European Journal of Cancer 122 (2019) 91–100

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

UCBG 2-04: Long-term results of the PACS 04 trial evaluating adjuvant epirubicin plus docetaxel in node-positive breast cancer and trastuzumab in the human epidermal growth factor receptor 2–positive subgroup

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Received 30 July 2019; received in revised form 9 September 2019; accepted 12 September 2019
Available online 18 October 2019

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https://doi.org/10.1016/j.ejca.2019.09.014

KEYWORDS
Breast cancer;
Adjuvant chemotherapy;
Taxanes;
Adjuvant trastuzumab

Abstract ***Purpose:*** We conducted a double-randomised phase III trial to evaluate a concomitant taxane-anthracycline regimen in node-positive breast cancer and the efficacy of trastuzumab in the human epidermal growth factor receptor 2 (HER2)–positive subpopulation.
Methods: A total of 3010 patients with node-positive breast cancer were randomly assigned to receive 6 cycles of 500 mg/m^2 of fluorouracil, 100 mg/m^2 of epirubicin and 500 mg/m^2 of cyclophosphamide (FEC) or 75 mg/m^2 of epirubicin and 75 mg/m^2 of docetaxel (ED). Patients with HER2-positive tumours were secondary randomly assigned to either trastuzumab or observation. The primary end-point was disease-free survival (DFS) in the two chemotherapy arms.
Results: After a 115-month median follow-up, DFS was not significantly better in the ED arm (DFS: 70%, 95% confidence interval [CI]: 67–72) than in the FEC arm (DFS: 68%, 95% CI: 65–70; hazard ratio [HR] = 0.88, 95% CI: 0.77–1.01; p = 0.064). The OS was not different between FEC (OS: 80%, 95% CI: 78–83) and ED (OS: 81%, 95% CI: 79–83); HR = 0.97, 95% CI: 0.81–1.16; p = 0.729). ED appeared more toxic. In the 528 HER2-positive subset, there was trend for a higher DFS, in the intention-to-treat population, in the trastuzumab arm (DFS: 68%, 95% CI: 61–74) than in the observation arm (DFS: 60%, 95% CI: 54–66; HR = 0.77, 95% CI: 0.57–1.03; p = 0.079). In the per-protocol population, DFS was significantly higher in the trastuzumab arm (DFS: 70%, 95% CI: 63–76) than in the observation arm (DFS: 59%, 95% CI: 53–65; HR = 0.69, 95% CI: 0.51–0.94; p = 0.0156). The OS was not different between these 2 arms.
Conclusion: This study did not show superiority of the concomitant anthracycline-taxane arm which was more toxic in high-risk node-positive breast cancer patients. Long-term results of the HER2-positive subpopulation are in line with those of the other adjuvant trastuzumab trials but quantitatively less pronounced mostly because of lack of power.

1. Introduction

The survival benefit of adjuvant chemotherapy for patients with node-positive early breast cancer is well established. Several polychemotherapy regimens that reduce the risk of relapse and death have been evaluated. Anthracycline-taxane combinations are among the most effective ones [1,2]. Both sequential and concomitant anthracycline-taxane regimens have been evaluated in this setting.

At the time the current trial was designed (late-1990s), the benefit of the anthracycline-taxane combinations was unknown and the appreciation of the risk of relapse was mostly based on the tumour burden. In addition, the results of the PACS 01 study on the sequential fluorouracil, epirubicin and cyclophosphamide (FEC)-docetaxel regimen were not available, and the 6FEC regimen was still a standard. The PACS 04 trial was designed to evaluate the efficacy of a concomitant taxane and anthracycline adjuvant regimen compared with an anthracycline-alone regimen in a broad population of patients with node-positive localised breast cancer. This trial also assessed the efficacy of one-year trastuzumab compared with observation in the human epidermal growth factor receptor 2 (HER2)–positive subset of patients, through double randomisation.

The trastuzumab efficacy and safety data in the 528 HER2-positive patients were previously reported, after a median 47-month follow-up [3].

We report here, for the first time, the long-term efficacy and safety results from this large, mature study comparing the epirubicin and docetaxel (ED) combination with the FEC regimen in 3010 patients, with 115-month median follow-up as well as an updated analysis of the trastuzumab efficacy in the HER2-positive subpopulation.

2. Patients and methods

2.1. Study design

The PACS 04 trial (NCT00054587) was a multicentre, international, open-label and double-randomised phase III trial conducted across 82 French and Belgian centres, sponsored by the French Breast Cancer Intergroup (UCBG). Patients were centrally randomly assigned to receive adjuvant treatment with either 6 cycles of FEC or 6 cycles of ED, with stratification for the centre and for the number of involved axillary nodes (1–3 versus $\geq$ 4). The subgroup of patients with HER2-positive breast cancer was additionally randomly assigned to receive 1 year of trastuzumab or no treatment (observation). The primary end-point was disease-

free survival (DFS) in the two chemotherapy arms. Secondary end-points included safety, DFS in the HER2-positive subpopulation, event-free survival (EFS) defined as DFS plus second primary cancer (breast or other) and overall survival (OS).

Patients provided written informed consent before enrolment. The protocol was approved by the French National Ethics Committee and committees of all participating institutions in Belgium, and the study was conducted in accordance with the Declaration of Helsinki and European Good Clinical Practice requirements.

2.2. Patients

Eligible women were 18–65 years old with a Word Health Organisation (WHO) performance status 0–1 and a histologically confirmed, unilateral, invasive breast adenocarcinoma. Patients required mastectomy or breast-conserving surgery with clear margins and axillary lymph node dissection with at least one involved lymph node from a minimum of 5 resected lymph nodes. Patients were required to have adequate bone marrow, renal and hepatic function and a left ventricular ejection fraction (LVEF) above 50%. All patients were required to have a negative metastatic workup.

2.3. Treatment

Adjuvant chemotherapy was to start within 42 days of initial surgery. In the FEC arm and ED arm, chemotherapy consisted of 6 courses, every 3 weeks, of 500 mg/m^2 of fluorouracil, 100 mg/m^2 of epirubicin and 500 mg/m^2 of cyclophosphamide (FEC) or of 75 mg/m^2 of epirubicin and 75 mg/m^2 of docetaxel (ED), respectively.

In the HER2-positive subgroup, patients randomised in the trastuzumab arm began their treatment after the completion of chemotherapy and radiotherapy. Trastuzumab was delivered every 3 weeks, for one year, at 6 mg/kg, except for the first loading dose which was at 8 mg/kg. Trastuzumab was initiated if the patient had received at least 4 cycles of chemotherapy and had an LVEF >55% (or between 50 and 55% with the cardiologist approval).

Regional lymph node irradiation was mandatory for all patients and breast irradiation in case of breast-conserving surgery. Radiotherapy began within 4 weeks after chemotherapy completion, and endocrine therapy was prescribed for patients with hormone receptor–positive disease defined as oestrogen receptor and/or progesterone receptor ≥ 10% by immunohistochemistry (IHC).

2.4. Assessments

Baseline examination included complete history, physical examination, chest X-ray, abdominal ultrasound, bone scintigraphy and LVEF determination.

HER2 status was analysed in 18 reference cancer centres, by IHC and fluorescent *in situ* hybridisation (FISH). HER2 positivity was defined either as an HER2 overexpression (3+) by IHC or as an HER2 amplification by FISH (i.e. HER2/CEP 17 ratio ≥2.2) in case of HER2 2 + by IHC. Details of the HER2 status assessments have been previously reported [3].

Patients were observed for relapse and survival every 4 months for the first 2 years, every 6 months for years 3–5 and annually for years 6–10. Annual examination included the same workup as baseline until year 5. Toxicity was evaluated in accordance with the WHO scale [4]. Assessments for cardiac toxicity in the HER2-positive population have been described elsewhere [3].

2.5. Statistical analysis

The sample size calculation was based on the number of patients required for the second randomisation. For an absolute improvement of 10% in the 3-year DFS rate (hazard ratio [HR]: 0.625), 460 randomised patients were required to ensure an 80% power and a 5% significance level (unilateral test). Assuming that about 10% of patients assigned to trastuzumab would not receive trastuzumab, 520 patients with HER2-positive tumours were required for the second randomisation. Assuming that 20% of breast cancers overexpress HER2, approximately 2600 patients were required for the study to detect an absolute difference of 6% in 5-year DFS in favour of the combined ED chemotherapy ($\beta = 0.08$, $\alpha = 0.05$), and with 3000 inclusions, the power of the comparison was 95% with a beta risk identical to the alpha risk, 0.05, bilateral test.

Statistical analyses were performed on the intention-to-treat (ITT) populations for the chemotherapy regimen analysis and on the ITT and per-protocol population – defined as the population that effectively received the treatment – for the trastuzumab analysis. In this per-protocol analysis, the 26 patients (10%) who had been assigned to the trastuzumab arm and who had never received it were analysed within the observation arm. Safety analysis was performed on the safety population, defined as all patients who received at least one dose of study treatment. DFS and OS rates were estimated by the Kaplan-Meier method. Treatment groups were compared using the log-rank test, stratified by the number of positive lymph nodes (1–3 versus ≥4).

The results of trastuzumab randomisation sub-study have been reported, after a planned interim analysis, when the target number of DFS events had been reached, with 47-month follow-up [3]. The updated

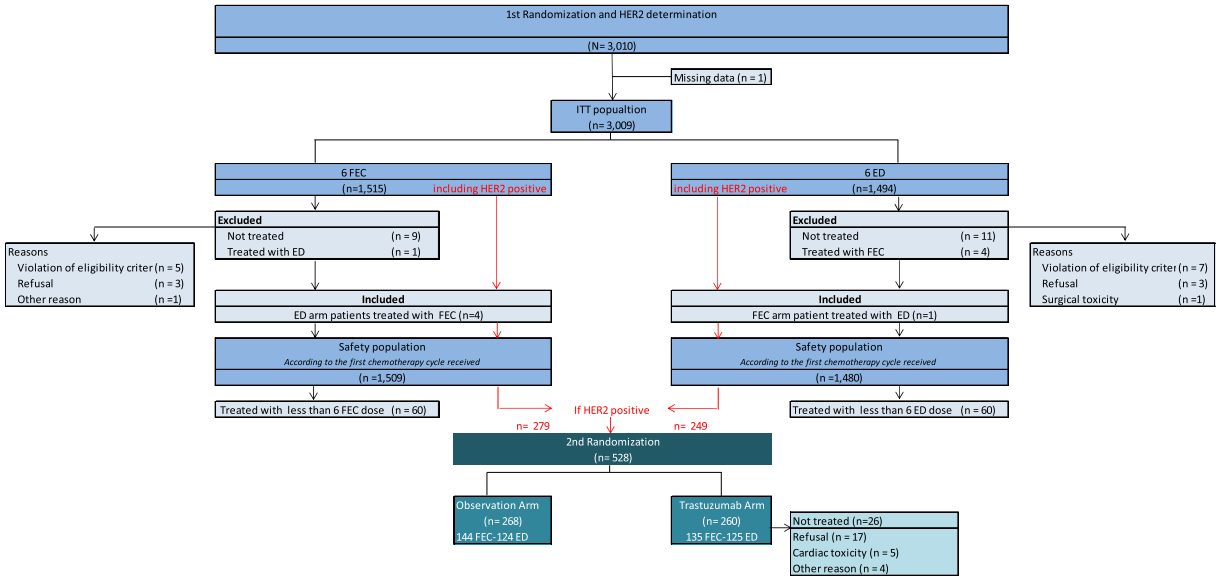

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. ITT, intention-to-treat; FEC, 500 mg/m^2 of fluorouracil, 100 mg/m^2 of epirubicin and 500 mg/m^2 of cyclophosphamide; ED, 75 mg/m^2 of epirubicin and 75 mg/m^2 of docetaxel; HER2, human epidermal growth factor receptor 2.

analysis reported here was realised with a 115-month median follow-up.

3. Results

3.1. Patients and treatment

The Consolidated Standards of Reporting Trials (CONSORT) diagram is presented in Fig. 1. A total of 3010 patients were randomised for the main chemotherapy question between February 2001 and August 2004, of whom 1515 were assigned to the FEC regimen and 1494 to the ED regimen (one missing data). Patients were analysed for safety according to the first chemotherapy cycle they actually received. The two chemotherapy arms were well balanced regarding well-known prognostic factors. Patients' clinical characteristics are summarised in Table 1.

In both arms, 96% of patients received 6 cycles of chemotherapy. The median relative dose intensity (RDI) was 98% for the 3 agents in the FEC arm and 99% for both agents in the ED arm. An RDI of chemotherapy ≥90% was reached in 86% of patients in the FEC arm and 92% in the ED arm. Dose intensities of each chemotherapy arm are reported in Table 2.

Regional lymph node radiotherapy was prescribed to 98% of patients and breast radiotherapy to 62% of patients. Endocrine therapy was prescribed to 99% of patients with hormone receptor–positive disease. Tamoxifen was prescribed for 5 years. After protocol amendment (Amendment N°18 on 10 March 2004), aromatase inhibitors were allowed for postmenopausal women. Overall, 88% of endocrine therapy consisted of tamoxifen and 12% of aromatase inhibitor (anastrozole or letrozole).

Among the 528 patients with HER2-positive tumours, 260 were assigned to the trastuzumab arm and 268 to the observation arm. In the trastuzumab arm, 26 patients (10%) did not receive any trastuzumab because of the patient's refusal (n = 17), cardiac toxicity (n = 5), progression (n = 2), second cancer (n = 1) and HER2-negative status (n = 1) (Fig. 1). Moreover, 58 patients (25%) did not complete the treatment, among whom 38 patients (15%) received trastuzumab for less than 6 months. The main reasons for early stop were cardiac toxicity (n = 41) and disease progression (n = 10). Both arms were well balanced for prognostic factors. Details of this subpopulation have previously been published [3].

3.2. Efficacy

3.2.1. Primary comparison of chemotherapy regimens

The median follow-up duration of the whole cohort was 115 months. Among the 3009 evaluable patients, 838 events occurred: 557 (67%) were distant metastases, 128 (15%) locoregional relapses, 87 (10%) contralateral breast cancers and 66 (8%) deaths. The proportion of these events was similar in both chemotherapy arms.

There was a non-significant trend for a better DFS in the ED arm (DFS: 70%, 95% confidence interval [CI]: 67–72) than in the FEC arm (DFS: 68%, 95% CI: 65–70; HR = 0.88, 95% CI: 0.77–1.01; p = 0.064). The OS was not different between the FEC arm (OS: 80%,

Table 1
Baseline clinical characteristics of the patients.

Characteristics	FEC arm (n = 1515)	ED arm (n = 1494)
Median age, years (range)	50 (23–65)	50 (22–66)
Menopausal status		
Pre-menopausal	613 (52%)	596 (52%)
Postmenopausal	558 (48%)	551 (48%)
Unknown	344	347
Surgery		
Breast-conserving	1078 (71%)	1018 (68%)
Mastectomy	437 (29%)	476 (32%)
Histological tumour size (cm)		
<2	568 (38%)	589 (40%)
2–5	798 (53%)	770 (52%)
≥5	133 (9%)	121 (8%)
Tumour grade		
I	178 (12%)	199 (14%)
II	691 (47%)	673 (46%)
III	613 (41%)	580 (40%)
Unknown	33	42
No. of positive nodes		
1–3	1026 (68%)	1006 (67%)
>3	489 (32%)	488 (33%)
Oestrogen receptor (ER) expression		
ER+	1170 (77%)	1152 (77%)
ER-	343 (23%)	342 (23%)
Unknown	2	0
Progesterone receptor (PR) expression		
PR+	926 (65%)	946 (67%)
PR-	508 (35%)	465 (33%)
Unknown	81	83
HER2 status		
HER2+	298 (20%)	265 (18%)
HER2-	1217 (80%)	1229 (82%)
TNBC		
Yes	174 (12%)	176 (12%)
No	1259 (88%)	1235 (88%)
Unknown	82	83

Abbreviation: FEC, 500 mg/m^2 of fluorouracil, 100 mg/m^2 of epirubicin and 500 mg/m^2 of cyclophosphamide; ED, 75 mg/m^2 of epirubicin and 75 mg/m^2 of docetaxel; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

95% CI: 78–83) and the ED arm (OS: 81%, 95% CI: 79–83; HR = 0.97, 95% CI: 0.81–1.16; p = 0.729) (Fig. 2).

The subgroup DFS analysis suggested a consistent trend in the subpopulation with that of the overall population except for the triple negative subgroup which seemed to benefit more from the FEC regimen containing an alkylating agent. However, interpretation remains cautious because of the low number of patients in this subpopulation (Fig. 3).

3.2.2. Trastuzumab in the HER2-positive subpopulation

In the ITT HER2-positive population, there was a trend for higher DFS in the trastuzumab arm (DFS: 68%, 95% CI: 61–74) than in the observation arm (DFS: 60%, 95% CI: 54–66; HR: 0.77, 95% CI: 0.57–1.03; p = 0.079). In the per-protocol population, DFS was significantly higher in the trastuzumab arm (DFS: 70%, 95% CI: 63–76) than in the observation arm (DFS: 59%, 95% CI: 53–65; HR: 0.69, 95% CI: 0.51–0.94; p = 0.0156) (Fig. 4).

Table 2
Summary of received chemotherapy in each arm.

Chemotherapy	6 FEC (n = 1509)	6 ED (n = 1480)
Received cycles (%)		
1–3 cycles	2	2.4
≥ 4 cycles	98	97.6
Median RDI (%)		
Fluorouracil	97.6	–
Epirubicin	97.6	98.8
Cyclophosphamide	97.8	–
Docetaxel	–	98.8
RDI ≥ 90% (%)		
Fluorouracil	87.2	–
Epirubicin	85.9	92.3
Cyclophosphamide	87.3	–
Docetaxel	–	92.4

Abbreviation: FEC, 500 mg/m^2 of fluorouracil, 100 mg/m^2 of epirubicin and 500 mg/m^2 of cyclophosphamide; ED, 75 mg/m^2 of epirubicin and 75 mg/m^2 of docetaxel; RDI, relative dose intensity.

The OS was not different in the trastuzumab arm as compared with the observation arm if analysing neither the ITT HER2-positive population (HR: 0.82, 95% CI: 0.56–1.21; p = 0.323) nor the per-protocol HER2-positive population (HR: 0.79, 95% CI: 0.54–1.17; p = 0.24).

3.2.3. Safety

We observed a higher rate of febrile neutropenia (32% versus 11%; p < 0.001), grade III–IV diarrhoea (3% versus 1%; p < 0.001) and grade II–IV neurotoxicity (4% versus 1%; p < 0.001) in the ED arm than in the FEC arm. Grade III–IV nausea and vomiting were more frequent with FEC than with ED (14% versus 8%; p < 0.001). Grade III–IV cardiac toxicity (congestive heart failure) was observed in 4 patients with FEC and in 2 patients with ED. Six toxic deaths were observed during or within 2 months after the end of chemotherapy: 5 in the ED arm and 1 in the FEC arm. Safety data are described in Table 3.

Long-term deaths linked to cardiac heart failure were observed in 3 patients and 1 patient in the FEC and ED arm, respectively. None of these patients had received trastuzumab.

Seventy-five patients developed a second non-breast primary cancer during the follow-up period (43 in the FEC arm and 32 in the ED arm). Among those, 12 were haematologic malignancies (7 in the FEC arm and 5 in the ED arm). The crude rates of second non-breast cancer and of second haematological malignancies were 2.5% and 0.4%, respectively, at 115 months.

4. Discussion

At 115-month median follow-up, PACS 04 did not demonstrate a significant DFS benefit in favour of ED

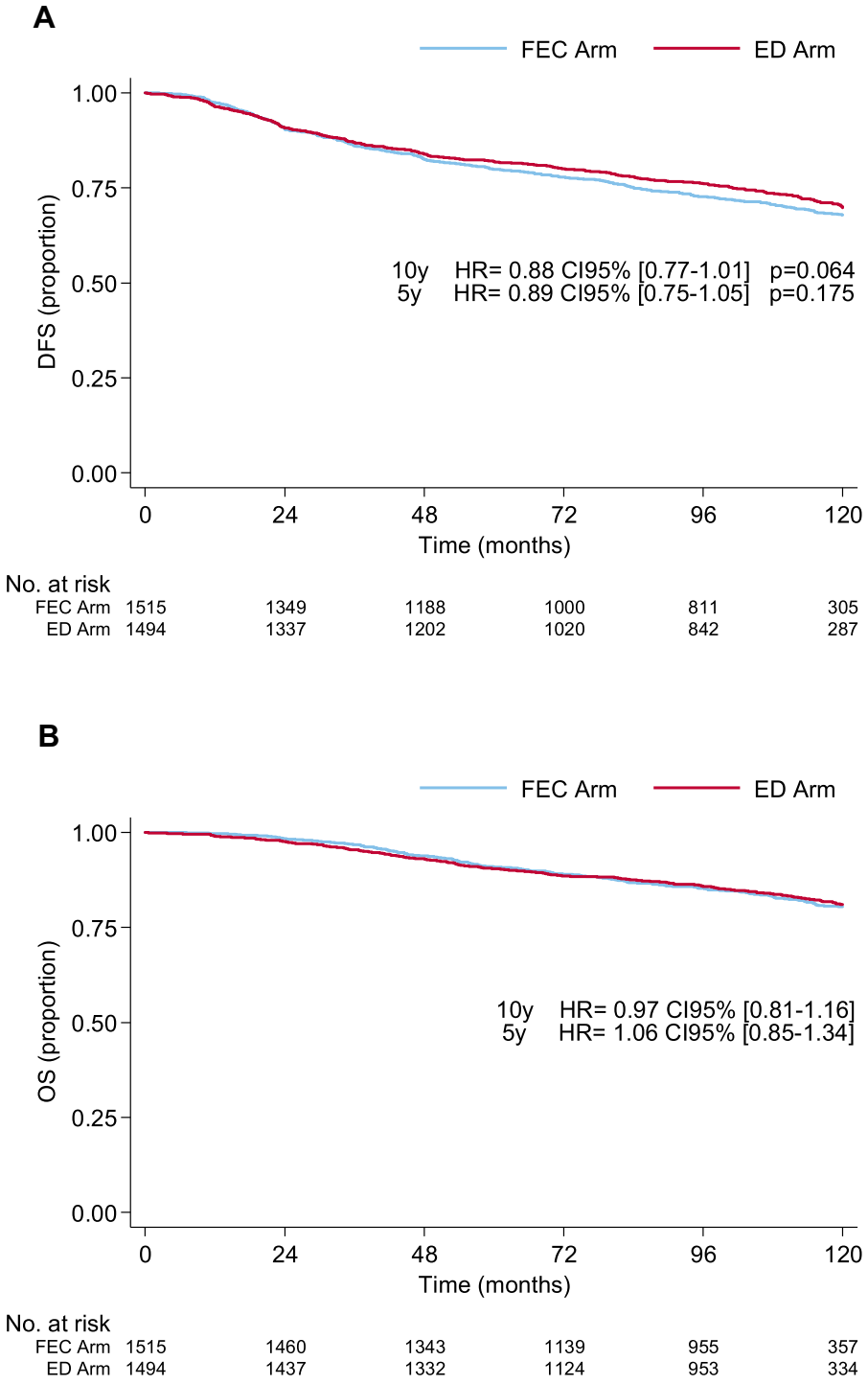

Fig. 2. Kaplan-Meier estimates of 10-year DFS and OS in the 2 chemotherapy arms. FEC, 500 mg/m^2 of fluorouracil, 100 mg/m^2 of epirubicin and 500 mg/m^2 of cyclophosphamide; ED, 75 mg/m^2 of epirubicin and 75 mg/m^2 of docetaxel; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.

compared with FEC in node-positive breast cancer. Nor was there an overall survival benefit in the taxane arm.

The benefit from concomitant taxane and anthracycline as adjuvant treatment has not been consistent in the literature. In the BCIRG 001 trial, TAC (docetaxel, doxorubicin and cyclophosphamide) clearly improved 10-year DFS (HR: 0.8; p = 0.0043) and 10-year OS (HR: 0.74; p = 0.002) compared with FAC (fluorouracil, doxorubicin and cyclophosphamide) for node-positive breast cancer patients [5]. In the BIG2-98 study, no benefit was seen from concurrent taxane and anthracycline regimen, whereas 8-year DFS and OS benefits were observed from sequential anthracycline and taxane regimen [6].

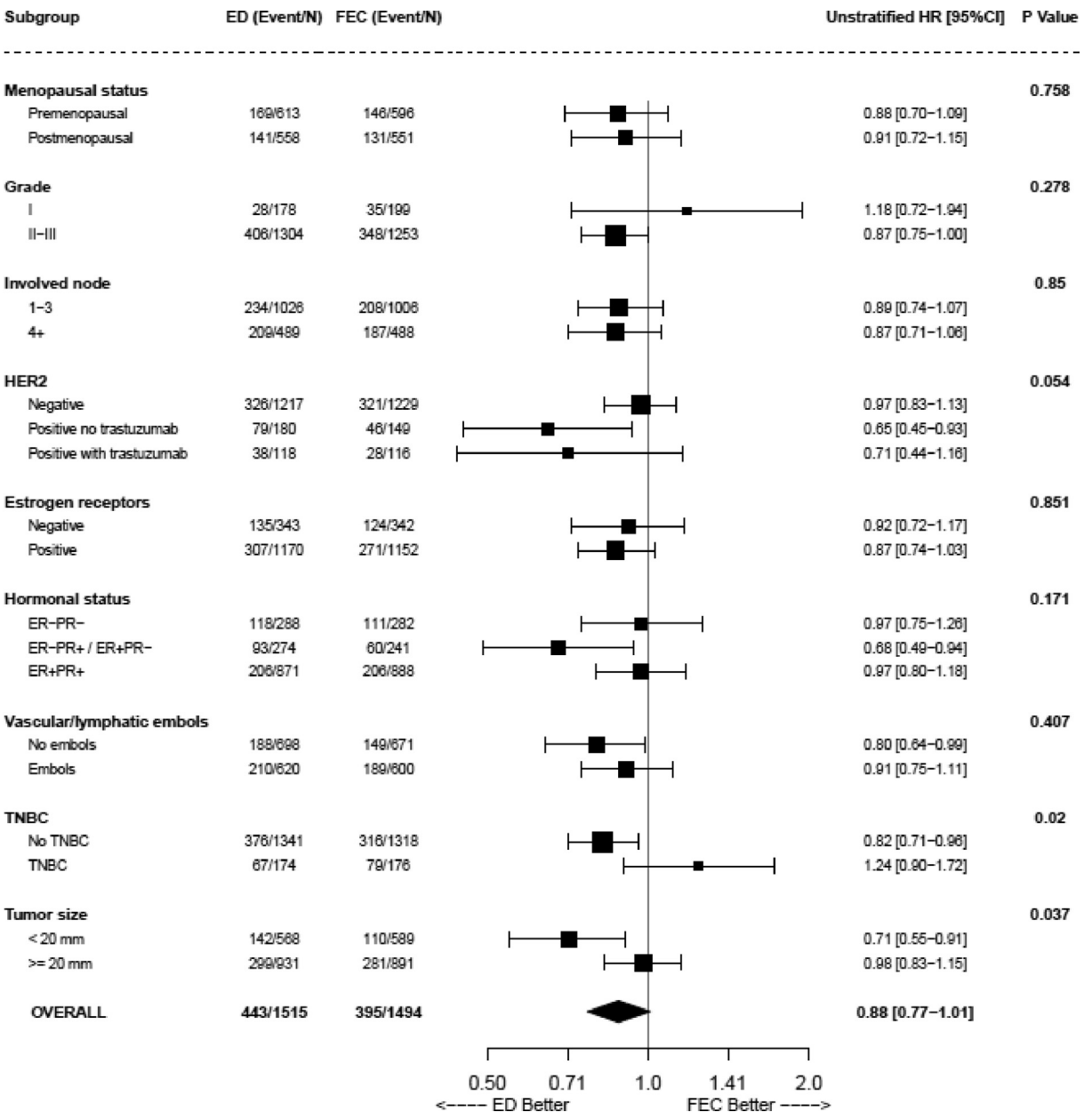

Fig. 3. Subgroup analysis of disease-free survival. Abbreviations: ER, oestrogen receptor; PR, progesterone receptor; TNBC, triple negative breast cancer. FEC, 500 mg/m^2 of fluorouracil, 100 mg/m^2 of epirubicin and 500 mg/m^2 of cyclophosphamide; ED, 75 mg/m^2 of epirubicin and 75 mg/m^2 of docetaxel; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; PR, Progesterone receptor; ER, oestrogen receptor.

Even if the superiority of combining anthracycline and taxane has clearly been demonstrated in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)meta-analysis [2] showing a reduction in the risk of recurrence (rate ratio [RR] 0.84; $2p < 0.0001$) and of death (RR: 0.86; $2p = 0.0002$), the dose and schedule seem very important. In the BCIRG 001 trial, in which the dose of doxorubicin is identical in both arms and docetaxel replaced fluorouracil, the TAC regimen is clearly a more intensive chemotherapy regimen than the control arm and is therefore associated with a higher risk of immediate toxicities. In the same way, in the BCIRG 005 study, the concomitant TAC regimen was associated with a higher haematologic toxicity and infection rate than the sequential AC-T regimen [7]. In the PACS 04 study and in the BIG 2-98, the lack of benefit in the concomitant arm might be explained by the epirubicin dose reduction in the investigational arm compared with that in the control arm, by the use of a suboptimal docetaxel dose and by the omission of an alkylating agent in the concomitant arm. Concurrent taxane-anthracycline regimens indeed require dose reduction for feasibility that may compromise the efficacy. Today, sequential regimen of anthracycline and

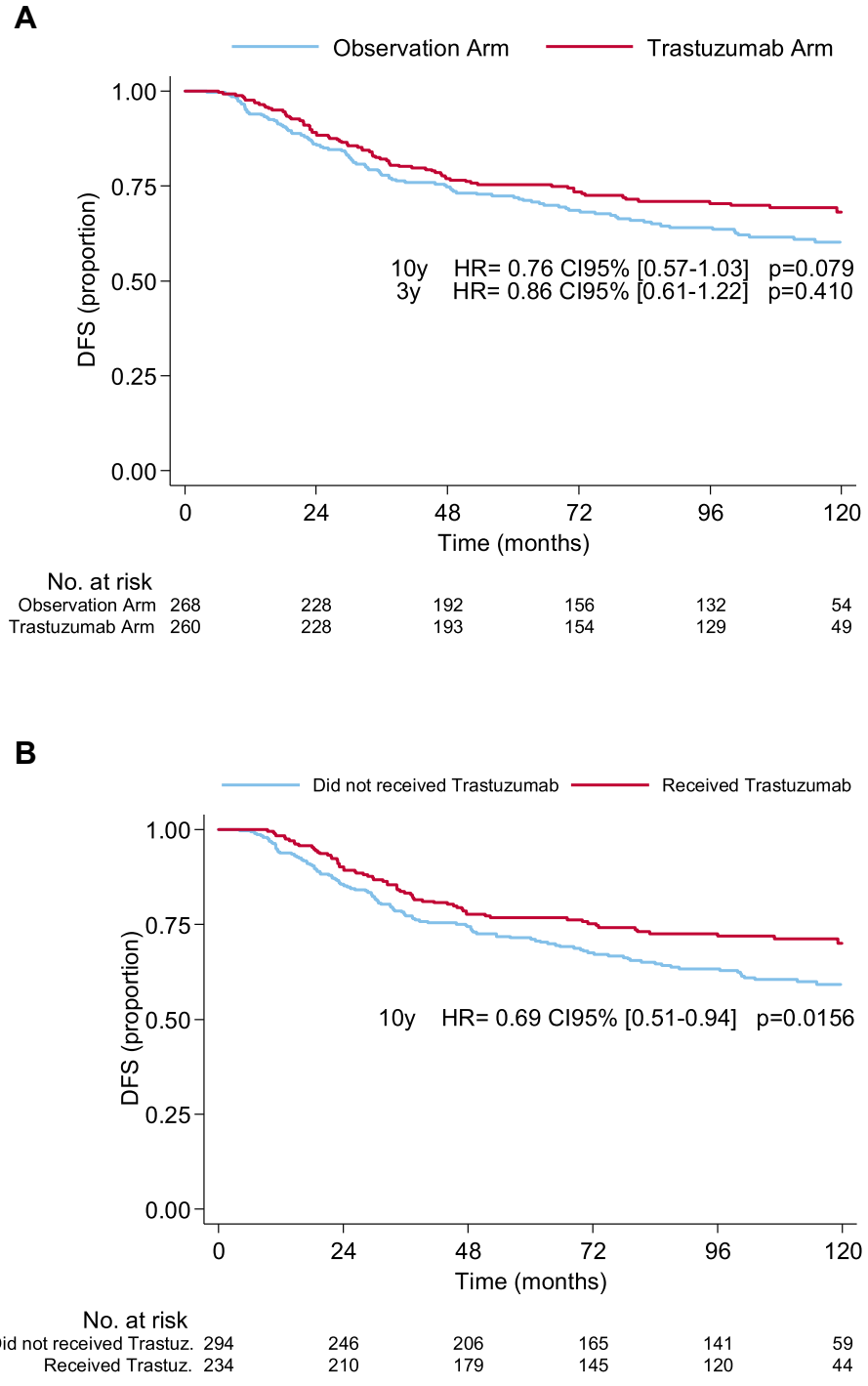

Fig. 4. Kaplan-Meier estimates of 10-year DFS in the HER2 population according to the ITT population (4A) and per-protocol population (4B). DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intention-to-treat.

taxane have clearly become standard, allowing an optimal dose intensity of anthracycline and of taxane (100 mg/m^2 of docetaxel every 3 weeks or 80 mg/m^2 of paclitaxel weekly) with acceptable toxicity [8,9]. In this regard, it is striking that the sequential administration of 3 cycles of FEC followed by 3 cycles of 100 mg/m^2 of docetaxel was superior to 6 cycles of FEC in our previous PACS 01 trial [10].

The strength of the PACS 04 trial is the large population, the long-term follow-up allowing 9.5 years efficacy and safety analyses.

The toxicity profile during chemotherapy, in both arms, was similar to that previously reported by others [7,11,12] with certain distinctions: the rate of febrile neutropenia was higher than that in previously reported studies and appeared especially high in the ED arm

Table 3
Chemotherapy-related adverse events (during chemotherapy and the following 2 months).

AE	6 FEC (n = 1509)	6 ED (n = 1480)	p
Haematologic gr III–IV (%)			
Anaemia	2.9	1.5	0.01
Thrombocytopenia	1.7	0.3	<0.001
Febrile neutropenia	10.7	31.5	<0.001
G-CSF (%)	31.0	43.2	<0.001
Gastrointestinal gr III–IV (%)			
Nausea vomiting	13.6	7.6	<0.001
Mucositis	3.2	3.3	0.85
Diarrhoea	0.5	2.8	<0.001
Neurotoxicity gr II–IV (%)	1.0	4.0	<0.001
Cardiac (n)			
LVEF<50%	35	34	
Arrhythmia gr III–IV	2	1	
LVEF gr III–IV	4	2	
Death	0	1[a]	
Toxic deaths (non-cardiac) (n)	1[b]	4[c]	

Abbreviations: AE, adverse event; gr, grade; LVEF, left ventricular ejection fraction; FEC, 500 mg/m^2 of fluorouracil, 100 mg/m^2 of epirubicin and 500 mg/m^2 of cyclophosphamide; ED, 75 mg/m^2 of epirubicin and 75 mg/m^2 of docetaxel; G-CSF, Granulocyte-Colony Stimulating Factor.
[a] Congestive heart failure.
[b] Pneumonia.
[c] One septic shock, 1 mesenteric infarction, 1 pulmonary embolism, 1 sudden death.

(32%), but patients did not receive primary Granulocyte-Colony Stimulating Factor (G-CSF) prophylaxis. This high rate of febrile neutropenia emphasises the need for primary prophylactic administration of G-CSF for concomitant anthracycline and taxane combination. The lower rate of peripheral neuropathy than that of other taxanes studies is related to the used WHO scale for evaluation of toxicities, which explains an apparent underestimation of peripheral neuropathy, as previously described in the literature [13].

Long-term cardiac toxicity was rare. This low long-term rate of cardiac toxicity seems contradictory with the high level of short-term cardiac toxicity in the trastuzumab subpopulation, previously reported [3]. This contradiction might, at least partly, be explained by very stringent rules for trastuzumab interruption in the PACS 04 study. Among the 41 patients who stopped trastuzumab for cardiac reason, only 6 had an LVEF <45% and 11 had an LVEF between 45% and 49%. Among the patients who stopped trastuzumab for cardiac toxicity, 59% would even not temporarily interrupt trastuzumab with the current cardiac monitoring rules.

Our observed rate of second primary non-breast cancer is similar to what has been reported by others [5]. The rate of haematologic malignancies is similar to that reported, among breast cancer survivors, in two recent analyses, based on a US cohort from the Surveillance, Epidemiology, and End Results (SEER) program [14] and on a French cohort from the French National Health Data System [15].

The 18% of patients from the PACS 04 study who had an HER2-positive disease were proposed randomisation for one-year sequential trastuzumab. Although we initially reported a lack of benefit of trastuzumab at 47-month follow-up, this long-term analysis demonstrates an improved DFS in the per-protocol population, together with a major trend for a benefit in the ITT population. OS was not different in either analysis.

There are several potential explanations for the lower effect of adjuvant trastuzumab in PACS 04 than in the other phase III adjuvant trials.

First, this sub-study lacked power to demonstrate a major benefit of trastuzumab, but its results are finally in line with those of the other such trials [16–20], as demonstrated by recent pooled analyses [21]. Furthermore, women with HER2-positive tumour were randomised for trastuzumab versus observation as soon as the HER2 status was known, at the beginning of chemotherapy. All of these patients were therefore randomised a long time before really initiating their trastuzumab therapy. This early randomisation explains the loss of patients due to low compliance, cardiac toxicity or early relapse. For this reason, the per-protocol analysis seemed more accurate than the ITT analysis. Moreover, 15% of patients received less than 6-month trastuzumab mainly because of cardiac events (again with very stringent stopping rules for trastuzumab). Most of these patients (60%) had received FEC chemotherapy.

Finally, concomitant administration of trastuzumab, starting with sequential taxane, is probably associated with a greater benefit of this drug [22]. Concurrent administration of trastuzumab was not possible in the PACS 04 study because of the FEC arm and an expected high rate of cardiotoxicity when combining anthracycline and trastuzumab.

Generally speaking, a limitation of PACS 04 study, as well as several first-generation taxane studies, is the selection of patients according to the lymph node status and not tumour biology. At the era of personalised medicine, more recent studies are dedicated to biological subtypes with different prognoses and different sensitivity to treatments. New strategies such as selection of patients after neoadjuvant treatment allow further progress of the adjuvant treatment. Still long-term information from older trials, with the methodological flaws of their time, remains important because those drugs are part of the backbone of the current adjuvant treatment. It remains important to know their strengths and limits and to keep the lessons we have learnt from these.

Role of funding sources

UNICANCER sponsored the study and collected the data and, along with the authors, analysed and

interpreted the data and managed the writing of the manuscript. The Ligue Nationale Contre le Cancer and Roche provided financial support for this study but had no role in study design, data collection, data analysis, data interpretation or writing of the report. The coordinating investigators had access to all study data and decided to submit this article for publication.

Conflict of interest statement

N.D. has led a research project funded by Roche, Novartis and Lilly. H.R. has received honoraria from Nanostring SAS, has been a consultant/advisor for Sandoz and has had travelling, accommodation and other expenses paid for by Roche and Amgen. The other authors have stated that they have no conflict of interest.

Acknowledgements

The authors thank the patients, Roche and the Ligue Nationale Contre le Cancer.

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