GS3-03: Impact of Anthracyclines in High Genomic Risk Node-Negative HR+/HER2- Breast Cancer

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Abstract Number: SESS-813

Background: The Anthracyclines in Early Breast Cancer (ABC) trials demonstrated no clear improvement in invasive disease-free survival with the addition of anthracycline to a taxane-containing chemotherapy for patients with hormone receptor-positive (HR+) breast cancer. Thus, an anthracycline-free regimen is often administered for lower risk patients with HR+/HER2- disease. However, the benefit of anthracyclines for patients with high Oncotype DX recurrence score (RS) has not been studied, despite the widespread use of RS to guide the use of adjuvant therapy for HR+ patients with 0-3 positive nodes.

Methods: We analyzed data from patients who received taxane + anthracycline/cyclophosphamide and similar regimens (T-AC) or taxane + cyclophosphamide (TC) chemotherapy in the TAILORx trial (NCT00310180), which enrolled patients with stage I/II, node-negative, HR+/HER2-negative breast cancer. Patients with an RS between 11 and 25 were randomized to endocrine therapy or endocrine therapy plus chemotherapy of physicians' choice, whereas patients with an RS > 26 received chemotherapy of physician's choice. Distant recurrence-free interval (DRFI), recurrence-free interval (RFI), distant recurrence-free survival (DRFS), recurrence-free survival (RFS), and overall survival (OS) were compared using adjusted hazard ratios (aHR) controlling for age, RS, grade, tumor size, and estrogen/progesterone receptor status. Outcomes were stratified by RS > 31 and < 31. Inverse probability of treatment weighting was used to estimate adjusted 5-year event rates for these outcomes, controlling for differences in the above covariates. Restricted cubic spline regression was used to estimate aHR for receipt of TAC (versus TC) for these endpoints as a function of RS.

Results: Of 2,528 cases that met eligibility, 437 were treated with T-AC and 2091 received TC. Treatment regimens in the T-AC group included anthracycline + cyclophosphamide (dose dense or standard) followed by taxane (n = 298, 68%), concurrent anthracycline, cyclophosphamide, and docetaxel (n = 59, 14%), and other anthracycline + taxane combinations (n = 80, 18%). All patients in the TC group received treatment with any taxane with cyclophosphamide. 32% had an RS >26 (n = 816) and 20% had an RS > 31 (n = 501). The mean age was 55 and median follow-up time was 7.3 years. Patients treated with T-AC had a higher RS (mean 30 vs 23), larger tumors (mean 20 mm vs 18 mm), and were more likely high grade (38% high grade vs 25%) than those treated with TC. In patients with an RS > 31 after adjusting for covariates, receipt of T-AC was associated with improved outcomes at 5 years, DRFI adjusted rate 97.5% with T-AC vs 89.4% with TC (aHR 0.27, p = 0.01), DRFS adjusted rate 96.5% with TAC vs 88.3% with TC (aHR 0.45, p = 0.03), RFI adjusted 5-year rate 95.7% with T-AC vs 87.7% with TC (aHR 0.31, p < 0.01), RFS adjusted 5-year rate 94.6% with T-AC vs 86.6% with TC; aHR 0.45, p = 0.02), and a trend towards improved OS at 5 years (adjusted rate 97.7% with T-AC vs 92.5% with TC; aHR 0.58, p = 0.22). Among cases with an RS <

31, receipt of T-AC was not associated with improved DRFI (aHR 1.12, p = 0.73), DRFS (aHR 1.09, p = 0.75), or other outcomes. Spline regression estimated the effect of T-AC over TC on DRFI at RS 20 to be aHR 0.84, (95% CI 0.30 – 1.39), at RS 30 aHR 0.63, (95% CI 0.14 – 1.12), at RS 40 aHR 0.54, (95% CI 0.18 – 0.90), and at RS 50 aHR 0.47, (95% CI 0.10 – 0.84) indicating increasing anthracycline benefit as RS increased.

Conclusions: Patients with early-stage, HR+/HER2-negative breast cancer and high RS values (> 31) may benefit from adjuvant taxane and anthracycline-containing therapy more than from TC. Genomic RS testing may predict anthracycline benefit more accurately than other factors such as nodal status.