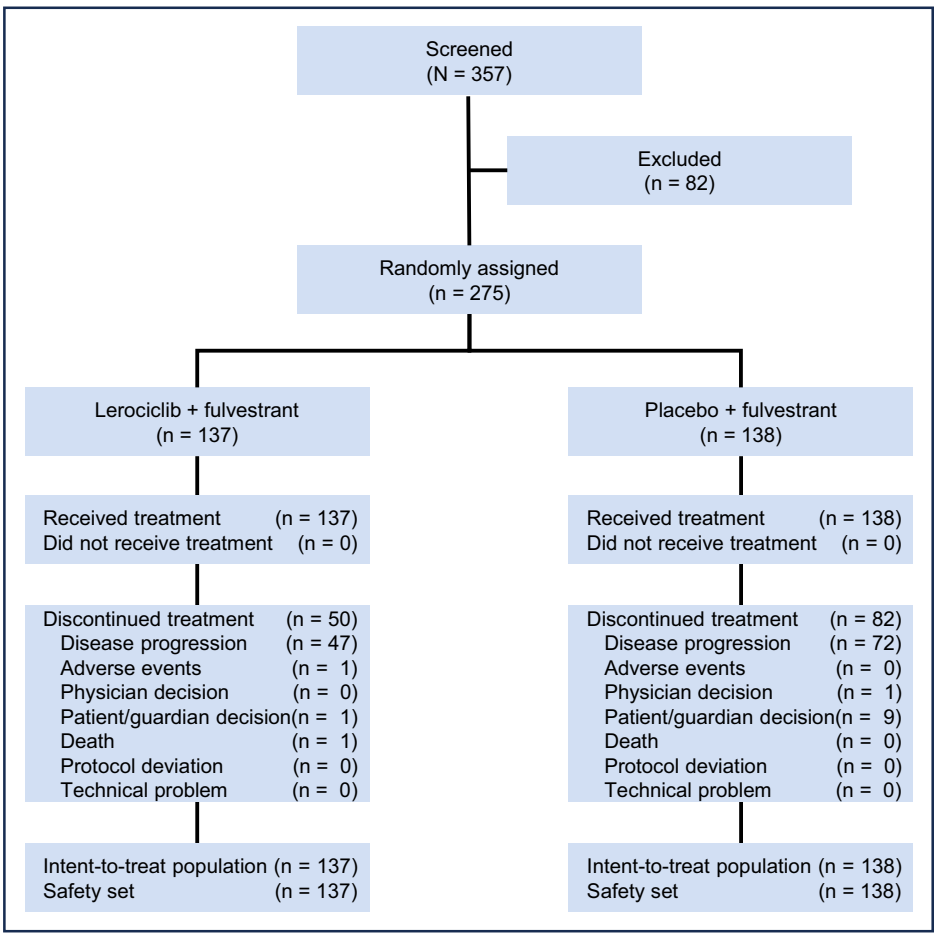

Fig. 1 | CONSORT diagram.

Table 1 | Patient and disease baseline characteristics

Characteristics	Lerociclib + Fulvestrant (*N* = 137), *n* (%)	Placebo + Fulvestrant (*N* = 138), *n* (%)
Age, years		
<65	120 (87.6%)	119 (86.2%)
≥65	17 (12.4%)	19 (13.8%)
ECOG PS		
0	73 (53.3%)	56 (40.6%)
1	64 (46.7%)	82 (59.4%)
Menopausal status		
Pre-/Perimeno-pausal women /men	57 (41.6%)	62 (44.9%)
Postmenopausal	80 (58.4%)	76 (55.1%)
Nature of disease		
Visceral metastasis	88 (64.2%)	86 (62.3%)
Liver metastasis	56 (40.9%)	48 (34.8%)
Bone only	19 (13.9%)	22 (15.7%)
Others	30 (21.9%)	30 (21.7%)
Metastatic sites		
<4	101 (73.7%)	106 (76.8%)
≥4	36 (26.3%)	32 (23.2%)
Sensitivity to endocrine treatment		
Primary resistance	34 (24.8%)	36 (26.1%)
Secondary resistance	103 (75.2%)	102 (73.9%)
Previous chemotherapy for recurrent/metastatic disease		
Yes	40 (29.2%)	40 (29.0%)
No	97 (70.8%)	98 (71.0%)
Previous lines of endocrine therapy		
1	137 (100%)	136 (98.6%)
2	0	2 (1.4%)
Hormone receptor status		
ER+ and PR+	109 (79.6%)	96 (69.6%)
ER+ and PR-	28 (20.4%)	42 (30.4%)
Previous endocrine therapy		
AI only	69 (50.4%)	73 (52.9%)
SERM only	51 (37.2%)	43 (31.2%)
AI and SERM	17 (12.4%)	22 (15.9%)
Measurable disease		
Yes	119 (86.9%)	121 (87.7%)
No	18 (13.1%)	17 (12.3%)

AI aromatase inhibitor; *ECOG PS* Eastern Cooperative Oncology Group performance status, *ER* estrogen receptor, *PR* progesterone receptor, *SERM* selective estrogen receptor modulator.

placebo arm (40.6%). Treatment discontinuation was mainly due to disease progression (34.3% in the lerociclib arm, 52.2% in the placebo arm). The median duration of drug exposure was 6.28 months (range: 0.6–12.1) in the lerociclib arm and 4.86 months (range: 0.4–12.5) in the placebo arm. The median average daily doses of lerociclib and matching-placebo were 283.67 mg and 297.55 mg, respectively.

Efficacy

A total of 125 PFS events, including documented disease progression or death without documented progression, were observed in the ITT population. Specifically, there were 48 events (35.0%) in the lerociclib arm (137 participants) and 77 events (55.8%) in the placebo arm (138 participants). The median follow-up time was 7.36 months for the lerociclib arm and 7.33 months for the placebo arm. The lerociclib arm demonstrated a superior median PFS of 11.07 months, compared with 5.49 months in the placebo arm (HR: 0.451; 95% CI: 0.311–0.656; $P = 0.000016$; Fig. 2A). BICR-assessed analysis provided consistent results for PFS (HR: 0.353; 95% CI: 0.228–0.547; $P = 0.000002$; Fig. 2B). The addition of lerociclib to fulvestrant improved PFS across all pre-specified patient subgroups, including patients with poor prognosis, such as primary ET resistance (HR: 0.374; 95% CI: 0.182–0.769), liver metastasis (HR: 0.487; 95% CI: 0.297–0.796), ≥4 metastatic sites (HR: 0.326; 95% CI: 0.160–0.665), received one line of chemotherapy for recurrent/metastatic disease (HR: 0.286; 95% CI: 0.138–0.593), and pre/perimenopausal women or men (HR: 0.471; 95% CI: 0.258–0.860) (Fig. 3). The pre-specified sensitivity analysis for investigator-assessed PFS, excluding patients (1) who had less than 80% of treatment compliance (9 patients, all due to COVID-19 pandemic); or (2) who didn't have any post-treatment radiological assessments (3 patients); or (3) whose baseline radiological assessment was uncomplete to allow appropriate post-treatment efficacy assessment (1 patient), further supported the primary analysis. The median PFS from the sensitivity analysis was 11.07 months in the lerociclib arm and 5.49 months in the placebo arm (HR: 0.462; 95% CI: 0.316, 0.676, $p < 0.0001$).

The investigator-assessed ORR (based on confirmed response) was 23.4% (95% CI: 16.27–30.44%) in the lerociclib arm and 8.7% (95% CI: 3.99–13.40%) in the placebo arm (Table 2). Three CRs (2.2%) were achieved in the lerociclib arm compared with no CRs (0%) in the placebo arm. Among patients with measurable disease at baseline, the ORR was 26.9% (95% CI: 18.92–34.86%) in the lerociclib arm and 9.9% (95% CI: 4.59–15.24%) in the placebo arm (Table 2). Due to the relatively short follow-up duration, DOR was not mature as of the data cut-off and the median DOR had not been reached in both arms, with 38 responders (86.4%) continuing the treatment at the time of the analysis. The DCR and CBR (lerociclib arm vs. placebo arm) were 81.8% (95% CI: 75.28–88.22%) vs. 71.0% (63.44–78.58%) and 48.2% (95% CI: 39.81–56.54%) vs. 24.6% (95% CI: 17.45–31.83%), respectively (Table 2). The ORR/DCR/CBR/DOR assessed by BICR were in line with the investigator assessments (Supplementary Table 1).

As of the data cut-off, OS results were not yet mature, with 9 deaths (6.6%) in the lerociclib arm and 13 deaths (9.4%) in the placebo arm (HR: 0.630, 95% CI: 0.267–1.484; median OS: not reached in both arms). An ad hoc analysis of OS was conducted (DCO: March 30, 2024) with a median follow-up duration of 23 months, at which time there were 32 and 43 deaths in the lerociclib arm and placebo arm, respectively. Median OS was not reached in either arm and the HR was 0.649 (95% CI: 0.410, 1.028) (Supplementary Fig. 1).

Pharmacokinetic (PK) samples were collected before the study drug dosing in the morning on Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, respectively. The mean of serum concentrations of lerociclib and its metabolite G1T30 ranged from 11.515 ng/mL to 16.556 ng/mL, and from 1.2545 ng/mL to 1.9259 ng/mL, respectively. The variations of the mean at different cycles are within the standard deviations of the mean at each cycle.

Safety

The safety population was the same as the ITT population (lerociclib, $n = 137$; placebo, $n = 138$). The most common treatment-emergent AEs of any grade were neutropenia, leukopenia, and anemia (Table 3). Grade 3 or higher AEs were reported in 57.7% and 15.2% of the patients in the lerociclib arm and the placebo arm, respectively (Table 4). The grade 3 or 4 AEs occurring in ≥3% of the patients in lerociclib arm were neutropenia (grade 3: 41.6%, grade 4: 5.1%, no febrile neutropenia), leukopenia (23.4%, grade 3 only), and thrombocytopenia (grade 3: 2.2%, grade 4: 1.5%) (Table 3).

Diarrhea was reported in 19.7% (no ≥grade 3) and 3.6% patients in lerociclib and placebo arms, respectively. AEs of ECG QTc

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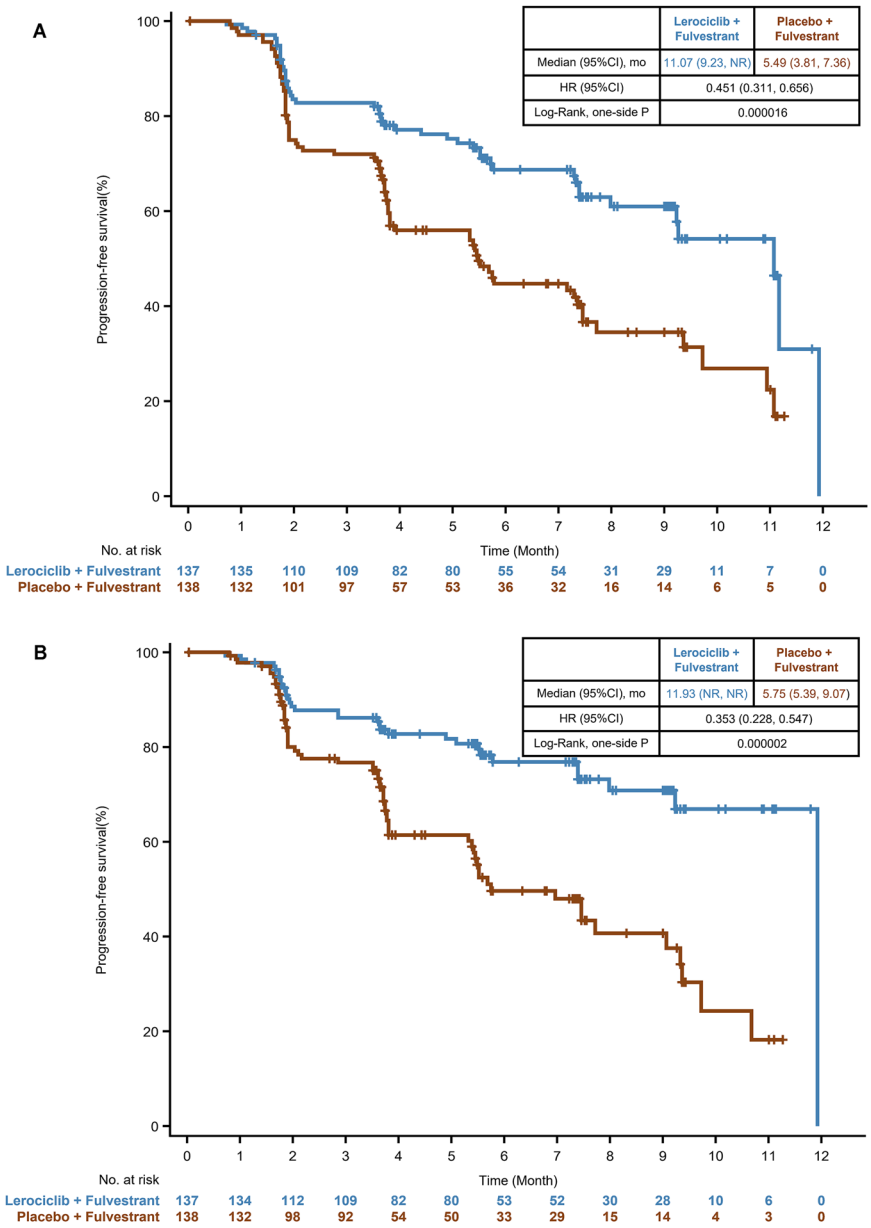

Fig. 2 | Kaplan–Meier analyses of progression-free survival in the intent-to-treat population (*n* = 275 patients). A Investigator-assessed and **B** Blinded Independent Central Review-assessed. HR hazard ratio. The hazard ratio (HR) was derived from a stratified Cox proportional hazards model, and the one-sided *p*-value was derived from the Log-Rank test. Source data are provided as a Source Data file.

prolongation (any grade) occurred in 4 patients (2.9%; all grade 1) receiving lerociclib plus fulvestrant and 2 patients (1.4%; 1 (0.7%) grade 2; 1 (0.7%) grade 3) receiving placebo plus fulvestrant. None of the prolonged QTc events led to treatment discontinuation. Pneumonitis due to any reason was reported by 2 (1.5%) patients in the lerociclib arm and 3 (2.2%) patients in the placebo arm; 1 patient in each arm reported grade 3 pneumonitis. Only 1 patient (0.7%), in the lerociclib plus fulvestrant arm, discontinued study treatment due to grade 3 pneumonitis. No venous thromboembolic events (VTE) were reported.

Serious AEs (SAEs) were reported in 5.8% of patients in the lerociclib arm and 8.0% of patients in the placebo arm (Table 4). SAEs that could possibly be attributed to the study drug were observed in 4.4% of patients on lerociclib and 4.3% of patients on placebo. SAEs in the lerociclib arm were sporadic with one patient (0.7%) in each of the AEs including neutropenia, leukopenia, infectious pneumonia, gastrointestinal infections, oral mucositis, vomiting, and interstitial lung disease.

The dose reduction as a result of AEs occurred in 52 (38.0%) patients receiving lerociclib compared with 3 (2.2%) receiving placebo. Only 1 patient (0.7%) discontinued lerociclib treatment due to AE.

There were 9 deaths (6.6%) in the lerociclib arm, one of which was due to AE (cerebral infarction, not considered treatment related by the investigator), while there were 13 deaths (9.4%) in the placebo arm, none of which were due to AEs.

Discussion

The LEONARDA-1 trial is the first phase 3 randomized controlled trial for lerociclib with continuous dosing schedule for the treatment of patients with HR+/HER2− ABC whose disease had progressed or relapsed following prior ET. Substantial clinical benefits of lerociclib were observed.

Addition of lerociclib to fulvestrant significantly reduced the risk of investigator-assessed disease progression/death by 54.9% (HR:

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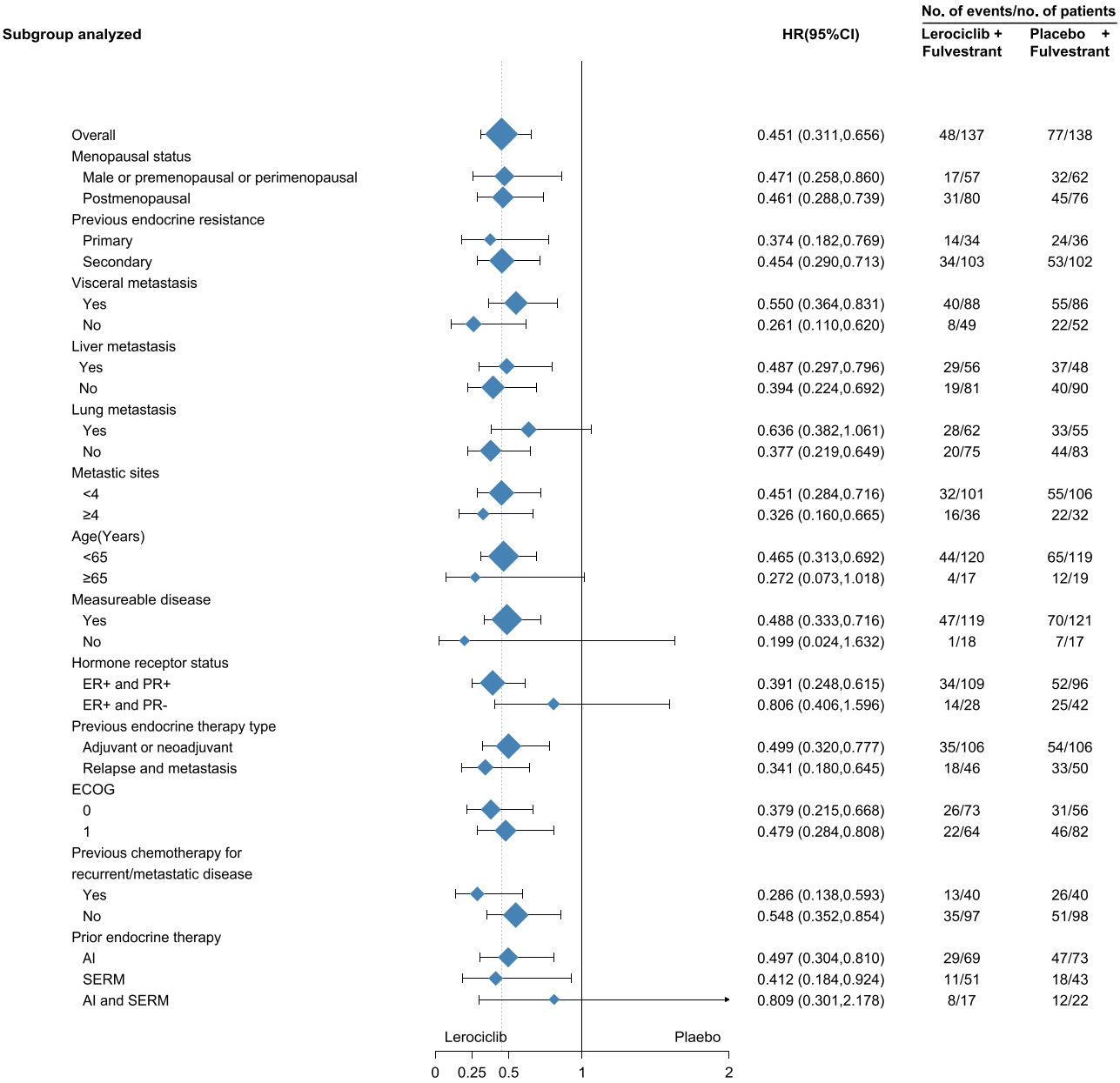

Fig. 3 | Subgroup analysis of progression-free survival (PFS) assessed by Investigator in the intent-to-treat population ($n = 275$ patients). HRs are for lerociclib versus placebo. PFS HRs are indicated by diamonds and 95% CIs are indicated by the crossing horizontal lines. Diamond size is proportional to the sample size of each patient subgroup. HRs were estimated based on the unstratified Cox proportional hazards model for the stratification factor related subgroups including menopausal status, visceral metastasis, liver metastasis; stratified Cox proportional hazards model for other subgroups and overall HR. ECOG Eastern Cooperative Oncology Group, ER estrogen receptor, HR hazard ratio, PR progesterone receptor. Source data are provided as a Source Data file.

0.451). Consistent results were observed in the BICR assessment (HR: 0.353) and across all subgroups.

The clinical efficacy of lerociclib in combination with fulvestrant was in line with other CDK4/6 inhibitors in combination with fulvestrant (PALOMA-3 with palbociclib, MONALEESA-3 with ribociclib, MONARCH-2 and MONARCH plus with abemaciclib, and DAWNA-1 with dalpiciclib)[7–15]. The inclusion/exclusion criteria varied among the CDK4/6 inhibitor phase 3 trials, and the LEONARDA-1 trial included a substantial proportion of patients with poor prognosis including patients with primary resistance to ET (25.5%), patients who received first-line chemotherapy in the recurrent and metastatic setting (29.1%; these patients were not included in MONALEESA-3, MONARCH-2 and MONARCH Plus), patients with visceral metastasis (63.3%), patients with liver metastasis (37.8%), and patients with over 4 sites of metastasis (24.7%). In these patients who typically have a poor prognosis, lerociclib demonstrated promising efficacy with improved PFS compared with placebo (medians of 9.26 vs 3.71 months in patients with primary resistance to ET; 11.07 vs 5.42 months in patients who received first-line chemotherapy in the recurrent and metastatic stage; 9.23 vs 3.81 months in patients with visceral metastasis; 7.39 vs 1.97 months in patients with liver metastasis; and 9.23 vs 3.65 months in patients with over 4 sites of metastasis). This evidence further supports the use of lerociclib-based therapy for a broad range and hard-to-treat patients with HR+/HER2− ABC.

Even though the current CDK4/6 inhibitors have moved to the first-line setting as the standard of care, CDK4/6 inhibitors still provide patients treatment benefits in the second-line setting due to the below considerations. Firstly, the CDK4/6 inhibitor first-line trials excluded

patients whose disease recurred while receiving the ET or within 12 months after completing ET. In the LEONARDA-1 study, over 60% (67.9% in lerociclib arm and 67.4% in placebo arm) of the patients were in the above-mentioned patient population. Therefore, a certain number of patients not having the opportunity to be treated in the first-line setting may obtain clinical benefit from the second-line setting. Secondly, according to the MAINTAIN and P-REALITY[21] studies, CDK4/6 inhibitor switching or cross-line treatment may also improve clinical outcomes. Thirdly, the SONIA study[22] demonstrated that first-line use of CDK4/6 inhibitor + ET does not provide statistically significant, nor clinically meaningful PFS benefit compared to second-line use in women with HR+, HER2− ABC; use in first-line prolongs the time on CDK4/6i by 16.56 months and increases toxicity and costs; second-line use may thus be a preferred option for the majority of patients.

The safety profiles of CDK4/6 inhibitors differ in terms of hematologic toxicity, gastrointestinal symptoms, and QT interval prolongation. Abemaciclib is associated with less hematologic toxicity and more gastrointestinal symptoms. On the other hand, palbociclib and dalpiciclib have induced a high percentage of grade 3 or 4 neutropenia. Ribociclib has a potential for QT interval prolongation. Physicians should carefully evaluate these different safety profiles before prescribing any of these drugs in their clinical practice. For instance, ribociclib may not be suitable for patients with cardiac diseases, while abemaciclib may not be the right choice for patients with preexisting gastrointestinal comorbidities[23]. The safety profile of lerociclib plus fulvestrant was very favorable and the AEs were well managed and only one patient (0.7%) discontinued treatment due to AE. The most common grade 3 or 4 events associated with lerociclib treatment were hematological toxicities (primarily neutropenia and leukopenia). The incidence of grade 3 or 4 neutropenia of lerociclib was 46.7% with a low incidence of grade 4 (5.1%), and no febrile neutropenia was reported. Neutropenia was effectively managed through dose interruption/reduction and/or the use of granulocyte colony-stimulating factor (G-CSF), with no cases of treatment discontinuation due to neutropenia. In addition, gastrointestinal toxicity including diarrhea, nausea and vomiting, a common adverse effect of abemaciclib and ribociclib, were observed in less than 20% of the patients treated with lerociclib and no grade 3 or 4 diarrhea was reported[7,12]. These findings suggest that the lerociclib may obtain overall advantages in terms of gastrointestinal and hematological toxicity although cross-trial comparisons are challenging and may introduce bias. Moreover, no VTE were reported; few cases of QTc prolongation were reported in each treatment arm; and the incidence of skin rash was low and similar between the lerociclib and placebo arms, both being around 4%. Finally, lerociclib did not pose an additional risk for hepatotoxicity.

The study has certain limitations. Firstly, it was exclusively conducted in Chinese patients. Even though the efficacy and safety data were in line with the results of the phase 2 study[18] conducted in western patients, further evaluation of the efficacy and tolerability of lerociclib

Table 2 | Best overall response (investigator-assessed)

Best overall response[a]	Lerociclib + Fulvestrantn (%)	Placebo + Fulvestrant *n* (%)
ITT population	*N* = 137	*N* = 138
CR	3 (2.2%)	0
PR	29 (21.2%)	12 (8.7%)
SD	80 (58.4%)	86 (62.3%)
SD ≥ 6 months	34 (24.8%)	22 (15.9%)
PD	23 (16.8%)	37 (26.8%)
NE	1 (0.7%)	0
NA	1 (0.7%)	3 (2.2%)
ORR (CR + PR)	32 (23.4%)	12 (8.7%)
95% CI	16.27%, 30.44%	3.99%, 13.40%
DCR (CR + PR + SD)	112 (81.8%)	98 (71.0%)
95% CI	75.28%, 88.22%	63.44%, 78.58%
CBR (CR + PR + SD ≥ 6 months)	66 (48.2%)	34 (24.6%)
95% CI	39.81%, 56.54%	17.45%, 31.83%
Measurable disease at baseline	*N* = 119	*N* = 121
CR	3 (2.5%)	0
PR	29 (24.4%)	12 (9.9%)
SD	64 (53.8%)	73 (60.3%)
SD ≥ 6 months	29 (24.4%)	20 (16.5%)
PD	22 (18.5%)	33 (27.3%)
NE	0	0
NA	1 (0.8%)	3 (2.5%)
ORR (CR + PR)	32 (26.9%)	12 (9.9%)
95% CI	18.92%, 34.86%	4.59%, 15.24%
CBR (CR + PR + SD ≥ 6 months)	61 (51.3%)	32 (26.4%)
95% CI	42.28%, 60.24%	18.59%, 34.30%

CBR clinical benefit rate, *CR* complete response, *ITT* intent-to-treat, *NA* not applicable, *NE* not evaluable, *ORR* objective response rate, *PD* progressive disease, *PR* partial response, *SD* stable disease.
[a]Using RECIST version 1.1; CR/PR was estimated based on confirmed response.

Table 3 | Treatment-emergent adverse events

Adverse event[a] (>10% in either arm)	Lerociclib + Fulvestrant (*N* = 137)			Placebo + Fulvestrant (*N* = 138)		
	All grade	Grade 3	Grade 4	All grade	Grade 3	Grade 4
Neutropenia	124 (90.5%)	57 (41.6%)	7 (5.1%)	6 (4.3%)	0	0
Leukopenia	119 (86.9%)	32 (23.4%)	0	9 (6.5%)	0	0
Anemia	47 (34.3%)	3 (2.2%)	0	14 (10.1%)	3 (2.2%)	0
ALT increased	32 (23.4%)	3 (2.2%)	0	28 (20.3%)	1 (0.7%)	0
Thrombocytopenia	27 (19.7%)	3 (2.2%)	2 (1.5%)	5 (3.6%)	0	2 (1.4%)
Diarrhea	27 (19.7%)	0	0	5 (3.6%)	0	0
AST increased	26 (19.0%)	1 (0.7%)	1 (0.7%)	31 (22.5%)	4 (2.9%)	0
Nausea	24 (17.5%)	0	0	11 (8.0%)	0	0
Lymphopenia	20 (14.6%)	3 (2.2%)	0	6 (4.3%)	0	0
Vomiting	18 (13.1%)	1 (0.7%)	0	4 (2.9%)	0	0
Fatigue	15 (10.9%)	1 (0.7%)	0	6 (4.3%)	0	0

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase.
[a]AE grade was based on Common Terminology Criteria for Adverse Events (CTCAE) version 1.1.

Table 4 | Treatment-emergent adverse events summary

	Lerociclib + Fulvestrant (*N* = 137)	Placebo + Fulvestrant (*N* = 138)
Any grade, *n* (%)	135 (98.5%)	111 (80.4%)
≥Grade 3, *n* (%)	79 (57.7%)	21 (15.2%)
Serious AE, *n* (%)	8 (5.8%)	11 (8.0%)
AE leading to treatment discontinuation, *n* (%)	1 (0.7%)	0
AE leading to death, *n* (%)	1 (0.7%)[a]	0

AE adverse event.
[a]Not treatment related.

plus fulvestrant in diverse populations may be considered. Secondly, the data on OS remains immature, warranting long-term investigation.

In conclusion, lerociclib, given at a dosage of 150 mg twice daily on a continuous schedule and in combination with fulvestrant, significantly improved PFS with a tolerable safety profile compared with placebo plus fulvestrant. These findings support the application of lerociclib plus fulvestrant as a treatment option for patients with HR+/HER2− ABC whose disease had progressed on prior ET.

Methods

Study design

LEONARDA-1 was a phase III, randomized, double-blind, and placebo-controlled study of fulvestrant with or without lerociclib in patients with HR+/HER2− ABC whose disease had progressed while receiving prior ET. This trial was preregistered at www.clinicaltrials.gov (ClinicalTrials.gov number: NCT05054751, Researcher View | GB491 Combined With Fulvestrant for HR+HER2- Locally Advanced or Metastatic Breast Cancer | ClinicalTrials.gov) on August 13, 2021.

Patients were randomly assigned (via an interactive, web-based response system) at a one-to-one ratio to receive Lerociclib or placebo (150 mg twice daily with food during each 28-day cycle) plus fulvestrant (500 mg intramuscularly on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1). Stratification factors include metastatic status (the presence of visceral metastasis versus bone lesion as the only metastasis versus others), menopausal status (postmenopausal versus pre-/perimenopausal), and number of previous endocrine therapy failure lines (one line versus two lines). All pre-/perimenopausal female or male patients were required to receive a gonadotropin-releasing hormone analog (goserelin or leuprorelin) during the study, starting at least 21 days before the first dose of the study medication. Treatment continued until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Lerociclib dose modifications, including interruption and up to two dose reductions, were permitted to manage adverse events (AEs). Fulvestrant dose modifications were not allowed.

All patients provided informed consent before joining the study. This study was performed in compliance with the Good Clinical Practice Guidelines and the Declaration of Helsinki. The study protocol and any modifications were approved by institutional ethics committee at each site. The study was conducted in 53 centers in China. The informed consent was obtained from all of the patients before the enrollment. Minor compensation (e.g., travel cost) was provided to the patients.

Patients

Eligible patients were 18-75 years old, male or female with histologically and/or cytologically confirmed HR+/HER2− ABC, regardless of menopausal status (pre-/perimenopausal women or men received a gonadotropin-releasing hormone agonist) and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Disease had to be measurable by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1)[24] or non-measurable bone-only disease (lytic, or mixed with lytic as the dominant presence). Patients were required to have disease that progressed while receiving (neo)adjuvant ET, or within 12 months from completion of (neo)adjuvant ET, or while receiving ET for ABC. Patients were allowed to receive one or two prior lines of ET and one prior line of chemotherapy for ABC. Key exclusion criteria included prior treatment with fulvestrant, or CDK4/6 inhibitors; presence of visceral crisis; evidence of uncontrolled CNS metastasis; a QT interval corrected for heart rate of >480 ms according to Fridericia's formula.

Procedures

Tumor response was assessed locally per RECIST (version 1.1) at screening, every 8 weeks after random assignment for 12 months, and every 12 weeks thereafter until disease progression, death, withdrawal of consent, or loss to follow-up per protocol. Patients underwent bone scintigraphy at baseline, and then repeated every 6 cycles starting from cycle 7. Imaging data were reviewed by investigators and centrally by BICR.

Hematologic and blood chemistry laboratory tests were performed on days 1 and 15 of the first cycle and day 1 of all remaining cycles. AEs were monitored and graded according to the Common Terminology Criteria for Adverse Events (version 5.0)[25]. Safety follow-up was conducted for at least 30 days after patients' last study treatment dose. All AEs were characterized by severity and whether they were related to the study drug.

Primary and secondary endpoints

The primary endpoint, the investigator-assessed PFS, was defined as the time from randomization to disease progression based on RECIST v1.1 or death for any reason, whichever occurs first. Key secondary endpoints reported here include PFS (assessed by BICR), ORR (*i.e.*, proportion of patients with complete response [CR] or partial response [PR]), DOR, DCR, CBR (percentage of patients with best response of CR, PR, or stable disease ≥6 months), safety and tolerability, OS and pharmacokinetic (PK) profile.

Statistical analysis

LEONARDA-1 study compared the investigator-assessed PFS of patients treated with Lerociclib with that of those treated with placebo. Assumptions for sample size calculation included a median PFS of 9 months with placebo plus fulvestrant and 16 months with lerociclib plus fulvestrant and a hazard ratio (HR) of 0.55, a randomization ratio of 1:1 between two arms, an accrual period of 14 months, a study duration of 24 months and a dropout rate of 25%. With a one-sided significance level of 2.5%, 119 PFS events were needed to ensure a 90% power to detect the superiority of Lerociclib plus fulvestrant over placebo plus fulvestrant. A sample size of 270 patients was required.

Efficacy was analyzed in the full analysis set, comprising all randomized patients, on an intent-to-treat (ITT) basis. Safety was analyzed in all randomized patients who received at least one dose of the study drug. Time-to-event survival curves were estimated using the Kaplan–Meier method and treatment effects were compared using the stratified log-rank test; HRs and the corresponding 95% CIs were estimated using a stratified Cox proportional hazards model; all stratification factors were the same as those used in the randomization system. A sensitivity analysis for investigator-assessed PFS was also performed excluding patients (1) who had less than 80% of treatment compliance; or (2) who didn't have any post-treatment radiological assessments; or (3) whose baseline radiological assessment was uncomplete to allow appropriate post-treatment efficacy assessment. The pre-specified subgroup analysis for PFS was done using an unstratified Cox proportional hazards model. The ORR and CBR were calculated and the corresponding 95% CIs were estimated using the Clopper–Pearson method; between-group comparisons were

implemented using the stratified Cochran–Mantel–Haenszel method. Safety was summarized using descriptive statistics. The data was collected using ClinFlash EDC. All statistical analyses were performed with SAS (Version 9.4; SAS Institute, Cary, NC).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The de-identified participant data related to this article (including Figs. 2 and 3, Supplementary Fig. 1) will be shared after lerociclib has been approved by major health authorities or 2 years after the study completion (March 30, 2024), whichever occurs later. Researchers who request the data should send a letter to Prof. Binghe Xu, the corresponding author (bhxu@hotmail.com), specifying the reasons for requiring the data. The leading study site and sponsor will check whether the request is subject to any intellectual property or confidentiality obligations and respond within 4 weeks from receiving the request. A signed data access agreement with the sponsor is required before accessing shared data. Use of the data must comply with the requirements of Human Genetics Resources Administration of China and other country- or region-specific regulations. The Study Protocol and statistical analysis plan are available in the Supplementary Information under Supplementary Notes 1 and 2, respectively. All other data are available in the main manuscript, supplementary information or source data file. Source data are provided with this paper.

Code availability

No custom code was used.

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Author contributions

B.X., Q.Z., and T.L. designed the study. B.X., Q.Z., Y.L., Z.T., T.S., C.S., X.L., Y.Y., B.Z., S.W., X.Z., C.H., X.Y., X.W., H.J., Z.C., F.Q., and X.W. contributed to patient enrollment and data acquisition. All authors involved in data interpretation. The manuscript was drafted by B.X., T.L., and D.Z.; reviewed and approved by all authors.

Competing interests

The authors declare the following competing interests: B.X. discloses receiving advisory fees from Novartis and AstraZeneca. D.Z. and T.L.

were employees of Genor Biopharma at the time of the study. The other authors declare no competing interests.

Additional information

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