These survival benefits were observed even though the study design resulted in 65% of control patients receiving H at disease progression. Cardiac dysfunction (CD) in the H + T arms occurred in 11% of patients aged <60 years and 21% of those aged >60 years. All CD events in those aged >60 years improved to grade 1 with treatment and H was continued. Conclusions: Patients with HER2-positive MBC who are more than 60 years of age appear to have a worse overall outcome than patients aged <60 years. This could be related to poor baseline prognostic characteristics. However, the survival benefit due to the addition of H to C in the older age group was significant. These data indicate that there is no reason to withhold first-line H + C therapy in older (age >60 years) patients with MBC.

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Capecitabine (Xeloda) in 162 patients with paclitaxel-pretreated mbc: updated results and analysis of dose modification

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Background: Capecitabine, a novel, oral, thymidine phosphorylase (TP)-activated fluoropyrimidine, exploits the high activity of TP in tumor cells to generate 5-FU preferentially at the tumor site. In the pivotal trial evaluating capecitabine in 162 heavily pretreated MBC patients, the response rate was 20% (29% in a subgroup of 42 patients resistant to both doxorubicin and paclitaxel), median time to progression (TTP) was 3.0 months and median overall survival (OS) was 12.8 months [Blum et al, JCO 1999]. Myelosuppression and alopecia were rare. We report updated results of this trial and an analysis of the impact of dose modification on efficacy.

Methods: 162 patients received capecitabine 1,250mg/m2 twice daily, days 1-14 every 21 days. The standard capecitabine dose modification scheme was applied if patients experienced grade 2 or more severe toxicities. A retrospective analysis was conducted to evaluate the impact of dose modification on efficacy.

Results: Median OS after 143 events is 11.6 months. Median TTP is 3.0 months. 54 patients (33%) required capecitabine dose reduction for adverse events. The dose was reduced to 75% of the starting dose after a median of 1.6 months in 45/162 patients (27%). A retrospective analysis demonstrated that patients requiring dose reduction for adverse events experienced no significant increase in risk of progression (hazard ratio 1.07, Wald test p=0.73) compared with those not requiring dose reduction.

Conclusions: Capecitabine monotherapy has shown considerable activity in heavily pretreated MBC. Dose modification from the standard starting dose to each patient's individually tolerable dose does not reduce efficacy. Given these results, capecitabine at a starting dose of 1,250mg/m2 twice daily, days 1-14, should be considered the reference treatment for patients whose disease has progressed with prior taxane therapy.

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Relationship of estrogen receptor (ER) status to clinical benefit in clinical trials of herceptin

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Background: HER2 proto-oncogene amplification and/or HER2 receptor overexpression is associated with poor prognosis in breast cancer. It has been reported that there is an inverse correlation between HER2 receptor levels and ER levels. It has also been suggested that targeting HER2 using Herceptin (H) may restore sensitivity to hormonal therapy in patients who have developed resistance. Therefore, we analysed the relationship of ER status to outcomes in the pivotal H trials and a trial of first-line H monotherapy. These trials demonstrated that H monotherapy is active as first- and second-line therapy for metastatic breast cancer and that H plus chemotherapy significantly improves survival. Methods: 805 HER2-positive patients (2+/3+ by IHC) were enrolled in these three clinical trials. A retrospective analysis was undertaken to compare the outcomes of ER+ and ER- patients treated with H. Tumors positive for the progesterone receptor (PR) respond to hormone therapy similarly to tumors that are ER+; therefore, ER-/PR+ tumors are included with ER+ tumors for the purpose of this analysis. Results: 50% of the 805 patients enrolled were ER+, 40% were ER-, and 10% were ER unknown. Outcomes are shown below.

First-line monotherapy (ER+ vs ER-): RR, 25 vs 29%; TTP, 3.8 vs 3.4 months; survival, 26 vs 20 months

Second/third-line monotherapy (ER+ vs ER-): RR, 16 vs 16%; TTP, 3.2 vs 3.0 months; survival, 14.2 vs 12.4 months

H + chemotherapy (ER+ vs ER-): RR, 53 vs 49%; TTP, 6.6 vs 7.0 months; survival, 25.4 vs 24.1 months

Conclusions: The above data support the conclusion that ER-/HER2+ patients and ER+/HER2+ patients have similar clinical outcomes when treated with H alone or H + chemotherapy. Therefore, ER status should not preclude testing for HER2 status and does not predict benefit from H in HER2+ patients.

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Results of two open label Multicentre phase II pilot studies with Herceptin in combination with docetaxel and platinum salts (Cis or Carboplatin) (TCH) as Therapy for Advanced Breast Cancer (ABC) in women with tumors over-expressing the HER2-neu proto-oncogene

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Preclinical data indicate that docetaxel (T) and/or platinum salts (C) are highly synergistic with Herceptin (H). This synergy, taken together with the activity of these drugs in ABC, and the need to develop non-anthracycline containing regimens with H, led to our performing two pilot studies to evaluate the safety and efficacy of T and H in combination with cisplatin (TCisH) or carboplatin (TCarboH). Both studies enrolled ABC patients whose tumors were positive for the HER2 alteration by immunohistochemistry (IHC) or fluorescent in-situ hybridization (FISH), with retrospective analysis by FISH planned on all primary tumors. T (75 mg/m2) and C (cis 75mg/m2, Carbo, AUC of 6) were given on day 1, and then q3wks up to 8 cycles. H was given on day 1 cycle 1 (4mg/kg) then continued weekly at 2mg/kg for 1 year or until progression.

Results: Enrollment is complete with 61 TCisH pts and 60 TCarboH pts. Interim results are on 34 TCisH pts (162 cycles) and 27 TCarboH pts (159 cycles). Pt characteristics for TCisH and TCarboH respectively were: prior adj chemo 56% and 67%, visceral mets 76% and 78%, liver mets 38% and 26%, lung mets 35% and 56%, bone mets 44% and 41%, and 3 or more organs involved 32% and 26%. Febrile neutropenia was 9% on TCisH and 11% on TCarboH, there was one grade 3 infection on TCarboH. G3-4 non-hematological toxicities for TCisH and TCarboH respectively were: nausea 12% and 7%, vomiting 6% and 4%, diarrhea 9% and 4%, stomatitis 3% and 11%, and neurosensory 3% and 0%. There were no G3-4 renal or ototoxicities. Grade 1-2 ototoxicities were seen in 18% of TCisH pts. One pt in each study developed CHF (1 prior cardiac history). Responses were seen in 26/34 (3 CRs, 23 PRs, ORR 76%) of TCisH pts HER2 positive by IHC, and in 10/14 (3 CRs, 7 PRs, ORR 71%) TCarboH patients HER2 positive by FISH.

Conclusion: These pilot studies show that the TCH combinations are feasible and are active in ABC, and justify their study in random assignment trials. BCIRG is conducting such studies in both the metastatic and adjuvant settings. Final results for all patients will be presented.

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Fractionated half'body irradiation (HBI) for widespread bone metastases (WSBM) from breast cancer: A randomized phase III trial of the international atomic energy agency (IAEA)

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Purpose: Find the fastest and most effective method to economically deliver fractionated HBI for WSBM from breast cancer.

Methods: Phase III trial with 3 arms for WSBM: (A) Control-Convent, daily fract. (15 Gy/5 fx/5 days); (B) Hyperfract. (8 Gy/2 fx/1 d); (C) Accel. Fract. (12 Gy/4 fx/2 d). Of 156 pts. entered, 72 (46%) had breast cancer primaries; 27, 25 and 20 pts. were random. to arms (A), (B) & (C) and constitute the subject of this analysis. All pts had initial and subseq. pain &