Estetrol for treatment of advanced ER+/HER2- breast cancer

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Introduction

A high dose of the fetal estrogen estetrol (E4) is anticipated to have anti-tumor effects in patients with advanced, anti-estrogen resistant, ER+/HER2- breast cancer (BC).[1,2] E4 treatment is also expected to improve patients' quality of life by treating the symptoms of estrogen deficiency due to the previous anti-estrogen therapy.[2] The main objectives of this study were to assess the safety and tolerability of three high doses of E4 (HDE4), to determine anti-tumor responses and to evaluate patient reported estrogen deficiency-related side effects.

Study Design and Methods

The ABCE4 study was a multi-center, open-label, phase IB/IIA, dose-escalation study performed in two centers in Germany (Trial registry no. NCT02718144). It was a 3+3 cohort design study, whereby successive cohorts of 3 patients received 20 mg, 40 mg and 60 mg E4 per day by oral administration. Dose limiting toxicity (DLT), safety and wellbeing were evaluated after 4, 8 and 12 weeks of treatment. Occurrence of DLTs at completion of phase IB after 4 weeks treatment determined escalation to the next higher dose. Objective anti-tumor effects were assessed by computer tomography scanning and evaluated according to RECIST criteria before and after 12 weeks of treatment. Thereafter treatment could continue based on an evaluation by the patient and her treating physician. In view of the small numbers required for this standard 3+3 design study no statistical testing was performed.

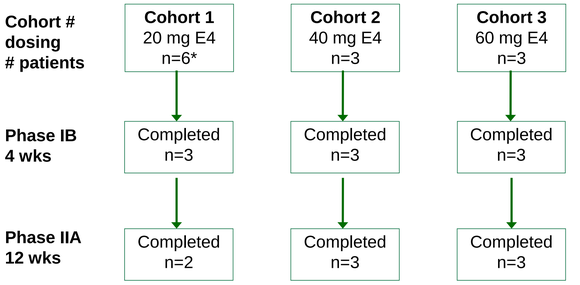

Figure 1 Subject disposition

* During Phase IB, one patient withdrew informed consent prior to starting treatment and two 2 patients died due to disease progression within 4 weeks of treatment

Results

A total of 12 postmenopausal women with progressive, heavily pre-treated advanced BC were enrolled of whom 11 received treatment. Nine patients completed Phase IB (see Table 1 for the baseline characteristics). One patient in the 20 mg group discontinued the study during Phase IIA due to disease progression after 9.5 weeks of E4 treatment. She died 3 weeks later. Eight patients completed both the Phase IB and IIA part of the study (Figure 1).

After 12 weeks of E4 treatment, five patients showed objective anti-tumor effects with stable disease in four patients and one complete response (Table 2). All five continued E4 treatment beyond the trial. Tumor assessment after 24 weeks of treatment confirmed stable disease in four of five patients investigated. Seven patients reported subjective improvement during E4 treatment.

None of the patients experienced a DLT. All three E4 doses were well tolerated by all patients. In total 31 adverse events were reported, mainly of mild or moderate intensity. The following six events were considered possibly related to E4 treatment by the investigator: endometrial hyperplasia, dry skin, pruritus, fatigue, vaginal hemorrhage and regurgitation. No drug-related SAEs were reported.

Conclusions

Daily doses of 20 mg, 40 mg and 60 mg E4 were well tolerated without DLTs, with anti-tumor effects in 5 of 9 patients, and favorable subjective effects in 7 of 9 patients, confirming the "Dual Efficacy" of HDE4. All doses of E4 met the criteria for further development of E4 for the treatment of anti-estrogen resistant advanced breast cancer.

Contact Information

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Table 1. Patient baseline characteristics

Parameter	Cohort 1: 20 mg E4			Cohort 2: 40 mg E4			Cohort 3: 60 mg E4		
Patient	1	2	3	4	5	6	7	8	9
Age, yrs	56	72	78	68	78	79	65	69	66
Duration since last natural menses, yrs	8	6	33	13	31	30	14	20[a]	20
Duration since BC diagnosis, yrs	8	5	37	23	13	16	8	16	20
Hormone receptor status	ER+/PR+	ER+/PR+	ER+/PR+	ER+/PR-	ER+/PR+	ER+/PR+	ER+/PR-	ER+/PR+	ER+/PR+
TNM stage	IV	IV	II	IV	IV	IV	IV	IV	IV
ECOG status	1	0	0	0	0	1	0	1	1
Recurrences	None	Local	None	None	None	None	None	None	None
Metastases	Li, Bo, LN pleura	Bo	Lu, LN	Lu	Li	Lu, Bo, LN	Li, Bo	Li	Lu, Li, Bo, LN
Complications	Pleural effusion, malignant ascites	None	None	Pleural effusion	None	None	None	None	Peritoneal metast.
Number of prior BC treatments[b]									
Endocrine therapy	2	3	2	6	4	3	5	3	4
Chemotherapy	3	-	-	5	5	2	6	4	5
Targeted therapy	1	-	-	2	1	-	1	2	-
Targeted+ Endocrine therapy	1	-	2	-	-	-	-	-	1

All women were at least 5 years postmenopausal; data are shown per patient in each cohort

[a] Surgical menopause

[b] Not including radiotherapy or surgery

BC, breast cancer; Bo, bone; E4, estetrol; ER, estrogen receptor; Li, liver; LN, lymph nodes; Lu, lung, PR, progesterone receptor; yrs, years

References

1. Singer et al. Antiestrogenic effects of the fetal estrogen estetrol in women with estrogen-receptor positive early breast cancer. Carcinogenesis. 2014;35:2447-51. doi: 10.1093/carcin/bgu144.
2. Coelingh Bennink et al. The use of high-dose estrogens for the treatment of breast cancer. Maturitas. 2017;95:11-23. doi: 10.1016/j.maturitas.2016.10.010.

Table 2. Anti-tumor response after 12 weeks of E4 treatment according to the RECIST criteria

Parameter	Cohort 1: 20 mg E4			Cohort 2: 40 mg E4			Cohort 3: 60 mg E4		
Patient	1	2	3	4	5	6	7	8	9
Evaluation of Target Lesions	PD	SD	CR	SD	SD	SD	PD	PD	PD
Evaluation of Non-Target Lesions	PD	Non-CR/ Non-PD	Non-CR/ Non-PD	Non-CR/ Non-PD	Non-CR/ Non-PD	Non-CR/ Non-PD	PD	-	PD
New Lesions	Yes	No	No	No	No	No	Yes	Yes	No
Response Type	PD	SD	CR	SD	SD	SD	PD	PD	PD
Response	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**	**No**

Data are shown per patient in each cohort

CR, complete response; SD, stable disease; PD, progressive disease