Results of Chemotherapy Alone, with Sequential or Concurrent Addition of 52 Weeks of Trastuzumab in the NCCTG N9831 HER2-Positive Adjuvant Breast Cancer Trial

Background: N9831 is the only randomized phase III trial comparing safety and efficacy of the addition of trastuzumab (H) to doxorubicin and cyclophosphamide then paclitaxel (Arm A: AC -->T) either following (Arm B: AC -->T-->H) or starting concurrently with paclitaxel (Arm C: AC -->T+H-->H) for women with resected Stage I-III invasive HER2+ breast cancer. The 3 yr cumulative incidence of NYHA class III or IV congestive heart failure or sudden cardiac death was previously reported: 3.3% in Arm C, 2.8% in Arm B (Perez EA, et al. JCO 2008). The comparison of AC -->T to AC -->T+H-->H was reported in a joint analysis of N9831 and NSABP B-31 in 2005 and updated in 2007, demonstrating a 52% reduction in risk of a disease event (Romond E et al, NEJM 2005; Perez EA, et al. ASCO 2007).

Materials and Methods: Primary endpoint is disease-free survival (DFS). At the second planned interim analysis of Arm A vs. Arm B, the O’Brien-Fleming boundary (OFB) was crossed. NCCTG Independent Data Safety Monitoring Committee approved the release of these data as well as data pertaining to Arm B vs. Arm C due to slow pace of events [expected 647 events in 4 yr follow-up period (f/u) vs. actual 334 events in 4.5 yr f/u]. Shortly thereafter, there were sufficient events to perform the first planned interim analysis of B vs. C. We present the results of each of these pairwise comparisons taking into account the potential for crossover to Arm C after the release of the joint analysis findings in 2005.

Results: From 5/2000 to 4/2005, 2448 eligible women were enrolled for the Arm A (n=1087) vs. Arm B (n=1097) comparison. Median f/u is 5/5 yrs. with 386 events. The addition of trastuzumab sequentially to AC -->T significantly improved DFS, univariately [HR(Arm B/Arm A)=0.70, 95% CI: 57-86%, logrank p=0.0005] and after adjusting for age, tumor size, number of positive nodes, and ER [PPH: HRadj=0.67 (95% CI: 0.55-0.82)]. 5 yr DFS was increased from 72% with AC -->T to 80% with AC -->T-->H. From 5/2000 to 4/2005, 1903 eligible women were enrolled for the Arm B (n=954 vs. Arm C (n=949) comparison. Median f/u is 5/3 yrs. with 312
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events. The log-rank p-value testing whether DFS differs with respect to starting time of trastuzumab was 0.019. [Not crossing pre-specified OFB for statistical significant]. After adjusting for tumor size, number of positive nodes, and ER, HR_{adj}(Arm C/Arm B)=0.75 (95% CI: 0.60-0.94)]. 5 yr DFS was increased from 80% with AC -->T-->H to 84% for AC -->T+H-->H.
Conclusions: DFS is significantly improved with the addition of 52 weeks of H (sequentially or concurrently) to AC -->T. There is a statistically significant 33% reduction in the risk of an event with the sequential addition of H following AC -->T. There is a strong trend for a 25% reduction in the risk of an event with starting H concurrently with T relative to sequentially after T. Therefore, based on a positive risk/benefit ratio, we recommend that trastuzumab be incorporated in a concurrent fashion with T chemotherapy.

Acknowledgements: NIH CA25224, Breast Cancer Research Foundation, Genentech.

Do the ASCO/CAP 2007 HER2 Testing Guidelines Improve Prediction of Benefit to Adjuvant Trastuzumab?: Data from North Central Cancer Treatment Group N9831 Adjuvant Trial

Background: In 2007, the American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) recommended new guidelines to define HER2 positivity by immunohistochemistry (3+ IHC: uniform intense membrane staining of >30% of invasive tumor cells) or fluorescent in situ hybridization (FISH+: HER2/CEP17 ratio >2.2). The original criteria used for enrollment in the pivotal N9831 trial conducted from 2000-2005 were IHC>10% (3+) or FISH ≥2.0.

Purpose: To investigate the impact of the ASCO/CAP guidelines on patient (pt) eligibility and disease free survival (DFS) compared to the originally used FDA-approved definitions.

Patients/Methods: This analysis included 2268 patients from the HER2+ N9831 adjuvant trastuzumab phase III trial. IHC was centrally performed at the Mayo Clinic using the DAKO HercepTest™ and was re-analyzed to determine the percent of tumor cells with 0, 1+, 2+, and 3+ staining intensities. DFS was compared between pts randomized to standard chemotherapy +/- concurrent trastuzumab (Arms A and C of the trial) within IHC/FISH subgroups using Cox proportional hazards regression stratified by hormone receptor and nodal status.

Results: Based on 2268 pts, 83 pts (3.7%) were 3+ by FDA-approved guidelines but not 3+ by the ASCO/CAP guidelines. Among these pts, 77% (64/83) were FISH amplified centrally by ASCO/CAP guidelines. Only 1.5% (34/2268) of pts eligible under FDA-approved definitions from N9831 in this sample set would not meet the ASCO/CAP guidelines. In 1441 patients randomized to standard chemotherapy +/- concurrent trastuzumab, the exploratory DFS hazard ratio (HR) associated with trastuzumab in IHC/FISH subgroups were as follows: ASCO/CAP HER2+ HR=0.59 (95% CI: 0.47-0.75; p<0.001); FDA-approved HER2+ HR=0.60 (95% CI: 0.47-0.75; p<0.001); ASCO/CAP HER2 normal (not positive) HR=0.74 (95% CI: 0.35-1.57; p=0.43); and FDA-approved HER2 normal HR=0.53 (95% CI: 0.22-1.26; p=0.15).

Conclusions: A small percentage (1.5%) of N9831 patients did not meet ASCO/CAP 2007 guidelines when applied retrospectively. Trastuzumab effect appeared similar for HER2+ patients regardless of ASCO/CAP or FDA-approved guidelines. Additional DFS analyses by IHC/FISH subgroups will be presented. We gratefully acknowledge support from the Breast Cancer Research Foundation, Genentech, and NIH CA 25224 for this study.
Paclitaxel-Related Peripheral Neuropathy Associated with Improved Outcome of Patients with Early Stage HER2+ Breast Cancer Who Did Not Receive Trastuzumab in the N9831 Clinical Trial

**Background:** Microtubules are crucial for spindle formation during mitosis and for cellular proliferation. The antineoplastic effect of paclitaxel is mainly related to its ability to bind the beta subunit of tubulin, thus preventing tubulin chain depolarization and inducing apoptosis. Tubulins are expressed in human peripheral nerves and the binding of paclitaxel to tubulin may lead to neuropathy. Peripheral neuropathy is a common dose limiting toxicity of paclitaxel. We hypothesized that the occurrence of peripheral neuropathy may correlate with outcome (disease-free survival; DFS).

**Methods:** This analysis sought to describe incidence of peripheral neuropathy following paclitaxel and its association to outcome (DFS) in patients who received paclitaxel (weekly x 12) in the adjuvant HER2+ intergroup trial N9831. Only eligible pts who initiated paclitaxel and did not have peripheral neuropathy at initiation of paclitaxel that were randomized to arms A (955 pts; chemotherapy alone) and C (889 pts; chemotherapy plus concurrent trastuzumab) of N9831 were included. Cox regression analysis stratified by ER/PR status and nodal status was used to compare DFS within arm between patients with and without peripheral neuropathy.

**Results:** Out of 1844 eligible pts, 379 developed neuropathy (20.5%). For pts in arm A, those who developed neuropathy had better DFS than pts who did not (3 yr DFS: 86.2% vs 81.8%; HR 0.65; p=0.01), despite lower doses of paclitaxel in the pts with neuropathy. Grade of neuropathy did not appear to impact DFS. No statistical difference was noted for pts treated in the trastuzumab-containing arm (3 yr DFS: 92.8% vs 91.1% for pts with neuropathy vs not; HR 0.79; p=0.34). There were no differences in paclitaxel dose intensity between arms A and C.

**Conclusion:** Patients with early stage HER2+ breast cancer who received adjuvant paclitaxel-containing chemotherapy in arm A and developed peripheral neuropathy had a better DFS than pts who did not develop neuropathy. This effect was possibly abrogated by the use of trastuzumab in Arm C. This side effect may represent effective bindings of paclitaxel to the target tubulin, lack of point mutations in tubulin at the paclitaxel binding site and/or lack of selective overexpression of β-III tubulin. This is a hypothesis generating study and additional analysis needs to be conducted from other large taxane-based trials.

Partial support from Genentech and the Breast Cancer Research Foundation