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Overall survival benefit for sequential doxorubicin–docetaxel compared with concurrent doxorubicin and docetaxel in node-positive breast cancer—8-year results of the Breast International Group 02-98 phase III trial†

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Background: In women with node-positive breast cancer, the Breast International Group (BIG) 02-98 tested the incorporation of docetaxel (Taxotere) into doxorubicin (Adriamycin)-based chemotherapy, and compared sequential and concurrent docetaxel. At 5 years, there was a trend for improved disease-free survival (DFS) with docetaxel. We present results at 8-year median follow-up and exploratory analyses within biologically defined subtypes.
Methods: Patients were randomly assigned to one of four treatments: (i) sequential control: doxorubicin (A) (75 mg/m^2) × 4 →classical cyclophosphamide, methotrexate, 5-fluorouracil (CMF); (ii) concurrent control: doxorubicin, cyclophosphamide (AC)(60/600 mg/m^2) × 4 →CMF; (iii) sequential docetaxel: A (75 mg/m^2) × 3 → docetaxel (T) (100 mg/m^2) × 3 → CMF and (iv) concurrent docetaxel: AT(50/75 mg/m^2) × 4 →CMF. The primary comparison evaluated docetaxel efficacy regardless of the schedule. Exploratory analyses were undertaken within biologically defined subtypes.
Results: Two thousand eight hundred and eighty-seven patients were enrolled. After 93.4 months of median follow-up, there were 916 DFS events. For the primary comparison, there was no significant improvement in DFS from docetaxel [hazard ratio (HR) = 0.91, 95% confidence interval (CI) = 0.80–1.05, $P = 0.187$]. In secondary comparisons, sequential docetaxel significantly improved DFS compared with sequential control (HR = 0.81, 95% CI = 0.67–0.99, $P = 0.036$), and significantly improved DFS (HR = 0.84, 95% CI = 0.72–0.99, $P = 0.035$) and overall survival (OS) (HR = 0.79, 95% CI = 0.65–0.98, $P = 0.028$) compared with concurrent doxorubicin–docetaxel. Luminal-A disease had the best prognosis. HRs favored addition of sequential docetaxel in all subtypes, except luminal-A; but this observation was not statistically supported because of limited numbers.

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Conclusion: With further follow-up, the sequential docetaxel schedule resulted in significantly better OS than concurrent doxorubicin–docetaxel, and continued to show better DFS than sequential doxorubicin-based control.
Key words: adjuvant, breast cancer, chemotherapy, docetaxel, doxorubicin, sequential

introduction

In early breast cancer, the role of adjuvant systemic chemotherapy for reducing recurrence and death is well established. The pivotal chemotherapy trials of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) showed long-term benefit in disease-free survival (DFS) and overall survival (OS) in node-positive and node-negative diseases [1]. Subsequently, some anthracycline-based regimens showed superiority to CMF [2,3]. In the late 1990s, docetaxel (Taxotere) showed superior efficacy over doxorubicin in metastatic disease [4], but its activity and optimal scheduling in early breast cancer were unclear. Many trials were undertaken to define the adjuvant role of taxanes. In 1998, the Breast International Group (BIG) launched the phase III, randomized trial 02-98 for women with node-positive early breast cancer to test novel incorporation of 3-weekly docetaxel into doxorubicin-based control, and to compare docetaxel given sequentially or concurrently with doxorubicin.

In 2006 after 5-year median follow-up and 732 events, the first BIG 02-98 efficacy results were reported [5]. Docetaxel incorporation improved DFS with borderline statistical significance compared with doxorubicin-based control [hazard ratio (HR) = 0.86, 95% confidence interval (CI) = 0.74–1.00; $P = 0.051$]. Superior DFS was suggested by sequential docetaxel compared with concurrent docetaxel–doxorubicin (HR = 0.83, 95% CI = 0.69–1.00), and compared with sequential doxorubicin-based control (HR = 0.79, 95% CI = 0.64–0.98).

Since the 1990s, understanding of breast cancer has been revolutionized by demonstration of heterogeneity in biology and treatment response [6], with a shift in risk assessment and treatment decisions away from staging alone towards the assessment of disease biology and estimation of tumor responsiveness. Molecular heterogeneity of tumors in the BIG 02-98 population, which was selected by node-positivity rather than biological features, makes interpretation and clinical application of results difficult for individual patients.

We present results at 8-year median follow-up and an unplanned, retrospective, exploratory analysis of efficacy within central laboratory determined biological subtypes.

patients and methods

study population

BIG 02-98 methodology has been reported by Francis et al. [5]. In brief, BIG 02-98 was a multicenter, prospective, non-blinded, randomized phase III adjuvant trial in women aged 18–70 years with clinical stage T1–3 breast cancer. Women had definitive surgical treatment (mastectomy or breast-conserving surgery) for invasive breast adenocarcinoma with ≥1 positive axillary lymph nodes of ≥8 resected nodes. The exclusion criteria included metastatic breast cancer and major co-morbidities. Institutional Ethics Committees at all participating sites approved the study. All patients provided written informed consent.

Estrogen receptor (ER) and progesterone receptor (PgR) were assessed locally. The human epidermal growth factor receptor 2 (HER2) status was not tested as it was not routine practice during trial recruitment. A primary tumor sample (blocks or slides) was required for a central pathology review.

study design and randomization

Patients were stratified by center, number of positive nodes (1–3 versus ≥4) and age (<50 versus ≥50 years). In a 2 × 2 trial design, the patients were randomly assigned to one of four treatments in an unbalanced 1:1:2:2 ratio. Arm A (sequential control): doxorubicin (A) 75 mg/m^2 × 4 every 3 weeks → classical CMF × 3; Arm doxorubicin, cyclophosphamide (AC) (concurrent control): AC 60/600 mg/m^2 × 4 every 3 weeks → CMF × 3; Arm A-T (sequential docetaxel, Taxotere): A 75 mg/m^2 × 3 every 3 weeks → docetaxel (T) 100 mg/m^2 × 3 every 3 weeks → CMF × 3; Arm AT (concurrent docetaxel): AT 50/75 mg/m^2 × 4 every 3 weeks → CMF × 3. The cumulative doxorubicin (Adriamycin) dose was higher in the control (A:300 mg/m^2; AC:240 mg/m^2) than the docetaxel arms (A-T:225 mg/m^2; AT:200 mg/m^2). A-T and AT had different docetaxel dose intensities but the same cumulative dose (300 mg/m^2). Chemotherapy duration was 30 weeks for A-T and 24 weeks for the other arms.

Five years of tamoxifen were indicated following chemotherapy for ER and/or PgR-positive disease, based on the local ER/PgR results. A protocol amendment in 2004 allowed aromatase inhibitors in postmenopausal women and ovarian suppression in premenopausal women. Adjuvant trastuzumab was not available at that time. Radiotherapy was indicated in all women treated with breast-conserving surgery and in some women post mastectomy according to the local guidelines.

transtax—biological subtypes

Primary tumor samples were stored centrally at Jules Bordet Institute, Brussels. Slide review, immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) were carried out on whole tissue sections from formalin-fixed paraffin-embedded (FFPE) samples centrally at the European Institute of Oncology, Milan, Italy. Tumor grade was centrally reviewed. Tumor specimens were stained for ER, PgR, HER2, Ki-67, EGFR, CK5/6 and CK14 [all the specific monoclonal or polyclonal (for HER2) antibodies were purchased from Dako, Glostrup, Denmark]. Immunohistochemical results were reported as percentage of invasive tumor cells showing definite immunoreactivity. FISH was carried out for HER2 according to the manufacturer's instructions (Vysis-Abbott).

Positivity thresholds were ER ≥ 1%; PgR ≥ 1%; HER2 = 3+ (>10% invasive tumor cells with intense and circumferential membrane staining) and/or FISH positive (*HER2*:CEP17 ratio ≥ 2); EGFR ≥ 1%; CK5/6 ≥ 1% and CK14 ≥ 1%. The Ki-67 threshold—high ≥14%—was based on work by Cheang et al. [7], in which 14% best discriminated between luminal-A and B tumors.

Biological subtypes were defined using central laboratory determined parameters. Four subtypes were defined: (i) luminal-A (highly endocrine responsive): ER positive, PgR positive, HER2 negative and Ki-67 low (if Ki-67 was missing, grade 1 was considered surrogate for low Ki-67; grade 2 cases were considered unassessable. The few ER-negative/PgR-positive cases were considered ER-positive/PgR-positive); (ii) luminal-B (moderately endocrine responsive): ER positive and PgR negative, independent of other parameters, or ER positive, PgR positive and at least

one of grade 3, HER2 positive and/or Ki-67 high; (3) HER2 positive: ER negative, PgR negative and HER2 positive and (iv) Triple negative: ER negative, PgR negative and HER2 negative. Triple-negative tumors were subdivided by basal-like marker expression: (iva) basal-like: positive for at least one of EGFR, CK5/6 and/or CK14; (ivb) Non-basal-like: negative for EGFR, CK5/6 and CK14.

statistical considerations

The primary study aim was to evaluate the efficacy of docetaxel regardless of the schedule, with DFS as primary end point. The primary comparison was docetaxel (A-T + AT) versus control (A + AC). Secondary comparisons were DFS between sequential arms (A-T versus A), concurrent arms (AT versus AC) and docetaxel arms (A-T versus AT), and OS among treatment arms. All randomly assigned patients were included in the intention-to-treat analysis.

DFS was defined as the interval from the date of randomization to the date of local, regional or metastatic relapse or second primary cancer or death for any cause. OS was calculated from the date of randomization to last follow-up or death from any cause. Statistics were carried out using SAS 9.1 and Minitab software. The Kaplan–Meier product-limit method was used to estimate DFS and OS, and the stratified log-rank test was used to compare DFS and OS among the treatment groups. HRs were calculated using a Cox model.

The primary efficacy analysis was planned for 5-year median follow-up, provided that 1215 events had occurred. A first interim-analysis by the independent data monitoring committee (IDMC) after 395 events supported study continuation. The study was subsequently amended by the steering committee in consultation with the IDMC when it became evident that the actual DFS event rate was much lower than anticipated: the primary analysis was replanned for 5-year median follow-up or 810 events. Descriptive analyses were planned after 8-year (1215 events) and 10-year median follow-up.

The primary aim of the exploratory Transtax substudy was to compare sequential docetaxel with doxorubicin-based controls within biologically defined tumor subtypes. The hypotheses were that (i) sequential docetaxel would be better than control in all subtypes, except luminal-A which is highly hormone sensitive; (ii) concurrent control would be better than sequential control in the triple-negative basal-like subset due to higher doses of DNA-damaging cyclophosphamide coupled with DNA repair dysfunction. Survival curves were estimated using the Kaplan–Meier method, and the curves for different classifications were compared using the log-rank test. Multivariate Cox regression models, with backward selection, were used to test the prognostic effect of subtypes after adjusting for other important prognostic variables. Comparisons were made relative to the largest subtype, luminal-B.

trial sponsors and funding

BIG 02-98 was conducted by BIG, with sponsorship and funding by sanofi-aventis. Transtax analyses were funded by Associazione Italiana Ricerca Cancro (AIRC), Milan, Italy. The coordinating group was the Breast European Adjuvant Studies Team with collaboration of eight BIG co-operative groups. Statistical analyses were carried out independently by the International Drug Development Institute.

results

efficacy analysis

Between June 1998 and June 2001, 2887 patients from 173 centers in 21 countries were enrolled. Patient characteristics are summarized in Table 1 and were well balanced between the treatment arms. Intervention and follow-up are summarized in Supplementary Table S1, available at *Annals of Oncology* online. In May 2009, the median follow-up was 93.4 months with 916 DFS events and 566 deaths. The actual event rate was lower than anticipated.

For the primary analysis (A-T + AT versus A + AC), addition of docetaxel did not improve DFS (HR = 0.91, 95% CI = 0.80–1.05, $P = 0.187$) or OS (HR = 0.91, 95% CI = 0.77–1.08, $P = 0.28$). For secondary end points, sequential docetaxel (A-T) improved DFS compared with sequential control (A) (HR = 0.81, 95% CI = 0.67–0.99, $P = 0.036$). Sequential docetaxel (A-T) was superior to concurrent docetaxel (AT), for both DFS (HR = 0.84, 95% CI = 0.72–0.99, $P = 0.035$) and OS (HR = 0.79, 95% CI = 0.65–0.98, $P = 0.028$), see Table 2 and Figure 1.

exploratory biological subtype analysis

FFPE primary tumors were provided by 2172 patients (75%). Central laboratory reassessment and categorization by IHC-defined biological subtypes were possible in 1777 patients (62%). The remaining 395 patients had inadequate tissue quantity and/or quality.

The substudy patients were representative of the entire population with no substantial differences in patient and tumor characteristics, or DFS and OS, compared with patients not included (data not shown). Patients per tumor subtype: luminal-A $N = 294$ (17%); luminal-B $N = 1034$(58%); HER2 positive $N = 149$ (8%) and triple negative $N = 300$ (17%). Of luminal-B tumors, 181 of 1034 (18%) were positive for HER2. Within triple-negative disease, 146 of 300 (49%) were basal-like and 42 (14%) were non-basal-like. The remaining 112 (37%) triple-negative tumors had inadequate tissue for EGFR, CK5/6 and/or CK14 determination. Patient characteristics according to subtype are summarized in Table 3.

Subtypes were prognostic for DFS (see Figure 2). DFS was most favorable for luminal-A, and least favorable for triple negative and HER2 positive. HR derived from pairwise comparison with luminal-B revealed HR = 0.66 (95% CI = 0.50–0.86, $P = 0.0018$) for luminal-A, HR = 1.75 (95% CI = 1.35–2.28, $P < 0.0001$) for HER2 positive and HR = 1.37 (95% CI = 1.11–1.69, $P = 0.0039$) for triple negative.

In the luminal-B subdivision, the 8-year DFS rates were 68.0% for luminal-B HER2 negative and were 58.5% for luminal-B HER2 positive. In the triple-negative subdivision, the 8-year DFS rates were 62.5% for basal-like and 47.1% for non-basal-like.

A multivariate DFS analysis included the following variables: age (<50 versus ≥50 years), body mass index (<30 versus ≥30), menopausal status, histopathological type, tumor size, grade, number of positive nodes (1–3 versus ≥4), mastectomy, chemotherapy (sequential versus concurrent), treatment (A + AC versus A-T + AT), radiotherapy, hormonotherapy usage and subtype (with comparison to luminal-B). After adjustment of statistically significant prognostic factors, luminal-A maintained a significantly better prognosis (HR = 0.74, 95% CI = 0.57–0.97, $P = 0.03$).

The substudy patients showed a trend favoring sequential docetaxel over control therapy for improved DFS (HR = 0.80,

Table 1. BIG 02-98: patient and tumor characteristics

	Total, $N = 2887$ %	Treatment arm			
		A ($N = 481$) %	AC ($N = 487$) %	A-T ($N = 960$) %	AT ($N = 959$) %
Age (years)					
Median	49 (range 21–0)	50	49	49	49
<35	7	6	8	6	7
35–49	47	46	47	47	46
50–65	43	43	43	43	42
>65	4	4	3	4	5
Menopausal status					
Premenopausal	54	53	54	53	55
Postmenopausal	41	41	40	42	40
missing	6	5	6	6	5
Tumor size (mm)					
<20	40	40	36	40	41
≥20	60	60	63	59	59
Histopathology					
Infiltrating ductal	80	81	83	83	81
Infiltrating lobular	13	13	10	11	13
Other	7	5	7	6	6
Number of positive nodes					
1–3	54	54	55	54	54
≥4	46	46	45	46	46
ER/PgR status (defined locally)					
ER+/PgR+	51	50	51	52	51
ER+/PgR−	12	12	11	11	13
ER−/PgR−	24	24	25	24	23
other	13	14	13	13	13
Hormonotherapy					
Received	74	71	74	74	75

A: sequential control = doxorubicin(A) 75 mg/m^2 × 4 → classical cyclophosphamide, methotrexate, 5-fluorouracil (CMF); AC: concurrent control = AC 60/600 mg/m^2 × 4 → CMF; A-T: sequential docetaxel = A 75 mg/m^2 × 3 → docetaxel(T) 100 mg/m^2 × 3 → CMF; AT: concurrent docetaxel = AT 50/75 mg/m^2 × 4 → CMF.

Table 2. BIG 02-98: DFS and OS

Comparison	DFS hazard ratio (HR; 95% CI)	*P* value	OS hazard ratio (95% CI)	*P* value
Primary comparison				
A-T + AT versus A + AC	0.91 [0.80–1.05]	0.187	0.91 [0.77–1.08]	0.28
Secondary comparison				
A-T versus A	0.81 [0.67–0.99]	0.036	0.86 [0.67–1.11]	0.24
AT versus AC	1.02 [0.84–1.23]	0.85	0.96 [0.76–1.21]	0.71
Secondary comparison				
A-T versus AT	0.84 [0.72–0.99]	0.035	0.79 [0.65–0.98]	0.028

A: sequential control = doxorubicin (A) 75 mg/m^2 × 4 → classical cyclophosphamide, methotrexate, 5-fluorouracil (CMF); AC: concurrent control = AC 60/600 mg/m^2 × 4 → CMF; A-T: sequential docetaxel = A 75mg/m^2 × 3 → docetaxel (T) 100 mg/m^2 × 3 → CMF; AT: concurrent docetaxel = AT 50/75mg/m^2 × 4 → CMF; CI: confidence interval; DFS: disease-free survival; OS: overall survival.

95% CI = 0.65–1.00). The HR favored docetaxel in all subtypes, except luminal-A, as expected. The test for heterogeneity, however, failed to reach statistical significance ($P = 0.38$) (see Figure 3A).

In triple-negative basal-like and non-basal-like subsets, concurrent control (higher cyclophosphamide dosing) was compared with sequential control. In both the groups, the HR favored concurrent AC, as expected. However, patient numbers were quite small, particularly for non-basal-like (see Figure 3B).

discussion

With 8-year follow-up in BIG 02-98, the incorporation of docetaxel regardless of the schedule showed no significant

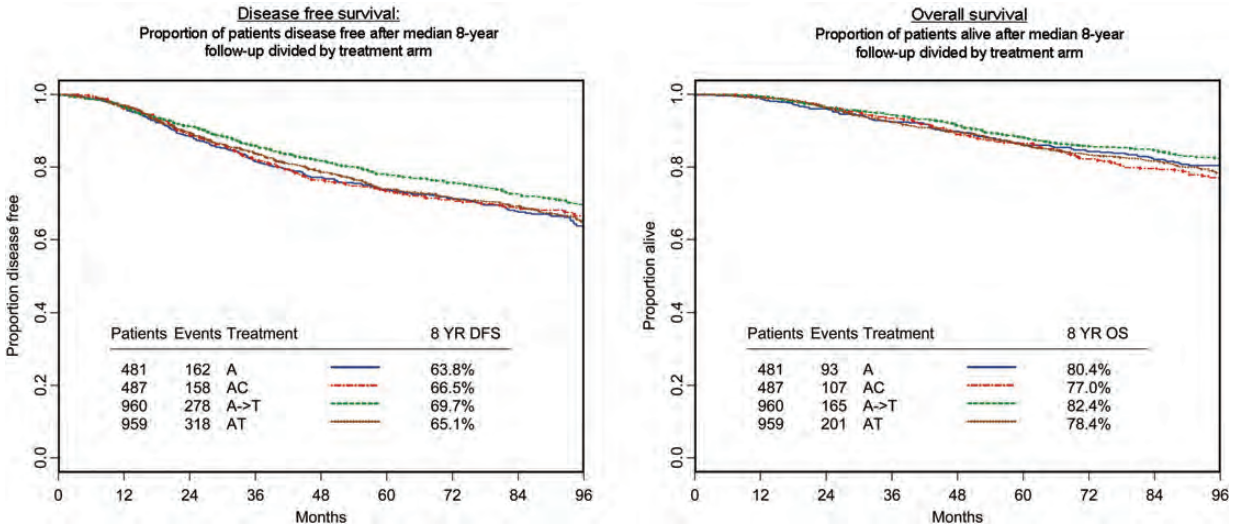

Figure 1. Disease-free survival (DFS) and overall survival (OS) at 8-year median follow-up divided by the treatment arm (Kaplan–Meier plots). (A) DFS; (B) OS. A: doxorubicin (A) → cyclophosphamide, methotrexate, 5-fluorouracil (CMF). AC: AC → CMF. A-T: A → docetaxel (T) → CMF. AT: AT → CMF.

difference in DFS compared with doxorubicin-based control in women with node-positive early breast cancer.

Sequential doxorubicin–docetaxel–CMF resulted in significant improvement in outcomes: better DFS than sequential doxorubicin–CMF (absolute improvement 5.9%, $P = 0.036$), and better DFS and OS than concurrent doxorubicin–docetaxel before CMF (absolute improvement DFS 4.6%, $P = 0.035$; OS 4.0%, $P = 0.028$). With longer follow-up and more deaths, the OS benefit suggested at 5 years now reaches nominal statistical significance.

Benefit from sequential but not concurrent docetaxel may be attributable to a higher docetaxel dose intensity (100 versus 75 mg/m^2), higher doxorubicin dose intensity (60 versus 50 mg/m^2) and longer treatment duration (30 versus 24 weeks). Concurrent docetaxel–doxorubicin requires dose reductions for feasibility which, in the absence of synergy, may compromise efficacy. Sequential therapy superiority is in keeping with the Norton–Simon hypothesis, which relates cytotoxic effects on the tumor size to tumor growth dynamics [8]. As a tumor shrinks, the regrowth rate increases, such that the chemotherapy level capable of initiating regression may be insufficient to maintain regression and produce cure. The slowing regression rate may be overcome by switching to alternative cytotoxics, which may also kill clones resistant to the initial drug(s) [8]. Intratumoral polyclonality may necessitate multiple drugs for micrometastatic disease eradication; not, however, at the expense of dose intensity as was required for concurrent docetaxel–doxorubicin.

In early breast cancer, addition of taxanes to anthracycline-based therapy has been tested in many clinical trials, with conflicting results [9–19]. Two meta-analyses have examined adjuvant taxanes in over 20 000 women [20,21]. De Laurentiis et al. [20] reported DFS benefit from taxane addition, independent of taxane type, ER status and nodal status. Laporte et al. [21] in an analysis restricted to docetaxel reported DFS and OS benefits in node-positive, but not node-negative disease. The meta-analyses have limitations and the results cannot be considered conclusive. A recently published meta-analysis by the Early Breast Cancer Trialists' Collaborative Group concluded that breast cancer mortality was reduced in randomized trials in which the addition of a taxane extended the duration of chemotherapy compared with the anthracycline-based control, while no significant difference in breast cancer mortality was observed in trials with taxane and control regimens of similar durations [22].

A consensus from available data is impeded by substantial heterogeneity in trial designs, use of paclitaxel (Taxol) or docetaxel, taxane doses, sequential or concurrent taxane administration, control therapy and follow-up duration. The extent to which docetaxel and paclitaxel results are interchangeable is unknown. Specifically for docetaxel, there is consensus for superiority of 3-weekly over weekly dosing [23], and dose-dependent activity [24]. However, debate persists regarding sequential or concurrent administration, and optimal partner drugs (see Supplement Table S2, available at *Annals of Oncology* online).

The absolute benefit in BIG 02-98 from sequential docetaxel compared with no docetaxel after 8-year follow-up is in keeping with 8-year results of PACS01. Compared with fluorouracil, epirubicin and cyclophosphamide (FEC)100, sequential FEC–docetaxel improved absolute DFS by 4.4% ($P = 0.035$) and OS by 5.2% ($P = 0.024$) [25]. Similarly, in TAXit216 addition of sequential docetaxel to E-CMF improved relapse-free survival (HR = 0.75, 95% CI = 0.59–0.96, $P = 0.039$) and OS (HR = 0.67, 95% CI = 0.48–0.94, $P = 0.017$) [26]. In contrast, the TACT trial reported no benefit but more toxicity from sequential FEC60-docetaxel compared with anthracycline-based control (HR = 0.95, 95% CI = 0.85–1.08. $P = 0.44$) [17], and preliminary ADEBAR results showed no difference between FEC120 and sequential EC-docetaxel (HR = 0.88, 95% CI: 0.69–1.11) [19].

No benefit was seen in BIG 02-98 for concurrent docetaxel over control. This is similar to PACS04 which compared ET and FEC100 [18], and E2197 which compared AT and AC [16]. In contrast, TAC (docetaxel, doxorubicin, cyclophosphamide) was superior to FAC (fluorouracil, doxorubicin, cyclophosphamide)

Table 3. BIG 02-98 exploratory biological subtype analysis: patient and tumor characteristics

	Total ($N = 1,777$) %	Luminal-A ($N = 294$) %	Luminal-B ($N = 1034$) %	HER2 positive ($N = 149$) %	Triple negative ($N = 300$) %
Age					
Median	49	51	49	50	49
Range	20–69	25–69	20–69	24–69	22–69
<35	7	4	7	9	9
35–49	46	43	48	12	45
50–65	43	49	41	46	43
>65	4	4	5	3	4
Menopausal status					
Premenopausal	53	47	55	47	54
Postmenopausal	42	45	41	49	42
missing	5	8	4	4	4
Tumor size (mm)					
<20	37	44	37	35	33
≥20	63	56	63	65	67
Histopathology					
Infiltrating ductal	83	70	83	93	90
Infiltrating lobular	11	23	11	1	4
Other	6	7	6	6	6
Number of positive nodes					
1–3	53	61	52	44	55
≥4	47	39	48	56	45
Grade[a]					
1	8	34	3	1	1
2	40	61	46	9	14
3	52	4	50	90	85
ER/PR status[a]					
ER+/PR+	66	99	85	0	0
ER+/PR−	9	1	15	0	0
ER−/PR−	25	0	0	100	100
other	1	1	0	0	0
HER2 positive[a]					
HER2 positive	19	0	18	100	0
Ki-67[a]					
High	80	0	97	98	96
Low	20	100	3	2	4
Hormonotherapy					
Received	72	94	90	18	16

[a]Central laboratory defined tumor features.

for DFS and OS in node-positive disease in BCIRG001 [12], and for DFS in high-risk node-negative disease in GEICAM 9805 [13], and TC (docetaxel, cyclophosphamide) was superior to AC for DFS and OS in USO 9735 [14].

Superiority of sequential docetaxel over concurrent docetaxel in BIG 02-98 concords with NSABP-B30, in which sequential AC × 4 followed by docetaxel × 4 improved DFS and OS compared with AT × 4 (DFS: HR = 0.80; $P = 0.001$; OS: HR = 0.83; $P = 0.03$), and improved DFS compared with concurrent TAC × 4 (DFS: HR = 0.83, $P = 0.01$) [27]. Like BIG 02-98, NSABP-B30 had substantial interarm differences in docetaxel and doxorubicin doses, and treatment duration. In contrast to BIG 02-98 and NSABP-B30, BCIRG005 showed TAC to be as effective as sequential AC-docetaxel [28], but higher cumulative doxorubicin and docetaxel doses in TAC pose increased risk for late toxicity. Ten-year follow-up of TAC-treated patients in BCIRG001 showed important cardiotoxicity [29].

In 1998 when BIG 02-98 commenced, CMF was a standard therapy, adjuvant trastuzumab for HER2-positive disease was not an option and molecular subtyping into biological subtypes beyond hormone receptor status was not a consideration. Disparities between 1998 and 2012 are testament to the progress made in diagnostics and therapy. However, how are the BIG 02-98 results applicable in current practice? In HER2-positive disease, HER2-targeted therapy plus chemotherapy is indicated and the current trial results are redundant. In HER2-negative disease, exploratory retrospective analysis by biological subtypes may identify subgroups likely to obtain the benefit observed in the biologically unselected trial population. Subtype-specific molecular events may impart taxane sensitivity.

The current biological subtype analysis was enabled by prospective tumor tissue collection and was strengthened by a central pathology review using current methods and thresholds. The prevalence of the HER2-positive subtype seems low (149/1777, 8%); however, HER2-positive tumors ($N = 330/1777$, 19%) were subtype classified as HER2 positive ($N = 149/149$) or luminal-B ($N = 181/1034$), depending on the ER status. The prevalence of subtypes was similar to BCIRG001 [30]. Both the studies used similar thresholds, including Ki-67 ≥14% in the distinction between luminal-A and B. The low prevalence of luminal-A tumors might, in part, be explained by investigators not proposing the trial for patients with low risk, good prognosis tumors. The prevalence of luminal-B was high (BIG 02-98: 58%; BCIRG001: 61%) compared with other analyses using similar parameters: among all BIG 02-98 luminal subtype patients, 78% were luminal-B (including luminal HER2-positive) compared with 41% in the pivotal validation series by Cheang et al. [7]. Higher rates of luminal-B disease may in part be a cohort selection-bias based on the nodal status (node-positive: BIG 02-98 and BCIRG001:100%; Cheang et al.: 42%). Furthermore, the validation assessed tissue microarray, while BIG 02-98 and BCIRG001 assessed whole sections. Ki-67 may be lower in tissue microarrays compared with whole sections due to non-homogenous intratumoral expression [31].

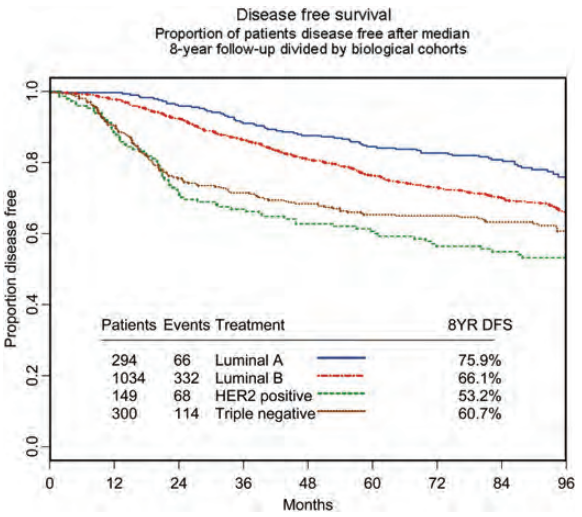

Figure 2. Prognostic evaluation of molecular subtypes: disease-free survival (DFS) analysis (Kaplan–Meier plots).

In this article, luminal-A disease had the best DFS and showed no differential chemosensitivity. Lack of taxane benefit in luminal-A is in keeping with exploratory analyses of docetaxel in BCIRG001 [30], and PACS01 [32]. Luminal-A disease, accounting for 35%–40% of all breast cancers, has not been shown in any trial to benefit from taxane addition, or indeed from any chemotherapy above and beyond the benefit of endocrine therapy [33].

HER2-postive and triple-negative subtypes had the worst DFS. In luminal-B, HER2-positive and triple-negative disease, there was no significant difference between treatment arms; however, HRs are in favor of sequential docetaxel. This trend is statistically relevant only in luminal-B patients, possibly because this is numerically the largest group. Subtype analyses from other adjuvant docetaxel trials have been reported. In BCIRG001, ER-negative tumors showed worse outcome, despite showing a better response to TAC over FAC [30]. There was significant DFS benefit from TAC over FAC in luminal-B disease ($P = 0.025$), and a trend in triple-negative and HER2-positive diseases. In PACS 01, the greatest docetaxel benefit was in the basal-like subtype [32]. GEICAM 9805 suggested greatest DFS benefit from docetaxel in HER2-negative patients, regardless of the hormone receptor status [13]. In TACT, the subgroup of patients with ER-negative, HER2-positive, node-

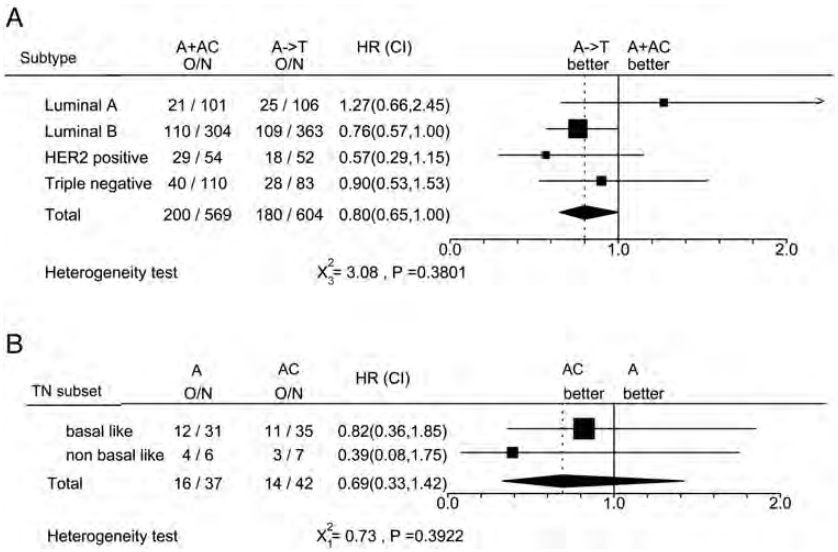

Figure 3. DFS analysis: predictive evaluation of molecular subtypes: (A). Predictive value of breast cancer subtypes comparing combined control arms (A + AC) with the sequential docetaxel arm (A-T). (B). Predictive value of basal-like and non-basal-like triple-negative subsets comparing concurrent control (AC) with the sequential control arm (A). A: doxorubicin (A) → cyclophosphamide, methotrexate, 5-fluorouracil (CMF); AC: AC → CMF; A ->T: A → docetaxel → CMF; CI: confidence interval; HR: Hazard ratio; N: number of patients exposed to the risk; O: number of observed events.

positive tumors benefited from the addition of docetaxel [17] (see Supplement Table S3, available at *Annals of Oncology* online).

It was hypothesized that the concurrent control therapy would be more active than the sequential control therapy in the triple-negative basal-like subset due to higher dosing of DNA damaging cyclophosphamide coupled with DNA repair dysfunction. Limited patient numbers in these cohorts prevent robust conclusions; however the HRs favor concurrent AC in both the groups.

In summary, with 8-year median follow-up, the incorporation of sequential docetaxel showed a statistically significant improvement in DFS compared with sequential doxorubicin-based control, and for both DFS and OS compared with concurrent administration of both drugs. Patients classified as luminal-A subtype had the best outlook compared with all other sybtypes, despite no differential chemosensitivity.

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Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making

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Background: As few older women with breast cancer receive adjuvant chemotherapy, we examined the barriers and perceptions of 24 UK NHS multidisciplinary breast cancer teams to offering this treatment to women ≥70 years.
Patients and methods: Questionnaires regarding 803 patients with newly diagnosed breast cancer were completed by specialist teams following discussion or outpatient consultation.
Results: Of 803 patients, 116 (14%), all <85 years, were offered chemotherapy and 66 (8%) received it. Only 94 of 309 (30%) of women with high-risk disease were offered chemotherapy, and 53 (17%) received it. The most common reasons for not offering chemotherapy were 'other treatments more appropriate' (usually patients with ER-positive tumours) or 'benefits too small' (63% and 54% of patients, respectively). Co-morbidities and frailty were less common reasons but became more frequent with increasing age. Recommendations regarding chemotherapy were made in the absence of documented HER2 and performance status in 29% and 33%, respectively. Treatment offered varied considerably between cancer centres.
Conclusions: National guidelines need development describing the minimally acceptable data for decision making, incorporating objective fitness measures and specific treatment recommendations. Such guidelines will require

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