Adjuvant systemic therapy for early breast cancer

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Abstract

Breast cancer-specific mortality has declined over the last two decades as a result of the introduction of screening programmes and advances in adjuvant systemic therapy. The most notable progress has been achieved in the case of Her2-positive disease, following the introduction of trastuzumab, a humanized monoclonal antibody targeting the extracellular domain of Her2. Indeed, addition of trastuzumab to chemotherapy for a total duration of 1 year increases progression-free survival (PFS) as well as overall survival (OS) compared with chemotherapy alone. In hormone receptor-positive disease, treatment with aromatase inhibitors (AIs) prolongs PFS compared with tamoxifen, and in some clinical trials they have been found to increase OS also. Chemotherapy remains the mainstay of treatment for patients with triple-negative disease and also plays a role in Her2-positive and high-risk hormone receptor-positive tumours. Although, overall, only limited progress has been achieved in this field, most trials suggest that the introduction of taxanes has resulted in improved outcomes. Dose-dense chemotherapy is superior to older adjuvant regimens comprising 3-weekly administration of paclitaxel, while high-dose chemotherapy with autologous stem cell support currently has no place in the treatment of breast cancer. Neoadjuvant chemotherapy increases the rate of breast-conserving surgeries; importantly, the pathological complete remission (pCR) rate has been identified as a surrogate for improved OS in hormone receptor-negative patients. Thus, clinical trials have aimed to increase pCR rates by addition of further cytotoxic substances or biologicals such as trastuzumab, lapatinib or bevacizumab. However, the optimum treatment strategy for hormone receptor-negative patients without pCR remains elusive. This review discusses recent developments and open questions in the field of adjuvant systemic therapy for early breast cancer.

Background

Breast cancer is the most prevalent malignant disease in women worldwide. The term encompasses a heterogeneous group of malignancies with major differences in terms of tumour biology and prognosis.

Depending on their gene expression profiles, breast tumours can be classified into different subtypes. The Stanford Group developed the classic ‘intrinsic classification’, which defines five subtypes: normal-like, basal-like, Her2-positive and luminal, which is further subdivided into luminal A (highly endocrine responsive with oestrogen receptor (ER) and progesterone receptor (PR) expression and with low grade and low proliferation rate) and a less endocrine-responsive subtype called luminal B. Basal-like breast cancers, on the other hand, typically lack hormone receptor expression and have a gene expression profile similar to myoepithelial cells of the basal epithelial layer of milk ducts. Subtypes predict response as well as prognosis; therefore, the intrinsic classification is an important tool aiding treatment decisions.

In the routine setting, receptor expression, Her2 overexpression or gene amplification as well as grade and proliferation rate are used as a clinical approximation.

Endocrine therapy remains the backbone of treatment for hormone receptor-positive breast cancer; additionally, chemotherapy may play a role in patients at increased risk of cancer recurrence. In patients with the Her2-positive subtype, the introduction of trastuzumab in addition to chemotherapy has a major impact on progression-free survival (PFS) as well as overall survival (OS). In triple-negative tumours, however, chemotherapy alone is the only treatment option currently available and only limited progress has been achieved.

In addition to the intrinsic classification, prognostic mRNA expression profiles, such as the 21-gene profile (OncotypeDX®) or the 70-gene profile (MammaPrint®),
are commercially available. In addition to high-quality histopathology and guidelines, those prognostic tools may refine the decision-making process in adjuvant therapy. Indeed, only patients at high risk of recurrence, as defined by the 21-gene recurrence score, seem to derive any benefit from adjuvant chemotherapy; increased use of those tools might therefore reduce the number of patients receiving adjuvant chemotherapy for early breast cancer. The on-going MindAct (NCT00433589) and TAILORx trials (NCT00310180) will eventually define the exact role of prognostic profiles.

This article reviews current concepts and trends in the field of adjuvant systemic treatment in early-stage breast cancer.

**Endocrine treatment**

Endocrine therapy is the preferred treatment modality in hormone receptor-positive breast cancer. Indeed, adjuvant endocrine treatment is almost always indicated in hormone receptor-positive breast cancers; in patients at higher recurrence risk, sequential administration of endocrine treatment after chemotherapy is indicated.

Tamoxifen was the backbone of hormonal treatment for nearly three decades. Response rates of up to 30% in metastatic disease have been reported. The Early Breast Cancer Trialists’ Collaborative Group established that adjuvant treatment of early-stage disease with tamoxifen for about 5 years reduced the recurrence rate by 47% and the mortality rate by 38% during the timespan from years 0 to 4.

Tamoxifen and its metabolites bind to the ER, thereby blocking binding of activating function 2 (AF-2). This receptor modulation causes antagonistic as well as oestrogenic effects. Oestrogenic effects reduce the risk of osteoporosis; on the downside, however, the incidence of thromboembolic events is increased and the risk of developing endometrial hyperplasia necessitates regular gynaecological examinations.

A newer class of drugs, aromatase inhibitors (AIs), reduce plasma oestrogen concentrations by inhibiting aromatase, an enzyme that facilitates the synthesis of oestrogens from androgenic precursors produced by the adrenal glands. Randomized clinical trials have demonstrated the superior efficacy of third-generation AIs to tamoxifen in postmenopausal women with advanced-stage breast disease. Based upon those results, trials evaluating the role of AIs in early-stage breast cancer were initiated.

**Aromatase inhibitors as adjuvant therapy**

In a total of 13 randomized adjuvant studies, AIs were evaluated in different settings: upfront (from the beginning of endocrine treatment instead of tamoxifen), sequentially after 2–3 years of tamoxifen (or the reverse sequence: AI followed by tamoxifen) or extended after 5 years of tamoxifen treatment; most studies have tested a sequential approach.

Major differences between the study designs complicate the comparability and interpretation of results. For example, trials excluding patients who had received prior adjuvant chemotherapy might have selected for low-risk patients. Furthermore, in switching trials, randomization after 2–3 years of tamoxifen excluded patients with early recurrences.

Despite this, most studies of AIs in the adjuvant setting suggest a benefit over tamoxifen, at least in terms of disease-free survival (DFS).

**Upfront therapy with aromatase inhibitors**

Two prospective randomized trials compared 5 years of AIs with 5 years of tamoxifen as adjuvant treatment for hormone receptor-positive early breast cancer.

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was intended as a three-arm study comparing anastrozole with tamoxifen or a combination of both agents. The combination arm was stopped early, as that arm was found to be equivalent to tamoxifen. At a median follow-up of 100 months, anastrozole was found to be superior in terms of DFS (hazard ratio (HR) 0.9; 95% confidence interval (CI) 0.82–0.99; $P=0.025$), whereas no significant difference in OS was observed (HR 1.0; 95% CI 0.89–1.12; $P=0.99$).

BIG 1-98, in contrast, was a four-arm trial in which tamoxifen was compared with letrozole and two sequencing arms, one conventional sequencing arm starting with tamoxifen, with a switch to letrozole, and a reverse sequencing arm starting with 2 years of letrozole followed by tamoxifen. At a median follow-up of 8.7 years, letrozole alone was significantly better than tamoxifen alone in the intention-to-treat analysis of DFS and OS (DFS HR 0.86; 95% CI 0.78–0.96; OS HR 0.87; 95% CI 0.77–0.99). No difference
was observed in the comparison of letrozole monotherapy with both switching strategies.

*Tamoxifen and aromatase inhibitor switching strategies*

Most studies of AIs in the adjuvant setting have employed switching strategies, usually starting with tamoxifen followed by an AI; the notable exception to this rule is the already mentioned reversed sequencing arm of BIG 1-98. Again, with the exception of BIG 1-98 and the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, all trials have compared sequential administration of tamoxifen and AIs with tamoxifen monotherapy. BIG 1-98, however, compared the switching arms with AI monotherapy; as outlined, no significant differences between the three arms were observed. The TEAM trial compared 5 years of exemestane with 30 months of tamoxifen followed by 30 months of exemestane. Again, no significant difference in favour of either arm was observed (DFS HR 0.97; 95% CI 0.88–1.08; \(P = 0.60\)).

In the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8, 3714 chemotherapy-naive patients were randomized to 5 years of tamoxifen or 2 years of tamoxifen followed by 3 years of anastrozole. Although the difference in terms of DFS did not reach statistical significance (HR 0.85; 95% CI 0.71–1.01; \(P = 0.067\)), ABCSG-8 found a benefit in terms of OS in the AI-containing arm (HR 0.78; 95% CI 0.62–0.98; \(P = 0.032\)). Thus, this is the only trial involving randomization after surgery to have found increased OS in the AI cohort.

The Arimidex Nolvadex 95 (ARNO 95) trial is the only other study of adjuvant AIs to report a survival benefit in the sequential arm (HR 0.53; 95% CI 0.28–0.99; \(P = 0.045\)). Here, however, it worth noting that randomization was performed after an initial phase of 2 years of adjuvant tamoxifen therapy. Thus, early relapsers were not included in the intention-to-treat (ITT) population. In ABCSG-8, selection for a low-risk population might result from the exclusion of patients with prior exposure to adjuvant chemotherapy. Thus, we suggest that the beneficial effect of adjuvant AIs is greatest in an endocrine-responsive low-risk population.

In line with this assumption, a recent prospectively planned biomarker analysis from the TEAM trial suggested that overall prognosis is poorer in patients with less endocrine-responsive disease [evaluated by the expression of epidermal growth factor receptor (EGFR), Her2 or Her3] than in EGFR-, Her2- and Her3-negative patients and found no evidence of additional benefit from adjuvant AIs.\(^7\)

Summarizing those data, adjuvant endocrine therapy of postmenopausal women should include AIs, especially when no prior chemotherapy was administered. However, the optimal treatment strategy – upfront versus sequential – remains unresolved.

*Aromatase inhibitors as extended adjuvant therapy*

Patients with hormone receptor-positive breast cancer remain at risk of disease recurrence even after 5 years of adjuvant tamoxifen. Thus, trials of extended endocrine therapy with AIs after 5 years of tamoxifen were instituted.

MA.17 compared 5 years of extended letrozole therapy with placebo after completion of 5 years of adjuvant tamoxifen. ABCSG-6a was an extension trial of ABCSG-6 comparing placebo with extended adjuvant endocrine therapy with 3 years of anastrozole. The third extended adjuvant treatment trial, National Surgical Breast and Bowel Project (NSABP) trial B-33, randomized patients to 5 years of extended therapy with exemestane or to placebo. Both MA.17 and ABCSG-6a reported a significant prolongation of DFS in the AI arms (MA.17: HR 0.68; 95% CI 0.55–0.83; \(P < 0.001\); ABCSG-6a: HR 0.62; 95% CI 0.40–0.96; \(P = 0.031\)), although no difference in OS was observed. In B-33, extension with exemestane resulted in a statistically non-significant improvement in terms of 4-year DFS (91% vs. 89%; relative risk = 0.68; \(P = 0.07\)).

Based on these results, both anastrozole given for 3 years and letrozole given for 5 years are reasonable options in postmenopausal patients with early-stage hormone receptor-positive breast cancer who have completed 5 years of adjuvant therapy with tamoxifen. The optimum duration of extended therapy is still unclear, but this issue is likely to be resolved by ABCSG trial 16 (NCT00295620), which compares 5 years and 2 years of extended adjuvant therapy. No data are currently available concerning any potential benefit of extended therapy after primary endocrine therapy with AIs instead of tamoxifen.
Neoadjuvant endocrine therapy

Neoadjuvant treatment today is well established in tumours not suitable for primary breast conservation. Usually, however, neoadjuvant chemotherapy is instituted. On the other hand, chemotherapy is less effective in highly endocrine-responsive disease, in which preoperative hormonal treatment offers a meaningful alternative.

Tamoxifen as primary treatment was first established in frail patients not fit for surgery and yielded a response rate of around 40%; a complete response rate of 15–30% was observed. In randomized trials comparing tamoxifen with surgery, OS outcomes were similar in both treatment groups, demonstrating the high activity of primary endocrine treatment. Later trials, therefore, were also conducted in younger postmenopausal women fit for breast cancer surgery.

The PO24 trial compared letrozol with tamoxifen, each given for a total duration of 4 months prior to breast cancer surgery. The response rate was 55% in the letrozole arm, compared with 36% in patients receiving tamoxifen. Furthermore, breast conservation was possible in 45% of letrozole patients compared with 35% of patients receiving tamoxifen. In contrast, the IMPACT trial, comparing anastrozole with tamoxifen, could not demonstrate a clear-cut benefit for AI over tamoxifen; however, a meta-analysis of four randomized trials comprising a total of 1160 patients found that AIs are superior to tamoxifen as neoadjuvant endocrine treatment. Preoperative AI treatment was more effective than preoperative tamoxifen in terms of clinical response rate (cCR 69.1% and 74.8%, respectively). Therefore, those substances should be used in further phase III trials. No differences were observed in biological activity, as changes in Ki67 levels were similar in the subgroups (Kruskal–Wallis test, \( P = 0.45 \)). Importantly, this trial did not find any differences between luminal A and luminal B subtype tumours in terms of clinical response or probability of breast conservation. Therefore, pending validation in further clinical trials, neoadjuvant endocrine may evolve into an attractive alternative to chemotherapy even in luminal B breast cancers.

Semiglazov et al. reported similar results in terms of pCR in a randomized phase II study comparing epirubicin plus paclitaxel every 3 weeks for four cycles with 3 months of endocrine treatment with either exemestane or anastrozole in 239 hormone receptor-positive primary breast cancer patients (pCR rate 6% vs. 3%, NS). This trial, although limited by the relatively small patient population, the lack of information on breast cancer subtypes as well as suboptimal chemotherapy regimen and treatment duration, strengthened the assumption that the effect of neoadjuvant endocrine therapy is often underestimated. Furthermore, Alba et al. demonstrated that exemestane may offer similar activity to epirubicin–cyclophosphamide (EC) followed by four cycles of docetaxel in women with low baseline Ki67.

Finally, the optimal duration of neoadjuvant endocrine treatment has not yet been resolved. Current recommendations, however, suggest that a minimum duration of 4–8 months might result in highest efficacy.

Fulvestrant

Fulvestrant is a pure anti-oestrogen without oestrogenic properties. In an early preoperative trial, 56 patients were randomly assigned to fulvestrant daily for 7 days prior to operation at daily doses of 6 or 18 mg or placebo. A significant reduction in terms of Ki67 expression was observed in both fulvestrant groups (median Ki67 labelling index 3.2 before compared with 1.1 after treatment; \( P < 0.05 \)).

Fulvestrant trial 0018 evaluated the relative effects of a single dose of long-acting fulvestrant at different dose levels (50 mg, 125 mg or 250 mg), continuous daily tamoxifen or placebo for 14–21 days prior to...
surgery in patients with primary breast tumours scheduled for surgery. All fulvestrant doses produced a statistically significant reduction in ER expression levels compared with placebo; in the 250 mg group, this reduction was significantly greater than that produced by tamoxifen.

Treatment with single-shot fulvestrant 250 mg had no effect in premenopausal women, while 750 mg significantly reduced expression of ER, PgR and Ki67. Currently, no information is available concerning the potential activity of fulvestrant 500 mg in premenopausal women.

Thus, although fulvestrant is well established for the treatment of postmenopausal women with metastatic breast cancer, it currently plays no role in early breast cancer outside clinical trials.

**Adjuvant endocrine therapy in premenopausal women**

Current American Society of Clinical Oncology (ASCO) guidelines recommend the use of tamoxifen for 5 years in premenopausal women with hormone receptor-positive early breast cancer. While the combination of tamoxifen with ovarian function suppression (OFS) with gonadotropin-releasing hormone (GnRH) agonists is superior to OFS alone, there is currently no clear-cut evidence that the combination of GnRH agonists plus tamoxifen is superior to tamoxifen alone. An on-going study will eventually help resolve this urgent question: the Suppression of Ovarian Function Trial (SOFT) is a three-arm study comparing tamoxifen with tamoxifen plus OFS, the third arm receiving a combination of the steroidal AI exemestane and OFS. The second question therefore likely to be answered by this trial is the role of AIs combined with OFS in premenopausal breast cancer patients. To date, only results from ABSCG trial 12 are available.

In ABSCG trial 12, 1803 patients were randomly assigned to 3 years’ treatment with tamoxifen or 3 years of anastrozole treatment. In both groups, the GnRH agonist goserelin was given as OFS. No patients with prior adjuvant chemotherapy were allowed, thereby selecting for a low-risk patient population. At a median follow-up of 47.8 months, DFS was 92.8% in the tamoxifen group and 92% in the anastrozole group (HR 1.10; 95% CI 0.78–1.53; P = 0.59). Thus, adjuvant AIs in combination with OFS appear to offer similar efficacy to tamoxifen; however, in contrast to postmenopausal women, the superiority of AIs could not be established. The reason for this observation is not entirely clear. In fact, patient number was too low to detect subtle differences between the subgroups. Also, there might be a difference between natural and drug-induced menopause. Therefore, the results from the SOFT trial are needed before a definitive conclusion concerning the potential role of AIs in premenopausal women can be drawn.

Standard endocrine treatment options are summarized in Table 1.

**Chemotherapy**

**Anthracyclines**

The Oxford Overview indicates that adjuvant chemotherapy reduces the risk of breast cancer recurrence by approximately 24%, and the risk of death by 15%. Women below the age of 50 years, as well as women aged 50–69 years, seem to derive the same relative benefit from adjuvant treatment. In hormone receptor-positive patients, a smaller relative benefit was observed. Development of modern chemotherapy regimens took decades, and still no international standard has been established.

Bonadonna and colleagues reported that adjuvant chemotherapy with cyclophosphamide, methotrexate (MTX) and 5-fluorouracil (5-FU) (CMF) resulted in superior PFS and OS to mastectomy alone. Thus, CMF and CMF-like regimens have been the standard of care in many countries for nearly 20 years.

Anthracyclines were incorporated into adjuvant regimens during the 1990s. NSABP study B-15 established that four cycles of doxorubicin and cyclophosphamide (AC) was equivalent to six cycles of CMF in terms of relapse-free survival.

**TABLE 1** Standard endocrine treatment options in early breast cancer

<table>
<thead>
<tr>
<th>Postmenopausal</th>
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<tr>
<td>Tamoxifen (5 years)</td>
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<td>Alternatively, ovarian function suppression (OFS) (2–3 years) in combination with tamoxifen (5 years) when no adjuvant chemotherapy is indicated (with or without zoledronic acid)</td>
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<table>
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<th>Premenopausal</th>
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<td>Tamoxifen (2–3 years) followed by AI (2–3 years)</td>
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<tr>
<td>AI (2 years) followed by tamoxifen (3 years)</td>
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<tr>
<td>Tamoxifen (5 years) followed by extended therapy with AI</td>
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and OS,\textsuperscript{44} while six cycles of FAC (5-FU 500 mg/m\textsuperscript{2}, doxorubicin 50 mg/m\textsuperscript{2}, cyclophosphamide 500 mg/m\textsuperscript{2}) was superior to six cycles of CMF in a Spanish Breast Cancer Research Group (GEICAM) trial.\textsuperscript{44} A meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) finally established the superiority of anthracycline-based regimens.\textsuperscript{45} While a number of different regimens of CMF and anthracycline-based chemotherapy were used, outcomes were consistently in favour of the anthracycline arms. The absolute benefit, although modest, was a difference in breast cancer mortality of 4\% at 10 years.\textsuperscript{46}

Identification of the optimal anthracycline dose took even longer. Increasing the dose of doxorubicin beyond 60 mg/m\textsuperscript{2} did not yield superior efficacy;\textsuperscript{47} epirubicin, however, demonstrates dose-dependent efficacy even beyond 60 mg/m\textsuperscript{2}, and the French FEC regimen (5-FU 500 mg/m\textsuperscript{2}, epirubicin 100 mg/m\textsuperscript{2}, cyclophosphamide 500 mg/m\textsuperscript{2}) is often cited as the optimal anthracycline-based regimen.\textsuperscript{48}

Anthracyclines inhibit topoisomerase-IIα (topo-IIα), a molecule active in DNA repair pathways. The gene coding for topo-IIα is located in close proximity to the Her2/neu gene (17q12–q21). When Her2 is amplified, this may be accompanied by the amplification of the topo-IIα gene as well, whereas isolated amplification of the topo-IIα is a rare event.\textsuperscript{49} In line with that assumption, a retrospective analysis of studies evaluating the role of anthracyclines in early breast cancer suggested that the relative benefit of anthracyclines to CMF might be restricted to Her2-positive cancers with consecutive topo-IIα overexpression.\textsuperscript{50} This theory, however, has not since been validated in prospective trials, and the general use of anthracycline-free regimens in Her2-negative disease cannot therefore be recommended.

**Taxanes**

Taxanes are cytotoxic agents first isolated from the yew tree; they interact with the β-subunit of tubulin and induce tubulin polymerization, thus interfering with the normal balance between polymerization and depolymerization, which leads to cell cycle arrest in the G2/M phase.\textsuperscript{51} With first-line response rates of up 70\%, taxanes are among the most active chemotherapeutic agents in breast cancer.\textsuperscript{52} In the metastatic setting, a lack of complete cross-resistance with anthracyclines has been reported.\textsuperscript{53,54} Thus, taxanes were introduced into the adjuvant setting in the 1990s.

Cancer and Leukaemia Group B (CALGB) Trial 9344 investigated different doses of doxorubicin (60 mg/m\textsuperscript{2}, 75 mg/m\textsuperscript{2} or 90 mg/m\textsuperscript{2}) plus cyclophosphamide in 3170 women with node-positive breast cancer. In a second randomization, patients were assigned to received four additional cycles of paclitaxel (175 mg/m\textsuperscript{2} every 3 weeks) or no further chemotherapy. Indeed, addition of paclitaxel improved DFS and OS.\textsuperscript{47} The design of the trial, however, drew some criticism, as the observed difference might have been caused simply by the longer duration of chemotherapy in the experimental arm (eight cycles vs. four cycles).

A study of similar design was conducted by the NSABP; in trial B-28, 3059 patients with node-positive breast cancer were randomized to four cycles of AC (doxorubicin 60 mg/m\textsuperscript{2} and cyclophosphamide 600 mg/m\textsuperscript{2}) or the same regimen followed by four cycles of paclitaxel (225 mg/m\textsuperscript{2} every 3 weeks). Again, DFS was superior in the taxane arm, yet no difference in terms of OS was observed.\textsuperscript{55}

This striking difference might be due to the higher percentage of patients completing all eight cycles of chemotherapy in CALGB 9344 compared with B-28 (> 90\% vs. 76\%). Furthermore, patients with hormone receptor-positive tumours received tamoxifen and chemotherapy concomitantly within B-28. In this context, it is important to note that South West Oncology Group (SWOG) trial 8814 suggested that concomitant administration of endocrine therapy and chemotherapy may be inferior to initiation of endocrine therapy after chemotherapy.\textsuperscript{56}

Breast Cancer International Research Group (BCIRG) trial 001 randomized 1491 patients to six cycles of FAC (5-FU 500 mg/m\textsuperscript{2}, doxorubicin 50 mg/m\textsuperscript{2}, cyclophosphamide 500 mg/m\textsuperscript{2}) or six cycles of TAC (docetaxel 75 mg/m\textsuperscript{2}, doxorubicin 50 mg/m\textsuperscript{2}, cyclophosphamide 500 mg/m\textsuperscript{2}). In hormone receptor-positive patients, tamoxifen was given sequentially. A relative 30\% reduction in the risk of death was observed in favour of the TAC arm (\textit{P} = 0.008).\textsuperscript{57} Therefore, although the FAC comparator arm was not optimally dose, this study strengthened the role of taxanes in the adjuvant setting.

Finally, Programme Adjuvant Cancer du Seins (PACS) 01 study compared six cycles of French FEC (FEC100; 5-FU 500 mg/m\textsuperscript{2}, epirubicin 100 mg/m\textsuperscript{2}, cyclophosphamide 500 mg/m\textsuperscript{2}), often regarded as being the ‘optimum’ anthracycline-based regimen, with three cycles of FEC followed by three cycles of docetaxel 100 mg/m\textsuperscript{2} in node-positive patients. Here,
a significant benefit in terms of DFS and OS, as well as a lower toxicity rate, was observed in favour of the taxane arm.48

Bases on these results, the inclusion of taxanes has become the standard of care in node-positive patients. The optimum dose and schedule, however, remain a matter of debate. In this context, the results of the Canadian MA.21 trial48 need to be taken into consideration.

In that study, the former North American standard regimen (four cycles of AC followed by four cycles of paclitaxel given every 3 weeks) was compared with 6 months of treatment with the Canadian CEF regimen, another sufficiently dosed anthracycline-based regimen. Surprisingly, Canadian CEF was superior to AC/T in terms of recurrence-free survival.58 Thus, paclitaxel administered every 3 weeks should no longer be part of adjuvant chemotherapy regimens.

In clear contrast to other adjuvant taxane studies, the Sequential Docetaxel as Adjuvant Chemotherapy for Early Breast Cancer (TACT) trial59 did not observe a benefit for docetaxel 100 mg/m² when given sequentially for four cycles after four cycles of FEC (5-FU 600 mg/m², epirubicin 60 mg/m², cyclophosphamide 600 mg/m²) compared with eight cycles of FEC or four cycles of epirubicin 100 mg/m² followed by four cycles of CMF.59 After a median follow-up of 62 months, DFS rates were similar in both treatment groups (HR 0.86; 95% CI 0.74–1.00; \( P = 0.05 \)).

Interestingly, DFS in the sequential docetaxel arm was superior to that in the concurrent docetaxel arm (HR 0.81; 95% CI 0.69–1.00) and the sequential control arm (HR 0.79; 95% CI 0.64–0.98).

**Dose-dense chemotherapy**

Dose-dense therapy is another concept to improve the efficacy of adjuvant treatment. In a prospective randomized trial of concomitant versus sequential conventional or dose-dense doxorubicin, cyclophosphamide and paclitaxel, Citron et al.60 observed a significant improvement in terms of DFS as well as OS with the use of dose-dense chemotherapy. A meta-analysis of dose-dense versus conventionally dosed chemotherapy regimens also suggested a significant benefit for the dose-dense arms (HR of death = 0.85; 95% CI 0.77–0.93).61 Whereas Intergroup trial 9741 directly compared the North American standard regimen, AC–paclitaxel with dose-dense AC–paclitaxel, most of the other regimens utilized differential or modified regimens.60,61 Importantly, dose-dense regimens were never compared with EC/AC followed by docetaxel. Furthermore, the aforementioned MA.21 trial58 did not establish superiority of dose-dense EC every 2 weeks plus paclitaxel (also administered every 2 weeks) over Canadian CEF. Thus, dose-dense regimens are just one potential standard for the treatment of early-stage breast cancer; 3-weekly paclitaxel should be considered suboptimal and should be replaced by dose-dense or weekly paclitaxel or 3-weekly docetaxel.

**Sequential or concomitant administration of anthracyclines or taxanes**

Furthermore, sequential administration of anthracyclines and taxanes may be superior to concomitant administration, although the results are not equivocal. A total of 2887 patients were accrued to BIG trial 2-98.62 This study randomized patients to one of four different regimens: docetaxel given concurrently with doxorubicin (four cycles of doxorubicin at 50 mg/m² plus docetaxel at 75 mg/m², followed by three cycles of CMF); docetaxel administered sequentially with doxorubicin (three cycles of doxorubicin at 75 mg/m², followed by three cycles of docetaxel at 100 mg/m², followed by three cycles of CMF); concurrent control (four cycles of doxorubicin at 60 mg/m² plus cyclophosphamide at 600 mg/m², followed by three cycles of CMF); or sequential control (four cycles of doxorubicin at 75 mg/m², followed by three cycles of CMF). Docetaxel-based adjuvant chemotherapy resulted in a borderline improvement in DFS compared with control (HR 0.86; 95% CI 0.74–1.00; \( P = 0.05 \)). Interestingly, DFS in the sequential docetaxel arm was superior to that in the concurrent docetaxel arm (HR 0.83; 95% CI 0.69–1.00) and the sequential control arm (HR 0.79; 95% CI 0.64–0.98).

BCIRG-005 randomly assigned 3289 patients to six cycles of TAC or four cycles of AC followed by four cycles of docetaxel at 3-weekly intervals. In contrast to the results above, after a median follow-up of 65 months, there was no difference in terms of DFS between the two treatment groups (DFS 79% in both arms; \( P = 0.98 \); HR 1.0; 95% CI 0.86–1.16). In terms of toxicity, more cases of febrile neutropenia and thrombocytopenia were observed in the TAC arm, while AC>T was associated with a higher rate of sensory neuropathy, nail changes and myalgia.63
Swain et al. randomized 5351 patients to four cycles of AC followed by four cycles of docetaxel or two experimental arms consisting of four cycles of concurrent AC–docetaxel or A–docetaxel. At a median follow-up of 73 months, superior OS was reported in the sequential AC–docetaxel group (83%) than in the A–docetaxel arm (OS 79%; HR 0.83; P = 0.03) and the concurrent AC–docetaxel arm (OS 79%; HR 0.86; P = 0.09). With the limitation of shorter chemotherapy duration, this trial therefore again suggests that sequential administration of anthracyclines and taxanes may be preferable to concurrent regimens.

**Anthracycline-free taxane-based regimen**

In patients not deemed eligible for 6–8 cycles of standard modern adjuvant regimens, TC × 4 (docetaxel 75 mg/m², cyclophosphamide 600 mg/m²) might constitute an appropriate alternative. Four cycles of TC was superior to four cycles of AC in US Oncology trial 9735 in terms of DFS. An update with longer follow-up even indicated a survival benefit associated with TC. The incorporation of docetaxel was associated with higher rates of myalgia, arthralgia, oedema and febrile neutropenia, whereas more cases of nausea and vomiting as well as one case of congestive heart failure were observed in the AC group. It is worth mentioning that TC was also reasonably well tolerated in older women with no excessive toxicity compared with their younger counterparts.

**Role of taxanes in node-negative patients**

Four cycles of A–docetaxel (doxorubicin 60 mg/m², docetaxel 60 mg/m²) was not superior to four cycles of conventional AC in 2882 patients with node-positive or node-negative tumours with primary tumour size larger than 1 cm. As in the TACT trial, the negative results may be attributable to the inclusion of node-negative patients. It is more likely, however, that the omission of cyclophosphamide had a negative impact on the efficacy of the experimental arm.

Summarizing the data on adjuvant taxanes, there is strong evidence to suggest that the inclusion of paclitaxel or docetaxel in the adjuvant chemotherapy of node-positive early breast cancer yields superior outcomes to non-taxane-containing regimens. As outlined, however, the evidence in node-negative patients is less clear. The TACT trial, which included high-risk node-negative patients, as well as North American Breast Cancer Intergroup Trial E 2197 did not show a benefit for the addition of docetaxel. Spanish Breast Cancer Research Group (GEICAM) trial 8701 randomly assigned 1060 node-negative early breast cancer patients with at least one high-risk factor for recurrence according to the 1998 St. Gallen Consensus Conference (tumour size >2 cm; negative hormone receptor status; grade 2 or 3; age < 35 years) to six cycles of FAC (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²) or six cycles of TAC (docetaxel 75 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²). At a median follow-up of 77 months, 473 patients in the TAC group (87.8%) and 426 patients in the FAC group (81.8%) were free of disease, corresponding to a 32% reduction in the risk of experiencing a DFS event in favour of the TAC group (HR 0.68; 95% CI 0.49–0.93; P = 0.01). Although a suboptimal dose of anthracyclines was used in the comparator arm, GEICAM 8701 is the only study specifically to have evaluated the role of taxanes in node-negative patients; the findings suggest that the addition of docetaxel might also prove beneficial in the adjuvant treatment of high-risk node-negative patients.

**Meta-analysis of taxane trials**

Finally, in spite of the outstanding questions, the Early Breast Cancer Trialists’ Collaborative Group overview suggests that taxanes make a valuable contribution to adjuvant chemotherapy regimens: the recurrence rate ratio of taxane-based to anthracyclines-based regimens in 20 000 women included in a prospective randomized studies was 0.83 (P < 0.00001). In terms of mortality, breast cancer mortality rate ratio was 0.46 (2P < 0.00001) in younger women and 0.66 (P = 0.00002) in older women.

Standard chemotherapy treatment options are summarized in Table 2.

**High-dose chemotherapy**

The dose-dependent activity of epirubicin is well established, and GOIOM (Gruppo Oncologico Italia Meridionale) trial 9902 observed no additional benefit when four cycles of docetaxel 100 mg/m² was added to four cycles of high-dose EC (epirubicin 120 mg/m², cyclophosphamide 600 mg/m²) over EC alone (5-year DFS 73.4% in both arms; HR 0.99; 95% 0.75–1.31; P = 0.95). These results suggest that any further increase in epirubicin dose beyond 90–100 mg/m² might increase the efficacy of anthracycline-based regimens.
The term ‘high-dose chemotherapy’, however, is usually applied only to chemotherapeutic regimens requiring autologous stem cell support; following promising phase II data, the concept was broadly utilized in breast cancer patients in the 1990s.73 Randomized clinical trials, however, could never establish a clear benefit of high-dose chemotherapy over conventionally dosed regimens, although a benefit in selected patient subgroups (such as Her2-negative, >10 positive lymph nodes) has been suggested.74

Recently, Berry et al.75 published an analysis of individual patient data from 15 prospective randomized trials that compared high-dose chemotherapy with conventional control without stem cell support. A total of 6210 patients were included. After correcting for trial, age, number of positive lymph nodes and hormone receptor status, high-dose chemotherapy significantly reduced the risk of recurrence (HR 0.87; 95% CI 0.81–0.93; P < 0.001). A non-significant reduction in the risk of death was also observed (HR 0.94; 95% CI 0.87–1.02; P = 0.13). On the downside, patients treated with high-dose chemotherapy experienced a significant increase in the risk of death after recurrence of 16% compared with patients in the control arms (HR 1.16; 95% CI 1.07–1.26; P < 0.01). In the subset of triple-negative patients, a significant 33% reduction in the risk of death was observed. However, Her2 status was available for only a limited number of patients, and no effect was seen in patients with hormone receptor-negative disease and unknown Her2 status. The authors therefore concluded that the observed benefit in triple-negative disease in probably spurious.

<table>
<thead>
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<th>TABLE 2</th>
<th>Standard chemotherapy regimens in early breast cancer</th>
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|**Her2-negative** | **CMF** | Cyclophosphamide (100 mg/m² p.o., d1–14), MTX (40 mg/m², d1 + 8), 5-FU (600 mg/m², d1–8), q28d, × 6
| | or | Cyclophosphamide (600 mg/m² d1 + 8), MTX (40 mg/m² d1 + 8), 5-FU (600 mg/m² d1–8), q28d, × 6
| | **AC** | Doxorubicin (60 mg/m²), cyclophosphamide (600 mg/m²), d1, q3w, × 4
| | **EC** | Epirubicin (90 mg/m²), cyclophosphamide (600 mg/m²), d1, q3w, × 4
| | **FEC** | 5-Fluorouracil (500–600 mg/m²), epirubicin (50–100 mg/m²), cyclophosphamide (500–600 mg/m²), d1, q3w, × 6
| | **CEF** | Cyclophosphamide (75 mg/m² p.o., d1–14), epirubicin (60 mg/m² d1 + 8), 5-FU (600 mg/m² d1–8), q28d, × 6
| | **TC** | Docetaxel (75 mg/m²), cyclophosphamide (600 mg/m²), d1, q3w, × 4
| | **ET** | Docetaxel (75 mg/m²), epirubicin (75 mg/m²), d1, q3w, × 6
| | **TAC** | Docetaxel (75 mg/m²), doxorubicin (50 mg/m²), cyclophosphamide (500 mg/m²), d1, q3w, × 6–8
| | **AC-T** | Doxorubicin (60 mg/m²), cyclophosphamide (600 mg/m²), d1, q2w, × 4, followed by paclitaxel (175 mg/m²), d1, q2w, × 4
| | or | Doxorubicin (60 mg/m²), cyclophosphamide (600 mg/m²), d1, q3w, × 4, followed by paclitaxel (80 mg/m²) weekly × 12
| | **EC-T** | Epirubicin (90 mg/m²), cyclophosphamide (600 mg/m²), d1, q3w, × 4, followed by docetaxel (100 mg/m²), d1, q3w, × 4
| **Her2-positive** | **Trastuzumab adjuvant (HERA style)** | Any chemotherapy (minimum EC × 4 or AC × 4, or CMF × 6) followed by trastuzumab (6 mg/kg) q3w (loading dose 8 mg/kg), total duration 52 weeks
| | **AC-TH** | Doxorubicin (60 mg/m²), cyclophosphamide (600 mg/m²), d1, q3w, × 4, followed by paclitaxel (80 mg/m²) weekly × 12
| | plus | Trastuzumab 2 mg/kg qw (loading dose 4 mg/kg), total duration 52 weeks
| | **EC-TH** | Epirubicin (90 mg/m²), cyclophosphamide (600 mg/m²), d1, q3w, × 4, followed by docetaxel (100 mg/m²), d1, q3w, × 4
| | plus | Trastuzumab 6 mg/kg q3w (loading dose 8 mg/kg), total duration 52 weeks
| | **TCH** | Docetaxel (75 mg/m²), carboplatin (AUC6), d1, q3w, × 6
| | plus | Trastuzumab 6 mg/kg q3w (loading dose 8 mg/kg), total duration 52 weeks

*Typically only used as neoadjuvant chemotherapy regimen.
†When administered as neoadjuvant regimen, trastuzumab may be given from the beginning of chemotherapy (concomitantly with EC).
The great advantage of this meta-analysis is the large sample size. While the largest of the individual trials had a statistical power to detect a 30% reduction in the risk of death, the study by Berry et al. had 80% power to detect a 10% reduction in breast cancer recurrences and 12% reduction in the risk of death. Thus, it is the best available analysis of high-dose chemotherapy. On the downside, the studies included were highly heterogeneous and, indeed, average weekly dose intensity and total dose intensity were higher in some of the control arms than in some of the high-dose chemotherapy arms during both the induction phase and the treatment phase. Thus, whether or not high-dose chemotherapy has any beneficial effect in selected patient subgroups, such as those with triple-negative tumours, remains in doubt. However, as most trials did not observe superior outcome in the high-dose arm and the focus of scientific interest today rests with targeted agents, it is highly unlikely that a trial of high-dose chemotherapy with stem cell support will ever again be initiated. Thus, high-dose chemotherapy plays no role in the adjuvant treatment of breast cancer.

Neoadjuvant chemotherapy

Preoperative chemotherapy was first used in the 1970s in patients with locally advanced inoperable breast cancer. National Surgical Breast and Bowel Project (NSABP) trial B-18 established that four cycles of preoperative chemotherapy with doxorubicin plus cyclophosphamide (AC) was equally as effective as four cycles of postoperative AC in operable disease. Today, the concept of neoadjuvant treatment has become a standard in operable disease, with the objective being to increase the rate of breast-conserving surgery and improve cosmesis. Over the last 30 years, a broad spectrum of different chemotherapeutic drugs have been used, with modern regimens encompassing anthracyclines as well as taxanes.

The largest neoadjuvant trial to date, NSABP B-27, included 2411 patients who were randomly assigned to four cycles of AC followed by surgery, AC followed by docetaxel and surgery or AC followed by surgery and adjuvant docetaxel. Incorporation of docetaxel into the neoadjuvant setting significantly reduced the incidence of local recurrence as a first event (P=0.0034); in addition, pCR was doubled by the addition of preoperative docetaxel, which was a significant positive predictor of OS (HR = 0.33; 95% CI 0.23–0.47; P < 0.0001). Thus, today a combination of taxanes and anthracyclines is usually administered in the neoadjuvant setting.

Other clinical trials have tested the inclusion of further chemotherapeutic agents such as capecitabine or gemcitabine. ABCSG trial 24 compared six cycles of ET (epirubicin 75 mg/m², docetaxel 75 mg/m²) plus granulocyte colony-stimulating factor (G-CSF) support with six cycles of ET plus capecitabine 1000 mg/m² b.i.d. for 2 weeks with 1 week’s rest. The triple combination resulted in a significantly increased pCR rate compared with ET alone (23.8% vs. 15.2%; P=0.036).

Those results are in contrast to the results of NSABP trial B-40, a study that tested the addition of capecitabine (C; 825 mg/m² b.i.d., days 1–14, every 21 days) or gemcitabine (G; 1000 mg/m², days 1 + 8, every 21 days) to four cycles of docetaxel followed by four cycles of AC. Here, no benefit of adding further cytotoxics was observed (pCR rate: docetaxel 32.7%; G + docetaxel 32%; C + docetaxel 29.7%).

The German Breast Group (GBG) trial GeparQuattro recruited 1509 patients, who received four cycles of EC (epirubicin 90 mg/m², cyclophosphamide 600 mg/m²). Patients were then randomly assigned to four cycles of docetaxel (100 mg/m²), four cycles of docetaxel plus capecitabine (docetaxel 75 mg/m², capecitabine 900 mg/m² b.i.d., days 1–14, every 21 days) or four cycles of docetaxel 75 mg/m² followed by four cycles of capecitabine 900 mg/m² b.i.d. for 2 weeks followed by 1 week’s rest. Treatment resulted in a pCR rate of 22.3% (EC–docetaxel), 19.5% (EC–docetaxel plus capecitabine) and 22.3% (EC–docetaxel–capecitabine). Thus, in line with the results of NSABP B-40, incorporation of capecitabine into the neoadjuvant setting did not result in higher pCR rates.

Differences between those trials might be explained by the lower dose of capecitabine in NSABP B-40 and GeparQuattro than in ABCSG-24, as a recently published randomized phase II trial suggested a dose-dependent efficacy of capecitabine in combination with docetaxel. However, it is also possible that the omission of cyclophosphamide in ABCSG-24 compromised the efficacy of the ET control group, thereby resulting in the relative advantage in the ET + capecitabine arm.

An increased rate of locoregional recurrence after neoadjuvant chemotherapy has been a matter of concern since it was suggested in a meta-analysis.
of neoadjuvant trials. It is, however, important to remember that the meta-analysis incorporated a number of studies in which breast cancer surgery was withheld in the neoadjuvant treatment groups. Thus, it is not proven that neoadjuvant treatment followed by optimal local therapy will increase the rate of locoregional recurrence.

As outlined, pCR may serve as surrogate for improved survival. Thus, pCR is often regarded as the most pertinent endpoint to assess the efficacy of neoadjuvant treatment. The prognostic role of pCR has also been established in Her2-positive disease. However, such a distinction (i.e. pCR or no-pCR) is overly simplistic, as the prognosis of patients with residual disease still varies depending on the grade of their response, which may range from near pCR to progression. Symmans et al. therefore established the residual cancer burden (RCB) score, which incorporates pathological measurements of primary tumour (size and cellularity) and nodal metastases (number and size). Indeed, the RCB score would seem to be a meaningful alternative to pCR as a primary endpoint in future clinical trials.

Trastuzumab

Targeted therapies such as trastuzumab, a monoclonal antibody targeting Her2, have also been introduced into the neoadjuvant setting. In a trial conducted by Buzdar et al., patients received four cycles of paclitaxel followed by four cycles of FEC with or without weekly trastuzumab for 24 weeks. After the inclusion of only 42 patients, a significant difference in pCR rate in favour of trastuzumab was observed and the trial was terminated (66.7% vs. 25%; \( P = 0.02 \)). These results have been verified by further trials. The NOAH trial included 228 patients with locally advanced Her2-positive breast cancer treated with doxorubicin plus paclitaxel followed by paclitaxel alone and then CMF with or without trastuzumab. Gianni et al. observed a pCR rate of 23% with chemotherapy alone, compared with 43% in the trastuzumab group (\( P = 0.002 \)). In the GeparQuattro trial, 445 Her2-positive patients were randomly assigned to four cycles of EC followed by four cycles of docetaxel (with or without capecitabine) with or without trastuzumab. The pCR rate (defined as no invasive or in situ residual tumours in the breast) was again doubled (31.7% in the trastuzumab group compared with 15.7% in the control group). In this context it is important to mention that, although epirubicin and trastuzumab were administered concomitantly, the short-term cardiac toxicity profile was similar in the two arms. A meta-analysis of eight neoadjuvant trials conducted by the German Breast Group and AGO (Arbeitsgemeinschaft Gynäkologische Onkologie; Working Group Gynaecologic Oncology) included a total of 6634 patients, 1407 of whom were Her2 positive; 671 of those had received neoadjuvant trastuzumab, while the remaining 736 had not. The reported pCR rate was 41.1% in trastuzumab-treated patients compared with 27.7% in the control group. Based on those results, trastuzumab should be part of neoadjuvant therapy for Her2-positive breast cancer.

Lapatinib and pertuzumab

Based on the successes of trastuzumab, other drugs targeting Her2, such as pertuzumab, a monoclonal antibody with a binding domain distinct from trastuzumab, and the tyrosine kinase inhibitor lapatinib have been evaluated in clinical trials.

GeparQuinto was a large prospective randomized trial of EC \( \times 4 \) followed by docetaxel \( \times 4 \) as chemotherapy backbone. Her2-positive patients were randomized to lapatinib or trastuzumab. So far, this is the only trial using a standard chemotherapy regimen that directly compares trastuzumab with lapatinib. In GeparQuinto, the pCR rate, defined by the absence of invasive tumour cells in breast and axilla, was significantly increased by the inclusion of trastuzumab (45% vs. 30%), with even higher pCR rates observed in hormone receptor-negative patients.

NeoAalto was a three-arm study evaluating the efficacy of trastuzumab, lapatinib or the combination of both agents in conjunction with paclitaxel. Targeted therapy was given alone for a run-in phase of 6 weeks, and concomitantly with chemotherapy for another 12 weeks. The pCR rate was higher in the trastuzumab group than in the lapatinib group, although this difference did not reach statistical significance (29.5% vs. 24.7%), a fact that might be explained by the non-standard paclitaxel-alone chemotherapy backbone and the relatively short treatment duration. The combination group, however, displayed a significantly higher pCR rate (51.3% vs. 29.5%) than both single-agent groups, although a higher rate of side-effects was observed and only 61% of patients in the combination group completed therapy as planned, compared with 92% in the trastuzumab group. It is imperative,
therefore, to evaluate if lapatinib combined with standard neoadjuvant chemotherapy is feasible and whether a combination of standard chemotherapy with lapatinib and trastuzumab might yield even higher pCR rates. Indeed, there is a strong rationale for combining lapatinib and trastuzumab: lapatinib stabilizes Her2 in the tumour cell membrane, thereby preventing Her2 receptor down-regulation due to antibody binding and potentially increasing trastuzumab activity.94

The third trial incorporating novel, Her2-targeted agents was NeoSphere, a four-arm study comparing docetaxel plus trastuzumab with docetaxel plus pertuzumab, docetaxel plus the combination of both Her2-targeted monoclonal antibodies, or trastuzumab plus pertuzumab without chemotherapy backbone.93 The total duration of neoadjuvant therapy in that trial was only 12 weeks, i.e. less than in NeoAltt0. The response rate in the four arms was 29% (docetaxel plus trastuzumab), 24% (docetaxel plus pertuzumab), 46% (docetaxel plus trastuzumab plus pertuzumab) and 17% (trastuzumab plus pertuzumab without chemotherapy). This trial is important as it directly compared two different anti-Her2 antibodies; however, the chemotherapy-free arm aroused the greatest interest. Indeed, this was the first clinical trial to indicate that Her2-targeted treatment as neoadjuvant therapy without additional chemotherapy has considerable activity and might be a valuable alternative to conventional regimens in patients not deemed eligible for chemotherapy.

Bevacizumab

The role of bevacizumab, a monoclonal antibody that binds the angiogenic growth factor VEGF (vascular endothelial growth factor), is also under investigation.80,95 The results from clinical trials reported so far are inconsistent.

NSABP B-40, a prospective randomized phase III trial, used a standard regimen of docetaxel × 4 followed by AC × 4 as chemotherapy backbone.86 As outlined above, the addition of other cytotoxics, such as capecitabine or gemcitabine, did not increase pCR rates. However the incorporation of bevacizumab into the neoadjuvant setting significantly increased the pCR rate, from 28.4% to 34.5% (P = 0.027). This effect was mainly driven by the increased pCR rate in hormone receptor-positive patients.

GeparQuinto (GBG-44), a trial conducted by the German Breast Group, has reported contradictory results.93 The addition of bevacizumab to chemotherapy consisting of EC × 4 followed by four cycles of docetaxel did not increase pCR rates in the total population of Her2-negative breast cancer patients. However, the pCR rate was significantly increased in the hormone receptor-negative subgroup.

Currently, the reason for these differences is not clear. Subtle differences in patient characteristics and study designs might play a role, and the final results of both studies are awaited with interest.

Trastuzumab and lapatinib

Background

Over 20 years ago, Slamon et al observed that Her2 (human EGFr-related 2)-positive tumours followed a highly aggressive disease course.96,97 Her2 is a ligand-less growth factor receptor, forming homo- or heterodimers with other members of the epidermal growth factor superfamily (EGFr = Her1, Her3, Her4), thereby activating downstream signalling pathways of tumour growth and survival. Based on these findings, biological therapies targeting Her2 were developed.

Trastuzumab (rhMab4D5), a monoclonal antibody directed against the extracellular domain of Her2, today is firmly established in Her2-positive early-stage and metastatic breast cancer. It has dramatically increased response rates as well as PFS and OS rates compared with chemotherapy alone.

Trastuzumab

Binding of trastuzumab to Her2 leads to inhibition of downstream signalling and eventually causes cell degradation. Different mechanisms of action have been suggested: internalization and degradation of Her2 receptor protein; p27 induction, thereby causing cell cycle arrest due to decreased cyclin-dependent kinase 2 (CDK2) activity; inhibition of DNA repair; and antibody-dependent cellular cytotoxicity.98

Phase II clinical trials have proven the activity of trastuzumab as a single agent in Her2-positive metastatic breast cancer.95,100 Based on these studies, large randomized trials were initiated. Clearly, the combination of trastuzumab and taxanes was superior to chemotherapy alone.101,102 Accordingly, trastuzumab was approved for the first-line treatment
of Her2-positive metastatic breast cancer in combination with taxanes.

**Trials of adjuvant trastuzumab**

Owing to its beneficial role in the palliative setting, trials of adjuvant trastuzumab were soon initiated. Six prospective randomized phase III studies included a total of more than 13,000 women. Five studies reported superior outcomes in terms of PFS in the trastuzumab arms: indeed, recurrence risk was cut by approximately 50%. With the exception of FinHer, OS also increased. The French PACS-04 study, on the other hand, was the only trial to report negative findings. Despite this, the results of these trials led to the approval of trastuzumab as adjuvant treatment for Her2-positive early breast cancer.

In this context, differences in the trial designs need to be considered. Node status, chemotherapy backbones and start of trastuzumab administration varied; thus, a number of questions remain unanswered.

**NSABP B-31 and NCCTG N9831**

NSABP B-31, a prospective, randomized phase III trial, randomized node-positive patients to the North American standard chemotherapy regimen of AC×4 followed by four cycles of paclitaxel every 3 weeks (or 12 cycles of weekly paclitaxel) with or without trastuzumab for a total duration of 1 year, which was started concomitantly with paclitaxel. The second North American study, NCCTG N9831, had a three-arm design. Two arms were identical to the corresponding arms of NSABP B-31, while a third arm started trastuzumab only after the end of chemotherapy, similar to the HERA trial. In contrast to B-31, patients with high-risk node-negative disease were also allowed to participate, although the rate of node-negative patients in the total population was rather low. Chemotherapy backbone in NCCTG N9831 was similar to that in NSABP B-31; therefore, an FDA-approved joint analysis comparing the two concurrent trastuzumab arms with the two control arms was conducted. The total patient number for this analysis was 3968, with 93% being node positive.

At a median follow-up of 2 years, the addition of trastuzumab significantly improved DFS (HR 0.48; 95% CI 0.39–0.59; P < 0.001). In addition, a significant benefit in terms of OS was observed (HR 0.67; 95% CI 0.48–0.93; P = 0.015). Updated results after a median follow-up period of 3.9 years were recently published. Here, a statistically significant reduction in DFS event rate in favour of the trastuzumab arm (P < 0.001) was observed. Furthermore, a 39% reduction in the risk of death was reported (P < 0.001), despite a considerable percentage of patients in the control groups crossing over to trastuzumab.

Another important aspect of NCCTG trial N9831 is the three-arm design. As outlined, a third arm with HERA-style sequential administration of chemotherapy and trastuzumab was included. The comparison of concomitant and sequential administration was eagerly awaited. Indeed, a strong trend towards better outcome was observed with the concomitant regimen. Absolute benefit in terms of DFS was 4.4% at 5 years’ follow-up (P = 0.019), although this did not cross the boundary for statistical significance (preset at 0.00116).

**HERA**

The largest of the adjuvant trastuzumab trials, HERA (Herceptin Adjuvant), was a prospective, randomized phase III trial including 5102 international non-US patients with Her2-positive node-positive or node-negative breast cancer. In contrast to the USA, in the early 2000s most other regions had no clearly defined adjuvant standard chemotherapy regimen. Therefore, a more pragmatic approach was chosen in HERA: a minimum of four cycles of adjuvant/neoadjuvant chemotherapy with or without radiotherapy was required; patients were then randomized to one of three treatment arms: control, trastuzumab for 12 months or trastuzumab for 24 months. It is also noteworthy that just over half of women had lymph node-positive disease; data on the efficacy of trastuzumab in node-negative patients therefore derive largely from the HERA study. At a median follow-up of 1 year, a significant reduction in recurrence-free survival was observed (HR 0.54; 95% CI 0.43–0.67; P < 0.0001). At 2 years’ follow-up, a significant reduction in the risk of death was also identified (HR 0.66; 95% CI 0.47–0.91; P = 0.0115). Importantly, a large percentage of patients crossed over to trastuzumab treatment from the control arm when the results become available. Thus, at 4 years’ follow-up, no significant difference in the risk of death was observed (HR 0.85; 95% CI 0.70–1.04; P = 0.11). In 885 patients (52%) who crossed over, treatment started after a median delay of 22 months after randomization. In that population, the crossover cohort experienced fewer DFS events than patients who remained in the observation group (HR 0.68;
95% CI 0.51–0.90; \( P = 0.0077 \), again emphasizing the efficacy of trastuzumab.\(^{106}\)

In the light of the N9831 results, the question remains whether a sequential design reduces the benefit of adjuvant trastuzumab. Furthermore, patients were randomized upon completion of conventional chemotherapy; this might select a more favourable patient population owing to the exclusion of patients with very early relapses and therefore overestimate the beneficial role of trastuzumab.

Results from the 2-year adjuvant trastuzumab arm are currently eagerly awaited.

**BCIRG 006**

Breast Cancer International Research Group (BCIRG) trial 006 is a randomized, three-arm, open-label study conducted at centres in the USA, Europe, South Africa, Asia and Venezuela.\(^{109}\) Two trastuzumab arms were compared with a control arm of AC \( \times 4 \) followed by docetaxel \( \times 4 \). The first trastuzumab arm used the same chemotherapy backbone; trastuzumab was initiated concurrently with docetaxel and given for a total duration of 52 weeks. The second trastuzumab arm used an anthracycline-free chemotherapy regimen of carboplatin–docetaxel plus trastuzumab upfront (TCH). A total of 3222 patients were accrued; 922 had node-negative tumours.

The results of BCIRG 006 were recently published. At a median follow-up of 65 months, DFS was 75% and OS 87% in the AC–docetaxel standard arm. The addition of trastuzumab to AC–docetaxel significantly decreased the risk of breast cancer recurrence (DFS 84%; HR 0.64; \( P < 0.001 \)) or death (OS 92%; HR 0.63; \( P < 0.001 \)) compared with AC–docetaxel. The results were similar in the TCH group (DFS 81%; HR 0.75; \( P = 0.04 \); OS 91%; HR 0.75; \( P = 0.04 \)). No significant difference was found between the two trastuzumab-containing regimens; in this context, however, it is important to note that the study was not powered to compare the two trastuzumab arms.

A significantly higher rate of cardiac dysfunction (seven patients) and acute secondary leukaemia (one patient) was observed in the anthracycline-containing arms. Thus, TCH appears to be a relatively well tolerated alternative to conventional anthracycline-containing regimen especially in patients presenting with cardiac risk factors.

**FinHER**

The design of this Finnish trial was radically different from that of the other adjuvant studies. Three cycles of docetaxel followed by FEC \( \times 3 \) was compared with 9 weeks of vinorelbine weekly, again followed by FEC \( \times 3 \). In Her2-positive patients, a second randomization to weekly trastuzumab (given concomitantly with docetaxel or vinorelbine) or control was performed. A total of 1010 node-positive or high-risk node-negative breast cancers were included; 232 were Her2 positive. Thus, FinHER is the smallest of the adjuvant trastuzumab studies; furthermore, the total duration of trastuzumab treatment was only 9 weeks compared with 52 weeks in the other studies. Despite this, a significant reduction in recurrence-free survival events was observed in the trastuzumab group (HR 0.42; 95% CI 0.21–0.83; \( P = 0.01 \)).\(^{110} \) In the overall population, adjuvant docetaxel was significantly more active than vinorelbine.

FinHER was the first study to ask whether short-course trastuzumab may also offer meaningful activity. Although the relative risk reduction in terms of DFS (HR 0.42) resembles data from other adjuvant studies, a direct randomized comparison of short-course and standard duration trastuzumab treatment is needed. Indeed, two such trials are currently on-going: SOLD (Synergism or Long Duration; NCT00593697) and PHARE (Protocol of Herceptin Adjuvant with Reduced Exposure; NCT00381901).

**PACS 04**

The French PACS 04 trial was the last of the large adjuvant trastuzumab trials to report results. Importantly, this was the first and only trial not to find a benefit in the trastuzumab cohort. A population of 3010 women with node-positive breast cancer was randomly assigned to six cycles of epirubicin plus docetaxel (both given at 75 mg/m\(^2\)) or six cycles of FEC (epirubicin dosed at 100 mg/m\(^2\)). Her2-positive patients were further randomized to 1 year of adjuvant trastuzumab or control. Thus, like the HERA trial, patients started on trastuzumab after the completion of conventional adjuvant chemotherapy.

At a median follow-up of 4 years, no additional benefit was observed in the trastuzumab arm (HR for relapse with trastuzumab 0.86; 95% CI 0.61–1.22; \( P = 0.41 \)).\(^{111} \)
With a total of 528 Her2-positive patients included, the study may have been underpowered to detect a subtle benefit in the trastuzumab group; the sequential design might also have contributed to the failure to detect any trastuzumab benefit. Indeed, there was one major difference between PACS 04 and HERA: randomization in PACS 04 was performed immediately the Her2 status became available after surgery, whereas, in HERA, patients were randomized after chemotherapy. As outlined, this might have selected a more favourable patient population. In the light of those results, concomitant administration of chemotherapy and trastuzumab may be generally preferable.

Summary of adjuvant trastuzumab trials

With the notable exception of PACS 04, the adjuvant trastuzumab trials offer compelling evidence that trastuzumab has clinically meaningful activity as adjuvant treatment of early breast cancer.

However, questions concerning the optimal time point of trastuzumab initiation, the role of anthracycline-free regimens and the optimum treatment duration remain unanswered for now. Limited data are also available concerning the role of trastuzumab in small Her2-positive tumours (pT1a, pT1b), as only a very small number of such patients were included in the adjuvant trials. In a combined retrospective analysis including 965 patients with small tumours, 10% presented with Her2-positive disease. These patients had a significantly higher rate of recurrences (HR 5.09; 95% CI 2.56–10.14; \( P < 0.0001 \)) and distant recurrences (HR 7.81; 95% CI 3.17–19.22; \( P < 0.0001 \)). Currently, in pT1b Her2-positive patients, adjuvant chemoimmunotherapy with trastuzumab is recommended.

Adjuvant trastuzumab: cardiac toxicity

Cardiac toxicity is usually the main safety issue with trastuzumab. This problem was first observed with the combination of doxorubicin and trastuzumab, and incidence in the adjuvant trials was much lower. Only 5% of all patients are expected to develop some form of cardiac dysfunction, and approximately 1% may develop symptomatic congestive heart failure; furthermore, cardiac dysfunction seems to be reversible in most cases. However, patients at increased risk for congestive heart failure (the elderly and those with hypertension, diabetes, coronary heart disease or valvular dysfunction) should be monitored closely.

The rate of cardiac toxicity was lower in HERA than in the North American trials. There are a number of possible reasons for this observation. First, the sequential design applied in HERA may have stretched the time interval between anthracyclines and trastuzumab administration; furthermore, the number of patients receiving anthracyclines as adjuvant treatment was lower and the eligibility threshold of left ventricular ejection fraction was more stringent (\( \geq 55\% \) compared with \( \geq 50\% \)). Thus, a sequential approach or the TCH regimen used in BCIRG006 appears preferable to AC/docetaxel as chemotherapy backbone in patients with known cardiac risk factors.

Conclusion

Recent developments have improved survival of patients with early-stage breast cancer. In particular, targeting Her2 with trastuzumab has dramatically improved the prognosis of patients with Her2-positive disease. Thus, trastuzumab today plays an important role in the adjuvant as well as neoadjuvant setting.

In endocrine-responsive disease, AIs have been shown to yield better outcome than tamoxifen. In triple-negative disease, however, only limited improvement has been achieved and conventional chemotherapy remains the backbone of treatment.

Conflicts of interest


<table>
<thead>
<tr>
<th>Generic name</th>
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<th>Manufacturer</th>
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<tbody>
<tr>
<td>Bevacizumab</td>
<td>Avastin</td>
<td>Hoffmann La-Roche, Basle, Switzerland</td>
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<td>Capecitabine</td>
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<tr>
<td>Zoledronic acid</td>
<td>Zometa</td>
<td>Novartis, Basle, Switzerland</td>
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