ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

PRO AND CON DISCUSSION

Anthracyclines in the treatment of patients with early breast cancer

THE CASE FOR ANTHRACYCLINES IN THE TREATMENT OF EARLY BREAST CANCER (DR GUARNERI)

In the past decades, systemic treatment for early-stage breast cancer (EBC) patients has undergone a profound evolution, driven by the progressively improving knowledge and understanding of breast tumor biology, with consequent outcome improvement. In this context, chemotherapy still represents a cornerstone of EBC treatment across different breast cancer (BC) subtypes. Once chemotherapy is considered, the next step is a careful risk—benefit balance aiming at choosing which specific regimen to offer. Within this framework, although anthracyclines have long been one of the mainstays of the cytotoxic therapy, in the last years their role has been challenged. Indeed, alongside with the concerns regarding anthracycline-related toxicity, the emergence of alternative active cytotoxic agents as well as targeted strategies to be combined with has progressively fueled the debate about de-escalating anthracyclines.

In order to properly and critically address this high-priority clinical issue, the following questions need to be answered:

Are the data supporting the use of anthracyclines no longer appropriate in the contemporary landscape of EBC treatment?

Are the data supporting chemotherapy de-escalation solid enough to enable us to safely withhold anthracyclines?

Are concerns regarding anthracycline long-term safety justified with cumulative doses reached with contemporary regimens?

The answers are no. The 2012 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) individual patient meta-analysis[1] has demonstrated that: (i) anthracycline-based regimens are superior to no adjuvant chemotherapy; (ii) anthracycline-based regimens are superior to chemotherapy regimens that contain neither anthracycline nor taxane; (iii) anthracycline—taxane combination is superior to anthracycline-based chemotherapy. The proportional risk reductions are little affected by age, nodal status, and estrogen receptor (ER) status. These data cannot be questioned; however, the past decades have been marked by the questioning of the actual indispensability of anthracyclines. One of the first pieces of evidence in this regard comes from the US-Oncology-9735 trial demonstrating survival benefit with docetaxel-based (TCx4) over anthracycline-based chemotherapy (ACx4) in unselected EBC patients.[2] However, the US-Oncology-9735 population was enriched for lower-risk patients.

Even when restricting the field to the human epidermal growth factor receptor 2 (HER2)-negative subgroup, available data do not support taxane-only as an equally effective alternative to anthracycline—taxane chemotherapy. The joint efficacy analysis of Anthracyclines in early Breast Cancer (ABC) trials failed to formally demonstrate the non-inferiority of six courses of taxane-based chemotherapy over anthracycline—taxane combination. Rather, an improvement of invasive disease-free survival (IDFS) was demonstrated for the anthracycline-based combination.[3] Similarly, a pooled analysis of ABC, West German Study Plan B (WSG Plan B) and Hellenic Oncology Research Group (HORG) trials was not able to prove the non-inferiority of taxanes versus anthra-taxanes.[4] Closing credits, the most recent update of the EBCTCG meta-analysis demonstrated a 15% proportional reduction and a 2.5% absolute reduction at 10 years in the risk of invasive recurrence for anthracycline—taxane combinations versus taxane-based regimen, independently of ER and nodal status.[5]

HER2-positive EBC deserves a separate discussion. First-generation adjuvant trials establishing trastuzumab as the standard of care mostly included anthracycline—taxane chemotherapy backbone.[6] The Breast Cancer International Research Group 006 (BCIRG-006) trial provided the first assumption of superimposable efficacy of sequential anthracycline—taxane and taxane-only chemotherapy.[7] However, the trial was not powered for a formal comparison, thus missing the opportunity to provide solid evidence supporting the use of anthracycline-free chemotherapy in combination with single HER2 blockade.

Aphinity and Katherine trials set new adjuvant standards for high-risk patients: dual HER2 blockade with trastuzumab—pertuzumab in the first case, and post-operative trastuzumab emtansine (T-DM1) in patients failing to achieve a pathologic complete response (pCR) after standard neoadjuvant chemotherapy including trastuzumab in the latter case.[8,9] Notably, ~77% of the patients in both trials have received anthracycline-based chemotherapy. Just to complete the scenario, the NeoSphere neoadjuvant trial, which firstly demonstrated the efficacy of pertuzumab—trastuzumab in the neoadjuvant setting, included four courses of post-operative anthracycline-based chemotherapy.[10] Two trials (TRAIN-2 and TRYPHAENA) specifically investigated whether the omission of anthracycline from the neoadjuvant backbone of dual HER2 blockade could provide a more favorable risk—benefit ratio, providing evidence that this de-escalated

approach does not seem to jeopardize the likelihood of pCR; however, none of these trials was statistically powered to formally establish the non-inferiority of omitting anthracycline.[11-13] In addition, in both of them, the de-escalated arm consisted of taxane + carboplatin, which is not unanimously considered a 'standard' de-escalation treatment; finally, the TRYPHAENA de-escalated arm, containing docetaxel, was associated with an unexpectedly high rate of non-cardiac toxicity, thus raising major concerns regarding a possible implementation of such an approach in clinical practice.

Therefore, unless clinically contraindicated, anthracycline-based chemotherapy is still the standard, with the exception of very-low-risk patients. Two single-arm phase II trials independently reported excellent survival rates of low-risk HER2-positive EBC patients receiving trastuzumab + taxane as adjuvant treatment, thus fueling the enthusiasm for this de-escalated approach, enough to build it up as the new adjuvant standard in HER2-positive EBC patients with small tumors and node-negative disease.[14,15] However, given the lack of a control standard arm, results from these trials should be considered assumptive rather than demonstrative.

A final consideration should be made for triple-negative (TN) EBC patients treated in the neoadjuvant setting. According to the results of the Create-X trial, post-operative capecitabine in patients with residual disease after standard neoadjuvant chemotherapy demonstrated survival improvement, setting a new option for this particularly poor-risk population.[16] Not surprisingly, standard chemotherapy was represented by anthracycline—taxane combination in 95% of the cases. More recently, KEYNOTE-522 trial demonstrated a pCR and event-free survival (EFS) advantage with the addition of pembrolizumab to standard chemotherapy over chemotherapy alone, leading to the approval of the first immune-checkpoint inhibitor in the early disease setting.[17] Again, the neoadjuvant chemotherapy backbone consisted of both taxane and anthracycline, further solidifying the value of such standard backbone in this clinical setting. Biological and clinical background further reinforces the use of anthracyclines in this particular context, to exploit the mechanisms of anthracycline-induced immunogenic cell death.

Of course, safety is a critical issue, in particular in a curative setting. The most feared anthracycline-related long-term effects are represented by cardiotoxicity and leukemia, the risk of both becoming concrete at cumulative doses which, however, are far above those reached with modern regimens. Indeed, sequential use of anthracycline and taxane has been shown to be particularly effective allowing a lower total dose of anthracyclines. The estimated risk of congestive heart failure and acute myeloid leukemia (AML) in a contemporary scenario is thus resized, and cardiac side-effects can be further scaled down by improving upfront patient selection, cardiac monitoring and preventive measures.[18] Moreover, the last EBCTCG meta-analysis showed no significant difference in death without recurrence and no difference in deaths from cardiovascular disease or leukemia was observed. Of course, longer follow-up is needed, but these data are reassuring.

THE CASE AGAINST ANTHRACYCLINES IN THE TREATMENT OF EARLY BREAST CANCER (DR DE AZAMBUJA)

Anthracyclines in the (neo)adjuvant treatment of breast cancer: why not to all patients?

Anthracycline-based chemotherapy has been the basis of curative therapy for patients with early BC since the 1990s.[19] However, while review evidence supported the use of anthracycline in the pre-taxane era,[20] in the modern era the issue of overtreatment in BC is being extensively discussed.

Of note, anthracycline use is associated with the risk of long-term toxicities, namely heart dysfunction or congestive heart failure and AML or myelodysplastic syndrome (MDS).[1] Hence, thanks to the availability of new effective therapies, and to a deeper biological knowledge of BC heterogeneity, with the possibility of better selection of patients according to their risk of recurrence and death, the de-escalation of anthracycline-containing regimens for selected patients is gaining increasing interest in clinical trials.

Intriguingly, at the San Antonio Breast Cancer Symposium (SABCS) 2021, the results of a patient-level meta-analysis comparing taxane with anthracycline versus taxane without anthracycline were presented. In all trials ($n = 16$, including 18 203 patients), a 15% proportional reduction and a 2.5% [95% confidence interval (CI) 0.9% to 4.2%] absolute reduction at 10 years in the risk of invasive recurrence for anthracycline + taxane versus taxane chemotherapy were observed. Moreover, proportional reduction in recurrence did not differ by ER or nodal status.

Despite these provocative results, it should be considered that, as a matter of fact, in contemporary clinical practice, there has been an increasing move toward anthracycline-free regimens for selected patients.

Indeed, early-stage and less aggressive BCs are expected to derive a smaller absolute benefit from adjuvant chemotherapy compared to those with larger or node-positive tumors, or with more aggressive biology, and remain at low risk for a recurrence of BC.[21-23] Thus, considering the potential life-altering toxicities associated with anthracyclines, it should be questioned whether the use of anthracyclines in these low-risk patients could potentially be harming more than helping them.[24]

Recent study results have added much to the discussion of de-escalating anthracycline-based chemotherapy in patients with early BC and are presented hereunder.

Which evidence we have according to breast cancer subtypes?

Triple-negative breast cancer. Triple negative comprises 10%-15% of all BCs and remains a heterogeneous and aggressive disease.[25] In the lack of more attractive chemotherapeutic options in the early setting, it seems reasonable to use an anthracycline—taxane-based chemotherapy as first option, preferably given as neoadjuvant

therapy.[18] Recently, the addition of carboplatin and pembrolizumab to an anthracycline—taxane regimen has shown to improve pCR and EFS.[17,26,27] At this moment, it is unlikely that anthracycline-based chemotherapy will be removed for this patient population, unless there are contraindications for anthracyclines.

HER2-positive breast cancer. Unlike triple negative, patients with HER2-positive BC, which comprises 15%-20% of all BCs, have been successfully treated with non-anthracycline-based chemotherapy and most efforts have focused on the identification of the ideal anti-HER2 partner. Today, patients with small (<2 cm) node-negative BC are treated with adjuvant weekly paclitaxel for 12 cycles and 1 year of trastuzumab, based on the long-term results of the Adjuvant Paclitaxel and Trastuzumab (APT) trial.[28] The 7-year disease-free survival (DFS) was 93% (95% CI 90.4% to 96.2%) with only four (1.0%) distant recurrences; 7-year overall survival (OS) was 95% (95% CI 92.4% to 97.7%) and 7-year recurrence-free interval (RFI) was 97.5% (95% CI 95.9% to 99.1%).[28]

The BCIRG-006 trial also tested a non-anthracycline adjuvant regimen, consisting of docetaxel, carboplatin and trastuzumab (TCH), for patients with early HER2-positive BC. At the final analysis with a median follow-up of 10.3 years, DFS and OS were similar in the anthracycline (AC-TH) and non-anthracycline (TCH) arms (10-year DFS 74.6% versus 73.0%, and 10-year OS rates 85.9% and 83.3%, in AC-TH and TCH arms, respectively), although they were not powered for comparison. The TCH arm showed lower rate of cardiac toxicity events (4 versus 21 cases of symptomatic congestive heart failure) and of leukemia (1 versus 7 cases). In terms of left ventricular ejection fraction (LVEF) decline >10%, 97 patients treated in the TCH arm experienced this event compared to 206 patients in the AC-TH arm ($P < 0.0001$).[29]

Notably, when moving to the neoadjuvant setting, these observations remained consistent. In the TRYPHAENA trial, a docetaxel—carboplatin-based neoadjuvant chemotherapy showed similar pCR and DFS rates compared with an anthracycline-based regimen, when added to dual HER2 blockade with trastuzumab and pertuzumab.[13]

More recently, the TRAIN-2 study demonstrated similar pCR rates and EFS between anthracycline and non-anthracycline regimens (pCR 67% versus 68%, $P = 0.75$, and 3-year EFS 92.7% versus 93.6%, respectively). However, the relatively small sample size ($n = 438$) and the under-representation of N2-3 tumors ($n = 67$) should be acknowledged. The anthracycline-based arm had more LVEF declines of ≥10% from baseline to <50% (7.7% versus 3.2%, respectively, $P = 0.044$). Two patients treated with anthracyclines developed acute leukemia.[30]

Research efforts are being made to de-escalate chemotherapy in HER2-positive early BC. In the West German Study Group - Adjuvant Dynamic marker- Adjusted Personalized Therapy (WSG-ADAPT) trial phase II trial, patients with hormone receptor (HR)-negative, HER2-positive early BC showed an excellent pCR rate of 90% after de-escalated neoadjuvant chemotherapy with 12-week paclitaxel, pertuzumab and trastuzumab, and pCR was strongly associated with survival outcomes.[31] The Paclitaxel/Trastuzumab/Pertuzumab in HER2-Positive BC (DAPHNE) trial is a single-arm pilot trial aimed to determine the feasibility of de-escalated adjuvant therapy (with trastuzumab/pertuzumab only) in patients with pCR following neoadjuvant paclitaxel, trastuzumab and pertuzumab.[32] Preliminary data showed a promising overall pCR rate of 55% (51/93 patients).[32] The long-term efficacy of this approach will be assessed in the ongoing COMprehensive use of Pathologic response ASSessment to optimize therapy in HER2 positive breast cancer (CompassHER2)-pCR trial (NCT04266249).

Taken together, all the above-mentioned information justifies the most recent National Comprehensive Cancer Network (NCCN) guidelines that removed anthracycline-based chemotherapy from the list of preferred options, stating that this regimen could be considered useful only in certain circumstances.[33]

Thus, the choice of an anthracycline-containing regimen should be discussed based on the potential risks and benefit expected for each specific patient, considering that higher benefit is expected in patients with higher-stage tumors (e.g. T3-4 or ≥N2 disease), which is an underrepresented population in clinical trials. This restricted indication would reduce the incidence of cardiac toxicity associated with the combination of chemotherapy and anti-HER2 agents.

Hormone receptor-positive, HER2-negative breast cancers. In HR-positive, HER2-negative BCs, which comprise ∼70% of all BCs, there is increasing evidence toward de-escalating chemotherapy and optimizing endocrine therapy, thanks to the availability of genomic signatures able to stratify patients according to their risk of recurrence.[34]

In patients with HER2-negative disease candidate to curative chemotherapy, the docetaxel—cyclophosphamide combination has been identified as one of the preferred regimens.[33] However, clinical trials comparing this combination with standard anthracycline and taxane-based sequential regimen in HER2-negative BC have produced mixed results thus far.

In a series of three adjuvant trials, docetaxel—cyclophosphamide was proven inferior to a combination of anthracyclines and taxanes in patients with HER2-negative, operable BC.[3] More recently, a phase III randomized trial demonstrated the non-inferiority of an anthracycline-free regimen (i.e. six cycles of docetaxel—cyclophosphamide) to standard anthracycline and taxane-based regimen (i.e. epirubicin and cyclophosphamide for 4 cycles followed by paclitaxel for 12 weeks) for operable patients with high-risk HER2-negative BC.[35]

The Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (EORTC 10041/BIG 3-04 MINDACT) study added another piece to this complex puzzle. In MINDACT, a phase III trial aimed to test whether patients with high clinical risk (i.e. T1-3 and

0 or 1-3 positive lymph nodes) and low genomic risk could avoid chemotherapy, similar DFS and OS between non-anthracycline- and anthracycline-based regimens were observed (5-year DFS 90.7% versus 88.8%, $P = 0.26$, and 5-year OS 96.3% versus 96.2%, $P = 0.72$, respectively). Of note, the trial was not powered to demonstrate the superiority of a given chemotherapy regimen.[36]

In the Trial Assigning Individualized Options for Treatment (TAILORx), a randomized trial aimed to demonstrate the non-inferiority of endocrine therapy alone versus the combination of chemo and endocrine therapy in patients with a recurrence score of 11-25 based on a 21-gene BC assay,[37] most patients randomized to the chemoendocrine arm received docetaxel—cyclophosphamide ($n = 589$, 42%). Similar IDFS and OS were observed with different chemotherapy regimens (5-year IDFS: 88.1%, 87.4%, 88.6% and 5-year OS: 95.8%, 96.7%, 97.2%, in patients receiving docetaxel—cyclophosphamide, anthracycline without a taxane and anthracycline plus a taxane, respectively).[38] Again, the trial was not powered to demonstrate differences between chemotherapy regimens, and these data should be considered only as exploratory.

Consistent with the available evidence, a retrospective real-world analysis including 17 788 patients with HR-positive, HER2-negative early BC candidate to receive chemotherapy based on a 21-gene assay showed that anthracyclines are prescribed more often to younger patients, with higher-stage tumors and with higher 21-gene recurrence scores, suggesting the tendency in clinical practice of avoiding the potential serious complications associated with anthracycline treatment in patients least likely to receive benefit.[39]

In conclusion, although anthracycline-based chemotherapy regimens have become standard in the (neo)adjuvant setting since the 1990s, its unselective use in the modern era is being increasingly questioned, due to the small magnitude of benefit in some subgroups and the associated unfavorable risk—benefit ratio. Most patients with HER2-positive or HR-positive/HER2-negative BCs candidate to (neo)adjuvant chemotherapy may benefit from a non-anthracycline-based regimen. The use of anthracyclines should be restricted to patients with a very high risk of recurrence (i.e. T3-4 or $\geq$N2 disease, or with high biological aggressiveness), who are still underrepresented in clinical trials. This strategy would reduce the risk of long-term toxicities, namely cardiotoxicity and hematologic malignancies.

REBUTTAL OF THE CASE AGAINST ANTHRACYCLINES IN THE TREATMENT OF EARLY BREAST CANCER

Having endorsed anthracyclines as standard component of chemotherapy for TN breast cancer (TNBC), let's focus on HER2-positive and HR-positive/HER2-negative subsets.

We already agreed that adjuvant weekly paclitaxel + 1 year of trastuzumab on the basis of the APT trial data can be an option for HER2-positive low-risk patients.[14]

However, here is a matter of reducing the burden of chemotherapy, relying on the synergistic effect of trastuzumab. And, if we want to be picky, given the CI associated with the 93% 7-year DFS rate of the APT trial, we cannot rule out a remarkably lower DFS benefit, down to 90.4%. Moreover, in the Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT) trial, the same schema of the APT trial produced a 3-year RFI of 94.3% (with the lower limit of the 95% CI of 89.9%); when at 3 years, the APT trial reported an IDFS of 98.7%. But these are the limits of single-arm trials. Regarding BCIRG-006, at 5 years, a 3% advantage in IDFS for the anthracycline-containing arm was reported. In the Aphinity trial, which set the combination of pertuzumab—trastuzumab as the new adjuvant standard regimen for high-risk patients, a 2.8% absolute difference at 6 years was reported. Of course, it is just a matter of how you look at the data.

Turning now to the neoadjuvant setting, I agree on the fact that available evidence overall suggests a possible more favorable risk—benefit ratio in favor of omitting anthracycline from the neoadjuvant backbone for HER-positive BC patients also receiving dual HER2 blockade.[11-13] However, again, (i) these trials did not formally demonstrate the non-inferiority of such de-escalated approach; (ii) carboplatin + paclitaxel does not represent an unanimously recognized standard 'de-escalated' arm; (iii) in anthracycline-containing arms, rate of symptomatic LVEF decline was generally very low, against the not-so-reassuring rates of non-cardiac events observed within the taxane-based arms, especially with docetaxel.

For these reasons, I would consider de-escalating anthracyclines only in selected cases at very low risk.

For the luminal subset, the situation is more complicated. Indeed, we currently lack solid evidence that could assist in the selection of patients for whom anthracycline may be safely omitted. In this context, as highlighted, phase III randomized clinical trials demonstrating the clinical utility of molecularly stratifying patients to identify those for whom chemotherapy can be confidently spared[37,40-42] provided us with intriguing considerations indirectly challenging the role of anthracycline in this clinical setting. However, none of those trials was powered to formally make comparisons across different regimens. Taken together, available evidence still supports anthracycline + taxane-based chemotherapy as the standard, and based on this, whenever chemotherapy is offered to a patient with HR-positive/HER2-negative BC, should not the question be: why would we offer an anthracycline-containing regimen; but rather, why wouldn't we?

REBUTTAL OF THE CASE FOR ANTHRACYCLINES IN THE TREATMENT OF EARLY BREAST CANCER

While my colleague is correct in detailing the data on the efficacy of anthracycline—taxane-based chemotherapy in patients with early BC, a few considerations have to be taken into account:

- Most of the practice-changing treatments come indeed from randomized superiority phase III trials. However, in HER2-positive disease, a phase II, single-arm, non-inferiority trial[14,28] was able to de-escalate therapy in patients with small node-negative HER2-positive early BC, and today, all international guidelines recommend 12 weeks of paclitaxel + 1 year of trastuzumab for these patients. This was a safe removal of anthracyclines.
- Another phase II non-inferiority study also demonstrated that T-DM1 could be used in small node-negative HER2-positive tumors,[43] thus de-escalating anthracyclines. However, this approach is considered only in selected cases.
- Phase III non-inferiority trials may not answer all the questions, as was the case for short durations of trastuzumab in the early setting.[44-47]
- A very recent pooled analysis of Plan B and Success C trials containing almost 6000 patients showed that anthracycline may not be required in most of the patients with intermediate- or high-risk HER2-negative early BC (no difference in DFS or OS) with the exception of lobular or pN2/pN3 tumors. In addition, adverse events were significantly higher with anthracycline-based regimens (76.3% versus 70.1%, $P < 0.001$).[48]
- A recent Surveillance, Epidemiology, and End Results (SEER) database publication including patients aged ≥66 years with node-negative TNBC compared patients receiving taxane-based ($n = 420$) versus anthracycline—taxane-based chemotherapy ($n = 275$), and showed inferior 3-year OS and cancer-specific survival (CSS) for anthracycline—taxane chemotherapy. The use of chemotherapy in general improved OS and CCS. However, the 3-year CSS was 93.7% with taxane compared to 89.8% ($P = 0.048$) for anthracycline—taxane. Similarly, 3-year OS was 91.0% for taxane and 86.4% for anthracycline—taxane chemotherapy ($P = 0.032$).[49]

I do agree with Dr Guarneri that most patients with TNBC will continue to receive anthracycline-based chemotherapy. However, subtypes such as HER2-positive or luminal BCs may not require an anthracycline-based chemotherapy, except for those with an important tumor burden. In HER2-positive disease, anthracyclines are no longer the preferred regimen in international guidelines (e.g. NCCN 2022).[33] In HER2-negative disease, taxane-based chemotherapy is one of the preferred regimens as well and remains a valuable therapeutic option for patients.

In terms of secondary hematologic diseases, among 92 110 older patients, adjuvant chemotherapy was associated with a small but significant increase in the risk of AML and MDS, especially with regimens that included anthracyclines (overall rates per 1000 person-years were 0.65 for AML and 1.56 for MDS). To confirm the safety of taxane-based regimen in terms of hematologic malignancies, longer follow-up is required.[50] Regarding cardiac safety, anthracycline-based chemotherapy confers more cardiac events compared to patients treated with taxane-based regimens.[51]

To conclude, anthracycline-based chemotherapy still has its indication for selected patients with BC, but certainly not for all patients. The choice of type of chemotherapy should take into account the risk of relapse, patients' risk factors and patients' preferences.

V. Guarneri[1]* & E. de Azambuja[2]*

[1]*Department of Surgery, Oncology and Gastroenterology; Oncology 2, Istituto Oncologico Veneto IOV IRCCS, Padova, Italy;*
[2]*Institut Jules Bordet and L'Université Libre de Bruxelles (U.L.B.), Brussels, Belgium*
(*E-mail: valentina.guarneri@unipd.it)
(*E-mail: evandro.azambuja@bordet.be).

Available online 19 April 2022

https://doi.org/10.1016/j.esmoop.2022.100461

ACKNOWLEDGEMENTS

Evandro de Azambuja thank Elisa Agostinetto, MD, Research Fellow at Institut Jules Bordet; Valentina Guarneri thank Federica Miglietta, MD, PhD Candidate at University of Padova.

FUNDING

None declared.

DISCLOSURE

VG reports Advisory Board: Eli Lilly, Novartis, Roche, MSD, Gilead, Eisai all outside the submitted work; Speaker's Bureau: Eli Lilly, Novartis, GSK, Amgen all outside the submitted work. EdA has declared: honoraria and/or advisory board participation from Roche/GNE, Novartis, Seattle Genetics, Zodiac, Libbs and Pierre Fabre; travel grants from Roche/GNE and GSK/Novartis; and research grant to his institution from Roche/GNE, Astra-Zeneca, GSK/Novartis and Servier.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. *Lancet*. 2012;379(9814):432-444.
2. Jones S, Holmes FA, O'Shaughnessy J, et al. 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*. 2009;27(8):1177-1183.
3. Blum JL, Flynn PJ, Yothers G, et al. 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*. 2017;35(23):2647-2655.
4. Ntellas P, Spathas N, Agelaki S, Zintzaras E, Saloustros E. Taxane & cyclophosphamide vs anthracycline & taxane-based chemotherapy as adjuvant treatment for breast cancer: a pooled analysis of randomized controlled trials by the Hellenic Academy of Oncology. *Oncotarget*. 2019;10(11):1209-1216.

5. Braybrooke J, Bradley R, Gray R, et al. Taxane with anthracycline versus taxane without anthracycline: an individual patient-level meta-analysis of 16,500 women with early-stage breast cancer in 13 randomised trials. *Cancer Res*. 2022;82(4_suppl):GS2-06.
6. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*. 2012;2012:CD006243.
7. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365(14):1273-1283.
8. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377:122-131.
9. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380(7):617-628.
10. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791-800.
11. van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(12):1630-1640.
12. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. 2013;24(9):2278-2284.
13. Schneeweiss A, Chia S, Hickish T, et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. *Eur J Cancer*. 2018;89:27-35.
14. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med*. 2015;372(2):134-141.
15. Jones SE, Collea R, Paul D, et al. Adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with HER2-amplified early stage breast cancer: a single-group, open-label, phase 2 study. *Lancet Oncol*. 2013;14(11):1121-1128.
16. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376:2147-2159.
17. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810-821.
18. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30(8):1194-1220.
19. de Boer RH, Chan A, Tran B, Wilcken N. Use of non-anthracycline regimens in early stage breast cancer in Australia. *Asia Pac J Clin Oncol*. 2011;7(1):4-10.
20. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet (London, England)*. 2005;365(9472):1687-1717.
21. Vaz-Luis I, Ottesen RA, Hughes ME, et al. Outcomes by tumor subtype and treatment pattern in women with small, node-negative breast cancer: a multi-institutional study. *J Clin Oncol*. 2014;32(20):2142-2150.
22. Fehrenbacher L, Capra AM, Quesenberry CPJ, Fulton R, Shiraz P, Habel LA. Distant invasive breast cancer recurrence risk in human epidermal growth factor receptor 2-positive T1a and T1b node-negative localized breast cancer diagnosed from 2000 to 2006: a cohort from an integrated health care delivery system. *J Clin Oncol*. 2014;32(20):2151-2158.
23. Curigliano G, Viale G, Bagnardi V, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol*. 2009;27(34):5693-5699.
24. Hurvitz SA, McAndrew NP, Bardia A, et al. A careful reassessment of anthracycline use in curable breast cancer. *NPJ Breast Cancer*. 2021;7(1):134.
25. Agostinetto E, Eiger D, Punie K, de Azambuja E. Emerging therapeutics for patients with triple-negative breast cancer. *Curr Oncol Rep*. 2021;23(5):57.
26. Poggio F, Bruzzone M, Ceppi M, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. *Ann Oncol*. 2018;29(7):1497-1508.
27. Poggio F, Tagliamento M, Ceppi M, et al. Adding a platinum agent to neoadjuvant chemotherapy for triple negative breast cancer: the end of the debate. *Ann Oncol*. 2021;33:347-349.
28. Tolaney SM, Guo H, Pernas S, et al. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2019;37(22):1868-1875.
29. Slamon DJ, Eiermann W, Robert NJ, et al. Abstract S5-04: Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH). *Cancer Res*. 2016;76(suppl 4):S5-04.
30. van der Voort A, van Ramshorst MS, van Werkhoven ED, et al. Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual ERBB2 blockade in patients with ERBB2-positive breast cancer: a secondary analysis of the TRAIN-2 randomized, phase 3 trial. *JAMA Oncol*. 2021;7(7):978-984.
31. Harbeck N, Gluz O, Christgen M, et al. De-escalated neoadjuvant pertuzumab+trastuzumab with or without paclitaxel weekly in HR-/HER2+ early breast cancer: ADAPT-HR-/HER2+ biomarker and survival results. *J Clin Oncol*. 2021;39(suppl 15):503.
32. Waks AG, Desai NV, Li T, et al. Abstract PD3-05: The DAPHNE trial: a feasibility study of chemotherapy de-escalation based on response to neoadjuvant paclitaxel-HP (THP) in HER2-positive breast cancer. *Cancer Res*. 2021;81(suppl 4). PD3-05.
33. Gradishar W, Moran M, Abraham J. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Available at https://www.nccn.org/. Accessed January 21, 2022.
34. Villarreal-Garza C, Ferrigno AS, De la Garza-Ramos C, et al. Clinical utility of genomic signatures in young breast cancer patients: a systematic review. *NPJ Breast Cancer*. 2020;6(1):46.
35. Yu K-D, Liu X-Y, Chen L, et al. Anthracycline-free or short-term regimen as adjuvant chemotherapy for operable breast cancer: a phase III randomized non-inferiority trial. *Lancet Reg Health West Pac*. 2021;11.
36. Delaloge S, Piccart M, Rutgers E, et al. Standard anthracycline based versus docetaxel-capecitabine in early high clinical and/or genomic risk breast cancer in the EORTC 10041/BIG 3-04 MINDACT phase III trial. *J Clin Oncol*. 2020;38(11):1186-1197.
37. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111-121.
38. Sparano JA, Gray RJ, Makower DF, et al. Clinical outcomes in early breast cancer with a high 21-gene recurrence score of 26 to 100 assigned to adjuvant chemotherapy plus endocrine therapy: a secondary analysis of the TAILORx randomized clinical trial. *JAMA Oncol*. 2020;6(3):367-374.
39. Henderson J, Adams P, Barber K. Factors determining anthracycline use in hormone receptor positive, early-stage breast cancer. *Clin Breast Cancer*. 2019;19(3):e475-e480.
40. Kalinsky K, Barlow WE, Gralow JR, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021;385(25):2336-2347.
41. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729.

42. Piccart M, van't Veer LJ, Poncet C, et al. 70-Gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *Lancet Oncol*. 2021;22(4):476-488.
43. Tolaney SM, Tayob N, Dang C, et al. Adjuvant trastuzumab emtansine versus paclitaxel in combination with trastuzumab for stage I HER2-positive breast cancer (ATEMPT): a randomized clinical trial. *J Clin Oncol*. 2021;39:2375-2385.
44. Conte P, Frassoldati A, Bisagni G, et al. Nine weeks versus 1 year adjuvant trastuzumab in combination with chemotherapy: final results of the phase III randomized Short-HER study. *Ann Oncol*. 2018;29:2328-2333.
45. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicentre, open-label, phase 3 randomised trial. *Lancet*. 2019;393:2591-2598.
46. Joensuu H, Fraser J, Wildiers H, et al. Effect of adjuvant trastuzumab for a duration of 9 weeks vs 1 year with concomitant chemotherapy for early human epidermal growth factor receptor 2-positive breast cancer: the SOLD randomized clinical trial. *JAMA Oncol*. 2018;4:1199-1206.
47. Earl HM, Hiller L, Vallier A-L, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet*. 2019;393:2599-2612.
48. de Gregorio A, Janni W, Friedl TWP, et al. The impact of anthracyclines in intermediate and high-risk HER2-negative early breast cancer—a pooled analysis of the randomised clinical trials PlanB and SUCCESS C. *Br J Cancer*. 2022. https://doi.org/10.1038/s41416-021-01690-6.
49. Schreiber AR, Kagihara J, Eguchi M, et al. Evaluating anthracycline + taxane versus taxane-based chemotherapy in older women with node-negative triple-negative breast cancer: a SEER-Medicare study. *Breast Cancer Res Treat*. 2022;191:389-399.
50. Rosenstock AS, Niu J, Giordano SH, et al. Acute myeloid leukemia and myelodysplastic syndrome after adjuvant chemotherapy: a population-based study among older breast cancer patients. *Cancer*. 2018;124:899-906.
51. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents. *Drug Saf*. 2000;22:263-302.