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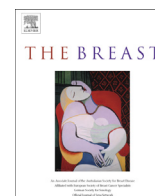
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Review

Current and future role of neoadjuvant therapy for breast cancer

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ABSTRACT

Neoadjuvant systemic chemotherapy is a possible therapeutic approach for the treatment of locally advanced operable, primarily non-operable or inflammatory breast cancer. Neoadjuvant systemic chemotherapy is an option for breast cancer patients who would require adjuvant chemotherapy otherwise based on clinical and histological examination and imaging. The use of neoadjuvant systemic therapy in operable breast cancer is currently increasing because of its advantages that include higher rates of breast conserving surgery and the possibility of measuring early in-vivo response to systemic treatment. The timing of axillary sentinel lymph node diagnosis (i.e. before or after neoadjuvant chemotherapy) is critical in that it may influence the likelihood of axillary preservation. It is not yet clear if neoadjuvant therapy might improve outcomes in certain subgroups of breast cancer patients. Neoadjuvant treatment modalities require a close collaboration between oncology professionals, including surgeons, gynecologists, medical oncologists, radiation oncologists, radiologists and pathologists. The most important parameter for treatment success and improved overall survival is the achievement of a pathologic complete response (pCR), although the role of pCR in patients with luminal A like tumours might be less informative. Identification of patient subgroups with high pCR rates may allow less invasive surgical or radiological interventions. Patients not achieving a pCR may be candidates for postoperative clinical trials exploring novel systemic treatments.

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Introduction

Therapy of patients with early breast cancer involves three principal treatment modalities: surgery, systemic therapy and radiation therapy. Traditionally, systemic therapy has been administered to breast cancer patients after surgery. Recently, however, neoadjuvant systemic therapy has been regarded as an equally effective option when compared to adjuvant therapy. While neoadjuvant antihormonal therapy is mainly recommended for hormone receptor positive postmenopausal patients, neoadjuvant chemotherapy (NACT) is increasingly utilized for all breast cancer subtypes. Neoadjuvant chemotherapy increases the rate of breast conserving surgery [1] and allows monitoring of treatment response, and provides unique opportunities for development of

both individualized treatment strategies and drug development. Modern treatment strategies are tailored to molecular subtypes [2], allowing for a more individualized approach to therapy. There is increasing evidence that a shift in the traditional sequence of treatment modalities may preferentially improve outcomes in certain subgroups of patients with early breast cancer [3,4].

Currently, the terms *neoadjuvant* and *primary systemic or pre-surgical* therapy are used. We recommend that in clinical trials, the term *neoadjuvant* be used when referring to a treatment given before surgery with therapeutic intent: The term *presurgical* should be used when referring to an intervention undertaken before surgery, with diagnostic intent to investigate the biologic or pharmacodynamic effect of a compound on breast cancer tissue. Presurgical trials are mostly referred to as biological window trials, such as those in which a short course of a compound is administered before surgery to test its short-term effect on a biologic or pharmacodynamic endpoint rather than a conventional efficacy endpoint. In the following manuscript we will use the term *neoadjuvant* as most of the clinical trials summarized in this review were conducted with therapeutic intent.

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Originally, it was recommended that neoadjuvant chemotherapy be only considered for women with large tumours or inflammatory disease. In the meantime, however, neoadjuvant chemotherapy is commonly used for the treatment of patients with high-risk operable primary breast cancer. Several international groups have developed guidelines for the use of neoadjuvant chemotherapy in operable breast cancer, with recommendations for patient selection and treatment regimens [5]. The guidelines provide the level of scientific evidence for each recommendation, and are the result of research collaborations (Table 1).

Defining patient groups for neoadjuvant chemotherapy

The results of the NSABP B-18 trial showed that breast conservation rates are higher after preoperative chemotherapy, especially in patients with tumours larger than 5 cm at study entry [6]. Although there were no significant differences in OS or DFS in protocol B-18, women younger than 50 years of age had more benefit from preoperative versus postoperative chemotherapy. In contrast, women aged 50 years and older had better outcomes with postoperative chemotherapy. These results were initially seen at 9 years median follow up and still persist after a median of 16 years [4]. These findings are in line with the overview analyses from the Early Breast Cancer Trialists' Collaborative Group which indicate that the effects of adjuvant chemotherapy are most apparent in younger women. It is possible that the benefit of neoadjuvant chemotherapy relative to postoperative chemotherapy could be age-dependent as well. Younger women are more likely to have oestrogen receptor (ER)-negative tumours and International Breast Cancer Study Group data suggest there may be a preferential benefit to early initiation of adjuvant chemotherapy in premenopausal women with ER-negative tumours [7]. These findings could help to explain why younger women seem to have a greater benefit from preoperative chemotherapy.

NSABP B-27 was a three arm, randomized, phase III trial of patients with invasive breast cancer treated with preoperative chemotherapy with AC (doxorubicin/cyclophosphamide) for 4 cycles followed by surgery alone, preoperative AC followed by preoperative docetaxel for 4 cycles followed by surgery, or AC followed by surgery followed by 4 cycles of postoperative docetaxel. Results from this study, which involved 2411 women, documented a higher pCR rate in patients treated preoperatively with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of preoperative AC. Disease free survival (DFS) and overall survival (OS) were not superior following the addition of docetaxel treatment in NSABP B-27. However in a subset analysis, a DFS advantage was observed (HR, 0.71; 95% CI, 0.55–0.91; $p = 0.007$) favouring preoperative versus postoperative docetaxel in patients experiencing a partial response to AC [8].

Role of surgery in neoadjuvant therapy

Systemic therapy administered prior to surgery can reduce the size and cellularity of the tumour, presenting unique challenges for surgeons, including increased difficulty in identifying the tumour bed and ensuring complete macroscopic and microscopic surgical excision. In order to enable optimal surgery, surgeons, oncologists, pathologists, radiologists and radiation-oncologists need to cooperate closely. The use of tissue marker clips before neoadjuvant therapy to mark the tumour facilitates later identification of the primary tumour area.

Available data suggest that locoregional therapy decisions should be based on both the pre-treatment clinical extent of disease and the response to neoadjuvant systemic therapy. An important advantage of pre-operative chemotherapy is that more

patients with larger tumours can be treated with breast conserving surgery. Most neoadjuvant chemotherapy or endocrine trials, such as NSABP-B18 and B 27 [9], EORTC 10902 [1], Fem-024 [10] and the AGO B and GBG-trials [11], report an increase in the percentage of patients that could be treated with breast conservation. Approx. 10–30% of the patients who were initially candidates for mastectomy were treated with breast conservation after neoadjuvant therapy [12].

A meta analysis of nine breast cancer trials comparing adjuvant and neoadjuvant therapy reported an increase in the relative risk of locoregional recurrence of 1.22 (CI 1.04–1.43) after neoadjuvant treatment [13]. However, the results were largely influenced by the trials in which surgery was either omitted or breast conservation therapy was achieved with radiation alone [13].

Four factors are independently associated with an increased risk of local recurrence: Clinical stage N2–N3 disease before neoadjuvant treatment, lymphovascular invasion, multifocal residual disease and pathologic residual tumour larger than 2 cm after neoadjuvant chemotherapy [14]. Simple techniques such as the use of tissue marker clips to indicate tumour location at the time of diagnosis ensure appropriate imaging after neoadjuvant therapy and can make later identification of the tumour area easier. In a retrospective analysis of patient records, it has been demonstrated that clip placement is associated with better local control, independent of stage and other clinicopathologic factors [15]. The risk ratio of local recurrence in this study was 3.7 if clip insertion was omitted, compared with patients who did have clip placement. 5-year local control was 98.6% in patients who had radiopaque clips placed versus 91.7% in patients who did not have tumour marker clips placed [15].

To ensure best outcomes, a multidisciplinary team should take the following aspects into account: Molecular analyses (ER, PR, HER2 status) from the diagnostic core needle biopsies to guide subsequent treatment, insertion of tissue marker clips before neoadjuvant therapy to improve the chance for breast conserving surgery and clinical and sonographic assessment of the axillary nodes prior to neoadjuvant therapy to determine the need for a sentinel node biopsy or axillary surgery after neoadjuvant chemotherapy.

In breast cancer patients with T1–T2 tumours, no palpable adenopathy and 1–2 positive sentinel lymph nodes (SLNs), the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial compared observation only to complete axillary lymph node dissection (ALND) following sentinel node biopsy [16]. No significant differences in disease-free survival (DFS) and overall survival (OS) were noted between the two groups at a median follow-up of 6.3 years. Patients with 1 or 2 SLNs containing macro- or micro-metastases who have had breast conserving surgery followed by tangential field radiation therapy and systemic therapy do not need further axillary lymph node dissection according to this landmark study. Importantly however, the Z0011-trial is not sufficient to provide recommendations concerning the management of axillary nodes after neoadjuvant therapy. To better understand the role of sentinel lymph node biopsies and ALND following neoadjuvant chemotherapy additional trials have been conducted.

In patients planning to receive neoadjuvant chemotherapy who have clinically negative axillary lymph nodes (ALNs) SLN biopsy can be considered. For those with clinically suspicious ALNs, the North American National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend consideration of either a core biopsy or FNA of these nodes, along with a sentinel node biopsy if FNA or core biopsy results are negative [17]. When administering neoadjuvant chemotherapy in women with clinically negative ipsilateral axillary nodes the current NCCN guidelines list SLN resection as the preferred option for surgical axillary staging. If the

Table 1

AGO guidelines: diagnosis and treatment of patients with primary and metastatic breast cancer – neoadjuvant (primary) systemic therapy (http://www.ago-online.de/fileadmin/downloads/leitlinien/mamma/maerz2014/de/2014D_12_Neoadjuvante_%28Primaere%29_systemische_Therapie.pdf, accessed March 20, 2014).

Guideline subject	Oxford LoE	Oxford grade	AGO grade
Indications			
Inflammatory BC	2b	B	++
Inoperable BC	1c	A	++
Large operable BC primarily requiring mastectomy and adjuvant CT with goal of breast conservation	1b	B	+
If similar post-operative adjuvant CT is indicated	1b	A	+*
Triple negative breast cancer (TNBC)			+
HER2-positive breast cancer	1b	B	+
Prediction of pCR			
Younger age	1a	A	+
Smaller tumour size	1a	A	++
Non-lobular histology	1a	A	+
Early clinical response	1b	A	+
Negative hormone receptor (HR)-status	1a	A	++
Triple negative breast cancer (TNBC)	1a	B	++
Positive HER2-status	1a	A	++
PAM50/MammaPrint LoE ₂₀₀₉ : III		B	±
Ki-67 LoE ₂₀₀₉ : I		A	+
Tumour-associated lymphocyte infiltration LoE ₂₀₀₉ : II		B	+
PIK3CA mutation LoE ₂₀₀₉ : II		B	+
Recommended chemotherapy schedules			
Adjuvant standard regimens for at least 18 weeks	1a	A	++
AC or EC → D q3w or P q1w	2b	A	++
DAC	2b	B	++
AP → CMF	1b	A	+
Taxane followed by anthracycline sequence	2b	B	+
Dose-dense regimens (e.g. E → P→CMF, E → P→C)	1b	B	+*
Capecitabine in combination with anthracycline and taxane	1b	B	±
Platinum in TNBC irrespective of BRCA1-mutation	2b	B	+*
Recommended methods of monitoring response			
Breast ultrasound	2b	B	++
Palpation	2b	B	++
Mammography	2b	B	++
MRI	2b	B	+
PET (-CT)	1b	D	±
Clip placement to mark tumour area	5	D	++
HER2-positive tumours			
Trastuzumab in combination with chemotherapy	1b	A	++
Lapatinib in combination with chemotherapy	1b	B	–
Lapatinib + Trastuzumab in combination with chemotherapy	2b	B	±
Pertuzumab + Trastuzumab in combination with chemotherapy	2b	B	+*
Two HER2-inhibitors without chemotherapy	2b	B	±
Procedures in case of early response (after 6–12 weeks of NST)			
Continue and complete all chemotherapy before surgery, i.e. ≥ 18 weeks of treatment	1b	A	++
In case of response after two cycles of TAC in HR+ breast cancer: give 8 instead of 6 cycles TAC	2b	C	+
Procedures in case of no early response			
In case of stable disease:			
Completion of NST, followed by surgery	2b	C	++
Continuation of NST with non cross-resistant regimen	2b	B	+
• AC or EC × 4 → D × 4 or Pw × 12	2b	B	+
• DAC × 2 → NX × 4	1b	B	+
In case of progressive disease:			

Table 1 (continued)

Guideline subject	Oxford LoE	Oxford grade	AGO grade
Stop NST, immediate surgery or radiotherapy	4	D	++*
Additional adjuvant chemotherapy with non-cross-resistant regimen	4	D	±*
Surgical procedures			
Intraoperative clip placement to mark tumour area	5	D	++
Adequate surgery after NST	2b	C	++
Microscopically clear margins	5	D	++
Excision within new margins	3b	C	+
Sentinel node biopsy			
Before neoadjuvant chemotherapy	2b	B	+
After neoadjuvant chemotherapy	3	B	±
Systemic therapy—timing of surgery and radiotherapy			
Surgery			
• After leucocyte nadir (2–4 weeks after last course of chemotherapy)	4	C	++
Radiotherapy after surgery	2b	B	++
• 2–3 weeks after surgery			
• Indication according to stage of disease before NST (cN+, cT3/4a-d)			
Systemic therapy after neoadjuvant systemic treatment			
Endocrine treatment in endocrine responsive disease	1a	A	++
Complete trastuzumab treatment for up to 1 year in HER2-positive disease	2b	B	++
In case of insufficient response	3	C	–
• Further chemotherapy	5	D	+
• Experimental treatments			

*Study participation recommended.

Abbreviations: AC, doxorubicin and cyclophosphamide; AGO, Working Group Gynecologic Oncology (Arbeitsgemeinschaft Gynäkologische Onkologie); AP, doxorubicin and paclitaxel; BC, breast cancer; BRCA1, breast cancer type 1 susceptibility gene; CT, chemotherapy; CMF, cyclophosphamide, methotrexate and fluorouracil; cN+, clinically positive node; cTX, clinical stage (X = 1–4); D, docetaxel; DAC, docetaxel, doxorubicin and cyclophosphamide; E, epirubicin; EC, epirubicin and cyclophosphamide; ER, estrogen receptor; LoE, level of evidence; MRI, magnetic resonance imaging; NST, neoadjuvant systemic therapy; NX, vinorelbine, capecitabine; P, paclitaxel; PARP, poly (ADP-ribose) polymerase; PET(-CT), positron emission tomography (computed tomography); PgR, progesterone receptor; qXw, every X weeks; w, weekly;

Oxford Levels of Evidence (Oxford Levels of Evidence and Grades of Recommendation. <http://www.cebm.net/index.aspx?o=1025>):

1a: Systematic review (with homogeneity) of randomized controlled trials.

1b: Individual randomized controlled trials (with narrow Confidence Interval).

1c: All or none.

2a - Systematic review (with homogeneity) of cohort studies.

2c - "Outcomes" Research; Ecological studies.

2b: Individual cohort study (including low quality randomized controlled trials; e.g. <80% follow-up)

3a: Systematic review (with homogeneity) of case-control studies.

3b: Individual Case-Control Study.

4: Case-series (and poor quality cohort and case-control studies).

5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

Oxford Grades of Recommendation (Oxford Levels of Evidence and Grades of Recommendation. <http://www.cebm.net/index.aspx?o=1025>):

A: consistent level 1 studies.

B: consistent level 2 or 3 studies or extrapolations from level 1 studies.

C: level 4 studies or extrapolations from level 2 or 3 studies.

D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

AGO Grades of Recommendation:

++: This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.

+: This investigation or therapeutic intervention is of limited benefit for patients and can be performed.

±: This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge a general recommendation cannot be given.

–: This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.

–/–: This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.

SLN is histologically negative, omission of the axillary dissection may be considered at the time of surgical therapy after neoadjuvant chemotherapy. If a pre-chemotherapy SLN excision is not performed, then a level I and II axillary dissection (or SLN excision with level I and II axillary dissection if SLN is positive) should be performed at the time of definitive surgical therapy. The false-negative rate of SLN biopsy in the post-chemotherapy setting is an important issue. The NCCN expert panel generally recommends a pre-chemotherapy SLN excision because it provides additional information to guide local and systemic treatment decisions.

To evaluate when it is best to perform a sentinel node biopsy the German SENTINA (SENTinel NeoAdjuvant) trial was initiated. This 4-arm prospective multicenter cohort study was conducted in 103 German and Austrian centers [18]. Clinically node-negative breast cancer patients underwent SLNB prior to neoadjuvant therapy (Arm A). If the sentinel node was positive (pN1), a second sentinel-lymph-node biopsy procedure was performed after neoadjuvant chemotherapy (Arm B). Women with clinically node-positive disease (cN+) received neoadjuvant chemotherapy. Those who converted to clinically node-negative disease after chemotherapy (ycN0; Arm C) were treated with sentinel-lymph-node biopsy and axillary dissection. Patients whose clinical nodal status remained positive (ycN1) underwent axillary dissection without sentinel-lymph-node biopsy (Arm D).

Out of 1737 eligible patients, 1022 underwent SLNB prior to neoadjuvant therapy with a detection rate of 99.1%. In 662 patients in arm A (64.8%), the sentinel node was histologically not involved, these patients had no axillary dissection after NACT. In 360 patients with a SLNB before and after neoadjuvant therapy the detection rate was 60.8% and the false-negative rate was 51.6% (Arm B). In 592 patients (Arm C) who had clinically suspicious or suspicious nodes by sonography before neoadjuvant therapy and a clinically or sonographically negative axillary status after neoadjuvant therapy the detection rate was 80.1% and the false negative rate was 14.2%. According to this study, the SLNB is a reliable diagnostic tool in the context of neoadjuvant therapy prior to treatment. The SLNB shows lower detection rates and higher false-negative rates after neoadjuvant therapy and/or SLNB. This limitation has to be considered if SLNB is planned after neoadjuvant therapy.

(ACOSOG) Z1071 trial enrolled 756 women from 136 institutions who had received neoadjuvant chemotherapy [19]. Following chemotherapy, patients underwent both SLN surgery and ALND. Of 663 evaluable patients with cN1 disease, 649 underwent chemotherapy followed by both SLN surgery and ALND. The SLN could not be identified in 46 patients (7.1%). One SLN was excised in 78 patients (12.0%). In 525 patients, 2 or more SLNs were removed, of which 215 were histologically negative. In 39 patients, the SLN was not involved but other lymph nodes obtained with ALND were involved, resulting in a false negative rate of 12.6%. The false negative rate was 10.8% if blue dye and radiocolloid were both used for mapping.

Based on these data, it is unclear whether ALND can be omitted after neoadjuvant therapy in clinical routine. Nevertheless, it may be possible in patients with proven nodal involvement (by fine-needle aspiration or core biopsy) that the ALND could be omitted in those patients who underwent mapping with radiocolloid and blue dye and have no histological involvement of at least two or more sentinel nodes after neoadjuvant therapy. However, this clinical approach needs validation in further studies before its implementation into routine practice.

Radiation therapy

In spite of the importance of radiation therapy in the multimodal approach to breast cancer treatment, there is limited evidence to guide its use following neoadjuvant therapy. Phase III

trials to date have focused primarily on the use of radiation therapy following surgery and adjuvant chemotherapy. Consequently, there are no well-established guidelines for radiation therapy following neoadjuvant chemotherapy. Studies involving patients treated with neoadjuvant therapy demonstrate that both, clinical stage prior to neoadjuvant chemotherapy and pathological response/extent of residual disease after neoadjuvant chemotherapy are independent predictors for locoregional failure [9,20].

In light of this, an appropriate approach may be to tailor treatment according to the individual response after neoadjuvant chemotherapy [21]. Patients with proven involvement of axillary lymph nodes before neoadjuvant treatment (by SNB or biopsy) who have a pathologic complete remission in the breast and the axilla may not need extensive postoperative radiotherapy of the regional lymph nodes. An Austrian study suggests that intraoperative radiotherapy could be implemented to replace postoperative boost and may be valid for these patients after neoadjuvant therapy [22]. The hypofractionated approach (40 Gy in 15 doses over 3 weeks) used in the START B trial from the UK is a new standard for adjuvant radiation therapy in patients with early breast cancer [23]. Whether this approach can be followed in patients after neoadjuvant therapy (and therefore reduce the radiation time from 5–6 weeks to 3–4 weeks (with or without boost), has to be addressed in future studies.

Pathological and molecular assessments in neoadjuvant therapy

Reliable pathological and molecular testing on tumour tissue is essential for treatment planning in breast cancer. However, methodologic differences in assays exist between institutions, and guidelines to ensure test quality and consistency have become very important to secure a high standard of care. To date, however, there is a lack of established guidelines regarding pathological assessment of tumour tissue following neoadjuvant chemotherapy. Moreover, a uniform definition of pCR is needed [24].

Information on the hormone receptor (HR) and HER2 status is required to effectively guide treatment in breast cancer. However, assessment of HR and HER2 status before neoadjuvant chemotherapy is not routinely used, and discordant results can occur. In the GeparQuattro trial, 27% of HER2-positive patients (based on local testing) tested centrally HER2-negative [25]. Thus, international breast cancer expert groups recommend that institutions performing neoadjuvant chemotherapy establish protocols to ensure reliable testing of HER2 and hormone receptors in the diagnostic core biopsy obtained before neoadjuvant therapy [3].

The proliferation marker Ki-67 has been shown to be an independent predictive and prognostic biomarker in early breast cancer. In a retrospective analysis including more than 1000 patients from the GeparTrio study, assessment of Ki-67 on pre-treatment core biopsies and on residual tumour provided valuable prognostic and predictive information for patients with all subtypes of breast cancer. Patients with a Ki-67 > 35% had a significantly worse outcome compared to patients with a Ki-67 < 35%. Ki-67 levels measured after neoadjuvant chemotherapy provided better prognostic information than pre-treatment levels. Post-treatment Ki-67 identifies groups of patients at high risk for relapse, for which additional post-surgical systemic treatment options should be developed [26]. However, implementation of Ki67 assessment in routine practice has been limited by difficulties in standardizing the assessment of Ki-67 between different pathology labs.

The role of pCR

One of the major benefits of neoadjuvant chemotherapy is the possibility to assess the clinical response of the primary tumour

which can range from a minimal response to pathologic complete response (pCR). In addition to the reduction in size, the cellularity of the tumour may change. The later effects often make it difficult for surgeons and pathologists to clearly identify the former tumour area and ensure clear resection margins. The insertion of a clip at the time of diagnosis can ensure the identification of the tumour area after multiple cycles of chemotherapy and improve the accuracy of the surgical excision and subsequent pathological assessment after neoadjuvant therapy.

Definition of pCR

To date, however, we do not have a uniform definition for pCR, which has made reporting and interpretation of data from neoadjuvant trials challenging. For example, some investigators have defined pCR as the absence of both in situ and invasive cancer following neoadjuvant chemotherapy, whereas others have considered only the invasive component in the definition. Some investigators have defined pCR as absence of residual cancer in the breast and regional lymph nodes at the time of definitive surgery, whereas others have defined pCR as a complete response in the breast, irrespective of axillary nodal involvement [8,9,11,27,28]. Adoption of a single term with a standard definition would facilitate comparison of clinical trial data.

Based on the work of the CTNeoBC consortium, the FDA has now proposed two definitions for the use in upcoming registrational trials [29]: Pathologic complete response (pCR) should be defined either as the absence of any residual invasive cancer (ypT0/is ypN0 in the current AJCC staging system) or any invasive and non-invasive cancer on haematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy. Eradication of the tumour from both the breast and lymph nodes (ypT0ypN0 or ypT0/isypN0) was associated with improved event free survival (EFS) and overall survival (OS) compared to eradication of the tumour from the breast alone (ypT0/is). Patients who achieved a pCR irrespective of residual DCIS in the breast (ypT0/isypN0) had an improved EFS (HR = 0.48) and OS (HR = 0.36) compared to those who did not. Impact of pCR is limited to patients with HR+/grade 3, HR-/HER2-, and HER2+ tumours. The data show comparable EFS or OS regardless of the presence or absence of DCIS. Definitions not considering nodal involvement or even including focal invasive residuals should no longer be used.

Predictive role of pCR

In clinical studies, the determination of pCR after neoadjuvant chemotherapy is a valid surrogate marker for long-term survival [3]. A recent meta-analysis including more than 6000 primary breast cancer patients after neoadjuvant systemic therapy demonstrated that pCR was significantly correlated with improved survival [11]. Patients achieving a pCR after neoadjuvant chemotherapy show a significantly improved DFS and OS compared to those without pCR. Hazard ratios between patients with and without pCR was highest if the ypT0ypN0 definition was used and decreased continuously when more residual disease was included in the definition. Other factors that were associated with a high pCR-rate include an adequate cumulative dose of anthracycline- and taxane-based neoadjuvant chemotherapy and the concurrent use of trastuzumab in patients with HER2-positive tumours. The use of capecitabine was only associated with an improved pCR-rate when the addition of capecitabine did not lead to a reduction of the delivered anthracycline dose [11].

Nevertheless, the CTNeoBC analysis failed to show a relationship between the improvements of the pCR rate and an improvement of

DFS when a potentially more active treatment was compared to a less active treatment. Currently, such an association has only been seen in one trial testing neoadjuvant trastuzumab in combination with chemotherapy where an increased pCR rate was associated with improved survival [30].

Clinical response is usually evaluated every three to four weeks after initiation of neoadjuvant chemotherapy. An important predictive marker of improved response to a taxane-anthracycline-based regimen is a negative hormone receptor status and high tumour grade. In these subgroups pCR-rates of up to 40% can be achieved [3]. Patients with triple negative breast cancer or patients with HER2-positive breast cancer failing to respond to an anthracycline-taxane- or trastuzumab-based neoadjuvant chemotherapy, respectively, have a poor prognosis [3,29]. Assessment of pCR is a suitable surrogate end point for patients with HER2-positive (nonluminal) and triple-negative breast cancer, less valid in those with luminal B (HER2-negative or positive) and probably not a good predictive test for patients with luminal A tumours [3,29] (Fig. 1).

Neoadjuvant endocrine therapy

For postmenopausal women with estrogen receptor (ER)-positive disease, neoadjuvant endocrine treatment is a possible treatment approach because of its established efficacy in the adjuvant setting. Historically, neoadjuvant endocrine therapy was reserved for elderly and frail patients with ER+ breast cancer. However, recent studies of this treatment modality in younger postmenopausal women showed no interaction between improved surgical outcomes and older age [31], justifying the increased acceptance of neoadjuvant endocrine therapy in younger postmenopausal women with good performance status. For premenopausal women, however, neoadjuvant endocrine therapy remains investigational.

Aromatase inhibitors are the agents of choice for neoadjuvant endocrine therapy as they lead to a significantly higher objective response rate and rate of conversion to breast-conserving surgery when compared to tamoxifen [32,33]. Endocrine neoadjuvant therapy should be given for a minimum of 4–8 months [34]. There is a strong rationale to study combinations of endocrine agents and signal transduction inhibitors in the neoadjuvant setting. Cross-talk between ER and growth factor receptor signalling pathways has been suggested as one of the mechanisms of endocrine resistance. A new approach to restore endocrine responsiveness in breast tumours might therefore be the combination of an aromatase inhibitor with a signal transduction inhibitor as a PI3K/mTOR antagonist. Baselga et al. conducted a neoadjuvant study in postmenopausal patients with ER-positive breast cancer, who received letrozole plus everolimus or letrozole alone. The combination of everolimus/letrozole demonstrated superior anti-proliferative effects and improved clinical response rates compared to letrozole alone (68.1% versus 59.1%) [35].

Neoadjuvant chemotherapy in clinical research

The neoadjuvant setting provides a unique opportunity to study the effect of systemic treatments on breast cancer biology and to identify clinically useful prognostic and predictive biomarkers.

A new generation of neoadjuvant clinical trials is exploring the addition of new biologic agents and alternative treatment schedules. So far, most neoadjuvant trials have enrolled unselected patients. However, the genomic complexity of breast cancer is now being recognized and incorporated into new trial designs. Molecular profiling of breast cancer has revealed gene expression patterns that are characteristic for the major molecular subtypes

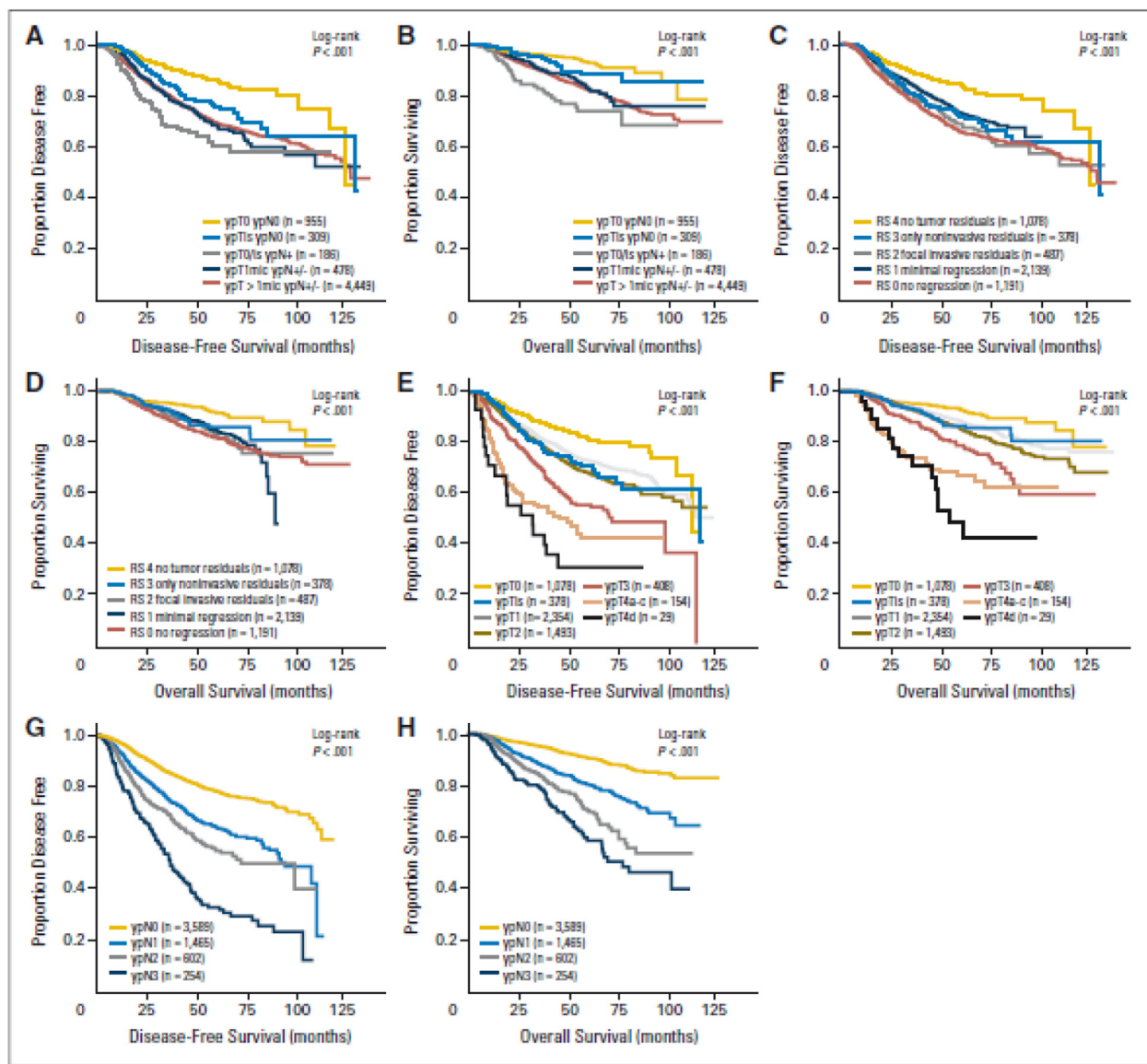


Fig. 1. Prognostic impact of various definitions of complete response on survival [3,29].

(luminal A and B, HER2-positive and basal-like). The identification of patient subgroups that may preferentially respond to neoadjuvant chemotherapy may help to improve treatment outcomes. In the past, adjuvant clinical trials have shaped our knowledge of early breast cancer care to date. However, these endeavours are resource-intensive, require the enrolment of large numbers of patients and extensive funding. Clinical trials using neoadjuvant therapy may allow us to address these important questions with fewer patients, at a reduced cost using pCR as a surrogate marker for efficacy.

Recently, the American Food and Drug Administration (FDA) released a guidance intended to assist clinician scientists in designing trials to support early approval of drugs to treat breast cancer in the neoadjuvant setting. The guidance describes a pathway to accelerated approval for promising drugs in early stages of development for breast cancer. The FDA may now grant approval for a new drug [or biological] product on the basis of an adequate and well-controlled clinical trial establishing that the drug has an effect on a surrogate endpoint such as the pCR rate which is reasonably likely to predict clinical benefit [36]. Despite advances

in adjuvant systemic therapy of breast cancer over the past few decades, there remains a significant unmet medical need for certain high-risk or poor prognosis populations of early-stage breast cancer patients. Developing highly effective new drugs for these populations has become a priority for the FDA. Considering pCR as an endpoint that would support accelerated approval in the neoadjuvant setting may thus expedite the development of breakthrough therapies to treat high-risk early-stage breast cancer. Following are examples of recently completed and ongoing studies in which assessment of efficacy using the surrogate marker pCR has helped and may help to expedite the development of novel treatment strategies for early stage breast cancer.

Early switch to a non-cross-resistant regimen – GeparTrio study

The aim of the GeparTrio study was to develop specific treatment strategies for patients with or without response to 2 cycles TAC (docetaxel, doxorubicin, cyclophosphamide). This study showed that a response-guided (switch to another chemotherapy in case of no early response or increased cycle number in case of an

early response) chemotherapy regimen is more effective compared to a non-individualized approach with a fixed number of cycles using the same chemotherapy agents [37]. Women who were treated with response-guided chemotherapy had a significantly longer DFS and OS (Fig. 2). Of note, subgroup analysis revealed that this difference was mainly restricted to patients with hormone-receptor-positive tumours. On the other hand, patients with triple negative breast cancer did not benefit from the switch to another chemotherapy or from increasing the number of cycles.

Neoadjuvant chemotherapy in younger patients

A recent study compared pCR rates and DFS of patients aged 35 or younger versus those above 35 years of age [38]. The data from eight studies included 8949 women with operable or locally advanced breast cancer who were treated with neoadjuvant chemotherapy. The pCR rate was significantly higher in very young patients when compared to those older than 35 years, but this difference was confined to the subgroup of patients with triple negative tumours. Surprisingly, better outcomes were seen for young women with luminal A-like tumours who achieved a pathologic complete response compared with those who did not. This was in contrast to other studies including older patients where pCR was not a predictor for improved DFS in patients with luminal A breast cancer.

Early neoadjuvant studies with HER2 inhibitors

Trastuzumab significantly improves pCR-rates when given as neoadjuvant treatment. For HER2-positive patients, recent studies including a meta-analysis confirmed that the higher pCR-rates achieved in those patients who received trastuzumab correlate with a significantly longer survival [11,39] (Fig.3). However, women with HER2-positive tumours without pCR have a very high risk of relapse. Novel treatment strategies are particularly needed for these patients.

The NOAH and the TECHNO trials were the first trials to demonstrate that HER2-positive patients achieving a pCR following neoadjuvant chemotherapy with anthracyclines, taxanes, and 12

weeks of trastuzumab had a significantly improved DFS and OS compared to those with residual tumour remaining after neoadjuvant therapy (Fig. 4) [30,40]. These data have now been confirmed by a recent meta-analysis [29].

The NOAH trial investigated the value of adding one year of trastuzumab (given as neoadjuvant and adjuvant treatment) to a neoadjuvant chemotherapy regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and fluorouracil in women with locally advanced or inflammatory breast cancer [30]. Trastuzumab significantly improved event-free survival in patients with HER2-positive breast cancer (3-year event-free survival, 71% with trastuzumab vs. 56% without; hazard ratio 0.59 [95% CI 0.38–0.90]; $p = 0.013$).

GeparQuattro study

In the GeparQuattro trial, adding trastuzumab to an anthracycline-taxane based regimen doubled the pCR-rate in HER2-positive patients when compared to patients with HER2-negative disease [41]. Although HER2 status is a good predictive marker for response to trastuzumab treatment, the truncated HER2 receptor may be an even better predictor of response to anti-HER2-treatment. In truncated HER2-receptors, the extracellular domain is split off (the residual HER2 receptor has a molecular weight of 95 kD, thus the name p95). In the GeparQuattro study the role of p95-expression as a predictive marker in patients with HER2-overexpression examined [42]. Interestingly, the pCR-rate was significantly higher in patients with p95-positive tumours (58.2%) than in patients with p95-negative tumours (32.6% ($p = 0.009$)). High levels of p95 expression lead to constitutive activation of the HER2 receptor and may result in a higher tumour proliferation. Further research is necessary to determine whether the improved pCR rate associated with p95 expression is caused by a better response to the chemotherapy or to trastuzumab.

GeparQuinto study

This randomized phase III study evaluated neoadjuvant chemotherapy and bevacizumab, everolimus or lapatinib in three

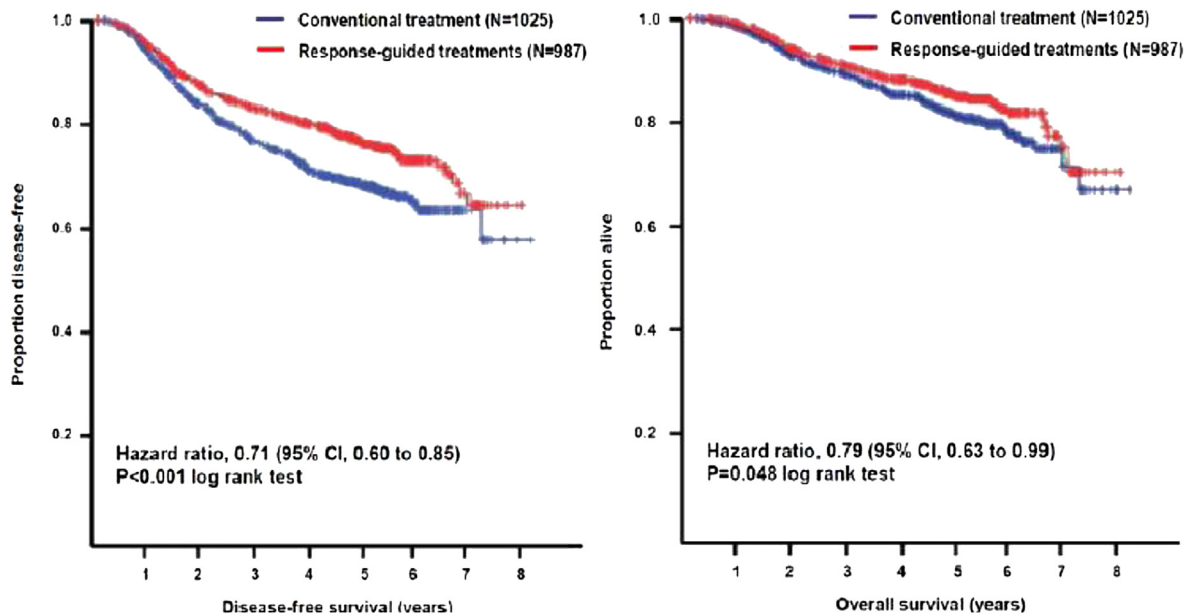


Fig. 2. GeparTrio study: DFS and OS after conventional (TACx6) vs. response guided (TACx8 or TAC-NX) treatment [37].

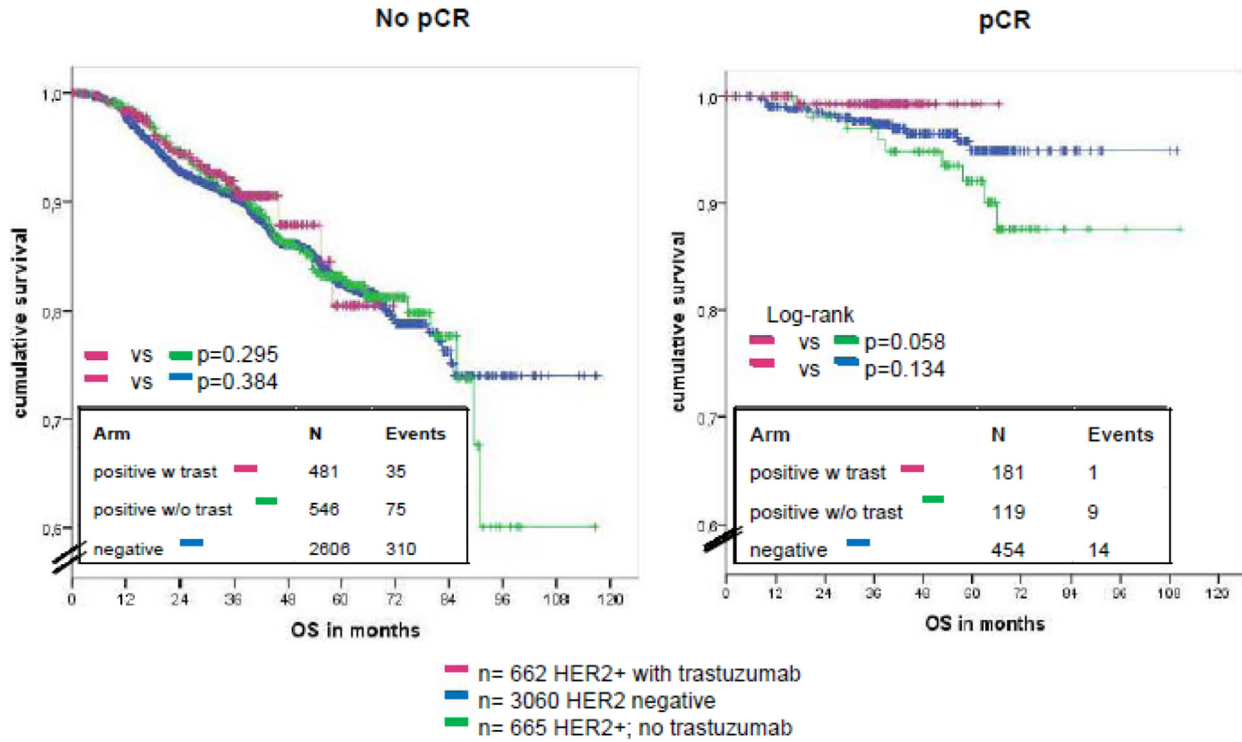


Fig. 3. pCR-rates in patients who had neoadjuvant trastuzumab correlate with a significantly longer survival [11,39].

distinct settings. 1948 HER2-negative patients were randomized in setting 1. They received 4 cycles EC (90/600 mg/m²) q3w followed by 4 cycles docetaxel (100 mg/m²) with or without bevacizumab 15 mg/kg q3w [43]. The pCR-rate (breast and axilla) was 14.9% in the chemotherapy-alone arm and 18.4% in the group receiving bevacizumab ($p = 0.04$). This difference was especially pronounced in the 663 patients with triple-negative tumours (HR = 1.67) (Fig. 5).

In setting 2, 620 patients with HER2 positive tumours were treated with EC → T chemotherapy and received either trastuzumab or lapatinib. The pCR-rate achieved by trastuzumab plus chemotherapy confirmed the results of the previous trials TECHNO and GearQuattro. The pCR-rate following chemotherapy in

combination with trastuzumab was 30.3% whereas the pCR-rate achieved by chemotherapy in combination with lapatinib plus chemotherapy was lower (22.7%; $p = 0.04$) [44].

In setting 3, non-responders to 4 × EC ± bevacizumab were randomized to receive paclitaxel 80 mg/m² for 12 weeks ± everolimus 5 mg/day. pCR-rates were very low in both arms, and no significant difference could be detected between both arms (5.6% for paclitaxel alone vs. 3.6% for paclitaxel plus everolimus) [45]. Response rates, too, were similar in both arms [45]. The addition of everolimus at a dose of 5 mg daily to 12 weeks paclitaxel did not improve the pCR rate in these patients. However, DFS and OS have to be awaited because pCR might not be the appropriate endpoint in this predominantly hormone-receptor-positive cohort.

NSABP B-40 study

After 4 cycles of neoadjuvant chemotherapy consisting of docetaxel or docetaxel plus gemcitabine or docetaxel plus capecitabine, patients received 4 cycles of neoadjuvant AC. Half of the patients also received neoadjuvant bevacizumab. The addition of bevacizumab significantly increased the rate of pathological complete response (28.2% without bevacizumab vs. 34.5% with bevacizumab, $p = 0.02$). In women with TNBC, there was only a non-significant trend favouring treatment with bevacizumab (47.3% vs. 51.3%, $p = 0.44$) [46].

The results of these studies indicate that the addition of bevacizumab to neoadjuvant chemotherapy can improve pCR rates. However, long-term outcome has to be awaited to fully understand the risk-benefit ratio of this treatment approach.

Dual blockade of the HER2-receptor with trastuzumab and lapatinib

The phase III study NSABP B-41 evaluated whether dual HER2 inhibition with trastuzumab plus lapatinib improves pathologic complete response rates when compared to trastuzumab alone

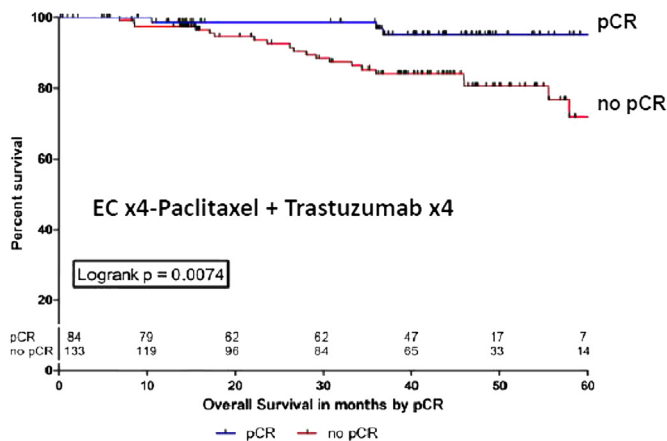


Fig. 4. Techno study overall survival [11,40].

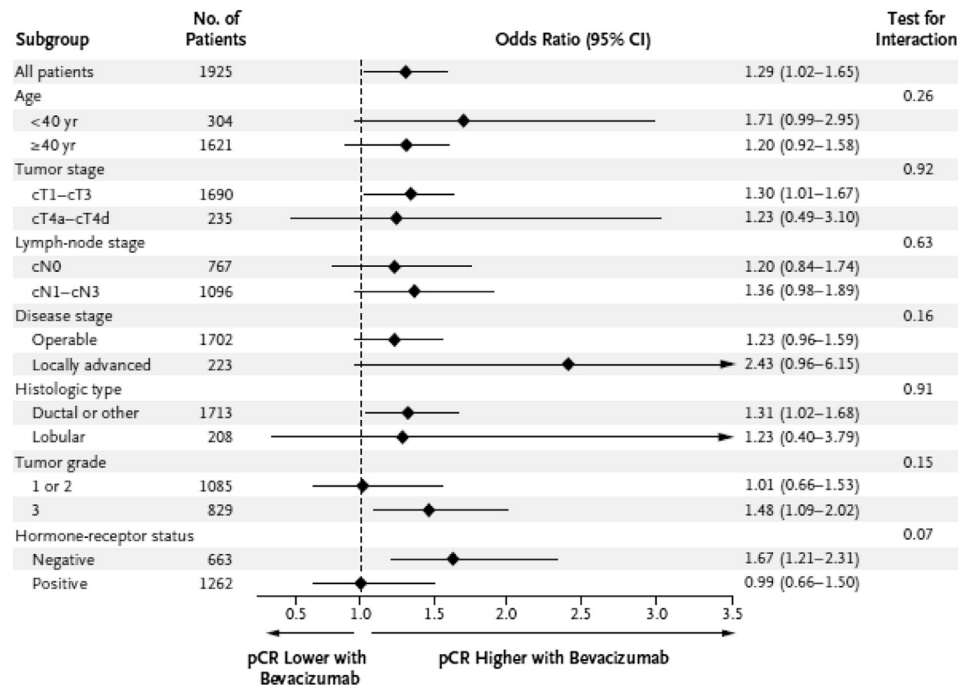


Fig. 5. pCR in GeparQuinto, HER-2-negative patients, according to subgroup. The analyses of subgroups according to tumour and node stage and hormone-receptor status were prespecified and stratified [43].

[47]. The combination of lapatinib and trastuzumab with chemotherapy resulted in higher pCR rates in both hormone receptor–positive and hormone receptor–negative cohorts when compared to single-agent HER2-directed therapy, but the difference was not statistically significant. In patients who had tumours with IHC3+ overexpression, pathologic complete responses were observed in 54.7%, 53.2%, and 71%, respectively ($p = 0.006$ for the combination vs. single agents). This suggests that combined HER2-targeted therapy may be of greatest value in patients with tumours with high levels of HER2 overexpression.

The international, randomized open-label multicenter phase III study Neo-ALTO compared the efficacy of lapatinib plus paclitaxel versus trastuzumab plus paclitaxel versus concomitant lapatinib and trastuzumab plus paclitaxel given as neoadjuvant treatment in HER2-overexpressing and/or amplified primary breast cancer. Following surgery patients received adjuvant FEC followed by the same targeted therapy as given in the neoadjuvant setting for an additional 34 weeks. The total duration of anti-HER2-treatment was 1 year. Of those patients treated with both trastuzumab and lapatinib 51.3% achieved a pCR compared to 29.5% with trastuzumab plus chemotherapy and 24.7% with lapatinib plus chemotherapy ($p \leq 0.0001$). The effect of the dual blockade was especially pronounced in women with hormone receptor-negative disease where 61.3% of the patients achieved a pCR with the dual blockade compared to 36.5% with trastuzumab and 33.8% with lapatinib alone. No cardiac dysfunctions were reported [48]. Patients who achieved pCR had significantly better EFS and OS compared with patients who had no pCR [49]. First DFS results of the ALTO trial were presented at the ASCO meeting 2014. At 4.5 years median follow-up, the dual HER2 blockade with trastuzumab plus lapatinib was not superior to trastuzumab alone in the adjuvant treatment of women with early HER2-positive breast cancer [50].

The approach of the dual blockade of the HER2 pathway is also supported by the results of the CHER-LOB study [51]. 121 patients received chemotherapy with either trastuzumab plus lapatinib,

with trastuzumab alone or with lapatinib alone. The combination of both HER2-inhibitors induced the highest pCR-rate (46.7%).

In summary, available data to date suggest that the combination of trastuzumab and lapatinib significantly increases pCR-rates. As increased pCR-rates have been associated with improved survival especially in patients with HER2 overexpressing tumours [29], dual blockade of the HER2 appears to be a promising future approach for the treatment of women with HER2-positive breast cancer.

Dual blockade of HER2-signalling with trastuzumab and pertuzumab

Pertuzumab is a monoclonal antibody inhibiting dimerization of HER2 with other HER-receptors. The neoadjuvant phase II study NEOSPHERE evaluated the efficacy of pertuzumab and trastuzumab plus docetaxel in 417 women with HER2-positive primary breast cancer [52]. The combination of both antibodies plus docetaxel significantly improved the pCR-rate (45.8%) when compared to docetaxel plus either antibody alone (29% after trastuzumab plus docetaxel and 24% after pertuzumab plus docetaxel, $p = 0.014$). The combination was not associated with increased toxicity or cardiac risk compared to trastuzumab plus chemotherapy. The dual HER2-blockade without concomitant chemotherapy induced a pCR-rate of 16.8%, which raises the important question which patients could benefit from targeted therapy alone without chemotherapy. Based on the results of the NEOSPHERE trial, the FDA granted accelerated approval to pertuzumab for the use in combination with docetaxel and trastuzumab for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.

The three arm TRYPHAENA study evaluated neoadjuvant administration of pertuzumab and trastuzumab with sequential or concomitant anthracycline-based or anthracycline-free chemotherapy [53]. A first analysis showed that the dual blockade was safe without increased risk of cardiac events. Regardless of

chemotherapy, the combination of pertuzumab and trastuzumab in the neoadjuvant setting resulted in high pCR rates (57%–66%) (Fig. 6).

New studies

GeparSixto. The multicenter, prospective, randomized, open-label phase II study GeparSixto was designed to evaluate the efficacy and safety of carboplatin in combination with paclitaxel and liposomal anthracycline (with trastuzumab+lapatinib in HER2-positive and with bevacizumab in triple negative breast cancer, TNBC) as neoadjuvant therapy in patients with untreated HER2-positive or triple-negative invasive breast cancer. All patients were treated with paclitaxel 80 mg/m² and liposomal doxorubicin 20 mg/m² weekly with or without carboplatin weekly at AUC 2 (amended to AUC 1.5 weekly) for a total duration of 18 weeks. Patients with HER2-positive disease receive trastuzumab 8 mg/kg every 3 weeks simultaneously to all cycles and lapatinib at a daily dose of 750 mg (first cycle) and escalated to 1000 mg if well tolerated. Patients with TNBC received bevacizumab 15 mg/kg i.v. day 1 q 21 simultaneously to all cycles. Stratification factors were breast cancer subtype (triple-negative vs. HER2+/HR+ vs. HER2+/HR-) and Ki 67 (<20% vs. ≥20%). The study included 319 triple-negative and 276 HER2-positive patients.

Results of the GeparSixto study showed an increase of the pCR rate from 37.2 to 46.7% by the addition of carboplatin. An absolute increase by >20% was observed in patients with TNBC (37.9% vs. 58.7%), but no increase in patients with HER2-positive breast cancer (36.3% vs. 33.1%) [54]. The observed high efficacy has to be weighed against the treatment discontinuations (39% for paclitaxel/non-pegylated liposomal doxorubicin (+bevacizumab/+trastuzumab/lapatinib) and 48% for paclitaxel/non-pegylated liposomal doxorubicin/carboplatin (+bevacizumab/+trastuzumab/lapatinib). A large biomarker program including BRCA mutations will try to identify subgroups of TNBC that derive even higher benefit from carboplatin. Also, results have to be set into context with the CALGB 40603 phase II study adding bevacizumab and/or carboplatin to weekly paclitaxel followed by dose-dense AC [55]. The addition of bevacizumab significantly increased pCR rates in the breast but not the pCR rates breast/axilla in stage II–III TNBC, and the pCR increase might be outweighed by increased toxicity. Thus, the routine use of bevacizumab in neoadjuvant chemotherapy for TNBC cannot be recommended. Consistent with the results of GeparSixto, adding carboplatin to neoadjuvant chemotherapy significantly increased pCR rates in the breast and breast/axilla.

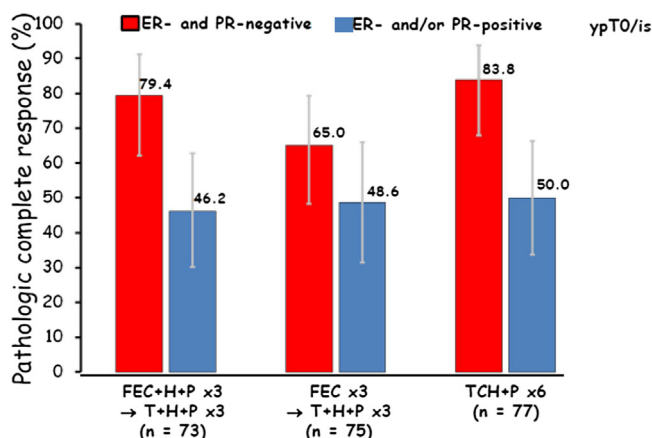


Fig. 6. pCR rates by hormone receptor status in the TRYPHAENA trial [53].

However, CALGB 40603 used a standard and better tolerated chemotherapy backbone and demonstrated a pCR benefit of carboplatin without bevacizumab and also the lack of interaction between these two agents. Results of correlative studies with subtype analysis to identify markers of response or resistance have to be awaited to decide whether carboplatin should be considered part of standard neoadjuvant therapy for stage II–III TNBC.

GeparSepto. The TECHNO, GeparQuattro and GeparQuinto trial demonstrated that the most effective neoadjuvant chemotherapy contains an anthracycline and a taxane. So far, the anthracycline was administered first, but two smaller phase II studies [56,57] and a larger phase-III-study [58] have demonstrated that the reverse sequence appears to increase efficacy. The multicenter, prospective, randomized, open-label phase III study GeparSepto compared paclitaxel to nab-paclitaxel followed by anthracycline in the neoadjuvant setting. Patients with HER2-positive tumours (central pathology confirmed) were treated with trastuzumab and pertuzumab concomitantly (Fig. 7). The study started accrual in August 2012 and achieved the targeted accrual of 1200 patients after 18 months. First results will be presented at the 2014 San Antonio Breast Cancer Symposium.

Future perspective and conclusions

Patients not achieving a pCR may be candidates for post-operative clinical trials exploring novel systemic treatments. The following novel compounds are currently being assessed in the post-neoadjuvant setting.

- Based on the phase III EMILIA study, which showed that trastuzumab emtansine (TDM-1) significantly improved survival of women with HER2-positive metastatic breast cancer [59], post-neoadjuvant treatment with TDM-1 is being compared with the continuation of trastuzumab in HER2-positive patients (Katherine study).
- Based on a randomized phase II study in patients with hormone-receptor-positive metastatic breast cancer showing an improvement of progression-free survival with a hazard ratio of 0.37 [60], palbociclib (PD-0332991), a novel cyclin-D kinase 4/6 inhibitor, is being explored in addition to endocrine treatment in patients with a high score in the clinical-pathologic stage (CPS) + E (estrogen receptor status) + G (grade) staging system (CPS-EG) [61] and no pCR (PENELOPE study).
- Hoosier Oncology Group is conducting a randomized phase-II-study in which patients with a triple negative breast cancer not achieving a pCR after a taxane- and anthracycline-based neoadjuvant chemotherapy are randomized to either cisplatin every 3 weeks × 4 cycles alone or in combination with PARP inhibition rucaparib (CLINICALTRIALS.GOV Identifier: NCT01074970).
- The international randomized phase III study GBG-82 – Olympia is evaluating the efficacy and safety of the PARP inhibitor olaparib (AZD-2281) versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed surgery and neoadjuvant or adjuvant chemotherapy. TNBC patients who did not achieve a pCR after at least six cycles of neoadjuvant chemotherapy containing anthracyclines or taxanes or the combination of both can be enrolled in the neoadjuvant group of the study, starting 1/2014 (BIG 6-13, NSABP B-55).

Another investigational PARP inhibitor is veliparib (ABT-888) which is currently being tested in combination with carboplatin in

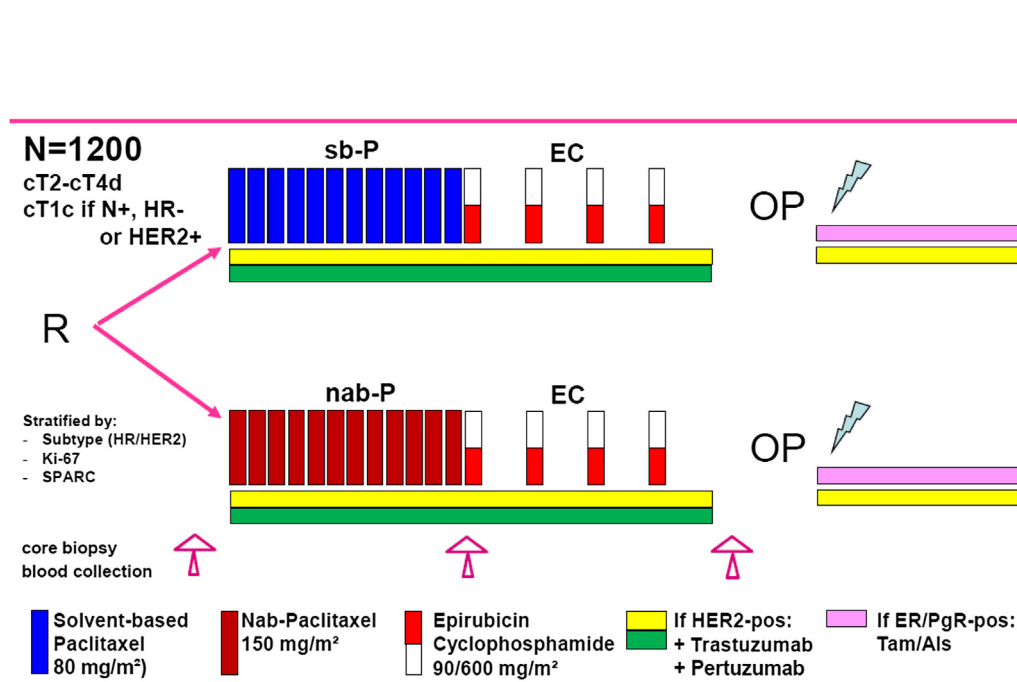


Fig. 7. Trial design of the GeparSepto study.

addition to standard neoadjuvant chemotherapy for early stage TNBC (M14-011, EudraCT 2013-002377-21).

For patients without a pCR, especially if a high proliferation can be detected in the residual tumour after neoadjuvant treatment, prognosis is still unfavourable and clinical trials exploring new targeted agents in this post-neoadjuvant indication may help to improve treatment outcomes. With the evolving knowledge on how best to perform neoadjuvant therapy in the various subtypes and how to use the information gained for the individual patient, neoadjuvant therapy is being increasingly used in patients with operable primary breast cancer. The importance of neoadjuvant therapy for clinical breast cancer research has recently been recognized by the FDA guidance to use pCR rate in breast cancer patients as a potential endpoint for accelerated approval regulations.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work (employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding)., MU has no conflicts to declare, GEK has no conflicts to declare, SP has no conflicts to declare, GvM: Research funds from Amgen, Celgene, Cephalon, GSK, Novartis, Pfizer, Roche, and Sanofi-Aventis, Honoraria from Amgen, Celgene, Roche and Sanofi-Aventis.

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