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Final 10-year results of the Breast International Group 2–98 phase III trial and the role of Ki67 in predicting benefit of adjuvant docetaxel in patients with oestrogen receptor positive breast cancer

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KEYWORDS
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Abstract ***Aim:*** Breast International Group (BIG) 2–98 is a randomised phase III trial that tested the effect of adding docetaxel, either in sequence to or in combination with anthracycline-based adjuvant chemotherapy, in women with node-positive breast cancer (BC). Here, we present the 10-year final trial safety and efficacy analyses. We also report an exploratory analysis on the predictive value of Ki67 for docetaxel efficacy, in the BIG 2–98 and using a pooled analysis of three other randomised trials.

Patients and methods: 2887 patients were randomly assigned in a 2 × 2 trial design to one of four treatments. The primary objective was to evaluate the overall efficacy of docetaxel on disease free survival (DFS). Secondary objectives included comparisons of sequential docetaxel versus sequential control arm, safety and overall survival (OS). Ki67 expression was centrally evaluated by immunohistochemistry.

Results: After a median follow-up of 10.1 years, the addition of docetaxel did not significantly improve DFS or OS (hazard ratio (HR) = 0.91, 95% confidence interval (CI) = 0.81–1.04; $P = 0.16$ and HR = 0.88, 95% CI = 0.76–1.03; $P = 0.11$, respectively). Sequential docetaxel did not improve DFS compared to the sequential control arm (HR = 0.86, 95% CI = 0.72–1.03; $P = 0.10$). In oestrogen receptor (ER)-positive tumours with Ki67 $\geqslant$ 14%, the addition of docetaxel resulted in 5.4% improvement in 10-year OS ($P = 0.03$, test for interaction = 0.1). In a multivariate model, there was a trend for improved DFS and OS in ER-positive patients with high Ki67 and treated with docetaxel (HR = 0.79, 95% CI = 0.63–1.01; $P = 0.05$ and HR = 0.76, 95% CI = 0.57–1.01; $P = 0.06$, respectively). A pooled analysis of four randomised trials showed a benefit of taxanes in highly proliferative ER-positive disease but not in low proliferating tumours (interaction test $P = 0.01$).

Conclusion: The DFS benefit previously demonstrated with sequential docetaxel is no longer observed at 10 years. However, an exploratory analysis suggested a benefit of docetaxel in patients with highly proliferative ER-positive BC.

1. Introduction

By the late 1990s, there was general agreement that the post-operative use of adjuvant anthracycline-containing cytotoxic chemotherapy regimens reduced the mortality of patients with operable breast cancer. The effect was marginal, but important, producing an approximate 5–10% increase in overall survival [1,2].

There was clearly a need to improve on these modest results by optimising the use of existing drugs, and by studying the incorporation of novel agents. Buzzoni, Bonadonna and colleagues reported that a sequential cross-over regimen in which single agent doxorubicin was followed by a phase of treatment with the classic 'CMF' regimen (cyclophosphamide, methotrexate and 5-flourouracil) produced significantly superior results compared to the strictly alternating use of the same drugs in the same doses [3,4]. The description of the prominent activity of the taxanes; paclitaxel and docetaxel, in the treatment of metastatic breast cancer in the 1990s provided a powerful rationale for their study in the adjuvant treatment of earlier stage disease [5–8].

One of the challenges facing investigators designing taxanes adjuvant trials, was devising appropriate control arms. CALGB and NSABP studied the addition of four cycles of paclitaxel to a four cycle anthracycline–cyclophosphamide doublet [9,10] with the addition of the taxane doubling the overall duration of chemotherapy. The Breast Cancer International Research Group studied the substitution of docetaxel for 5-flourouracil in a six-cycle FAC regimen [11]. The Breast International Group (BIG) designed a prospective random assignment phase III trial which studied the addition of docetaxel to a doxorubicin regimen followed by cyclophosphamide/methotrexate/5-flourouracil regimen. In this study, docetaxel was administered either in combination with doxorubicin, or sequenced following it, and control arm patients received a 6-month anthracycline-based chemotherapy regimen. At five years of follow-up we reported that the sequential but not the concurrent inclusion of docetaxel improved disease free survival [11]. We also reported that taxane therapy was generally well-tolerated, but toxicity including myelosuppression and neurotoxicity was seen. These data were included in the EBCTG meta-analysis of random assignment trials of taxanes versus non-taxane containing adjuvant chemotherapy which confirmed a benefit for taxanes, and taxanes have been a standard of care in adjuvant chemotherapy for more than a decade [12]. Less is known concerning the durability of adjuvant taxane benefit, and in this paper we report ten year safety and efficacy data. The BIG 2–98 trial also included a

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translational component (referred to as the TransTAX study), and in this paper we also report the predictive significance of Ki67 expression.

2. Patients and methods

2.1. Patients and study design

BIG 2–98 (ClinicalTrials.gov identifier of BIG 2–98: NCT00174655), is a multicenter, prospective, open labelled, randomised phase III adjuvant trial. Women had definitive surgical treatment (mastectomy or breast-conserving surgery) for invasive breast adenocarcinoma with $\geqslant 1$ positive axillary lymph nodes of $\geqslant 8$ resected nodes. Key exclusion criteria included metastatic breast cancer and other serious illness or medical condition. Institutional ethics committees at all participating sites approved the study. All patients provided written informed consent prior to study entry. Patients were stratified by centre, number of positive nodes (1–3 versus $\geqslant 4$) and age (<50 versus $\geqslant 50$ years). In a 2×2 trial design, the patients were randomly assigned to one of four treatments in a 1:1:2:2 ratio as follows: Arm 1 (sequential control): (A) doxorubicin 75 mg/m^2 $\times$ 4 every 3 weeks $\rightarrow$ classical CMF $\times$ 3; Arm 2 (concurrent control): (AC) doxorubicin, cyclophosphamide 60/600 mg/m^2 $\times$ 4 every 3 weeks $\rightarrow$ CMF $\times$ 3; Arm 3 (sequential docetaxel): (A–T) A 75 mg/m^2 $\times$ 3 every 3 weeks $\rightarrow$ docetaxel (T) 100 mg/m^2 $\times$ 3 every 3 weeks $\rightarrow$ CMF $\times$ 3; Arm 4 (concurrent docetaxel): (AT) AT 50/75 mg/m^2 $\times$ 4 every 3 weeks $\rightarrow$ CMF $\times$ 3.

Five years of tamoxifen were indicated following chemotherapy for patients with ER and/or progesterone receptor (PgR)-positive disease, based on the local hormone receptor results. A protocol amendment in 2004 allowed aromatase inhibitors in postmenopausal women and ovarian suppression in premenopausal women.

Full details and CONSORT diagram were previously reported [11,13].Patients were followed up to 10 years from recruitment of the last patient. During the follow-up period, investigators were required to take history and perform physical examination, and record adverse events. Follow-up visits were every 3 months for the first two years, every 6 months for years 3–5 and then once a year. It was the decision of the treating physician to decide if the adverse events reported during the follow-up period were possibly related to the treatment. No specific cardiac studies were requested throughout follow-up. Potential adverse events were defined according to the NCI common toxicity criteria (1998) and further tests were done as clinically indicated.

2.2. Central pathology review and staining

A primary tumour sample (blocks or slides) was required for central pathology review. Primary tumour samples were stored centrally at the Institut Jules Bordet, Brussels, Belgium. Slide review, immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH) were carried out on whole tissue sections from formalin-fixed paraffin-embedded (FFPE) samples centrally at the European Institute of Oncology, Milan, Italy. Tumour grade was centrally reviewed. Immunostaining experiments for the localisation of ER and PgR, HER2 protein and Ki-67 antigen were carried out on consecutive tissue sections using an automated immunostainer (Autostainer, Dako, Glostrup, Denmark). The following primary antibodies were used: the 1D5 monoclonal antibody (mAb) to ER (Dako, at 1/100 dilution), the 1A6 mAb to PgR (Dako, 1/800), the MIB-1 mAb to the Ki-67 antigen (Dako, 1/100) and the polyclonal antiserum (Dako, 1/800) to the HER2 protein.

Only nuclear reactivity was taken into account for ER, PgR and Ki-67 antigen, and the results were recorded as the percentage of immunoreactive cells over at least 2000 neoplastic cells. Ki-67 was assessed by a single pathologist. FISH was carried out for HER2 according to the manufacturer's instructions (Vysis-Abbott). Positivity thresholds were ER $\geqslant$ 1%; PgR $\geqslant$ 1%; HER2 = 3+ (>10% invasive tumour cells with intense and circumferential membrane staining) and/or FISH positive (HER2:CEP17 ratio $\geqslant$ 2).

2.3. Statistical analysis

The primary study objective was to evaluate the efficacy of docetaxel regardless of the schedule, with disease free survival (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 vs A), concurrent arms (AT vs AC) and docetaxel arms (A-T vs AT), and overall survival (OS) among treatment arms. All randomly assigned patients were included in the intention-to treat analysis. Further Supplementary information is available in the online version of the paper. The article was written in accordance with Reporting Recommendations for Tumour Marker Prognostic Studies guidelines (REMARK) [16].

3. Results

3.1. Efficacy analysis

Between 1998 and 2001, the BIG 2–98 phase III trial enroled 2887 patients with node positive breast cancer. Patient characteristics, intervention and follow-up were previously reported [11,13]. In June 2012, after a median follow-up of 10.1 years (max 12.9 years) and 1072 DFS events, docetaxel treatment did not significantly improve DFS or OS compared to the control arms (Univariate DFS: HR = 0.91, 95% confidence interval

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(CI) = 0.81–1.04; $P = 0.16$; OS: HR = 0.88, 95% CI = 0.76–1.03; $P = 0.11$). In secondary comparisons, no significant differences were observed when sequential docetaxel was compared with the sequential control (Univariate DFS: HR = 0.86, 95% CI = 0.72–1.03, $P = 0.10$; OS: HR = 0.85, 95% CI = 0.68–1.06; $P = 0.15$) or with concurrent doxorubicin–docetaxel (Univariate DFS: HR = 0.88, 95% CI = 0.7–1.02; $P = 0.09$; OS: HR = 0.84, 95% CI = 0.7–1.01; $P = 0.06$) (Table 1). When sub-group analysis was performed based on local pathology, no significant differences where observed for the primary and secondary comparisons in patients with no positive hormone receptor or patients with at least one positive hormone receptor (non-centrally reviewed data) (Supplementary Tables 1 and 2).

Central pathology review was available for 2173 (67%) patients of whom 1492 were ER-positive, 300 triple negative (ER-negative, PgR-negative, HER2-negative) and 150 HER2-positive ER negative (other cases were excluded due to at least one missing data). Sub-group analysis based on a central pathology review similarly showed no benefit of docetaxel treatment in terms of DFS or OS compared to control arms in any of the subtypes possibly because the trial was not designed and powered to detect such differences (Supplementary Table 3).

3.2. Safety analysis

The long-term safety profile was reassuring with only four patients developing grade 3–4 cardiac toxicity following the completion of adjuvant therapy during 10 years of median follow up. Worsening or development of treatment-related neurotoxicity (any grade) following the completion of adjuvant chemotherapy occurred in 1.6% and 1% of patients in the docetaxel and non-docetaxel-based regimens, respectively. In general, adverse events that evolved or worsened during the follow-up period and that were probably related to treatment, were rare in comparison to toxic effects during the treatment phase [11] (Supplementary Table 4). The type of new primary cancers reported were in line with secondary cancers observed in breast cancer populations reported in the literature [14]. The incidence of secondary contralateral breast cancer was relatively low in both treatment arms (Supplementary Table 5).

3.3. Association between Ki67, DFS and OS, in ER-positive tumours

We further analysed the predictive value of Ki67 expression for the efficacy of docetaxel in patients with ER-positive breast cancer. Of 1492 ER-positive tumour specimens, 1198 patients had Ki67% levels available (80.2%) and were included in this analysis (Fig. 1 flowchart). For the Ki67% translational outcome analysis, patients were dichotomised according to the percentage of Ki67% as centrally evaluated. The Ki67% threshold of high $\geqslant$14% was based on work by Cheang et al. [15], in which 14% best discriminated between high and low proliferative ER-positive tumours (such analysis for triple negative and HER2 positive was less relevant as >90% in these subgroups had high Ki67). Table 2 reports the patient characteristics for patients with Ki67 analysis. 892 (74.4%) had Ki67 $\geqslant$14%. As expected, tumours with Ki67 $\geqslant$14% were significantly associated with higher histological grade, tumour stage, HER2 positivity and PgR negativity (Table 2).

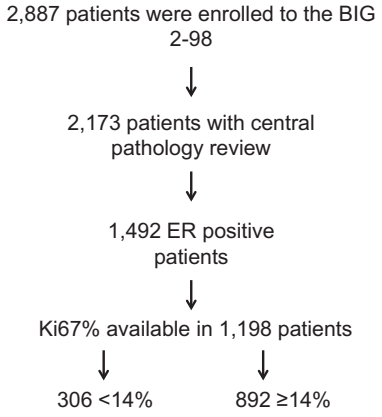

Fig. 1. Study flowchart shows the process for tumour blocks and patient selection.

Table 1
Breast International Group (BIG) 2–98: primary and secondary comparisons for the 10 year follow-up analysis. 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; CI: confidence interval; DFS: disease-free survival; OS: overall survival.

Comparison	DFS hazard ratio (HR; 95% CI)	*P* value	OS hazard ratio (HR; 95% CI)	*P* value
Primary comparison				
A–T + AT versus A + AC	0.91 [0.81–1.04]	0.16	0.88 [0.76–1.03]	0.11
Secondary comparison				
A–T versus A	0.86 [0.72–1.03]	0.1	0.85 [0.68–1.06]	0.15
AT versus AC	0.96 [0.81–1.15]	0.6	0.91 [0.74–1.13]	0.39
A–T versus AT	0.88 [0.76–1.02]	0.09	0.84 [0.7–1.01]	0.06

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Table 2
Sub-study patient characteristics (oestrogen receptor (ER) positive patients with Ki67 levels available).

Characteristics	Ki67 <14% ($N = 306$)		Ki67 ⩾14% ($N = 892$)		P value (<14% versus ⩾14%)
Age at randomisation, years					
Mean ± std	50.1 ± 8.4		48.8 ± 9.1		0.03
Median (range)	50 (25–69)		49 (20–69)		
No. of involved nodes, No (%)					
1–3	184	(60%)	461	(52%)	0.01
4–10	91	(30%)	306	(34%)	
>10	31	(10%)	125	(14%)	
Tumour size, No (%)					
⩽2 cm	126	(41%)	315	(36%)	0.07
>2 cm	179	(59%)	571	(64%)	
pTx	1		6		
Tumour grade, No (%)					
G1–G2	230	(79%)	478	(55%)	<0.001
G3	61	(21%)	391	(45%)	
Gx	15		23		
PR, No (%)					
PR−	21	(7%)	94	(11%)	0.047
PR+	284	(93%)	787	(89%)	
Missing info	1		11		
HER2, No (%)					
HER2−	289	(96%)	734	(83%)	<0.001
HER2+	13	(4%)	149	(17%)	
Missing info	4		9		
Taxane, No (%)					
No	105	(34%)	260	(29%)	0.09
Yes	201	(66%)	632	(71%)	
Seq/combined, No (%)					
Sequential	159	(52%)	450	(50%)	0.65
Combined	147	(48%)	442	(50%)	
Median follow-up, years (95% confidence interval (CI))	10.2 (10.0–10.5)		10.3 (10.1–10.4)		
Number of deaths	45 (14%)		230 (25%)		
Number of events (disease-free survival (DFS))	85 (27%)		345 (38%)		

In the absence of adjuvant taxanes, patients in the Ki67 ⩾14% group had significantly shorter 10-year DFS and OS compared to patients with tumours exhibiting Ki67 <14% (58.1 [95% CI = 51.7–64.0] versus 72.9% [95% CI = 62.9–80.6]; $P < 0.006$ and 70.5 [95% CI = 64.4–75.8) versus 86.3% [95% CI = 77.5–91.8]; $P < 0.0001$, respectively). On limiting the analysis to the subgroup of tumours with Ki67 ⩾14%, taxane resulted in 5.4% improvement in 10-year OS (75.9% [95% CI = 72.2–79.2] versus 70.5% [95% CI = 64.4–75.8], $P = 0.03$) (Fig. 2). Supplementary Table 6 reports univariate analysis of the different variables' association with DFS and OS. The interaction test between Ki67 and taxane was $P = 0.10$ for OS and $P = 0.37$ for DFS. Multivariate analysis was subsequently performed for age, LN, size, histological grade, PgR status and HER2 status. We found that adjuvant taxane chemotherapy showed a trend to improved DFS and OS among ER positive patients with high Ki67 ⩾14% (HR = 0.79 95% CI = 0.63–1.01 $P = 0.05$; and HR = 0.76 95% CI = 0.57–1.01 $P = 0.06$ respectively). By contrast, there was no benefit of adjuvant taxane chemotherapy in the group with Ki67 <14% (Table 3). In the multivariate analysis, the tests for interaction between Ki67 and taxane for DFS and OS were $P = 0.43$ and $P = 0.15$ respectively.

STEPP analyses were used to evaluate 5- and 10-year DFS according to treatment regimen and quantitative values of Ki67, and showed a trend towards differential benefit of docetaxel versus no docetaxel according to the value of Ki67, especially at 5 years (Supplementary Fig. 1).

In order to explore whether Ki67% adds to common pathological grading, we analysed Ki67% data according to the histological grade. We found that a relatively high percentage (>50%) of low-intermediate grade tumours (grades 1–2) have high Ki67% (>14) and those with Ki67 >14% show a trend to improved DFS although not statistically significant ($P = 0.14$) (Supplementary Fig. 2).

Finally, we performed a descriptive pooled analysis of four prospective randomised studies (including our own) that evaluated the role of Ki67 as single variant in predicting the usefulness of taxanes in luminal cancers

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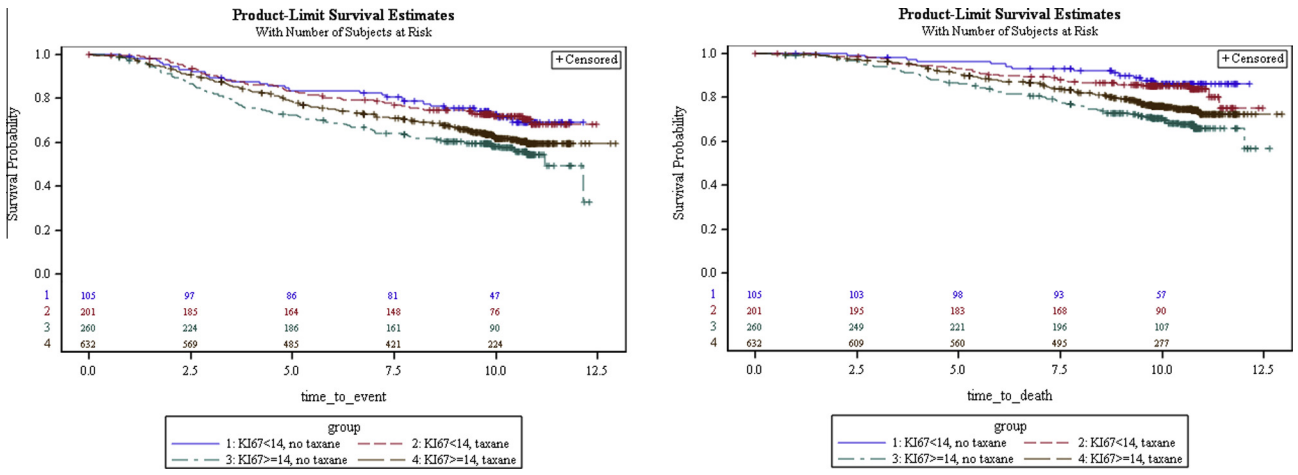

Fig. 2. Disease free survival (DFS) and overall survival (OS) after 10 years follow-up. Kaplan–Meier analyses of DFS (Right) and OS (left) stratified by Ki67% levels and docetaxel treatment.

Table 3
Cox multivariate regression analysis of disease-free survival (DFS) and overall survival (OS) according to Ki67 and taxane treatment after adjustment to: Age, size, lumor nodes (LN), grade, HER2 and PR expression in the oestrogen receptor (ER) positive sub study group.

	N		OS		DFS	
			Hazard ratio (HR) (95% confidence interval (CI))	*P*-value	HR (95% CI)	*P*-value
All pts	1131	KI67 ⩾ 14%	1.46 (1.03–2.06)	0.03	1.21 (0.94–1.57)	0.14
No taxane	337	KI67 ⩾ 14%	1.94 (0.96–3.90)	0.06	1.26 (0.78–2.03)	0.35
Taxane	794	KI67 ⩾ 14%	1.29 (0.87–1.93)	0.21	1.17 (0.86–1.59)	0.31
All pts	1131	Taxane	0.83 (0.64–1.08)	0.17	0.83 (0.67–1.03)	0.09
Ki67 < 14	285	Taxane	1.13 (0.54–2.35)	0.75	0.92 (0.56–1.52)	0.75
Ki67 ⩾ 14	846	Taxane	0.76 (0.57–1.01)	0.06	0.79 (0.63–1.01)	0.05

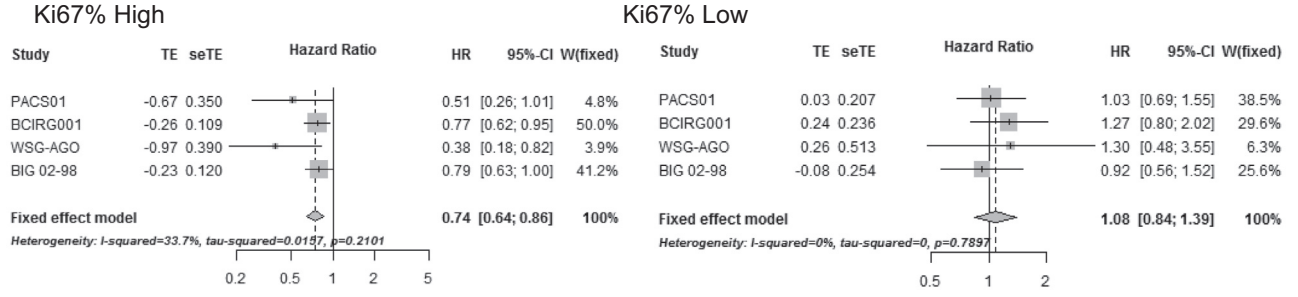

Fig. 3. Pooled analysis of the effect of taxane chemotherapy on disease free survival (DFS), stratified by level of KI-67 in oestrogen receptor (ER) positive patients. TE = treatment effect log (HR), seTE = standard error of the treatment effect, W = weight.

(Supplementary Table 7) [11,16–20]. The results of this analysis showed a benefit of taxanes only in highly proliferative ER-positive disease (interaction test $P = 0.01$) (Fig. 3).

4. Discussion

In this paper we report that the previously observed benefit for the addition of sequential docetaxel following doxorubicin in the A-CMF regimen for patients with lymph node positive breast cancer in the BIG 2–98 trial is no longer significant at ten years of follow-up. In this mature report, there is no significant difference in disease-free or overall survival.

During the last 15 years, more than 44,000 patients have been recruited to randomised clinical trials that compared a taxane-plus-anthracycline based regimen to anthracycline-based control regimens. Heterogeneity in the design of these trials and variety in treatment comparisons have complicated meta-analyses. In one of the most comprehensive efforts in the field, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysed the results for all such trials to test for a taxane effect [12]. The EBCTCG showed that adding four additional cycles of a taxane to a fixed

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anthracycline-based control regimen reduces breast cancer mortality. However, in trials where the chemotherapy was counterbalanced in control regimens by extra cycles of other drugs, there was no significant advantage to taxanes. In the BIG 2–98 trial, the non-docetaxel arms were counterbalanced by increasing the number of doxorubicin cycles (from 3 to 4) or by adding cyclophosphamide to doxorubicin. It is possible that the A-CMF regimen represented a more rigorous standard control comparison than other anthracycline regimens. It contains more drugs, and administers more cycles than any of the other regimens.

In a recent update of the ECOG1199 trial, Sparano and colleagues showed after median follow-up of 10 years that the superiority of weekly paclitaxel or three-weekly docetaxel schedule (post anthracycline-based regimen) persists [21]. It was suggested that triple negative patient benefit more from the weekly paclitaxel and ER positive patients benefit more from the three-weekly docetaxel arms. The dose-dense regimen that showed superiority in the CALGB-9741 [22] seems to be equivalent to 6xTAC which is equivalent to a non-dose-dense regimen as demonstrated in the NSABP-B38 and BCIRG005 respectively [23,24]. Notably, a recent update of the BCIRG001 demonstrated that the initial therapeutic advantage seen at the 5-year follow-up with a docetaxel-containing adjuvant regimen (TACx6 versus FACx6) is maintained at 10 years [17].

Ki67 could be used to differentiate between luminal A and Luminal B cancers [25–27].The 13th St Gallen International Breast Cancer Conference (2013) Expert Consensus Panel has provided new recommendations to distinguish between luminal A and luminal B tumours [28]. It is suggested that levels of $<14\%$ for Ki67% or a PgR $\geqslant 20\%$ best correlated with the Luminal-A subtype [29,30]. One problem with Ki67 IHC is its low reproducibility [31,32]. In our study Ki67 IHC was performed centrally, and its predictive and prognostic roles in the ER positive subgroup was explored.

Decisions about adjuvant chemotherapy for ER positive breast cancers are complex and sometimes an 'all or none' approach is used, which means that if a physician decides to administer chemotherapy, an anthracycline-taxane regimen is considered. Even newer advanced clinical tools such as the Oncotype DX® 21-gene recurrence score (RS) assay are able to quantify the likelihood of distant recurrence and to predict the potential magnitude of chemotherapy benefit but not to assess the benefit form the addition of taxanes [33]. Data provided in this study suggest that Ki67 identifies a high proliferative subset of patients with ER-positive breast cancer who derive greater benefit from adjuvant docetaxel.

Three previous unplanned exploratory analyses of three large adjuvant trials (BCIRG001, PACS01, WSG-AGO) evaluated the role of Ki67 as a single variable in predicting the usefulness of taxane in the management of luminal cancers and showed that patients with ER-positive/Ki67-high tumours benefit from taxanes while those with ER-positive/Ki67-low, do not [11,16,19,20]. Our study (BIG 2–98), although not demonstrating a significant interaction between taxanes and Ki67, supports the hypothesis that high Ki67 could identify patients with ER-positive breast cancer who derive more benefit from adjuvant taxanes. Although heterogeneity in the design of these trials, variety in treatment comparisons and different Ki67% cut-offs complicate the interpretation of data, we performed a descriptive pooled analysis of these studies and found the same pattern; greater benefit of taxanes in highly proliferative ER-positive disease (Fig. 3). This raises the questions whether the 'All or none' paradigm should be revised as it is becoming clearer that low absolute risk implies low absolute benefit. Indeed, in a recent meta-analysis, it was demonstrated that high Ki67 ER-positive patients have a worse prognosis and were found to be more sensitive to chemotherapy in general [34]. Perhaps ER positive patients with low proliferating tumours (Ki67 $<14\%$) can be spared from taxanes even if it is decided to administer chemotherapy.

In summary, this is one of the largest of the few adjuvant trials reporting on the 10-year outcome of adjuvant docetaxel in patients with node positive breast cancer. Incorporating docetaxel into adjuvant therapy showed a long term safety profile but did not result in an overall improvement in DFS or OS on considering all patients (level one evidence). Pooled analysis of four prospective randomised studies in ER positive tumours suggested benefit from taxanes only in patients with ER-positive/high Ki67 breast cancers (level two evidence).

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2015.03.018.

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