Trastuzumab in the adjuvant setting: a practical review

Trastuzumab is a monoclonal antibody directed against the product of the *HER2/neu* oncogene. The HER2 protein is overexpressed in approximately 20% of human breast cancers and is associated with adverse prognosis. Randomized studies in patients with HER2-positive advanced breast cancer demonstrated an increased response rate and survival when trastuzumab was added to chemotherapy. These results prompted the conduction of several large trials with trastuzumab in the adjuvant setting. Approximately 16,000 women with HER2-positive early breast cancer have been randomized in trials assessing the efficacy of trastuzumab added to adjuvant chemotherapy. All of these trials, except one, have confirmed superior outcomes of the experimental trastuzumab-containing arms over chemotherapy alone. Owing to these results, adjuvant regimens with trastuzumab and chemotherapy are now the standard of care for patients with HER2-positive operable breast cancer. However, because of different designs, these trials leave several questions open, which have practical as well as scientific implications. A debate exists around sequential or concomitant administration of trastuzumab with chemotherapy, treatment duration, minimization of cardiac risks and role of anthracyclines in trastuzumab-based regimens. This article will analyze the currently available data on trastuzumab in the adjuvant setting and discuss critical issues regarding its use.

KEYWORDS: adjuvant chemotherapy ■ breast cancer ■ chemotherapy ■ HER2 ■ trastuzumab

Valentina Rossi[1]*, Stefania Redana[1]*, Andrea Milani[1], Elena Geuna[1], Giorgio Valabrega[1], Massimo Aglietta[1] & Filippo Montemurro[†1]

[1]Fondazione del Piemonte per l'Oncologia/Division of Medical Oncology I, Institute for Cancer Research & Treatment (IRCC), Strada Provinciale 142, Km 3.95, 10060 Candiolo, Torino, Italy
[†]Author for correspondence:
Tel.: +39 011 993 3251
Fax: +39 011 993 3299
filippo.montemurro@ircc.it
**Authors contributed equally*

Breast cancer is the most frequent cancer among women worldwide [1]. Owing to screening programs and increased awareness of the importance of early diagnosis, breast cancer is operable at presentation in most patients. Owing to the risk of microscopic systemic involvement, surgery of nonmetastatic disease is usually followed by adjuvant medical treatments. Chemotherapy and endocrine therapy effectively reduce the risk of disease recurrence and death after surgery by controlling the growth of micrometastases [2]. More recently, the monoclonal antibody trastuzumab, which targets the product of the *HER2* oncogene, has been confirmed as an important component of adjuvant regimens in patients whose tumors carry this abnormality [3].

The *HER2* oncogene, which is located on chromosome 17, encodes a transmembrane tyrosine kinase protein belonging to the EGF receptor family, together with HER1 (EGF receptor 1), -3 and -4 [4]. Since no specific ligand has been identified for HER2, this receptor is believed to act by forming homo- or hetero-dimers with other members of the EGF receptor family, activating a cascade of cell signaling involved in cell cycle progression and regulation, and proliferation and apoptosis.

HER2 is amplified, with consequent overexpression of its product (HER2 positivity), in approximately 20% of human breast cancers [5]. Tumors bearing this alteration display an aggressive clinical behavior characterized by early relapse, visceral metastatic spread and resistance to endocrine manipulation [5,6]. By contrast, HER2 positivity predicts a benefit from anthracycline-based chemotherapy [7]. Owing to these features, HER2 was identified as a potential pharmacological target. Trastuzumab is the first humanized monoclonal antibody specifically directed against this oncogene product that was made available for clinical use [8–10]. In women with HER2-positive advanced breast cancer, the addition of trastuzumab to chemotherapy resulted in a significant improvement in response rate, progression-free survival and overall survival (OS) compared with chemotherapy alone [11,12]. The results obtained in the metastatic setting and the favorable toxicity profile of trastuzumab prompted its testing in the management of operable disease. Four large international and two smaller single-country randomized trials comparing chemotherapy with or without trastuzumab have been published or presented at international meetings (**Figure 1**) [13–20].

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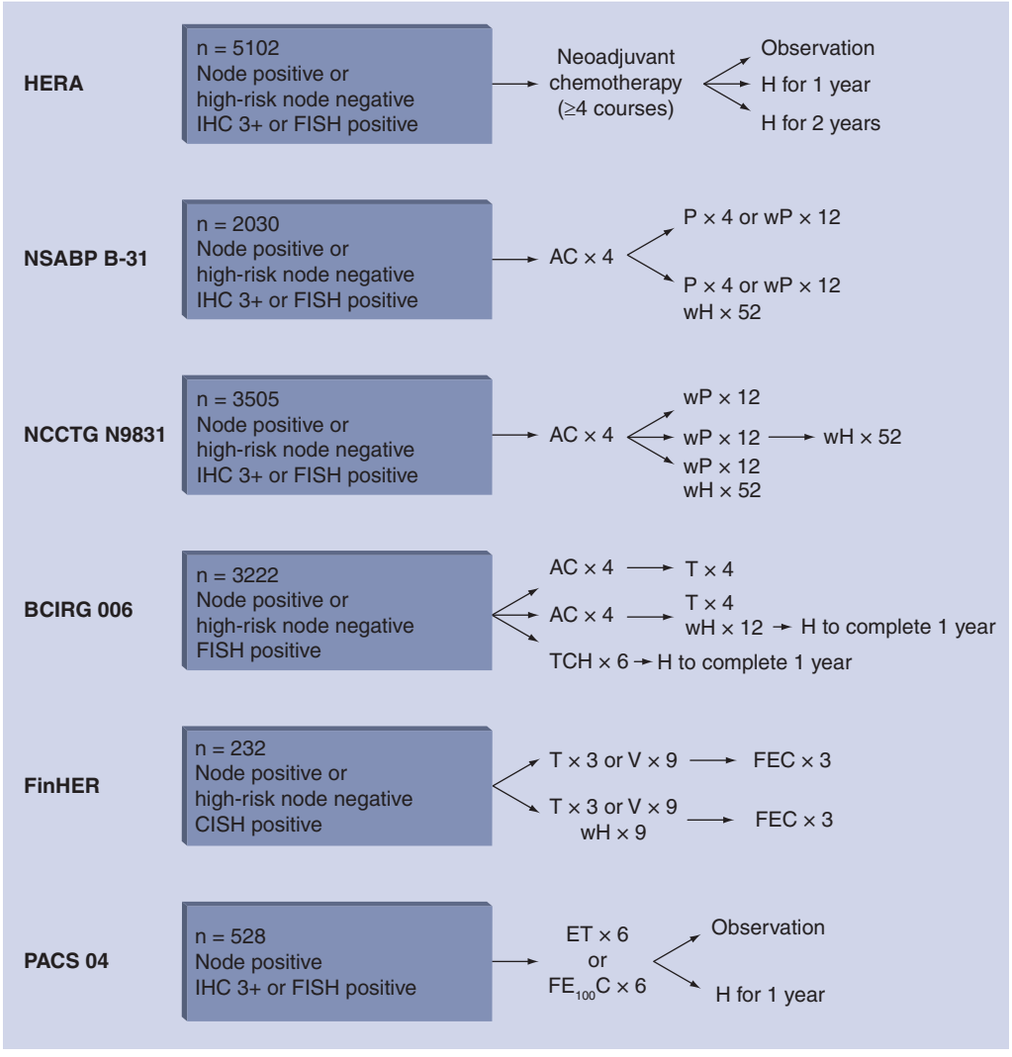

Figure 1. Available clinical trials with trastuzumab in the adjuvant setting. In the HERA trial, 94% of patients had received anthracycline-based adjuvant chemotherapy. Median cumulative doses of doxorubicin were 239 and 238 mg/m^2 among patients in the experimental and conventional arms, respectively. Median cumulative doses of epirubicin were 397 and 405 mg/m^2 among patients in the experimental and conventional arms, respectively.
AC: Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2; BCIRG: Breast Cancer International Research Group; CISH: Chromogenic *in situ* hybridization; ET: Epirubicin 75 mg/m^2 plus docetaxel 75 mg/m^2; $FE_{100}C$: 5-fluorouracil 500 mg/m^2 plus epirubicin 100 mg/m^2 plus cyclophosphamide 500 mg/m^2; FEC: 5-fluorouracil 600 mg/m^2 plus epirubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2; FinHER: Finland Herceptin; H: Trastuzumab loading dose 8 mg/kg followed by 6 mg/kg every 3 weeks; HERA: Herceptin Adjuvant; IHC: Immunohistochemistry; NCCTG: North Central Cancer Treatment Group; NSABP: National Surgical Adjuvant Breast and Bowel Project; P: Paclitaxel 175 mg/m^2 every 3 weeks; T: Docetaxel 100 mg/m^2 every 3 weeks; TCH: Docetaxel 75 mg/m^2 plus a carboplatin area under the curve of 6 every 3 weeks and trastuzumab loading dose 4 mg/kg then 2 mg/kg weekly; V: Vinorelbine 25 mg/m^2 every week; wH: Trastuzumab loading dose 4 mg/kg followed by 2 mg/kg every week; wP: Paclitaxel 80 mg/m^2 every week.

A recent meta-analysis of five of these trials demonstrated that the addition of trastuzumab to adjuvant chemotherapy reduces the risk of relapse by 38% and the risk of death by 34% [3]. One striking feature of all the adjuvant trials with trastuzumab except one is the consistency of results despite some major differences in trial design.

In fact, when establishing trastuzumab-containing adjuvant combinations, investigators had to consider lessons learned from studies with trastuzumab in the metastatic setting. For example, as a single agent, trastuzumab is active when administered to a subset of appropriately selected HER2-positive patients [8–10]. However, it is the combination with chemotherapy, as previously

demonstrated in preclinical models, that allows the full exploitation of its clinical potential [21]. Cardiac dysfunction has been associated with trastuzumab use. Prior exposure or concomitant administration with anthracyclines significantly increases the risk of developing cardiac dysfunction during trastuzumab treatment [11]. Although trastuzumab is administered at least until tumor progression in metastatic patients, its optimal duration in a surgically treated and potentially cured patient is unknown. Investigators took different approaches in dealing with this background of information on trastuzumab.

As shown in FIGURE 1, trastuzumab was administered concomitantly with taxanes after or before an anthracycline-based combination, or after the conclusion of any neoadjuvant or adjuvant chemotherapy and radiation therapy, or with a nonanthracycline-based regimen. In most of the trials, the duration of adjuvant trastuzumab was 1 year; however, one trial is currently investigating a longer duration and another evaluated a short-course of just 9 weeks concomitantly with chemotherapy. This article will detail the results of clinical trials and focus on open questions emerging from the use of trastuzumab in this setting.

Pharmacology of trastuzumab

In the 1990s, several groups obtained monoclonal antibodies directed against HER2, showing therapeutic potential in HER2-overexpressing cell lines [22,23]. The first antibody available for clinical use was the product of the humanization of a murine monoclonal antibody called 4D5, which was selected for its potency and specificity [24]. This product was called trastuzumab, which is 95% human and 5% murine. In HER2-overexpressing human breast cancer xenografts, trastuzumab showed a dose-dependent growth inhibition [25]. Further valuable knowledge in this field was provided by Pegram *et al.* who, in a *HER2*-transfected MCF-7 xenograft model, evaluated potential interactions between trastuzumab and a wide array of cytostatic drugs used in the treatment of breast cancer [26]. This series of elegant experiments revealed synergistic interactions with cisplatin, docetaxel, thiotepa, cyclophosphamide, vinorelbine and etoposide. Additive effects were observed with doxorubicin, paclitaxel, vinblastine and methotrexate, whereas the combination of trastuzumab with 5-fluorouracil showed antagonism.

The mechanism of action of trastuzumab and its interaction with cytostatic drugs have not been fully elucidated [27]. One of the first hypotheses is that it may enhance HER2 downregulation on the cell surface and accelerate its endocytic degradation [28]. Other potential mechanisms include antiangiogenetic effects [29], inhibition of the PI3K/Akt pathway [30], interference with chemotherapy or radiation-induced DNA damage repair mechanisms [26,31], and antibody-dependent cell cytotoxicity triggering [32].

The murine antibody 4D5 caused maximal tumor growth inhibition at concentrations of 1–23 µg/ml. Owing to greater affinity for HER2, the humanized antibody trastuzumab was expected to have at least the same effect in the same range of concentrations. Therefore, clinical dosing sought to determine minimum serum trough concentrations between 10 and 20 µg/ml, which could be successfully achieved with weekly intravenous administrations. A loading dose of 4 mg/kg of bodyweight, followed by weekly doses of 2 mg/kg was established as the conventional schedule for trastuzumab alone or in combination with chemotherapy. The elimination half-life of trastuzumab was initially believed to be 8.3 days, on the basis of the assumption of dose-related nonlinear pharmacokinetics, with the elimination half-life increasing with increasing dosage [33]. However, population pharmacokinetic analysis of data from the initial Phase I, II and III studies suggested a half-life of 28.5 days [34]. Subsequent studies evaluated a more convenient 3-weekly schedule consisting of a loading dose of 8 mg/kg of bodyweight, followed by 6 mg/kg every 3 weeks [35]. Plasma trough levels of trastuzumab were similar to those achieved with weekly dosing and no unexpected changes in the toxicity profile occurred (TABLE 1). The half-life of trastuzumab was between 18 and 27 days, confirming the population pharmacokinetic data (TABLE 1). Although never formally compared, both the weekly and the 3-weekly schedules are considered equivalent. More recently, based on a potential gain in clinical benefit if high trastuzumab concentrations are obtained early during treatment, Leyland-Jones *et al.* evaluated an intensive loading regimen of trastuzumab in 72 women with HER2-positive advanced breast cancer [36]. In this study, trastuzumab was administered at 6 mg/kg intravenously every week for 4 consecutive weeks, and then every 3 weeks. At 3 weeks from the first administration, this intensive loading regimen achieved a median estimated trough concentration of trastuzumab of 119 mg/l, which is almost twice as high as the steady-state concentration achieved

with conventional dosing. No unexpected toxicities occurred and the clinical activity was encouraging.

Adjuvant trials

National Surgical Adjuvant Breast & Bowel Project B31 & North Central Cancer Treatment Group N9831 studies

Owing to similarities in design, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 study and two arms of the North Central Cancer Treatment Group (NCCTG) N9831 study were analyzed jointly (Figure 1) [16]. For both studies, the backbone chemotherapy regimen was a sequence of doxorubicin and cyclophosphamide and paclitaxel (see legend to Figure 1 for treatment details). From May 2003, investigators in the NSABP B31 study could also opt for the weekly paclitaxel schedule. Trastuzumab was administered concomitantly with paclitaxel in the experimental arm of the NSABP B31 study and in one of the two experimental arms of the NCCTG N9831 study, and continued for 1 year. At a median follow-up of 2 years, the combined analysis of these two trials showed that trastuzumab halved the hazard of disease progression and reduced the hazard of death by 33% (Table 2). The NCCTG N9831 study included a second experimental arm in which trastuzumab was administered sequentially to chemotherapy (Figure 1). Results of this arm of the trial have recently been presented at the 32nd San Antonio Breast Cancer Symposium (Table 2) [19]. In addition, the sequential trastuzumab-containing arm confirmed superior outcomes compared with chemotherapy alone. A direct comparison of the two trastuzumab-based arms showed a disease-free survival (DFS) advantage of concomitant oversequential administration (Table 2). The implications of these results will be addressed in a later section of this article.

The Breast Cancer International Research Group 006 study

The backbone chemotherapy regimen for the conventional and for one of the two experimental arms of the Breast Cancer International Research Group (BCIRG) 006 study was a sequence of doxorubicin and cyclophosphamide followed by docetaxel (Figure 1) [20]. In the first experimental arm, trastuzumab was administered concomitantly with docetaxel and continued for 1 year (AC-TH). The second experimental arm was introduced to test an anthracycline-free regimen. Trastuzumab was administered concomitantly with docetaxel and carboplatin for six cycles, then continued as monotherapy for 1 year. Both docetaxel and carboplatin were chosen owing to their potentially synergistic interaction with trastuzumab [26,37]. The latest planned efficacy analysis, which was presented at the 32nd San Antonio Breast Cancer Symposium, confirmed the superiority of both trastuzumab-containing arms compared with chemotherapy alone (Table 2) [20]. At a median follow-up of 65 months, AC-TH and docetaxel plus carboplatin reduced the hazard of progression by 36 and 25%, respectively, compared with the sequence of doxorubicin and cyclophosphamide followed by docetaxel (Table 2). The difference in DFS events in the two trastuzumab-containing arms was not statistically significant ($p = 0.21$). Furthermore, AC-TH and docetaxel plus carboplatin resulted in improved OS (Table 2). Again, the difference in OS events in the two trastuzumab-containing arms was not statistically significant ($p = 0.14$).

The Herceptin Adjuvant study

In contrast to the aforementioned clinical trials, in the Herceptin Adjuvant (HERA) study patients were randomized to observation or

Table 1. Main pharmacokinetic parameters of trastuzumab administered alone every 3 weeks.

Parameter	Cycle 10 (three patients)		Cycle 12 (15 patients)	
	Mean	***CV (%)***	***Mean***	***CV (%)***
C_{min}	66.0 µg/ml	39	72.3 µg/ml	9
C_{max}	203 µg/ml	7	237 µg/ml	12
t_{max} (hours after start of infusion)	1.7 h	22	2.7 h	45
AUC last	45.036 µg•h/ml	10	55.529 µg•h/ml	35
$t_{1/2}$	27.04 days	0.92	18.29 days	1.83
Clearance	8.8 ml/h	24	8.2 ml/h	57

AUC last: Area under the serum concentration–time curve up to the last sampling; C_{max}: Maximum serum concentration; C_{min}: Minimum serum trough concentration; CV: Coefficient of variation; $t_{1/2}$: Terminal half-life; t_{max}: Time to C_{max}. Adapted from [35].

Table 2. Summary of the adjuvant trials with chemotherapy and trastuzumab.

Parameter	NSABP B31 plus NCCTG N9831	NCCTG N9831	HERA	BCIRG 006	FinHER	PACS-04
Participants (n)	3968	3133	3401	3222	232	528
Design	AC→P AC→PH	a: AC→P b: AC→P→H c: AC→PH→H	CT→observation CT→H (1 year)	a: AC→T b: AC→TH c: TCH	T or V + H→FEC FEC	FEC or ET→H FEC or ET
Median FU	2 years	>5 years	4 years	65 months	64 months	4 years
HR for DFS	0.48 (p < 0.0001)	b vs a: 0.70 (p = 0.0005) c vs b: 0.77 (p = 0.019)	0.76 (p < 0.0001)	b vs a: 0.64 (p < 0.001) c vs a: 0.75 p = 0.04	0.65† (p = 0.12)	0.86 (p = 0.41)
Absolute DFS gain	18.2% at 4 years	b vs a: 8.2% at 5 years c vs b: 4.4% at 5 years	6.4% at 4 years	b vs a: 9% at 65 months c vs a: 6% at 65 months	7.6% at 64 months	3% at 3 years
HR for OS	0.67 (p = 0.014)	b vs a: 0.86 (p = 0.218) c vs b: 0.79 (p = 0.135)	0.85 (p = 0.109)	b vs a: 0.63 (p = 0.001) c vs a: 0.77 (p = 0.033)	0.55 (p = 0.094)	1.27 (p > 0.05)
Absolute OS gain	4.8% at 3 years	NR	1.6% at 4 years	b vs a: 5% at 65 months c vs a: 4% at 65 months	9% at 64 months	-1% at 4 years

†*Time-to-distant metastases.*
A: Doxorubicin; BCIRG: Breast Cancer International Research Group; C: Carboplatin; CT: Chemotherapy; DFS: Disease-free survival; ET: Epirubicin 75 mg/m² plus docetaxel 75 mg/m²; FEC: 5-fluorouracil plus epirubicin plus cyclophosphamide; FinHER: Finland Herceptin; FU: Follow-up; H: Trastuzumab; HERA: Herceptin Adjuvant; HR: Hazard ratio; NCCTG: North Central Cancer Treatment Group; NR: Not reported; NSABP: National Surgical Adjuvant Breast and Bowel Project; OS: Overall survival; P: Paclitaxel; T: Docetaxel; V: Vinorelbine.

trastuzumab for 1 or 2 years following the completion of at least four cycles of chemotherapy, either neoadjuvant or adjuvant, and of radiotherapy if needed (Figure 1) [13]. A large number of chemotherapy regimens were allowed, including anthracycline and/or taxane-free combinations. At a median follow-up of 4 years, the administration of trastuzumab for 1 year yielded a 24% reduction of the hazard of relapse (Table 2) [15]. An advantage in OS had emerged at 2 years of follow-up [14], but it lost statistical significance at the most recent update. The high number of patients in the observation arm crossing over to trastuzumab after the disclosure of the results may be partly responsible for this effect. The comparison of trastuzumab for 2 years versus observation is not yet available.

The Finland Herceptin study

The Finland Herceptin (FinHER) trial was designed as a head-to-head comparison of two adjuvant chemotherapy regimens in 1010 patients with node-positive or 'high-risk' node-negative breast cancer (Figure 1) [18]. The two regimens were sequences of either docetaxel (three cycles) or weekly vinorelbine (11 weeks) followed by 5-fluorouracil plus epirubicin plus cyclophosphamide. Of these patients, 232 had HER2-positive breast cancer and underwent a second randomization to trastuzumab administered concomitantly with docetaxel or vinorelbine for 9 weeks, or to docetaxel or vinorelbine without trastuzumab. The initial results of this trial showed a 58% (hazard ratio [HR]: 0.42; p = 0.01) reduction in the hazard of recurrence or death in patients randomized to trastuzumab [38]. A subsequent report with a median follow-up of 62 months showed that trastuzumab was still associated with a trend towards better OS (Table 2) [18]. However, a significant advantage in distant DFS compared with chemotherapy alone was only observed in patients receiving trastuzumab with docetaxel.

The PACS 04 study

The PACS 04 study was designed to compare two adjuvant chemotherapy regimens in 3010 female patients with node-positive operable breast cancer (Figure 1) [17]. Patients were randomized to either 5-fluorouracil plus epirubicin 100 mg/m² and cyclophosphamide, or epirubicin plus docetaxel, both administered every 3 weeks for six cycles. The 528 patients whose diseases were HER2-positive underwent a second randomization to trastuzumab, which was administered upon the completion of chemotherapy and radiotherapy, when needed, and continued for 1 year or to observation.

In contrast to the HERA trial and the sequential arm of the NCCTG N9831 study, trastuzumab added sequentially to chemotherapy was associated with a statistically nonsignificant trend towards a reduction in the hazard of relapse and with no effect on survival, compared with chemotherapy alone (Table 2). Possible reasons for these contrasting results have been discussed recently by HERA trial investigators [39]. The PACS 04 enrolled a small number of patients, giving it a much smaller statistical power compared with the HERA trial. Furthermore, patients were randomized before the completion of adjuvant chemotherapy, while in the HERA trial randomization occurred at the end of chemotherapy. Therefore, in the HERA trial, patients experiencing very early disease relapse and chemotherapy-related cardiotoxicity were not included. Finally, one main difference between these two studies is that approximately 90% of the patients assigned to trastuzumab in the HERA trial were able to complete the planned treatment, compared with only 68% in the PACS 04 trial. This latter figure resulted from 26 patients who were assigned to trastuzumab but did not start it, either because of refusal (17 patients), chemotherapy-related cardiac toxicity (five patients) or other reasons (four patients), and from 58 additional patients discontinuing treatment mainly because of trastuzumab-related cardiac toxicity (41 patients) and disease progression (ten patients). In the intent-to-treat analysis, reduced adherence to trastuzumab may have diluted the effect of this monoclonal antibody in the experimental arm of the PACS 04 trial.

Who should receive adjuvant trastuzumab?

Target identification

The assessment of HER2 status in tumor cells is the first critical step in the evaluation of eligibility for trastuzumab. Immunohistochemistry (IHC) is used to determine HER2 protein expression, whereas FISH and chromogenic *in situ* hybridization (CISH) are used to identify *HER2* gene amplification. FISH evaluates the ratio between the average number of gene copies and the average number of centromeres of the chromosome where the gene of interest is located. CISH is very similar to FISH but utilizes conventional peroxidase or alkaline phosphatase reactions visualized under a standard bright-field microscope to evaluate the average number of copies of the gene of interest.

The predictive value of HER2 status with respect to response to trastuzumab-based therapy was studied in the populations of patients enrolled in initial trials in the metastatic setting. These studies revealed that trastuzumab activity was restricted to patients whose tumors expressed HER2 at the highest level (complete and intense staining in >10% of invasive tumor cells, corresponding to a score of 3+ on a semiquantitative scale ranging from 0 to 3+) and to *HER2*-amplified tumors (*HER2*:CEP17 ratio ≥2) [40]. Furthermore, 20–25% of tumors scoring 2+ at IHC were found to be *HER2*-amplified by FISH and derived significant benefit from trastuzumab-based therapy.

According to the testing algorithm developed on the basis of these observations, HER2 assessment in the adjuvant trials was performed by either IHC, with subsequent evaluation of gene status in patients with an IHC score of 2+ or by FISH/CISH (Table 3).

The two North American trials initially allowed randomization based on the results of local laboratories and were subsequently amended to introduce centralized testing before randomization. This was necessary owing to the finding of a high rate of discordance between results of the local and the approved reference laboratories, a known issue with HER2 testing [41]. All the other trials had patient tumor samples tested at centrally designated laboratories.

Table 3. HER2 assessment in the adjuvant trials.

Definition	NSABP B31 plus NCCTG N9831	HERA	BCIRG 006	FinHER	PACS-04
HER2 status	3+ (IHC) or amplified (FISH)	3+ (IHC) or amplified (FISH)	Amplified (FISH)	Amplified (CISH)	3+ (IHC) or amplified (FISH)
Type of assessment	B31†: NSABP approved reference laboratories N9831†: registration after local testing, treatment assigned after central testing	Designated central laboratory	Designated central laboratory	Designated central laboratory	18 reference laboratories performed HER2 testing

†Amended at some point after study initiation based on unacceptable discordance rates.
BCIRG: Breast Cancer International Research Group; CISH: Chromogenic in situ *hybridization; FinHER: Finland Herceptin; HERA: Herceptin Adjuvant; IHC: Immunohistochemistry; NCCTG: North Central Cancer Treatment Group; NSABP: National Surgical Adjuvant Breast and Bowel Project.*

The initial discordant cases offered the possibility to perform subgroup analyses of the effects of trastuzumab in patients with HER2-negative disease. Paik *et al.* identified a total of 174 patients enrolled in the NSABP B31 study (9.7% of the total) whose tumor was found to be HER2-negative (both by IHC and FISH) by central analysis [42]. Surprisingly, in these patients, trastuzumab was associated with a significant reduction in the hazard of relapse (HR: 0.34; p = 0.014), which was of the same magnitude of that observed in patients with *HER2* amplification (HR: 0.4; p < 0.0001) or with IHC 3+ (HR: 0.48; p < 0.0001). Other intriguing data were presented by investigators of the NCCTG N9831 study [43]. In a total of 53 patients with HER2-overexpressing (IHC 3+) breast cancers lacking *HER2* amplification, trastuzumab showed a trend towards a DFS benefit (HR: 0.61; p = 0.57). Conversely, an IHC score of less than 3+ in *HER2*-amplified patients was not associated with trastuzumab benefit (HR: 0.98;p = 0.97). Similar to the results presented by Paik *et al.*, in patients with HER2-negative disease (both by IHC and FISH) trastuzumab provided a not statistically significant trend towards a benefit in DFS (HR: 0.51; p = 0.13). These results do not support the use of trastuzumab in patients whose tumors are HER2-negative by classical criteria, but should be considered hypothesis generating. In fact, adjuvant therapy is aimed at eradicating micrometastatic disease in apparently disease-free patients. Conversely, the predictivity of HER2 status with respect to trastuzumab activity was established in the metastatic setting, where the burden of disease is higher. Therefore, it is possible that trastuzumab may provide significant benefit in patients with early breast cancer with a mechanism of action that does not require *HER2* amplification but, rather, normal HER2 epitope expression. Another intriguing hypothesis has been suggested by studies evaluating circulating tumor cells, where a clinically significant proportion of patients with HER2-negative primary tumors are found to have HER2-positive circulating tumor cells [44,45].

In summary, although newer guidelines for HER2 testing have recently been released [46], target identification in candidates for adjuvant trastuzumab should rely on the same criteria used in the adjuvant trials (Table 3).

Risk of relapse

In the randomized adjuvant trials with trastuzumab, the main criteria for the definition of risk of relapse and, consequently, eligibility for adjuvant chemotherapy were tumor diameter, loco-regional lymph nodal status and, in two trials, hormone receptor status combined with tumor diameter (Table 4). Two studies enrolled only women with node-positive breast cancer, whereas the others also enrolled patients with high-risk node-negative breast cancer with some differences in the definition between trials (Table 4). In all the trials that separately reported the effects of trastuzumab according to risk category (i.e., node-positive vs node-negative tumors) no differences were observed in the proportional reduction in tumor-related events, such as relapse or death. This suggests that the benefits of adding trastuzumab to chemotherapy do not depend on the baseline risk profile.

One open question is whether trastuzumab may benefit patients with HER2-positive lymph node-negative tumors smaller than 1 cm ($pT1_{a/b}$), a category that has not been included in adjuvant trials. In the presence of hormone receptor expression and normal HER2 status, these tumors carry a very low risk of relapse, even in the absence of adjuvant medical treatments [47]. However, in HER2-positive tumors, an aggressive underlying biology translates into an increased risk of distant spread, even when tumors are at a very early stage. In fact, retrospective analyses and population-based studies demonstrate that prognosis of smaller HER2-positive $pT1_{a/b}$ breast cancers without lymph node involvement in the absence of trastuzumab treatment is not different from that of pT1c tumors [48–52]. One such study also included patients who had received adjuvant trastuzumab. A large California Cancer Registry was used to compare outcomes of node-negative $pT1_{a/b}$ at two different time points: before and after the introduction of adjuvant trastuzumab [53]. The breast cancer-specific 5-year OS was significantly shortened in HER2-positive breast cancer patients compared with their HER2-negative counterparts in the period between 2000 and 2004. By contrast, there was no significant difference from 2005 to 2007, when patients began to be treated with adjuvant trastuzumab therapy. Obviously, owing to the inherent limitations caused by their design, the results of these studies must be interpreted with caution.

At present, adjuvant trastuzumab is registered in populations defined by the same inclusion criteria used in the adjuvant trials. In the absence of stronger medical evidence regarding $pT1_{a/b}$ tumors, choices should be individualized. Additional variables should be taken into account,

Table 4. Main patients' characteristics in the adjuvant trials.

Feature	NSABP B31	NCCTG N9831	HERA	BCIRG 006	FinHER	PACS-04
Inclusion criteria	Node positive	Node positive High-risk Node negative (T > 2 cm ER and/or PgR positive, or T > 1 cm ER and PgR negative)	Node positive High-risk Node negative (T > 1 cm)	Node positive High-risk Node negative (NA)	Node positive High-risk Node negative (T > 2 cm PgR negative)	Node positive
T < 2 cm	39%	39%	40%	40%	40%	51%
n = 0	0%	12%	32%	29%	10%	0%
n = 1–3	57%	49%	39%	29%	60%	67%
n > 3	33%	39%	33%	28%	30%	33%

BCIRG: Breast Cancer International Research Group; ER: Estrogen receptor; FinHER: Finland Herceptin; HERA: Herceptin Adjuvant; n: Number of positive axillary lymph nodes; NA: Definition not available; NCCTG: North Central Cancer Treatment Group; NSABP: National Surgical Adjuvant Breast and Bowel Project; PgR: Progesterone receptor; T: Tumor diameter.

such as endocrine sensitivity, tumor grade and proliferation index, but also the patient's age and comorbidity.

Cardiac safety

Investigators faced with the design of adjuvant trastuzumab-based experimental arms had to deal with the intrinsic cardiac toxicity of trastuzumab, an issue that had emerged from the early studies in the metastatic setting. When administered alone, trastuzumab is associated with a low rate of cardiac side effects, consisting mainly of asymptomatic and reversible left ventricular ejection fraction (LVEF) dysfunction, occurring especially in patients with prior exposure to anthracyclines and/or with pre-existing cardiovascular risk factors. Concomitant administration of trastuzumab with anthracyclines in the pivotal trial resulted in a concerning increase in the frequency and severity of cardiac toxicity, with a 27% incidence of congestive heart failure [11]. Furthermore, at the time the adjuvant studies were planned no information was available on the long-term consequences of the exposure to trastuzumab on heart function. Consequently, patients enrolled in the adjuvant clinical trial were selected on the basis of cardiac prerequisites that were, in some studies, very strict (Table 5), as were criteria to stop trastuzumab in the case of asymptomatic or symptomatic toxicity (Table 6). All the studies required the baseline LVEF, measured either by ultrasonography or multiple gated acquisition scan, to be above the Institutional lower normal limit, which was usually 50–55%. Regular LVEF monitoring was mandated (every 3 months in most of the trials) in patients remaining asymptomatic during treatment. As a result, in general, the incidence of cardiac events was acceptable across the trials, with differences that merit being discussed (Table 6) [13,17,20,38,54–56].

Table 5. Summary of cardiac eligibility criteria in the published randomized trials.

Criteria	NSABP B31	NCCTG N9831	HERA	FinHER	PACS-04
Angina pectoris requiring medication	X	X	X		
Arrhythmia requiring medication	X	X	X	X	
Severe conduction abnormality	X	X			
Clinically significant valvular disease	X	X	X		
Cardiomegaly on chest x-ray	X	X			
Left ventricular hypertrophy on US	X				
Poorly controlled hypertension	X	X	X	X	
Clinically significant pericardial effect		X			
History of myocardial infarction	X	X	X	X	
History of congestive heart failure	X	X	X	X	X
Cardiomyopathy	X	X			
LVEF prerandomization	Normal (NS)†	Normal (NS)†	≥55%	Normal (NS)	>50%

†If LVEF declined more than 15 percentage points after four cycles of doxorubicin and cyclophosphamide, the patient was not randomized even in the presence of values within the normal range.
FinHER: Finland Herceptin; HERA: Herceptin Adjuvant; LVEF: Left-ventricular ejection fraction; NCCTG: North Central Cancer Treatment Group; NS: Not specified; NSABP: National Surgical Adjuvant Breast and Bowel Project; US: Ultrasonography.

Concomitant administration of trastuzumab with taxanes, after the completion of an anthracycline-based chemotherapy resulted in a slightly higher incidence of cardiac events, compared with sequential administration of single-agent trastuzumab upon the completion of any chemotherapy. However, in the two North American trials, approximately 20% of patients could not start or complete the assigned trastuzumab treatment on account of symptomatic cardiotoxicity, inability to start trastuzumab owing to a LVEF drop after AC, and asymptomatic cardiac toxicity. By contrast, in the HERA trial, only 5.2% of the patients discontinued trastuzumab because of cardiac toxicity.

In the BCIRG 006 study, the omission of anthracyclines resulted in reduced cardiac toxicity in the TCH arm, compared with the AC-TH arm.

A short-term treatment with trastuzumab before anthracycline exposure resulted in a low incidence of symptomatic congestive heart failure in the FinHER trial [18]; however, the small number of patients involved precludes firm conclusions on this subject. The hypothesis that a short exposure to trastuzumab before anthracycline treatment may reduce the incidence of cardiac toxicity is currently being investigated in a prospective trial [57].

In general, the cumulative incidence of cardiac events increased gradually during the scheduled trastuzumab treatment period [54,55,58] and plateaued during follow-up. A practical consequence of this observation is that, while regular cardiac monitoring by LVEF assessment every 3 months is generally advised in patients on treatment, its role during patient follow-up is undefined at present.

Another practical issue is whether the acceptably low rates of cardiac toxicity observed in clinical trials is reproducible in clinical practice, where patients do not represent a strictly selected population such as those enrolled in experimental studies. Indeed, we and others have observed that as many as 12–18% of the patients may need trastuzumab discontinuation even if the cardiologically safer sequential strategy is employed [59,60]. The application of algorithms of trastuzumab discontinuation or prosecution in asymptomatic patients with LVEF drop [56] and the establishment of trastuzumab-based regimens that minimize the risk of cardiac toxicity represent two possible areas of intervention. The anthracycline-free TCH regimen used in the BCIRG 006 study, for example, has been approved by several healthcare systems for use in patients with contraindications to anthracyclines.

Table 6. Summary of cardiac toxicity findings.

Parameter	NSABP B31	NCCTG N9831	HERA	BCIRG 006	FinHER	PACS-04
Stopping criteria	Symptomatic CHF Asymptomatic absolute LVEF decline of >15 percentage points from baseline, or 10–15 percentage points from baseline to below the lower limit of the normal	Symptomatic CHF Asymptomatic absolute LVEF decline of >15 percentage points from baseline, or 10–15 percentage points from baseline to below the lower limit of normal	Symptomatic CHF with a LVEF drop to <45% Symptomatic CHF with an LVEF absolute reduction of ≥10 percentage points from baseline values to <50% Asymptomatic absolute reduction of ≥10 percentage points from baseline values to <50%	NR	Symptomatic CHF Asymptomatic absolute LVEF drop >10 percentage points from baseline	LVEF of <45% ≥15% decrease in LVEF from baseline to between 45 and 50% If the LVEF ranged from 45 to 50% with a relative decline of <15%, or the LVEF ranged from 50 to 55% the cardiologist's advice was sought regarding discontinuation of H
Symptomatic toxicity	AC→P: 0.9% AC→PH→H: 3.8%	AC→P: 0.3% AC→PH→H: 3.8% AC→P→H: 2.8%	1 year of T: 0.8% Observation arm: 0%	AC–T: 0.7% AC–TH→H: 2.0% Cost–effectiveness: 0.4%	CT with T: 0.9% CT without T: 1.7%	CT with T: 1.5% CT without T: 0.4%
Asymptomatic toxicity	AC→P: NR AC→PH→H: 11.7%	AC→P: 0.5% AC→PH→H: 6.6% AC→P→H: 5.05	1 year of T: 3.6% Observation arm: 0.6%	NR	CT with T: 6.8% CT without T: 10.5%	CT with T: 3.8 % CT without T: 0.4 and 1.5%

AC: Doxorubicin-cyclophosphamide; BCIRG: Breast Cancer International Research Group; CHF: Congestive heart failure; CT: Chemotherapy; FinHER: Finland Herceptin; H: Trastuzumab; HERA: Herceptin Adjuvant; LVEF: Left-ventricular ejection fraction; NCCTG: North Central Cancer Treatment Group; NR: Not reported; NSABP: National Surgical Adjuvant Breast and Bowel Project; P: Paclitaxel; PH: Paclitaxel and trastuzumab; T: Docetaxel; TH: Docetaxel and trastuzumab.

Trastuzumab-related cardiac toxicity is usually reversible upon discontinuation of this monoclonal antibody and administration of cardiac medications. However, a significant proportion of patients either do not recover completely, or are required to remain on cardiac therapy for long periods of time [61]. Therefore, involvement of the cardiologist in the management of patients who are candidates to receive trastuzumab treatment to evaluate the patient's cardiac risk profile is a necessary measure to minimize cardiac risk and take proactive measures for patients presenting with risk factors. Furthermore, markers that could help predict patients more likely to develop reversible or irreversible cardiotoxicity are actively studied. An elevation of troponin I during trastuzumab, for example, has been shown to correlate with irreversible trastuzumab-related cardiac toxicity [62].

Another promising approach is the early use of β-blockers and angiotensin-converting enzyme inhibitors to prevent trastuzumab-related cardiotoxicity [63]. By counteracting myocardial remodeling, these drugs have a well-established role in patients with trastuzumab-related cardiac toxicity. A prospective, randomized trial demonstrated that the use of β-blockers and angiotensin-converting enzyme inhibitors administered concomitantly with trastuzumab was associated with a smaller decrease in mean LVEF (4.7 vs 10.3 percentage points; $p < 0.001$) when compared with untreated patients [64].

Interestingly, concurrent administration of conventional anthracyclines resulted in a low incidence of cardiac events in studies conducted in the neoadjuvant setting [65,66]. It is difficult to ascertain whether these low rates of cardiac toxicity are caused by the particular clinical setting or just to accurate selection of patients. Therefore, at present, the concomitant administration of trastuzumab and anthracyclines should not be used in clinical practice or outside the context of clinical trials.

Trastuzumab in the adjuvant setting: timing, scheduling & duration

Timing

Breast cancer is a collection of different biological entities. Biological diversity translates into different clinical behavior [67,68]. For example, the kinetics of relapse (either local or distant) over time after surgery is different according to hormone receptor status. Hormone receptor-positive tumors display a smooth peak of relapse at approximately 3 years after surgery, but as much as 50% of relapses occur beyond 5 years following surgery [69]. By contrast, the hazard for relapse in HER2-positive tumors is higher in the first 2–3 years after surgery and tends to decrease to baseline thereafter [70]. Intriguing observations suggest that HER2-positive cells may be particularly sensitive to growth factors that are produced in response to surgical trauma and scarring, possibly contributing to early relapse [71]. On these premises, it would appear reasonable that trastuzumab treatment should be started as early as possible after the diagnosis of operable, HER2-positive breast cancer. Unfortunately, investigators facing the challenge of designing the randomized trials had to concentrate on safety issues and on the strategy for combining chemotherapy and trastuzumab in experimental arms (concomitant or sequential). Therefore, timing of trastuzumab initiation was the result of the strategy adopted rather than a prespecified research hypothesis.

Trastuzumab was initiated at the end of chemotherapy and, if needed, radiotherapy in the HERA and the PACS 04 trials. The HERA investigators reported a median time between surgery and trastuzumab initiation of 8.4 months (interquartile range of 7.1–9.6 months). This long time period might have impaired trastuzumab efficacy in patients with very aggressive, HER2-positive disease. The timing in the PACS 04 trial was presumably similar, although not specifically reported in the study. As previously illustrated, the PACS 04 study was the only one not demonstrating a trastuzumab-related benefit compared with chemotherapy alone. Obviously, any cross-comparison between these two trials is not appropriate. However, both the HERA and the PACS 04 investigators reported annualized DFS hazard rates for the experimental and the control arms [14,72]. Interestingly, both trials demonstrated that the hazard for patients in the control arms was significantly higher than that of patients receiving trastuzumab over the initial 18–24 months. Afterwards, both hazard curves tended to fall to lower values and to overlap. This confirms that much, if not all, the beneficial effect of trastuzumab in the sequential strategy is limited to the initial months after randomization. In both studies, patients undergoing adjuvant radiotherapy had to complete treatment before initiating trastuzumab therapy. This design was probably adopted to minimize the risk of increased treatment-related toxicities. This risk is suggested by preclinical evidence demonstrating that x-ray exposure of breast cancer cells can induce HER2 overexpression [73]. Furthermore, DNA repair mechanisms

have been demonstrated to be impaired when HER2-positive MCF-7 cells and *in vivo* experimental tumors are exposed to trastuzumab and concurrent irradiation [31]. However, an analysis of the NCCTG N9831 study, where radiotherapy and trastuzumab were administered concomitantly, did not reveal an increase in the incidence of acute adverse events [74]. Based on these results, there would be no reason to delay the administration of trastuzumab to allow completion of adjuvant radiotherapy.

In the NSABP B31 study, and in the concomitant arms of the NCCTG N9831 and BCIRG 006 studies, trastuzumab was started approximately 3 weeks after the final administration of doxorubicin and cyclophosphamide. The median interval from surgery and trastuzumab was approximately 4 months. In the FinHER trial and in the docetaxel plus carboplatin arm of the BCIRG 006 trial, trastuzumab was initiated a few weeks after surgery. Any attempts at evaluating how early initiation in these trials could have affected results or considering initiating trastuzumab even earlier, before surgery in the context of a neoadjuvant regimen, would be purely speculative. However, the BCIRG 006 trial does not demonstrate an advantage of docetaxel plus carboplatin over AC-TH. In fact, the data suggest a slight superiority, if any, of AC-TH over docetaxel plus carboplatin [20].

Chemotherapy & schedule

The high rates of tumor response yielded by associations of trastuzumab with paclitaxel, vinorelbine or platinum salts were anticipated on the basis of preclinical synergism [26,75]. Furthermore, while single-agent trastuzumab seems to have a cytostatic effect, its combination with chemotherapy results in enhanced cell killing [76]. Furthermore, HER2-positive tumors are sensitive to anthracyclines [77,78]. Investigators in the NSABP-B31, NCCTG N9831, BCIRG 006 and FinHER studies realized these concepts and established experimental trastuzumab-containing regimens in which this antibody was administered concomitantly with taxanes or vinorelbine. Anthracyclines were included in all of these studies with the exception of the docetaxel plus carboplatin arm of the BCIRG 006 study. Anthracycline and taxane-containing combinations, where trastuzumab was administered concomitantly with taxanes, achieved the highest reductions in the risk of relapse and death over each respective comparator (Table 2). In addition, in the FinHER study, patients receiving vinorelbine and trastuzumab had no benefit compared with patients receiving vinorelbine alone before 5-fluorouracil plus epirubicin plus cyclophosphamide. By considering these results it would appear that, in patients with HER2-positive operable breast cancer, the efficacy of trastuzumab can be maximized when optimal chemotherapy is chosen and when this monoclonal antibody overlaps with taxanes. The results of the HERA trial challenge this conclusion because the choice of the type of chemotherapy and number of cycles was left to the discretion of the investigator, and because trastuzumab was not administered concomitantly with chemotherapy. Despite these profound differences in scheduling, the initial analyses of clinical outcomes confirmed reductions in the hazard of relapse that were similar to those reported by the other large trials (Table 2). However, it is worth noting that longer follow-up of the HERA trial demonstrated a smaller reduction in the hazard of relapse compared with the initial results. Furthermore, in a subset analysis presented at the time of the initial publication, a total of 873 patients received a taxane- and an anthracycline-containing neoadjuvant or adjuvant regimen. While the overall HR for relapse was 0.54, in patients receiving anthracycline and taxanes, the HR for relapse was 0.77 (95% CI: 0.53–1.16). Intriguingly, this HR is similar to that of the sequential arm of the NCCTG N9831 trial (0.70; 95% CI: 0.57–0.86) and only slightly better than that of the PACS 04 trial (0.86; 95% CI: 0.61–1.22). In our opinion, these HRs suggest that trastuzumab may lose part of its therapeutic efficacy when administered sequentially following the completion of anthracycline- and taxane-based adjuvant chemotherapy.

Duration

Most of the patients enrolled in the adjuvant clinical trials received 1 year of trastuzumab. While in the metastatic setting there is a general consensus that trastuzumab should be continued at least until tumor progression or unacceptable toxicity, there is no specific rationale to decide its duration in a patient who has undergone curative surgery. Therefore, the choice of 1 year was empirical and leaves an open question regarding whether different durations may be associated with similar or improved outcomes. The HERA study included a third arm evaluating 2 years of trastuzumab, but results are not available yet. On the other hand, the results of the FinHER trial, where shorter duration (9 weeks) and concomitance with chemotherapy provided improvements in clinical outcomes in the range

Table 7. Estimates of the incremental cost–effectiveness ratio of trastuzumab for early breast cancer.

Study	Source of data	Treatment effect	Estimated carryover benefit	ICER	Ref.
NICE, UK (trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer)	HERA trial at 1 year	HR: 0.54	5 years	£18,000/QALY	[108]
Liberato *et al.*	HERA trial at 1 year	HR: 0.54	5 years	€11,228/QALY and US$16,199/QALY	[79]
Liberato *et al.*	NSABP B31-NCCTG N9831 at 2 years	HR 0.48	5 years	€14,861/QALY and US$18,970/QALY	[79]
Kurian *et al.*	NSABP B31-NCCTG N9831 at 2 years	NR	2 years	US$39,982/QALY	[80]
Garrison *et al.*	NSABP B31-NCCTG N9831 at 2 years	NR	5 years	US$34,201/QALY	[81]
Skedgel *et al.*	HERA trial at 2 years	RR: 0.754	5 and 3 years	CAN$70,292/QALY (5 years), CAN$127,862/QALY (3 years)	[82]
Lidgren *et al.*	HERA trial at 2 years	HR: 0.64	Lifetime and 5 years	€36,000/QALY €66,800/QALY (3 years)	[83]
Shiroiwa *et al.*	HERA trial at 2 years	HR: 0.64	5 years	€17,000/life-year gained	[84]
Dedes *et al.*	FinHER Median FU of 3 years	HR: 0.42	5 years	Cost saving	[85]
Neyt *et al.*	FinHER Median FU of 3 years	HR: 0.42	Lifetime	€668/life-year gained (stage I) Cost saving (stage II and III)	[86]

FinHER: Finland Herceptin; FU: Follow-up; HERA: Herceptin Adjuvant; HR: Hazard ratio; ICER: Incremental cost–effectiveness ratio; NCCTG: North Central Cancer Treatment Group; NR: Not reported; NSABP: National Surgical Adjuvant Breast and Bowel Project; QALY: Quality-adjusted life-year; RR: Relative risk.

of those reported by larger trials, were provocative. Two randomized trials, the Synergism Or Long Duration (SOLD) trial [101] and the ShortHER trial [102], are currently comparing 9 weeks versus 12 months of adjuvant trastuzumab and are based on the FinHER observation. Furthermore, the Protocol of Herceptin Adjuvant with Reduced Exposure (PHARE [103] and the Persephone [104] trials are currently comparing 6 versus 12 months of adjuvant trastuzumab. These are large-scale clinical trials with a planned accrual of several thousand patients and will hopefully provide an answer to the issues regarding the duration of treatment with trastuzumab.

Conclusion & future perspective

Trastuzumab has represented a major step forward in the treatment of HER2-positive breast cancer. Its use in patients with operable disease increases the cure rate over chemotherapy alone. However, after an effort that has involved several thousand women in prospective clinical trials, some questions on its optimal use are still open. Owing to its favorable toxicity:benefit ratio, trastuzumab should be part of the adjuvant treatment of all patients with HER2-positive operable breast cancer at risk of relapse. However, recent results from the adjuvant trials demonstrate that the choice of the chemotherapy regimen, the timing of trastuzumab administration and its scheduling are also critical on both efficacy and toxicity. The most significant example is represented by the sequence of doxorubicin and cyclophosphamide followed by trastuzumab administered concomitantly with either paclitaxel or docetaxel. This strategy seems to be one of the most active in the clinical trials. However, a significant proportion of patients in the NSABP B31 and NCCTG N9831 had to discontinue

treatment on account of either symptomatic or asymptomatic cardiac toxicity. Considering that patients in these trials were accurately selected on the basis of cardiac prerequisites, the rates of patients not receiving the intended treatment in clinical practice may be even higher. The optimization of the use of trastuzumab in operable patients is necessary considering how trastuzumab impacts on healthcare resources. Table 7 summarizes studies analyzing the cost:benefit ratio of adjuvant trastuzumab using the results from randomized trials. There is a general consensus that the increased costs are within commonly accepted thresholds. However, a wide variability exists depending primarily on projected long-time efficacy and duration of trastuzumab. Establishing optimal duration, improving on adherence of patients to the planned schedule of trastuzumab by reducing cardiac toxicity and studying alternative strategies in patients at a lower risk of relapse would likely result in an improvement in the cost–effectiveness of adjuvant trastuzumab.

While most of these relevant clinical issues are still just a matter of discussion, research in the field of HER2-positive disease is rapidly moving forward. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) [105], Neoadjuvant (NEO)-ALTTO [106] and NSABP-B44 trials [107], just to cite a few, are evaluating the inclusion of newer biologically targeted therapies, such as the dual tyrosine kinase inhibitor lapatinib or the monoclonal antibody directed against VEGF, bevacizumab, in adjuvant chemotherapy programs. These trials are planned to accrue several thousands of patients and some have completed patient recruitment. Results of these trials will clarify whether the prognosis of patients with HER2-positive operable

Executive summary

Mechanism of action

- Trastuzumab is a humanized monoclonal antibody of the IgG1 type.
- It binds to an epitope on the extracellular portion of the HER2 tyrosine-kinase receptor.
- The exact mechanism accounting for HER2's antitumor activity is not presently known. It may act by triggering antibody-dependent cell cytotoxicity or by inhibiting the downstream signaling of HER2.

Pharmacokinetics

- Trastuzumab is administered intravenously. Two schedules are commonly accepted: a loading dose of 4 mg/kg of bodyweight, followed by weekly doses of 2 mg/kg; or a loading dose of 8 mg/kg of bodyweight, followed by 3-weekly doses of 6 mg/kg.
- The trastuzumab concentration in plasma achieved with this scheduling is well beyond the concentration that has been demonstrated to cause maximal tumor growth inhibition in preclinical models.

Clinical activity

- As a single agent in metastatic breast cancer patients, selected on the basis of HER2 overexpression or *HER2* gene amplification, trastuzumab induces tumor regression in approximately 25% of cases.
- In combination with chemotherapy, in particular with taxanes, response rates to trastuzumab have been observed as high as 70%. Furthermore, compared with chemotherapy alone, it prolongs progression-free and overall survival.
- Trastuzumab has modest intrinsic cardiotoxicity, which is enhanced when it is administered with anthracyclines.

Use in the adjuvant setting

- Six randomized trials accruing approximately 16,000 women with HER2-positive operable breast cancer have demonstrated that the addition of trastuzumab to chemotherapy reduces the hazard of relapse by 36% and of death by 34%.
- The clinical trials differed in design and in the strategy of combining trastuzumab with chemotherapy.

Candidates for adjuvant trastuzumab

- Patients with HER2-positive breast cancer, whose risk of relapse is defined by positive axillary lymph node status, or by a tumor diameter larger than 1 cm are strong candidates for adjuvant trastuzumab.
- A possible benefit from trastuzumab has also been suggested in patients with smaller tumors, but no prospective data on the risk:benefit ratio are available in these patients.
- Patients with no major cardiac comorbidities are also good candidates.

Optimal scheduling

- Current data point toward a possible superiority of regimens of anthracycline followed by taxanes, with trastuzumab therapy initiated concomitantly with taxanes.
- A taxane-based, anthracycline-free regimen used in one of the trials is a promising alternative and is associated with reduced cardiac toxicity.
- The conventional duration of adjuvant trastuzumab therapy is 1 year.

Future developments

- Studies are ongoing to determine whether shorter or longer duration of treatment may yield different results.
- Newer biologically targeted agents are being actively investigated to evaluate whether the prognosis of HER2-positive operable breast cancer patients can be further improved.

breast cancer can be improved beyond what is achieved with the addition of trastuzumab to adjuvant chemotherapy.

Financial & competing interests disclosure

Filippo Montemurro has received honoraria from GlaxoSmithKline SPA, the manufacturer of lapatinib, for scientific lectures. This collaboration does not have any direct relevance to the content of this manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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