

LIST OF SUPPLEMENTAL CONTENT

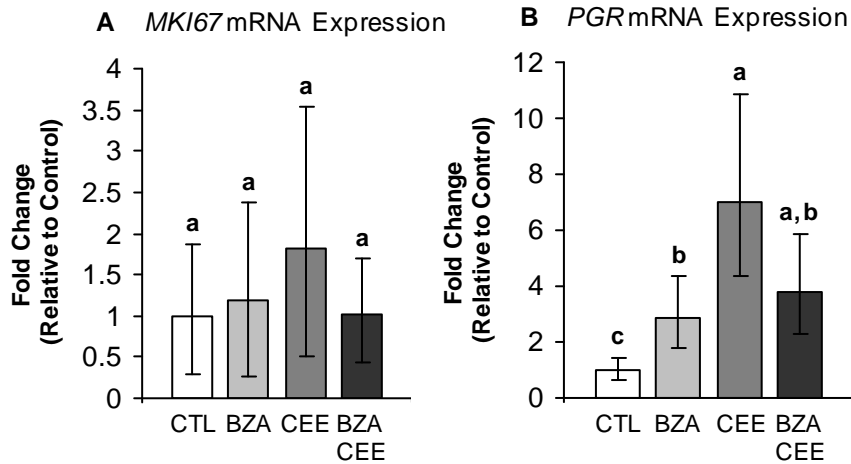
Supplemental Content 1: File name 'Ethun_Breast Effects of Bazedoxifene with CEE_Supplemental Content 1.ppt'. Figure displaying mRNA expression of *MKI67* (A) and *PGR* (B).

Supplemental Content 2: File name 'Ethun_Breast Effects of Bazedoxifene with CEE_Supplemental Content 2.doc'. Table displaying '*Genes Regulated by 0.45 mg/d CEE treatment in the Breast*'.

Supplemental Content 3: File name 'Ethun_Breast Effects of Bazedoxifene with CEE_Supplemental Content 3.doc'. Table displaying '*Bazedoxifene-agonized Genes in BZA+CEE Co-therapy*'.

Supplemental Content 4: File name 'Ethun_Breast Effects of Bazedoxifene with CEE_Supplemental Content 4.doc'. Table displaying '*Treatment Effects of Bazedoxifene and CEE on Genes Related to Estrogen Metabolism*'

SUPPLEMENTAL CONTENT 1 (REVISION).



Relative gene expression of progesterone receptor (*PGR*) and the proliferation marker, *MKI67*. (A) No significant difference in *MKI67* expression was observed among treatment groups (non-parametric Kruskal-Wallis). (B) Treatment with BZA, CEE, and BZA+CEE significantly increased *PGR* expression relative to control ($P < 0.01$ for all). A trend for a significant difference in *PGR* expression was observed between CEE and BZA+CEE ($P = 0.051$, ANOVA). Values represent means \pm 95% CI. Treatment groups not connected by the same letter are significantly different.

SUPPLEMENTAL CONTENT 2.

Genes Regulated by 0.45 mg/d CEE treatment in the Breast^a

Gene Symbol	Gene Name	CEE-regulated Direction vs. Control
IGFBP1	Insulin-like growth factor binding protein 1	Up
<i>C1orf173</i>	Chromosome 1 open reading frame 173	Up
TFF1	Trefoil factor 1	Up
<i>MCCC2</i>	Methylcrotonoyl-Coenzyme A carboxylase 2 (beta)	Up
TFF3	Trefoil factor 3 (intestinal)	Up
PGR	Progesterone receptor^b	Up
<i>HIST3H2A</i>	Histone cluster 3, H2a	Up
<i>ASPN</i>	Asporin	Up
<i>SGK493</i>	Protein kinase-like protein SgK493	Up
<i>KLK11</i>	Kallikrein-related peptidase 11	Up
GREB1	GREB1 protein	Up
IGSF1	Immunoglobulin superfamily, member 1	Up
<i>KLK12</i>	Kallikrein-related peptidase 12	Up
PPM1K	Protein phosphatase, Mg²⁺/Mn²⁺ dependent, 1K	Up
<i>SYT13</i>	Synaptotagmin XIII	Up
<i>PACRG</i>	PARK2 co-regulated	Up
<i>MAGED2</i>	Melanoma antigen family D, 2	Up
<i>C2orf80</i>	Chromosome 2 open reading frame 80	Up
<i>CLGN</i>	Calmegin	Up
STC2	Stanniocalcin 2	Up
<i>CACNA1D</i>	Ca ⁺⁺ channel, voltage-dependent, L type, alpha 1D subunit	Up
RET	Ret proto-oncogene	Up
<i>NTNG1</i>	Netrin G1	Up
<i>CSRNP3</i>	Cysteine-serine-rich nuclear protein 3	Up
<i>NR2C2</i>	Nuclear receptor subfamily 2, group C, member 2	Down
<i>SLC4A8</i>	Solute carrier family 4, sodium bicarbonate cotransporter, member 8	Up
<i>DACHI</i>	Dachshund homolog 1 (Drosophila)	Up
IRS1	Insulin receptor substrate 1	Up
<i>FXYP3</i>	FXYP domain containing ion transport regulator 3	Up
<i>RNASE1</i>	Ribonuclease, RNase A family, 1 (pancreatic)	Up
<i>DDX4</i>	DEAD (Asp-Glu-Ala-Asp) box polypeptide 4	Up
MYB	V-myb myeloblastosis viral oncogene homolog (avian)	Up
<i>TFCP2L1</i>	Transcription factor CP2-like 1	Down
<i>AGR2</i>	Anterior gradient homolog 2 (Xenopus laevis)	Up
<i>C4orf30</i>	Chromosome 4 open reading frame 30	Down
<i>UQCRC2</i>	Ubiquinol-cytochrome c reductase core protein II ^c	Up
<i>NELL1</i>	NEL-like 1 (chicken)	Up
<i>IL22RA2</i>	Interleukin 22 receptor, alpha 2	Down

^a Gene names are listed in descending order of significance level (pair-wise comparison between control and CEE-alone, fold change > 2, adjusted *P* values 0.01 – 0.05).

^b Commonly up-regulated by BZA treatment compared to control.

^c Contrarily down-regulated by BZA+CEE treatment compared to control.

Bold terms represent genes well-known to be up-regulated by estrogen therapy in human breast cancer cells.⁴⁰⁻⁴² N = 4 for each treatment group.

SUPPLEMENTAL CONTENT 3.*Bazedoxifene-agonized Genes in BZA+CEE Co-therapy*^a

Gene Symbol	Gene Name	Fold Change CEE vs. BZA/CEE
<i>IGHA1</i>	Immunoglobulin heavy constant alpha 1	3.28
<i>CCL5</i>	Chemokine (C-C motif) ligand 5	2.79
<i>MDM4</i>	Mdm4 p53 binding protein homolog (mouse)	2.67
<i>GZMK</i>	Granzyme K (granzyme 3, tryptase III)	2.49
<i>UBD</i>	Ubiquitin D	2.31
<i>HLA-DPA1</i>	Major histocompatibility complex, class II, DP alpha 1	2.21
<i>GZMB</i>	Granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1)	2.10

^a Filtered dataset generated in Genesifter software program using a pair-wise comparison between CEE and BZA+CEE at a fold change (FC) > 2, adjusted $P < 0.05$, Benjamini & Hochberg correction. All genes were not significantly regulated by BZA, CEE, and BZA+CEE compared to control, except for *IGHA1* (CEE down-regulated compared to control, FC 3.58). N = 4 for each treatment group.

SUPPLEMENTAL CONTENT 4. *Treatment Effects of Bazedoxifene and CEE on Genes Related to Estrogen Metabolism*^a

	Control	BZA 20 mg/d	CEE 0.45 mg/d	BZA + CEE 20 mg/d + 0.45 mg/d	<i>P</i> value (ANOVA)
<i>CYP19</i>	1.00 (0.71 - 1.33)	0.78 (0.59 - 0.99)	0.65 (0.45 - 0.87)	0.98 (0.73 - 1.27)	0.105
<i>HSD17B1</i>	1.00 (0.77 - 1.25)	1.25 (0.79 - 1.79)	1.05 (0.81 - 1.32)	1.32 (0.94 - 1.75)	0.498
<i>HSD17B2</i>	1.00 (0.71 - 1.33)	1.70 (1.09 - 2.48)	1.65 (1.09 - 2.33)	1.88 (1.28 - 2.63)	0.102
<i>STS</i>	1.00 (0.73 - 1.31)	1.03 (0.77 - 1.32)	0.92 (0.70 - 1.16)	1.15 (0.84 - 1.51)	0.665
<i>SULT1E1</i>	1.00 (0.72 - 1.31)	0.97 (0.71 - 1.27)	0.90 (0.64 - 1.21)	1.21 (0.87 - 1.60)	0.492
N	22	22	24	25	

^a Values represented as means (95% CI); expressed relative to control (1.0)