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

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## Background

The estrogen receptor (ER) as a nuclear transcription factor alters the transcription of estrogen sensitive genes to which the progesterone receptor gene belongs. The ER has also been described to exert non genomic effects by interacting with several cell signalling pathways that do not initially involve increases in gene transcription. 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 progesterone receptor (PgR) expression would be decreased or absent. Therefore lack of PgR expression could be a surrogate marker of altered growth factor signalling. The aim of this study was to investigate if PgR expression may act as a predictive factor for response to neoadjuvant chemotherapy and long-term outcome in breast cancer patients.

## Materials and Methods

5613 patients with primary breast cancer, follow-up, positive ER expression; HER2+/- or unknown from overall 10 (n=9785) German neoadjuvant trials receiving an anthracycline and taxane based chemotherapy were included.

The pathologic complete response (pCR)(ypT0, ypN0), long term survival data (disease free survival (DFS), distant disease free survival (DDFS), overall survival (OS) and local recurrence free survival (LRFS)) were compared according to their PgR expression, overall and in subgroups defined by HER2.

**Table 1: Baseline characteristics**

| | All ER+ patients N (valid%) | ER+ PgR – N (valid%) | ER+ PgR+ N (valid%) | p-value between PgR groups |
|---|---|---|---|---|
| Tumor stage | | | | 0.304 |
| cT1 | 403 (7.2) | 87 (7.5) | 316 (7.2) | |
| cT2 | 3559 (63.9) | 744 (63.8) | 2815 (63.9) | |
| cT3 | 919 (16.5) | 181 (15.5) | 738 (16.8) | |
| cT4a-c | 407 (7.3) | 82 (7.0) | 325 (7.4) | |
| cT4d | 281 (5.0) | 72 (6.2) | 209 (4.7) | |
| Nodal stage | | | | 0.004 |
| cN0 | 2720 (49.3) | 528 (45.7) | 2192 (50.2) | |
| cN1 | 2517 (45.6) | 550 (47.6) | 1967 (45.1) | |
| cN2 | 227 (4.1) | 60 (5.2) | 167 (3.8) | |
| cN3 | 56 (1.0) | 18 (1.6) | 38 (0.9) | |
| Histological type | | | | <0.001 |
| Ductal invasive | 4351 (78) | 950 (81.1) | 3401 (77.2) | |
| Lobular invasive | 901 (16.2) | 142 (12.1) | 759 (17.2) | |
| others | 326 (5.8) | 79 (6.7) | 247 (5.6) | |
| Tumor grade | | | | <0.001 |
| 1 | 283 (5.2) | 38 (3.4) | 245 (5.7) | |
| 2 | 3570 (66) | 654 (58.2) | 2916 (68) | |
| 3 | 1557 (28.8) | 431 (38.4) | 1126 (26.3) | |
| HER2 status | | | | <0.001 |
| Negative | 3301 (74.7) | 598 (63.8) | 2703 (77.7) | |
| positive | 1116 (25.3) | 340 (36.2) | 776 (22.3) | |

## Results

Tumors lacking PgR expression (1172 patients) were of significantly higher grade, tended to have an advanced clinical nodal involvement and were more likely to demonstrate HER2 positivity.
pCR rates were significantly higher in PgR negative patients in the entire cohort (13.8% v 7.5%; p<0.001) as well as in the HER2 negative subgroup (11.2% v 5.8%; p<0.001) whereas there was no significant difference in the HER2 positive (22.1% v 18%; p=0.117).
After adjusting for known predictive factors in the multivariable logistic regression analysis PgR negativity was an independent predictive factor for pCR overall (OR 1.755; p<0.001) and in the HER2 negative patients (OR 1.992; p<0.001).
Patients with PgR negative disease had a significantly worse DFS, OS, DDFS and LRFS (p<0.001, respectively). Multivariable Cox regression analysis revealed that PgR was an independent prognostic factor (OS: HR 1.575, CI 1.309-1.895; DFS: HR 1.456, CI 1.261-1.68; DDFS: HR 1.467, CI 1.26-1.709; LRFS: HR 1.625, CI 1.255-2.106). This was also observed in the HER2+ (OS: HR 2.192, CI 1.424-3.373; DFS: HR 1.687, CI 1.248-2.279; DDFS: HR 1.878, CI 1.353-2.606; LRFS: HR 1.727, CI 1.077-2.769) and HER2- subgroups (OS: HR 1.801, CI 1.406-2.308; DFS: HR 1.58, CI 1.306-1.912; DDFS: HR 1.592, CI 1.299-1.95; LRFS: HR 1.517, CI 1.07-2.151). Interestingly, in the PgR negative tumors HER2 status did not influence long-term outcome.

**Figure 1: Disease free (DFS), distant disease free (DDFS), local recurrence free (LRFS) and overall survival (OS) in patients with ER positive and PgR positive or negative breast cancer treated with neoadjuvant chemotherapy. A: OS, B: DFS, C: DDFS, D: LRFS**

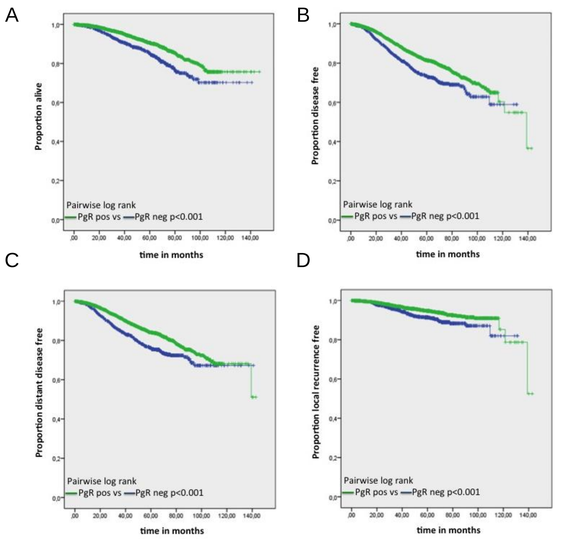



**Figure 2: Disease free (DFS), distant disease free (DDFS), local recurrence free (LRFS) and overall survival (OS) in patients with ER positive and PgR negative breast cancer with and without pCR treated with neoadjuvant chemotherapy. A: OS, B: DFS, C: DDFS, D: LRFS**

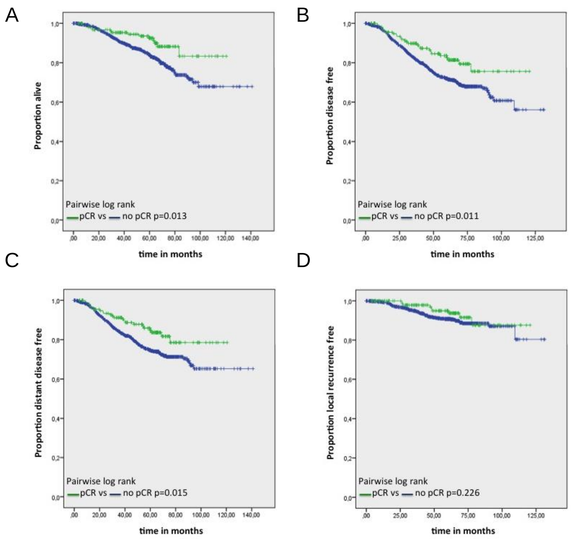
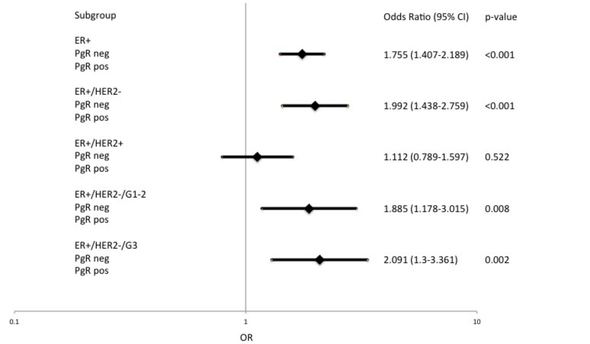



**Figure 3: Forrest Plot for multivariable logistic regression model demonstrating the odds of achieving a pCR overall and in subgroups after adjustment for age, tumor stage and nodal stage at baseline, histological type and study**




## Conclusions

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 and therefore its status should be considered when deciding on systemic treatment.

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