Results: Cytostatic treatment was prematurely stopped in 119 pts (4.4%) receiving FEC-DG and in 103 pts (3.8%) with FEC-D (p = 0.21). Dose reduction >20% (3.97% vs 2.90%) and postponement of treatment cycles >7die (22.85% vs 14.19%) was rare, but more frequent in the FEC-DG arm (both p < 0.001). G-CSF support was applied in 850 (29.2%) vs. 602 pts (20.7%, p < 0.001). Toxicities NCI grade >2 which occurred with incidence >1% or significantly different in the two arms are depicted in Table 1. Afebrile and febrile neutropenia and anemia did not differ between the two arms, but thrombocytopenia was more frequent in FEC-DG (1.7%, p = 0.007). Hand-foot syndrome and neuropathy was more frequent in the FEC-D arm (p = 0.09 and p = 0.02, respectively).

Conclusion: Severe adverse effects were rare in both treatment arms. The addition of gemcitabine to FEC-D adjuvant chemotherapy increases toxicity moderately. These findings will have to be interpreted in the context of survival outcome results.

Table 1

Toxicity	Grade >2		Percentage		p-value
	FEC-DG	FEC-D	FEC-DG	FEC-D	
Neutropenia	504	508	0.3490	0.3458	0.9984
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0×10⁹/L, fever ⩾38.5°C)	42	59	0.0291	0.0402	0.4454
Anemia	31	20	0.0215	0.0136	0.4556
Thrombocytopenia	25	6	0.0173	0.0041	0.0070
SGPT (ALT) (serum glutamic pyruvic transaminase) elevation	68	28	0.0471	0.0191	0.0004
GGT (Gamma-Glutamyl transpeptidase)	45	34	0.0312	0.0231	0.6205
Vomiting	55	58	0.0381	0.0395	0.9981
Nausea	43	45	0.0298	0.0306	0.9994
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	24	26	0.0166	0.0177	0.9971
Diarrhea patients without colostomy	41	39	0.0284	0.0265	0.9927
Fatigue (lethargy, malaise, asthenia)	40	46	0.0277	0.0313	0.9539
Bone pain	28	44	0.0194	0.0300	0.3381
Thrombosis/embolism	28	22	0.0194	0.0150	0.8396
Arthralgia (joint pain)	24	29	0.0166	0.0197	0.9409
Headache	21	10	0.0145	0.0068	0.2469
Myalgia	20	37	0.0139	0.0252	0.1809
Dyspnea	19	24	0.0132	0.0163	0.9175
Hand-foot skin reaction	15	33	0.0104	0.0225	0.0876
Neuropathy	9	28	0.0062	0.0191	0.0227

239 Poster

Economic assessment of late extended adjuvant letrozole following a prolonged therapy break from Tamoxifen – MA-17 post-unblinding analysis

J. Karnon[1], F. di Trapani[2], S. Kaura[2]. [1]University of Adelaide, Public Health, Adelaide, Australia; [2]Novartis Pharmaceuticals, Oncology, East Hanover, USA

Background: The MA17 study was a randomized double-blind placebo-controlled trial of 5 years of letrozole (LET) 2.5 mg/d in 5187 post-menopausal women (median age 62 yrs) with early breast cancer after 5 years of adjuvant tamoxifen (TAM). Due to significant improvement in disease-free survival with LET, the study was unblinded at the first interim analysis (mean follow-up 2.4 years). At this point (median time from TAM, 2.5 years), patients receiving placebo (PLAC) were offered LET. 1,655 patients accepted LET, 613 patients elected no treatment. After a median 2 year follow-up, DFS and DDFS were highly significantly improved in the PLAC-LET group after adjusting for differential demographics and disease characteristics. This analysis estimates the incremental cost per QALY gained (ICQ) of 5 years LET after the observed 2.5 year therapy break after TAM versus no extended adjuvant therapy from a national health service perspective.

Methods: A Markov model described the natural history of breast cancer via contralateral tumour, locoregional, and distant recurrence, also accounting for the effects of osteoporosis. Annual contralateral, recurrence and osteoporosis rates were obtained from the PLAC arm of the post-unblinding analysis, to which the adjusted HRs for the PLAC-LET group were applied. Effects of osteoporosis and recurrent events, and health state utilities were informed by published studies. Costs (2006 £) of breast-cancer care were obtained from a primary costing study in 2006. A probabilistic sensitivity analysis was undertaken, and all outcomes were discounted at 3.5% annually.

Results: The results show that the PLAC-LET group gain 14.14 QALYs compared to 13.84 in the PLAC group, lifetime costs £8,477 and

£4,524, respectively. The mean incremental cost per QALY is £13,154. The probabilistic sensitivity analysis estimates a 95% credible interval of £9,153–27,094, with an 87% probability of cost-effectiveness at a £20,000 value of a QALY.

Conclusions: Late extended adjuvant Letrozole therapy after a prolonged therapy break from Tamoxifen (1−5 years) is a cost-effective use of health care resources.

240 Poster

99mTc-MIBI elimination by a tumor and response to chemotherapy in locally advanced breast cancer patients

S.M. Portnoj[1], S.V. Shiryaev[2], A.A. Odjarova[2], O.A. Anurova[3], K.P. Laktionov[1], D.A. Rjabchikov[1]. [1]N.N. Blokhin Russian Cancer Research, Surgical Department of the Female Reproductive System Tumors, Moscow, Russian Federation; [2]N.N. Blokhin Russian Cancer Research, Laboratory of the Radioisotope Diagnose, Moscow, Russian Federation; [3]N.N. Blokhin Russian Cancer Research, Pathological Department, Moscow, Russian Federation

Aim: To estimate predictive significance of 99mTc-MIBI accumulation and elimination by tumor on the effectiveness of neoadjuvant chemotherapy in locally advanced breast cancer patients.

Materials and Methods: Investigation of accumulation and elimination of 99mTc-MIBI by tumor was performed in 45 breast cancer patients (stages: IIa − 1, IIb − 1, IIIa − 7, IIIb − 31, IIIc − 5 patients) before the beginning of chemotherapy (CAF, FAC, docetaxel, 3−6 cycles). 99mTc-MIBI was introduced intravenously (555 MBq), with the following two-phase (in 15 min and in average 3 hours) static scintigraphy of a breast. Coefficient of relative accumulation (CRA) of 99mTc-MIBI in tumors in 15 min after injection (CRA1), CRA after 3 hours (CRA2), and percent of elimination (PE) were calculated [PE = (CRA1 − CRA2)×100/CRA1]. All patients were operated. "No residual tumor" and "Microscopic residual tumor" were united as "pathological effect".

Results: Clinical effect was observed in 82% (complete effect in 6, partial effect in 31, stabilization in 7, and progression in 1 patient). Pathological effect was observed in 29% (no residual tumor in 4, and microscopic residual tumor in 9 cases). The levels of CRA1 and CRA2 did not influence on the frequency of clinical or pathological effects. In patients with high level of the PE pathological effect was not attained (see table). High level of the PE was reviewed more rarely (2p < 0.05) in patients with ER− HER2neu− tumors (19%), than in patients with ER+ HER2neu− tumors (47%), and than in patients with HER2neu+ tumors (75%).

Table. PE level and frequency of clinical and pathological effects

PE level	Frequency of clinical effects	Frequency of pathological effects
Low (<21%)	87% (26/30)	43%* (13/30)
High (>22%)	73% (11/15)	0%* (0/15)

*- 2p < 0.05.

Conclusion: Our first results confirm the main hypothesis: rapid 99mTc-MIBI elimination by a tumor predicts the low pathological response to chemotherapy. Detection of the high level of 99mTc-MIBI PE by tumor can indicate that neoadjuvant target therapy may be more preferential, than chemotherapy.

241 Poster

Safety and feasibility of biweekly neoadjuvant gemcitabine, epirubicin, and albumin bound nab-paclitaxel (GEA) in locally advanced breast cancer – results of a phase II study

D. Daniel[1], B. Daniel[1], R. Inhorn[2], Y. Naot[3], J. Zubkus[4], L. Simons[4], D. Knauer[5], V. Trieu[5], N. Desai[5], D. Yardley[4]. [1]Chattanooga Oncology and Hematology Associates PA, Hem/Onc, Chattanooga TN, USA; [2]Mercy Hospital, Hem/Onc, Portland ME, USA; [3]ICON, Hem/Onc, Jacksonville FL, USA; [4]Sarah Cannon Research Institute, Hem/Onc, Nashville TN, USA; [5]Abraxis Bioscience, Hem/Onc, Los Angeles CA, USA

Background: The triplet combination of gemcitabine (G), anthracyclines and taxanes have demonstrated significant activity as neoadjuvant therapy. Nab-paclitaxel is a novel albumin-bound form of paclitaxel that allows for the preferential delivery of paclitaxel to the site of the tumor via gp60/caveolin-1 transcytosis and the albumin binding protein SPARC. In preclinical models as well as in a phase III metastatic breast cancer trial, single agent nab-pacltiaxel was shown to increase both response rate and TTP compared with standard solvent based paclitaxel. In this multicenter phase II study, the

safety and feasibility of combining biweekly nab-paclitaxel with gemcitabine and epirubicin in the neoadjuvant setting is evaluated.

Methods: Eligibility: Clinical T1c-T4-d and/or N0−3, M0 breast cancer (T1N0M0 excluded). ER/PR/HER2 status were obtained for all pts. ECOG PS 0−2, normal LVEF, normal organ function. Treatment: 6 cycles neoadjuvant G 2000 mg/m^2, epirubicin 50 mg/m^2, and nab-pac 175 mg/m^2 q14 days followed by surgery. Post operative therapy: 4 cycles G 2000 mg/m^2 and nab-paclitaxel 220 mg/m^2 q14 days. Primary prophylaxis with myeloid growth factors was required with all cycles. Optional archival tumor tissue was obtained and evaluated for SPARC by immunohistochemistry; assessments were performed and scored on a 0−3 level (0 = absent, 1 = weak, 2 = moderate, 3 = strong).

Results: 123 pts have enrolled in this study. Median age 51 (29−72). ECOG PS 0 − 90%. Median tumor size 4.5 cm. Histology: 78% ductal, 9% lobular, 13% others. 42% ER and PR negative. 55% clinical T3/T4 and 66% lymph node positive at presentation. Grade 3/4 toxicity present in >5% of patients consisted of neutropenia 10% (febrile neutropenia 1 pt), thrombocytopenia 5% with arthralgias, fatigue, and infection each in 7%. 20 pts did not complete study treatment for the following reasons: disease progression 7, toxicity 3 patient/MD request 5, and other 5. Total of 1049 cycles were administered. pCRs have been noted in 21 pts (22%) patients. Full safety data as well as efficacy data will be presented.

Conclusion: Neoadjuvant biweekly GEA demonstrates a favorable safety profile and activity. Currently correlation between pathological responses and the expression of SPARC, a biomarker for poor prognosis, is being assessed.

242   Poster

Zoledronic acid (ZA) as adjuvant therapy for women with early stage breast cancer and disseminated tumor cells (DTC) in bone marrow (BM)

A. Lin[1], J. Park[1], M. Melisko[1], A. Goga[1], M. Moasser[1], D. Moore[1], H. Rugo[1]. [1]University of California-San Francisco, Comprehensive Cancer Center, San Francisco CA, USA

Background: The presence of DTC in the BM is associated with an increased risk of distant recurrence and death from cancer in women with early stage breast cancer (ESBC), particularly when these cells are detected after completion of adjuvant systemic therapy. Clodronate in pts with DTC at BC diagnosis reduced the incidence of metastases and improved survival. ZA is significantly more potent than clodronate in inhibiting bone resorption. We designed a pilot study to evaluate ZA in pts with ESBC with DTC. Decrease in DTC could serve as a surrogate marker of antitumor effect.

Methods: DTCs are detected by immunomagnetic enrichment + flow cytometry: BM is enriched with anti-EpCAM-conjugated iron particles, DTC are detected with EpCAM, CD45, and nucleic acid content. Pts with stage I−III BC are evaluated for DTC with a unilateral BM aspiration following neoadjuvant or adjuvant CTX; eligibility was defined as >4 DTC/ml, which is 2.5 SD > than 50 normal BM (Park, *Proc ASCO* 2002). Pts receive 4 mg of ZA IV monthly × 2 years (yrs). Concomitant hormone therapy was allowed. Serum creatinine and toxicity are evaluated monthly and urinary n-telopeptide is measured at 0, 2, 4, 6, 12, and 24 months (mos). Repeat BM aspirations are performed at 1 and 2 yrs.

Results: 45 pts are enrolled in this study. We report an interim analysis of baseline and one yr BM results. The mean DTC at baseline is 25.4 DTC/ml (range 4.9–333 DTC/ml), and the mean follow-up period is 16.2 mos (range: 1 to 31 mos). Baseline DTC >30 DTC/ml predicts for distant recurrence ($p = 0.007$). 24/31 pts (77%) had a decrease in DTC from baseline to 1 yr ($p = 0.02$). Mean urinary n-telopeptide levels for 0, 2, 4, 6, and 12 mos are 42, 20, 16, 16, and 15 nM BCE/mM creatinine respectively ($p < 0.001$). To date, 14 pts have had BM aspirations at 2 yrs. Five breast cancer recurrences occurred during the first yr of study enrollment (average time to recurrence 5.2 mos); all pts were node+, and negative for ER, PR, Her2/neu. ZA was well tolerated with only 1 pt discontinuing study treatment due to side effects.

Discussion: Serial detection of DTC in BM is feasible in women with ESBC. High baseline BM DTCs predicted for early recurrence in women with high risk disease. This preliminary data suggests that ZA may decrease the number of DTC in ESBC. Urinary n-telopepetide decreases over time, as expected. The study is ongoing, updated data will be presented.

243   Poster

Clinical impact of upfront adjuvant aromatase inhibitor (AI) therapy

J. Gligorov[1], D. Azria[2], M. Namer[3]. [1]APHP Tenon University Paris VI, Medical Oncology, Paris, France; [2]Centre Val d'Aurelle, Radiation Oncology, Montpellier, France; [3]Centre Azuréen de Cancérologie, Medical Oncology, Mougins, France

Background: ATAC and BIG 1-98 evaluate the efficacy of initial adjuvant AIs vs tamoxifen (TAM) in postmenopausal women with hormone-dependent breast cancer. ATAC originally compared anastrozole (ANA) with TAM and a combination of both for 5 years. BIG 1-98 is unique, as it compares 5 years of monotherapy with TAM or letrozole (LET) and the sequential use of both agents in either order. There were notable differences in trial design, population, and impact on early distant metastasis (DM), a proposed surrogate for survival.

Methods: Trial designs, analyses, and data were evaluated from the two initial adjuvant AI trials, ATAC and BIG 1-98. Efficacy results from the BIG 1-98 primary core analysis (PCA) at 25.8 months of follow-up (FU) and monotherapy arms analysis at 51 months (51M) are reviewed. Patient (pt) populations from the BIG 1-98 PCA and 51M differ. The PCA includes events in the monotherapy and sequential arms until 30 days post treatment switch (n = 8010). The 51M compares the monotherapy arms (n = 4922). ATAC (n = 6241) results at 68 and 100 months of FU are also reviewed. Pt eligibility varied; hormone receptor positivity was required for BIG 1-98; 99.7% of pts were hormone receptor-positive (HR+), compared with only 84% in ATAC. Only HR+ pt data were considered.

Results: The unique design of BIG 1-98 allowed for different analyses. A significant 27% reduction in the risk of DM was seen with LET in the planned PCA (P = 0.0012) and 19% (P = 0.03) in the 51M analysis. The ATAC trial did not proceed as originally planned, and no significant reduction in DM was reported at 33 months of FU. In ATAC, at 68 months of FU, the risk of DM was not significant with ANA (hazard ratio = 0.84, P = 0.06), but a significant 16% risk of DM was noted at 100 months (P = 0.022). Retrospective analyses done for BIG 1-98 at 2 years and ATAC at 2.5 years identified DM as the most common site of recurrence. LET reduced the DM risk by 30%, ANA by 7%.

Conclusions: ANA and LET prevent early recurrence more effectively than TAM. However, only LET in BIG 1-98 showed a pronounced early impact on DM, which is the most lethal recurrence.

244   Poster

TEACH phase III study of lapatinib after completion of adjuvant chemotherapy in trastuzumab-naive women with HER2-overexpressing breast cancer

B. Moy[1], J.D. Maltzman[2], E. Rappold[2], D. Finkelstein[3], L.S. Williams[2], P.E. Goss[1]. [1]Massachusetts General Hospital, Dept of Medicine, Boston MA, USA; [2]GlaxoSmithKline, Medicine Development Center, Collegeville PA, USA; [3]Massachusetts General Hospital, Dept of Biostatistics, Boston MA, USA

Background: Trastuzumab (Herceptin®; T) is a standard adjuvant treatment for high-risk HER2-positive (HER2+) early breast cancer (BC) patients (pts) receiving primary chemotherapy. However, T is not available to HER2 + pts who were diagnosed before T became available, live where T is not available to them, or have hypersensitivity to T. These pts are vulnerable to HER2-driven recurrences and therefore eligible for evaluation of an alternate anti-HER2 therapy. Lapatinib (Tykerb®, L) is a potent, oral selective, reversible, inhibitor of EGFR (ErbB1) and HER2 (ErbB2) receptor tyrosine kinases and has activity in both T-pretreated and T-naive HER2+ metastatic BC. TEACH (Tykerb® Evaluation After Chemotherapy) is a global randomized, double-blind, placebo-controlled phase III trial evaluating the role of L for reducing risk of relapse in T-naive HER2+ early-stage BC.

Methods: Women who have completed primary neo- or adjuvant chemotherapy without T for HER2+ (3+ by IHC or FISH+) invasive BC (stages I−IIIc) and are clinically or radiographically disease free are eligible. The primary endpoint is disease-free survival; secondary endpoints are overall survival, recurrence-free intervals, rate of CNS metastases, toxicity, and quality of life. Pts are randomized to L 1500 mg daily or placebo for 1 year and stratified by time from diagnosis, nodal involvement, and hormone receptor status.

Results: Between Aug 2006 and Dec 2007, 2404 pts have been randomized, approximately half from the EU, 16% from North America, and the remaining from the rest of the world. The table summarizes key patient demographics and disease characteristics as of November 20, 2007.

Conclusions: TEACH is a pioneer trial assessing benefit of adjuvant L in T-naive pts who received chemotherapy and thus have a significant risk of recurrence. Current data reflect a relatively lower risk pt population drawn from a wide distribution of nations. Accrual is ahead of schedule