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SHORT COMMUNICATION

Meta-analysis of concomitant compared to sequential adjuvant trastuzumab in breast cancer: the sooner the better

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Abstract Adjuvant trastuzumab (T) significantly reduces the risk of progression and death in HER-2 positive high-risk early breast cancer. The differential benefit of T, administered either sequential or concomitant, has been calculated with 2 comparative meta-analyses of randomized trials. We have meta-analyzed sequential and concomitant arms of 6 T adjuvant trials separately and then calculated the pooled hazard ratios (HRs) for disease-free survival (DFS) and overall survival (OS) in both meta-analyses. Primary cardiac event rates have also been meta-analyzed. In the concomitant T meta-analysis, HRs for DFS and OS were 0.62 and 0.68, respectively ($P < 0.0001$ and <0.00001 for both endpoints). Conversely, in the sequential T meta-analysis, HRs for DFS and OS were, respectively, 0.74 and 0.87, where P is, however, significant only in the first comparison ($P < 0.00001$ and $P = 0.09$). Relative risks (RRs) for major cardiac events (severe cardiac hearth failure or death) are 2.44 ($P = 0.07$) in the concomitant T meta-analysis and 8.35 ($P < 0.0001$) in the sequential T meta-analysis. Concomitant adjuvant T therapy seems to give a significant and greater benefit than sequential administration in both DFS and OS, and the number of cases of severe cardiotoxicity does not seem to be higher in concomitant administration than in the sequential one.

Keywords Breast cancer · Adjuvant trastuzumab · Concomitant · Sequential · Adjuvant chemotherapy

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Introduction

Trastuzumab (T) is a humanized monoclonal antibody (MoAb) that binds to a specific epitope of HER-2 protein on breast cancer (BC) cells' surface. This interaction inhibits the signal transduction induced by other peptide growth factors that interact with their own receptors. Therefore, the net result is cellular growth inhibition. The initial demonstration of the therapeutic benefit achieved with T and the criteria used to select individuals suitable for treatment with this drug were obtained from trials conducted in women with metastatic BC. Afterward, several randomized phase-III trials have provided clear and consistent evidence that the addition of T to a taxane and/or anthracycline-containing adjuvant chemotherapy regimen significantly reduces the likelihood of disease relapse and death among women with HER-2-positive early BC, but at the cost of a slight increase in the incidence of cardiac dysfunction. Concerning the additional effects of anthracyclines on cardiac toxicity, lead researchers have carried out studies in which adjuvant T was administered in association with taxanes after a previous course of (epi)doxorubicin alone without T. In some studies, T was administered in an anthracycline-free combination (taxane- and platinum-based) after the entire course of adjuvant chemotherapy, while in some others, the administration of T has been performed for only 9 weeks instead of the standard 1-year course.

The question of whether concurrent (with chemotherapy and thereafter) trastuzumab is better than sequential trastuzumab (i.e., starting after completion of chemotherapy) has not been exhaustively answered yet. The updated results of the NCCTG N9831 trial have recently confirmed that sequential trastuzumab-based therapy following chemotherapy reduces recurrence risk. However, a strong

trend for higher disease-free survival (hazard ratio [HR] 0.75) has been observed with the concurrent use of T and paclitaxel chemotherapy in comparison to the sequential treatment. These data support the standard North American practice of administering adjuvant T concurrently with taxane-based chemotherapy and then continuing the administration of adjuvant T for a total duration of 1 year [1]. An early administration of T (with or without previous anthracyclines) during adjuvant therapy for the treatment of HER-2 positive BC could become the worldwide standard of care, if better results in terms of benefit (i.e. overall survival [OS] other than PFS) were achieved without a significantly increased burden of severe cardiac toxicity (cardiac death or severe cardiac hearth failure [CHF]). Trastuzumab-related cardiac changes are mostly manifested by an asymptomatic decrease in left ventricular ejection fraction (LVEF), or less often by clinical heart failure. In contrast to anthracyclines, T-associated cardiac dysfunctions do not seem to be related to cumulative dose and can be more often reversed with treatment discontinuation; rechallenge is often tolerated after recovery. We have performed 2 comparative meta-analyses to investigate whether concomitant T (meta-analysis of concomitant T vs. control arms) offers a different benefit in terms of DFS and OS compared to sequential T (meta-analysis of sequential T vs. control arms) in major randomized, controlled phase-III trials. Also, the different relative risk (RR) (if any) of primary cardiac endpoints (severe CHF and death) was calculated through a meta-analysis of cardiac events.

Results

We have identified six eligible trials [1, 2–9], for a total of 13,331 patients with HER-2-positive early breast cancer, 7,138 of which have been assigned to chemotherapy combined with T and 6,193 to chemotherapy alone. The characteristics of the included trials are summarized in Table 1. The median follow-up ranged between 2.9 and 5.5 years.

In the 'concomitant' analysis, the DFS was significantly longer in the T arm (HR 0.62, 95% CI 0.49, 0.78; $P < 0.0001$), although significant heterogeneity was reported ($P = 0.002$). The OS was significantly longer in the T arm (HR 0.68, 95% CI 0.59, 0.78; $P < 0.00001$), with no significant heterogeneity ($I^2 = 0\%$; $P = 0.63$) (Fig. 1).

In the 'sequential' analysis, the DFS was significantly longer in the T arm (HR 0.74, 95% CI 0.67, 0.83; $P < 0.00001$), with no significant heterogeneity ($P = 0.41$). The OS, however, was not significantly longer in the T arm (HR 0.87, 95% CI 0.75, 1.02; $P = 0.09$), without any heterogeneity ($I^2 = 0\%$; $P = 0.48$) (Fig. 2).

All RCTs were available also for the determination of the risk of primary cardiac events. In the 'concomitant' analysis, when considering only the arms in which T had been administered for 1 year (5 arms, 7,226 patients), a non-significantly increased risk of severe cardiac events was found in the T arm (RR 2.44, 95% CI 0.93, 6.35, $P = 0.07$), which became, however, significant after excluding non-anthracyclines containing trials (RR 3.79; $P = 0.0005$) (Table 2).

In the 'sequential' analysis, a significantly increased risk of severe cardiac events was found in the T arm (RR 8,35, 95% CI 2.98, 23.40, $P < 0.0001$), with no significant heterogeneity ($P = 0.74$).

Discussion

Randomized trials have definitively shown that the administration of adjuvant trastuzumab in the treatment of HER-2-positive BC decreases the risk of recurrence and mortality by more than 30%. A benefit in survival was confirmed even at the latest follow-up of large adjuvant trials, with the exception of the HERA trial, where the HR for survival at 4 years was a non-significant 0.86. Patients were offered two options: sequential T treatment (for 1 year after the completion of adjuvant anthracycline and/or taxane-based chemotherapy as in the HERA trial, for example) or concomitant T treatment (for 1 year starting from the taxane part of adjuvant treatment with or without a previous course of anthracycline as in North American trials). The first interim analysis of sequential versus concomitant T arms of the NCCTG 9831 trial has recently affirmed that concomitant T administration has reduced the risk of progression and survival by 25 and 21%, raising the question of T-administration timing. If the concomitant administration of T confirmed a gain in OS compared to the sequential one, the standard practice of the administration of T would change, at least in European countries. The American practice actually consists in administering T concomitantly to the taxane-based portion of adjuvant chemotherapy, according to the (North American) adjuvant trial designs.

The results of our 2 comparative meta-analyses confirm that the advantages of concomitant administration of T are greater and more robust compared to the ones observed with sequential administration in terms of OS (HR 0.70 in concomitant arms and 0.87 in sequential arms, even though this last one is not significant). The benefits achieved in terms of DFS are similar, even though they were found to be higher in magnitude in concomitant T arms (HR 0.64 and 0.74). The data of the NCCTG 9831 trial and our meta-analyses have *de facto* replicated metastatic-setting trial

Table 1 Characteristics of trastuzumab-adjuvant trials included in the meta-analysis

Study (ref.)/ year	Median follow-up (years)	No pts	Tumor characteristics	Treatment regimens and no pts per arm	Cross over (%)	DFS HR	OS HR	Primary cardiac events RR	LVEF decrease events (RR)
NCCTG9831 Perez/2009° Perez/2008*	5.5 for A versus B 5.3 for B versus C	3,133	Early-stage invasive breast cancer, node positive or high-risk node negative (tumor >1 cm if HR negative or >2 cm if HR positive)	°° A: AC → P (1,087) B: AC → P → T × 1 year overall (1,097) C: AC → PT → T × 1 year overall (949)	255/958	B versus A 0.67 ($P = 0.0005$) C versus B 0.75 ($P = 0.019$)	B versus A 0.86 ($P = 0.281$) C versus B 0.79 ($P = 0.135$)	C versus A: 9.5 (19 vs 2) B vs A: 8.03 (20 vs 2)	C vs A: 2.11 (57 versus 31) B versus A: 1.46 (46 vs 31)
BCIRG 006 Slamon/2009	65 months	3,222	Node positive or high-risk node negative	$ A: AC → D (1,073) B: AC → DT → T × 1 year overall (1,074) C: Carboplatin +DT → T × 1 year overall (1,075)	23/1,073	0.64 0.75	0.63 0.77	2.95 (21 vs 79 and 0.57 (4 vs 7) B versus A and C versus A	0.84 (97 vs 114) and 1.66 (194 vs 114) for C va A and B versus A
NSABP B31 Perez/2007@ Tan Chiu/ 2005@@ Rastogi/ 2007@@@	2.9 (5 for cardiac analysis)	1,736	Early-stage node positive invasive breast cancer	@@@@ A: AC → P (872) B: AC → PT × 1 year overall (864)	158/1,021	@ 0.48 joint analysis ($P < 0.00001$)	@ 0.65 joint analysis ($P = 0.0007$)	@@@ 4.79 (35 vs 7)	@@ According to CREC analysis: (289 vs 138) 2.01
HERA Gianni/2009	4	5,090	Early-stage invasive breast cancer, node positive or high-risk node negative (tumor >1 cm)	# A: CT ± RT → observation (1,698) B: CT ± RT → T × 1 year overall (1,703) C: CT ± RT → T × 2 years overall (1,689)	885/1,698 arm A	0.76 ($P < 0.0001$) B vs A	0.85 ($P = 0.1087$)	13.29 (13 vs 1)	4.87 (62 vs 13)
FinHer/2009	62 months	232	Early-stage, node-positive or node-negative breast cancer (>2 cm and PgR negative)	## A: D o V → CEF (116) B: D o V +T × 9 weeks → CEF (116)	Not reported	0.65 (distant DFS: $P = 0.12$)	0.55 ($P = 0.094$)	0.5 (1 vs 2 events)	0.71 (7 vs 10 events)

Table 1 continued

Study (ref.)/ year	Median follow-up (years)	No pts	Tumor characteristics	Treatment regimens and no pts per arm	Cross over (%)	DFS HR	OS HR	Primary cardiac events RR	LVEF decrease events (RR)
PACS04 Spielmann 2009	47 months	528	Operable invasive node positive breast cancer	§ 6 cycles CT → T × 1 year overall (260) 6 cycles CT → observation (268) (after both RT and CT)	Not reported	0.86 ($P = 0.41$)	1.27 (p not significant)	4 vs 1 §§ (4.12)	37 vs 11 §§§ (3.47)

Ref reference, *no* number, *DFS* progression-free survival, *OS* overall survival, *HR* hormone receptor, *NSABP* national surgical adjuvant breast and bowel project, *NCCTG* north central cancer treatment group, *HERA* herceptin adjuvant trial, *BCIRG* breast cancer international research group, *FinHer* finland herceptin trial, *LVEF* left ventricular ejection fraction, *CT* chemotherapy, *AC* doxorubicin/cyclophosphamide, *P* paclitaxel, *D* docetaxel, *V* vinorelbine, *T* trastuzumab, *RR* relative risk, *PACS* Programmes d'Actions Concertées

°NCCTG9831 trial only analysis; *cardiac safety only; °°60 mg/m2 doxorubicin and 600 mg/m2 cyclophosphamide every 3 weeks for four cycles followed by 12 weekly doses of 80 mg/m2 paclitaxel were compared with the same regimen plus a 4-mg/m2 loading dose of trastuzumab followed by weekly doses of 2 mg/kg for 51 weeks

$: 60 mg/m2 doxorubicin and 600 mg/m2 cyclophosphamide every 3 weeks for four cycles followed by 100 mg/m2 docetaxel on day 1 of each 21-day cycle were compared with the same regimen plus a 4-mg/kg concurrent loading dose of trastuzumab followed by 2 mg/kg weekly for 12 weeks subsequently followed by 6 mg/kg every 3 weeks for 14 cycles and with carboplatin AUC6 plus docetaxel 75 mg/m2 60 mg/m2 plus a 4-mg/kg concurrent loading dose of trastuzumab followed by 2 mg/kg weekly for 18 weeks subsequently followed by 6 mg/kg every 3 weeks for 7 cycles

@ joint analysis of concomitant arms of NSABPB31 and NCCTG9831, @@ LVEF analysis of NSABPB31 only (CREC:independent Cardiac Review and Evaluation Committee), @@@ update of cardiac events analysis of NSABPB31 only, @@@@ 60 mg/m2 doxorubicin and 600 mg/m2 cyclophosphamide every 3 weeks for four cycles followed by 175 mg/m2 paclitaxel every 3 weeks for four cycles were compared with the same regimen plus a 4-mg/kg loading dose of trastuzumab followed by weekly doses of 2 mg/kg for 51 weeks

The HERA trial allowed the administration of several alternative chemotherapy regimens; chemotherapy was anthracycline based in 94% of patients; 26% received a taxane and 76% received radiotherapy. Patients had to have received at least four cycles of an approved chemotherapy regimen. In all cases, the maximum cumulative dose of doxorubicin was 360 mg/m2, and the maximum cumulative dose of epirubicin was 720 mg/m2. For trastuzumab, a loading dose of 8 mg/kg i.v. was followed by 6 mg/kg every 3 weeks for 1 or 2 years (data on 2 years administration not available)

finHER: 100 mg/m2 docetaxel on day 1 of each 21-day cycle or 25 mg/m2 vinorelbine on days 1, 8, and 15 of the 21-day cycle and 600 mg/m2 fluorouracil, 60 mg/m2 epirubicin, and 600 mg/m2 cyclophosphamide on day 1 of each 21-day cycle were compared with the same regimen plus a 4-mg/kg loading dose of trastuzumab followed by weekly doses of 2 mg/kg for 9 weeks

§6 FE100C regimen included fluorouracil 500 mg/m2, epirubicin 100 mg/m2, and cyclophosphamide 500 mg/m2 (at day 1 of a 21-day cycle; 6 ED75 regimen included epirubicin 75 mg/m2 and docetaxel 75 mg/m2 (day 1 q day 21). T loading dose 8 mg/kg → maintenance dose 6 mg/kg q3w × 18; §§: symptomatic congestive heart failure; §§§: LVEF <50% for this analysis

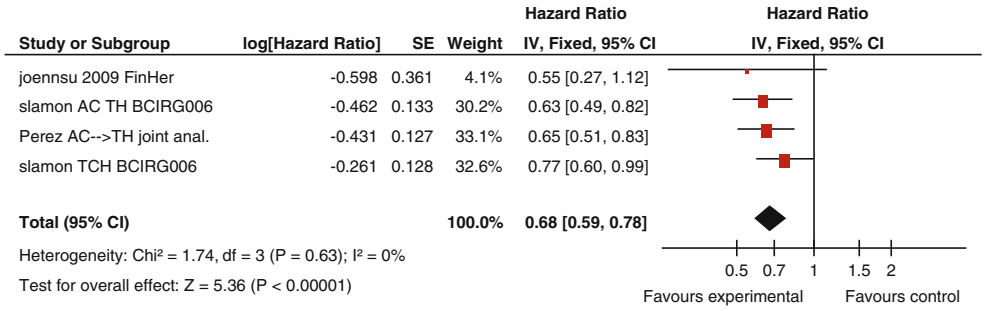

Fig. 1 Forrest plots for OS with concomitant T + chemotherapy versus chemotherapy alone

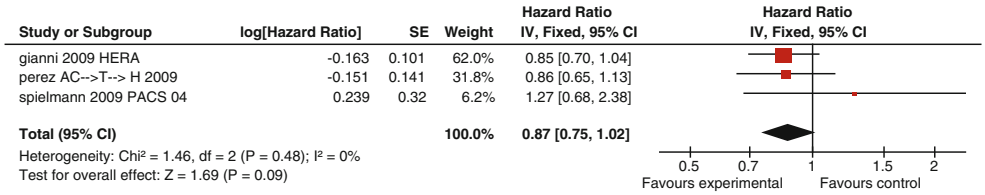

Fig. 2 Forrest plots for OS with sequential T + chemotherapy versus chemotherapy alone

Table 2 Cardiotoxicity definitions in the adjuvant trastuzumab trials

Study	Primary cardiac endpoint	Additional cardiac safety endpoints reported
NCCTG9831	Cardiac event rate: defined as death or NYHA class III/IV symptoms with either decline in LVEF > 10% from baseline to < 55%, or decline in LVEF >5% to < LLN	Asymptomatic decrease in LVEF requiring discontinuation of trastuzumab
BCIRG 006	Cardiac death or grade 3/4 CHF, grade 3/4 cardiac ischemia/infarction, grade 3/4 cardiac arrhythmia (grade 3 CHF is symptomatic CHF responsive to treatment, LVEF between 20% and 39%; grade 4 CHF is refractory CHF, LVEF > 20%)	Patients with >10% relative LVEF decline from baseline
NSABP B31	Cardiac event rate: defined as death or NYHA class III/IV symptoms with either decline in LVEF > 10% from baseline to <55%, or decline in LVEF > 5% to < LLN	Patients with symptoms of CD not meeting criteria for a cardiac event. Asymptomatic decrease in LVEF requiring discontinuation of trastuzumab
HERA	Cardiac death or severe CHF defined as NYHA class III/IV symptoms and LVEF < 50% with an absolute decrease of ≥ 10% from baseline	Symptomatic CHF, including severe CHF (any degree of symptoms and LVEF < 50% with a decrease of ≥10% from baseline at any time). Decrease in LVEF (LVEF < 50% with absolute Decrease of ≥10% from baseline at any time)
FinHer/2009	Unknown	Cardiac death and CHF/MI (not otherwise defined). Patients with ≥1 measurement of LVEF ≥15% below baseline. Patients with decline in LVEF > 10% resulting in LVEF < 50%
PACS04 (no prespecified cardiac endpoints)	Trastuzumab treatment was stopped if LVEF dropped below 45%, or if LVEF was between 45 and 50% together with a relative decrease of 15% or more	If LVEF ranged between 45 and 50% together with a relative decrease less than 15%, or If LVEF ranged between 50 and 55%, a cardiologist's advice was requested to decide about trastuzumab discontinuation. No trastuzumab reintroduction was allowed

NSABP national surgical adjuvant breast and bowel project, *NCCTG* north central cancer treatment group, *HERA* herceptin adjuvant trial, *BCIRG* breast cancer international research group, *FinHer* finland herceptin trial, *NYHA* New York heart association, *LVEF* left ventricular ejection fraction, *LLN* lower limit of normal, *CHF* congestive heart failure, *CD* cardiac dysfunction; *MI* myocardial infarction

results, where the combination of taxane and T provided a greater survival-related benefit compared to taxane alone, although only very few patients crossed over from monotherapy arms to T [10–18]. Trastuzumab plus taxanes also appear to give better results than trastuzumab alone [19, 20]. In summary, administering T after the conclusion of adjuvant chemotherapy seems to dilute and cancel the outcome benefit with longer follow-up.

There are several explanations for this difference. First of all, in the HERA trial, that retained 62% of its weight in the sequential T meta-analysis, 65% of the patients in the observational arm crossed over to T after the release of adjuvant T data, achieving a greater survival benefit compared to the no-crossover population. This crossover effect could potentially decrease the long-term survival benefit. Second, only 26% of the patients in the HERA sequential trial have received adjuvant taxanes, in contrast to other trials, such as the North American ones, where taxanes were administered to almost all patients in concomitant T arms. A meta-analysis of 13 trials (22,903 patients) testing the efficacy of the addition of taxanes to anthracycline-based adjuvant chemotherapy came also to the conclusion [21] that the addition of a taxane as adjuvant chemotherapy significantly improves both DFS (pooled HR 0.83) and OS (pooled HR 0.85) in an unselected setting. This resulted in an absolute five-year risk reduction by 5% for DFS and by 3% for OS.

The rationale for combining T and cytotoxic agents, however, is also provided by preclinical studies suggesting strong additive or synergistic interactions between T and multiple drugs, including anthracyclines, taxanes, platinum analogs, vinorelbine, and cyclophosphamide [22]. In a group of 297 women with metastatic BC who received either paclitaxel or cyclophosphamide plus epirubicin, the women whose tumors were HER2-positive showed significantly longer PFS and OS under a taxane-containing regimen, while no differences were observed between the two regimens in those whose tumors were HER2-negative [23]. These results have been confirmed by some [24, 25], but not all studies [26]. In the adjuvant setting, the interaction between the HER-2 status and the benefit obtained from taxanes was evaluated in a subset of 1,322 women treated in the CALGB 9,344 trial (which showed a more significant improvement in terms of DFS and OS in women with node-positive BC with four cycles of adjuvant paclitaxel after AC rather than four cycles of AC alone) who had tissue blocks available for analysis [27]. In a prespecified analysis, a significant benefit was obtained from the addition of paclitaxel after AC in women with HER-2-positive cancers, while no evidence of benefit was recorded in the subgroup with ER-positive, HER2-negative tumors. Overall, this meta-analysis demonstrates that the administration of taxanes and T should become the standard of care for the treatment of HER-2 positive BC in adjuvant setting and that it should be early and concomitant.

Despite close monitoring, long-term concomitant treatment with chemotherapy and T has been associated with a small but real increase in the risk of myocardial dysfunction and possibly arrhythmias [28]. In general, T-related cardiac dysfunctions appear to be less severe and more reversible than the ones associated with anthracyclines. However, a full characterization of long-term cardiac side effects associated with adjuvant trastuzumab needs longer follow-up. Early reports from 4 major randomized trials suggest that approximately 2–3% of women who are administered T for 1 year after anthracycline-based adjuvant chemotherapy will develop symptomatic congestive heart failure, while a higher percentage (7–17%) will experience an asymptomatic decline in LVEF. The results of our cardiac outcome meta-analysis show that the RRs of a cardiac event are 2.44 and 8.35 in concomitant arms and in sequential arms, respectively ($P = 0.07$ and $P < 0.0001$). After the exclusion of the anthracycline-free arm from the BCIRG 006 trial, the result is slightly worse, but still significant, in the concomitant meta-analysis (RR 3.79; $P = 0.0005$), and is half the one achieved in the sequential meta-analysis. In particular, our meta-analysis shows that, in terms of primary cardiac outcomes, the incidence of cardiac adverse events is generally low (2.18 and 1,39% in concomitant and sequential T arms, respectively) and of similar magnitude in 2 comparative analyses. This is probably due to the strict (cardiologic) inclusion criteria that made it possible to exclude patients who had developed cardiac toxicity after a course of anthracyclines.

In the pivotal phase-III trial assessing the benefit of adding T to cytotoxic therapy in metastatic patients [13], the incidence of cardiac dysfunction with T plus AC chemotherapy was 27%, compared to the 8% of AC alone, and it was higher also with T plus paclitaxel versus paclitaxel alone (13 vs. 1%). On the other hand, the incidence of NYHA class-III to -IV heart failure was markedly lower with T alone (2–4%) and with paclitaxel plus T (2 vs. 1% for paclitaxel alone), but it was 16% with AC plus T (compared to 4% with AC alone). Thus, it can be said that, after completing the initial anthracycline-containing chemotherapy course, a therapy with T and a concomitant taxane is generally safe and not more cardiotoxic than sequential T administration, provided that no history of heart failure or cardiac disease exists, that no cardiac symptoms have occurred during the initial chemotherapy and that post-anthracycline LVEF is adequate (may be >55%).

Other modalities of T administration (shorter duration or anthracyclines-free schedules) seem to increase its risk/benefit ratio in adjuvant setting.

Conclusion

Despite the weakness of a non-individual patient data meta-analysis, where the HR and the number of events have been calculated from published trials, it seems demonstrated that the concomitant administration of T during adjuvant chemotherapy improves the outcome of

HER-positive breast cancer patients compared to the sequential administration and that its benefit is greater and more significant than in sequential trials, in particular in terms of OS. Cardiotoxicity is increased, but the RR obtained in the concomitant T meta-analysis was not significant. Conversely, the risk of a major cardiac event is significantly increased in the concomitant analysis only after the exclusion of the anthracycline-free arm from the BCIRG006 trial. Inferior outcome in the sequential T meta-analysis may be probably due to less frequent use of taxanes in sequential trials (e.g. HERA and PACS 04 studies) and significant crossover rate.

In conclusion, adjuvant T should be always administered, if medically feasible, concomitantly and not sequentially to a taxane-containing chemotherapy (with or without a previous course of anthracyclines), provided that cardiac risk factors are excluded.

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