PROTOCOL

STUDY TITLE: Phase II trial of EVEROLIMUS ± Trastuzumab in hormone-refractory metastatic breast cancer

STUDY DRUG:	HERCEPTIN® (Trastuzumab) EVEROLIMUS (EVEROLIMUS)
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1. INTRODUCTION

1.1 The median survival for hormone receptor-positive metastatic breast cancer has improved significantly over the past 15 years (1). However, eventually all hormone receptor-positive metastatic breast cancers develop resistance to hormonal therapies (acquired resistance). Most patients who are considered to have hormone-refractory metastatic breast cancer are treated with chemotherapy, which is generally minimally effective and has inherent increases in toxicity. A better understanding of the molecular mechanisms responsible for hormone-resistance could lead to the discovery of more effective, less toxic therapies.

1.2 Mechanisms of hormone-resistance

Much of our current understanding of the molecular mechanisms responsible for hormone-resistance comes from clinical and pre-clinical models of selective estrogen receptor modulator (SERM)- resistance.

Transfection of HER2 into estrogen receptor (ER)-positive breast cancer cells renders them resistant to tamoxifen (2). Breast cancers that have high levels of HER2 expression are felt to be somewhat intrinsically resistant to hormonal therapies, including tamoxifen and aromatase inhibitors (3,4). These findings suggest the likely possibility that HER2 plays a significant role in *de novo* hormone-resistance.

There is increasing data to suggest that an increase in HER2 protein expression plays a role in acquired hormone-resistance. SERM-resistant breast cancer cells *in vitro* and *in vivo* have an increase in the expression of members of the epidermal growth factor family, including HER2, compared to SERM-sensitive breast cancer cells (5).

We recently analyzed primary and metastatic breast cancers in patients treated with tamoxifen for HER2 expression. As can been seen in table 1-1 below there was a significant increase in the level of expression of HER2 protein in the metastatic tamoxifen-treated breast cancers (6). This, together with the preclinical data outlined above confirms a likely role of HER2 in cancers with acquired hormone-resistance.

Table 1-1 Mechanisms of Hormone-Resistance

	At diagnosis	At recurrence	p
ER	79%	59%	P=0.035
PR	34%	22%	P=0.13
HER2/neu (2+,3+)	27%	53%	P=0.01

1.3 Rationale for use of trastuzumab in hormone-refractory disease

Although preclinical and clinical tamoxifen-resistant breast cancers exhibit an incremental increase in HER2 (5,6), the degree of over-expression is at most 2+ by IHC and is not gene amplified. However, trastuzumab inhibits SERM-stimulated breast cancer growth *in vivo*, despite the low level of HER2 protein expression (7). The use of trastuzumab in this model was associated with an increase in apoptosis.

Although the presence of HER2 gene amplification is an important predictor of outcome to trastuzumab-based chemotherapy and to single agent trastuzumab in patients with metastatic breast cancer, emerging data suggests this may not be the case for patients with early stage breast cancer. Paik et al (8) recently correlated disease-free survival (DFS) in the NSABP B-31 trial in patients treated with adjuvant trastuzumab-based chemotherapy with HER2 expression and amplification. The use of adjuvant trastuzumab-based chemotherapy improved DFS compared to chemotherapy alone by greater than 50% regardless of whether cancers were HER2 gene-amplified or not, and regardless of the level of expression of HER2 protein. Most interestingly, DFS was improved by 50% with the use of trastuzumab-based chemotherapy compared to chemotherapy alone in patients with tumors that did not exhibit HER2 gene amplification and had only 1+ expression of HER2 protein.

The fact that cancers with low to moderate levels of HER2 expression, such as those seen in hormone-resistant cancers, may respond to trastuzumab supports this proposal to examine the use of trastuzumab in hormone-refractory breast cancers.

1.4 Rationale of mTOR inhibition in hormone-refractory and HER2-positive breast cancer

An increase in downstream signaling has been documented in tamoxifen-resistant preclinical models, through constitutive activation of the Akt pathway, PTEN loss and an increase in upstream receptors, including members of the EGFR and IGFR families (9). mTOR inhibition has been demonstrated to be more effective preclinically in cell lines with increased Akt signaling, PTEN loss and/or increased upstream signaling (10,11). Additionally, mTOR inhibitors, such as Rapamycin and Everolimus, have been demonstrated to increase Akt activity, while decreasing downstream effectors of cell signaling (12, 13). This increase in Akt activity is felt to be due to a feedback mechanism (12,13). Therefore, the concept of using an mTOR inhibitor with an agent that blocks upstream signaling via the Akt pathway is a rational combination which is currently being examined in patients with trastuzumab-resistant HER2-positive metastatic breast cancer.

In summary, hormone-resistance is mutifactorial but increased expression of HER2 and downstream signaling appear to play an important role. Based on these findings, together with the findings of Paik et al (8) demonstrating that trastuzumab is effective in cancers with low to moderate HER2 protein expression, we propose that the use of trastuzumab alone or in combination with mTOR inhibition could circumvent hormone-resistance in patients with metastatic breast cancer.

1.5 Trastuzumab Clinical Experience

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 (14). 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 (15). 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 (16). 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 that in the pivotal clinical trials

1.5.1 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 Trastuzumab 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 postapproval 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 postmarketing 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-Trastuzumab antibodies in this patient was not associated with clinical signs or symptoms.

1.5.2 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 in 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) (17). 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 (18), and in combination with paclitaxel (175 mg/m^2) (19), confirmed that a two-compartment model best describes the PK of trastuzumab. Model-independent analysis of the 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 (14,15,20). In the trastuzumab q3 weekly monotherapy study (18), 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 (19), 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.

1.6 EVEROLIMUS AND mTOR INHIBITION

1.6.1 PI3K / AKT / mTOR pathway as a molecular target in cancer

mTOR (mammalian target of rapamycin) is a key protein kinase present in all cells which regulates cell growth, proliferation and survival. mTOR is mainly activated via the P13 kinase pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of P13 kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the

pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development.

mTOR (mammalian target of rapamycin) is a serine-threonine kinase which is a member of the larger PI3K (phosphatidylinositol 3-kinase) family and present in all cells. The main known functions of mTOR include the following (21):

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels, facilitating cell-cycle progression from G1-S phase in appropriate growth conditions.
- The PI3K (mTOR) pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors.
- The mTOR pathway is involved in the production of pro-angiogenic factors e.g. vascular endothelial growth factor (VEGF) and in endothelial cell growth and proliferation directly.
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates protein translation, including the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.

In breast cancer, overactivation of PI3K or Akt1 can be as high as 40%, whereas mutations or loss of heterozigozity at PTEN locus are much less frequent (22).

Preclinical rationale is established for the combination of an mTOR inhibitor with trastuzumab; loss of PTEN predicts resistance to trastuzumab (23). It has been shown that in PTEN-deficient cells PI3K inhibition rescued trastuzumab resistance in vitro and in vivo (24-25).

There is evidence that PI3K-AKT pathway activity contributes to ErbB2-associated tumor growth, and resistance to ErbB2 inhibition (26-27).

1.6.2 Overview of EVEROLIMUS

EVEROLIMUS (everolimus) is a derivative of rapamycin. EVEROLIMUS has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. It is approved in Europe since 2003 (trade name: Certican®) for the prevention of organ rejection in patients with renal and cardiac transplantation. Approval for Certican® was also granted in Australia, South Africa, the Middle East, Central and South America, the Caribbean and some Asian countries.

EVEROLIMUS is being investigated as an anticancer agent based on its potential to act

- directly on the tumor cells by inhibiting tumor cell growth and proliferation
- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF production and VEGF-induced proliferation of endothelial cells)

1.6.3 Preclinical studies of EVEROLIMUS

EVEROLIMUS inhibits the proliferation of a range of human tumor cell lines *in-vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to µM. EVEROLIMUS also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) in *vitro*, with particular potency against VEGF-induced proliferation suggesting that EVEROLIMUS may also act as an antiangiogenic agent. The antiangiogenic activity of EVEROLIMUS was confirmed in vivo. EVEROLIMUS selectively inhibited VEGF-dependent

angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with EVEROLIMUS showed a significant reduction in blood vessel density when compared to controls.

The potential of EVEROLIMUS as an anticancer agent was shown in rodent models. EVEROLIMUS is orally bioavailable, residing longer in tumor tissue than in plasma in a s.c mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of EVEROLIMUS indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to EVEROLIMUS *in vitro*.

EVEROLIMUS administered daily p.o. was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and "relative resistant" *in vitro*. In general, RAD was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated s.c. implant model of angiogenesis and reduced vascularity (vessel density) of EVEROLIMUS-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

It is not clear which molecular determinants predict responsiveness of tumor cells to EVEROLIMUS. Molecular analysis has revealed that relative sensitivity to EVEROLIMUS *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein; in some cases (i.e., GBM) there is also a correlation with PTEN status.

In vivo studies investigating the anti-tumor activity of EVEROLIMUS in experimental animal tumor models showed that EVEROLIMUS monotherapy typically reduced tumor cell growth rates rather than produced regressions or stable disease. These effects occurred within the dose range of 2.5 to 10 mg/kg, p.o. once a day.

In preclinical models, the administration of EVEROLIMUS is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, noteably phosphorylated-S6 (p-S6) and p-4E-BP1, and occasionally with an increase in the phosphorylation AKT, a protein upstream of the mTOR signaling pathway. Study [CEVEROLIMUSA2107] explored MPD (molecular pharmacodynamic) changes in tumor at different doses and schedules of EVEROLIMUS (weekly 20, 50 and 70 mg or daily 5 and 10 mg).

All significant adverse events observed in toxicology studies with EVEROLIMUS in mice, rats, monkeys and minipigs were consistent with its anticipated pharmacological action as an antiproliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

1.6.4 Clinical experience with EVEROLIMUS

1.6.4.1 EVEROLIMUS pharmacokinetics

The pharmacokinetic characteristics of EVEROLIMUS have been extensively investigated in the context of the drug's development as an immunosuppressant in solid organ transplantation where EVEROLIMUS was administered twice daily as a part of an immunosuppressant, multi-drug regimen consistently including cyclosporin A and glucocorticoids. Recent Phase I studies provide steady-state pharmacokinetics for both the weekly and daily schedules at varying dose levels in patients with advanced cancers.

EVEROLIMUS is rapidly absorbed after oral administration, with a median time to peak blood levels (t_{max}) of 1-2 hours postdose. The extent of absorption is estimated at above 11%. The area under the blood concentration-time curve (AUC) is dose-proportional over the dose range tested while maximum blood concentration C_{max} appears to plateau at dose levels higher than 20 mg. The terminal half-life in cancer patients averaged 30 hours, which is similar to that in healthy subjects. Inter-patient variability is moderate with the coefficient of variation (CV) of approximately 50%. A high-fat meal altered the absorption of EVEROLIMUS with 1.3 hour delay in $t_{max,}$ a 60% reduction in C_{max} and a 16% reduction in AUC. In whole blood, approximately 80% of EVEROLIMUS is contained in red blood cells. Of the fraction of drug contained in plasma, 74% is protein-bound. The apparent distribution volume (Vz/F) after a single dose was 4.7 L/kg. EVEROLIMUS is eliminated by metabolism, mainly by hydroxylation, then excreted into the feces >80%.

EVEROLIMUS is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. EVEROLIMUS is also a substrate of P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systematically

absorbed EVEROLIMUS may be influenced by medicinal products that interact with CYP3A4 and/or P-glycoprotein. *In vitro* studies showed that EVEROLIMUS is a competitive inhibitor of CYP3A4 and of CYP2D6 substrates, potentially increasing the concentrations of medicinal products eliminated by these enzymes. In two phase III clinical trials in patients following kidney transplantation, strong inhibitors of CYP3A4 (azoles, antifungals, cyclosporine, erythromycin) have been shown to reduce the clearance of EVEROLIMUS therapy thereby increasing EVEROLIMUS blood levels. Similarly, Rifampin, a strong inducer of CYP3A4, increases the clearance of EVEROLIMUS thereby reducing EVEROLIMUS blood levels. Caution should be exercised when co-administering EVEROLIMUS with CYP3A4 inhibitors or inducers.

Pharmacokinetic drug to drug interactions with cancer agents are being evaluated in ongoing phase Ib studies. Based on currently available results, gemcitabine (study 2101 part 2) and paclitaxel (study 2104) did not alter EVEROLIMUS pharmacokinetics to a clinically relevant extent whereas imatinib notably increased EVEROLIMUS exposure with a mean increase in AUC by a multiple of 3.7 for EVEROLIMUS administered weekly and two-fold for EVEROLIMUS administered daily (study 2206). Exposure to EVEROLIMUS in the presence of letrozole did not exceed that in monotherapy (study 2108). Co-administration of EVEROLIMUS did not influence pharmacokinetics of

gemcitabine, imatinib or letrozole. Exposure to paclitaxel in the presence of EVEROLIMUS was slightly decreased (average by 23%).

EVEROLIMUS pharmacokinetics in transplant patients was investigated in special populations such as subjects with hepatic or renal impairment, various ethnic groups and pediatric renal transplant patients. In subjects with mild–moderate hepatic impairment, mean AUC to EVEROLIMUS is increased by 3-fold whilst renal impairment does not affect the pharmacokinetics of EVEROLIMUS. Age, weight (both over the adult range) and gender do not affect the pharmacokinetics of EVEROLIMUS to a clinically relevant extent. Also, pharmacokinetics does not alter in Japanese or Asian patients whereas black patients have 21% higher clearance compared to non-blacks. In children, the apparent clearance of EVEROLIMUS increases linearly with body surface. The clearance per square meter of body surface area is 12-fold higher compared with adult patients.

1.6.4.2 Pharmacodynamic studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition in a peripheral biomarker (S6 kinase inhibition in peripheral blood mononuclear cells) suggests that 5-10 mg daily should be an adequate dose to produce a high-degree of sustained target inhibition. Furthermore, molecular pharmacodynamic (MPD) studies using IHC in biopsied tumor tissue assessed the degree of inhibition and its duration (for p-S6, p-4E-BP1 and p-Akt expression) with the daily and weekly dosing. The pathologist was blinded for the biopsy sequence. There was almost

complete inhibition of p-S6 at all doses and schedules studied (p=0.001). Preliminary results suggest a dose-related decrease in p-4E-BP1 and increase in p-Akt expression with maximal effect at 10 mg daily and ≥ 50 mg weekly. The study results are provided in Table 1-2.

Table 1-2 p-S6, p-4E-BP1 and p-Akt expression at various doses of EVEROLIMUS

Dose of Everolimus	p-S6 inhibition (mean %)	p-4E-BP1 inhibition (mean %)	p-Akt activation (mean %)
Daily 5 mg (n=3)	100.0	48.0	22.2
Daily 10 mg (n=6)	92.5	58.2	45.5
Weekly 20 mg (n=5)	96.7	5.9	32.7
Weekly ≥ 50 mg (n=6)	100.0	63.8	63.1

Reference: EVEROLIMUS Investigator's Brochure 2005

1.6.4.3 Phase I and II oncology studies

Data are available from phase I clinical studies of EVEROLIMUS given as a single agent to 147 patients with advanced solid tumors. Such studies included various doses and schedules (weekly dosing, range 5-70 mg and daily dosing 5-10 mg). Approximately, 46% of patients reported rash or erythema and 40% of the patients presented with stomatitis/mucositis. The most frequent adverse events suspected to be drug-related observed in three studies using EVEROLIMUS as a single agent are listed in Table 1-3.

Table 1-3 Adverse events suspected to be drug-related in ≥10% of patients with advanced cancers reported in Phase I EVEROLIMUS monotherapy studies (C2101, C2102 and 2107)

	Weekly			Daily		
	5-30 mg n=30	**50 mg n=18**	**70 mg n=38**	**5mg n=16**	**10 mg n=45**	**Total n=147**
No. Pts with AEs						
Any event	23 (1)	17 (2)	38 (10)	14 (1)	43 (14)	135 (28)
By event						
- Rash	5	8	18	10	27 (1)	68 (1)
- Stomatitis/mucositis	6	8 (2)	16 (2)	6 (1)	23 (3)	59 (8)
- Fatigue	8	7 (1)	14 (1)	1	17 (1)	47 (3)
- Nausea	5	4	8	2	18 (1)	37 (1)
- Anorexia	1	6	10	3	15	35
- Diarrhea	1	7	7	-	9	24
- Vomiting	4	5	5	-	10	24
- Headache	7	4	6	6	4	20
- Pruritus	2	1	6	3	4	16
- Infections[1]	1	3	3 (1)	1	6 (2)	14 (3)
- Constipation	-	1	2	2	9	14

The numbers of patients (by dose level and dose schedule) who have reported grade ≥3[1] toxicities is given in brackets.

[1]. events included in brackets reached no more than grade 3 severity

[2] Infections noted as drug-related included:

Herpes simplex: 5 pts (1 at 50 mg/wk; 1 at 5mg/d; 3 at 10 mg/d)
Oral candidiasis: 5 pts (1 at 50 mg/wk; 3 at 70 mg/wk, 1 at 10 mg/d)
Pneumonia (gr3) 1 pt (10 mg/d)
Pustular rash 1 pt (20 mg/wk)
Rhinitis 2 pts (50 mg/wk)
URT Infection 1 pt (50 mg/wk
Urinary Tract Infect 1 pt (50 mg/wk)

Reduced blood cell counts at the initiation of treatment are frequent but remain mostly within the normal range or limited to grade 1 although a grade 3 neutropenia was a DLT in one patient as was a grade 3 thrombocytopenia in a patient receiving EVEROLIMUS with letrozole where pharmacodynamic interaction is unlikely. This suggest that some patients may be particularly sensitive to the myelosuppressive effect of EVEROLIMUS making it necessary to monitor carefully blood cell counts at initiation of treatment.

Metabolic changes (hyperlipidemia and hyperglycemia) may be observed during treatment with EVEROLIMUS. Both events may be medically managed. Hyperlipidemia has been reported as an ADR in 10% of patients although review of the laboratory values suggests that as many as a quarter of patients develop grade 1-2 hyperlipidemia on treatment, mostly hypercholesterolemia. Hyperglycemia has been reported as an adverse event in 7% of patients. Grade 3 hyperglycemia has been observed, especially in diabetics receiving EVEROLIMUS treatment. Therefore, patients with diabetes should have their blood glucose monitored carefully and their medications adjusted, as needed, to maintain adequate control of their blood glucose levels.

In Novartis-sponsored clinical trials, symptomatic non-infectious pneumonitis has been reported as a serious adverse event in less than 1% of patients out of approximately 1000 cancer patients treated with EVEROLIMUS as of April 30, 2006. This adverse event has been noted in the Investigators' Brochure. Corticosteroids were often administered to the patients with symptomatic pneumonitis.

Novartis has recently received reports of low grade non-infectious pneumonitis in cancer patients treated with EVEROLIMUS. Most of these reports involve patients with no respiratory symptoms (CTC grade 1 pneumonitis: radiographic findings only) or mild severity (CTC grade 2: symptomatic, not interfering activities of daily living), and were from two investigator-sponsored (private IND) trials, as follows:

- In a study of patients with advanced renal cell carcinoma receiving 10 p.o. mg/day, 15/20 patients reviewed by an independent radiologist were noted to have lung infiltrates consistent with pneumonitis on routine chest CT scans performed to follow the patients' thoracic metastases.
- In a study of patients with advanced breast cancer, 7/18 patients treated with EVEROLIMUS 10 mg/d and 2/16 patients treated with EVEROLIMUS 70 mg/week, had findings consistent with pneumonitis. In this study, two patients, one on the daily RAD arm and one on the weekly EVEROLIMUS arm, developed severe (grade 3) pneumonitis which resolved after EVEROLIMUS was discontinued.

In both studies, most patients had radiological changes with mild or no symptoms and have continued EVEROLIMUS treatment without developing symptoms. The reason for an increased rate of reported low-grade pneumonitis among oncology patients in these studies is unclear. Both studies included serial chest CT scans allowing prolonged, detailed evaluation of the lung parenchyma; the dosage and drug exposure in these phase 2 trials is generally longer than in the phase 1 experience. In addition, the dosage of EVEROLIMUS used in the treatment of cancer patients is substantially higher than that given routinely in the organ transplant setting. Everolimus (EVEROLIMUS) is approved at a daily dose of 0.75 mg twice a day guided by therapeutic drug monitoring (3-8 ng/ml) in combination with cyclosporine microemulsion in many regions of the world for renal and cardiac transplantation. In phase 3 trials investigating everolimus in renal and cardiac transplantation, the overall reported rate of pneumonitis ranged from 0.0 to 1.4%. The spontaneous reporting rate for pneumonitis following exposure to commercially available everolimus in transplantation is very low (0.08% or 84.4 events/100,000 patient-years). Refer to the latest version of the EVEROLIMUS Investigator's Brochure and safety letters (Investigator Notifications) for the most up to date information available.

1.6.5 EVEROLIMUS combination with trastuzumab

To investigate the potential for EVEROLIMUS/trastuzumab combinations, trastuzumab-sensitive ErbB2-overexpressing breast carcinoma cells (BT474, SKBR3), with known sensitivity to EVEROLIMUS (IC50 for antiproliferative activity = sub nM), were incubated with increasing concentrations of trastuzumab in the presence of an optimal EVEROLIMUS concentration and effects on proliferation were analyzed. In both lines, increased antiproliferative effects were observed with the combination as compared to the single agents. Statistical analysis indicated significant positive interactions between EVEROLIMUS and trastuzumab ($p < 0.001$ BT474; $p = 0.035$ SKBR3, two-way ANOVA). Based on this promising in vitro data, the combination was also assessed in an athymic mouse BT474 orthotopic mammary tumor model. Ten estrogen pellet-bearing animals per group were treated three times per week (MWF) with EVEROLIMUS (5mg/kg p.o.), trastuzumab (2 mg/kg i.p.), the combination or vehicle control. Antitumor activity was observed with the single agents and was increased with the combination; a result indicating positive interaction between the two agents that reached near significance ($p = 0.060$, two-way ANOVA). A second experiment also showed increased activity of the combination. Based on body weights, treatments were well tolerated. Taken together, these data suggest that combinations of EVEROLIMUS and trastuzumab may have application in the treatment of ErbB2/HER2-overexpressing breast cancer patients, although further dose/regimen optimization may be required.

The ability of everolimus to re-sensitize HER2-positive breast cancers to trastuzumab has recently been evaluated (28). Patients with HER2-positive cancers who had been previously treated with both taxanes and trastuzumab were treated with paclitaxel and trastuzumab in combination with everolimus (phase 1 schedule 5mg daily, 10mg daily or 30mg weekly). There were two DLTs, one patient with febrile neutropenia who received 5mg daily dose of everolimus and one patient with a confusional state who received 30mg weekly dose. Other toxicities included stomatitis and anemia. Out of 13 patients eligible for efficacy assessment, 46% had a partial response and 91% of patients had disease control for > 16 weeks. This trial will proceed to a phase 2 trial in which patients with taxane and trastuzumab-resistant HER2-positive metastatic breast cancer will be treated with paclitaxel, trastuzumab and everolimus 10mg daily. This data supports the hypothesis that mTOR inhibition can re-sensitize HER2-positive cancers to trastuzumab.

1.7 Correlative Studies

1.7.1 Biopsies or surgical specimens at the time of initial diagnosis wil be evaluated for the expression of HER2, ER, PR, EGFR, and downstream effector proteins, including Akt, PI3K, PTEN, MAPK, mTOR, S6, 4-EBP. Total and phosphorylated proteins will be measured.

1.7.2. Patients must have a biopsy of their cancer in the metastatic setting to assess HER2-expression. In general, it can be difficult to obtain biopsies in patients with metastatic breast cancer because of an inaccessibility of metastatic sites amenable to biopsy without increased morbidity. This may be especially true in these patients with hormone receptor-positive disease, which may have bone as the only site of metastases.

1.7.3 Pre-treatment biopsies will be evaluated for the expression of HER2, ER, PR, EGFR, and downstream effector proteins, including Akt, PI3K, PTEN, MAPK, mTOR, S6, 4-EBP. Total and phosphorylated proteins will be measured.

1.7.4 Post-treatment biopsies will be evaluated for the expression of HER2, ER, PR, EGFR, and downstream effector proteins, including Akt, PI3K, PTEN, MAPK, mTOR, S6, 4-EBP. Total and phosphorylated proteins will be measured.

1.7.5 We will compare the expression of these proteins in the primary biopsy/surgical specimen with the pre-treatment biopsies. Based on our preliminary studies, we anticipate an increase in HER2 and EGFR, with a concomitant decrease in ER and PR in the pre-treatment biopsies, compared to the primary specimens.

1.7.6 Response to trastuzumab and everolimus will be correlated with the expression of total and phosphorylated proteins (HER2, ER, PR, EGFR, and downstream effector proteins, including Akt, PI3K, PTEN, MAPK, mTOR, S6, 4-EBP).

2. OBJECTIVES

To evaluate the benefit of everolimus with hormonal therapy in patients with hormone-refractory breast cancer.

2.1 PRIMARY OBJECTIVES

- Assess the response rate everolimus in combination with hormonal therapy in patients with hormone-refractory metastatic breast cancer

2.2 SECONDARY OBJECTIVES

- Assess the clinical benefit rate (response rate plus stable disease for ≥ 24 weeks) of everolimus in combination with hormonal therapy in patients with hormone-refractory metastatic breast cancer
- Assess time to progression of everolimus in combination with hormonal therapy in patients with hormone-refractory metastatic breast cancer
- Correlate response rate and clinical benefit in patients with hormone-refractory breast cancer treated with everolimus with the expression of HER2 and downstream effector proteins in pre-treatment biopsies
- Assess the response rate, clinical benefit rate and time to progression in patients treated with trastuzumab in combination with everolimus following disease progression on everolimus in combination with hormonal therapy in patients with hormone-refractory metastatic breast cancer
- Evaluate the safety of everolimus alone or with trastuzumab in combination with hormonal therapy in patients with hormone-refractory metastatic breast cancer

3. STUDY DESIGN

- Patients will continue to take most recent hormonal therapy (tamoxifen, anastrozole, letrozole, exemestane, fulvestrant, etc)
- Patients receive everolimus 10mg daily PO

- Patients will be asked to have a biopsy performed prior to study entry (but must have had a biopsy in the metastatic setting demonstrating 1+ or 2+ HER2-expression by IHC) and when they come off study (both biopsies are optional)
- At the time of disease progression patients will continue everolimus and start trastuzumab (6mg /kg three weekly with 8mg/kg loading dose) in combination with hormonal therapy

3.1 Description of the Study

This is an open-label phase II trial in patients with hormone-refractory metastatic breast cancer (defined as disease progression within 6 months of most recent hormonal therapy). Patients will continue most recently prescribed hormonal therapy and receive everolimus 10 mg daily. Thirty-four patients will be recruited*. Patients will be followed for response rate, clinical benefit, time to progression and safety.

At the time of disease progression patients will be offered combination therapy with trastuzumab and will continue on hormonal therapy.

*Prior to protocol version 12, the study had 2 arms: Patients were randomized to receive trastuzumab (6mg/kg every 3 weeks) or everolimus 10 mg daily. Thirty-nine patients were the target enrollment goal for each arm for a total of 78 subjects. Protocol version 12 modified the study to a single-arm study. The discontinued tratuzumab arm had already enrolled subjects prior to this modification. The on-going enrollment target for the evrolimus arm was subsequently adjusted to 34.

3.2 Rationale for Study Design

Acquired resistance to hormonal therapy is associated with an increase in the expression of HER2 protein. In preclinical models, trastuzumab inhibits breast cancer growth despite the fact that HER2 is only moderately expressed. This is the rationale for evaluating the use of trastuzumab in hormone-refractory metastatic breast cancer. The PI3-kinase pathway has been demonstrated to be involved in hormone-resistance and mTOR inhibitors are currently in phase 3 trials of patients with hormone receptor-positive metastatic breast cancer. In preclinical models, mTOR inhibition using everolimus is associated with an increase in Akt signaling, which can sensitize cancer cells to upstream inhibition, with trastuzumab.

3.3 Outcome Measures

Response rate will be measured after 6 and then every 12 weeks using RECIST criteria (see appendix B), and is the primary endpoint.

Clinical benefit (response rate plus stable disease) will be assessed after 6 weeks then every 3 months (12 weeks).

Patients will be followed for **time to progression**.

Patients who receive combination therapy with trastuzumab and everolimus at disease progression will have response rate and clinical benefit rate assessed after 6 and then every 3 months (12 weeks). Patients will be followed for time to progression.

The **safety** of the combination of trastuzumab and/or everolimus in combination with hormonal therapy will be monitored continuously over the study period.

3.3.1 Primary Outcome Measure

Assess the response rate everolimus in combination with hormonal therapy in patients with hormone-refractory metastatic breast cancer. Response rate will be measured after 6 and then every 12 weeks of therapy and then every 3 months (12 weeks) using RECIST criteria.

3.3.2 Secondary Outcome Measures

3.3.2.1 Assess the clinical benefit rate of everolimus in combination with hormonal therapy in patients with hormone-refractory metastatic breast cancer. Clinical benefit will be measured after 6 and then every 12 weeks of therapy and then every 3 months using RECIST criteria.
3.3.2.2 Assess time to progression of everolimus in combination with hormonal therapy in patients with hormone-refractory metastatic breast cancer
3.3.2.3 Assess the response rate, clinical benefit rate and time to progression in patients treated everolimus in combination with hormonal therapy with the addition of trastuzumab at disease progression after 6 and then every 12 weeks of therapy and then every 3 months using RECIST criteria
3.3.2.4 Correlate response rate and clinical benefit rate in patients with hormone-refractory breast cancer treated with everolimus with the expression of HER2 and downstream effector proteins in pre-treatment biopsies
3.3.2.5 Evaluate safety of everolimus alone or with trastuzumab and hormonal therapy

3.4 Safety Plan

Patients will be evaluated at each study visit for the duration of their participation in the study (see Section 4.5 and Appendix A, Study Flowchart).

Specific potential safety issues for this trial are outlined below.

3.4.1 Trastuzumab

3.4.1.1 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 Trastuzumab. 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) (Seidman et al. 2001). 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.

3.4.1.2 Management of Cardiac Safety

All patients must have a baseline evaluation of cardiac function including a measurement of LVEF by either MUGA or ECHO prior to entry into the study. Only patients with normal LVEF (≥50% or institutional normal) should be entered into this study. All should have regular cardiac monitoring throughout the study. It is suggested that the first evaluation occur 3 months after the initiation of Trastuzumab therapy. During the course of Trastuzumab therapy, patients should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). The diagnosis must be confirmed using the same method used to measure LVEF at baseline (either ECHO or MUGA).

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). 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) for example after 4 weeks and then every 3 months 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 a

symptomatic 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). 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 3-1 Management of Cardiac Toxicity of Trastuzumab

	Ejection fraction	**Procedure**
Symptoms of CHF		Hold trastuzumab Treat with CHF medications Consider cardiology consult If ejection fraction increases to normal range consider restarting trastuzumab based on breast cancer risk If ejection fraction doesn't increase to normal range, patient will be removed from the study
Asymptomatic		
	Decrease of less 20 percentage points but within range of normal limits	Continue trastuzumab Repeat ejection fraction measurement in 4 weeks
	Decrease of ≥ 20 percentage points and/or below range of	Hold trastuzumab

	normal	Treat with CHF medications Repeat ejection fraction measurement in 4 weeks If ejection fraction increases to normal range consider restarting trastuzumab based on breast cancer risk If ejection fraction doesn't increase to normal range, patient will be removed from the study

3.4.1.3 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.

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.

Table 3-2 Management of infusion reactions associated with trastuzumab

Grade of reaction	Procedure
Mild to moderate	Treat with analgesic/antipyretic and/or antihistamine
Serious	Supportive care Withdrawal of trastuzumab may be necessary

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 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 Trastuzumab.

3.4.2 Everolimus

Adverse events most frequently observed with EVEROLIMUS are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, diarrhea and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (CTC grade 1-2).

3.4.2.2 Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis/oral mucositis/mouth ulcers due to EVEROLIMUS should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with EVEROLIMUS as mouth ulcers, rather than mucositis or stomatitis. If examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.

2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of EVEROLIMUS metabolism, therefore leading to higher EVEROLIMUS exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

3.4.2.3 Management of hyperlipidemia and hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia (>2.5 x upper normal limit) should be treated with a statin or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors. Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia. Grade 3 ***hyperglycemia*** has been observed in patients receiving EVEROLIMUS therapy. In almost all cases the affected patients had an abnormal fasting glucose at baseline. Based on this finding, we suggest that optimal glucose control should be achieved before starting a patient on EVEROLIMUS and should be monitored during EVEROLIMUS therapy.

Table 3-3 Criteria for dose-modification in case of suspected EVEROLIMUS toxicity and re- initiation of EVEROLIMUS treatment

Toxicity	Actions
Non-hematological toxicity	
Grade 2 (except pneumonitis – refer to Table 3-2)	If the toxicity is tolerable to the patient, maintain at 10mg daily. If the toxicity is intolerable to patient, interrupt EVEROLIMUS until recovery to grade ≤1. Then reintroduce EVEROLIMUS at 5mg daily. If event returns to grade 2, then interrupt EVEROLIMUS until recovery to grade ≤1. Then reintroduce EVEROLIMUS at 5mg every other day.
Grade 3 (except hyperlipidemia* and pneumonitis see Table 3-2)	Interrupt EVEROLIMUS until recovery to grade ≤1. Then reintroduce EVEROLIMUS at 5mg every other day. For pneumonitis consider the use of a short course of corticosteroids.
Grade 4	Discontinue EVEROLIMUS.
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	Interrupt EVEROLIMUS until recovery to grade ≤1 (>75 x10^9/L). Then reintroduce EVEROLIMUS at 5mg daily. If thrombocytopenia again returns to grade 2, interrupt EVEROLIMUS until recovery to grade ≤1. Then reintroduce EVEROLIMUS at 5mg every other day
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt EVEROLIMUS until recovery to grade ≤1 (platelets ≥ 75 x10^9/L). Then resume EVEROLIMUS at 5mg every other day. If grade 3 thrombocytopenia recurs, discontinue EVEROLIMUS.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Discontinue EVEROLIMUS.
Grade 3 Neutropenia (neutrophils <1, ≥0.5 x10^9/L)	Interrupt EVEROLIMUS until recovery to grade ≤1 (neutrophils ≥ 1.5 x 10^9/L). Then resume EVEROLIMUS at 5mg daily. If ANC again returns to Grade 3, hold EVEROLIMUS until the ANC ≥ 1.5 x 10^9/L. Then resume EVEROLIMUS dosing at 5mg every other day. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt EVEROLIMUS until recovery to grade ≤ 1 (neutrophils ≥ 1.5 x 10^9/L). Then resume EVEROLIMUS at 5mg every other day. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue EVEROLIMUS.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt EVEROLIMUS until resolution of fever and neutropenia to grade ≤ 1. Hold further EVEROLIMUS until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume EVEROLIMUS at 5mg every other day. If febrile neutropenia recurs, discontinue EVEROLIMUS.
Grade 4 febrile neutropenia (life-threatening)	Discontinue EVEROLIMUS.
Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks	Discontinue EVEROLIMUS

3.4.2.4 Management of non-infectious pneumonitis

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving EVEROLIMUS therapy. . Non-infectious pneumonitis has been associated with EVEROLIMUS and other mTOR inhibitors. In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray every 3 months is required if a CT scan of chest is not used for disease evaluations. Additional chest X-rays/CT scans may be done, when clinically necessary. If non-infectious pneumonitis develop, consultation with a pulmonologist should be considered. Management of non-infectious pneumonitis suspected to be associated with EVEROLIMUS and dose modifications instructions are provided in Table 3-4.

Table 3-4 Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	EVEROLIMUS Dose Adjustment
Grade 1	CT scans with lung windows.	No specific therapy is required	Administer 100% of EVEROLIMUS dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to within normal limits. Consider a bronchoscopy.	Symptomatic only. Rule out infection. Prescribe corticosteroids if cough is troublesome.	Reduce EVEROLIMUS dose until recovery to $\leq$ grade 1. EVEROLIMUS may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to $\leq$ grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest.; Repeat each subsequent Cycle until return to within normal limits. Bronchoscopy is recommended.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to $\leq$ grade 1. May restart protocol treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit. Patients will be withdrawn from the study if they fail to recover to $\leq$ grade 1 within 3 weeks.
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to within normal limits. Bronchoscopy is recommended.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

All interruptions or changes to study drug administration must be recorded.

3.5 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 requirements.

4. MATERIALS AND METHODS

4.1 Subjects

4.1.1 Subject Selection

4.1.2 Inclusion Criteria

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

- Hormone-refractory metastatic breast cancer defined as disease progression within 6 months from starting most recent hormonal therapy
- At least one line of endocrine therapy in the metastatic setting
- Candidate for hormonal therapy (ER and/or PR-positive at primary diagnosis and at metastatic diagnosis where tissue is available)
- HER2/neu-negative breast cancer by standard criteria (IHC < 3+ or FISH-negative if IHC 3+) at primary diagnosis
- Must have a biopsy in the metastatic setting with HER2 expression of 1+ or 2+ by IHC
- If biopsy of metastatic lesion is performed prior to study entry, HER2 expression by IHC must be 1+ or 2+.
- Histologically confirmed, measurable or evaluable disease. If disease is measurable RECIST criteria should be used (please refer to Appendix B).
- Life expectancy > 6 months
- Age >18 years
- ECOG performance status ≤ 2
- Adequate bone marrow function as indicated by the following:

  ANC >1500/μL

  Platelets ≥100,000/μL

  Hemoglobin >10 g/dL
- Adequate renal function, as indicated by creatinine ≤1.5× upper limit of normal (ULN)
- Adequate liver function, as indicated by bilirubin ≤1.5× ULN
- INR ≤ 1.3 (or ≤ 3 on anticoagulants)
- AST or ALT <2× ULN unless related to primary disease.

- Signed informed consent
- Adequate birth control
- Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.

4.1.3 Exclusion Criteria

Patients will be excluded from the study based on the following criteria:

- Prior treatment with trastuzumab or other HER2-directed therapies or with an mTOR inhibitor within 12 months of study entry (when cancer was not definitely hormone refractory)
- HER2 0 or 3+ by IHC on pre-treatment biopsy of metastatic lesion (if performed)
- Active infection
- Uncontrolled central nervous system metastases
- Life-threatening, visceral metastases
- Pregnant or lactating women
- Prior chemotherapy within the last 4 weeks
- Prior radiation therapy within the last 4 weeks; prior radiation therapy to indicator lesion (unless objective disease recurrence or progression within the radiation portal has been documented since completion of radiation).
- Concomitant malignancies or previous malignancies within the last 5 years, with the exception of adequately treated basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix.
- History of significant cardiac disease, cardiac risk factors or uncontrolled arrhythmias
- Ejection fraction <50% or below the lower limit of the institutional normal range, whichever is lower
- Hypersensitivity to trial medications
- Emotional limitations
- Prior treatment with any investigational drug within the preceding 4 weeks. Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent
- uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN
- liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis
- A known history of HIV seropositivity

- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of EVEROLIMUS (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection)
- Patients with an active, bleeding diathesis
- Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Hormonal contraceptives are not acceptable as a sole method of contraception. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of EVEROLIMUS)
- Patients who have received prior treatment with an mTOR inhibitor (sirolimus, temsirolimus, everolimus).
- Symptomatic intrinsic lung disease or extensive tumor involvement of the lungs, resulting in dyspnea at rest
- Taking any of the following agents:
    - chronic treatment with systemic steroids or another immunosuppressive agent
    - live vaccines
    - drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A

4.1.4 Patient Registration and Randomization

Each site must submit the following study documentation prior to beginning patient enrollment on the study:

- IRB approval letter
- IRB approved informed consent(s) and HIPAA
- IRB assurance number
- Study specific FDA Form 1572 for PI
- Current CV (within 1 year of date, signed and dated) for PI and Co-Investigators listed on FDA Form 1572
- Medical Licenses for PI and Co-Investigators listed on 1572
- Lab License, certificates, and Normal Lab Values (NLV) for labs listed on FDA Form 1572
- Signed original Financial Disclosure Form for PI and Co-Investigators listed on FDA Form 1572
- Signed original Signed Investigator Signature Page

All **original** documents will be kept on file in the WCI Clinical Trials Office.
All copies of the above should be filed in a study-specific regulatory binder at the site.

Registration and Randomization Procedure:

All regulatory documents (as stated in Section 4.0) must be received and approved by Emory before patient registration will be permitted for each site. When a suitable candidate has been identified for enrollment, the following steps should be taken:

- Obtain signed informed consent and authorization for the release of personal health information from patient or guardian.

- Complete the eligibility criteria and verify that all eligibility requirements as stated above have been met.

- Submit the following to Emory via fax at 404-778-4389:
  - Signed informed consent
  - Authorization for the release of personal health information from parent or guardian.
  - Completed Eligibility Criteria Form.

- Following receipt of completed Eligibility Criteria form, Emory will assign study-specific patient ID and randomize patient to trastuzumab or everolimus. Site will receive email notification of patient ID and assigned study arm via email within 48 hours (2 business days) of submission of Eligibility Criteria form.

4.2

4.2 Study Treatment

Trastuzumab and everolimus will be provided free of charge by Genentech and Novartis. The Sponsor Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (C.F.R.), Part 312.57 and 312.62 and Genentech requirements.

4.3.1 Trastuzumab Formulation

Trastuzumab is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each vial of Trastuzumab contains 400 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.

4.3.2 Trastuzumab Dosage, Preparation, Administration, and Storage

a. Dosage

The recommended initial loading dose is 8 mg/kg (for q3wk dosing schedules) Trastuzumab administered as a 90-minute infusion. The recommended maintenance Trastuzumab dose is 6 mg/kg q3wk and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. Trastuzumab 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 Trastuzumab 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 Trastuzumab. Immediately upon reconstitution with BWFI, the vial of

Trastuzumab 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, Trastuzumab must be reconstituted with Sterile Water for Injection (see PRECAUTIONS). Trastuzumab 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 Trastuzumab needed, based on a loading dose of 8 mg Trastuzumab /kg body weight for q3wk dosing schedules and the recommended maintenance dose of 6 mg Trastuzumab/kg body weight for q3wk dosing schedules. Calculate the correct dose using 21 mg/mL Trastuzumab 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 Trastuzumab and polyvinylchloride or polyethylene bags have been observed.

c. Administration

Treatment may be administered in an outpatient setting by administration of a 4 mg/kg Trastuzumab loading dose for weekly dosing schedules (OR 8 mg/kg Trastuzumab loading dose for q3wk dosing schedules) by intravenous (IV) infusion over 90 minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** If Trastuzumab is being administered concomitantly with chemotherapy, Trastuzumab administration should precede chemotherapy administration. 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 2 mg/kg Trastuzumab weekly (OR 6 mg/kg

Trastuzumab q3wk) may be administered over 30 minutes. If chemotherapy is discontinued during the treatment phase, either because of completing a planned number of cycles of chemotherapy, or because of chemotherapy related toxicity, Trastuzumab should be continued until \ disease progression or unacceptable toxicity related specifically to Trastuzumab.

Table 4-1

Trastuzumab Infusion Time and Post-Infusion Observation Period

Trastuzumab 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.

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

d. Storage

Vials of Trastuzumab 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 Trastuzumab 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 Trastuzumab solution should be used immediately and any unused portion must be discarded. DO NOT FREEZE TRASTUZUMAB THAT HAS BEEN RECONSTITUTED.

The solution of Trastuzumab 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 Trastuzumab has been shown to be stable for up to 24 hours at room temperature 15°C–25°C; however, since diluted Trastuzumab contains no effective preservative the reconstituted and diluted solution should be stored refrigerated (2°C–8°C).

4.3.3 Trastuzumab Dosage Modification

Dose modification of Trastuzumab is not permitted.

4.3.4 Trastuzumab Overdosage

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

4.3.5 Everolimus

Everolimus will be supplied by Novartis as tablets in 5mg strength. The drug will be packaged in blisters containing 10 tablets per blister. Blisters and packaging labels will be compliant with local regulations and be printed in local language. They will supply no information about the patient.

Upon receipt, everolimus should be stored according to the instructions specified on the drug labels. Everolimus should be opened only at the time of administration as the drug is both hygroscopic and light-sensitive.

These instructions should also be made clear to the patient for storage and self-administration of everolimus at home.

4.4 Concomitant and Excluded Therapy

All medications and non-drug therapies taken within 30 days prior to starting study treatment should be reported to the Principal Investigator.

The investigator should instruct the patient to notify the study site about any new medications (including over-the-counter drugs and herbal/alternative medications) he/she takes after the start of study treatment. Patients must be instructed not to take any additional medications (including over-the-counter products and herbal/alternative medications) during the trial without prior consultation with the investigator. All medications (other than study treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts study treatment must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Concurrent administration of EVEROLIMUS and strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir) and inducers (such as rifampin,,rifabutin) should be avoided. Provided there is no alternative treatment available, patients should be closely monitored for potential toxicities.
- Concurrent administration of EVEROLIMUS and moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin) should

also be avoided if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of EVEROLIMUS).

- Competitive inhibition could occur when EVEROLIMUS is combined with drugs which are also CYP3A4 substrates. Therefore caution should be exercised in such cases.
- Co-administration with substrates, inducers, or inhibitors of P-glycoprotein should be avoided, if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of EVEROLIMUS).
- Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided.
- In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- EVEROLIMUS may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with EVEROLIMUS.
- Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with EVEROLIMUS is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The coadministration of EVEROLIMUS and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state

4.4.1 Antineoplastic therapy

The administration of anticancer agents other than study medication, including chemotherapy, investigational agents, and biologic agents is NOT permitted while patients are enrolled in this study. The need for other anti-cancer therapy will be attributed to disease progression and will require the patient to be withdrawn from study treatment.

Palliative radiotherapy for local peripheral metastases not being used as target lesions is permitted, but the need for such therapy may be an indication of disease progression and should be discussed prior to administration. Radiotherapy for central metastases (e.g., vertebral, mediastinal) is not permitted. Patients requiring such therapy prior to completion of the study should be considered to have progression of disease and study treatment should be discontinued.

No other investigational cancer medication/therapies should have been taken within the last 4 weeks prior to study entry and any cancer medication / therapies given to a patient within 4 weeks after the last dose of study treatment also must be recorded.

4.4.2 Bisphosphonates

Patients who enter the study on bisphosphonates may continue this therapy. The need to start bisphosphonate therapy on study will be considered as an indication of disease progression and the patient will be discontinued from protocol therapy.

4.4.3 Hematopoietic growth factors and antibiotics

Hematopoietic growth factors and antibiotics should not be administered prophylactically during cycle 1 for patients undergoing study treatment and should be used in future cycles only in patients with documented cytopenia in previous cycles in accordance with the guidelines established by the American Society of Clinical Oncology, available on the following website [http://www.asco.org/ac/1,1003,_12-002138,00.asp]. Exception is made for recombinant erythropoietin-like product (such as Procrit®) which may be received throughout the study.

4.4.4 Anti-emetics

Approximately 25% of patients experience nausea when treated with EVEROLIMUS alone and 16% experience vomiting. The majority of nausea and vomiting events is of Grade 1 or 2. EVEROLIMUS is best classified as having moderate emetogenic potential, therefore prophylactic treatment with appropriate anti-emetic agents as per local institutional guidelines is recommended.

4.4.5 Analgesics

Baseline analgesics for tumor-related pain should be maintained during the study.

However, an increase in analgesic use or a step up on the WHO analgesic ladder for control of tumor-related pain may indicate disease progression. If an increase in analgesic medication from baseline is required during the study, the patient should be evaluated for progression of disease.

4.4.6 Systemic corticosteroids

Prolonged (greater than 2 weeks in duration) treatment with systemic corticosteroid treatment is not allowed during the study. Prolonged treatment with topical steroids should be discussed with the Principal Investigator.

4.4.7 P-glycoprotein (P-gp) inhibitors

Patients receiving any concomitant medications known to inhibit P-gp function (e.g., verapamil, diltiazem, nicardipine, cyclosporine, quinine) will not be excluded from the study but these medications should be avoided.

4.4.8 Cytochrome p450 enzymes

EVEROLIMUS is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Therefore the following advice should be followed:

- Wherever possible, drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A should be avoided as systemic therapy in association with EVEROLIMUS as these can alter its metabolism (see Table 4-2).
- Patients should also refrain from herbal/alternative remedies and grapefruit juice

Table 4-2 Clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A

Substrates	
Antibiotics[1]: clarithromycin* erythromycin telithromycin* **Anti-arrhythmics:** quinidine **Benzodiazepines:** alprazolam diazepam midazolam triazolam **Immune Modulators:** cyclosporine tacrolimus (FK506) **HIV Protease Inhibitors:** indinavir* ritonavir* saquinavir* **Prokinetic:** cisapride **Antihistamines:** astemizole	**Calcium Channel Blockers:** amlodipine diltiazem felodipine nifedipine nisoldipine nitrendipine verapamil **HMG CoA Reductase Inhibitors[2]:** cerivastatin lovastatin simvastatin **Miscellaneous:** buspirone haloperidol methadone pimozide quinine sildenafil tamoxifen trazodone vincristine

Inducers		
Carbamazepine Phenobarbital Phenytoin	Rifabutin* Rifampin*	St John's wort Troglitazone

Inhibitors		
Amiodarone Cimetidine Clarithromycin Diltiazem Erythromycin	Fluvoxamine* Grapefruit juice Seville orange juice or product Indinavir Itraconazole* Ketoconazole* Voriconazole* Posaconazole*	Mibefradil Nefazodone* Nelfinavir* Troleandomycin Verapamil

Based on: Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104 and [http://www.medicine.iupui.edu/flockhart/clinlist.htm as of July 13, 2006]

* asterisk denotes strong inhibition/ induction

Please note:

Strong inhibitor implies that it can cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates

Moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates.

(Distinction is not always categorical as interaction can vary according to conditions).

1. Macrolide antibiotics: Azithromycin is not a CYP3A substrate. It may therefore be employed where antibiotherapy with a macrolide is desirable in a patient being treated with EVEROLIMUS

.2. Statins: Atorvastatin and pravastatin may be administered concomitantly with EVEROLIMUS, since a PK interaction study has shown that there is no relevant PK interaction

4.5 Study Assessments

- Evaluation of subject's cardiac function by either MUGA or echocardiogram

4.5.1 Assessments during Treatment

- Monitor CBC, chemistries, etc. per institutional guidelines.
- Repeat measurements of LVEF using the same methodology as used at baseline will be obtained at 3 months (Week 12) following initiation of Trastuzumab and thereafter as clinically indicated. If Trastuzumab is discontinued for a decline in LVEF, a repeat measure of LVEF will be obtained in 1 month to assess whether the decline has resolved.

4.5.2 Follow-Up Assessments

Patients will have repeat staging performed at 6-weeks and then every 12 weeks with CT scans ± bone scans or PET scans. Repeat staging may be performed earlier if there is clinical evidence to suggest disease progression.

4.6 Discontinuation of Protocol-Specified Therapy

Protocol-specified therapy may be discontinued for any of the following reasons:

- Progressive disease

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

4.7 Subject Discontinuation

Patients may discontinue taking one (or more) of the study treatments for the reason of an adverse event and yet continue to receive the other treatments if this is felt to be in the best interests of the patient.

Each study treatment discontinuation will be captured separately in the corresponding Drug Administration CRF. All discontinuations from the study must be recorded in the Study Completion CRF.

Patients may voluntarily withdraw from the study or be discontinued from it at the discretion of the investigator at any time. The reason for premature discontinuation of a subject must be recorded on the CRF.

4.8 Study Discontinuation

The Principal Investigator or the study sponsors 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

4.9 Statistical Methods

4.9.1 Efficacy Analysis

4.9.1.1 Primary Endpoint

The primary objective of this study is to to evaluate response rate. One stage design will be adopted for these trials conduct. We will test the null hypothesis that the response rate is 1.0% versus the alternative hypothesis that the response rate is 10.0%. A sample size of 34 patients achieves 86% power to detect a difference of 0.09 using a one-sided binomial test. The target significance level is 0.1. The actual significance level achieved by this test is 0.045. For the secondary objective of the study where patients are given trastuzumab after disease progression, we expect that about 50% of the patients will progress. Therefore, a sample size of 17 patients treated with the two agents achieves 52% power to detect a

difference of 0.0900 using a one-sided binomial test the same target significance level as the primary objective.

This trial will be monitored by the WCI DSMBThe probability of observing 9 or 10 patients with disease progression at 8 weeks is 0.24 if the probability of disease progression at 6 weeks is 0.0.75. Patients will be evaluable for response after 6, and then every 12 weeks.

4.9.1.2 Secondary Endpoints

The secondary objectives of this study are to (i) Assess time to progression of everolimus in combination with hormonal therapy in patients with hormone-refractory metastatic breast cancer, (ii) Correlate response rate and clinical benefit in patients with hormone-refractory breast cancer treated with everolimus with the expression of HER2 and downstream effector proteins in pre-treatment biopsies, (iii) assess time to progression, response rate and clinical benefit rate of trastuzumab in combination with endocrine therapy in patients with hormone-refractory metastatic breast cancer with disease progression on prior everolimus, and (iv) Evaluate safety of combination of everolimus with and without trastuzumab with hormonal therapy and For (i), Kaplan-Meier curves will be used to estimate the survival curve of time to progression. We then estimate the median time to progression by constructing a 95% confidence interval.
For (ii), ordinary logistic regression will be carried out to correlate response with HER2 expression and key biomarkers obtained from pre-treatment biopsies after adjusting for relevant baseline covariates such as age, etc… The dependent variable is response which is binary, and the independent variables of interest are HER2 expression and key biomarkers expressions. We will also correlate time to progression with HER2 expression and key biomarker levels using the Cox proportional hazards model.
For (iii), The tolerability and safety of everolimus with and without trastuzumab will be monitored by the WCI DSMB.

4.9.1.3 Correlative studies

Patients are required to have a biopsy as standard of care before starting the study treatment, and be asked to have a biopsy when they discontinue treatment.
Primary diagnostic biopsies and surgical specimens, pre-treatment and post-treatment biopsies will be evaluated for the expression of targeted proteins (see section 1.7). We will compare the expression of these proteins in the primary
biopsy/surgical specimen with the pre-treatment biopsies, and in the pre-treatment biopsies compared to the post-treatment biopsies.
Biopsy specimens will be shipped to Emory University and Dr. Elisavet Paplomata at: 1365 Clifton Road, Atlanta, GA 30322. The tissue selected to be shipped should be invasive breast cancer. Tissue will be shipped as paraffin embedded tissue and fresh tissue (if available).

4.9.2 Safety Analysis

Patients will be followed continuously for adverse events which will be graded according to ECOG grading system through the Winship Cancer Institute DSMB. An analysis of safety will be performed after 10 patients have been enrolled. The incidence of clinically significant CHF will monitored continuously. Symptomatic CHF is defined as the occurrence of objective findings on clinical examination (e.g., rales, S3, elevated jugular venous pressure) and confirmed

by chest X-ray and either MUGA or ECHO. Difference in risk based on prior anthracycline exposure as well as risk factors such as ECHO performance status and smoking status will be explored.

4.9.3 Missing Data

Any missing data will be excluded from the statistical analysis.

4.10 Data Quality Assurance

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

4.11 Data and Safety Monitoring Plan

The data safety monitoring plan will be implemented by Dr. Elisavet Paplomata, the Principal Investigator (P.I.) of this study. The plan is based on self-monitoring, internal CTO real time monitoring using the quality assurance committee, and monitoring via Winship Cancer Institute ("WCI") Data Safety Monitoring Committee (DSMC) as per WCI CTO standard operating procedure. Dr. Paplomata and the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain one spread sheet which will summarize all the patient data for patients actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual patient. During the weekly meeting the group will review the eligibility criteria for each new patient. In addition, during these meeting the group will review all the toxicity (AE/SAE) logs, case report form completion and roadmap for each patient on the trial. Documentation of the discussions during these meetings are completed, filed and forwarded to the Winship Cancer Institute ("WCI") Data Safety Monitoring Committee (DSMC) at WCI. The WCI has two internal monitoring committees. The first is the quality assurance and quality monitoring committee which will perform a review of the first and then on a regular ongoing basis for selected patient enrolled on the trial to confirm that the trial is being conducted appropriately. The second monitoring process involves DSMC. The WCI DSMC is responsible for providing data safety-monitoring oversight for this protocol. Any comments that are generated by the WCI DSMC are forwarded to the IRB. The P.I. and the study investigators will discuss any required modifications to this study at the weekly meetings. No modifications to this study are implemented until they are submitted for review and approved by the Emory University IRB. The comments from the WCI DSMC are forwarded to the IRB at the time of the annual renewal of this study or sooner if warranted and requested by the WCI DSMC.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will oversee the conduct of this study. This committee will review all pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy. The committee will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. Reviews will occur annually for studies that are low risk or moderate risk. High risk studies will be reviewed every 6 months. The committee reserves the right to conduct additional audits if necessary at any time-point. The Principal Investigator is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study. The PI will also notify the DSMC of the study status within 2 months before

the next annual review is due. The charter for the Winship DSMC is available upon request to the investigator or other study-related personnel.

The WCI DMSC does not tolerate protocol deviations, but does recognize that they occur unintentionally. Any protocol violations are reviewed and reported to the WCI DSMC, IRB, and all other designated regulatory agencies as required by the study protocol.

All study data reviewed and discussed during these meetings with the PI and the investigators and the WCI DSMC is kept confidential. Any breach in confidentiality during the conduct of the study is reported to the PI, WCI DSMC, sponsor, and the IRB.

4.11.1 Monitoring of Subsite(s)

At the study initiation, the PI, regulatory specialist and research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The subsites will have internal monitoring meetings. These meetings will include the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain one spread sheet which will summarize all the patient data for patients actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual patient. The spread sheet will be shared with Emory PI. Teleconferences will be conducted at least once monthly between the PI at Emory and the research team at the subsites. The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the principal investigators at each site.

4.11.2 Data Safety and Monitoring Committee at Emory

The Monitoring Committee consists of faculty members, a research nurse, the Clinical Trials Director and/or Associate Director, the Medical Director of Clinical Trials, the Director of the Phase I Program and The Regulatory and Compliance Manager The Monitoring Committee reviews all auditing, Data and Safety Monitoring Board (DSMB) composition and reports, and recommends corrective action if needed to the PI. The Monitoring Committee may initiate an external audit of any trial at any time if it determines such action to be necessary. The Monitoring Committee will review all internally audited trials annually. Egregious data insufficiency is reported to the Associate Director of Clinical Research who notifies the CTRC as part of the CTRC PRMS function. If deficiencies are discovered during the annual review, the Monitoring Committee will first inform the PI. If the deficiencies cannot be corrected, the Monitoring Committee will involve the PI's direct supervisor and may refer the protocol to the Associate Director of Clinical Research for corrective action including possible termination of the trial. The Associate Director of Clinical Research has the authority to terminate trials for cause.

5. REPORTING OF ADVERSE EVENTS

5.1 Adverse Event and Reporting Definitions

An **adverse event** (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, without any judgment about causality. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

An adverse event is considered a **serious adverse event** (SAE) if it results in any of the following outcomes:

1) Results in death
2) Is a life-threatening (ie, its occurrence places the patient or subject at immediate risk of death)
3) Requires inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) Is a congenital anomaly/birth defect
6) Is an important medical event that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected Adverse Event

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected Adverse Events

An adverse event is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

5.1.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix D) will be utilized for AE reporting. If specific grading is not available in the CTCAE for a particular AE's severity/intensity, the investigator is to revert to the general definitions of Grade 1 through 5 and use his/her best medical judgment. The 5 general grades are: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening or disabling, Grade 5 = death related to AE.

Attribution of the AE:
Investigators are required to assess whether there is a reasonable possibility that trastuzumab caused or contributed to the adverse event. The following general guidance may be used.

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

5.2 Reporting of Serious Adverse Events Associated with Trastuzumab

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

Dr. Elisavet Paplomata

Tel: 404-778-1900

AND:

Novartis Pharmaceuticals CS&E

FAX (888-299-4565),

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (888-299-4565), to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of it's occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

AND Emory IRB

1599-001-1AV

Institutional Review Board

Emory University, 1599 Clifton Road,

Atlanta, GA 30322

Tel: 404-712-0720

Fax: 404-727-1358

Email: IRB@emory.edu

Webpage: http://emory.edu/IRB/

5.2.1 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 or Novartis 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 or Novartis 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 Trastuzumab or everolimus if the investigator believes:

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

6. INVESTIGATOR REQUIREMENTS

6.1 Study Initiation

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

- 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
- A signed Clinical Research Agreement

6.2 Study Completion

The following materials are requested by Genentech and Novartis 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.

6.3 Informed Consent

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

6.4 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.

Dr. Paplomata 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. Dr. Paplomata 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 and Novartis (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 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, Novartis, the U.S. FDA, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.6 Study Medication Accountability (If Applicable)

If study drug will be provided by Genentech, the recipient will acknowledge receipt of the drug by returning the INDRR-1 form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the NCI drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech and Novartis for everolimus.

6.7 Disclosure of Data

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

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, Novartis and the IRB for each study site, if appropriate.

6.8 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 and Novartis will notify the Principal Investigator of these events.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with U.S. FDA IND regulations and with the record retention policies of the relevant national and local health authorities.

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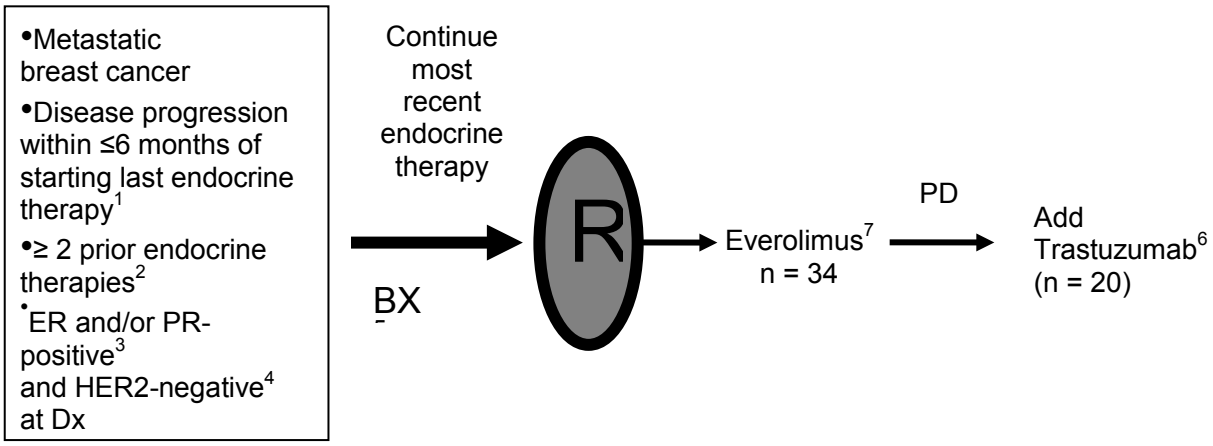
FIGURE 1

STUDY SCHEMA



(1) Any endocrine therapy allowed.
(2) Patients must have had at least one line of endocrine therapy for metastatic disease.
(3) On primary and subsequent biopsies,
(4) HER2 ≤ 2+ by IHC and/or FISH-negative
(5) Biopsies optional prior to study entry and at study discontinuation (but must have a biopsy in the metastatic setting demonstrating HER2 1+ or 2+ by IHC
(6) Trastuzumab IV 8 mg loading dose-> 6 mg 3 weekly
(7) Everolimus 10 mg daily PO

APPENDIX A
Study Flowchart

	Days –14 to 1	Day 1	Daily	Every 4 weeks while on everolimus	Every 3 weeks while on trastuzumab	Every 12 Weeks	Study Termination[10]
Trastuzumab (HERCEPTIN®) administration		X			X[1]		
Everolimus (EVEROLIMUS)		X	X				
Hormonal therapy		X	X[2]				
Complete medical history	X	X		X			
Complete physical exam	X	X		X			
Clinical assessment	X	X		X			
Weight, height	X	X		X			
ECOG performance status	X	X		X			
Toxicity evaluation	X	X		X			
Vital signs	X	X		X			
ECG (12-lead)	X[9]						
MUGA scan/echocardiogram	X[9]					X[3]	
Serum pregnancy test	X						
Tumor assessment	X[4,9]					X[4]	X
Hematology (CBC, diff., platelets)	X[5]			X			
Coagulation (PT/INR)	X[6]						
Chemistry panel (including lipid panel)	X[7]			X[7]			
Biopsy	X[8]						X[8]

(1) Trastuzumab 6mg/kg 3 weekly following loading dose 8mg/kg. Given at disease progression. Initially the patients will be seen in clinic every 4 weeks while on everolimus alone. After the addition of Trastuzumab the schedule will switch to 3 weeks to coincide with trastuzumab infusions.
(2) Any prior hormonal therapy is allowed (for example: tamoxifen, toremifene, anastrozole, letrozole, fulvestrant, estrogen, megestrol acetate, androgens).
(3) Assessment of ejection fraction (by MUGA, first pass or ECHO) must be done at baseline, 3 months ± 1 week (Week 12) following initiation of trastuzumab and then every 12 weeks if clinically indicated. Any patient with symptoms suggestive of cardiac failure should be worked up immediately.
(4) Staging will be performed using CT scans: chest, abdomen and pelvis. First staging assessment will be done at baseline, after 6 weeks ± 2 days, then every 12 weeks ± 1 week until progression.
(5) Hematology should include hemoglobin, hematocrit, red blood cells (RBC), platelets, total and differential white blood cells.
(6) The coagulation profile should include a prothrombin time (PT/INR).
(7) Chemistry Panel should include: potassium, magnesium (optional), calcium, chloride, bicarbonate, creatinine, blood urea nitrogen, fasting glucose, albumin, total protein, AST, ALT, total bilirubin, alkaline phosphatase, fasting lipid profile (triglycerides, total cholesterol, HDL, and LDL). These assessments should be performed at screening and Day 1 of each cycle. Fasting lipid profile should only be repeated every 2 cycles for patients on everolimus only and every 3 cycles for patients on everolimus plus trastuzumab
(8) Patients will be asked to have an optional biopsy at baseline and when they come off study. In order to be eligible all patients must have a biopsy in the metastatic setting demonstrating 1+ or 2+ expression of HER2
(9) EKG (12-lead), MUGA scan/Echocardiogram, and Tumor assessment: within 4 weeks of baseline
(10) <u>No long-term follow-up is required but patients will be followed off study.</u>

APPENDIX B
Response Evaluation Criteria in Solid Tumors (RECIST Criteria)

The RECIST criteria should be used to assess response to treatment. Only subjects with measurable disease should be entered in the study. Measurable disease is defined as the presence of one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥2.0 cm with conventional techniques (or as ≥1.0 cm by spiral CT). Evaluable lesions should be followed for the assessment of response. Non-measurable lesions include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitic carcinomatosis, abdominal masses that are not confirmed by CT, and cystic lesions.

All measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.

- Complete response (CR)

  Disappearance of all evidence of tumor for at least two cycles of therapy. Tumor markers must be normal.

- Partial response

  At least a 30% decrease in the sum of the longest diameter of target lesions, taking a reference the baseline sum longest diameter.

- Stable disease (SD)

  Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

- Progressive disease (PD)

  At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the beginning of treatment or the appearance of one or more new lesions.

- Clinical progressive disease

Subjects, who in the opinion of the treating physician investigator have had a substantial decline in their performance status and have clinical evidence of progressive disease may be classified as having progressive disease.

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

APPENDIX D
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 uptitrated 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 ßblockade 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 uptitration 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. Clinicalreevaluation 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-failureassociated 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 cointervention (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 cointervention; 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 of digoxin (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.

HFSA Guidelines
Appendix D
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 D
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 E
FDA MedWatch 3500 Form