The Still Long and Winding Road to Neoadjuvant Systemic Therapy as the Standard of Care in Breast Cancer

Richard Greil

IIIrd Medical Department with Hematology, Medical Oncology, Hemostaseology, Infectious Disease and Rheumatology at the Private Medical University Hospital Salzburg and Laboratory for Immunological and Molecular Cancer Research, Salzburg, Austria

Initially neoadjuvant systemic therapy (NST) for breast cancer was developed for improving cure rates. It was based on the findings of Bernie Fisher in xenograft models showing that resection of the primary increased tumor cell release and fostered the growth of micrometastases probably via induction of proangiogenic factors. In turn neoadjuvant endocrine and cytotoxic therapy were able to counteract this effect [1–3]. Since then, the aims of NST have been defined and analyzed in clinical and translational research settings as follows: (i) to increase disease-free survival (DFS), overall survival (OS) and cure rates, (ii) to reduce the initial tumor mass in unresectable breast cancer otherwise requiring mastectomy to a degree allowing resection or breast conserving therapy (BCT), (iii) to define new prognostic and predictive markers, (iv) to enable the proof of principle of modern molecular therapies by serial biopsies and molecular workup during initial treatment, and (v) to proceed on the way to an individually tailored therapy. Recently two consensus conferences of experts in the field came to the conclusions, that NST was a reasonable treatment alternative appropriate in any condition where postoperative adjuvant therapy was indicated [4, 5]; and ‘from the standpoint of operable breast cancer, NST should be offered to all patients who are expected to be candidates for adjuvant systemic chemotherapy, ... and offering NST in patients who are expected to be candidates for adjuvant therapy is appropriate regardless of tumor size’ [4]. However, although these statements are very definite and conclusive and the conceptual framework of NST is stunning, this position paper is required by the editors to ask whether or not such definite statements are supported by sufficient data as currently available.

Is NST More Efficient Than Adjuvant Therapy?

Metaanalysis and crucial findings: A metaanalysis of 9 trials with 3,946 patients did not prove any difference in DFS or OS

of patients treated by chemotherapy either pre- or postoperatively [6]. However, inclusion criteria varied considerably and approximately half of the trials and the majority of patients attributed to the neoadjuvant arm of this analysis had also received postoperative treatment, thus conceptually confusing the analysis [7]. Also, it may be argued that many of the previous regimens combined in the metaanalysis used drug regimens not efficiently enough to allow benefits to emerge. Indeed, anthracycline-taxane containing regimens must now be considered superior to other regimens in terms of induction of complete pathological remissions (pCR), DFS and OS as compared to anthracycline containing standard regimens in the neoadjuvant and adjuvant setting [8], although the exact role of sequential vs. concurrent application of the drugs, the impact of dose density and the optimal number of cycles remain unresolved. The NSABP B27 trial is seminal since it used the most efficient drugs currently available and after 4 cycles of neoadjuvant doxorubicin and cyclophosphamide (AC) randomly placed docetaxel as the most efficient individual drug either before or after surgery. Surprisingly, the addition of docetaxel after 4 cycles of AC either prior to or after surgery did not significantly impact DFS or OS at all [20]. However, the subset of patients who achieved a clinical partial remission (cPR) after AC, did significantly better when receiving neoadjuvant but not when receiving adjuvant docetaxel. This is interesting, since this was a rare trial showing such a difference but also surprising for several reasons:

(i) Both, clinical nonresponders and also those with a complete clinical response (cCR) to AC did not benefit from the addition of docetaxel, independent of whether given before or after surgery. The authors discuss this finding as a result of a complete cross-resistance to docetaxel in AC-nonresponders but this remains very hypothetical since they do not show the relevant data. It also seems unlikely since the response rate to docetaxel in anthracycline refractory patients is 30% in the metastatic setting [9]. In addition, in the small Aberdeen trial,

at least 55% of patients not responding to 4 cycles of CVAP achieved a cPR or cCR and 2% even achieved a pCR with further 4 cycles of docetaxel [10]. Although the authors refer to the GEPARTRIO trial in making their point of an initial complete cross-resistance in AC nonresponders it has to be stated that patients in GEPARTRIO received an upfront triple combination with TAC and a secondary treatment with capecitabine and vinorelbine or prolongation of TAC [11]. Apparently this trial only shows that patients with initial resistance to the most efficient triple combination including anthracycline and docetaxel less frequently but still achieve a cCR and pCR after prolonged treatment with the same protocol (22.5 and 3.1%, respectively) and possess only few further efficient options which are not equivalent to the power of docetaxel as a rescue protocol (21.9% cCR and 7.3% pCR, respectively). If these trials contribute anything to the interpretation of the NSABP B27 trial then they challenge rather than support the interpretations of their findings.

(ii) Surprisingly within the same NSABP B27 trial, patients with complete clinical remission after AC show opposite though statistically insignificant effects of adjuvant vs. neoadjuvant docetaxel in favor of adjuvant treatment.

In conclusion, there is no convincing evidence that neoadjuvant sequential therapy with the same drugs as postoperative adjuvant therapy leads to better results in terms of long-term tumor control. That more intense therapy leads to higher pCR rates or better outcome is not surprising. In fact, an OS benefit has been reported for patients responding to CVAP and receiving 4 further cycles of docetaxel instead of continuation of CVAP in the Aberdeen trial [12]. Care has to be given to avoid overinterpretation of pCR rates. They define an intrinsically sensitive tumor clone but do not *eo ipso* prove the benefit of neoadjuvant over adjuvant treatment. Conceptually pCR rates cannot be validated in trial designs with a perioperative or strictly adjuvant arm as a comparator to pure NST, therefore they should not simultaneously be reported as surrogate markers for increased overall outcome in randomized trials with such a design. For adequate comparison, patients with a pCR after e.g. 4 cycles of anthracyclines would have to be randomized to either 4 further cycles of a taxane given either pre- or postoperatively to clarify the effect of the chemotherapy-surgery timing sequence.

Downstaging and breast conserving therapy: Improvements in BCT is one of the major clinical advantages advocating NST. Downstaging rates allowing BCT for patients initially deemed resectable only by mastectomy vary between 17 and 90% [13–15]. In a metaanalysis of 9 trials BCT was observed more often in the neoadjuvant than in the adjuvant arm in 6 trials [6]. These enormous differences in efficacy and the 3 negative trials in the metaanalysis warrant caution: The variable inclusion criteria of the trials, the lack of unifiable definition criteria for primary and secondary resectability, and the lack of trials ever comparing the reproducibility of these criteria or the surgeons' decisions particularly within multicenter studies re-

quire consideration. The individual patient selection by the surgeons both initially as well as at the end of NST may significantly impact the results. This may be further underlined by two facts:

(i) The clinical response to NST and downstaging results as determined by ultrasound or mammography are poorly correlated [16]. False positive rates are in the range of 20–65%, and even more disappointing in many patients with a proven pCR ultrasound measured the residual tumor mass in the size of 1–4 cm. False negative results vary between 10 and 57% for the 3 techniques when compared with the results of pathological examination. Even in clinically progressing patients, pCR can be seen [17]. In 14–20% of patients clinical size estimations differ by more than ± 1 cm. MRI has been supposed to be superior to other radiologic techniques in this regard, but 50% of cases with a CR in MRI still demonstrated residual tumor cells in histology [18]. It is well known that in response to NST the tumor may eccentrically split up into small nests which remain undetectable by any imaging procedure currently available. These facts defer the locoregional treatment decision and diminish the potential of narrowing the resection margins below the initial tumor volume. In fact, up to a quarter of patients are resected with positive margins demonstrating the difficulty in surgical decision making [19]. Considering this, the differences in sensitivity and specificity of staging methods used to define adequate downstaging for BCT and the experience and a priori attitude of the specialists might more significantly impact the BCT rates than the type of NST chosen and might confound the degree of objective benefit in downstaging by NST.

(ii) A change from mastectomy to BCT includes criteria like cosmetic satisfaction by the surgical result expected. This aspect can be influenced by both the qualification of individual surgeons or centers and the aesthetic sense of patients and physicians involved.

Change of therapy in trials tailoring therapy to NST response:

The above-mentioned results provide difficulties in the adequate stratification of patients according to their response to NST. This difficulty is intrinsic to the histologically eccentric response pattern mentioned earlier. PET or PET/CT imaging cannot overcome this problem due to their resolution limits and thus are currently of no help in better defining the area of resection. However, these techniques may help in better defining response to treatment and should be considered novel surrogate markers requiring the definition of their exact value in prospectively randomized trials rather than replacing currently existent markers *per se*. Also, optimal time and technique still remain undefined.

Can We Harm Patients by NST?

Delay in surgery as a conceptual disadvantage? Given the fact that long-term OS is similar in the groups of patients treated

with either NST or adjuvant therapy [6], there does not seem to be a disadvantage for patients due to delay of surgery. In addition, the high proportion of responding patients and the valuable fraction of pCR as well its prognostic effect on DFS and probably OS seem to suggest that patients are safe as long as the tumor is responding or at least not increasing in volume. Even in the latter case, it may be argued that the observation of the tumor under treatment may allow to adequately and timely change to a non-cross-resistant type of systemic therapy and in fact, patients without response to an anthracycline benefited in terms of clinical remission and even pCR from a change to drugs and regimens deemed non-cross-resistant in several trials [10].

The safety approach of NST relies on the concept that shrinkage of the visible tumor mass is representative of a single tumor cell clone feeding the tumor development. However, tumors are composed of cells with different biology and sensitivity to chemotherapy. Cells partly resistant to a certain regimen might acquire full-blown resistance during such a treatment approach and a small proportion of ab initio resistant cells may grow up and also start to build up micrometastases. In addition, it has become clear that tumor stem cells might be the relevant clonogenic source of the longevity of the tumor, that these cells are rare, that they may behave differently in terms of drug sensitivity than more differentiated tumor cells building the visible 'iceberg' of the tumor and that such tumor stem cells might exist in breast cancer [21–24]. These concerns are supported by the clinical experience that breast cancers sometimes shrink during the first few treatment cycles but later on stabilize or even increase in size [10]. Therefore, an initial resection of the tumor might avoid some of these theoretical disadvantages by just resecting fully or partly resistant tumor cells and probably by reducing or eliminating the tumor stem cell pool. While NST is supposed to sterilize micrometastases prior to surgery, recent data demonstrate that tumors responding to therapy shed tumor cells into circulation to the same degree as progressive cancers [25].

Certainly, these findings are hypotheses at best, but retrospective analyses have shown that the resection of the primary breast tumor at diagnosis increased the overall survival of patients with clinically overt metastases [26] to a degree (i.e. a 39% risk reduction in mortality) probably beyond the effects most of the drugs we are using in the treatment of metastatic breast cancer [27]. Similar results have been observed in metastatic renal cell cancer, thus supporting the major biological role of the primary tumor and the clinical benefit of its (early) surgical resection [28, 29].

In conclusion we have to bear in mind that all randomized trials are comparisons of cohorts. The similar or equal overall results of adjuvant and neoadjuvant treatments tell us that the sum of patients benefiting and probably acquiring disadvantages are comparable between neoadjuvant and adjuvant approaches. This does not mean that individual patients might

not do better with the other type of treatment, but only that our tools for adequate definition of surrogate markers and optimal patient selection require improvement.

Is downstaging to BCT associated with a lower tumor control rate? The degree of downstaging has impact on survival. Patients achieving pCR survive longer than those who do not [30–32]. Patients who require NST to become treatable by BCT more often relapse [32] and also may have a shorter survival [33]. This suggests that initial tumor volume and pattern of spread retain their prognostic value and that at least they cannot be simply overcome by NST per se under all circumstances [34]. Attempts have been made to adequately define risk factors for relapse after NST, BCT and adequate radiotherapy in patients with an initial tumor size >5cm [35, 36]. When 4 risk groups were defined, patients with a prognostic index of 2 showed a 16% absolute difference in locoregional recurrences after BCT or mastectomy and this difference increased to 42% in patients with a prognostic index of 3.4. The proportion of these intermediate and higher-risk groups made up 20% of all patients. Thus, patients have to be carefully selected for NST with subsequent BCT even when modern radiotherapy is added to the post-surgical management.

Do NST and BCT select for or overlook a different neoplastic clone? In the NSABP B27 trial the pCR rate of the invasive cancer component increased substantially within the group receiving neoadjuvant 4 × AC + 4 × docetaxel [20]. This is not surprising since these patients received twice the number of cycles of preoperative chemotherapy than the other 2 groups. However, the number of residual DCIS only found in the resected specimens nearly doubled in this arm (7.2% in the 4×AC→4×D→S arm vs. 4.4% in the AC→S vs. 3.6% in the 4×AC→S→4×D arm) although the resected specimens should have been smaller than in the other cohorts.

Are long-term side effects of more aggressive therapy in balance with the benefits of pCR rates and long-term tumor control? The number of second tumors more than doubled in the NSABP B27 trial i.e. 3.7 vs. 1.6% for pre- vs. postoperative docetaxel. The exact types of tumors and their stages are not given, and only long-term observation will show whether these second cancers will affect overall outcome. Following the hypothesis that particular patients with a pCR after NST benefit in terms of DFS or even OS, ever more aggressive induction therapies will be provoked to achieve this goal. As long as the patients who will achieve such a pCR cannot reliably be defined a priori the whole cohort of patients will be exposed to substantially more relevant long-term toxicity. Caution is warranted not to neglect second cancers, myelodysplastic syndromes and leukemias which carry a prognosis worse than breast cancer thus counteracting the benefits of NST. It is now clear that BCT after NST requires radiotherapy for adequate locoregional tumor control. An increased risk of second lung cancers has been reported following irradiation both after mastectomy and lumpectomy, particularly in smokers (for review see [37]). This finding could not be confirmed

by other researchers [38]. The risk – if existing – may depend on radiation dosage and fields as well as predisposing factors but warrants consideration at least in the long-term follow-up of certain patients.

Is NST safe and equally, less, or more toxic than adjuvant therapy? Little evidence is available that NST could exert more toxicity than the same treatment given after surgery. With conventional systemic therapies no interference with the results and complications of surgery are to be expected. However, this may change when new molecular tools like antiangiogenic agents are used which may disturb wound healing. Careful evaluation of such complications and their frequency in the neoadjuvant vs. adjuvant setting will have to be performed.

Does NST negatively impact the adequate choice of locoregional staging and treatment? Sentinel node biopsy (SNB) has become the standard of care for early stages of breast cancer undergoing resection and adjuvant therapy. The initial axillary status as well as the status of nodes after the downstaging attempt by NST carry significant implications for the adequate choice of treatment of the axilla. However, conclusions as to the suitability of SNB after NST in practice and the interpretation of the results are completely divergent [4, 34]. This uncertainty has particular implications for the planning of radiotherapy.

Is Adequate Patient Selection Possible?

Are there patients particularly or barely benefiting from NST?

Patient selection is important in patients undergoing NST. Patients with large tumors (>5 cm), a lobular histology, low histologic grade, multicentricity and estrogen receptor (ER) or progesterone receptor (PR) positivity have a lower probability of achieving a degree of tumor reduction which allows for BCT [35, 39]. Based on these risk factors, a nomogram for prediction of BCT has been developed which is valid for NST with anthracyclines with or without paclitaxel [40]. The risk score for relapse after BCT vs. mastectomy [36] came up with clinical N2, N3 disease, lymphovascular invasion, residual pathologic primary size >2 cm and pathologically multifocal residual disease as risk factors. Risk factors for predicting failure to achieve BCT in large tumors obviously differ from those for relapse after BCT. Therefore, for adequate patient selection, future research should address the question of how to define risk factors which allow to predict downstaging and relapse probability simultaneously and upfront.

Is pCR a reasonable endpoint to be addressed by NST and can we select patients with a high chance for achieving it? NST is associated with clinical response rates of 60–90%, which translate into a small pCR rate of 3–16% [41] and a tiny OS benefit of 2–11% as compared to nil, i.e. that of adjuvant therapy, depending on the risk profile of patients included. This raises concerns regarding the validity of the biological

and clinical concepts NST is based on. Most but not all trials have confirmed pCR as a prognostic marker predicting for recurrence-free survival after NST and thus pCR has not only become a surrogate endpoint in trial design, but also a target for second surrogate marker definitions by clinical and molecular methods.

CR patients still have a lifelong and substantial risk of recurrence. 25% of pCR and 42% of cCR patients with residual microscopic tumor had relapsed after 9 years in NSABP B18 [32]. In good concordance with these clinical findings 42% of patients with a pCR after NST still had viable non-apoptotic tumor cells within their bone marrow [42]. Circulating tumor cells have been demonstrated in the blood of patients more than 20 years after the resection of the primary tumor and in the absence of any sign of clinical recurrence [43]. Provocatively, but without phenotypic proof, these persistent epithelial cells have been advocated as dormant breast cancer stem cells with the capacity to re-grow at any time after treatment [44, 45], however, only a part of these cells may have such stem cell properties. Thus pCR by itself does not mean cure, the subset of pCR patients who remain in persistent CR is ill defined as are the surrogate markers for this patient population. Finally, it remains unclear whether the timing and dosing of an initial therapeutic hit, whether applied neoadjuvantly or adjuvantly is sufficient to alter the microenvironment and or the stem cell biology in such a dramatic manner that late relapses are still causally attributable to these interventions. It remains unresolved whether differences in the timing, sequence and type of adjuvant or neoadjuvant systemic therapy may have such a persistently different effect on the clonal capacity.

The definition of pCR is inconsistent with some reports defining it by the absence of any cancer cell whether invasive or in situ and both within the primary and the lymph nodes while others accept residual DCIS components or neglect the axillary lymph node status. Also histologic criteria are not uniform. Not surprisingly pCR rates vary widely between trials.

Do We Have the Tools for Reliably Testing the Proof of Principle in Biologicals?

What is the target cancer population? At present it is unclear how different tumor cell populations can be hit by a variety of cytotoxic agents. We do not know the optimal target cell which should be hit, i.e. the average tumor cell in the visible bulk, the presumed tumor stem cell, circulating tumor cells or dormant cells in marrow and other tissues. Also the role of the treatment of the microenvironment and the consequence for preparing or inhibiting the outgrowth of a tumor cell with the capacity to ultimately kill the host is unclear. These questions become ever more important with the armamentarium of molecular agents targeting neoangiogenesis or stroma cells. In fact, in one third of patients still in remission circulating tumor cells can be seen up to two decades after resection of a

breast cancer. This is in concordance with murine data and with the recent perception that breast cancer might be a chronic disease. Factors deciding over the appearance of an overt tumor during the lifetime of the patient may vary and are unknown. The contribution of these different cell populations, the connex of their regulation and the optimal timing of their targeting during either neoadjuvant or adjuvant treatment remains to be determined. This has significant implications for the adequate surrogate markers for novel neoadjuvant (and adjuvant) research concepts.

Are gene arrays helpful in governing treatment decisions? Gene arrays are a powerful tool for directing treatment decisions in the future. Arrays are under development to predict pCR following multi-agent NST [46], and others may be suited to define resistance to certain agents like docetaxel [47]. However, the adequate choice of the platform, the reproducibility of findings and even the optimal choice of trial design, the choice of control populations in cohort vs. matched pair analyses, the molecular or clinical definition of the groups to be compared and the evaluation of the results are under investigation. Enormous efforts will be required to bring these tools into everyday practice [48]. Meanwhile, simpler parameters are

being evaluated, such as downregulation of Ki-67 and signaling pathways involving certain growth factor receptors [47]. However, large scale prospective trials testing for the robustness and reproducibility of these factors during NST are still lacking.

Conclusions

In conclusion, the only benefit of NST which is currently proven is the downsizing of tumor volume to allow for BCT in up to 50% of carefully selected patients and at experienced centers at the price of a decreased locoregional control rate [49]. For patients with the chance of BCT at presentation, NST may not offer any benefit and may complicate surgical decision-making particularly concerning the axilla [34]. NST is an adequate and valuable tool for careful research of strategies trying to improve predictive and prognostic markers as well as tailored therapies with the vast majority of work necessary to reach the goal ahead of us. However, for primary resectable disease, these questions should exclusively be approached in clinical trials.

References

- Fisher B, Gunduz N, Saffer EA: Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases. *Cancer Res* 1983;43:1488–1492.
- Fisher B, Gunduz N, Saffer EA: Interrelation between tumor cell proliferation and 17-fluoresceinated estrone binding following primary tumor removal, radiation, cyclophosphamide, or tamoxifen. *Cancer Res* 1983;43:5244–5247.
- Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E: Presence of a growth-stimulating factor in serum following primary tumor removal in mice. *Cancer Res* 1989;49:1996–2001.
- Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, Blohmer JU, Eiermann W, Jackesz R, Jonat W, Lebeau A, Loibl S, Miller W, Seeber S, Semiglazov V, Smith R, Souchon R, Stearns V, Untch M, von Minckwitz G: Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: An update. *J Clin Oncol* 2006;24:1940–1949.
- Schwartz GF, Hortobagyi GN: Proceedings of the consensus conference on neoadjuvant chemotherapy in carcinoma of the breast, April 26–28, 2003, Philadelphia, PA. *Cancer* 2004;100:2512–2532.
- Mauri D, Pavlidis N, Ioannidis JP: Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis. *J Natl Cancer Inst* 2005;97:188–194.
- Popat S, Smith IE: Re: Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis. *J Natl Cancer Inst* 2005;97:858; author reply 858–859.
- Hutcheon AW HS: Primary systemic chemotherapy of large and locally advanced breast cancer. *American Society of Clinical Oncology 2004 Educational Book* 2004:63–79.
- Nabholtz JM, Senn HJ, Bezwoda WR, Melnychuk D, Deschenes L, Douma J, Vandenberg TA, Rapoport B, Rosso R, Trillet-Lenoir V, Drbal J, Molino A, Nortier JW, Richel DJ, Nagykalnai T, Siedlecki P, Wilking N, Genot JY, Hupperets PS, Pannuti F, Skarlos D, Tomiak EM, Murawsky M, Alakl M, Aapro M, et al.: Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 study group. *J Clin Oncol* 1999;17:1413–1424.
- Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, Ah-See AK, Eremin O, Walker LG, Sarkar TK, Eggleton SP, Ogston KN: Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel. *J Clin Oncol* 2002;20:1456–1466.
- von Minckwitz G, Blohmer JU, Raab G, Lohr A, Gerber B, Heinrich G, Eidtmann H, Kaufmann M, Hilfrich J, Jackisch C, Zuna I, Costa SD: In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: The gepartrio pilot study. *Ann Oncol* 2005;16:56–63.
- Hutcheon AW, Heys SD, Sarkar TK: Neoadjuvant docetaxel in locally advanced breast cancer. *Breast Cancer Res Treat* 2003;79 (Suppl 1):S19–S24.
- Smith IE, Lipton L: Preoperative/neoadjuvant medical therapy for early breast cancer. *Lancet Oncol* 2001;2:561–570.
- Rouzier R, Pusztai L, Delaloge S, Gonzalez-Angulo AM, Andre F, Hess KR, Buzdar AU, Garbay JR, Spielmann M, Mathieu MC, Symmans WF, Wagner P, Atallah D, Valero V, Berry DA, Hortobagyi GN: Nomograms to predict pathologic complete response and metastasis-free survival after preoperative chemotherapy for breast cancer. *J Clin Oncol* 2005;23:8331–8339.
- Beriwal S, Schwartz GF, Komarnicky L, Garcia-Young JA: Breast-conserving therapy after neoadjuvant chemotherapy: Long-term results. *Breast J* 2006;12:159–164.
- Chagpar AB, Middleton LP, Sahin AA, Dempsey P, Buzdar AU, Mirza AN, Ames FC, Babiera GV, Feig BW, Hunt KK, Kuerer HM, Meric-Bernstam F, Ross MI, Singletary SE: Accuracy of physical examination, ultrasonography, and mammography in predicting residual pathologic tumor size in patients treated with neoadjuvant chemotherapy. *Ann Surg* 2006;243:257–264.
- Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, Margolese R, Theoret H, Soran A, Wickerham DL, Wolmark N: The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from national surgical adjuvant breast and bowel project protocol b-27. *J Clin Oncol* 2003;21:4165–4174.
- Belli P, Costantini M, Malaspina C, Magistrelli A, Latorre G, Bonomo L: MRI accuracy in residual disease evaluation in breast cancer patients treated with neoadjuvant chemotherapy. *Clin Radiol* 2006;61:946–953.
- Fukutomi T: Clinical practice and outcome of breast-conserving treatment: The effectiveness of preoperative systemic chemotherapy. *Breast Cancer* 2006;13:147–151.
- Bear HD, Anderson S, Smith RE, Geyer CE, Jr., Mamounas EP, Fisher B, Brown AM, Robidoux A, Margolese R, Kahlenberg MS, Paik S, Soran A, Wickerham DL, Wolmark N: 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;24:2019–2027.

- 21 Dontu G, Liu S, Wicha MS: Stem cells in mammary development and carcinogenesis: Implications for prevention and treatment. *Stem Cell Rev* 2005;1: 207–214.
- 22 Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF: Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci U S A* 2003;100:3983–3988.
- 23 Ponti D, Zaffaroni N, Capelli C, Daidone MG: Breast cancer stem cells: An overview. *Eur J Cancer* 2006;42:1219–1224.
- 24 Dean M, Fojo T, Bates S: Tumour stem cells and drug resistance. *Nat Rev Cancer* 2005;5:275–284.
- 25 Pantel K, Brakenhoff RH: Dissecting the metastatic cascade. *Nat Rev Cancer* 2004;4:448–456.
- 26 Rapiti E, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP, Chappuis PO, Bouchardy C: Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol* 2006;24: 2743–2749.
- 27 Morrow M, Goldstein L: Surgery of the primary tumor in metastatic breast cancer: Closing the barn door after the horse has bolted? *J Clin Oncol* 2006; 24:2694–2696.
- 28 Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R: Radical nephrectomy plus interferon- α -based immunotherapy compared with interferon α alone in metastatic renal-cell carcinoma: A randomised trial. *Lancet* 2001;358:966–970.
- 29 Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, Caton JR, Jr., Munshi N, Crawford ED: Nephrectomy followed by interferon α -2b compared with interferon α -2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001;345:1655–1659.
- 30 Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, Cruz AB, Jr., Fisher ER, Wickerham DL, Wolmark N, DeCillis A, Hoehn JL, Lees AW, Dimitrov NV: Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from national surgical adjuvant breast and bowel project b-18. *J Clin Oncol* 1997;15:2483–2493.
- 31 Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margolese RG, Cruz AB, Jr., Hoehn JL, Lees AW, Dimitrov NV, Bear HD: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998;16:2672–2685.
- 32 Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B: Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from national surgical adjuvant breast and bowel project b-18. *J Natl Cancer Inst Monogr* 2001;96–102.
- 33 van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L: Preoperative chemotherapy in primary operable breast cancer: Results from the european organization for research and treatment of cancer trial 10902. *J Clin Oncol* 2001;19:4224–4237.
- 34 Sachelarie I, Grossbard ML, Chadha M, Feldman S, Ghesani M, Blum RH: Primary systemic therapy of breast cancer. *Oncologist* 2006;11:574–589.
- 35 Rouzier R, Mathieu MC, Sideris L, Youmsi E, Rajan R, Garbay JR, Andre F, Marsiglia H, Spielmann M, Delaloge S: Breast-conserving surgery after neoadjuvant anthracycline-based chemotherapy for large breast tumors. *Cancer* 2004;101: 918–925.
- 36 Huang EH, Strom EA, Perkins GH, Oh JL, Chen AM, Meric-Bernstam F, Hunt KK, Sahin AA, Hortobagyi GN, Buchholz TA: Comparison of risk of local-regional recurrence after mastectomy or breast conservation therapy for patients treated with neoadjuvant chemotherapy and radiation stratified according to a prognostic index score. *Int J Radiat Oncol Biol Phys* 2006;66:352–357.
- 37 Deutsch M, Land SR, Begovic M, Wieand HS, Wolmark N, Fisher B: The incidence of lung carcinoma after surgery for breast carcinoma with and without postoperative radiotherapy. Results of national surgical adjuvant breast and bowel project (nsabp) clinical trials b-04 and b-06. *Cancer* 2003;98: 1362–1368.
- 38 Fowble B, Hanlon A, Freedman G, Nicolaou N, Anderson P: Second cancers after conservative surgery and radiation for stages i-ii breast cancer: Identifying a subset of women at increased risk. *Int J Radiat Oncol Biol Phys* 2001;51:679–690.
- 39 Cristofanilli M, Gonzalez-Angulo A, Sneige N, Kau SW, Broglio K, Theriault RL, Valero V, Buzdar AU, Kuerer H, Buchholz TA, Hortobagyi GN: Invasive lobular carcinoma classic type: Response to primary chemotherapy and survival outcomes. *J Clin Oncol* 2005;23:41–48.
- 40 Rouzier R, Pusztai L, Garbay JR, Delaloge S, Hunt KK, Hortobagyi GN, Berry D, Kuerer HM: Development and validation of nomograms for predicting residual tumor size and the probability of successful conservative surgery with neoadjuvant chemotherapy for breast cancer. *Cancer* 2006;107: 1459–1466.
- 41 Jones RL, Smith IE: Neoadjuvant treatment for early-stage breast cancer: Opportunities to assess tumour response. *Lancet Oncol* 2006;7:869–874.
- 42 Fehm T, Becker S, Becker-Pergola G, Sotlar K, Gebauer G, Durr-Storzer S, Neubauer H, Wallwiener D, Solomayer EF: Presence of apoptotic and nonapoptotic disseminated tumor cells reflects the response to neoadjuvant systemic therapy in breast cancer. *Breast Cancer Res* 2006;8:R60.
- 43 Meng S, Tripathy D, Frenkel EP, Shete S, Naftalis EZ, Huth JF, Beitsch PD, Leitch M, Hoover S, Euhus D, Haley B, Morrison L, Fleming TP, Herlyn D, Terstappen LW, Fehm T, Tucker TF, Lane N, Wang J, Uhr JW: Circulating tumor cells in patients with breast cancer dormancy. *Clin Cancer Res* 2004;10:8152–8162.
- 44 Waterworth A: Introducing the concept of breast cancer stem cells. *Breast Cancer Res* 2004;6:53–54.
- 45 Wicha MS, Liu S, Dontu G: Cancer stem cells: An old idea—a paradigm shift. *Cancer Res* 2006;66: 1883–1890; discussion 1895–1886.
- 46 Ayers M, Symmans WF, Stec J, Damokosh AI, Clark E, Hess K, Lecoche M, Metivier J, Booser D, Ibrahim N, Valero V, Royce M, Arun B, Whitman G, Ross J, Sneige N, Hortobagyi GN, Pusztai L: Gene expression profiles predict complete pathologic response to neoadjuvant paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide chemotherapy in breast cancer. *J Clin Oncol* 2004; 22:2284–2293.
- 47 Noguchi S: Predictive factors for response to docetaxel in human breast cancers. *Cancer Sci* 2006;97:813–820.
- 48 Andre F, Mazouni C, Hortobagyi GN, Pusztai L: DNA arrays as predictors of efficacy of adjuvant/neoadjuvant chemotherapy in breast cancer patients: Current data and issues on study design. *Biochim Biophys Acta* 2006.
- 49 Cinieri S, Orlando L, Colleoni M: Primary systemic therapy on local advance breast cancer, where are we going? *Ann Oncol* 2006;17 Suppl 7:vii18-vii21.