According to Prof Steger, neoadjuvant treatment regimens resulting in high pathologic complete response (pCR) rates are needed for patients with HER2-positive breast cancer because they are correlated with favorable prognoses. Although N in combination with H is highly effective in HER2-positive breast cancer, this regimen is unsuitable because of high cardiotoxicity. HER2-positive breast cancer cells have, however, been shown to produce high levels of vascular endothelial growth factor, he added.

Consequently, the Phase 2 Study of Neoadjuvant Trastuzumab + Docetaxel + Non-pegylated Liposome-Encapsulated Doxorubicin (NPLD) ± Bevacizumab in HER2-Positive Early Breast Cancer [ABCSG-32; NCT01367028] was conducted to evaluate the cardiotoxicity and efficacy of N and B in combination with DH in the neoadjuvant treatment of early HER2-positive breast cancer.

Inclusion criteria included patients ≥ 18 years with (1) pathologically confirmed invasive primary breast adenocarcinoma, with or without palpable lymph nodes, who were scheduled for taxane-containing neoadjuvant systemic therapy and (2) HER2 protein overexpression as determined by immunohistochemistry 3 + or by *HER2* (c-erbB2) gene amplification according to fluorescent in situ hybridization or chromogenic in situ hybridization of the primary tumor. Exclusion criteria included patients with metastatic disease, HER2-negative disease, or a history of prior local or systemic antitumor therapy.

This open-label phase 2 trial enrolled 100 patients with biopsy-proven, invasive, early HER2-positive breast cancer who were randomized to 6 cycles (every 21 days) of the following:

DH: D (100 mg/m^2) + H (8/6 mg/kg; n = 25)
DHB: DH + B (15 mg/kg; n = 25)
DHN: D (75 mg/m^2) + H + N (50 mg/m^2; n = 26)
DHNB: D (75 mg/m^2) + H + N + B (15 mg/m^2; n = 24)

All patients received pegfilgrastim (6 mg, subcutaneously) on day 2.

Cardiotoxicity was low in all 4 regimens, with only 3 cardiac toxicity events documented (DH, n = 0; DHB, DHN, and DHNB, all n = 1). A cardiac toxicity event was defined as the occurrence of symptomatic left ventricular dysfunction, NYHA class 2 to 4; an asymptomatic drop of ejection fraction > 15% from baseline or < 50%; or the appearance of significant arrhythmias requiring treatment.

Although noncardiac toxicity was also acceptable, it was more pronounced in patients receiving the 3- and 4-drug combinations (Table 1).

All 4 regimens were highly effective. The overall pCR rate was 52%, with 63% and 62% of patients experiencing pCR in the DHN and DHNB regimens, respectively. The total pCR rate was also highest after DHN (58%) and DHNB (57%).

Table 1. Noncardiac Toxicity of the 4 Neoadjuvant Regimens, No.

	All	DH	DHB	DHN	DHNB
Patients	100	25	25	26	24
Events					
Serious adverse	50	8	12	14	16
Significant safety	114	23	31	29	31

B, bevacizumab; D, docetaxel; H, trastuzumab; N, nonpegylated liposomal doxorubicin.
Reproduced with permission from G Steger, MD.

Prof Steger concluded that neoadjuvant DH, DHB, DHN, and DHNB can be safely administered to patients with HER2-positive early breast cancer. He emphasized, however, that although noncardiac toxicity is acceptable, its increase with the 3- and 4-drug combinations may lead to early treatment termination in some patients.

Interim Safety Analysis of nP in High-Risk Early Breast Cancer

Written by Nicola Parry

Stefanie Noeding, MD, Gynecologic-Oncology Practice, Hannover, Germany, presented data from the first interim safety analysis of the Study of Nab-Paclitaxel in High-Risk Early Breast Cancer [GAIN2; NCT01690702], demonstrating acceptable initial toxicity profiles.

According to Dr Noeding, owing to acute and cumulative toxicities, combination chemotherapy requires compromises in drug dosage and treatment intervals. The sequential use of monotherapies, however, allows for the use of high doses of single agents and dose-dense treatment intervals, and such regimens have been very effective in cases of early breast cancer with high risk of recurrence [Moebus V et al. *J Clin Oncol.* 2010].

Compared with the solvent-based taxanes, paclitaxel and docetaxel, nab-paclitaxel (nP) provides a more favorable toxicity profile and a higher efficacy and might therefore be preferable in an intense dose-dense regimen [Ibrahim NK et al. *J Clin Oncol.* 2005].

Consequently, the GAIN2 study was an adjuvant phase 3 trial in patients with high-risk early breast cancer that was designed to compare a predefined intense dose-dense adjuvant treatment (epirubicin followed by nP followed by cyclophosphamide [ddEnPC]) with a dose-dense tailored therapy. In the study, single doses

are adjusted depending on individual hematologic and nonhematologic toxicities (dose-dense and dose-tailored epirubicin or cyclophosphamide followed by dose-dense and dose-tailored docetaxel [dtEC-dtD]).

This multicenter, prospective, randomized, open-label phase 3 trial randomized 2886 patients 1:1 to receive ddEnPC or dtEC-dtD. Inclusion criteria included women aged 18 to 65 years with pathologically confirmed high-risk breast cancer, defined as HER2-positive or triple-negative tumors irrespective of nodal status; luminal B–like tumors with Ki67 proliferation marker levels >20%; or luminal A–like tumors with Ki67 ≤20% and ≥4 involved lymph nodes. The primary end point was the invasive disease-free survival in patients with primary node-positive or high-risk node-negative breast cancer.

This first safety analysis comprises data from the first 200 patients who completed chemotherapy. With respect to hematologic adverse events (AEs), the rates of febrile neutropenia grade 3 to 4 (14.1% vs 5.0%; $P=.031$) and thrombocytopenia grade 3 to 4 (14.1% vs 5.0%; $P=.031$) were significantly increased in the ddEnPC arm. Similarly, with respect to nonhematologic AEs, significantly more patients in the ddEnPC arm developed anorexia grade 1 to 4 (28.3% vs 13.9%; $P=.015$). There was no significant difference between the 2 treatment arms with respect to AEs of special interest (cranial nerve palsies, anaphylaxis, or macular edema).

According to Dr Noeding, more patients in the ddEnPC arm required dose reductions because of hematologic toxicities (28% vs 11%; $P=.002$). Dose escalation to the maximum tolerated dose was possible in half of the patients receiving dtEC-dtD, whereas 7% of patients required dose reduction in the fourth cycle of docetaxel.

Because of acceptable toxicity profiles in both arms in these first 200 patients, the study will proceed as originally planned. An additional safety analysis will be performed after 900 patients have completed chemotherapy, and efficacy analyses are planned 60 months after the end of accrual.

Docetaxel Added to Anthracycline Regimens Benefits Patients With Highly Proliferative ER-Positive Breast Cancer

Written by Nicola Parry

Amir Sonnenblick, MD, PhD, Free University of Brussels, Brussels, Belgium, presented data from the 10-year final safety and efficacy analyses of the Intergroup Phase 3 Trial to Evaluate the Activity of Docetaxel, Given Either Sequentially or in Combination With Doxorubicin, Followed by *Cyclophosphamide*, Methotrexate, and Fluorouracil (CMF), in Comparison to Doxorubicin Alone, or in Combination With Cyclophosphamide, Followed by CMF, in the Adjuvant Treatment of Node-Positive Breast Cancer Patients [BIG 2-98; NCT00174655]. The results demonstrated that the addition of docetaxel to anthracycline-based adjuvant chemotherapy may benefit patients with estrogen receptor (ER)–positive breast cancer.

According to Prof Sonnenblick, adding taxanes to an anthracycline-based chemotherapy regimen in the adjuvant setting has become a standard approach in the management of patients with breast cancer. However, long-term outcomes data are still lacking regarding the safety and efficacy of this approach.

This trial randomized 2887 patients with lymph node–positive breast cancer to 1 of 4 treatment arms:

Arm A: Sequential control—doxorubicin (75 mg/m^2) for 4 cycles, followed by CMF.

Arm AC: Concurrent control—doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) for 4 cycles, followed by CMF.

Arm A-T: doxorubicin (75 mg/m^2) for 3 cycles, followed by docetaxel (100 mg/m^2) for 3 cycles, followed by CMF.

Arm AT: doxorubicin (50 mg/m^2) plus docetaxel (75 mg/m^2) for 4 cycles, followed by CMF.

The primary objective was to determine the efficacy of docetaxel, regardless of schedule, on disease-free survival (DFS). However, after 10 years and 1072 DFS events, docetaxel treatment did not improve DFS (HR, 0.91; 95% CI, 0.81 to 1.04; $P=.16$) or overall survival (OS; HR, 0.88; 95% CI, 0.76 to 1.03; $P=.11$), compared with control arms.

Similarly, there was no significant difference in DFS (HR, 0.86; 95% CI, 0.72 to 1.03, $P=.1$) or OS (HR, 0.85; 95% CI, 0.68 to 1.06; $P=.15$) between sequential docetaxel and sequential control or in DFS (HR, 0.88; 95% CI, 0.76 to 1.02; $P=.09$) or OS (HR, 0.84; 95% CI, 0.7 to 1.01; $P=.06$) between sequential docetaxel and concurrent doxorubicin-docetaxel.

In a multivariate model, however, data showed a trend for improved DFS (HR, 0.79; 95% CI, 0.63 to 1.01; $P=.05$) and OS (HR, 0.76; 95% CI, 0.57 to 1.01; $P=.06$) in patients with ER-positive breast cancer with high levels of Ki67 proliferation marker (≥14%) who were treated with docetaxel.

There were no significant long-term safety issues. Grade 3 to 4 cardiac toxicity was recorded in only 4 patients, and