TNT Results: Carboplatin Improves Patient Outcomes in Advanced *BRCA1/2*-Mutated BC

Written by Nicola Parry

Andrew Tutt, MB, ChB, PhD, King's College London, London, United Kingdom, shared results from the Triple Negative Breast Cancer Trial [TNT; NCT00532727], a randomized phase 3 trial of carboplatin compared with docetaxel in estrogen receptor (ER)–, progesterone receptor (PR)–, and human epidermal growth factor receptor 2 (HER2)–negative breast cancer (BC). Although the data showed no difference in survival among patients treated with either drug, carboplatin did provide benefit for those with *BRCA1* or *BRCA2* gene mutations.

Although triple-negative BC (TNBC) is a heterogeneous disease, distinct subgroups are associated with *BRCA1/2* gene mutation, including immunohistochemical and gene expression basal-like subtypes [Sharma P et al. *Breast Cancer Res Treat.* 2014; Lehmann BD et al. *J Clin Invest.* 2011; Parker JS et al. *J Clin Oncol.* 2009; Cheang MCU et al. *Clin Cancer Res.* 2008]. However, although data have demonstrated sensitivity of some triple-negative and *BRCA1/2* gene mutation–associated BCs to platinums [Isakoff SJ et al. *J Clin Oncol.* 2014; Telli ML et al. *J Clin Oncol.* 2013; Bryski T et al. *Breast Cancer Res.* 2012], studies have not compared single-agent platinum chemotherapy with standard of care and mechanistically distinct taxanes in these patient populations.

The TNT trial was conducted in women (n = 376) with metastatic or recurrent, locally advanced TNBC or *BRCA1/2* gene mutation–associated BC. Patients were enrolled if they had ER-negative, PR-negative, and HER2-negative BC, or a known *BRCA1/2* gene mutation. Exclusion criteria included adjuvant taxane therapy within the past 12 months, previous platinum therapy, or non-anthracyclines for metastatic BC. Participants were randomized 1:1 to receive either carboplatin (C; area under the curve 6) or docetaxel (D; 100 mg/m^2) every 3 weeks for 6 cycles or until disease progression.

The primary end point was objective response rate (ORR). Secondary end points included progression-free survival (PFS), overall survival (OS), crossover treatment ORR, and toxicity. At a median follow-up of 11 months, ORR, median PFS, and median OS were similar in both treatment groups (Table 1).

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Table 1. TNT Results

	C	D	Absolute Difference, C – D (95% CI)	*P* Value
Objective response rate, %	31.4	35.6	–4.2 (–13.7 to 5.3)	.44
Median PFS, mo	3.1	4.5		
Restricted mean survival to 15 mo	4.8	5.2	–0.4 (–1.1 to 0.3)	.29
Median OS, mo	12.4	12.3		
Restricted mean survival to 15 mo	10.7	10.8	–0.2 (–1.1 to 0.8)	.31

C, carboplatin; D, docetaxel; OS, overall survival; PFS, progression-free survival.

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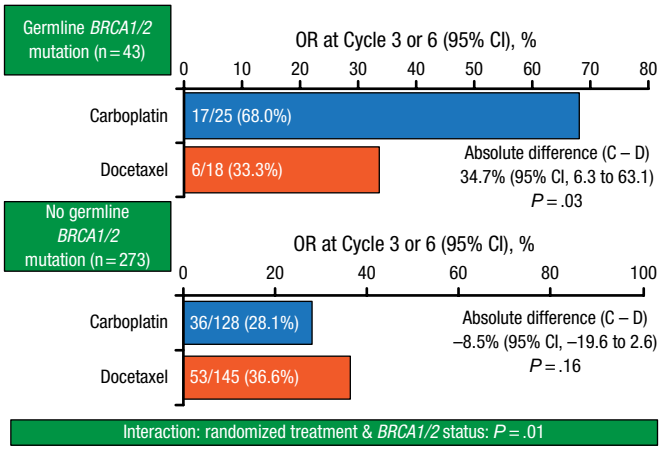
Figure 1. Objective Response in Patients With and Without BRCA Gene Mutations



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