Adjuvant Therapy for HER2 Positive Breast Cancer: Are Anthracyclines Still Necessary?

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Abstract: Anthracyclines are integral components of most adjuvant chemotherapy regimens for surgically removed early breast cancer and are central to the accepted treatment standards. Recently the standard anthracycline regimen of doxorubicin plus cyclophosphamide was found to be inferior in preventing recurrence of breast cancer when compared to cyclophosphamide and docetaxel, questioning the necessity to expose patients to the potential cardiotoxicity of anthracycline in the adjuvant setting. Trastuzumab, a humanized monoclonal antibody against the extracellular domain of the human epidermal growth factor receptor 2 (HER2) has become the cornerstone of treatment of breast cancers that overexpress HER2 in the neo-adjuvant and metastatic setting. Unfortunately, the combination of anthracyclines and trastuzumab produces a high incidence of cardiotoxicity as seen in early trials of metastatic breast cancer. Five adjuvant trials combining trastuzumab with different anthracycline-based regimens have been reported, all of them revealing similar efficacy in reducing recurrence of breast cancer. The trastuzumab adjuvant trial 006 from the Breast Cancer International Research Group shows for the first time that a nonanthracycline-containing regimen with trastuzumab has equivalent efficacy in decreasing the recurrence of breast cancer, with less incidence of cardiotoxicity when compared to anthracycline-containing trastuzumab adjuvant regimens. Further trials are needed to determine the optimal length of adjuvant therapy with trastuzumab, as well as long-term side effects with special attention to cardiotoxicity.

In the United States, an estimated 182,460 cases of invasive breast cancer will be diagnosed this year and approximately 40,480 women are expected to die from this disease,[1] these statistics make breast cancer the most commonly diagnosed malignancy among women. A great amount of progress has been made in recent years in terms of understanding tumor biology and in the development of more specific and tailored therapies in the metastatic and adjuvant treatment of breast cancer.

Anthracyclines are important in optimizing the adjuvant treatment of breast cancer and are indicated for therapy regardless of the extent of nodal involvement, hormone receptor status, or human epidermal growth factor receptor 2 (HER2) expression level of the tumor. These agents are integral components of most regimens and are central to the accepted treatment standards.

Approximately 15%–25% of breast cancers either overexpress the HER2 protein or have an amplification of the c-erbB2 proto-oncogene, encoding for the HER2 protein. HER2 plays an important role in processes of normal cellular growth, differentiation, and survival. Overexpression of HER2 is considered an early and stable event and is associated with aggressive behavior in the tumor.[2,3] Homo or hetero-dimerization with other members of the epidermal growth factor receptor (EGF-R) superfamily leads to increased signaling and molecular events that lead to potential metastases, undifferentiated phenotype, decreased apoptosis, and less estrogen sensitivity.[4] Trastuzumab (Herceptin, Genentech), a humanized monoclonal antibody against the extracellular domain of HER2, has been shown to benefit patients with HER2-positive metastatic breast cancer administered weekly or every 3 weeks, alone[5] or in combination with chemotherapy.[6] Cardiotoxicity has been reported in 1.4% of women who received the drug as monotherapy for metastatic disease.[5] This effect on the heart increases when trastuzumab is combined with anthracyclines[6] and is seen to a lesser degree when trastuzumab is combined with taxanes.[7] The effectiveness of trastuzumab in the treatment of advanced breast cancer has prompted its evaluation in the adjuvant setting; herein we discuss the adjuvant trastuzumab trials, including the results from the Breast Cancer International Research Group (BCIRG) 006 trial, in which the combination of docetaxel (Taxotere, Sanofi-Aventis), carboplatin, and trastuzumab has reported equal efficacy in reducing the recurrence of breast cancer that overexpresses HER2, when compared to anthracycline-containing regimens.

Overview of Selected Adjuvant Chemotherapy Trials With Anthracyclines

A large number of randomized adjuvant chemotherapy trials have evaluated the use of anthracyclines (Table 1). The National Surgical Adjuvant Breast and Bowel Project (NSABP) studies B-15 and B-23 found that a regimen of 4 cycles of doxorubicin plus cyclophosphamide (AC) was equivalent to 6 cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with respect to event-free survival, relapse-free survival (RFS), and overall survival (OS) in breast cancer patients regardless of nodal status, age, or estrogen receptor (ER) status. However, it was evident that AC offered the advantages of a shorter treatment course with fewer side effects.[8,9] The National Cancer Institute of Canada evaluated both moderate risk (1–3 positive nodes) and high risk (>4 positive nodes) premenopausal women receiving either cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) or CMF. Patients fared better on the CEF regimen than on CMF; 63% of the CEF group remained relapse-free after 5 years compared with 53% of the CMF group (P=.009). OS rates for CEF and CMF were 77% and 70%, respectively (P=.03).[10] In the setting of node-negative disease, in a planned pooled efficacy analysis of the National Epirubicin Adjuvant Trial and the Scottish Cancer Trials Breast Group BR9601 trials, 28% of the 2,391 patients enrolled in the 2 studies had node-negative disease. The trials compared the classic CMF regimen with 100 mg/m^2 epirubicin followed by CMF (ECMF) and found that ECMF produced significantly better RFS with a relative risk reduction (RRR) of 30% (P=.0003) and OS (RRR, 36%; P=.0001), irrespective of nodal status.[11]

The addition of paclitaxel after AC has been shown, in the NSABP 28 study, to improve disease-free survival (DFS at 5 years, 76% [AC→paclitaxel] vs 72% [AC]; RRR, 17%; P=.006) without OS improvement data at the present time.[12] Overall, these studies established the role of anthracyclines in early node-positive breast cancer; these regimens are at least equivalent (ie, AC) or superior to CMF (ie, 5-fluorouracil, epirubicin, and cyclophosphamide). In a similar design, the Cancer and Leukemia Group B study 9344 demonstrated improvement in DFS (AC [65%] vs AC + paclitaxel [70%]; P=.0011) and OS (AC [77%] vs AC + paclitaxel [80%]; P=.0089).[13]

Based on studies of cyclophosphamide and docetaxel (TC) in metastatic breast cancer that showed high efficacy and no cardiac toxicity,[14] a randomized adjuvant trial was conducted comparing TC with standard-dose AC in the adjuvant treatment of women with stage I–III invasive breast cancer with complete surgical excision of the primary tumor, with a primary endpoint of DFS.[15] Comparison at 5 years showed that the DFS rate for patients receiving TC was 86% versus 80% for patients receiving AC (RRR, 33%; P<.015). OS at 5 years had not reached statistical significance, with 90% of patients alive in the group treated with TC versus 87% on AC (RRR, 24%; P=.13). In a recent update, Jones and colleagues[16] also reported a survival advantage (82 vs 87%, respectively; RRR, 31%; P=.032). This study is of overwhelming importance because it is the first adjuvant study in which a nonanthracycline-containing arm has shown superiority over AC. The RRR of replacing anthracycline with docetaxel (AC vs AT) resulted in a larger benefit than adding 4 cycles of paclitaxel to AC. Moreover, 16% of all patients enrolled in this trial were 65 years or older. Most US-based trials in the

Table 1. Summary of Selected Randomized Adjuvant Chemotherapy Trials of Anthracycline-containing Regimens

Study	N	Endpoints	Treatment	Results	Conclusions
NSABP B15[9]	2,194 (node-positive)	OS	AC × 4, CMF × 6; AC × 4→6 months of rest→ CMF × 3	62.3% DFS, 83% OS (3-year)	AC × 4 not superior to CMF × 6 but less toxic, less costly
NSABP B23[8]	2,008 (node-negative/ ER-negative)	RFS, EFS, S	AC × 4, AC × 4 + tam (5 years); CMF × 6; CMF × 6 + tam (5 years)	RFS, 87% in AC and CMF groups; (*P*=.6); OS, 90% for AC, 89% for CMF (5-year)	No significant difference in all 4 groups for RFS (*P*=.96), EFS (*P*=.8), or S (*P*=.8)
NCIC[10] MA.05	710 (node-positive)	RFS, OS	CEF 120 vs CMF epirubicin 120 days 1, 8	DFS (5 years), 63% vs 53% (*P*=.009); OS (5 years); 77% vs 70% (*P*=.03)	~19% RRR for death; ~29% RRR for relapse. Moderate dose density is reasonable approach
NEAT[11]	2,021 (NEAT); 370 (SCTBG)	RFS, OS	NEAT: E (100 mg/m^2) × 4→ cCMF × 4 versus cCMF × 6; SCTBG BR9601: E (100 mg/m^2) × 4→ CMF × 4 vs CMF × 8	ECMF: RFS, RRR, 30% (*P*=.003); OS, RRR, 24% (*P*=.0001).	ECMF advantage regardless of node status, age, ER status.
NSABP 28[12]	3,060	DFS, OS	AC × 4 versus AC × 4→ T × 4	5 year DFS, 76% (AC × 4→P) vs 72% (AC) RRR, 17% (*P*=.006); OS: No difference between groups	The addition of T to AC resulted in significant improvement in DFS but no significant improvement in OS
CALGB 9344[13]	3,121	DFS, OS	AC × 4 versus AC × 4→ T × 4	5 year DFS, 65% vs 70%; RRR, 17% (*P*=.0011) 5 year OS, 77% vs 80%; RRR, 18% (*P*=.0098)	The addition of T to AC demonstrated improvement in DFS and OS.
Jones et al[15]	1,016	DFS	AC × 4 versus docetaxel/C × 4	5 year DFS, 86% (TC) vs 80% (AC); RRR, 33% (*P*<.015). 5 year OS, 82% (AC) vs 87% (TC); RRR, 31% (P=.032)	At 5 years, TC was associated with a superior DFS

AC=doxorubicin and cyclophosphamide; CALGB=Cancer and Leukemia Group B; CEF=cyclophosphamide, epirubicin, and 5-fluorouacil; CMF=cyclophosphamide, methotrexate, 5-fluorouacil; cCMF=classical CMF; DFS=disease-free survival; E=epirubicin; ECMF=epirubicin followed by CMF; EFS=event-free survival; ER=estrogen receptor; NCIC=National Cancer Institute of Canada; NEAT=National Epirubicin Adjuvant Trial; NSABP=National Surgical Adjuvant Breast and Bowel Project; OS=overall survival; RFS=relapse-free survival; RRR=relative risk reduction; S=survival; SCTBG=Scottish Cancer Trials Breast Group; T=paclitaxel; tam=tamoxifen; TC=docetaxel and cyclophosphamide.

adjuvant setting have less than 10% of patients in this age group.[16] These intriguing results have caused researchers to question the necessity of incorporating anthracyclines in the adjuvant treatment of breast cancer in node-positive, as well as in high-risk node-negative, patients.

Overview of Adjuvant Clinical Trials With Trastuzumab

Over the past decade, 5 phase III randomized clinical trials with over 13,000 participants have evaluated the use of trastuzumab in addition to chemotherapy for early-stage breast cancer (Table 2); interim results of these trials have been reported. All the trastuzumab adjuvant trials enrolled patients with HER2-positive (immunohistochemistry 3+/fluorescence in situ hybridization [FISH] amplified or chromogenic in situ hybridization amplified) invasive breast cancer resected by lumpectomy or mastectomy. Patients had either node-positive or node-negative disease, with the exception of the NSABP 31 trial, which did not include participants with node-negative disease. All patients were to receive adjuvant chemotherapy and

Table 2. Summary of Adjuvant Trastuzumab Chemotherapy Trials

Study	N	Endpoints	Treatment	Results	Grade III-IV Heart Failure
HERA[17]	5,090 (HER2-positive, node-negative/positive, stage ≥T1c, LVEF ≥55%)	DFS, RFS, DDFS, OS	H, 8 mg→6 mg every 3 weeks (2 years); H, 8 mg → 6 mg every 3 weeks (1 year); No T	H (1 year) vs no H: 2 years DFS 80.6% vs 74.3%; RRR, 36% (*P*<.001); OS 92.4% versus 89.7%; RRR, 34% (*P*=.0115)	1.7% (H arm) vs 0.06%
NSABP B-31/ NCCTG N9831[18]	3,505 (HER2-positive, node-positive/ high-risk, node-negative)	DFS, OS	N9831: arm A, AC every 3 weeks × 4→ T (80 mg/week) × 12; arm B, AC × 4 → T (80 mg/week) × 12 → H (1 year); arm C, AC × 4 → T (80 mg/week) × 12 + H (1 year). B31: arm 1, AC every 3 weeks × 4 → T (175 mg) every 3 weeks × 4; arm 2, AC every 3 weeks × 4 → T (175 mg) every 3 weeks × 4 + H (1 year)	DFS at 3 years, AC→ T + H vs AC→T: 87% vs 75%; RRR, 52% (*P*<0.001); OS at 3 years, AC→TH vs AC→T 94.3% vs 91.7% RRR, 33% (*P*=0.015)	4.1% (H arm) vs 0.8% NSABP B-31 2.9% (H arm) vs 0 NCCTG N9831
finHer (Finland)[21]	232	RFS	Arm 1: docetaxel every 3 weeks × 3 or V every week × 8→ FEC every 3 weeks × 3. Arm 2: docetaxel every 3 weeks × 3 or V every week × 8 + H every week × 9→FEC every 3 weeks × 3	RFS and OS at 3 years favors H-containing arm. 89% vs 78% RRR, 58% (*P*=.01); OS 89.7% vs 96.3%; RRR, 59% (*P*=0.07)	0
BCIRG 006[19,20]	3,200 (node-positive or high-risk node-negative, HER2-positive, normal LVEF)	DFS, OS	Arm 1: AC × 4 → docetaxel × 4. Arm 2: AC × 4 → docetaxel × 4 + H every week × 12 → H every week × 40. Arm 3: docetaxel + C × 6 + H every week × 18 → H every week × 34 (no anthracycline)	DFS at 3 years, AC→ docetaxel + H vs AC→ docetaxel: 83% vs 77% RRR, 39% (*P*<0.001); TCH→H vs AC→ docetaxel 82% vs 77% RRR, 33% (*P*=.0003)	0.4% (ACT) vs 1.8% (AC/docetaxel +H) vs 0.4 % (TCH)

AC=doxorubicin and cyclophosphamide; ACT=doxorubicin, cyclophosphamide, docetaxel; BCIRG=Breast Cancer International Research Group; C=cisplatin or carboplatin; CHF=congestive heart failure; DDFS=distant disease-free survival; DFS=disease-free survival; FEC=5-fluoracil, epirubicin, cyclophosphamide; H=trastuzumab; HERA=Herceptin Adjuvant; HR=hormone receptor; LVEF=left ventricular ejection fraction; NCCTG=North Central Cancer Treatment Group; NSABP=National Surgical Adjuvant Breast and Bowel Project; OS=overall survival; RFS=relapse-free survival; RRR=relative risk reduction; T=paclitaxel; TCH=docetaxel, carboplatin and trastuzumab; V=vinorelbine.

appropriate radiotherapy and hormonal therapy. Locally advanced or distant disease was not permitted in any trial. Cardiac eligibility criteria differed among the trials. The Herceptin Adjuvant (HERA) trial[17] required patients to have a normal left ventricular ejection fraction (LVEF ≥55% as measured by echocardiography or multiple-gated acquisition scan) after completion of chemotherapy and radiotherapy, whereas in the B-31 and N9831 trials,[18] baseline LVEF was required to be greater than or equal to 50% after completion of chemotherapy. In the BCIRG 006 trial,[19,20] baseline LVEF was required to be 50% or higher after surgery before the initiation of adjuvant therapy. Additional cardiac exclusion criteria included a history of myocardial infarction, congestive heart failure (CHF), coronary artery disease, angina pectoris requiring medication, uncontrolled hypertension, clinically significant valvular disease, or unstable arrhythmias.

The HERA trial[17] is an international, multicenter, randomized, controlled trial comparing 1 year or 2 years of trastuzumab therapy given every 3 weeks to observe (no trastuzumab) patients with HER2-positive early breast cancer who had completed locoregional therapy and at least 4 cycles of neo-adjuvant or adjuvant chemotherapy from a list of approved regimens (eg, AC, epirubicin+cyclophosphamide, 5-fluorouracil+adriamycin+cyclophosphamide, epirubicin+paclitaxel, doxorubicin+paclitaxel, CMF). Analysis at 2-year follow up reported a statistically significant reduction in disease recurrence, as well as a significant improvement in OS in the trastuzumab and non-trastuzumab groups, respectively. About one-third of the patients received anthracyclines, and less than 10% received taxanes, but the rate of recurrence was still in the 40-50% range. Ongoing studies testing the duration of trastuzumab (6 vs 12 months and 1 vs 2 years) are ongoing and not yet reported.

The combined analysis of The North Central Cancer Treatment Group trial N9831 and NSABP-31[18] showed a significant improvement in DFS for trastuzumab given concurrently with 4 courses of paclitaxel either every week or every 3 weeks after a combination of 4 cycles of AC and continued for 1 year compared with the same chemotherapy schedule without trastuzumab.

In a smaller study, FinHer trial patients were randomized to 3 cycles of docetaxel or vinorelbine followed by 3 cycles of CEF. This study also showed an improvement in DFS after only 9 weeks of trastuzumab therapy given at the start of treatment concurrently with adjuvant chemotherapy.[21] OS benefit has not been shown in this particular study.

The BCIRG 006 trial showed more of the same DFS benefit when trastuzumab was administered either with docetaxel or after AC. This study was unique because it used a different taxane—docetaxel. Another novelty of this trial was that it tested a completely nonanthracycline arm, which contained docetaxel, carboplatin, and trastuzumab (TCH).[19,20] This third arm was designed to avoid cardiotoxicity by not including an anthracycline and to combine drugs that had shown the greatest amount of synergy in preclinical models. Another theoretical advantage was that therapy with trastuzumab started immediately and was not delayed.

The findings of all the trastuzumab trials are indeed remarkable in that they suggest that the addition of trastuzumab to anthracycline-based chemotherapy, either with or without a taxane, may reduce the recurrence rate by approximately 50%. The magnitude of this benefit is such that the use of trastuzumab reduces the risk for tumor recurrence in women with HER2-positive, high-risk breast cancer to rates of recurrence typical of patients with HER2-negative cancers.

Rationale for the Combination of Trastuzumab and Platinum Salts

The rationale for the combination of trastuzumab with platinum salts and docetaxel comes from in vitro and in vivo preclinical laboratory studies[22] that demonstrated that trastuzumab interacts synergistically with cisplatin, carboplatin, and docetaxel. In contrast, the cytotoxic effects of paclitaxel or doxorubicin in combination with trastuzumab in vitro are additive.[23] The synergistic effects of platinum salts and trastuzumab are the result of trastuzumab-induced attenuation of DNA repair that follows platinum-induced DNA damage[24] and suggest a complex molecular interaction between HER2 signal transduction and DNA repair pathways.[25] The underlying mechanism of the synergy between docetaxel and trastuzumab is still under investigation, but preliminary data indicate that it may be the result of increased apoptosis.[26] The University of California at Los Angeles-Oncology Research Network and BCIRG conducted 2 phase II studies to evaluate docetaxel and trastuzumab in combination with either cisplatin or carboplatin in the treatment of women with advanced breast cancer that overexpresses HER2. These studies showed that combinations of docetaxel, a platinum salt, and trastuzumab are feasible and active in patients with advanced breast cancers that overexpress HER2. Overall response rates in these studies were 79% (95% CI, 66–89%) and 58% (95% CI, 44–70%), and median time to progression was 9.9 months (95% CI, 8.3–13.1) and 12.7 months (95% CI, 8.6–15.5), respectively.[7] These studies demonstrated an acceptable toxic profile and only 1 patient in each study developed reversible CHF. These results defined the combination of TCH as an option in the treatment of metastatic breast that overexpresses the HER2 protein.

Is TCH Enough?

BCIRG 006, a randomized phase III adjuvant clinical trial, compared 2 trastuzumab-containing regimens, 1 with anthracycline/taxane and 1 with a nonanthracycline, to a standard anthracycline/taxane regimen in patients with HER2-positive early-stage breast cancer. In a preliminary report with a 23-month median follow-up, DFS was significantly better in both trastuzumab arms as compared to AC followed by docetaxel (RRR, 51% and 39% for AC/docetaxel/trastuzumab and TCH, respectively).[19] After a median follow-up of 36 months, DFS continued to be superior in the trastuzumab-containing arms: 83% (AC/docetaxel/trastuzumab) versus 77% (AC/docetaxel); (RRR, 39%; P<.001) and 82% (TCH; RRR, 33%; P=.0003). Grade 3 or 4 heart failure differed significantly between the 2 trastuzumab-containing arms, with 4 patients in both the AC/docetaxel and TCH groups, compared to 20 patients in the AC/docetaxel/trastuzumab group, developing CHF (0.4%, 0.4% vs 1.8%; *P*=.0015).[20] At 3 years of follow-up, analysis of BCIRG 006 reaffirmed that adding trastuzumab to a traditional anthracycline/taxane adjuvant regimen is significantly advantageous in terms of both DFS and OS. In addition, the inclusion of the nonanthracycline arm demonstrated that a similar degree of efficacy can be achieved without the use of anthracyclines.

Subset Analysis of BCIRG 006 for Coamplification of Topoisomerase IIα

Topoisomerase IIα (Top2α) is an essential cellular enzyme that functions in the segregation of newly replicated chromosome pairs, in chromosome condensation, and in altering DNA superhelicity. DNA topoisomerases participate in nearly all biologic processes governing DNA and untangle intertwined DNA strands before cell division by transiently breaking and then re-ligating duplex strands of DNA.[27] Top2α can be found to be coamplified in up to 35% of breast cancer tumors that overexpress HER2; the amplification of Top2α leads to the overexpression of the Top2α protein, and ultimately, to a better response to anthracyclines.[28] In a study of advanced breast cancer, all patients with a complete response to a Top2α inhibitor had a Top2α amplification,[29] whereas patients with HER2 amplification and progressive disease, despite chemotherapy, had Top2α deletion. In a retrospective study of an adjuvant breast cancer trial, the benefit of anthracycline-containing chemotherapy was only seen in women with amplified HER2 breast cancer who also had a simultaneous amplification of Top2α.[30]

To analyze the possibility that certain subgroups within the HER2-positive population may achieve greater benefit from anthracycline-based chemotherapy, a retrospective analysis of 2,990 participants of the BCIRG 006 trial demonstrated that 1,788 (60%) had gene amplification of HER2, determined by FISH but not Top2α; 145 patients (5%) had amplification of HER2 and deletion of Top2α, and 1,057 patients (35%) had coamplification of HER2 and Top2α. When patients with coamplification of both HER2 and Top2α were stratified by treatment arm, all 3 treatment arms had an equivalent outcome if Top2α was coamplified (AC/docetaxel/trastuzumab vs AC/docetaxel: *P*=.336; TCH vs AC/docetaxel: *P*=.648). However, patients with non-coamplified tumors had significantly superior outcomes with either the AC/docetaxel/trastuzumab arm or TCH arm compared to the AC/docetaxel arm (*P*<.001).[20] These findings indicate that at 36 months of follow-up, adjuvant treatment with TCH appears to have a similar effect to AC/docetaxel/trastuzumab in women with coamplification of Top2α, suggesting that testing patients for coamplification of Top2α may not be necessary to tailor adjuvant therapy of female patients with overexpression of HER2.

Conclusions

For patients with HER2 nonamplified or negative early breast cancer in which adjuvant treatment with AC used to be the choice of treatment (standard or low risk early breast cancer [eg, lymph node-negative or ER-positive disease]), for patients with cardiac problems, or for elderly women, adjuvant chemotherapy with TC produces a superior DFS and OS at 5 years. The US Oncology Group is currently conducting a large randomized adjuvant chemotherapy trial for HER2-negative female participants comparing 6 cycles of docetaxel combined with cyclophosphamide and doxorubicin against 6 cycles of TC.

The results of the 5 trastuzumab adjuvant trials indicate that the addition of at least 1 year of trastuzumab to anthracycline- and taxane-containing chemotherapy provides substantial benefit for women with HER2-positive breast cancer both in terms of disease recurrence and survival. However, there are still some unanswered questions, such as the optimal duration of trastuzumab therapy and long-term safety data of trastuzumab, especially with regard to cardiac toxicity.

The BCIRG 006 trial is different because it tested for the first time in the adjuvant setting a nonanthracycline-containing arm. One of the benefits of this combination is that patients are exposed earlier to trastuzumab, thus shortening the duration of adjuvant intravenous therapy by 9–52 weeks; additionally, cardiotoxicity is comparable to the nontrastuzumab arm. Cardiotoxicity of TCH is approximately 4%, and that of the anthracycline combination AC-TH is 20%.

Preliminary data indicate that only a minority of patients (approximately 1/3 of all HER2 amplified cases) also have Top2α coamplified. Although Top2α is believed to be one of the targets for anthracyclines, it is not clear whether anthracyclines really represent an advantage in this subset of patients

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