# Factors Affecting Treatment Choice in HER2 Positive Metastatic Breast Cancer

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BY

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## ABSTRACT

Women with HER2 positive breast cancer have decreased overall survival and may have a poorer response to treatment. Evidence suggests that disparities exist in treatment and outcomes in individuals with diverse racial and ethnic backgrounds, the elderly, individuals that are obese, hormone receptor positive, those with comorbid conditions, those treated in various regions of the country, and in different treatment settings.

Trastuzumab (Herceptin®) is an anti-HER2 monoclonal antibody and was the first targeted therapy developed for the treatment of HER2 positive metastatic breast cancer. With its approval by the U.S. Federal Drug Administration in 1998, trastuzumab became the standard of care for treatment of HER2 positive MBC. This study examined differences in treatment, specifically trastuzumab use, and outcomes in these various groups treated for HER2 positive metastatic breast cancer. A conceptual framework guided by the fourth version of Andersen's health service utilization model was developed to better understand treatment patterns in these various groups. A prospective observational database called RegistHER was the source of the data.

The first outcome evaluated was whether the frequency of use of optimal therapy (antibody) varied by group. Using logistic regression, this study showed no difference in use of optimal treatment in participants based on region of the country, race, obesity status or comorbid conditions. Differences in these groups might be seen given larger sample sizes. There were differences seen in individuals treated in different settings, the elderly, and those in that are ER/PR positive. Although women who are hormone receptor positive are eligible for treatment with hormones, consideration should be given to concurrent or sequential treatment with antibody therapy in those women that are HER2 positive.

The second outcome evaluated was the time to start of treatment (in days). Logistic regression showed no variables were significant for this outcome indicating that race, age, obesity status, treatment setting, region of the country, hormone receptor status, the presence of cardiac disease and comorbid conditions did not affect time to start of treatment in this sample of patients from the RegistHER database.

The third outcome evaluated was time to progression of disease. Using Cox regression, those who were ER/PR positive had a reduced risk of having progressive disease than their ER/PR negative counterparts. Not surprisingly,

those with ER/PR positive disease did better than those that were ER/PR negative since those that have HR negative disease typically have a poorer prognosis than their HR positive counterparts. An unplanned sub-analysis showed that when you look at just those that are HR positive and compare those who got antibody to those that did not get antibody, both groups progressed at about the same rate.

RegistHER, a registry with the largest cohort of HER2 positive MBC patients followed to date, is important because it provides a unique opportunity to characterize treatment patterns in this subset of individuals with breast cancer. In this evaluation of the database, important information regarding use of optimal treatment and time to progressive disease for women with HER2- positive breast cancer was described. Given the findings, this additional data may guide clinical decision-making for healthcare providers and their HER2 positive breast cancer patients and ultimately improve outcomes.

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# CHAPTER I. BACKGROUND

## A) Statement of the problem

Cancer is the second leading cause of morbidity and mortality in the developed world, as well as in some developing countries. In 2008 there were about 1.4 million people diagnosed with cancer and more than 10.8 million people with a history of cancer alive in the U.S. (American Cancer Society, ACS Facts & Figures, 2008).

Breast cancer is the most frequently diagnosed tumor in women, and human epidermal growth factor receptor type 2 (HER2) overexpression occurs in 20-30% of invasive breast carcinomas. Trastuzumab (Herceptin®) is an anti-HER2 monoclonal antibody and was the first targeted therapy developed for the treatment of HER2 positive metastatic breast cancer (MBC). With its approval by the U.S. Federal Drug Administration in 1998, trastuzumab became the standard of care for treatment of HER2 positive MBC. Because of the benefits of trastuzumab in terms of overall tumor response rate, duration of response, time to disease progression and duration of survival, any treatment of HER2 positive MBC that does not include this therapy is sub-optimal. A review of the literature indicates that there may be certain sub-groups in the population that are not receiving optimal cancer treatment.

**B) Rationale for the study**

Interestingly, cancer outcomes are not equal across all groups of adults (Ashing-Giwa & Singer, 2006; Freyer et al., 2006). This study will explore differences in treatment and outcomes in various groups treated for HER2 positive MBC. There is evidence to suggest that disparities exist in the treatment and outcomes of different groups with diverse racial and ethnic backgrounds (including African Americans and Hispanics), as well as in the elderly. Although the most common cancer sites are the same for women (breast, colon and lung) and men (prostate, colon and lung) of different racial and ethnic groups, mortality rates are higher in various ethnic groups (ACS Facts & Figures, 2008).

For example, African Americans have the highest death rate and shortest survival of any racial and ethnic group in the U.S. for most cancers (ACS Cancer Facts & Figures for African Americans, 2008). The cause of this is complex but likely is from a combination of factors including socioeconomic disparities in work, wealth, income, education, housing and overall standard of living, economic and social barriers to high quality prevention, early detection and treatment services and the impact of racial discrimination on all of these factors. In addition, there is evidence suggesting that treatment of elderly people with cancer is not as aggressive as treatment of their younger counterparts (Freyer et al., 2006). There

are also a few studies that indicate a difference in treatment choice based on the region of the country in which the person with breast cancer lives (Sturgeon et al., 2004; Nattinger et al., 1992), as well as one study indicating that obese women with breast cancer have a higher mortality rate than non-obese women (Wee et al., 2000). All of these factors (race, age, region of the country, and obesity) were evaluated in this study. Other factors that were evaluated include the hormone receptor status of the women being treated for metastatic breast cancer and whether or not such women had comorbid conditions including a history of cardiac disease. Evaluating trends and outcomes in sub-optimal treatment is important as interventions can be designed to target populations. In this study some of these groups will be targeted.

**C) Study overview**

This study evaluated treatment patterns and outcomes in women with HER2 positive MBC. This was done by assessing the use of optimal therapy with trastuzumab, as well as the time between diagnosis and start of treatment. Additionally, response to treatment was evaluated. Groups that were evaluated included those with different racial and ethnic backgrounds, the elderly, individuals who are obese, those with positive hormone receptors, as well as those with comorbid conditions including cardiac disease. Treatment patterns and response to treatment by region of the country, as well as whether the individual

was treated in an academic or community setting, will also be evaluated. RegistHER, a prospective observational study of patients with newly diagnosed HER2 positive MBC was used for this analysis.

**Primary aim**

To evaluate the differences in treatment patterns and outcomes in women with HER2 positive MBC in the following groups:

- Women treated in an academic setting compared to a community setting;
- Women treated in different regions of the country (Midwest, Northeast, Southeast, Southwest, and West);
- Elderly women (three groups were defined as ≥ 65 years old, ≥ 75 years old, and age as a continuous variable) compared to non-elderly women (< 65 years old and < 75 years old);
- Women with different racial and ethnic backgrounds (African American and Hispanic compared to white);
- Obese women (three groups were defined as BMI > 30, BMI > 40 and BMI as a continuous variable) compared to non-obese women;
- Women positive for estrogen and progesterone receptors (ER/PR) compared to women who are ER/PR negative;

- Women with comorbid conditions compared to women with no such history;
- Women with a history of cardiac disease compared to women with no such history.

**Hypotheses**

- Factors indicative of limited access to healthcare will be associated with sub-optimal treatment patterns in the following groups of women with HER2 positive MBC: elderly, women with different racial and ethnic backgrounds (African American and Hispanic compared to white), obese women, women that are ER/PR positive, and women with comorbid conditions including a history of cardiac disease. Region of the country (Midwest, Northeast, Southeast, Southwest and West) and setting (academic or community) will impact treatment patterns.
- The time between diagnosis of HER2 positive MBC and start of therapy will be longer for the following groups of women with HER2 positive MBC: elderly, women with different racial and ethnic backgrounds (African American and Hispanic compared to white), obese women, women that are ER/PR positive, and women with comorbid conditions including a history of cardiac disease.

Region of the country (Midwest, Northeast, Southeast, Southwest and West) and setting (academic or community) will impact treatment patterns.

- Time to progressive disease for HER2 positive MBC will be less favorable (shorter in duration measured in days) in the following groups: elderly, women with different racial and ethnic backgrounds (African American and Hispanic compared to white), obese women, women that are ER/PR positive, and women with comorbid conditions including a history of cardiac disease. Region of the country (Midwest, Northeast, Southeast, Southwest and West) and setting (academic or community) will impact treatment patterns.

# CHAPTER II. LITERATURE REVIEW

## A) Incidence of HER2 positive metastatic breast cancer

Breast cancer is a major public health problem in the United States and is the most frequently diagnosed tumor in women. Worldwide, breast cancer is the second most common cancer and the most common cause of cancer death in women (Parkin et al., 2002). In 2008 in the United States, more than 180,000 new cases of breast cancer were diagnosed, and over 40,000 women died of this disease (ACS Facts & Figures, 2008). Women diagnosed with early stage disease do significantly better than those diagnosed with advanced disease. The 5-year survival rate is only 25% for women who present with metastatic disease, compared with 98% and 80% for those who present with localized and regional disease, respectively (Surveillance Epidemiology and End Results Program (SEER), 2007). Women with breast cancer cells that overexpress the HER2 receptor or that have a high copy number of its gene (about 20-30% of invasive breast cancers) have decreased overall survival and typically have a poorer response to treatment (Hudis, 2007). Overexpression of HER2 is detected by either immunohistochemical analysis (IHC) or fluorescent in situ hybridization (FISH) testing.

HER2 overexpression may indicate more aggressive disease as well as disease that is more difficult to treat, including resistance to nonanthracycline chemotherapies (Ross & Fletcher, 1998) and hormonal therapies such as tamoxifen (Konecny et al., 2003). Additionally, women with HER2 positive breast tumors have shorter disease-free intervals after adjuvant therapy, and shortened overall survival compared to women with HER2-normal breast tumors (Slamon et al., 1987; Ross & Fletcher, 1998).

**B) Standard treatment of HER2 positive metastatic breast cancer**

Trastuzumab (Herceptin®), an anti-HER2 monoclonal antibody, was the first targeted therapy developed for the treatment of HER2 positive MBC and has become a crucial part of treatment. Trastuzumab, which was approved for the treatment of HER2 positive MBC by the FDA in 1998, provides substantial clinical benefits. These benefits include improvement in overall tumor response rate, duration of response, time to disease progression and duration of survival when used alone or when used in combination with chemotherapeutic agents (Osoba, Slamon, Burchmore & Murphy, 2002). Trastuzumab is generally well tolerated and has a well established safety profile. The most serious adverse events that have occurred include infusion-related reactions, pulmonary toxicity

and cardiomyopathy. These adverse events are seen most often when trastuzumab is given concurrently with anthracycline chemotherapy (Bell, 2001).

The pivotal randomized clinical trial that showed the activity of trastuzumab in combination with chemotherapy enrolled 469 patients with previously untreated, HER2 positive MBC (Slamon et al., 2001). Patients in this trial received first-line chemotherapy either alone or in combination with trastuzumab. Patients who had not previously received an adjuvant anthracycline received chemotherapy consisting of doxorubicin or epirubicin combined with cyclophosphamide. In this trial, paclitaxel was administered in those who had received an anthracycline previously. The primary end point of the study was time to disease progression, which increased from 4.6 months among patients who received chemotherapy alone to 7.4 months among those who received trastuzumab in addition to chemotherapy ($p<0.001$). Trastuzumab was also associated with an increase in the objective response rate (50% vs. 32%, $p< 0.001$) and a longer duration of response (median, 9.1 vs. 6.1 months, $p< 0.001$). A subsequent randomized trial of docetaxel alone or with trastuzumab had similar results (Marty et al., 2005). Trastuzumab in combination with chemotherapy remains the standard of care for women with HER2 positive MBC. Treatment of HER2 positive MBC that does

not include trastuzumab in women where there is not a contraindication is sub-optimal.

In addition to treating with the right regimen, timely treatment of breast cancer is crucial. Cutting delays in treating breast cancer saves lives, according to a review of more than 100,000 cases worldwide. Women waiting three months or more for treatment are less likely to survive beyond five years than those benefiting from shorter delays, according to the study (Jones, 1999). Additionally, delays in treatment may be more common in certain racial and ethnic groups. A population-based study by Gorin et al. (2006) which defined treatment delays as 1 month or more found African American women experienced the most delays in initial diagnosis and initiation of breast cancer treatment, relative to women of other racial/ethnic subgroups. Despite the limitations of a claims database used for this study, the magnitude and direction of the findings are consistent across the research, suggesting the critical importance of reducing these delays. Timely initiation of treatment has been shown to improve survival, and may help to lessen the mortality differences among racial/ethnic groups.

### C) Health disparities in cancer

Access to medical care varies greatly within subgroups of the population in the United States. The U.S. Department of Health and Human Services (2000) defined health disparities as differences in the occurrence, frequency, death, and burden of disease and other unfavorable health conditions that exist among specific population groups. Health disparities, as opposed to differences, refer to gaps in the quality of health and healthcare across racial, ethnic, and socioeconomic groups. As Table 1 suggests, disparities impact women with different racial and ethnic backgrounds, the uninsured, those with lower incomes, younger women, elderly women, and women in rural and inner-city communities (Millman, 1993). Healthcare disparities are a concern in the detection, diagnosis and treatment of breast cancer (Susan G. Komen for the Cure, 2007).

Despite significant advances in therapy, many women with breast cancer are still not getting the treatment they need. For individuals without insurance, the cost of treatment can be devastating. Women with lower incomes and those of minority racial and ethnic backgrounds are less likely to be offered the latest tests or treatments (Intercultural Cancer Council, 2006). Consequently, they are more likely to suffer side effects from conventional, less specific treatments and are more likely to die of breast cancer (Intercultural Cancer Council, 2006). Additionally, greater psychological distress including depression, hopelessness,

hostility, conflict and stress have been shown as well as reduced social support in individuals of minority racial and ethnic backgrounds as well as those with low socioeconomic status (Fontaine & Bartlett, 2000).

Table 1. Identified Groups Affected by Disparities in Breast Cancer Detection, Diagnosis and Treatment

| **Factors Affecting Disparities in Breast Cancer** |
|---|
| • Minority racial and ethnic backgrounds |
| • Uninsured |
| • Lower income |
| • Younger age |
| • Older age |
| • Living in rural communities |
| • Living in inner-city communities |
| • Lower education level |
| • Lack of access to providers and services |
| • Language barriers |
| *Millman, 1993 |

**D) Treatment in an academic setting compared to the community setting**

There have been a few studies evaluating the difference in treatment of cancer in academic settings compared to community settings. As mentioned above, in a study evaluating treatment patterns for breast cancer, Nattinger (1992) found breast-conserving treatment (lumpectomy) was used more often in academic

settings than in community settings. In a study by Chaudhry et al. (2001), survival by status of teaching hospital was evaluated. The study found that women with node-negative breast cancer and tumors less than or equal to 20 mm in diameter who were initially seen in an academic setting had significantly better survival than women with similar tumors seen in a community hospital. Survival among women with larger tumors was not statistically significantly different for the two types of settings. A number of other studies in different disease states have evaluated treatment disparities finding that either outcome was the same for patients treated in these settings or outcomes were improved when treatment was given in the academic setting (Chaudhry et al., 2001).

**E) Regional differences**

Little current literature was found that evaluates regional differences in the treatment patterns and mortality rates of individuals with breast cancer. Historical studies from the 1970's evaluated incidence and geographic variation of breast cancer across the continental United States (Blot et al., 1977). One study by Sturgeon et al. (2004) evaluated the mortality relative risk in women with breast cancer across regions of the United States. This study found that in white women ages 50–64 years, the mortality relative risk for the Northeast compared to the South was 1.48 in 1950–1959 and 1.15 in 1990–1999. Rates increased in all regions from the 1950s to 1960s but more substantially in the South. Rates

increased slightly in the 1970s in all regions, declined slightly in the Northeast, Midwest and West but not in the South in the 1980s. In the 1990's rates declined more in the Northeast, Midwest and West than in the South. Among similarly aged black women, the relative risk for the Northeast compared to the South was 1.13 and 1.0 in 1970–1979 and 1990-1999, respectively. Among these women, rates increased in all regions in the 1980s; in the 1990s rates declined in the Northeast, Midwest and West but continued to increase in the South. Therefore, regional differences are clearly demonstrated in this study by region and race.

In another study evaluating treatment patterns for breast cancer, Nattinger (1992) found substantial geographic variation in the use of breast-conserving surgery across the United States. This study used national data on Medicare claims for inpatient care provided in 1986 to study 36,982 women 65 to 79 years of age, who had local or regional breast cancer and underwent either mastectomy or breast-conserving treatment (local excision, quadrantectomy, or subtotal mastectomy). Of the 36,982 women, 12.1 percent had breast-conserving surgery and 87.9 percent had a mastectomy. The frequency of breast-conserving surgery ranged from 3.5 percent to 21.2 percent in various states. The highest rate of use was in the Middle Atlantic states (20.0 percent) and New England (17.2 percent), and the lowest was in the East South Central states (5.9 percent) and the West South Central states (7.3 percent). Breast-conserving treatment was used more often in

urban than in rural areas, in teaching hospitals than in nonteaching hospitals, in large hospitals than in small hospitals, and in hospitals with on-site radiation therapy or geriatric services than in others.

As in the study by Nattinger, it is predicted that there will be similar variability in the use of optimal treatment for MBC by region. Comparisons will be made in these groups in terms of access to optimal treatment, time between diagnosis of HER2 positive MBC and start of therapy, and response to therapy.

**F) Health disparities in the elderly**

Breast cancer in elderly women is already a significant public health problem. Elderly women have a six fold higher breast cancer incidence rate and eight fold higher mortality rate compared with non-elderly women (Alburg et al., 2001). The risk of developing breast cancer increases with age. In elderly women with MBC, undertreatment due to the risk of side-effects and the patient's inability to tolerate chemotherapy and/or biologic therapy has been reported (Freyer et al., 2006). However, the assumption of the patient's inability to tolerate treatment is often not based on objective assessment but is based on the patient's age alone

(Freyer et al., 2006). In other words, the elderly are sometimes treated with less aggressive therapy solely based on their age.

A few retrospective studies have documented significant undertreatment by disease stage of the elderly breast cancer population (65 years of age and older) (Mandelblat et al., 2000; Wanebo et al., 1997). However, there is little information available documenting the pattern of treatment of elderly women with HER2 positive disease. In a small subset of patients (n=55), Freyer et al. (2006) reported that trastuzumab was used more frequently in younger patients: 9% versus 2% ($p < 0.001$).

Another study evaluated the treatment patterns of women age 55 years or older with newly diagnosed breast cancer and examined the association between age and ethnicity/race on treatment selection. This cross-sectional survey of 401 women showed older patients were less likely to receive lymph node dissection after lumpectomy (OR=0.48) and chemotherapy (OR=0.22) (Naeim et al., 2006).

Another study by Hurria et al. (2003) looked at the very old (≥75 years). In this retrospective study of 216 patients with a diagnosis of stage I, II, or III breast cancer, increased age ($P<0.01$) and increased comorbidity score ($p=0.01$) were

identified as independent prognostic variables for not receiving combined local treatment. Increased age did not correlate with increased comorbidity (p=0.48) (Hurria et al., 2003) further supporting that the elderly should be offered the same treatment options as their younger counterparts.

## G) Health Disparities in individuals of different racial and ethnic backgrounds

Research has found that individuals of different racial and ethnic backgrounds are less likely to receive standard therapy. Reasons for this are complex and interrelated but include a lack of access to medical resources, lower socio-economic status, and cultural barriers (Avanian et al., 1993; Breen et al., 1999; Bickell et al., 2000; Li et al., 2003; Stevenson-Perez, 1998; Voti et al., 2006).

### i. African Americans

African Americans have the highest death rate and shortest survival of any racial and ethnic group in the U.S. for most cancers (ACS Cancer Facts & Figures for African Americans, 2008). Although racial disparities have decreased over the last decade, in 2003 the death rate for all cancers combined continued to be 35% higher in African American men and 18% higher in African American women than in white men and women (Smigal et al., 2006).

In 2008, over 150,000 African American women were newly diagnosed with breast cancer and over 60,000 women died of their disease (ACS Cancer Facts & Figures for African Americans, 2008). In breast cancer, the most common cancer diagnosis among African American women, about 20,000 new cases are expected to occur in 2008. African American women with breast cancer are less likely than white women to survive 5 years: 77% versus 90% respectively (Shavers & Brown, 2002). The difference can be attributed to both later stage at detection and poorer stage-specific survival. A study by Naeim et al. (2006) showed that African American women were less likely to receive hormone therapy (OR=0.36) or chemotherapy (OR=0.50). Additionally, aggressive tumor characteristics associated with poorer prognosis appear to be more common in African American women and may also contribute to their lower survival rates (Bradley, Given & Roberts, 2001).

**ii. Hispanic**

About 14% of the total U. S. population identifies themselves as Hispanic or Latino according to U. S. Census Bureau population estimates. About 40,000 new cancer cases in men and over 40,000 cases in women were diagnosed in Hispanics in 2006 (Kirby, Taliaferro & Zuvekas, 2006). The most common site of cancer in Hispanic women is breast cancer with 14,300 cases (34% of all

cancer diagnosis) and 1,740 deaths (16% of all cancer deaths). The incidence of breast cancer in Hispanic women is 40% lower than that of non-Hispanic white women. Possible explanations for this low incidence are differences in reproductive pattern (younger age at first birth and larger number of children) and lower use of hormone-replacement therapy (Diaz, 2002).

Given the socioeconomic disparities in the Hispanic population, it is possible that there is a difference in how this population is treated with regard to breast cancer. In the U.S., Hispanics have lower levels of education than non-Hispanic whites and are more likely to live in poverty. In 2000, 48% of Hispanics had less than a high school education compared with 15% of non-Hispanic whites. About 23% of Hispanics in the U.S. lived in poverty compared with 8% of non-Hispanic whites (Phillips, Mayer & Aday, 2000). Additionally, many Hispanics face financial, structural, and personal barriers to receiving health care. Financial barriers include inadequate health insurance and low personal income. Structural barriers include poor geographic access to providers and lack of transportation to and from providers. Personal barriers to care include cultural and linguistic factors. Among Hispanic women, 17% report they have no usual source of medical care, compared to 7% of non-Hispanic whites (Phillips, Mayer & Aday, 2000).

**H) Health disparities in individuals who are obese**

Systematic undertreatment of breast cancer in overweight and obese women may contribute to the poorer prognosis in these women. Some evidence exists suggesting that obese women with breast cancer do not do as well as non-obese women in terms of survival. For instance, compared to thinner women, obese women have higher mortality rates for breast cancer (Wee et al., 2000). It is unclear whether this is due to some genetic difference in the disease in obese women or whether it is related to some other factor such as access to care. Access to health care for obese women has recently shown up in the literature as potentially being problematic. Recent studies suggest that obese women receive preventive services such as papanicolaou (Pap) smears and clinical breast exams less often than normal weight women (Fontaine et al., 1998; Adams et al., 1993).

Griggs et al. (2006) investigated treatment patterns in overweight and obese women undergoing breast cancer adjuvant chemotherapy. In this retrospective cohort study of 9672 women treated with doxorubicin hydrochloride and cyclophosphamide, 62% had a BMI of at least 25, 31% were overweight, 17% were obese, and 14% were severely obese (BMI > 35). This study found overweight and obese women with breast cancer often received intentionally

reduced doses of adjuvant chemotherapy. Administration of initial and overall full weight-based doses of adjuvant chemotherapy in overweight and obese women is likely to improve outcomes in this group of patients (Griggs et al., 2006). No literature was found, however, exploring whether or not obese women have equal access to treatment for HER2 positive MBC.

**I) Health disparities by hormone receptor status**

At the present time, there is no reason why women with HER2 positive hormone receptor (HR) positive breast cancer should not receive antibody therapy. About half of HER2 positive breast cancers are also HR positive (Basi & Mackey, 2007). For these women with HR positive disease, hormonal agents such as tamoxifen and aromatase inhibitors (for postmenopausal women) are treatment options. Because there are interactions between HER-2 and estrogen receptors, it has been hypothesized that HER2 positive tumors may be less responsive to endocrine treatments (De Laurentiis et al., 2005). However, there is no data to suggest that use of the monoclonal antibody trastuzumab is not effective in women with HER-2 and HR positive disease. In fact, there are a number of studies that show that it is efficacious to include monoclonal antibody therapy in the treatment of women with HER2 and HR positive disease. A study by Brufsky et al. (2005) found that overall response rate and time to progression were

significantly higher in patients treated with chemotherapy plus trastuzumab than in those treated with chemotherapy alone, irrespective of HR status. Another study demonstrated that trastuzumab plus anastrozole as first-line therapy for postmenopausal women with HER2 and HR positive MBC is effective and well tolerated (Basi & Mackey, 2007). Large-scale clinical trials evaluating the use of trastuzumab with hormonal therapy are ongoing (Jones, 2003). There are no studies looking at whether or not women with HR positive breast cancer have equal access to treatment with monoclonal antibody therapy for their HER2 positive breast cancer. This analysis of RegistHER will further evaluate this effect.

**J) Health disparities in those with comorbid conditions**

Table 2 lists the reported comorbid conditions in RegistHER. Because of the risk of CV toxicity with trastuzumab, this comorbidity was evaluated separately from the other comorbid conditions included in Table 2. The presence of comorbid conditions can limit the treatment options available for patients with any disease. In patients with breast cancer, this can mean limited or no use of effective therapies such as chemotherapy or monoclonal antibody therapy. As mentioned earlier, the study by Hurria et al. (2003) showed an increased comorbidity score ($p=0.01$) was identified as an independent prognostic variable for not receiving

combined local treatment. Additionally, a study by Maskarinec et al. (2003) evaluated 1,052 breast cancer patients' survival times in relation to demographics, disease characteristics, comorbidity, and treatment patterns. In this study, comorbidity and treatment patterns were significant in predicting survival (Maskarinec et al., 2003). Consequently, despite advances in cancer therapy, many patients with early stage breast cancer eventually progress to metastatic disease and the presence of comorbid conditions has been identified as a prognostic indicator in early stage breast cancer (Michaud, 2008).

Table 2. Comorbid Conditions as Per Patient Report

| **Comorbid Conditions** |
| --- |
| • Cardiac disease<br>  - Arrhythmias<br>  - CHF<br>  - Hypertension with complications<br>  - Myocardial infarction<br>  - Peripheral vascular disease<br>  - Unstable angina<br>• Pulmonary disease<br>• Dementia<br>• Hemiplegia/Paraplegia<br>• Cerebrovascular disease/Stroke<br>• Diabetes<br>• Gall bladder disease<br>• Liver disease<br>• Coagulopathy<br>• Renal disease<br>• Other malignancy<br>*per RegistHER |

## CHAPTER III. CONCEPTUAL FRAMEWORK

Treatment of breast cancer is primarily a clinical decision for a specific patient in a specific clinical scenario. However, given the availability of targeted antibody therapy for those with HER2 positive disease and the well-documented effectiveness of this therapy, the question of access to optimal treatment arises. In order to better understand treatment patterns in various groups, a conceptual framework guided by the fourth version of Andersen's health service utilization model (Andersen, 1995) was used.

The Andersen model (Figure 1) was developed to better understand why families use health services, to measure equitable access to health care, and to assist in the development of policies to promote access. This model originally focused on the family unit, but in subsequent revisions the focus changed to the individual as the unit of analysis because of the difficulty developing measures at the family level.

In the revised model, health services are determined by societal factors, health services system factors, and individual factors. This revised model emphasizes the dynamic nature of a health services use model and includes health status outcomes. Feedback loops are used to show that not only do predisposing factors,

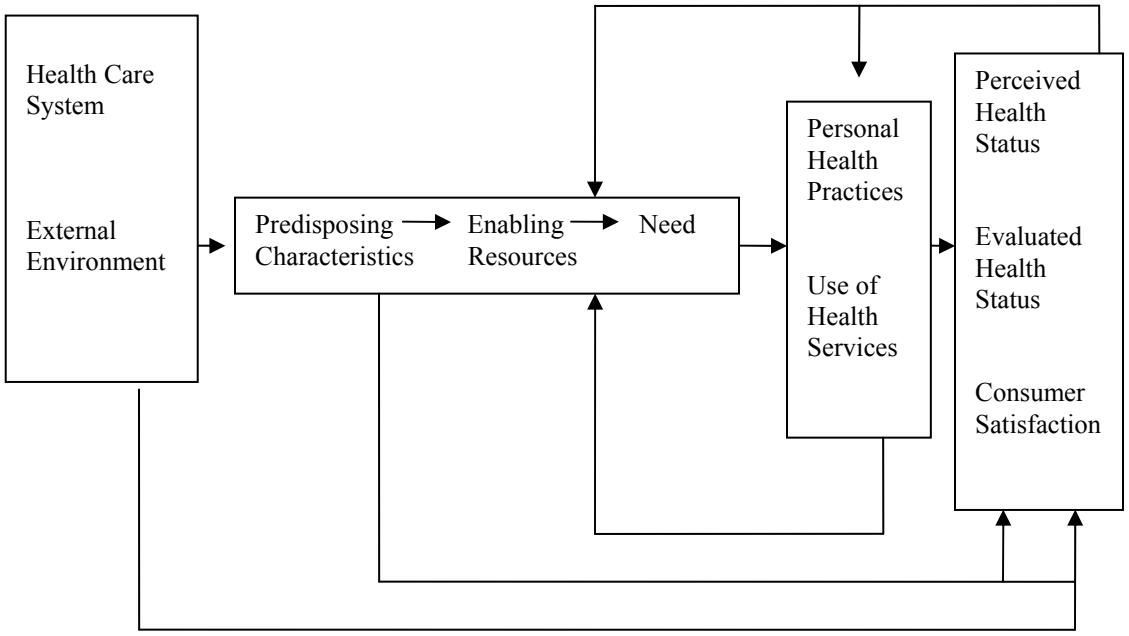
resources, and perceived need affect outcomes but that outcomes in turn affect subsequent predisposing factors and perceived need for services as well as health behavior.

The environment component of this model includes the health care system (encompassing policy issues, resources, organization and access to the system) and the external environment (including physical, political, and economic components). Individual factors are categorized as need, enabling factors, and predisposing factors. Need includes an individual's perceived and evaluated functional capacity, symptoms, and general state of health. Enabling factors encompass family and community resources and accessibility to those resources. Predisposing factors include age, sex, marital status, education, race and ethnicity, occupation, as well as a set of beliefs including attitude toward health services, knowledge about their disease, and their values.

Health behavior in this model includes the personal health practices of the individual and the use of health services (the type, site, purpose and time interval between visits). In versions three and four of this model, health outcomes were added which include the following components: the individual's perceived health status, the individual's evaluated health status, and consumer satisfaction (convenience, availability, financing, provider characteristics and quality of care).

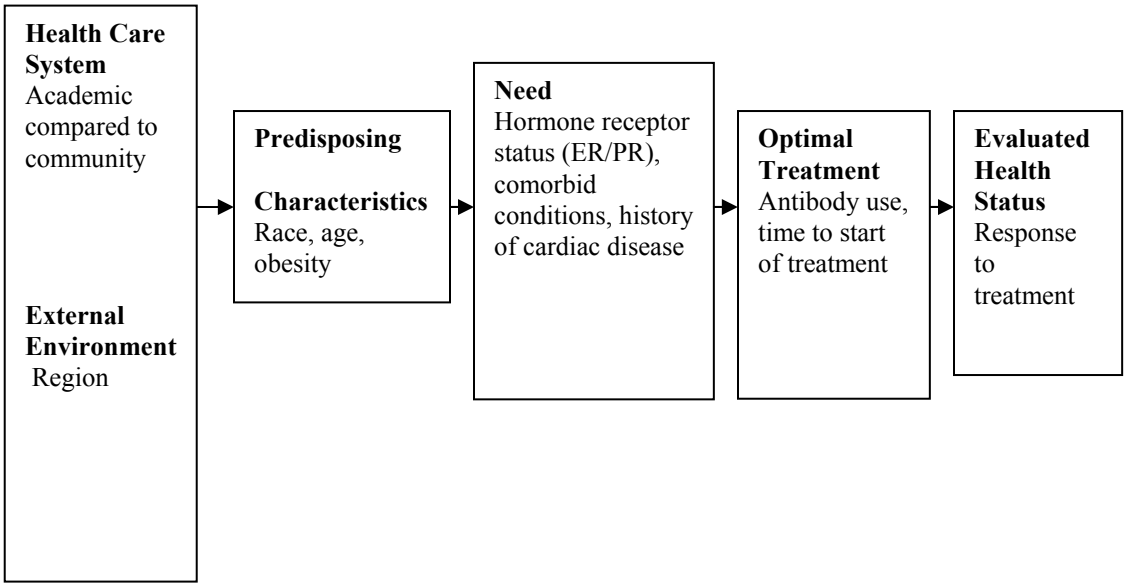
**Figure 1: Andersen Model – Phase 4***

Environment Population Characteristics Health Behavior Outcomes




*Andersen, R. (1995). Revisiting the behavioral model and access to medical care: does it matter? *Journal of Health and Social Behavior*, 36, 1-10.

**Figure 2: Conceptual Framework**



### A) Factors influencing treatment patterns and response

Aspects of this model can be enhanced to better guide future investigations regarding treatment of HER2 positive breast cancer (Figure 2).

#### i. Healthcare system variables

Academic compared to community setting: As noted in Chapter 2, there is evidence that setting impacts optimal treatment choice as well as survival in breast cancer (Nattinger et al., 1992; Chaudhry et al., 2001).

#### ii. External environment variables

Region of the country: Healthcare resources are different across geographic regions which may influence treatment patterns in breast cancer across the country (Sturgeon et al., 2004). Breast-conserving treatment was used more often in urban than in rural areas, in teaching hospitals than in non-teaching hospitals, in large hospitals than in small hospitals, and in hospitals with on-site radiation therapy or geriatric services than in others (Nattinger et al., 1992).

**iii. Predisposing variables**

Race: Research has found that individuals of different racial and ethnic backgrounds, those with lower incomes, and the uninsured are less likely to receive standard therapy (Avanian et al., 1993; Breen et al., 1999; Bickell et al., 2000; Li et al., 2003; Stevenson-Perez, 1998; Voti et al., 2006).

Age: Older age is associated with undertreatment in many diseases including MBC (Freyer et al., 2006). The assumption of the patient's inability to tolerate treatment is often not based on risk of side-effects or comorbidity. The elderly are sometimes treated with less aggressive therapy solely based on their age. Thus age might be an important predisposing factor that could influence treatment patterns and outcomes in women with MBC.

For this study, the cut points of ≥ 65 years and ≥ 75 years were used for each of the analyses. The cut point of ≥ 65 years of age was chosen because most of the reviewed retrospective studies have documented significant undertreatment by disease stage of the elderly breast cancer population (≥ 65 years of age) so the results of this study can be compared to the results of other studies. The very old breast cancer population (≥ 75 years of age) was chosen because this group is often excluded from retrospective analysis and clinical trials. Additionally, the amount of information available to guide treatment in this

population of women is limited, and as life expectancy continues to increase, this information may be used to guide treatment decisions for the very elderly person with breast cancer.

Obesity: Some evidence exists suggesting that obese women with breast cancer do not do as well as non-obese women in terms of survival. Compared to thinner women, obese women have higher mortality rates for breast cancer (Wee et al., 2000). As described in Chapter 2, pap smears and clinical breast exams are given less often in obese women than normal weight women (Fontaine et al., 1998; Adams et al., 1993). The Centers for Disease Control classifications on obesity were used to guide the cut points for this study. Per the Body Mass Index (BMI) Scale, a score of more than 30 indicates obesity and a score of more than 40 indicates morbid obesity. Consequently, the cut points of 30 and 40 on the BMI scale were used for the analysis on of this study.

**iv. Need variables**

Hormone receptor status: As discussed in Chapter 2, women with HER2 positive disease get similar clinical benefit from trastuzumab regardless of HR status (Basi & Mackey, 2007; Brufsky et al., 2005).

Comorbid conditions: Despite these advances in cancer therapy, many patients with early stage breast cancer eventually progress to metastatic disease. The presence of comorbid conditions has been identified as a prognostic indicator in early stage breast cancer (Michaud, 2008). A history of cardiovascular (CV) disease was also evaluated separately because of the increased risk of CV toxicity (Rastogi et al., 2007) with this therapy. There is a significant increase in the three-year cumulative incidence of New York Heart Association class III and IV congestive heart failure and cardiac death when trastuzumab was used with chemotherapy compared with chemotherapy alone (4.1% vs 0.8%).

**v. Outcome variables**

Use of antibody therapy: As discussed in Chapter 2, use of the monoclonal antibody trastuzumab in combination with chemotherapy remains the standard of care for women with MBC. Anyone who received trastuzumab therapy during their treatment will be included in this group for this outcome variable.

Treatment within 30 days: Timely treatment of breast cancer is crucial. As outlined in Chapter 2, women waiting three months or more for treatment have poorer survival (Jones, 1999). Additionally, a study by Gorin et al. (2006) suggested that a delay of more than one month from diagnosis to treatment is

detrimental. In this study, initiation of treatment within 30 days was used as the cut off for this outcome variable because waiting longer than 30 days is potentially detrimental to outcomes in this group of women.

Time to progression: The participant's time to progression in this study was given in days. A classification of shorter time to progressive disease was seen as a negative outcome for this study.

**B) Study Hypotheses**

All of the following sub-hypotheses will be tested individually in univariate analyses and then in multivariate analysis as follows:

**i. Sub-study I hypothesis**

**$H_{A\text{-}1}$:** The healthcare system variable of academic or community setting is associated with the likelihood of receiving biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A\text{-}1a}$**: Women treated in academic settings have a higher odds of being prescribed biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A-2}$**: After controlling for the healthcare system variable, the introduction of the external environment variable of region of the country (Midwest, Northeast, Southwest, Southeast, and West) further explains differences among women likely to receive biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A-2a}$**: Women that live in the Northeast have a higher odds of being prescribed biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A-3}$**: After controlling for the healthcare system and external environment variables, the introduction of predisposing variables of age, race and obesity further explain differences among women likely to receive biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A-3a}$**: Elderly ( $\geq$ 65 years old and $\geq$ 75 years old) women have a lower probability of receiving biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A-3b}$**: African American and Hispanic women have a lower probability of receiving biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A-3c}$**: Obese women (BMI > 30 and BMI > 40) have a lower probability of receiving biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A-4}$**: After controlling for the healthcare system variables, external environment variables, and predisposing variables, the needs variables of comorbid conditions, history of cardiac disease, and hormone receptor status further explain differences among women likely to receive biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A-4a}$**: Patients with comorbid conditions and a history of cardiac disease have a lower probability of receiving biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**$H_{A-4b}$**: Patients with positive hormone receptor status (ER/PR positive) have a lower probability of receiving biologic therapy (trastuzumab) following a diagnosis of HER2 positive MBC.

**ii. Sub-study II hypothesis**

**$H_{A-5}$:** The healthcare system variable of academic or community setting is associated with time to treatment following a diagnosis of HER2 positive MBC.

**$H_{A-5a}$**: Women treated in academic settings will have a shorter time to treatment than women treated in a community setting following a diagnosis of HER2 positive MBC.

**$H_{A-6}$**: After controlling for the healthcare system variable, the introduction of the external environment variable of region of the country (Midwest,

Northeast, Southeast, Southwest, and West) further explains differences in time to treatment following a diagnosis of HER2 positive MBC.

**$H_{A-6a}$**: Women that live in the Northeast will have a shorter time to treatment than women treated in a community setting following a diagnosis of HER2 positive MBC.

**$H_{A-7}$**: After controlling for the healthcare system and external environment variables, the introduction of predisposing variables of age, race and obesity further explain differences in time to treatment following a diagnosis of HER2 positive MBC.

**$H_{A-7a}$**: Elderly ( $\geq$ 65 years old and $\geq$ 75 years old) women will have a longer time to treatment following a diagnosis of HER2 positive MBC.

**$H_{A-7b}$**: African American and Hispanic women will have a longer time to treatment following a diagnosis of HER2 positive MBC.

**$H_{A-7c}$**: Obese women (BMI > 30 and BMI > 40) will have a longer time to treatment following a diagnosis of HER2 positive MBC.

**$H_{A-8}$**: After controlling for the healthcare system variables, external environment variables, and predisposing variables, the needs variables of comorbid conditions, history of cardiac disease, and hormone receptor status further explain differences in time to treatment following a diagnosis of HER2 positive MBC.

**$H_{A-8a}$**: Patients with comorbid conditions and a history of cardiac disease will have a longer time to treatment following a diagnosis of HER2 positive MBC.

**$H_{A-8b}$**: Patients with positive hormone receptor status (ER/PR positive) will have a longer time to treatment following a diagnosis of HER2 positive MBC.

### iii. Sub-study III hypothesis

**$H_{A-9}$:** The healthcare system variable of academic or community setting is associated with time to progressive disease following a diagnosis of HER2 positive MBC.

**$H_{A-9a}$**: Women treated in academic settings have a more favorable time to progressive disease following a diagnosis of HER2 positive MBC.

**$H_{A-10}$**: After controlling for the healthcare system variable, the introduction of the external environment variable of region of the country (Midwest, Northeast, Southwest, Southeast, and West) further explains differences in time to progressive disease following a diagnosis of HER2 positive MBC.

**$H_{A-10a}$**: Women with HER2 positive MBC that live in the Northeast have a favorable time to progressive disease.

**$H_{A-11}$**: After controlling for the healthcare system and external environment variables, the introduction of predisposing variables of age, race and obesity further explain differences in time to progressive disease following a diagnosis of HER2 positive MBC.

**$H_{A\text{-}11a}$**: Elderly ( ≥ 65 years old, ≥ 75 years old and age as a continuous variable) women with HER2 positive MBC will have a shorter time to progressive disease.

**$H_{A\text{-}11b}$**: African American and Hispanic women with HER2 positive MBC will have a shorter time to progressive disease.

**$H_{A\text{-}11c}$**: Obese women (BMI > 30 and BMI > 40) with HER2 positive MBC will have a shorter time to progressive disease.

**$H_{A\text{-}12}$**: After controlling for the healthcare system variables, external environment variables, and predisposing variables, the needs variables of comorbid conditions, a history of cardiac disease and hormone receptor status further explain differences in time to progressive disease following a diagnosis of HER2 positive MBC.

**$H_{A\text{-}12a}$**: Patients with comorbid conditions and a history of cardiac disease will have a shorter time to progressive disease.

**$H_{A\text{-}12b}$**: Patients with positive hormone receptor status (ER/PR positive) will have a shorter time to progressive disease.

# CHAPTER IV. METHODS

## A) Registries

A patient registry is an organized system that uses observational study methods to collect uniform data. These data are used to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and serve predetermined scientific, clinical, or policy purposes (Agency for Healthcare Research and Quality (AHRQ), 2007). Data are collected in such a way that the management of patients is determined by the caregiver and patient together and not by the registry protocol. The registry is designed to fulfill specific purposes, and these purposes are defined before collecting and analyzing the data. In other words, the data collection is purpose driven rather than the purpose being data driven (AHRQ, 2007).

The registry captures data elements with specific and consistent data definitions. The data are collected in a uniform manner for every patient in terms of the type of data collected as well as the frequency of collection. The data collected include data from the clinical status of the patient (e.g., history, examination, laboratory test) including the types of data that clinicians would use for the diagnosis and management of patients. At least one element of registry data collection is active, meaning that some data are collected specifically for the

purpose of the registry (usually collected from the patient or clinician) rather than inferred from sources (administrative, billing, pharmacy databases, etc.) that are collected for another purpose.

A patient registry can be a powerful tool for the following reasons: (1) to observe the course of disease, (2) to understand variation in treatment and outcomes, (3) to examine factors that influence prognosis and quality of life, (4) to describe care patterns, including appropriateness of care and disparities in the delivery of care, (5) to assess effectiveness, (6) to monitor safety, and (7) to change behavior through feedback of data (AHRQ, 2007).

Patient registries and randomized controlled trials (RCTs) have important and complementary roles in evaluating patient outcomes. Patient registries collect data in a comprehensive manner (with few excluded patients) and therefore produce outcome results that may be generalizable to a wide range of patients. They also evaluate care as it is actually provided, because care is not assigned, determined, or even recommended by a protocol. As a result, the outcomes reported may be more generalizable and representative of what is achieved in real-world practice. Patient registries also offer the ability to evaluate patient outcomes when clinical trials are not practical (e.g. rare diseases), and they may be the only option when clinical trials are not ethically acceptable. They are a

powerful tool when randomized controlled trials are difficult to conduct, such as in surgery or when very long-term outcomes are desired.

**B) Database description - RegistHER**

RegistHER is a prospective observational study of 1031 patients with newly diagnosed HER2 positive MBC treated in community and academic settings. This study was designed to record long-term clinical outcomes and address treatment related questions. Participants were enrolled on this study between January 2003 and February 2006 and were followed for a minimum of three years, or until death or study discontinuation. There were no strict inclusion or exclusion criteria, no randomization, and no predefined treatment or follow-up. HER2 positive status was determined by institutional standards. Electronic case report forms were submitted through a secure web-based system and initial data collection included the following items: demographics, height, weight, Eastern Cooperative Oncology Group (ECOG) performance status, albumin level, cardiac history, comorbidities, stage of disease, pregnancy status, tumor characteristics (date of initial and metastatic breast cancer diagnosis, sites of metastasis, estrogen and progesterone receptor status, HER2 positive status), therapy log, evaluation of responses, prior adjuvant therapy and radiotherapy, serious adverse events, study discontinuation, as well as patient status (alive or dead).

The RegistHER study represents the largest cohort of HER2 positive MBC patients followed to date and provides a unique opportunity to characterize treatment patterns in this subset of individuals with breast cancer. Information on who receives optimal treatment is currently lacking. This observational cohort, with its large sample, wide geographic distribution of patients, and substantial range of prescribed treatment regimens may provide data to guide clinical decision-making for healthcare providers and their HER2 positive breast cancer patients.

To minimize patient selection bias, investigators were encouraged to ask all eligible patients in their practice, as opposed to a selected subset of eligible patients, to participate in the study. Steps were taken to evaluate the degree of case ascertainment in this study, which included two separate surveys of study site investigators to understand how patients were being identified for enrollment and to assess any potential bias in how patients were selected for enrollment. First, a simple survey was faxed to all sites, which determined that: a) sites tended to use multiple sources to identify eligible patients in their practice, minimizing the chances of only enrolling selected subsets of eligible patients, and b) periodic

review of patient medical charts (about 60%) and/or pathology reports (about 45%) were the most common sources used by sites to identify eligible patients.

Subsequently, approximately 15% of the close to 300 site investigators (which included an even mix of low, intermediate, and high enrolling sites, as well as sites that had yet to enroll any patients) were asked to participate in an additional survey that involved describing in greater detail the process used to identify eligible patients at their sites. This survey was conducted via in-person visits or telephone interviews. Overall, 65% (27/41) of targeted sites agreed to participate and among those who agreed to participate, 96% (26/27) were determined to have appropriate standard methods in place to identify eligible patients for RegistHER. Processes described included regular review of patient medical charts prior to scheduled patient visits, referral of eligible patients directly from the physician to the research coordinator, attendance of study coordinators at weekly staff meetings where all patients seen at a practice were reviewed and eligible patients identified, and the periodic review of available clinical information (e.g., on-site cancer registry databases, diagnosis codes in billing records and pathology or chemotherapy logs).

## C) Subjects

The subjects in the registry have all been enrolled in the RegistHER database. In this study, elderly was defined as women 65 years of age and older and 75 years of age and older (in two separate groups) as calculated from their self-reported date of birth. Additionally, for sub-study III age was treated as a continuous variable. Racial background of the participant was also given by self-report using the following categories: white, black, Asian or Pacific Islander, Hispanic, American Indian or Alaskan Native, or other (the participant was to specify if they chose other). Obesity status was calculated using the patient's measured weight and height to calculate their body mass index (BMI higher than 30 was considered obese and BMI higher than 40 was considered morbidly obese; BMI was also treated as a continuous variable (Centers for Disease Control, 2008)). BMI, calculated from a person's weight and height, is a reliable indicator of body fat for people. The calculation is based on the following formulas:

$$\text{Formula: weight (lb) / [height (in)]}^2 \text{ x } 703$$

BMI was calculated by dividing weight in pounds (lbs) by height in inches (in) squared and multiplying by a conversion factor of 703.

Regional differences were defined by the following categories using the zip codes of their treating institution: Midwest, Northeast, Southeast, Southwest and West. Academic or community status was decided by report of the treating institution.

Comorbid conditions including a history of cardiac disease were defined per patient self-report (see Table 2). Hormone receptor status was determined by medical records from the patient chart. No data from this database are available on the financial status of the women who participated in the study or their insurance situation. Consequently, this study evaluated only the above variables to see if comparisons could be made across these groups in terms of access to optimal treatment, time between diagnosis of HER2 positive MBC and start of therapy (suboptimal therapy was be defined as a treatment delay greater than 30 days), and time to progressive disease.

The first two outcome variables related to optimal treatment (antibody use and time to start of therapy) were collected by medical record abstraction. The third outcome variable, response to therapy, was determined by clinician rating (complete response, stable disease/partial response, progressive disease, or other). Days to first progressive disease was collected from medical records.

**D) Data collection procedures and instruments**

Data were collected on participants in this registry at the time of enrollment and every three months thereafter. The data collected focused on the following: demographic information, height and weight, comorbid conditions including a

history of cardiac disease, HR status, treatment for MBC, physician reported tumor response and method of assessments, and survival status. Patients received care according to the institution's standard practice. Patient data were entered into electronic case report forms (eCRF) by means of a web-based electronic data capture (EDC) system (www.registHER.com). To ensure continued high level of data quality, initial and on-going training and meetings were held for site staff and investigators, and the eCRF was designed to be simple and convenient for the sites to complete.

**E) Study variables**

All variables in this study were summarized in Table 3 and operational definitions were provided.

Table 3: Study variables

| | Measurement Method/ Operational Definition | Type of Variable |
|---|---|---|
| **Variables** | | |
| **Predisposing Characteristics** | | |
| Age - elderly or non-elderly | Date of Informed consent (mm/dd/yyyy) - Date of birth (mm/dd/yyyy) = Age of participant. Age of the participant was evaluated in 3 categories: 1) ≥ 65 years old (Aim 1, 2, and 3), 2) ≥ 75 years old (Aim 1, 2, and 3), and 3) as a continuous variable (Aim 3 only). Evaluated at baseline. | Categorical/Continuous |
| Race | Race of the participant was categorized as white, black, Asian or Pacific islander, Hispanic, American Indian or Alaskan native, or other. Evaluated at baseline. | Categorical |
| Obesity Status – obese or non-obese | Height (cm or in), weight (kg or lb); BMI was calculated using BMI ($kg/m^2$) = weight (lbs) * 703/height $(in)^2$. Obesity status of the participant was evaluated in 3 categories: 1) BSA > 30, 2) BSA > 40 and 3) as a continuous variable. Evaluated at baseline. | Categorical/Continuous |
| **External Environment** | | |
| Regional differences | Regions were defined as the region in which the patient was treated and will be divided into 5 areas of the country including: Midwest, Northeast, Southeast, Southwest, West.* Evaluated at baseline. | Categorical |
| **Health Care System** | | |
| Academic or community | Participant's site of enrollment was classified as either academic or community. Evaluated at baseline. | Categorical |
| **Need** | | |
| Comorbid Conditions | Yes or no (see Table 2 for a list of conditions). Cardiovascular (CV) disease history was compared to those with no CV disease. Evaluated at baseline. | Categorical |
| Hormone Receptor status | ER status: positive, negative, unknown, PR status: positive, negative, unknown; Participants were considered ER positive and/or PR positive if estrogen receptors are positive using either ELISA or IHC. Evaluated at baseline. | Categorical |
| **Outcome Variables** | | |
| Optimal Treatment – Antibody use | Metastatic therapy log evaluated for antibody use - Optimal therapy for participants was defined as those who have received the monoclonal antibody trastuzumab on the metastatic therapy log. | Categorical |
| Optimal Treatment – Start of therapy | Start date of metastatic therapy – date of metastatic diagnosis (mm/dd/yyyy-mm/dd/yyyy); Start of therapy | Categorical |

| | | |
|---|---|---|
| | was defined for participants as the number of days from the date of metastatic diagnosis to the start of treatment. Suboptimal therapy was defined as a treatment delay greater than 30 days. | |
| Response to therapy | Response to treatment for participants was defined as a complete response, stable disease/partial response, progressive disease, or other and was measured in days from first progressive disease. | Continuous |

*States included for each geographic site region were:
NORTHEAST: *Delaware*, District of Columbia, Connecticut, Maryland, Maine, Massachusetts, New Hampshire, *Rhode Island, Vermont*, New Jersey, New York, Pennsylvania
MIDWEST: Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, *Kansas*, Minnesota, Missouri, Nebraska, *North Dakota*, South Dakota.
SOUTHEAST: Florida, Georgia, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana.
SOUTHWEST: Oklahoma, Texas, Arizona, New Mexico; WEST: Idaho, Montana, *Wyoming*, Colorado, *Utah*, Nevada, Alaska, California, *Hawaii*, *Oregon*, Washington.
States whose names are italicized did not have any RegistHER study sites.

## F) Statistical Analysis

All analyses were based on data available in RegistHER as of December 31, 2006. Statistical analyses were performed in Stata (Stata 10 Corp. College Station, Texas) and included descriptive analyses, bivariate and multivariate analyses, and Cox proportional hazards analyses. Comparisons were made between groups referenced in the above table for outcomes of access to optimal treatment which included the monoclonal antibody trastuzumab, time between diagnosis of HER2 positive MBC, start of therapy, and response to therapy.

A power analysis using Stata was conducted to determine the number of participants needed in this study for analyses of each sub-study hypotheses.

Logistic regression was used to examine sub-study hypotheses 1 and 2. The model tested whether the independent variables (treatment setting, region, race, age, obesity, hormone receptor status, comorbid conditions, and history of cardiac disease) predicted the dependent variables (antibody use and start of treatment within 30 days of diagnosis,Yes/No). The alpha for the test of this model was set at 0.05. To achieve power of .80 and a medium effect size, a sample size of 300 is required to detect a significant model so there were satisfactory patient numbers for this study (Hsieh, Block, Larsen, 1998).

Cox regression was used to examine Aim 3. There are two assumptions that must be satisfied with Cox regression. With the first assumption, non-informative censoring, the design of the underlying study must ensure that the mechanisms giving rise to censoring of individual subjects are not related to the probability of an event occurring. In this study participants were followed until death and there was a very low drop out rate so this assumption was satisfied. The second assumption in the Cox model is that of proportional hazards meaning the survival curves for two strata must have hazard functions that are proportional over time, also satisfied in this evaluation of the RegistHER database.

Time-to-event analysis, in this case time to progression of disease, involves estimating the probability that an event will occur at a different point in time. Time to progression was calculated in days for each participant. If multiple progression of disease timepoints were recorded, only the first was used for the analysis. The starting time was measured from entry into study. Data was censored if no progression occurred or if participants dropped out of the study.

The model tested whether the independent variables (treatment setting, region, race, age, obesity, hormone receptor status, comorbid conditions, and a history of cardiac disease) predicted the dependent variable (time to progressive disease). The alpha for the test of this model was set at 0.05. To achieve power of .80 and a medium effect size, a sample size of 364 is required to detect a significant model so there are satisfactory patient numbers for this study as well (Hsieh, Block, Larsen, 1998). Exact p-values were reported and 0.05 was used as the standard for statistical significance.

**i. Descriptive analysis**

All study variables were analyzed descriptively. Numbers and percents were provided for dichotomous and polychotomous variables. Means, medians, standard deviations, and percentiles were calculated for continuous variables.

These results were stratified by the following study groups: age, race, obesity, regional differences, treatment setting, comorbid conditions, cardiac disease and HR status. Bivariate comparisons of baseline characteristics and outcome measures between cohorts were conducted with either t-tests, chi-square tests or other nonparametric tests, depending on the distribution of study variables.

**ii. Sequential logistic regression**

Univariate logistic regression was first utilized to examine the relationship between each predictor variables and outcome variables. The 95% confidence intervals of the odds ratios for each variable and associated p-values were reported. To evaluate differences in treatment patterns and outcomes in women with HER2 positive breast cancer with regard to use of chemotherapy and biologic therapy, the medication therapy log was analyzed to see if antibody therapy was given to the participant. If it was, the participant was grouped as having received optimal therapy. If not, the participant was grouped as having received sub-optimal therapy. Logistic regression was used to evaluate differences in each of the following groups. Participants treated in academic settings were compared to those treated in community settings. Various regions of the country (Midwest, Northeast, Southwest, Southeast, and West) were compared. Elderly ( $\geq$ 65 years old and $\geq$ 75 years old) women were compared

with non-elderly women (< 65 years old and < 75). Individuals with different racial and ethnic backgrounds (African American and Hispanic) were compared to the participants that were categorized as white. Obese women were compared to non-obese women. Individuals that were HR positive were compared to those that were HR negative. Individuals with comorbid conditions were compared to those with no comorbid conditions. Individuals with a history of cardiac disease were compared to those with no history of cardiac disease. Logistic regression was used to predict if the use of the antibody trastuzumab was less frequent for: those treated in community settings, the elderly, racial and ethnic minorities, obese women, those that were HR positive, those with comorbid conditions and those with a history of cardiac disease.

To evaluate the time between diagnosis of HER2 positive MBC and start of therapy, the difference between the date of metastatic disease diagnosis and metastatic disease therapy was calculated (in days) from the medication therapy log. If treatment was received within 30 days, participants were grouped as having received optimal therapy. If not, the participant was grouped as having received sub-optimal therapy. Logistic regression was used to evaluate differences in each of the above groups and to predict if the time between diagnosis of HER2 positive MBC and start of therapy was longer for: those

treated in community settings, the elderly, racial and ethnic minorities, obese women, those that were HR positive, those with comorbid conditions, and with a history of cardiac disease. The multivariate modeling strategy was analogous to that used for the first outcome. Additionally, for the above two aims, various regions of the country (Midwest, Northeast, Southeast, Southwest, and West) were compared using logistic regression.

**iii. Cox proportional hazards regression**

In addition to using logistic regression to evaluate Aim 2, Cox Proportional Hazards regression was used so that time to treatment could be treated as a continuous variable. To evaluate time to progression, Cox proportional hazards regression was used to predict if there is a relation to response to therapy (first incidence of progressive disease as measured in days) for HER2 positive MBC in each of the groups: those treated in a community setting, the elderly, racial and ethnic minorities, obese women, those that are HR positive, those with comorbid conditions, and those with a history of cardiac disease. Additionally, various regions of the country (Midwest, Northeast, Southwest, Southeast, and West) were compared using this method. Participants were censored if they were lost to follow-up or did not yet have progressive disease at the time of their follow-up evaluations.

**Multistage multivariate logistic regression - Use of trastuzumab**

Initial Model I-1: **Log (odds of use of trastuzumab therapy) = β0 + β1 * X1**

**X1** = all Healthcare System variables

Refitted Model I-1: **Log (odds of use of trastuzumab therapy) = β0 + β1 * $X1^+$**

$\mathbf{X1^+}$ = significant Healthcare System variables

Initial Model I-2: **Log (odds of use of trastuzumab therapy) = β0 + β1 * X1 + β2 * X2**

**X1** = all Healthcare System variables

**X2** = all External Environment variables

Refitted Model I-2: **Log (odds of use of trastuzumab therapy) = β0 + β1 * $X1^+$ + β2 * $X2^+$**

$\mathbf{X1^+}$ = significant Healthcare System variables

$\mathbf{X2^+}$ = significant External Environment variables

Initial Model I-3: **Log (odds of use of trastuzumab therapy) = β0 + β1 * X1 + β2 * X2 + β3 * X3**

**X1** = all Healthcare System variables

**X2** = all External Environment variables

**X3** = all predisposing characteristics

Refitted Model I-3: **Log (odds of use of trastuzumab therapy) = β0 + β1 * $X1^+$ + β2 * $X2^+$ + β3 * $X3^+$**

$X1^+$ = significant Healthcare System variables

$X2^+$ = significant External Environment variables

$X3^+$ = significant predisposing characteristics

Initial Model I-4: **Log (odds of use of trastuzumab therapy) = β0 + β1 * X1 + β2 * X2 + β3 * X3 + β4 * X4**

**X1** = all Healthcare System variables

**X2** = all External Environment variables

**X3** = all predisposing characteristics

**X4** = all needs variables

Refitted Model I-4: **Log (odds of use of trastuzumab therapy) = β0 + β1 * $X1^+$ + β2 * $X2^+$ + β3 * $X3^+$ + β4 * $X4^+$**

$X1^+$ = significant Healthcare System variables

$X2^+$ = significant External Environment variables

**$X3^+$** = significant predisposing characteristics

**$X4^+$** = all needs variables

Interactions between significant variables will be evaluated:

Two-way Interactions for Model I-4: **Log (odds of use of trastuzumab therapy) = $\beta 0 + \beta 1 * X1^+ + \beta 2 * X2^+ + \beta 3 * X3^+ + \beta 4 * X4^+ + \beta_{ij} * X_i^+ * X_j^+$**

*for all significant variables $X_i^+ * X_j^+$

**Multistage multivariate logistic regression - Time to start of treatment**

Initial Model II-1: **Log (odds of start of therapy in 30 days) = $\beta 0 + \beta 1 * X1$**

**X1** = all Healthcare System variables

Refitted Model II-1: **Log (odds of start of therapy in 30 days) = $\beta 0 + \beta 1 * X1^+$**

**$X1^+$** = significant Healthcare System variables

Initial Model II-2: **Log (odds of start of therapy in 30 days) = $\beta 0 + \beta 1 * X1 + \beta 2 * X2$**

**X1** = all Healthcare System variables

**X2** = all External Environment variables

Refitted Model II-2: **Log (odds of start of therapy in 30 days) = β0 + β1 * X1$^{+}$ + β2 * X2$^{+}$**

**X1**$^{+}$ = significant Healthcare System variables

**X2**$^{+}$ = significant External Environment variables

Initial Model II-3: **Log (odds of start of therapy in 30 days) = β0 + β1 * X1 + β2 * X2 + β3 * X3**

**X1** = all Healthcare System variables

**X2** = all External Environment variables

**X3** = all predisposing characteristics

Refitted Model II-3: **Log (odds of start of therapy in 30 days) = β0 + β1 * X1**$^{+}$ **+ β2 * X2**$^{+}$ **+ β3 * X3**$^{+}$

**X1**$^{+}$ = significant Healthcare System variables

**X2**$^{+}$ = significant External Environment variables

**X3**$^{+}$ = significant predisposing characteristics

Initial Model II-4: **Log (odds of start of therapy in 30 days) = β0 + β1 * X1 + β2 * X2 + β3 * X3 + β4 * X4**

**X1** = all Healthcare System variables

**X2** = all External Environment variables

**X3** = all predisposing characteristics

**X4** = all needs variables

Refitted Model II-4: **Log (odds of start of therapy in 30 days) = β0 + β1 * $X1^+$ + β2 * $X2^+$ + β3 * $X3^+$ + β4 * $X4^+$**

**$X1^+$** = significant Healthcare System variables

**$X2^+$** = significant External Environment variables

**$X3^+$** = significant predisposing characteristics

**$X4^+$** = all needs variables

Interactions between significant variables will be evaluated:

Two-way Interactions for Model II-4: **Log (odds of start of therapy in 30 days) = β0 + β1 * $X1^+$ + β2 * $X2^+$ + β3 * $X3^+$ + β4 * $X4^+$ + $\beta_{ij}$ * $X_i^+$ * $X_j^+$**

*for all significant variables $X_i^+$ * $X_j^+$

**Cox Proportional Hazards – Time to Progression**

Initial Model III-1: **Log (time to progression) = β0 + β1 * X1**

**X1** = all Healthcare System variables

Refitted Model III-1: **Log (time to progression) = β0 + β1 * $X1^+$**

**$X1^+$** = significant Healthcare System variables

Initial Model III-2: **Log (time to progression) = β0 + β1 * X1 + β2 * X2**

**X1** = all Healthcare System variables

**X2** = all External Environment variables

Refitted Model III-2: **Log (time to progression) = β0 + β1 * $X1^+$ + β2 * $X2^+$**

**$X1^+$** = significant Healthcare System variables

**$X2^+$** = significant External Environment variables

Initial Model III-3: **Log (time to progression) = β0 + β1 * X1 + β2 * X2 + β3 * X3**

**X1** = all Healthcare System variables

**X2** = all External Environment variables

**X3** = all predisposing characteristics

Refitted Model III-3: **Log (time to progression) = β0 + β1 * $X1^+$ + β2 * $X2^+$ + β3 * $X3^+$**

**$X1^+$** = significant Healthcare System variables

**$X2^+$** = significant External Environment variables

**$X3^+$** = significant predisposing characteristics

Initial Model III-4: **Log (time to progression) = β0 + β1 * X1 + β2 * X2 + β3 * X3 + β4 * X4**

**X1** = all Healthcare System variables

**X2** = all External Environment variables

**X3** = all predisposing characteristics

**X4** = all needs variables

Refitted Model III-4: **Log (time to progression) = β0 + β1 * $X1^+$ + β2 * $X2^+$ + β3 * $X3^+$ + β4 * $X4^+$**

**$X1^+$** = significant Healthcare System variables

**$X2^+$** = significant External Environment variables

**$X3^+$** = significant predisposing characteristics

**$X4^+$** = all needs variables

Interactions between significant variables will be evaluated:

Two-way Interactions for Model III-4: **Log (time to progression) = β0 + β1 * $X1^+$ + β2 * $X2^+$ + β3 * $X3^+$ + β4 * $X4^+$ + $\beta_{ij}$ * $X_i^+$ * $X_j^+$**

*for all significant variables $X_i^+$ * $X_j^+$

# CHAPTER V. RESULTS

## A) Sub-study I: Antibody Use

### i. Descriptive statistics

There were 1031 individuals in the RegistHER database. Only 10 patients were males (<1%) so they were excluded from the rest of the analysis. The average age of the study sample was 55 ± 12 (Mean ± SD). The median age of participants in this study was 53 with a range in age from 20 to 92 years. There were 216 women 65 years and older on this study (22%) and 68 women were 75 years or older (7%).

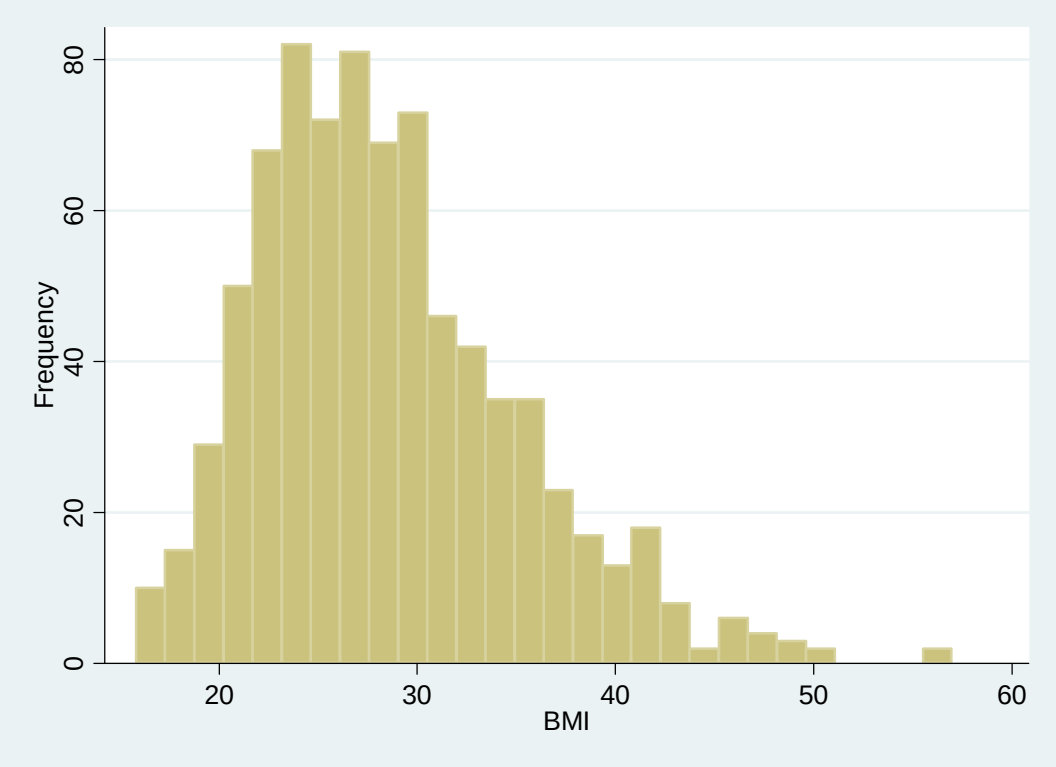
Table 4. RegistHER Database – Predisposing Characteristics

| ***Variable*** | ***Frequency*** | ***Percent*** |
|---|---|---|
| ***Sex*** (n=1031) | | |
| Men | 10 | <1 |
| Women | 1,021 | 99 |
| ***Age*** (n=1021) | | |
| 0-65 | 805 | 79 |
| 65-74 | 148 | 15 |
| ≥75 | 68 | 7 |
| ***Race*** (n=1021) | | |
| White | 806 | 79 |
| Black | 131 | 13 |
| Hispanic | 57 | 6 |
| Other Race | 27 | 3 |
| ***Obesity*** (n=1021) | | |
| BMI ≤ 30 | 520 | 51 |
| BMI > 30 | 501 | 49 |
| BMI > 40 | 268 | 26 |

Data regarding race were gathered from the participants by self-report using the following categories: White, Black, Asian or Pacific Islander, Hispanic, American Indian or Alaskan Native, or other (the participant was to specify if they chose other). Twenty-one percent of the participants in this trial indicated that they were of a race other than white. Thirteen percent (131 participants) classified themselves as African American, six percent (57 participants) classified

themselves as Hispanic, three percent (27 participants) classified themselves other race (27 participants).

Figure 3. Distribution by BMI




After calculating obesity status as measured by BMI, 51% of participants were obese and 49% were not obese with a BMI ≤ 30 (see Figure 3). Twenty-six percent were morbidly obese with a BMI > 40. Forty-four percent of participants were positive for ER and PR and 56% of patients were negative for one or both

receptors. Seventy-two percent of those in the study reported having comorbid disease (see Table 2 for specific categories). A history of cardiac disease was reported in 83% of participants.

Table 5. RegistHER Database - Needs

| *Variable* | *Frequency* | *Percent* |
|---|---|---|
| ***Hormone Status*** (n=816) | | |
| Positive | 358 | 44 |
| Negative | 458 | 56 |
| ***Other Comorbid Diseases*** (n=1021) | | |
| Yes | 732 | 72 |
| No | 289 | 28 |
| **Cardiac Disease** (n=1021) | | |
| Yes | 847 | 83 |
| No | 174 | 17 |

Eighty-two percent of the participants in this study were treated in a community setting and 18% were treated in an academic setting. When broken down by region of the country, the largest group of participants was in the Southeast (32%), 23% of participants were in the Midwest, 20% of participants were in the Northeast, 13% in the West and 12% in the Southwest. When compared to the expected distribution of MBC cases across the U. S. based on American Cancer Society (ACS) estimates, the geographic distribution of HER2 positive MBC

patients in RegistHER included more women from the Midwest and Southeast, and fewer from the Southwest and West than the national data (Table 7).

Table 6. RegistHER Database – Healthcare System

| ***Variable*** | ***Frequency*** (n=1020) | ***Percent*** |
|---|---|---|
| ***Treatment Setting*** | | |
| Academic | 187 | 18 |
| Community | 833 | 82 |

Table 7. RegistHER Database – External Environment

| ***Region of the Country**** | RegistHER | | Estimated HER2 positive MBC from ACS for years 2004 & 2005 | |
|---|---|---|---|---|
| | ***Frequency*** (n=1020) | ***Percent*** | ***Frequency*** (n=10,679) | ***Percent*** |
| Southwest | 119 | 12 | 2498 | 23 |
| West | 129 | 13 | 2519 | 24 |
| Northeast | 210 | 21 | 2815 | 26 |
| Midwest | 237 | 23 | 1033 | 10 |
| Southeast | 325 | 32 | 1815 | 17 |

For the analysis of research hypothesis $H_{A-1}$ - $H_{A-4}$ use of the antibody trastuzumab was evaluated. Thirty five percent of participants did not receive

optimal therapy with antibody treatment in this registry (65% did receive optimal therapy).

Table 8. Frequency of Antibody Use

| ***Antibody Use*** | ***Frequency*** (n=1020) | ***Percent*** |
|---|---|---|
| Did not receive antibody | 358 | 35 |
| Received antibody | 652 | 65 |

**ii. Analysis of research hypotheses $H_{A-1}$**

Hypothesis $H_{A-1}$ along with sub-hypotheses $H_{A-1a}$ addressed the relationship between the proposed healthcare system variable of academic or community setting and the use of optimal therapy with the antibody trastuzumab. The results from univariate logistic regression supported sub-hypothesis $H_{A-1a}$ indicating that location of treatment either academic or community setting strongly related to the use of antibody treatment with trastuzumab (p=0.01) (Table 9). The odds ratio is a measure of effect size, and it is defined as the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. The confidence interval characterizes the uncertainty about the true value of a

population parameter. A wide confidence interval indicates that more data should be collected before anything definitive can be said about the parameter. Specifically, patients treated at a community center had a significantly lower likelihood of being treated with trastuzumab (41% less likely to receive trastuzumab) and the odds ratio associated was 1.594 (95% CI: [1.118, 2.271]). Since this confidence interval is relatively narrow and the lower limit is greater than 1 (1.118), this estimate is likely precise. In a multivariate logistic regression model (Model I-1) adjusted for all significant variables (treatment setting, elderly ≥ 75 years, ER/PR positive, and cardiac disease), treatment setting remained significantly associated with the likelihood of receiving trastuzumab and likelihood was much lower in the community setting (Table 10).

Table 9. Univariate Logistic Regression for Use of Antibody

| | Number of observations | Log likelihood | LR $chi^2$ | Prob > $chi^2$ | Pseudo $R^2$ | Odds Ratio | Std. Err. | z | P>z | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Race*** | 1010 | -655.324 | 2.68 | 0.444 | 0.002 | | | | | | |
| Black | | | | | | 0.948 | 0.189 | -0.27 | 0.789 | 0.642 | 1.400 |
| Hispanic | | | | | | 0.689 | 0.191 | -1.34 | 0.179 | 0.400 | 1.186 |
| Other | | | | | | 1.462 | 0.655 | 0.85 | 0.397 | 0.607 | 3.519 |
| ***Elderly*** | | | | | | | | | | | |
| Elderly ≥75 | 1010 | -653.526 | 6.27 | 0.012 | 0.005 | 0.525 | 0.134 | -2.52 | 0.012 | 0.318 | 0.866 |
| ***Obese*** | | | | | | | | | | | |
| ***Treatment Setting*** | 1010 | -653.186 | 6.95 | 0.008 | 0.005 | 1.594 | 0.288 | 2.58 | 0.010 | 1.118 | 2.271 |
| ***Region*** | 1010 | -655.309 | 2.71 | 0.608 | 0.002 | | | | | | |
| Midwest | | | | | | 1.321 | 0.240 | 1.53 | 0.125 | 0.925 | 1.884 |
| Northeast | | | | | | 1.068 | 0.197 | 0.36 | 0.721 | 0.744 | 1.534 |
| Southwest | | | | | | 1.184 | 0.267 | 0.75 | 0.455 | 0.760 | 1.843 |
| West | | | | | | 1.033 | 0.224 | 0.15 | 0.880 | 0.676 | 1.580 |
| ***ER/PR positive*** | 809 | -497.026 | 53.33 | 0.001 | 0.051 | 0.3342 | 0.051 | -7.18 | 0.001 | 0.248 | 0.451 |
| ***Comorbid Conditions*** | 1010 | -656.563 | 0.20 | 0.656 | 0.001 | 1.067 | 0.156 | 0.45 | 0.655 | 0.802 | 1.421 |
| ***Cardiac Disease*** | 1010 | | | | 0.003 | 1.431 | | | 0.036 | 1.024 | 1.99 |

Notes: Setting is either academic or community; Elderly ≥65 and ≥75 were analyzed separately. Elderly ≥65, $r^2 = 0.002$, OR = 0.797, p = 0.153. Age as a continuous variable $r^2 = 0.001$, OR = 0.995, p = 0.339. Obese BMI > 30 and > 40 were analyzed separately. BMI > 40, $r^2 = 0.002$, OR 1.264, p = 0.126. Obese as a continuous variable $r^2 = 0.000$, OR= 0.998, p = 0.881.

Table 10. Multivariate Logistic Regression Results for Use of Antibody (with significant variables)

| | **Number of observations** | **Log likelihood** | **LR chi2** | **Prob > chi2** | **Pseudo R2** | **Odds Ratio** | **Std. Err.** | **z** | **P>z** | **Lower 95% CI** | **Upper 95% CI** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model I-1**<br>**Health Care System** | | | | | | | | | | | |
| Treatment Setting | 1010 | -653.186 | 6.95 | 0.008 | 0.005 | 1.594 | 0.288 | 2.58 | 0.010 | 1.118 | 2.271 |
| ***Model I-2***<br>***Healthcare System + External Environment*** | | | | | | | | | | | |
| | 1010 | -651.498 | 10.33 | 0.066 | 0.008 | | | | | | |
| Treatment Setting | | | | | | 1.688 | 0.327 | 2.70 | 0.007 | 1.154 | 2.467 |
| Midwest | | | | | | 1.335 | 0.243 | 1.59 | 0.112 | 0.934 | 1.906 |
| Northeast | | | | | | 1.005 | 0.188 | 0.03 | 0.979 | 0.697 | 1.449 |
| Southwest | | | | | | 0.950 | 0.229 | -0.21 | 0.830 | 0.593 | 1.522 |
| West | | | | | | 1.024 | 0.223 | 0.11 | 0.912 | 0.669 | 1.568 |
| ***Model I-3***<br>***Healthcare System + External Environment + Predisposing Characteristics*** | | | | | | | | | | | |
| | 1010 | -649.002 | 15.32 | 0.032 | 0.012 | | | | | | |
| Treatment Setting | | | | | | 1.577 | 0.298 | 2.41 | 0.016 | 1.089 | 2.285 |
| Black | | | | | | 0.927 | 0.186 | -0.38 | 0.706 | 0.625 | 1.374 |
| Hispanic | | | | | | 0.681 | 0.190 | -1.37 | 0.169 | 0.393 | 1.178 |
| Other | | | | | | 1.404 | 0.633 | 0.75 | 0.452 | 0.580 | 3.399 |
| Elderly ≥75 | | | | | | 0.531 | 0.161 | -2.09 | 0.037 | 0.293 | 0.961 |
| Obesity | | | | | | 0.954 | 0.132 | -0.34 | 0.733 | 0.726 | 1.252 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Model I-3 Refitted*** | | | | | | | | | | | |
| | 1010 | -650.429 | 12.47 | 0.002 | 0.012 | | | | | | |
| Treatment Setting | | | | | | 1.653 | 0.282 | 2.44 | 0.013 | 1.113 | 2.455 |
| Elderly ≥75 | | | | | | .546 | 0.140 | -2.36 | 0.018 | 0.330 | .902 |
| ***Model I-4*** ***Healthcare System + External Environment + Predisposing Characteristics + Need*** | | | | | | | | | | | |
| | 809 | -487.632 | 72.12 | 0.001 | 0.068 | | | | | | |
| Treatment Setting | | | | | | 1.851 | 0.400 | 2.85 | 0.004 | 1.212 | 2.827 |
| Elderly ≥75 | | | | | | .541 | 0.169 | -1.97 | 0.049 | 0.294 | .997 |
| ER/PR Positive | | | | | | .305 | 0.048 | -7.56 | 0.001 | 0.224 | .415 |
| Comorbid Conditions | | | | | | 1.256 | 0.220 | 1.30 | 0.194 | 0.890 | 1.77 |
| Cardiac Disease | | | | | | 1.259 | 0.256 | 1.09 | 0.276 | 0.832 | 1.904 |
| ***Model I-4 Refitted*** | | | | | | | | | | | |
| | 809 | -489.382 | 68.62 | 0.001 | 0.067 | | | | | | |
| Treatment Setting | | | | | | 1.847 | 0.400 | 2.89 | 0.004 | 1.210 | 2.818 |
| Elderly ≥75 | | | | | | 0.481 | 0.146 | -2.41 | 0.049 | 0.266 | 0.872 |
| ER/PR Positive | | | | | | 0.313 | 0.049 | -7.46 | 0.001 | 0.231 | 0.425 |
| | | | | | | | | | | | |
| Notes: Setting is either academic or community; Elderly ≥65 and ≥75 were analyzed separately. Elderly ≥ 65 years $r^2 = 0.007$, OR = 1.421, p= 0.452. Obese BMI > 30 and > 40 were analyzed separately. BMI > 40, $r^2 = 0.007$, OR =1.267, p = 0.123. | | | | | | | | | | | |

### iii. Analysis of research hypotheses $H_{A-2}$

The relationship between the external environment variable of region of the country (Midwest, Northeast, Southeast, Southwest and West) was examined in hypothesis $H_{A-2}$ and its sub-hypotheses $H_{A-2a}$. Univariate logistic regression showed that there is no relationship between region of the country in which you are treated and your likelihood of receiving antibody therapy. The region of the country in which the participants live did not impact the use of antibody therapy (Table 9).

In a multivariate regression model, region of the country was not a significant predictor of optimal treatment with the antibody trastuzumab. Therefore, region of the country was not retained for the final model (Table 10).

### iv. Analysis of research hypotheses $H_{A-3}$

The relationship between predisposing variables (age, race and obesity) and the use of optimal therapy with the antibody trastuzumab were examined in hypothesis $H_{A-3}$ and its sub-hypotheses $H_{A-3a,}$ $H_{A-3b,}$ $H_{A-3c.}$ Univariate logistic regression showed that there is no relationship between the needs variables of race and obesity and the likelihood of receiving antibody therapy (Table 9). Age greater than 65 years did not show a relationship, however, the very old group

(≥75 years) had a significantly lower likelihood of being treated with trastuzumab (48% less likely to receive trastuzumab) and the odds ratio associated was 0.525 (95% CI: [0.318, 0.866]). The confidence interval is very narrow, so the estimate is likely precise.

Race and obesity were not significant predictors of optimal treatment with the antibody trastuzumab by themselves or combined with healthcare system and external environment variables, however, age ≥75 remained significant in a multivariate regression model including all other significant variables (treatment setting, ER/PR positive, and cardiac disease) (Table 10).

**v. Analysis of research hypotheses $H_{A-4}$**

The relationship between the needs variables (comorbid conditions, cardiac disease and hormone receptor status) was examined in hypothesis $H_{A-4}$ and sub-hypothesis $H_{A-4a}$ and $H_{A-4b.}$ Univariate logistic regression showed that hormone receptor status strongly related to the use of antibody treatment with trastuzumab ($p<0.001$) (Table 9). Specifically, patients who were ER/PR positive were 67% less likely to be treated with trastuzumab, and the odds ratio associated was 0.334 (95% CI: [0.248, 0.451]). Having comorbid conditions was not a significant predictor of optimal treatment with the antibody trastuzumab; however, having a history of cardiac disease was with an odds ratio of 1.431 (95% CI: [1.024,

1.999]). However, in a multivariate regression model including other significant variables (treatment setting, elderly ≥ 75 years, ER/PR positive); having a history of cardiac disease was not a significant predictor (Table 10).

**vi. Multivariate Analysis of Aim I with all Variables**

Table 10 illustrates the findings when all variables for Aim 1 were run in a multivariate analysis. Three variables remained significant, treatment setting ($p= 0.015$), age ≥ 75 years ($p = 0.048$), and those that were ER/PR positive ($p<0.001$).

**vii. Interactions for Model I-4**

Two-way interactions for all significant variables in univariate analysis were evaluated (age ≥ 75 years, ERPR status, and treatment setting). Interactions were evaluated to see if any two of the variables were not simply additive but had a multiplicative effect when analyzed together. Since the consequence of an interaction is that the effect of one variable depends on the value of another, it was important to evaluate synergy between the individual variables. As illustrated in Table 11, interactions between these variables were significant.

Table 11. Interactions for Significant Antibody Use Variables

| Interactions* | N | Pseudo R2 | Odds Ratio | P>z | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| | 809 | 0.066 | | | | |
| Age | | | 0.453 | 0.012 | 0.245 | 0.839 |
| ERPR status | | | 0.311 | 0.000 | 0.229 | 0.422 |
| Treatment setting | | | 1.812 | 0.006 | 1.184 | 2.774 |
| Interaction | | | 2.524 | 0.470 | 0.205 | 31.045 |

* Two-way interactions for all significant variables were included in Model I-4

Table 12. Occurrence of History of Cardiac Disease by Age

| History of Cardiac Disease | Age < 75 years (n=953) | Age ≥ 75 years (n=68) |
|---|---|---|
| Yes (n=847) | 809 | 38 |
| No (n=174) | 144 | 30 |

To further explore possible explanations for why having a history of cardiac disease was not significant when run with the other significant variables of age, treatment setting and HR status, data for Tables 12, 13 and 14 were compiled. There were adequate patient numbers in all of the groups so sample size was

probably not a factor. It is unclear why this variable became not significant but could be something unique to this particular sample.

Table 13. Occurrence of History of Cardiac Disease by Treatment Setting

| **History of Cardiac Disease** | **Academic Setting** (n=187) | **Community Setting** (n=833) |
|---|---|---|
| Yes (n=847) | 164 | 683 |
| No (n=174) | 23 | 151 |

Table 14. Occurrence of History of Cardiac Disease Hormone Receptor Status

| **History of Cardiac Disease** | **ER/PR Positive** (n=358) | **ER/PR Negative** (n=458) |
|---|---|---|
| Yes (n=847) | 307 | 373 |
| No (n=174) | 51 | 85 |

## B) Sub-study II: Time to treatment

### i. Descriptive statistics

For the analysis of research hypothesis $H_{A-5}$ - $H_{A-8}$ the time to treatment following a diagnosis of HER2 positive MBC was evaluated. Twenty-six percent of women were not treated within thirty days following their diagnosis of MBC.

Table 15. Time to Treatment

| **Time to treatment** | **Frequenc y** (n=961) | **Percent** |
|---|---|---|
| > 30 days | 250 | 26 |
| ≤ 30 days | 711 | 734 |

### ii. Analysis of research hypotheses $H_{A-5}$

Hypothesis $H_{A-5}$ along with sub-hypotheses $H_{A-5a}$ addressed the relationship between the proposed healthcare system variable of academic or community setting and the time to treatment following a diagnosis of HER2 positive MBC. The results from univariate logistic regression do not support sub-hypothesis $H_{A-5a}$ indicating that the location of treatment in either an academic or community setting was not related to the time to initiation of treatment following a diagnosis of HER2 positive MBC (Table 16).

Table 16. Univariate Logistic Regression Results for Start of Treatment

| | Number of observations | Log likelihood | LR chi2 | Prob > chi2 | Pseudo R2 | Odds Ratio | Std. Err. | z | P>z | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Race*** | 961 | -549.091 | 3.53 | 0.318 | 0.003 | | | | | | |
| Black | | | | | | 1.205 | 0.278 | 0.81 | 0.418 | 0.767 | 1.893 |
| Hispanic | | | | | | 0.739 | 0.227 | -0.99 | 0.324 | 0.405 | 1.348 |
| Other | | | | | | 1.974 | 1.085 | 1.24 | 0.216 | 0.672 | 5.798 |
| ***Elderly*** | | | | | | | | | | | |
| Elderly ≥75 | 961 | -550.847 | 0.01 | 0.906 | 0.001 | 0.965 | 0.291 | -0.12 | 0.905 | 0.534 | 1.743 |
| ***Obese*** | 961 | -550.830 | 0.05 | 0.827 | 0.001 | 1.033 | 0.152 | 0.22 | 0.827 | 0.774 | 1.378 |
| ***Treatment Setting*** | 961 | -550.766 | 0.18 | 0.675 | 0.001 | 0.924 | 0.174 | -0.42 | 0.674 | 0.639 | 1.335 |
| ***Region*** | 961 | -548.472 | 4.76 | 0.312 | 0.004 | | | | | | |
| Midwest | | | | | | 1.057 | 0.222 | 0.27 | 0.791 | 0.701 | 1.595 |
| Northeast | | | | | | 0.789 | 0.163 | -1.15 | 0.252 | 0.527 | 1.183 |
| Southwest | | | | | | 0.873 | 0.217 | -0.55 | 0.585 | 0.536 | 1.421 |
| West | | | | | | 0.662 | 0.156 | -1.75 | 0.080 | 0.416 | 1.051 |
| ***ER/PR Positive*** | 768 | -436.661 | 1.24 | 0.266 | 0.001 | 1.205 | 0.203 | 1.11 | 0.267 | 0.867 | 1.676 |
| ***Comorbid Conditions*** | 961 | -550.851 | 0.01 | 0.935 | 0.001 | 0.987 | 0.161 | -0.08 | 0.935 | 0.716 | 1.360 |
| ***Cardiac Disease*** | 961 | | | | 0.002 | 1.309 | | | 0.152 | 0.905 | 1.894 |

Notes: Setting is either academic or community; Elderly ≥65 and ≥75 were analyzed separately. Elderly ≥65 $r^2$ 0.001, OR = 0.994, p = 0.973. Obese BMI > 30 and > 40 were analyzed separately. BMI > 40, $r^2$ =0.002, OR 0.807, p = 0.193.

### iii. Analysis of research hypotheses $H_{A-6}$

The relationship between the external environment variable of region of the country (Midwest, Northeast, Southeast, Southwest and West) was examined in hypothesis $H_{A-6}$ and its sub-hypotheses $H_{A-6a}$. Univariate logistic regression showed that there is no relationship between region of the country in which you are treated and the time to treatment following a diagnosis of HER2 positive MBC (Table 16).

### iv. Analysis of research hypotheses $H_{A-7}$

The relationship between predisposing variables (age, race and obesity) and the time to treatment following a diagnosis of HER2 positive MBC was examined in hypothesis $H_{A-7}$ and its sub-hypotheses $H_{A-7a}$, $H_{A-7b}$, $H_{A-7c}$. Univariate logistic regression showed that there is no relationship between the predisposing variables of age, race and obesity and the time to treatment following a diagnosis of HER2 positive MBC (Table 16).

### v. Analysis of research hypotheses $H_{A-8}$

The relationship between the needs variables (comorbid conditions, history of cardiac disease and hormone receptor status) and the time to treatment following a diagnosis of HER2 positive MBC was examined in hypothesis $H_{A-8}$ and sub-hypotheses $H_{A-8a}$ and $H_{A-8b}$.. Univariate logistic regression showed that there is no relationship between the needs variables of comorbid conditions, history of cardiac disease, and hormone receptor status and the time to treatment following a diagnosis of HER2 positive MBC (Table 16).

Consistent with univariate results, none of the variables were significant in multivariate analyses, and the estimate of explained variance (pseudo R2) was negligible (see Table 17).

Table 17. Multivariate Logistic Regression Results for Start of Treatment

| | Number of observations | Log likelihood | LR chi2 | Prob > chi2 | Pseudo R2 | Odds Ratio | Std. Err. | z | P>z | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model I-1**<br>**Healthcare System** | | | | | | | | | | | |
| Treatment Setting | 961 | -550.766 | 0.18 | 0.675 | 0.000 | 0.924 | 0.174 | -0.42 | 0.674 | 0.639 | 1.335 |
| ***Model I-2***<br>***Healthcare System + External Environment*** | | | | | | | | | | | |
| ***Region*** | 961 | -548.472 | 4.76 | 0.312 | 0.004 | | | | | | |
| Midwest | | | | | | 1.057 | 0.222 | 0.27 | 0.791 | 0.701 | 1.595 |
| Northeast | | | | | | 0.789 | 0.163 | -1.15 | 0.252 | 0.527 | 1.183 |
| Southwest | | | | | | 0.873 | 0.217 | -0.55 | 0.585 | 0.536 | 1.421 |
| West | | | | | | 0.662 | 0.156 | -1.75 | 0.080 | 0.416 | 1.051 |
| ***Model I-3***<br>***Healthcare System + External Environment + Predisposing Characteristics*** | | | | | | | | | | | |
| | 961 | -549.061 | 3.59 | 0.733 | 0.003 | | | | | | |
| Black | | | | | | 1.200 | 0.278 | 0.79 | 0.430 | 0.763 | 1.890 |
| Hispanic | | | | | | 0.736 | 0.227 | -0.99 | 0.320 | 0.403 | 1.346 |
| Other | | | | | | 1.975 | 1.087 | 1.24 | 0.216 | 0.672 | 5.806 |
| Elderly ≥75 | | | | | | 0.960 | 0.336 | -0.12 | 0.906 | 0.483 | 1.905 |
| Obesity | | | | | | 1.031 | 0.153 | 0.21 | 0.836 | 0.771 | 1.380 |
| ***Model I-4***<br>***Healthcare System + External Environment + Predisposing Characteristics + Need*** | | | | | | | | | | | |
| | 775 | -440.035 | 2.90 | 0.408 | 0.003 | | | | | | |
| ER/PR Positive | | | | | | 1.173 | 0.197 | 0.95 | 0.341 | 0.845 | 1.630 |
| Comorbid | | | | | | 1.131 | 0.208 | 0.67 | 0.504 | 0.788 | 1.622 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Conditions | | | | | | | | | | | |
| Cardiac Disease | | | | | | 1.245 | 0.271 | 1.01 | 0.314 | 0.813 | 1.908 |
| Notes: Setting is either academic or community; Elderly ≥65 and ≥75 were analyzed separately. Elderly ≥ 65 years $r^2 = 0.000$, OR = 1.015, p= 0.942. Obese BMI > 30 and BMI > 40 were analyzed separately. Obese BMI > 40 $r^2 = 0.000$, OR = 1.049, p = 0.746. | | | | | | | | | | | |

### vi. Analysis of Aim 2 using Cox Regression with time to treatment as a continuous variable

The results from Cox Proportional Hazards regression indicated that none of the variables tested affect the time to progression of metastatic disease. This is consistent with the results from univariate and multivariate logistic regression using a cut-off point of 30 days discussed above (Table 18).

Table 18. Cox Proportional Hazards Model for Start of Treatment

| | **Number of observations** | **Number of failures** | **Time at risk** | **Log likelihood** | **LR chi2** | **Prob > chi2** | **Haz. Ratio** | **Std. Err.** | **z** | **P>z** | **Lower 95% CI** | **Upper 95% CI** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 768 | 571 | 19960 | -3500.802 | 8.62 | 0.801 | | | | | | |
| ***Race*** | | | | | | | | | | | | |
| Black | | | | | | | 0.961 | 0.120 | -0.32 | 0.748 | 0.753 | 1.226 |
| Hispanic | | | | | | | 0.856 | 0.169 | -0.79 | 0.429 | 0.582 | 1.259 |
| Other | | | | | | | 1.165 | 0.330 | 0.54 | 0.590 | 0.669 | 2.030 |
| ***Elderly*** (≥75) | | | | | | | 0.841 | 0.173 | -0.84 | 0.402 | 0.562 | 1.260 |
| ***Obese*** | | | | | | | 1.036 | 0.092 | 0.4 | 0.688 | 0.870 | 1.234 |
| ***Treatment Setting*** | | | | | | | 0.965 | 0.122 | -0.28 | 0.777 | 0.753 | 1.236 |
| ***Region*** | | | | | | | | | | | | |
| Midwest | | | | | | | 1.292 | 0.208 | 1.59 | 0.111 | 0.942 | 1.770 |
| Northeast | | | | | | | 1.042 | 0.165 | 0.26 | 0.794 | 0.764 | 1.422 |
| Southeast | | | | | | | 1.191 | 0.181 | 1.15 | 0.249 | 0.885 | 1.605 |
| West | | | | | | | 1.037 | 0.188 | 0.2 | 0.841 | 0.727 | 1.479 |
| ***ER/PR Positive*** | | | | | | | 1.100 | 0.094 | 1.11 | 0.268 | 0.929 | 1.301 |
| ***Comorbid Conditions*** | | | | | | | 1.029 | 0.099 | 0.3 | 0.763 | 0.852 | 1.244 |
| Notes: Obese = BMI ≥ 30; Setting is either academic or community; Elderly ≥ 65 years HR =1.014, p= 0.906. | | | | | | | | | | | | |

### vii. Interactions for Model I-4

Since no variables were significant for the analysis of Aim 2, interactions were not evaluated.

## C) Sub-study III: Response to treatment

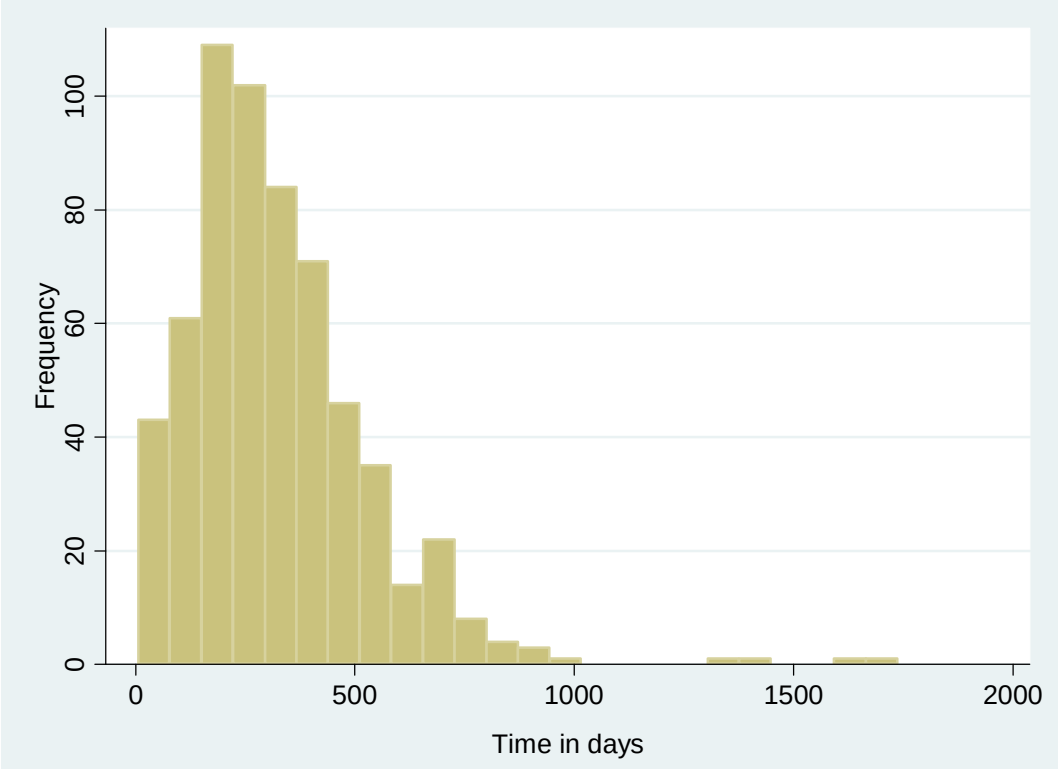
### i. Descriptive statistics

The mean time to progression for the participants in this study was 325 days (minimum 6 days and maximum of 1737 days) (Table 19). Figure 4 depicts the distribution of time to progression for participants.

Table 19. Time to Progression

| **Variable** | **Mean** | **Standard Deviation** | **Minimum** | **Maximum** |
|---|---|---|---|---|
| ***Time to Progression*** | 324.975 | 205.930 | 6 | 1737 |

Figure 4. Distribution of Time to Progression




### ii. Analysis of research hypotheses $H_{A-9}$

Hypothesis $H_{A-9}$ along with sub-hypotheses $H_{A-9a}$ addressed the relationship between the proposed healthcare system variable of academic or community setting and response and hazard ratios were evaluated. The hazard ratio is a ratio of the rates at which patients are progressing in the two groups. A hazard ratio of 1 corresponds to equal treatments; a hazard ratio of 2 means that twice as many patients in one group are progressing proportionately compared to the other group; and a hazard ratio of 0.5 is the reverse, with half as many patients in one group progressing at any point in time compared to the other group. The results from Cox Proportional Hazards regression do not support sub-hypothesis $H_{A-9a}$ indicating that location of treatment either academic or community center did not affect the time to progression of metastatic disease (Table 20).

Table 20. Cox Proportional Hazards Model for Time to Progression

| | **Number of observations** | **Number of failures** | **Time at risk** | **Log likelihood** | **LR chi2** | **Prob > chi2** | **Haz. Ratio** | **Std. Err.** | **z** | **P>z** | **Lower 95% CI** | **Upper 95% CI** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Race*** | 1007 | 607 | 386951 | -3741.561 | 3.94 | 0.268 | | | | | | |
| Black | | | | | | | 1.199 | 0.145 | 1.50 | 0.135 | 0.945 | 1.519 |
| Hispanic | | | | | | | 1.298 | 0.231 | 1.46 | 0.143 | 0.915 | 1.839 |
| Other | | | | | | | 0.942 | 0.256 | -0.22 | 0.826 | 0.553 | 1.604 |
| ***Elderly*** (≥75) | 1007 | 607 | 386951 | -3742.212 | 2.63 | 0.105 | 1.306 | 0.207 | 1.69 | 0.092 | 0.957 | 1.781 |
| ***Obese*** (BMI >30) | 1007 | 607 | 386951 | -3742.111 | 2.84 | 0.092 | 1.147 | 0.093 | 1.68 | 0.092 | 0.978 | 1.345 |
| ***Treatment Setting*** | 1007 | 607 | 386951 | -3741.961 | 3.14 | 0.077 | 1.203 | 0.123 | 1.80 | 0.071 | 0.984 | 1.470 |
| ***Region*** | 1007 | 607 | 386951 | -3741.132 | 4.79 | 0.309 | | | | | | |
| Midwest | | | | | | | 1.119 | 0.168 | 0.75 | 0.455 | 0.833 | 1.502 |
| Northeast | | | | | | | 1.181 | 0.180 | 1.09 | 0.274 | 0.877 | 1.591 |
| Southwest | | | | | | | 1.211 | 0.173 | 1.34 | 0.180 | 0.915 | 1.601 |
| West | | | | | | | 0.935 | 0.162 | -0.39 | 0.699 | 0.666 | 1.312 |
| ***ER/PR Positive*** | 805 | 493 | 304230 | -2937.383 | 4.52 | 0.034 | 0.824 | 0.075 | -2.12 | 0.034 | 0.688 | 0.986 |
| ***Comorbid Conditions*** | 1007 | 607 | 386951 | -3743.519 | 0.02 | 0.888 | 0.987 | 0.089 | -0.14 | 0.888 | 0.827 | 1.179 |
| ***Cardiac Disease*** | 1007 | 607 | 386951 | -3743.018 | 1.02 | 0.312 | 0.896 | 0.096 | -1.02 | 0.306 | 0.726 | 1.106 |

Notes: Setting is either academic or community; Elderly ≥65 and ≥75 were analyzed separately. Elderly ≥ 65 years HR =1.019, p= 0.852; Elderly as a continuous variable HR=0.997, p=0.372. Obese BMI > 30 and BMI > 40 were analyzed separately. Obese BMI > 40 HR = 1.004, p = 0.596; Obese as a continuous variable HR = 1.001, p = 0.771.

Table 21. Cox Proportional Hazards Model for Time to Progression and Significant Variables

| | Number of observations | Number of failures | Time at risk | Log likelihood | LR chi2 | Prob > chi2 | Haz. Ratio | Std. Err. | z | P>z | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Model I-1*** ***Healthcare System*** | | | | | | | | | | | | |
| Treatment Setting | 1007 | 607 | 386951 | -3741.960 | 3.14 | 0.077 | 1.203 | 0.123 | 1.80 | 0.071 | 0.984 | 1.470 |
| ***Model I-2*** ***Healthcare System + External Environment*** | | | | | | | | | | | | |
| ***Region*** | 1007 | 607 | 386951 | -3741.132 | 4.79 | 0.309 | | | | | | |
| Midwest | | | | | | | 1.119 | 0.168 | 0.75 | 0.455 | 0.833 | 1.502 |
| Northeast | | | | | | | 1.181 | 0.180 | 1.09 | 0.274 | 0.877 | 1.591 |
| Southwest | | | | | | | 1.211 | 0.173 | 1.34 | 0.180 | 0.915 | 1.601 |
| West | | | | | | | 0.935 | 0.162 | -0.39 | 0.699 | 0.666 | 1.312 |
| ***Model I-3*** ***Healthcare System + External Environment + Predisposing Characteristics*** | | | | | | | | | | | | |
| | 1007 | 607 | 386951 | -3738.5632 | 9.93 | 0.128 | | | | | | |
| Black | | | | | | | 1.187 | 0.144 | 1.41 | 0.158 | 0.935 | 1.506 |
| Hispanic | | | | | | | 1.285 | 0.230 | 1.40 | 0.160 | 0.906 | 1.824 |
| Other | | | | | | | 0.940 | 0.255 | -0.23 | 0.821 | 0.552 | 1.602 |
| Elderly ≥75 | | | | | | | 1.432 | 0.272 | 1.89 | 0.059 | 0.987 | 2.078 |
| Obesity BMI > 30 | | | | | | | 1.144 | 0.094 | 1.63 | 0.103 | 0.973 | 1.344 |
| ***Model I-4*** ***Healthcare System + External Environment + Predisposing Characteristics + Need*** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 805 | 493 | 304230 | -2937.275 | 5.21 | 0.157 | | | | | | |
| ER/PR Positive | | | | | | | 0.830 | 0.077 | -2.02 | 0.044 | 0.693 | 0.995 |
| Comorbid Conditions | | | | | | | 0.968 | 0.099 | -0.32 | 0.752 | 0.792 | 1.183 |
| Cardiac Disease | | | | | | | 0.917 | 0.115 | -0.69 | 0.488 | 0.718 | 1.171 |
| **Refitted Model I-4** | | | | | | | | | | | | |
| ER/PR Positive | 805 | 493 | 304230 | -2937.383 | 4.52 | 0.034 | 0.824 | 0.075 | -2.12 | 0.034 | 0.688 | 0.986 |
| Notes: Setting is either academic or community; ≥ 65 years HR = 0.941, p= 0.620; elderly as a continuous variable HR= 0.997, p=0.324. Obese BMI > 30 and BMI > 40 were analyzed separately. Obese BMI > 40 HR = 1.108 , p = 0.254. | | | | | | | | | | | | |

### iii. Analysis of research hypotheses $H_{A-10}$

The relationship between the external environment variable of region of the country (Midwest, Northeast, Southwest, Southeast and West) and the time to progressive disease was examined in hypothesis $H_{A-10}$ and its sub-hypotheses $H_{A-10a}$. Cox Proportional Hazards regression showed that the region of the country in which you are treated did not affect the time to progression of metastatic disease (Table 20). In a multivariate Cox Proportional Hazards regression model including significant values for the healthcare system variable (academic compared to community setting) and the external environment variable (region of the country), no significant values were found (Table 21).

### iv. Analysis of research hypotheses $H_{A-11}$

The relationship between predisposing variables (age, race and obesity) and the time to progressive disease was examined in hypothesis $H_{A-11}$ and sub-hypotheses $H_{A-11a}$, $H_{A-11b}$, $H_{A-11c}$. Cox Proportional Hazards regression showed that the predisposing variables of age, race and obesity did not affect the time to progression of metastatic disease. Elderly was defined three different ways: ≥65 years, ≥75 years, and as a continuous variable. Obesity was defined three different ways: BMI > 30, BMI > 40 and as a continuous variable (Table 20). In a multivariate Cox Proportional Hazards regression model including significant

values for the healthcare system variable (academic compared to community setting), the external environment variable (region of the country), and the predisposing variables (age, race and obesity), no significant values were found (Table 21).

### v. Analysis of research hypotheses $H_{A-12}$

The relationship between the needs variables (comorbid conditions, history of cardiac disease and hormone receptor status) and the time to progressive disease was examined in hypothesis $H_{A-12}$ and sub-hypotheses $H_{A-12a}$ and $H_{A-12b.}$ Univariate logistic regression showed that there is no relationship between the needs variables of comorbid conditions or history of cardiac disease and time to progressive disease. Hormone receptor status, however, did significantly affect time to progressive disease ($p=0.034$), both limits of the 95% confidence interval were less than one (95% CI:[0.688, 0.986]) consistent with statistical significance. People in the ER/PR positive group had a reduced risk of having progressive disease than their ER/PR negative counterparts with a hazard ratio of 0.824 (Table 20). In a multivariate Cox Proportional Hazards regression model including values for the healthcare system variable (academic compared to community setting), the external environment variable (region of the country), and the predisposing variables (age, race and obesity), hormone receptor status continued to significantly affect time to progressive disease (Table 21). Figure 5

shows the Kaplan-Meier failure estimates. As depicted by this graph, those who are ER/PR negative fail faster than those who are ER/PR positive.

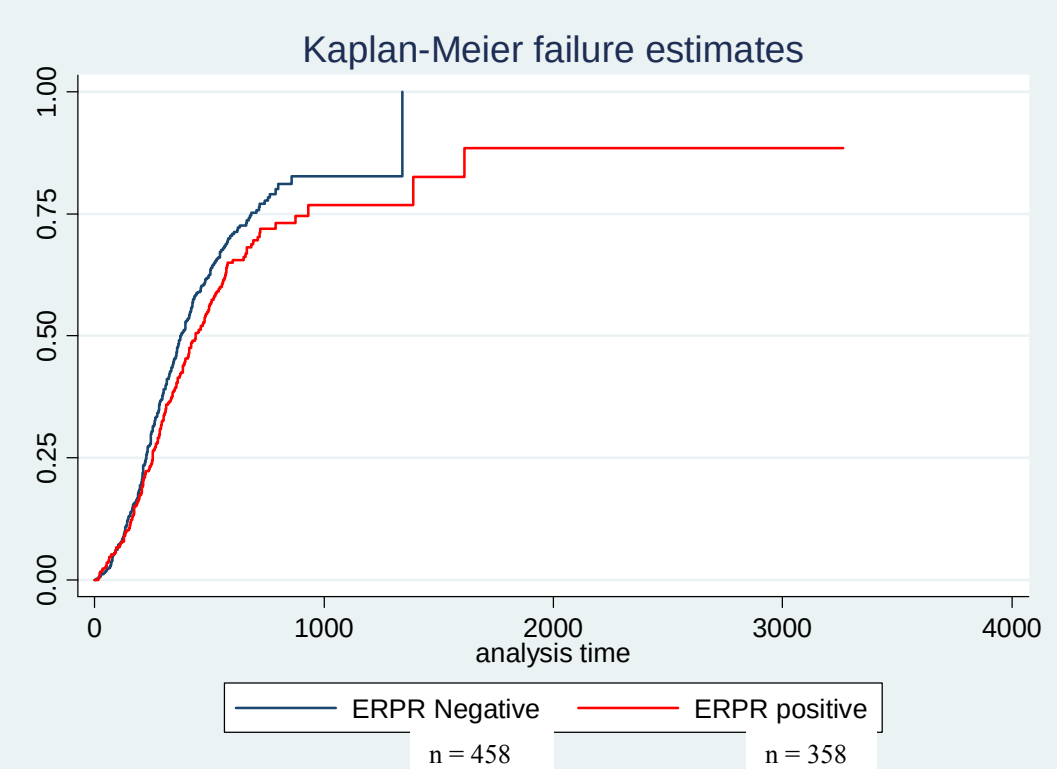
**vi. Interactions for Model I-4**

Interactions for Aim 3 were not evaluated since there was only one significant variable found (ER/PR status).

**vii. Additional Analyses**

Additional analyses were run to further explain the time to progression outcome variable. Figure 5 depicts the Kaplan-Meier (KM) failure estimates for hormone receptor status. Those that were ER/PR negative had a faster rate of failure than those who were ER/PR positive.

Figure 5. Kaplan-Meier Failure Estimates for Hormone Receptor Status




When those that were ER/PR positive were analyzed separately for time to progression, those who received antibody had a hazard ratio of 1.036 indicating that they progressed at about the same rate as those who had not received antibody (Table 22). This finding was not significant (p=0.801). Figure 6 depicts this with virtually overlapping KM curves.

**Table 22.** Cox Proportional Hazards Model for Aim 3 and the Need Variable (Hormone Status) for ER/PR Positive Participants Only

| | Number of observations | LR chi2 | Prob > chi2 | Haz. Ratio | Std. Err. | z | P>z | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| **Received Antibody** | 353 | 0.6 | 0.801 | 1.036 | 0.145 | 0.25 | 0.801 | 0.787 | 1.364 |

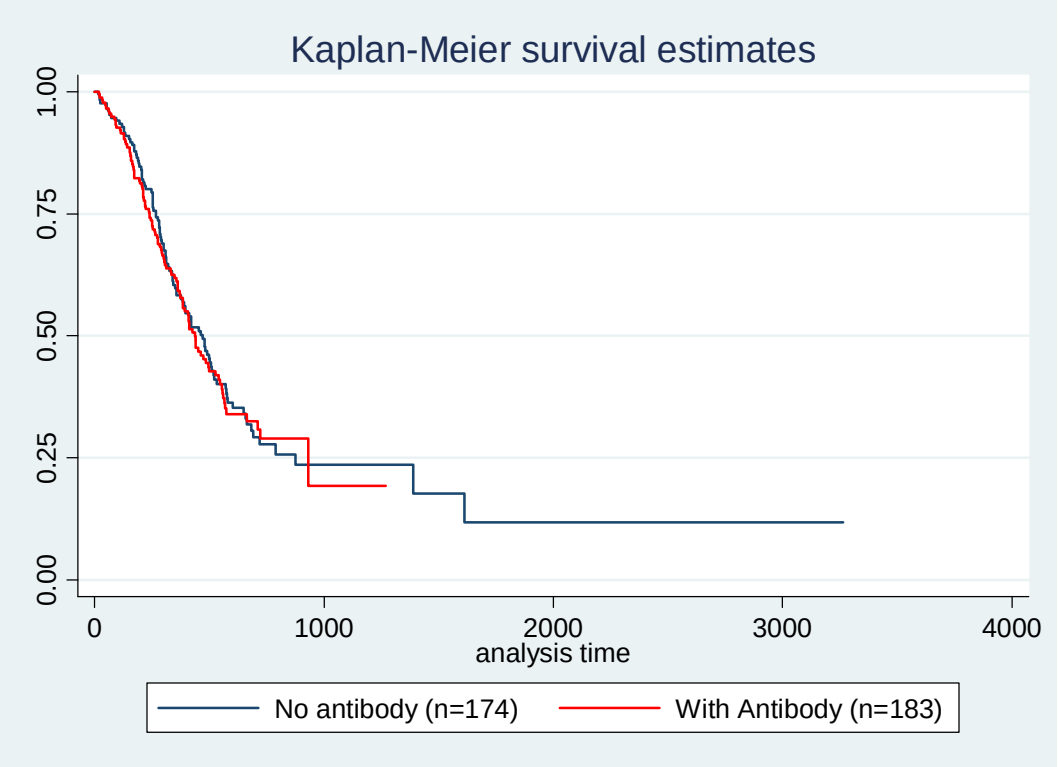
*n=174 patients received no antibody, n=183 patients received antibody

Table 23 describes all significant outcomes for Aims 1, 2 and 3.

Table 23. Results for Aims 1, 2 and 3

| | Aim 1 Odds Ratio | Aim 2 Odds Ratio | Aim 3 Hazard Ratio |
|---|---|---|---|
| ***Healthcare System*** | | | |
| Treatment Setting | 1.594* | 0.924 | 1.203 |
| ***External Environment*** | | | |
| Midwest | 1.335 | 1.057 | 1.119 |
| Northeast | 1.005 | 0.789 | 1.181 |
| Southwest | 0.950 | 0.873 | 1.211 |
| West | 1.024 | 0.662 | 0.935 |
| ***Predisposing Characteristics*** | | | |
| Black | 0.927 | 1.201 | 1.187 |
| Hispanic | 0.681 | 0.736 | 1.285 |
| Other | 1.404 | 1.975 | 0.940 |
| Elderly ≥75 | 0.531* | 0.90 | 1.432 |
| Obesity | 0.954 | 1.031 | 0.997 |
| ***Need*** | | | |
| ER/PR Positive | 0.308* | 1.197 | 0.828* |
| Comorbid Conditions | 1.301 | 1.161 | 0.954 |
| | | | |
| * p≤ 0.05, multivariate | | | |
| | | | |
| N | 1010 (except 809 for ER/PR positive) | 961 (except 768 for ER/PR pos) | 1007 (except 805 for ER/PR positive) |

Figure 6. Kaplan-Meier Survival Estimates for those that are ER/PR positive and treated with antibody compared to no antibody



# CHAPTER VI. DISCUSSION AND CONCLUSIONS

## A) Sub-study I: Antibody Use

The clinical benefit from the use of the monoclonal antibody trastuzumab in the treatment of HER2 positive MBC is well established (Osoba, Slamon, Burchmore & Murphy, 2002). However, retrospective trials in breast cancer have demonstrated a trend in the underutilization of optimal therapy in certain groups including the elderly (Freyer et al., 2006), those of different racial and ethnic backgrounds (Avanian et al., 1993; Bickell et al., 2000; Li et al., 2003; Stevenson-Perez, 1998; Voti et al., 2006), obese women (Wee et al., 2000), those from different regions of the country (Nattinger, 1992), those treated in a community setting (Chaudhry et al., 2000), those with comorbid conditions (Maskarinec et al., 2003) and those with hormone positive disease (Brufsky et al., 2005). This study evaluated each of these groups in relation to the use of trastuzumab and found that overall, 35% of the women in this study did not receive trastuzumab in the course of their treatment for MBC. This finding adds to the growing body of literature demonstrating sub-optimal use of antibodies.

The Andersen model was used as the conceptual framework in this study to examine the relationship between use of antibody therapy and a variety of

predictor variables. Specifically, the use of the antibody trastuzumab to treat HER 2 positive MBC was hypothesized to be a function of their healthcare system, external environment, predisposing characteristics and their need variables. Each of these four components was hypothesized to make an independent contribution to the understanding of differences in use of the antibody. It was also hypothesized that the effects of the healthcare system and external environment would be modified by the introduction of predisposing characteristics and need variables would further modify the effects of the healthcare system, external environment and predisposing characteristics. Accordingly, predictors included in this study were grouped as healthcare system, external environment, predisposing and need variables, and their effects on use of monoclonal antibodies were tested through hierarchical models. The results showed Andersen's model could be applied to 1) guide selection of important predictor variables, and 2) explain a portion of the variance in the use of monoclonal antibody therapy. There were four factors associated with use of monoclonal antibody therapy in this study. Age $\geq$ 75 years, the treatment setting of the participant (academic or community), hormone receptor status (ER/PR positive), and a history of cardiac disease all were significant factors for the use of monoclonal antibody therapy. However, in multivariate analysis, only the first 3 were independent predictors.

The elderly participants who were age ≥ 75 years were 52% less likely to receive monoclonal antibody therapy than their younger counterparts, after adjustment for other covariates (Table 10). As noted in the literature review, studies typically have evaluated patient groups over 65 or over the 75 year mark. Being elderly should not be a basis for a treatment decision; however, it seems that it is in the case of HER2 positive disease in the RegistHER database.

The treatment setting of the participant was also significant. Those treated in an academic setting were 85% more likely to receive monoclonal antibody therapy than those treated in a community setting, after adjustment for other covariates (Table 10). Reasons for this are unclear, although one could speculate that cost may be more of an issue in the community setting and the financial situation of a community practice may indeed dictate treatment choices. Another factor could be comfort level with newer therapies. Oncologists that practice in academic settings may be more used to a broader group of therapies due to access to these modalities in clinical trials so may be more likely utilize newer therapies including monoclonal antibodies with their patients.

Interestingly, hormone receptor status of the participant also made an impact. Participants that were ER/PR positive were 69% less likely to receive antibody therapy than those that were hormone receptor negative, after adjustment for other

covariates (Table 10). Having positive estrogen and progesterone receptors makes the individual with breast cancer eligible for an additional type of therapy (hormone therapy) but should not make the patient ineligible for monoclonal antibody therapy. As mentioned earlier, treatment with trastuzumab in the setting of HER2 positive ER/PR positive MBC is efficacious. It is difficult to discern why patients in this group were not offered this therapy. Perhaps there is a perception that trastuzumab is not indicated in this setting or that only hormones or chemotherapy are efficacious.

Not surprisingly, having a history of cardiac disease decreased risk of receiving antibody therapy (57% less likely to receive trastuzumab). Given the increased risk of cardiac toxicity with this treatment, it is probable that many of these individuals did not qualify for antibody administration based on cardiac function tests. In the multivariate model, however, history of cardiac disease was not significant when the variables of age, HR status and treatment setting were added. It is unclear why it was no longer significant. Exploratory analysis of participant number per group was done in Tables 12, 13 and 14 which showed it is unlikely due to the sample size in each group.

Interestingly, none of the other variables affected use of antibody therapy. It was hypothesized that all of the variables, including region of the country, race,

obesity, and comorbid conditions would; however, they did not. Given the number of studies that have found race to be a factor in poorer outcomes, it was refreshing to see that in this study in the evaluated population, race did not affect use of optimal therapy.

**B) Sub-study II: Time to treatment**

Timely initiation of treatment for MBC has been an issue in numerous studies (Gorin et al., 2006; Jones, 1999). Conflicting data vary on the importance of initiation of treatment within a certain time period ranging from 1-3 months. In the RegistHER database, 26% of patients did not start therapy within 30 days of diagnosis of HER2 positive MBC.

Andersen's model was adopted as the conceptual framework to analyze the relationship between time to start of treatment and a variety of predictor variables. Similar to the findings on the use of monoclonal antibody therapy, the model provided theoretical guidance in selection of predictor variables to explain differences in the time to treatment in HER2 positive MBC. However, only a small percentage of the overall variation in the time to treatment was explained by Andersen's model. This may reflect that time to treatment is a more complex health service utilization phenomenon, and the application of Andersen's model is of limited use in this scenario. The one variable that trended toward significance

in univariate analysis was the region of the country (West, p=0.08). It is possible that with more participants, region of the country would have been a factor in discerning if patients are treated in a timely manner. No other variables were significant indicating that race, age, obesity status, treatment setting, hormone receptor status and the presence of comorbid conditions did not affect time to start of treatment in this sample of patients from the RegistHER database. Given the importance of timely treatment for MBC, it was promising to see that none of the variables evaluated in this analysis affected time to start of treatment.

**C) Sub-study III: Response to treatment**

Response to treatment is an important outcome indicator in oncology. The first incidence of progressive disease measured in days indicated a negative outcome for this study. A significant relationship was found between time to progression of disease and hormone receptor status. Those who were ER/PR positive had a reduced risk of having progressive disease than their ER/PR negative counterparts (HR =0.824, p= 0.034, CI = 0.688 to 0.986) (Table 21 and Figure 5). The confidence interval is very narrow so the estimate is likely precise. It was not surprising that those with ER/PR positive disease did better than those that were ER/PR negative since those that have HR negative disease typically have a poorer prognosis than their HR positive counterparts. An unplanned sub-analysis showed that those who where ER/PR positive and received antibody had a hazard

ratio of 1.036 when compared to those who received no antibody indicting that there was no impact of antibody use in this subpopulation (p=0.801) (Table 22 and Figure 6). The confidence interval was fairly wide so further investigation is needed before any conclusions can be drawn.

The treatment setting in which the participant was seen approached significance (p=0.071) with those treated in an academic center having reduced risk of progressive disease compared to their counterparts treated in a community setting (HR = 1.203, CI 0.984 to 1.470). The relationship between progression of disease and age with patients older than ≥ 75 years approached significance (p=0.092) with those ≥ 75 years having increased likelihood of progression compared to their younger counterparts (HR = 1.306, CI 0.958 to 1.781). Similarly, the relationship between progression of disease and obesity approached significance (p=0.092) with obese participants being more likely to have progressive disease than their non-obese counterparts (HR = 1.147, CI 0.978 to 1.345). Given these trends and the wide confidence intervals found, further work is needed to rule out age, obesity and setting as predictors of this outcome.

**D) Fit with the Andersen Model**

The Andersen Conceptual Framework was very helpful in categorizing groups for this evaluation of RegistHER looking at health disparities. Because of its focus on the individual versus the family unit, it was easy to use the groups defined by the registry with the groups defined by the Andersen model. Additionally, because of the focus of this model on the multiple influences on health services' use and health status, it was a good fit with this analysis. The environmental factors of the health care system (setting in which the person was treated – academic versus community) and the external environment (region of the country in which they lived) were critical factors to evaluate based on the literature review. The population characteristics including the person's predisposing characteristics (race, age and obesity status) as well as their need variables (hormone receptor status, comorbid conditions and history of cardiac disease) were also key variables for this evaluation based on the investigator's clinical experience as well as previous research that was performed.

A limitation of using this model for this analysis was the limited data that were available in some of the categories. For instance, there was no information on the personal health practices of participants in the registry or their use of health care services, their perceived health status, or their satisfaction with services provided. Additionally, there was no information for the enabling resources category which

would have included the family and community resources that were available as well as access to those resources.

Other models were evaluated for use in this analysis but none were as good of a fit for various reasons. Many health disparities models focus on the family as the unit and since the data in the registry was on individuals, these models were not a fit. Other models, such as the Planned Care Model, focused on the health care practice, and since minimal information was available on the practice setting, these models were also not a good fit with this analysis (Wagner et al., 1996). The Andersen model was a useful tool to better understand health behavior.

**Summary**

There are some interesting findings from this study regarding use of optimal treatment in women with HER2 positive MBC. This study showed no difference in use of optimal treatment in participants based on region of the country, race, obesity status or comorbid conditions. Differences in these groups might be seen given larger sample sizes. There were differences seen with multivariate analyses in individuals treated in different settings (academic or community), the elderly (≥ 75 years), and those that are ER/PR positive.

The one variable that was significant for both use of optimal treatment and evaluated time to progression was HR status. Participants that were HR positive for ER and PR were treated with antibody therapy less often than their ER/PR negative counterparts. Reasons for lack of use of optimal treatment in this group are unclear but suggest an educational need for providers. Although these women are eligible for treatment with hormones, consideration should be given to concurrent or sequential treatment with antibody therapy in those women that are HER2 positive.

The other interesting finding in this group was that those who were ER/PR positive had a reduced risk of having progressive disease compared to their ER/PR negative counterparts. An unplanned sub-analysis showed that when you look at those who are HR positive and compare those who got antibody to those that did not get antibody, the rates of progressive disease were nearly identical in the two groups. It is unclear if a longer time to disease progression would be seen in the antibody treated group if a larger sample size was used.

One surprising finding from this study was that so few of the variables affected outcomes. When reflecting on why this could be the case, a number of possibilities come to mind. Oncology drug development has been a dynamic area for decades, and it is possible that the oncology community embraces new

research findings and novel treatments for their patients. It is possible that the level of awareness of the healthcare community as well as individuals with cancer is high and the use of new treatment modalities is quickly embraced. It is also possible that given the remarkable efficacy of this drug in this specific population of women with HER 2 positive MBC, that programs were set up by the company who developed the drug to allow access to those in need but who do not have insurance or could not afford the treatment. It is also possible that clinicians who participated in RegistHER are more progressive as evidenced by their participation in research and more willing to embrace newer therapies. Whatever the reason, it was great to find that in most cases, participants in RegistHER received optimal treatment.

## E) Strengths and Limitations

*Strengths*

High participation and minimal patient loss to follow-up were key strengths of this registry. The data set is a strength. Only 4% (44/1031) of patients were lost to follow-up for reasons other than death and only 3% (33/1071) of patients screened for enrollment chose not to participate in the study. Several factors played a role in the extraordinary levels of initial and ongoing participation in this

study. Having a convenient and simple electronic data capture system for data collection encouraged and maintained site participation. Newsletters and periodic meetings that brought together staff from each of these sites helped maintain interest in the study. Initial site training and establishment of an ongoing helpline for the sites reduced data errors and ensured that the data collected was of high quality.

*Limitations*

As with any secondary data analysis, data points to be collected for this study were predefined and missing some key demographic data. It would have been valuable to examine other contributing factors besides race and ethnicity including socio-economic status, health insurance status, employment status, language barriers, education level and marital status of the participants in the study. It would also have been interesting to include other ethnic groups in the study if there was better representation in the sample. Additionally, in this study comorbidities were evaluated as a group (aside from cardiac disease) but in future studies it might be interesting to evaluate comorbidies individually to see if there was an impact on use of optimal therapies. The Andersen model also includes outcomes of perceived health status and consumer satisfaction, so it would have been interesting to look at these additional outcomes as well. As this is a very

large database of HER2 positive women, findings from this study can direct the development of prospective future studies.

Additionally, the participating clinical sites may not be completely representative of all sites, and there is the potential that participants may represent healthier patients who received better care. Additionally, the presence of selection bias cannot be completely ruled out. Since women at participating sites may be more likely to participate in research, participants recruited at those sites may not be completely representative of women with MBC across the country. These factors could reduce the generalizability of the results to all HER2 positive MBC patients.

Given the large numbers of patients enrolled and the diversity in geographic region and practice types, it is less likely that this study population represents an unusual subset of HER2 positive MBC patients. In fact, compared with expected distribution of breast cancer cases across the U.S. based on estimates from the American Cancer Society, the geographic distribution of HER2 positive MBC patients in RegistHER was reasonably comparable (see Table 7). However, there were more patients in RegisterHER from the Southeast and Midwest and fewer

from the Southwest and West compared to the ACS data. This is likely due to the presence of personnel in these areas to recruit participation in the study and the willingness of the investigators to participate from the various regions of the country signaling biased representation.

Additionally, due to the nature of observational data, this study is limited in its ability to establish any causal relationship. Therefore, no causal relationship can be proven between factors associated with the use of monoclonal antibody therapy and time to start of therapy for HER2 positive MBC. Similarly, this study was not able to prove any causal relationship between use of time to progression and the previously stated predictors.

**F) Implications for nurses and recommendations for future research**

This study examined the use of monoclonal antibody therapy and time to treatment of HER2 positive MBC and time to progression of disease. Andersen's model was successfully applied in this study as a conceptual framework. The predictor variables were hypothesized to be the healthcare system, external environment, predisposing variables and need variables. These variables were

hypothesized to be associated with the use of monoclonal antibodies, the time to treatment, and progression of disease.

A number of variables did not influence the use of optimal treatment or response to treatment including the region of the country in which the participant lived, their race, obesity status, or whether or not the individual had comorbid conditions. In this evaluation of RegistHER, these groups were treated the same as their counterparts. Having a history of cardiac disease was significant in univariate analysis but for unknown reasons was not significant in multivariate analysis with other significant predictors.

When optimal treatment with monoclonal antibody therapy was evaluated, it became evident that education regarding the use of this therapy in special populations is needed. These populations include the elderly (≥75 years) and those with ER/PR positive disease. For unknown reasons, these populations are not receiving standard of care as often as others. Accordingly, investigation into why and education of healthcare providers may help to eliminate this disparity. As was noted in the literature review, it seems that elderly patients often times do not get the therapies they need based solely on their age. Although it was not shown in the analysis of this registry, suboptimal treatment in this group could have an effect on outcomes.

In the case of those with ER/PR positive disease, it is again unclear why this group is not getting optimal treatment for their HER2 positive disease. Further exploration into the reasoning behind why and education of healthcare providers could impact frequency of use of optimal treatment and ultimately outcomes in this group.

Additionally, barriers to use of antibody therapy in community settings should be evaluated. It is unclear whether the disparity in monoclonal antibody use is an access issue related to finances or an educational issue related familiarity with monoclonal antibodies. Exploration into whether or not there are system or process issues with access to particular therapies should be explored. As stated above, education of healthcare providers as to the importance of use of optimal therapy is critical.

To answer the remaining questions above and to explore areas of the Andersen model that were not evaluated in this analysis, follow-up studies should be conducted. Any further studies should include not only the variables evaluated in this analysis but also contributing factors from the Andersen model such as socio-economic status, health insurance status, employment status, language barriers, education level and marital status of the participant in the study. Since the

Andersen model includes outcomes of perceived health status and consumer satisfaction, it would be interesting to look at these additional outcomes as well in future studies. Ideally, a prospective longitudinal study evaluating the multiple influences on health status and access to health services would be beneficial so that specific interventions can be targeted to gain a better understanding of health behavior and ultimately inform health policy.

RegistHER, a registry with the largest cohort of HER2 positive metastatic breast cancer patients followed to date, is important because it provides a unique opportunity to characterize treatment patterns in this subset of individuals with breast cancer. In this evaluation of this database, important information regarding use of optimal treatment and evaluated health status of women with HER2 positive MBC was described. These findings may guide clinical decision-making for healthcare providers and their HER2 positive MBC patients and ultimately improve outcomes.

## Appendix 1: IRB Notification

Date: Fri, 16 May 2008 15:04:14 -0500 (CDT)
From: irb@umn.edu
To: gall0097@umn.edu
Subject: 0805E32261 - PI Gallagher - IRB - Exempt Study Notification

The IRB: Human Subjects Committee determined that the referenced study is exempt from review under federal guidelines 45 CFR Part 46.101(b) category #4 EXISTING DATA; RECORDS REVIEW; PATHOLOGICAL SPECIMENS.

Study Number: 0805E32261

Principal Investigator: Eva Gallagher

Title(s):
Factors Affecting Treatment Choice in HER2+ Breast Cancer

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This e-mail confirmation is your official University of Minnesota RSPP notification of exemption from full committee review. You will not receive a hard copy or letter.
This secure electronic notification between password protected authentications has been deemed by the University of Minnesota to constitute a legal signature.

The study number above is assigned to your research. That number and the title of your study must be used in all communication with the IRB office.

If you requested a waiver of HIPAA Authorization and received this e-mail, the waiver was granted. Please note that under a waiver of the HIPAA Authorization, the HIPAA regulation [164.528] states that the subject has the right to request and receive an accounting of Disclosures of PHI made by the covered entity in the six years prior to the date on which the accounting is requested.

If you are accessing a limited Data Set and received this email, receipt of the Data Use Agreement is acknowledged.

This exemption is valid for five years from the date of this correspondence and will be filed inactive at that time. You will receive a notification prior to inactivation. If this research will extend beyond five years, you must submit a new application to the IRB before the study's expiration date.

Upon receipt of this email, you may begin your research. If you have questions, please call the IRB office at (612) 626-5654.

You may go to the View Completed section of eResearch Central at http://eresearch.umn.edu/ to view further details on your study.

The IRB wishes you success with this research.

## Appendix 2: Correspondence Regarding Conflict of Interest

---------- Forwarded message ----------
From: "bexxx001" <bexxx001@umn.edu>
To: <gall0097@umn.edu>
Subject: RE: Factors Affecting Treatment Choice in HER2+ Breast Cancer--conflict question
Date: Fri, 16 May 2008 14:55:28 -0500

Thank you, Eva. This looks fine.
I will notify the IRB not to hold this for conflict review.
Meg

-----Original Message-----
From: gall0097@umn.edu [mailto:gall0097@umn.edu]
Sent: Thursday, May 15, 2008 4:05 PM
To: Meg
Subject: Re: Factors Affecting Treatment Choice in HER2+ Breast Cancer--conflict question

Hi Meg,
Thanks so much for your email. I am a PhD student at the U of MN and also am an employee of Genentech, the owner of the database I am using for my thesis. I don't see any direct conflict of interest as I do not see a direct benefit to Genentech from the outcomes of this study but I wanted to make sure that all are aware that I am an employee of the company.

Please let me know if I can provide any additional information.

Thank you!

Eva

On May 14 2008, Meg wrote:

Hello Eva:
I am writing from the Office of Regulatory Affairs as I am in charge of conflict of interest management at the U of M and received the email below from the IRB informing me of a potential conflict of interest disclosure you made on your application "Factors Affecting Treatment Choice in HER2+ Breast Cancer".

Will you please provide me with additional information about why you believe you have a conflict with this research?
Your IRB application can not be approved until I notify them that your potential conflict is managed, if necessary.
Thanks so much in advance for your response.
Meg

Meg Becker Adson

Associate Director
Office of Regulatory Affairs
612.625.5488
Bexxx001@umn.edu

From: Rachel Blixt [mailto:blix0009@umn.edu]
Sent: Wednesday, May 14, 2008 10:17 AM
To: bexxx001@umn.edu
Subject: Exempt Study COI?

Hi Meg,

I received this application info---
Study: 0805E32261
PI: Gallagher, Eva M
Status: Active
Title: Factors Affecting Treatment Choice in HER2+ Breast Cancer

The PI indicates she has a conflict of interest, but she says she hasn't disclosed it.
Thanks! Rachel

Rachel Blixt
Exempt Research Administrator, IRB
Research Subjects' Protection Programs
University of Minnesota
420 Delaware Street SE MMC 820
Minneapolis, MN 55455

612-625-9186 (direct line and voicemail)

612-626-5654 (RSPP reception)
612-626-6061 (fax)
blix0009@umn.edu
http://www.research.umn.edu/subjects

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