

Safety, Pharmacokinetics, and Preliminary Activity of CDK4/6 Inhibitor FCN-437c in Chinese Female Patients with HR+HER2- Advanced Breast Cancer (ABC) From Phase Ia Study

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Abstract

Purpose: This is a phase Ia, first-in-human study aiming to assess the safety, maximum tolerated dose (MTD), pharmacokinetic (PK) and anti-tumor activity of FCN-437c, CDK4/6 inhibitor, as monotherapy in patients with HR+HER2- ABC (advanced breast cancer) who failed standard of care.

Methods: Regular 3+3 dose escalation design was utilized with starting dose of 50 mg per day for 3 weeks on -1 week off treatment in a 28-day cycle. Seventeen eligible female patients with HR+HER2- ABC were enrolled at different dose levels: 50 mg (n = 3), 100 mg (n = 3), 200 mg (n = 3), 300 mg (n = 6) and 450 mg (n = 2).

Results: Two patients in the 450 mg dose group experienced DLT of grade 4 thrombocytopenia and neutropenia respectively, and no DLT was observed in other dose levels. The most frequently reported TEAEs was hematological, including leukopenia (94.1%), neutropenia (88.2%), anemia (64.7%) and thrombocytopenia (47.1%). Major grade 3-4 TEAEs were neutropenia and leukopenia, occurring in 11 (64.7%) and 8 (47.1%) patients, respectively. The exposure increased almost in proportion to given dose ranging from 50 to 200 mg. At multiple dose levels from 200 to 450 mg, there appeared to be a trend of saturation. MTD was determined to be 300 mg. Of 15 measurable patients, nine (60.0%) had the best response of stable disease and no objective response was observed.

Conclusions: FCN-437c has established an acceptable safety profile with no unexpected signals compared to other CDK4/6 inhibitors. (NCT04488107, Jul 13th 2020)

Introduction

Breast cancer (BC) has become the most common life-threatening malignancies in women worldwide. Although many approaches have been developed for the diagnosis and treatment of BC, the 5-year survival rate of metastatic BC remains at 27% [1]. CDK4/6 has been found to play an important role in cell proliferation and are often dysregulated in BCs, particularly in HR-positive BCs [2, 3]. Cyclin D1 is a transcriptional target of ER and forms complexes with CDK4/6 [4]. Activation of the CDK4/6-cyclinD1 complex contributes to the hyperphosphorylation of retinoblastoma (Rb) protein, which causes inactivation of the cell growth-inhibitory by releasing E2F transcription factors and the cell-cycle progression from G1 to S phase [5, 6]. Because of the essential role of this pathway in cell cycle regulation, inhibition of CDK4/6 has been regarded as a promising target for anti-tumor therapies. Small molecule CDK4/6 inhibitors may block tumor cell growth by binding to ATP-binding domain of CDK4/6 kinase and dephosphorylate Rb protein, resulting in cell cycle arrest in G1 phase [7].

The emergence of second generation selective CDK4/6 inhibitors has targeted tumors with the expression of CDK4/6 with meaningful prolongation of progression-free survival over endocrine therapy alone [8]. To date, three orally bioavailable CDK4/6 inhibitors, palbociclib (Ibrance, PD0332991), ribociclib (Kisqali, LEE011) and abemaciclib (Verzenio, LY2834219), have been FDA-approved as standard of care against HR + HER2- metastatic breast cancer in combination with aromatase inhibitors (AI) as initial therapy and

with fulvestrant after disease progression following first line endocrine therapy or as monotherapy for heavily pre-treated patients. However, the treatment with CDK4/6 inhibitors is limited for patients with brain metastases. Only abemaciclib demonstrated a confirmed objective intracranial response of 6% in a phase II study in 58 patients with brain metastases secondary to HR + HER2- metastatic breast cancer and 38% of the patients showed a decrease in the sum of intracranial target lesions. Intracranial clinical benefit rate (CR + PR + SD persisting for ≥ 6 months) was 25% and median PFS was 4.4 months (95% CI, 2.6–5.5) [9].

FCN-437c is an oral, second generation, potent CDK4/6 dual inhibitor which selectively inhibits the kinase activities of CDK4 and CDK6 kinases and had no inhibitory activity against CDK1, CDK2 or CDK5 kinases. In *in vitro* studies, FCN-437c showed inhibitory effects on cell proliferation in human breast cancer cell lines MCF7 and MCF/ARO, which was comparable to or greater than ribociclib and palbociclib. FCN-437c also showed a synergistically *in vitro and in vivo* anti-tumor effect in combination with fulvestrant on MCF7 cell line and xenograft models comparable to ribociclib and palbociclib, while that on MCF7/ARO xenograft models FCN-437c was more potent than ribociclib and palbociclib. In addition, FCN-437c represents favorable physical and pharmacokinetic (PK) properties with good penetration through blood brain barrier, and an acceptable toxicity profile in non-clinical studies.

Methods

Study design and treatment:

This is a phase Ia, multi-center, open-label, single arm dose- escalation clinical trial of FCN-437c to treat the female patients with advanced HR + HER2- breast cancer. The primary objective of the study was to evaluate the safety, tolerability and to determine the MTD of FCN-437c as a single agent. In addition, this study evaluated the pharmacokinetics characteristics of FNC-437c as a single dose and continuous dose, and preliminary anti-tumor activity.

Dose-escalation was conducted following a 3 + 3 study design with starting dose of 50mg. 50 mg, 100 mg, 200 mg, 300 mg, 450 mg and 600 mg per day were set as main dose level for escalation. Patients were administered a single oral dose of FCN-437c under fasting conditions for PK run in of 7 days, and following a continuous treatment once daily for 21 days and 7 days break in a 28-day cycle. DLT was evaluated during the DLT observation period, including the PK run in period (7 days) and the first cycle (28 days). MTD was considered as the highest dose level with no more than 33% DLT of assessable patients during the DLT evaluation period. All screened patients provided a signed informed consent form (ICF) and agreed to comply with the study protocol. This study was conducted in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice as defined by the International Conference on Harmonization.

Patients:

Adult female patients (≥ 18 years old) must have a histological or cytological confirmation of HR + HER2-advance breast cancer, who had disease progression after standard therapy or for whom no standard therapy is available, was eligible for this study. Patients should have at least one measurable lesion based on RECIST Version 1.1 or only have bone metastatic lesions. Life expectancy should exceed at least 12 weeks and the Eastern Cooperative Oncology Group (ECOG) performance status score was 0 or 1. Patients who recently underwent major surgery, chemotherapy, radiotherapy, antibodies or other investigational drugs within 28 days, or patients previously treated with any CDK4/6 inhibitor were excluded from this study. Patients were also excluded if they had uncontrolled central nervous system metastases or presented with cardiac dysfunction such as average QTc > 470 ms in 3 sequential 12-lead ECGs, arrhythmia with clinical significance according to NYHA (New York Heart Association) Grade 3 or 4 congestive heart failure or have potential for prolongation of the QTc interval.

Safety assessments:

DLT was assessed during DLT observation period (7 days PK run in and 28 days since C1D1). DLT was defined as (1) hematological toxicities: Grade 4 neutropenia lasting ≥ 3 days; Grade 3 thrombocytopenia with hemorrhage; Grade 3 or 4 febrile neutropenia ($> 38^{\circ}\text{C}$ for 1 hour or $> 38.3^{\circ}\text{C}$) (2) non-hematological toxicities (alopecia excluded): Grade 2 increased AST/ALT with Grade 2 increased total bilirubin; QTc interval ≥ 501 ms (mean value of at least two ECGs) or QTc interval prolongation ≥ 60 ms from baseline; Grade 3 nausea, vomiting and/or diarrhea, electrolyte disturbances lasting for more than 3 days, which cannot be controlled or recovered to Grade 1 with supportive care; and other non-specified \geq Grade 3 non hematological toxicities. (3) advance events leading to dose suspension for more than 28 days or intolerable AEs (adverse events) with clinical significance judged by the investigator. Adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03. Laboratory analyses were performed on days 1 and 15 of cycles 1 and then on day 1 of each subsequent cycle. 12-lead electrocardiogram, Eastern Cooperative Oncology Group performance status and vital signs were assessed on D1 of each cycle.

Pharmacokinetic assessments:

Blood samples for single dose PK evaluation were collected on pre-dose and 0.5h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 48 h, 72 h, 120 h, 168 h post-dose. Blood samples for multi-dose PK evaluation were collected on cycle1 D21(pre-dose and 0.5h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h post-dose), D22(24 h post-dose), D23(48 h post-dose), D24(72 h post-dose) and on pre-dose of cycle2 Day 1 (192 h post-dose). Steady-state values were calculated by combining data collected on pre-dose of Cycle1 Day 15, D21, D22. Plasma samples were assayed using a validated liquid chromatography-tandem mass spectrometry assay.

The PK parameters including $\text{AUC}_{(0-\text{last})}$, $\text{AUC}_{(0-24)}$, $\text{AUC}_{(0-\infty)}$, C_{max} , T_{max} , $t_{1/2}$, CL/F and accumulation ratio (R_{AUC} , RC_{max}) were analyzed and calculated by the non-compartmental model of Phoenix® WinNonlin 6.4 or higher version (Pharsight Corp., Certara, Princeton, NJ, USA) from the individual plasma concentration data of FCN-437c. Plasma concentration and PK parameters of FCN-437c were assessed through descriptively analysis.

Efficacy assessments:

Radiographic tumor assessment was performed at screening and once every 8 weeks (\pm 7 days) until disease progression, intolerable toxicity, death. Efficacy endpoints including ORR (confirmed partial or complete response), CBR (objective response or stable disease for \geq 24 weeks) and investigator-assessed PFS was assessed based on RECIST Version 1.1

Statistical Methods:

Sample size was estimated based on 3 + 3 study design. All statistical analyses were performed with SAS® 9.2 or higher version (SAS Institute, Inc., Cary, N.C., USA) except for the calculation of pharmacokinetic parameters with Phoenix® WinNonlin 6.4 or higher version (Pharsight Corp., Certara, Princeton, NJ, USA). DLT was summarized by counts and percentages. Safety data were summarized using descriptive statistics in patients who received \geq 1 dose of study treatment (as-treated population). For efficacy, confirmed objective response rate (ORR), clinical benefit rate (CBR) and 95% Clopper Pearson confidence interval will be calculated. Progression-free survival (PFS), duration of response (DOR) and overall survival (OS) for survival analysis will be carried out by using Kaplan-Meier curve according to the investigator's evaluation.

Results

Patients and treatment

Between Feb 13th. 2019 to Apr.15th 2020, 17 patients were enrolled in 3 study centers in Mainland China and received FCN-437c at doses ranging from 50 to 450mg in a 3-week-on and 1-week-off schedule: 50mg (n = 3), 100mg (n = 3), 200mg (n = 3), 300 mg (n = 6) and 450 mg (n = 2) mg. Most of the patients were \leq 65 years, with a median age of 45.0 years. Most of patients are ECOG performance status grade 1 (84.2%). Patients were heavily pretreated, 100% failed to prior both hormone therapy and chemotherapy. A summary of patient characteristics is provided in Table 1.

All of 12 discontinued patients were due to disease progression, the other 5 patients are still on the treatment. Five patients had completed the study, 4 deaths and 1 completed the one-year follow-up per protocol.

As of the cut-off date on Aug. 10th 2020, the median follow-up duration was 8.71 months (95%CI: 4.53–10.84). Median planned treatment duration was 112 days (56, 216), and the median actual treatment duration was 81days (43, 157). The mean relevant dose intensity was 85.4%, 70.6% of patients received over 80% of the planned dose.

Table 1
Patient characteristics and disposition at baseline

	All (n = 17)
Median age, years (range)	45.0 (35–67)
Median weight, kg(range)	65.50 (50.00, 80.50)
ECOG performance status, n (%)	
0	3 (17.6%)
1	14 (82.4%)
Prior antitumor therapies, n (%)	
Any	17 (100.0%)
Surgery	14 (82.4%)
Chemotherapy	17 (100.0%)
Radiotherapy	10 (58.8%)
Endocrine therapy	17 (100.0%)
Targeted therapy	1 (5.9%)

Safety and tolerability

Two patients in the 450 mg dose group had experienced DLTs and was regarded as intolerable. No DLT was observed in 300mg and lower dose level.

Table 2 shows study drug-related TEAEs that occurred with a frequency of at least 10%. The most frequently reported hematological TEAEs (treatment emergent adverse events) was leukopenia (16/17 pts, 94.1%), neutropenia (15/17 pts, 88.2%), anemia (11/17 pts, 64.7%) and thrombocytopenia (8/17 pts, 47.1%), followed by non-hematological toxicities reported were prolonged electrocardiogram QT interval (5/17 pts, 29.4%), hypoalbuminemia (5/17 pts, 29.4%) and rash (5/17 pts, 29.4%). To be noted, there was no G3 or higher non-hematological treatment related AE reported in the study.

There was no dose adjustment or interruption at 50 and 100mg dose level. Since 200mg, a total of 6 patients had dose reduction (35.3%) and 10 patients had dose interruption (58.8%) due to neutropenia. No SAE was reported and no TEAE led to drug permanent discontinuation. There were 4 death reported in the study considered as study drug irrelevant, one was due to respiratory failure which was not considered to be drug related per investigator and the other 3 patients' death reason were unclear because the family was unable or refused to provide. All patients were in compliance of study drug (median: 100%, range 99%-100%).

Table 2
Study drug-related TEAEs in > 10% of patients (n = 17)

AE, n(%)	Grade	50mg	100mg	200mg	300mg	450mg	Total
		(N = 3)	(N = 3)	(N = 3)	(N = 6)	(N = 2)	(N = 17)
Total	All	3 (100.0)	3 (100.0)	3 (100.0)	6 (100.0)	2 (100.0)	17 (100.0)
	Grade 3/4	0 (0.0)	0 (0.0)	3 (100.0)	6 (100.0)	2 (100.0)	11 (64.7)
Leukopenia	All	2 (66.7)	3 (100.0)	3 (100.0)	6 (100.0)	2 (100.0)	16 (94.1)
	Grade 3/4	0 (0.0)	0 (0.0)	2 (66.7)	5 (83.3)	1 (50.0)	8(47.0)
Neutropenia	All	2 (66.7)	2 (66.7)	3 (100.0)	6 (100.0)	2 (100.0)	15 (88.2)
	Grade 3/4	0 (0.0)	0 (0.0)	3 (100.0)	6 (100.0)	2 (100.0)	11 (64.7)
Anemia	All	0 (0.0)	0 (0.0)	3 (100.0)	6 (100.0)	2 (100.0)	11 (64.7)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	All	0 (0.0)	0 (0.0)	1 (33.3)	5 (83.3)	2 (100.0)	8 (47.1)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (5.9)
Prolonged Electrocardiogram QT interval	All	1 (33.3)	0 (0.0)	2 (66.7)	2 (33.3)	0 (0.0)	5 (29.4)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoalbuminemia	All	1 (33.3)	1 (33.3)	1 (33.3)	1 (16.7)	1 (50.0)	5 (29.4)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	All	1 (33.3)	0 (0.0)	2 (66.7)	1 (16.7)	1 (50.0)	5 (29.4)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	All	1 (33.3)	0 (0.0)	0 (0.0)	2 (33.3)	1 (50.0)	4 (23.5)

	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	All	0 (0.0)	1 (33.3)	2 (66.7)	0 (0.0)	1 (50.0)	4 (23.5)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Proteinuria	All	2 (66.7)	1 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	4 (23.5)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	All	3 (100.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	4 (23.5)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	All	0 (0.0)	0 (0.0)	1 (33.3)	2 (33.3)	1 (50.0)	4 (23.5)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	All	1 (33.3)	0 (0.0)	0 (0.0)	1 (16.7)	1 (50.0)	3 (17.6)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypercholesterolaemia	All	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	3 (17.6)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperglycaemia	All	0 (0.0)	0 (0.0)	1 (33.3)	1 (16.7)	1 (50.0)	3 (17.6)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertriglyceridaemia	All	0 (0.0)	1 (33.3)	1 (33.3)	1 (16.7)	0 (0.0)	3 (17.6)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	All	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (50.0)	3 (17.6)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	All	0 (0.0)	1 (33.3)	0 (0.0)	1 (16.7)	1 (50.0)	3 (17.6)

	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	All	0 (0.0)	0 (0.0)	1 (33.3)	2 (33.3)	0 (0.0)	3 (17.6)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperuricaemia	All	0 (0.0)	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	2 (11.8)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypocalcaemia	All	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	All	0 (0.0)	0 (0.0)	1 (33.3)	1 (16.7)	0 (0.0)	2 (11.8)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	All	0 (0.0)	0 (0.0)	1 (33.3)	1 (16.7)	0 (0.0)	2 (11.8)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	All	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	2 (11.8)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	All	0 (0.0)	0 (0.0)	1 (33.3)	1 (16.7)	0 (0.0)	2 (11.8)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decreased	All	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (11.8)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight increased	All	0 (0.0)	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	2 (11.8)
	Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	All	0 (0.0)	0 (0.0)	1 (33.3)	1 (16.7)	0 (0.0)	2 (11.8)

Pharmacokinetics characteristics

The plasma concentration-time data and pharmacokinetics profile of FCN-437c were determined in all 17 patients following single dose on D1 and multiple dose on C1D21, which are shown in Fig. 1 and Table 3, respectively. The correlation of exposure and dose after multi-dose administration are shown in Table 4.

On Single dose administration

FCN-437c was absorbed rapidly to maximum concentration (T_{max}) with a median time ranging from 3.0 to 3.5 hours. Mean $t_{1/2}$ ranged from 37.1 to 50.6 hours. Mean Vd/F ranged from 4020 to 13210 mL/Kg. The exposure (C_{max} and $AUC_{0-\infty}$) increased almost in proportion with dose following a single dose from 50 to 450 mg.

On Multi-dose administration

Mean C_{max} , $C_{av-ss 24h}$, $AUC_{0-\infty}$, AUC_{0-24} ranged from 378 ~ 1723 ng/ml, 245 ~ 1136 ng/ml, 18568 ~ 71273 ng•h/mL, 5889 ~ 27253 ng•h/mL, respectively from the dose of 50 to 200mg. The exposure increased almost in proportion with dose following a multi-dose from 50 to 200mg. In multiple dose at 200–450 mg dose level, there appeared to be a trend of saturation. After repeated administration, FCN-437c accumulated in the human body. Mean accumulation ratio for $AUC_{0-\infty}$ (R_{AUC}) and C_{max} (R_{Cmax}) ranged from 1.59 to 3.12 and 1.24 to 1.63, respectively.

Table 3
Pharmacokinetics parameters of FCN-437c

Mean ± SD	50mg	100mg	200mg	300mg	450mg
D1: Following single dose					
C _{max} (ng/mL)	240 ± 78.9	316 ± 121	1477 ± 376	1092 ± 489	1839
T _{max} (h) [1]	3.00 (1.00 ~ 3.00)	3.00 (1.00 ~ 4.00)	3.00 (2.00 ~ 3.00)	3.50 (2.00 ~ 4.00)	3.50 (3.00 ~ 4.00)
AUC _{0-∞} (ng•h/mL)	6115 ± 1015	12003 ± 6242	45146 ± 12812	34648 ± 13642	51591
t _{1/2} (h)	50.6 ± 3.42	40.9 ± 14.0	42.5 ± 3.18	43.6 ± 9.50	37.1
MRT (h)	58.7 ± 9.06	48.7 ± 13.3	50.1 ± 6.96	51.9 ± 15.0	40.2
Vd/F (mL/kg)	9893 ± 1057	8674 ± 2537	4020 ± 1079	9765 ± 3341	13210
Cl/F (mL/h/kg)	136 ± 11.3	173 ± 118	66.3 ± 20.7	158 ± 62.4	248
C1D21: Following multiple doses					
C _{max} (ng/mL)	378 ± 122	469 ± 179	1723 ± 983	1653 ± 457	1730
T _{max} (h)*	3.00 (2.00 ~ 3.00)	4.00 (3.00 ~ 8.00)	4.00 (3.00 ~ 4.00)	4.00 (3.00 ~ 4.00)	4
AUC _{0-∞} (ng•h/mL)	18568 ± 4437	22566 ± 16691	71273 ± 35143	56592 ± 12149	58803
t _{1/2} (h)	52.1 ± 8.20	38.8 ± 24.3	45.1 ± 14.1	27.9 ± 2.67	36.6
R _{AUC}	3.12 ± 1.00	1.88 ± 0.701	1.61 ± 0.819	1.59 ± 0.456	3.04
Vd/F (mL/kg)	3531 ± 1312	4222 ± 894	3301 ± 2243	3408 ± 704	6858
Cl/F (mL/h/kg)	46.0 ± 11.7	98.7 ± 58.6	47.6 ± 26.1	86.1 ± 24.4	130
R _{Cmax}	1.63 ± 0.458	1.58 ± 0.525	1.24 ± 0.838	1.50 ± 0.643	2.12
AUC _{0-24h} (ng•h/mL)	5889 ± 2138	7871 ± 3109	27253 ± 17592	25098 ± 5019	23615
C _{av-ss} _{24h} (ng/mL)	245 ± 89.1	328 ± 130	1136 ± 733	1046 ± 209	984
DF _{24h}	0.802 ± 0.222	0.712 ± 0.245	0.863 ± 0.236	0.820 ± 0.194	1.12
[1] T _{max} (h): median (range)					

Mean ± SD	50mg	100mg	200mg	300mg	450mg
<p>C_{max}: Maximum concentration; t_{1/2}: Half life; T_{max}: Time to C_{max}; AUC_{0-∞}: Area Under the Curve from 0 h after administration to infinite time point; MRT: mean residence time; V_d/F: Apparent volume of distribution per unit of body weight; Cl/F: Apparent volume of the central compartment cleared of drug per unit time; RAUC: Ratio of AUC_{0-∞}; RC_{max}: Ratio of maximum concentration; AUC_{0-24 h}: Area Under the Curve from 0 h after administration to 24h; C_{av-ss 24h}: Average steady state concentration from 0 h after administration to 24h; DF: DF = 100%×(C_{max}-C_{min})/C_{av}</p>					

Table 4
The correlation of Exposure and Dose after multi-dose administration

Dose	DR	C _{max}	ER	AUC _{0-∞}	ER	AUC ₀₋₂₄	ER	C _{av-ss0-24}	ER	Trough Con.	ER
50	1	378	1	18568	1	5889	1	245	1	188	1
100	2	469	1.24	22566	1.22	7821	1.33	328	1.34	299	1.59
200	4	1723	4.56	71273	3.84	27253	4.63	1136	4.64	812	4.33
300	6	1870	4.95	56592	3.05	25098	4.26	1046	4.27	730	3.89
450	9	1730	4.58	58803	3.17	23615	4.01	984	4.02	661	3.52
<p>DR: dose ratio; ER: exposure ratio. The dose of 50mg was set to 1 and the other doses were compared to 50 mg. The exposure (C_{max}, AUC_{0-∞}, AUC₀₋₂₄, C_{av-ss 24h}, Trough concentration) of 50mg was set to 1, and the exposure of the other doses were compared to the exposure of 50mg respectively.</p>											

Efficacy

Fifteen patients had post baseline assessment. Nine stable disease was observed (60%), no response was reported (ORR 0%) and 6 patients' disease progressed. One SD maintained over 6 months at data cut-off date and CBR was 6.7%. Median PFS was 3.91 months (95%CI: 2.07–7.62), while median OS was not reached due to short follow-up period. The tumor shrinkage and maintain time are referred to Fig. 2 and the response data summary in Table 5.

Table 5
Clinical efficacy of single agent FCN-437c

Best of Response	Total (n = 15)
Complete Response, n (%)	0 (0.0%)
Partial Response, n (%)	0 (0.0%)
Stable Disease, n (%)	9 (60.0%)
Progressive Disease, n (%)	6 (40.0%)
Not Evaluable, n (%)	0 (0.0%)
ORR, % (95%CI)	0.0% (0.00% ~ 21.80%)
CBR, % (95%CI) ^[1]	6.7% (0.17% ~ 31.95%)
Median PFS, months (95%CI)	3.91 (2.07 ~ 7.62)
Median OS, months (95%CI)	NR (7.98 - NA)
[1] CBR is defined as the proportion of patients with confirmed CR & PR and SD lasting for ≥ 6 months.	
NR: Not reached; NA: Not applicable	

Discussion

This phase Ia dose-escalation study enrolled adult female patients with advanced/metastatic HR + HER2-breast cancer to evaluate safety and tolerability of FCN-437c, an oral CDK4/6 inhibitor. The preliminary safety data from these 17 patient have demonstrated acceptable safety profile. The majority AEs reported were myelosuppression, such as leukopenia, neutropenia and anemia, which were manageable and reversible with supportive care and were strongly correlated with dose level. Two patients in 450 mg dose group experienced DLTs in the third week after the initiation of the first cycle in the continuous dose treatment period, one G4 thrombocytopenia lasting for 11 days and one G4 leukopenia for 7 days. No DLT was reported in 300mg and lower dose level. Neutropenia and leukopenia were the most frequently reported Grade 3 and 4 AEs that occurred in patients in 200–450 mg dose groups, and were the main reason for dose reduction and dose interruption. In general, the hematological toxicity of FCN-437c is very similar to that established by palbociclib and ribociclib. The most common AEs induced by these two agents are also hematological toxicities and the primary Grade 3/4 AE is neutropenia, which is reported in 66.4% and 59.3% patients in registration trials when combined with AIs, respectively [10, 11].

Patients in different dose level groups also experienced mild to moderate non-hematological AEs, all of which were Grade 1 or 2. Prolonged electrocardiogram QT interval, hypoalbuminemia and rash were the most common observed non-hematological toxicities. It is nice to see that only G1 or G2 QTcF prolongation happening to 5 patients (29.4%) in this phase 1a study. Ribociclib has been reported with high prevalence of prolongation of QTc interval. Based on the results from MONALEESA-7, an increase of

more than 60 ms from baseline in the QTcF interval occurred in 32 (10%) of 335 patients in the ribociclib group and led to dose interruptions or reductions in 13 (4%) of the patients [12].

By contrast, abemaciclib is reported with less frequent hematological toxicities such as Grade 3/4 neutropenia found only in 21.1% patients, but higher incidence of diarrhea, nausea, fatigue and creatinine increased [13, 14], which are not very common with FCN-437c treatment, only 3,2 and 4 patients reported diarrhea, nausea and fatigue respectively, all of which are G1 or G2, no creatinine increase was reported as study drug related in this study.

By using non-compartmental model, pharmacokinetics characteristics and parameters were analyzed based on FCN-437c plasma concentration. The exposure (C_{max} and $AUC_{0-\infty}$) increased almost in proportion with dose following a single dose from 50 to 450 mg. The exposure (C_{max} , $AUC_{0-\infty}$, AUC_{0-24} , $Cav-ss_{24h}$) increased almost in proportion with dose following a multi-dose from 50 to 200mg. The concentration of FCN-437c reached steady state at Cycle 1 Day 15. As the dose increased, the average trough concentration increased in nearly equal proportion after multi-dose administration from 50 to 200mg. In multiple dose at 200–450 mg dose level, there appeared to be a trend of saturation. The elimination characteristics were similar between single dose and multiple dose in each cohort. After repeated administration, FCN-437c accumulated in the human body. Mean accumulation ratio for $AUC_{0-\infty}$ and C_{max} ranged from 1.59 to 3.12 and 1.24 to 1.63, respectively. The variation between individuals is large based on the existing data, like the similar drug ribociclib. In addition, comparing the *in vivo* exposure levels at the same dose, FCN-437c is higher than ribociclib: Following a single dose, the C_{max} (1477 ± 376 ng/ml) of FCN-437c in the 200mg dose group has exceeded the average C_{max} (933, 340–3200 ng•h/ml) of ribociclib in the 600mg dose group; Following a multi-dose, the C_{max} (1723 ± 983 ng/ml) and AUC_{0-24} (27253 ± 17592 ng•h/ml) of FCN-437c in the 200mg dose group were also equivalent to the C_{max} (1940, 859-5860ng/ml) and AUC_{0-24h} (26600, 9960–89600 ng•h/ml) of ribociclib in the 600 mg dose group.

MTD was established as 300 mg QD on the basis of safety profile. Considering that the occurrence of Grade 3/4 hematological AEs was much higher in 300mg dose group than that in 200 mg and resulted in more dose interruption and adjustment, there appears to be a trend of the exposure saturation from 200mg to 450mg, thus the recommended phase II dose was determined as 200 mg for further development.

As of the three marketed CDK4/6 inhibitors, combination therapies with endocrine agents (aromatase inhibitors or fulvestrant) significantly improved PFS and OS over the placebo plus endocrine agents in patients with HR + HER2- metastatic breast cancer in first- and second-line settings, regardless of endocrine therapy strategies, treatment lines, the number of metastatic sites or menopausal status [15, 16]. However, minor antitumor activities were demonstrated with palbociclib and ribociclib as single agent. Barely patients achieved partial response and approximately 30% of the patients had stable disease in phase I trials [17–19]. In phase II trial MONARCH-1, abemaciclib alone showed a confirmed objective response rate at 19.7% and clinical benefit rate at 42.4% among 132 heavily pre-treated patients, with a

median PFS of 6.0 months and a median OS of 17.7 months [20]. Therefore, abemaciclib has become the only CDK4/6 inhibitor approved as monotherapy for the treatment of patients with HR + HER2- advanced breast cancer with disease progression following prior endocrine therapy and chemotherapy.

Similar to palbociclib and ribociclib, FCN-437c as monotherapy showed modest tumor activity, however, there seems to be high potential anti-tumor capability of the combination with hormone therapy, given 60% of the patients exhibited stable disease with long disease control period by monotherapy, which is likely to be better than that from palbociclib and ribociclib phase 1 studies, warranting further exploration of the combination therapy in phase 2 study.

In conclusion, this study indicated a favorable safety profile of oral administration of single agent FCN-437c on a 3/1 schedule and the toxicities were generally tolerable and manageable. Major AEs were hematological toxicities and 200mg was determined to be recommended dose for further development based on the comprehensive assessment of safety and pharmacokinetics results. 60% of the patients exhibited stable disease with long disease control period by monotherapy warranted to explore the clinical antitumor activity of the combinations with other endocrine therapies. A phase II trial of FCN-437c is now ongoing in combination with letrozole or fulvestrant in female advanced/metastatic HR + HER2- breast cancer patients.

Declarations

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The authors declare no potential conflicts of interest.

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Not applicable

Code availability:

Not applicable

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Ethics approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (No. 1806186-8-1808), Cancer Hospital of the University of Chinese Academy of Sciences (No. IRB-[2019]619) and Sir Run Run Shaw Hospital (No. 20190927-14).

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Informed consent was obtained from all individual participants included in the study.

Consent for publication (include appropriate statements):

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