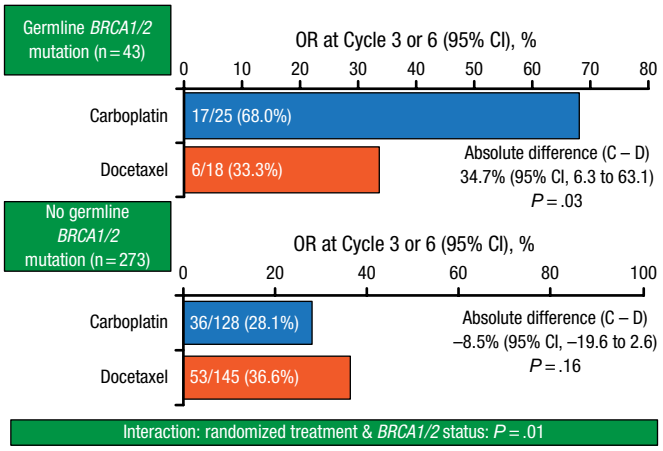
Figure 1. Objective Response in Patients With and Without BRCA Gene Mutations



BRCA, breast cancer gene; C, carboplatin; D, docetaxel; OR, objective response.
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However, carboplatin therapy was associated with significantly improved ORR (68.0% vs 33.3%; $P = .03$; Figure 1) in patients with *BRCA1/2* gene mutations, in whom median PFS was 6.8 months, compared with 3.1 months for mutation-negative patients.

In the docetaxel group, median PFS was 4.8 and 4.6 months, respectively, among patients with and without *BRCA1/2* gene mutations.

With respect to other disease subtypes, only patients with nonbasal-like disease responded differently to the 2 treatments, with a significantly increased ORR in the docetaxel group (16.7% vs 73.7%; absolute difference, –55.5%; 95% CI, –82.4 to –28.6; $P < .01$).

The safety data were as anticipated for both drugs. Carboplatin was generally better tolerated than docetaxel, with febrile neutropenia and neuropathy significantly more common in the docetaxel group (both $P < .01$).

Prof Tutt emphasized that the results of this trial support *BRCA1/2* genotyping to guide therapy choice in advanced triple-negative and familial BC.

AC and Weekly Paclitaxel Improve Outcomes in TNBC

Written by Nicola Parry

Joseph A. Sparano, MD, Montefiore Medical Center, Bronx, New York, USA, shared the 10-year results of the E1199 trial: A Phase 3 Study of Doxorubicin-Cyclophosphamide Followed by Paclitaxel or Docetaxel Given Weekly or Every 3 Weeks in Patients With Axillary Node-Positive Breast Cancer [BC; NCT00004125]. In the complete study population, adjuvant weekly paclitaxel and docetaxel Q3W significantly improved outcomes compared with paclitaxel Q3W, when administered sequentially after doxorubicin-cyclophosphamide (AC) therapy, and weekly paclitaxel improved outcomes in patients with triple-negative breast cancer (TNBC).

According to Dr Sparano, the E1199 trial was designed to compare taxane type and schedule as a component of adjuvant chemotherapy in localized BC [Sparano JA et al. *N Engl J Med*. 2008]. All participants received 4 cycles of standard AC therapy Q3W, and were randomized to 1 of 4 taxane arms: paclitaxel 175 mg/m^2 Q3W for 4 doses (P3) or 80 mg/m^2 weekly for 12 doses (P1); or docetaxel 100 mg/m^2 Q3W for 4 doses (D3), or 35 mg/m^2 weekly for 12 doses (D1). Patients received hormonal therapy according to standard of care. The primary end point was disease-free survival (DFS).

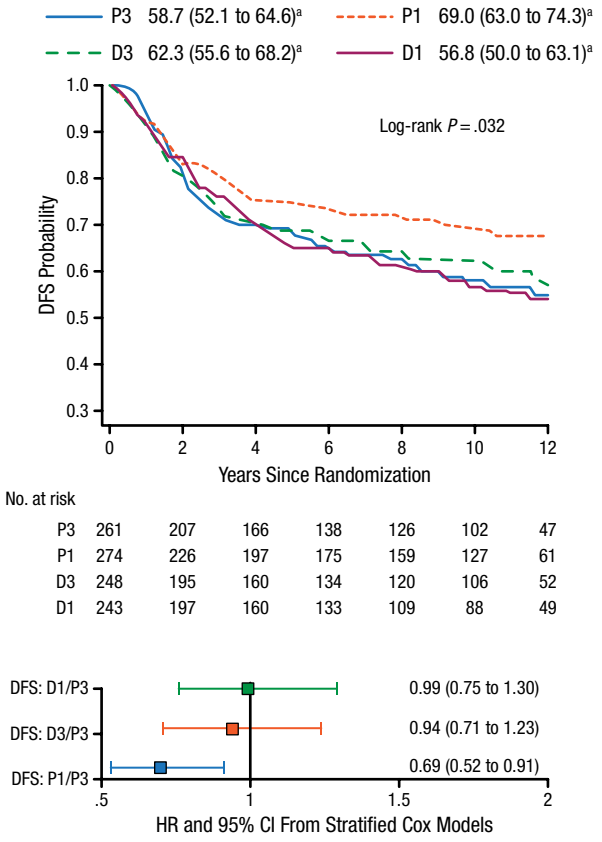
Dr Sparano reported that 1639 DFS events and 1283 deaths were recorded in 4950 patients at a median follow-up of 12.1 years. He added that primary comparisons showed no significant difference in outcomes with respect to taxane type (P1 + P3 vs D1 + D3; overall survival [OS], log-rank $P = .977$; DFS, log-rank $P = .322$) or schedule (P1 + D1 vs P3 + D3; OS, log-rank $P = .795$; DFS, log-rank $P = .876$). However, OS ($P = .007$) and DFS ($P < .001$) were significant when analyzed using a taxane-by-schedule interaction test, similar to reported 5-year outcomes.

With respect to secondary outcomes, there was a significant improvement in DFS (HR, 0.79; 95% CI, 0.68 to 0.90) and a trend toward increased OS (HR, 0.86; 95% CI, 0.73 to 1.00) with D3 compared with P3. Similar results were reported for DFS (HR, 0.84; 95% CI, 0.73 to 0.96) and OS (HR, 0.87; 95% CI, 0.75 to 1.02) for P1 compared with P3.

With respect to BC subtype, P1 was the most effective taxane regimen in patients with TNBC (n = 1025). This regimen was associated with increased OS (75% vs 66%; HR, 0.69, 95% CI, 0.50 to 0.94; $P = .094$) and DFS (69% vs 59%; HR, 0.69; 95% CI, 0.52 to 0.91; $P = .032$; Figure 1) compared with standard therapy (P3). Dr Sparano added that similar benefits were not seen with D3.

For patients whose BC was hormone receptor–positive and human epidermal growth factor receptor-2–negative

Figure 1. Improvement in DFS With Weekly Paclitaxel in Patients With TNBC



DFS, disease-free survival; D1, weekly docetaxel; D3, every-3-weeks docetaxel; P1, weekly paclitaxel; P3, every-3-weeks paclitaxel; TNBC, triple-negative breast cancer.

[a]10-y rate, % (95% CI).

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or of unknown status, Dr Sparano said that, although 5-year data showed a trend for improved outcomes in the taxane arms, this was not consistently seen in the updated analysis. At a median follow-up of 12.1 years in this patient population, there was a nonsignificant trend toward increased OS (81.6% vs 79.6%; HR, 0.87; 95% CI, 0.69 to 1.08) favoring D3 compared with P3. DFS was also improved in this group compared with P3 (75.3% vs 69.4%; HR, 0.76; 95% CI, 0.63 to 0.91). However, similar benefits were not seen in association with P1.

Although these data demonstrate benefit of AC and weekly paclitaxel therapy in patients with TNBC, Dr Sparano emphasized that outcomes can still be improved in this population. A pending trial [NRG-BR003] will investigate the effect of adding carboplatin to AC and weekly paclitaxel in this setting, he concluded.

TP53 Mutations Are Associated With Increased Pathologic Complete Response in HER2-Positive BC

Written by Lynne Lederman

Katherine A. Hoadley, PhD, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA, presented the mutational analysis of the Paclitaxel and Trastuzumab With or Without Lapatinib in Treating Patients With Stage II or Stage III Breast Cancer That Can Be Removed by Surgery trial [CALGB 40601; NCT00770809].

CALGB 40601 was a neoadjuvant trial in which patients with human epidermal growth factor receptor 2 (HER2)–positive clinical stage II or III breast cancer (BC) had a pretreatment biopsy research tissue sample taken at random assignment to weekly paclitaxel (T) plus trastuzumab (H) plus lapatinib (L) for 16 weeks (n = 118); or T plus H for 16 weeks (n = 120); or T plus L for 16 weeks (n = 67) [Carey LA et al. ASCO 2013 (abstr 500)]. A second research tissue sample was obtained at surgery following the neoadjuvant treatment. There was no statistically significant difference between treatment groups in pathologic complete remission (pCR) rates. RNA from pretreatment samples were correlated with pCR by intrinsic subtype in all arms (n = 265). The pCR rate for the HER2-enriched subtype (n = 82) has twice the pCR rate (70%) as luminal A (n = 80; 34%) or luminal B (n = 80; 36%) [Carey LA et al. *J Clin Oncol.* 2014].

The mutational analysis evaluated 181 HER-positive pretreatment tumors and correlated 9 genes (*TP53*, *PIK3CA*, *GATA3*, *AKT1*, *ERBB2*, *MAP3K1*, *MAP2K4*, *TRPS1*, and *MALAT1*) with pCR rates. To increase the power to detect somatic mutations, UNCeqR, a program that integrates RNA and DNA sequencing, was used [Wilkerson MD et al. *Nucleic Acids Res.* 2014].

A median of 62 total mutations (interquartile range 32-118) was found. The number of mutations varied significantly by intrinsic subtype ($P < .001$) and by *TP53* mutation status ($P < .001$). The HER2-enriched and luminal B subtypes had higher numbers of mutations. *TP53* mutations also correlated with higher numbers of mutations.

TP53 had a mutation frequency of 56%, *PIK3CA* had a mutation frequency of 20%, and the rest of the 9 genes had a mutation frequency of < 10%. *TP53* mutations were significantly associated with pCR. In the overall population, the odds ratio was 3.67 ($P < .001$) for pCR vs wild type for those with mutated *TP53*; the odds ratio was 5.23 ($P = .007$) for pCR with luminal A mutations vs wild type. No other genes examined were correlated with pCR.