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CLINICAL TRIAL

Outcome after neoadjuvant chemotherapy in estrogen receptor-positive and progesterone receptor-negative breast cancer patients: a pooled analysis of individual patient data from ten prospectively randomized controlled neoadjuvant trials

Marion T. van Mackelenbergh[1,4] · Carsten Denkert[2] · Valentina Nekljudova[1] · Thomas Karn[3] · Christian Schem[4] · Frederik Marmé[5] · Elmar Stickeler[6] · Christian Jackisch[7] · Claus Hanusch[8] · Jens Huober[9] · Peter A. Fasching[10] · Jens-Uwe Blohmer[2] · Sherko Kümmel[11] · Volkmar Müller[12] · Andreas Schneeweiss[5] · Michael Untch[13] · Gunter von Minckwitz[1] · Karsten E. Weber[1] · Sibylle Loibl[1]

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Abstract

Purpose The estrogen receptor (ER) is involved in control of progesterone receptor (PgR) expression and lack of PgR may be also a surrogate of altered growth factor signaling. The aim of this study was therefore to investigate PgR expression as predictive factor for response to neoadjuvant therapy and long-term outcome.

Methods Five thousand and six hundred and thirteen patients with primary breast cancer and positive ER expression from ten German neoadjuvant trials of anthracycline and taxane-based chemotherapy were included. Pathologic complete response (pCR), disease-free survival (DFS), distant disease-free survival (DDFS), overall survival (OS), and local recurrence-free survival (LRFS) were compared according to PgR expression.

Results The lack of PgR expression (1172 patients) was associated with grade 3 (38.4 vs. 26.3%; $p < 0.001$), nodal involvement (>cN2) (6.8% vs. 4.7%; $p = 0.004$), and HER2 positivity (36.2 vs. 22.3%; $p < 0.001$). pCR rates of PgR-negative tumors were higher in the entire cohort (13.8 vs. 7.5%; $p < 0.001$) and in the HER2-negative subgroup (11.2 vs. 5.8%; $p < 0.001$). In multivariable logistic regression, PgR negativity was an independent predictive factor for pCR overall (OR 1.76; $p < 0.001$) and in the HER2-negative patients (OR 1.99; $p < 0.001$). Patients with PgR-negative disease had significantly worse outcome ($p < 0.001$, respectively). Multivariable Cox regression analysis revealed that PgR was an independent prognostic factor for DFS, OS, DDFS, and LRFS.

Conclusion ER-positive/PgR-negative breast carcinomas are associated with higher response but also worse long-term outcome after neoadjuvant therapy. PgR negativity is an independent predictive factor for pCR after neoadjuvant chemotherapy in ER-positive HER2-negative breast cancer.

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✉ Marion T. van Mackelenbergh
marion.vanmackelenbergh@gbg.de

[1] German Breast Group, c/o GBG Forschungs GmbH, Martin-Behaim-Straße 12, 63263 Neu-Isenburg, Germany

[2] Charite Berlin, Institute of Pathology and German Cancer Consortium (DKTK), Partner Site, Berlin, Germany

[3] Universitätsklinikum Frankfurt, Frankfurt, Germany

[4] Universitätsklinikums Schleswig-Holstein Kiel, Kiel, Germany

[5] Universitätsklinikum Heidelberg, Heidelberg, Germany

[6] Universitätsklinikum Aachen, Aachen, Germany

[7] Sana Klinikum Offenbach, Offenbach, Germany

[8] Universitätsklinikum München, Munich, Germany

[9] Universitätsklinikum Ulm, Ulm, Germany

[10] Department of Gynecology and Obstetrics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany

[11] Kliniken Essen Mitte, Essen, Germany

[12] Universitätsklinikum Hamburg, Hamburg, Germany

[13] Helios Kliniken Berlin-Buch, Berlin, Germany

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Introduction

The estrogen receptor (ER) is a member of the nuclear transcription factor family. Upon binding of estrogen, it forms dimers and binds either directly to estrogen response elements in the promoter region of target genes to alter the transcription of estrogen-sensitive genes including the progesterone receptor gene (*PGR*) [1]. This direct binding to estrogen response elements has been described as the classical function of the ER. However, the ER can also act as a coactivator of several other transcription factors. Despite its classical genomic or nuclear effects, the ER has been described to exert non-genomic effects by interacting with several cell signaling pathways that do not initially involve upregulation of gene transcription. These interaction partners of the ER comprise members of the HER family, PI3K, Akt, and src which exert their effects by phosphorylating the ER and leading to ligand-independent activation [2, 3]. For several of these interactions, a resulting increase in cell proliferation and tumorigenesis has been detected. These different patterns of action of the ER lead to the assumption that in tumors that utilize the non-genomic ER activity in order to stimulate tumorigenesis and proliferation PgR expression would be decreased or absent. Therefore, the lack of PgR expression could be a surrogate marker of altered growth factor signaling.

ER-positive and PgR-negative tumors have been described to represent a specific subset of breast cancers that comprises more aggressive features [4]. Among patients that were treated with endocrine therapy alone, PgR expression has been shown in a retrospective analysis to be an independent predictive factor for benefit from therapy [5]. On the other hand, in the trials comparing tamoxifen with an aromatase inhibitor the PgR status did not identify patients with a relative greater benefit from the aromatase inhibitor over tamoxifen [6, 7]. In order to classify breast cancer intrinsic subtypes by immunohistochemistry, Prat et al. [8] used a 20% cutoff of PgR expression in addition to ER, HER2, and Ki67 expression to differentiate luminal A from B tumors and predict benefit from endocrine therapy alone.

Only limited data exist of ER-positive breast cancer patients lacking PgR expression on response to neoadjuvant chemotherapy and long-term outcome. Therefore, the aim of this study was to address this issue in a large cohort of 5613 prospectively treated breast cancer patients and compare chemotherapy response and long-term outcome in patients with hormone receptor-positive tumors with or without PgR expression.

Materials and methods

Patients

Patients participating in ten prospectively randomized trials conducted in Germany studying neoadjuvant systemic therapy in operable and non-operable primary breast cancer were eligible for these analyses.

An overview of the Gepardo trial [9], GeparDuo [NCT00793377, www.clinicaltrials.gov] [10], GeparTrio pilot [11] and main study [NCT00544765] [12, 13], GeparQuattro [NCT00288002] [14], AGO 1 [not registered] [15], Prepare [NCT00544232] [16, 17], and Techno [NCT00795899] has been previously published [18, 19]. In addition, patients participating in the GeparQuinto trial [NCT00567554] [20, 21] and GeparSixto trial [NCT01426880] [22] were as well included. Written informed consent for study participation and data collection was obtained from all patients and all trials were approved by the respective ethics committees.

Main eligibility criteria [20, 21, 23] were comparable in the aforementioned trials and all of them used an anthracycline and taxane-based chemotherapy backbone. Patients included in the analysis had available information on ER and PgR status at baseline (in the majority centrally determined). The cutoff for PgR expression was set at 1%. Patients with missing information on hormone receptor status and negative ER expression were excluded. For survival analyses, patients with missing follow-up data were excluded. Anti-HER2 treatment was administered to all patients with HER2-positive disease as part of the (neo)adjuvant therapy within the TECHNO, GeparQuattro, GeparQuinto, and GeparSixto study. All patients with ER- and/or PgR-positive tumors received adjuvant endocrine treatment for at least 5 years according to the AGO-breast commission guidelines [24]. Conventional adjuvant radiotherapy was recommended as outlined in the AGO-breast commission guidelines [25].

Objectives and endpoints

The aim of this study was to analyze if baseline characteristics, and response to and outcome after neoadjuvant chemotherapy differ in patients with negative PgR status compared to patients with positive PgR status in ER-positive breast cancer. The primary objective was to compare survival data (disease-free survival (DFS)) overall and in subgroups defined by HER2 status and grading. In addition, we assessed the effect of PgR expression on overall

survival (OS), locoregional recurrence-free survival (LRFS), distant disease-free survival (DDFS), and pathologic complete response (pCR), overall and in subgroups defined by HER2 status and grading.

DFS was defined as time in months from randomization to relapse either local or distant, secondary malignancy, or death irrespective of the underlying reason. Pathological complete response was defined in accordance with current FDA recommendations as ypT0 ypN0 (no microscopic evidence of residual viable tumor cells invasive or non-invasive) in any resected specimens of the breast and axillary nodes [26].

Statistics

From overall 9785 patients participating in these trials, individual data of baseline characteristics, histo-pathological results at surgery, and follow-up were extracted for this combined analysis from the original data bases. As defined in the protocols, patients with missing data on histopathological response were counted as having no pCR.

Baseline parameters, type of surgery, and pCR were compared between PgR-positive and PgR-negative patients using cross-tables and two-sided Pearson χ^2 test. Time-to-event parameters were analyzed using the Kaplan–Meier product-limit method and compared between groups using the log-rank test. Univariable and multivariable Cox proportional hazards regression analyses were performed to calculate hazard ratios (HR) and 95% CI for PgR status and covariates. Odds ratios for pCR as well as 95% CI and corresponding p values were calculated using multivariable logistic regression analysis. All reported p values are two-sided, and $p \leq 0.05$ was considered statistically significant. No adjustment for multiple comparisons has been made. SPSS, Version 22 for windows (IBM, Armonk, NY, USA) was utilized to perform the analyses.

Results

In total, 5613 patients participating in the aforementioned 10 neoadjuvant trials showed positive ER expression and had available PgR status. 1172 (20.9%) of these were lacking PgR expression. Breast cancer patients with the absence of PgR expression were more likely to be diagnosed with tumors of higher grade both overall ($p < 0.001$) and in the subgroups defined by HER2 status ($p < 0.001$ for HER2 negative and $p = 0.022$ for HER2 positive) (Table 1). Moreover, they tended to have a clinical nodal involvement ($p = 0.004$). PgR-negative tumors were in comparison to PgR expressing tumors more likely to demonstrate HER2 positivity ($p < 0.001$) (Table 1). Regarding the patients' age, PgR negativity tended to occur more frequently in patients 50 years and older, which resulted in patients being more often postmenopausal, overall and in subgroups defined by HER2 (Table 1).

Analyses of time-to-event endpoints

During a median follow-up period of 62 (0–147) months, 1062 relapses (18.9%), 312 (5.6%) locoregional recurrences, 926 distant events (16.5%), and 612 (10.9%) deaths were observed.

Survival analyses demonstrated that women with ER-positive and PgR-negative primary breast cancer receiving neoadjuvant chemotherapy had a significantly higher risk of relapse than patients with PgR-positive tumors (PgR− vs. PgR+: adj. HR 1.456, CI 1.261–1.680, $p < 0.001$) (Table 2). Similarly, this significant survival disadvantage for patients with PgR-negative tumors could be observed for overall survival (OS) (PgR− vs. PgR+: adj. HR 1.575, CI 1.309–1.895, $p < 0.001$), DDFS (PgR− vs. PgR+: adj. HR 1.467, CI 1.260–1.709, $p < 0.001$), and LRFS (PgR− vs. PgR+: adj. HR 1.625, CI 1.255–2.106, $p < 0.001$) (Fig. 1, Table 2). Patients lacking PgR expression of their tumors combined with negative HER2 status had a significantly worse DFS (PgR− vs. PgR: adj. HR 1.580, CI 1.306–1.912, $p < 0.001$), OS (PgR− vs. PgR+: adj. HR 1.801, CI 1.406–2.308, $p < 0.001$), DDFS (PgR− vs. PgR+: adj. HR 1.592, CI 1.299–1.950, $p < 0.001$ and LRFS (PgR− vs. PgR+: adj. HR 1.517, CI 1.070–2.151, $p = 0.019$) (Fig. 2, Table 2). This could also be observed in the HER2-positive subgroup (Supplemental Figure 1) (Table 2). Interestingly, in patients with ER- and HER2-positive tumors who did not achieve a pCR, negative PgR expression segregated patients with a worse prognosis regarding OS, DFS, DDFS, and LRFS (Fig. 3). A significantly worse survival of PgR-negative patients was also seen in HER2-negative tumors of grades 1 and 2 for DFS, OS, DDFS, and LRFS (Table 2). If ER-positive, HER2-negative and PgR-negative tumors were compared to triple-negative breast cancer (TNBC) regarding their long-term outcome, ER-positive breast cancer lacking PgR expression still demonstrated significantly longer DFS, OS, DDFS, and LRFS periods than TNBC (Supplemental Figure 2).

After adjustment for known prognostic factors in the multivariable Cox regression analysis, PgR status was an independent prognostic factor for local and distant recurrence as well as overall survival in the entire cohort and in subgroups defined by HER2 status and grading (Table 2).

Women with ER-positive and PgR-negative tumors not achieving a pCR (ypT0 ypN0) had a worse DFS, OS, and DDFS, but not LRFS compared to women with pCR (Fig. 4).

Table 1 Baseline characteristics

	ER+ $N = 5613$			p value between PgR groups	ER+ HER2− $N = 3305$		p value between PgR groups	ER+ HER2+ $N = 1117$		p value between PgR groups
	All patients N Valid (%)	PgR− N Valid (%)	PgR+ N Valid (%)		PgR− N Valid (%)	PgR+ N Valid (%)		PgR− N Valid (%)	PgR+ N Valid (%)	
Tumor stage	–	–	–	0.304	–	–	0.094	–	–	0.571
cT1	403	87	316	–	39	209	–	38	71	–
	7.2%	7.5%	7.2%	–	6.6%	7.8%	–	11.2%	9.2%	–
cT2	3559	744	2815	–	388	1699	–	203	482	–
	63.9%	63.8%	63.9%	–	65.2%	63.1%	–	60.1%	62.6%	–
cT3	919	181	738	–	83	433	–	47	116	–
	16.5%	15.5%	16.8%	–	13.9%	16.1%	–	13.9%	15.1%	–
cT4a-c	407	82	325	–	44	225	–	25	59	–
	7.3%	7%	7.4%	–	7.4%	8.4%	–	7.4%	7.7%	–
cT4d	281	72	209	–	41	126	–	25	42	–
	5%	6.2%	4.7%	–	6.9%	4.7%	–	7.4%	5.5%	–
Missing	44	–	–	–	–	–	–	–	–	–
Nodal stage	–	–	–	**0.004**	–	–	**0.021**	–	–	0.125
cN0	2720	528	2192	–	264	1327	–	150	350	–
	49.3%	45.7%	50.2%		45.3%	49.7%	–	44.2%	46%	
cN1	2517	550	1967		279	1209	–	161	373	
	45.6%	47.6%	45.1%		47.9%	45.3%	–	47.5%	49%	
cN2	227	60	167	–	26	104	–	26	32	
	4.1%	5.2%	3.8%	–	4.5%	3.9%		7.7%	4.2%	
cN3	56	18	38	–	14	28		2	6	
	1.00%	1.6%	0.9%	–	2.4%	1%		0.6%	0.8%	
Missing	93	–	–	–	–	–	–	–	–	–
Histological type	–	–	–	**<0.001**	–	–	0.24	–	–	**0.006**
Ductal invasive	4351	950	3401	–	462	2051	–	310	667	–
	78%	81.1%	77.2%	–	77.3%	76.2%	–	91.2%	86.3%	–
Lobular invasive	901	142	759	–	95	490	–	13	72	–
	16.2%	12.1%	17.2%	–	15.9%	18.2%	–	3.8%	9.3%	–
Others	326	79	247	–	41	151	–	17	34	–
	5.8%	6.7%	5.6%	–	6.9%	5.6%	–	5%	4.4%	–
Missing	35	–	–	–	–	–	–	–	–	–
Tumor grade	–	–	–	**<0.001**	–	–	**<0.001**	–	–	**0.022**
1	283	38	245	–	28	161	–	5	26	
	5.2%	3.4%	5.7%	–	4.8%	6.1%	–	1.5%	3.5%	
2	3570	654	2916	–	333	1894	–	180	452	
	66%	58.2%	68%	–	57.2%	71.6%	–	54.9%	60.5%	
3	1557	431	1126	–	221	590	–	143	269	
	28.8%	38.4%	26.3%	–	38%	22.3%	–	43.6%	36%	
Missing	203	–	–	–	–	–	–	–	–	
HER2 status	–	–	–	**<0.001**	–	–	–	–	–	
Negative	3301	598	2703	–	–	–	–	–	–	
	74.7%	63.8%	77.7%	–	–	–	–	–	–	
Positive	1116	340	776	–	–	–	–	–	–	
	25.3%	36.2%	22.3%	–	–	–	–	–	–	
Missing	1196	–	–	–	–	–	–	–	–	

Table 1 continued

	ER+ $N = 5613$			p value between PgR groups	ER+ HER2− $N = 3305$		p value between PgR groups	ER+ HER2+ $N = 1117$		p value between PgR groups
	All patients N Valid (%)	PgR− N Valid (%)	PgR+ N Valid (%)		PgR− N Valid (%)	PgR+ N Valid (%)		PgR− N Valid (%)	PgR+ N Valid (%)	
Menopause status	–	–	–	**<0.001**	–	–	**<0.001**	–	–	**<0.001**
Premenopausal	2150	330	1820	–	188	1299	–	129	430	
	53.4%	39.8%	57%	–	37.2%	54.8%	–	44.6%	64.9%	
Postmenopausal	1875	500	1375	–	318	1071	–	160	233	
	46.6%	60.2%	43%	–	62.8%	45.2%	–	55.4%	35.1%	
missing	1588	–	–	–	–	–	–	–	–	
Age group	–	–	–	**<0.001**	–	–	**<0.001**	–	–	**<0.001**
<40	809	148	661	–	78	364	–	36	162	
	14.4%	12.6%	14.9%	–	13%	13.5%	–	10.6%	20.9%	
40–49	1956	308	1648	–	143	1005	–	106	319	
	34.9%	26.3%	37.2%	–	23.9%	37.2%	–	31.2%	41.1%	
≥50	2834	716	2118	–	377	1334	–	198	295	
	50.6%	61.1%	47.8%	–	63%	49.4%	–	58.2%	38%	
	0.2%		–	–	–	–	–	–	–	
Type of surgery	–	–	–	0.303	–	–	0.331	–	–	0.182
Breast conserving	3654	744	2910	–	358	1692		209	515	
	68%	66.7%	68.3%	–	63%	65.2%		64.5%	68.7%	
Mastectomy	1719	371	1348	–	210	904		115	235	
	32%	33.3%	31.7%	–	37%	34.8%		35.5%	31.3%	
Missing	240	–	–	–	–	–	–	–	–	
pCR (ypT0 ypN0)	–	–	–	**<0.001**			**<0.001**			0.117
No pCR	5106	1010	4096		531	2545		265	636	
	91.2%	86.2%	92.5%		88.8%	94.2%		77.9%	82%	
pCR	493	162	331		67	158		75	140	
	8.8%	13.8%	7.5%		11.2%	5.8%		22.1%	18%	
Missing	14									

p values determined by two-sided Pearson χ^2 test, statistically significant p values are indicated in bold

Analyses with pCR as endpoint

In hormone receptor-positive tumors, a pCR after neoadjuvant chemotherapy (ypT0 ypN0) was more likely to be achieved in PgR-negative tumors (Table 1). In the entire cohort, 13.8% of patients lacking PgR expression achieved a pCR compared to 7.5% in the PgR-positive group ($p < 0.001$). If patients were also selected for HER2 negativity, 11.2% of the PgR negative showed a pCR compared to 5.8% with PgR expression ($p < 0.001$). However, there was no significant difference in pCR rates in the HER2-positive subgroup (22.1 vs. 18%; p = 0.117).

After adjusting for known predictive factors and trial in the multivariable logistic regression analysis, PgR status was an independent predictive factor for increased pCR rate overall (OR 1.755; CI 1.407–2.189, $p < 0.001$) and in the HER2− group of patients (OR 1.992; CI 1.438–2.759, $p < 0.001$) (Fig. 5). If these HER2− patients were subgrouped by grading, grade 3 tumors showed a slightly higher odds ratio for achieving a pCR (OR 2.091; CI 1.300–3.361, $p = 0.002$).

As previously mentioned, PgR status not only predicted for an increased pCR rate, but also patients achieving a pCR had a significant survival benefit.

Table 2 Multivariable Cox regression analysis for DFS, DDFS, LRFS, and OS overall and in different biological subgroups (adjusted for age, pCR, tumor stage, nodal stage, histological type, and study)

	OS				DFS				DDFS				LRFS			
	HR	95% CI		*p* value	HR	95% CI		*p* value	HR	95% CI		*p* value	HR	95% CI		*p* value
ER+ $N = 5162$																
PgR+	1.00				1.00				1.00				1.00			
PgR−	1.575	1.309	1.895	<0.001	1.456	1.261	1.68	<0.001	1.467	1.26	1.709	<0.001	1.625	1.255	2.106	<0.001
ER+ HER2− $N = 3079$																
PgR+	1.00				1.00				1.00				1.00			
PgR−	1.801	1.406	2.308	<0.001	1.58	1.306	1.912	<0.001	1.592	1.299	1.95	<0.001	1.517	1.07	2.151	0.019
ER+ HER2+ $N = 1026$																
PgR+	1.00				1.00				1.00				1.00			
PgR−	2.192	1.424	3.373	<0.001	1.687	1.248	2.279	0.001	1.878	1.353	2.606	<0.001	1.727	1.077	2.769	0.023
ER+ HER2− G 1–2 $N = 2320$																
PgR+	1.00				1.00				1.00				1.00			
PgR−	1.703	1.234	2.35	0.001	1.656	1.308	2.098	<0.001	1.606	1.247	2.068	<0.001	1.848	1.199	2.847	0.005
ER+ HER2 − G 3 $N = 750$																
PgR+	1.00				1.00				1.00				1.00			
PgR−	1.954	1.305	2.926	0.001	1.398	1.006	1.943	0.046	1.526	1.075	2.164	0.018	1.133	0.615	2.087	0.688

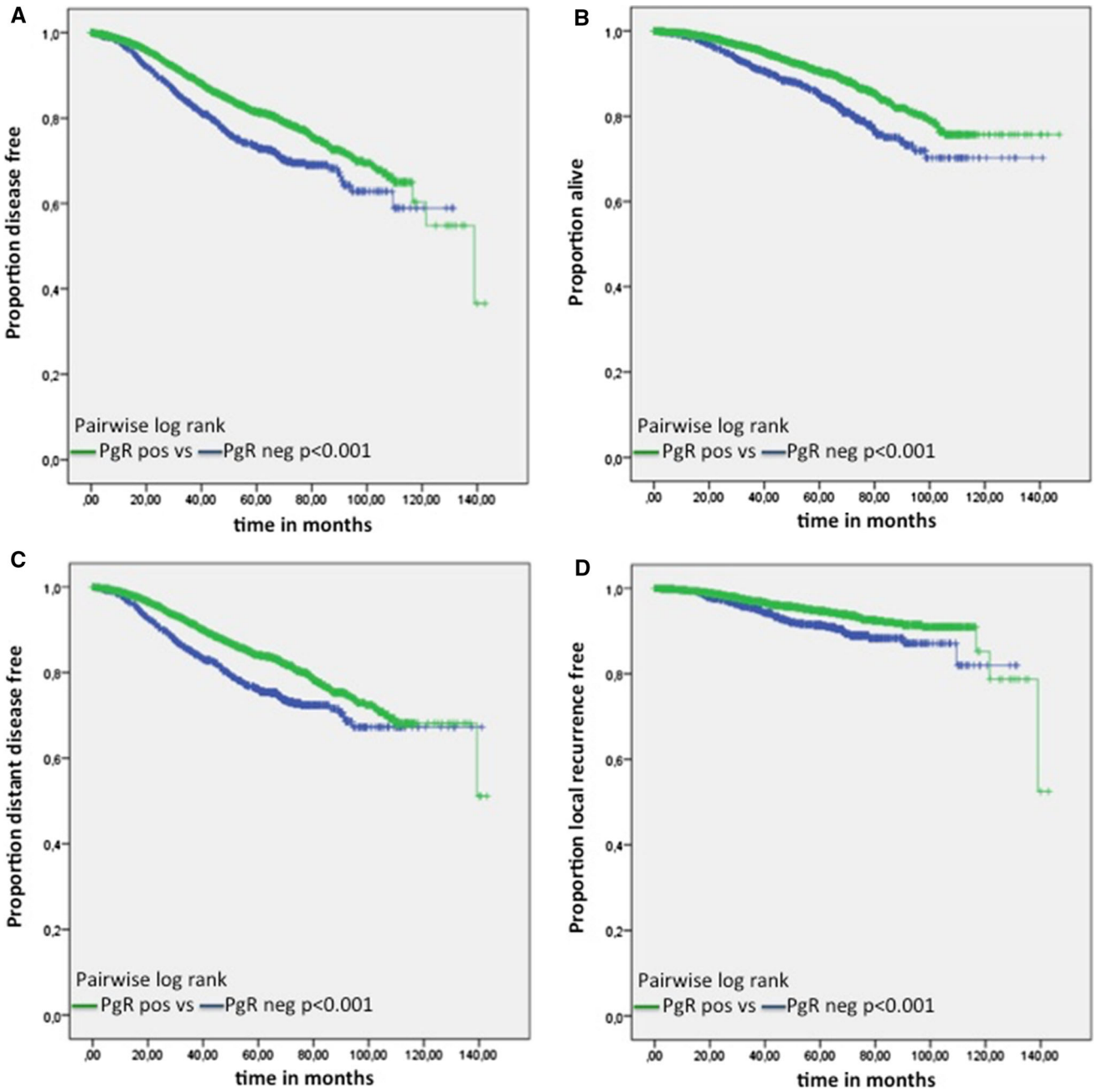

Fig. 1 Disease-free survival (DFS), overall survival (OS), distant disease-free survival (DDFS), and local recurrence-free survival (LRFS) in patients with ER-positive breast cancer with PgR positivity or negativity treated with neoadjuvant chemotherapy. **a** DFS, **b** OS, **c** DDFS, **d** LRFS

Discussion

In this retrospective study of 5613 patients, we observed that PgR expression in ER-positive primary breast cancer patients treated with neoadjuvant anthracycline and taxane-based chemotherapy is of prognostic relevance as patients lacking PgR expression suffer from worse outcome. In addition, we observed that PgR negativity predicts for a pCR after neoadjuvant chemotherapy in the HER2-negative subgroup. The importance of hormone receptor expression on outcome of breast cancer has long been recognized and influences therapeutic decisions of oncologists on a regular basis. It is well known that hormone receptor-positive breast cancer patients have a lower risk of recurrence and subsequent mortality [27]. Nevertheless, only few studies have focussed on the differences in outcome regarding PgR expression in hormone receptor-positive breast cancer [28–30] reporting a higher risk of mortality in PgR-negative patients. A retrospective pooled analysis of breast cancer trials

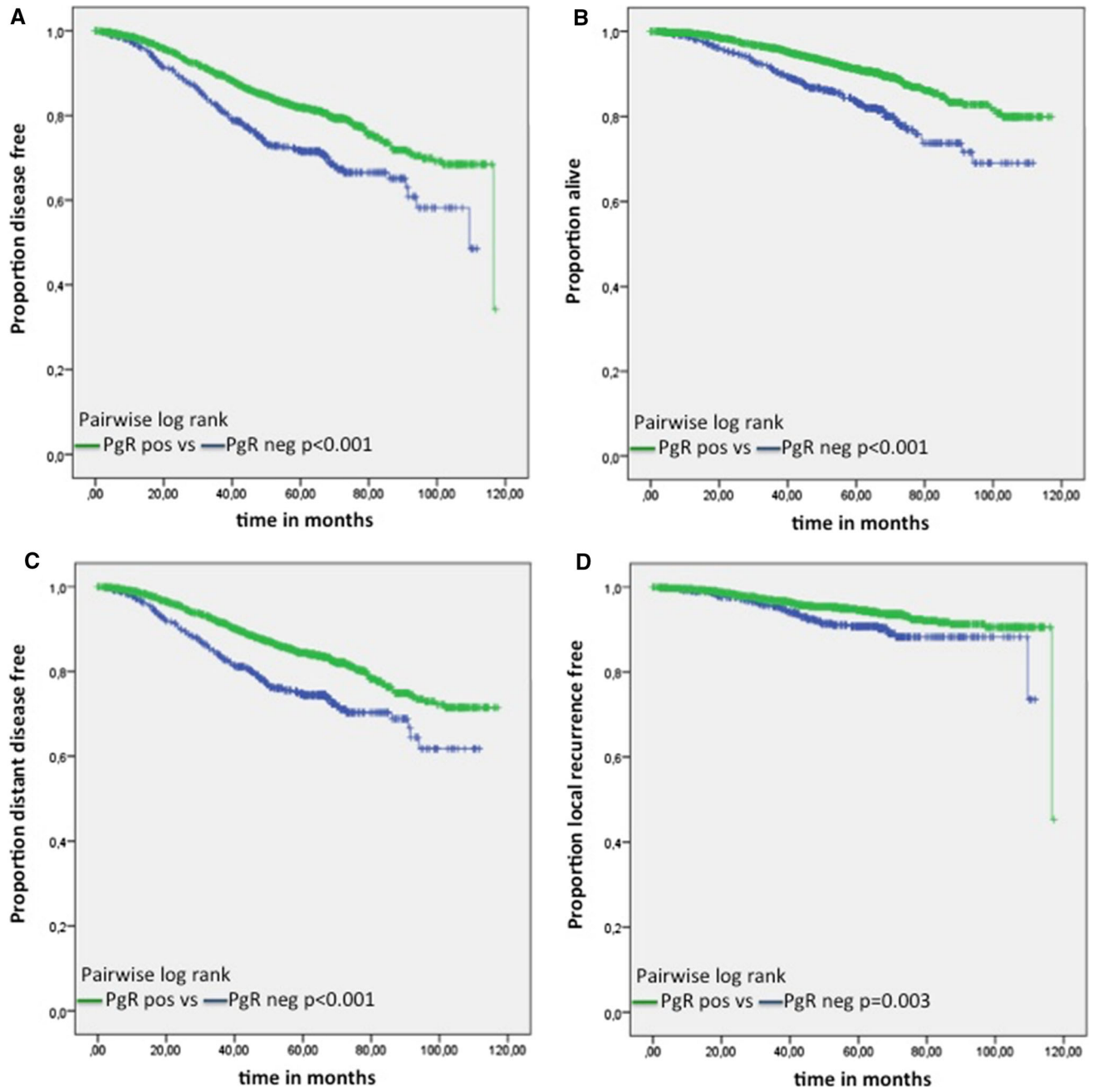

Fig. 2 Disease-free survival (DFS), overall survival (OS), distant disease-free survival (DDFS), and local recurrence-free survival (LRFS) in patients with ER-positive, HER2-negative tumors and PgR positivity or negativity treated with neoadjuvant chemotherapy. **a** DFS, **b** OS, **c** DDFS, **d** LRFS

described that PgR status can improve the prediction of patient outcome [31]. On the other hand, a recent study reported that an immunohistologically determined high PgR expression was more often detected in patients with favorable prognostic factors [8].

A predictive value of PgR expression on response to endocrine therapy has been investigated previously. Several studies have reported that the risk of recurrence after endocrine therapy with tamoxifen was independent of PgR expression and ER status was the only predictive factor [32, 33]. Moreover, the PgR expression status had no effect on the superior efficacy of an aromatase inhibitor over tamoxifen in early breast cancer patients [6, 34]. Regarding the prediction which patients benefit from chemotherapy, it has been reported in several trials that hormone receptor-negative patients obtain the greater benefit and are more likely to achieve a pCR in the neoadjuvant setting compared to hormone receptor-positive patients. In the

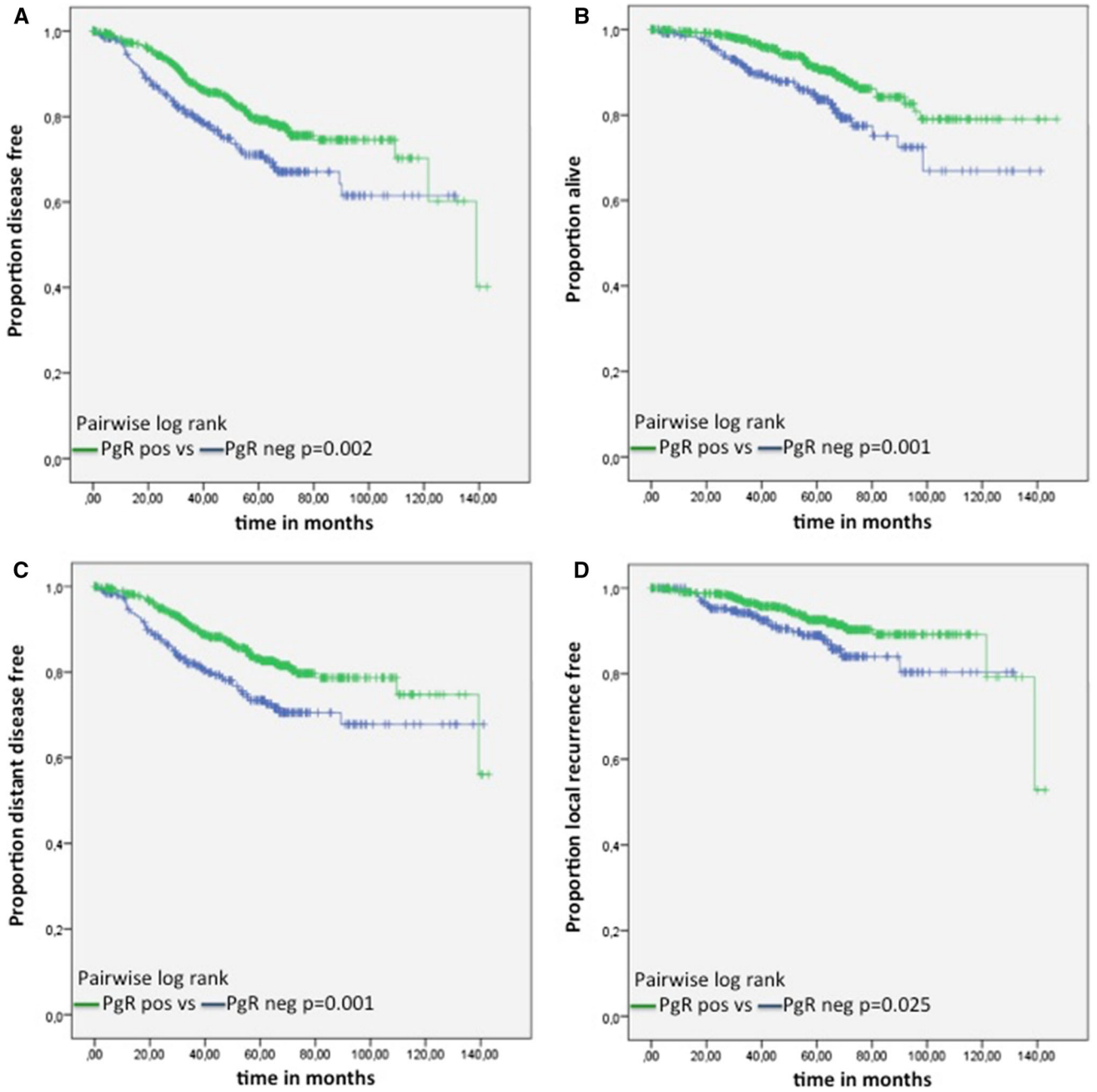

Fig. 3 Disease-free survival (DFS), overall survival (OS), distant disease-free survival (DDFS), and local recurrence-free survival (LRFS) in patients with ER-positive, HER2-positive, and PgR-positive or PgR-negative breast cancer treated with neoadjuvant chemotherapy who did not achieve a pCR. **a** DFS, **b** OS, **c** DDFS, **d** LRFS

adjuvant setting, data from randomized trials demonstrated that low or absent expression of ER and PgR was predictive for a benefit from adding chemotherapy to endocrine treatment, and in one trial low or absent PgR expression in ER-positive tumors predicted for an additional benefit from chemotherapy [7].

The here presented data including patients from ten neoadjuvant trials demonstrated that patients with ER-positive tumors lacking PgR expression suffered not only from worse recurrence free but also overall survival although having received neoadjuvant chemotherapy in addition to endocrine treatment. This suggests that the previously described poorer prognosis for PgR-negative tumors also prevails in this cohort of patients qualifying for neoadjuvant chemotherapy. Moreover, negative PgR status was in this cohort associated with several characteristics of more aggressive tumors like high grade and advanced nodal involvement. Interestingly, the expression of PgR has

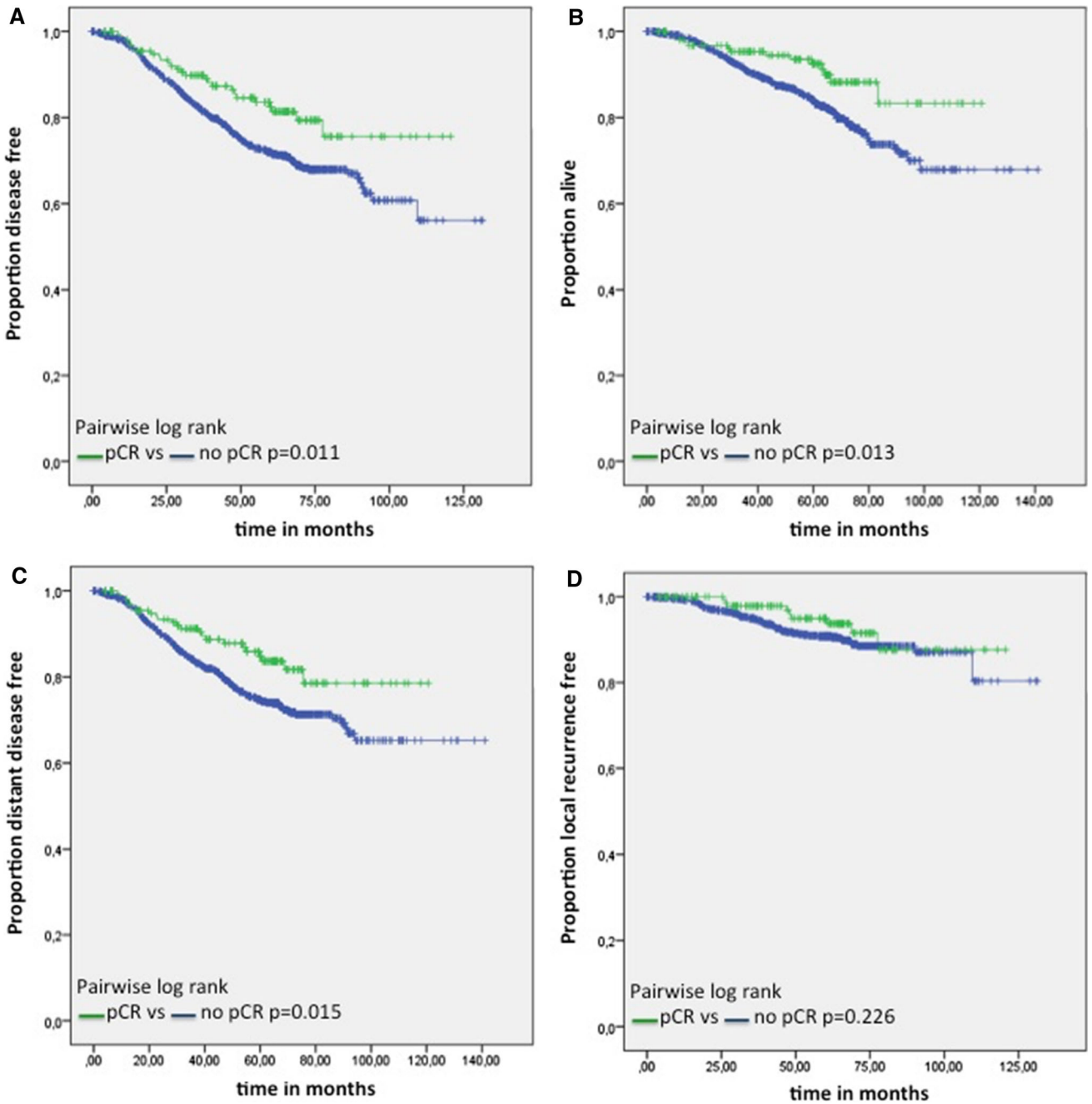

Fig. 4 Disease-free survival (DFS), overall survival (OS), distant disease-free survival (DDFS), and local recurrence-free survival (LRFS) in patients with ER-positive and PgR-negative breast cancer with and without pCR treated with neoadjuvant chemotherapy. **a** DFS, **b** OS, **c** DDFS, **d** LRFS

been described as being dependent on the activation of ER as a transcription factor [35]. Therefore, the absence of PgR in ER-positive breast cancer might assume an ER functioning in the non-classical manner. Numerous studies have reported that altered growth factor signaling is able to interact with ER signaling leading to its non-genomic activity resulting in decreased or absent PgR expression [36]. Several growth factors have been found to interact with ER signaling and one of these is HER2 [37] whose overexpression and amplification in this cohort occurred more often in the absence of PgR expression. This would suggest the existence of a potential crosstalk of HER2 and ER in these particular tumors rendering them a more aggressive phenotype. However, PgR negativity also occurred in HER2-negative tumors and it could be assumed that in these tumors other growth factor pathways might be overexpressed as a molecular profiling study previously reported [4]. Interestingly, in the HER2-negative cohort of

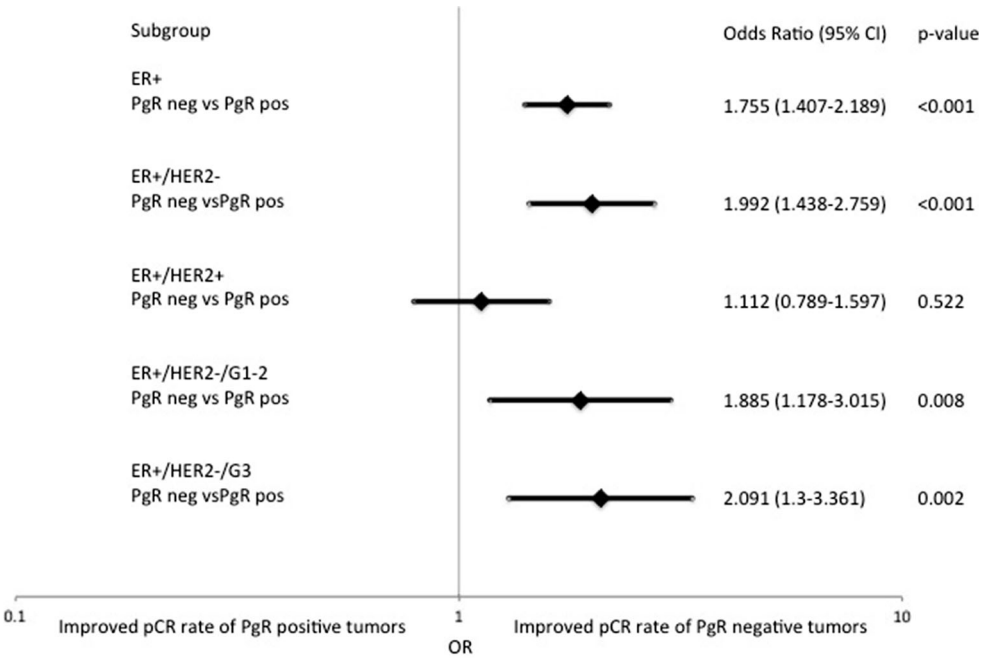

Fig. 5 Forrest Plot for multivariable logistic regression model demonstrating the odds ratios of achieving a pCR with respect to the PgR status by subgroup after adjustment for age, tumor stage and nodal stage at baseline, histological type, and study (ER+ $N = 5307$, ER+/HER2− $N = 3163$, ER+/HER2+ $N = 1056$, ER+/HER2−/G1–2 $N = 2372$, ER+/HER2−/G3 $N = 791$)

ER estrogen receptor, PgR progesterone receptor, CI confidence interval, HER2 human epidermal growth factor receptor, G grading

this study not only patients' outcome was worse in the absence of PgR, but these patients were also significantly more likely to achieve a pCR. Moreover, the previously described outcome advantage for patients achieving a pCR after neoadjuvant chemotherapy could also be observed in the PgR-negative cohort [23].

The here presented retrospective analyses represent the largest cohorts of ER-positive and PgR-negative patients that were treated with neoadjuvant chemotherapy and have long-term outcome data available. Nevertheless, the issue that patients were treated within several different trials receiving different treatment regimens has to be considered when interpreting the results. Also the fact that patients included in the GeparSixto trial were HER2 positive in addition to hormone receptor expression has to be considered. However, all patients received an anthracycline and taxane backbone as neoadjuvant treatment and data collection was managed within the trials centrally.

This analysis demonstrates that ER-positive and PgR-negative tumors represent a specific subset in primary breast cancer patients associated with higher response but also worse long-term outcome after neoadjuvant chemotherapy. Interestingly, PgR negativity served as an independent predictive factor for achieving a pCR after neoadjuvant chemotherapy in ER-positive HER2-negative breast cancer and therefore its status should be considered when deciding on systemic treatment for breast cancer patients.

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Compliance with ethical standards

Conflict of interest Peter Fasching is a consultant for Novartis, Pfizer, and Roche and receives funding from Novartis. Claus Hanusch is a consultant for Roche, Pfizer Amgen, Asrazeneca, Celgene, and Novartis. Sherko Kuemmel is a consultant for Roche, Amgen, Novartis, Genomic Health, Cellgene, Tewa, and Dairdi-Saulay and receives funding from Roche. Frederik Marme acts as a consultant for Roche, AstraZeneca, Novartis, Amgen, and Genomic Health and receives remuneration from the aforementioned companies. All remaining authors declare that there exists no conflict of interest.

References

1. Silva CM, Shupnik MA (2007) Integration of steroid and growth factor pathways in breast cancer: focus on signal transducers and activators of transcription and their potential role in resistance. Mol Endocrinol 21:1499–1512. doi:10.1210/me.2007-0109
2. Migliaccio A, Di Domenico M, Castoria G, de Falco A, Bontempo P, Nola E et al (1996) Tyrosine kinase/p21ras/MAP-kinase pathway activation by estradiol-receptor complex in MCF-7 cells. EMBO J 15:1292–1300
3. Dutertre M, Smith CL (2003) Ligand-independent interactions of p160/steroid receptor coactivators and CREB-binding protein (CBP) with estrogen receptor-alpha: regulation by phosphorylation sites in the A/B region depends on other receptor domains. Mol Endocrinol 17:1296–1314

4. Creighton CJ, van de Vijver MJ, Foekens JA, Klijn JG, Horlings HM et al (2009) Molecular profiles of progesterone receptor loss in human breast tumors. Breast Cancer Res Treat 114:287–299. doi:10.1007/s10549-008-0017-2
5. Bardou VJ, Arpino G, Elledge RM, Osborne CK, Clark GM (2003) Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. J Clin Oncol 21:1973–1979. doi:10.1200/JCO.2003.09.099
6. Dowsett M, Allred C, Knox J, Quinn E, Salter J, Wale C et al (2008) Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the arimidex, tamoxifen, alone or in combination trial. J Clin Oncol 26:1059–1065. doi:10.1200/JCO.2007.12.9437
7. Viale G, Regan MM, Maiorano E, Mastropasqua MG, Golouh R, Perin T et al (2008) Chemoendocrine compared with endocrine adjuvant therapies for node-negative breast cancer: predictive value of centrally reviewed expression of estrogen and progesterone receptors–International Breast Cancer Study Group. J Clin Oncol 26:1404–1410. doi:10.1200/JCO.2007.10.6393
8. Prat A, Cheang MC, Martin M, Parker JS, Carrasco E, Caballero R et al (2013) Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. J Clin Oncol 31:203–209. doi:10.1200/JCO.2012.43.4134
9. von Minckwitz G, Costa SD, Raab G, Blohmer JU, Eidtmann H, Hilfrich J et al (2001) Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 19:3506–3515
10. von Minckwitz G, Raab G, Caputo A, Schutte M, Hilfrich J, Blohmer JU et al (2005) Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol 23:2676–2685. doi:10.1200/JCO.2005.05.078
11. von Minckwitz G, Blohmer JU, Raab G, Lohr A, Gerber B, Heinrich G et al (2005) In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study. Ann Oncol 16:56–63. doi:10.1093/annonc/mdi001
12. von Minckwitz G, Kummel S, Vogel P, Hanusch C, Eidtmann H, Hilfrich J et al (2008) Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 100:552–562. doi:10.1093/jnci/djn089
13. von Minckwitz G, Kummel S, Vogel P, Hanusch C, Eidtmann H, Hilfrich J et al (2008) Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 100:542–551. doi:10.1093/jnci/djn085
14. Untch M, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H et al (2010) Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. J Clin Oncol 28:2024–2031. doi:10.1200/JCO.2009.23.8451
15. Untch M, Mobus V, Kuhn W, Muck BR, Thomssen C, Bauerfeind I et al (2009) Intensive dose-dense compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer. J Clin Oncol 27:2938–2945. doi:10.1200/JCO.2008.20.3133
16. Untch M, Fasching PA, Konecny GE, von Koch F, Conrad U, Fett W et al (2011) PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF versus a standard-dosed epirubicin/cyclophosphamide followed by paclitaxel ± darbepoetin alfa in primary breast cancer–results at the time of surgery. Ann Oncol 22:1988–1998. doi:10.1093/annonc/mdq709
17. Untch M, von Minckwitz G, Konecny GE, Conrad U, Fett W, Kurzeder C et al (2011) PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer–outcome on prognosis. Ann Oncol 22:1999–2006. doi:10.1093/annonc/mdq713
18. Untch M, Fasching PA, Konecny GE, Hasmuller S, Lebeau A, Kreienberg R et al (2011) Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 29:3351–3357. doi:10.1200/JCO.2010.31.4930
19. von Minckwitz G, Untch M, Nuesch E, Loibl S, Kaufmann M, Kummel S et al (2011) Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 125:145–156. doi:10.1007/s10549-010-1228-x
20. von Minckwitz G, Eidtmann H, Rezai M, Fasching PA, Tesch H, Eggemann H et al (2012) Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 366:299–309. doi:10.1056/NEJMoa1111065
21. Untch M, Loibl S, Bischoff J, Eidtmann H, Kaufmann M, Blohmer JU et al (2012) Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. Lancet Oncol 13:135–144. doi:10.1016/S1470-2045(11)70397-7
22. von Minckwitz G, Schneeweiss A, Loibl S, Salat C, Denkert C, Rezai M et al (2014) Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 15:747–756. doi:10.1016/S1470-2045(14)70160-3
23. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA et al (2012) Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 30:1796–1804. doi:10.1200/JCO.2011.38.8595
24. http://www.ago-online.de/fileadmin/downloads/leitlinien/mamma/march2012/14_2012E_Breast_Cancer_Specific_Situations.pdf
25. http://www.ago-online.de/fileadmin/downloads/leitlinien/mamma/march2012/13_2012E_Adjuvant_Radiotherapy.pdf
26. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N et al (2014) Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384:164–172. doi:10.1016/S0140-6736(13)62422-8
27. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA et al (2000) Molecular portraits of human breast tumours. Nature 406:747–752. doi:10.1038/35021093
28. Mohsin SK, Weiss H, Havighurst T, Clark GM et al (2004) Progesterone receptor by immunohistochemistry and clinical outcome in breast cancer: a validation study. Mod Pathol 17:1545–1554. doi:10.1038/modpathol.3800229
29. Dunnwald LK, Rossing MA, Li CI (2007) Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res 9:R6. doi:10.1186/bcr1639
30. Grann VR, Troxel AB, Zojwalla NJ, Jacobson JS, Hershman D, Neugut AI (2005) Hormone receptor status and survival in a

population-based cohort of patients with breast carcinoma. Cancer 103:2241–2251. doi:10.1002/cncr.21030
31. Salmen J, Neugebauer J, Fasching PA, Haeberle L, Huober J, Wockel A et al (2014) Pooled analysis of the prognostic relevance of progesterone receptor status in five German cohort studies. Breast Cancer Res Treat 148:143–151. doi:10.1007/s10549-014-3130-4
32. Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, Gray R, Clarke M, Cutter D et al (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 378:771–784. doi:10.1016/S0140-6736(11)60993-8
33. Dowsett M, Houghton J, Iden C, Salter J, Farndon J, A'Hern R et al (2006) Benefit from adjuvant tamoxifen therapy in primary breast cancer patients according oestrogen receptor, progesterone receptor, EGF receptor and HER2 status. Ann Oncol 17:818–826. doi:10.1093/annonc/mdl016
34. Viale G, Regan MM, Dell'Orto P, Mastropasqua MG, Maiorano E, Rasmussen BB et al (2011) Which patients benefit most from adjuvant aromatase inhibitors? Results using a composite measure of prognostic risk in the BIG 1-98 randomized trial. Ann Oncol 22:2201–2207. doi:10.1093/annonc/mdq738
35. Horwitz KB, McGuire WL (1978) Estrogen control of progesterone receptor in human breast cancer. Correlation with nuclear processing of estrogen receptor. J Biol Chem 253:2223–2228
36. Arpino G, Weiss H, Lee AV, Schiff R, De Placido S, Osborne CK et al (2005) Estrogen receptor-positive, progesterone receptor-negative breast cancer: association with growth factor receptor expression and tamoxifen resistance. J Natl Cancer Inst 97:1254–1261. doi:10.1093/jnci/dji249
37. Arpino G, Wiechmann L, Osborne CK, Schiff R (2008) Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. Endocr Rev 29:217–233