Breast Cancer Research and Treatment (2019) 174:27–37
https://doi.org/10.1007/s10549-018-5055-9

REVIEW

Anthracycline and taxane-based chemotherapy versus docetaxel and cyclophosphamide in the adjuvant treatment of HER2-negative breast cancer patients: a systematic review and meta-analysis of randomized controlled trials

Rafael Caparica[1] · Marco Bruzzone[2] · Francesca Poggio[3] · Marcello Ceppi[2] · Evandro de Azambuja[1] · Matteo Lambertini[1]

Received: 14 September 2018 / Accepted: 16 November 2018 / Published online: 21 November 2018

Abstract

Purpose Standard adjuvant chemotherapy for HER2-negative breast cancer consists generally in an anthracycline and taxane-based regimen (A+T). The TC (docetaxel and cyclophosphamide) regimen arises as a potential alternative, although individual randomized controlled trials (RCTs) could not demonstrate the non-inferiority of TC over A+T. This is a systematic review and meta-analysis of RCTs comparing 6 cycles of TC versus sequential A+T in the adjuvant treatment of HER2-negative breast cancer.

Methods A systematic literature search was performed to identify RCTs comparing TC versus A+T. Disease-free survival (DFS) and overall survival (OS) were assessed. Subgroup analyses of DFS according to hormone receptor status, lymph node involvement, and menopausal status were performed. Hazard ratios (HRs) and 95% confidence intervals (CI) for DFS and OS were extracted from each trial, and a pooled analysis was conducted using the random-effect model. The Higgins' *I*-Squared Test was used to quantify heterogeneity.

Results Seven RCTs were included (12,741 patients). Overall, no difference was observed between TC and A+T in DFS (HR 1.08, 95% CI 0.96–1.20) and OS (HR 1.05; 95% CI 0.90–1.22). A trend favoring A+T was observed in hormone receptor-negative (HR 1.12, 95% CI 0.93–1.34) and N2 patients (HR 1.25; 95% CI 0.82–1.90). Emesis/vomiting, mucositis, thrombocytopenia and sensory neuropathy were significantly more frequent with A+T.

Conclusion As adjuvant treatment of HER2-negative breast cancer, sequential A+T regimen was associated with increased risk of toxicities and no clear survival benefit as compared to 6 cycles of TC. Higher-risk patients may benefit the most from A+T, whilst TC may be an efficacious and less toxic alternative for lower-risk patients.

Keywords Breast cancer · Adjuvant chemotherapy · Anthracyclines · Taxanes

Introduction

Adjuvant chemotherapy significantly reduces the risk of recurrence and improves overall survival (OS) of breast cancer patients [1]. The sequential administration of a taxane with anthracycline and cyclophosphamide-based chemotherapy (A+T) is considered the standard adjuvant regimen in HER2-negative early breast cancer [2–4]. Although anthracyclines represent an important component of adjuvant chemotherapy, they are associated with several possible short and long-term adverse events, including myelosuppression, emesis/vomiting, heart failure, myelodysplasia, and leukemia [4, 5]. In an attempt to avoid these toxicities,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-018-5055-9) contains supplementary material, which is available to authorized users.

✉ Matteo Lambertini
matteo.lambertini85@gmail.com

[1] Department of Medical Oncology, Institut Jules Bordet and Université Libre de Bruxelles (ULB), Boulevard de Waterloo 121, 1000 Brussels, Belgium

[2] Clinical Epidemiology Unit, Ospedale Policlinico San Martino, Genova, Italy

[3] Department of Medical Oncology, U.O. Oncologia Medica 2, Ospedale Policlinico San Martino, University of Genova, Genova, Italy

alternative chemotherapy regimens have been studied such as the combination of docetaxel plus cyclophosphamide (TC) for 4 cycles, which demonstrated to be superior to 4 cycles of doxorubicin plus cyclophosphamide [6]. Based on these findings and given the aforementioned safety concerns, the percentage of patients receiving a non-anthracycline regimen in the adjuvant setting has increased over time [7].

More recently, a next generation of randomized controlled trials (RCTs), most of which were non-inferiority studies, compared the standard sequential A+T regimens with 6 cycles of TC as adjuvant chemotherapy. No single RCT was able to demonstrate the non-inferiority of TC versus A+T [8–11]. To provide updated evidence on the controversial but crucial topic of adjuvant chemotherapy de-escalation, we performed a systematic literature review and a meta-analysis of RCTs that compared 6 cycles of TC versus sequential A+T in HER2-negative early breast cancer patients.

Methods

This study is a systematic review and meta-analysis based on published data of RCTs that compared 6 cycles of TC versus sequential A+T as adjuvant chemotherapy in HER2-negative breast cancer patients.

Objectives

Primary objective was to compare the efficacy of TC versus A+T in terms of disease-free survival (DFS). Secondary endpoints included OS, rates of adverse events grade ≥ 3 (emesis/vomiting, mucositis, diarrhea, anemia, neutropenia, febrile neutropenia, thrombocytopenia, sensory neuropathy, and heart failure), treatment-related deaths and treatment interruption due to toxicities.

Subgroup analyses of DFS were performed to evaluate if treatment effect varied according to hormone receptor status (positive and negative), number of positive lymph nodes (N1 and N2), and menopausal status (premenopausal and postmenopausal).

Data sources and search strategy

A literature search in PubMed, Embase, the Cochrane Library, and conference proceedings from major oncology conferences (ASCO, ESMO and SABCS) was performed with no date restriction up to June 15, 2018. The search strategy was developed using the Patient, Intervention, Comparator and Outcome (PICO) framework and comprised the keywords related to "breast cancer", "adjuvant", "chemotherapy", "anthracycline", and "taxane". Two reviewers (RC and FP) independently evaluated the titles and the abstracts of the identified records; a third author (ML) reviewed the search results to apply the eligibility criteria. Cross-referencing from relevant studies and review articles on the topic was performed to confirm that all eligible trials were included.

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines for systematic reviews [12], and registered before study initiation in the PROSPERO database (registration number CRD42018090962; full protocol available in the website).

Selection of the articles

Eligible studies had to meet the following inclusion criteria: RCTs with published, presented, or otherwise publically available data; RCTs that included HER2-negative early breast cancer patients; RCTs comparing TC versus A+T; information available at least on DFS; and published in English. For RCTs fulfilling these criteria but with multiple arms or factorial design, only the results of the arms of interest were included.

Excluded studies were RCTs including only HER2-positive patients, non-randomized studies, studies for which insufficient or no results were available at the time of the literature search, and studies not published in English.

Statistical analysis

For the efficacy analysis (DFS and OS), HRs were calculated for the comparison of TC versus A+T. A HR < 1 favors TC (i.e., better DFS/OS with TC), whilst a HR > 1 favors A+T (i.e., better DFS/OS with A+T). For the safety analysis, the odds ratio (OR) for each adverse event was calculated by comparing TC versus A+T. An OR < 1 indicates that the adverse event was more frequent with TC, whilst an OR > 1 indicates that the adverse event was more frequent with A+T. For each OR or HR estimates, 95% confidence intervals (CIs) were computed.

Pooled ORs or HRs using the random-effects model were computed with the method of DerSimonian and Laird. The Higgins' I^2 index was computed to obtain a quantitative measure of the degree of inconsistency in the results of the included studies. To assess whether the pooled OR/HR estimates were stable or strongly dependent on one or few studies, sensitivity analyses were conducted by interactively recalculating the pooled OR/HR estimates after exclusion of each single study. All reported p values were two-sided. All statistical analyses and the generation of forest plot were conducted using Stata Software Version 13.1 (StataCorp LP). The Cochrane risk of bias assessment tool was employed to assess the quality of the data obtained and the risk of bias in each study (Supplementary material, Table 1) [13].

Table 1 Characteristics of the studies included in the meta-analysis

Trial	Patients	Population	Objective	Medium follow-up	Chemotherapy	Prophylatic G-CSF
HORG Mavroudis et al. [9]	650	HER2 negative, N ≥ 1	TC NI to A+T in 3-year DFS HR for NI - 1.53	A+T arm—46 months TC arm—47 months	TC x6 Versus FEC x3 + docetaxel x3	Mandatory for A+T, optional for TC
ABC Trials Blum et al. [8]	4.156	HER2 negative, N ≥ 1 OR N0 high risk (TNBC, T2, grade 3, Oncotype DX ≥ 25)	TC NI to A+T in iDFS HR for NI - 1.18	39.6 months	TC x6 Versus AC + docetaxel or paclitaxel	Mandatory for A+T, optional for TC
DBCG 07-READ Ejlertsen et al. [10]	2.012	TOP2A not overexpressed, N1 OR N0 high risk (age ≤ 39 years, T2, grade ≥ 2, TNBC, HER2 positive)	TC superiority to A+T in 3-year DFS 36% improve in 3-year DFS	69 months	TC x6 Versus EC x3 + docetaxel x3	Mandatory for all patients
PlanB + SuccessC Wolfgang et al. [11]	5.923	PlanB HER2 negative, TNBC N1, or N0 high risk (*T* ≥ 2, grade ≥ 2, Hormone receptor-negative, age ≤ 35 years, PAI-1 high expression) OR Hormone receptor-positive and N ≥ 2, or N1 with a RS > 11 SuccessC HER2 negative, N ≥ 1 OR N0 high risk (*T* ≥ 2, grade 3, age ≤ 35 years, TNBC)	TC NI to A+T in 5-year DFS 4.4% absolute NI margin[a]	62 months	TC x6 Versus EC x4 + docetaxel x4	N/A

G-CSF, Granulocyte monocyte colony stimulating factor; HER2, human epidermal growth factor receptor type 2; TC, docetaxel + cyclophosphamide; FEC, fluorouracil + epirubicin + cyclophosphamide; A+T, anthracycline and taxane-based regimen; TNBC, triple-negative breast cancer; AC, doxorubicin + cyclophosphamide; TOP2A, topoisomerase IIa; EC, epirubicin + docetaxel; PAI-1, plasminogen activator inhibitor-1; RS, 21-gene recurrence score assay; NI, non-inferiority

[a]This is the objective of the PlanB study

Results

From the initial 501 records that were identified, four were included (Fig. 1). Among them, two were RCTs (HORG and DBCG 07-READ), one was a pooled analysis of three RCTs (ABC trials comprising three studies: USOR06-090, NSABP B-46-I/USOR07132, and NSABPB-49), and one was a conference abstract corresponding to the pooled analysis of two RCTs (PlanB + SuccessC) [8–11] (Table 1). A total of 12,741 patients were included.

The DBCG READ-07 trial allowed the inclusion of HER2-positive patients (11% of the study population): this was a stratification factor and all these patients received standard treatment with trastuzumab combined to chemotherapy [10]. The DBCG READ-07 trial included only patients without amplifications of topoisomerase IIa (TOP2A) because at the time of study conception, TOP2A was considered a potential predictor of benefit from anthracyclines. However, more recent studies did not confirm the role of TOP2A as a predictive biomarker [14–16]. Nevertheless, to take into account the inclusion of a selected patient population, efficacy results are presented both overall and after excluding the DBCG READ-07 trial.

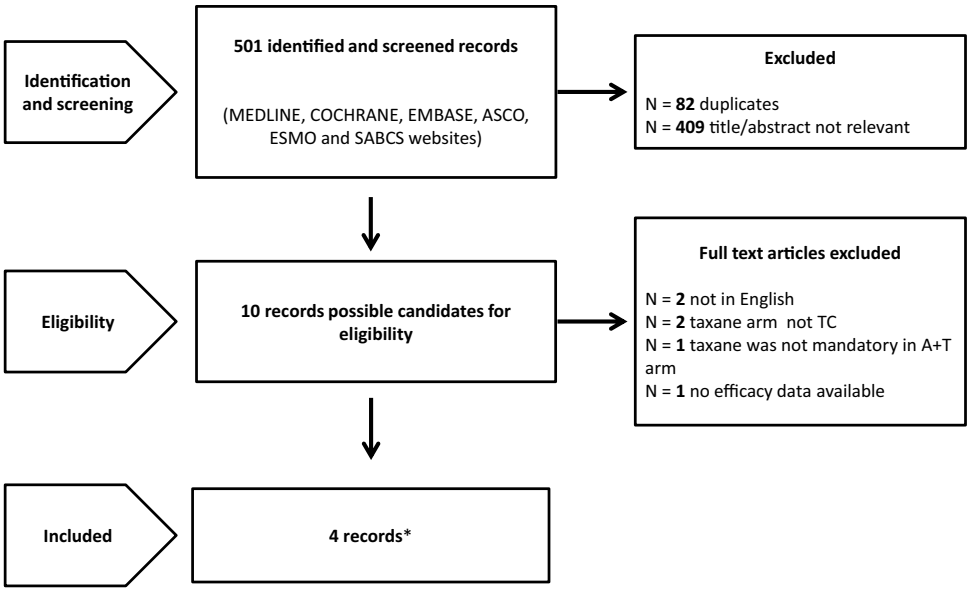

Fig. 1 PRISMA flow chart illustrating the literature search and the study selection for the meta-analysis. *Pooled efficacy data from the PlanB and SuccessC trials presented at ASCO 2018 were included; for the toxicity analysis, we included the PlanB study abstract presented at ASCO 2017 (since the pooled analysis PlanB + SuccessC presented at ASCO 2018 did not report data on toxicities). Abbreviations: ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; SABCS, San Antonio Breast Cancer Symposium

Efficacy analyses

Disease-free survival

All studies reported DFS results [8–11]. No significant difference was observed between TC and A+T in the overall population (HR 1.08; 95% CI 0.96–1.20; $p = 0.193$) with no significant heterogeneity ($I^2 = 1.2\%$, $p_{heterogeneity} = 0.386$; Fig. 2a). At the sensitivity analyses, DFS results did not change significantly; after excluding the DBCG READ-07 study, the pooled HR for DFS was 1.09 (95% CI 0.94–1.27; $p = 0.240$) (Supplementary material, Table 2A).

Three studies reported DFS in hormone receptor-positive patients ($N = 11{,}143$) [8–10]. No significant difference was observed between TC and A+T (HR 1.05; 95% CI 0.86–1.27; $p = 0.653$) with no significant heterogeneity ($I^2 = 0\%$, $p_{heterogeneity} = 0.664$; Fig. 3a). Sensitivity analysis is provided as Supplementary material, Table 3A. All studies reported DFS in hormone receptor-negative patients ($N = 1598$) [8–11]. No significant difference was observed between TC and A+T (HR 1.12; 95% CI 0.93–1.34; $p = 0.237$) with no significant heterogeneity ($I^2 = 9.0\%$, $p_{heterogeneity} = 0.348$; Fig. 3b). Sensitivity analysis is provided as Supplementary material, Table 3B.

Two studies reported DFS according to lymph node status (N1 and N2) [8, 9]. In N1 patients ($N = 2242$), no significant difference was observed between TC and A+T (HR 1.06; 95% CI 0.65–1.73; $p = 0.823$; Fig. 4a), with no significant heterogeneity ($I^2 = 49.7\%$, $p_{heterogeneity} = 0.159$). In N2 patients ($N = 678$), no significant difference was observed between TC and A+T (HR 1.25; 95% CI 0.82–1.90; $p = 0.300$; Fig. 4b), with no significant heterogeneity ($I^2 = 0\%$, $p_{heterogeneity} = 0.400$).

Two studies reported DFS according to menopausal status [9, 10]. In premenopausal patients ($N = 1251$), no significant difference was observed between TC and A+T (HR 0.78; 95% CI 0.56–1.09; $p = 0.140$), with no significant heterogeneity ($I^2 = 0\%$, $p_{heterogeneity} = 0.874$; Fig. 5a). Similarly, in postmenopausal patients ($N = 1411$), no significant difference was observed between TC and A+T (HR 1.16; 95% CI 0.83–1.61; $p = 0.395$), with no significant heterogeneity ($I^2 = 14.1\%$, $p_{heterogeneity} = 0.281$; Fig. 5b).

Overall Survival

All studies reported OS results for the overall population [8–11]. No significant difference was observed between TC and A+T (HR 1.05; 95% CI 0.90–1.22; $p = 0.555$) with no significant heterogeneity ($I^2 = 0\%$, $p_{heterogeneity} = 0.850$; Fig. 2b). Sensitivity analysis is reported as Supplementary material, Table 2B; after excluding the DBCG READ-07 study, the pooled HR for OS was 1.02 (95% CI 0.86–1.21; $p = 0.825$).

Safety analyses

For the safety analysis, a total of 9145 patients were included. Considering that the latest abstract of the PlanB + SuccessC trials included in the efficacy analysis did not contain data on toxicities, this information was retrieved from a previously presented abstract of the PlanB study [17]. All sensitivity analyses for the safety results are reported as Supplementary material Table 4.

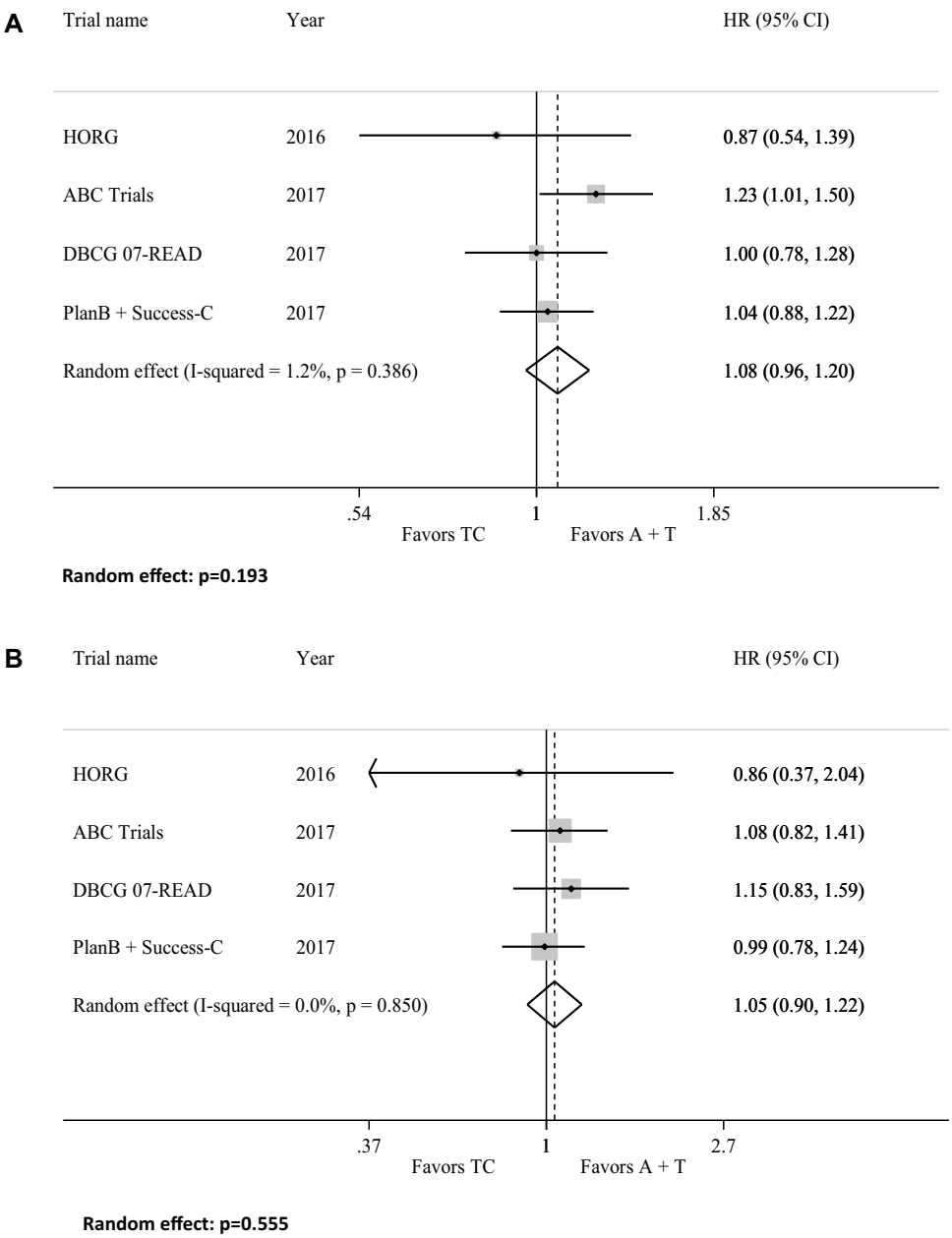

Fig. 2 Forest plots and the pooled hazard ratios with the respective *p* values for disease-free survival (**a**) and overall survival (**b**) in the overall population. Abbreviations: HR, hazard ratio; CI, confidence intervals; TC, docetaxel and cyclophosphamide; A+T, anthracycline and taxane-based chemotherapy

Emesis/vomiting

Grade ≥ 3 emesis/vomiting was significantly less frequent with TC (39 out of 4597 patients [0.8%]) in comparison with A+T (129 out of 4548 patients [2.8%]; OR 4.36; 95% CI 1.47–12.94; $p = 0.008$; Fig. 6 and Supplementary material Fig. 1A). A significant heterogeneity between studies was observed ($I^2 = 81.5\%$, $p_{\text{heterogeneity}} = 0.001$); this appeared to be mainly driven by the ABC trials. After excluding this study, the results confirmed the higher risk of emesis/vomiting with A+T (Supplementary material Table 4A).

Mucositis

Grade ≥ 3 mucositis was significantly less frequent with TC (45 out of 4597 patients [1%]) in comparison with A+T (114 out of 4548 patients [2.5%]; OR 2.57; 95% CI 1.81–3.64; $p < 0.001$; Fig. 6 and Supplementary material Fig. 1B), with no significant heterogeneity ($I^2 = 0$, $p_{\text{heterogeneity}} = 0.776$).

Diarrhea

There was no significant difference in grade ≥ 3 diarrhea between TC (164 out of 4597 patients [3.5%]) and A+T (169

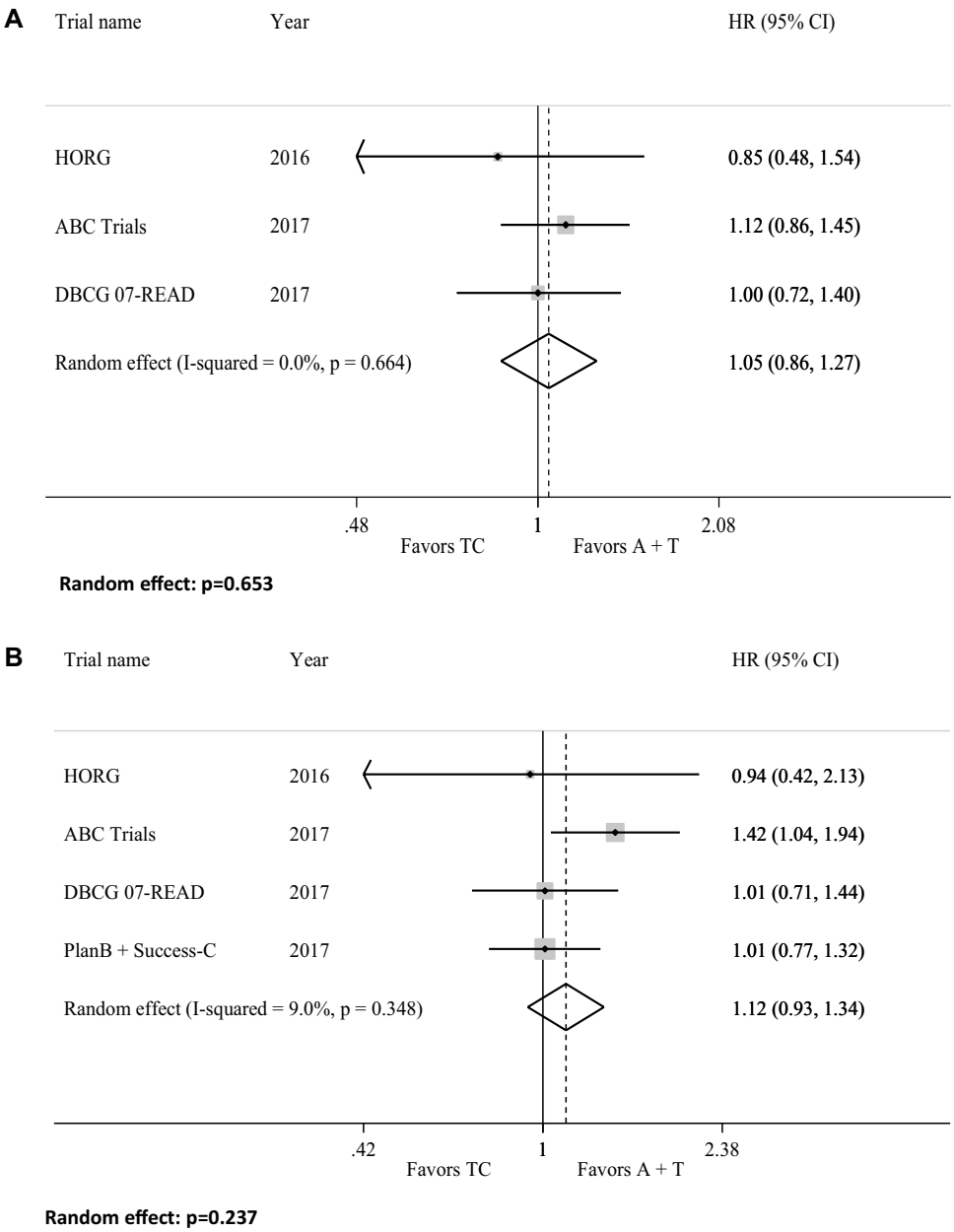

Fig. 3 Forest plots and the pooled hazard ratios with the respective *p* values for disease-free survival in hormone receptor-positive (**a**) and negative (**b**) patients. Abbreviations: HR, hazard ratio; CI, confidence intervals; TC, docetaxel and cyclophosphamide; A+T, anthracycline and taxane-based chemotherapy

out of 4548 patients [3.7%]; OR 1.05, 95% CI 0.84–1.30; $p = 0.682$; Fig. 6 and Supplementary material Fig. 1C), with no significant heterogeneity ($I^2 = 0$, $p_{\text{heterogeneity}} = 0.798$).

Febrile neutropenia

There was no significant difference in febrile neutropenia between TC (274 out of 4597 patients [5.9%]) and A+T (264 out of 4548 patients [5.8%]; OR 1.02; 95% CI 0.62–1.66; $p = 0.947$; Fig. 6 and Supplementary material Fig. 1D). A significant heterogeneity between studies was observed ($I^2 = 81.3\%$, $p_{\text{heterogeneity}} = 0.001$); this appeared to be mainly driven by the DBCG 07-READ study. After excluding this study, a higher risk of febrile neutropenia for TC was observed (OR 0.78; 95% CI 0.63–0.96; $p = 0.019$) with no significant heterogeneity ($I^2 = 0$, $p_{\text{heterogeneity}} = 0.682$; Supplementary material Table 4D).

Neutropenia

Neutropenia was reported in 3 RCTs [8, 9, 17]. There was no significant difference in grade ≥ 3 neutropenia between TC (1041 out of 3591 patients [28.9%]) and A+T (1044 out of 3554 patients [29.3%]; OR 0.72, 95% CI 0.38–1.36; $p = 0.300$; Fig. 6 and Supplementary material Fig. 1E). A significant heterogeneity between studies was observed ($I^2 = 96.3\%$, $p_{\text{heterogeneity}} < 0.001$) but there was

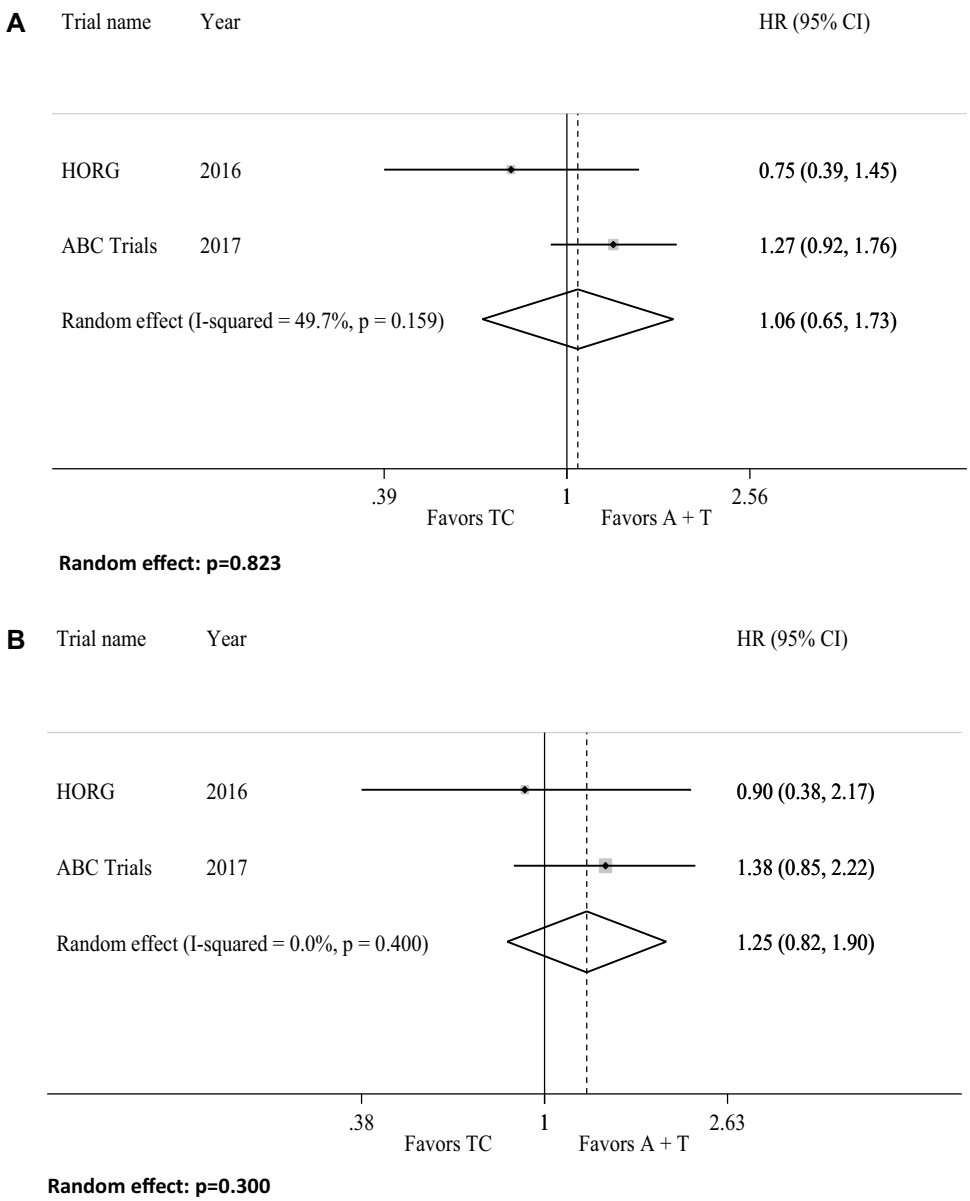

Fig. 4 Forest plots and the pooled hazard ratios with the respective *p* values for disease-free survival in N1 (**a**) and N2 (**b**) patients. Abbreviations: HR, hazard ratio; CI, confidence intervals; TC, docetaxel and cyclophosphamide; A+T, anthracycline and taxane-based chemotherapy

no evidence that this was independently driven by a single trial (Supplementary material Table 4E).

Anemia

Anemia was reported in 2 RCTs [8, 9]. There was no significant difference in grade ≥ 3 anemia between TC (23 out of 2413 patients [0.9%]) and A+T (32 out of 2387 patients [1.3%]; OR 1.42; 95% CI 0.83–2.43; $p = 0.202$; Fig. 6 and Supplementary material Fig. 1F), with no significant heterogeneity ($I^2 = 0\%$, $p_{\text{heterogeneity}} = 0.365$).

Thrombocytopenia

Thrombocytopenia was reported in 2 RCTs [8, 9]. Grade ≥ 3 thrombocytopenia was significantly less frequent with TC (10 out of 2413 patients [0.4%]) in comparison to A+T (48 out of 2387 patients [2%]; OR 4.73; 95% CI 2.41–9.28; $p < 0.001$; Fig. 6 and Supplementary material Fig. 1G), with no significant heterogeneity ($I^2 = 0\%$, $p_{\text{heterogeneity}} = 0.429$).

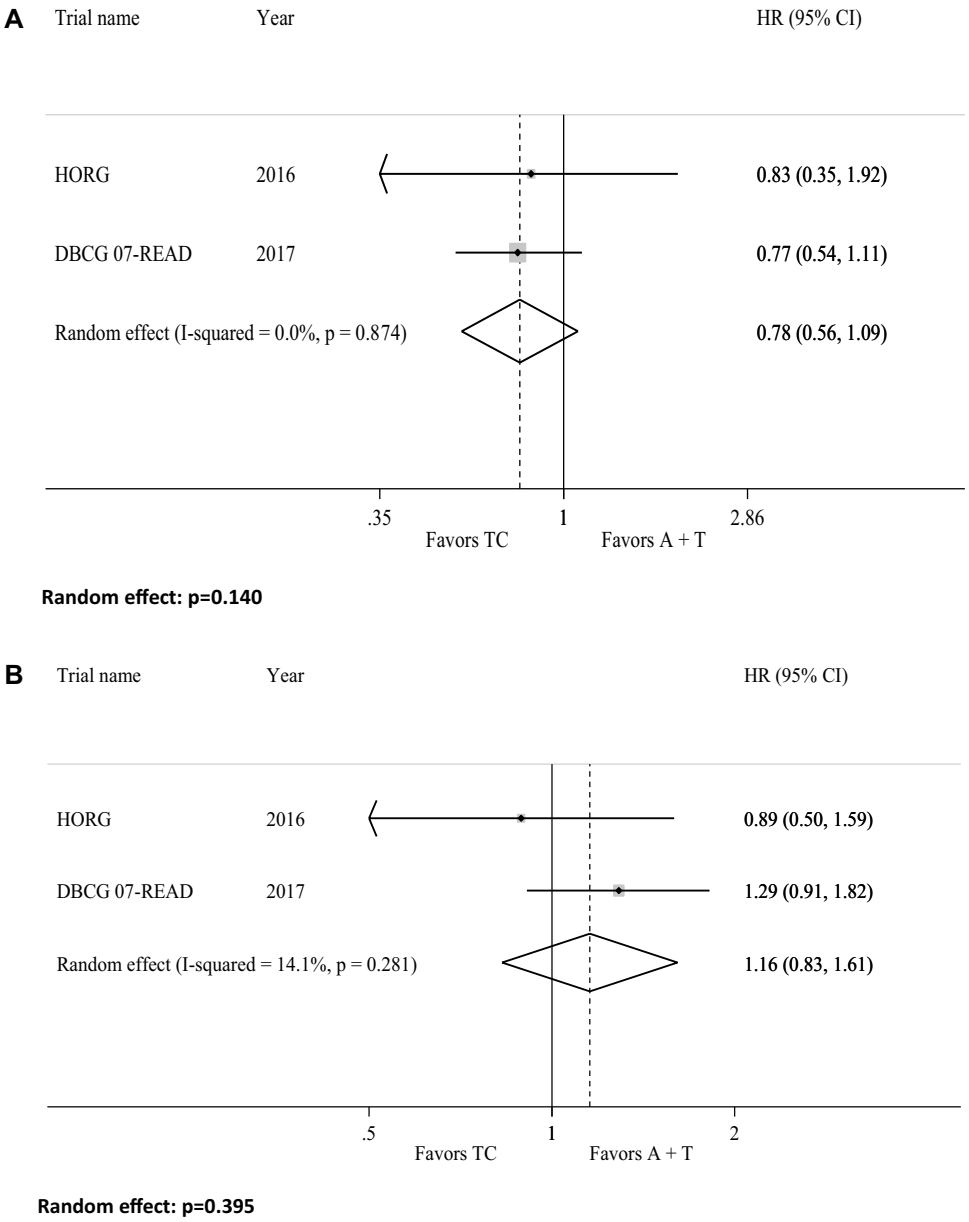

Fig. 5 Forest plots and the pooled hazard ratios with the respective *p* values for disease-free survival in premenopausal (**a**) and postmenopausal women (**b**). Abbreviations: HR, hazard ratio; CI, confidence intervals; TC, docetaxel and cyclophosphamide; A+T, anthracycline and taxane-based chemotherapy

Heart failure

There was no significant difference in grade ≥ 3 heart failure between TC (9 out of 4597 patients [0.2%]) and A+T (15 out of 4548 patients [0.3%]; OR 1.36; 95% CI 0.58–3.15; $p = 0.477$; Fig. 6 and Supplementary material Fig. 1H), with no significant heterogeneity ($I^2 = 0\%$, $p_{\text{heterogeneity}} = 0.489$).

Sensory neuropathy

Grade ≥ 3 sensory neuropathy was significantly less frequent with TC (121 out of 4597 patients [2.6%]) in comparison to A+T (197 out of 4548 patients [4.3%]; OR 1.71; 95% CI 1.33–2.19; $p < 0.001$; Fig. 6 and Supplementary material Fig. 1I), with no significant heterogeneity ($I^2 = 4.1\%$, $p_{\text{heterogeneity}} = 0.372$).

Treatment-related deaths

There was no significant difference between TC (7 out of 4597 patients [0.1%]) and A+T (10 out of 4548 patients [0.2%]; OR 1.12; 95% CI 0.20–6.43; $p = 0.899$), with no significant heterogeneity ($I^2 = 45.3\%$, $p_{\text{heterogeneity}} = 0.140$; Supplementary material Fig. 1J).

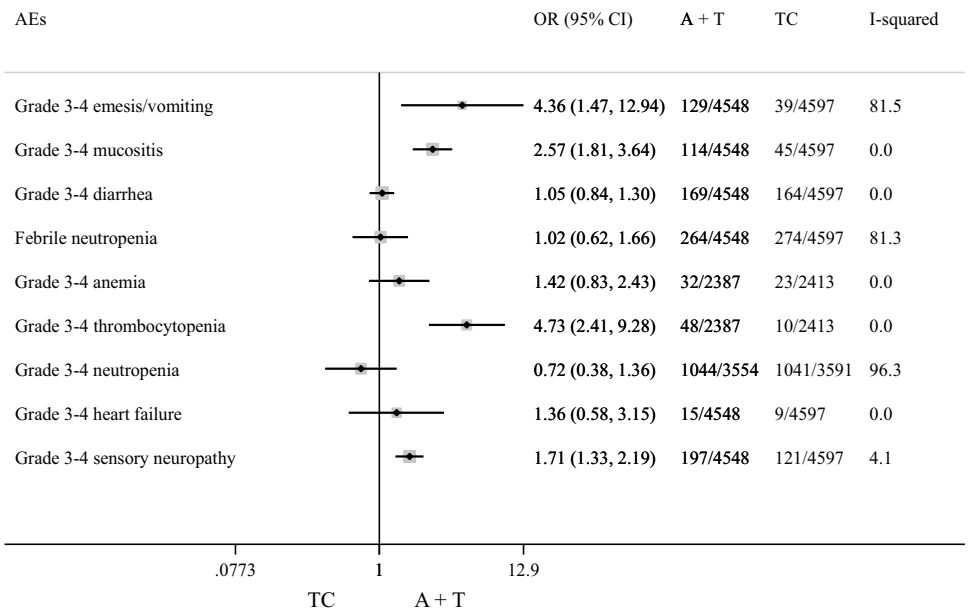

Fig. 6 Forest plot of the safety analyses, with the OR for the evaluated toxicities. Abbreviations: OR, odds ratio; CI, confidence intervals; TC, docetaxel and cyclophosphamide; A+T, anthracycline and taxane-based chemotherapy

Treatment interruption due to toxicities

The frequency of treatment interruption due to toxicities was reported in 3 RCTs. There was no significant difference between TC (194 out of 2508 patients [7.7%]) and A+T (177 out of 2487 patients [7.1%]; OR 0.84; 95% CI 0.40–1.79; $p=0.659$). A significant heterogeneity between studies was observed ($I^2=89.2\%$, $p_{\text{heterogeneity}}<0.001$; Supplementary material Fig. 1K); this appeared to be mainly driven by the PlanB study. After excluding this study, more treatment interruptions due to toxicities were observed for TC than A+T (OR 0.63; 95% CI 0.43–0.92; $p=0.015$) with no significant heterogeneity ($I^2=21.8\%$, $p_{\text{heterogeneity}}=0.258$; Supplementary material Table 4I).

Discussion

This meta-analysis reports updated evidence on the feasibility of chemotherapy de-escalation by using 6 cycles of the TC regimen instead of sequential A+T as adjuvant treatment of HER2-negative breast cancer patients. By pooling the results from 7 RCTs including a total of 12,741 patients, neither DFS nor OS difference was observed between TC and A+T in the overall population. Emesis/vomiting, mucositis, thrombocytopenia and sensory neuropathy were more frequent with A+T.

For interpreting these results, it should be highlighted that most of the included RCTs were designed to evaluate the non-inferiority of TC as compared to A+T, with different non-inferiority margins defined in each study [8–11]. Hypothetically, using as a reference the most conservative non-inferiority margin applied in the ABC trials (HR > 1.18, corresponding to an absolute maximum difference of 2% in 5-year DFS) [8], the upper limit of the HR for DFS of the present meta-analysis (HR 1.08, 95% CI 0.96–1.20) would exceed the non-inferiority margin to consider TC non-inferior to A+T.

When considering the benefit from adjuvant treatments, an adequate estimation of recurrence risk based on a combination of clinical and biological features is crucial. Specifically, hormone receptor status is amongst the most important predictive and prognostic factors [18]. Although the relative risk reduction provided by taxanes added to an anthracycline-based regimen is similar in both subgroups, the absolute risk reduction is less pronounced in patients with hormone receptor-positive (1%) than in those with hormone receptor-negative (2.6%) disease considering their different recurrence risk [19]. Given the modest absolute gain obtained from chemotherapy and the pronounced benefit of endocrine therapy, patients with lower-risk hormone receptor-positive breast cancer but candidates to systemic cytotoxic therapy may be those who could potentially benefit the most from chemotherapy de-escalation strategies [19, 20]. Our subgroup analysis demonstrated no clear superiority of A+T versus TC in patients with hormone receptor-positive disease, supporting the hypothesis that TC may be an adequate alternative for this subgroup, although the wide range of the HR precludes definitive conclusions. Considering that hormone receptor-positive disease comprises a heterogeneous group of tumors, the advent of genomic tests can help in identifying the subgroup of patients who may really benefit from de-escalation strategies [21–23]. Notably, a trend favoring A+T was observed in patients with hormone receptor-negative disease.

Chemotherapy-induced amenorrhea is a frequent adverse event in premenopausal women [24, 25]. In patients with hormone receptor-positive disease, the hormonal deprivation induced by chemotherapy can contribute to its anti-tumoral effects [24–28]. Although there was no significant difference between TC and A+T, we observed a trend favoring TC in the premenopausal subgroup. Notably, the RCTs included in this analysis used 6 cycles of cyclophosphamide (a highly gonadotoxic agent) for TC as compared with 3 to 4 for A+T. Although no information is reported on the type of adjuvant endocrine therapy used in the RCTs, tamoxifen alone was considered standard of care at that time. More recently, the benefit of a more potent hormonal suppression in higher-risk premenopausal patients has been demonstrated [29]. Therefore, although this information was not available in the RCTs, it can be speculated that the higher cumulative dose of cyclophosphamide with TC may have resulted in higher incidence of chemotherapy-induced amenorrhea and subsequent ovarian suppression in premenopausal patients, which may justify the observed trend favoring TC in this subgroup [26].

Lymph node status is also an important prognostic factor in breast cancer [30]. We observed a trend favoring A+T in the N2 subgroup, suggesting that patients with higher recurrence risk may benefit the most from a more intense chemotherapy regimen. However, the limited sample size and the absence of statistical significance preclude definitive conclusions.

From a safety perspective, we observed that emesis/vomiting, mucositis, thrombocytopenia, and sensory neuropathy were more frequent with A+T than TC. However, no differences in the rates of treatment interruptions or treatment-related deaths were observed between the two regimens. In addition, there was no difference in heart failure rate, although a longer follow-up is needed to obtain a more precise estimation of this event. Despite TC is considered a high-risk regimen for febrile neutropenia [31–34], no difference in the frequency of this adverse event was observed between the two chemotherapy regimens. Nevertheless, after excluding the DBCG 07-READ (the only RCT with mandatory prophylactic G-CSF in the TC arm), TC was associated with higher rates of febrile neutropenia than A+T. These results further reinforce the current recommendations to use prophylactic G-CSF when the TC regimen is used [31, 32].

Some limitations to be considered in the interpretation of our meta-analysis include the difficulty to perform non-inferiority assumptions. In addition, data were retrieved from published articles or proceedings of major conferences; individual-patient level data were not available. The missing data in some of the studies limited the sample size for the subgroup analyses. No safety data from the pooled analysis of the PlanB + SucessC trials were available, and the evaluation of long-term toxicities was not possible considering the relatively short follow-up of these RCTs. The lack of long-term follow-up and the subsequent limited number of events may also limit the interpretation of OS results. Nevertheless, despite the aforementioned limitations, this meta-analysis included only phase III RCTs, being the first to report updated data on the pros and cons about the controversial topic of adjuvant chemotherapy de-escalation in HER2-negative breast cancer.

In conclusion, our meta-analysis showed that sequential A+T was associated with an increased risk of toxicities and no survival benefit when compared to 6 cycles of TC as adjuvant chemotherapy in patients with HER2-negative early breast cancer. Patients with higher-risk features (e.g., those with hormone receptor-negative disease or N2 status) may represent the subgroups that benefit the most from more intensive chemotherapy regimens (A+T), whilst TC may be an efficacious and less toxic alternative for lower-risk patients.

Acknowledgements Matteo Lambertini acknowledges the support from the European Society for Medical Oncology (ESMO) for a Translational Research Fellowship at the Institut Jules Bordet (Brussels, Belgium).

Compliance with ethical standards

Conflict of interest Evandro de Azambuja received honoraria from Roche-Genentech, research grant from Roche–Genentech (to the insitution) and travel grants from Roche-Genentech and GlaxoSmithKline outside the submitted work. Matteo Lambertini served as a consultant for Teva and received honoraria from Theramex outside the submitted work All the other authors declare no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Sonnenblick A, Piccart M (2015) Adjuvant systemic therapy in breast cancer: quo vadis? Ann Oncol 26:1629–1634. https://doi.org/10.1093/annonc/mdv108
2. Senkus E, Kyriakides S, Ohno S et al (2015) Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 26:v8–v30. https://doi.org/10.1093/annonc/mdv298
3. Denduluri N, Chavez-MacGregor M, Telli ML et al (2018) Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol 36:2433–2443. https://doi.org/10.1200/JCO.2018.78.8604
4. Swain SM, Tang G, Geyer CE et al (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. https://doi.org/10.1200/JCO.2012.48.1275
5. Steinherz LJ (1991) Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 266:1672. https://doi.org/10.1001/jama.1991.03470120074036

6. Jones S, Holmes FA, O'Shaughnessy J et al (2009) Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. J Clin Oncol 27:1177–1183. https://doi.org/10.1200/JCO.2008.18.4028
7. Giordano SH, Lin Y-L, Kuo YF et al (2012) Decline in the use of anthracyclines for breast cancer. J Clin Oncol 30:2232–2239. https://doi.org/10.1200/JCO.2011.40.1273
8. Blum JL, Flynn PJ, Yothers G et al (2017) Anthracyclines in early breast cancer: the ABC trials—USOR 06–090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). J Clin Oncol 35:2647–2655. https://doi.org/10.1200/JCO.2016.71.4147
9. Mavroudis D, Matikas A, Malamos N et al (2016) Dose-dense FEC followed by docetaxel versus docetaxel plus cyclophosphamide as adjuvant chemotherapy in 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. https://doi.org/10.1093/annonc/mdw274
10. Ejlertsen B, Tuxen MK, Jakobsen EH et al (2017) Adjuvant cyclophosphamide and docetaxel with or without epirubicin for early *TOP2A* -normal breast cancer: DBCG 07-READ, an open-label, phase III, randomized trial. J Clin Oncol 35:2639–2646. https://doi.org/10.1200/JCO.2017.72.3494
11. Wolfgang et al (2018) Pooled analysis of two randomized phase III trials (PlanB/SuccessC) comparing six cycles of docetaxel and cyclophosphamide to sequential anthracycline taxane chemotherapy in patients with intermediate and high risk HER2-negative early breast cancer (n = 5,923). J Clin Oncol 36:522–522. https://doi.org/10.1200/JCO.2018.36.15_suppl.522
12. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339:b2535–b2535. https://doi.org/10.1136/bmj.b2535
13. Higgins JPT, Altman DG, Gotzsche PC et al (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928–d5928. https://doi.org/10.1136/bmj.d5928
14. Knoop AS, Knudsen H, Balslev E et al (2005) Retrospective analysis of topoisomerase IIa amplifications and deletions as predictive markers in primary breast cancer patients randomly assigned to cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide, epirubicin, and fluorouracil: Danish Breast Cancer Cooperative Group. J Clin Oncol 23:7483–7490. https://doi.org/10.1200/JCO.2005.11.007
15. Won HS, Lee KE, Sung SH et al (2014) Topoisomerase II alpha and microtubule-associated protein-tau as a predictive marker in axillary lymph node positive breast cancer. Tumori. https://doi.org/10.1700/1430.15820
16. Leo AD, Desmedt C, Bartlett JMS et al (2011) HER2 and TOP2A as predictive markers for anthracycline-containing chemotherapy regimens as adjuvant treatment of breast cancer: a meta-analysis of individual patient data. Lancet Oncol 12:1134–1142. https://doi.org/10.1016/S1470-2045(11)70231-5
17. Harbeck N, Prospective (2017) WSG phase III PlanB trial: final analysis of adjuvant 4xEC→4x doc vs. 6x docetaxel/cyclophosphamide in patients with high clinical risk and intermediate-to-high genomic risk HER2-negative, early breast cancer. J Clin Oncol 35:504
18. Colleoni M, Sun Z, Price KN et al (2016) Annual hazard rates of recurrence for breast cancer during 24 years of follow-up: results from the International Breast Cancer Study Group Trials I to V. J Clin Oncol 34:927–935. https://doi.org/10.1200/JCO.2015.62.3504
19. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2012) Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. The Lancet 379:432–444. https://doi.org/10.1016/S0140-6736(11)61625-5
20. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2015) Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 386:1341–1352. https://doi.org/10.1016/S0140-6736(15)61074-1
21. Perou CM, Sørlie T, Eisen MB et al (2000) Molecular portraits of human breast tumours. Nature 406:747–752. https://doi.org/10.1038/35021093
22. Cardoso F, van't Veer LJ, Bogaerts J et al (2016) 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 375:717–729. https://doi.org/10.1056/NEJMoa1602253
23. Sparano JA, Gray RJ, Makower DF et al (2018) Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 379:111–121. https://doi.org/10.1056/NEJMoa1804710
24. Lambertini M, Goldrat O, Clatot F et al (2017) Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. Curr Opin Oncol 29:243–252. https://doi.org/10.1097/CCO.0000000000000380
25. Lambertini M, Moore HCF, Leonard RCF et al (2018) Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient–level data. J Clin Oncol 36:1981–1990. https://doi.org/10.1200/JCO.2018.78.0858
26. Zhao J, Liu J, Chen K et al (2014) What lies behind chemotherapy-induced amenorrhea for breast cancer patients: a meta-analysis. Breast Cancer Res Treat 145:113–128. https://doi.org/10.1007/s10549-014-2914-x
27. Lambertini M, Campbell C, Bines J et al (2018) Adjuvant anti-HER2 therapy, treatment-related amenorrhea, and survival in premenopausal HER2-positive early breast cancer patients. JNCI J Natl Cancer Inst. https://doi.org/10.1093/jnci/djy094
28. Lambertini M, Viglietti G, de Azambuja E (2018) Impact of ovarian function suppression in premenopausal women with estrogen receptro-positive early breast cancer. Curr Opin Oncol. https://doi.org/10.1097/CCO.0000000000000491
29. Francis PA, Pagani O, Fleming GF et al (2018) Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med 379:122–137. https://doi.org/10.1056/NEJMoa1803164
30. Metzger-Filho O, Sun Z, Viale G et al (2013) Patterns of recurrence and outcome according to breast cancer subtypes in lymph node–negative disease: results from International Breast Cancer Study Group Trials VIII and IX. J Clin Oncol 31:3083–3090. https://doi.org/10.1200/JCO.2012.46.1574
31. Smith TJ, Bohlke K, Lyman GH et al (2015) Recommendations for the use of WBC growth factors: American society of clinical oncology clinical practice guideline update. J Clin Oncol 33:3199–3212. https://doi.org/10.1200/JCO.2015.62.3488
32. Aapro MS, Bohlius J, Cameron DA et al (2011) 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 47:8–32. https://doi.org/10.1016/j.ejca.2010.10.013
33. Chan A, Fu WH, Shih V et al (2011) Impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving docetaxel plus cyclophosphamide chemotherapy. Support Care Cancer 19:497–504. https://doi.org/10.1007/s00520-010-0843-8
34. Soong D, Haj R, Leung MG et al (2009) High rate of febrile neutropenia in patients with operable breast cancer receiving docetaxel and cyclophosphamide. J Clin Oncol 27:e101–e102. https://doi.org/10.1200/JCO.2009.23.0508