Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC®T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC®TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study

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Background: This study evaluates the benefit of two trastuzumab-based (H) regimens in HER2 amplified breast cancer with the intent of integrating H to maximize efficacy and minimize known cardiotoxicity.

Material and Methods: HER2 amplified (centralized FISH) patients with axillary lymph node (LN) positive or high risk LN negative were randomized to either AC (60/600 mg/m2 q3wk x4) followed by T (100 mg/m2 q3wk x 4) or two H-containing regimens; AC followed by T with H x 1 year (q1wk during chemo/q3wk during FUP) or TCarbo (75 mg/m2 / AUC6 q3wk x 6) with H x 1 year. Patients were prospectively stratified by positive LN (0, 1-3 vs 4+) and hormone receptor (HR) status. Patients with HR+ tumors received hormonal therapy for 5 yrs after chemotherapy. The primary endpoint was disease-free survival (DFS) with 80% power (0.05 significance level) to detect an absolute difference of 7%. Secondary endpoints included OS, safety, including cardiotoxicity (symptomatic events -CHF, gr3/4 ischemia/infarction, gr3/4 arrhythmia- and asymptomatic LVEF decline). We report the results of the first planned, protocol-mandated interim analysis conducted after 322 events (breast cancer relapse, second primary malignancy or death).

Results: A total of 3222 pts (1073 in AC-T, 1074 in AC-TH and 1075 in TCH) were recruited between Apr 2001 and Mar 2004. At a median follow-up of 23 months, the two H-containing arms have both met the DFS endpt: hazard ratio of 0.49 with AC-TH, p-value=0.00000048 and 0.61 with TCH, p-value=0.00015 (as compared to AC-T). At this time, there is no statistically significant difference btw the two H-containing arms perhaps due to the small number of events currently separating them. Symptomatic cardiac events: AC-T: 1.2% vs AC-TH: 2.3%, p-value=0.046; AC-T vs TCH: 1.2%, p value=1.00. Absolute LVEF decline >15% and below lower limit of normal occurred in 0.6% pts in AC-T, 2.4% in AC-TH and 0.4% in TCH arms respectively (AC-T vs AC-TH (p=0.001); AC-T vs TCH (p=0.54).

Discussion: Result of this trial confirms the benefit of H when combined with docetaxel (AC-TH) or with docetaxel and carboplatin (TCH) without an anthracycline. There are fewer severe cardiac adverse events when H is administered without prior A. Longer follow-up is needed in order to confirm whether non-A-based adjuvant H regimens will have efficacy comparable to A-based regimens.