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

long-term treatment-related neurotoxicity occurred in only 1.6% and 1.0% of patients in the docetaxel- and non-docetaxel-based regimens, respectively.

Although the addition of docetaxel to anthracycline-based adjuvant chemotherapy did not improve DFS or OS, the data suggested a benefit of sequential docetaxel in patients with highly proliferative ER-positive breast cancer, concluded Prof Sonnenblick.

Trial Will Evaluate Niraparib vs Placebo in Platinum-Sensitive Patients With Ovarian Cancer

Written by Maria Vinall

Niraparib is a potent oral PARP1 and PARP2 (poly [ADP-ribose] polymerase) inhibitor with antitumor activity in germline BRCA mutation (gBRCAmut) ovarian cancer and BRCA-negative (non-gBRCAmut) high-grade serous ovarian cancer (HGSOC).

Niraparib demonstrated antitumor activity in a recent phase 1 (dose-finding) trial of patients with advanced solid tumors (half the population enriched for *BRCA1* and *BRCA2* mutations) [Sandhu SK et al. *Lancet Oncol.* 2013]. Niraparib was well tolerated in this study, with a relatively low rate of grade 3 and 4 toxicities. The most common grade 3 or 4 treatment-related adverse events were anemia and thrombocytopenia (9% and 8% for grade 3 and 1% and 7% for grade 4, respectively) and 4% each for fatigue and neutropenia grade 3. Among study participants with sporadic HGSOC, 3 of 4 platinum-sensitive patients achieved RECIST responses (Response Evaluation Criteria in Solid Tumors). Based on these results, further trials were recommended.

Mansoor R. Mirza, MD, Oncology, Nordic Society of Gynaecologic Oncology and Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, presented the study design of an ongoing niraparib maintenance study examining platinum-sensitive patients with ovarian cancer and deleterious gBRCA^{mut} or high-grade serous histology non-gBRCA^{mut} (NOVA; NCT01847274).

The repeating 28-day maintenance cycle begins with screening and is followed by evaluation of gBRCA mutation status. From there, randomization occurs in 2 groups: gBRCA^{mut} (n = 180) and non- gBRCA^{mut} (n = 180). Each group is further divided into 2 groups: those receiving 300 mg of niraparib and those receiving placebo. After this, end points are assessed.

Women are eligible to participate in this phase 3 trial who are aged ≥ 18 years with histologically confirmed ovarian cancer, including either a tumor with HGSOC histology or known gBRCA^{mut}, and who have completed ≥ 2 courses of platinum-containing therapy with documented platinum sensitivity (complete or partial remission; no measurable lesion > 2 cm and normal CA125 or > 90% decrease during the last platinum regimen). Patients must also have an Eastern Cooperative Oncology Group score of 0 to 1 and normal organ function.

The primary study objective is to evaluate the effect of niraparib (300 mg, QD) on progression-free survival (PFS). Secondary objectives include additional measures of clinical benefit: patient-reported outcomes; PFS2, defined as the time from treatment randomization to the assessment of progression on a subsequent anticancer therapy or death by any cause; chemotherapy-free interval; and overall survival. Corrected QT intervals will be evaluated in a subset of patients. Other secondary objectives are to evaluate the safety and tolerability of niraparib versus placebo, the concordance of the centralized *BRCA* mutation test and a candidate companion diagnostic test with respect to gBCRA^{mut} patients, and the effects of food on the pharmacokinetics of niraparib.

The efficacy of oral niraparib will be determined by PFS as assessed by RECIST 1.1 via computed tomography or magnetic resonance imaging every 2 cycles through cycle 14, then every 3 cycles. Other end points are assessed by various targeted questionnaires. Analysis of 2 independent patient cohorts (deleterious gBRCA^{mut} and high-grade serous or high-grade predominantly serous histology non-gBRCA^{mut}) is being conducted under the hypothesis that patients with gBRCA mutations are enriched for responsiveness to niraparib. Pharmacokinetics will be assessed in all patients, and food effects will be assessed in a subset of patients who ingest a high-fat meal. This trial is being conducted in Europe, the United States, and Canada.

Niraparib is also being investigated in a phase 3 trial in patients with Her2-negative, germline *BRCA* mutation–positive breast cancer [BRAVO; NCT01905592].

Everolimus Safe and Effective for Advanced pNET: Final Results of RADIANT-3

Written by Brian Hoyle

Final overall survival (OS) and safety results of the phase 3 Everolimus and Octreotide in Patients With Advanced Carcinoid Tumor trial [RADIANT-3; NCT00412061] have bolstered previous findings that everolimus is effective and safe in the treatment of advanced pancreatic neuroendocrine tumors (pNET).