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Dalpiciclib in combination with letrozole/anastrozole or fulvestrant in HR-positive and HER2-negative advanced breast cancer: results from a phase Ib study

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Abstract

Background: Dalpiciclib is a novel cyclin-dependent kinase 4/6 inhibitor which showed tolerability and preliminary efficacy as monotherapy for pretreated advanced breast cancer (BC).

Objectives: To further assess dalpiciclib with endocrine therapy (ET) in hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative BC.

Design: A multicenter, open-label, phase Ib trial.

Methods: Patients with locally recurrent or metastatic BC were enrolled in five cohorts. Patients without prior treatment for advanced disease (cohorts 1–2) were given dalpiciclib (125 or 150 mg) plus letrozole/anastrozole; patients who progressed after ET (cohorts 3–5) were given dalpiciclib (125, 150, or 175 mg) plus fulvestrant. Dalpiciclib was administered orally once daily in 3-weeks-on/1-week off schedule. The primary endpoint was safety.

Results: A total of 58 patients received dalpiciclib with letrozole/anastrozole and 46 received dalpiciclib with fulvestrant. No maximum tolerated dose of dalpiciclib was reached with letrozole/anastrozole or fulvestrant. Across all cohorts, 86.7%–93.8% of patients had a grade ⩾3 adverse event, with the most common being neutropenia (grade 3, 40.0% for dalpiciclib 175 mg and 61.8%–87.5% for lower doses; grade 4, 46.7% and 4.2%–20.6%, respectively) and leukopenia (grade 3, 80.0% for 175 mg and 33.3%–54.2% for lower doses; grade 4, 0% for all doses). At tested dose levels, steady-state areas under the concentration curve and peak concentration of dalpiciclib increased with dose when combined with letrozole/anastrozole and fulvestrant. Dalpiciclib at 150 mg was associated with a numerically higher objective response rate in both patients untreated for advanced disease (67.6%; 95% confidence interval (CI) 49.5–82.6) and patients progressing after ET (53.3%; 95% CI 26.6–78.7); as of July 30, 2022, the median progression-free survival with dalpiciclib 150 mg was 24.1 months (95% CI 16.9–46.0) with letrozole/anastrozole and 16.7 months (95% CI 1.9–24.1) with fulvestrant.

Conclusion: Dalpiciclib plus letrozole/anastrozole or fulvestrant showed an acceptable safety profile. The recommended phase III dose of dalpiciclib was 150 mg.

Trial registration: ClinicalTrials.gov identifier: NCT03481998.

Keywords: advanced breast cancer, CDK4/6 inhibitor, endocrine therapy, HR-positive and HER2-negative

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Introduction

Breast cancer (BC) holds the highest prevalence among malignant tumors worldwide, representing one-fourth of all cancer cases and causing one-sixth of all cancer-related deaths among women.[1] Hormone receptor-positive (HR+) tumors are the predominant BC subtype, constituting over 70% of cases.[2] While endocrine therapy (ET) is a mainstay treatment strategy for HR+ BC, most patients eventually develop resistance and are left with limited alternatives beyond chemotherapy.[3] This highlights the critical need for innovative therapies that can either delay or overcome this endocrine resistance.

Cyclin-dependent kinases 4 and 6 (CDK4/6) play crucial roles in cell proliferation, by regulating the transition from G1 to S phase of the cell cycle via the phosphorylation of the tumor-suppressor retinoblastoma protein.[4] Elevated expression of cyclin D1, which complexes with and activates CDK4/6, is a common feature of HR+ BC; this overexpression has been implicated in resistance to ET and is associated with a poor prognosis.[5] Pivotal phase III studies demonstrated that the addition of CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib to standard ET (first-line: nonsteroidal aromatase inhibitors (NSAIs) or tamoxifen; later-line: fulvestrant) improved survival outcomes compared with ET alone in patients with HR+/human epidermal growth factor receptor 2 (HER2)− advanced BC.[6–15] These results have led to the approval of the three CDK4/6 inhibitors by the US Food and Drug Administration and the European Medicines Agency for use in both the first-line and later-line treatment settings.

Dalpiciclib (SHR6390) is a novel, orally administered, selective CDK4/6 inhibitor, with comparable potency against CDK 4 and 6 (half maximal inhibitory concentration, 12.4 and 9.9 nM, respectively). In HR+ BC cell line and xenograft models, dalpiciclib exhibited robust antitumor activity and could overcome conditioned ET resistance; additionally, synergistic effects were observed when combined with ET.[16] In a previous phase I trial, dalpiciclib monotherapy has demonstrated tolerability and preliminary clinical activity in patients with heavily pretreated HR+/HER2− BC.[17] Herein, we conducted a phase Ib trial to further assess the safety, pharmacokinetics (PK), and efficacy of dalpiciclib in combination with ET in HR+/HER2− advanced BC.

Methods

Study design and patients

This was a multicenter, open-label, multi-cohort, phase Ib trial conducted in China (NCT03481998). The primary objective was to evaluate the safety and tolerability of dalpiciclib in combination with letrozole/anastrozole or fulvestrant in patients with HR+/HER2− advanced BC and to establish the recommended dose for subsequent development. The trial originally included a phase II indication expansion part. However, the sponsor decided that patients enrolled in phase Ib part have provided sufficient information to determine the recommended phase III dose and initiated the phase III trials of dalpiciclib combinations directly (NCT03927456 in combination with fulvestrant; NCT03966898 in combination with letrozole/anastrozole).[18,19]

Eligible patients were women aged 18–75 years, of any menopausal status, and had pathologically confirmed HR+/HER2− locally advanced or metastatic BC not amenable to curative resection or radiotherapy and not indicated for chemotherapy. HR+ was defined as ER+ and/or PR+, which required ⩾10% of tumor cells showing positive staining, as assessed by the institutional pathology department. Premenopausal or perimenopausal women were required to receive a gonadotropin-releasing hormone analog during the study, starting at least 14 days before the first study dose. Postmenopausal status was defined as having undergone bilateral oophorectomy, aged ⩾60 years, or aged <60 years but having experienced natural menopause (i.e. spontaneous cessation of regular menstrual cycles for ⩾12 consecutive months, without any other pathological or physiological causes). Patients were sequentially enrolled to one of five study cohorts (cohort 1–2 or cohort 3–5) based on prior treatment. For cohorts 1–2, patients were required to receive no previous systemic therapy for recurrent or metastatic BC; neoadjuvant or adjuvant ET was allowed if the recurrence-free interval was >12 months from completion of ET. For cohorts 3–5, patients were required to have radiographically confirmed relapse or disease progression during adjuvant ET but after the first 2 years, or ⩽12 months from completion of adjuvant ET, or >6 months after initiating first-line ET for recurrent or metastatic disease; up to one line of previous chemotherapy was allowed for locally recurrent/metastatic BC. Other inclusion criteria for all cohorts included an Eastern Cooperative

Oncology Group performance status of 0–1, a life expectancy of ⩾12 weeks, measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, adequate organ, and bone marrow functions. Key exclusion criteria were HER2+ disease (defined as immunohistochemistry 3+, HER2/CEP17 ⩾2 by fluorescence in situ hybridization, or HER2 gene copy number ⩾6), uncontrolled central nervous system metastasis, previous exposure to other CDK4/6 inhibitors, fulvestrant, or everolimus, important cardiac event within 6 months, and serious infection within 4 weeks.

The study was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. The study protocol and all amendments were approved by the independent ethics committee at each participating site. All patients provided written informed consent before enrollment.

Treatment

In cohorts 1–2, dalpiciclib was administered orally at doses of either 125 or 150 mg once daily for 3 weeks, followed by 1 week off in 4-week cycles. This was combined with an NSAI, either letrozole at 2.5 mg or anastrozole at 1.0 mg, taken orally once daily. In cohorts 3–5, dalpiciclib was given at doses of 125, 150, or 175 mg once daily, also on a 3-week-on/1-week-off schedule, in combination with fulvestrant. Fulvestrant at 500 mg was administered intramuscularly on day 1 and day 15 of the first cycle, and then on day 1 of each subsequent 4-week cycle. Based on efficacy, safety, and PK data from the phase I trial of dalpiciclib monotherapy, where doses ranging from 25 to 175 mg were evaluated in pretreated BC,[17] the initial plan for this study was to assess dalpiciclib at doses of 125–150 mg in combination with ET; a cohort of dalpiciclib at 175 mg with fulvestrant was subsequently added through a protocol amendment (June 30, 2019) to fully explore the performance of dalpiciclib at the higher dose. Treatment continued until disease progression, unacceptable toxicity, consent withdrawal, or investigator's decision. Treatment tolerability was assessed in the first cycle. The dose level was deemed tolerable if ⩽33% of patients experienced clinically significant toxicity (defined as grade 4 hematological toxicity, grade 3 thrombocytopenia with apparent clinical bleeding, grade ⩾3 neutropenia with infection or fever ⩾38.5°C, and grade ⩾3 nonhematological toxicity (excluding laboratory abnormalities, untreated nausea, vomiting, and diarrhea, or adverse events (AEs) considered tolerable by the patients, such as alopecia)). Dose interruption or reduction of dalpiciclib was permitted after the initiation of the second cycle of treatment.

Assessment

Safety was monitored from the time of informed consent until 30 days after the last study dose; AEs were graded according to Common Terminology Criteria for AEs, version 4.03. Tumor evaluation was done using CT or MRI at screening, every 2 cycles for the first 14 cycles, and every 4 cycles thereafter. Tumor response was assessed by the investigator according to RECIST v1.1. A complete response (CR) or partial response (PR) was required to be confirmed with a subsequent scan at least 4 weeks after the first documentation.

For PK analysis, blood samples were collected on day 1 (predose, and 1, 2, 3, 4, 5, 6, 8, 10, 24 h postdose), day 19 (predose), day 20 (predose), day 21 (predose, and 1, 2, 3, 4, 5, 6, 8, 10, 24 h postdose), and day 22 through day 27 (every 24 h) of cycle 1.

Outcomes

The primary endpoint was safety. Secondary endpoints were PK parameters of dalpiciclib given in combination with letrozole, anastrozole, or fulvestrant, objective response rate (ORR; proportion of patients with CR or PR as the best overall response), duration of response (DoR; time from first documented response to first objective progression or death from any cause), disease control rate (DCR; proportion of patients with CR, PR, or stable disease (SD) lasting ⩾6 weeks), and progression-free survival (PFS; time from enrollment to first objective progression or death from any cause) per investigator according to RECIST v1.1.

Statistical analysis

For cohorts 1–2, approximately 15 patients were planned to be enrolled for the letrozole and anastrozole regimens, respectively; for cohorts 3–5, approximately 15 patients were planned for each cohort. The number of evaluable patients required for each cohort for tolerability and PK assessment was 8–15 patients.

Safety was analyzed in patients who received at least one dose of study treatment and had post-treatment safety evaluation data. Efficacy was analyzed in patients who received at least one study dose and had at least one post-baseline tumor radiographic evaluation according to the frequency prespecified in the protocol. PK was analyzed in treated patients who had evaluable post-treatment PK data. Safety data were summarized using descriptive statistics. ORR and DCR were evaluated with point estimates, with 95% confidence intervals (CIs) calculated using the Clopper–Pearson method. PFS and DoR were estimated using the Kaplan–Meier method, and the associated 95% CIs were calculated using the Brookmeyer–Crowley method. PK parameters were estimated by non-compartmental method using Phoenix WinNonlin 8.1 (Certara Inc., Princeton, NJ, USA). Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition and baseline characteristics

Between March 27, 2018 and July 30, 2020, 104 patients with HR+/HER2− advanced BC were enrolled and treated with dalpiciclib plus letrozole/anastrozole ($n=58$) or fulvestrant ($n=46$). As of the data cutoff of July 30, 2022, 18 (31.0%) patients receiving dalpiciclib with letrozole/anastrozole and 7 (15.2%) patients receiving dalpiciclib with fulvestrant remained on treatment (Supplemental Figure S1). Baseline patient and disease characteristics by cohort are shown in Table 1. Across cohorts, most patients had ⩾2 metastatic sites (56.3%–86.7%) and visceral metastases (50.0%–86.7%). Among patients enrolled for dalpiciclib plus fulvestrant, 7 (15.2%) had prior chemotherapy for recurrent/metastatic BC.

Tolerability and safety

During cycle 1, clinically significant toxicities were reported for three patients treated with dalpiciclib plus letrozole/anastrozole (dalpiciclib 125 mg, $n=1$ (4.2%); 150 mg, $n=2$ (5.9%)) and seven patients treated with dalpiciclib plus fulvestrant (dalpiciclib 125 mg, $n=1$ (6.3%); 150 mg, $n=2$ (13.3%); 175 mg, $n=4$ (26.7%)), with all cases being grade 4 neutropenia. No maximum tolerated dose (MTD) of dalpiciclib was reached with letrozole/anastrozole or fulvestrant.

Treatment exposure is provided in detail in Supplemental Table S1. In patients receiving dalpiciclib with letrozole/anastrozole, grade 3–4 AEs were reported for 87.5%–91.2% of patients across cohorts, predominantly neutropenia (grade 3, 61.8%–75.0%; grade 4, 4.2%–20.6%) and leukopenia (grade 3, 52.9%–54.2%; grade 4, 0%; Table 2 and Supplemental Table S2). The most common non-hematological AEs were increased aspartate aminotransferase (AST; grade 1–2, 38.2%–41.7%; grade 3–4, 0%) and increased alanine aminotransferase (ALT; grade 1–2, 33.3%–35.3%; grade 3–4, 0%; Table 2). AEs led to dose reduction of dalpiciclib in 8.3% of patients in the 125 mg cohort and 32.4% in the 150 mg cohort (Supplemental Tables S3 and S4). One patient in the 125 mg cohort discontinued treatment due to AE (cerebral infarction, judged as treatment unrelated by the investigator). Serious AEs possibly related to study treatment were reported for 3 of 58 (5.2%) patients, including 2 (vertigo and deep vein thrombosis) in the 125 mg cohort and 1 (pneumonia) in the 150 mg cohort. There were no treatment-related deaths.

In patients receiving dalpiciclib with fulvestrant, grade 3–4 AEs occurred in 86.7%–93.8% of patients across cohorts; the most common were neutropenia (grade 3, 40.0% for dalpiciclib 175 mg and 73.3%–87.5% for lower doses; grade 4, 46.7% and 6.3%–13.3%, respectively) and leukopenia (grade 3, 80.0% for 175 mg and 33.3%–50.0% for lower doses; grade 4, 0% for all doses). There was one case of febrile neutropenia in the dalpiciclib 175 mg cohort. The most frequent non-hematological AEs were increased AST (grade 1–2, 18.8%–46.7%; grade 3–4, 0%) and increased ALT (grade 1–2, 12.5%–33.3%; grade 3–4, 0%; Table 2). Dose reductions of dalpiciclib were required for 12.5%, 33.3%, and 73.3% of patients in the 125, 150, and 175 mg cohorts, respectively (Supplemental Tables S3 and S4); treatment discontinuation due to AE occurred in 1 patient (increased gamma-glutamyltransferase) in the 125 mg cohort. Two serious AEs (4.3% of 46 patients) possibly related to study treatment were reported, with 1 each in the 150 mg (osteomyelitis) and 175 mg (anemia) cohorts. No treatment-related death occurred.

Pharmacokinetics

The PK profiles of dalpiciclib after a single dose and at steady state, when combined with letrozole 2.5 mg, anastrozole 1 mg, and fulvestrant

Table 1. Baseline characteristics.

Characteristic	Dalpiciclib 125 mg + letrozole/ anastrozole (*n* = 24)	Dalpiciclib 150 mg + letrozole/ anastrozole (*n* = 34)	Dalpiciclib 125 mg + fulvestrant (*n* = 16)	Dalpiciclib 150 mg + fulvestrant (*n* = 15)	Dalpiciclib 175 mg + fulvestrant (*n* = 15)
Age, years	55.5 (50–63)	54 (47–61)	48 (44.5–51.5)	59 (47–63)	51 (39–57)
ECOG performance status					
0	8 (33.3)	10 (29.4)	9 (56.3)	6 (40.0)	3 (20.0)
1	16 (66.7)	24 (70.6)	7 (43.8)	9 (60.0)	12 (80.0)
Menopausal status					
Postmenopausal	21 (87.5)	25 (73.5)	4 (25.0)	9 (60.0)	9 (60.0)
Pre-/peri-menopausal	3 (12.5)	9 (26.5)	12 (75.0)	6 (40.0)	6 (40.0)
Hormone receptor status					
ER-positive	24 (100)	33 (97.1)	16 (100)	15 (100)	15 (100)
PR-positive	20 (83.3)	25 (73.5)	12 (75.0)	12 (80.0)	10 (66.7)
No. of metastatic sites					
1	8 (33.3)	11 (32.4)	7 (43.8)	5 (33.3)	2 (13.3)
2	7 (29.2)	12 (35.3)	4 (25.0)	3 (20.0)	8 (53.3)
3	7 (29.2)	7 (20.6)	3 (18.8)	5 (33.3)	2 (13.3)
⩾4	2 (8.3)	4 (11.8)	2 (12.5)	2 (13.3)	3 (20.0)
Visceral metastases	16 (66.7)	17 (50.0)	11 (68.8)	13 (86.7)	11 (73.3)
Lung	14 (58.3)	17 (50.0)	5 (31.3)	7 (46.7)	7 (46.7)
Liver	2 (8.3)	2 (5.9)	9 (56.3)	8 (53.3)	8 (53.3)
Bone metastases	10 (41.7)	20 (58.8)	8 (50.0)	8 (53.3)	10 (66.7)

Data are *n* (%) or median (IQR). Percentages may not total 100 due to rounding.
ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IQR, interquartile range; PR, progesterone receptor.

500 mg, are presented in Figure 1 and Supplemental Tables S5 and S6. After a single dose with letrozole/anastrozole, the median time to peak concentration (T_{max}) of dalpiciclib ranged 2.0–3.0 h at doses of 125–150 mg. At steady state (day 21), the median T_{max} of dalpiciclib ranged 3.0–4.0 h and the geometric mean terminal half-life ($t_{1/2}$) ranged 48.0–53.6 h; the geometric mean accumulation ratio for peak concentration ($R_{ac,Cmax}$) and area under the concentration–time curve ($R_{ac,AUC}$) was 1.95–2.26 and 2.77–3.27, respectively. The exposure ($C_{max,ss}$ and AUC_{ss}) of dalpiciclib at steady state increased with dose of 125–150 mg, when combined with letrozole/anastrozole; the exposure of dalpiciclib was irrespective of the NSAI partner (Supplemental Table S5). The PK parameters of letrozole and anastrozole when combined with dalpiciclib are provided in Supplemental Table S7. At steady state, the geometric mean $R_{ac,Cmax}$ and $R_{ac,AUC}$ ranged 4.36–4.86 and 6.25–6.41, respectively, for letrozole, and 3.29–3.45 and 3.66–4.15, respectively, for anastrozole. The exposure ($C_{max,ss}$ and AUC_{ss}) of letrozole/anastrozole was similar when combined with dalpiciclib at doses of 125 and 150 mg.

After a single dose with fulvestrant, the median T_{max} of dalpiciclib was 3.0 h at doses of 125–175 mg. At steady state (day 21), the median T_{max} of dalpiciclib was 4.0 h and the geometric mean $t_{1/2}$ ranged 48.3–50.2 h; the geometric mean $R_{ac,Cmax}$ and $R_{ac,AUC}$ ranged 1.98–2.47 and 2.70–3.53, respectively. The exposure ($C_{min,ss}$, $C_{max,ss}$,

Table 2. Adverse events.

Event	Dalpiciclib 125 mg + letrozole/ anastrozole (*n* = 24)		Dalpiciclib 150 mg + letrozole/ anastrozole (*n* = 34)		Dalpiciclib 125 mg + fulvestrant (*n* = 16)		Dalpiciclib 150 mg + fulvestrant (*n* = 15)		Dalpiciclib 175 mg + fulvestrant (*n* = 15)	
	Any grade	Grade ⩾3	Any grade	Grade ⩾3	Any grade	Grade ⩾3	Any grade	Grade ⩾3	Any grade	Grade ⩾3
Hematological toxicities										
Neutropenia	24 (100)	19 (79.2)	33 (97.1)	28 (82.4)	16 (100)	15 (93.8)	15 (100)	13 (86.7)	15 (100)	13 (86.7)
Leukopenia	24 (100)	13 (54.2)	32 (94.1)	18 (52.9)	16 (100)	8 (50.0)	14 (93.3)	5 (33.3)	15 (100)	12 (80.0)
Anemia	15 (62.5)	2 (8.3)	13 (38.2)	0	6 (37.5)	0	3 (20.0)	0	12 (80.0)	1 (6.7)
Thrombocytopenia	8 (33.3)	0	10 (29.4)	0	4 (25.0)	0	4 (26.7)	0	8 (53.3)	1 (6.7)
Non-hematological toxicities										
AST increased	10 (41.7)	0	13 (38.2)	0	3 (18.8)	0	7 (46.7)	0	7 (46.7)	0
ALT increased	8 (33.3)	0	12 (35.3)	0	2 (12.5)	0	4 (26.7)	0	5 (33.3)	0
Upper respiratory tract infection	6 (25.0)	0	7 (20.6)	0	2 (12.5)	0	4 (26.7)	0	4 (26.7)	0
Nausea	5 (20.8)	0	5 (14.7)	0	2 (12.5)	0	3 (20.0)	0	5 (33.3)	0
Rash	3 (12.5)	0	7 (20.6)	0	3 (18.8)	0	1 (6.7)	0	5 (33.3)	0
Asthenia	4 (16.7)	0	5 (14.7)	0	2 (12.5)	0	0	0	0	0
Arthralgia	3 (12.5)	0	6 (17.6)	0	1 (6.3)	0	1 (6.7)	0	1 (6.7)	0
Influenza-like illness	6 (25.0)	0	3 (8.8)	0	0	0	0	0	1 (6.7)	0
Stomatitis	1 (4.2)	0	7 (20.6)	0	1 (6.3)	0	2 (13.3)	0	2 (13.3)	0
ECG QT interval prolonged	2 (8.3)	0	6 (17.6)	1 (2.9)	1 (6.3)	0	3 (20.0)	0	2 (13.3)	0
Diarrhea	2 (8.3)	0	5 (14.7)	0	1 (6.3)	0	1 (6.7)	0	1 (6.7)	0
GGT increased	3 (12.5)	1 (4.2)	3 (8.8)	1 (2.9)	2 (12.5)	2 (12.5)	0	0	2 (13.3)	2 (13.3)
Hot flush	1 (4.2)	0	5 (14.7)	0	1 (6.3)	0	1 (6.7)	0	0	0
Urinary tract infection	3 (12.5)	0	3 (8.8)	0	2 (12.5)	0	1 (6.7)	0	2 (13.3)	0
Headache	3 (12.5)	0	3 (8.8)	0	1 (6.3)	0	1 (6.7)	0	1 (6.7)	0
Blood creatinine increased	4 (16.7)	0	2 (5.9)	0	1 (6.3)	0	3 (20.0)	0	4 (26.7)	0
Blood bilirubin increased	2 (8.3)	0	2 (5.9)	0	1 (6.3)	0	2 (13.3)	0	3 (20.0)	0

Data are *n* (%). AEs occurring in ⩾10% of patients receiving dalpiciclib either with letrozole/anastrozole or fulvestrant are listed.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; GGT, gamma-glutamyltransferase.

and AUC_{ss}) of dalpiciclib at steady state increased slightly greater than dose-proportionally over the range of 125–175 mg when combined with fulvestrant (Supplemental Table S6).

Efficacy

Change in size of target lesion from baseline for individual patients is shown in Figure 2. Among 58 patients with no prior treatment for advanced

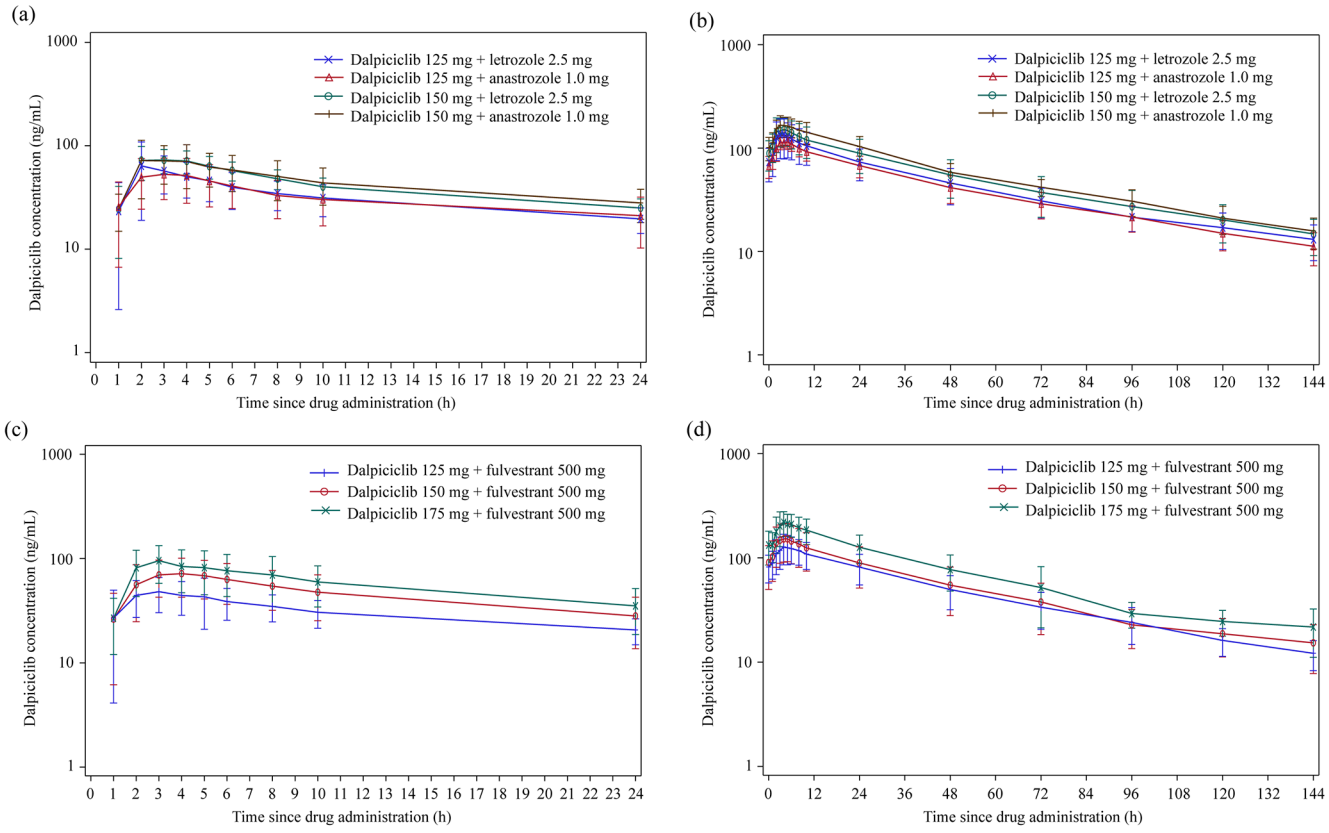

Figure 1. Plasma concentration–time curve of dalpiciclib (semi-log scale). (a) After a single dosing of dalpiciclib with letrozole/anastrozole. (b) After multiple dosing of dalpiciclib with letrozole/anastrozole. (c) After a single dosing of dalpiciclib with fulvestrant. (d) After multiple dosing of dalpiciclib with fulvestrant. Data are mean ± standard deviation.

BC, 1 (1.7%) CR, 37 (63.8%) PR, and 18 (31.0%) SD were recorded with dalpiciclib plus letrozole/anastrozole; the activity of the combination was consistent regardless of the NSAI partner. The ORR was 62.5% (95% CI 40.6–81.2) and 67.6% (95% CI 49.5–82.6) for the 125 and 150 mg cohort, respectively, and the DCR was 100% (95% CI 85.8–100) and 94.1% (95% CI 80.3–99.3), respectively (Table 3). Durable responses were observed in both cohorts (Supplemental Figure S2). As of data cutoff, median PFS was 38.7 months (95% CI 27.6–not reached (NR)) in the 125 mg cohort and 24.1 months (95% CI 16.9–46.0) in the 150 mg cohort.

Among 46 patients progressing after ET, 1 (2.2%) CR, 23 (50.0%) PR, and 15 (32.6%) SD were recorded with dalpiciclib plus fulvestrant. The ORR was 50.0% (95% CI 24.7–75.4), 53.3% (95% CI 26.6–78.7), and 53.3% (95% CI 26.6–78.7) for the 125, 150, and 175 mg cohorts, respectively, and the DCR were 87.5% (95% CI 61.7–98.5), 80.0% (95% CI 51.9–95.7), and 86.7% (95% CI 59.5–98.3), respectively. As of data cutoff, median DoR ranged 10.2 months to NR (Supplemental Figure S3), and median PFS ranged 12.0–16.7 months across cohorts, with numerically longer DoR and PFS observed in the 150 mg cohort (Table 3).

Discussion

Dalpiciclib is a novel CDK 4/6 inhibitor that has recently gained approval in China both for use with letrozole/anastrozole in previously untreated HR+/HER2− advanced BC and with fulvestrant in relapsed or progressed disease, based on the DAWNA-1 and -2 phase III trials.[18,19] In this phase Ib trial, we established the synergic efficacy of dalpiciclib with ET in the treatment of HR+/HER2− BC and provided data supporting the regimen selection for confirmatory phase III investigations. At the recommended phase III dose of 150 mg, dalpiciclib in combination with letrozole/anastrozole resulted in an ORR of 67.6%

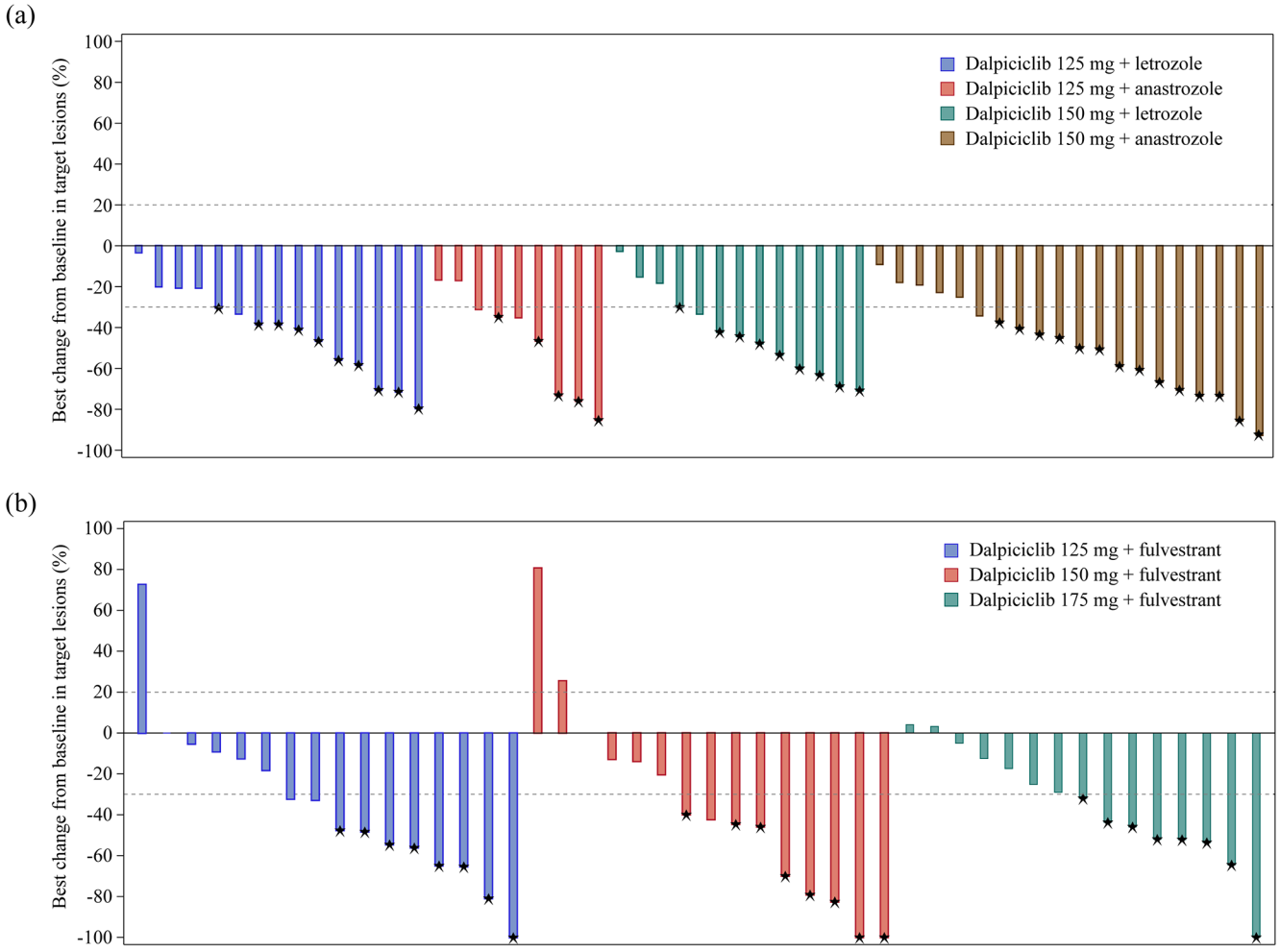

Figure 2. Best percentage change from baseline in the sum of diameters in target lesions. (a) Patients treated with dalpiciclib plus letrozole/anastrozole. (b) Patients treated with dalpiciclib plus fulvestrant.
*Confirmed response.

and a median PFS of 24.1 months, while the combination with fulvestrant yielded an ORR of 53.3% and a median PFS of 16.7 months. These encouraging efficacy outcomes with dalpiciclib 150 mg and ET combinations were further validated in the DAWNA-2 (dalpiciclib with letrozole/anastrozole: ORR, 57%, median PFS, 30.6 months) and DAWNA-1 (dalpiciclib with fulvestrant: ORR, 27%; median PFS, 15.7 months) trials in the same treatment settings.[18,19] Additionally, the manageable safety profile with dalpiciclib 150 mg and ET combinations observed in this study has also been confirmed in the subsequent phase III trials.

In our previous phase I trial, the recommended dose for single-agent dalpiciclib was determined to be 150 mg. Considering a potential drug–drug interaction, dalpiciclib was tested up to 175 mg in combination with ET. While the MTD for dalpiciclib was not reached during the prespecified period for clinically significant toxicity assessment, a notable proportion of patients experienced late-onset equivalent toxicities (overall rate of grade 4 neutropenia, 46.7%) in the 175 mg cohort and dose reduction was required by >70% of patients. Therefore, dalpiciclib at a dose of 175 mg was not recommended for further clinical development. The tolerability and safety profile of dalpiciclib plus ET observed in this study was generally consistent with dalpiciclib and ET monotherapy, with no new safety signals noted.[6–15,17] Overall, the most common grade 3–4 AEs with dalpiciclib plus ET were neutropenia and leukopenia (predominantly

Table 3. Efficacy outcomes.

Variable	Dalpiciclib 125 mg + letrozole/ anastrozole (*n* = 24)	Dalpiciclib 150 mg + letrozole/ anastrozole (*n* = 34)	Dalpiciclib 125 mg + fulvestrant (*n* = 16)	Dalpiciclib 150 mg + fulvestrant (*n* = 15)	Dalpiciclib 175 mg + fulvestrant (*n* = 15)
Best overall response					
CR	0	1 (2.9)	0	1 (6.7)	0
PR	15 (62.5)	22 (64.7)	8 (50.0)	7 (46.7)	8 (53.3)
SD	9 (37.5)	9 (26.5)	6 (37.5)	4 (26.7)	5 (33.3)
PD	0	1 (2.9)	2 (12.5)	3 (20.0)	2 (13.3)
Not evaluable	0	1 (2.9)	0	0	0
ORR (95% CI), %	62.5 (40.6–81.2)	67.6 (49.5–82.6)	50.0 (24.7–75.4)	53.3 (26.6–78.7)	53.3 (26.6–78.7)
DoR (95% CI), mo	44.2 (31.0–NR)	25.8 (14.7–NR)	15.7 (9.4–NR)	NR (3.7–NR)	10.2 (5.5–14.8)
DCR (95% CI), %	100 (85.8–100)	94.1 (80.3–99.3)	87.5 (61.7–98.5)	80.0 (51.9–95.7)	86.7 (59.5–98.3)
Median PFS (95% CI), mo	38.7 (27.6–NR)	24.1 (16.9–46.0)	12.0 (3.7–20.2)	16.7 (1.9–24.1)	12.9 (9.1–16.6)

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

grade 3 events in the 125–150 mg cohorts), which are known class effects of CDK4/6 inhibitors, particularly those with comparable potencies against CDK4 and CDK6; in contrast, gastrointestinal toxicities, a common AE of abemaciclib, are rarely reported with dalpiciclib.[6–15] According to subgroup analysis from the global phase III PALOMA-3 trial[20] and findings from the phase III PALOMA-4 trial from China,[21] there appeared to be an increased risk of neutropenia in Asian patients treated with CDK4/6 inhibitors. In this study, the incidence of neutropenia observed with dalpiciclib (125–150 mg) plus ET in Chinese patients was in line with that reported for palbociclib plus letrozole (grade 3, 72%; grade 4, 12.5%) in the PALOMA-4 trial.[21] Neutropenia was effectively managed with dose modifications and standard supportive care (e.g. granulocyte colony-stimulating factor), and none resulted in treatment discontinuation. Moreover, the incidence of febrile neutropenia (none in the 125–150 mg cohorts) and infection-related serious AEs were rare. The most common non-hematological toxicity observed with dalpiciclib plus ET were low-grade liver enzyme abnormalities. Given the lack of a clear dose relationship of dalpiciclib with these events, the hepatotoxicities might be at least partly attributed to the ET component (i.e. letrozole/anastrozole or fulvestrant) of the combination. In our subsequent randomized phase III trials of dalpiciclib in the front-line and later-line settings,[18,19] comparable incidence and severity of liver enzyme abnormalities were observed for dalpiciclib plus ET and ET alone in patients with BC, suggesting that the addition of dalpiciclib to ET was not associated with increased risk of hepatic toxicities. Importantly, the incidence of grade ⩾3 increased AST and ALT was consistently very low in the present study (0%) and phase III trials of dalpiciclib combinations (0–2%; all grade 3). These data compared favorably with the rates reported in trials involving other CDK4/6 inhibitors[6–15] and supported long-term use of the dalpiciclib combination therapies.

In this study, the ORRs achieved with the combination of dalpiciclib and either letrozole/anastrozole or fulvestrant (50.0%–67.6%) were markedly higher than previously reported for dalpiciclib[17] or the corresponding ETs[7–9,11–14] used as monotherapies at the equivalent dose levels in the treatment of HR+/HER2− advanced BC, suggesting a synergic effect of dalpiciclib with these ETs. Generally consistent clinical activity was observed with dalpiciclib plus letrozole and anastrozole, which was supported by the similar PK profile of dalpiciclib when given with these two NSAIs. Across cohorts, dalpiciclib 150 mg combinations were associated with a numerically higher ORR in both patients untreated for

advanced disease (67.6%, 95% CI 49.5–82.6) and patients progressing after ET (53.3%, 95% CI 26.6–78.7). While cross-trial comparison should be interpreted with caution, the median PFS of 24.1 months (95% CI 16.9–46.0) and 16.7 months (95% CI 1.9–24.1) achieved with dalpiciclib 150 mg in combination with letrozole/anastrozole as a first-line treatment, and in combination with fulvestrant as a later-line treatment for HR+/HER2− advanced BC appeared promising, in the context of outcomes observed with approved combination regimens of palbociclib, ribociclib, and abemaciclib in the same setting.[7,9,11–13] Notably, remarkable antitumor activities were also observed with the dalpiciclib 125 mg combinations, particularly in previously untreated patients. The interpretation of efficacy was complicated by crucial aspects such as the nonrandomized design and potentially unbalanced distribution of disease prognostic factors, and the relatively small sample sizes. PK analysis showed that the steady-state exposure of dalpiciclib increased with dose of 125–150 mg when combined with letrozole/anastrozole or fulvestrant. Considering the potential inter-patient pharmacokinetic variability, part of patients may derive optimal efficacy from the higher dose. This notion supports a starting dose of 150 mg for dalpiciclib, with the implementation of dose modification if necessary. Of note, the determination of dalpiciclib at 150 mg as the RP3D with ET was made before the enrollment of 175 mg cohort. This decision was based on the favorable efficacy and safety profile with the 150 mg regimen demonstrated in this study, prior observations of reduced tolerability and no signal of improved efficacy at 175 mg as monotherapy, and the absence of apparent drug–drug interactions in the 125–150 mg cohorts in this study. Importantly, the efficacy, safety, and PK data generated in this study for dalpiciclib in combination with ET across a range of doses provide valuable insights and reference information for study designs employing different disease settings and treatment regimens. A phase III study (NCT04842617) with a planned sample size of over 5000 patients is currently ongoing, to assess dalpiciclib in combination with ET as adjuvant treatment for patients with HR+/HER2− high-risk early BC.

The study has some limitations. Firstly, the study population comprised only Chinese patients, and therefore, the efficacy and safety of dalpiciclib in patients of other ethnicities require further investigation. Secondly, the relatively small sample size of patients in the early-phase trial and the sequential enrollment of patients into the study cohorts, as opposed to a randomized approach, could introduce complexities and potential biases in data interpretation.

Conclusion

In summary, dalpiciclib plus letrozole/anastrozole or fulvestrant showed an acceptable safety profile, with hematological toxicities as the most common AEs. The recommended phase III dose of dalpiciclib was 150 mg.

Declarations

Ethics approval and consent to participate

The study was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. The study protocol and all amendments were approved by the independent ethics committee at each participating site (Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College; Harbin Medical University Cancer Hospital; The affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital; West China Hospital, Sichuan University; Sir Run Run Shaw Hospital; The First Affiliated Hospital of Zhengzhou University; The First Affiliated Hospital of China Medical University). All patients provided written informed consent before enrollment.

Consent for publication

Not applicable.

Author contributions

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Competing interests

S.L., G.X., and X.Z. were employees of Hengrui Pharmaceuticals at the time of study. All other authors have no conflicts to declare.

Availability of data and materials

Datasets supporting the conclusions of the study are presented in the paper or are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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