Chidamide combined with fulvestrant in the treatment of HR-positive,HER2-negative advanced breast cancer after failure of previous endocrine therapy: A single-arm, single-center, phase 2 study

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Abstract

Background Chidamide is an oral subtype-selective histone deacetylase inhibitor that has been used as an anti-cancer agent.
Methods Eligible patients were treated with oral chidamide (30 mg twice weekly) plus intramuscular fulvestrant (500 mg on days 1 and 15 of cycle one, and then on day one of each subsequent 28 day cycle) until disease progression or toxicity related intolerance. Premenopausal women received a concomitant GnRH analogue. The primary endpoint was progression-free survival.
Results Between Mar 8, 2021, and Mar 20, 2024, a total of 30 patients were enrolled. The median progression-free survival for the entire cohort was 6.3 months (95% CI 5.0–9.0). The ORR was 10%, with a DCR of 83.3% (partial response + stable disease) and CBR of 23.3%.
Conclusions Chidamide combined with fulvestrant showed encouraging antitumor activity and tolerable toxicity in pts with HR+/HER2- advanced breast cancer that had progressed after previous endocrine therapy.

Introduction

- Chidamide, an orally administered, subtype-selective histone deacetylase (HDAC) inhibitor, exerts multifaceted antitumor effects through epigenetic regulation. Mechanistically, chidamide selectively modulates HDAC isoforms to induce chromatin remodeling and transcriptional reprogramming of key oncogenic pathways[3].
- The landmark ACE trial [1] established the clinical efficacy of chidamide in combination with exemestane for HR+/HER2- advanced breast cancer progressing after prior endocrine therapy, leading to its regulatory approval for this indication and prompting updates to breast cancer diagnosis and treatment guidelines in China.
- Strikingly, preclinical studies have shown that chidamide synergizes with anti-estrogen (ER) therapies by promoting ER re-expression in ER-negative cells, inhibiting aromatase, and suppressing EGFR-mediated bypass signaling [2-3]
- This phase II study was conducted to evaluate the efficacy and safety of chidamide combined with fulvestrant in pts with HR+/HER2- advanced breast cancer who progressed after first-line endocrine therapy.

Methods and Materials

- Eligible pts were women aged 18-75 years with histologically confirmed HR-positive, HER2-negative, advanced invasive breast cancer, whose disease relapsed or progressed after at least one endocrine therapy with or without a CDK4/6i.
- Eligible patients were treated with oral chidamide (30 mg twice weekly) plus intramuscular fulvestrant (500 mg on days 1 and 15 of cycle one, and then on day one of each subsequent 28 day cycle) until disease progression or toxicity related intolerance. Premenopausal women received a concomitant GnRH analogue.
- The primary endpoint is progression-free survival (PFS) and the secondary endpoints include overall response rate (ORR), duration of response (DoR), disease control rate (DCR), overall survival (OS), and safety.

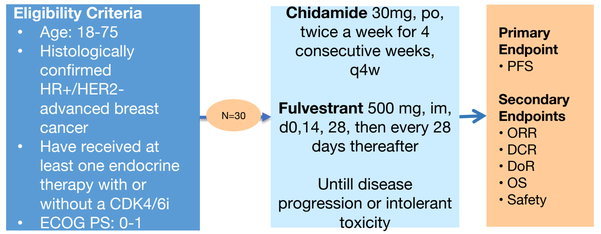


Figure 1. Study design

Table 1. Baseline characteristics

Baseline characteristics		N (%)
Median age, years (range)		54.5 (31-70)
Menopausal status	Premenopausal	7 (23%)
	Postmenopausal	23 (77%)
Sites of metastases	Non-visceral	6 (20%)
	Visceral	24 (80%)
	Lung	13 (43%)
	Liver	11 (37%)
Number of previous treatments for metastatic disease	1	6 (20%)
	2	11 (37%)
	3	9 (30%)
	≥4	4 (13%)
Prior CDK4/6i for metastatic disease	Yes	12 (40%)
	No	18 (60%)
Progesterone receptor status	Positive	19 (63%)
	Negative	11 (37%)

Results

- Between March 8, 2021, and March 20, 2024, in total 30 participants were included in our final analysis. The median age was 54.5 years (range 31–70), with all 30 (100%) patients having an Eastern Cooperative Oncology Group Performance Status of 1. Visceral metastases were present in 80% (n = 24) of cases, and 50% (n = 15) exhibited metastases in >3 anatomical sites. The median number of prior chidamide treatments was 2 (range 1–4). In total, 40% (n = 12) had undergone prior CDK4/6i therapy. Baseline characteristics was shown in Table 1.
- As shown in table 2 and figure 2, the mPFS was 6.3 months (95% CI 5.0–9.0). The ORR was 10%, with a DCR of 83.3% and CBR of 23.3%. Treatment related adverse events of any grade occurred in 30 (100%) patients, of those 9 (30%) were ≥ grade 3. The most frequent hematologic toxicities included leukopenia (all-grade: 67%; grade 3–4: 19%),No treatment-related deaths occurred.

Table 2 Anti-tumor response (N=30)

Best Response	%(n/N)
PR	10 (3/30)
SD≥ 6months	13.3(4/30)
SD < 6months	60(18/30)
PD	16.7 (5/30)
ORR, % (95% CI)	10% (2.11%-26.53%)
DCR , % (95% CI)	83.3% (65.3%-94.4%)

Figure 2. Kaplan-Meier curves for PFS (N=30)

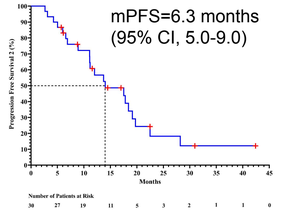


Figure 3. Swimming plot of duration of response (N=30)

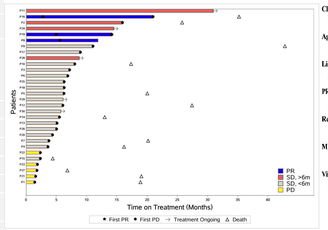
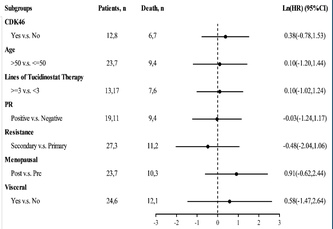


Figure 4. Forest Plot for PFS (N=30)



Discussion

- Treatment decisions after resistance to first-line endocrine therapy remain controversial. In this prospective study, the enrolled patient population exhibited a substantial overall tumor burden, with 80% presenting visceral metastases and 50% demonstrating metastatic involvement of more than three anatomical sites. Despite these poor prognostic features, the regimen demonstrated promising efficacy. Notably, the subgroup with visceral metastases maintained a PFS of 6.08 months.
- Optimal post-CDK4/6i progression strategies remain elusive. In this study, 40% of the cohort was comprised of pts with prior CDK4/6i exposure. Notably, the subgroup with disease that progressed after CDK4/6i treatment demonstrated a median mPFS of 5.09 months.

Table 3: Adverse events with frequency ≥ 10% (N=30)

Adverse Events	All grade n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)
leucopenia	20 (67)	14 (47)	4 (13)	2 (6)
Neutropenia	14 (47)	8 (27)	4 (13)	2 (6)
Nausea	13 (43)	11 (37)	2 (7)	0
Thrombocytopenia	12 (40)	11 (37)	1 (3)	1 (3)
Diarrhea	6 (20)	6 (20)	0	0
Vomiting	5 (17)	4 (13)	1 (3)	0
Fatigue	5 (17)	5 (17)	0	0
AST increased	5 (17)	5 (17)	0	0
ALT increased	5 (17)	5 (17)	0	0

Conclusions

This study confirms the efficacy and safety of chidamide combined with fulvestrant in pts with HR+/HER2- advanced breast cancer. However, it has several limitations that should be acknowledged. First, the relatively small sample size, single-center design, and short median follow-up duration of 6.3 months may limit the generalizability of our findings. Additionally, restricted drug availability during the initial study period resulted in most pts being CDK4/6 inhibitor-naïve prior to receiving chidamide treatment. Variability heterogeneity in treatment adherence and differences in response assessment intervals may also have introduced bias in the evaluation of PFS. Despite these limitations, this study represents one of the first prospective investigations in this setting and offers valuable real-world evidence supporting the clinical feasibility of the chidamide and endocrine therapy combination in HR+/HER2- MBC pts.

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