Pharmacologic Regimens in HER2+ Breast Cancer and the Effects of Radiotherapy in Smokers

Covering early stage HER2+ breast cancer (BC) was Dr. Arlene Chan, who discussed the findings of a 3-yr analysis from a phase 3 randomized trial looking at neratinib (N), an irreversible pan-HER tyrosine kinase inhibitor, after trastuzumab-based adjuvant therapy.

This exploratory analysis of invasive disease-free survival (iDFS) demonstrated a consistent benefit in patients receiving N, particularly in patients with centrally confirmed HER2+ disease, patients who completed trastuzumab treatment within 1 yr, and patients with hormone receptor-positive disease.

Dr. Dennis Slamon later presented a 10-yr follow-up analysis of the BCIRG-006 trial, which compared doxorubicin plus cyclophosphamide followed by docetaxel (AC-T), doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC-TH), and docetaxel, carboplatin, and trastuzumab (TCH) in HER2+ early BC.

Conclusions show that while there is no statistical advantage of AC-TH over TCH, there is a significant efficacy advantage of AC-TH and TCH over the non-trastuzumab regimen (AC-T) in DFS and overall survival. Unfortunately, there were 5-fold more congestive heart failures in AC-TH than in TCH, a higher rate of leukemia, and a higher rate of sustained loss of left ventricular ejection fraction >10%.

Dr. Carolyn Taylor ended the session with a talk about the late side effects of modern BC radiotherapy, particularly in smokers vs nonsmokers. She concluded that for nonsmokers, the combined risks of radiotherapy total <1%. However, for women who have smoked since adolescence and continue to smoke after radiotherapy, the predicted risk is “a few percent.”

Dr. Taylor and her group looked at 75 randomized trials that included >40,000 women. The estimates of doses used in trials (10 Gy to lungs, 6 Gy to the heart) and modern doses (5 Gy to lungs, 4 Gy to the heart) were used to calculate excess rate ratios per Gy for lung cancer (12% per Gy) and cardiac mortality (4% per Gy). These excess rate ratios likely apply to modern doses and population-based data and can be used to predict 30-yr risk from typical modern radiotherapy.

Modern radiotherapy may increase a nonsmoking, 50-yr-old woman’s risk of dying from lung cancer by age 80 from 0.5% to 0.8%, and her risk from dying from heart disease from 1.8% to 2.0%. But for a woman who has smoked since adolescence and continues to smoke, modern radiotherapy may increase her risk for death from lung cancer from 9.4% to 13.8%, and her risk of dying from heart disease from 8.0% to 8.6%.

Dr. Taylor closed by saying that smoking cessation at time of radiotherapy may avoid much of the risk since most of the lung cancer risk starts >10 yr after radiotherapy.
Anastrozole vs Tamoxifen in Ductal Carcinoma in Situ

On Friday afternoon, Dr. Jack Cuzick presented data on a trial that randomized 2980 postmenopausal women with locally excised ER+ ductal carcinoma in situ (DCIS) to 5 yr of treatment with anastrozole or tamoxifen. He and his group evaluated the recurrence rates of all breast cancer (BC), including DCIS.

Primary results showed a projected recurrence rate of 7.4% in the tamoxifen arm and 6.6% in the anastrozole arm, which met the non-inferiority criterion of the trial. They saw no impact on recurrent DCIS overall. Differences were restricted to reductions in invasive cancer (20% with tamoxifen, 47% with anastrozole), though the differences did not reach statistical significance. Interestingly, anastrozole appeared to favor HER2- and ER+ recurrences, though the difference was not significant. However, the benefit of anastrozole on ER+/HER2- recurrences was significant. When data was combined with that from NSABP B-35, the overall reduction in recurrence with anastrozole was found to be 21% (statistically significant).

The 2 drugs exhibited different side effect profiles. Dr. Cuzick pointed out that there were 11 cases of endometrial cancer in the tamoxifen group, compared to 1 in the anastrozole arm. Vasomotor and gynecologic symptoms, such as hot flashes and vaginal bleeding, were also higher in the tamoxifen group (45% vs 60%). Expectedly, musculoskeletal effects and fractures were more common with anastrozole. But one unexpected finding, which was not seen in previous trials, was an increase in cerebrovascular accidents and transient ischemic attacks with anastrozole. Despite the difference in side effects, adherence was almost identical between the arms (67% at 5 yr).

Next, Dr. Patricia Ganz presented patient-reported outcomes from the NSABP B-35 trial, which compared anastrozole vs tamoxifen in postmenopausal HR+ patients with DCIS undergoing lumpectomy with radiotherapy.

The primary aim of the trial was to look at BC-free interval, a composite endpoint looking at time to any BC event. Investigators found a statistically significant difference favoring anastrozole (95.5% vs 89.2%) at 10 yr. Dr. Ganz acknowledged that this difference did not emerge until 8 yr later (ie, beyond the median follow-up time of the IBIS-II trial).

In the secondary quality of life analysis, no change and no difference in physical function, mental function, fatigue, and depression scales between the two arms was seen. But tamoxifen was associated with increased severity of vasomotor and bladder control symptoms, compared to anastrozole. And patients on anastrozole showed increased severity of musculoskeletal symptoms and vaginal symptoms, compared to tamoxifen. Increased joint pain at 6 mo was reported in both groups, but was higher in the anastrozole arm. Patients <60 yr of age had significantly lower rates of vasomotor symptoms, which were worse in the tamoxifen group. Younger women also had more vaginal and gynecologic symptoms, which were worse in the anastrozole group.

Updated Abstracts

SS-02: NERATINIB AFTER TRASTUZUMAB-BASED ADJUVANT THERAPY IN EARLY-STAGE HER2+ BREAST CANCER: 3-YEAR ANALYSIS FROM A PHASE 3 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL (ExteNET)


Background: Neratinib (Puma Biotechnology Inc), an irreversible pan-HER tyrosine kinase inhibitor, was evaluated in a phase 3 randomized, placebo-controlled, double-blind trial (ExteNET) to assess for improved invasive DFS (iDFS) in women with early-stage HER2+ breast cancer (BC) after trastuzumab-based therapy (clinicaltrials.gov NCT00876709). Primary efficacy analysis at 2-yrs demonstrated iDFS of 93.9% and 91.6% neratinib and placebo, respectively (HR 0.67, 95% CI 0.50-0.91; P=0.009). Greater benefit was observed in hormone-receptor (HR)-positive and centrally-confirmed HER2 subsets - HR 0.51, p=0.001 and HR 0.51 p=0.002, respectively [Chan et al. ASCO 2015]. We report an exploratory analysis of efficacy after 3-ys of follow-up.

Methods: Women with HER2+ BC were randomly assigned to oral neratinib 240 mg/day or matching placebo for 1 year, stratified by nodal status, HR-status and prior trastuzumab regimen. The study was initiated in April 2009 with recruitment ceased in October 2011, limiting follow-up to 2 years. In January 2014, follow-up was restored to 5 years. During year 1, physical examinations were performed at 3-monthly intervals, at 4-monthly intervals in year 2 and then 6-monthly to 5-years; with mammography performed annually. Patients were asked to re-consent following ethics approval of the January 2014 protocol amendment. During years 3 to 5, disease-free survival (DFS) and survival events were identified from medical records. A descriptive analysis of iDFS, to investigate the durability of neratinib effect was performed after 3-yr of follow-up. Data for overall survival remains blinded until 248 events have occurred. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using stratified Cox proportional-hazards models.

Results: The intention-to-treat population included 2840 patients (neratinib, N=1420; placebo, P=1420). Central HER2 testing has now been performed in 2041 (81%) pts. Three-yr iDFS for ITT population demonstrated HR 0.74, [95% CI 0.56-0.96]. In the ITT pts who were randomized within 1-yr of trastuzumab completion, DFS HR 0.72 [0.54-0.95]. For pts who had centrally-confirmed (cc) HER2-positive disease , DFS HR 0.70 [0.50-0.98]. Pts with HR-positive disease had 3-yr iDFS HR 0.57 [0.39-0.82] and HR-negative pts HR 0.96 [0.67-1.45]. Overall survival data are not yet mature.

Conclusions: Exploratory analysis at 3-ears supports the significant benefit seen in the primary analysis of 12-months of neratinib following adjuvant trastuzumab-based therapy. Patients who consistently derived the greatest benefit were 1) patients who received neratinib within 12 months of completing adjuvant trastuzumab; 2) centrally confirmed HER2 positive patients and 3) HR-positive patients.
P6-05-05: LONG-RANGE EXPRESSION ANALYSIS REVEALS NEW LUMINAL SUBGROUPS ASSOCIATED WITH DIFFERENT PATIENT OUTCOMES

Mankovich A., Agrawal V., Banerjee N., Dimitrova N. Philips Research North America

Breast cancer subtyping using gene expression is well established in breast cancer research and gaining traction in the clinical setting. While it is known that there are large chromosomal regions affected by copy number polymorphisms, histone modifications, and other spanning alterations, it is not clear whether expression patterns regulate such regional changes. We present a method to integrate any type of expression data - here, we analyze mRNA, lincRNA, and mRNA and lincRNA together - and quantify long-range expression patterns affecting large regions of the genome.

TCGA alignment and gene expression RNA-Seq data for breast cancer were generated at the Carolina Center for Genome Sciences, UNC at Chapel Hill. We examined 715 samples which each had at least partial data for ER/PR/HER2 status and complete data for PAM50 subtype assignment. Our method defines long-range expression within a window of a particular length (e.g., 100 Kb, 1 Mb). We take the mean weighted expression values for all genes that fall within each window and concatenate these windows to obtain larger chromosome-wide patterns. The final chromosome-wide vectors are joined to represent long-range expression patterns across the whole genome. We retain the top 10% most varying windows. Then, we apply hierarchical clustering, perform survival analysis, and evaluate enrichment of clinically meaningful subtypes using hypergeometric test.

Hierarchical clustering across each analysis revealed clear separation of all PAM50-classified breast cancer subtypes at 1 Megabase resolution in the available data set. Interestingly, clustering of samples (n = 715) using 247 bins revealed distinct subgroups at each level of analysis - mRNA, lincRNA, and mRNA plus lincRNA. At these levels, three clusters contained significant enrichment for Her2-amplified (mRNA, p=1.5E-35; lincRNA, p=1.8E-26; mRNA + lincRNA, p=1.4E-33), Normal-like (mRNA, p=8.9E-82; lincRNA, p=1E-71; mRNA + lincRNA, p=1.6E-77), and Basal-like (mRNA, p=9.2E-67; lincRNA, p=6.9E-93; mRNA + lincRNA, p=8.2E-72) breast cancer. In view of the association of these mRNA clusters with PAM50 classifications, it is surprising that less than 10% of the genes in the analysis were overlapped (42 of the 465 intersected with 1734 genes in the original PAM50 study). The Luminal clusters exhibited a more diverse clustering pattern; however, the lincRNA and combined analyses were capable of delineating Luminal A from Luminal B and into several subclusters. These subclusters, interestingly, differed in overall survival, particularly amongst the Luminal A/B mixed subgroups in the lincRNA (about a 16% 5-year OS delta) and combined (10% 5-year OS delta) analyses.

Hierarchical clustering relying on long-range expression regions at 1 Megabase resolution produces clusters that are enriched with well-known clinically relevant subtypes. A surprising finding is the capability for this method to reveal existing PAM50 subtypes across non-coding, intergenic regions. Of special interest is the demarcation of Luminals into different survival profiles using this method. To date, this is the first study to our knowledge that attempts to analyze and reveal existing and novel breast cancer subtypes across large regions of the genome and in long intergenic non-coding regions.