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.

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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.

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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.

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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