Ann Surg Oncol (2012) 19:1508–1516
DOI 10.1245/s10434-011-2108-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

# Recommendations from an International Consensus Conference on the Current Status and Future of Neoadjuvant Systemic Therapy in Primary Breast Cancer

**Manfred Kaufmann[1], Gunter von Minckwitz[2], Elefhterios P. Mamounas[3], David Cameron[4], Lisa A. Carey[5], Massimo Cristofanilli[6], Carsten Denkert[7], Wolfgang Eiermann[8], Michael Gnant[9], Jay R. Harris[10], Thomas Karn[1], Cornelia Liedtke[11], Davide Mauri[12], Roman Rouzier[13], Eugen Ruckhaeberle[1], Vladimir Semiglazov[14], W. Fraser Symmans[15], Andrew Tutt[16], and Lajos Pusztai[17]**

[1]Department of Gynecology and Obstetrics and Breast Unit, Goethe University, Frankfurt, Germany; [2]German Breast Group, Neu Isenburg, Germany; [3]Aultman Cancer Center, Canton, OH; [4]Edinburgh Cancer Research Center, University of Edinburgh, Edinburgh, Scotland, UK; [5]Division of Hematology-Oncology, University of North Carolina, Chapel Hill, NC; [6]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA; [7]Institute of Pathology, University Hospital Charité, Berlin, Germany; [8]Women's Hospital, Red Cross Clinics, Munich, Germany; [9]Department of Surgery, Medical University of Vienna, Vienna, Austria; [10]Department of Radiation Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [11]Department of Gynecology and Obstetrics, University Hospital Muenster, Muenster, Germany; [12]Department of Medical Oncology, General Hospital of Lamia, Lamia, Greece; [13]Department of Obstetrics and Gynecology, Hôpital Tenon, Paris, France; [14]N.N. Petrov Research Institute of Oncology, St. Petersburg, Russia; [15]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; [16]Breakthrough Breast Cancer Research Unit, Guy's Hospital Campus, King's College London School of Medicine, London, UK; [17]Department of Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

**ABSTRACT** The use of neoadjuvant systemic therapy (NST) for the treatment of primary breast cancer has constantly increased, especially in trials of new therapeutic regimens. In the 1980 s, NST was shown to substantially improve breast-conserving surgery rates and was first typically used for patients with inoperable locally advanced or inflammatory breast cancer. Investigators have since also used NST as an in vivo test for chemosensitivity by assessing pathologic complete response. Today, by using pathologic response and other biomarkers as intermediate end points, results from trials of new regimens and therapies that use NST are aimed to precede and anticipate the results from larger adjuvant trials. In 2003, a panel of representatives from various breast cancer clinical research groups was first convened in Biedenkopf to formulate recommendations on the use of NST. The obtained consensus was updated in two subsequent meetings in 2004 and 2006. The most recent conference on recommendations on the use of NST took place in 2010 and forms the basis of this report.



First Received: 20 January 2011;
Published Online: 23 December 2011

M. Kaufmann
e-mail: M.Kaufmann@em.uni-frankfurt.de

Since the last consensus meeting on neoadjuvant systemic therapy (NST) in 2006, knowledge has increased on intrinsic subtype responses, different chemotherapy and trastuzumab regimens' response evaluation, and the use of sentinel lymph node biopsy (SLNB).[1] The aim of this update was to integrate this new knowledge into the current practice of NST in primary breast cancer.

## METHODS

In September 2010, an international panel of representatives of breast cancer clinical research groups was convened in Biedenkopf, Germany, for a fourth meeting on NST in operable breast cancer (Table 1). The panel comprised experts in medical oncology, breast surgery, diagnostics, pathology, radiation oncology, and modern genomic methods in breast cancer (six members from the United States and 13 from six different European countries). The presentations

**TABLE 1** Panel members and titles of presentations at the meeting

| Panel member | Presentation title |
|---|---|
| Davide Mauri, Roditsa Lamia, Greece | General: Neoadjuvant vs. Adjuvant |
| Manfred Kaufmann, Frankfurt, Germany (Chair) | Local Treatment: Surgery of the breast, axilla (SLN) |
| Jay R. Harris, Boston, USA | Local Treatment: Radiotherapy |
| Massimo Cristofanilli, Philadelphia, USA | Pathology, Subentities: Inflammatory, local advanced |
| Andrew Tutt, London, UK | Pathology, Subentities: *BRCA1/2* |
| Lisa Carey, Chapel Hill, USA | Pathology, Subentities: Triple negative/lobular |
| Michael Gnant, Wien, Austria | Systemic Treatment: Chemotherapy |
| Wolfgang Eiermann, München, Germany | Systemic Treatment: Trastuzumab |
| David Cameron, Edinburgh, UK | Systemic Treatment: Endocrine |
| Vladimir Semiglazov, St.Petersburg, Russia | Systemic Treatment: Chemotherapy Versus Endocrine |
| Gunter v. Minckwitz, Neu-Isenburg, Germany (Chair) | Systemic Treatment: New agents |
| William Fraser Symmans, Houston, USA | Response Assessment: PET/MRI, Pathology |
| Roman Rouzier, Paris, France | Response Prediction: Nomograms |
| Carsten Denkert, Berlin, Germany | Response Prediction: Histology (conventional) |
| Lajos Pusztai, Houston, USA | Response Prediction: Gene Signatures |
| Cornelia Liedtke, Münster, Germany | Long Term Outcome: Postoperative Endocrine Treatment |
| Elefhterios Mamounas, Canton, Ohio, USA (Chair) | New Trials, Future Aspects |
| Thomas Karn, Frankfurt, Germany | (meeting protocol, manuscript preparation) |
| Eugen Ruckhäberle, Frankfurt, Germany | (meeting protocol, manuscript preparation) |

on the different aspects of NST were solicited to provide an overview of current knowledge (Table 1). Presenting panel members were charged with reviewing all available data from published prospective clinical trials of NST (published reports indexed on Medline) and abstracts published in the proceedings of the American Society of Clinical Oncology (ASCO), San Antonio Breast Cancer Symposium (SABCS), European Cancer Organisation (ECCO), European Society for Medical Oncology (ESMO), and European Breast Cancer Conference (EBCC). The presentations were discussed, and 12 questions were debated to formulate a consensus. The recommendations in this article were approved by all panelists.

## RECOMMENDATIONS

### *What Are the Medical Aims of NST?*

The most important clinical goals of NST are to improve disease-free and overall survival and enable more limited surgery. The general research goal is to learn how to individualize systemic therapy, with tumor response used as a metric. NST also maximizes benefits of a multidisciplinary approach because a decision on timing and type of local and systemic treatment needs to be agreed on by all treating physicians with critical input from breast imagers and pathologists.

The proven benefits of NST justifying its routine clinical use include the following: it improves disease-free survival and overall survival to the same extent as postoperative chemotherapy; it increases breast-conserving surgery (BCS) rates in patients with operable locally advanced breast cancer (clinical stages IIIA except of T3N1M0, IIIB, and IIIC); and it reduces the extent of resection in cancers >2 cm even if a patient is a candidate for BCS.[2,3] The extent of residual cancer after NST is a powerful prognostic marker.[4,5]

Still-unproven benefits of NST may include the following: the opportunity to monitor response during NST with the potential of an adjustment in systemic therapy; an improvement in cosmetic outcome for candidates for BCS at diagnosis; and a decrease in the extent of axillary surgery by downstaging nodes and performing SLNB after NST.[1] However, prospective trials have not yet established beyond doubt that the omission of full axillary dissection is safe when initially pathologically positive nodes yield negative SLNB samples after NST.

Some of the above benefits demonstrated for NST in trials may also apply to neoadjuvant endocrine therapy (NET). However, far fewer studies and knowledge on NET are available. NST also represents and important research tool in clinical trials to identify molecular predictors of response, to identify pharmacodynamic markers and allow direct examination of drug effects on targets through serial biopsies, and to permit rapid identification and comparison of promising new systemic treatments that could be prioritized for validation in the adjuvant setting.[6]

*Who Should or Should Not Be Considered for NST?*

Generally, any patient who is a candidate for adjuvant systemic chemotherapy can be considered for NST. The main expected benefit from NST is reduction of the extent of surgery. Patient preference should always be taken into account. However, patients with inoperable or inflammatory breast cancer should be recommended to receive NST.[7] Patients who desire BCS but are less than optimal candidates should, in the absence of contraindications to radiotherapy, be counseled about the benefits of NST. The largest benefit by NST is realized in those patients who have a high likelihood for a pathologic complete response (triple-negative or high-grade estrogen receptor [ER]-positive, and HER2-positive breast cancer).[4] If disease manifests with axillary involvement, NST may even convert disease to be pathologically node negative, providing the opportunity for less extensive axillary surgery and decrease in the need for locoregional radiotherapy. However, evidence for this potential benefit is evolving, and considerable debate exists, especially as a result of differences in management and clinical structures between the United States and Europe.

Patients with small (<2 cm) tumors and those with ER-positive low-grade cancers or pure (classic) invasive lobular cancers have the smallest expected benefit from NST (Fig. 1).[4,8,9] However, clinical responses are common, and surgical downstaging of inoperable cancers may still be possible.[10,11]

NST should not be recommended routinely when there is uncertainty regarding the appropriateness of chemotherapy (i.e., small [<2 cm], ER-positive/HER-2neu negative, or low or intermediate grade with clinically negative nodes). Such a patient may be treated with adjuvant hormone therapy only.

*How Should pCR Be Defined?*

The definition of pCR (pathologic complete response) should be based on histopathologic assessment, including absence of invasive cancer in both breast and lymph nodes.[4] Patients with complete response in the breast but positive lymph nodes in the axilla have a far worse prognosis than patients with true pCR.[12] The presence, extent, and classification of ductal carcinoma-in situ (DCIS) should be reported separately.[13]

*Which Histopathologic Assessments of the Surgical Specimen Are Required?*

Minimal assessment includes the identification of the tumor bed (this is easier after inserting a clip before NST) and radiographic examination of resected specimen to ensure all suspicious calcifications and involved regions are removed.[14] Complete macroscopic examination and immunohistochemistry of ER, progesterone receptor, and HER2 must be performed unless they were already established by the original diagnostic core biopsy. Repeat

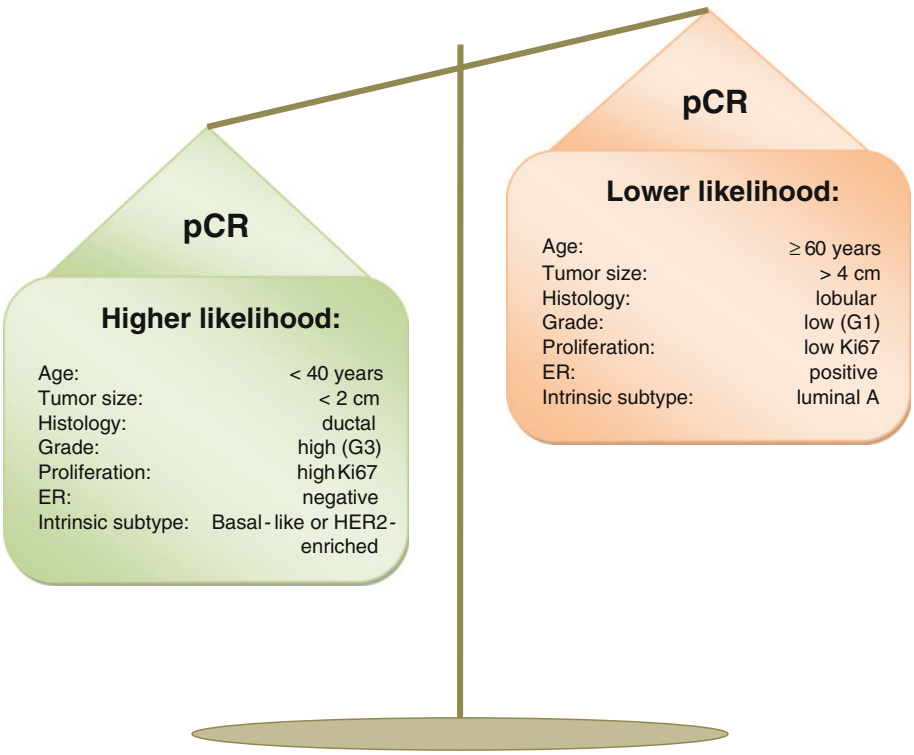


**FIG. 1** Likelihood of pCR in NST of breast cancer

receptor determination is not necessary if good-quality results are available. The sentinel nodes should be sliced serially at a 2-mm distance.[15] Routine immunohistochemistry for isolated tumor cells in lymph nodes is not indicated because their prognostic impact is still uncertain.

A standardized protocol for assessment of invasive tumor size and percent cellularity should be used (e.g., http://www.mdanderson.org/breastcancer_RCB).

### *Can pCR Serve as a Surrogate Marker for Outcome?*

For nearly all recently completed and ongoing NST trials, pCR is the primary end point. In every individual study and a recent overview, pCR has been consistently shown to be associated with excellent long-term survival (Table 2). Unfortunately, 60–85% of patients do not experience pCR, even with modern regimens.[4,5] Long-term survival of patients with residual cancer depends on its extent and baseline prognosis.[5] For example, low-grade cancers have low pCR rates but often favorable survival.[4] Small differences in pCR rates between arms in randomized trials may not translate into relevant survival differences unless unrealistically large sample sizes are pursued. Thus, observed differences in pCR have to be validated by long-term outcome to change clinical practice. Similar to other outcome measures, comparisons of pCR rates between independent trials are not sufficiently reliable to establish superior regimens because subtle differences in patient characteristics, such as ER and grade, can have substantial impact.

For NET, pCR is less frequent and not the appropriate early surrogate of long-term benefit. Clinical response and changes in proliferation rate may be more relevant as metrics of drug activity. Ki67 or newly described preoperative endocrine prognostic index have shown promising results but will require validation.[16]

### *How Can Clinical and Pathologic Response Be Predicted and Monitored?*

To monitor response, mandatory baseline elements include physical examination of breast and nodal areas, breast ultrasound and mammogram, and a minimum of two or three core-cut biopsy samples. Banking further tissue is strongly encouraged. Core biopsy samples should be assessed for ER, progesterone receptor, and HER2 assessment according American Society of Clinical Oncology/College of American Pathologists guidelines.[17,18] If DCIS is found, ER and DCIS grade should be reported separately to avoid confusion with the invasive component.

We strongly encourage imaging of axillary lymph nodes and diagnostic fine-needle aspiration of suspicious nodes. Ultrasound or magnetic resonance imaging (MRI) may be appropriate methods to assess nodal status, depending on local expertise and access.[19–21] Placement of a radiopaque clip is important unless malignant calcifications define the invasive cancer bed. MRI of the breast may be helpful to define the extent of disease when mammography is suboptimal as a result of dense breast parenchyma or in lobular cancer with indistinct margins, or in cases of inflammatory breast cancer.[22] Bilateral breast MRI may also be included for women with the *BRCA1* or *BRCA2* mutation. Positron emission tomography–computed tomography and other methods should only be used in clinical studies.

SLNB should only be considered for patients with clinically negative axilla at time of diagnosis. Optimal timing of SLNB is controversial.[23,24] We recommend performing SLNB after NST in those patients whose axilla is clinically negative by ultrasound or by fine-needle aspiration. In those with biopsy-confirmed axillary lymph node involvement before NST, full axillary lymph node dissection is recommended after NST while we await data from further clinical studies. An important ongoing prospective clinical trial that will clarify many of the issues concerning SLNB in the context of NST is the ACOSOG-Z1072 trial. It is important to note, however, that the above-mentioned discussion pertains to patients with large operable breast cancers and should not be extrapolated to those with locally advanced disease, including patients with inflammatory breast cancer, because the accuracy of SLNB after NST has not been convincingly demonstrated in these groups.

Monitoring during treatment must include clinical breast examination before each cycle. The frequency and nature of imaging assessment during chemotherapy is controversial. Most of us thought that breast imaging should be repeated after completion of NST before surgery to assess residual disease and plan surgical procedures; minimal requirements for the surgeon include clinical examination, mammogram, ultrasound, and, in selected cases of, e.g., lobular cancer, MRI.[19] Imaging may also be repeated sooner in order to document tumor response or disease progression. However, there are no clinical trial data to support or reject the use of serial imaging during NST. When repeat imaging is used, the same method should be used as performed at baseline.

Changes in the planned regimen should only be carried out in cases of clinical and radiological progression or unacceptable toxicity. Providing less than a standard course as a result of a mistaken assumption of lack of response can jeopardize long-term survival (extrapolated from adjuvant studies where reducing treatment intensity has led to reduced efficacy).[25] It is important to realize that pathologic response is common even if imaging suggests stable disease, and a minority of these patients may even experience pCR.

**TABLE 2** pCR vs. long-term outcomes in neoadjuvant systemic treatment

| Study | Treatment | pCR (%) | DFS, EFS, DMFS, RFS | OS |
|---|---|---|---|---|
| Aberdeen[61] | CVAP ($n = 50$) | bpCR | 3-y DFS | 3-y OS |
| | vs. CVAP → D ($n = 47$) | 16 vs. 34% | 77% vs. 90% | 84% vs. 97% |
| | | $P = 0.035$ | $P = 0.03$ | $P = 0.05$ |
| AGO[62] | EP ($n = 335$) | bpCR | 5-y DFS | 5-y OS |
| | vs. E → P ($n = 333$) | 10 vs. 18% | 50% vs. 70% | 77% vs. 83% |
| | | $P = 0.008$ | HR = 0.71 (0.54–0.92), $P = 0.011$ | HR = 0.83 (089–0.99), $P = 0.041$ |
| SICOG 9908[63] | EP q3w ($n = 100$) | tpCR | 5-y DMFS | 5-y OS |
| | vs. EPCis qw ($n = 100$) | 6 vs. 16% | 55% vs. 73% | 69% vs. 82% |
| | | $P = 0.02$ | $P = 0.04$ | $P = 0.07$ |
| NOAH[64] | AP → P → CMF ($n = 113$) | tpCR | 3-y EFS | 3-y OS |
| | vs. id + H ($n = 115$) | 19 vs. 38% | 56% vs. 71% | 79% vs. 87% |
| | | $P = 0.001$ | HR = 0.59 (0.38–0.90), $P = 0.013$ | HR = 0.62, $P = 0.114$ |
| MDACC Buzdar[65] | P → FEC ($n = 19$) | tpCR | 3-y DFS | NA |
| | vs. Id + H (N = 23) | 26 vs. 65%, $P = 0.016$ | 85.3 vs. 100%, $P = 0.041$ | |
| NSABP B-27[66] | AC + TAM ($n = 804$) | bpCR | 8-y DFS | 8-y OS |
| | vs. AC + TAM → surg → D ($n = 805$) | 13 vs. 14.5 vs. 26% | 59 vs. 62 vs. 62% | 74 vs. 75 vs. 75% |
| | vs. AC + TAM + D ($n = 802$) | $P < 0.001$ (I + II vs. III) | NS | NS |
| ACCOG[67] | AC ($n = 180$) | tpCR | RFS (median follow-up 32 mo) NS | Median follow-up 32 mo |
| | vs. AD ($n = 183$) | 16 vs. 12%, $P = 0.43$ | | NS |
| MDA[68] | CAF ($n = 87$) | bpCR | 2-y DFS | NA |
| | vs. P ($n = 87$) | 8 vs. 17%, $P = 0.11$ | 89 vs. 94%, $P = 0.44$ | |
| Baldini[69] | CED ($n = 77$) | tpCR | 5-y DFS | 5-y OS |
| | vs. dose-dense CEF ($n = 73$) | 2.6 vs. 4.1% NS | 48% vs. 60%, $P = 0.18$ | 52 vs. 54%, $P = 0.64$ |
| TOPIC[70] | AC ($n = 215$) | bpCR | 5-y RFS | 5-y OS |
| | vs. ECisF ($n = 211$) | 25 vs. 24% | 63 vs. 62% | 74 vs. 82% |
| | | $P = 0.9$ | HR = 1.05 (0.77–1.44), $P = 0.77$ | HR = 0.76 (0.51–1.13), $P = 0.18$ |
| TOPIC2[71] | AC ($n = 211$) | bpCR | 2-y DFS | 2-y OS |
| | vs. VE ($n = 240$) | 12 vs. 12%, NS | HR = 1.18 (0.80–1.73) | HR = 1.41 (0.86–2.32) |
| | | | $P = 0.24$ | $P = 0.27$ |

Adapted from Debled and Mauriac[60]

*A* doxorubicin, *bpCR* pathologic complete response in breast, *C* cyclophosphamide, *Cis* cisplatin, *D* docetaxel, *DFS* disease-free survival, *DMFS* distant metastasis-free survival, *E* epirubicin, *EFS* event-free survival, *F* 5-fluorouracil, *H* herceptin, *HR* hazard ratio, *M* methotrexate, *NS* not significant, *OS* overall survival, *P* paclitaxel, *RFS* relapse-free survival, *Tam* tamoxifen, *tpCR* pCR in breast and axilla, *V* vincristine, *X* capecitabine

*Prediction of Response*

Characteristics for a higher likelihood for a pCR are presented in Fig. 1. However, pCR cannot be predicted with certainty (positive predictive values of markers range 30–50%).[26] There is clinical value in partial response occurring in >75% of patients allowing lesser surgery if concentric shrinkage occurs. The use of clinical and molecular variables, particularly as proper multivariate prediction models, can help select patients most likely to benefit from NST.[27] We encourage the use of nomograms (e.g., http://www.mdanderson.org/pcr/) because they are currently as good as or better than gene signatures in their predictive strength.[28,29] There may be value in developing predictors of nonresponse to a particular therapy. However, there are important conceptual limitations: first, very high accuracy is needed to justify not administering an established chemotherapy that prolongs survival in randomized trials, and second, the test does not define what alternative treatment may work.

*Which Treatments Should Be Used for Which Patients, and for How Long?*

In routine practice, the same regimens should be used for NST as in the adjuvant setting (anthracyclines and taxanes concurrently or sequentially for at least 6 cycles or 6 months, respectively). All chemotherapy should be provided before surgery rather than split into preoperative and postoperative phases.

Trastuzumab should be provided to all patients with HER2 overexpressing cancers, except those with cardiac comorbidities. Published data based on a relatively small number of highly selected patients suggest that trastuzumab can be safely administered concurrently with an attenuated epirubicin dose for 4 cycles followed by concurrent trastuzumab and a taxane in patients without cardiac comorbidity; this modality represents a highly effective regimen that produces pCR rates of approximately 50%.[30,31] Such a regimen represents an attractive option for younger woman with normal cardiac function who have a higher risk for recurrence. Cardiac monitoring is similar to the adjuvant setting, and patients must be informed according to the guidelines of the U.S. Food and Drug Administration.[32–34]

NET with aromatase inhibitors for at least 4 months represents an option particularly for postmenopausal patients with ER-positive cancers.[35–40] Young patients with low ER expression, high Ki67 levels, or HER2-positive cancers are generally not appropriate for NET outside of a trial. On the other hand, patients with pure lobular, tubular, and low-grade mucinous tumors are not optimal candidates for NST with chemotherapy.

For pure lobular cancers, the extent of surgery should be planned according to the initial extent of the primary tumor as pCR is infrequent.[11] Metaplastic breast cancer is treated much like invasive ductal carcinoma. *BRCA* mutation carriers seem to respond at least similarly to current standard anthracycline/taxane NST as sporadic breast cancer.[41] BCS and radiotherapy results in similar rates of local recurrence in the same quadrant as observed in sporadic breast cancer. However, women with the *BRCA* mutation may elect for mastectomy or bilateral mastectomy because of the higher risk of second new primary breast cancers.[42] Initial BCS can be considered, particularly in those with a high competing risk of distant recurrence that will dominate early risk.

Platinum salts, bevacizumab, or PARP inhibitors, although appearing promising as active agents in triple-negative cancers and *BRCA* mutation carriers, currently should only be provided within the context of clinical trials.[43–46]

For breast cancer diagnosed during pregnancy, NST should include the same chemotherapy regimens as in nonpregnant women, except that antimetabolites and trastuzumab should not be provided because of limited toxicity data regarding the fetus for those agents.[47]

During the review process of this article, the first results of neoadjuvant trials of trastuzumab with lapatinib or pertuzumab in HER2-positive breast cancer became available.[48,49] These preliminary data suggest that NST based solely on biologicals may also be effective and might become an additional variant to NST and NET.

*How Should Surgery Be Performed?*

Surgery after NST is necessary for every patient.[50] So far, there are no data defining a group that does not need surgery. Ideally, surgery should be performed by a surgeon who specializes in breast disease. BCS is performed with the goal of resecting as little tissue as possible. Resection size should be planned according to the size of residual disease after NST. In cases of complete clinical response, resection is still required because in most cases, microscopic residual disease exists. Clearly negative margins for both invasive cancer and DCIS are required, and the same margin rules apply as in primary surgery.[50,51] Specimen radiography is frequently helpful in assessing margins. Patients with inflammatory breast cancer, persistent positive margins after repeat margin resection, multicentric lesions (more than 2 lesions in different quadrants), with widespread DCIS or microcalcifications or planned prophylactic contralateral mastectomy should not be considered for BCS.[52] Breast reconstruction follows the same rules and has the same controversies as with primary surgery. The axillary nodal surgery provides prognostic and predictive information, improves local control, and can influence therapeutic decision making.

*When and How Should Radiotherapy Be Performed?*

After BCS, irradiation of the breast is indicated to decrease local recurrence. Hypofractionated protocols may be considered according to guidelines for adjuvant treatment.[53] Data on the need for radiotherapy after mastectomy are still being collected.[54] In general, radiotherapy is guided by initial clinical stage and by pathologic findings at the time of surgery. Radiotherapy is indicated for all node-positive patients after NST and patients with locally advanced cancer or inflammatory breast cancer.[55] Additional studies are needed on postmastectomy radiotherapy in node-negative patients after NST.

*Which Postsurgical Systemic Treatment Should Be Recommended?*

The recommendations for postsurgical treatment generally mirror those from the adjuvant setting with endocrine treatment according to guidelines. In cases of a receptor switch, patients with at least one ER-positive result should be given the benefit of doubt and should receive adjuvant endocrine therapy unless it is contraindicated by other medical reasons.[56] For HER2-positive disease, trastuzumab therapy that lasts at least 1 year is indicated. Benefit from bisphosphonates remains to be confirmed in additional randomized trials, and such therapy is not currently considered standard.[57–59] Patients who have extensive residual cancer after a full course (4–6 months) of anthracycline–taxane neoadjuvant chemotherapy remain at high risk, and if possible, they should be referred for participation in clinical trials.

*What Role Will NST Trials Play in the Future?*

NST trials offer the ideal treatment setting to (1) discover and validate biomarkers of response, (2) test the cytotoxic activity of new agents and help prioritize regimens for confirmatory adjuvant trials, and (3) learn about the mode of action of drugs. However, we emphasize that the use of early stage investigational drugs in the context of NST has the potential to harm individuals by unexpected toxicities or by the risk of missing the opportunity for cure by administering effective systemic therapies. Thus, clinical trials of new regimens in NST should be structured in such a way that patients do not miss out on proven potentially curative therapies.

*What Are Key Research Topics for NST in the Next 5 Years?*

Key research questions include the identification and validation of markers of activity and early surrogates of benefit from endocrine therapies as well as drug- or regimen-specific molecular response predictors with clinically useful predictive accuracy. Studies on new therapeutic agents need to be performed to further increase pCR rates. Could local therapy, particularly surgery, be safely omitted for patients with pCR (as observed in head and neck and anal cancers)? Post-NST adjuvant trials in patients who do not experience a pCR and have a poor prognosis are badly needed. Finally, multinational forces should join together to avoid duplication of NST studies; they ought to design complimentary trials with seamless integration of follow-up of larger adjuvant studies.

**ACKNOWLEDGMENT** We thank the independent BANSS Foundation, Biedenkopf, Germany, for financial support, and the GBG GmbH, Neu Isenburg, Germany for logistical support of the meeting. All members of the panel had input in the discussion and formulation of the article. This consensus symposium received financial support from the BANSS Foundation, a nonprofit body based in Biedenkopf an der Lahn, Germany. Both the symposium and the preparation of this article was conducted independent of the pharmaceutical industry. The report was drafted in its entirety by the meeting participants without any paid assistance.

## REFERENCES

1. Kaufmann M, von Minckwitz G, Bear HD, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives, 2006. *Ann Oncol.* 2007;18:1927–34.
2. Kaufmann M, Hortobagyi GN, Goldhirsch A, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J Clin Oncol.* 2006;24:1940–9.
3. Caudle AS, Hunt KK. The neoadjuvant approach in breast cancer treatment: it is not just about chemotherapy anymore. *Curr Opin Obstet Gynecol.* 2011;23:31–6.
4. Von Minckwitz G, Kaufmann M, Kuemmel S, et al., for the GBG and AGO-B Study Groups. Correlation of various pathologic complete response (pCR) definitions with long-term outcome and the prognostic value of pCR in various breast cancer subtypes: results from the German neoadjuvant meta-analysis. *J Clin Oncol.* 2011;29(Suppl.):1028.
5. Montagna E, Bagnardi V, Rotmensz N, et al. Pathological complete response after preoperative systemic therapy and outcome: relevance of clinical and biologic baseline features. *Breast Cancer Res Treat.* 2010;124:689–99.
6. Kaufmann M, Pusztai L; Biedenkopf Expert Panel Members. Use of standard markers and incorporation of molecular markers into breast cancer therapy. *Cancer.* 2011;117:1575–82.
7. Robertson RM, Bondy M, Yang W, et al. Inflammatory breast cancer. *CA Cancer J Clin. CA Cancer J Clin.* 2010;60:351–75.
8. Boughey JC, Wagner J, Garrett BJ, et al. Neoadjuvant chemotherapy in invasive lobular carcinoma may not improve rates of breast conservation. *Ann Surg Oncol.* 2009;16:1606–11.
9. Boughey JC, Peintinger F, Meric-Bernstam F, et al. Impact of preoperative versus postoperative chemotherapy on the extent and number of surgical procedures in patients treated in randomized clinical trials for breast cancer. *Ann Surg.* 2006;244:464–70.
10. Kim SI, Sohn J, Koo JS, Park SH, Park HS, Park BW. Molecular subtypes and tumor response to neoadjuvant chemotherapy in

patients with locally advanced breast cancer. *Oncology.* 2010;79: 324–30.
11. Huober J, von Minckwitz G, Denkert C, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. *Breast Cancer Res Treat.* 2010;124:133–40.
12. Penault-Llorca F, Abrial C, Raoelfils I, et al. Comparison of the prognostic significance of Chevallier and Sataloff's pathologic classifications after neoadjuvant chemotherapy of operable breast cancer. *Hum Pathol.* 2008;39:1221–8.
13. Mazouni C, Peintinger F, Wan-Kau S, et al. Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. *J Clin Oncol.* 2007;25:2650–5.
14. Gralow JR, Burstein HJ, Wood W, et al. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. *J Clin Oncol.* 2008;26:814–9.
15. Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. *Cancer.* 2002;95:681–95.
16. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst.* 2008; 100:1380–8.
17. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC; American Society of Clinical Oncology; College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Arch Pathol Lab Med.* 2010;134(7):e48–72
18. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol.* 2007;25:118–45.
19. Londero V, Bazzocchi M, Del Frate C, et al. Locally advanced breast cancer: comparison of mammography, sonography and MR imaging in evaluation of residual disease in women receiving neoadjuvant chemotherapy. *Eur Radiol.* 2004;14:1371–9.
20. Schott AF, Roubidoux MA, Helvie MA, et al. Clinical and radiological assessments to predict breast cancer pathologic complete response to neoadjuvant chemotherapy. *Breast Cancer Res Treat.* 2005;92:231–8.
21. Roubidoux MA, LeCarpentier GL, Fowlkes JB, et al. Sonographic evaluation of early-stage breast cancers that undergo neoadjuvant chemotherapy. *J Ultrasound Med.* 2005;24:885–95.
22. Yang WT, Le-Petross HT, Macapinlac H, et al. Inflammatory breast cancer: PET/CT, MRI, mammography, and sonography findings. *Breast Cancer Res Treat.* 2008;109:417–26.
23. van Deurzen CH, Vriens BE, Tjan-Heijnen VC, et al. Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer patients: a systematic review. *Eur J Cancer.* 2009;45:3124–30.
24. Schwartz GF, Tannebaum JE, Jernigan AM, Palazzo JP. Axillary sentinel lymph node biopsy after neoadjuvant chemotherapy for carcinoma of the breast. *Cancer.* 2010;116:1243–51.
25. Budman DR. Dose and schedule as determinants of outcomes in chemotherapy for breast cancer. *Semin Oncol.* 2004;31(6 Suppl. 15):3–9.
26. Caudle AS, Gonzalez-Angulo AM, Hunt KK, et al. Predictors of tumor progression during neoadjuvant chemotherapy in breast cancer. *J Clin Oncol.* 2010;28:1821–8.
27. Rouzier R, Pusztai L, Delaloge S, et al. Nomograms to predict pathologic complete response and metastasis-free survival after preoperative chemotherapy for breast cancer. *J Clin Oncol.* 2005;23:8331–9.
28. Lee JK, Coutant C, Kim YC, et al. Prospective comparison of clinical and genomic multivariate predictors of response to neoadjuvant chemotherapy in breast cancer. *Clin Cancer Res.* 2010; 16:711–8.
29. Tabchy A, Valero V, Vidaurre T, et al. Evaluation of a 30-gene paclitaxel, fluorouracil, doxorubicin, and cyclophosphamide chemotherapy response predictor in a multicenter randomized trial in breast cancer. *Clin Cancer Res.* 2010;16:5351–61.
30. von Minckwitz G, Kaufmann M, Kümmel S, et al. Integrated meta-analysis on 6402 patients with early breast cancer receiving neoadjuvant anthracycline-taxane ± trastuzumab containing chemotherapy. *Cancer Res.* 2009;69(Suppl. 2):79.
31. Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. *Clin Cancer Res.* 2007;13:228–33.
32. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet.* 2010;375(9712):377–84.
33. Guarneri V, Frassoldati A, Bottini A, et al. Safety and activity report of a randomized phase II trial of preoperative anthracycline-based chemotherapy plus lapatinib, trastuzumab or both in HER2 positive breast cancer: CHERLOB Trial. *Cancer Res.* 2009;69(Suppl. 3):1093.
34. Rayson D, Suter T, van der Vegt S, et al. Interim results of BACH: randomized phase ii trial evaluating the safety of two chemotherapy regimens as adjuvant therapy in patients with HER2-positive breast cancer: PLD + cyclophosphamide + trastuzumab (PLD + C + H), or doxorubicin + cyclophosphomide (A + C), each followed by paclitaxel + trastuzumab (T + H). *Cancer Res.* 2009;69(24 Suppl. 3):2085.
35. Mathew J, Asgeirsson KS, Jackson LR, Cheung KL, Robertson JF. Neoadjuvant endocrine treatment in primary breast cancer—review of literature. *Breast.* 2009;18:339–44.
36. Smith IE, Dowsett M, Ebbs SR, et al.; IMPACT Trialists Group. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol.* 2005;23:5108–16.
37. Eiermann W, Paepke S, Appfelstaedt J, et al.; Letrozole Neo-Adjuvant Breast Cancer Study Group. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Ann Oncol.* 2001;12:1527–32.
38. Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor–positive breast cancer. *Cancer.* 2007;110:244–54.
39. Cataliotti L, Buzdar AU, Noguchi S, et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor–positive breast cancer: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial. *Cancer.* 2006;106:2095–103.
40. Ellis MJ, Buzdar A, Unzeitig GW, et al. ACOSOG Z1031: A randomized phase II trial comparing exemestane, letrozole, and

anastrozole in postmenopausal women with clinical stage II/III estrogen receptor-positive breast cancer (abstract LBA513). *J Clin Oncol.* 2010;28(Suppl.):18 s.
41. Fourquet A, Stoppa-Lyonnet D, Kirova YM, Sigal-Zafrani B, Asselain B; Institut Curie Breast Cancer Study Group; Institut Curie Breast Ovary Cancer Risk Study Group. Familial breast cancer: clinical response to induction chemotherapy or radiotherapy related to *BRCA1/2* mutations status. *Am J Clin Oncol.* 2009;32:127–31.
42. Pierce LJ, Phillips KA, Griffith KA, et al. Local therapy in *BRCA1* and *BRCA2* mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. *Breast Cancer Res Treat.* 2010;121:389–98.
43. Byrski T, Gronwald J, Huzarski T, et al. Pathologic complete response rates in young women with *BRCA1*-positive breast cancers after neoadjuvant chemotherapy. *J Clin Oncol.* 2010;28: 375–9.
44. Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. *J Clin Oncol.* 2010;28:1145–53.
45. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med.* 2009;361:123–34.
46. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. *Lancet.* 2010;24;376(9737):235–44.
47. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. Cancer. 2006;106:237–46.
48. Gianni L, Pienkowski T, Im YH, et al. Neoadjuvant pertuzumab (P) and trastuzumab (H): antitumor and safety analysis of a randomized phase II study ("NeoSphere"). *Cancer Res.* 2011; 70:S3–2.
49. Baselga J, Bradbury I, Eidtmann H, et al. First results of the NeoALTTO Trial (BIG 01-06/EGF 106903): a phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer. *Cancer Res.* 2011;70:S3–3.
50. Kaufmann M, Morrow M, von Minckwitz G, Harris JR; Biedenkopf Expert Panel Members. Locoregional treatment of primary breast cancer: consensus recommendations from an international expert panel. *Cancer.* 2010;116:1184–91.
51. Houssami N, Macaskill P, Marinovich ML, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer.* 2010;46:3219–32.
52. Dawood S, Merajver SD, Viens P, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. *Ann Oncol.* 2011;22:515–23.
53. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys.* 2011;22:515–23.
54. Mamounas EP, Anderson SJ, Bear HD, et al. Predictors of locoregional failure (LRF) in patients receiving neoadjuvant chemotherapy (NC): results from combined analysis of NSABP B-18 and NSABP B-27 (abstract 90). Presented at the 2010 ASCO Breast Cancer Symposium.
55. Buchholz TA, Tucker SL, Masullo L, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. *J Clin Oncol.* 2002;20:17–23.
56. Pusztai L, Viale G, Kelly CM, Hudis CA. Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. *Oncologist.* 2010;15:1164–8.
57. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med.* 2009; 360:679–91.
58. Coleman RE, Winter MC, Cameron D, et al.; AZURE (BIG01/04) Investigators. The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. *Br J Cancer.* 2010;102:1099–105.
59. Aft R, Naughton M, Trinkaus K, et al. Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: an open label, randomised, phase 2 trial. *Lancet Oncol.* 2010;11:421–8.
60. Debled M, Mauriac L. Neoadjuvant chemotherapy: are we barking up the right tree? *Ann Oncol.* 2010;21:675–9.
61. Hutcheon AW, Heys SD, Sarkar TK; Aberdeen Breast Group. Neoadjuvant docetaxel in locally advanced breast cancer. *Breast Cancer Res Treat.* 2003;79(Suppl. 1):S19–S24.
62. Untch M, Möbus V, Kuhn W, et al. Intensive dose-dense compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer. *J Clin Oncol.* 2009;27:2938–45.
63. Frasci G, D'Aiuto G, Comella P, et al. Preoperative weekly cisplatin, epirubicin, and paclitaxel (PET) improves prognosis in locally advanced breast cancer patients: an update of the Southern Italy Cooperative Oncology Group (SICOG) randomised trial 9908. *Ann Oncol.* 2010;21:707–16.
64. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet.* 2010;375:377–84.
65. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol.* 2005;23:3676–85.
66. Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol.* 2006;24:2019–27.
67. Evans TR, Yellowlees A, Foster E, et al. Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: an anglo-celtic cooperative oncology group study. *J Clin Oncol.* 2005;23:2988–95.
68. Buzdar AU, Singletary SE, Theriault RL, et al. Prospective evaluation of paclitaxel versus combination chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. *J Clin Oncol.* 1999;17:3412–17.
69. Baldini E, Gardin G, Giannessi PG, et al. Accelerated versus standard cyclophosphamide, epirubicin and 5-fluorouracil or cyclophosphamide, methotrexate and 5-fluorouracil: a randomized phase III trial in locally advanced breast cancer. *Ann Oncol.* 2003;14:227–32.
70. Smith IE, A'Hern RP, Coombes GA, et al. TOPIC Trial Group. A novel continuous infusional 5-fluorouracil-based chemotherapy regimen compared with conventional chemotherapy in the neoadjuvant treatment of early breast cancer: 5 year results of the TOPIC trial. *Ann Oncol.* 2004;15:751–58.
71. Chua S, Smith IE, A'Hern RP, et al. TOPIC Trial Group. Neoadjuvant vinorelbine/epirubicin (VE) versus standard adriamycin/cyclophosphamide (AC) in operable breast cancer: analysis of response and tolerability in a randomised phase III trial (TOPIC 2). *Ann Oncol.* 2005;16:1435–41.