

EDUCATIONAL HIGHLIGHTS FROM DATA PRESENTED AT THE

**30TH ANNUAL SAN ANTONIO
BREAST CANCER SYMPOSIUM (SABCS)**

**NEW ADVANCES
IN THE TREATMENT OF
BREAST CANCER**



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NEW ADVANCES IN THE TREATMENT OF BREAST CANCER

The field of breast cancer treatment has seen enormous growth since the introduction of anthracyclines almost three decades ago. As knowledge about the molecular biology of breast cancer has increased, so has the complexity of treating this heterogeneous disease. Successive improvements in reducing recurrence and mortality with anthracyclines over cyclophosphamide, methotrexate, and fluorouracil (CMF), and taxanes over anthracyclines have added up to significant gains over no therapy at all ^[1]. The availability of hormonal and targeted therapies has added further gains in certain subsets of women with breast cancer. Most recently, genetic and molecular testing for disease targets and predictors of response to therapy has opened up the potential for customised treatment programmes ^[2].

The 30th Annual San Antonio Breast Cancer Symposium (SABCS) featured several presentations reporting the latest clinical data on the use of systemic therapy in different adjuvant combinations as well as treatment options in metastatic breast cancer.

Evolution of systemic adjuvant therapies

A satellite symposium at this year's SABCS entitled 'Adjuvant Chemotherapy: From Receptors to Regimens to Real Patients,' featured a historical review of adjuvant breast cancer treatment by Miguel Martín (Servicio de Oncología Médica, Hospital Universitario San Carlos, Madrid, Spain).

Historical perspective

"The adjuvant treatment of breast cancer has moved from an empirical approach in the 20th century to a molecular/genomic approach in the 21st century," said Dr. Martín. Disease stage-based treatment has evolved to a focus on tumour biology, while risk estimation is now based on molecular factors in addition to TNM (Tumour, Nodes, and Metastases) staging. Even the concept of breast cancer as a single disease has changed to an understanding that it is a family of diseases. With this understanding, a treatment paradigm based on tailored therapy as opposed to 'chemotherapy for all' is emerging.

In the 1980s, anthracycline-based combinations became the standard adjuvant chemotherapy for breast cancer, as studies demonstrated an absolute increase of 4% in disease-free survival (DFS) over CMF ^[3,4]. However, anthracyclines are associated with long-term adverse effects, including severe cardiac toxicity and increased risk of leukemia and myelodysplastic syndrome (MDS). Taxanes entered the picture in the 1990s, with nine first-generation randomised studies comparing anthracycline-based combinations with and without a taxane ^[5-13]. "All of these trials except one ^[13] showed an absolute increase in DFS with taxanes ranging from 4% to 7%," noted Dr. Martín. A meta-analysis of 9,670 patients reported a reduced risk of relapse (relative risk [RR]: 0.84; $p < 0.0001$) and mortality (RR: 0.84; $p < 0.0001$) with taxanes ^[14].

Second-generation trials evaluated dose-intensified and sequential regimens. The Intergroup C9741 trial reported a

significant improvement in DFS with dose-dense (q2wk) paclitaxel, doxorubicin (A) and cyclophosphamide (C) over the standard dose regimen (q3wk) ^[15]. An analysis of relative risk of recurrence according to hormone receptor (HR) status in several taxane trials (for paclitaxel) showed a somewhat greater benefit in HR-negative patients ^[16].

A retrospective analysis of the CALGB 9344 study found that paclitaxel is effective in Human Epidermal growth factor Receptor-Receptor (HER 2)-positive patients but not in HER2 negative patients (HER2-) ^[17]. DFS was improved by paclitaxel in HER2-, ER (oestrogen receptor)-negative patients ($p = 0.002$) and HER2+, ER- patients ($p = 0.001$). The GEICAM 9906 trial found that HER2-, HR- patients were the only subgroup to derive significant benefit from paclitaxel ($p = 0.0254$) ^[10]. Finally, trials of adjuvant trastuzumab report improved DFS and overall survival (OS) in patients with HER2+ breast cancer ^[18-20]. "Advances in molecular biology are changing our conception of breast cancer and improving the prediction of risk and response to therapy," concluded Dr. Martín.

The worldwide overview: new results for systemic adjuvant therapies

In order not to miss moderate gains from treatment, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) shares data every five years (1985, 1990, 1995, 2000, 2005-2006). Analyses have shown that by many moderate gains, treatment has almost halved the UK and US breast cancer mortality rate for the 35-69 age group. Further, moderate gains are still considered to be achievable and worthwhile.

In the present 2005-2006 update, Sir Richard Peto (Medical Sciences Division, University of Oxford, Oxford, UK) again showed the improvements in reducing recurrence and mortality with CMF over no chemotherapy and with anthracyclines over CMF. For the first time, Prof. Peto

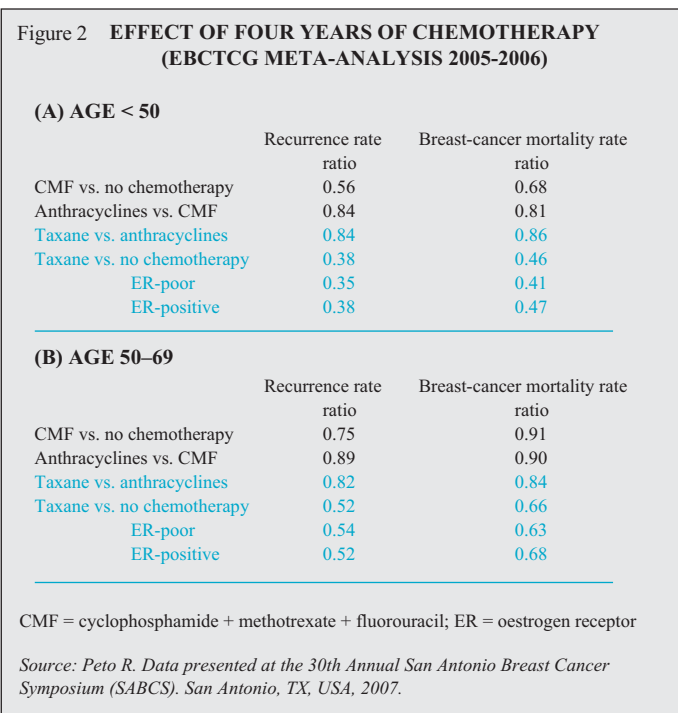
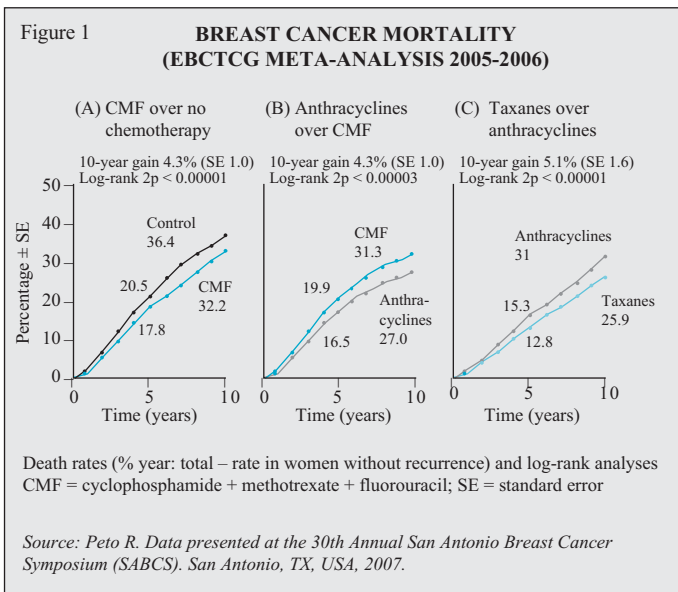
presented the significant benefit with taxanes-based chemotherapy as compared to anthracyclines, independent of hormone receptor status and age, though longer follow-up is needed for exact impact of taxanes in early breast cancer patients (Figures 1 and 2).

axillary nodes involved). Effects were compared to standard-dose chemotherapy in terms of DFS, breast-cancer-specific survival (BCSS) and OS. Data indicated that HDC with autologous haematopoietic stem-cell transplantation after surgery significantly improves DFS (hazard ratio [HR] = 0.87; $p = 0.0005$) but has at most a modest effect on BCSS. Moreover, HDC does not extend the OS (HR = 0.94) of breast-cancer patients. He concluded that these new findings, based on analysis of 6,200 patients from 15 trials, should close the book on this controversial treatment.

Controversy anthracycline-free vs. anthracycline-based treatment

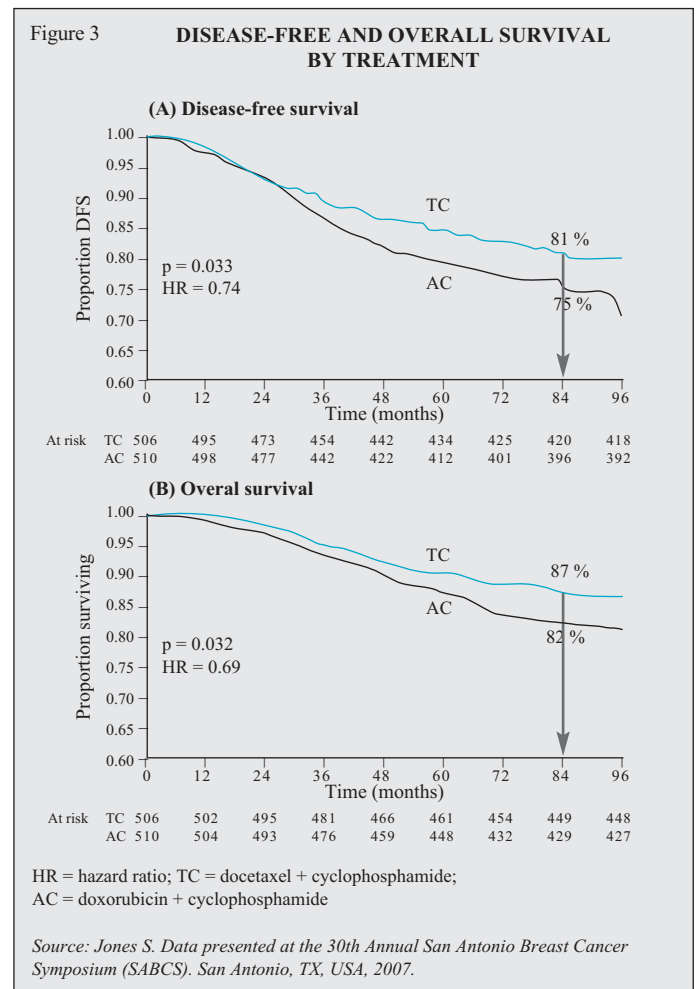
US Oncology Adjuvant Trial 9735

Steve Jones (US Oncology Research, Houston, TX, USA) presented the extended follow-up and analyses by age of the US Oncology Trial 9735 investigating the anthracycline-free combination of docetaxel and cyclophosphamide (TC) versus doxorubicin and cyclophosphamide (AC) in women with early operable breast cancer [21]. The patients were randomised to doxorubicin (60 mg/m² IV day 1) plus cyclophosphamide (600 mg/m² IV day 1) or docetaxel (75 mg/m² IV day 1) plus cyclophosphamide (600 mg/m² IV day 1), every 21 days for four cycles.



High-dose chemotherapy with autologous stem-cell support versus standard-dose chemotherapy

David A. Berry (Division of Quantitative Sciences, MD Anderson Cancer Center, Houston, TX, USA) presented an MDACC-EBMT (European Group for Blood and Marrow Transplantation) meta-analysis from 15 randomised adjuvant trials and the impact of high-dose chemotherapy (HDC) for primary breast cancer at high risk (at least four



At a median follow-up of seven years, four cycles of TC compared to four cycles of AC was superior for DFS and OS. DFS was 81% with TC (n = 506) versus 75% with AC (n = 510; HR = 0.74; p = 0.033). OS was significantly better for patients receiving TC (87%) versus AC (82%; HR = 0.69; p = 0.032; Figure 3). DFS and OS were better in both younger (<65) and older (≥ 65) patients receiving TC than in those receiving AC but p values were not calculated because of the small sample size. DFS was also superior with TC versus AC in a limited sample of HER2+ patients (HR = 0.73) and HER2- patients (HR = 0.56). An exploratory analysis showed that the hazard ratios for DFS favoured TC in all subgroups, including ER/PgR- and ER/PgR+ patients.

Grade 3/4 anaemia was more common in patients aged 65 and over who received AC (5%) versus TC (<1%). In patients younger than 65 the result was less than 1% for TC and 1% for AC. Grade 3/4 febrile neutropenia was more common in the TC patients aged 65 years and over (8%) versus AC (4%). In patients younger than 65 years grade 3/4 febrile neutropenia was 4% in the TC arm versus 2% in the AC arm. Grade 3/4 non-haematologic toxicities were relatively low and similar in both treatment and age groups. Three additional long-term fatal toxicities occurred — congestive heart failure (CHF), MDS, and myelofibrosis — all in patients receiving AC. “TC is a highly effective, modestly toxic, non-anthracycline adjuvant chemotherapy regimen that should now be considered a standard treatment for early breast cancer and that deserves further study in new clinical trials,” concluded Dr. Jones.

Role of anthracycline-based therapy in the adjuvant treatment of breast cancer

With reference to the superiority of a non-anthracycline (TC) over an anthracycline-containing regimen (AC), Dennis J. Slamon (Division of Hematology/Oncology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA) reviewed the role of anthracyclines in the adjuvant treatment of breast cancer as determined by molecular subtypes of the disease. The CALGB 8541 trial found no difference in outcome associated with anthracycline dose in HER2- patients, but HER2+ patients had better DFS (p < 0.001) and OS (p < 0.001) with higher doses. The NSABP B-15 study reported improved outcomes with anthracycline-based therapy versus CMF in HER2+ patients but not in HER2- patients. The MA.5 trial found an increase in relapse-free survival (p = 0.003) and OS (p = 0.06) with fluorouracil plus epirubicin plus cyclophosphamide (FEC) vs. CMF but no difference in HER2- patients^[3]. A meta-analysis of six trials showed that HER2+ patients had better OS with anthracycline therapy compared to HER2- patients^[22].

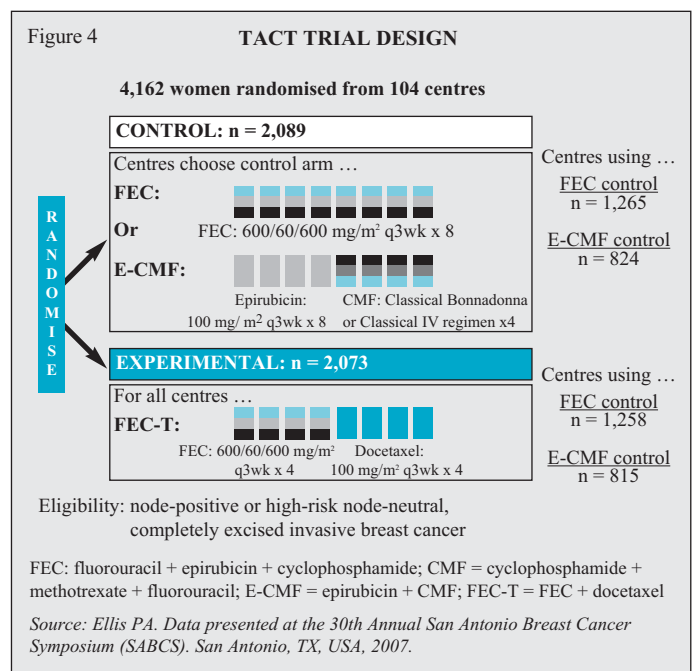
In the BCIRG 006 trial in HER2+ patients, DFS was significantly better in the two trastuzumab (H) arms

(AC-TH 83%; TCH 82%) than in the AC-T control arm (77%). The difference was much larger in the topoisomerase IIa non-coamplified patients, with 83% DFS in the AC-TH arm and 81% DFS in the TCH arm versus 71% in the AC-T arm. In the topoisomerase IIa coamplified patients, DFS outcomes were identical for all three treatment arms. The BCIRG 005 study analysed the topoisomerase IIa status in over 1,600 HER2- patients. None of these patients showed topoisomerase IIa amplification, indicating that topoisomerase IIa amplification does not occur in the absence of HER2 amplification. Prof. Slamon suggested that the superior efficacy of anthracyclines appears to derive from their effects on topoisomerase IIa coamplification, occurring only in 8% of all breast cancers. He closed his presentation with the provocative question: “What is the role of anthracyclines in the adjuvant treatment of breast cancer?”

The UK TACT trial

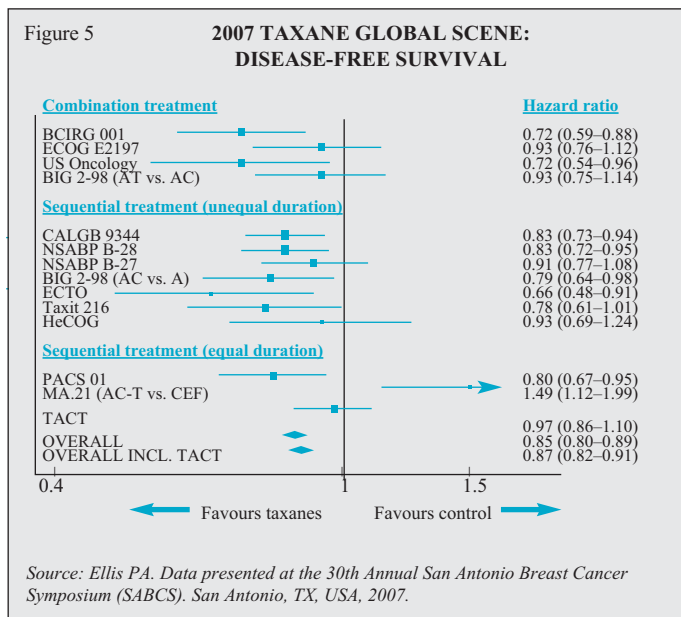
The UK TACT trial evaluated outcomes of sequential docetaxel-based chemotherapy versus standard anthracycline-based chemotherapy of equivalent duration. Paul A. Ellis (Department of Medical Oncology, Guy's, King's, and St. Thomas' Hospital, London, UK) presented the preliminary safety and efficacy results of the trial^[23].

A total of 4,162 women, with high-risk invasive breast cancer (~20% node-negative), were randomised to FEC (n = 2,523) or E-CMF (n = 1,639) as the control or to FEC-T (n = 2,073). FEC consisted of fluorouracil plus epirubicin plus cyclophosphamide (600/60/600 mg/m² q3wk x 8 cycles). E-CMF consisted of epirubicin (100 mg/m² q3wk x 4 cycles) plus CMF (4 cycles). FEC-T consisted of FEC (600/60/600 mg/m² q3wk x4) followed by docetaxel (100 mg/m² q3wk x 4). The primary end point was DFS.



Five-year DFS was 74.7% for the FEC-T arm versus 73.9% for the control arm (HR = 0.97; 95% confidence interval [CI] 0.86–1.10; $p = 0.62$). Five-year OS was 82.0% for the FEC-T arm versus 81.8% for the control arm (HR = 0.98; 95% CI 0.84–1.14; $p = 0.76$). Analysis of DFS by subgroups showed no benefit of FEC-T over control for ER+ patients (HR 1.06; 95% CI 0.90–1.25; $p = 0.50$). For ER- patients receiving FEC-T, the HR was 0.87 (95% CI 0.71–1.05; $p = 0.15$). By HER2 status, HRs were 1.02 (95% CI 0.87–1.21; $p = 0.74$) for HER2- patients and 0.89 (95% CI 0.70–1.12; $p = 0.32$) for HER2+ patients. Analysis by combined ER and HER2 status in node-positive patients showed that HER2+ ER- patients had an HR of 0.70 (95% CI 0.49–1.01) favouring FEC-T. The rates of grade 3/4 haematologic and non-haematologic toxicities were higher in the FEC-T arm than in the control arm ($p < 0.001$).

Dr. Ellis finished his presentation with an overview of the impact of taxane-based chemotherapy for adjuvant treatment of early breast cancer. He showed that even with the incorporation of the preliminary UK-TACT data, taxanes appear to have added significant value as systemic adjuvant treatment for breast cancer (Figure 5). Dr. Ellis concluded with the question “Have we reached the end of the era asking ‘one size fits all’ questions in large adjuvant clinical trials?”



Tailor-made treatment: one size fits all?

Prognostic and predictive value of the 21-gene recurrence score assay

With reference to the quote of Dr. Ellis and in line with the development of customised treatment programmes,

Kathy S. Albain (Department of Hematology and Oncology, Loyola University, Chicago, IL, USA) presented data on the prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER+ breast cancer. Data were derived from the phase III trial S8814 showing DFS and OS benefit of CAF (cyclophosphamide plus doxorubicin plus fluorouracil) added to tamoxifen (T) at 10 years, especially if T followed CAF (CAF-T), in this patient population. RT-PCR (reverse transcription-polymerase chain reaction) analyses of the 21 genes for the recurrence score (RS) for DFS and OS were conducted by the SWOG Statistical Center using tumour blocks or unstained slides of the T and CAF-T arms of S8814. The RS was shown to be prognostic for T-treated patients with positive nodes. Moreover, it is predictive of added CAF benefit in those patients whose tumours have a high RS. A low RS may define a group of women with positive nodes who do not appear to benefit from anthracycline-based adjuvant chemotherapy.

Contributions from The Netherlands

Predictive value of the Amsterdam 70-gene signature

S. Mook (The Netherlands Cancer Institute, Amsterdam, The Netherlands) presented a poster on predicting outcomes in breast cancer patients using the Amsterdam 70-gene profile. The aim of the study^[24] was to identify low-risk breast cancer patients who have excellent disease outcomes. A total of 106 patients with 1–3 positive nodes were selected from the first validation study of the 70-gene profile^[25]. The patients were classified as having a good prognosis 70-gene signature (41%) or a poor prognosis signature (59%).

At a median 10.3 years follow-up, OS was 98% for patients with a good prognosis signature versus 64% for patients with a bad prognosis signature ($p < 0.01$). On multivariate analysis, the 70-gene signature was a strong independent prognostic factor for OS (HR = 5.3; 95% CI 1.2–22.5; $p = 0.025$).

In patients with a good prognosis signature, there was no significant difference in outcomes between patients treated and those not treated with adjuvant chemotherapy. These results suggest that incorporating the 70-gene profile into clinical decision making might lead to reconsideration of adjuvant chemotherapy.

Study acronyms

BCIRG 001, 005, 006	Breast Cancer International Research Group trials 001, 005, 006
CALGB 8541, 9344	Cancer and Leukemia Group B trials 8541, 9344
ECOG 1199, E2197	Eastern Cooperative Oncology Group trials 1199, E2197
ECTO	European Cooperative Trial in Operable breast cancer
GEICAM 9906	Grupo Español de Investigación en Cáncer de Mamma trial 9906
HeCOG	Hellenic Cooperative Oncology Group
MA.5, MA.21	National Cancer Institute of Canada Clinical Trials Group studies MA.5, MA.21
NSABP B-15, B-27, B-28	National Surgical Adjuvant Breast and Bowel Project studies B-15, B-27, B-28
PACS-01	Phase III Randomized Study of Adjuvant Fluorouracil, Epirubicin and Cyclophosphamide, in Women with Stage I Breast Cancer trial 01
TACT	Taxotere as Adjuvant Chemotherapy Trial

References

- Peto R. The worldwide overview: New results for systemic adjuvant therapies. SABCS 2007 (Plenary Lecture 1).
- Goldhirsch A, et al. Progress and promise: Highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol* 2007;18:1133–1144.
- Pritchard KI, et al. *HER2* and responsiveness of breast cancer to adjuvant chemotherapy. *New Engl J Med* 2006;354:2103–2111.
- Knoop AS, et al. Retrospective analysis of topoisomerase IIa amplifications and deletions as predictive markers in primary breast cancer patients randomly assigned to cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide, epirubicin, and fluorouracil: Danish Breast Cancer Cooperative Group. *J Clin Oncol* 2005;23:7483–7490.
- Henderson IC, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 2003;21:976–983.
- Mamounas EP, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. *J Clin Oncol* 2005;23:3686–3696.
- Martin M, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005;352:2302–2313.
- Roché H, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: The FNCLCC PACS 01 trial. *J Clin Oncol* 2006;24:5664–5671.
- Jones SE, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* 2006;24:5381–5387.
- Rodríguez-Lescure Á, et al. Subgroup analysis of GEICAM 9906 trial comparing six cycles of FE₉₀C (FEC) to four cycles of FE₉₀C followed by 8 weekly paclitaxel administrations (FECp): Relevance of *HER2* and hormonal status (HR). *J Clin Oncol* 2007;25(Suppl.):10598.
- Bianco AR, et al. Sequential Epirubicin-Docetaxel-CMF as adjuvant therapy of early breast cancer: results of the Taxit216 multicenter phase III trial. *J Clin Oncol* 2006;24(Suppl.):LBA520.
- Crown JP, et al. Docetaxel (T) given concurrently with or sequentially to anthracycline-based (A) adjuvant therapy (adjRx) for patients (pts) with node-positive (N+) breast cancer (BrCa), in comparison with non-T adjRx: First results of the BIG 2-98 Trial at 5 years median follow-up (MFU). *J Clin Oncol* 2006;24(Suppl.):LBA519.
- Goldstein L, et al. E2197: Phase III AT (doxorubicin/docetaxel) vs. AC (doxorubicin/cyclophosphamide) in the adjuvant treatment of node positive and high risk node negative breast cancer. *J Clin Oncol* 2005;23(Suppl.):512.
- Bria E, et al. Benefit of taxanes as adjuvant chemotherapy for early breast cancer: Pooled analysis of 15,500 patients. *Cancer* 2006;106:2337–2344.
- Hudis C, et al. Five year follow-up of INT C9741: Dose-dense (DD) chemotherapy (CRx) is safe and effective. *Breast Cancer Res Treat* 2005;94(Suppl. 1):S20–S21 (Abstr. 41).
- Martin M, et al. Benefit from adjuvant taxanes and endocrine responsiveness in breast cancer. *Breast* 2007;16(Suppl. 2):S127–S131.
- Hayes DF, et al. *HER2* and response to paclitaxel in node-positive breast cancer. *N Engl J Med* 2007;357:1496–1506.
- Romond EH, et al. Trastuzumab plus adjuvant chemotherapy or operable *HER2*-positive breast cancer. *N Engl J Med* 2005;353:1673–1684.
- Smith I, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in *HER2*-positive breast cancer: A randomised controlled trial. *Lancet* 2007;369:29–36.
- Slamon D, et al. BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in *Her2neu* positive early breast cancer patients. 29th SABCS. San Antonio, TX, USA, 2006 (Abstr. 52).
- Jones S, et al. Extended follow-up and analysis by age of the US Oncology Adjuvant trial 9735: Docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/cyclophosphamide and is well-tolerated in women 65 or older. *Breast Cancer Res Treat* 2007;106:S5 (Abstr. 12).
- Gennari A, et al. A pooled analysis on the interaction between *HER-2* expression and responsiveness of breast cancer to adjuvant chemotherapy. *Breast Cancer Res Treat* 2006;100(suppl 1):S19 (Abstr. 41).
- Ellis PA, et al. Preliminary results of the UK Taxotere as Adjuvant Chemotherapy (TACT) Trial. *Breast Cancer Res Treat* 2007;106:S21 (Abstr. 78).
- Mook S, et al. The Amsterdam 70-gene signature predicts outcome in breast cancer patients with 1-3 positive axillary lymph nodes. *Breast Cancer Res Treat* 2007;106:S63 (Abstr. 1064).
- Van de Vijver MJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* 2002;347:1999–2009.

