Original Article

Tucidinostat plus exemestane for postmenopausal patients with advanced, hormone receptor-positive breast cancer: a long-term safety and overall survival update from the randomised, double-blind, placebo-controlled, phase 3 trial

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Background: The ACE study previously demonstrated that tucidinostat (chidamide), a subtype-selective histone deacetylase (HDAC) inhibitor, plus exemestane significantly improved progression-free survival (PFS) in advanced hormone receptor-positive (HR^+) breast cancer patients with a manageable safety profile. The analysis of long-term safety and overall survival (OS) is presented here.

Methods: ACE is a randomized, double-blind, placebo-controlled, phase 3 trial comparing tucidinostat 30 mg/twice weekly plus exemestane 25 mg/day versus placebo plus exemestane 25 mg/day in postmenopausal patients with advanced, HR^+ breast cancer. The primary endpoint was PFS, and OS was the secondary endpoint.

Results: Of the 365 patients enrolled between July 2015, and June 2017, 244 were assigned to tucidinostat plus exemestane (tucidinostat group) and 121 to placebo plus exemestane group (placebo group). Baseline characteristics were well balanced between groups. The median follow-up from randomization to data cut-off (February 25, 2021) of this analysis was 26.5 months (range, 13.9–45.5 months). A total of 231 deaths (63.3%) from 365 patients occurred, including 155 deaths (63.5%) in the tucidinostat group and 76 deaths (62.8%) in the placebo group. The median OS was 30.3 months (95% CI, 26.7–36.7) in the tucidinostat group and 30.3 months (95% CI, 24.8–38.1) in the placebo group. The safety profiles of both tucidinostat and placebo groups remained consistent with those previously reported, and no new safety signals were observed with longer follow-up. Neutropenia of grade 3 or 4 occurred in 51.6% of the patients in the tucidinostat group and 2.5% of the patients in the placebo group. Adverse events (AEs) that led to treatment discontinuations from any cause occurred in 28 (11.5%) patients in the tucidinostat group and 4 (3.3%) in the placebo group.

Conclusions: Although tucidinostat in combination with exemestane had produced a clinically meaningful and statistically significant improvement in the primary endpoint PFS, the ACE study did not show a prolongation of the secondary endpoint OS in the tucidinostat combination regimen. Ongoing studies have been considered in terms of potential identification of what patient subpopulations could benefit most from the tucidinostat combination regimens in advanced HR^+ breast cancer.

Keywords: Chidamide/tucidinostat; histone deacetylase inhibitor (HDAC inhibitor); breast cancer; safety; overall survival (OS)

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Introduction

Currently, combination of targeted therapies with established endocrine regimens has played a major role in the treatment of endocrine resistant hormone receptor-positive (HR^+) metastatic breast cancer, including cyclin-dependent kinase (CDK) 4/6, mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinase (PI3K), and histone deacetylase (HDAC) inhibitors combined with endocrine drugs.

Aberrant gene expression due to epigenetic aberrations is involved in disease progression and drug resistance in different types of cancer. Epigenetic alterations can be modulated or reversed with HDAC inhibitors, which modify the status of acetylation on histone and non-histone proteins to affect not only the cancer cell but also the tumor microenvironment (1-3). Tucidinostat, also known as chidamide, is a novel and orally active benzamide class of HDAC inhibitor to selectively inhibit activity of HDAC1, 2, 3 and 10. Functioning as a genuine epigenetic modulator, tucidinostat induces growth arrest and apoptosis in tumor cells and enhances cellular antitumor immunity (4,5). Tucidinostat has also demonstrated to downregulate estrogen-independent growth factor signaling pathways and restores sensitivity to anti-estrogen agents (6). In a phase 3 trial (ACE study), the combination of tucidinostat with exemestane, compared with exemestane alone, significantly improved progression-free survival (PFS) in advanced HR^+ breast cancer patients with a manageable safety profile (7). The overall survival (OS) was not reported before due to the premature data. The current report is to update the results of long-term safety and the secondary endpoint of OS from the ACE trial.

Highlight box

Key findings

- Tucidinostat in combination with exemestane did not show a prolongation of the secondary endpoint OS.

What is known and what is new?

- Tucidinostat in combination with exemestane had produced a clinically meaningful and statistically significant improvement in the primary endpoint PFS.
- The ACE study did not show a prolongation of the secondary endpoint OS in the tucidinostat combination regimen.

What is the implication, and what should change now?

- Ongoing studies have been considered in terms of potential identification of what patient subpopulations could benefit most from the tucidinostat combination regimens in advanced HR^+ breast cancer.

Methods

Trial design and patients

Details of the ACE trial were described previously (7). Briefly, eligible patients were postmenopausal women with confirmed estrogen receptor-positive (ER^+) and/or progesterone receptor-positive (PgR^+), human epidermal growth factor receptor-2-negative ($HER2^-$), advanced breast cancer, whose disease relapsed or progressed after at least one endocrine therapy. Patients, stratified according to the presence of visceral metastases, were randomly assigned (2:1) to receive oral tucidinostat plus exemestane or placebo plus exemestane. 30 mg tucidinostat or matching placebo was given orally twice a week for 4 consecutive weeks in a 4-week cycle. Patients also took 25 mg exemestane orally daily. Patients continued to receive treatment until disease progression, development of unacceptable toxic effects, loss to follow-up, or withdrawal of consent. Dose modifications up to two dose reductions of tucidinostat or placebo were permitted if intolerable adverse events (AEs) occurred. After discontinuation of study treatment, all patients (unless they withdrew consent or were lost to follow-up) were followed continuously for survival at least every 3 months. Post study anticancer medications were recorded. Double-blinding was maintained after the primary PFS analysis until this analysis.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from every patient before screening and enrolment. The ethics committee at each

Table 1 Summary of adverse events

Adverse events	Tucidinostat group (n=244)	Placebo group (n=121)
All-cause adverse events of grade 3/grade 4, n (%)	174 (71.3)	16 (13.2)
All-cause serious adverse events, n (%)	59 (24.2)	10 (8.3)
Adverse events leading to treatment discontinuation, n (%)	28 (11.5)	4 (3.3)
Adverse events leading to dose reduction, n (%)	142 (58.2)	7 (5.8)

participating center approved the study.

Endpoints

As previously reported, the primary endpoint in the ACE trial was investigator-assessed PFS per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Secondary endpoints were OS, objective response, clinical benefit, duration of response, and safety (defined as the frequency and severity of AEs and laboratory abnormalities). Safety was assessed continuously in the safety population until 30 days after the last dose of study treatment, as previously reported.

Statistical analysis

The ACE study was not powered and hypothesized for the secondary endpoints. The Kaplan-Meier method was applied to estimate the distribution of OS between the two treatment groups, and we used a prespecified Cox proportional-hazards model adjusted for visceral metastases to estimate treatment effect, which was expressed as a hazard ratio with a 95% CI.

On the basis of the calculated sample size and preplanned study duration, no interim analyses were planned or done. All statistical analyses were done in SAS (version 9.4), and all P values reported are two sided.

Results

Patients and treatment

Of the 365 patients enrolled between July 2015, and June 2017, 244 were assigned to tucidinostat plus exemestane (tucidinostat group) and 121 to placebo plus exemestane group (placebo group). Baseline characteristics were well balanced between groups (7). The median follow-up from randomization to data cut-off (February 25, 2021) of this analysis was 26.5 months (range, 13.9–45.5 months). Median treatment duration was 24 weeks (range, 8–44 weeks) in the tucidinostat group and 16 weeks (range, 8–40 weeks) in the placebo group. Six patients (2.5%) in the tucidinostat group and 4 patients (3.3%) in the placebo group were still receiving study treatment.

Safety

With longer follow-up, the safety profiles of both tucidinostat and placebo groups (*Tables 1*,*2*) remained consistent with those previously reported for the ACE study (7). Neutropenia of grade 3 or 4 occurred in 51.6% of the patients in the tucidinostat group and 2.5% of the patients in the placebo group; leucopenia of grade 3 or 4 occurred in 21.7% and 2.5% of the patients, respectively; thrombocytopenia of grade 3 or 4 occurred in 27.9% and 3.3% of the patients, respectively; and anemia of grade 3 or 4 occurred in 4.1% and 1.7% of the patients, respectively. Most hematological AEs were largely asymptomatic and manageable by supportive care. No febrile neutropenia was reported in either treatment group. Non-hematological AEs of grade 3 or 4 were uncommon. Events of grade 3 or 4 from any causes that occurred at a frequency of more than 2% of the patients in the tucidinostat group were hypokalemia (6.1% *vs.* 0.8% in the placebo group), hypertriglyceridemia (4.9% *vs.* none), increased γ-glutamyl transferase (4.5% *vs.* 2.5%), hyperglycemia (2% *vs.* none), and increased blood creatine phosphokinase (2.0% *vs.* none; *Table 2*).

Additional 11 patients had experienced serious adverse events (SAEs) from any cause since the primary analysis, including 8 in the tucidinostat group and 3 in the placebo group. In total, SAEs from any cause occurred in 59 (24.2%) of 244 patients in the tucidinostat group and 10 (8.3%) of 121 patients in the placebo group. Compared with the primary report (7) additional 3 patients in the tucidinostat group had at least one treatment-related SAE. No treatment-related SAE occurred in more than 2% of the patients in either group. No treatment-related deaths were reported in the study. Three deaths occurred in

Table 2 Adverse events from any cause occurring in ≥10% of patients in the tucidinostat group

Adverse events	Tucidinostat group (n=244)		Placebo group (n=121)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any adverse events, n (%)	234 (95.9)	174 (71.3)	99 (81.8)	16 (13.2)
Neutropenia, n (%)	199 (81.6)	126 (51.6)	32 (26.4)	3 (2.5)
Leucopenia, n (%)	195 (79.9)	53 (21.7)	32 (26.4)	3 (2.5)
Thrombocytopenia, n (%)	185 (75.8)	68 (27.9)	17 (14.0)	4 (3.3)
Anaemia, n (%)	85 (34.8)	10 (4.1)	26 (21.5)	2 (1.7)
Hyperglycaemia, n (%)	65 (26.6)	5 (2.0)	19 (15.7)	0
Hypertriglyceridaemia, n (%)	64 (26.2)	12 (4.9)	16 (13.2)	0
Hypokalaemia, n (%)	64 (26.2)	15 (6.1)	5 (4.1)	1 (0.8)
Nausea, n (%)	62 (25.4)	1 (0.4)	7 (5.8)	0
Hypocalcaemia, n (%)	61 (25.0)	2 (0.8)	5 (4.1)	0
Diarrhoea, n (%)	55 (22.5)	4 (1.6)	9 (7.4)	0
Increased aspartate aminotransferase, n (%)	54 (22.1)	1 (0.4)	28 (23.1)	4 (3.3)
Increased alanine aminotransferase, n (%)	52 (21.3)	1 (0.4)	23 (19.0)	2 (1.7)
Urinary tract infection, n (%)	51 (20.9)	1 (0.4)	8 (6.6)	0
Anorexia, n (%)	48 (19.7)	3 (1.2)	11 (9.1)	0
Increased γ-glutamyl transferase, n (%)	47 (19.3)	11 (4.5)	17 (14.0)	3 (2.5)
Cough, n (%)	41 (16.8)	2 (0.8)	16 (13.2)	0
Fatigue, n (%)	38 (15.6)	1 (0.4)	13 (10.7)	0
Vomiting, n (%)	36 (14.8)	1 (0.4)	4 (3.3)	0
Weight loss, n (%)	35 (14.3)	2 (0.8)	8 (6.6)	0
Hypoalbuminaemia, n (%)	33 (13.5)	0	7 (5.8)	0
Upper respiratory tract infection, n (%)	31 (12.7)	2 (0.8)	10 (8.3)	1 (0.8)
Fever, n (%)	28 (11.5)	0	9 (7.4)	0
Increase blood creatine phosphokinase, n (%)	26 (10.7)	5 (2.0)	2 (1.7)	0

the tucidinostat group during or within 30 days of study treatment because of progression of breast cancer.

The most frequent reason for treatment discontinuation was disease progression, which occurred in 182 (74.6%) of 244 patients in the tucidinostat group and 107 (88.4%) of 121 patients in the placebo group. AEs that led to treatment discontinuations from any cause occurred in 28 (11.5%) patients in the tucidinostat group and 4 (3.3%) in the placebo group. Dose reductions because of AEs from any cause occurred in 142 (58.2%) patients in the tucidinostat group and 7 (5.8%) in the placebo group. Hematological AEs were the most frequent reasons for dose reductions in the tucidinostat group, including neutropenia (80, 32.8%), thrombocytopenia (71, 29.1%), and leucopenia (41, 16.8%).

OS

At the data cut-off of this analysis, 231 deaths (63.3%) from 365 patients occurred, including 155 deaths (63.5%) in the tucidinostat group and 76 deaths (62.8%) in the placebo group. The median OS was 30.3 months (95% CI, 26.7–36.7) in the tucidinostat group and 30.3 months (95% CI, 24.8–38.1) in the placebo group (*Figure 1*). No significant difference was observed in OS between the two groups

(hazard ratio =1.050; 95% CI, 0.798–1.383; P=0.7259).

Post study treatment

A total of 190 patients (77.9%) in the tucidinostat group and 98 patients (81.0%) in the placebo group received new anticancer medications after discontinuation of study treatment. Chemotherapy and hormonal therapy were the most common post study treatments (*Table 3*). Other anticancer medications after discontinuation of study treatment included targeted therapies and radiotherapy. In general, similar medication profiles and numbers of post study treatments were noted in the two groups (*Table 3*).

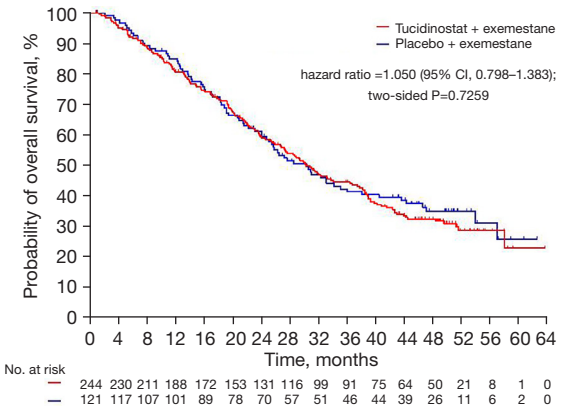

Figure 1 Kaplan-Meier plots of overall survival. CI, confidence interval.

Discussion

The ACE study adopted a multicenter, randomized, double-blind, placebo-controlled design. The enrolled population consisted of postmenopausal, $HR^+/HER2^-$, locally advanced or metastatic breast cancer patients who had experienced recurrence or progression after endocrine therapy. A total of 365 enrolled patients in mainland of China were randomly allocated to tucidinostat plus exemestane group (tucidinostat group) and placebo plus exemestane group (placebo group) at a ratio of 2:1. The primary endpoint was PFS assessed

Table 3 New anticancer medications after discontinuation of study treatment

Patients	Tucidinostat group (n=244)	Placebo group (n=121)
Received at least one new treatment, n (%)	190 (77.9)	98 (81.0)
Chemotherapy, n (%)	155 (63.5)	79 (65.3)
Radiotherapy, n (%)	17 (7.0)	13 (10.7)
Endocrine therapy, n (%)	114 (46.7)	62 (51.2)
Fulvestrant	66 (27.0)	41 (33.9)
Aromatase inhibitor	47 (19.3)	21 (17.4)
Tamoxifen	30 (12.3)	19 (15.7)
Others	11 (4.5)	7 (5.8)
Targeted therapy, n (%)	49 (20.1)	20 (16.5)
CDK4/6 inhibitor	22 (9.0)	6 (5.0)
mTOR inhibitor	18 (7.4)	8 (6.6)
VEGFR inhibitor	22 (9.0)	8 (6.6)
PARP inhibitor	1 (0.4)	3 (2.5)
HER2 inhibitor	3 (1.2)	1 (0.8)
Others, n (%)	41 (16.8)	20 (16.5)
Number of treatments, n (%)		
0	54 (22.1)	23 (19.0)
1–2	108 (44.3)	55 (45.5)
≥3	82 (33.6)	43 (35.5)

CDK, cyclin-dependent kinase; mTOR, mammalian target of rapamycin; VEGFR, vascular endothelial growth factor receptor; PARP, poly (adenosine diphosphate-ribose) polymerase; HER2, human epidermal growth factor receptor-2.

by the investigator, while OS was one of the secondary endpoints. As of March 9, 2018, the study achieved its primary endpoint, with the median PFS of 7.4 months (95% CI, 5.5–9.2) in the tucidinostat group and 3.8 months (95% CI, 3.7–5.5) in the placebo group, respectively (hazard ratio =0.755; P=0.0336). The results evaluated by an independent review committee (IRC) showed that the median PFS of the tucidinostat group and the placebo group were 9.2 months (95% CI, 7.2–10.9) and 3.8 months (95% CI, 3.6–7.4), respectively (hazard ratio =0.713; P=0.024). Similar to the tucidinostat monotherapy, the combination of tucidinostat and exemestane was associated with a manageable safety profile, with the hematological toxicities as the most common AEs. In November 2019, tucidinostat was approved for the indication by China National Medical Products Administration (NMPA). As of February 25, 2021, the study met its criteria for completion, with an additional follow-up time of approximately 3 years. Long-term safety data analysis showed that the categories and incidence of AEs of the tucidinostat plus exemestane regimen were basically consistent with the previous report, and no new safety signals were identified. The median OS of the tucidinostat group and the placebo group were 30.3 months (95% CI, 26.7–36.7) and 30.3 months (95% CI, 24.8–38.1) (hazard ratio =1.050; P=0.7259).

Patients with $HR^+/HER2^-$ breast cancer are usually with long survival durations and receive multiple lines of therapy. Under such a circumstance, PFS may be the most meaningful metric of treatment outcome, and are recommended and typically used in pivotal phase 3 trials as a primary endpoint, with OS being an additional endpoint (8). This study did not show a prolongation of OS in the tucidinostat combination regimen compared with that of exemestane alone, which could be potentially related to several issues. First, the primary endpoint of this study was PFS, and the statistical power of OS was not considered in the trial design and sample size determination. In fact, the statistical power fell far short of what was needed for testing the secondary OS endpoint, and 2:1 randomization made even a less power under such a situation. Second, as reported previously, compared with some other studies on advanced $HR^+/HER2^-$ breast cancer, patients enrolled in the ACE trial were younger and potentially less to have prior endocrine therapy in the advanced-disease setting (7), which might contribute to relatively longer OS shown in this study. For example, we observed a longer median OS in the single-agent exemestane group (30.3 months) than that reported in SoFEA study (21.6 months) (9). Third, very similar profiles of new anticancer treatment for post-study patients between the two groups were noted, including the number lines of treatment and treatment categories applied (*Table 3*). While these treatments reflected the common medical practice for post-study patients from our trial, they may lead to bias in the analysis and interpretation of OS comparison between the groups (8).

Conclusions

Taken together, the small sample size lacking power for the detection of secondary endpoints and relatively adequate use of post-study therapies make it unsurprising that the ACE study did not show an OS benefit in the tucidinostat combination regimen versus exemestane alone. Nevertheless, the ACE study represents a clear step forward in the development of HDAC inhibitors as epigenetic therapy in advanced $HR^+/HER2^-$ breast cancer (10). Meanwhile, ongoing efforts have been taken on the potential identification of reliable biomarkers, as well as the best treatment plans or sequencing (e.g., post CDK4/6 inhibitor therapy), to select patients who could benefit most from the tucidinostat combination regimens in advanced HR^+ breast cancer (11).

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Footnote

Data Sharing Statement: https://tbcr.amegroups.com/article/view/10.21037/tbcr-23-31/dss

Peer Review File: Available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-23-31/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-23-31/coif). ZN reports that he works in Chipscreen Biosciences Ltd. SW, CG, QZ, YY and TS serve as unpaid editorial board members of *Translational Breast Cancer Research* from March 2022 to February 2024. ZJ serves as the Editor-in-Chief of *Translational Breast Cancer Research*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from every patient before screening and enrolment. The ethics committee at each participating center approved the study.

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