Adjuvant treatment of early breast cancer

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Introduction

The 2005 St. Gallen consensus guidelines represent a major shift from adjuvant treatment decision making based primarily on "risk of relapse" towards treatment decision-making based primarily on endocrine responsiveness.

For tumours exhibiting a molecular profile that leaves little doubt about response to hormonal manipulation, the selection of the endocrine treatment offering the best benefit versus risk ratio for the individual woman is the priority. The addition of a few chemotherapy (CT) cycles prior to the start of adjuvant endocrine therapy will be considered in patients at high risk of relapse (such as those with $\geqslant$4 positive nodes).

For tumours exhibiting molecular features that leave uncertainty about responsiveness to endocrine therapy, more weight will be given to the role of sequential chemo-endocrine treatment and of the selection of endocrine agents that may have a greater chance of activity when these molecular features are present.

Finally, it is for non-endocrine responsive tumours that extreme care will need to be taken in selecting the adjuvant CT regimen, since it will represent the only "weapon" against potential micrometastases. These tumours are likely to be the ones that benefit most from the introduction of non cross resistant cytotoxic agents in the treatment scheme, as well as from fine tuning of cytotoxic dose and schedule.

In order to make these delicate treatment decisions in the optimal way, oncologists need to have broad knowledge of the benefits and risks associated with adjuvant treatment modalities.

This article attempts to provide this knowledge in a concise way.

Tailoring adjuvant therapies: a high priority in 2005

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, updated with 15 years of follow up of all randomised trials in this setting, reinforces the evidence of efficacy of adjuvant systemic therapies in reducing disease recurrence and mortality in early breast cancer (EBC) [1]. These data provide average estimations of relative and absolute treatment benefits in the global population studied and are suboptimal for the appraisal of the complex heterogeneity of breast cancer (BC) [2].

Tailoring of adjuvant endocrine therapy (tamoxifen, ovarian ablation) has been based on the hormone receptor status of tumours: additional molecular markers or molecular ' signatures' are urgently needed now that aromatase inhibitors (AI) are entering the adjuvant scene, in order to identify subgroups that derive particular benefit from these more expensive agents.

Tailoring of adjuvant CT has been lacking so far: patients at higher risk of relapse (typically those with node positive disease) have been offered the more aggressive regimens in view of the incremental average gain in efficacy provided by these regimens in randomised trials. Retrospective, but now overwhelming, evidence indicates a much greater magnitude of CT benefit in estrogen receptor (ER) negative disease as compared to ER positive disease [3]. The next generation of prospective trials should ideally be run separately in hormone receptor positive and negative BC, allowing sufficient power for the identification of optimal systemic treatments for these two different diseases.

The use of microarray technology as a tool to dissect the molecular heterogeneity of BC and to improve treatment tailoring is increasing exponentially, with no routine clinical application thus far. Perou et al. [4] first described differences in gene expression profiles between clinically ER positive and ER negative BC tumours. Sorlie et al. [5] later refined the ER positive and negative tumour classification with the identification of different subgroups with distinct molecular signatures, each associated with distinct clinical outcomes.

Van de Vijver et al. [6] discovered a 70-gene prognostic signature in node negative BC patients without prior exposure to systemic therapy: the expression profile outperformed traditional clinical and pathological criteria in identifying patients with or without distant metastases. They claimed that the use of this signature would reduce the fraction of

women receiving adjuvant CT by about 30%. These challenging hypotheses need to be validated before such a prognostic molecular signature is implemented in clinical practice. For this reason, prior to the launch of a large prospective randomised trial (MINDACT), an external, independent validation of the 70-gene Amsterdam signature [6] based on 301 patients followed for a median of 10 years was conducted [7]. The 70-gene prognostic signature outperformed the Nottingham Prognostic Index, the St. Gallen 2003 criteria, and ' Adjuvant! On Line' in predicting time to distant metastases and overall survival. The women classified as low risk by the gene signature had a projected 5-year distant metastases free survival of 95% and a projected 10-year survival of 88%.

The European Organisation for the Research and Treatment of Cancer (EORTC) TRANSBIG multinational project MINDACT is the first large prospective trial that will investigate the role of the gene expression signature identified by Dutch researchers [6] as a tool to improve CT decision making for node negative EBC. This very ambitious trial could upgrade the gene signature level of evidence from a score of 3 to a score of 1, and lead to a major change in BC clinical practice.

This ' bench to bed-side' research process is critical if one wants to avoid both over-treatment, with its potential for severe complications, and under-treatment with deleterious consequences for patient survival.

Cytotoxics brought onto the adjuvant scene in the last decade

The role of new cytotoxics such as taxanes, capecitabine, gemcitabine, and platinum compounds in the adjuvant setting is reviewed in this section.

Taxanes

The role of taxanes in the adjuvant setting is still under evaluation, despite promising preliminary results. In the literature, 19 trials evaluated the role of taxanes in this setting, with an expected accrual of 35,500 patients. So far, 8 trials have generated mature results, which are summarized in Table 1. The latest St. Gallen Consensus expert panel [16] has confirmed that there is still no level-1 evidence for the use of taxanes in the adjuvant setting for node negative BC. Regarding node positive BC patients, the expert panel remains divided in view of the suboptimal design of these trials, which mix hormone responsive and non-responsive populations and lack proper control of other variables, such as treatment duration.

The Cancer and Leukemia Group B (CALGB) 9344 study [8], in which 3,121 node positive BC patients were included, evaluated whether increasing the dose of doxorubicin or adding of paclitaxel to a standard adjuvant CT regimen would improve disease free (DFS) and overall survival (OS). At 69 months median follow up, there was a statistically significant reduction in the risk of recurrence (17%) and death (18%) in the paclitaxel-containing arm. An unplanned subset analysis demonstrated a significant improvement in recurrence free survival (RFS) only for patients with ER negative tumours.

In the National Surgical Adjuvant Breast Project (NSABP) B-28 trial [9], 3,060 node positive BC patients were randomly treated either with the combination of cyclophosphamide and doxorubicin or the same regimen followed by paclitaxel. After a median follow up of 64 months, there was a statistically significant reduction in the risk of relapse, but no statistically significant reduction in the risk of death in the paclitaxel arm. The subset analysis according to HR and lymph node status did not demonstrate a significant difference regarding DFS, RFS and OS between the two arms. Of note, concomitant CT and tamoxifen administration in this trial is a potential confounding factor.

In the Breast Cancer International Research Group (BCIRG) 001 trial [11], 1,491 node positive BC patients were randomised to receive either $FA_{50}C$ (fluorouracil, doxorubicin 50 mg/m^2, and cyclophosphamide) or TAC (docetaxel, doxorubicin 50 mg/m^2, and cyclophosphamide). At a median follow up of 55 months, there was a statistically significant reduction in the risk of relapse (28%) and death (30%) in the docetaxel-containing arm. The improved DFS was independent of both HR and HER2 status. The magnitude of taxane-associated benefit appeared to be larger in the subset of 1–3 positive nodes as compared to the subset with more extensive nodal involvement.

The PACS 01 trial [13] compared 6 cycles of $FE_{100}C$ (fluorouracil, epirubicin 100 mg/m^2, cyclophosphamide) to 3 cycles of $FE_{100}C$ followed by 3 cycles of docetaxel (100 mg/m^2) in 1,999 women with node positive BC. At 60 months of follow up, there was a statistically significant reduction in the risk of recurrence and death for the sequential docetaxel arm (17% and 23%, respectively). A preplanned subset analysis suggests that the benefit is confined to patients with 1–3 positive nodes and to patients older than 50 years.

In a small M.D. Anderson trial [10], 524 patients were randomised to receive either 4 cycles of paclitaxel followed by 4 cycles of fluorouracil,

Table 1
Taxanes in the adjuvant setting[a]

Study	Eligibility	Patients (n)	Regimens	Follow-up (mo)	Outcome	Comments
Paclitaxel monotherapy						
CALGB9344 (Henderson et al 2003 [8])	Node positive	3121	AC × 4 AC × 4 → P × 4 (A = 60, 75 or 90)	69	Increased DFS (HR 0.83; CI 0.73–0.94) and increased OS (HR 0.82; CI 0.71–0.95)	Subset analysis showed paclitaxel more beneficial in ER negative/unknown
NSABP B28 (Mamounas et al 2005 [9]	Node positive	3060	AC × 4 AC × 4 → P × 4	64	Increased RFS (HR 0.83; CI 0.73–0.95) No difference in OS	paclitaxel equally effective in ER positive and ER negative
MDACC (Buzdar et al 2002 [10])	N0 or node positive	524[b]	FAC × 4 P × 4 → FAC × 4	60	No significant difference in RFS	Non-significant trend suggesting paclitaxel beneficial in ER negative patients
Docetaxel monotherapy/combination						
BCIRG 001 (Martin et al 2003 [11])	Node positive	1491	FAC × 6 DAC × 6	55	DFS: absolute benefit of 7% at 5 years (HR 0.72); also Increased OS (HR 0.70)	Subgroup with 1–3 positive nodes seems to benefit the most
NSABP B-27 (Bear et al 2004 [12])	Neoadjuvant	2411	AC × 4 AC × 4 → D × 4		No significant difference in DFS and OS	
PACS 01 (Fumoleau et al 2004 [13])	Node positive	1999	FEC (100) × 6 FEC(100) × 3 → D×3	60	DFS improved with docetaxel (HR 0.83; CI 0.69–0.99); OS also improved (HR 0.77)	More pts in the FEC100 group with receptor negative tumor (22% vs 19%); women older than 50 years and those with 1–3 positive nodes benefit the most
US Oncology 9735 (Jones et al 2001 [14])	Stage I–III Node positive and negative	1015	AC × 4 DC × 4	43	Not reported	Long-term follow up needed
E 2197 (Goldstein et al 2005 [15])	Node negative (T > 1 cm) or Node positive	2952	AC × 4 AD × 4	59	No difference in DFS or OS	Better than expected outcome for both regimens

[a] D: docetaxel; F: 5-fluorouracil, A: doxorubicin, C: cyclophosphamide; E: epirubicin; P: paclitaxel; RFS: relapse-free survival; DFS: disease-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval

[b] 174 neoadjuvant; 350 adjuvant.

doxorubicin, and cyclophosphamide (FAC) or 8 cycles of FAC alone. At 60 months follow up, there was no statistically significant difference in RFS and OS between the two arms, although a trend favoured the taxane regimen.

In the neoadjuvant setting, the NSABP B-27 trial [12], conducted in 2,411 patients with operable BC, was designed to determine the effect of adding docetaxel after 4 cycles of preoperative doxorubicin and cyclophosphamide (AC). Despite a doubling in pathologic complete response rate, there was no statistically significant difference in terms of DFS and OS favouring the taxane arm. Like in NSABP-B28, tamoxifen was given concurrently with CT.

One relatively small but interesting trial, US Oncology 9735 [14], suggests that a non anthracycline, taxane-based regimen (docetaxel + cyclophosphamide) might be as good as 4 cycles of AC (doxorubicin-cyclophosphamide), while the larger Intergroup/E2197 trial found no advantage of AT $\times$ 4 (doxorubicin-docetaxel) over AC $\times$ 4 [15].

Up to now, adequately dosed anthracycline regimens remain an acceptable standard of adjuvant CT. The EBCTCG meta-analysis [1] with 15 years follow up, demonstrates that on average these regimens continue to be significantly more effective than CMF regimens in reducing disease recurrence and mortality from BC. There was no significant excess of secondary leukaemia and cardiac deaths, but long-term cardiac sequelae may occur and are not detected by overviews.

Unfortunately the place of taxanes in the adjuvant setting has not yet been validated with a level-1 evidence, due to trial design limitations. However, the threshold for prescribing anthracyclines followed by taxanes has been lowered for tumours devoid of HR, those showing a worrisome genetic make-up or when there is a fear of anthracycline-induced cardiotoxicity (HER2 overexpressing tumours fulfil the last two criteria).

Another important aspect to be considered is the high cost of treatment due to the increased use of epirubicin and taxanes in CT regimens [17]. Our public health systems are in jeopardy and this aspect should motivate an accelerated transition from empirical oncology (' one shoe fits all') to molecular oncology which will depend on high quality translational research linked to the clinical trials [18].

Capecitabine

Capecitabine with its oral bioavailability and favourable side-effect profile is a very attractive drug for the adjuvant setting. Capecitabine has demonstrated to be active in the metastatic setting, both as a single agent [19] and in combination with other agents such as docetaxel, paclitaxel, vinorelbine and anthracyclines [20]. Moreover, capecitabine combined with docetaxel has shown an improved OS when compared to docetaxel alone in metastatic BC [21].

Recently, the interim analysis of a randomised phase II trial in the neoadjuvant setting has shown that docetaxel/capecitabine provided higher clinical and pathological response rates compared to doxorubicin/cyclophosphamide (AC) in 121 eligible patients with stage II/III BC [22].

Capecitabine as a single agent is currently being evaluated in a phase III trial comparing capecitabine with CMF or AC regimens in elderly patients with early BC (NO17629). Capecitabine-based combinations, with paclitaxel and docetaxel, are also being evaluated in phase III trials as treatment for EBC (IDO1-580) (*www.clinicaltrials.gov*). A large registration study, conducted by US Oncology, compares postoperative treatment with four cycles of AC followed by four cycles of either docetaxel monotherapy or capecitabine/docetaxel. Capecitabine/docetaxel will be compared to anthracycline-based regimens in the large MINDACT trial, with particular attention paid to long-term sequelae, which are hoped to be reduced in the non anthracycline-based arm.

Gemcitabine

This pyrimidine nucleoside antimetabolite has shown activity in a variety of solid tumours, with a favourable toxicity profile. As a single agent, gemcitabine yields response rates ranging from 14% to 37% as first-line treatment for advanced BC, and 12% to 30% as salvage therapy for patients previously treated with anthracyclines and/or taxanes. Phase II studies reported high response rates in combination with vinorelbine, platinum, and taxanes [23].

Five hundred and twenty-nine metastatic breast cancer (MBC) patients were randomly assigned to receive either paclitaxel (every 3 weeks) and gemcitabine, or paclitaxel alone. The combination arm reported higher response rates, longer time to progression, and longer survival [24].

Many randomised phase III trials are ongoing to identify the place of gemcitabine in the adjuvant setting: the Cancer Research Campaign Clinical Trials is comparing the effectiveness of adjuvant paclitaxel, epirubicin, and cyclophosphamide with or without gemcitabine in 3,000 patients (*www.clinicaltrials.gov*). The tAnGo trial [25] will examine the sequence

of epirubicin and cyclophosphamide (EC) followed by paclitaxel alone or combined with gemcitabine in 3,000 EBC patients. Finally, a phase III trial conducted by the NSABP is comparing the DFS of three treatment arms in 4,800 node positive EBC patients: a dose dense (every 2 weeks) regimen of doxorubicin, cyclophosphamide, paclitaxel with or without gemcitabine and docetaxel, doxorubicin and cyclophosphamide.

Platinum compounds

Platinum compounds, which are widely used in oncology, are also active in metastatic BC, especially in first-line treatment [26], but the availability of less toxic drugs with more convenient ways of administration has limited their use in this setting. Preclinical studies have indicated that there is a synergy between platinum salts and the monoclonal antibody trastuzumab in human BC cell lines that overexpress HER2/neu [27].

These findings have led to two open-label phase II trials conducted by the Breast Cancer International Research Group (BCIRG) in HER2 overexpressing metastatic BC patients [28]. BCIRG 101 and UCLA-ORN have evaluated 2 platinum compounds, cisplatin and carboplatin, respectively, in combination with docetaxel and trastuzumab, in 124 patients. Overall response rates were 79% and 58%, respectively.

Both overall response (52% versus 32%; $p=0.04$) and time to progression (11.2 months versus 6.9 months; $p=0.007$) were significantly improved by the addition of platinum salts in a randomised phase III study in 188 HER2 overexpressing MBC patients treated with trastuzumab and paclitaxel, with or without carboplatin [29]. The ongoing BCIRG 007, which plans to enrol 466 patients with stage IIIb/IV BC that overexpress HER2, compares docetaxel and trastuzumab with or without carboplatin.

In the adjuvant setting, BCIRG is also running a large randomised study of 3,150 patients (BCIRG 006) comparing docetaxel, trastuzumab and carboplatin to doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab.

New uses of older cytotoxic drugs

The development of new drugs is not the only way to improve the survival impact of adjuvant CT. The manipulation of ' old' drugs with new doses and schedules, such as with the dose dense and metronomic approaches, could further improve the efficacy of adjuvant CT for EBC patients, particularly for those with HR negative tumours.

Dose dense chemotherapy

Historically, the interval between CT cycles has been dictated by neutrophil recovery kinetics. With most myelosupressive agents used alone or in combination, peripheral granulocyte nadirs are reached around days 10–15 following CT administration and recovery is achieved around day 21. Norton and Simon [30] developed a mathematical kinetic model in order to determine the most effective way of administering non cross resistant cytotoxic drugs in an attempt to eradicate the cancer cell population. As a result of this work, they recommended sequential administration of these agents given in a dose-dense fashion.

A large phase III adjuvant trial was designed to validate this concept: the Intergroup Trial 9741, coordinated by the Cancer and Leukaemia Group B (CALGB) [31]. The study included 2,005 node positive BC patients in a two by two factorial design to test the two hypotheses that dose dense (every two weeks) and sequential (instead of concurrent) administration of CT regimens incorporating doxorubicin, cyclophosphamide and paclitaxel would improve DFS and OS. At a median follow up of 36 months, the sequential dose dense regimen demonstrated a statistically significant improvement in terms of DFS (85% versus 81%) and OS (92% versus 90%). The estimated 4-year DFS was 82% versus 75%.

Venturini et al. [32] used accelerated FEC (every 2 weeks) versus standard FEC in 1,214 node negative high risk, and node positive BC patients. This smaller study showed only a trend of improved OS in the dose dense arm.

The toxicity data in these two trials did not show statistically significant differences between the conventional and dose dense arms, at least in terms of short-term risks.

The majority of the other dose dense trials published have had negative results, probably explained by several trial design limitations. These include insufficient power, asymmetric arms with respect to drug administered, and/or use of sub-optimal doses [33].

Metronomic chemotherapy

Preclinical models elegantly show that the frequent administration of chemotherapeutic agents at lower doses (the so called ' metronomic' schedule) may optimize their anti-angiogenic properties [34]. Metronomic CT may be able to circumvent drug resistance by targeting normal tumour endothelial cells rather than genetically unstable tumour cells [35].

The IBCSG–22-00 trial is an ongoing randomised, open-label, multicenter study exploring the role of

metronomic CT (oral cyclophosphamide and methotrexate for 1 year) as consolidation therapy after completion of anthracycline or CMF-based adjuvant CT in approximately 1,330 EBC patients with HR negative BC (*www.clinicaltrials.gov*).

Weekly paclitaxel has been successfully used in the treatment of advanced BC. The CALGB 9840 trial [36] conducted in 577 patients showed superiority of the weekly schedule over the 3-weekly schedule in terms of time to disease progression. Regarding toxicity, there was slightly less myelosuppression but more neurotoxicity with the weekly schedule when compared to the 3-weekly schedule of paclitaxel.

The ECOG1199/Intergroup trial should provide important information related to the relative merits of conventionally timed (3-weekly) versus metronomic CT. Around 5,000 patients have been randomised in one of four arms, containing standard AC followed by either docetaxel or paclitaxel given according to a weekly or 3-weekly schedule (*www.clinicaltrials.gov*).

Optimal adjuvant endocrine therapy

Endocrine therapy is a key player in the adjuvant treatment of early BC, as evidenced by the demonstration that tamoxifen and, more recently, the AI, have had a profound impact on the course of early endocrine-responsive BC.

Postmenopausal EBC patients (Table 2)

The results of the 2005 EBCTCG meta-analysis [1] confirm that adjuvant hormone therapy for ER positive EBC in postmenopausal patients has a major long-term impact on DFS and BC mortality. Until recently, tamoxifen has been considered the gold standard treatment for all HR positive patients. However, several large trials using AI are now challenging this privileged position. AI have so far been explored (a) as replacement for or in combination with tamoxifen (ATAC and BIG 1-98 trials), (b) sequentially after 2–3 years of tamoxifen (ITA, IES, ARNO 95 and ABCSG 8 trials), and (c) sequentially after 5 years of tamoxifen (MA.17 trial).

Benefits associated with the introduction of AI in the adjuvant setting

(a) AI upfront. In the ATAC (Arimidex and Tamoxifen Alone or in Combination) trial [37], a randomised double-blind placebo controlled study, 9,366 postmenopausal patients with operable BC were randomised to receive anastrozole (1 mg daily), tamoxifen (20 mg daily), or the combination for 5 years. In this very large trial, 84% of patients had ER positive and/or PgR positive tumours. The combination arm was discontinued, as this arm showed no benefit over tamoxifen alone on the second analysis. The last update of results at a median follow-up of 68 months [38] favours anastrozole in patients with ER positive disease, with statistically significant hazard ratios (HR) for DFS (primary endpoint of the study), time to recurrence, contralateral BC, and time to distant recurrence. However, there is as yet, no statistically significant difference between the anastrozole and tamoxifen arms in terms of OS. A retrospective subgroup analysis shows a 57% reduction in the HR for recurrence with anastrozole compared to tamoxifen in women with ER positive and PgR negative tumours [44].

The IBCSG 18-98 / BIG 1-98 trial compared (A) tamoxifen (5 years) to (B) letrozole (5 years), to (C) tamoxifen (2 years) followed by letrozole (3 years), to (D) letrozole (2 years) followed by tamoxifen (3 years). Accrual was completed in May 2003 with the inclusion of 8,028 patients. First results based on the comparison of initial treatment assignment to letrozole in arms B and D versus initial assignment to tamoxifen in arms A and C were presented after a median follow-up of 25.8 months [41]. A statistically significant difference in DFS, time to recurrence, and time to distant metastases favours the use of letrozole.

b) Sequence of tamoxifen followed by AI. In the small Italian Tamoxifen Arimidex (ITA) randomised trial, 426 postmenopausal patients treated with adjuvant tamoxifen for around 2 years continued treatment either with tamoxifen or anastrozole for a total of 5 years of endocrine therapy. Updated analysis at a median follow-up of 52 months confirms that the risk of relapse was statistically significantly lower in the sequential arm [40].

The Intergroup Exemestane Study (IES)/BIG 2-97 was a large double-blind, randomised trial that enrolled 4,742 postmenopausal women with ER positive or unknown primary BC who were disease-free after completion of 2–3 years of tamoxifen adjuvant therapy. Patients were randomised to receive exemestane or to continue tamoxifen in order to complete a total of 5 years of adjuvant endocrine therapy. At the time of a third planned interim analysis with a median follow-up of 37.4 months [39], the HR for DFS, the primary study endpoint, and for contralateral BC showed a statistically significant reduction in the exemestane group compared to the tamoxifen group. So far, only a trend for improved in OS is seen in favour of the sequential arm.

Table 2
Adjuvant phase III trials incorporating aromatase inhibitors in postmenopausal patients[a]

Trial	Patient characteristics	Treatment arms	FU (mo)	Results (Hazard Ratio)					Comments
				DFS	OS	TTR	CLBC	TTDR	
ATAC Trialists group [37,38]	9366 pts 84% HR+ 61% N neg 64% tu $\leqslant$ 2 cm 20% CT	Tamoxifen $\times$ 5 years Anastrozole $\times$ 5 years Tamoxifen + Anastrozole (discontinued)	68	0.87 (0.78–0.97) p = 0.01	0.97 (0.85–1.12) p = 0.7	0.79 (0.70–0.90) p = 0.0005	0.58 (0.38–0.88) p = 0.01	0.86 (0.74–0.99) p = 0.04	Subgroup analysis for DFS: HR+: 0.79 ER+PgR+: 0.84 ER+PgR–: 0.43
IES trial BIG 2-97 [39]	4742 pts 81% HR+ 51% N neg 37% CT	Tamoxifen 5 years Tamoxifen 2–3 years $\rightarrow$ Exemestane 2–3 years	37.4	0.73 (0.62–0.85) p = 0.0001	0.83 (0.67–1.02) p = 0.08	Not reported	0.50 (0.26–0.97) P = 0.04	Not reported	No significant detrimental impact on QoL (FACT-ES) (Fallowfield LJ et al, Breast Cancer Res Treat 2004)
ITA trial [40]	426 pts All ER+ N+	Tamoxifen 5 years Tamoxifen 2–3 years $\rightarrow$ Anastrozole 2–3 years	52	0.42 (0.26–0.66) p = 0.0001 (EFS)	Not reported	Not reported	Not reported	Not reported	HR of PFS 0.43 (0.25–0.73) p = 0.001
BIG 1-98 [41]	8028 pts All HR+ 52% N– 37% tu > 2cm 25% CT	A. Tamoxifen 5 years B. Letrozole 5 years C. Tamoxifen 2 years $\rightarrow$ Letrozole 3 years D. Letrozole 2 years $\rightarrow$ Tamoxifen 3 years	25.8	0.81 (0.70–0.93) p = 0.003 5-year	0.86 (p = 0.16)	0.72 (p = 0.0002)	0.4% vs 0.7% (p = 0.125)	0.73 (p = 0.0012)	Subgroup analysis: N+ HR 0.71 Previous CT HR 0.70
MA.17 BIG 1-97 [42]	5187 pts 98% HR+ 50% N– 46% CT	Tamoxifen 4.5–6.0 years $\rightarrow$ Placebo Tamoxifen 4.5–6.0 years $\rightarrow$ Letrozole 5 years	2.4 yr	0.57 (p = 0.00008) 4-year	No difference	Local, metastatic recurrence, or contralateral BC 0.57 (0.43–0.75) p = 0.00008			Subgroup analysis: N+ (40% reduction risk) and N– (53% reduction risk) for 3-year DFS in letrozole arm Survival benefit in N+ No detrimental impact on QoL (SF-36 and MENQOL)
ABCSG 8/ ARNO 95 [43]	3123 pts All HR+ 74% N– 70% T1	Tamoxifen 5 years Tamoxifen 2 years $\rightarrow$ Anastrozole 3 years	26	0.60 (0.44–0.81) p < 0.0009 (EFS)	0.76 (0.52–1.12) p = 0.16	Not reported	0.61 (0.42–0.87) p = 0.0067 $\downarrow$ DRFS		

[a] DFS: disease-free survival; OS= overall survival; TTR: time to recurrence; CLCB: contralateral breast cancer; TTDR: time to distant recurrence; HR: hormone receptor; ER: estrogen receptor; PgR: progesterone receptor; EFS: event-free survival; DRFS: distant recurrence free survival; CT: chemotherapy; tu: tumour size.

Table 3
Risk associated with adjuvant AI (AI versus tamoxifen in all trials except MA 17: AI versus placebo)

Bone	Vascular	Other
Anastrozole (ATAC [37,38,45] and ABCSG 8/ARNO 95 [43] trials)		
Arthralgias: 35.6% vs 29.4% ($p < 0.0001$) OR 1.32 (1.19–1.47) (ATAC)	Cardiovascular: 4.1% vs 3.4% ($p = 0.1$) OR 1.23 (ATAC) 0.37% vs 0.19% ($p = 0.51$) OR 2.0 (ABCSG8/ARNO)	Endometrial invasive cancer (ATAC): 0.2% vs 0.8% ($p = 0.02$) OR 0.29
Fractures: 11% vs 7.7% ($p < 0.0001$) OR 1.49 (1.25–1.77) (ATAC) 1.0% vs 2.1% ($p = 0.01$, NS) OR 2.14 (ABCSG 8/ARNO 95)	Cerebrovascular: 2.0% vs 2.8% ($p = 0.03$) OR 0.70	Hot flushes (ATAC): 35.7% vs 40.9% ($p < 0.0001$) OR 0.80
	Venous thromboembolic: 2.8% vs 4.5% ($p = 0.0004$) OR 0.61 (ATAC) 0.4% vs 0.1% ($p = 0.17$) OR 0.28 (ABCSG8/ARNO)	Vaginal bleeding (ATAC): 5.4% vs 10.2% ($p < 0.001$) OR 0.50 Vaginal discharge (ATAC): 3.5% vs 13.2% ($p < 0.0001$) OR 0.24
Letrozole (MA.17 [42] and BIG 1-98 [41] trials)		
Arthralgias: 21.3% vs 16.6% ($p < 0.001$) (MA.17)	Cardiovascular: 4.1% vs 3.6% ($p = 0.40$) (MA.17) 3.6% vs 2.5% (p-value not reported) (BIG 1-98)	Endometrial cancer: OR 0.40 ($p = 0.078$) (BIG 1-98)
Fractures: 5.8% vs 4.1% ($p = 0.0006$) OR 1.44 (BIG 1-98) 3.6% vs 2.9% ($p = 0.24$) (MA.17)		Hot flushes: 47.2% vs 40.5% ($p < 0.001$) (MA.17)
Exemestane (IES trial [39])		
Arthralgias: 19.8% vs 13.1% ($p < 0.001$)	Cardiovascular: 0.9% vs 0.4% ($p = 0.02$, NS)	Gynaecological symptoms: 5.8% vs 9% ($p < 0.001$)
Fractures: 3.1% vs 2.3% ($p = 0.08$)	Venous thromboembolic: 1.9% vs 3.3% ($p < 0.001$)	Hot flushes: 42% vs 40% ($p = 0.28$)

The results from ABCSG 8 (2,262 postmenopausal patients with endocrine sensitive BC) and ARNO 95 (962 postmenopausal patients with endocrine sensitive BC) were combined for the efficacy analysis of switching from adjuvant tamoxifen to anastrozole after two years of tamoxifen [43]. At a median follow-up of 28 months, there was a statistically significant 40% reduction in events, which included recurrences, second BC and deaths – and a highly significant improvement in the distant RFS in the anastrozole-containing arm.

c) Extended AI. One large trial was designed to test whether the extension of adjuvant treatment beyond 5 years with an AI could improve outcome. In the NCIC CTG MA.17/BIG 1-97 trial, 5,187 postmenopausal women treated with approximately 5 years (4.5–6) of tamoxifen were randomised to receive either letrozole or a placebo for 5 more years [42]. A first planned interim analysis, at a median follow-up of 2.4 years, showed a significantly higher rate of DFS in the letrozole group: an absolute difference of 2.2% with an actuarial projection of an absolute difference of 6% in the rate of events over 4 years. This unexpected and robust difference led to the early unblinding of the study.

Safety of AI (Table 3)

Given all these "positive" trials and the optimistic view that OS benefits will emerge with longer patient follow-up, the main concern with adjuvant use of AI is their long-term side effects. Whereas tamoxifen has been shown to prevent bone loss and maintain an appropriate lipid balance, AI may affect bone turnover and lipid balance due to estrogen deprivation. Several safety issues, including bone fractures, lipid profile changes, cardiac and vascular events, were defined as important for specific clinical investigations. Table 3

summarizes our current knowledge in this field at a point with relatively short follow-up.

In the ATAC trial, patients treated with anastrozole had significantly lower rates of hot flushes, vaginal bleeding and discharge, endometrial cancer, and cerebrovascular or venous thromboembolic events than those receiving tamoxifen. On the other hand, anastrozole-treated women showed significantly higher rates of joint symptoms and bone fractures [45].

Preliminary results from the ABCSG 8/ARNO 95 [43] trial did not demonstrate any statistically significant detrimental effect for the anastrozole arm in terms of bone fractures, thromboembolic and cardiovascular events.

In comparison with placebo (MA.17 trial) [42], letrozole induced more arthralgias and hot flushes, while the slightly higher incidence of bone fractures and cardiovascular events is not statistically different from the rate observed in the placebo group.

In comparison with tamoxifen (BIG 1-98) [41], letrozole induced significantly more bone fractures. As far as severe ischemic cardiovascular disease is concerned, the incidence figures reported so far are 3.6% for letrozole and 2.5% for tamoxifen (p-value not reported).

In comparison with tamoxifen, exemestane induced less venous thromboembolic events, gynaecological symptoms and a similar rate of hot flushes (Table 3). In contrast, arthralgias were more common and particular attention will need to be paid to cardiovascular events, which show a non significant higher rate in the exemestane group [39].

More mature data are clearly awaited.

Practical recommendations for clinical practice

There has been an attempt to produce therapeutic guidelines given the rapidly growing body of knowledge gained from these large adjuvant trials.

ASCO' s 2005 Technology Assessment Committee concluded that optimal adjuvant hormonal therapy for a postmenopausal woman with HR positive BC should include an AI either as initial therapy or after treatment with tamoxifen [46]. However, based on the published trials, it is not possible to determine the optimal strategy for the individual patient.

In 2005, three BC responsiveness categories were identified by the St. Gallen Consensus Panel [16]: endocrine responsive, endocrine response uncertain and endocrine non-responsive. Patients in the former group are likely to benefit most from endocrine therapy alone, while those in the latter group are likely to benefit from CT alone. Adjuvant use of CT followed by endocrine therapy should be preferred for the newly defined intermediate category.

Of note, endocrine responsiveness is becoming the most important feature for adjuvant therapy decision making, surpassing ' risk of relapse' . Tamoxifen, AI or a sequence of tamoxifen followed by AI are all considered valid options by the St. Gallen Consensus Panel and choice must be based on comorbidities and patient or physician preference.

Future hope: choice of optimal endocrine therapy based on the tumour molecular profile

Current research efforts are directed at the discovery of molecular signatures that might identify those patients most responsive to tamoxifen or to an AI. The assumption is that the former group will be an ideal candidate for the sequencing strategy while the latter should be offered an AI upfront. However, none of this research has reached level-1 evidence today. The most mature data are those generated by Paik and colleagues [47] (level-2): their recurrence score, obtained by the RT-PCR evaluation of 21 genes in paraffin-embedded tumour material from node-negative BC patients, identifies a group of women with excellent prognosis following adjuvant tamoxifen.

Premenopausal EBC patients

The optimal management of premenopausal EBC patients remains an area with many uncertainties.

EBCTCG Overview

The 2005 EBCTCG overview, including almost 8,000 women aged under 50 with ER positive or unknown EBC with a minimum of 5-years follow up convincingly confirms the positive impact of ovarian ablation (OA) or suppression on both BC recurrence and mortality [1]. However, these effects are not as extreme as seen in earlier meta-analyses, when OA was not tested against effective systemic therapy. No data indicate that these effects are different between OA and ovarian suppression and between women aged <40 and women aged 40–49.

Ovarian ablation

a) As alternative to CT (Table 4). The ZEBRA trial [48] is the largest study to directly compare ovarian suppression and CT. This trial randomised 1,640 premenopausal women with node positive BC to receive either 6 cycles of CMF or 2 years of goserelin. For those women with ER positive tumours, the two arms resulted in equivalent DFS and OS at a median follow-up of 6 years. In contrast, CMF yielded

Table 4
Randomized clinical trials assessing ovarian ablation (OA) versus chemotherapy (CT) in premenopausal EBC patients[a]

Trial	Patient characteristics	Treatment arms	FU (y)	Hazard ratio			Comments
				EFS	DFS	OS	
ZEBRA (Kaufmann et al 2003 [48])	1640 pts 70% 1–3 LN+, 25% 4–9 LN+ 80% ER +	Z × 2 years vs CMF × 6	6	–	1.18 (1.02–1.37) p = 0.29	1.21 (0.99–1.49) p = 0.067	In the 270 ER+ pts, improved OS with OA; CMF better for ER– (HR: 1.76; p = 0.0006) No differences on basis of nodal status
Scottish trial, 2002 [49]	332 pts LN– or LN+ 60% ER+	OA vs Oral CMF × 6–8 (± prednisolone)	10.7	0.95 (0.71–1.26) p = 0.70 1.00 (0.75–1.32) p = 0.97	–	1.01 (0.74–1.37) p = 0.96 1.06 (0.78–1.44) p = 0.71	10% crossover treatment or TAM or no ttx after randomization (potential bias)
Scandinavian trial (Ejlertsen et al 1999 [50])	732 pts LN+ and/or TU > 5 cm HR+	OA vs IV CMF × 9	68 mo	–	67% vs 66% (5-year) (ns)	78% vs 82% (5-year) (ns)	68% of pts in the CMF arm became amenorrheic
GABG IV A 93 (Von Minckwitz et al 2004 [51])	771 pts	Z × 2 years vs IV CMF × 3	4.9	–	0.81 (0.56–1.17) p = 0.24		

[a] EFS: event-free survival; OS: overall survival; DFS: disease-free survival; HR: hormone receptor; ER: estrogen receptor; C: cyclophosphamide; M: methotrexate; F: 5-fluorouracil; OA: ovarian ablation; LN: lymph nodes; TU: tumour; mo: months; FU: follow up; ns= not statistically significant; IV: intravenous.

superior DFS and OS compared to goserelin in the subgroup of women with ER negative tumours.

The Scottish [49], Scandinavian [50] and German [51] trials did not demonstrate statistically significant differences between the CMF and OA arms regarding DFS and OS. Interestingly, in the Scottish trial improved survival was demonstrated in the subgroups of women with significant levels of ER who were treated with ovarian ablation and in women with low scores of ER treated with 6 months of oral CMF.

The trials comparing OA plus tamoxifen to CT in premenopausal women with HR positive EBC did not demonstrate significant differences in DFS and OS (Table 5).

The GROCTA trial, which enrolled 244 node positive EBC patients, compared OA (by surgery, radiation, or 2 years of goserelin) plus 5 years of tamoxifen with 6 cycles of oral CMF [52]. At a follow-up of 76 months, there was no statistically significant difference in DFS and OS. This trial was considered underpowered, particularly for survival.

In the FASG 06 trial, 3 years of triptorelin plus tamoxifen was compared to 6 cycles of FEC_{50} in 333 node positive EBC patients [53]. At a median follow-up of 54 months, there was no statistically significant difference between the two treatment approaches regarding DFS and OS.

Another small French trial [54] compared FAC with OA and tamoxifen in 162 node positive EBC patients. This trial was stopped early due to poor accrual and is thus underpowered.

The ABCSG 5 trial compared goserelin for 3 years plus tamoxifen for 5 years to 6 cycles of IV CMF in 1,045 EBC patients [55]. At a median follow-up of 42 months, combination endocrine therapy was associated with a statistically significant improvement in DFS compared to CMF, with no difference in OS.

A recent trial has compared 2 years of leuproreline with 6 cycles of IV CMF in 599 node positive BC patients and has failed to demonstrate a difference in both DFS and OS [56].

Unfortunately, the absence of tamoxifen in the CT arms of all these trials and the use of different CMF regimens with a variable propensity for ovarian failure undermine in part their clinical relevance.

b) Following CT (Table 6). CT-induced amenorrhea has been shown to have an impact on survival [59]. The trials incorporating OA after adjuvant CT did not establish definitive benefit. However, the subgroup of HR positive premenopausal patients who do not become amenorrheic with CT may benefit from the addition of OA (IBCSG VIII) [58].

Intergroup 0101 [57] is a randomised trial involving 1,504 premenopausal eligible patients that compared CAF for 6 cycles, or CAF for 6 cycles followed by LH-RH agonist for 5 years, or CAF for 6 cycles followed by the combination of LH-RH plus tamoxifen for 5 years. At 6 years of follow up, only the tamoxifen-containing arm demonstrated a statistically significant improvement in time to treatment relapse (TTR).

The IBCSG coordinated PERCHE trial will enrol 1,750 premenopausal women with HR positive EBC to evaluate the efficacy and safety of adding adjuvant CT to OA plus either tamoxifen or exemestane for 5 years (*www.ibcsg.org*).

Combined endocrine therapy

Few trials have compared tamoxifen with or without OA (Table 7) and only very recent trials, which have just started accrual, are investigating OA in association with an AI. The ZIPP trial [60] included 2,631 women randomised in four arms: a 2-year treatment of either tamoxifen, LH-RH agonist, or the combination of both, and a control arm without any treatment. At 4.3 years median follow up, there was a statistically significant event-free survival and OS in favour of the LH-RH agonist arm. INT0142 was a prospective randomised trial designed to compare DFS, OS and quality of life of adjuvant tamoxifen 5 years alone or with OA. The study accrued slowly and was closed before obtaining its accrual target, and survival analyses consequently are underpowered [61].

Tamoxifen alone may also be an effective adjuvant therapy, but there are no trials comparing its efficacy to CT or to OA in the adjuvant setting.

Two trials coordinated by the IBCSG and run under the BIG umbrella will contribute to answering these important questions. SOFT is an ongoing phase III trial aiming to recruit 3,000 patients that will compare the efficacy of OA associated with tamoxifen or exemestane to tamoxifen alone in premenopausal women with HR positive tumour. TEXT is a phase III randomised study in 1,845 HR positive premenopausal patients that will evaluate the efficacy and safety of OA (LH-RH) plus exemestane compared with OA plus tamoxifen for 5 years (*www.ibcsg.org*).

The ABCSG-12 trial is another ongoing study with a projected accrual of 1,250 premenopausal women with HR positive EBC that compares adjuvant endocrine treatment with ovarian suppression (goserelin) plus anastrozole or tamoxifen for 3 years [62].

Table 5
Randomized clinical trials assessing ovarian ablation (OA) + Tamoxifen vs chemotherapy (CT) in premenopausal EBC patients[a]

Trial	Patient characteristics	Treatment arms	FU (mo)	Hazard ratio			Comments
				RFS	DFS	OS	
GROCTA (Boccardo et al 2000 [52])	244 pts ER+ 86% LN+ 91% premenop	OA (Surg/Rtx/Z×2y) + T×5y vs Oral CMF×6	76	–	No difference	No difference	Underpowered particularly for survival
FASG 06 (Roche et al 2000 [53])	333 pts HR+ LN+	Triptoreline + T×3y vs FEC 50 × 6	54	–	91.7% vs 80.9% (p = 0.12)	97% vs 92.9% (p = 0.18)	
Roche et al (1996) [54]	162 pts HR+ LN+ 84% premenop	OA + T×2y vs FAC×6	84	–	No difference	No difference	Low accrual, unbalance between arms, prematurely stopped
ABCSG 5 (Jakesz et al 2002 [55])	1045 pts HR+ 50% LN+	Z×3y + T×5y vs CMF×6 (i.v.)	5 y	5-year: 81% vs 76% (p = 0.037)	–	No difference	
Wallwiener et al (2004) [56]	599 pts HR+ LN+	Leuprorelin × 2y vs CMF (i.v.) × 6		83% vs 80.9% (ns)	–	98.7% vs 97.2% (ns)	

[a] RFS: relapse-free survival; OS: overall survival; DFS: disease-free survival; HR: hormone receptor; ER: estrogen receptor; C: cyclophosphamide; A: adriamycin; M: methotrexate; F: 5-fluorouracil; OA: ovarian ablation; LN: lymph nodes; TU: tumour; mo: months; FU: follow up; ns: not statistically significant; Z: Zoladex; i.v: intravenous.

Table 6
Randomized clinical trials assessing chemotherapy (CT) vs CT + OA ± Tam in premenopausal EBC patients[a]

Trial	Patient characteristics	Treatment arms	FU (y)	Hazard ratio		Comments
				DFS	OS	
Intergroup 0101 (Davidson et al 1999 [57])	1504 pts HR+ 59% 1–3 LN+ 29% < 40 y	CAF × 6 CAF × 6 → Z × 5y CAF × 6 → Z + T × 5y	6	–	–	Addition of T to CAF improved TTR (1-sided p values <0.01) No arm CAF × 6 → T
IBCSG VIII, 2003 [58]	1063 pts 68% ER+ T1-T3N0 Pre- and perimenopausal	Z × 2y CMF × 6 CMF × 6 → Z × 1.5y	5.7	No difference	No difference	Subgroup analysis: better survival for ER– treated with CMF (with our without Z), Z equivalent to CMF for ER+

[a] EFS: event-free survival; OS: overall survival; DFS: disease-free survival; HR: hormone receptor; ER: estrogen receptor; C: cyclophosphamide; A: adriamycin; M: methotrexate; F: 5-fluorouracil; OA: ovarian ablation; LN: lymph nodes; TU: tumour; mo: months; FU: follow up; ns: not statistically significant; Z: Zoladex.

Table 7
Randomized clinical trials assessing Tamoxifen (T) vs T + OA in premenopausal EBC patients[a]

Trial	Patient characteristics	Treatment arms	FU (y)	Hazard ratio		Comments
				EFS	OS	
ZIPP trial (Lars 1999 [60])	2631 pts 42% LN+ 43% previous CT	T × 2 years Z × 2 years T + Z × 2 years No hormonal therapy	4.3	Better with Z (HR 0.77 p = 0.001)	Better with Z (HR 0.84 p = 0.12, NS)	Benefit independent of adjuvant T or CT
INT 0142 (Robert et al 2003 [61])	345 pts LN– HR+	T T + OA	5	underpowered	underpowered	Prematurely closed

[a] EFS: event-free survival; OS: overall survival; DFS: disease-free survival; HR: hormone receptor; ER: estrogen receptor; C: cyclophosphamide; A: adriamycin; M: methotrexate; F: 5-fluorouracil; OA: ovarian ablation; LN: lymph nodes; TU: tumour; mo: months; FU: follow up; ns: not statistically significant; Z: Zoladex.

New biological agents

Trastuzumab

Trastuzumab is a therapeutic monoclonal antibody targeting the human epidermal growth factor receptor type 2 (HER2), a cell-surface tyrosine kinase receptor overexpressed in 25–30% of BC [63]. Active as a single agent, trastuzumab in combination with standard CT prolongs the survival of women with advanced BC [64]. This activity in the metastatic setting and the known association of HER2 overexpression with poor prognosis prompted the launch of adjuvant clinical trials examining its potential role in early BC.

Four randomised trials of adjuvant trastuzumab have recruited more than 13,500 overexpressing HER2, node positive, or high risk node negative EBC patients worldwide [65]. Three of these trials disclosed early, highly positive results at the 2005 ASCO meeting, which are summarized in Table 8.

In the NSABP B-31, a phase III trial sponsored by US National Cancer Institute, a total of 2,700 patients were randomised to receive either AC followed by 3-weekly paclitaxel alone or in combination with trastuzumab weekly for a total of 52 weeks. The primary endpoint was OS.

The NCCTG N9831 trial aimed to include 3,300 patients randomised to receive one of three treatment arms: AC for 4 cycles followed by weekly paclitaxel for 12 cycles, or AC followed by weekly paclitaxel followed by trastuzumab weekly for 1 year, or the same CT schedule but trastuzumab administered upfront in combination with paclitaxel. The primary endpoints are DFS and cardiac tolerability. A decision was taken by the National Cancer Institute to pool the NSABP

Table 8
Phase III randomized trials of adjuvant trastuzumab in EBC[a]

	Pooled analysis of NSABP-B31/NCCTG-N9831		HERA	
	Control: AC → P	AC → P + trastuzumab	Control: NIL	Trastuzumab × 1 year[b]
Number of patients	1679	1672	1693	1694
Median follow up	2 years		1 year	
HR for disease-free survival	0.48 ($2p = 3 \times 10^{-12}$)		0.54 ($p < 0.0001$)	
HR for time to distant recurrence	0.47 ($2p = 8 \times 10^{-10}$)		NA	
HR for distant-disease free survival	NA		0.51 ($p < 0.0001$)	
HR for overall survival	0.67 ($2p = 0.015$)		0.76 ($p = 0.26$)	
Cumulative incidence of severe cardiac events	0.6%	4%	0.1%	0.5%

[a] EBC: early breast cancer; A: doxorubicin; C: cyclophosphamide; P: paclitaxel; HR: hazard ratio; NA: not available.
[b] No results available as yet for trastuzumab × 2 years.

B-31 and NCCTG N9831 trials in order to increase the power of treatment comparisons.

The HERA trial, a collaboration between the Breast International Group, F. Hoffmann-La Roche, non-affiliated collaborative groups and independent centres, investigates the role of trastuzumab independently from previous neo/adjuvant chemotherapeutic regimens in 5,082 patients. In this 3-arm design, trastuzumab is administered every 3 weeks for 1 or 2 years, and compared with an observation arm. The primary endpoint is DFS.

The interim analyses of the HERA results and pooled results from the Northern American trials presented at the 2005 ASCO meeting indicate a drastic reduction in the risk of relapse as well as distant relapse (*www.asco.org*). Overall survival is also enhanced in the US trials, while a favourable trend emerges in HERA (HR 0.78, p-value NS), which has the shortest median follow-up (1 year instead of 2). Severe congestive heart failure is a potential serious adverse effect of trastuzumab in all three trials. The risk appears to be higher in the US trials, which initiated trastuzumab sooner than in HERA, where trastuzumab was administered at completion of adjuvant CT and radiotherapy. Longer follow-up is essential in order to better quantify this risk in all three studies.

The BCIRG trial has not yet reported results: it has three arms comparing AC for 4 cycles followed by docetaxel every 3 weeks for 4 cycles with AC for 4 cycles followed by docetaxel every 3 weeks for 4 cycles with concomitant administration of trastuzumab weekly and then trastuzumab alone every 3 weeks for 1 year, or carboplatin and docetaxel every 3 weeks for 6 cycles concomitant with trastuzumab weekly followed by trastuzumab alone every 3 weeks for one year. The recruitment was completed with 3,150 patients and first results are expected by the end of 2005.

Perspectives

Several new agents appear to be good candidates for incorporation into adjuvant regimens, pending the availability of more safety and efficacy data in advanced disease. Four examples are given below.

The HER2 antigen is a compelling antigen for a cancer vaccine because it is overexpressed on some cancer cells relative to normal tissues, and it is known to be immunogenic in both animal models [66] and humans [67]. There are good reasons to speculate that HER2 vaccines, capable of eliciting both antibody and T cell responses, could be more effective than antibody therapy alone, at least in some BC patients. Based on this rationale, phase I trials of vaccination in the adjuvant setting of high risk BC patients are ongoing to evaluate the safety and immunogenicity of serial vaccinations of HER2 recombinant protein (GSK 719125).

One contributing factor to the ultimate failure of trastuzumab may be the collateral activation of the other members of the HER family in tumour cells [68]. The development of additional targeted molecular therapies against multiple members of the HER family may thus have a greater impact on inhibiting cell proliferation and angiogenesis. CI 1033 is an orally available targeted therapy that interferes directly with the ATP binding site of the HER family members (EGFR, HER2, HER3, HER4), resulting in irreversible inhibition of the activation of these receptors and their subsequent downstream mitogenic signalling pathways [69]. Phase I trials have been conducted with doses ranging from 2 to 1000 mg, and with weekly and chronic daily schedules. The most common adverse effects were diarrhoea, rash, and nausea/vomiting at low grades. Results of an open-label, randomised multicenter phase Ib study with 3 dose levels of CI 1033 conducted in 168 patients with MBC are pending.

Lapatinib is a reversible potent inhibitor of both HER1 and HER2 tyrosine kinases. It induces growth arrest and/or tumour cell apoptosis in HER1 and HER2 dependent tumour cell lines and xenografts [70]. This oral drug is well tolerated in phase I trials as single agent, in doses ranging from 175 to 1800 mg/day. The most frequent adverse events were cutaneous rash, diarrhoea, anorexia, fatigue, stomatitis and nausea/vomiting, usually grade 1 or 2 [71]. This drug has also been evaluated in phase I trials in combination with CT (paclitaxel) [72], trastuzumab [73], and letrozole [74]. Phase II and III trials as single agent or in combination with these agents are ongoing in advanced and inflammatory BC (EGF 30008, EGF 30001, EGF 100151, EGF 20002, EGF 20008) (*www.clinicaltrials.gov*).

RAD001 is a potent oral inhibitor of the mTOR pathway, which plays a central role in the regulation of cell growth and survival as well as angiogenesis in BC. Preclinical results with RAD001 show high sensitivity of BC cell lines in vitro [75]. The combination of RAD001 and letrozole has demonstrated in vitro additive/synergistic effects in inhibiting the proliferation of aromatase expressing MCF7 breast cancer cells [76]. A phase I trial [77] was conducted in metastatic BC patients treated with letrozole for a minimum of 4 months and for whom no objective response had been observed. The combination of letrozole (2.5 mg/day) and RAD001 (up to 10 mg/day) had a good toxicity profile, with no grade 3/4 toxicities. One complete response was reported.

Finding the optimal way to introduce these new agents into the adjuvant treatment of HER2 overexpressing BC presents us with an exciting challenge for the coming years.

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