CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER: CASE 10107

STUDY TITLE: Safety and Efficacy of Single Agent Adjuvant Trastuzumab (Herceptin®) in Older Women with Early-Stage and Locally Advanced Breast Cancer: A Phase II Trial

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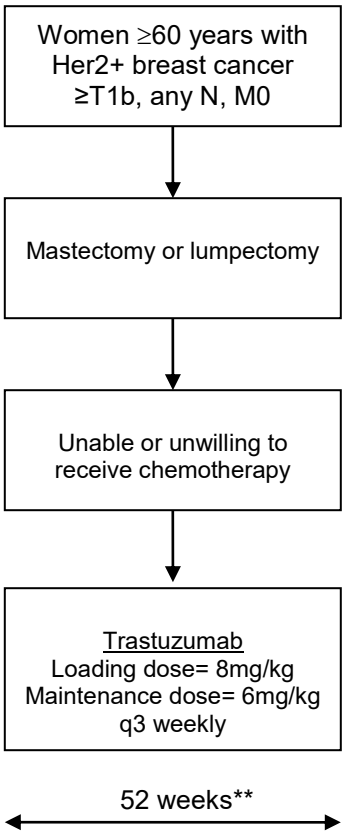
TABLE OF CONTENTS

TABLE OF CONTENTS (cont'd)

TABLES AND FIGURES

APPENDICES

STUDY SCHEMA



**Adjuvant radiation therapy and endocrine therapy may be given as per institutional standard during this period

1. INTRODUCTION

1.1 BACKGROUND

Persons 65 years and older are the fastest growing segment of the population in America and by 2030 will account for 20% of the US population.[1,2] They however bear a disproportionate burden of the incidence and mortality of cancer and account for more than 50% of all new cancers that occur in the US including breast cancer.[2,3] Because the most important risk factor for breast cancer is age and because of recent gains in life expectancy, these proportions are expected to increase. Unfortunately older cancer patients are more likely to receive sub-optimal cancer treatment[4-6], and are consistently under-represented in clinical trials of new cancer therapies.[7,8] With the dramatic shift in the demographics of the aging population it is imperative that treatment strategies tailored to the needs of the older cancer patients are developed.

Evaluation of the biology of breast cancer by age has suggested that estrogen–receptor positive, low S phase, low tumor grade and Her-2 negative tumors are more common among older than younger women.[9-11] Inspite of this favorable tumor profile and recent advances in breast cancer therapy this has not translated into any major survival advantage for older women with breast cancer as compared with their younger counterparts.[12] There is evidence that receipt of sub-optimal treatment by older women may be contributing to this poor outcome.[4] In addition there is a reluctance among clinicians to include older women in breast cancer clinical trials.[8] Under-representation has been found to be particularly striking in Southwest Oncology Group (SWOG)` breast cancer trials, with the percentage of elderly patients participating in SWOG trials and the general population being nine percent and 49%, respectively.[13]This has led to a paucity of efficacy data and a lack of definitive recommendations for the use of adjuvant chemotherapy in women 70 yrs and older with breast cancer.[14]

Trastuzumab (herceptin; Genentech, South San Francisco, CA) is a humanized mono-clonal antibody targeting the extracellular domain of the human epidermal growth factor receptor 2 (HER2) protein. Amplification or overexpression of Her2 is seen in approximately 25-30% of invasive breast cancers and is associated with an unfavorable prognosis.[15] Trastuzumab as a single agent and also in combination with chemotherapy has proven to be efficacious in the treatment of Her2-positive breast cancer in the metastatic setting resulting in response rates of 34% and 50%, respectively.[16,17] The benefit of this approach and the poor prognosis associated with this disease has recently led to a number of pivotal phase III trials in the adjuvant setting which have all demonstrated statistically significant increases in disease-free survival when trastuzumab is used either concurrently with or sequential to docetaxel, after anthracycline-based chemotherapy.[18,19] The role of single agent trastuzumab in the adjuvant setting, however, has not been explored.

The main adverse effect associated with trastuzumab is cardiotoxicity. Concurrent use of anthracycline-based chemotherapy with trastuzumab in the metastatic setting was associated with an overall cardiac dysfunction rate of 27%[16]. Furthermore trastuzumab use in the adjuvant setting in combination with paclitaxel was associated with a 4.1% cardiac event rate and an asymptomatic decline in left ventricular ejection fraction of

14%, resulting in an overall cardiac dysfunction rate of 18%[19,20]. In contrast use of single agent trastuzumab as a first line agent in the metastatic setting was associated with a cardiac event rate of only 2% [17] and an overall cardiac dysfunction rate of up to 7%.[21,22] .There is no data of single agent use of trastuzumab in the adjuvant setting. However, the existing data does suggest that use of trastuzumab concurrently with or sequentially after chemotherapy is associated with a much increased risk of cardiotoxicity.

Table 1: Incidence of Cardiac Dysfunction in Adjuvant and Metastatic Trials of Trastuzumab

Study	% NYHA Class III-IV CHF	
	Control arm	**Trastuzumab arm**
Adjuvant Studies		
NSABP B-31	0.8	4.1
N9831	0	2.9
HERA	0	0.6*
BCIRG 006**	.95†	1.33‡ - 2.34§
FinHer¶	0	0
Metastatic Studies		
Vogel (JCO 1999)	No control arm	2 (Trastuzumab alone)
Cobleigh (JCO, 1999)	No control arm	5 (Trastuzumab)
Slamon (NEJM, 2001)	3 (AC alone) 1 (Paclitaxel)	16 (AC + Trastuzumab) 2 (Paclitaxel + trastuzumab)

*1-yr trastuzumab arm; **Includes: Grade 3 or 4 arrhythmias, Grade 3 or 4 cardiac ischemia / infarction; †AC→T; ‡TCH; §AC→TH; ¶Small sample size.

Consistent with the under-representation of older women in breast cancer clinical trials of chemotherapy[8,13], trastuzumab was administered to only 257 patients (6%) who were 65 years and older (124 (adjuvant) and 133 (metastatic)) out of 4443 women who participated in clinical trials of trastuzumab that led to FDA-approval.[23] Besides cardiac dysfunction, limitations in data collection and differences in study design of the two studies of trastuzumab in the adjuvant setting precluded a determination of whether the toxicity profile of trastuzumab in older patients was different from younger patients. The reported clinical experience was also not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of trastuzumab treatment in older patients was different from that observed in patients <65 years of age.

Since older women bear a disproportionate burden of the incidence and mortality associated with breast cancer it is paramount that they receive optimal treatment just like their younger counterparts. However based on the existing literature several questions remain unanswered as these results cannot be generalized to the older population. Is trastuzumab safe and effective in older breast cancer patients considering age-related changes in physiology and an increased incidence of comorbidities? Will single agent adjuvant trastuzumab be less cardiotoxic but yet still effective? The risk-benefit profile in older patients remains poorly understood and this study is designed to address these questions.

1.2 SIGNIFICANCE

This study is significant because it seeks to address an important question in a subset of the population that has been consistently under-represented in clinical trials. Our long-term goal is to develop effective and tolerable therapeutic interventions for the treatment of breast cancer in older women. The objective for this particular study is to determine the tolerability and efficacy of adjuvant trastuzumab in older women. Trastuzumab is particularly attractive because except for cardiotoxicity it has a favorable safety profile, and has been proven to be very effective in the adjuvant setting for younger patients with Her2 positive breast cancer.[18,19] These attributes suggest that with careful patient selection this biological agent may play a significant role in the management of breast cancer in older women and therefore this option should be explored. Currently there are no published data from phase II or III trials on the safety of trastuzumab in older breast cancer patients nor is there efficacy data on use of single agent adjuvant trastuzumab in the management of breast cancer. Contrary to what was previously believed a recent review of trastuzumab cardiotoxicity data appears to suggest that declines in LVEF are more sustained.[24] The long-term implications of trastuzumab cardiotoxicity therefore remain unclear. Long-term cardiac monitoring data, which will be collected in this study, will be particularly useful since increasing age is a risk factor for trastuzumab related cardiactoxicity,[20] and cardiac diseases generally. It is our expectation that at the completion of this study when the safety and efficacy of single agent trastuzumab in the adjuvant setting has been demonstrated, physicians will be more inclined to enroll older patients in trials that address the safety of trastuzumab in combination with chemotherapy and or with other biologic agents. It is in the light of this missing safety and efficacy data that we propose to conduct this study, to answer critical safety and efficacy questions related to the care of older women with early stage breast cancer. Findings from this study will afford the opportunity to inform the debate on the role of systemic therapy in older women with breast cancer.

1.3 HER2 OVEREXPRESSION AND BREAST CANCER

Growth factors and their receptors play critical roles in development, cell growth, differentiation, and apoptosis.[25] Such receptors span the cell membrane, with the extracellular domain binding specific growth factors and the intracellular domain transmitting growth signals. Interaction of the extracellular domain with its cognate ligand often results in intracellular activation of tyrosine kinase activity. Overexpression of human epidermal growth factor receptor 2 (HER2, also known as *erb*B2, neu, and p185HER2) is observed in approximately 25-30% of human breast cancers.[15] HER2 overexpression has been reported to only rarely occur in the absence of gene amplification. [26,27] High level of HER2 expression has been correlated with poor clinical outcome.[15]

Several lines of evidence support a direct role for HER2 overexpression in the pathogenesis and poor clinical course of human tumors.[28] When the mutated gene is transfected into murine fibroblast (NIH 3T3) cells, it causes transformation, and the resulting cells are tumorigenic in the nude mice.[29,30] Additionally, transgenic mice that overexpress the rodent homolog of the human HER2 gene develop breast cancer.[31] Finally, specific antibodies to the extracellular domain of HER2 inhibit the experimental growth of tumors that overexpress the gene.[32-34] These data suggest a direct role for HER2 in both malignant transformation and enhanced tumorigenicity. Therefore a

strategy to antagonize the abnormal function of overexpressed HER2 was developed to improve the course of patients with HER2-overexpressing tumors. Monoclonal antibodies directed against the HER2 protein were developed and humanized to minimize the likelihood of immunogenicity. One of these antibodies (trastuzumab) was very effective in inhibiting both in vitro and in vivo proliferation of human breast cancer tumor cells overexpressing the HER2 protein and in mediating antibody-dependent cellular cytotoxicity in the presence of human effector cells.[35]

There is substantial preclinical evidence that inhibition of signal transduction pathways can potentiate the cytotoxic activity of chemotherapeutic drugs. Indeed, trastuzumab has been shown to have synergy, in vitro and in vivo, with several chemotherapeutic drugs including cisplatin, doxorubicin, thiotepa, etoposide, vinorelbine, and taxanes.[36-41] Given this promising preclinical data, Trastuzumab was tested in the clinic both as a single agent and in combination with chemotherapy.

Amplification or overexpression of Her1 is also seen in approximately 15-50% of women with invasive breast cancers, and is also associated with an unfavorable prognosis.[42] Inhibition of both her1 and Her2 receptor types should therefore improve optimal inhibition of tumor growth and survival. Recently, Lapatinib ditosylate (GW572016/Tykerb®; Glaxo-SmithKline, Research Triangle Park, NC) has been developed as an oral dual TK inhibitor targeting both the ErbB-1 and ErbB-2 receptors and has shown promising activity in preclinical investigations[43-45] and clinical trials mainly in the advanced breast cancer[46].Geyer, et al,[46] in their pivotal randomized controlled trial of lapatanib plus capecitabine versus capecitabine alone among locally advanced and metastatic her2+ breast cancer patients, heavily pretreated with combination chemotherapy demonstrated a 51% proportional reduction in time to progression in the combination-therapy arm in comparison with the capecitabine alone without increase in serious toxic effects or symptomatic cardiac events. It is unclear how many women enrolled in this trial were 65 years and older. However the median age of participants in the combination arm was 54 years and in the capecitabine alone arm was 51 years.

1.4 HERCEPTIN CLINICAL EXPERIENCE IN THE ADJUVANT SETTING

In November 2006 the FDA approved trastuzumab for use as part of a treatment regimen containing doxrubicin, cyclophosphamide and paclitaxel for the treatment of patients with HER2 overexpressing, node positive breast cancer based on the results of two pivotal randomized, open-label, clinical trials with a total of 3752 patients who were randomized in the studies prior to a pre-specified interim analysis.[19] The data from both arms in NSABP-31 and two of the three study arms in N-9831 were pooled for efficacy analyses. Breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (N-9831) or was required to be performed at a reference laboratory (NSABP-31). Patients with a history of active cardiac disease based on symptoms, abnormal electrocardiographic, radiologic, or left ventricular ejection fraction findings or uncontrolled hypertension (diastolic >100 mmHg or systolic >200 mmHg) were not eligible. Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by paclitaxel alone or paclitaxel plus trastuzumab. In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m2 and

cyclophosphamide 600 mg/m2. Paclitaxel was administered either weekly (80 mg/m2) or every 3 weeks (175 mg/m2) for a total of 12 weeks in NSABP-31; paclitaxel was administered only by the weekly schedule in the N9831. Trastuzumab was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a dose of 2 mg/kg weekly for a total of 52weeks. Radiation therapy, if administered, was initiated after the completion of chemotherapy. Disease-free survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death, was the primary endpoint of the combined efficacy analysis. A total of 3752 patients were included in the efficacy analyses. Overall, there were 1,736 patients in the B-31 trial and 1,615 patients in N-9831, and at the time of the combined analysis, the median follow-up was 2.0 years. Compared with the control arm, the trastuzumab arm showed a statistically signficant increase in 3-year disease-free survival (DFS), 75.4% vs 87.1% respectively, $p<0.0001$;HR=0.48, 95% CI (0.39-0.59). The cumulative incidence of class III or IV heart failure was 0.8% in the control group and 4.1% in the trastuzumab group.

Three other important trials in addition to the two pivotal trials described above validate the use of trastuzumab in the adjuvant treatment of breast cancer. The HERA (Herceptin Adjuvant) trial focused on determining the optimal duration of trastuzumab for early-stage breast cancer.[18] Patients were randomized to one of three arms: observation, trastuzumab every 3 weeks for 1 year, or trastuzumab every 3 weeks for 2 years. Trastuzumab was dosed with 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks thereafter. Patients had either node-negative disease if tumor size >1cm (32.1%) or node-positive disease, and all patients had HER2-positive tumors. At a median follow-up of 2 years, the addition of trastuzumab to neoadjuvant and adjuvant chemotherapy resulted in a statistically signficant improvement in DFS (86.1% vs 78%) and overall survival (96.9% vs 93.6%). Further analysis is expected to determine if 2 years is superior to a year of treatment.

The BCIRG 006 trial aimed at maximizing the efficacy of trastuzumab while minimizing cardiac toxicity.[47] The trial enrolled 3,222 patients with node-positive or high-risk lymph node-negative HER2-positive tumors to 1 of 3 arms: doxorubicin-cyclophosphamide every 3 weeks for 4 cycles followed by docetaxel every 3 weeks for 4 cycles (ACT); or the same regimen plus 52 weeks of trastuzumab,weekly during chemotherapy then every 3 weeks during follow-up (ACTH); or docetaxel-carboplatin every 3 weeks for 6 cycles plus 52 weeks of trastuzumab with the same schedule as given in arm 2 (TCH). At a 36 month follow-up, presented at the 2006 San Antonio Breast Conference, the 2 trastuzumab arms showed a statistically significant improvement in DFS compared with the control arm. Symptomatic cardiac events and an LVEF decline >15% were statistically significantly greater in the ACTH group compared with the ACT. There was no statistically significant difference between the ACT and TCH groups in terms of cardiac side-effects. This trial shows that fewer cardiac events are observed when trastuzumab is administered without prior anthracycline-based therapy. There was no statistically significant difference in terms of disease free survival across the two trastuzumab-containing arms.

The FinHer trial involved 1,010 patients randomized to docetaxel every 3 weeks for three doses versus 9 weeks of vinorelbine followed, in both groups, by three weeks of

cyclophosphamide, epirubicin, and fluoruracil (CEF).[48] The 232 patients found to be HER2 positive were randomized to receive weekly trastuzumab for 9 weeks with docetaxel or vinorelbine. This trial enrolled women with axillary node-positive disease or women with node-negative breast cancer with tumors >2cm and progesterone-receptor negative. After a median follow-up of 3 years, they found that recurrence was less frequent amongst women receiving docetaxel/CEF with 42/502 recurrences compared with 71/507 recurrences in the vinorelbine/CEF arm at 3 years. They also found that trastuzumab for 9 weeks was effective in preventing breast cancer recurrence, with 12/115 events in the trastuzumab arm compared with 27/116 events in the arm without trastuzumab (p= 0.01).

1.5 HERCEPTIN CLINICAL EXPERIENCE IN METASTATIC BREAST CANCER

The clinical benefit of trastuzumab in women with metastatic breast cancer has been demonstrated in two pivotal studies.

A large Phase II trial (H0649g) assessed the activity of trastuzumab as a single agent in 222 women with HER2 overexpressing metastatic breast cancer with progressive disease after one or more chemotherapy regimens.[49] A blinded, independent response evaluation committee identified 8 complete and 26 partial responses, for an objective response rate of 15% in the intent-to-treat population (95% confidence interval, 11% to 21%). The median duration of response was 9.1 months, and the median duration of survival was 13 months. The most common adverse events, which occurred in approximately 40% of patients, were mild to moderate infusion-associated fever and/or chills. These symptoms usually occurred only during the first infusion. The most clinically significant event was cardiac dysfunction, which occurred in 4.7% of patients.

A large, open-label, randomized Phase III study (H0648g) in 469 patients with HER2-positive metastatic breast cancer was conducted to evaluate the efficacy of trastuzumab in combination with chemotherapy as first-line treatment. Patients who were anthracycline-naïve were randomized to receive either anthracycline plus cyclophosphamide (AC) or trastuzumab plus AC. Patients who had received prior anthracyclines in the adjuvant setting were randomized to receive either paclitaxel or trastuzumab plus paclitaxel. Patients randomized to trastuzumab and chemotherapy measurably benefited in comparison to patients treated with chemotherapy alone in terms of time to disease progression, overall response rate, median duration of response, and survival. As determined by an independent Response Evaluation Committee (REC), trastuzumab prolonged median time to disease progression from 4.6 months to 7.4 months ($p<0.001$), improved the overall response rate (complete and partial responses) from 32% to 50% ($p<0.001$), and increased median duration of response from 6.1 to 9.1 months ($p<0.001$). Compared to chemotherapy alone, the addition of trastuzumab significantly lowered the incidence of death at one year from 33% to 22% ($p=0.008$) and increased median overall survival 24% from 20.3 months to 25.1 months ($p=0.046$). The observed survival advantage remained despite crossover of 66% of patients initially randomized to chemotherapy alone who elected to receive trastuzumab upon disease progression.[50] Fever/chills were observed with the initial trastuzumab infusion in approximately 25% of patients. Class III or IV cardiac dysfunction was observed in 16% of the Trastuzumab +

AC subgroup; increasing age was an associated risk factor for the development of cardiotoxicity in this treatment cohort.

Based on these data, trastuzumab was approved by the U.S. Food and Drug Administration (FDA) for use in HER2-overexpressing metastatic breast cancer in combination with paclitaxel for first-line treatment and as a single agent for patients failing prior chemotherapy for metastatic disease. However, current usage patterns of trastuzumab indicate that the drug is now being used in a broader array of circumstances than in the pivotal clinical trials. Since initiation of the pivotal clinical trials, docetaxel has become a commonly used taxane in the treatment of metastatic breast cancer [51] and new data have emerged on the weekly use of paclitaxel[52]. Trastuzumab has been studied in combination with paclitaxel and docetaxel using a variety of doses and schedules with promising results.[53-55] In addition, the combination of trastuzumab with vinorelbine has recently been studied.[56] In this study, 30 of 40 women treated with trastuzumab (4 mg/kg x 1, 2 mg/kg weekly thereafter) and vinorelbine (25 mg/m^2 weekly, with dose adjusted each week for neutrophil count) responded to therapy, for an overall response rate of 75% (95% confidence interval 57% to 89%). Neutropenia was the only grade IV toxicity. No patients had symptomatic heart failure. Grade 2 cardiotoxicity was observed in 3 patients; prior cumulative doxorubicin dose in excess of 240 mg/m^2 and borderline pre-existing cardiac function were associated with this toxicity.

1.6 SAFETY

Experience with trastuzumab administration has shown that the drug is relatively safe. The most significant safety signal observed during clinical trials was cardiac dysfunction (principally clinically significant heart failure [CHF]), particularly when Herceptin was given in combination with an anthracycline-containing regimen. Much of the cardiac dysfunction was reversible on discontinuation of trastuzumab.

In addition, during the first infusion with trastuzumab, a symptom complex most commonly consisting of fever and/or chills was observed in approximately 40% of patients. The symptoms were usually mild to moderate in severity and controlled with acetaminophen, diphenhydramine, or meperidine. These symptoms were uncommon with subsequent infusions. However, in the post approval setting, more severe adverse reactions to trastuzumab have been reported. These have been categorized as hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary events. Rarely, these severe reactions culminated in a fatal outcome.

There are no adequate or well-controlled studies in pregnant women, and animal reproduction studies are not always predictive of human response. Therefore, trastuzumab should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus. In the post marketing setting, oligohydramnios (decreased amniotic fluid) has been reported in women who received trastuzumab during pregnancy, either in combination with chemotherapy or as a single agent. Given the limited number of reported cases, the high background rate of occurrence of oligohydramnios, the lack of clear temporal relationships between drug use and clinical findings, and the lack of supportive findings in animal studies, an association between trastuzumab and oligohydramnios has not been established.

Trastuzumab appears to be relatively nonimmunogenic. Only 1 of 903 patients evaluated developed neutralizing antibodies to trastuzumab. The development of anti-Herceptin antibodies in this patient was not associated with clinical signs or symptoms.

1.7 CLINICAL PHARMACOKINETICS OF TRASTUZUMAB

A Phase I single dose study (H0407g) of intravenous trastuzumab infusions ranging from 10-500 mg resulted in dose-dependent pharmacokinetics (PK) with serum clearance of trastuzumab decreasing with an increasing dose at doses <250 mg. PK modeling of trastuzumab concentration-time data from 7 patients that were administered doses of 250 mg and 500 mg had a mean half-life of 5.8 days (range 1-32 days). Additionally, PK modeling showed that weekly trastuzumab doses ≥250 mg resulted in serum trough levels of >20 □g/mL that was above the minimum effective concentration observed in preclinical xenograft studies in tumor-bearing mice. The Phase I data supported the weekly dosing schedule that was implemented in all subsequent Phase II and Phase III clinical trials. A weight-based dose schedule was adopted after two Phase II trials (H0551g and H0552g) suggested that inter-subject variability in trastuzumab PK was related to body weight. These findings resulted in a trastuzumab dose schedule of a 4 mg/kg loading dose followed by a weekly 2 mg/kg maintenance dose utilized in the two pivotal Phase III trials (H0648g and H0649g) that were the basis of the BLA filing and subsequent FDA approval of trastuzumab for HER2+ metastatic breast cancer.

The trastuzumab PK data from studies H0407g (Phase I), H0551g (Phase II), and H0649 (pivotal) have been subsequently reanalyzed by a population PK approach using nonlinear mixed effect modeling (NONMEM).[57] A linear two-compartment model best described the concentration-time data, and accounted for the accumulation of trastuzumab serum concentrations seen in the Phase II and Phase III clinical studies. A covariate analysis was conducted using the subjects from these single agent studies to evaluate the effect of pathophysiologic covariates (e.g. age, weight, shed antigen) on the PK parameter estimates. The covariates, that significantly influenced clearance, were the level of shed antigen and the number of metastatic sites. Volume of distribution was significantly influenced by weight and shed antigen level. Additionally, data from the Phase III study, H0648g, were added to assess the influence of concomitant chemotherapy on trastuzumab PK. Importantly, chemotherapy (AC or paclitaxel) did not significantly alter trastuzumab PK. The estimated half-life of trastuzumab based on the final model was 28.5 days.

Analysis of data obtained from two Phase II studies which utilized a loading dose of 8 mg/kg trastuzumab followed by a 6 mg/kg maintenance dose administered every 3 weeks (q3 week) as a single-agent[40], and in combination with paclitaxel (175 mg/m^2)[58], confirmed that a two-compartment model best describes the PK of trastuzumab. Model-independent analysis of the data obtained in these studies gives comparable PK parameter estimates to those obtained by the population PK model, thus confirming the validity of the population PK model. In addition, the population PK model adequately predicted trastuzumab serum concentrations obtained independently in these studies. After two treatment cycles, trastuzumab exposure were similar to those measured in the once weekly dosing regimen used in the pivotal trials. Trough levels were in excess of the targeted serum concentrations established from preclinical xenograft models, and as expected, peak levels were greater than those observed upon weekly administration. The

apparent half-life of trastuzumab in these studies was determined to be approximately 21 days, and the PK was supportive of a q3 week dosing schedule.

The efficacy and safety results from these Phase II studies with q3 week dosing do not appear to be different from those with weekly dose-schedules[16,49,59]. In the trastuzumab q3 weekly monotherapy study[40], 105 patients with HER2+ metastatic breast cancer were treated, with an objective response rate of 19% (23% in patients with measurable centrally confirmed HER2+ disease). The median baseline LVEF was 63%, which did not significantly change during the course of the study. One patient experienced symptomatic CHF, which resolved with medical treatment for CHF and discontinuation of trastuzumab. In the study of q3 weekly trastuzumab and paclitaxel[58], 32 patients were treated with an investigator-assessed response rate of 59%. Ten patients had a decrease in LVEF of 15% or greater. One patient experienced symptomatic CHF, which improved symptomatically after medical therapy for CHF and discontinuation of trastuzumab.

1.8 PHYSIOLOGIC CARDIAC MARKER STUDIES BACKGROUND AND RATIONALE

The pathophysiology of trastuzumab-related cardiac dysfunction remains undefined with several hypotheses being proposed. These include drug-drug interactions, the induction of immune-mediated destruction of cardiomyocytes, and defects in HER2 signaling required for maintenance of cardiac contractility.[60] HER2 may also play a role in myocyte survival, which may then be impaired during treatment with trastuzumab[61,62]. What is definitely known about trastuzumab-related cardiotoxicity is that it is different from that induced by anthracyclines. Cardiac biopsy specimens have revealed no anthracycline-like morphologic abnormalities and unlike anthracycline-induced cardiotoxicity it is largely reversible.[63]

Currently, existing literature suggest that detection of trastuzumab related cardiac toxicity is best accomplished by serial measurements of left ventricular ejection fractions by either multiple-gated acquisition scans or echocardiography techniques[20] These measurements do not, however, provide early detection of abnormalities. A plausible explanation for the lack of early detection of cardiac abnormalities may be attributable to physiologic compensations for significant damage, with abnormalities only becoming evident when physiologic compensations are no longer possible. The need for a screening tool that could reveal trastuzumab related cardiac toxicity in a more sensitive and immediate manner cannot be over emphasized and hence the rationale for measuring plasma physiologic cardiac markers in this study and to determine it's correlation with trastuzumab-related cardiac dysfunction.

Cardiac troponin, a component of the myocardial contractile apparatus, is released after just one cycle of chemotherapy and is more frequently abnormal with each cycle in patients who ultimately develop left ventricular dysfuction[64]. Pretreatment levels of N-terminal brain natriuretic protein (NT-proBNP) has also shown promise regarding the prediction of trastuzumab-related cardiac toxicity and requires further exploration[65] Lastly, inflammatory immune activation is an important feature of chronic heart failure and therefore physiologic markers such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) levels maybe useful as early predictors of trastuzumab-related cardiac dysfunction.[66-68]

1.9 COMPREHENSIVE GERIATRIC ASSESSMENT BACKGROUND AND RATIONALE

Comprehensive Geriatric Assessment (CGA) is a multidisciplinary evaluation which assesses function, comorbidity, nutrition, cognition, emotional, psychological and social support, and a review of medication list for polypharmacy and drug interactions. It is a key tool currently recommended as an integral part of the treatment and follow-up of the older patient with cancer.[69] The rationale for integrating the principles of geriatrics evaluation into oncology care for older cancer patients is to use this assessment to determine an estimation of life expectancy and treatment tolerance, allowing a common language beyond that provided by chronological age. The expectations are that this approach will result in improved treatment outcomes in older patients with cancer.

Domains of the Comprehensive Geriatric Assessment

Functional status

Functional status refers to a patient's ability to perform routine daily tasks and is an independent predictor for mortality in both the geriatric[70] and geriatric-oncology[71] population. Impaired functional status also increases the risk of toxicity due to chemotherapy.[72] An accurate assessment of functional status will therefore increase identification of those at risk for non-adherence to chemotherapy and those at increased risk of dying from cancer. The commonly used performance status scores (eg, Karnofsky or Eastern Cooperative Oncology Group (ECOG) scales tend to under-represent the degree of functional impairment in the older patient.[73] Functional state is better reflected by the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales. ADLs are the skills that are necessary for basic living, and include feeding, grooming, transferring, and toileting. IADLs are required to live independently in the community and include activities such as shopping, managing finances, preparing meals, housekeeping, and taking medications.

Co-morbidity

Co-morbidity is an important factor to consider in determining the prognosis of patients with a cancer diagnosis. As an individual ages, the number of comorbid medical conditions increases making comorbidity an important domain of a CGA.[1] Co-morbidity adversely impacts survival[74], and tolerance to chemotherapy[75]. The impact of comorbidity on survival was well illustrated by a longitudinal observational study of 936 women with breast cancer ages 40 to 84. Patients who had three or more comorbid medical conditions had a 20-fold higher rate of mortality from causes other than breast cancer and a fourfold higher all-cause mortality rate compared to those who had no comorbid medical conditions.[74] The adverse impact of comorbidity on chemotherapy tolerance was illustrated in a study of patients age ≥70 years with advanced non–small cell lung cancer.[75] In this study patients with a Charlson Comorbidity Index of ≥2 were more likely to discontinue chemotherapy earlier than patients with a comorbidity score <2. Because comorbidity has been shown to be independent of functional status is it is important that both domains are assessed when evaluating an older patient with cancer.[76]

Cognitive function

Cognitive function plays an important role in the outcome of the older patient with cancer and therefore is an important domain that needs to be assessed. In the geriatric oncology

population dementia is associated with a lack of diagnosis of cancer until discovery at death[77], advanced stage at diagnosis[78], receipt of suboptimal therapy[78], and survival[79]. Additionally, an assessment of cognitive status is important prior to treatment in order to ensure the process of informed consent, that the patient can comply with instructions regarding supportive medications or oral agents, and in order to understand and remember to seek medical attention if side effects develop.

Nutrition

The adverse impact of weight loss and low Body Mass Index (BMI) have been demonstrated in all older patients including those with cancer.[80,81] In a study among older cancer patients enrolled in 12 chemotherapy protocols of the Eastern Cooperative Oncology Group (ECOG) weight loss was associated with a lower performance status, a decrease in chemotherapy response rates in women with breast cancer, and was found to be an independent prognostic factor for survival.[82] The importance of a thorough nutritional assessment and the development of interventions to improve nutritional status among malnourished older cancer patients cannot be overemphasized.

Social support and psychological state

Social isolation has been linked to an increased vulnerability to psychological distress among geriatric patients[83] and an increase in mortality among both geriatric and oncology patients. [84,85] Additionally studies of geriatric assessment show that 14-40% of older patients have depressive symptoms. Depression among older patients with cancer is associated with receipt of sub-optimal therapy[86], increased toxicity to chemotherapy[72], and increased mortality[72]. An assessment of the social support and psychological state of an older cancer patient is therefore essential as an appropriate intervention is likely to improve outcomes among older patients with cancer.

Polypharmacy

Age-related physiological changes include a decrease in total body water, an increase in body fat, a decrease in renal function, a decrease in hepatic mass and blood flow, and decrease in bone marrow reserve. Polypharmacy is prevalent among older patients. In the older cancer patient age-related changes in physiology, polypharmacy and cancer therapy can contribute to drug interactions and adverse drug events. A CGA of an older cancer patient should therefore include a review of prescribed medications with the discontinuation of nonessential medications, evaluation of potential drug interactions, and a review of expected side effects from prescribed medications.

Below is a table of validated instruments for evaluation of the domains described above that will be utilized in this study.

Table 2: Validated Comprehensive Geriatric Assessment Instruments and Corresponding Domains	
Instrument	**Domain**
Lawton's nine-item Instrumental Activities of Daily Living (IADL)[87]	Functional Status
Katz's Activity of Daily Living (ADL)[88]	
Timed up and go test[89]	
Karnofsky Physician-Rated Performance Rating Scale (KPS)[90]	
Number of falls in the last 6 months[91]	
Mini-nutritional assessment (MNA)[92]	Nutritional Status Assessment
Body Mass Index[93]	
Percent Unintentional Weight Loss in the Last 6 Months[82]	
Medical Outcomes Study (MOS) Social Support Subscale (Emotional/information and Tangible subscales)[94]	Social Functioning and Support
MOS Social Activity Limitations Measure[95]	
Charlson Comorbidity Index[96]	Comorbidity
Cumulative Index Rating Scale Geriatrics (CIRS-G)[97]	
Folstein's Mini-mental State Examination (MMSE)[98]	Cognitive Function Assessment
Clock Drawing Test[99,100]	
Geriatric Depression Scale (GDS)[101]	Assessment of Emotional/Psychological state
Functional Pain Scale[93]	Pain Assessment
List of Medications	Poly-pharmacy

Table 2: Validated Comprehensive Geriatric Assessment Instruments and Corresponding Domains	
Instrument	**Domain**
Minnesota Leisure Time Activity Questionnaire	Cardiovascular Health Study Frailty Index[102]
Questions on exhaustion	
Grip Strength	
15ft walk speed	
Unintentional weight loss in 12 months	
Vulnerable Elders Survey[103,104]	Assessment of Vulnerability
Functional Assessment of Cancer Therapy (FACT-B)[105]	Quality of Life

2.0 OBJECTIVES

2.1 PRIMARY OBJECTIVE

2.1.1 Evaluate the three-year cumulative incidence of cardiac events in women 60 years and older with Her2-positive breast cancer who receive single agent trastuzumab in the adjuvant setting.

2.2 SECONDARY OBJECTIVES

2.2.1 Evaluate the one-year cumulative incidence of asymptomatic cardiac left ventricular dysfunction in women 60 years and older with Her2-positive breast cancer who receive single agent trastuzumab in the adjuvant setting.

2.2.2 Evaluate long-term cardiac toxicity (five-year cumulative incidence of cardiac events) in women 60 years and older with Her2-positive breast cancer who receive single agent trastuzumab in the adjuvant setting.

2.2.3 Assess the relation between physiologic markers of chronic heart failure and trastuzumab-related cardiac dysfunction in women 60 years and older with Her2-positive breast cancer who receive single agent trastuzumab.

2.2.4 Assess the relation between pro-inflammatory cytokines and trastuzumab-related cardiac dysfunction in women 60 years and older with Her2-positive breast cancer.

2.2.5 Determine the effect of single agent trastuzumab on the Health-related Quality of Life (HRQOL), functional, cognitive, and mental status of women 60 years and older with Her2-positive breast cancer.

2.2.6 Determine the five-year disease-free and overall survival in women 60 years and older with Her2-positive breast cancer who receive single agent trastuzumab in the adjuvant setting.

3.0 STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open label, single arm, multi-institutional, phase II pilot study. One hundred and twenty-four patients 60 years and older with early-stage HER2+ invasive breast cancer who undergo appropriate primary tumor therapy (mastectomy or lumpectomy) with either sentinel or axillary lymph node dissection, will be enrolled and undergo treatment with single agent Trastuzumab at 8mg/kg IV loading dose, followed by 6mg/kg IV every three weeks to complete 52 weeks of treatment. Patients will receive additional adjuvant radiation therapy and/or endocrine therapy according to standard institutional practice. Patients will be followed prospectively for five years after entry into study or until death, whichever comes first.

Participating institutions include the Seidman Cancer Center and its satellites, Cleveland, Ohio, University of Pittsburgh, Pittsburgh, Pennsylvania, Wake Forest University, Winston-Salem, North Carolina and University of Miami, Florida.

3.2 RATIONALE FOR STUDY

As described in section 1.1, older patients bear a disproportionate burden of the incidence and mortality of cancer. However, they are consistently under-represented in clinical trials, particularly, breast cancer clinical trials of chemotherapy. This has led to a paucity of efficacy data and a lack of definitive recommendations for the use of adjuvant chemotherapy in women 70 yrs and older with breast cancer.[14] Consistent with other breast cancer clinical trials of chemotherapy[8,13], trastuzumab was administered to only 274 patients (6%) who were 65 years and older (141 (adjuvant) and 133 (metastatic)) out of 4443 women who participated in clinical trials of trastuzumab that led to FDA-approval.[106] Besides cardiac dysfunction, limitations in data collection and differences in study design of the two studies of trastuzumab in adjuvant treatment of breast cancer precluded a determination of whether the toxicity profile of trastuzumab in older patients was different from younger patients. The reported clinical experience was also not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of trastuzumab treatment in older patients was different from that observed in patients <65 years of age.. Other clinical trials of trastuzumab have also been largely limited to younger patients. A total of 16% of patients enrolled in the HERA trial were older than 60 years of age and BCIRG006 limited patient enrollment to those who were less than 70

years old.[106] The need, therefore, for clinical trials of trastuzumab specifically developed for older patients cannot be overemphasized.

Results from a Phase II study, demonstrates the efficacy and safety of single agent trastuzumab as a first-line agent in the metastatic setting. In this study 114 women with *HER2*-overexpressing metastatic breast cancer were randomized to receive first-line treatment with trastuzumab 4 mg/kg loading dose, followed by 2 mg/kg weekly, or a higher 8 mg/kg loading dose, followed by 4mg/kg weekly. Randomization was used to ensure that estimates of the efficacy outcomes within each dose level would not be biased by assigning patients with worse prognosis to the higher dose group. Response rates in111 assessable patients with 3+and 2+*HER2* overexpression by immunohistochemistry (IHC) were 35% (95% CI, 24.4% to 44.7%) and none (95% CI, 0% to 15.5%), respectively. The response rates in108 assessable patients with and without *HER2* gene amplification by fluorescence in situ hybridization (FISH) analysis were 34% (95% CI, 23.9% to 45.7%) and 7% (95% CI, 0.8% to 22.8%), respectively. There was no clear evidence of a dose-response relationship for response, survival, or adverse events. Cardiac dysfunction occurred in two patients (2%); both had histories of cardiac disease and did not require additional intervention after discontinuation of trastuzumab. This study demonstrates the efficacy and safety of single agent trastuzumab in the metastatic setting and forms the basis for the need for further exploration of single agent trastuzumab in the adjuvant setting, particularly among older patients who may have pre-existing cardiac disease that may not allow the administration of trastuzumab in combination with chemotherapy. Also since advanced aged has been identified as a risk factor for the development of trastuzumab-related cardiac toxicity[19], a cautious approach is needed when clinical trials of trastuzumab, that specifically focuses on older patients, are designed and hence the decision to utilize trastuzumab as a single agent in this trial.

A Phase I PK study (H0407g) supported a weekly dosing schedule that was implemented in all subsequent Phase II and Phase III clinical trials. A weight-based dose schedule was adopted after two Phase II trials (H0551g and H0552g) suggested that inter-subject variability in trastuzumab PK was related to body weight. These findings resulted in a trastuzumab dose schedule of a 4 mg/kg loading dose followed by a weekly 2 mg/kg maintenance dose utilized in the two pivotal Phase III trials (H0648g and H0649g) that were the basis of the BLA filing and subsequent FDA approval of trastuzumab for HER2+ metastatic breast cancer. Subsequently, two Phase II studies utilized a loading dose of 8 mg/kg trastuzumab followed by a 6 mg/kg maintenance dose administered every 3 weeks (q3 week) as a single-agent[40], and in combination with paclitaxel (175 mg/m^2)[58].The efficacy and safety results from these Phase II studies with q3 week dosing do not appear to be different from those with weekly dose-schedules[16,17,49].Similarly, in the adjuvant setting trials utilizing a weekly dose schedule[19,48], a 3 weekly dose schedule[18], or a combination of both[47] have all demonstrated efficacy.

Because of the lack of safety and efficacy data on trastuzumab use among older women with breast cancer, the demonstrated efficacy of trastuzumab as a single agent in the metastatic setting, the association between the risk of trastuzumab-related cardiac toxicity and advanced age, and the need for a pragmatic yet effective dosing schedule that encourages clinical trials participation among older breast cancer patients, we have

developed an exploratory study to evaluate the safety and efficacy of single agent trastuzumab therapy at 8mg/kg loading dose, then 6mg/kg every 3 weeks for a total of 52 weeks as adjuvant treatment for older breast cancer patients with HER2-positive breast cancer who are unwilling or unable to undergo treatment with chemotherapy.

3.3 ASSESSMENTS

3.3.1 DEMOGRAPHIC AND BASELINE ASSESSMENTS

Assessments prior to registration

- Subject to sign the informed consent form
- Initiate completion of study eligibility form
- Documentation of immunohistochemical (IHC) staining for HER2 protein of 3+ intensity or HER2 gene amplification by FISH testing.

Note: Subject must be documented as having HER2 overexpression prior to initiation of additional screening assessments outlined subsequently in this section. Assessment for HER2 expression or gene amplification should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Centralized testing is not required.

A written informed consent form must also be signed by all participants prior to screening assessments, and before any study-specific assessments are initiated.

Screening Assessments

- Demographic data: date of birth, race, gender, height in centimeters, body weight in kilograms, and ECOG Performance Status.
- Medical history including details of malignancy: date of diagnosis, primary tumor type, histology, ER and PR status, stage of cancer, relevant prior surgical procedures, and prior and concomitant medications within 3 weeks of first dose of trastuzumab.
- Baseline Echocardiogram (ECHO) or MUGA scan may be completed within 3 months of current breast cancer diagnosis. The same method used at screening should be used throughout the study period.

Assessments within 21 days prior to first dose

- Physical examination
- Medical history, ECOG Performance Status
- Vital signs (blood pressure, pulse rate, body temperature, height, and body weight)
- Baseline laboratory tests (complete blood count (CBC), electrolytes, liver function tests, and physiological markers of cardiac function
- Baseline Quality of Life and Comprehensive Geriatric Assessment

Testing for physiologic cardiac markers (IL-6, TNF-alpha, Troponin-I, and BNP) will be centralized. Testing will be done at the Translational Research Core Laboratory at the Case Comprehensive Cancer Center Cleveland, Ohio. All serum samples for such tests

will therefore require shipping to the Case Comprehensive Cancer Center. Please see appendix D for instructions on how to handle serum samples and shipment details.

Note: After all baseline and screening evaluations have been completed, determine if the subject is eligible for the study by reviewing the inclusion and exclusion criteria.

3.3.2 ASSESSMENTS DURING STUDY CONDUCT

Assessments every 3 weeks during trastuzumab monotherapy

- Vital signs (blood pressure, pulse rate, body temperature, and body weight)
- Record any non-serious and serious adverse events (AE) and assign appropriate toxicity grade (NCI CTCAE version 3, published March 31, 2003)
- Hematology (CBC with differential)
- Complete Metabolic profile

Assessments every 6 weeks during trastuzumab monotherapy

- Serum cardiac physiologic markers
- Limited history
- Physical examination
- ECOG Performance Status

Assessment every 4 weeks until return of normal cardiac function

- Echocardiogram (ECHO) or MUGA scan for patients with significant left ventricular cardiac dysfunction requiring trastuzumab to be with held

Assessment every 3 months until end of year one

- Echocardiogram (ECHO) or MUGA scan

Assessment every 6 months until end of year one

- Quality of Life and Comprehensive Geriatric Assessment
- Cardiac history

Assessment every 6 months for years 2-5 or until disease-free or survival Endpoint is reached, whichever comes first

- Hematology (CBC with differential)
- Complete Metabolic profile
- Limited history including cardiac history
- Physical examination
- ECOG Performance Status
- Vital signs (blood pressure, pulse rate, body temperature, and body weight)
- Record any non-serious and serious adverse events (AE) and assign appropriate toxicity grade (NCI CTCAE version 3, published March 31, 2003)

Assessment at 60 months

- cardiac history
- physical examination
- cardiac markers
- ECHO or MUGA scan

3.4 OUTCOME MEASURES

3.4.1. PRIMARY OUTCOME MEASURE

The primary outcome measure is the three-year cumulative incidence of cardiac events and is defined by any one of the following events;

- Definitive cardiac death; due to CHF, MI, or documented arrhythmia
- Any possible/probable cardiac death over the three-year follow-up period defined as a sudden unexpected death within 24 hours after a definitive cardiac event , and without definitive documented alternative cause.
- Signs and symptoms of congestive heart failure (CHF). CHF will be defined as follows: New York Heart Association (NYHA) class III or IV symptoms with either a decrease from baseline in LVEF of more than 10 percentage points to less than 55% or a decrease of more than 5 percentage points to less than the lower limit of normal. Class III is characterized by symptoms of dyspnea with activities such as climbing a flight of stairs, whereas class IV symptoms are present at rest. LVEF will be determined with either a MUGA or echocardiogram.

Cardiac Assessment for primary outcome measure

- MUGA scans or echocardiogram will be required at study entry, at 3, 6, 9, and at 12months after study entry to assess primary outcome measure.
- Additional MUGA scans or echocardiograms after 12 months will be at treating physician's discretion except for one dditional MUGA scan or echocardiogram that will be performed at 60 months for long-term cardiac monitoring.
- Patients who develop significant left ventricular dysfunction will have MUGA scans at four week intervals until return of normal function.
- Cardiac history every 6 months until end of study.

Analysis of primary outcome measure

Descriptive statistics, such as means, median, range, and frequencies, will be used to describe subjects' cardiac toxicity profile. The incidence of cardiac dysfunction and its confidence interval will be estimated using Wilson's method.[107] Potential factors that predict the incidence will be identified by Cox proportional hazards regression.

3.4.2 SECONDARY OUTCOME MEASURES

3.4.2.1. The one-year cumulative incidence of asymptomatic left ventricular cardiac dysfunction defined as an asymptomatic decrease in LVEF from baseline of at least ten percentage points to below the lower limit of normal or an absolute

decrease of >15 percentage points leading to a permanent discontinuation of trastuzumab before completion of one year of trastuzumab therapy.

3.4.2.2. The five-year cumulative incidence of asymptomatic left ventricular cardiac dysfunction defined as an asymptomatic decrease in LVEF from baseline of at least ten percentage points to below the lower limit of normal or an absolute decrease of >15 percentage points at 60 months..

3.4.2.3. The five-year cumulative incidence of cardiac events and defined as above under section 3. 4.1.

3.4.2.4. Mean change in plasma cardiac markers from baseline to mid-treatment, and from baseline to end of treatment.

3.4.2.5. Mean change in pro-inflammatory cytokines from baseline to mid treatment, and from baseline to end of treatment. Similar analysis as above will be done.

3.4.2.6. Mean change in QOL and CGA scores from baseline to mid treatment, and from baseline to end of treatment. Differences in QOL and GCA scores will be examined by paired *t*-test.

3.4.2.7. Disease-free survival (DFS) defined as the time from initiation of treatment to the date of first loco-regional or distant treatment failure, ignoring any intervening contralateral breast cancers or other second primary cancers. Deaths without evidence of recurrence will be treated censoring events.

Appearance of DCIS or LCIS either in the ipsilateral or in the contralateral breast will not be considered as an event for DFS (but must be reported on the Follow-Up Form).

3.4.2.8. Overall survival defined as the time from initiation of treatment to the date of death from any cause and censored to the date of last follow-up for survivors.

Diagnosis of treatment failure

The diagnosis of first treatment failure depends on evidence of recurrent disease, which can be classified as either suspicious or acceptable. In either case, this should be specified and reported. Acceptable evidence of treatment failure according to site is defined below. Any events not included in this section are considered unacceptable as evidence of recurrent disease. Treatment failures include: local, regional, and distant failures. To ensure consistency with definitions used in pivotal trials of trastuzumab therapy intervening contra-lateral breast cancers and second primary cancers will not be considered treatment failures.[19] The date of treatment failure is the time of first appearance of a suspicious lesion, later proven to be a definitive recurrence or metastasis. All events described below should be recorded on the Follow-up Form

Local failure
Local failure is defined as a tumor recurrence in any soft tissues of the ipsilateral (or in the case of bilateral, either) conserved breast or the chest wall, mastectomy scar, and/or skin.

Acceptable for recurrence in ipsilateral conserved breast: positive cytology or histology
Acceptable for recurrence in chest wall, mastectomy scar, and/or skin: positive cytology or histology or evidence of new lesions (by CT or MRI) without any obvious benign etiology.

Suspicious: a visible or palpable lesion.
Appearance of DCIS or LCIS either in the ipsilateral or in the contralateral breast is not considered a treatment failure.

Treatment after local relapse for patients who received breast-conserving surgery:
Patients may continue to receive the protocol treatment after resection of a relapse in the ipsilateral conserved breast, an option that reflects the controversy concerning therapy for reappearance of disease in the ipsilateral breast. Continued treatment is only allowed when there is no evidence of loco-regional disease outside the breast or of distant disease at the time of breast relapse. Details of the local treatment for the conserved breast relapse must be recorded on the Follow-up Form. Patients who develop a local relapse other than a relapse in the ipsilateral conserved breast should change therapy.

Regional failure
Regional failure is defined as a tumor recurrence in the ipsilateral axillary lymph nodes, extranodal soft tissue of the ipsilateral axilla, ipsilateral internal mammary lymph nodes, and/or ipsilateral supraclavicular lymph nodes. For patients with bilateral breast cancer at randomization, failure in the previously-listed regional nodes should be recorded as regional failure (rather than distant) on the Follow-Up Form. The side (right or left) of the nodes should be recorded.

Acceptable: positive cytology or histology or evidence of new lesions by CT or MRI without a benign etiology.
Suspicious: a visible or palpable lesion.

Contralateral breast failure
Appearance of invasive breast cancer ,DCIS or LCIS in the contralateral breast is not considered an event for DFS.

Distant failure
Tumors in all areas other than those defined above are considered distant metastases. The following criteria apply:

Bone marrow
Acceptable: positive cytology, aspiration or biopsy.
Suspicious: unexplained depression of peripheral blood counts and/or a leucoerythroblastic blood picture.

Lung
Acceptable: positive cytology or histology or a positive CT or MRI without obvious benign etiology or evidence of progressive disease. (Progressive disease is confirmed by two X-rays with the second showing worsening disease.)
Suspicious: new radiological lesion(s).

Pleura
Acceptable: positive cytology or histology.
Suspicious: new pleural effusion.

Bone
Acceptable: positive cytology or histology or a positive X-ray, MRI, or CT, one bone scan with new multiple lesions and no obvious benign etiology.
Suspicious: skeletal symptoms or positive scan showing only one new lesion (until confirmed by other imaging study).

Liver
Acceptable: positive cytology or histology, or positive CT or MRI without an obvious benign etiology, or evidence of progressive disease by ultrasound. (Progressive disease in this case is confirmed by two ultrasounds with the second showing worsening disease).
Suspicious: any two of the following: hepatomegaly on physical examination, equivocal ultrasound and abnormal liver function test.

Central nervous system
Acceptable: positive cytology or histology. Positive MRI or CT when the clinical picture is suspicious.
Suspicious: any other clinical findings suggestive of this diagnosis.

Distant lymph nodes, not including ipsilateral supraclavicular lymph nodes, or, for cases with bilateral invasive cancers, supraclavicular or axillary nodes on either side.
Acceptable: positive cytology or histology, or enlarged lymph nodes in CT or MRI, or progressive disease by physical exam without an obvious benign etiology.
Suspicious: evidence of enlarged lymph nodes by physical exam.
For patients with bilateral breast cancer at randomization, failure in the axillary lymph nodes, extranodal soft tissue of the axilla, internal mammary lymph nodes, and/or supraclavicular lymph nodes on either the right or left side should be recorded as regional failure (rather than distant) on the Follow-Up Form. The side (right or left) of the recurrence should be recorded.

Other sites
Acceptable: positive cytology or histology or evidence of progressive disease if only indirect means of diagnosis were used (e.g., X-ray).
Suspicious: clinical and radiological evidence of a tumor.

Second (non-breast) primary
Any positive diagnosis of a second (non-breast) primary is not considered a treatment failure. Patients may continue to receive the protocol treatment after a second (nonbreast) primary is diagnosed.

Death without cancer event
Any death without a prior cancer event described in 3.4.5.2 above is not considered a treatment failure.

Other noteworthy events
The following events should be recorded on the Follow-up Form. These events are NOT considered treatment failures, but must be recorded.

- ipsilateral and contralateral breast cancer *in situ*
- cervical carcinoma *in situ*
- bladder cancer *in situ*
- basal or squamous cell carcinoma of the skin

Assessment schedule for plasma cardiac markers

Every 6 weeks during trastuzumab monotherapy

- N-terminal Brain Natriuretic Protein (NT-proBNP)
- Troponin-I

Analysis:
Pearson's correlation will be used to determine the correlation between cardiac markers and LVEF, and logistic regression to determine if cardiac markers can predict for cardiotoxicity.

Assessment Schedule for Pro-inflammatory Cytokines

Every 6 weeks during trastuzumab monotherapy

- Interleukin-6 (IL-6)
- Tumor Necrosis Factor Alpha (TNF-α)

Analysis:
Pearson's correlation will be used to determine the correlation between pro-inflammatory cytokines and LVEF, and logistic regression to determine if cardiac markers can predict for cardiotoxicity

Assessment Schedule for QOL and CGA Assessments

Assessment at baseline (prior to the first dose of Trastuzumab)

- Quality of Life and Comprehensive Geriatric Assessment

Assessment at 6 months

- Quality of Life and Comprehensive Geriatric Assessment

Assessment at 12 months

- Quality of Life and Comprehensive Geriatric Assessment

Analysis
Differences in QOL and GCA scores will be examined by paired *t*-test.

Cox proportional hazards regression models will be used to test domains of the CGA as potential predictors of cardiac toxicity and disease-free survival.

3.5 SAFETY PLAN

Patients will be evaluated at each study visit for the duration of their participation in the study (see Section 4.0 (Study Calendar)).

Specific potential safety issues for this trial are outlined below.

3.5.1 Cardiac Dysfunction.

Signs and symptoms of cardiac dysfunction were observed in a number of women who received Trastuzumab alone or in combination with chemotherapy, most often anthracycline-based treatment. Cardiac dysfunction was observed most frequently among patients who received Trastuzumab plus AC chemotherapy (28%), compared with those who received AC alone (7%), Trastuzumab plus paclitaxel (11%), paclitaxel alone (1%), or Trastuzumab alone (7%). Severe disability or fatal outcome due to cardiac dysfunction was observed in ~1% of all patients.

The nature of the observed cardiac dysfunction was similar to the syndrome of anthracycline-induced cardiomyopathy. The signs and symptoms of cardiac dysfunction usually responded to treatment. Complete and partial responses were observed among patients with cardiac dysfunction. The risk appears to be independent of tumor response to therapy. Analysis of the clinical database for predictors of cardiac dysfunction revealed only advanced age and exposure to an anthracycline as possible risk factors. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy, often including discontinuation of Trastuzumab. In many cases, patients were able to resume treatment with Herceptin. In a subsequent study using weekly paclitaxel and Trastuzumab as first-line treatment for metastatic breast cancer, the observed incidence of serious cardiac dysfunction was 3% (N=95).[108] Since the occurrence of cardiac dysfunction in the Trastuzumab plus chemotherapy trial was an unexpected observation, no information is available regarding the most appropriate method for monitoring cardiac function in patients receiving Trastuzumab. Significant advances in the understanding and treatment of CHF have been made in the past several years, with many of the new drugs demonstrating the ability to normalize cardiac function. Patients who develop symptoms of congestive heart failure while on Trastuzumab should be treated according to the HFSA guidelines (Appendix D).

Management of Cardiac Safety for Adjuvant Breast Cancer Protocols

All patients must have a MUGA scan or ECHO at baseline, and on a regular schedule throughout the course of the study. Investigators are strongly urged to schedule MUGA scans/ECHOs at the same radiology facility where the patient's baseline MUGA scan/ECHO was done whenever possible. MUGA scans/ECHOs are required at protocol-specified time points and after any patient has any of the following: discontinuation of protocol therapy, congestive heart failure, breast cancer recurrence, or a second primary cancer. When a cardiac event occurs, the Cardiac Report Form must be faxed in within 14 days of learning of the event.

Post surgical radiation therapy may be required in patients at risk for recurrence. Whenever possible, irradiation to the internal mammary nodes should be avoided because of the concern for possible additional cardiotoxicity from the combination of Trastuzumab and radiation therapy. Efforts should be taken to ensure that the volume of the heart irradiated is minimal. Investigators are encouraged to discuss cardiac toxicity concerns with their radiation oncologists to ensure careful planning of the ports of ***left-sided*** lesions.

Cardiac Safety Criteria for initiation of Herceptin

Asymptomatic Patients

If a patient does not have significant symptoms related to LV dysfunction, administration of Trastuzumab will depend on the absolute change in LVEF between baseline and follow-up assessments.
Trastuzumab should be initiated in an asymptomatic patient if:

a) The LVEF increased or stayed the same;
b) The LVEF decreased by ≤15 percentage points but is still at or above the lower limit of normal for the radiology facility.

Trastuzumab is ***PROHIBITED*** in an asymptomatic patient if:

a) The LVEF decreased ≤15 percentage points and is below the limit of normal for the radiology facility:
b) The LVEF decreased by 16 percentage points or more (regardless of lower limits of normal for the radiology facility)

Symptomatic Patients
If a patient has significant symptoms related to left ventricular (LV) dysfunction, cardiac ischemia, or arrhythmia, initiation of trastuzumab is prohibited.

Management of Symptomatic Cardiac Changes.
Patients who develop signs and symptoms of CHF should have Trastuzumab held and should receive treatment for CHF as prescribed by the HFSA (e.g., ACE inhibitors, angiotensin-II receptor blockers, β-blockers, diuretics, and cardiac glycosides, as needed; see Appendix C for HFSA guidelines). Consideration should be given to obtaining a cardiac consultation.

If the symptoms of CHF resolve with treatment, and cardiac function improves, trastuzumab may be continued after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO) is strongly recommended until cardiac function has normalized.

Management of Asymptomatic Decreases in LVEF.
Trastuzumab may be continued in patients experiencing an asymptomatic absolute decrease in LVEF of <20 percentage points from baseline, when the ejection fraction remains within the imaging center's range of normal limits. Repeat measures of LVEF

should be obtained using the methodology selected at baseline. Close follow-up of such patients is recommended. Patients with an asymptomatic absolute decrease in LVEF of ≥20 percentage points or an ejection fraction below the range of normal limits, should have trastuzumab held and be considered for treatment of incipient CHF as prescribed by the HFSA (e.g., ACE inhibitors, angiotensin-II receptor blockers, β-blockers, diuretics, and cardiac glycosides, as needed; see Appendix C for HFSA guidelines). In light of the variability inherent in the assessment of ejection fraction, consideration should be given to repeating the study to confirm an observed decline. Repeat measures of LVEF should be obtained using the same methodology selected at baseline. If trastuzumab has been discontinued for an asymptomatic decline in LVEF, a repeat measure of LVEF will be obtained in 1 month to determine if the decline has resolved.

If cardiac function improves, trastuzumab may be restarted after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO), using the methodology selected at baseline, is strongly recommended until cardiac function has normalized.

Table 3 below summarizes rules governing trastuzumab suspension in the event of asymptomatic decline in LVEF

Table 3: Asymptomatic Decrease in LVEF: Percentage Points from Baseline

Relationship of LVEF to radiology facility's LLN	**Decrease of <10 percentage points**	**Decrease of 10 to 15 percentage points**	**Decrease of ≥16 percentage points**
Within normal limits	Continue	Continue	Hold and repeat MUGA/echocardiogram after 4 weeks
1-5 percentage points below LLN	Continue and repeat MUGA/echocardiogram after 4 weeks	Hold and repeat MUGA/echocardiogram after 4 weeks	Hold and repeat MUGA/echocardiogram after 4 weeks
≥ 6 percentage points below LLN	Continue and repeat MUGA/echocardiogram after 4 weeks	Hold and repeat MUGA/echocardiogram after 4 weeks	Hold and repeat MUGA/echocardiogram after 4 weeks

3.5.2 Infusion-Associated Symptoms. During the first infusion with trastuzumab, a symptom complex consisting of chills and/or fever is observed in approximately 40% of patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent trastuzumab infusions. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine.

3.5.3 Serious Infusion-Associated Events. Serious adverse reactions to trastuzumab infusion including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently. In rare cases (4 per 10,000), these events were associated with a clinical course culminating in a fatal outcome. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of trastuzumab as indicated.

3.5.4 Hematologic Toxicity and Neutropenic Infections In the clinical trials, an increased incidence of anemia was observed in patients receiving trastuzumab plus chemotherapy compared with patients receiving chemotherapy alone. The majority of these anemia events were mild or moderate in intensity and reversible; none resulted in discontinuation of trastuzumab therapy.

In the clinical trials, the per-patient incidences of moderate to severe neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. In the post marketing setting, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving trastuzumab and myelosuppressive chemotherapy, although in controlled clinical trials (pre- and post-marketing), the incidence of septic deaths was not significantly increased. The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of trastuzumab on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated.

Secondary acute leukemia or myelodysplastic syndrome has been reported in 4 of approximately 1200 patients who participated in trastuzumab clinical trials. Patients treated with chemotherapeutic agents are known to be at increased risk for secondary leukemia. The observed incidence of leukemia among trastuzumab-treated patients appears to be consistent with the expected incidence of leukemia among patients treated with chemotherapy for metastatic breast cancer (7). Therefore, the contribution of trastuzumab to the etiology of acute leukemia or myelodysplastic syndrome in these cases is unclear.

Management of Hematologic Toxicities
Care should be taken to carefully monitor the patient's hematologic status throughout the course of the trial. Use of hematopoietic growth factors to ameliorate hematologic toxicity is at the discretion of the physician investigator and should be in accordance with the American Society of Clinical Oncologists (ASCO) guidelines.

Please refer to the HERCEPTIN® Investigator Brochure for a detailed description of the safety profile of Herceptin.

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

3.6 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirement

4.0 STUDY PARAMETERS AND CALENDAR

Table 4: Study Calendar for Screening, Treatment and Surveillance Period						
	Screening	**Treatment**			**Surveillance**	
	Pre study period	**Week 1**	**Weeks 2-51**	**Week 52 End of Treatment**	**Year 2 to end of year 3**	**Year 4 to end of Year 5**
Eligibility	✓					
Review study procedures	✓					
Sign informed consent	✓					
Demographics	✓					
Baseline history and Physical Examination	✓					
Cardiac History	✓		Every 6 months	✓	Every 6 months	Every 6 months
Administer QOL and CGA tools	✓		Every 6 months	✓		
CBC, Complete Metabolic profile	✓		Every 3 weeks	✓	Every 6 months	Every 6 months
Cardiac markers	✓		Every 6 weeks	✓	†	Cardiac Markers only @60mths
MUGA/Echo*	✓		Every 3 months	✓		@60mths
Loading dose of trastuzumab		✓				
Maintenance dose of trastuzumab			Every 3 weeks	✓		
Limited physical examination and history			Every 6 weeks	✓	Every 6 months	Every 6 months
Assessment of adverse events			Every 3 weeks	✓		
†Cardiac markers will not be tested during the surveillance period *MUGA/ECHO measurements will be done every 4 weeks for patients who develop significant left ventricular cardiac dysfunction requiring trastuzumab to be held.						

5.0 MATERIALS AND METHODS

5.1 SUBJECTS

5.1.1 Inclusion Criteria

Patients will be included in the study based on the following criteria:

- Women with histologically confirmed adenocarcinoma of the breast
- Immunohistochemical staining for Her2 protein of 3+ intensity or Her2 gene amplification of ≥ 2.0 by FISH testing.
- Life expectancy > 6 months, age ≥60 years
- ECOG performance status ≤ 2
- Node positive disease irrespective of tumor size
- Node negative disease:

  TNM Stage (AJCC Cancer Staging Manual 6th edition) T1b-T4, N0-3, M0, irrespective of hormonal status

- Baseline LVEF ≥ lower limit of normal for a particular institution
- Complete surgical removal of invasive cancer by mastectomy or lumpectomy
- Complete staging work-up with CT of chest, abdomen, and pelvis plus bone scan or alternatively with PET scan for stage II and higher disease, or as determined by symptoms for all other stages. Additional staging work-up as per symptoms.
- Adequate bone marrow function as indicated by the following:

  ANC >1000/μL

  Platelets ≥100,000/μL

  Hemoglobin >10 g/dL

- Adequate liver function, as indicated by bilirubin ≤1.5× ULN

  Adequate renal function, as indicated by creatinine ≤1.5× upper limit of normal (ULN)

- AST or ALT <2× ULN unless related to primary disease.
- Signed informed consent

5.1.2 Exclusion Criteria

- Enrollment after more than 120 days from the last day of mastectomy or lumpectomy
- Patients able to tolerate and willing to receive chemotherapy
- Prior chemotherapy for current malignancy
- Prior herceptin therapy

Active cardiac disease

- Myocardial infarction (asymptomatic changes on EKG suggestive of old MI is not an exclusion)
- Angina pectoris requiring anti-anginal treatment
- Documented congestive heart failure (CHF)
- Current use of any therapy specifically for CHF
- Cardiac arrhythmia requiring medication
- Current uncontrolled hypertension (diastolic >100 mmHg or systolic > 200 mmHg)
- Clinically significant valvular abnormality (associated with New York Heart Association (NYHA) class II, III, or IV symptoms)
- Clinically significant pericardial effusion (associated with New York Heart Association (NYHA) class II, III, or IV symptoms)

Past cardiac disease

- Prior myocardial infarction (asymptomatic changes on EKG suggestive of old MI is not an exclusion)
- Prior history of CHF
- History of cardiomyopathy

Other diseases and conditions

- Evidence of metastatic breast cancer (clinical or radiological evidence)
- Active infection
- Concomitant malignancies or previous malignancies within the last 3 years, with the exception of adequately treated basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix.
- Hypersensitivity to trastuzumab

5.1.3 Inclusion of Women and Minorities

This study will be open to women of all ethnic backgrounds who meet eligibility criteria. Accrual targets will not be specific for ethnic groups.

5.2 REGISTRATION PROCEDURES

This is a single arm trial that does not require randomization. Case Comprehensive Cancer Center will be the coordinating institution for the study. To enter eligible patients on study, investigators from participating institutions listed on the cover sheet will register patients by contacting the Study Coordinator at (216) 844-1545. The following information will be requested: a registration card, copy of the informed consent which may be obtained by investigators of participating institutions or their designee, and a copy of the signed eligibility checklist. These must be submitted prior to a patient starting treatment. These documents can be faxed to (216) 201-5013. All patients enrolled on the study will be entered into a secure database at Case Comprehensive Cancer Center called Oncore database.

5.3 TREATMENT PLAN

5.3.1 Trastuzumab Administration and Supportive Measures

5.3.1.1 Loading dose of trastuzumab: Patients will receive an 8mg/kg IV loading dose on day 1.

5.3.1.2 Maintenance Phase of trastuzumab:
Every 3 week schedule: 6 mg/kg IV every 3 weeks to complete 52 weeks of treatment

5.3.1.3 The initial dose of trastuzumab will be administered over 90 minutes. If this first dose is well tolerated, subsequent infusion times may be shortened to 30 minutes. If the initial or a subsequent dose is not well tolerated (i.e. fevers, chills, or rigors), subsequent infusion times may be shortened only after a dose is well tolerated.

5.3.1.4 If during the maintenance phase with trastuzumab monotherapy a dose of trastuzumab is delayed the dose of trastuzumab should not be made up and reloading doses are not to be given.

5.3.1.5 Treatment is permitted in an asymptomatic patient if:

- The LVEF increased or stayed the same OR
- The LVEF decreased by ≤15 percentage points, but is still at or above the radiology facility's lower limit of normal (LLN)

5.3.1.6 Treatment is prohibited in an asymptomatic patient if:

- The LVEF decreased by ≤15 percentage point and is below the radiology facility's lower limit of normal limit

- The LVEF decreased by 16 percentage point or more, regardless of the radiology facility's LLN

See Table under section 3.5.1

5.4 STUDY TREATMENT

Genentech will supply Herceptin.

5.4.1 Herceptin Formulation

Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each vial of Herceptin contains 440 mg of trastuzumab, 9.9 mg of L-histidine HCl, 6.4 mg of L-histadine, 400 mg of α,α-trehalose dihydrate, and 1.8 mg of polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection (BWFI) USP, containing 1.1% benzyl alcohol as a preservative, yields 21 mL of a multidose solution containing 21 mg/mL trastuzumab, at a pH of ~6.

5.4.2 Herceptin Dosage, Preparation, Administration, and Storage

a. Dosage

The recommended initial loading dose is 8 mg/kg Herceptin administered as a 90-minute infusion. The recommended maintenance Herceptin dose is 6 mg/kg q3wk and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. Herceptin may be administered in an outpatient setting. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS (see ADMINISTRATION).

b. Preparation

Use appropriate aseptic technique. Each vial of Herceptin should be reconstituted with 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multidose solution containing 21 mg/mL Herceptin. Immediately upon reconstitution with BWFI, the vial of Herceptin must be labeled in the area marked "Do not use after" with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, Herceptin must be reconstituted with Sterile Water for Injection (see PRECAUTIONS). Herceptin which has been reconstituted with SWFI must be used immediately and any unused portion discarded. Use of other reconstitution diluents should be avoided. Determine the dose of Herceptin needed, based on a loading dose of 8 mg Herceptin/kg body weight or a maintenance dose of 6 mg Herceptin/kg body weight. Calculate the correct dose using 21 mg/mL Herceptin solution. Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% sodium chloride, USP. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

No incompatibilities between Herceptin and polyvinylchloride or polyethylene bags have been observed.

c. Administration
Treatment may be administered in an outpatient setting by administration of an 8 mg/kg Herceptin loading dose by intravenous (IV) infusion over 90 minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** Patients should be observed for fever and chills or other infusion-associated symptoms (see ADVERSE REACTIONS). If prior infusions are well tolerated subsequent doses of 6 mg/kg Herceptin q3wk may be administered over 30 minutes.

Table 5

Herceptin Infusion Time and Post-Infusion Observation Period

Herceptin Dose		Infusion Time (minutes)	Post-Infusion Observation Period (minutes)
First infusion	8 mg/kg	90	60
Second infusion	6 mg/kg	30 [a]	30 [a]
Third and subsequent infusions	6 mg/kg	30 [a]	None [a]

[a] Only if previous dose was well tolerated.

Herceptin should not be mixed or diluted with other drugs. Herceptin infusions should not be administered or mixed with Dextrose solutions.

d. Storage
Vials of Herceptin are stable at 2°C–8°C (36°F–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of Herceptin reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2°C–8°C (36°F–46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted Herceptin solution should be used immediately and any unused portion must be discarded. DO NOT FREEZE HERCEPTIN THAT HAS BEEN RECONSTITUTED.

The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for injection, USP, may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use. Diluted Herceptin has been shown to be stable for up to 24 hours at room temperature 15°C–25°C; however, since diluted Herceptin contains no effective preservative the reconstituted and diluted solution should be stored refrigerated (2°C–8°C).

5.4.3 Herceptin Dosage Modification

- No dose modifications are permitted.

- No cardioprotective drugs are permitted. There are no data for the use of cardioprotective agents such as dexrazoxane (Zinecard®)

5.4.4 Toxicities

5.4.4.1 Infusion-associated symptoms

5.4.4.1.1 During the first infusion, a symptom complex of fever and/or chills may occur. These are usually mild-to-moderate and may be accompanied by nausea, vomiting, headache, dizziness, rigors, pain, hypotension, rash, and asthenia. These symptoms occur infrequently during subsequent infusions.

5.4.4.1.2 Serious adverse reactions to Trastuzumab infusion include dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress have been reported infrequently. In rare cases (4 per10,000) these events were associated with a clinical course culminating in fatal outcome.

5.4.4.2 Cardiac Dysfunction

5.4.4.2.1 Trastuzumab may result in clinically manageable left ventricular systolic dysfunction, and occasionally advanced congestive heart failure (CHF) in a small proportion of patients. The incidence and severity of cardiac dysfunction has been greatest in patients who received Trastuzumab in combination with an anthracycline. In the pooled NSABP/NCCTG experience, the risk of cardiac events was 4% among those treated with chemotherapy and trastuzumab, as compared with .6% for those given chemotherapy alone. There are data suggesting that the risk is lower when sequential chemotherapy followed by trastuzumab is given Furthermore, older patients and those patients with borderline normal LVEF at baseline may be at greater risk for cardiac events. The incidence of class III or IV cardiac dysfunction was 2% for those receiving concurrent paclitaxel plus trastuzumab.[22] The risk of cardiac toxicity is

substantially lower in patients who received trastuzumab alone. Cardiac dysfunction appears to improve in most patients who receive supportive medical treatment.

5.4.4.2.2 Individual patients should have their MUGA scans/echocardiograms performed at the same radiology facility to eliminate variability between facilities.

5.4.4.2.3 Asymptomatic decrease in LVEF:
Decision to continue or stop is based on the measured ejection fraction as it relates to the radiology facility's LLN and change in ejection fraction from baseline. See section 3.5.1 for guidelines for performing MUGA scan/echocardiogram and management of patients who have an asymptomatic decrease inLVEF from baseline.

5.4.4.2.4 If trastuzumab is not started or discontinued during therapy, MUGA scan/echocardiogram still needs to be done at 12 weeks and at 1 year.

5.4.4.2.5 Trastuzumab must be permanently discontinued when two consecutive "hold" categories occur.

5.4.4.2.6 Trastuzumab must be permanently discontinued when three intermittent "hold" categories occur.

5.4.4.2.7 At the discretion of the investigator, trastuzumab may also be permanently discontinued prior to the occurrence of three intermittent "hold" categories.

5.4.4.2.8 If LVEF is maintained at a "continue and repeat MUGA/echocardiogram" or improves from a "hold" to a "continue and repeat MUGA/echocardiogram" category, additional MUGA scans/echocardiogram prior to the next scheduled MUGA scan/echocardiogram will be at the discretion of the investigator.

5.4.4.3 Symptomatic decrease in LVEF

5.4.4.3.1 Grade 3 CHF

5.4.4.3.1.1 Monitor for signs and symptoms of CHF (i.e. dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc)

5.4.4.3.1.2 If patient develop these signs and symptoms,

hold treatment.

5.4.4.3.1.3 Confirm diagnosis of CHF with either a MUGAscan/echocardiogram. A chest x-ray is also required. Once a diagnosis of CHF is confirmed, trastuzumab must be permanently discontinued and reported as an adverse event.

5.4.4.3.1.4 Follow-up at 3, 6, and 12 months from time of CHF diagnosis with MUGA scan/echocardiogram.

5.4.4.3.2 Grade 4 CHF (severe refractory CHF or requiring intubation)

5.4.4.3.2.1 Discontinue treatment, and report as an adverse event.

5.4.4.3.2.2 Follow-up at 3, 6, and 12 months with MUGA/echocardiogram.

5.4.4.4 Ischemia

5.4.4.4.1 Grade 1

5.4.4.4.1.1 Continue treatment with frequent monitoring.

5.4.4.4.2 Grade 2

5.4.4.4.2.1 Hold treatment and conduct cardiac evaluation.

5.4.4.4.2.2 Based on this evaluation, treatment may be continued at the discretion of the investigator.

5.4.4.4.3 Grade 3 or 4

5.4.4.4.2.3 Discontinue treatment.

5.4.4.5 Arrhythmia

5.4.4.5.1 Grade 1

5.4.4.5.1.1 Continue treatment with careful monitoring OR hold treatment and conduct cardiac evaluation.

5.4.4.5.1.2 Based on cardiac evaluation, treatment with trastuzumab and may continue or discontinue at the discretion of the investigator.

5.4.4.5.2 Grade 2

5.4.4.5.2.1 Hold treatment and conduct cardiac evaluation.

5.4.4.5.2.2 Based on cardiac evaluation, treatment with trastuzumab may continue or discontinue at the discretion of the investigator.

5.4.4.5.3 Grade 3 or 4

5.4.4.5.3.1 Discontinue trastuzumab.

5.4.4.6 Myocardial Infarction

5.4.4.6.1 Discontinue treatment

5.4.4.7 Fever

5.4.4.7.1 Grade 1 (38°C - 39°C [100.4° - 102.2°F] OR Grade 2 (39.1°C - 40°C [102.3° - 104°F]

5.4.4.7.1.1 Stop infusion and give antipyretics. Once temperature is <38°C, resume infusion at a slower rate.

5.4.4.7.2 Grade 3 (>40°C [104°]) OR Grade 4 (40°C [104°F] for 24 hours)

5.4.4.7.2.1 Stop infusion immediately and give antipyretics

5.4.4.7.2.2 Monitor patient for a minimum of one hour

5.4.4.7.2.3 If temperature drops to <38°C within 3 hours, resume infusion at a slower rate.

5.4.4.7.2.4 If fever does not resolve within 3 hours, inpatient monitoring is strongly recommended.

5.4.4.7.2.5 If temperature drops to <38°C within 3 days, re-challenge at a slower rate.

5.4.4.7.2.6 If temperature remains >38°C after 3 days, abandon this administration and subsequent administration is at the discretion of the investigator

5.4.4.8 Chills

5.4.4.8.1 Treat with acetaminophen and/or diphenhydramine hydrochloride. Meperidine may be given at the investigator's discretion.

5.4.4.9 Gastrointestinal

5.4.4.9.1 Diarrhea

5.4.4.9.1.1 Any grade

Any anti-diarrheal medication may be given at the investigator's discretion.

5.4.4.10 Allergy/Immunology

5.4.4.10.3 Allergic reaction/hypersensitivity (including drug fever) Stop the infusion and give diphenhydramine Hydrochloride. If toxicity resolves within 3 hours, treatment in next dose is allowed at a slower rate and under close observation. If toxicity does not resolve in 3 hours, overnight observation is recommended and

treatment in the next dose under close observation is at the discretion of the investigator.

5.4.4.11 Pulmonary

5.4.4.11.1 Any (e.g. Adult Respiratory Distress Syndrome[ARDS], pneumonitis/pulmonary infiltrates, etc)

Delay trastuzumab until cause is known. If pneumonitis/fibrosis, or pulmonary infiltrate is confirmed, and the relationship to trastuzumab cannot be excluded, trastuzumab must be permanently discontinued.

5.4.4.12 Hematologic Toxicity

5.4.4.12.1 Anemia

An increased incidence of anemia has been observed in patients receiving trastuzumab plus chemotherapy compared with patients receiving chemotherapy alone. The majority of these anemia events were mild or moderate in intensity and reversible. None resulted in discontinuation of trastuzumab.

5.4.4.12.2 Neutropenia

In randomized controlled clinical trials designed to assess the impact of the addition of trastuzumab to chemotherapy, the incidence of moderate to severe neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with chemotherapy as compared to those who received chemotherapy alone. The pathophysiologic basis for exacerbation of neutropenia has not been determined.

5.4.4.12.3 Secondary acute leukemia or myelodysplastic syndrome

Incidence of approximately 4 in 1200 patients who participated in trastuzumab clinical trials. Patients treated with chemotherapeutic agents are known to be at increased risk of secondary leukemia. The observed incidence of leukemia among trastuzumab-treated patients appears to be consistent with the expected incidence of leukemia among patients treated with chemotherapy for metastatic breast cancer.[25] The contribution of trastuzumab to the etiology of acute

leukemia or myelodysplastic syndrome in these cases is unclear.

5.4.5 Herceptin Overdosage

There is no experience with overdosage in human clinical trials. Single doses higher than 500 mg have not been tested.

5.5 ANCILLARY THERAPY

5.5.1 Patients should receive full supportive care, including transfusions of blood or blood products, antibiotics, antiemetics, etc., when appropriate.

5.5.2 Treatment with other chemotherapeutic agents or biologic agents may not be administered except for hormonal therapy given for patients with hormone positive disease, steroids given for adrenal failure, hormones administered for non- disease-related conditions (insulin for diabetes, synthroid for hypothyroidism); and intermittent use of dexamethasone as an antiemetic

5.5.3 Use of Growth Factors

5.5.3.1 Erythropoetin (EPO) and Related Agents. The use of EPO is permitted at the discretion of the treating physician.

5.5.3.2 Filgrastim (G-CSF) and Related Agents. The use of filgrastim is permitted at the discretion of the treating physician

5.6 CONCOMITANT AND EXCLUDED THERAPY

5.6.1 Radiation Therapy

5.6.1.1 Patients who undergo lumpectomy (breast conserving surgery) must receive breast radiation therapy. This may be performed according to local institutional standards. Patients may be treated with conventional, whole breast radiation, or partial breast radiation, administered by external beam or brachytherapy.

5.6.1.2 Radiation therapy will begin after completion of primary surgery (lumpectomy or mastectomy if indicated)

5.6.1.3 Patients undergoing mastectomy may receive chest wall and nodal radiation according to local institutional standards.

5.6.1.4 Patients may receive adjuvant trastuzumab as per protocol during radiotherapy.

5.7 STUDY ASSESSMENTS

See section 3.3 for study assessments

5.8 DISCONTINUATION OF PROTOCOL-SPECIFIED THERAPY

Trastuzumab may be discontinued for any of the following reasons:

- Recurrent disease
- Unacceptable toxicity
- Patient election to discontinue therapy (for any reason)
- Physician's judgment

5.9 SUBJECT DISCONTINUATION

Even after a patient agrees to take part in this study, she may stop study therapy or withdraw from the study at any time. If she stops study therapy but still allows the study doctor to submit follow-up information, she should continue to be followed according to the study schedule. Alternatively, she may choose to have no further interaction regarding the study. In this case, the investigator must provide documentation of the patient's decision to fully withdraw from the study in the case report form. No special tests are needed at the time of discontinuation. Patients who choose to discontinue the study cannot resume participation at a later date.

Since this is a non-randomized study, patients who fully withdraw from the study should be replaced.

The reason for premature discontinuation of a subject must be recorded on the Case Report Form.

5.10 STUDY DISCONTINUATION

Genentech Study Center, and the Principal Investigator have the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording are inaccurate or incomplete
- Study protocol not followed

5.11 STATISTICAL METHODS

5.11.1 Study Design

This is an open label, single arm, phase II pilot study evaluating the safety and efficacy of single agent adjuvant trastuzumab at 8mg/kg IV loading dose, followed by 6mg/kg IV every three weeks to complete 52 weeks of treatment, among women 60 years and older.

5.11.2 End Points

5.11.2.1 Primary End-point

The primary outcome measure is the incidence of cardiac events over a three-year follow-up period and is defined by any one of the following events;

- Definitive cardiac death; due to CHF, MI, or documented arrhythmia
- Any possible/probable cardiac death over the three-year follow-up period defined as a sudden unexpected death within 24 hours after a definitive cardiac event , and without definitive documented alternative cause.
- Signs and symptoms of congestive heart failure (CHF). CHF will be defined as follows: New York Heart Association (NYHA) class III or IV symptoms with either a decrease from baseline in LVEF of more than 10 percentage points to less than 55% or a decrease of more than 5 percentage points to less than the lower limit of normal. Class III is characterized by symptoms of dyspnea with activities such as climbing a flight of stairs, whereas class IV symptoms are present at rest.

5.11.2.2 Secondary End-points

- The three-year cumulative incidence of asymptomatic left ventricular cardiac dysfunction defined as an asymptomatic decrease in LVEF from baseline of at least ten percentage points to below the lower limit of normal or an absolute decrease of >15 percentage points leading to a permanent discontinuation of trastuzumab before completion of one year of therapy.

- The five-year cumulative incidence of cardiac events for long term cardiac monitoring and defined as above under section 5.11.2.1

- Mean change in plasma cardiac markers from baseline to mid treatment, and from baseline to end of treatment.

- Mean change in pro-inflammatory cytokines from baseline to mid treatment, and from baseline to end of treatment.

- Mean change in QOL and CGA scores from baseline to mid treatment, and from baseline to end of treatment.

- Disease-free survival (DFS) defined as the time from treatment initiation to the date of first loco-regional or distant treatment failure, ignoring any intervening contra-lateral breast cancers or other second primary cancers. Deaths without evidence of recurrence will be treated as censoring events.

- Overall survival defined as the time from treatment initiation to the date of death from any cause and censored to the date of last follow-up for survivors.

5.11.3 Sample Size Justification

The target accrual of this study is 124 patients. The primary endpoint used in the sample size calculation is the cumulative incidence of cardiac events over a three-year period. We hypothesize that the incidence (P) of cardiac events in this trial will be no bigger than 4% and that incidence of cardiac events bigger than 10% is considered unacceptable. With a type I error of 0.05, the estimated sample size based on a two-sided chi-square test is 113. With 10% attrition rate, the sample size required for this study is 124 patients. With 124 patients, the power to test the null hypothesis H_0: $P \leq 0.04$ vs. H_a: $P > 0.1$ is above 80%. By the accrual rate of 7 patients per institution per year, the enrollment is expected to complete within about 3.5 years. Our acceptable cardiac toxicity rate of 4% is derived from NSABP-B31[20] study, in which the three-year cumulative incidence of symptomatic cardiac dysfunction was 4.1%. Our unacceptable cardiac toxicity rate of 10% is derived from an overall cardiac dysfunction rate of up to 7%[21,22] associated with the use of single agent trastuzumab in the metastatic setting.

Early Stopping Rules

A formal interim analysis plan will be used to monitor the cardiotoxicity rate, defined as the number of cardiotoxicity events divided by the person-years of follow-up at that time. This is an estimate of the hazard of cardiotoxicity, assuming an exponential distribution for time to cardiotoxicity. The timing of the interim analyses will be based on the number of cardiotoxicity events; analyses will occur when the cumulative number of events is 3, 6, 9, as well as at one year after enrollment of the last patient. Thus, there will be up to three interim analyses. At each interim analysis, we will use an exact one-sided Poisson test to test the null hypothesis that the exponential hazard is less than or equal to 0.0136 (corresponding to a 4% 3-year event rate) versus the alternative hypothesis that it is 0.0351 or higher (corresponding to a 10% 3-year cardiotoxicity event rate). A Lan-DeMets type I error spending function with overall type I error rate of 0.05 will be used to determine the significance level used at each analysis. If the null hypothesis is rejected, then the trial will be stopped. If the 3-year cardiotoxicity event rate is 10%, with 124 patients enrolled uniformly over two years and followed an additional 3 years, and allowing for 10% exponential loss due to death or dropout over 3 years, approximately 12 (11.78) cardiotoxicity events within 3-years of enrollment will be observed by the end of the study. Therefore, the interim analyses occurring at 3, 6, and 9 cumulative events correspond approximately to information times of 0.25, 0.50, and 0.75. Alternatively, if the true 3-year cardiotoxicity rate is 4%, then the expected total number of cardiotoxicities observed over 3 years among the 124 patients is only 4.7. Although interim analyses will be based on testing the exponential hazard, for the primary analysis the 3-year incidence of cardiotoxicity will be estimated using the Kaplan-Meier method.

5.11.4 ACCRUAL ESTIMATES AND RATE

Accrual estimates
Five institutions are participating in this study. With an accrual rate of 7 patients per institution per year we expect to accrue 124 participants into the study within 3.5 years.

5.11.5 Statistical Analysis

- Descriptive statistics, such as means, median, range, and frequencies, will be used to describe subjects' cardiac toxicity profile.
- Time to incidence of cardiac events will be measured from the date of treatment initiation to the date of cardiac event and censored at the date of last follow-up or the date of death due to non cardiac causes for those who do not have a cardiac event. The cumulative incidence of cardiac events and its 95% confidence interval will be estimated using Kaplan-Meier[104].
- Potential factors that predict the incidence of cardiac toxicity will be identified by multivariable Cox proportional hazards analysis.[109]
- Pearson's correlation will be used to determine the correlation between cardiac markers and LVEF.
- The difference in mean QOL and CGA scores from baseline to mid treatment, and from baseline to end of treatment will be examined by paired *t*-test.
- The Kaplan-Meier method[110] will be used to estimate disease-free survival and overall survival.
- Cox proportional hazards regression models[109] will be used to test selected variables as potential predictors of disease-free-survival and overall survival.
- All eligible subjects who received at least one dose of trastuzumab will be included in survival (time-to-event) analysis.
- All statistical testing will be two-sided and level of significance will be assumed at 5%.

5.11.6 Missing Data

Completion of all scheduled protocol forms is part of the routine delinquency assessment for all collaborating institutions. Adherence to the assessment schedule will be encouraged by means of proactive reminders to the participating institutions. The Data coordinating staff at Case Comprehensive Cancer Center will continue to monitor missing information at different assessment points. If the proportion of missing information is related to specific centers or specific assessments, interventions will be developed in order to correct problems in the data collection process and to bring delinquent centers back in line with the protocol. If all efforts to collect information on a scheduled questionnaire fail, the center will be required to submit a Missing Data Form to the study coordinator at Case Comprehensive Cancer Center. Despite these precautions, a certain amount of missing data is expected. The information from patients with missing data will be reviewed in order to determine whether the data analytic procedures will be biased. Subjects with missing data will be reviewed for imbalances in factors such as treatment adherence, collaborating

center, and reasons for non-adherence. Mean scores on the primary measures will be compared for patients with or without missing data at different assessment points in order to investigate whether missing data is arising from a systematic error and likely to introduce a bias into the analysis. If no missing data mechanism can be detected following this review, the data will be analyzed assuming the missing data are at random. In the case of item non-response, summed scores will be computed using the mean from the other items in the analysis. If a missing data mechanism appears to be present, we will undertake to develop an appropriate analytic strategy to control for the potential bias and, if possible, to impute the missing values. The appropriateness of alternative strategies will depend upon both the pattern (e.g., item non-response versus intermittent missing forms versus complete dropouts) and the severity of the missing data problem. For example, an appropriate strategy could
involve the stratification of the patients in the study in terms of the completeness of their data for key time periods (e.g., 6 months or 1 year) and the comparison of results from separate analyses for each group or it could involve the implementation of more sophisticated imputation procedures designed to model a missing data mechanism within the framework of a repeated measure analysis. We will also present sensitivity analyses based on varying assumptions about the missing-data mechanism.

5.12 DATA QUALITY ASSURANCE

We will conduct the trial according to the ICH Good Clinical Practice guidelines. Keeping accurate and consistent records is essential in a multi-institutional study. To ensure good quality data, all randomization, baseline, intervention, and follow-up forms will be signed by an investigator at each site or their designee. Monthly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team twice a year.

5.13 DATA SAFETY AND MONITORING PLAN

This protocol will adhere to the policies of the Seidman Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations. The data and safety committee will review all serious adverse events and toxicity reports as well as annual reviews.

6. REPORTING OF ADVERSE EVENTS

6.1 ADVERSE EVENT AND REPORTING DEFINITIONS

With the occurrence of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Genentech Drug Safety any **serious adverse event**, whether **expected** or **unexpected**, and which is assessed by the investigator to be **reasonably or possibly related** to or caused by

Herceptin. All events meeting these criteria will be reported for the time period beginning with any amount of exposure to Herceptin through the protocol-defined follow-up period. Serious criteria, definitions, and guidance for reporting follow.
An **adverse event (AE)** is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Serious adverse events (SAE) are adverse events occurring at any dose which meet one or more of the following **serious criteria**:

Results in **death** (i.e. the AE caused or led to death)

Is **life-threatening** (i.e. the AE placed the subject at immediate risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe)

Requires or prolongs inpatient **hospitalization** (i.e. the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)

Is **disabling** (i.e. the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)

Is a **congenital anomaly/birth defect** (i.e., an adverse outcome in a child or fetus of a subject exposed to the study drug prior to conception or during pregnancy)

Does not meet any of the above serious criteria but **may jeopardize the subject** and **may require medical or surgical intervention** to prevent one of the outcomes listed above

Expected adverse events are those adverse events that are **listed** or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those **not listed** in the Package Insert (P.I.) or current Investigator Brochure (I.B.). This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

6.2 REPORTING OF SERIOUS ADVERSE EVENTS ASSOCIATED WITH HERCEPTIN

All SAEs that are serious and reasonably or probably related to the use of

Herceptin (this applies to both expected and unexpected events) should be recorded on a MedWatch 3500 Form (Appendix D) and faxed to:

Genentech Drug Safety Contact Line

Tele: 1-888-835-2555

Fax: (650) 225-4682/ (650) 225-4683

AND:

Cynthia Owusu, Principal Investigator

Tele: 1-216-844-7670

Fax: 1-216- 844-5234

AND:

Leda Dumadag, Study Coordinator

Tele : 1-216 844-8098

Fax: 216-201-4341

MedWatch 3500 Reporting Guidelines:
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500 form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500 report and submitting as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted). The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above.

Study Drug Relationship:

The investigator will determine which events are associated with the use of study drug. For reporting purposes, an AE should be regarded as possibly related to the use of Herceptin® if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and Herceptin administration; and/or
- There is a biologically plausible mechanism for Herceptin to cause or contribute to the AE; and
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

Reporting to the FDA in compliance with 21 CFR 321 .32 (FDA reporting of IND safety report).

The sponsor shall notify the FDA:

- Written reports of any adverse experience associated with the use of the drug that is both serious and unexpected.
- The sponsor shall notify the FDA by telephone or facsimile transmission of any unexpected fatal or life-threatening experience as associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsors initial receipt of the information.
- If the results of a sponsor's investigation shows that an adverse drug experience not initially determined to be reportable, is so reportable , the sponsor shall report such experience in a written safety report as soon as possible, but no later than 15 calendar days after the determination is made.

7. INVESTIGATOR REQUIREMENTS

7.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with Genentech or a Genentech representative:

- Original U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.

- Current *curriculum vitae* of the Principal Investigator
- Written documentation of IRB approval of protocol and informed consent document
- A copy of the IRB-approved informed consent document from all participating institutions
- A signed Clinical Research Agreement

7.2 STUDY COMPLETION

The following materials are requested by Genentech when a study is considered complete or terminated:

- A summary, prepared by the Principal Investigator, of the study, and/or a study manuscript, and/or a study abstract submitted to scientific conferences.

7.3 INFORMED CONSENT

An informed consent template will be provided, and the final IRB-approved document must be provided to Genentech for regulatory purposes.

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

7.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific adverse event requirements that investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

7.5 STUDY MONITORING REQUIREMENTS

Site visits may be conducted by an authorized Genentech representative to inspect study data, subjects' medical records, and CRFs in accordance with current U.S. GCPs and the respective local and national government regulations and guidelines (if applicable).

The Principal Investigator will permit authorized representatives of Genentech, the U.S. FDA, and the respective national or local health authorities to inspect facilities and records relevant to this study.

7.6 DATA MANAGEMENT ISSUES

A data coordinator will be assigned to the study. The data manager will have the responsibilities which include study compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. Case Comprehensive Cancer Center will be the coordinating institution for this study. All data collected for this study will be transferred via fax (216 844 8599) and will be entered into a secure database (Oncore) at the Case Comprehensive Cancer Center. In addition source documentation will be available to support the computerized patient record. Source documentation will be stored in a locked filing cabinet under the supervision of the Principal Investigator.

7.7 STUDY MEDICATION ACCOUNTABILITY (IF APPLICABLE)

Trastuzumab will be provided by Genentech.

7.8 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, Genentech, and the IRB for each study site, if appropriate.

7.9 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified. Genentech will notify the Principal Investigator of these events.

8. 0 PROTECTION OF HUMAN SUBJECTS

All institutional, FDA, and Federal regulations concerning informed consent and peer judgment will be fulfilled.

8.1 ETHICS

The trial will be conducted in full agreement with the principles of the Declaration of Helsinki and International Committee on Harmonization guidelines for good clinical practice. The trial protocol will be approved by the institutional review board. Written informed consent will be obtained from each subject before start of the study after explaining the objectives, methods, and potential benefits/risks of the study. It will also be explained to subjects that they are free to refuse participation in the study or withdraw from the study at any time. A patient's decision not to participate or choosing to withdraw from the study will in no way compromise the patient's continued care.

8.2 PRIVACY AND CONFIDENTIALITY

All information collected during the study will be maintained in a confidential manner in compliance with regulations enacted pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Patient records may be inspected by auditing agencies to satisfy regulatory requirements.

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APPENDIX A
National Cancer Institute Common Toxicity Criteria
obtained from http://ctep.cancer.gov/forms/CTCAEv3.pdf

APPENDIX B
HFSA Guidelines
Recommendations for Pharmacological Therapy:
Left Ventricular Systolic Dysfunction

ß-Adrenergic Receptor Blockers

Background for Recommendations

The single most significant addition to the pharmacological management of heart failure since the publication of previous guidelines involves the use of ß-receptor antagonists. This represents a noteworthy departure from traditional doctrine in which ß-blocking agents were classified as contraindicated in the setting of left ventricular systolic dysfunction. A solid foundation of both clinical and experimental evidence now firmly supports their use in heart failure with the aim of reducing both morbidity and mortality (16,22,23).

ß-Blocker therapy for heart failure has been advocated by some investigators since the 1970s (24). During the subsequent 2 decades, many small- to medium-sized placebo-controlled trials, which used a variety of agents, showed several common findings: 1) the use of ß-blockers in mild to moderate heart failure was generally safe when initiated at low doses and gradually up titrated under close observation; 2) improvement in left ventricular ejection fraction was observed in all trials that lasted at least 3 months; and 3) there was wide variability in the effects of ß blockade on exercise tolerance but improvement in outcome and symptomatic benefits was noted in many studies. These generally positive findings stimulated additional, large-scale clinical trials that have provided an impressive body of evidence that supports the use of ß-blockers in patients with heart failure caused by left ventricular systolic dysfunction. The recommendations that follow are derived from nearly 2 decades of research that include basic science data, animal models, and clinical trial experience in over 10,000 patients (25,26).

Although this is a major advance in efficacy, identification of appropriate candidates for ßblocker therapy is essential to ensure safe and effective treatment. Prescribing physicians should understand the potential risks of ß-blocker therapy, as well as the benefits. The interested practitioner who is unfamiliar with ß-blocker initiation and titration may first seek further education and counsel from sources such as the Heart Failure Society of America or local and regional heart failure specialty centers.

Recommendation 1. ß-blocker therapy should be routinely administered to clinically stable patients with left ventricular systolic dysfunction (left ventricular ejection fraction less than or equal to 40%) and mild to moderate heart failure symptoms (ie, NYHA class II-III, Appendix A) who are on standard therapy, which typically includes ACE inhibitors, diuretics as needed to control fluid retention, and digoxin (Strength of Evidence = A).

The most persuasive outcome in heart failure management remains all-cause mortality. Combined endpoints, including mortality or hospitalization and mortality or hospitalization for heart failure, have also emerged as key outcomes. These latter

endpoints reflect a more comprehensive assessment of the influence of therapy on quality of life and disease progression and are assuming more importance as mortality rates decline with treatment advances. The substantial beneficial effect of ß-blocker therapy on these endpoints has been well shown in clinical trials of symptomatic patients (NYHA class II - III) treated with carvedilol, bisoprolol, or metoprolol controlled release/extended release (CR/XL) (27-29). Trials with these agents encompass the combined, worldwide experience with ß-blocker therapy in patients with chronic heart failure who were stable on background therapy, including ACE inhibitors (over 90%) and diuretics (over 90%). Digoxin was common as background therapy, particularly in studies conducted in the United States. Trial results indicate that both selective and nonselective ßblockers, with and without ancillary properties, have significant efficacy in heart failure. ß-Blocking agents with intrinsic sympathomimetic activity appear to have a negative impact on survival and should not be used in heart failure patients.

Metoprolol. The MDC Study was an early trial that included 383 patients with heart failure caused by nonischemic causes, NYHA class II-III symptoms, and a left ventricular ejection fraction of less than or equal to 40% (30). Patients with coronary artery disease were excluded. Study results showed a 34% reduction in risk in patients treated with metoprolol, although this strong trend toward benefit (P = .058) was entirely attributable to a reduction in the frequency of cardiac transplantation listing in the treatment group. In fact, the absolute number of deaths in the metoprolol group was higher than in the placebo group (23 *v* 19, P = .69).

The MERIT-HF Trial evaluated the effect of metoprolol CR/XL with all-cause mortality as the primary endpoint. The trial included 3,991 patients with NYHA class II-IV heart failure, although 96% of the study patients were functional class II or III (31). In this study, investigators were allowed to select the starting dose of metoprolol CR/XL. Seventy-nine percent chose 25 mg as the starting dose for class II patients, and 77% chose 12.5 mg for class III-IV patients. The target dose was 200 mg and doses were up-titrated over a period of 8 weeks. Premature discontinuation of blinded therapy occurred in 13.9% of those treated with metoprolol CR/XL and 15.3% of those in the placebo group (P = .90). The study results revealed a 34% reduction in mortality in the metoprolol group (relative risk of .66; 95% confidence interval [CI], .53 to .81; p=.0062 after adjustment for interim analyses), with annual mortality rates of 11% in the placebo and 7.2% in the metoprolol CR/XL group (29).

Bisoprolol. The CIBIS Study evaluated the effects of bisoprolol in 641 patients with left ventricular systolic dysfunction caused by ischemic or nonischemic causes and NYHA class III-IV heart failure (32). The primary endpoint was all-cause mortality, and hospitalization for worsening heart failure was one of the secondary outcomes of interest. The initial bisoprolol dose was 1.25 mg/day, which was increased to a maximum dose of 5 mg/day. The trial found no significant reduction in all-cause mortality in patients treated with bisoprolol (20% reduction bisoprolol *v* placebo, P = .22) (32). The risk of hospitalization was significantly reduced by 34% (28% placebo group *v* 19% bisoprolol group, P < .01).

The favorable trends seen in CIBIS led to the larger CIBIS II Study, which ultimately was prematurely terminated as a result of a significant reduction in mortality in the bisoprolol arm (28). These results were obtained in 2,647 patients who were followed for an average of 1.3 years. Over 80% of the patients were judged to be NYHA class III at enrollment. Background therapy included ACE inhibitors in 96% and diuretic in 99% of the study patients, whereas 52% were taking digoxin. In contrast to the original CIBIS study, CIBIS II had a similar starting dose of 1.25 mg but had a greater target dose of 10 mg daily of bisoprolol. More stringent criteria for defining ischemic cardiomyopathy were used. Treatment with bisoprolol reduced the annual mortality rate by 34% (13.2% placebo *v* 8.8% bisoprolol; hazard ratio .66; 95% CI, .54 to .81; *P*< .0001). Hospitalizations for worsening heart failure were also decreased by 32% (18% placebo *v* 12% bisoprolol, hazard ratio .64; 95% CI, .53 to .79; *P*< .0001). Although a post hoc analysis of the CIBIS Study had suggested benefit might be consigned to patients without coronary disease, the survival benefit, with significant reductions apparent in both ischemic or nonischemic patients, was not influenced by disease origins.

Carvedilol. Carvedilol, a nonselective ß-blocker and □-blocker, has been extensively investigated for treatment of heart failure caused by left ventricular systolic dysfunction. In the United States carvedilol trials, 4 separate study populations were examined and the data from 1,094 patients were combined to evaluate the effect of carvedilol therapy on the clinical progression of heart failure (27). Clinical progression was defined as worsening heart failure leading to death, hospitalization, or, in one study, a sustained increase in background medications. Patients with a left ventricular ejection fraction of 35% or less and NYHA class II-IV were eligible if they tolerated 6.25 mg of carvedilol twice per day for a 2-week, open-label, run-in period. Although this run-in phase biased the ultimately randomized patient population, less than 8% of eligible patients failed the open-label challenge. Target dosages for the studies were 50 to 100 mg/day of carvedilol that were administered in divided doses twice daily. Patients completing the run-in period were randomized based on results from their 6- minute walk test into mild, moderate, or severe trials. These studies were prematurely terminated (median follow-up 6.5 months) by the Trial Data and Safety Monitoring Board because of reduced mortality across the 4 combined trials of patients treated with carvedilol.

Data from these combined trials indicated a substantial benefit from carvedilol treatment. The risk of mortality was 65% lower (7.8% placebo *v* 3.2% carvedilol; 95% CI, 39% to 80%; *P*< .001) and the combined risk of hospitalization or death was reduced by 38% (20% on placebo *v* 14% on carvedilol; 95% CI, 18% to 53%; *P*< .001). A significant mortality reduction was also noted when deaths that occurred in the run-in period were included in the analysis. The statistical validity of the survival analysis across the trials has been questioned because mortality was not the primary endpoint, and only 1 of the 4 trials achieved a significant result when analyzed based on the primary endpoint. Nevertheless, the magnitude of the survival benefit and the reduction in hospitalization were impressive. The survival benefit was not influenced by the cause of disease, age, gender, or baseline ejection fraction. Overall, 7.8% of the placebo group and 5.7% of the carvedilol group discontinued study medication. Data from the individual trials, PRECISE and MOCHA, which evaluated patients with moderate to severe heart failure, found that carvedilol reduced the risk of the combined endpoint of mortality or heart failure hospitalization by 39% to 49% (33,34). The MOCHA Study provided strong

evidence for increased benefit from higher dosages (25 mg twice per day) versus lower dosages (6.25 mg twice per day) of carvedilol, so up titration of carvedilol dosages to 25 mg twice per day is generally recommended. However, favorable effects were noted at 6.25 mg twice per day, so intolerance of high doses should not be a reason for discontinuation of therapy.

The Australia-New Zealand Carvedilol Trial enrolled 415 patients with ischemic cardiomyopathy and a left ventricular ejection fraction of less than 45% (35). Although patients with NYHA functional classes I-III were eligible, the majority enrolled were NYHA functional class I (30%) or II (54%). ACE inhibitors were used in 86% of the participants, whereas 76% were on diuretic therapy, and 38% were on digoxin. This trial also had a run-in phase during which 6% of the patients discontinued ß-blocker therapy. During an average follow-up of 19 months, carvedilol decreased the combined risk of all-cause mortality or any hospitalization by 26% (relative risk .74; 95% CI, .57 to .95; *P*= .02). Overall mortality was 12.5% in the placebo group and 9.6% in the carvedilol group which was not statistically significant (relative risk .76; 95% CI, .42 to 1.36; $P > .10$).

Unreported or Ongoing Trials. Studies that are underway will provide additional data concerning specific aspects of the efficacy of ß-blocker therapy in heart failure. The effect of bucindolol on mortality and morbidity in patients with moderate to severe heart failure has been evaluated in the BEST Study. This study enrolled a substantial number of women so the potential influence of gender on the efficacy of ß-blocker therapy can be investigated. The trial has been stopped, and no results are available for analysis.

The COPERNICUS Trial is designed to assess the effect of carvedilol treatment on disease progression and survival in patients with advanced heart failure with symptoms at rest or on minimal exertion. The COMET protocol is a 3,000 patient study that directly compares the survival benefit of carvedilol versus metoprolol. This trial will provide important data concerning the relative efficacy of a selective ß-blocker versus a nonselective ß-blocker with ancillary properties.

Recommendation 2. ß-blocker therapy should be considered for patients with left ventricular systolic dysfunction (left ventricular ejection fraction less than or equal to 40%) who are asymptomatic (ie, NYHA class I) and standard therapy, including ACE inhibitors (Strength of Evidence = C).

Data from the SOLVD Prevention Trial prospectively illustrated the efficacy of ACE inhibitors in delaying the onset of heart failure symptoms and the need for treatment or hospitalization for heart failure in asymptomatic patients with a left ventricular ejection fraction less than or equal to 35% (36). Similar controlled, clinical trial data that support the use of a ß-blocker in this clinical circumstance are not available. However, significant support for the use of ßblocker therapy in patients with asymptomatic left ventricular dysfunction can be derived from clinical trials in coronary artery disease and hypertension. Previous data indicate that ß-blocker therapy should be used in patients after myocardial infarction (MI) and in patients with myocardial revascularization who have good symptomatic and functional recovery but residual ventricular systolic dysfunction. Trials in hypertension indicate that ß-blocker therapy decreases the risk of developing heart failure. Given the potential of ß-blockers to retard disease progression

and improve ventricular function, the risk to benefit ratio seems sufficiently low to support ß-blocker use in asymptomatic patients with left ventricular dysfunction, especially when the dysfunction is marked, and coronary artery disease is present.

Recommendation 3. To maximize patient safety, a period of clinical stability on standard therapy should occur before ß-blocker therapy is instituted. Initiation of ß-blocker therapy in patients with heart failure requires a careful baseline evaluation of clinical status (Strength of Evidence = B).

Initiation of ß-blocker therapy has the potential to worsen heart failure signs and symptoms. This risk increases with the underlying severity of the heart failure that is present. To minimize the likelihood of worsening failure, a period of treatment with standard therapy and evidence of clinical stability without acute decompensation or fluid overload is recommended before initiation of ß-blocker therapy. The majority of the large-scale, ß-blocker heart failure trials required that chronic heart failure be present 3 months or more before initiation of ß-blocker therapy. Patients enrolled in these trials were typically treated with ACE inhibitors (if tolerated), diuretic, and digoxin for at least 2 months and were observed to be clinically stable for 2 to 3 weeks before beginning ß-blocker therapy. Thus, many heart failure clinicians favor a minimum of 2 to 4 weeks of clinical stability on standard therapy before ß-blocker therapy is instituted. Likewise, most clinicians discourage the initiation of ß-blocker therapy in the hospital setting after treatment for new or decompensated heart failure (with or without associated inotrope administration). Some experienced clinicians initiate ß-blocker therapy in the hospital in selected patients who have responded well to inpatient treatment and who can be followed closely after discharge.

Recommendation 4. There is insufficient evidence to recommend the use of ß-blocker therapy for inpatients or outpatients with symptoms of heart failure at rest (ie, NYHA class IV) (Strength of Evidence = C).

ß-Blocker therapy cannot be routinely recommended for NYHA class IV patients because there are currently no clinical trial data to indicate favorable long-term efficacy and safety of ßblocker therapy in this patient population. A substantial body of observational data indicates that successful institution of ß-blocker therapy in patients with this degree of heart failure is problematic. If used, these agents may precipitate deterioration, and patients so treated should be monitored by a physician who has expertise in heart failure.
The number of patients with class IV heart failure at the time of ß-blocker initiation in controlled clinical trials is small. Available trials, which report data on patients with severe heart failure mostly labeled as NYHA class III, show the potential problems of ß-blocker therapy in this part of the heart failure spectrum. This experience is reflected in a 14-week study that evaluated the effects of ß-blocker therapy in 56 patients (51 NYHA class III and 5 NYHA class IV at randomization) with severe left ventricular dysfunction (average left ventricular ejection fraction of 16% ± 1% and left ventricular filling pressure of 24 mm Hg ± 1 mm Hg) (37). These patients had significant impairment of exercise capacity (mean VO2 max of 13.6 mL/kg/min ± 0.6 mL/kg/min) despite ACE-inhibitor, digoxin and diuretic therapy. Patients were believed to be clinically stable (requiring no medication adjustments) for a 2-week period before an open-label challenge was conducted. Seven patients (12%) failed to complete the open-label, run-in period,

during which 5 died and 2 had nonfatal adverse reactions. Clinical parameters did not distinguish these patients from those who were able to continue in the trial. Eighteen of the 49 patients (37%) completing the run-in period experienced worsened dyspnea or fluid retention during this phase. Also, 22% experienced dizziness and required medication adjustment, which delayed up-titration during the run-in. Subsequently, an additional 12% of the patients randomized to carvedilol withdrew from the blinded arm of the study. One of the United States carvedilol trials studied patients with severe left ventricular dysfunction who had markedly reduced exercise capacity as assessed by the 6-minute walk test (38). In this trial, 131 patients with a mean left ventricular ejection fraction of 22% and severe impairment in quality of life underwent a 2-week, open-label challenge phase of 6.25 mg of carvedilol twice per day. Ten of these 131 patients (8%) were unable to complete this run-in phase, most because of worsening heart failure, dyspnea, or dizziness. Subsequently, 11% of the patients randomized to carvedilol withdrew, as did a similar number of patients (11%) in the placebo group. In the recently completed large-scale BEST Trial, the mortality trend in NYHA class III-IV patients favored the ß-blocker bucindolol, but the difference from placebo was not significant. Further analysis of these preliminary findings is necessary, but the data suggest that the striking benefit of ß-blockers in mild-to-moderate heart failure may not be extrapolated to those with severe symptoms.

Recommendation 5. ß-Blocker therapy should be initiated at low doses and up-titrated slowly, generally no sooner than at 2-week intervals. Clinical reevaluation should occur at each titration point and with worsening of patient symptoms. Patients who develop worsening heart failure or other side effects after drug initiation or during titration require adjustment of concomitant medications. These patients may also require a reduction in ß-blocker dose and, in some cases, temporary or permanent withdrawal of this therapy (Strength of Evidence = B).

ß-Blocker therapy should be initiated at doses substantially less than target doses. Clinical trials required patient reassessment at up-titration of each dose. This careful evaluation by trained nurses and/or heart failure specialists likely contributed to the relatively low withdrawal rates and safety profiles observed in the clinical trials.
Treatment for symptomatic deterioration may be required during ß-blocker titration, but with appropriate adjustments in therapy, most patients can be maintained and generally achieve target doses. There is a risk of worsening heart failure, and vasodilatory side effects may occur with certain agents. Worsening heart failure is typically reflected by increasing fatigue, lower exercise tolerance, and weight gain. Increased diuretic doses may be required for signs and symptoms of worsened fluid retention. Treatment options also include temporary down-titration of the ß-blocker to the last tolerated dose. Abrupt withdrawal should be avoided. A minimum period of stability of 2 weeks should occur before further up-titration is attempted. Hypotensive side effects may often resolve with reduction in diuretic dose. Temporary reductions in ACE inhibitor dose may be helpful for symptomatic hypotension not obviated by staggering the schedule of vasoactive medications. Administration of carvedilol with food may alleviate vasodilatory side effects as well.

If ß-blocker treatment is interrupted for a period exceeding 72 hours and the patient is still judged a candidate for this therapy, drug treatment should be reinitiated at 50% of the previous dose. Subsequent up-titration should be conducted as previously described.

Recommendation 6. In general, patients who experience a deterioration in clinical status or symptomatic exacerbation of heart failure during chronic maintenance treatment should be continued on ß-blocker therapy (Strength of Evidence = C).

Clinical decompensation that occurs during stable maintenance therapy is less likely caused by chronic ß-blocker therapy than other factors (diet or medication noncompliance, ischemia, arrhythmia, comorbid disease, infection, or disease progression). In these situations, maintaining the current ß-blocker dose while relieving or compensating for the precipitating factor(s) is most often the best course. Data from patients randomized to continue or discontinue ß-blocker therapy in this setting are not currently available. However, studies of the withdrawal of ß-blocker therapy in patients with persistent left ventricular systolic dysfunction but improved and stable clinical heart failure have revealed a substantial risk of worsening heart failure and early death after discontinuation of ß-blocker therapy (39,40).

Recommendation 7. Patient education regarding early recognition of symptom exacerbation and side effects is considered important. If clinical uncertainty exists, consultation with clinicians who have expertise in heart failure and/or specialized programs with experience in ß-blocker use in patients with heart failure is recommended (Strength of Evidence = B).

In certain patients, frequent return visits for dose-titration may be difficult to accommodate in a busy clinical practice. Trained personnel, including nurse practitioners, physicians' assistants, and pharmacists with physician supervision, may more efficiently perform patient education and reevaluation during up-titration. Heart failure specialty programs are more likely to have the resources to provide this follow-up and education (41). Consultation or referral may be particularly beneficial when the clinical heart failure status of the patient is uncertain or problems arise during initiation of therapy or dose-titration that may cause unwarranted discontinuation of therapy. Ideal patients for ß-blocker therapy should be compliant and have a good understanding of their disease and their overall treatment plan. Patients should be aware that symptomatic deterioration is possible early in therapy and that symptomatic improvement may be delayed for weeks to months.

Unresolved Therapeutic Issues

Combining ß-Blocking Agents With Amiodarone Therapy. Concomitant use of amiodarone was generally precluded in the trials evaluating carvedilol and most other ß-blockers. However, the use of this agent for rate control of atrial arrhythmia or for maintenance of sinus rhythm is common in heart failure patients. Drug interactions between ß-blockers and amiodarone are possible, including symptomatic bradycardia, and may limit the maximum tolerated dose of the ß-blocker. When the combination is used, the smallest effective dose of amiodarone should be employed. Given the lack of a

clear survival benefit, amiodarone is not a substitute for ß-blocker therapy in heart failure patients who are candidates for this therapy.

Implantation of Cardiac Pacemakers. Given the strength of evidence that supports ß-blocker therapy in patients with symptomatic heart failure, some physicians would consider pacemaker implantation when symptomatic bradycardia or heart block occur during the initiation of this therapy, although no data are available to support such use. Consideration should be given, after weighing risks and benefits, to the withdrawal of other drugs that may have bradycardia effects.

Duration of Therapy. Whether patients experiencing marked improvement in left ventricular systolic dysfunction and heart failure symptoms during therapy can be successfully withdrawn from ß-blocker therapy remains to be established. Concern continues that such patients would experience worsening after ß-blocker withdrawal, either in systolic function or symptoms, over a time period that is undefined. Until clinical trial data indicate otherwise, the duration of ßblocker therapy must be considered indefinite.

Digoxin

Background for Recommendations

Although little controversy exists as to the benefit of digoxin in patients with symptomatic left ventricular systolic dysfunction and concomitant atrial fibrillation, the debate continues over its current role in similar patients with normal sinus rhythm. Recent information regarding digoxin's mechanism of action and new analyses of clinical data from the DIG Trial and the combined PROVED and RADIANCE Trial databases provide additional evidence of favorable efficacy that was unavailable to previous guideline committees (42-47). In fact, this information has recently formed the basis of Food and Drug Administration (FDA) approval of digoxin for the treatment of mild to moderate heart failure (48). Digoxin, a drug that is inexpensive and can be given once daily, represents the only orally effective drug with positive inotropic effects approved for the management of heart failure. The committee's consensus is that digoxin, when used in combination with other standard therapy, will continue to play an important role in the symptomatic management of the majority of patients with heart failure.

The efficacy of digoxin for the treatment of heart failure caused by systolic dysfunction has traditionally been attributed to its relatively weak positive inotropic action that comes from inhibition of sodium-potassium adenosine triphosphatase (ATPase) that results in an increase in cardiac myocyte intracellular calcium. However, in addition to positive inotropy, digitalis has important, neurohormonal-modulating effects in patients with chronic heart failure, including a sympathoinhibitory effect that cannot be ascribed to its inotropic action (49,50). Digoxin also ameliorates autonomic dysfunction as evidenced by studies of heart rate variability, which indicates increased parasympathetic and baroreceptor sensitivity during therapy (51).

Recommendation 1. Digoxin should be considered for patients who have symptoms of heart failure (NYHA class II-III, Strength of Evidence = A and NYHA class IV, Strength of Evidence = C) caused by left ventricular systolic dysfunction while receiving standard therapy.

Digoxin increases left ventricular ejection fraction and alleviates symptomatic heart failure as evidenced by drug-related improvement in exercise capacity and reductions in heart-failure associated hospitalization and emergency room visits. Digoxin should be used in conjunction with other forms of standard heart failure therapy including ACE inhibitors, diuretics and ß-blockers.

The DIG Trial, a randomized, double-blind, placebo-controlled trial in over 7,000 patients with heart failure, showed a neutral effect on the primary study endpoint and mortality from any cause during an average follow-up of approximately 3 years (42). In the main trial, 6,800 patients with left ventricular ejection fraction less than or equal to 45% were randomized to digoxin or placebo, in addition to diuretics and ACE inhibitors. A total of 1,181 deaths occurred on digoxin (34.8%) and 1,194 on placebo (35.1%) for a risk ratio of .99 (95% CI, .91 to 1.07; $P = .80$). These results differ from other oral agents with inotropic properties that have been associated with an adverse effect on mortality. In addition, the need for hospitalization and co intervention (defined as increasing the dose of diuretics and ACE inhibitors or adding new therapies for worsening heart failure) was significantly lower in the digoxin group, even in those patients who were not previously taking digoxin. Fewer patients on digoxin compared with placebo were hospitalized for worsening heart failure (26.8%*v* 34.7%; risk ratio .72; 95% CI, .66 to .79; $P < .001$). These long-term data are consistent with recent results obtained from an analysis of the combined PROVED and RADIANCE databases (45). In this analysis, patients who continued digoxin as part of triple therapy with diuretics and an ACE inhibitor were much less likely to develop worsening heart failure (4.7%) than those treated with a diuretic alone (39%, $P < .001$), diuretic plus digoxin (19%, $P = .009$) or diuretic plus an ACE inhibitor (25%, $P = .001$).

Although there are no clinical trial data (level A evidence) for the efficacy of digoxin in patients with NYHA Class IV heart failure, there is evidence that digoxin works across the spectrum of left ventricular systolic dysfunction. A prespecified subgroup analysis of patients enrolled in the DIG Trial with evidence of severe heart failure (as manifested by left ventricular ejection fraction less than 25%, or cardiothoracic ratio [CTR] greater than .55) showed the benefit of digoxin (48). The following reductions in the combined endpoint of all-cause mortality or hospitalization were seen on digoxin compared with placebo: 16% reduction (95% CI, 7% to 24%) in patients with a left ventricular ejection fraction of less than 25%, and a 15% reduction (95% CI, 6% to 23%) in patients with a CTR of greater than .55 (43). Reductions in the risk of the combined endpoint of heart-failure related mortality or hospitalization were even more striking: 39% (95% CI, 29% to 47%) for patients with left ventricular ejection fraction less than 25%, and 35% (95% CI, 25% to 43%) for patients with a CTR greater than .55 (48).

Evidence for the efficacy of digoxin in patients with mild symptoms of heart failure has been provided by a recent retrospective, cohort analysis of the combined PROVED and RADIANCE data (52). The outcome of patients in these trials who were randomized to digoxin withdrawal or continuation was categorized by using a prospectively obtained heart failure score based on clinical signs and symptoms. Patients in the mild heart failure group (heart failure score of 2 or less) who were randomized to have digoxin withdrawn were at increased risk of treatment failure and had deterioration of exercise capacity and left ventricular ejection fraction compared with patients who continued digoxin (all $P <$

.01). Patients in the moderate heart failure group who had digoxin withdrawn were significantly more likely to experience treatment failure than either patients in the mild heart failure group or patients who continued digoxin (both $P < .05$). These data suggest that patients with left ventricular systolic dysfunction benefit from digoxin despite only mild clinical evidence of heart failure.

In summary, a large body of evidence supports the efficacy of digoxin in patients with symptomatic heart failure caused by left ventricular systolic dysfunction. Digoxin has been shown to decrease hospitalizations, as well as emergency room visits; decrease the need for co intervention; and improve exercise capacity (42-44,53,54). Taken as a whole, these clinical trial data provide support for digoxin's beneficial effect on morbidity and neutral effect on mortality (42).

Recommendation 2. In the majority of patients, the dosage of digoxin should be .125 mg to .25 mg daily (Strength of Evidence = C).

Recent data suggest that the target dose of digoxin therapy should be lower than traditionally assumed. Although higher doses may be necessary for maximal hemodynamic effects (55), beneficial neurohormonal and functional effects appear to be achieved at relatively low serum digoxin concentrations (SDC) typically associated with daily doses of .125 mg to .25 mg of digoxin (55-57). The utility of lower SDC is supported by recent clinical trial data; the mean SDC achieved in the RADIANCE Trial was 1.2 ng/mL and in the DIG Trial was 0.8 ng/mL (42,44). Recent retrospective, cohort analysis of the combined PROVED and RADIANCE databases indicates that patients with a low SDC (less than .9 ng/mL) were no more likely to experience worsening symptoms of heart failure on maintenance digoxin than those with a moderate (.9 to 1.2 ng/mL) or high (greater than 1.2 ng/mL) SDC (41). All SDC groups were significantly less likely to deteriorate during follow-up compared with patients withdrawn from digoxin.

Therefore, patients with left ventricular systolic dysfunction and normal sinus rhythm should be started on a maintenance dosage of digoxin (no loading dose) of .125 or .25 mg once daily based on ideal body weight, age, and renal function For patients with normal renal function, a dosage of digoxin of .25 mg/day will be typical. Many patients with heart failure have reduced renal function and should begin on .125 mg daily. In addition, patients with a baseline conduction abnormality, or who are small in stature or elderly, should be started at .125 mg/day, which can be up-titrated if necessary. Once dosing has continued for a sufficient period for serum concentration to reach steady state (typically in 2 to 3 weeks), some clinicians consider the measurement of a SDC, especially in elderly patients or those with impaired renal function in which the digoxin dose is often not predictive of SDC. SDC measurements may be considered when 1) a significant change in renal function occurs; 2) a potentially interacting drug (amiodarone, quinidine, or verapamil) is added or discontinued; or 3) confirmation of suspected digoxin toxicity is necessary in a patient with signs or symptoms and/or electrocardiographic changes consistent with this diagnosis. Samples for trough SDC should be drawn more than 6 hours after dosing. Otherwise, the result is difficult to interpret because the drug may not be fully distributed into tissues.

Recommendation 3. In patients with heart failure and atrial fibrillation with a rapid ventricular response, the administration of high doses ofdigoxin (greater than .25 mg) for the purpose of rate control is not recommended. When necessary, additional rate control should be achieved by the addition of ß-blocker therapy or amiodarone (Strength of Evidence= C).

Digoxin continues to be the drug of choice for patients with heart failure and atrial fibrillation. However, the traditional practice of arbitrarily increasing the dose (and SDC) of digoxin until ventricular response is controlled should be abandoned because the risk of digoxin toxicity increases as well. Digoxin alone is often inadequate to control ventricular response in patients with atrial fibrillation, and the SDC should not be used to guide dosing to achieve rate control. Therefore, digoxin should be dosed in the same manner as in a patient with heart failure and normal sinus rhythm.
Digoxin slows ventricular response to atrial fibrillation through enhancement of vagal tone. However, with exertion or other increases in sympathetic activity, vagal tone may decrease and ventricular rate accelerate. Addition of a ß-blocker or amiodarone 1) complements the pharmacological action of digoxin and provides more optimal rate control; 2) allows the beneficial clinical effects of digoxin to be maintained; and 3) limits the risk of toxicity that may occur if digoxin is dosed to achieve a high SDC (58). For patients who have a contraindication to ßblockers, amiodarone is a reasonable alternative. If amiodarone is added, the dose of digoxin should be reduced, and the SDC should be monitored so that the serum concentration can be maintained in the desired range. Some clinicians advocate the short-term, intravenous administration of diltiazem for the acute treatment of patients with very rapid ventricular response, especially those with hemodynamic compromise. This drug is not indicated for long-term management because its negative inotropic effects may worsen heart failure.

Unresolved Therapeutic Issues

Combination With ß-blockers. ß-Blocker therapy has become pivotal in the management of heart failure. However, the majority of patients enrolled in controlled clinical trials that study the efficacy of digoxin were not taking ß-blockers. Therefore, it is uncertain whether or not digoxin should be routinely included as part of a ß-blocker regimen for symptomatic heart failure caused by left ventricular systolic dysfunction. There are attractive features of combining digoxin with ß-blocker therapy in the treatment of heart failure. The majority of heart failure patients have coronary artery disease and may be at risk for transient episodes of myocardial ischemia that could cause catecholamine release and sudden cardiac death. Combining digoxin with a ß-blocker may preserve the beneficial effects of digoxin on the symptoms of heart failure while minimizing the potential detrimental effects of this therapy on catecholamine release in the setting of ischemia (47).

Combination with Diuretics. Non-potassium-sparing diuretics can produce electrolyte abnormalities such as hypokalemia and hypomagnesemia, which increases the risk of digoxin toxicity. The combination of digoxin with a potassium- sparing diuretic would be a potentially safer alternative. Further study will be necessary to carefully elucidate the efficacy and safety of combining digoxin with these agents.

Anticoagulation and Antiplatelet Drugs
Background for Recommendations

Patients with heart failure are recognized to be at increased risk for thromboembolic events that can be arterial or venous in origin. In addition to atrial fibrillation and poor ventricular function (which promote stasis and increase the risk of thrombus formation), patients with heart failure have other manifestations of hypercoagulability. Evidence of heightened platelet activation; increased plasma and blood viscosity; and increased plasma levels of fibrinopeptide A, ßthromboglobulin, D-dimer, and von Willebrand factor (59-61) have been found in many patients. Despite a predisposition, estimates regarding the incidence of thromboemboli in patients with heart failure vary substantially between 1.4 and 42 per 100 patient years (62-65). Although variability in the reported incidence likely results from differences in the populations studied and the methods used to identify these events, the consensus is that pulmonary and systemic emboli are not common in heart failure patients. Traditionally, the issue of anticoagulation in patients with heart failure centered on warfarin. Growing recognition of the importance of ischemic heart disease as a cause of heart failure suggests that the role of antiplatelet therapy must be considered in patients with this syndrome as well.

Previous guidelines have recommended warfarin anticoagulation in patients with heart failure complicated by atrial fibrillation and in heart failure patients with prior thromboembolic events (18,19). Warfarin anticoagulation specifically was not recommended in patients with heart failure in the absence of these indications. There have been no randomized, controlled trials of warfarin in patients with heart failure. Therefore, recommendations regarding its use, in the absence of atrial fibrillation or clinically overt systemic or pulmonary thromboemboli, must be made on the basis of cohort data and expert opinion. The likely incidence of thromboembolic events and the possibility of averting them with warfarin are important considerations for any guideline recommendation. In addition, the potential beneficial effects of warfarin on coronary thrombotic events, independent of embolic phenomenon, must be taken into account. The substantial clinical trial data that reflect the beneficial effects of antiplatelet therapy in patients with ischemic heart disease suggest that new guideline recommendations for heart failure should address the role of this form of therapy in patients with left ventricular dysfunction.

Anticoagulation

Recommendation 1. All patients with heart failure and atrial fibrillation should be treated with warfarin (goal, international normalized ratio (INR) 2.0 to 3.0) unless contraindicated (Strength of Evidence = A).

The committee agrees with previous guideline recommendations that concern warfarin therapy in patients with heart failure complicated by atrial fibrillation. The benefit of warfarin anticoagulation in this setting is well established through several randomized trials (66). Patients with heart failure commonly have atrial fibrillation. Warfarin anticoagulation should be implemented in all of these patients unless clear contraindications exist.

Recommendation 2. Warfarin anticoagulation merits consideration for patients with left ventricular ejection fraction of 35% or less. Careful assessment of the risks and benefits of anticoagulation should be undertaken in individual patients (Strength of Evidence = B).

Cohort analyses examining the relationship between warfarin use and noncoronary thromboembolism in patients with heart failure have not consistently yielded positive findings (62,63,65,67-69). It is possible that the lack of consistent benefit was related to the low incidence of identifiable embolic events in these populations. However, these studies do not make a convincing argument for the use of warfarin to prevent embolic events in the absence of atrial fibrillation or a previous thromboembolic episode.

In contrast, a recent cohort analysis of the SOLVD population focused on the relation between warfarin use and the risk of all-cause mortality rather than risk for embolic events (70). After adjustment for baseline differences, patients treated with warfarin at baseline had a significantly lower risk of mortality during follow-up (adjusted hazard ratio .76; 95% CI, .65 to .89, $P = .0006$). In addition to a mortality benefit, warfarin use was also associated with a significant reduction in the combined endpoint of death or hospitalization for heart failure (adjusted hazard ratio .82; 95% CI, .72 to .93, $P = .002$). In the SOLVD population, the benefit associated with warfarin use was not significantly influenced by 1) presence or absence of symptoms (treatment trial *v* prevention trial), 2) randomization to enalapril or placebo, 3) gender, 4) presence or absence of atrial fibrillation; 5) age, 6) ejection fraction, 7) NYHA class, or 8) origins of disease.

The benefit associated with warfarin use in the cohort analysis of the SOLVD population was related to a reduction in cardiac mortality. Specifically, there was a significant reduction among warfarin users in deaths that were identified as sudden, in deaths associated with heart failure, and in fatal MI. In contrast (yet in agreement with previous cohort analyses), there was no significant difference in deaths considered cardiovascular but noncardiac, including pulmonary embolism and fatal stroke. Some caution is needed in consideration of this finding because the number of cardiovascular deaths that were noncardiac was far less than the number of cardiac deaths.

Reduction in ischemic events is one potential explanation for the apparent benefit from warfarin in the SOLVD Study. Warfarin users showed a reduced rate of hospitalization for unstable angina or nonfatal MI. Prior investigations of patients after acute MI showed that warfarin anticoagulation, when started within 4 weeks, reduces the incidence of fatal and nonfatal coronary events, as well as pulmonary embolus and stroke (71).

As with other post hoc, cohort analyses, it is possible that the findings from the SOLVD Study may result from differences between the treatment groups that were not identified and for which statistical correction could not adequately adjust. For this reason, evidence from any cohort study must be considered less powerful compared with evidence derived from randomized, controlled trials. Nevertheless, in the absence of randomized data, the SOLVD cohort analysis represents reasonable evidence to support more aggressive use of warfarin anticoagulation than previously recommended in patients with reduced left ventricular ejection fraction and sinus rhythm. The data from this analysis provide no information regarding the ideal warfarin dose in this patient population. Therefore, the

dosing recommendation should likely conform to that derived from previous randomized trials performed in patients without mechanical prosthetic valves (INR 2.0 to 3.0).

Antiplatelet Drugs

Recommendation 1. With regard to the concomitant use of ACE inhibitors and acetylsalicylic acid (ASA), each medication should be considered on its own merit for individual patients. Currently, there is insufficient evidence concerning the potential negative therapeutic interaction between ASA and ACE inhibitors to warrant withholding either of these medications in which an indication exists (Strength of Evidence =C).

Strong evidence supports the clinical benefit of aspirin in ischemic heart disease and atherosclerosis (72-75). However, recent post hoc analyses of large randomized trials involving ACE inhibitors in heart failure and post-MI suggest the possibility of an adverse drug interaction between ASA and ACE inhibitors (76-78). A retrospective cohort analysis of the SOLVD Study found that patients on antiplatelet therapy (assumed to be ASA in the great majority of patients) derived no additional survival benefit from the addition of enalapril. Data from CONSENSUS II and GUSTO-1 in post-MI patients, suggest not only no additive benefit, but the possibility of a negative effect on mortality from the combination of ASA and ACE inhibition. In contrast, an unadjusted, retrospective registry study in patients with chronic coronary artery disease did not support an adverse interaction (79). Interestingly, in an adjusted analysis of the subset of patients with heart failure in this study, the beneficial effects of aspirin seemed less evident in patients taking ACE inhibitors. Despite these provocative post hoc findings, no prospective studies have yet been reported that concern the possible adverse interaction between ACE inhibitors and aspirin. To date, there is no clear evidence of harm from the combination of ASA and ACE inhibitors in patients with heart failure (76).

There is also some evidence that the potential interaction between ASA and ACE inhibitors may be dose related. A recent meta-analysis of all hypertension and heart failure patients who have received both ASA and ACE inhibitors suggests that ASA at doses equal to or less than 100 mg showed no interaction with ACE inhibitors (80). Any interaction, if observed, occurred at higher doses of aspirin.

A potential mechanism for the hypothesized adverse interaction between ASA and ACE inhibitors in patients with heart failure involves prostaglandin synthesis. ACE inhibition is believed to augment bradykinin which, in turn, stimulates the synthesis of various prostaglandins that may contribute vasodilatory and other salutary effects. In the presence of ASA, the bradykinin-induced increase in prostaglandins should be attenuated or blocked, which potentially reduces the benefits of ACE inhibition. Invasive hemodynamic monitoring has shown that the acute hemodynamic effect of enalapril is blunted by concomitant administration of aspirin (81). Another possibility is that ASA and ACE inhibitors act in a similar fashion in heart failure, therefore no added benefit is gained from the combination. ACE inhibitors appear to reduce ischemic events in heart failure patients possibly through antithrombotic effects, which could mimic those of antiplatelet agents. Recent study results that suggest ASA may have independent

beneficial action on ventricular remodeling support the hypothesis of similar mechanisms of action for ACE inhibitors and ASA (82).

Development of the adenosine diphosphate (ADP) antagonists, ticlopidine and clopidogrel, provides alternative therapy for platelet inhibition that does not appear to influence prostaglandin synthesis (83). In direct comparison with aspirin, large-scale clinical trial results have established the efficacy of clopidogrel in the prevention of vascular events in patients with arteriosclerotic disease (84). Clinical data are limited with ADP antagonists in heart failure. However, hemodynamic evaluation found a similar reduction in systemic vascular resistance in heart failure patients treated with the combination of ACE inhibitors and ticlopidine versus ACE inhibitors alone, which suggests no adverse hemodynamic interaction with ACE inhibition with this type of antiplatelet compound (85). Definitive resolution of the therapeutic implications of the ASA/ACE inhibitor interaction and the appropriate alternative therapy, if any, in heart failure awaits the results of additional clinical research studies.

Angiotensin II Receptor Blockers

Background for Recommendations

Angiotensin ll (AT) receptor blockers (ARBs) differ in their mechanism of action compared with ACE inhibitors. Rather than inhibiting the production of AT by blockade of ACE, ARBs block the cell surface receptor for AT. ARBs that are currently available are selective and only effectively inhibit the AT1 subtype of this receptor. Theoretical benefits of ARBs include receptor blockade of AT produced by enzymes other than ACE and maintenance of ambient AT to maintain or increase stimulation of AT2 receptors. AT1 receptor antagonism is important because this receptor appears to mediate the classical adverse effects associated with AT in heart failure. In contrast, the AT2 receptor subtype appears to counterbalance AT1 receptor stimulation by causing vasodilation and inhibiting proliferative and hypertrophic responses (86). Thus, the selective receptor blockade of the current ARBs may be particularly advantageous. Theoretical concerns about ARB therapy include the potential deleterious effects of increased AT levels and AT2 receptor-mediated enhancement of apoptosis. Whether ARBs have beneficial effects similar to ACE inhibitors on the course of coronary artery disease remains to be determined. ARBs may or may not influence bradykinin concentrations, which are anticipated to rise with ACE inhibitor therapy and may contribute to their efficacy.

The hemodynamic actions of ARBs have, thus far, been similar to ACE inhibitors for reduction of blood pressure in hypertension and lowering of systemic vascular resistance in heart failure (87). ARBs have a similar mild-to-modest effect on exercise capacity and produce a comparable reduction in norepinephrine relative to ACE inhibitors (88).

Recommendation 1. ACE inhibitors rather than ARBs continue to be the agents of choice for blockade of the renin-angiotensin system in heart failure, and they remain the cornerstone of standard therapy for patients with left ventricular systolic dysfunction with or without symptomatic heart failure (Strength of Evidence = A).

At present, it is not possible to predict where ARBs will ultimately reside among accepted therapies for heart failure. Although the initial small ELITE Trial suggested a greater benefit from a losartan dosage of 50 mg daily than from a captopril dosage of 50 mg 3 times daily on mortality in elderly patients with heart failure (89), the ELITE II Mortality Trial, which included more than 3,000 patients (90), showed no comparative benefit from losartan and a trend for a better outcome and fewer sudden deaths with captopril (91). This result provides no evidence that the low dose (50 mg) of losartan that was tested is better than an ACE inhibitor for treating heart failure, but it does not exclude the efficacy of a higher dose designed to provide continuous inhibition of the AT1 receptor. Tolerability of losartan was better than of captopril, primarily because of an ACEinhibitor cough. But the well-established efficacy of the ACE inhibitors on outcome in the post-MI period, in diabetes, in atherosclerosis, and in heart failure mandates that this drug group remains agents of choice for inhibiting the renin-angiotensin system in heart failure. The RESOLVD Trial suggested no major differences in efficacy of candesartan and enalapril, with a trend favoring enalapril during the study period of 43 weeks (92). The OPTIMAAL and VALIANT Studies will provide information specifically about the role of ARBs versus ACE inhibitors in the post-MI population.

Currently, ACE inhibitors continue to be regarded as the therapy of choice to inhibit the renin-angiotensin system in patients with asymptomatic and symptomatic left ventricular dysfunction. There is no current rationale to recommend initiating ARBs in patients with new onset heart failure or for switching from a tolerated ACE-inhibitor regimen to an ARB in patients with chronic heart failure.

Recommendation 2. All efforts should be made to achieve ACE inhibitor use in patients with heart failure caused by left ventricular dysfunction. Patients who are truly intolerant to ACE inhibitors should be considered for treatment with the combination of hydralazine and isosorbide dinitrate (Hyd-ISDN) (Strength of Evidence = B) or an ARB (Strength of Evidence = C).

Previous large-scale trials do not specifically address the role of ARB and Hyd-ISDN in patients who are intolerant to ACE inhibitors. One arm of the CHARM Study has been specifically designed to test the effectiveness of candesartan in patients with systolic dysfunction who are intolerant to ACE inhibitors. The primary endpoint in this study will be a composite of cardiovascular death and time until first hospitalization for heart failure. For now, ARBs offer a reasonable alternative in the heart failure or post-MI patient who is truly intolerant to ACE inhibition. Intolerance because of cough should always trigger a careful reevaluation for congestion. If congestion is present, cough should abate with increases in diuretic that should allow ACE-inhibitor use to continue (93). It should be emphasized that patients intolerant to ACE inhibitor because of renal dysfunction, hyperkalemia, or hypotension are often intolerant to ARBs as well. ACE inhibitor intolerance because of persistent symptomatic hypotension in advanced heart failure may represent severe dependence on the hemodynamic support of the renin-angiotensin system, which generally would predict hypotension with ARB use as well.

The combination of Hyd-ISDN has not been studied in the post-MI population, but sufficient experience exists to support its use in the ACE-inhibitor-intolerant patient with

symptomatic heart failure. Hydralazine blocks the development of nitrate tolerance, which argues for the use of combination therapy. Although they were not studied alone in a heart failure mortality trial, oral nitrates represent another reasonable alternative for patients intolerant to both ACE inhibitors and hydralazine.

Unresolved Therapeutic Issues

Combination Therapy With ACE Inhibitors and ARBs. Interest has grown in the potential utility of combining ACE inhibitors and ARBs in patients with heart failure. Initial data suggest that the combination yields more vasodilation and decreased blood pressure than either agent alone. The addition of losartan to an ACE inhibitor has been found to improve exercise capacity compared with an ACE inhibitor alone (94). Preliminary data from the RESOLVD Trial suggest that ventricular dilation and neuroendocrine activation may be best reduced with combination therapy, but other endpoints were not clearly affected. Trials are currently underway to determine the safety, as well as benefit, of more complete blockade of the renin-angiotensin system. The Val-HeFT Trial is a large-scale investigation of the effect of valsartan in addition to ACE inhibitors on morbidity and mortality in symptomatic patients with heart failure caused by systolic dysfunction. One arm of the CHARM Study will also examine the effect of the addition of candesartan in patients with symptomatic, systolic dysfunction treated with an ACE inhibitor. Preliminary data from the RESOLVD Trial suggest that combination therapy may be even more efficacious when used in conjunction with ß-blocker treatment. Results from Val-HeFT and CHARM in the subset of patients treated with ß-blocker therapy will provide more information concerning this strategy.

Combination therapy represents a rational option when treating severe hypertension or other vasoconstriction but cannot, at present, be recommended as routine therapy in the absence of a proven superiority to ACE-inhibitor therapy alone.

Appendix B
Criteria for NYHA functional classification for chronic heart failure patients, functional capacity (130)

CLASS 1	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
CLASS 2	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
CLASS 3	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.
CLASS 4	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

HFSA Guidelines
Appendix B
Glossary of Clinical Trials

AVID	Antiarrhythmics Versus Implantable Defibrillators
BEST	Beta-blocker Evaluation of Survival Trial
CAMIAT Trial	Canadian Amiodarone Myocardial Infarction Arrhythmia
CAPRIE Events	Clopidogrel vs Aspirin in Patients at Risk of Ischemic
CASH	Cardiac Arrest Study Hamburg
CHF-STAT Therapy	Congestive Heart Failure-Survival Trial of Antiarrhythmic
CHARM	Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity
CIBIS	Cardiac Insufficiency BIsoprolol Study
CIBIS II	Cardiac Insufficiency Bisoprolol Study II
CIDS	Canadian Implantable Defibrillator Study
COMET	Carvedilol or Metoprolol European Trial
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
CONSENSUS II	Cooperative New Scandinavian Enalapril Survival Study II
COPERNICUS Trial	Carvedilol Prospective Randomized Cumulative Survival
DEFINITE Evaluation	Defibrillators in Nonischemic Cardiomyopathy Treatment
DIAMOND Dofetilide	Danish Investigation of Arrhythmia and Mortality on
DIG	Digitalis Investigation Group
ELITE	Evaluation of Losartan In The Elderly
ELITE II	Losartan Heart Failure Survival Study - ELITE II
EMIAT	Infarction Amiodarone Trial
GESICA en Argentina	Grupo de Estudio de Sobrevida en Insuficiencia Cardiaca
GUSTO 1	Global Utilization of Streptokinase and TPA for Occluded coronary arteries
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MADITII	Multicenter Automatic Defibrillator Implantation Trial II
MDC	Metoprolol in Dilated Cardiomyopathy trial
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Heart Failure
MOCHA	Multicenter Oral Carvedilol in Heart-failure Assessment
MTT	Myocarditis Treatment Trial
OPTIMALL	Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan
PRECISE	Prospective Randomized Evaluation of Carvedilol In Symptoms and Exercise
PROVED	Prospective Randomized study Of Ventricular failure and the Efficacy of Digoxin

RADIANCE	Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme
RALES	Randomized Aldactone Evaluation Study
RESOLVD	Randomized Evaluation of Strategies for Left Ventricular Dysfunction
SAVE	Survival And Ventricular Enlargement
SCD-HeFT	Sudden Cardiac Death in Heart Failure: Trial of prophylactic amiodarone versus implantable defibrillator therapy
SOLVD	Studies Of Left Ventricular Dysfunction
SWORD	Survival With Oral D-sotalol
ValHeFT	Valsartan Heart Failure Trial
VALIANT	Valsartan in Acute Myocardial Infarction

APPENDIX C
FDA MedWatch 3500 Form

APPENDIX D
Handling and Shipping Instructions for Serum Bound For
Case Comprehensive Cancer Center

Sample Handling Instructions

Herceptin trial CASE 10107

Collection and processing

Draw one 4.5 mL serum separator tube for TNFalpha, IL-6 and Troponin levels, and one 4.5ml EDTA-containing tube for BNP determination per time point. Allow serum separator tubes to clot for 30 minutes at room temperature before centrifugation. Centrifuge all tubes at 1500 x g at 4° C for 10 min. Divide the serum and plasma each into four 0.5 mL aliquots (use 1.8ml screw cap cryovials). Store at -70° C or colder, and batch ship every month. Ship Mon-Wed only to the address below. Label the aliquots in indelible marker as follows:

Patient ID, initials (FML)	Patient ID, initials (FML)
Date, draw time	Date, draw time
Timepoint	Timepoint
Serum (TNF, IL-6, Troponin)	Plasma (BNP)
Dr. Owusu, Herceptin	Dr. Owusu, Herceptin

Shipping Address

ATTN: Erin Hohler
University Hospitals of Cleveland
Rainbow Babies and Children's Hospital, room 693
11100 Euclid Ave
Cleveland, OH 44106
Please include a Shipping Manifest (see template provided).

Please email Erin Hohler the tracking number on day of shipment erin.hohler@case.edu.
Please call Erin Hohler if there are any questions 216-844-5562.

IL-6, TNFalpha, Troponin and BNP Analytical Method

Serum levels of IL-6 and TNFalpha are determined using commercially available multi-plex enzyme-linked immunosorbent assay (ELISA) kits (Meso-Scale Discovery, Gaithersburg, MD). All samples are run in duplicate with appropriate controls. Analytes are detected and quantitated using a MesoScale Discovery electrochemiluminesence instrument model Sector 2400 Imager. Troponin analyses are run on an automated analyzer using immunoassay technique (StreamLab system, Siemens, USA). The BNP is determined using a chemiluminesce automated analyzer (Centaur analyzer, Siemans, USA).