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)

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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

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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

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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

with a goal of ~3000 pts. The success of enrollment demonstrates the feasibility of conducting an adjuvant trial in pts remote from their primary BC diagnosis.

Characteristic	Randomized population (N = 2103)
Mean age, yr (range)	51.9 (24−87)
Postmenopausal, %	66
Ethnicity, %	
European	72
East Asian	16
American Indian/Alaskan	5
African	3
Other	4
Stage at diagnosis, %	
I	19
II	56
III	24
Time from diagnosis $\leqslant$4 yr, %	73
Hormone receptor ER/PR positive, %	57
Axillary lymph node positive, %	57

245 Poster

Neoadjuvant docetaxel (DOC 75) followed by fluorouracil, epirubicin, cyclophosphamide (FEC 100) in primary operable breast cancer: results of a multicenter phase II trial

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Background: Combination regimens of an anthracycline and a taxane have been widely used as preoperative systemic therapy in patients with operable breast cancer. Our previous study (JBCRG01: FEC 100 followed by DOC 75, Toi et al, SABCS 2006 #1037), showed most tumors responded to docetaxel despite non response to FEC. However, due to the toxicity of FEC, completion rate of DOC was only 80%. To resolve issues from the JBCRG01 trial, we evaluated the efficacy and safety of neoadjuvant therapy with the reverse regimen DOC 75 followed by FEC 100 (JBCRG03).

Material and Methods: Eligible women had T1c−3N0M0, T1−3N1M0 operable breast cancer. Chemotherapy consisted of 4 cycles of DOC (75 mg/m^2) every 3 weeks followed by 4 cycles of FEC (F: 500 mg/m^2, E: 100 mg/m^2, C: 500 mg/m^2) every 3 weeks. The primary endpoint was pathologic response rate; secondary endpoints were safety, efficacy and a subset analysis of biomarkers.

Results: From October 2005 to October 2006, 137 women were enrolled and 135 were evaluable. The median age was 46 (range, 24−62) with 70% being premenopausal. All patients had ECOG Performance Status of 0 and 54% were node positive. 73% of patients had tumor stage T2, 9% T1, and 18% T3. Hormone status was: ER positive 64%, PgR positive 47%, both negative 33%. HER2 (IHC) status: positive (3+) 23%, negative 77%. Patient characteristics were similar to JBCRG01. 6 patients stopped chemotherapy because of progressive disease during DOC treatment. In DOC–FEC treatment, completion rates of DOC and FEC were 85% and 79%, respectively. The overall response rate was 79% with 21% CR. Addition of FEC improved overall response rate from 64% to 79%. Grade 3−4 hematological toxicity included leucopenia 58%, neutropenia 69%, and febrile neutropenia 15%. Grade 3 non-hematological toxicity included nausea 2%, vomiting 2%, fatigue 2%, anorexia 2%, diarrhea 1%, and weight loss 1%. There were no reports of grade 4 non-hematological toxicity.

Conclusions: The regimen of DOC 75 followed by FEC 100 as primary therapy for early stage breast cancer was an active regimen with an acceptable rate of severe toxicity. Further analyses including translational research are needed to evaluate the benefit of taxane first administration in the neoadjuvant setting.

246 Poster

Optimal timing and duration of the use of an aromatase inhibitor (AI) in the adjuvant treatment of postmenopausal hormone receptor-positive (HR+) breast cancer (BC)

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Introduction: It is clear that AIs have a central role to play in the adjuvant treatment of postmenopausal HR+ BC. They are more effective than tamoxifen (TAM) and generally have a better side-effect profile. However uncertainty exists as to whether they should be offered as the initial adjuvant treatment, or whether they are more effective after an initial "priming" period with TAM, where relative benefits appear to be larger. There is uncertainty between the efficacy of the different AIs and the timing of treatment.

Methods: Models are presented, based on published data from 8 trials, to evaluate the use of an AI upfront compared with sequencing it after varying periods of initial treatment with TAM. We model recurrence rates for the first 10 and 20 years of follow-up using only the reported hazard ratios. Historically, carryover effect had only been demonstrated with TAM as documented in the EBCTCG overview; however, it is now reported to be significantly greater with AIs [1].

Results: These models indicate that initial or early treatment always dominates a strategy of using TAM for 5 years initially. Using current data to estimate hazard ratios suggests that starting with an AI dominates a 2-year initial use of TAM followed by 3 years of an AI, even though the reduction in hazard ratios after switching may be larger after the switch has taken place. Based on data from the extended treatment studies of 5 years of an AI after 5 years of TAM, and the ATLAS study of 5 vs 10 years of TAM, we also model a range of 10-year treatment plans.

Conclusions: While it is clear that the current evidence suggesting use of an AI upfront, in the first 5 years of adjuvant treatment, is the best strategy, additional clinical trials results (ie, BIG 1-98 comparing upfront vs sequencing) will provide additional information regarding the optimal time to introduce an AI. Available evidence also supports continued treatment beyond 5 years in some patients, but no data exist on the optimal duration of treatment with an AI.

References

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247 Poster

Long-term results and comparative analysis of normo fractionated (NF) and hypo fractionated (HF) adjuvant radiotherapy after breast conserving surgery in elderly

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Purpose: To evaluate the results of elderly breast cancer (BC) patients (pts) treated with adjuvant once-weekly HF radiotherapy (RT).

Patients and Methods: Between 1995 and 1999, 401 patients older than 70 yrs were treated with conservative surgery and then adjuvant RT at the Institut Curie for non-metastatic BC. The surgery consisted of lumpectomy and lymph node dissection (LND) followed by NF RT, delivered to the total dose (TD) of 50 Gy in 25 fractions (fr.) to the breast +/− boost or HF: once weekly in five fr. of 6.5 Gy to a TD of 32.5 Gy to the breast. The regional LN were irradiated in NF group. Pts are regularly followed up and toxicity is evaluated. Hormonal treatment (HT) was delivered to all RH positive pts.

Results: There were 347 pts in the NF RT and 54 pts in HF RT group. The median follow-up was 92 months (9–143). In NF 36% of pts were older than 80 yrs vs 87% in HF group. The cause specific survival at 5 and 10 yrs was as follows: 96% and 89% for NF vs 93% and 85% for HF (p 0.3). HT was mostly neoadjuvant in HF pts (35%) and adjuvant in 91% in NF group. There was no significant difference in the local control between 2 groups with p 0.65, at 5 and 10 yrs, as follows: 95% and 89% for NF and 94% and 91% for HF. No metastatic disease was found at 5 and 10 yrs: 94% and 90% in NF and 93% and 91% in HF. The treatment tolerance and cosmetic results were comparable also between the 2 groups of patients.

Conclusions: The HF RT scheme resulted to providing excellent long-term local control, in mild early reactions and acceptable late toxicity. This treatment represents a good alternative in elderly with equal results in term of cause specific survival, local control, and metastatic rates, compared to NF RT. Large prospective randomised trials are needed to confirm these results.