Sequential vs concurrent epirubicin and docetaxel as adjuvant chemotherapy for high-risk, node-negative, early breast cancer: an interim analysis of a randomised phase III study from the Hellenic Oncology Research Group

Dimitrios Mavroudis*,1, Emmanouil Saloustros2, Ioannis Boukovinas3, Pavlos Papakotoulas4, Stylianos Kakolyris5, Nikolaos Ziras6, Charalampos Christophylakis7, Nikolaos Kentepozidis8, Georgios Fountzilas9, Georgios Rigas10, Ioannis Varthalitis11, Konstantinos Kalbakis1, Sofia Agelaki1, Dora Hatzidaki12 and Vasilios Georgoulias12

1Department of Medical Oncology, University Hospital of Heraklion, Heraklion, Greece; 2Oncology Unit, General Hospital of Heraklion 'Venizelio', Heraklion, Greece; 3Department of Medical Oncology, Bioclinic, Thessaloniki, Greece; 42nd Department of Medical Oncology, 'Theageneio' Cancer Center, Thessaloniki, Greece; 5Department of Medical Oncology, University Hospital of Alexandroupolis, Alexandroupolis, Greece; 62nd Department of Medical Oncology, 'Metaxas' Cancer Center, Piraeus, Greece; 7Department of Medical Oncology, 401 General Military Hospital, Athens, Greece; 8Department of Medical Oncology, 251 Airforce Hospital, Athens, Greece; 9Aristotle University of Thessaloniki, Thessaloniki, Greece; 10Chemotherapy Unit, General Hospital of Volos ‘Achilopoulio’, Volos, Greece; 11Department of Oncology, General Hospital of Chania, Chania, Greece and 12Hellenic Oncology Research Group (HORG), Athens, Greece

Background: Sequential anthracyclines and taxanes are standard adjuvant chemotherapy for patients with high-risk axillary node-positive breast cancer. We compared a sequential to a concurrent regimen in high-risk node-negative early breast cancer.

Methods: Patients were eligible if they had tumours >2 cm or T1c with two of the following characteristics: no oestrogen receptor (ER) and progesterone receptor (PR) expression, histological grade III, Ki67 >40% and vascular, lymphovascular or perineural invasion. They were randomised to receive four cycles of epirubicin 90 mg m⁻² followed by four cycles of docetaxel 75 mg m⁻² (sequential regimen) or six cycles of epirubicin 75 mg m⁻² plus docetaxel 75 mg m⁻² (concurrent regimen). All chemotherapy cycles were administered every 21 days with G-CSF prophylaxis only for the concurrent arm. The primary endpoint was disease-free survival (DFS).

Results: Between 2001 and 2013, 658 women received the sequential (n=329) or the concurrent (n=329) regimen. The median age was 53 years, 43.9% of the patients were premenopausal and of the tumours 44.2% were ≤2 cm, 52.7% histological grade 3 and 35.3% hormone receptor-negative. After a median follow-up of 70.5 months, there were 29 (8.8%) vs 42 (12.8%) disease relapses (P=0.102) and 11 (3.3%) vs 19 (5.8%) deaths (P=0.135), in the sequential and concurrent arm, respectively. The 5-year DFS rates were 92.6% vs 88.2% for sequential and concurrent arm, respectively. There were no toxic deaths.

Conclusions: Sequential compared with the concurrent administration of anthracyclines and taxanes is associated with a non-significant but possibly clinically meaningful improvement in DFS. In the era of molecular selection of patients for adjuvant chemotherapy, this study offers valuable information for the optimal administration of anthracyclines and taxanes in patients with node-negative disease.

*Correspondence: Professor D Mavroudis; E-mail: medoncsec@med.uoc.gr

Received 25 September 2016; revised 7 March 2017; accepted 12 April 2017; published online 22 June 2017

© 2017 Cancer Research UK. All rights reserved 0007–0920/17
Adjuvant chemotherapy reduces significantly the risk of recurrence and death for women with early breast cancer (Early Breast Cancer Trialists’ Collaborative Group (EBCTCG), 2005). The addition of a taxane to an anthracycline-containing regimen is associated with further reduction in the risk of disease relapse and death (Saloustros et al., 2008).

In phase 3 trials in metastatic breast cancer setting, the concurrent administration of doxorubicin and docetaxel has been proven to be superior to doxorubicin–cyclophosphamide and doxorubicin, cyclophosphamide, and docetaxel (also known as the TAC regimen) superior to fluorouracil, doxorubicin, and cyclophosphamide (Mackey et al., 2002; Nabholz et al., 2003). In early breast cancer, the concurrent vs sequential administration of anthracyclines and taxanes has been investigated in at least four studies: the Breast Cancer International Research Group (BCIRG) 005 (Mackey et al., 2016), the Breast International Group (BIG) 02–98 (Oakman et al., 2013), the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-30 and B-38 trials (Swain et al., 2010, 2013). A significant benefit in both disease-free survival (DFS) and overall survival (OS) has been shown for sequential over concurrent regimens in a meta-analysis including three of these studies (Sha et al., 2012). In all these studies, only patients with node-positive disease have been included.

Owing to the relative lack of data for sequential and concurrent chemotherapy in node-negative early disease and given the fact that the benefit of taxanes in the adjuvant setting was independent of the nodal status (Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) et al., 2012), we compared the sequential vs the concurrent administration of anthracyclines and taxanes in patients with node-negative, high-risk disease. This question is crucial, especially in the era of precision medicine when molecular signatures are being used to select the patients for whom adjuvant chemotherapy is beneficial (Cardoso et al., 2016).
type of surgery) on DFS and OS was examined in a multivariate analysis using the Cox model. All tests were conducted at a two-sided alpha level of 0.05, and all CIs were given at a two-sided 95% level. Clinical data were held centrally (Clinical Trial Office, Hellenic Oncology Research Group) and analysed using the SPSS (version 22.0) program. Data were current as of May 2015.

RESULTS

Patients. Between June 2001 and August 2013, 724 patients were assessed, of whom 658 (91%) were found to be eligible. Forty-five patients did not meet all the eligibility criteria and 21 patients withdrew their consent. Therefore, 658 patients were centrally randomized to the sequential (n = 329 patients) or concurrent (n = 329 patients) treatment arm (Figure 1). The treatment groups were well balanced regarding prognostic characteristics (Table 1). The median age was 52 years (range: 28–78). Forty-four percent of the patients were premenopausal at diagnosis. The tumour was positive for ER, PR, or both in 64% of the patients and negative for both hormonal receptors in 36%. Finally, 60% of the patients had undergone breast-conservation, and 40% mastectomy.

Treatment. Patients on the sequential arm received a median of 8 (range: 3–8) cycles of treatment, whereas on the concurrent arm, they received a median of 6 (range: 2–6) cycles. The proportion of women who received all eight cycles of the sequential regimen was 96.7% vs 96.4% for the concurrent arm who received all six cycles (P = 0.122). The main reason for treatment discontinuation was adverse event probably associated with the treatment in 2.4% and 2.1% (P = 0.794) of the patients for the sequential and the concurrent arm, respectively. In both arms treatment discontinuation was mainly due to non-haematologic toxicities. Treatment was administered on time without delay in 96.7% and 96.4% of cycles (P = 0.557). Dose reduction for toxicity was required in 1.2% and 3% of administered cycles, in the sequential vs the concurrent group (P = 0.001). A total of 8 patients in the sequential and 11 in the concurrent group were lost to follow-up (P = 0.641; Figure 1).

Disease-free and overall survival. After a median follow-up of 70.5 months, 71 (10.8%) patients experienced disease recurrence (local n = 16, distant n = 44) or cancer in the contralateral breast (n = 11), and 30 (4.5%) patients died. According to the protocol, the number of events for the interim analysis had been reached and due to the better outcome of the sequential arm, the steering committee decided to report the results.

The DFS events were distant relapses in ~66% of the cases in both groups (Table 2). Although the median DFS has not yet been reached, there was a trend favoring the sequential administration (HR: 1.591; 95% CI: 0.990–2.556; P = 0.055). Figure 2A illustrates the Kaplan–Meier curves for DFS in the two treatment groups. The 5-year DFS rates were 88.2% and 92.6% for the groups receiving concurrent and sequential treatment, respectively. An unplanned subgroup analysis for the 188 triple-negative patients, revealed a similar trend; the 5-year DFS rates were 91.4% vs 82.2% in favour of the sequential arm (HR: 1.93; 95% CI: 0.886–4.205; P = 0.098). However, for patients with hormone receptor positive, HER2-negative disease no difference was found; the 5-year DFS was 92.5% vs 92.2% for the sequential and the concurrent group (HR: 1.185; 95% CI: 0.592–2.371; P = 0.631).

Figure 2B shows the Kaplan–Meier curves for OS. The estimated 5-year OS rates were excellent in both groups; 96.3% for the

Figure 1. CONSORT diagram.
Interestingly, this trend towards better OS was more pronounced in DFS (HR: 1.683, 95% CI: 1.056–2.683, P = 0.078). The Table 3 summarises the most commonly reported adverse events. Patients in the sequential group despite the lower cumulative dose of chemotherapy received (sequential: 360 mg m⁻² epirubicin and 300 mg m⁻² docetaxel vs concurrent: 450 mg m⁻² epirubicin and 450 mg m⁻² docetaxel) were at higher risk for grade 2–4 neutropenia (54% vs 41%), presumably due to primary G-CSF prophylaxis in the concurrent arm. However, grade 2–4 febrile neutropenia was more common on the concurrent arm (6% vs 2.7%). The incidence of grade 2–4 neuropathy in the two groups was relatively low (0.3% vs 0.6%). Finally, grade 2–4 non-haematologic toxicities like chemotherapy-induced nausea and vomiting, constipation and nail toxicity were more common in the sequential arm, whereas patients in the concurrent group were at higher risk for oedema. There were no significant cardiac toxicity or toxic deaths.

**DISCUSSION**

We present the first study, to the best our knowledge, comparing the sequential vs concurrent administration of anthracyclines and taxanes as adjuvant therapy in patients with node-negative but high-risk early breast cancer. After a median follow-up of ~6 years and 10.7% of the patients experiencing disease relapse, a preplanned interim analysis showed a non-statistically significant but possibly clinically meaningful trend towards longer DFS and OS in favour of the sequential administration of epirubicin and docetaxel. Moreover, the observed increased haematologic toxicity of the sequential regimen was not clinically harmful. The higher incidence of neutropenia did not result in more febrile neutropenia events, whereas there were no significant differences in the non-haematologic toxicities.

Anthracyclines and taxanes are recommended for the adjuvant treatment of women with operable breast cancer. Several regimens are being used by clinicians, including standard dose sequential, concurrent and dose-dense sequential (Saloustros et al, 2014). However, due to the relative paucity of data from head-to-head comparisons between these regimens, there is no consensus for the optimal chemotherapy regimen.

The sequential vs concurrent administration has been tested so far only in the population of node-positive early breast cancer. The concurrent TAC (docetaxel, doxorubicin and cyclophosphamide) was not superior in DFS and OS to the sequential AC → T regimen, according to the 10-year analysis of the BCIRG-005 study. At 10-years, the DFS rates were 66.5% in the AC → T arm and 66.3% in the TAC arm (P = 0.749), whereas OS was 79.9% and 78.9% (P = 0.506), respectively (Mackey et al, 2016). The efficacy was comparable across all stratification subgroups. Likewise, due to primary G-CSF support, the toxicity was more acceptable in the TAC than AC → T therapy. The BIG 02-98 trial compared the sequential vs the concurrent docetaxel arm (A 75 mg m⁻² × 3 cycles → T 100 mg m⁻² × 3 cycles → CMF × 3 cycles vs AT 50/75 mg m⁻² × 4 cycles → CMF × 3 cycles) in patients with infiltrated lymph nodes. Sequential docetaxel significantly improved DFS (HR: 0.84, 95% CI: 0.72–0.99, P = 0.035) and OS (HR: 0.79, 95% CI: 0.65–0.98, P = 0.028) compared to the concurrent doxorubicin–docetaxel, after 8 years of median follow-up (Oakman et al, 2013). In the context of NSABP B-30 trial, 5351 patients were randomly assigned to four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel (AC → T) vs four cycles of doxorubicin and docetaxel and vs four cycles of concurrent group and 98.7% for the sequential one. A trend for prolonged median OS was observed in favour of the sequential treatment group (HR: 1.896; 95% CI: 0.902–3.987, P = 0.091). Interestingly, this trend towards better OS was more pronounced for patients with triple-negative tumours (HR: 3.369; 95% CI: 0.940–12.081, P = 0.062).

From the exploratory variables included in the univariate analysis, only hormone receptors had a significant influence on DFS (HR: 1.683, 95% CI: 1.056–2.683, P = 0.029), whereas the type of treatment had a marked trend but not statistically significant (HR: 1.591, 95% CI: 0.990–2.556, P = 0.055). The interaction between treatment arms and hormone receptors was also examined and a statistically significant association was revealed (HR: 2.157, 95% CI: 1.174–3.963, P = 0.013). The multivariate analysis confirmed this association (HR: 2.125, 95% CI: 1.152–3.921, P = 0.029), whereas the type of hormone receptors had a significant influence on OS (HR: 1.591, 95% CI: 0.990–2.556, P = 0.055). The interaction between treatment arms and hormone receptors was also examined.
doxorubicin, cyclophosphamide, and docetaxel (Swain et al., 2010). After a median follow-up of 73 months, OS was improved in the AC–T group (8-year OS, 83%) compared with the doxorubicin–docetaxel group (OS 79%; \( P = 0.03 \)) or the concurrent-TAC group (OS 79%; \( P = 0.09 \)). According to a meta-analysis of these studies, the sequential taxane- and anthracycline-based regimen resulted in a significant 12% reduction in mortality over the concurrent administration in patients with early-stage, node-positive breast cancer (Swain et al., 2013).

The more recently reported NSABP B38 trial compared the TAC regimen vs the dose-dense AC \( \times 4 \) followed by paclitaxel \( \times 4 \). No significant differences in efficacy were shown (Swain et al., 2013). Febrile neutropenia and diarrhoea were more common with TAC, and neuropathy, anaemia, transfusions and erythropoietin use with dose dense AC\( \rightarrow \)paclitaxel. In both of these studies (Swain et al., 2013; Mackey et al., 2016), cyclophosphamide was included in the concurrent regimen. This observation raises the question whether the omission of cyclophosphamide in the concurrent arm of the other two studies, the BIG 02-98 and NSABP B-30, favored the sequential regimens.

Cyclophosphamide administration was not a ‘cofounding factor’ in our study, as it was not administered in either arm. However, in contrary to the NSABP B30 trial (Swain et al., 2010), which suggested that both a longer course (sequential regimen) and a higher dose of docetaxel are important for maximum efficacy, our study showed that for node-negative patients, less chemotherapy administered over a longer course is actually more beneficial. Given the results from recently presented trials, showing that in terms of invasive DFS, docetaxel plus cyclophosphamide \( \times 6 \) was inferior to taxane plus anthracycline (Blum et al., 2017; Mavroudis et al., 2016), we conclude that for high-risk node-negative patients anthracyclines and taxanes are crucial for maximising clinical benefit. However, our study raises the question whether maximum benefit can be achieved with less cumulative chemotherapy dose.
An interesting issue in the interpretation of our data is the observation, based on an unplanned analysis, that the sequential regimen may be more active in patients with triple-negative tumours; 5-year DFS rates 91.4% vs 82.2% in favour of the sequential arm. Subset analyses of the other sequential vs concurrent taxane trials have shown contradictory results. Although no subtype specificity was observed in the BIG 02-98 and BCIRG trials, NSABP B-32 and B-38 trials suggested that the sequential regimen may be superior for patients with ER-negative tumours. Our results for triple-negative tumours should be interpreted with caution as this analysis has not been preplanned, and the sequential arm. Subset analyses of the other sequential vs concurrent arm. It seems highly unlikely that changes in dosing schedules will result in any substantial clinical benefit. Moreover, attempts to improve outcomes with combination regimens by adding more chemotherapeutic agents to anthracyclines and taxanes, have not been successful. Studies that will help us determine optimal treatments based on tumour biology seem to be more promising. The recently reported MINDACT (Microarray in Node-Negative and 1–3 Node-Positive Disease May Avoid Chemotherapy) trial showed that molecular analysis might improve the selection of patients with node-negative disease who derive benefit from adjuvant chemotherapy (Cardoso et al., 2016). The ongoing TAILORx (Trial Assigning Individualised Options for Treatment) study will address the question whether the addition of chemotherapy to hormonal therapy for women with node-negative, ER-positive breast cancer and intermediate Oncotype DX (Genomic Health, Redwood City, CA, USA) recurrence score improves outcome. In the era of molecular selection of patients with node-negative disease for whom adjuvant chemotherapy is indicated, we believe that our study provides valuable information regarding the optimal use of the most active drugs to achieve a better clinical outcome.

### ACKNOWLEDGEMENTS

This study was funded by the Hellenic Oncology Research Group.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### ETHICAL STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Sequential vs concurrent chemotherapy for breast cancer

women with HER2-negative, axillary lymph node-positive early breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG). Ann Oncol 27: 1873–1878.

Nabholtz JM, Falkson C, Campos D, Szanto J, Martin M, Chan S, Pienkowski T, Zaluski J, Pinter T, Krazkowski M, Vorobiof D, Leonard R, Kennedy I, Azil N, Murawsky M, Riva A, Pouillart P (2003) Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol 21: 968–975.

Oakman C, Francis PA, Crown A, Quinaux E, Buyse M, De Azambuja E, Margeli Vála M, Andersson M, Nordensjöld B, Jakesz R, Thürlimann B, Gutierrez J, Harvey V, Punzalan L, Dell’orto P, Larmsint D, Steinberg I, Gelber RD, Piccart-Gebhart M, Viale G, Di Leo A (2013) Overall survival benefit for sequential doxorubicin-docetaxel compared with concurrent doxorubicin and docetaxel in node-positive breast cancer-8-year results of Breast International Group 02-98 phase III trial. Ann Oncol 24: 1203–1211.

Saloustros E, Malamos N, Boukouvina I, Kakolyris S, Kouroussis C, Athanasiadis A, Óziris N, Kenterpodis N, Makrantonakis P, Polyzos A, Christophyllakis C, Georgoulia V, Mavroudis D (2014) Dose-dense paclitaxel versus docetaxel following FEC as adjuvant chemotherapy in axillary node-positive early breast cancer: a multicenter randomized study of the Hellenic Oncology Research Group (HORG). Breast Cancer Res Treat 148: 591–597.

Saloustros E, Mavroudis D, Georgoulas V (2008) Paclitaxel and docetaxel in the treatment of breast cancer. Expert Opin Pharmacother 9: 2603–2616.

Sha N, Wang S, Yao C, Xu Z, Zhang Y, Zhang Y, Lin Y (2012) Sequential versus concurrent anthracyclines and taxanes as adjuvant chemotherapy for early breast cancer: A meta-analysis of phase III randomized control trials. Breast 21: 389–393.

Swain SM, Jeong JH, Geyer CE, Costantino JP, Pajon ER, Fehrenbacher L, Atkins JN, Polikoff J, Vogel VG, Erban JK, Rastogi P, Livingston RB, Perez EA, Mamounas EP, Land SR, Ganz PA, Wolmark N (2010) Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med 362: 2053–2065.

Swain SM, Tang G, Geyer CE, Rastogi P, Atkins JN, Donnellan PP, Fehrenbacher L, Azar CA, Robidoux A, Polikoff JA, Bruksky AM, Biggs DD, Levine EA, Zapas JL, Provencher L, Northfelt DW, Paik S, Costantino JP, Mamounas EP, Wolmark N (2013) Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: The NSABP B-38 Trial. J Clin Oncol 31: 3197–3204.

This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 4.0 Unported License.