

Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006

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Received 5 April 2007; accepted 13 April 2007

Neoadjuvant (primary systemic) treatment has become a standard option for primary operable disease for patients who are candidates for adjuvant systemic chemotherapy, irrespective of the size of the tumor. Because of new treatments and new understandings of breast cancer, however, recommendations published in 2006 regarding neoadjuvant treatment for operable disease required updating. Therefore, a third international panel of representatives of a number of breast cancer clinical research groups was convened in September 2006 to update these recommendations. As part of this effort, data published to date were critically reviewed and indications for neoadjuvant treatment were newly defined.

Key words: breast cancer, neoadjuvant therapy, recommendations

introduction

Neoadjuvant systemic therapy (NST) has become a frequently used option for systemic therapy in primary operable breast cancer. The quintessence of the last meeting is that all patients with a clear indication for adjuvant cytotoxic treatment can be offered chemotherapy preoperatively. These recommendations focus on early response to NST and on tailoring therapy to response and biological and histological markers. A chapter dealing with radiotherapy has been added. As before [1], the manuscript refers to operable breast cancer only but recent results demonstrate that patients with locally advanced disease have comparable benefits from the same neoadjuvant treatment [2].

methods

In September 2006, an international panel of representatives of a number of breast cancer clinical research groups was convened for a third

biannual meeting in Biedenkopf, Germany. The panel members comprised experts in the areas of medical oncology, breast surgery, breast diagnostics, pathology, radiodiagnostics, and radiation oncology. Available data from all prospective clinical trials of NST in patients with operable breast cancer, including abstracts published in the proceedings of meetings of ASCO (American Society of Clinical Oncology), SABCS (San Antonio Breast Cancer Symposium), ECCO (European Conference of Clinical Oncology), ESMO (European Society of Medical Oncology), and EBCC (European Breast Cancer Conference), were critically reviewed the objectives of updating the recommendations published in 2006.

recommendations

aims of primary systemic treatment

Three main goals for NST in operable breast cancer were defined:

- to reduce mortality from breast cancer with reduced toxicity;
- to improve surgical options;
- to acquire early information on response and biology of the disease.

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Response to neoadjuvant chemotherapy is used in clinical research as an intermediate endpoint for breast cancer recurrence and survival.

candidates for NST

As stated in the earlier recommendations a meta-analysis of the published results showed no difference between neoadjuvant therapy and adjuvant therapy in terms of survival and overall disease progression. The individual patient data from these trials are currently being analysed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Therefore, neoadjuvant treatment can be offered as a standard treatment and as an alternative to adjuvant treatment to all patients who are expected to be candidates for adjuvant systemic chemotherapy.

in which patients is NST with cytotoxic agents the preferred treatment?

- 1 Breast conserving surgery (BCS) is not possible or is likely to be suboptimal in terms of cosmesis.

- 2 Patients whose tumors express markers of good response to chemotherapy (low or absent hormone-receptor status, high-grade, non-lobular invasive histology, high Ki67, luminal B) should be considered for NST.

in which patients is NST with endocrine agents the preferred treatment? Endocrine NST alone would be appropriate mainly for patients in whom BCS is not possible or likely to be suboptimal in terms of cosmesis *and* who are not candidates for neoadjuvant or adjuvant cytotoxic chemotherapy *and* in whom predictive markers for endocrine responsiveness or chemotherapy unresponsiveness are present (estrogen receptor (ER) and progesterone receptor (PgR) positive, low grade, invasive lobular histology, low Ki67).

appropriate type of NST

Anthracycline- and taxane-based therapies are widely used. Capecitabine and Gemcitabine have been recently incorporated into trials assessing neoadjuvant chemotherapy (Table 1) [3–5]. Most trials are still ongoing.

Table 1. Current running and closed but unpublished neoadjuvant trials

Author/Trial	No. of patients	Regimen 1	Regimen 2	Regimen 3	Aim
ABCSG-24	460	EDX	ED		pCR 16 vs. 27%
ABCSG-24H		EDXH	EDH		pCR
EORTC (Lapatax), phase I	84	FECx3-Dx3+L	FECxe-Dx3+H		50%pCR in the 2nd regimen
EORTC (pre-ALTTO)	250	L 3weeks	H 3xweekly	H+L 3w	Change in apoptotic and EGFR pathway
EORTC	1860	No taxane	Taxane		PFS stratified by p53
EORTC II	490	AP-CMX	AP-CMF		
French	200	CEX-D	FEC-D		
German Breast Group (Geparquattro)	1510	AC-D (+H)	AC-DX (+H)	AC-D-X (+H)	To evaluate the X and the duration of the treatment. To evaluate H in Her-2 positive tumors
German Breast Group (Geparquinto I)	1300	EC-DX	ECB-DXB		pCR with or without B
German Breast Group (Geparquinto II)	540	EC-Pw	EC-PwRad001		Comparing the pCR in patients not responding to initial four cycles of EC
German Breast Group (Geparquinto III)	600	ECH-DXH	ECL-DXL		pCR with H compared to L
Korean	200	XD	AC		
MDACC	930	XD-FEC	P-FEC		
Neo-ALTTO	450	L+P	H+P	H+L+P	
NSABP (NSABP-B40)	2000	D-AC+/-B	DX-AC+/-B	DG-AC+/-B	Adding capecitabine or gemcitabine to docetaxel followed by AC, with or without bevacizumab, will increase the breast pCR rates addition of bevacizumab to 3 docetaxel/anthracycline-based regimens will increase breast pCR rates
REMAUS 02	340	ECx4-Dx4	ECx4-Dx4+H	ECx4-Dx4+ celecoxib	pCR H randomized in HER2+ Coxib in HER2-
Royal Marsden (POETIC)		Periop AI			
UK (Neo-TANGO)	800	P (dd)-EC	EC-P (dd)	GP (dd)-EC	

A, doxorubicin; E, epirubicin; P, paclitaxel; D, docetaxel; V, vincristine; F, 5-fluorouracil; C, cyclophosphamide; G, gemcitabine; N, vinorelbine; M, methotrexate; X, capecitabine; B, bevacizumab; H, trastuzumab; L, lapatinib; Rad 001, everolimus; AI, aromatase inhibitor; w, weekly; dd, dose-dense.

Combined or sequential use of anthracyclines and taxanes are both acceptable.

Trastuzumab should be incorporated into the regimen in patients with Her-2/neu positive disease, but concomitant use with an anthracycline (preferably one with lower cardiac toxicity, e.g. epirubicin/pegylated doxorubicin) should only occur in clinical trials. The concomitant application of trastuzumab and epirubicin seems safe as demonstrated in the Geparquattro trial of the German Breast Group and the MD-Anderson trial [6].

There are limited data on the use of preoperative endocrine treatment in premenopausal patients. A combination of Gonadotropin Releasing Hormone analogue (GnRH) and letrozole in premenopausal patients with ER and PgR $\geq 10\%$ with a median duration of 5 and 4 months, respectively, demonstrated a pCR of 3% and a rate of breast conservation of 42% [7]. A tailored approach of chemoendocrine therapy with or without an AI demonstrated pCR rates of 7% and 11%, respectively, and BCS rates of 62% and 58%, respectively [8]. However, none of the approaches can be used as a routine therapy. As has been stated before, chemotherapy and tamoxifen should be delivered sequentially but no such data exist for ovarian function suppression (OFS). Hence, the concomitant use of any indicated chemotherapy with GnRH might be considered as acceptable in women with a desire of pregnancy [9]. A combined chemoendocrine approach, including an aromatase inhibitors (AI), is investigational.

The AIs are well-established in the neoadjuvant endocrine treatment of postmenopausal women with hormone-responsive tumors. The IMPACT trial could not demonstrate a significant benefit in terms of the clinical response rate for the AIs over tamoxifen [10].

appropriate duration of NST

It has been accepted that the chemotherapy should be completed before surgery, except for the rare patient in whom disease progression during treatment threatens to make the patient inoperable. At least six cycles should be administered over 4 to 6 months. Endocrine treatment should be given for 4 to 6 months before proceeding to surgery [11].

early response evaluation

To avoid unnecessary toxicity without potential for benefit from the treatment, early response evaluation should be performed. The time of response evaluation depends on the treatment given and should be performed 6–9 weeks after the start of treatment.

Patients with an early clinical response seem to derive the most benefit from a non cross-resistant regimen. In patients with insufficient early response, especially progressive disease, a switch of treatment should be considered. The aim in those patients is to spare toxicity because they gain little, if any, benefit from a non cross-resistant regimen.

predictors of response or resistance

Predicting the chance of response to treatment before starting NST is an important research goal. Patients with a low chance of a pCR, and especially a low chance of a clinically useful response, might then be spared unnecessary toxicity [12].

Patients whose tumors express markers predictive of chemo-response are the best candidates for neoadjuvant chemotherapy. Negative hormone receptor status is one of the strongest predictive markers for chemo-response in general. Tumors completely lacking such receptors were found to be particularly sensitive to preoperative cytotoxic agents, but despite a pathological complete remission rate exceeding 40%, survival of patients with this phenotype was reported in several studies to be shorter than for those with receptor-positive tumors [13–15].

Several neoadjuvant trials demonstrate a difference between lobular invasive and ductal invasive carcinomas in terms of response to NST and BCS [16–18]. However, there is still a debate as to whether the lower response rate of lobular cancers to NST translates into a worse overall survival.

Recently, investigations have concentrated on predicting response to specific therapies based on various biological markers. Her-2/neu was one of the most intensively studied ones. So far there is no clear evidence that Her-2/neu positive breast cancers respond better than negative ones to anthracycline- and taxane-based chemotherapy [19–20]. Her-2/neu negative breast cancer patients might respond better to a taxane than to an anthracycline treatment [21]. Topoisomerase II α has been demonstrated to be an independent predictor of clinical tumor response, especially to anthracycline, but in a gene array, analysis failed to predict pCR [22, 23]. It is unlikely that a single biologic marker will ever be able to differentiate definitively between responders and non-responders [24].

An alternative to measuring one specific marker is to use a combination of different markers and/or the establishment of a specific gene-expression profile that can predict response to neoadjuvant therapy. Gene-expression profiling has become quite popular, but has so far failed to identify a definitive population that should be spared chemotherapy, nor has this approach identified a population that has more than an 80% chance of a pCR (Table 2).

It is well known that patients with a pCR have a better overall survival than those who did not achieve a pCR. Data are limited regarding the prognostic significance of residual *in situ* ductal cancer (DCIS) [25, 26]. Apart from the pCR in the breast, one of the most important prognostic factors after neoadjuvant therapy is the post-treatment lymph node status [27].

Chemosensitivity testing is investigational and should not be used outside clinical trials.

imaging. Imaging is an important adjunct to neoadjuvant therapy. Before starting therapy, it helps to identify the extent of the disease; during therapy it can be used to evaluate response; and after NST, it may assist with evaluation of the extent of residual tumor and to guide surgery. It will be important to identify accurate methods for measuring early treatment response in order to maximize treatment effect and minimize treatment toxicity without benefit.

Clinical examination based on palpable change in tumor size is the most common method for monitoring treatment effect. However, it seems advisable to perform ultrasound and clinical examination in combination with mammography

for response evaluation to rule out over as well as under-estimation of response [28]. In case of ambiguous results, multicentricity, and lobular invasive cancers, a quantitative contrast-enhanced Magnetic Resonance Imaging (MRI) might be helpful [29] (Table 3). Some studies have shown MRI to be superior to mammography, ultrasound, and clinical examination in evaluating the extent of the tumor [30]. The agreement of pathologic residual tumor size with mammography or sonography residual tumor is moderate, especially in lobular invasive cancers [31, 32]. Investigations suggest that findings on MRI strongly correlate with the pathological response [33]. At the time of surgery, MRI may therefore help to identify residual disease more accurately.

Studies in the neoadjuvant setting demonstrate that [F-18] Fluorodeoxyglucose Positron Emission Tomography (FDG PET) might predict pathologic response at 2 to 3 months after the start of chemotherapy [34–36]. Combining FDG PET and MRI for response evaluation was shown to be complementary [37]. However, changes in imaging generally manifest themselves later than changes in underlying tumor function, e.g. vascular density and permeability [38]. Newer techniques, such as proton magnetic resonance spectroscopy, diffusion weighted imaging [39], interstitial fluid pressure [40] and Doppler ultrasound are under investigation.

local treatment: surgical issues and radiotherapy

surgical management of the breast. Breast surgery after primary chemotherapy should be performed according to the guidelines for breast surgery without prior systemic therapy. Breast-conservation techniques include lumpectomy, wide excision, and quadrantectomy [41]. For medium and large breasts, dermoglandular flaps can be used to fill the excision site. If intramammary glandular flaps are used or if reduction mammoplasty techniques are used, the initial tumor location should be marked by clips to allow planning of subsequent breast irradiation [42].

If mastectomy is indicated, postoperative radiotherapy is also indicated in most of these patients, and therefore breast reconstruction should usually be delayed until 6–12 months after completion of breast irradiation.

Data on breast conservation after neoadjuvant chemotherapy is limited, but several studies have demonstrated that NST can increase the feasibility of breast conservation without adversely affecting survival. There are some factors that might influence the success of BCS, such as tumor size, lymphatic invasion, nodal status, or diffuse microcalcifications [43, 44]. Also, some data suggest that converting young patients who were not candidates for breast conservation to lumpectomy candidates with NST may be associated with

Table 2. Gene expression profiles for predicting pCR

Author	n	Objective	PST	Genes	Accuracy % (95%CI)	PPV/NPV %	N
Ayers et al. (2004) [64]	42	ypT0/is	PAC-FAC	74	85 (52–94)	100/73	18
Hannemann et al. (2005) [65]	48	ypT0/is	AC/AD				
Thuerigen et al. (2006) [66]	100	ypT0/is	GE-D GEDoc	512	88 (75–95)	64/95	48
Hess et al. (2006) [67]	133	ypT0/is ypN0	PAC-FAC	26	76 (62–87)	52/92	51
Rody et al. (2005) [68]	50	ypT0	TAC	70			
Chang et al. (2003) [69]	24	cRR	D	92	100		
Iwao-Koizumi et al. (2005) [70]	44	cRR	D	85	80	73	
Cleator (2006) [71]	40	cRR	AC	293	67		
Gianni et al. (2005) [72]	86	pCR	AP-P	Ass		Sign association	

A, doxorubicin; E, epirubicin; P, paclitaxel; D, docetaxel; F, 5-fluorouracil; C, cyclophosphamide; G, gemcitabine; PPV, positive predicate value; NPV, negative predictive value.

Table 3. Prediction of pathological response by clinical evaluation

Author	n	Correlation coefficient with pathological tumor size with presurgical tumors size				
		Physical examination	Mammography	Sonography	MRI	Others
Forouhi et al. (1994) [56]	35	0.88	0.96	0.94	–	–
Gawne-Caine (1995) [57]	16	0.74	0.85	0.61		
Herrada et al. (1997) [58]	100	0.73	0.6	0.65		
Akashi-Tanaka et al. (2001) [59]	57	0.57	0.56	0.55		
Fiorentino et al. (2001) [60]	141	0.68	0.29	0.33		
Bodini et al. (2004) [61]	73	0.58			0.72	
Chagpar et al. (2006) [32]	189	0.42	0.42	0.41		
Peintinger et al. (2006) [31]	162		0.66			
Belli et al. (2006) [62]	45				0.97	
Akazawa et al (2006) [63]	38	0.55		0.48	0.90	

MRI, Magnetic Resonance Imaging.

a higher risk of local recurrence. However, this does not appear to compromise patient overall outcomes.

Surgical planning and execution should take into account the size of the original tumor and the response to NST [45].

surgical management of the axilla. The standard surgical procedure for staging the axilla has been axillary dissection, aiming at removal of at least 10 axillary lymph nodes. Sentinel lymph node biopsy (SLN) before the start of NST is an option that has been advocated by some. The accuracy of SLN biopsy for determining lymph-node status before primary surgery has been confirmed in a metaanalysis with pooled data from 69 trials with more than 8000 patients [46]: 30% of patients with T1 tumours had involved lymph nodes.

SLN biopsy after NST is an acceptable approach in patients with clinically tumor-free axillary lymph nodes after NST. It may be performed with accuracy that is comparable to that in primary surgery patients [47]. The identification rate (pooled estimate 90%) and the false-negative rate (pooled estimate 12%) for SLN biopsy reported in a recent meta-analysis were similar for patients with and without preoperative chemotherapy [48]. The SLN biopsy procedure and histologic examination should be performed according to the consensus recommendations [49, 50]. However, this procedure is still controversial after neoadjuvant chemotherapy and should therefore be used with caution in patients presenting with grossly positive nodes, and only in patients with a clinically negative axilla after chemotherapy. Patients should be informed by the surgeon that this approach is unproven. Intraoperative frozen sections of the SLN should be performed. In the subsequent paraffin histology, step sections, as well as immunohistochemical staining for epithelial markers such as cytokeratins, should be performed. If the frozen section and the definitive histology show no tumor cells in the SLN, axillary dissection is not needed and the axilla can be considered tumor-free. If SLN mapping fails or if the SLN is positive for metastases ($> 0.2\text{mm}$), then standard axillary dissection should be carried out.

We cannot yet identify any patients with certainty who might forego excision of the primary tumor site. Whether we could spare the patient the operation on the axilla has not been systematically investigated in those patients who respond well to NST and have a clinically negative axilla.

radiotherapy. It has been proven that systemic treatment and radiotherapy are independent factors influencing the outcome of patients with operable breast cancer [51]. However, the addition of preoperative radiotherapy to NST in patients with operable tumors has not yet been adequately proven to be effective. Limited data demonstrate additional benefits in terms of higher rates of pCR and BCS, especially in T3 and T4 tumors. Regardless, since up to one-third of patients with clinical complete remission after NST still have pathologic evidence of residual tumor in the breast, radiotherapy alone cannot replace adequate surgery [52].

It appears that postmastectomy radiation therapy is beneficial in patients with an initial T3 or T4 tumors, even in those who subsequently achieved a pCR, because the rate of locoregional recurrence remains high in these patients [53].

Postmastectomy radiotherapy is not justified in patients with T1 or T2 disease and one to three involved lymph nodes because of the low 5-year risk of local regional recurrence in these patients [54]. However, since the number of involved lymph nodes can be altered by NST, postmastectomy radiotherapy should also be considered in patients who present initially with clinically positive lymph nodes.

potential risk for local recurrence

Some patients will not be good candidates for breast conservation after NST, regardless of response. For example, women with pathologically proven multi-centric disease, should generally undergo mastectomy. It is not clear that they will benefit from NST outside of a clinical trial, unless they present with locally advanced or inoperable disease. Younger patients (< 40) who undergo breast-conserving treatment that was not possible without NST may have a higher local recurrence rate than other patients, but this does not necessarily compromise patient survival, and may reflect the biology of breast cancer in this population more than the choice of treatment. Since these women are often the most emphatic in desiring breast conservation, age should not be a contraindication to using NST to achieve this goal.

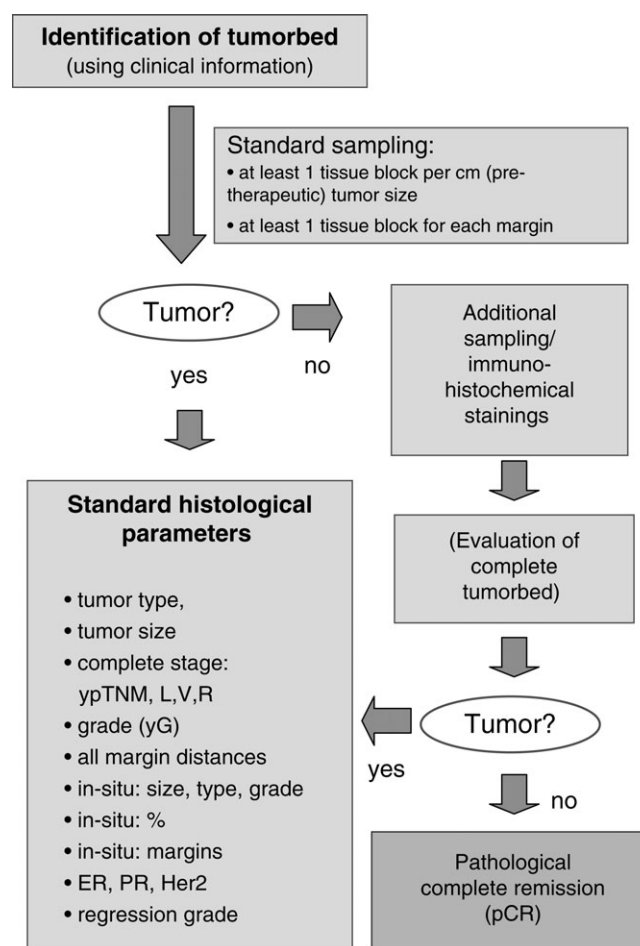


Figure 1. Standardized histopathological approach to the assessment of breast cancer specimen from neo-adjuvant chemotherapy.

Table 4. Four essential parameters the surgeon should provide to the pathologist for each tumor resection specimen from neoadjuvant therapy

Clinical information	Why is this information important for the pathologist?
1. A neoadjuvant therapy has been performed (cytotoxic or endocrine).	Different histopathological approaches after neo-adjuvant therapy: <ul style="list-style-type: none"> • modified tumor classification (ypTNM) and regression grading have to be reported; • histological changes in poor-responders may be very uncharacteristic and may therefore not be recognized without clinical information.
2. The pretherapeutic tumor size and localization.	The histopathological evaluation for complete pathological response is dependent on the size and localization of the pretherapeutic tumor bed which cannot necessarily be determined from the resection specimen itself.
3. Localization of residual tumor foci in clinical and imaging approaches.	To reduce local recurrences after neoadjuvant therapy, an adequate sampling of margins is mandatory. Since residual tumor may be discontinuously located close to the margins, an exact clinical description of the localization is needed.
4. Clinical response.	In the setting of clinical complete response, the macroscopic evaluation and the sampling will be extended. Histological workup time will be much shorter if this information is given when sending the specimen.

The Early Breast Cancer Trialists' Collaborative Group demonstrated in the 2006 meta-analysis a slightly increased risk for local recurrence (by absolute 3%) for patients with neoadjuvant therapy. However, the analysis includes some old trials with less efficient chemotherapy regimens, which are not used any longer. Reports from single institutions and more modern treatment could not demonstrate a negative effect. Another meta-analysis on this issue suggested that higher local recurrence rates after NST are mostly the result of trials that allowed RT alone without surgery after NST [55]. The risk of local recurrence may be optimized by efficient communication between surgeons and pathologists.

standardized pathology approach

Before starting any NST, a core biopsy should be performed to confirm the diagnosis of invasive cancer and to obtain predictive markers such as histological subtype, tumor grading according to Elston and Ellis, ER and PgR status and Her-2/neu status.

The surgical specimen should be examined in a standardized approach (Figure 1). The pathologist should determine the size of residual tumor (invasive and non-invasive separately), the tumor free margins in all six directions of the specimen, the regression score (using one of the national or international scoring systems) and repeat the ER, PgR, and Her-2/neu assessments at least for initially negative disease. For nodal status the pathology report should give the total number of nodes, the number of positive nodes with information on the size of the metastatic foci and regressive changes, as well as the number of nodes with therapy-induced regressive changes, but without residual tumor cells. All tumor parameters should be reported according to the TNM system with the addition of "y" to indicate the status post therapy.

Conversely, the pathologist needs to be given clinical information (Table 4) for optimization of the histopathological work up. Quality control can be assured by spot-checking and monitoring of pathology reports.

conclusion and recommendations

For patients to be treated with NST chemotherapy, at least six cycles of an anthracycline- and taxane-containing regimen should be planned and given preoperatively over 4–6 months.

Trastuzumab should be included in the regimen for patients with Her-2 positive tumors. The concurrent use of Trastuzumab with an anthracycline containing regimen should only be given in clinical trials.

LHRH analogues in premenopausal patients are investigational.

Primary endocrine therapy with aromatase inhibitors (AIs) should be offered to women if the tumor is expected to be highly endocrine responsive.

Concepts for clinical trials related to NST:

- large adjuvant trials should be preceded by adequately powered randomized neoadjuvant trials to support the validity of the scientific question and the statistical design;
- role of RT in pCR patients (need and schedule);
- RT and surgery trials need to be funded.

Outside clinical trials:

- patients need to be referred to a breast surgeon and a radiation oncologist before initiating NST (multidisciplinary management approach is mandatory);
- to avoid extensive local relapse, close follow-up by members of all involved disciplines is needed throughout the course of treatment and after completion of therapy;
- SLN biopsy can be offered to women after neoadjuvant therapy.

acknowledgements

We thank the independent BANSS-Foundation, Biedenkopf, Germany, for supporting the meeting.

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