SUPPLEMENTAL METHODS

Inclusion Criteria Human Breast Cancer Cases

Inclusion criteria for this study were as follows: invasive breast cancer; no neo-adjuvant and, for the lymph-node negative (LNN) cases only, no adjuvant systemic therapy; for the 1st line tamoxifen cases only, estrogen receptor (ER, *ESR1*) positive primary tumors and endocrine therapy naive; no previous other cancer (except basal cell skin cancer or early-stage cervical cancer stage Ia/Ib); detailed clinical follow up available; ≥100 mg frozen tissue available; ≥ 30% invasive tumor cell nuclei in the sample. All remaining isolated RNA samples that required more than 25 rounds of real-time PCR for detectable products of our 3 reference genes at a fixed input of 10 ng total RNA and at a threshold of 0.1 were considered of insufficient quality and were excluded from further analysis.

Determination of Clinico-pathological and Biological Factors

Lymph-node negativity and tumor size was based on pathological examination by regional pathologist. After primary surgery, a representative part of the tumor was selected by the pathologist, frozen in liquid nitrogen, and sent to our department for routine determination of ER and progesterone receptor (PR, *PGR*) by ligand binding assay (LBA) (*1*). Tumor cytosols were prepared and processed as recommended by the E.O.R.T.C. and the cut-off used to classify tumors as ER or PR positive at protein level was 10 fmol/mg cytosolic protein (*2*). *ESR1*, *PGR* and human epidermal growth factor receptor 2 (HER2, *ERBB2*) expression were also determined by real-time PCR with cut points used for *ESR1* = 0,2, *PGR* = 0.1 and *ERBB2* = 0.18 (mRNA levels relative to reference genes) as described before (*3,4*). Genomic Grade Index (GGI), a gene expression pattern of histological tumor grade, was determined by real-time PCR based on the expression of 4 proliferation marker genes as described before (*5*).

Human Breast Cancer Cases with 1st Line Tamoxifen Treatment

For prediction of therapy response a cohort of 224 hormonal treatment-naive ER-positive patients who received 1st line tamoxifen treatment for recurrent disease were analyzed (*6,7*). Of the 224 patients from this cohort, 24 patients presented with distant metastasis at diagnosis or developed distant metastasis (including supraclavicular lymph node metastasis) within 1 month after primary surgery (M1-patients). These 24 patients and the 200 patients who developed a first recurrence during follow-up [19 patients with local-regional relapse (LRR), 181 patients with distant metastasis (DM)] were treated with first-line tamoxifen. All patients were ER positive and anti-hormonal therapy naive, but 33 patients received adjuvant chemotherapy. The median time between primary surgery and start of therapy was 24 months (range, 0-120 months). The median follow-up of patients alive at end of follow up was 93 months (range, 9-240 months) after primary surgery, and 51 months (range, 4-178 months) after start of 1st line tamoxifen therapy. For 132 patients (59%), disease progression within 6 months after start first-line was controlled by tamoxifen therapy. At the end of the follow-up period, 215 (96%) patients had developed tumor progression and 186 (83%) patients had died. Progression-free survival (PFS) was defined as the time elapsed between initiation of tamoxifen therapy and first detection of disease progression as defined by standard International Union Against Cancer criteria for objective response (*8*).

In Vitro Autoradiography Assay

Tissue sections were incubated with 10^{-9} M of the radioligands for 1 h, without and with 10^{-6} M of unlabeled tracer as control for non-specific binding. Unlabeled Tyr^4-bombesin (Sigma-Aldrich) and octreotide (Covidien) were used to block gastrin releasing peptide receptor (GRPR) and somatostatin receptor subtype 2 (SSTR2), respectively. Following incubation unbound radioligands were removed and slides were exposed to super-resolution phosphor screens (Perkin Elmer) for 72 h and read using the cyclone (Perkin Elmer). Tissue sections of PC3 xenografts (GRPR-positive, SSTR2-negative) and H69

xenografts (SSTR2-positive, GRPR-negative) were used as positive and negative controls (*9,10*). Autoradiography results of the tumor containing areas of the tissue sections were quantified using OptiQuant Software (Perkin Elmer) and expressed as digital light units/mm^2 (DLU/mm^2). Specific binding was determined by subtracting DLU/mm^2 of blocked tissue sections from the DLU/mm^2 of the unblocked tissue sections. Standards containing a known amount of the added radiotracer solution were also quantified and used to determine the percentage of added dose that was bound to the tumors. In addition, hematoxylin and eosin (H&E) staining was performed on adjacent sections (5 μm) to determine tumor content of the sections.

Statistics

For the analyses the STATA statistical package v,11 and v13,1 and IBM statistics SPSS version 21 were used. Differences in continuous levels were assessed with the Mann-Whitney U test and between categorized variables with the Fisher Exact Probability Test, both using patient and tumor characteristics as grouping variables. The strength of associations between continuous variables were tested with the Spearman rank correlation (Rs). Univariate and multivariate Cox regression was used to analyze the association between clinico-pathological factors and *GRPR*, *SSTR2* and c-x-c chemokine receptor 4 (*CXCR4*) mRNA expression with disease-free, metastasis-free, and overall survival (DFS, MFS and OS, respectively) and with MFS, respectively. A Cox proportional hazard model was used to calculate the hazard ratios (HRs) and the 95% confidence interval (95% CI) of variables and in multivariate analysis adjusted for covariates in the analyses of MFS. For the multivariate Cox regression analysis the log-transformed continuous levels of the receptors was separately introduced in the base multivariate model that included the following factors: age, menopausal status, pathological tumor size, genomic grade index (GGI) and *ESR1*, *PGR* and *ERBB2* mRNA levels.

Survival curves were constructed from MFS and progression free survival (PFS) data using the Kaplan-Meier estimator for survival. The logrank rest was used to test for differences. All P-values are two-sided and $P<0.05$ was considered statistically significant.

SUPPLEMENTAL RESULTS

GRPR, _SSTR2_ and _CXCR4_ Associations with Clinico-pathological, Biological Factors and Prognosis in M0 LNN and LNP Patients

Supplemental Table 1A displays the correlation of *GRPR*, *SSTR2* and *CXCR4* measured in the primary tumor with clinico-pathological and biological factors in the M0 patient group with LNN and LNP tumors. A representative group of M0 LNP patients was added to the study to investigate the influence of positive nodal status on the correlation of *GRPR*, *SSTR2* and *CXCR4* with clinco-pathological and biological factors.

Contrary to associations found in the LNN M0 patient group (Table 1), high *GRPR* mRNA expression was not associated with tumor size in the LNN and LNP M0 patient group. In addition, contrary to its association with favorable prognostic features (*ESR1* and *PGR* positivity, negative *ERBB2* and favorable GGI), higher *GRPR* mRNA levels were associated with LNP tumors.

Concerning *SSTR2* expression, contrary to the LNN patient group, *SSTR2* expression was not significantly correlated with *ERBB2* expression. Furthermore, there was a positive significant correlation with smaller pathological tumor size.

There were no differences in correlation of *CXCR4* expression with biological and clinical factors in the LNN M0 patient group and the LNN and LNP M0 patient group.

Supplemental Table 2 displays the association of *GRPR*, *SSTR2* and *CXCR4* in the systemic adjuvant therapy naive LNN patients.

No significant association was observed between *GRPR* and *SSTR2* mRNA levels and prognosis. However high CXCR4 mRNA levels were associated with favorable DFS, MFS and OS.

GRPR, _SSTR2_ and _CXCR4_ Associations with Clinico-pathological and Biological Factors; and Association with PFS After 1st Line Tamoxifen Treatment in the Cohort of _ESR1_-positive Breast Cancer Patients with Recurrent Disease That Received 1st Line Tamoxifen Treatment

Supplemental Table 1B displays the association of *GRPR*, *SSTR2* and *CXCR4* measured in the primary tumor with biological and clinical factors in the cohort that received 1st line tamoxifen treatment. Within this cohort *GRPR* showed significant positive associations with *PGR*, *ERBB2* and GGI. *SSTR2* expression showed a significant positive association with *PGR* expression and high *CXCR4* mRNA levels were associated with ≤70% invasive tumor cells.

Supplemental Table 3 displays the association of *GRPR* mRNA levels and PFS on 1st line tamoxifen treatment. High *GRPR* mRNA levels were associated with a prolonged PFS after this type of treatment.

Supplemental Table 1A. Associations of *GRPR*, *SSTR2* and *CXCR4* mRNA levels in LNN and LNP M0 patients

Characteristic	No of patients*		GRPR mRNA (x10^{-2}) Median	GRPR mRNA (x10^{-2}) Interquartile range	SSTR2 mRNA (x10^{-2}) Median	SSTR2 mRNA (x10^{-2}) Interquartile range	CXCR4 mRNA (x10^{-2}) Median	CXCR4 mRNA (x10^{-2}) Interquartile range
All patients in this cohort	**878**	**100%**	**1.09**	**8.25**	**0.61**	**1.79**	**11.49**	**12.85**
Age at surgery (years)								
≤40	78	9%	1.52	12.48	0.78	3.02	14.06	13.17
41-55	319	36%	1.26	9.10	0.61	1.66	11.31	13.00
56-70	290	33%	0.71	7.20	0.54	1.86	11.78	11.39
>70	191	22%	1.09	6.92	0.63	1.60	10.46	12.46
P[†]			*0.63*		*0.62*		*0.12*	
Menopausal status								
Premenopausal	347	40%	1.47	10.94	0.65	1.90	11.60	13.84
Postmenopausal	531	60%	0.90	6.65	0.57	1.57	11.38	12.07
P[†]			*0.12*		*0.17*		*0.31*	
Surgery								
Lumpectomy	419	48%	0.70	8.40	0.62	1.87	11.67	13.13
Ablation	459	52%	1.19	8.02	0.59	1.60	11.33	12.26
P[†]			*0.24*		*1.00*		*0.33*	
Pathological tumor size								
pT1	336	38%	1.27	8.68	0.69	1.85	11.95	13.18
pT2+unknown	479	55%	0.99	7.93	0.59	1.93	11.19	12.63
pT3 + pT4	63	7%	0.90	8.25	0.41	0.92	11.37	12.10
P[†]			*0.10*		***0.0411***		*0.48*	
Nodal status (positive nodes)								
LNN	684	78%	0.72	7.07	0.58	1.75	11.78	13.13
LNP (1 to 3)	87	10%	4.14	11.73	0.84	3.12	9.91	9.64
LNP (>3 or N=2 and >0)	107	12%	2.25	8.96	0.64	1.47	10.90	12.73
P[†]			***0.0001***		*0.19*		*0.05*	
ESR1 mRNA status[‡]								
Negative < 0.2	214	24%	0.09	0.14	0.31	0.40	14.68	13.93
Positive ≥ 0.2	664	76%	3.28	11.28	0.82	2.58	10.74	11.26
P[§]			***< 0.001***		***< 0.001***		***< 0.001***	
PGR mRNA status[‡]								
Negative < 0.1	348	40%	0.13	0.47	0.34	0.65	13.97	14.27
Positive ≥ 0.1	529	60%	4.31	12.48	0.94	2.96	10.39	10.93
P[§]			***< 0.001***		***< 0.001***		***< 0.001***	
ERBB2 mRNA status[‡]								
Negative < 18	736	84%	1.21	9.13	0.62	1.95	11.32	12.71
Positive ≥ 18	138	16%	0.33	3.73	0.50	1.04	13.28	12.75
P[§]			***0.0004***		*0.09*		*0.26*	
Grade (GGI)								
1	292	33%	3.66	11.86	0.76	2.25	9.90	10.57
2	289	33%	1.10	7.60	0.63	2.43	11.12	13.81
3	289	33%	0.18	2.67	0.38	1.10	13.76	13.46

	P[§]			***< 0.001***		***< 0.001***		***< 0.001***	
% Invasive tumor cells									
≤ 70%		374	43%	1.19	7.90	0.63	1.89	13.01	13.92
> 70%		504	57%	1.03	8.57	0.55	1.71	10.44	11.50
	P[†]			*0.89*		***0.0377***		***< 0.001***	

** Due to missing numbers not all categories add up to 878.*

† P for Mann-Whitney U or Kruskal-Wallis test when appropriate.

‡ ESR1, PGR and ERBB2 were determined by real-time PCR, cut point were as follows ESR1=0.2, PGR=0.1 and ERBB2=18.0 (mRNA level relative to reference gene set).

§ P for Spearman rank correlation test.

Supplemental Table 1B. Associations of *GRPR*, *SSTR2* and *CXCR4* mRNA levels in patients that received 1st line tamoxifen treatment

Characteristic	No of patients*		GRPR mRNA ($x10^{-2}$) Median	GRPR mRNA ($x10^{-2}$) Interquartile range	SSTR2 mRNA ($x10^{-2}$) Median	SSTR2 mRNA ($x10^{-2}$) Interquartile range	CXCR4 mRNA ($x10^{-2}$) Median	CXCR4 mRNA ($x10^{-2}$) Interquartile range
All patients in this cohort	224	100%	2.38	9.01	0.68	2.51	8.79	9.12
Age at primary surgery (years)								
≤50	68	30%	2.63	9.82	1.40	3.00	8.48	7.97
>50	156	70%	2.22	8.31	0.53	2.35	8.79	9.41
P†			*0.81*		***0.005***		*0.70*	
Menopausal status at primary surgery								
Premenopausal	26	12%	4.97	16.48	1.32	3.22	5.50	8.86
Postmenopausal	167	75%	2.31	9.21	0.58	2.47	8.81	9.64
P†			*0.59*		***0.028***		*0.36*	
Age at start 1st line tamoxifen (years)								
≤50	54	24%	2.38	11.92	1.23	2.90	7.51	8.03
>50	170	76%	2.37	8.16	0.62	2.37	8.82	9.42
P†			*0.88*		***0.047***		*0.38*	
Surgery primary tumor								
Lumpectomy	86	38%	2.36	7.57	1.00	2.56	8.89	8.71
Ablation	138	62%	2.39	9.34	0.64	2.45	8.56	9.37
P†			*0.38*		*0.39*		*0.72*	
Pathological tumor size								
pT1	60	27%	1.27	4.73	0.77	2.70	8.48	9.29
pT2	130	58%	3.06	10.49	0.77	3.12	8.33	8.03
pT3 + pT4	28	13%	1.17	6.54	0.56	1.03	10.45	12.30
P†			*0.13*		*0.13*		*1.00*	
Nodal status (positive nodes)								
LNN	101	45%	1.53	7.45	0.71	2.60	8.34	8.82
LNP (1 to 3)	74	33%	4.33	10.28	0.70	2.47	9.41	8.79
LNP (>3 or N=2 and >0)	36	16%	3.01	8.96	0.71	2.57	8.81	11.57
P†			*0.24*		*0.99*		*0.76*	
M-stage primary tumor								
M0 no distant metastases	200	89%	2.24	8.42	0.74	2.63	8.35	8.87
M1 distant metastases	24	11%	4.51	10.96	0.42	1.76	10.46	9.38
P†			*0.53*		*0.36*		*0.41*	
ESR1 mRNA status primary tumor‡								
Negative < 0.2	0	0%						
Positive ≥ 0.2	224	100%	2.38	9.01	0.68	2.51	8.79	9.12
P†								
PGR mRNA status primary tumor‡								
Negative < 0.1	55	25%	0.58	1.82	0.32	1.66	8.83	9.58
Positive ≥ 0.1	169	75%	4.16	10.16	0.85	2.77	8.35	8.60
P§			***< 0.001***		***< 0.001***		*0.09*	

ERBB2 mRNA status primary tumor‡									
Negative < 18		191	85%	2.79	9.79	0.67	2.66	8.31	9.41
Positive ≥ 18		33	15%	0.69	4.52	0.68	1.68	10.40	9.66
	P§			***0.002***		*0.58*		*0.31*	
Grade (GGI)									
1		75	33%	1.09	6.03	0.46	1.78	8.83	8.79
2		72	32%	2.04	6.47	1.20	3.24	9.83	9.78
3		73	33%	4.07	10.58	0.72	2.93	7.66	8.04
	P§			***0.022***		*0.16*		*0.16*	
% Invasive tumor cells									
≤ 70%		86	38%	3.00	8.20	0.63	2.26	11.33	9.31
> 70%		138	62%	1.96	9.80	0.72	2.79	7.48	7.64
	P†			*0.78*		*0.85*		***0.001***	
Adjuvant systemic therapy									
None		191	85%	2.12	7.71	0.68	2.60	8.34	9.37
Chemotherapy		33	15%	4.48	14.02	0.57	1.67	10.42	9.31
Endocrine therapy		0							
	P†			*0.18*		*0.86*		*0.38*	
Disease free interval (years)									
≤ 1		60	27%	1.61	6.67	0.53	1.83	8.83	10.67
1- 3		100	45%	3.15	9.77	0.73	2.58	8.13	7.76
> 3		64	29%	1.29	8.59	0.92	3.38	9.23	10.39
	P†			*0.58*		*0.31*		*0.77*	
Dominant site of relapse									
Soft		21	9%	6.24	12.06	0.64	2.85	7.53	10.65
Bone		120	54%	2.53	7.75	0.77	2.29	8.79	7.32
Viscera		83	37%	1.59	8.38	0.45	2.83	9.49	10.67
	P†			*0.32*		*0.47*		*0.96*	

** Due to missing numbers not all categories add up to 224.*

† P for Mann-Whitney U or Kruskal-Wallis test when appropriate.

‡ ESR1, PGR and ERBB2 were determined by real-time PCR, cut points were as follows ESR1=0.2, PGR=0.1 and ERBB2=18.0 (mRNA level relative to reference gene set).

§ P for Spearman rank correlation test.

Supplemental Table 2. Cox univariate and multivariate analysis for DFS, MFS and OS in LNN patients

Factor	No. of patients*	Univariate DFS analysis HR	95% CI		*P*	Univariate MFS analysis HR	95% CI		*P*	Univariate OS analysis HR	95% CI		*P*	Multivariate MFS analysis† HR	95% CI		*P*
	684													**Base model (n=677)**			
Age at surgery (years)																	
≤40	60	1				1				1				1			
41-55	252	0.65	0.45	0.95	***0.027***	0.87	0.56	1.34	*0.53*	0.90	0.56	1.43	*0.65*	0.87	0.56	1.36	*0.55*
56-70	218	0.57	0.39	0.85	***0.005***	0.77	0.49	1.20	*0.25*	0.90	0.56	1.46	*0.68*	0.74	0.38	1.44	*0.38*
>70	154	0.59	0.39	0.91	***0.015***	0.74	0.46	1.20	*0.22*	1.17	0.71	1.93	*0.54*	0.70	0.34	1.41	*0.31*
Menopausal status																	
Premenopausal	273	1				1				1				1			
Postmenopausal	411	0.83	0.65	1.05	*0.11*	0.87	0.67	1.12	*0.29*	1.14	0.87	1.49	*0.33*	1.08	0.65	1.79	*0.77*
Pathological tumor size																	
pT1	307	1				1				1				1			
pT2+unknown	351	1.40	1.10	1.78	***0.007***	1.34	1.03	1.74	*0.031*	1.43	1.09	1.88	***0.011***	1.29	0.99	1.69	*0.06*
pT3 + pT4	26	1.94	1.07	3.51	***0.030***	2.21	1.21	4.03	*0.010*	2.09	1.08	4.04	***0.028***	2.26	1.23	4.17	***0.009***
Grade (GGI)																	
1	227	1				1				1				1			
2	229	1.26	0.93	1.69	*0.13*	1.32	0.96	1.83	*0.09*	1.45	1.03	2.05	*0.04*	1.33	0.95	1.87	*0.10*
3	224	1.55	1.16	2.07	***0.003***	1.59	1.16	2.17	***0.004***	1.82	1.31	2.55	***<0.001***	1.73	1.18	2.53	***0.005***
ESR1 primary tumor																	
Negative < 0.2	184	1				1				1				1			
Positive ≥ 0.2	500	1.14	0.87	1.50	*0.33*	1.12	0.83	1.50	*0.46*	0.94	0.70	1.26	*0.67*	1.49	1.02	2.17	***0.038***
PGR primary tumor																	
Negative < 0.1	285	1				1				1				1			
Positive ≥ 0.1	399	0.90	0.71	1.14	*0.37*	0.95	0.73	1.22	*0.67*	0.79	0.61	1.03	*0.08*	1.03	0.73	1.45	*0.88*
ERBB2 primary tumor																	
Negative < 18	574	1				1				1				1			
Positive ≥ 18	107	1.31	0.98	1.77	*0.07*	1.30	0.94	1.79	*0.11*	1.38	1.00	1.93	*0.05*	1.20	0.86	1.67	*0.28*
														Additions to the base model			
GRPR primary tumor																	
Log-transformed continuous	684	1.01	0.96	1.06	*0.64*	1.00	0.96	1.06	*0.79*	0.97	0.92	1.02	*0.23*	‡			
GRPR primary tumor																	
50% low	342	1				1				1				‡			
50% high	342	1.12	0.89	1.42	*0.33*	1.06	0.83	1.37	*0.63*	0.87	0.67	1.13	*0.30*				
SSTR2 primary tumor																	
Log-transformed continuous	684	1.02	0.94	1.10	*0.70*	0.99	0.91	1.08	*0.80*	0.96	0.88	1.04	*0.32*	‡			

SSTR2 primary tumor																	
50% low	343	1				1				1				‡			
50% high	341	0.98	0.77	1.23	*0.83*	0.95	0.73	1.22	*0.66*	0.84	0.65	1.10	*0.21*				
CXCR4 primary tumor																	
Log-transformed continuous	684	0.82	0.70	0.95	*0.009*	0.80	0.68	0.94	*0.008*	0.76	0.64	0.90	***0.001***	0.76	0.64	0.90	***0.001***
CXCR4 primary tumor																	
50% low	342	1				1				1							
50% high	342	0.79	0.63	1.00	*0.049*	0.75	0.58	0.97	*0.028*	0.71	0.54	0.92	***0.011***	0.71	0.55	0.91	***0.011***

** Due to missing numbers, not all categories add up to 684.*

† Factors were separately introduced to the base multivariate model that included the following factors: age, menopausal status, pathological tumor size, GGI and ESR1, PGR and ERBB2 mRNA status.

‡ Multivariate MFS analysis was not performed since univariate data is not significant.

Supplemental Table 3. Cox univariate and multivariate analysis for PFS on 1st line tamoxifen treatment

Factor	No. of patients	Univariate analysis HR	95% CI		*P*	Multivariate analysis HR	95% CI		*P*
	224					**Base model**			
Age at start 1st line tamoxifen (years)									
≤ 50	54	1			*0.11*	1			*0.68*
50-70	112	0.83	0.59	1.16		0.99	0.67	1.45	
> 70	58	0.65	0.44	0.97		0.84	0.53	1.35	
Disease free interval (years)									
≤ 1	60	1			***<0.001***	1			***<0.001***
1-3	100	0.56	0.40	0.78		0.50	0.35	0.71	
> 3	64	0.44	0.30	0.64		0.40	0.27	0.59	
Dominant site of relapse									
Soft	21	1			*0.27*	1			***0.043***
Bone	120	1.49	0.88	2.52		2.05	1.17	3.60	
Viscera	83	1.28	0.75	2.21		1.92	1.07	3.46	
ESR1 primary tumor									
Log-transformed continuous	224	0.82	0.75	0.9	***<0.001***	0.85	0.76	0.95	***0.005***
PGR primary tumor									
Log-transformed continuous	224	0.91	0.85	0.97	***0.005***	0.94	0.87	1.02	*0.12*
ERBB2 primary tumor									
Negative, < 18	191	1			***0.003***	1			***0.046***
Positive, ≥ 18	33	1.78	1.22	2.6		1.56	1.01	2.41	
Adjuvant chemotherapy									
No	191	1			*0.41*	1			*0.68*
Yes	33	1.18	0.80	1.73		1.10	0.71	1.70	
						Additions to the base model*			
GRPR primary tumor									
Log-transformed continuous	224	0.92	0.86	0.99	***0.030***	0.95	0.88	1.03	*0.22*
GRPR primary tumor									
1-75% low	168	1			***0.011***	1			***0.031***
25% high	56	0.65	0.47	0.91		0.68	0.48	0.97	
GRPR primary tumor									
25% low	56	1			*0.09*	1			*0.18*
25% intermediate-low	56	0.93	0.63	1.38		1.04	0.68	1.57	
25% intermediate-high	56	0.99	0.67	1.46		1.11	0.72	1.71	
25% high	56	0.63	0.42	0.94		0.72	0.47	1.11	

** Factors were separately introduced to the base multivariate model that included the following factors: age, disease free interval, dominant site of relapse, adjuvant chemotherapy and ESR1 and PGR mRNA levels and ERBB2 mRNA status.*

REFERENCES

1. Foekens JA, Portengen H, van Putten WL, et al. Prognostic value of estrogen and progesterone receptors measured by enzyme immunoassays in human breast tumor cytosols. *Cancer Res.* 1989;49:5823-5828.

2. Revision of the standards for the assessment of hormone receptors in human breast cancer; report of the second E.O.R.T.C. Workshop, held on 16-17 March, 1979, in the Netherlands Cancer Institute. *Eur J Cancer.* 1980;16:1513-1515.

3. Sieuwerts AM, Usher PA, Meijer-van Gelder ME, et al. Concentrations of TIMP1 mRNA splice variants and TIMP-1 protein are differentially associated with prognosis in primary breast cancer. *Clin Chem.* 2007;53:1280-1288.

4. Van Agthoven T, Sieuwerts AM, Meijer-van Gelder ME, et al. Relevance of breast cancer antiestrogen resistance genes in human breast cancer progression and tamoxifen resistance. *J Clin Oncol.* 2009;27:542-549.

5. Toussaint J, Sieuwerts AM, Haibe-Kains B, et al. Improvement of the clinical applicability of the Genomic Grade Index through a qRT-PCR test performed on frozen and formalin-fixed paraffin-embedded tissues. *BMC Genomics.* 2009;10:424.

6. Sieuwerts AM, Lyng MB, Meijer-van Gelder ME, et al. Evaluation of the ability of adjuvant tamoxifen-benefit gene signatures to predict outcome of hormone-naive estrogen receptor-positive breast cancer patients treated with tamoxifen in the advanced setting. *Mol Oncol.* 2014;8:1679-1689.

7. Sieuwerts AM, Meijer-van Gelder ME, Timmermans M, et al. How ADAM-9 and ADAM-11 differentially from estrogen receptor predict response to tamoxifen treatment in patients with recurrent breast cancer: a retrospective study. *Clin Cancer Res.* 2005;11:7311-7321.

8. Therasse P, European Organisation for R, Treatment of Cancer Data C. Evaluation of response: new and standard criteria. *Ann Oncol.* 2002;13 Suppl 4:127-129.

9. Taylor JE, Theveniau MA, Bashirzadeh R, Reisine T, Eden PA. Detection of somatostatin receptor subtype 2 (SSTR2) in established tumors and tumor cell lines: evidence for SSTR2 heterogeneity. *Peptides.* 1994;15:1229-1236.

10. Schroeder RP, de Visser M, van Weerden WM, et al. Androgen-regulated gastrin-releasing peptide receptor expression in androgen-dependent human prostate tumor xenografts. *Int J Cancer.* 2010;126:2826-2834.