ORIGINAL RESEARCH ARTICLE

Phase I Study and Pilot Efficacy Analysis of Entinostat, a Novel Histone Deacetylase Inhibitor, in Chinese Postmenopausal Women with Hormone Receptor-Positive Metastatic Breast Cancer

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Abstract

Background Previous clinical trials have demonstrated that entinostat in combination with exemestane had good tolerability and significant clinical efficacy in patients with advanced hormone receptor positive (HR+) and HER2 negative (HER2−) metastatic breast cancer (MBC) in the USA. However, no clinical trials have been conducted in Chinese populations.

Objective To investigate the safety, pharmacokinetics, and pilot efficacy of entinostat with or without exemestane in Chinese postmenopausal patients with locally advanced or metastatic HR+ /HER2− MBC.

Patients and methods Nineteen patients received entinostat for 4 weeks (dose-limiting toxicity (DLT) observation stage) at 3, 5, or 7 mg/week, with a "3+3" dose-escalation design and in combination with exemestane thereafter (extended treatment stage: entinostat, 3 or 5 mg/week; exemestane, 25 mg/day). An additional 21 patients were enrolled to assess the entinostat (5 mg) plus exemestane (25 mg) pharmacokinetic profile and potential efficacy.

Results The peak entinostat serum concentration and area under the curve increased dose proportionally, without significant interaction between entinostat and exemestane. Entinostat was well tolerated at all doses. The most common grade 3/4 adverse effects (AEs) included neutropenia (31.6%) and thrombocytopenia (15.8%). In the DLT observation stage, grade 3/4 AEs accounted for 16.7% in the 5 mg group with one suspicious DLT (G3 ventricular tachycardia) and 33.3% in the 7 mg group. In the extended treatment stage, 2/16 patients achieved partial response and three patients experienced stable disease (> 12 weeks). The median progression-free survival was 9.41 months for the additional 21 patients, who experienced grade 3/4 AEs of neutropenia (38%), thrombocytopenia (9.5%), anemia (9.5%), and fatigue (9.5%).

Conclusion Entinostat with exemestane showed reasonable safety, tolerability, and encouraging efficacy in Chinese patients with HR+/HER2− MBC. These results support further evaluation in a randomized, double-blind Phase III study with a weekly 5 mg entinostat dose in a Chinese population.

Trial Registration NCT02833155.

Key Points

For Chinese HR+/HER2− metastatic breast cancer patients, 5 mg entinostat with exemestane showed promising efficacy with good tolerability.

With regard to the PK profile, no significant accumulation of entinostat was observed and the PK characteristics of entinostat were not affected by exemestane.

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1 Introduction

Approximately two-thirds of breast cancer patients belong to the hormone receptor-positive (HR+) subtype, and can be treated with hormonal therapy [1]. However, the 5-year survival rate of patients with advanced disease after recurrence and metastasis is only 25%; eventually all of these patients progress to endocrine-therapy resistance, and approximately 15–20% of patients are resistant to endocrine therapy at the time of initial treatment [2]. Therefore, overcoming resistance to endocrine therapy is an important focus in the effort to improve clinical practice, with implications for the clinical diagnosis and treatment of breast cancer [3]. Breast cancer treatment strategies have been greatly improved in recent years due to the introduction of novel drugs, including CDK4/6 inhibitors [4, 5], anti-PD-1 antibodies [6], and epigenetic modulators [7]. These drugs have provided clinicians with new options for treatments, and they have notable benefits in progression-free survival (PFS) improvement for breast cancer patients [3]. However, despite the wide range of treatment options available, patients with HR+ metastatic breast cancer still have a relatively poor prognosis after inevitable treatment resistance [1].

Epigenetic dysfunction has been reported in breast cancer [8], and targeting epigenetic abnormalities with various modulators has shown anti-cancer efficacy in vivo and in vitro [9–11]. Histone deacetylases (HDACs), which remove the acetyl groups from lysines that have been *N*-acetylated by histone acetylases, target epigenetic changes in tumors and alter gene regulation; they have recently become important targets for anti-tumor drug design [12]. HDAC inhibitors (HDACIs) can modulate the structure of chromosomes and regulate tumor cell sensitivity to various anti-tumor treatments [13], making HDACIs a current research hotspot in the field of cancer therapy. Multiple HDACIs have shown efficacy for the treatment of solid tumors and hematological malignancies [14].

Entinostat is a benzamide-derivative with promising therapeutic effects in patients with breast cancer. In 2013, it was granted "breakthrough designation" by the US Food and Drug Administration for combination therapy with exemestane for the treatment of postmenopausal women with estrogen receptor-positive advanced breast cancer [15]. Combination therapy with entinostat plus exemestane was generally well tolerated, and prolonged PFS (from 2.3 to 4.3 months) and overall survival (OS; from 19.8 to 28.1 months) of patients with estrogen receptor-positive advanced breast cancer in a signal-finding phase II randomized controlled study (ENCORE 301) [15].

Hence, entinostat in combination with exemestane demonstrated good tolerability and significant clinical efficacy in patients in the USA with advanced HR+ and HER2-negative (HER2−) breast cancer. However, no clinical trials had been conducted in Chinese populations. The aim of the present study was to evaluate the safety, tolerability, and pharmacokinetic profile of entinostat alone and in combination with exemestane in Chinese postmenopausal patients with locally advanced or metastatic HR+ / HER2− metastatic breast cancer.

2 Patients and Methods

2.1 Patient Eligibility

Patients were eligible for enrollment based on the following criteria: (1) postmenopausal women aged ≤ 65 years; (2) estrogen receptor- and/or progesterone receptor-positive (> 1%) breast cancer, confirmed by pathology; (3) previously treated with a non-steroidal aromatase inhibitor (letrozole/anastrozole), with disease progression or relapse afterwards; (4) Eastern Cooperative Oncology Group Performance Status 0–1; (5) a life expectancy of > 3 months; and (6) adequate organ and bone marrow functions. Patients were excluded if they had received prior treatment with an HDACI.

2.2 Study Design

This was a multicenter, open-label, phase I study conducted in China to determine the safety, pharmacokinetics, and efficacy of entinostat in postmenopausal women with HR+/ HER2− advanced breast cancer. The study included two stages. Stage I comprised four treatment cycles (4 weeks per cycle), during which patients received one of three doses (3, 5, or 7 mg) of entinostat orally on a weekly basis. We assessed dose-limiting toxicity (DLT) and tolerability. After stage I, patients could voluntarily participate in Stage II, in which they were given either 3 or 5 mg of entinostat weekly in combination with 25 mg exemestane orally per day, until the occurrence of disease progression (PD), intolerable adverse effects (AEs), or the patient withdrawing consent (see Fig. 1). We enrolled a further 21 patients to investigate the potential interactions between entinostat and exemestane. They received entinostat (5 mg/week) plus exemestane 25 mg/day until PD or intolerable AEs.

The study was approved by the Independent Ethics Committee (EC) of the National Cancer Center/Cancer Hospital, and written informed consent was obtained from all patients before their enrollment in this study. All interventions were performed in accordance with the Declaration of Helsinki guidelines of the International Conference for Harmonization/Good Clinical Practice. The study was registered at ClinicalTrials.gov (NCT 02833155).
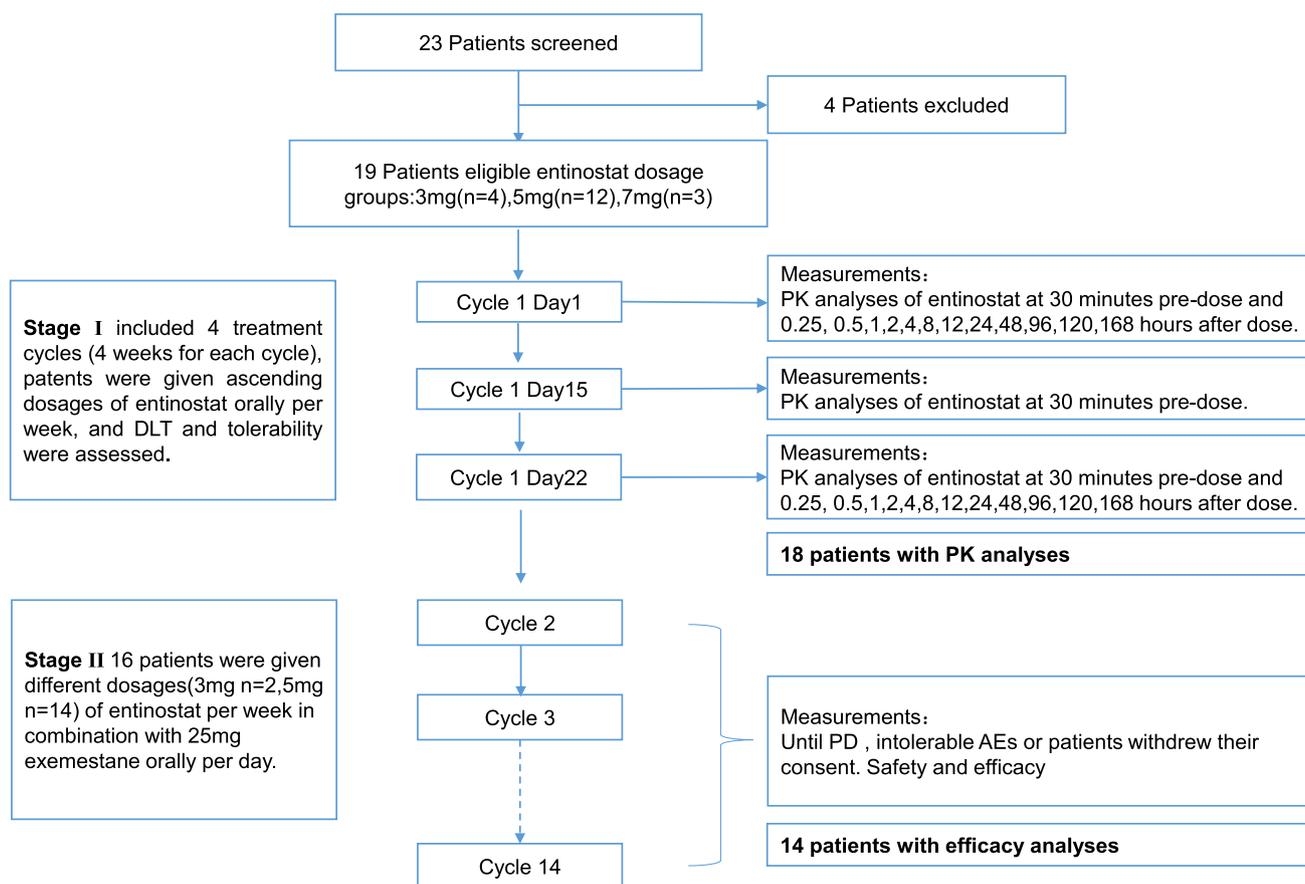
Fig. 1 Study flowchart. *PK* pharmacokinetics, *PD* disease progression, *AE* adverse effect, *DLT* dosage-limited toxicity

2.3 Dose Escalation

The trial followed the traditional "3+3" design. The first stage of the trial consisted of three doses of entinostat (3, 5, and 7 mg). Three patients were administrated 3 mg entinostat/week orally for 4 weeks. If no DLT was observed, patients were enrolled in the next dose group. But if one case of DLT occurred, three more patients would be enrolled in the initial dose group. If no more than one case of DLT occurred in this dose group, we escalated to the next dose group. If two patients in one dose group experienced DLT, then this dose was considered the maximum tolerated dose and dose escalation stopped.

According to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0), DLT was defined as an intolerable grade 2 AE that led to discontinuation of treatment or that could not recover to grade 1 during the treatment stage (alopecia excluded), any grade 3 non-hematological AE, or a grade 4 hematological AE.

2.4 Patient Evaluation

Safety evaluations were performed on days 1, 8, 15, and 22 in Stage I, and once every month for Stage II of the treatment. Safety assessments included vital sign measurements, laboratory tests, and electrocardiograms. The efficacy of the treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1. Complete response (CR) or partial response (PR) was confirmed at least 4 weeks after the initial response.

2.5 Pharmacokinetic Analysis

Blood samples for pharmacokinetic analyses of entinostat were collected on days 1 and 22 in both stages. We collected samples 30 min prior to drug administration on days 1, 15, and 22, and at several time points after each dose: 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 96, 120, and 168 h. The plasma concentration of entinostat was measured using a validated liquid chromatography–tandem mass

spectrometry method. The blood samples were stored at −70 °C until testing. Pharmacokinetic analysis was performed using Phoenix WinNonlin version 6.3 (Pharsight, Mountain View, CA, USA). A standard non-compartmental method was used to calculate the peak plasma concentration (C_{max}), the time to C_{max} (t_{max}), the total area under the concentration-time curve ($AUC_{0-\infty}$), and the elimination half-life ($t_{1/2}$).

3 Results

3.1 Patient Characteristics

From August 2016 to July 2018, we enrolled 19 patients, all of whom participated in Stage I of the treatment plan, and 16 of whom participated in Stage II. Baseline characteristics of these enrolled patients are summarized in Table 1. To investigate the potential interaction between entinostat and exemestane, we enrolled an additional 21 patients from May 2018 to July 2018 who received 5 mg entinostat once per week plus 25 mg exemestane daily until PD or intolerable AE.

3.2 Entinostat Dose Escalation

In Stage I, no patients experienced a DLT in any of the dose groups. In Stage II, one patient in the 5 mg entinostat group (1/14, 7.1%) had CTCAE grade 3 arrhythmia, and required medical care. Median tolerance limit (MLT) was not achieved throughout the trial.

3.3 Safety

Nineteen patients were enrolled in Stage I of the treatment plan, in which entinostat was administered as a monotherapy (four in the 3 mg group, 12 in the 5 mg group, and three in the 7 mg group). All 19 patients experienced entinostat-related AEs (100%), of whom 16 patients continued to Stage II of the treatment plan (two in the 3 mg entinostat plus exemestane group and 14 in the 5 mg entinostat plus exemestane group). Three patients in the 7 mg group in Stage I were transferred to the 5 mg group in Stage II due to safety concerns. The AEs that occurred in two or more patients are shown in Table 2. In Stage I, no CTCAE grade 3 AE occurred in the 3 mg/week group. Two subjects in the 5 mg/week group had four cases of CTCAE grade 3 AE. One subject in the 7 mg/week group experienced a CTCAE grade 3 AE. In prolonged Stage II, no grade 3 AE occurred in the 3 mg/week group. Ten subjects in the 5 mg/week group experienced 38 CTCAE grade ≥ 3 AEs.

We also assessed the safety of the regimen in the 21 patients who provided blood samples for pharmacokinetic analysis. Those patients experienced grade 3/4 AEs as follows: neutropenia (38%), thrombocytopenia (9.5%), anemia (9.5%), and fatigue (9.5%).

In the DLT observation stage, one suspicious DLT (G3 ventricular tachycardia) occurred in the 5 mg group. Subject 0105 did not have coronary heart disease or other heart-related basic diseases before the clinical trial. The baseline screening ECG indicated sinus rhythm and normal outcome. In the clinical study, palpitation symptoms were closely observed during treatment. The patient's 24-h dynamic electrocardiogram indicated sinus tachycardia. The cardiologist preliminarily made a diagnosis of "ventricular tachycardia"

Table 1 Baseline characteristics of the enrolled patients

| Characteristic | Entinostat dose (mg/day) cohorts | | | | |
| | Stage I (n = 19) | | | Stage II (n = 16) | |
	3 mg	5 mg	7 mg	3 mg	5 mg
Median age, years (range)	53.5 (41–60)	53.0 (40–65)	53.0 (35–56)		
ECOG					
0	4	12	3	2	13
1	0	0	0	0	1
HR					
ER+	4	12	3	2	14
PR+	1	11	2	1	12
Prior treatment					
Chemotherapy	4	12	3	2	14
Hormone therapy	4	12	3	2	14
Radiotherapy	4	7	3	2	9

ECOG Eastern Cooperative Oncology Group, *ER+* estrogen receptor-positive, *PR+* progesterone receptor-positive

Table 2 Entinostat-related adverse events (AEs) of all grades in the two stages

	Entinostat dose cohorts				
	Stage I			Stage II	
AE	3 mg	5 mg	7 mg	3 mg	5 mg
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Leukopenia	3 (75)	7 (58.3)	0	0	10 (71.4)
Neutropenia	3 (75)	4(33.3)	2 (66.7)	2 (100)	10 (71.4)
Anemia	2 (50)	0	0	0	5 (35.7)
Thrombocytopenia	0	2 (16.7)	0	0	6 (42.9)
AKP elevation	0	2 (16.7)	0	0	4 (28.6)
ALT elevation	0	2 (16.7)	0	0	0
AST elevation	0	2 (16.7)	0	0	2 (14.3)
α-HBDH elevation	0	2 (16.7)	0	0	2 (14.3)
Γ-GT elevation	0	2 (16.7)	0	0	3 (21.4)
Debilitation	0	2 (16.7)	0	0	0
Fatigue	0	2 (16.7)	0	0	0
Chest pain	0	2 (16.7)	0	0	0
Nausea	0	4 (33.4)	0	0	0
Abdominal pain	0	2 (16.7)	0	0	0
Back pain	0	3 (25)	0	0	0
Palpitation	0	2 (16.7)	0	0	0
Headache	0	3 (25)	0	0	0
Flatulence	0	2 (16.7)	0	0	0
Serum phosphate decrease	0	0	0	0	7 (50)
Creatinine phosphokinase increase	0	0	0	0	6 (42.9)
Creatine increase	0	0	0	0	4 (28.6)
Serum albumin decrease	0	0	0	0	2 (14.3)
Serum Ca^{2+} decrease	0	0	0	0	2 (14.3)
Serum Na+ decrease	0	0	0	0	2 (14.3)
Serum urea increase	0	0	0	0	2 (14.3)
LDH increase	0	0	0	0	2 (14.3)
Hypoalbuminemia	0	0	0	0	3 (21.4)
Hypoproteinemia	0	0	0	0	3 (21.4)
Hypocalcemia	0	0	0	0	2 (14.3)
Hypokalemia	0	0	0	0	2 (14.3)
Diarrhea	0	0	0	0	3 (21.4)
Limb pain	0	0	0	0	2 (14.3)

AKP alkaline phosphatase, *ALT* alanine aminotransferase, AST aspartate aminotransferase, *α-HBDH* α-hydroxybutyrate dehydrogenase, *γ-GT* γ-glutamyl transferase, *LDH* lactate dehydrogenase

Table 3 Clinical responses

	Entinostat dose		
Response	3 mg ($n = 2$)	5 mg ($n = 9$)	7 mg→5 mg ($n = 3$)
CR	0	0	0
PR	0	2	0
SD	1	1	1
PD	1	6	2

CR complete response, *PR* partial response, *SD* stable disease, *PD* disease progression

and gave her the appropriate medication, which met the termination criterion of "grade 3 ventricular arrhythmia." The patient was followed up for 35 days after withdrawal, and the symptoms of conscious palpitation were relieved. On 10 February 2017 (the 41st day after the last medication), no ventricular arrhythmia was observed in the 24-h dynamic electrocardiogram.

3.4 Efficacy

Of the 16 patients who completed the treatment plan (Stages I and II), only 14 patients were evaluated for therapeutic efficacy (Table 3). Of these 14 patients, none achieved CR. Two patients in the 5 mg group in both stages achieved PR. Three patients from all three treatment groups experienced stable disease. Nine patients from the three groups experienced PD. The overall response rate (ORR), defined as the combined rates of patients who achieved CR and PR, was 2/14 (14.3%) (Fig. 2A). Survival analysis showed that the PFS of the enrolled patients, counted from the date of the first dose of entinostat, was 85.5 days in the 5 mg group (95% confidence interval (CI): 78–201), and 90 days in the 7 mg→5 mg cohort (95% CI: 85–426). None of the patients in the 3 mg group experienced PR.

For the 21 patients enrolled to assess the pharmacokinetic profile of entinostat (5 mg) administered in combination with exemestane (25 mg), the ORR (CR+PR) was 9.52% (95% CI: 1.17–30.38) and the clinical benefit rate (CBR, CR+PR+SD over 24 weeks) was 42.86% (95% CI: 21.82–65.98) (Fig. 2B). The median PFS was 9.41 months (Fig. 3).

3.5 Pharmacokinetics

Blood samples from all 19 patients in Stage I were collected for analysis of the pharmacokinetics of entinostat. The values of the pharmacokinetic indexes are shown in Table 4A and B. Regression analysis showed a linear relationship between AUC_{0-168} and entinostat dose, but the relationship
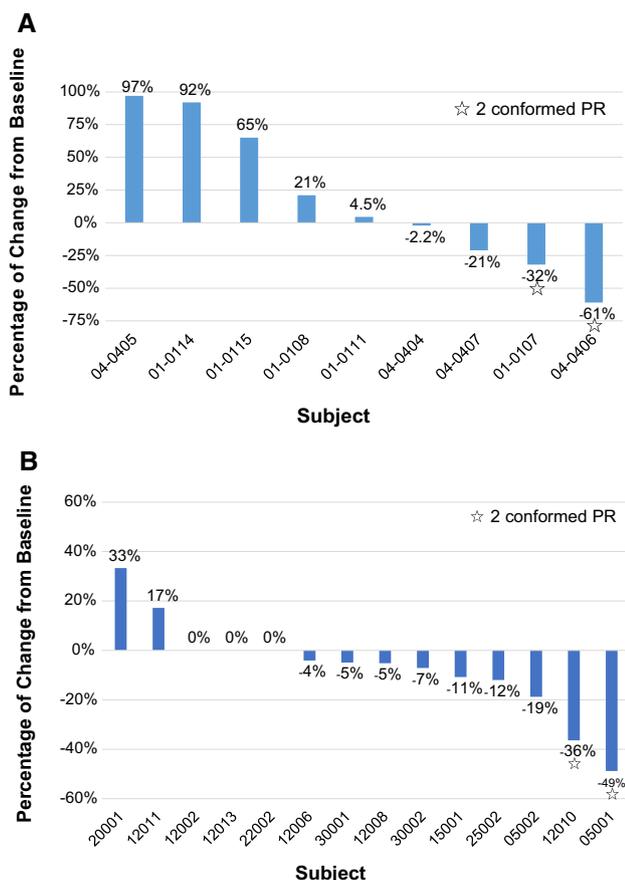
A

B

Fig. 2 Antitumor clinical activity of the combination of entinostat and exemestane. Maximum reduction of target lesion from baseline in Stage II enrolled patients with efficacy analysis (**A**). Of the additional 21 subjects, 14 had measurable target lesions (**B**)

between C_{max} and dose was unclear due to the relatively small sample size.

The PK profile of the additional 21 subjects suggested that there was no significant interaction between entinostat and exemestane (see Table 4C).

4 Discussion

The purpose of this phase I trial was to assess the safety and pharmacokinetics of entinostat in Chinese patients with locally recurrent/metastatic breast cancer. We chose the dosage of entinostat based on the data collected from previous Phase I and Phase II trials of entinostat performed outside China [15, 16], i.e., oral administration of 3, 5, and 7 mg entinostat once weekly for Stage I.

In the three dose groups of this study, entinostat-related adverse events were mostly mild or moderate, and no DLT events occurred during the DLT observation period. Subject 0105 in the 5 mg/week group had adverse events during the

extended treatment period, classified as grade 3 ventricular arrhythmia (MedDRA code as "ventricular arrhythmia"), which was determined by the investigator to be possibly related to the study drugs. The adverse events were considered to have appeared during Stage I and worsened to level 3 during Stage II, which was classified as DLT. The remaining subjects tolerated treatment well without any serious AEs related to the study drugs. Most of the subjects' symptoms were self-relieved or no longer appeared, without affecting the follow-up treatment process.

Since only one DLT occurred (arrhythmia) in the 5 mg group, and the patient's symptoms were relieved after symptomatic treatment, we concluded that the patients showed good tolerance to these dosages. However, based on the results of the dose-escalation phase, and the dose of entinostat used in the Phase III trial in the USA, we changed the dose group from 7 mg in Stage I to 5 mg in Stage II.

The most common AEs observed in this trial were hematological toxicities, including leukocytopenia, neutropenia, thrombocytopenia, and anemia. This differed from what had been observed in previous clinical trials conducted in the USA, in which the most common AEs were nausea, vomiting, and fatigue [15, 16]. Interestingly, the AE spectrum observed in this trial was similar to that observed for another HDACI, chidamide, in Chinese patients with advanced breast cancer [17]. We believe that these distinct AE spectra may be attributable to the genetic characteristics of the different ethnic groups. Although entinostat is associated with more toxicity than hormonal therapy, the level of toxicity is considered acceptable for this patient population.

We also compared the safety profile and efficacy of entinostat with those of an HDACI that has been approved in China for the treatment of breast cancer, chidamide, using the published data from its crucial, market-launching Phase III trial (NCT02482753) [17]. In combination with exemestane, chidamide treatment yielded a median PFS of 7.4 months, with neutropenia in 51% and thrombocytopenia in 28% of patients. In this trial, entinostat in combination with exemestane yielded a longer median PFS (9.41 months), and lower occurrence rates of neutropenia and thrombocytopenia (33% and 10%, respectively).

There was no significant difference in major pharmacokinetic parameters between the breast cancer subjects on day 1 and day 22 after entinostat administration. The median T_{max} of each dose group on day 1 and day 22 was about 0.5 h; the median $T_{1/2}$ was between 38.3 and 65.3 h; the median C_{max} was 44.5–150.0 ng/mL; the median AUC_{0-168h} was 451–1180 h·ng/mL, and the AUC_{0-168h} and C_{max} improved with the increase in dose. The AUC_{0-168h} and C_{max} in the dosages range of 3–7 mg have a linear trend, but the linear relationship is not clear yet. The primary cause was due to the small amount of samples, and high individual variation of tumor patients in the 3 and 5 mg dose groups
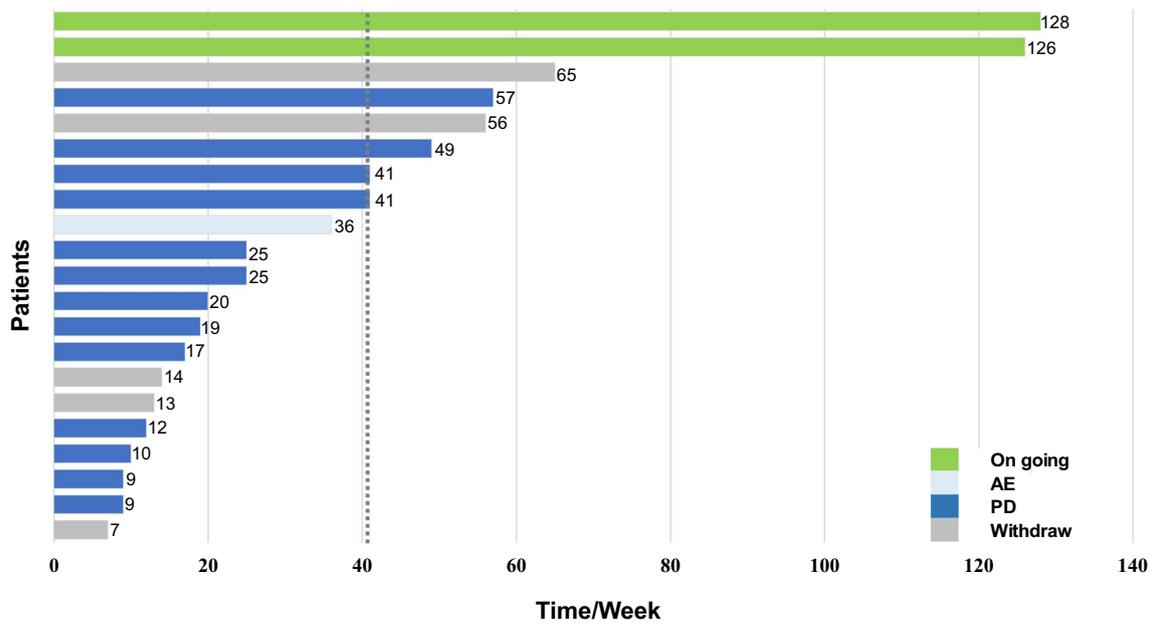
Fig. 3 Potential efficacy of additional 21 patients enrolled to assess the entinostat (5 mg) plus exemestane (25 mg) pharmacokinetic profile

Table 4 Pharmacokinetic index values for entinostat and exemestane

(A)

Compound	Day	Dose	Cohort	C_{max}	t_{max}	AUC_{inf}	$t_{1/2}$	CL/F
		(mg)	N	(ng/mL)	(h)	(h·ng/mL)	(h)	L/h
Entinostat	1	3	3*	49.2 ± 8.38	0.50 (0.25, 0.53)	572 ± 122	38.3 (14.3, 218)	5.42 ± 1.26
		5	12	101 ± 62.1	0.50 (0.25, 7.92)	1070 ± 364	51.7 (33.8, 156)	5.08 ± 1.31
		7	3	154 ± 39.2	0.55 (0.50, 1.0)	1380 ± 206	48.1 (42.5, 87.6)	5.15 ± 0.76

(B)

Compound	Day	Dose	Cohort	C_{max}	t_{max}	AUC_{inf}	$t_{1/2}$	CL/F	AR
		(mg)	N	(ng/mL)	(h)	(h·ng/mL)	(h)	L/h	/
Entinostat	22	3	3*	55.7 ± 38.2	0.47 (0.28, 7.92)	609 ± 44.3	65.3 (61.2, 66.7)	4.94 ± 0.36	1.30 ± 0.19
		5	12	107 ± 63.2	0.50 (0.25, 8.00)	1310 ± 349	61.9 (40.2, 195)	4.00 ± 0.85	1.46 ± 0.19
		7	3	122 ± 76.1	0.50 (0.23, 2.00)	1650 ± 452	56.2 (53.6, 127)	4.45 ± 1.14	1.38 ± 0.12

(C)

Compound	Stage	Cohort	$t_{1/2}$	t_{max}	C_{max}	AUC_{0-t}
	mg/dose	N	(h)	(h)	(ng/mL)	(h•ng/mL)
Exemestane	Lead in 25 mg	21	6.24 (1.87, 14.0)	1.02 (0.50, 8.03)	17.0 (5.66, 70.5)	54.6 (27.5, 128)
	Combo 25 mg	21	5.68 (2.22, 7.98)	3.95 (1.95, 12.00)	13.0 (5.06, 57.4)	58.8 (27.1, 109)

AUC area under the plasma concentration-time curve, *CL/F* oral clearance, *Cmax* maximum plasma concentration, $t_{1/2}$ half-life

t_{max} and $t_{1/2}$ are shown as median (Min., Max.), and otherparameters are shown as mean ± SD

COVANCE-EOC103 China Ph I PK report;

*1 subject with an AUC extrapolated percentage > 30%

The data are included in the descriptive statistics

should also be considered. On the 22nd day after entinostat administration, the drug had basically reached steady state [18]. The mean accumulation ratio (AR_AUC_{0-168h}) of entinostat in breast cancer subjects was between 1.30 and 1.46 after four doses of the drug, indicating that entinostat had no significant accumulation in breast cancer subjects [19]. The single-dose administration in the Phase I clinical study in China was similar to the plasma concentration and exposure of entinostat combination with exemestane study, and the pharmacokinetic characteristics of entinostat were not affected by exemestane.

4.1 Limitations

The limitations of this study include the lack of tissue and serum collection prior to and during the study. Collection of tissue and serum samples in future studies will facilitate the observation of changes in lysine acetylation, which will further improve treatment strategies and patient selection. Indeed, the association between HDAC inhibition and entinostat-induced acetylation of lysine should be demonstrated in planned confirmatory studies. An on-going randomized, double-blind Phase III trial in Chinese metastatic breast cancer patients (NCT03538171) might provide further insight into the efficacy of entinostat plus exemestane combination therapy.

4.2 Conclusion

In conclusion, we found that entinostat in combination with exemestane was well tolerated in this cohort of Chinese patients and showed encouraging efficacy in reducing tumor volumes. Based on our results, we recommend administration of 5 mg entinostat once weekly in combination with exemestane as a promising treatment option for patients with advanced breast cancer.

Declarations

Conflicts of interest Jiani Wang, Qingyuan Zhang, Qiao Li, Yuxin Mu, Jing Jing, Huiping Li, Wei Li, Jingfen Wang, Guohua Yu, Xian Wang, Quchang Ouyang, Jing Hao, Liang Lu, Li Zhou, Jin Guan, Qing Li, and Binghe Xu declare that they have no conflicts of interest that might be relevant to the contents of this article.

Ethics approval This clinical trial received EC approval.

Consent of participate This clinical trial obtained informed consent from all participated subjects.

Consent for publication Not applicable.

Availability of data and material The datasets generated and analyzed during the current study are not publicly available due the confidential requirements of the new product, but are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors' contributions Conception and design: Q. Li and B. Xu. Development of methodology: Q. Li, J. Wang, Q. Li, B. Xu. Acquisition of data (acquired and managed patients, provided facilities, etc.): J. Wang, Q. Zhang, Q. Li, Y. Mu, J. Jing, H. Li, W. Li, J. Wang, G. Yu, X. Wang, Q. Ouyang, Q. Li, and B. Xu. Analysis and interpretation of data (e.g., statistical analysis, computational analysis): L. Lu, L. Zhou, J. Guan, J. Hao, and J. Wang. Writing, review, and/or revision of the manuscript: J. Wang, Q. Li, and B. Xu. Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Wang, Q. Zhang, Q. Li, and Y. Mu. Study supervision: Q. Li and B. Xu.

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