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Original article

# Selecting the neoadjuvant treatment by molecular subtype: How to maximize the benefit?

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A B S T R A C T

The relationship between achievement of a pathologic complete response (pCR) and favorable long-term outcome varies among breast cancer subtypes. We aimed to highlight which neoadjuvant treatment strategy could be most successful in each breast cancer subtype. A recent FDA meta-analysis on randomized neoadjuvant breast cancer trials suggests that the survival differences of patients with or without a pCR were less pronounced in luminal A-like tumors, despite the overall favorable prognosis of these patients. Moreover, even though the strong prognostic effect of pCR in HER2 positive and TNBC, the NOAH study was the only trial which showed a trend in surrogacy of pCR for long-term outcome in HER2-positive subtype. Results from GeparTrio study suggest that patients with hormone-positive tumors might need a response-guided approach, with either an intensification of treatment in case of an early response or a change to other chemotherapy in case of no early response. Furthermore, data from German neoadjuvant trials confirm that an increasing number of chemotherapy cycles is associated with a higher pCR rate, especially in patients with HER2-positive/hormone-positive tumors. In line with these suggestions, Tryphaena study showed a pCR rate that exceeding the 60% threshold, the highest pCR results presented in a large multicenter study. In TNBC, the highest pCR rate in the German neoadjuvant studies was obtained with the simultaneous application of docetaxel, doxorubicin and cyclophosphamide for 6 cycles. However, as shown in GaparQuinto and NSABP 40 trials, treatment effect in TNBC might be further maximized by adding bevacizumab, and two randomized neoadjuvant trials are expected this year to report data on the efficacy of carboplatin.



## Introduction

Over the last two decades, the use of neoadjuvant chemotherapy (NAC) in operable disease has become more popular based on the observation that outcomes with the same kind of chemotherapy given neoadjuvantly or adjuvantly are similar [1,2].

However, compared to the adjuvant approach, NAC offers the advantages of real-time monitoring and confirmation of treatment effect in terms of pathologic complete response (pCR) [3,4]. Several trials have shown that achievement of a pCR after chemotherapy strongly correlates with favorable long-term outcome [5]. Despite that this relationship varies among breast cancer subtypes, treatment strategies maximizing pCR rates probably will result in optimal sustained benefits for patients.

We will examine results of previous neoadjuvant studies and meta-analysis to draw conclusions on which neoadjuvant treatment strategies are most suitable in the corresponding breast cancer subtype to achieve an optimal short and potentially by this also an optimal long-term effect.

## Correlation of pCR with survival

Recent meta-analyses on patient data level provide strong evidence of association between breast cancer subtypes and the odds of achieving pCR [6,7]. Differences in survival between patients with or without a pCR were largest in patients with HER2-positive/hormone-receptor (HR)-negative and triple negative breast cancer (TNBC) [5]. Despite this strong prognostic effect of pCR in these two

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subtypes, a recent global meta-analysis initiated by FDA on 13,000 patients from randomized neoadjuvant chemotherapy trials could not show that an improvement of pCR by one over the other chemotherapy consistently translated into a longer disease-free survival – which is a prerequisite for a surrogate outcome marker [8]. It is speculated that the reported increases of pCR rates in these trials were to moderate to result in detectable survival benefits.

The survival differences of patients with or without a pCR were less pronounced in patients with hormone-receptor-positive disease, especially in luminal A-like tumors (ER/PgR-positive, HER2-negative, grade 1–2) [9]. Despite the overall favorable prognosis of patients with this subtype, a pCR is infrequently been observed and the risk of relapse is almost as high as in patients without a pCR of this subtype. One explanation for this observation is that patients with HR-positive tumors receive a relevant part of their treatment, i.e. endocrine treatment, only after surgery.

## Maximizing outcome in hormone-receptor-positive disease

As shown in a German pooled analysis [7], patients with HR-positive tumors irrespective of HER2 status achieved a higher rate of pCR with every two more cycles of treatment. This might go in line with the moderate sensitivity of HR-positive tumors to chemotherapy. In addition, a higher cumulative dose of anthracyclines, but not of taxanes was associated with a higher pCR rate in the group of patients with HR-positive/HER2-negative tumors. However, no correlation of these observations with long-term outcome has so far been reported.

The GeparTrio trial [3] examined the possibility to modify neoadjuvant treatment according to an early response assessment. Treatment was either intensified (two additional cycles of treatment) in case of an early response or change (to another chemotherapy) in case of no early response. PCR rates differed by a factor of 4 between patients with or without an early response, but not between the randomized treatment strategies. However, both, intensification and the change of treatment based on early response assessment resulted in a better disease-free survival compared to a conventional fixed treatment with the same chemotherapy. This response-guided approach was most beneficial for patients with HR-positive tumors. The discrepant results for the pCR and the disease-free survival endpoint of the study might be explained by the less relevant prognostic impact of pCR in HR-positive disease and that therefore pCR differences are not necessarily required.

## Treatment strategies in HER2-positive disease

Adding trastuzumab to NAC in patients with HER2-positive tumors doubled pCR rate in comparison to chemotherapy alone and it was as well associated with longer event-free survival. In the NOAH trial [10], regression analysis confirmed that treatment with trastuzumab was the only variable to significantly affect event-free survival. In the FDA analysis [8], the NOAH study was the only study that showed such a high association and led at least to a trend that surrogacy of pCR for outcome is existing in this subtype. Other trials have shown lower pCR rates for lapatinib in combination with chemotherapy when compared to a trastuzumab chemotherapy combination or even a trastuzumab/lapatinib/chemotherapy combination. This goes in line to early observations from the ALTTO study [11] where the arm using lapatinib alone in combination with chemotherapy was closed early.

Data from German neoadjuvant breast cancer trials suggest that an increasing number of chemotherapy cycles is associated with an augmented pCR rate especially in patients with HER2-positive/HR-positive tumors, so that treatment duration might be relevant also in this specific setting [7]. This is supported by recent results from the Tryphaena study [12] that assessed the addition of pertuzumab to standard preoperative treatment in patients with early HER2-positive breast cancer. Patients received 6–8 cycles of a taxane-based chemotherapy including either as well an anthracycline or carboplatin and received anti-HER2-treatment with trastuzumab and pertuzumab. The observed pCR rates were exceeding the 60% threshold and are so far the highest pCR results presented in a large multicenter study.

**Table 1**
Systemic treatment for breast cancer subtypes optimized based on lessons learnt from recent neoadjuvant studies.

| Subtype | NAC |
|---|---|
| Luminal-like/HER2-negative | EC – Pw (or reverse)<br>TAC × 2 → response-guided chemotherapy |
| HER2-positive | EC(H) – TH (or reverse)<br>FECHP – THP or TCHP (P if available) |
| TNBC | TAC<br>EC – Pw<br>(+bevacizumab? +carboplatin?) |

E = epirubicin; C = cyclophosphamide; Pw = paclitaxel weekly; T = docetaxel; A = doxorubicin; F = 5-fluorouracil; H = trastuzumab; P = pertuzumab.

## Are there optimal treatment strategies in TNBC?

The highest pCR rates for TNBC in the German neoadjuvant studies were observed for TAC, the simultaneous application of docetaxel, doxorubicin and cyclophosphamide for 6 cycles. In fact, a response after only 2 cycles TAC was associated with a better disease-free survival compared to patients without an early response [13]. A neoadjuvant study from Shanghai randomizing TAC vs TC [14] is expected to report soon in how far doxorubicin is an important part of this regimen in TNBC. Treatment effect might be further maximized by adding bevacizumab to neoadjuvant chemotherapy. The GeparQuinto trial [15] showed that bevacizumab significantly increased the pCR rate among patients with HER2-negative disease, restricted primarily to patients with TNBC. However, the NSABP B40 trial [16] asking a similar question demonstrated again an in increase in pCR rate by the addition of pCR but this was more prominent in HR-positive/HER2-negative disease. As well, the addition of bevacizumab to adjuvant chemotherapy in the BEATRICE study did not improve disease-free survival [17]. Considering that in the adjuvant setting we're dealing with possible microscopic metastases that haven't developed a sufficient blood supply yet, the effect of such an anti-angiogenic drug might be different in the neoadjuvant setting. So long-term outcome observations of the two neoadjuvant bevacizumab studies [15,16] are to be awaited before drawing final conclusions. Two randomized neoadjuvant trials are expected this year to report data on the efficacy of carboplatin in TNBC. The GeparSixto study [18] examines the addition of weekly carboplatin given simultaneously to weekly paclitaxel, weekly pegylated doxorubicin and bevacizumab in 300 patients with TNBC and 300 patients with HER2-positive tumors, and the CALGB 40603 study [19] examines the addition of 3 weekly carboplatin as well as bevacizumab in a 2 by 2 factorial design in 446 patients treated with a chemotherapy backbone of weekly paclitaxel followed by dose-dense doxorubicin/cyclophosphamide.

## Conclusion

Table 1 provides a recommendation of currently or in the near future available treatment regimen for the various breast cancer

subtypes in conclusion to the above discussed experience from past neoadjuvant studies. For patients with HR-positive/HER2-negative tumors a chemotherapy, e.g. anthracycline-cyclophosphamide followed by a taxane (or the reverse sequence) for a total duration of 24 weeks might results in the highest pCR rates. An alternative might be a response-guided approach starting with TAC. For patients with HER2-positive tumors a similar sequential chemotherapy approach together with trastuzumab might be most beneficial, especially for HR-positive tumors. In case, pertuzumab is available, this second antibody can be added to either a similar sequence or to a taxane–carboplatin-combination. As in TNBC, response to the first couple of chemotherapy cycles is predetermine outcome of patients, a simultaneous combination of a taxane and an anthracycline might be of advantage. The role of bevacizumab and carboplatin in this subtype will be further defined by already fully accrued neoadjuvant studies.

## Conflict of interest disclosure

Gunter von Minckwitz has worked as a consultant for Eisai, Novartis, Celgene, Amgen, Roche, Genomic Health, Boerhringer, Novartis, Bayer and Celgene. He has also received speaker's bursaries from Novartis, Celgene, Amgen, Roche, Genomic Health,-Boehringer, Novartis and Ratiopharm.

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