

Study Participation Improves Treatment Strategies and Individual Patient Care in Participating Centers

W. JANNI¹, M. KIECHLE², H. SOMMER¹, B. RACK¹, K. GAUGER²,
M. HEINRIGS¹, D. STEINFELD³, D. AUGUSTIN⁴,
W. SIMON⁵, N. HARBECK² and K. FRIESE¹
(on behalf of the ADEBAR Study Group)

¹Frauenklinik Innenstadt of the LMU Munich;

²Frauenklinik, Klinikum rechts der Isar of the TU Munich;

³Zentralklinikum Augsburg, ⁴Mammazentrum Ostbayern, Deggendorf;

⁵Robert-Bosch-Krankenhaus, Stuttgart, Germany

Abstract. *Background:* The ADEBAR study is a prospective multicenter Phase III trial to examine whether high-risk breast cancer patients (≥ 4 involved axillary lymph nodes) benefit from a sequential anthracycline-docetaxel regimen compared to standard chemotherapy with anthracyclines. With a median recruitment of 33 patients per month at 198 actively-recruiting centers, the ADEBAR study was the best recruiting study in Germany until the end of the trial. *Materials and Methods:* A standardized questionnaire was sent to all participating centers in order to determine the extent to which treatment strategies and patient care are affected by participation in the ADEBAR study. The questionnaire covered 5 areas of interest: previous inclusion of patients at the same tumor stage in other studies, the type of chemotherapy received by comparable patients previously outside the study, change in the intensity of medical care since participating in the ADEBAR study, the information gained through participation in the study and changes in the overall quality of medical care. *Results:* 51.0% ($n=98$) of the questionnaires were returned, from which 3 were excluded from the analysis due to being incomplete. In the year preceding the ADEBAR study, 63.2% of participating centers had not entered their high-risk patients into a clinical trial. Before participating in the ADEBAR protocol, 44.2% of patients with the same indication had received inadequate therapy by today's standards, such as CMF, EC/CMF or 4x EC. 59.0% of the centers noted an increase in the intensity of patient care as a

result of participation in the study, independent of the care provided purely because of the study. By being part of a research network, with a regular flow of information via newsletters, study meetings and the like, 80.0% noted an improvement in their professional knowledge in the field of breast cancer. Moreover, 31.6% of the centers reported an improvement in the overall quality of their patient care since the start of the trial. *Conclusion:* The results of the survey demonstrate that both physicians and patients benefit from participation in clinical trials as this is associated with optimized decision-making as regards therapy and patient care.

The arguments put forward by critics of participation in clinical trials range from deriving personal benefit from the financial support provided by the research industry to the social aspects of study meetings, and from the scientific emphasis on individuals to businesses exerting their influence. It is reasonable to assume that, in addition to logistical and personal reasons and time constraints, sceptical considerations of this nature result in only a fraction of patients with breast cancer in Germany being included in clinical scientific studies.

However, the example of breast cancer in particular demonstrates the benefits of scientific advances, which have undoubtedly resulted in significant improvements in the medical care of patients. Whereas less than one hundred years ago, the standard operative treatment was the Halsted radical mastectomy (15) with no significant systemic treatment options available, (3) nowadays, the radical nature of the operation can be reduced to a minimum by breast-conserving techniques (5, 13, 18, 29, 33, 36) and by axillary sentinel lymph node excision (22, 34, 35, 37). At the same time, the systematic use of cytostatic and endocrine forms of treatment has achieved a significant increase in overall life expectancy for patients treated in line with current standards of therapy (1, 2, 9).

Correspondence to: PD Dr. med. Wolfgang Janni, I. Frauenklinik Innenstadt, Maistr. 11, 80337 Munich, Germany. Tel: 089-5160-4111, 0177-8090258, Fax: 089-5160-4622, e-mail: wolfgang.janni@med.uni-muenchen.de

Key Words: Breast cancer, study participation, metastasis, cancer recurrence, prognosis.

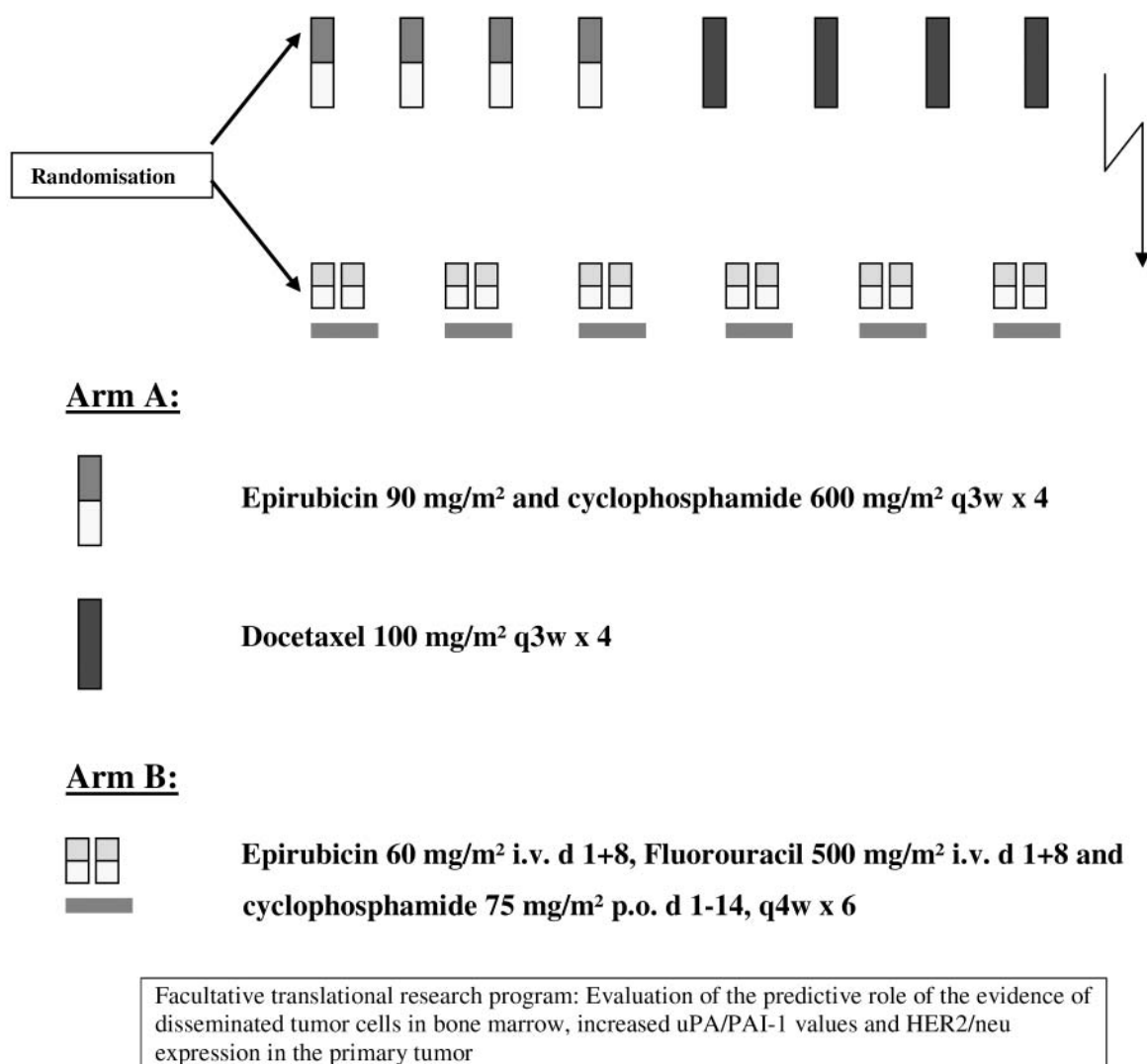


Figure 1. Study design of the ADEBAR study.

This development, which has resulted in definite advantages for the individual breast cancer patient, was only made possible as a result of clinical trials. The contribution made by trials conforming to GCP (*Good Clinical Practice*) to improvements in medical care should therefore be undisputed (7). The aim of the following evaluation was to analyze the extent to which conducting a prospective randomized Phase III study affects the current medical care of participating patients, the treatment practices and current state of knowledge of the investigating physicians, irrespective of the knowledge gained later from the actual findings of the study.

Materials and Methods

ADEBAR study design. The ADEBAR study is a prospective multicenter Phase III trial to evaluate whether high-risk breast

cancer patients (>4 involved lymph nodes) benefit from a sequential anthracycline-docetaxel regimen (E90C-D: 4 cycles epirubicin [E] 90 mg/m² BSA plus cyclophosphamide [C] 600 mg/m² BSA q21d, followed by 4 cycles docetaxel [D] 100 mg/m² BSA q21d) compared to anthracycline-containing standard chemotherapy (FE₁₂₀C: 6 cycles E60 mg/m² BSA d 1+8, 5-fluorouracil 500 mg/m² BSA d 1+8 and C 75 mg/m² BSA d 1-14, q28d) (Figure 1). The primary objective of the study is the comparison of the relapse-free survival time after randomization, while the secondary objectives of the study involve analysis of overall survival, toxicity and quality of life. An additional optional translational research program is investigating the predictive value of the HER2/neu, uPA and PAI1 status of the primary tumor and the effect of treatment on the presence of disseminated tumor cells in the bone marrow.

The inclusion criteria were:

- Primary breast carcinoma pT₁₋₄, pN₂₋₃, pM₀ with ≥4 axillary lymph node metastases.

- R0 resection (margins of resection free from invasive carcinoma), axillary lymphadenectomy (≥ 10 lymph nodes removed) no more than 5 weeks before the start of chemotherapy.
- Women between 18 and 70 years of age.
- Performance status < 2 on the ECOG scale.
- Life expectancy of at least 32 weeks.
- Adequate bone marrow reserve: leucocytes $\geq 3.0 \times 10^9/l$ and platelets $\geq 100 \times 10^9/l$.
- Serum creatinine, SGOT, SGPT, alkaline phosphatase, bilirubin, albumin within 1.5 times the reference laboratory's normal range.
- Guarantee of regular follow-up for the duration of the trial.
- Understanding of the study design and written informed consent.

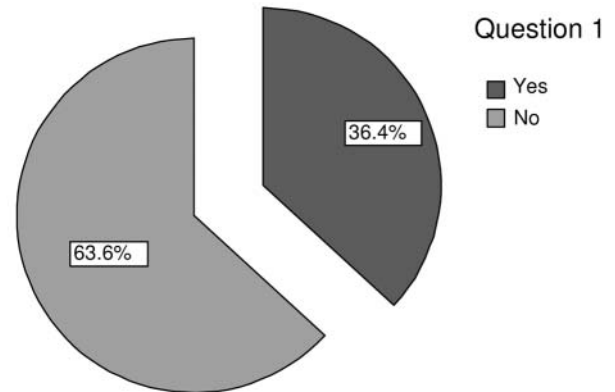
The exclusion criteria were:

- Clinical, histopathological or radiological evidence of distant metastases (M1).
- Inflammatory breast cancer (p T 4d).
- Previous or concomitant treatment with other cytotoxic or antineoplastic drugs.
- A second primary malignancy (except *in situ* carcinoma of the cervix or basal cell carcinoma).
- Manifest pre-existing cardiac damage (cardiomyopathy with impaired ventricular function (NYHA $> II$), arrhythmias requiring medication, myocardial infarction or angina pectoris within the last 6 months, uncontrolled arterial hypertension).
- Known hypersensitivity to docetaxel, epirubicin, 5-fluorouracil, cyclophosphamide or other medication in the study protocol.
- Participation in another clinical trial within 3 weeks prior to inclusion.
- Pregnant or lactating patients (premenopausal women must use effective contraception).

Patients with hormone receptor positive breast cancer (estrogen and/or progesterone receptor $\geq 10\%$) received tamoxifen 20 mg/d *p.o.*, while postmenopausal patients in whom tamoxifen was contraindicated were given an anti-aromatase agent for 5 years. Patients with positive hormone receptor status who were aged below 40 years, or menstruated within 6 months after completion of chemotherapy, or with LH < 20 mIU/ml, FSH < 20 mIU/ml and E2 > 20 pg/ml also received goserelin 3.6 mg q1m s.c. for 2 years.

Questionnaire. In August 2004 a questionnaire with 5 multiple-choice questions was sent to all 198-actively-recruiting ADEBAR study centers. The questionnaire contained the following questions:

- In the last year *prior* to taking part in the ADEBAR study, have you entered the relevant patients (breast cancer, ≥ 4 lymph nodes) in another therapy optimizing study (not an observational study)? (Answer options: Yes/No)
- Which chemotherapy schedule did comparable patients with the same tumor stage receive prior to your center's participation in the ADEBAR study? (CMF day 1 every 3 weeks, CMF day 1 and 8 every 4 weeks, EC [90/600], EC/CMF, FEC100 [Bonneterre, 100 mg epirubicin], FEC120 [Levine, 120 mg epirubicin], other schedule)
- Has the intensity of the medical care of the patients (not including paperwork) changed as a result of participation in the ADEBAR study? (decreased, stayed the same, increased)
- As a result of participation in the ADEBAR study, do you receive additional information which actually helps to improve the medical care of patients (*e.g.*, through information in the study protocol, the central trial office, the ADEBAR newsletter or the study meeting)? (does not apply, hardly applies, applies to a minor degree, definitely applies)



Question 1: In the last year *prior* to taking part in the ADEBAR study, have you introduced the relevant patients (breast cancer, ≥ 4 lymph nodes) in another therapy optimizing study (not an observational study)? (49.5% of the questionnaires available for analysis)

Figure 2. Previous study participation.

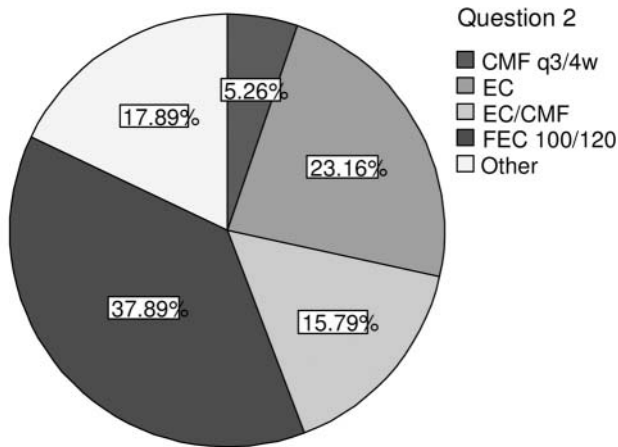
- In your estimation, has the overall quality of the medical care of patients (taking into account the various influencing factors, such as therapeutic efficacy, adverse effects, intensity of care) changed as a result of recruitment into the ADEBAR study? (worsened, stayed the same, improved)

Results

ADEBAR study procedure. In the period from September 1, 2001 to October 31, 2004, 1,248 patients (624 patients in treatment arm A, 624 patients in treatment arm B) were included in the ADEBAR trial. Out of 218 registered study centers, 198 study centers (91%) actively participated in patient recruitment. The tumor characteristics of tumor size ($p=0.24$), axillary lymph node status ($p=0.84$) and hormone receptor status ($p=0.78$) were distributed equally between both therapy groups.

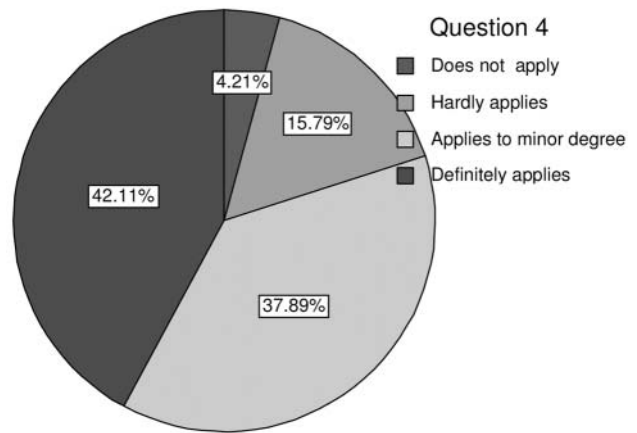
Results of the survey. The questionnaire was completed by 98 study centers and returned to the central trial office (49.5%). Three questionnaires were excluded from further analysis on account of incomplete answers to the questions (≥ 1 unanswered question), so that the results of 95 questionnaires were utilized.

Almost two thirds of the study centers (63.2%) had not entered their breast cancer patients with a comparable indication in any clinical scientific study prior to participation in the ADEBAR study (Figure 2). Prior to participation in the ADEBAR study, 37.9% of patients with the same indication (at least four axillary lymph node metastases) received anthracycline-based chemotherapy in triple combination and adequate dosage (FEC120 or FEC100), while 23.2% of the centers treated the patients in question with EC chemotherapy, 15.8% of the centers treated them



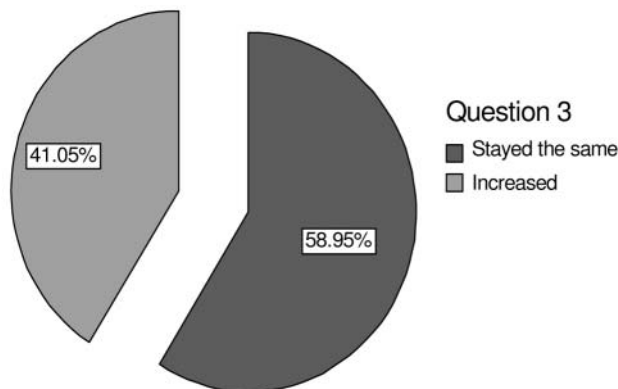
Question 2: Which chemotherapy scheme were comparable patients with the same tumor stage receiving *prior to* your center participating in the ADEBAR study? (49.5% of the questionnaires available for analysis)

Figure 3. *Previous study participation.*



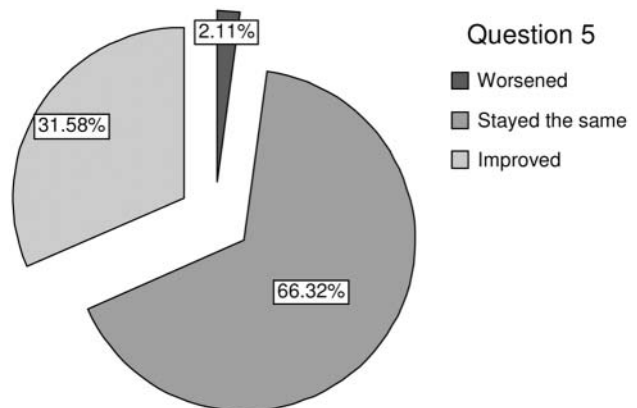
Question 4: As a result of participating in the ADEBAR study, do you receive additional information which actually helps to improve the medical care of patients (*e.g.* through information in the study protocol, the central trial office, the ADEBAR newsletter or the study meeting)? (49.5% of the questionnaires available for analysis)

Figure 5. *Additional information.*



Question 3: Has the intensity of the medical care of the patients (not counting paperwork) changed as a result of participating in the ADEBAR study? (49.5% of the questionnaires available for analysis)

Figure 4. *Intensity of medical care.*



Question 5: In your estimation, has the overall quality of medical care (taking into consideration the various factors of influence, such as oncological safety, adverse effects, intensity of care) of patients changed as a result of recruitment into the ADEBAR study? (49.5% of the questionnaires available for analysis)

Figure 6. *Overall quality of medical care.*

according to the EC/CMF schedule, and 5.3% of the centers used a CMF regimen. A different chemotherapy schedule, not named in the questionnaire, was given in 17.9% of the centers (Figure 3). In summary, before participating in the ADEBAR study, patients in at least 44.2% of the centers received cytostatic therapy (CMF, EC/CMF, EC) which did not meet the therapy standard of adequately-dosed anthracycline-containing polychemotherapy with three drugs (38).

By their own admission, the intensity of medical care (not including paperwork) had increased in 41.1% of the study

centers since participation in the ADEBAR study (Figure 4). Eighty percent of the centers stated that they received information as a result of participation in the study which helped to improve the quality of medical care (Figure 5). According to reports from 31.6% of the centers, the overall quality of medical care improved as a result of participation in the study, taking into account the various influencing factors, such as therapeutic efficacy, adverse effects and intensity of care, whereas it deteriorated in only 2.1% of cases (Figure 6).

Discussion

The present evaluation shows that the majority (63%) of the centers participating in the ADEBAR study had not entered their breast cancer patients with the same indication into any clinical trial before the beginning of this study. Before participating in the ADEBAR study, 44.2% of these patients received treatment, such as CMF, EC/CMF, or 4x EC, which is inadequate to today's standards. By participating in the study, and as a result of the flow of information associated with it (*e.g.*, through the study protocol, newsletter and study meetings), 80% of the centers recorded an improvement in their knowledge of breast cancer. In the opinion of the authors, these results support the hypothesis that carrying out the study has a positive effect on the current medical care of participating patients, irrespective of the knowledge gained later from the actual findings of the study.

In broad areas of oncology, clinical research has made the chance of recovery possible to an extent which was unimaginable only a few decades ago. Diseases such as seminoma (10) or choriocarcinoma are curable today in the majority of cases, even in the advanced, metastatic stage. The prospects for success are distinctly lower in solid malignancies such as breast cancer, which are characterized by early hematogenous tumor cell dissemination and resistance to systemic therapy (19, 24). Nevertheless, the prognosis in breast cancer has been improved substantially using cytostatic and endocrine therapies (1, 2, 9), while today's standard operative therapy is significantly less invasive (5, 13, 18, 20-22, 29, 33-37). At the same time, however, prospective randomized studies are necessary to qualify unrealistic hopes in new forms of therapy and to avoid excessive adverse effects in the future, as was demonstrated in the past by the example of high-dose chemotherapy of breast cancer (4, 11, 12).

Given the undoubted importance of clinical trials, the reasons for centers not to participate in clinical research projects are diverse and require further study. In a previous survey of two German clinical research groups (the Arbeitsgemeinschaft Gynakologische Onkologie Studien-gruppe Ovarialkarzinom [AGO-OVAR] or the Nord-Ostdeutsche Gesellschaft für Gynakologische Onkologie [NOGGO]), 85 institutions gave their reasons for non-participation (30). The most commonly-noted arguments were limited resources for documentation (84.7%), or for informing patients (82.4%), and the high costs of treatment in the study (65.9%). About 47.1% of non-participants stated that patients refused informed consent and that taking part in a trial is an additional burden. Administrative services refused permission to take part in the survey in 4.7% of all cases. The authors conclude that an inadequate infrastructure is the main barrier that must be overcome in

order to improve study participation. In addition, the high percentage of ADEBAR study centers (63%) which did not participate in clinical trials prior to ADEBAR indicate that feasible study designs and support offered by a leading research group may increase study compliance.

A satisfactory response cannot be given at present to the question of whether participating in a study produces direct benefits for the patients concerned, regardless of the scientific advances for future generations of patients. The frequently cited work of Gnant (14), presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2000, and was met with widespread interest, is not yet available as a full publication. Based on the results of a tumor stage-adjusted matched pair analysis of 7,738 patients, the author came to the conclusion that the probability of overall survival can be significantly improved by participation in a clinical trial ($p < 0.00001$) (14). In addition to the fact that the data were not checked *via* a medical journal peer review process, method-related doubts make it more difficult to interpret the findings. It is not impossible that the increased survival advantage attributed to participation in the study is caused by the effect of selecting patients with a more favorable morbidity profile (*healthy patient effect*).

In a more recent study, Hébert-Croteau *et al.* assessed the impact of participation in clinical trials, with treatment according to guidelines or non-systematic treatment, among 1,727 women with localized breast cancer (17). Using individuals not treated according to guidelines for systemic therapy as reference, the adjusted hazard ratio of death was 0.70 (95% confidence interval (CI): 0.54-0.90, $p = 0.006$) in those treated according to current guidelines and 0.45 (95% CI: 0.27-0.73, $p = 0.001$) in those participating in research (17). Particularly in the case of ovarian cancer, similar results support a survival benefit through participation in clinical trials (8, 16). The beneficial effect of study participation might be explained in several ways: some of the patients benefit from a superior treatment in positive randomized trials, all patients may benefit from more intensive care prescribed by protocols and patients will benefit from standardized treatment as study protocols are thoroughly reviewed by ethics review committees (16, 27, 31, 39). In addition, patients with cancer should be encouraged to enrol in clinical trials on the basis of the unquestionable role of trials in improving treatment for future patients (25).

There is ample evidence of the benefits of standardized therapy that conforms to medical guidelines which is not only more cost effective (23), but also any deviation from the recommended chemotherapy dosage may result in a demonstrable reduction in life expectancy (6). Phase III studies offer a largely secure basis for the controlled delivery of a therapy of known efficacy. While the standard therapy arm is normally derived from the currently valid

"gold standard" (e.g., the FEC120 scheme within the ADEBAR study), on ethical grounds alone experimental therapies are only employed as a study arm when efficacy is assumed to be at least equivalent to this. The present study demonstrates that, prior to the ADEBAR study, patients in at least 44% of the centers were treated with chemotherapy regarded as inadequate to today's standards (38). The proportion of centers (17.9%) which employed other chemotherapy schedules not named in the questionnaire suggests that the proportion of patients receiving inadequate therapy may in reality be even higher.

The basis for satisfactory implementation of standard therapy is the adequate flow of information to the attending physician (28, 32). This information must include both the principles for carrying out the therapy and also various options for the successful treatment of complications associated with the therapy. Clinical studies should offer a platform which improves the provision of this information. The responsibilities of a central trial office, in addition to carefully developing a study protocol and arranging an objective review of it (by ethics committees and by certification procedures for seals of approval), should include the continuous passing on of relevant information which helps ensure the optimal treatment of patients within the study. Thus, newsletters or study meetings can be used to pass on recent conference reports and therapy standards, as well as reports on serious adverse events (SAE) or study-specific instructions for treatment. The feedback from 80% of the study centers indicating that they had received information which helped to improve the quality of medical care, confirms that carrying out the study makes a contribution to this flow of information.

The potential shortcomings of this study comprise the survey's response rate of approximately 50% and the potential subjectivity of responses in this survey. It is impossible to know how far the treatment in the non-responding centers corresponds to that of the responding centers. In addition, the rating of treatment quality by the centers themselves might not accurately reflect the treatment reality. However, the key findings of this study, such as the change in chemotherapy regimens, are objective and reproducible. The scope of this study explicitly was not to demonstrate survival benefits acquired by study participation and the results should be interpreted with great caution and must not lead to the conclusion that it can substantiate an overall benefit of participation in clinical trials.

Conclusion

In conclusion, the results of the survey support the belief that participation in a clinical trial has a positive effect on the overall quality of the medical care of patients. Of course, this effect is difficult to objectify and quantify. Even the

results of this survey do not provide clear evidence of patient-specific benefit as a result of participation in a study. However, for method-related reasons, prospective data on the prognostic effect of study participation will also not be available in the future. Nevertheless, the contribution of clinical trials to the improvement in standards of therapy in breast cancer remains undisputable, based on the fact that, according to the estimate of Sir R. Peto of the Early Breast Cancer Trialists' Collaborative Group, the mortality of breast cancer in 2010 might only be half as high as it would have been without the progress made in recent decades (26).

The authors declare that they have no competing interests.

References

- 1 Early Breast Cancer Trialists' Collaborative Group: Ovarian Ablation for Early Breast Cancer. *Cochrane Database Syst Rev* CD000485, 2000.
- 2 Tamoxifen for Early Breast Cancer. *Cochrane Database Syst Rev* CD000486, 2001.
- 3 Beatson GT: On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet* 74: 1896.
- 4 Berger A: High dose chemotherapy offers little benefit in breast cancer. *BMJ* 318: 1440, 1999.
- 5 Blichert TM, Rose C, Andersen JA, Overgaard M, Axelsson CK, Andersen KW and Mouridsen HT: Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. *Danish Breast Cancer Cooperative Group. J Natl Cancer Inst Monogr* 11: 19-25, 1992.
- 6 Bonadonna G and Valagussa P: Dose-response effect of adjuvant chemotherapy in breast cancer. *N Engl J Med* 304: 10-15, 1981.
- 7 Dixon JR Jr: The International Conference on Harmonization Good Clinical Practice Guideline. *Qual Assur* 6: 65-74, 1998.
- 8 du Bois A, Rochon J, Lamparter C and Pfisterer J: Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer. *Int J Gynecol Cancer* 15: 183-191, 2005.
- 9 Early Breast Cancer Trialists' Collaborative Group: Multi-agent chemotherapy for early breast cancer. *Cochrane Database Syst Rev* CD000487, 2002.
- 10 Einhorn LH: Ifosfamide in germ cell tumors. *Oncology* 65: 73-75, 2003.
- 11 Farquhar C, Basser R, Hetrick S, Lethaby A and Marjoribanks J: High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. *Cochrane Database Syst Rev* CD003142, 2003.
- 12 Farquhar C, Basser R, Marjoribanks J and Lethaby A: High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer. *Cochrane Database Syst Rev* CD003139, 2003.
- 13 Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, Fisher E, Deutsch M, Caplan R, Pilch Y *et al*: Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 320: 822-828, 1989.

- 14 Gnant M: Impact of participation in randomized clinical trials on survival of women with early-stage breast cancer – an analysis of 7985 patients. *Proc ASCO*. 2000. (Abstract)
- 15 Halsted WS: The results of radical operation for the cure of carcinoma of the breast. *Ann Surg* 46: 1-19, 1907.
- 16 Harter P, Du Bois A, Schade-Brittinger C, Burges A, Wollschlaeger K, Gropp M, Schmalfeldt B, Huober J, Staehle A and Pfisterer J: Non-enrolment of ovarian cancer patients in clinical trials: reasons and background. *Ann Oncol*, 2005.
- 17 Hebert-Croteau N, Brisson J, Lemaire J and Latreille J: The benefit of participating to clinical research. *Breast Cancer Res Treat* 91: 279-281, 2005.
- 18 Jacobson JA, Danforth DN, Cowan KH, d'Angelo T, Steinberg SM, Pierce L, Lippman ME, Lichter AS, Glatstein E and Okunieff P: Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med* 332: 907-911, 1995.
- 19 Janni W, Rack B, Schindlbeck C, Strobl B, Rjosk D, Braun S, Sommer H, Pantel K, Gerber B and Friese K: Association of persistence of isolated tumor cells (ITC) in bone marrow (BM) of breast cancer patients with risk for relapse. *Proc ASCO*, 2004 (Abstract).
- 20 Janni W, Rjosk D, Dimpfl TH, Haertl K, Strobl B, Hepp F, Hanke A, Bergauer F and Sommer H: Quality of life influenced by primary surgical treatment for stage I-III breast cancer-long-term follow-up of a matched-pair analysis. *Ann Surg Oncol* 8: 542-548, 2001.
- 21 Janni W, Sommer H, Strobl B, Rack B, Klanner E, Hantschmann P, Rammel G, Harms G and Dimpfl T: Progress in the early diagnosis of breast carcinoma during the years 1981-1990. Results of a longitudinal study. *Dtsch Med Wochenschr* 128: 601-606, 2003.
- 22 Kuhn T, Bembek A, Buchels H, Decker T, Dunst J, Mullerleile U, Munz DL, Ostertag H, Sautter-Bihl ML, Schirrmeister H, Tulusan AH, Untch M, Winzer KJ and Wittekind C: Sentinel node biopsy in breast carcinoma. Interdisciplinary agreement consensus of the German Society for Serology for quality controlled application in routine clinical testing. *Pathologe* 25: 238-243, 2004.
- 23 Minter RM, Spengler KK, Topping DP, Flug R, Copeland EM and Lind DS: Institutional validation of breast cancer treatment guidelines. *J Surg Res* 100: 106-109, 2001.
- 24 Pantel K and Brakenhoff RH: Dissecting the metastatic cascade. *Nat Rev Cancer* 4: 448-456, 2004.
- 25 Peppercorn JM, Weeks JC, Cook EF and Joffe S: Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* 363: 263-270, 2004.
- 26 Peto R: 2003 (personal communication).
- 27 Rahman ZU, Frye DK, Buzdar AU, Smith TL, Asmar L, Champlin RE and Hortobagyi GN: Impact of selection process on response rate and long-term survival of potential high-dose chemotherapy candidates treated with standard-dose doxorubicin-containing chemotherapy in patients with metastatic breast cancer. *J Clin Oncol* 15: 3171-3177, 1997.
- 28 Randal J: Study evaluates information on breast cancer Web sites. *J Natl Cancer Inst* 96: 430, 2004.
- 29 Sarrazin D, Le MG, Arriagada R, Contesso G, Fontaine F, Spielmann M, Rochard F, Le-Chevalier T and Lacour J: Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncol* 14: 177-184, 1989.
- 30 Sehouli J, Kostromitskaia J, Stengel D and Du Bois A: Why institutions do not participate in ovarian cancer trials – results from a survey in Germany. *Onkologie* 28: 13-17, 2005.
- 31 Stiller CA: Centralised treatment, entry to trials and survival. *Br J Cancer* 70: 352-362, 1994.
- 32 Thornton H: Evidence-based information. *Lancet* 353: 2249, 1999.
- 33 van-Dongen JA, Bartelink H, Fentiman IS, Lerut T, Mignolet F, Olthuis G, van-der-Schueren E, Sylvester R, Winter J and van-Zijl K: Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. *J Natl Cancer Inst Monogr* 15-18, 1992.
- 34 Veronesi U, Paganelli G, Viale G, Galimberti V, Luini A, Zurrada S, Robertson C, Sacchini V, Veronesi P, Orvieto E, De Cicco C, Intra M, Tosi G and Scarpa D: Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series. *J Natl Cancer Inst* 91: 368-373, 1999.
- 35 Veronesi U, Paganelli G, Viale G, Luini A, Zurrada S, Galimberti V, Intra M, Veronesi P, Robertson C, Maisonneuve P, Renne G, De Cicco C, De Lucia F and Gennari R: A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 349: 546-553, 2003.
- 36 Veronesi U, Salvadori B, Luini A, Greco M, Saccozzi R, Del-Vecchio M, Mariani L, Zurrada S and Rilke F: Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,973 patients. *Eur J Cancer* 31A: 1574-1579, 1995.
- 37 Veronesi U and Zurrada S: Present and future of sentinel node lymphadenectomy in breast cancer. *Recent Results Cancer Res* 157: 221-227, 2000.
- 38 von Minckwitz G, Brunnert K, Costa SD, Friedrichs K, Jackisch C, Gerber B, Harbeck N, Junkermann H, Mobus V, Nitz U, Schaller G, Scharl A, Thomssen C and Untch M: Evidence-based recommendations on primary treatment of carcinomas of the breast. *Zentralbl Gynakol* 124: 293-303, 2002.
- 39 Ward LC, Fielding JW, Dunn JA and Kelly KA: The selection of cases for randomised trials: a registry survey of concurrent trial and non-trial patients. The British Stomach Cancer Group. *Br J Cancer* 66: 943-950, 1992.

Received January 9, 2006

Accepted June 14, 2006