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Herceptin®: the future in adjuvant breast cancer therapy

Martine J Piccart-Gebhart
Chemotherapy Unit, Institut Jules Bordet, 1000 Brussels, Belgium.

New drugs for the treatment of breast cancer are generally introduced into clinical practice in the metastatic setting. However, it is well known that therapeutic response improves when drugs are used earlier in the disease. Therefore, once drugs have shown a major therapeutic impact in the metastatic setting, investigation in the adjuvant setting should be prioritized. Herceptin® has shown significant efficacy and an ability to extend survival in human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer patients and is well tolerated. Four major randomized, multicenter adjuvant clinical trials of Herceptin® in patients with HER2-positive primary breast cancer have been started or are planned. The designs of these trials are described. With a total of over 12 000 patients, these studies should provide the information necessary to confirm the clinical potential of Herceptin® as adjuvant therapy. The inclusion of a variety of regimens, including different durations of Herceptin® therapy in the Herceptin® Adjuvant (HERA) Trial, will allow the optimal therapeutic approach to be identified, and the size and generally pragmatic designs should encourage clinicians to enroll patients. The establishment of the role of Herceptin® in the adjuvant setting will offer women with HER2-positive primary breast cancer the chance for improved survival. This is particularly important given that HER2-positive breast cancer patients form a high-risk group with a poor overall prognosis. [© 2001 Lippincott Williams & Wilkins.]

Key words: Adjuvant therapy, breast cancer, clinical trials, HER2, Herceptin®.

Correspondence to MJ Piccart-Gebhart, Chemotherapy Unit, Institut Jules Bordet, Rue Héger-Bordet 1, 1000 Brussels, Belgium.
Tel: (+32) 2 541 3111; Fax: (+32) 2 538 0858;
E-mail: mpiccart@ulb.ac.be

Introduction

Amplification of the human epidermal growth factor receptor-2 (HER2) gene and subsequent overexpression of the encoded protein are known to be early events in breast cancer pathogenesis,[1–3] with up to 60% of ductal carcinomas *in situ* being HER2-positive.[4,5] HER2 gene amplification has been implicated in malignant transformation, tumorigenesis and the acquisition of aggressive growth characteristics by preclinical studies,[6–10] and appears to play a significant role in the development of breast cancer.[11] These and other observations regarding the prognostic and predictive value of HER2[12,13] have led to the development of the humanized anti-HER2 monoclonal antibody Herceptin®.

Herceptin® has been approved in many countries for the treatment of women with HER2-positive metastatic breast cancer based on data from pivotal clinical trials showing that: women with HER2-positive metastatic breast cancer who received Herceptin® in combination with chemotherapy achieved a 50% response rate compared to 32% for those receiving chemotherapy alone;[14,15] women who received Herceptin® in addition to chemotherapy lived on average 25% longer than those who received chemotherapy alone;[16] Herceptin® is effective as monotherapy, producing durable responses;[17] and that Herceptin® is well tolerated and does not produce the dose-limiting adverse events that are typical of cytotoxic chemotherapy.[16,17]

The introduction of Herceptin® in the metastatic setting is typical of anticancer drug development and is designed to ensure that the effect of any unexpected toxicity is minimized. This underestimates the true benefit of new therapies because it is well known that response to therapy improves when drugs are used earlier in the disease. For this reason, it is widely believed that the full benefits of recently introduced chemotherapeutic agents and hormonal therapies in the adjuvant setting have not yet been realized.[18,19] However, there can be little doubt that there has been significant progress in adjuvant therapy of breast

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cancer over the last two decades: the collaborative Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis[20] has confirmed the ability of adjuvant hormonal or cytotoxic therapy to increase disease-free and overall survival. These treatments in combination with surgical and radiotherapy have become integrated into modern adjuvant treatment algorithms.[21,22] However, considerable scope for improvement of efficacy remains despite these advances and trials to investigate the potential for adjuvant therapy using these agents continue.[22,23]

As outlined above, it is reasonable to expect that therapy targeting HER2 will have clinical benefit when used as adjuvant therapy. When attempting to demonstrate the utility of new drugs such as Herceptin® in the adjuvant setting, a number of considerations need to be addressed: the need for potentially effective drugs to be introduced as early as possible, the need for trials that are designed so that the most useful outcomes are studied and the need for large trials that are powered to show clinically relevant differences between therapies.[23] Recently initiated trials as well as several that are in an advanced stage of planning will investigate the efficacy and safety of Herceptin® in adjuvant breast cancer therapy. These trials, which are described below, have been designed in such a way that data regarding the utility of Herceptin® in the treatment of primary breast cancer should be available as early as possible.

Trials in adjuvant breast cancer

Four major adjuvant trials in breast cancer will examine the role of Herceptin® in the prevention of disease recurrence. Two of these trials [National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and Intergroup Trial N9831] are being conducted in North America and both are examining how to use Herceptin® with the American standard treatment regimen of anthracycline/cyclophosphamide followed by a taxane. This approach to adjuvant therapy is widely accepted in North America based on trial data published by Henderson *et al.*[24] and the involvement of most major institutions in this trial. However, this approach is not standard outside of the US. The international Breast Cancer International Research Group (BCIRG) 006 Trial (involving North America, Europe and elsewhere) is in the late planning stages, as is the Herceptin® Adjuvant (HERA) Trial [Breast International Group (BIG)/Roche] that will involve many countries outside North America. These latter two trials will study adjuvant regimens other than those being investigated in the NSABP and Intergroup trials. All four of these trials are described below.

NSABP B-31 Trial

The design of the NSABP B-31 Trial is shown in Figure 1. This US National Cancer Institute (NCI)-sponsored phase

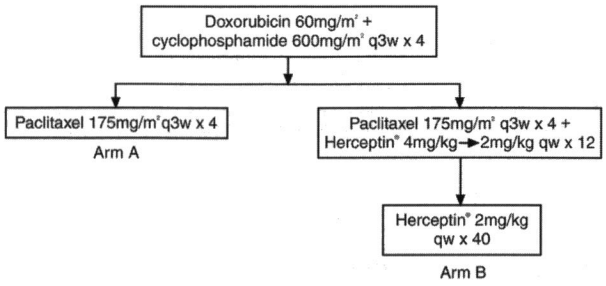

Figure 1. Study design for NSABP Trial B-31.

III trial is being conducted at more than 100 centers across the USA and Canada. It will assess the efficacy and safety of the combination of Herceptin® and chemotherapy in the treatment of 2700 patients with node-positive breast cancer whose tumors overexpress the HER2 protein by immunohistochemistry (IHC) or demonstrate HER2 gene amplification by fluorescence *in situ* hybridization (FISH). The protocol is being conducted in two stages.

Stage 1 will evaluate 1000 patients for cardiac safety and compare the toxicity of adding weekly Herceptin® to adjuvant paclitaxel following doxorubicin/cyclophosphamide with that of the same regimen without Herceptin®. If the drug-related adverse effects are determined to be acceptable, the study will progress to Stage 2. This second stage will accrue an additional 1700 patients and will study the efficacy of adding Herceptin® to the standard chemotherapy regimen of doxorubicin/cyclophosphamide followed by paclitaxel in prolonging overall and disease-free survival.

Women with node-positive, HER2-positive breast cancer who are operable with either lumpectomy plus irradiation or mastectomy will be recruited. There must be no evidence of metastatic disease. HER2 positivity will be defined as a confirmed score of 3+ by IHC and/or a positive FISH test. Cardiac function will have to be normal at baseline as assessed by multigated radionuclide angiography (MUGA) scan and there must be no history of cardiac disease. Cardiac safety will be analyzed after accrual of 200, 600 and 1000 patients.

Patients are initially treated with a combination of doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 i.v. every 3 weeks for 4 courses. The patients are then randomized to either paclitaxel (175 mg/m^2 i.v. every 3 weeks for 4 courses) alone or in combination with Herceptin® (4 mg/kg i.v. initial dose followed by 2 mg/kg weekly) after stratification for number of positive nodes, type of surgery (lumpectomy, mastectomy), tamoxifen administration and choice of radiotherapy. Weekly Herceptin® administration will be continued for a total of 52 weeks (12 weeks in combination with paclitaxel and 40 weeks alone). Patients in either treatment arm whose tumors are estrogen receptor (ER)- or progesterone-receptor (PgR)-positive will also receive tamoxifen (20 mg/day) for 5 years. Tamoxifen is

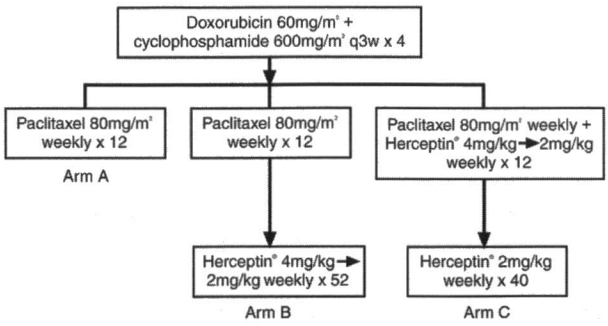

Figure 2. Study design for Intergroup Trial N9831.

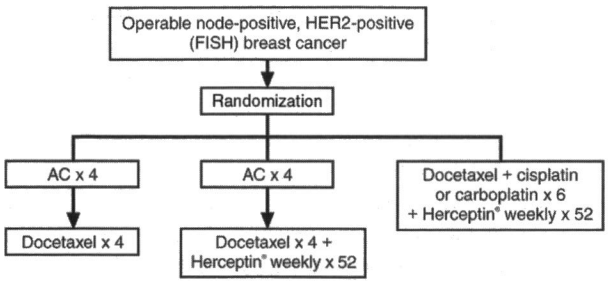

Figure 3. Study design for BCIRG Trial 006.

optional for those with ER- or PgR-negative tumors. The primary endpoints of the trial will be overall survival and safety.

Currently (as of May 2001), 457 of the planned 2700 patients have been recruited. It is estimated that complete accrual will take about 4.75 years and patients will be followed for a further 5 years.

Intergroup Trial N9831

The Intergroup Trial N9831 is also an NCI-sponsored phase III trial with a similar design and protocol to that of the NSABP trial. The treatment protocol is summarized in Figure 2. The primary differences are that paclitaxel is administered on a weekly schedule rather than a 3-weekly schedule, and that administration of Herceptin® both in combination with and following paclitaxel will be investigated. The weekly schedule for paclitaxel coincides with the currently recommended standard regimen of weekly Herceptin®. The study has the following objectives: to compare the disease-free survival of HER2-positive breast cancer when treated with doxorubicin/cyclophosphamide followed by paclitaxel with or without Herceptin®; to compare the cardiotoxicities of these treatments in these patients; to compare overall survival of these patients when treated with one of these regimens; to determine whether higher circulating levels of the extracellular domain of HER2 ($HER2^{ECD}$) or autoantibodies to HER2 and HER1 prior to treatment predict for disease-free and overall survival in these patients; and to determine the concordance of HER2 overexpression with disease-free and overall survival in this patient population.

Women with node-positive, HER2-positive breast cancer who are operable with either lumpectomy plus irradiation or mastectomy will be recruited. HER2 status has to be confirmed by a IHC 3+ and/or positive FISH test result. Patients with evidence of metastatic disease or cardiac disease are not eligible. Intergroup Trial N9831 is a randomized, multicenter study expected to recruit a total of 3000 patients over 4.5 years.

Before randomization, patients are stratified by number of positive lymph nodes (axillary dissection with 1–3 versus 4–9 versus ≥10 nodes versus positive sentinel node with no axillary dissection) and receptor status (ER- or PgR-positive versus other). All patients will receive initial treatment with doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 i.v. every 3 weeks for 4 courses. They will then be randomized to one of three treatment arms. The first arm will receive paclitaxel 80 mg/m^2 i.v. weekly for 12 weeks. The second arm will receive the same paclitaxel dose which will be followed immediately by Herceptin® (4 mg/kg initial dose i.v. followed by 2 mg/kg weekly) for a total of 52 weeks. The third arm will receive paclitaxel and Herceptin® concurrently for 12 weeks, with Herceptin® continued alone for a further 40 weeks. All ER- and PgR-positive patients will receive oral tamoxifen daily for 5 years, starting no later than 5 weeks after the last dose of paclitaxel. Follow-up for up to 15 years is planned.

This study will therefore address several key questions. It will determine the role of weekly paclitaxel in adjuvant breast cancer treatment and the impact of Herceptin® on survival. Additionally, it will determine whether a 3-month delay between doxorubicin exposure and Herceptin® therapy decreases the incidence of potential cardiotoxicity. As of May 2001, 242 patients had been enrolled.

BCIRG 006 Trial

The design of the BCIRG 006 Trial is shown in Figure 3. This trial is starting accrual (four patients enrolled in the US as of May 2001) and it is intended that operable, node-positive, HER2-positive breast cancer patients will be recruited. HER2 positivity will be determined by FISH analysis of HER2 gene amplification. Approximately 3000 patients will be randomized to three arms. One arm will receive anthracycline/cyclophosphamide for 4 courses followed by docetaxel for 4 courses. The second arm will receive the same therapy but with the addition of Herceptin® (4 mg/kg initial dose i.v. followed by 2 mg/kg weekly) for a total of 52 weeks, with the initial doses being administered concomitantly with docetaxel. The third arm will not receive anthracycline/cyclophosphamide, but will immediately

receive docetaxel plus cisplatin or carboplatin for 6 courses with concurrent Herceptin® given for a total of 52 weeks.

The design of the BCIRG trial is controversial in that platinum analogs are not widely used in the treatment of breast cancer due to their toxicity. Preclinical data, however, indicate that Herceptin® has significant synergy with these agents[25] and some of the early trials of Herceptin® in metastatic breast cancer indicated that the combination has activity.[26] Preliminary reports of two open-label pilot phase II trials (BCIRG 101 and 102) examining docetaxel plus cisplatin (BCIRG 101) or carboplatin (BCIRG 102) plus Herceptin® suggest that the combination is active (response rates above 70% based on analysis of approximately 50% of patients in these trials) and that toxicity is characteristic of these agents used alone with no exacerbation of side effects.[27]

HERA Trial

In contrast to North America, in Europe and the rest of the world there is not one standard approach to adjuvant therapy for breast cancer. This is partly due to a more conservative approach to accepting that the anthracycline/cyclophosphamide followed by taxane strategy is most effective, particularly with the publication of data suggesting that adding taxanes to anthracycline/cyclophosphamide may not produce a sustained improvement in survival.[28] This lack of acceptance and the absence of pan-European cooperative groups is reflected in the ongoing research activity in adjuvant breast cancer in Europe: over 25 different treatment schedules are currently being examined in about 85 clinical trials (Piccart M, Goldhirsch A. unpublished observation). In an effort to reduce wasteful duplication of efforts and to encourage collaboration for difficult/high-priority trials, a consortium of breast cancer adjuvant study groups was formed 4 years ago. The BIG has members from throughout Europe as well as Canada, Australia, New Zealand, South Africa and South America. The BIG is planning the multicenter, randomized phase III HERA Trial in collaboration with Roche.

The HERA Trial, which became active in October 2001, will recruit over 3200 women with HER2-positive primary breast cancer. The study design is such that following primary chemotherapy, patients will be randomized to treatment with Herceptin® for either 1 or 2 years (8 mg/kg initial dose i.v. followed by 6 mg/kg 3-weekly) or to observation (for design, see Figure 4). The primary objective will be to compare disease-free survival between the 1-year Herceptin® and observation groups, and between the 2-year Herceptin® and observation groups. Secondary objectives will include: overall survival, cardiac safety, overall safety, recurrence-free survival, and a comparison of all outcomes in the 1- and 2-year Herceptin® groups.

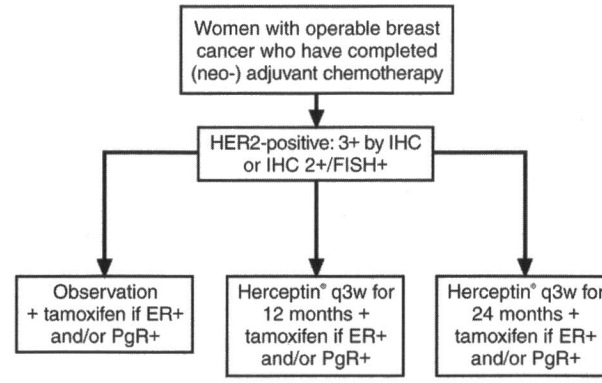

Figure 4. Study design for the HERA Trial.

Patients will be accrued to the HERA Trial over about 4 years. HER2 positivity will be defined as a 3+ score on IHC or a positive FISH test. All patients must have had their primary breast cancer adequately excised and have completed radiotherapy if indicated. A baseline left ventricular ejection fraction (LVEF) above 55% following chemotherapy and radiotherapy is required. As there is wide variation in accepted management practices between the participating countries and even centers within a country, patients treated using most neo-adjuvant and adjuvant chemotherapy regimens will be eligible, with a restriction on cumulative anthracycline dose prior to Herceptin® (<360 mg/m^2 doxorubicin or <720 mg/m^2 epirubicin). Stratification following chemotherapy but prior to randomization will be performed based on number of positive nodes, type of chemotherapy, receptor status and endocrine therapy and age. ER- and/or PgR-positive patients will receive oral tamoxifen or standard hormonal therapy according to individual center policy.

This trial has several interesting features. The first is the pragmatic approach to prior chemotherapy allowed. It is hoped that allowing patients who have received any standard adjuvant chemotherapy regimen will ensure rapid recruitment, that as many centers from as many countries as possible are involved, and that Herceptin® is shown to be generally active and well tolerated following any type of adjuvant chemotherapy. To this end, allowed prior chemotherapy regimens include non-anthracycline-based, e.g. CMF (Bonnadonna regimen, 6–9 cycles of a regimen in which cyclophosphamide is administered i.v. or 3 cycles of a regimen including oral cyclophosphamide in women aged >65 years), anthracycline-based (including FAC/CAF × 6–8, FEC/CEF × 6–8, AC/EC × 4–6, AC/EC or A/E × 4 followed by CMF × 3 or 4), anthracyclines combined with/followed by taxane-based regimens (AC × 4 followed by taxane × 4–6, AT/ET × 4–6, TAC × 4–6 or FAC/FEC × 4 followed by taxane × 4) and any other regimen that is part of an approved chemotherapy trial.

Another interesting feature of the trial is the use of a 3-weekly Herceptin® regimen. The current standard regimen of Herceptin® in metastatic breast cancer is an initial dose of 4 mg/kg i.v. followed by subsequent weekly administration of 2 mg/kg i.v. until disease progression. However, in the adjuvant setting, where women are often asymptomatic, this frequency of administration may result in non-compliance with long-term therapy. The use of 3-weekly Herceptin® is therefore considered more attractive in the adjuvant setting and is being investigated in ongoing clinical trials.

Phase I/II trials of Herceptin® using fixed single and multiple doses of the drug[26,29] indicated that Herceptin® doses of between 100 and 500 mg produced minimum serum trough concentrations of 50–55 μg/ml, were well tolerated and had antitumor activity. Furthermore, serum half-life increased from 1.1 to 23 days as the dose of Herceptin® increased. On the basis of these data and considerations of adjusting dose based on body weight, an initial dose of 4 mg/kg with subsequent weekly doses of 2 mg/kg was chosen for use in the pivotal clinical trials of Herceptin®,[14–17] in which the significant clinical benefit of Herceptin® was demonstrated, and is the currently accepted schedule in clinical practice. This dose schedule produced mean steady-state serum Herceptin® concentrations of about 60 μg/ml when Herceptin® was administered as monotherapy.[17] Based on the pharmacokinetic and clinical data outlined above, administering Herceptin® at higher doses than were used in the pivotal trials would allow a longer dose interval to be used with good tolerability while maintaining serum concentrations similar to those observed in the pivotal clinical trials.

These considerations have led to the initiation of a trial to examine the pharmacokinetics and safety of 3-weekly Herceptin® in combination with paclitaxel, also administered every 3 weeks.[30,31] Herceptin® is administered as an initial i.v. dose of 8 mg/kg followed by 6 mg/kg every 3 weeks in combination with paclitaxel 175 mg/m^2 every 3 weeks. To date, 32 patients have been enrolled and pharmacokinetic and safety data have been reported. These data indicate that the 3-weekly Herceptin® regimen produces mean serum trough concentrations similar to those observed when weekly Herceptin® was administered in combination with 3-weekly paclitaxel in the pivotal phase III trial. As expected, peak serum Herceptin® concentrations are higher and the half-life is longer (27 days) than those in the pivotal phase III trial.[32] Hematologic side effects observed to date are typical of paclitaxel, and non-hematologic side effects are typical of the known toxicities of Herceptin® and paclitaxel. Furthermore, cardiotoxicity has so far occurred rarely, with New York Heart Association grade II heart failure (slight limitation of physical activity, but comfortable at rest) affecting only one patient.

These data support the use of the 3-weekly Herceptin® regimen in the HERA Trial. It is expected that the regimen will be well tolerated, and the similarity in serum Herceptin® concentrations with 3-weekly and weekly dosing suggests that efficacy may be similar.

A further unique feature of the HERA Trial is the comparison of two durations of Herceptin® therapy. Whereas the NSABP, Intergroup and BCIRG trials are all examining Herceptin® administered for 1 year, either alone or in combination with chemotherapy, patients receiving Herceptin® in the HERA Trial will receive the drug for either 1 or 2 years. This design will provide additional data regarding duration of therapy and is based on a number of observations. First, withdrawal of Herceptin® is associated with rapid tumor regrowth in preclinical studies.[32] Second, data from trials in metastatic breast cancer suggest that the efficacy of therapy improves when Herceptin® is used for extended periods.[33] Finally, data indicate that breast cancer recurrence shows two peaks at between 1 and 2 years and at 5 years after adjuvant therapy.[34] Given the likelihood that HER2-positive breast cancers contribute to the first peak, it will be interesting to determine whether extending the duration of Herceptin® therapy in the adjuvant setting has significant effects on survival.

Conclusions

Evidence that the introduction of anthracyclines has improved outcomes in women with primary breast cancer, together with data indicating that adding hormonal therapy to chemotherapy reduces relapse rates and that a regimen of anthracycline/cyclophosphamide followed by a taxane may provide additional benefit, indicate that continuous progress is being achieved in the treatment of early breast cancer. However, the identification of therapies that are more effective, better tolerated and acceptable to patients remains a priority, particularly for high-risk patient groups. HER2-positive patients are known to have significantly reduced disease-free and overall survival, and to show altered responses to some standard therapies, including hormonal therapy and anthracyclines. Furthermore, HER2 gene amplification/protein overexpression is known to be an early event in breast cancer development with a role in oncogenesis. HER2 oncogene targeting using the humanized anti-HER2 monoclonal antibody Herceptin® has proven efficacy in HER2-positive metastatic breast cancer patients. Herceptin® is an ideal agent for study in the treatment of primary breast cancer based on these features and particularly its tolerability. This has led to the design and initiation of a number of trials of Herceptin® as adjuvant therapy.

The designs of the recently started and soon to be initiated randomized, multicenter clinical trials of Herceptin® in the adjuvant treatment of primary breast cancer

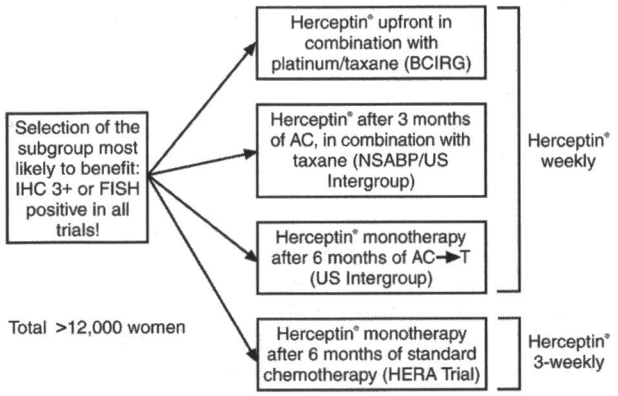

Figure 5. Overview of major trials of Herceptin® in the adjuvant treatment of HER2-positive primary breast cancer.

discussed above are summarized in Figure 5. These trials will take several years to accrue the large numbers of patients that are necessary to provide the statistical power to detect clinically relevant results, although it is likely that preliminary safety data will be available within 12 months. The pragmatic design of the trials and the involvement of major cooperative groups will ensure that accrual is as rapid as possible. Furthermore, the long duration of follow-up required to provide statistically robust data on the major endpoints of disease-free and overall survival will be supported by the involvement of the cooperative groups.

The protocols of the four trials discussed here are flexible enough to allow the inclusion of the different regimens that are used in different regions and institutions to treat primary breast cancer. This pragmatic approach should encourage physicians to enroll patients in these trials. Furthermore, it will demonstrate which agent(s) is most effective when used either in combination with or prior to Herceptin® in the adjuvant setting and will provide important information regarding the safety of Herceptin®. Another interesting aspect of these trials will be the opportunity to assess the efficacy and safety of the 3-weekly Herceptin® regimen, as well as its potential to improve patient convenience and compliance. Finally, data regarding the optimal duration of Herceptin® therapy will be produced.

It is believed that these four major trials will, in the most timely manner possible, clarify the role of Herceptin® in the adjuvant setting with the hope of offering women with HER2-positive primary breast cancer the chance for improved survival.

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