

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

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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.

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: <i>BRCA1/2</i>
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
Eleftherios 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 an 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.

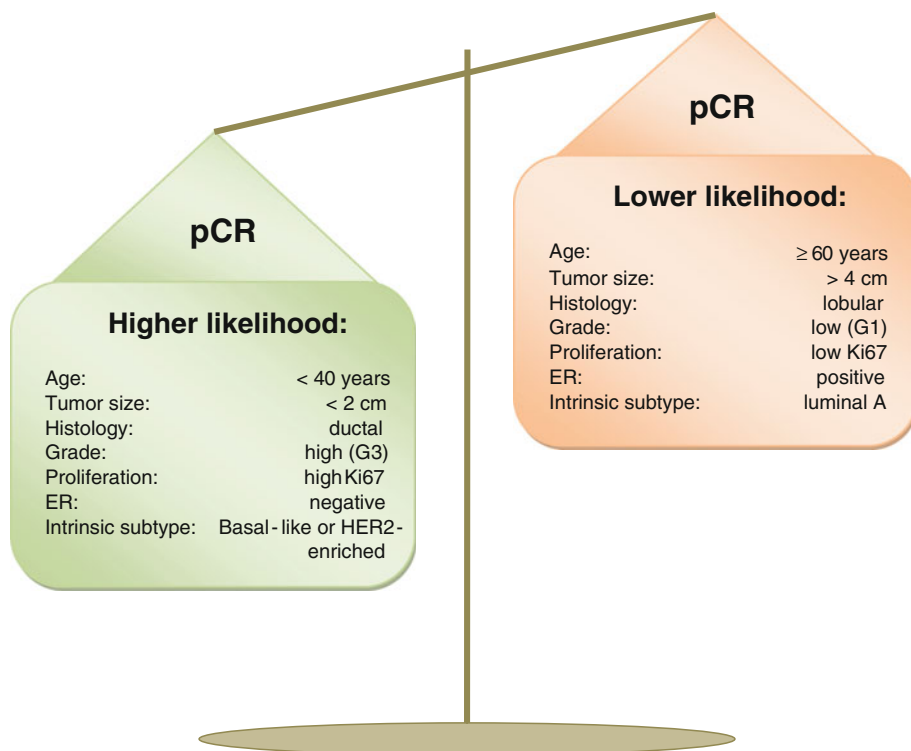
How Should pCR Be Defined?

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% P = 0.035	77% vs. 90% P = 0.03	84% vs. 97% P = 0.05
AGO ⁶²	EP (n = 335)	bpCR	5-y DFS	5-y OS
	vs. E → P (n = 333)	10 vs. 18% P = 0.008	50% vs. 70% HR = 0.71 (0.54–0.92), P = 0.011	77% vs. 83% HR = 0.83 (0.89–0.99), 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% P = 0.02	55% vs. 73% P = 0.04	69% vs. 82% 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% P = 0.001	56% vs. 71% HR = 0.59 (0.38–0.90), P = 0.013	79% vs. 87% 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% P < 0.001 (I + II vs. III)	59 vs. 62 vs. 62% NS	74 vs. 75 vs. 75% NS
ACCOG ⁶⁷	AC (n = 180)	tpCR	RFS (median follow-up 32 mo)	Median follow-up 32 mo
	vs. AD (n = 183)	16 vs. 12%, P = 0.43	NS	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% P = 0.9	63 vs. 62% HR = 1.05 (0.77–1.44), P = 0.77	74 vs. 82% 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) P = 0.24	HR = 1.41 (0.86–2.32) P = 0.27

Adapted from Debled and Mauriac⁶⁰

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.

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