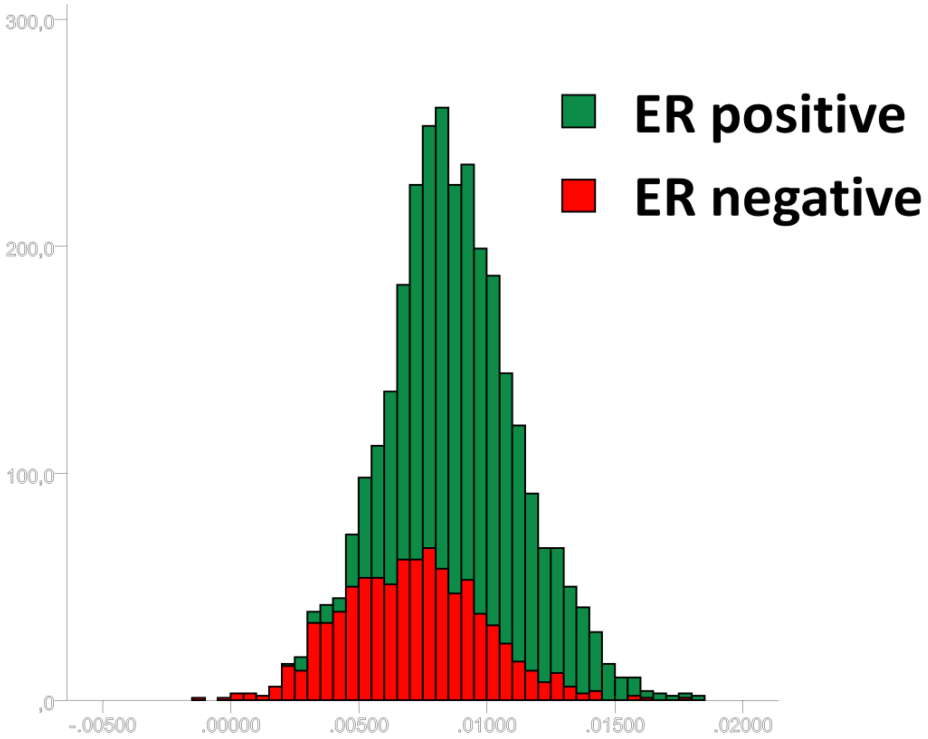
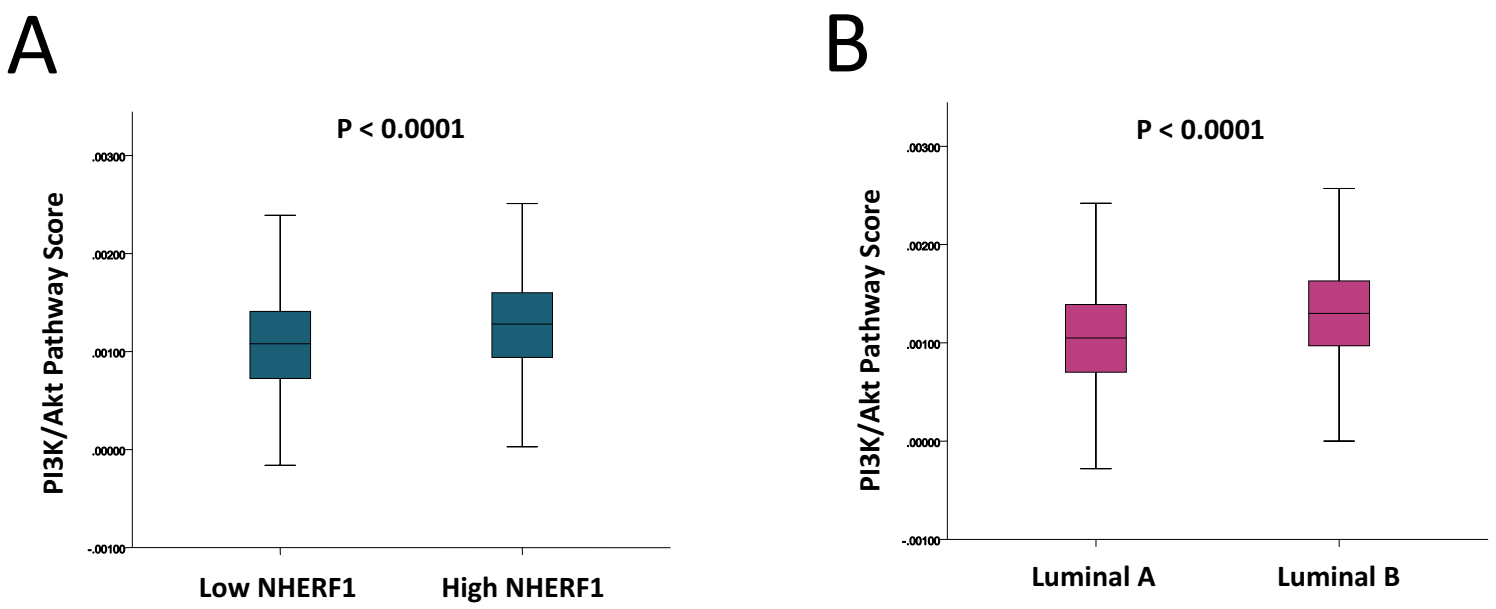


Supplementary Figure S1: NHERF1 expression is associated with the ER status of the tumor

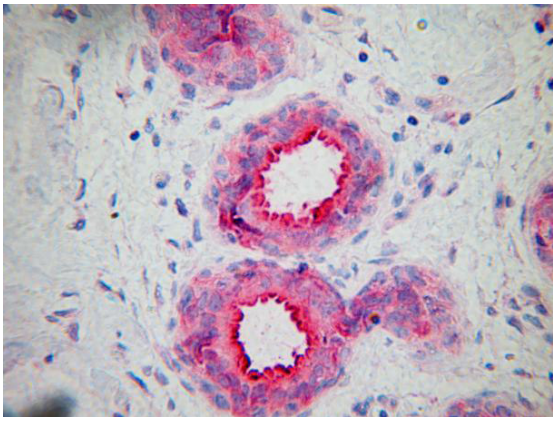
Shown is the distribution of normalized NHERF1 mRNA expression values measured by Affymetrix microarrays among 2158 ER positive and 872 ER negative invasive breast cancer samples. Highest expression of NHERF1 was observed among ER positive tumors.



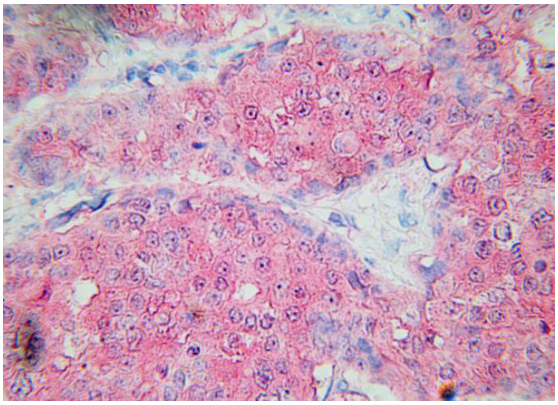
Suppl. Figure S2: **Association of NHERF1 expression with activation of PI3K/Akt pathway**

The PI3K/Akt pathway activation score as described by Creighton et al. (Breast Cancer Res. 2010;12(3):R40. Epub 2010 Jun 22.) was analyzed in 2158 ER positive tumors. Samples were either stratified according to NHERF1 expression in (A) or Luminal A vs Luminal B subtype according to Hugh et al. (J Clin Oncol. 2009; 27(8):1168) in (B). Higher scores for PI3K/Akt pathway activation were observed in tumors with high NHERF1 expression and those of the Luminal B subtpye (P<0.0001 for both, Mann-Whitney U test).

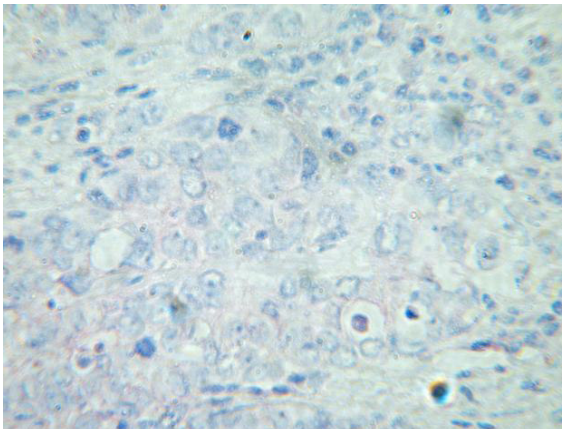
A



B



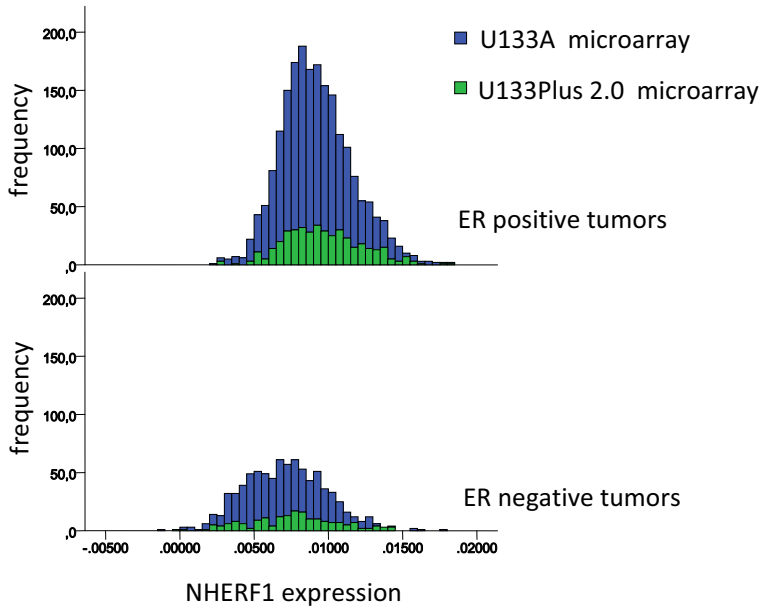
C



Supplementary Figure S3: Immunohistochemical detection of NHERF1 expression

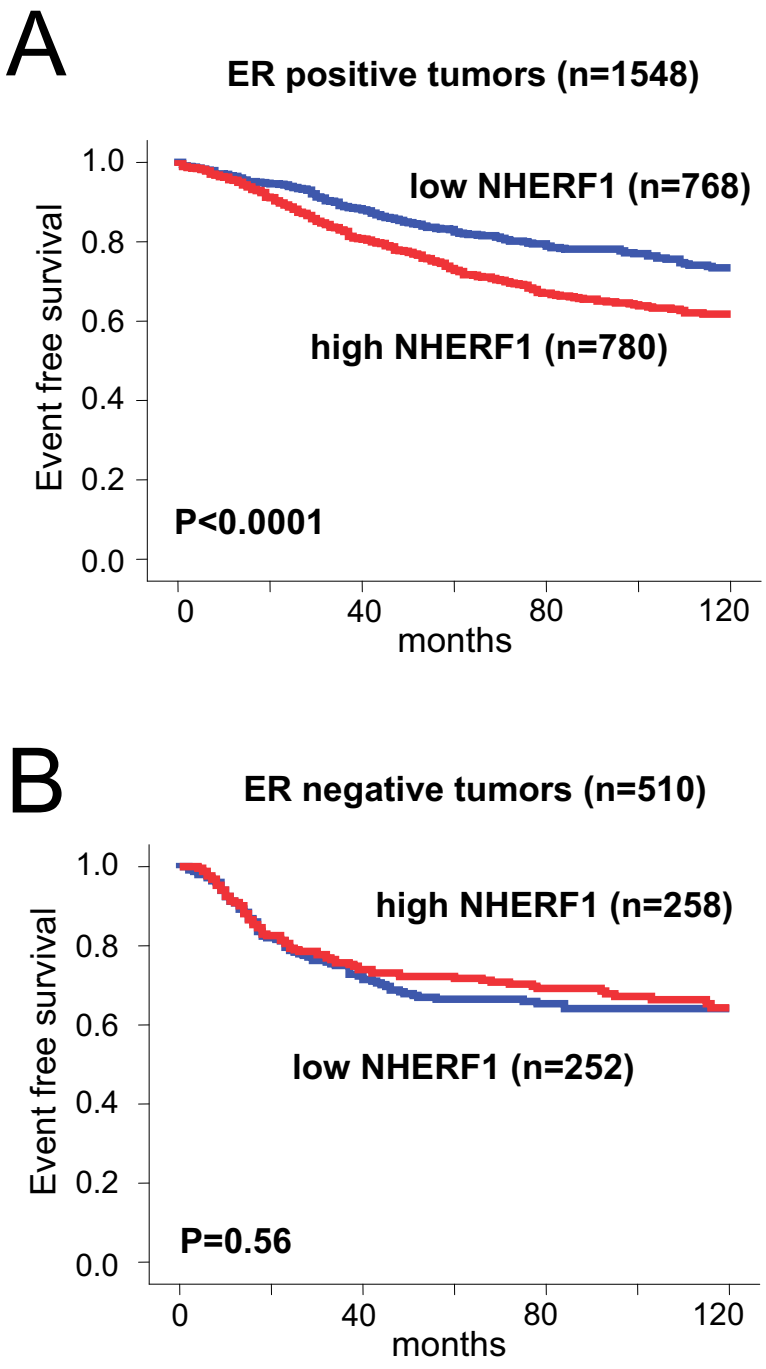
Immunohistochemical detection of NHERF1 protein expression in breast tissue samples using a monoclonal antibody directed against the human NHERF1 protein (LS-C15004, LifeSpan Biosciences Inc., Seattle, WA; red staining, blue counterstain).

A) Normal breast tissue showing apical localization of NHERF1 protein.
B) Representative examples of an ER positive tumor showing diffuse cytoplasmatic distribution of NHERF1 protein.
C) Example of an ER negative breast cancer sample lacking strong NHERF1 expression.



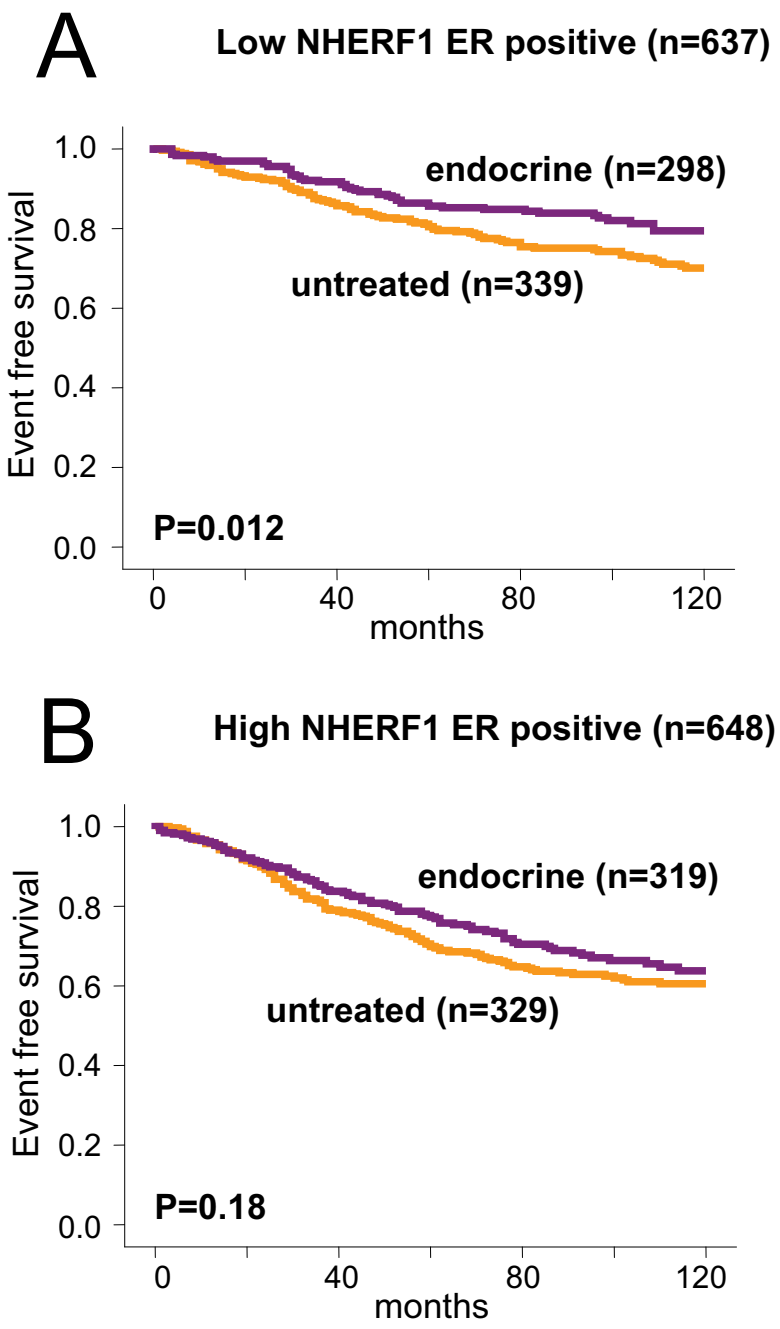
Supplementary Figure S4: Analysis of a potential bias for NHERF1 expression between Affymetrix U133A and U133Plus2 microarray formats.

The distribution of NHERF1 expression values in ER positive (upper panel) and ER negative (lower panel) breast cancer samples is given. Blue colour was used for samples profiles on U133A microarrays and green colour for samples profiled on U133Plus2.0 microarrays. Roughly similar distribution of NHERF1 expression were observed between the two Affymetrix formats.



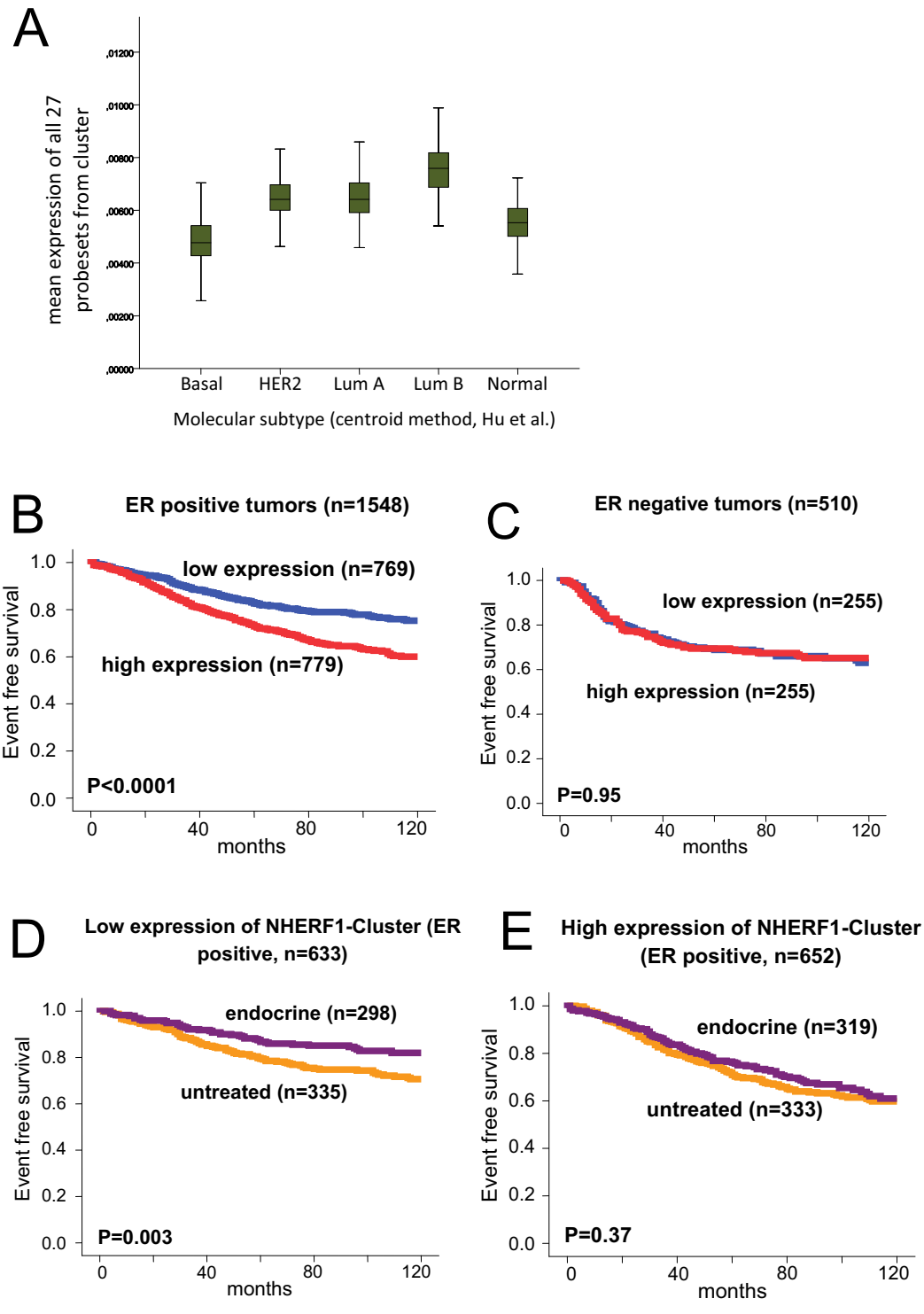
Supplementary Figure S5: Kaplan Meier analysis of NHERF1 using separate median splits in each sub-dataset

Since the analyzed expression data were assembled from several different datasets possible confounding effects could have been introduced by systematic technical differences. Therefore the Kaplan Meier survival analysis according to NHERF1 expression presented in Figure 3 was validated by performing the median split of NHERF1 expression separately on an individual dataset by dataset basis here. As in Figure 3 separate analysis were performed among ER positive (A) and ER negative (B) tumors.

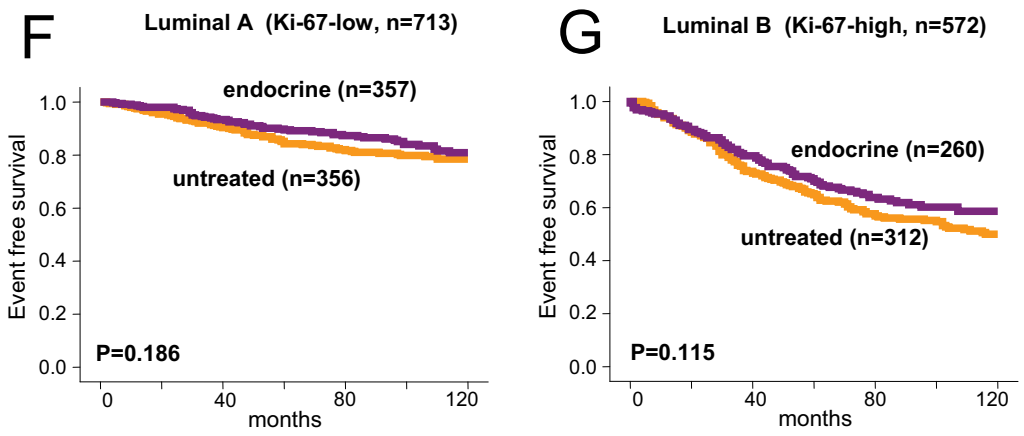


Supplementary Figure S6: **Analysis of predictive value of NHERF1 for response to endocrine treatment in ER positive breast cancer using separate median splits in each sub-dataset**

Since the analyzed expression data were assembled from several different datasets possible confounding effects could have been introduced by systematic technical differences. Therefore the analysis of event free survival of ER positive breast cancer patients according to treatment with endocrine therapy in the *low NHERF1* (A) and *high NHERF1* (B) subgroups of tumors presented Figure 4 was validated by performing the median split of NHERF1 expression separately on an individual dataset by dataset basis here. Similar as in Figure 4 a significant difference in event free survival between endocrine treated patients and patients without systemic treatment (P=0.012) was observed only in the subgroup with low NHERF1 expression.



Supplementary Figure S7 ***- continued -***



Supplementary Figure S7: **Analysis of the prognostic/predictive value of the combined *luminal B like* gene cluster**

As a combined expression metric for all genes from the luminal-B-like cluster the arithmetic mean of the expression values of all 27 probesets from the cluster was used. Panel (A) demonstrates the expression of this combined value among the different molecular subtypes according to the centroid method using the intrinsic gene set from Hu et al. (as in Figure 2D). For survival analyses a median split of the combined expression value of the luminal-B-like cluster was performed separately in the ER positive and ER negative subgroups. This stratification was done on an individual dataset by dataset basis to avoid biases from technical differences in array analyses. Panels (B) and (C) demonstrates the survival of patients stratified according to the luminal-B-like cluster either in the ER positive (B) or ER negative (C) subgroups as in Figure 3 of the main manuscript. Panels (D) and (E) demonstrates the influence of endocrine therapy among ER positive tumors with either low (D) or high (E) expression of the luminal-B-like gene cluster as in Figure 4 of the main manuscript. For comparison a similar analysis as in (D) and (E) is also shown for luminal A and luminal B tumors defined on the basis of Ki-67 as a metric for proliferation in panels (F) and (G) respectively. In this analysis Ki-67 as proliferation marker had no significant predictive value for the response to endocrine treatment.

Supplementary Table S1: Summary of Affymetrix microarray datasets used in this study.

			% of samples									
Dataset	Data Source	No. of samples	Age ≤ 50	Tumor size ≤ 2 cm	LNN	ER pos.	G3	System. treatment	Median follow up months	No. of relapses	event type	Reference
Rotterdam	GSE2034, GSE5327	344	n.a.	n.a.	n.a.	62	n.a.	286 untreated, 58 n.a.	86	118	DMFS	A, B
Mainz	GSE11121	200	35	56	100	84	23	untreated	92	41	DMFS	C
TransBIG	GSE7390	198	69	37	100	68	42	untreated	117	91	RFS	D
Oxford-Untreated	GSE2990 (n=61), GSE6532 (n=8)	69	44	64	100	71	41	untreated	121	29	RFS	E
London	GSE6532	87	6	35	33	98	23	endocrine	137	28	RFS	F
London-2	GSE9195	77	5	44	53	96	41	endocrine	98	13	RFS	G
Oxford-Tamoxifen	GSE6532	109	14	34	64	98	19	endocrine	61	30	RFS	F
Veridex-Tam	GSE12093	136	n.a.	n.a.	100	100	n.a.	endocrine	85	20	DMFS	H
Frankfurt-3	This study	52	6	9	61	98	10	endocrine	56	19	RFS	I
Stockholm	GSE1456	159	n.a.	n.a.	n.a.	79	42	yes / no	85	40	RFS	J
Uppsala	GSE3494 (n=251), GSE6232 (n=5), GSE4922 (n=1), GSE2990 (n=1)	258	22	51	65	80	22	yes / no	118	91	RFS	K, L
San Francisco	E-TABM-158	118	46	33	43	69	54	yes / no	68	36	DMFS	M
New York	GSE2603	99	37	9	34	58	n.a.	n.a.	65	27	DMFS	N
Frankfurt	This study	119	55	50	56	66	47	chemotherapy	39	29	RFS	O
Frankfurt-2	This study	67	51	0	49	58	30	chemotherapy	n.a.	n.a.	-	P
MDA133	www.mdanderson.org	133	41	9	30	63	58	chemotherapy	n.a.	n.a.	-	Q
EORTC	GSE1561	49	n.a.	n.a.	n.a.	57	n.a.	chemotherapy	n.a.	n.a.	-	R
Edinburgh	GSE5462	116	n.a.	n.a.	n.a.	100	n.a.	endocrine	n.a.	n.a.	-	S
expO	GSE2109	301	31	32	47	67	49	n.a.	n.a.	n.a.	-	T
Signapore	GSE5364	183	n.a.	n.a.	n.a.	55	n.a.	n.a.	n.a.	n.a.	-	U
Genentech	GSE12763	30	n.a.	n.a.	n.a.	70	n.a.	n.a.	n.a.	n.a.	-	V
Boston	GSE3744	40	n.a.	n.a.	n.a.	30	100	n.a.	n.a.	n.a.	-	W
Berlin	GSE6596	24	21	63	n.a.	67	46	n.a.	n.a.	n.a.	-	X
Paris	GSE13787	23	n.a.	n.a.	n.a.	0	100	n.a.	n.a.	n.a.	-	Y
Tampa	GSE10780	39	n.a.	n.a.	n.a.	70	n.a.	n.a.	n.a.	n.a.	-	Z
TOTAL:		3030	35	36	70	74	38		80	629		

Remarks: The TransBIG cohort contains independent replicate samples from 19 patients of Uppsala cohort and 22 patients of Oxford-Untreated cohorts. Affymetrix HG-U133A microarrays were applied in all studies except for datasets expO, London, London-2, Genentech, Boston, Paris, and Tampa where the identical ProbeSets from HG-U133Plus arrays were used.

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Supplementary Table S2: Genes in the *Luminal B – like* gene cluster

Gene Symbol	Gene Name	Affymetrix probesets	Chrom.Loc.
BCAS4	breast carcinoma amplified sequence 4	220588_at	20q13.13
CANT1	calcium activated nucleotidase 1	46323_at, 221732_at	17q25.3
CNNM4	cyclin M4	218900_at	2q11.2
CRABP2	cellular retinoic acid binding protein 2	202575_at	1q23.1
CXorf40	chromosome X open reading frame 40	212961_x_at, 213315_x_at, 214112_s_at	Xq28
DDR1	discoidin domain receptor tyrosine kinase 1	1007_s_at, 207169_x_at, 210749_x_at, 208779_x_at	6p21.33
HSPB1	heat shock 27kDa protein 1	201841_s_at	7q11.23
LGALS3BP	lectin, galactoside-binding, soluble, 3 binding protein	200923_at	17q25.3
MAGED2	melanoma antigen family D, 2	208682_s_at, 213627_at	Xp11.21
NKAIN1	Na+/K+ transporting ATPase interacting 1	219438_at	1p35.2
NSF	N-ethylmaleimide-sensitive factor	202395_at	17q21.31
PNPO	pyridoxamine 5'-phosphate oxidase	218511_s_at	17q21.32
SEMA3F	semaphorin-3F	206832_s_at, 209730_at	3p21.31
SHROOM2	shroom family member 2	204967_at	Xp22.2
SLC9A3R1	NHERF1	201349_at	17q25.1
TMEM106C	transmembrane protein 106C	201764_at	12q13.11
WFS1	Wolfram syndrome 1	202908_at	4p16.1
WWP1	WW domain containing E3 ubiquitin protein ligase	212637_s_at, 212638_s_at	8q21.3

Supplementary Table S4: Information on variables from *Supplementary Table S3*

VARIABLE	CODE
combi_id	singular ID
sample	sample name
dataset	dataset
GSE	GEO series
Array_type	GEO platform
GSM_No	GEO GSM number
lymph_node_status	"0=lymph node negative; 1=N1"
age50	"1= age over 50yr; 2= age up to 50yr"
t1vsrest	"1= tumor size up to 2cm; 2= tumor size >2cm"
g12vs3	"Histol.Grading 12=G1 or G2; 3=G3 "
er_bio	"biochemical ER status (1=positive; 2=negative)"
pr_bio	"biochemical PgR status (1=positive; 2=negative)"
her2 bio	"biochemical HER2 status (1=positive; 2=negative)"
fu mon	follow up time (months)
event01	"event status (1=event; 0=censored)"
fu_120	follow up time censored at 120 months
ev120	"event status (1=event; 0=censored) censored at 120 months"
ev_type	"event type (1=any relapse; 2=distant metastasis)"
treat3class	"adjuvant treatment (1= no adjuvant treatment; 2= endocrine treatment; 3=cytotoxic treatment)"
ESR1_205225_at	magnitude normalized Log2-MAS5
PGR_208305_at	magnitude normalized Log2-MAS5
HER2_216836_s_at	magnitude normalized Log2-MAS5
MKI67_212020_s_at	magnitude normalized Log2-MAS5
MKI67_212021_s_at	magnitude normalized Log2-MAS5
MKI67_212022_s_at	magnitude normalized Log2-MAS5
MKI67_212023_s_at	magnitude normalized Log2-MAS5
MKI67_mean	mean of four MKI67 probeset magnitude normalized Log2-MAS5
ESR_0.0075	"ER status according ESR1_205225_at cutoff 0.0075 (1=positive; 2=negative); [Karn et al. Breast Cancer Res Treat. 2010; 120:567]"
PGR_m0.0078	"PgR status according PGR_208305_at cutoff -0.0078 (1=positive; 2=negative); [Karn et al. Breast Cancer Res Treat. 2010; 120:567]"
HER2_0.0135	"HER2 status according HER2_216836_s_at cutoff 0.0135 (1=positive; 2=negative); [Karn et al. Breast Cancer Res Treat. 2010; 120:567]"
MolSubType_Hugh	"Molecular subtype of tumors according to Hugh et al. (J Clin Oncol. 2009, 27:1168); ERpos LumA/Lum B splitted by median Ki-67 among ER pos; ERpos/HER2pos tumors defined as LumB; ERneg/PgRpos tumors regarded as ERneg/PgRneg"
MolSubType_Hu306	"Molecular subtype of tumors according to Hu et al. (BMC Genomics. 2006; 7:96) using the SSP method of Weigelt et al. (Lancet Oncol. 2010; 11:339)"
NHERF1_201349_at	magnitude normalized Log2-MAS5
Median_NHERF1_by_ER	"1=low NHERF1 expression, 2=high NHERF1 expression; median split separately in ERpos and ERneg subgroup"

Supplementary Table S5: **Multivariate Cox Regression analysis of NHERF1 and Ki-67 expression and standard parameters among ER positive tumors**

Parameter	n=786	HR	95% CI	P-Value
NHERF1 (high vs. low)	361 vs. 425	1.22	0.93-1.61	0.15
Ki-67 (high vs. low)	317 vs. 469	2.43	1.84-3.22	**<0.001**
lymph node status (LNN vs. N1)	505 vs. 281	1.19	0.91-1.55	0.21
patient age (>50yr vs. ≤50 yr)	532 vs. 254	0.95	0.72-1.25	0.70
histological grading (G3 vs. G1-2)	186 vs. 600	1.09	0.81-1.46	0.58
tumor size (≤ 2cm vs. > 2cm)	340 vs. 446	0.57	0.43-0.77	**<0.001**
HER2 status (pos. vs. neg.)	47 vs. 739	1.26	0.80-2.01	0.32
PgR status (pos. vs. neg.)	597 vs. 189	0.92	0.69-1.23	0.56

Supplementary Table S6: **Multivariate Cox Regression analysis of expression of the Luminal-B-like-Cluster and Ki-67 expression and standard parameters among ER positive tumors**

Parameter	n=786	HR	95% CI	P-Value
Luminal-B-like-Cluster (high vs. low)	396 vs. 390	1.40	1.07-1.83	**0.015**
Ki-67 (high vs. low)	317 vs. 469	2.39	1.81-3.14	**<0.001**
lymph node status (LNN vs. N1)	505 vs. 281	1.18	0.90-1.55	0.22
patient age (>50yr vs. ≤50 yr)	532 vs. 254	0.93	0.70-1.22	0.58
histological grading (G3 vs. G1-2)	186 vs. 600	1.09	0.81-1.46	0.57
tumor size (≤ 2cm vs. > 2cm)	340 vs. 446	0.58	0.43-0.77	**<0.001**
HER2 status (pos. vs. neg.)	47 vs. 739	1.25	0.79-1.99	0.34
PgR status (pos. vs. neg.)	597 vs. 189	0.92	0.69-1.23	0.57