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Meta-analysis of Lapatinib plus Capecitabine versus Capecitabine in the Treatment of HER2 Positive Breast Cancer

Lynda Smith
St. Cloud State University

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Meta-analysis of Lapatinib plus Capecitabine versus Capecitabine in the Treatment of HER2 Positive Breast Cancer

by

Lynda Kay Smith

A Thesis
Submitted to the Graduate Faculty of
St. Cloud State University
in Partial Fulfillment of the Requirements
for the Degree of
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Shiju Zhang, Chairperson
Joyce Simones
David Robinson
Abstract

BACKGROUND:

Breast cancer is the most common type of cancer in women despite advances in research and detection methods. Approximately 25 to 30 percent of newly diagnosed cases of breast cancer will overexpress HER2, human epidermal growth factor receptor 2, and are at a greater risk for disease progression and poorer clinical outcomes. The traditional treatment is associated with irreversible cardiac dysfunction. An alternative treatment involving lapatinib plus capecitabine has been reported in some randomized controlled clinical trials comparing treatment outcomes. To quantify the effectiveness of lapatinib plus capecitabine combination therapy versus capecitabine monotherapy in treating metastatic breast cancer, a systemic review seems necessary. In this thesis, meta-analysis was performed to synthesize the ratio of the odds of patient death or disease progression for breast cancer patients who are treated with a combination therapy to the odds for patients who are treated with monotherapy.

METHODS:

Several randomized clinical trials are identified comparing combination therapy lapatinib plus capecitabine versus capecitabine monotherapy in women with metastatic HER2 positive breast cancer that had disease progression after treatment with regimens that included an anthracycline, a taxane, and trastuzumab. Patients in the treatment arm received lapatinib dosed at 1,500 mg per day continuously plus capecitabine 2,000 mg per square meter of body surface area on days 1 through 14 of a 21 day cycle. Patients in the control arm received capecitabine at a dose of 2,500 mg per square meter of body surface area on days 1 through 14 of a 21 day cycle. Mantel–Haenszel fixed effect meta-analysis was used to combine the data to evaluate frequency
of the events between combination therapy and monotherapy treatments in a heavily pre-treated metastatic breast cancer population.

CONCLUSION:

Three eligible clinical trials were identified, reporting outcomes on 1,131 women. Mantel–Haenszel fixed effect analysis showed the event occurred 26.7 percent less frequently for women treated with combination lapatinib plus capecitabine (odds ratio [OR], 0.733; 95 percent confidence interval [CI], 0.565 to 0.952) than patients treated with capecitabine monotherapy. The use of lapatinib plus capecitabine should be evaluated in clinical trial for newly diagnosed HER2 positive patients or older patients who might otherwise be exposed to potential serious adverse side effects as a result of the current first line treatment or patients that have a pre-existing heart condition.
Acknowledgements

I dedicate my thesis work to my family who has taught me to apply an immense amount of work for the things that I aspire to achieve while continually offering love and support. I will appreciate all they have done; you are my best cheerleaders. A special gratitude to my sibling, Pamela, Janice, Sharon, Scott, Andrea, and Jenny, whose support and words of encouragement kept me motivated and driven to succeed.

To my mother, Marion, though absent, you are ever near, still missed, still loved, and ever dear. Your memory is my gift with which I’ll never part. I have you forever in my heart.
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Chapter I: INTRODUCTION

Breast cancer is the most common type of cancer in women despite advances in research and detection methods. Breast cancer is the second most common cancer in the world, and by far the most frequent cancer among women with an estimated 1.67 million newly diagnosed cases in 2012 resulting in over 400,000 deaths worldwide (World Health Organization, 2015). Public health data suggests that the global burden of breast cancer in women, measured by incidence and mortality, is substantial and on the rise. There is an increasing number of global health initiatives to address breast cancer including efforts by Susan G. Komen for the Cure ©, the Breast Health Global Initiative, the U.S. Centers for Disease Control and Prevention, the American Cancer Society, the National Cancer Institute, and ongoing work by leading oncology societies in different parts of the world.

In the United States an estimated 234,190 (2,350 men and 231,840 women) will be diagnosed with breast cancer; and, an estimated 40,730 (440 men and 40,290 women) will die from breast cancer in 2014 (Jemal, Siegel, Xu & Ward 2014). Approximately 25 to 30 percent of newly diagnosed cases of breast cancer will overexpress HER2, human epidermal growth factor receptor 2, and are at greater risk for disease progression and poorer clinical outcomes (Geyer et al. 2008; Cameron et al. 2010). The HER proteins are transmembrane receptors which regulate: cell growth, survival, adhesion, migration, and differentiation (Hudis, 2007). In some breast cancers, HER2 is over-expressed and causes breast cells to reproduce uncontrollably.

In 1998, the FDA approved: doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab as first-line treatment for women with HER2 positive breast cancer. This first line treatment for naïve HER2 positive breast cancer showed biological activity in controlling breast cancer growth. The chemotherapy regimen is abbreviated as AC→TH followed by H maintenance for 1
year. The A refers to Adriamycin® (doxorubicin, Ben Venue Laboratories, Inc., Bedford, OH), the C refers to Cytoxan® (cyclophosphamide, Bristol-Myers Squibb, New York, NY), the T refers to Taxol® (paclitaxel, Bristol-Myers Squibb, New York, NY), and H refers to Herceptin® (trastuzumab, Genetech, San Francisco, CA).

Unfortunately, this treatment regime is associated with irreversible cardiac dysfunction which can develop into congestive heart failure (CHF) that can manifest at any time during treatment and may also occur years and possibly decades after treatment has completed (Bowles et al., 2012). A retrospective study of 12,000 women who received breast cancer treatment between 1999 and 2007 reported that patients who received chemotherapy agents such as: anthracyclines and trastuzumab have a 20 percent increased risk of developing congestive heart failure within five years after finishing chemotherapy (Bowles et al. 2012; Pinder, Duan, Goodwin, Hortobagyi & Giordano, 2007). Nevertheless, the side effect profiles of the chemotherapy agents, especially when used in combination, must be factored into treatment decision to maximize quality of life and prolonging patient survival. This is of particular importance to breast cancer survivors because the development of congestive heart failure is more pronounced in older patients and females.

Patients that have disease progression or reoccurrence following treatment with: anthracycline, a taxane, and trastuzumab have limited treatment options available due to a lack of other HER2 antagonists. The data is pooled from HER2 positive metastatic or advanced breast cancer clinical trials of combination therapy of lapatinib plus capecitabine versus capecitabine monotherapy. In this thesis, meta-analysis was performed to synthesize the ratio of the odds of patient death or disease progression for breast cancer patients who are treated with a combination therapy to the odds for patients who are treated with monotherapy.
Chapter II: LITERATURE REVIEW

The scientific advancement in treatment of breast cancer is as varied as the history of breast cancer. In understanding the significant side effects that chemotherapy drug(s) pose to the patient, one is required to comprehend the significance of the treatment options available to women who have been diagnosed with breast cancer.

History of Breast Cancer

The history of breast cancer is unique. This type of cancer can be seen by the naked eye as a result of the transformation of the breast structure. The treatment option for women diagnosed with breast cancer begins with a journey through the history of medicine.

The ancient Greek physician Hippocrates, the founder of Western Medicine, in 460 B.C. reported the earliest documented case of breast cancer. He noted that women developed hard lumps in their breast tissue which would swell and turn black. Hippocrates theorized that the women suffered from a humoral disease, a systemic imbalance of the humors (blood, phlegm, yellow and black bile) resulting in illness and death (Random History, 2008).

A major advancement of medicine occurred in the late 1700s when Dr. Henri Le Dran proposed that breast cancer was a single-site disease which surgery alone could cure (Random History, 2008). Since the patient was not anesthetized, the need for quickness, and not surgical skill, left women with horrible disfigurements of the chest wall. The women endured chronic pain and swelling in the arms from impaired lymphatic circulation (Random History, 2008).

The introduction of anesthesia in the mid-1800s allowed surgeons to have more time to skillfully remove the breast tissue. The radical mastectomy was introduced by Dr. William Halstead. A radical mastectomy, more commonly called, a bilateral radical mastectomy in modern terms, is the complete removal of: both breasts, both pectoral chest muscles (major and
minor) and the axillary lymph nodes in a single surgical procedure (Donegan & Spratt, 2002). The radical mastectomy was gold standard in the treatment of breast cancer for 100 years until the development of chemotherapeutic agents in the mid-1900s (Random History, 2008). Unfortunately, women still endured chronic pain and swelling following the surgery.

In 1955, Dr. George Crile argued that breast cancer was a systemic disease and argued against the radical mastectomy indicating the procedure as too invasive and unnecessary. He proposed a more conservative mastectomy that only removed the breast cancer and some of the surrounding tissue but not the entire breast. The hormone estrogen receptor was also identified during this time period and became a useful tool in classifying breast cancer.

The introduction of radiotherapy, hormone therapy, and chemotherapy in the 1970s improved the survival chance of some women; however, a large majority of women still died from the disease (Donegan & Spratt, 2002). In 1980s, researchers identified a receptor that was over-expressed in some breast cancer; the HER2 receptor. This was recognized as a cancer distinguisher, useful in staging and categorizing various breast cancers. The correlation between the estrogen receptor and HER2 status was not fully understood until the development of chemotherapy drugs and hormone antagonists which could block or inhibit the specific receptors. The current knowledge of HER2 positive and estrogen receptor status is what medical oncologists and researchers are using to develop new chemotherapy treatments in the search of a cure for breast cancer.

A journey through the history of breast cancer has shown that as medical knowledge has increased; the treatments and surgical options available to women have advanced; the survival outcome of this deadly disease has improved. The national awareness which breast cancer has received in the past two decades has increased funding, both privately and nationally, in hopes of
finding a cure. The efforts by organizations like Susan G. Komen for the Cure © and highlighting October as National Breast Cancer Awareness Month has taken breast cancer out of the closet and into the living rooms of the American household. The treatment options available for women in the twenty-first century are a vast improvement than what was offered in Hippocrates’ time.

**Chemotherapeutic Agents**

A discussion of the drugs utilized and the significant side effects is needed to comprehend the potential risks women accept when starting chemotherapy treatment. The following drugs are commonly used in the first line treatment for metastatic breast cancer: Adriamycin® (doxorubicin, Ben Venue Laboratories, Inc., Bedford, OH), Cytoxan® (cyclophosphamide, Bristol-Myers Squibb, New York, NY), Taxol® (paclitaxel, Bristol-Myers Squibb, New York, NY), Herceptin® (trastuzumab, Genetech, San Francisco, CA), lapatinib (Tykerb® or Tyverb®, GlaxoSmithKline, Research Triangle Park, NC), and capecitabine (Xeloda®, Roche, San Francisco, CA).

Doxorubicin mode of action is to impede the DNA topoisomerase which repairs damaged DNA and generating free radical that cause damage to the cell membrane, DNA, and proteins. Doxorubicin is associated with irreversible cardiac dysfunction. Cardiac dysfunction is defined as any alteration in the normal function of the heart. Cardiac dysfunction can occur at any dose of doxorubicin which can manifest as the potentially fatal congestive heart failure (CHF) occurring at any time during therapy, even months to years after termination of treatment (Adriamycin [package insert]. Bedford, OH: Ben Venue Laboratories, Inc.; 2006).

Cyclophosphamide and paclitaxel are two chemotherapy agents are not associated with life threatening side effects, but they are still cytotoxic agents. Cyclophosphamide crosslinks DNA
strands by the addition of an alkyl group of guanine which inhibits DNA replication leading to cellular apoptosis. Paclitaxel stabilizes the microtubules preventing disassembly during cell division stopping the cell life cycle. Cyclophosphamide and paclitaxel are associated with myelosuppression (also known as bone marrow suppression). Myelosuppression is a condition in which bone marrow activity is decreased resulting in fewer red blood cells, white blood cells, and platelets. Prolonged myelosuppression can result in bacterial, fungal, or viral infections that can delay treatment. Myelosuppression is dose related and normally resolves upon a dose reduction or termination of treatment.

Trastuzumab is a human monoclonal antibody which targets the extracellular domain of the HER2 receptor that inhibits the phosphorylation of key proteins needed to regulate the cell life cycle. The breast cancer cells that have been treated with trastuzumab induce immune cells to kill the cancer cell. The antibody-dependent cell cytotoxicity is an important mechanism in killing the cancer cells (Hudis, 2007). Trastuzumab was a pivotal advancement in the treatment of breast cancer. In 2001, research showed that trastuzumab can increase the incidence of cardiac dysfunction when used in combination with doxorubicin, cyclophosphamide, and paclitaxel which was an unexpected complication based on preclinical trials (Slamon et al., 2001). Unfortunately, trastuzumab is associated with a natural and acquired resistance which can develop during the course of treatment and recurrences following trastuzumab therapy still occur.

Lapatinib is the first orally available dual inhibitor of both the HER2 and EGFR (epidermal growth factor receptor) tyrosine kinases; a dual inhibitor may benefit more patients due to the role of EGFR and HER2 in the progression of various cancers including, but not limited to, breast, colon, head and neck, and bladder cancers (Kopper, 2008). Lapatinib blocks the
intracellular domain of the HER2 and EGFR receptors which prevents phosphorylation of key proteins that regulate the cell life cycle, resulting in mechanisms that lead to cell death. The role of the EGFR and HER2 in cellular proliferation, differentiation and survival provides strong rationale for utilizing chemotherapy agents, such as lapatinib, that block EFGR or HER2 signaling pathways in tumors that overexpress EFGR or HER2 (Tevaarwerk & Kolesar, 2009). Lapatinib is associated with hepatotoxicity and left ventricle ejection fraction (LVEF) decline that may be severe and result in death (Tykerb® or Tyverb® [package insert], GlaxoSmithKline, Research Triangle Park, NC, 2015).

Capecitabine is an orally available chemotherapeutic agent used in the treatment of metastatic breast and colorectal cancers. Capecitabine is a prodrug that is enzymatically converted into 5-fluorouracil (5FU) by thymidine phosphorlase which is present at a higher concentration within tumor cells (Walko & Lindley, 2005). The higher concentration of 5FU inhibits deoxyribonucleic acid (DNA) synthesis in cancer cells thus sparing healthy tissue. The primary side effect of capecitabine is hand-foot syndrome. Hand-foot syndrome is a thickening of the skin on the hand and feet that cause severe pain, numbness and/or peeling of the skin. This reversible side effect is dose dependent and will resolve upon a dose reduction of capecitabine or discontinuation of treatment.

Clinical Trials

The women who have developed irreversible cardiac dysfunction or have progressive disease after trastuzumab therapy had few treatment options available until the FDA approved lapatinib in 2007. The FDA approved lapatinib in combination with capecitabine for the treatment of HER2 positive breast cancer for those patients who had disease progression while on or after
trastuzumab therapy. The treatment regimen of lapatinib and capecitabine shows clinical benefit in the treatment of locally advanced (Stage III) or metastatic (Stage IV) breast cancer.

The combination treatment of lapatinib and capecitabine showed a 51% increase in the time to tumor progression (TTP), as elaborated by Geyer et al (2006) in the New England Journal of Medicine. The research also demonstrated no increase of serious side effects or decrease in the left ventricle ejection fraction (LVEF). However, this study was biased on the population selection; the eligibility criteria required that the women have normal cardiac function before starting investigational treatment.

The EGF100151 study by Cameron et al. (2010) showed a need for further research to determine which patients may have a survival benefit with the addition of lapatinib to chemotherapy treatments. The TTP was increased in this study which implies that lapatinib and capecitabine are clinically beneficial to women who have failed trastuzumab therapy. This study also showed no increase in cardiac toxicity in the treatment arm.

Kaufman, Stein, Casey and Newstat (2008) suggest although breast cancer is currently incurable, by utilizing the new treatment therapies and strategies, it may allow breast cancer to be managed as a chronic disease. The research demonstrated a longer TTP then the capecitabine monotherapy. This study also analyzed the benefit of lapatinib and capecitabine in treating brain metastasis since both drugs cross the blood-brain barrier. Trastuzumab, however, does not. Lapatinib plus capecitabine fills a void after the patient had disease progression while on trastuzumab.

**Mantel-Haenszel Meta-Analysis Method**

Meta-analysis, the methodologies of synthesizing existing evidence to answer a clinical or other research question, is a dynamic area of research. The furor of methodological activity
reflects the clinical importance of meta-analysis and its potential to provide conclusive answers, rather than incremental knowledge contributions. When the original data is unavailable, researchers have to combine the evidence in a two stage process, retrieving the relevant summary effects statistics from publications and using a suitable meta-analysis model to calculate an overall effect estimate.

The Mantel-Haenszel (MH) meta-analysis method which can be used to calculate odds ratio (OR), risk ratio (RR), and risk difference (RD) (Mantel & Haenszel, 1959). The MH method is based on either a fixed effect or random effect model, where the weight is assigned to each study based on that study alone. Under the fixed effect model, there is an assumption that only one true effect exists which underlies all the studies in the meta-analysis. However, the random effects model incorporates an assumption that the different studies are estimating different, yet related, intervention effects. In both models, the observed effect size in a study is assumed to estimate the corresponding population effect with random error that stems only from the chance factor associated with subject level sampling error in that study from the population of potential subjects. When comparing randomized control trials the goal is to detect incidence of a single health outcome between different study groups (Borenstein, Hedges, Higgins, & Rothstein, 2009).

**Heterogeneity**

Heterogeneity refers to the various responses to a given treatment among included studies. It can relate to the biological differences among individuals, but also to other differences that are not as easily detectable (Leandro, 2008). Heterogeneity has two sources of variability that explain the differences in a set of studies utilized in a meta-analysis. One source of variability is due to sampling error. Sampling error variability is always present in a meta-analysis, because
every study uses different study patients and no two patients are identical. The other source of heterogeneity is the between-study variability, which can appear in a meta-analysis when there is true heterogeneity among population effect size estimated by the individual studies. The between-studies variability is due to the influence of an indeterminate number of characteristics that vary among the studies.

**Publication Bias**

The one type of publication bias that occur in meta-analysis is sampling bias where only studies showing significant difference are published, this implies that some complete studies are not published and the results resides in the investigator’s “file drawer” a term coined by psychologist Robert Rosenthal in 1979. Non-publication is not a direct result of a rejected manuscript, but a failure of the investigator to write up and submit the trial results (Rosenthal, 1979). Since published studies are easier to identify and retrieve than unpublished studies, or studies that resulted in negative or null findings; the studies used in a meta-analysis may over-represent published work and exaggerate statistical significance
Chapter III: STUDY DESIGN AND METHODS

The studies enrolled randomized patients to receive lapatinib plus capecitabine or capecitabine monotherapy within strata defined according to disease stage and the presence or absence of visceral disease (metastatic disease) to other organs such as: bones, liver, lung, and/or brain. The eligibility criteria for enrollment was documented HER2 positive status by immunohistochemistry or gene amplification by fluorescence in situ hybridization, locally advanced or metastatic breast cancer, and minimum prior treatment(s) that included an anthracycline, a taxane, and trastuzumab.

**Trial Identification**

I performed a computerized search of MEDLINE database (last search, October 26, 2014), online proceedings of the San Antonio Breast Cancer Symposium (years 2008-2014; last searched October 26, 2014), and the online proceeding of the American Society of Clinical Oncology (ASCO) Annual Meeting (years 2005-2014; last search October 26, 2014), using the combinations of the following keywords: “breast cancer”, “lapatinib”, “capecitabine”, “HER2”, “neoplasm” and “chemotherapy.” I reviewed the reference list of every published clinical article used in the meta-analysis to find any missing relevant studies.

The extractor used the trial eligibility schema (figure 1) to determine which clinical trials met the research conditions. The following information was recorded about each eligible clinical trial used in the meta-analysis: first author, journal name and year of publication, number of patients assign to each treatment arm, the number of outcome events recorded, and the dosing schedule for both treatment arms.
Potentially relevant published articles identified (n= 86)

Reports of nonclinical trials excluded (n= 63)
- Review papers
- Not studies on humans

Clinical trials screened on basis of title or abstract (n= 23)

Exclude because non randomized controlled trials (n= 17)
- Single treatment arm

Randomized controlled trials reviewed in detail (n= 6)

Randomized, controlled trials excluded (n= 3)
- Duplicate reports of previous trials
- Novel capecitabine dosing

Eligible randomized clinical trials (n=3)

Figure 1

Trial identification schema
Study Treatment Protocol

Patients in the treatment arm received lapatinib dosed at 1,500 mg per day continuously plus capecitabine 2,000 mg per square meter of body surface area on days 1 through 14 of a 21 day cycle. Patients in the control arm received capecitabine at a dose of 2,500 mg per square meter of body surface area on days 1 through 14 of a 21 day cycle. Baseline characteristics of the women enrolled in the clinical trials is listed in table 1.

Table 1
Baseline Characteristics of Women Included in the Analysis

<table>
<thead>
<tr>
<th>Gender (female/male)</th>
<th>Lapatinib + Capecitabine</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cameron</td>
<td>Geyer</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>207 / 0</td>
<td>206 / 0</td>
</tr>
<tr>
<td>Cancer Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB / IIIC</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>IV</td>
<td>199</td>
<td>156</td>
</tr>
<tr>
<td>Median TTP</td>
<td>18.8 months</td>
<td>8.4 months</td>
</tr>
<tr>
<td>Observation Duration</td>
<td>180–220 weeks</td>
<td>70–80 weeks</td>
</tr>
</tbody>
</table>

The study patients were all female for the clinical trials. The Cameron and Geyer studies reflect a balanced participant number of stage III patients in each arm, but in the Kaufman study reports 96 percent of the participants had stage IV cancer with no additional information provided. Stage IIIB or IIIC locally advanced breast cancer means that the patient does not have a tumor is distant organ such as: bone, brain, liver, or lung. Stage IV is commonly defined as metastatic breast cancer and it has all the characteristics of Stage III with the inclusion of a tumor found in one or more of the distant organs listed above.
Median time to tumor progression (TTP) reflects the length of time from start of treatment until 50 percent of the women experience death or disease progression the termination criteria for treatment. Study observation duration is estimated based on the Kaplan-Meier curve. The baseline characteristics were used to check the data integrity, since the numbers reported in the journal articles are very similar. The additional information provided by table 1 provides enough evidence that the clinical trials are unique and data reported is accurate.

**Mantel-Haenszel Method**

When the studies have a dichotomous (binary) data the results of each study can be presented in a 2×2 table (Table 2) giving the number of participants who experience the event or do not experience the event (non-event) in each of the two study groups treatment or control.

<table>
<thead>
<tr>
<th>Study</th>
<th>Event</th>
<th>Non-Event</th>
<th>Total Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>$A_i$</td>
<td>$B_i$</td>
<td>$N_{1i}$</td>
</tr>
<tr>
<td>Control</td>
<td>$C_i$</td>
<td>$D_i$</td>
<td>$N_{2i}$</td>
</tr>
</tbody>
</table>

The Mantel-Haenszel (MH) odds ratio is an alternative way of comparing how likely events are between two groups. The odds ratio is simply the odds of the event occurring in one group divided by the odds of the event occurring in the other group. I will use $OR_i$ to denote the odds ratio (effect size) for each $i^{th}$ study.

**MH Raw Odds Ratio Formula**

$$OR_i = \frac{(A_i / B_i)}{(C_i / D_i)}$$
Re-arrange above formula to this.

\[ OR_i = \frac{A_i \times D_i}{B_i \times C_i} \]

MH Variance Formula

\[ V_i = \frac{n_i}{B_i \times C_i} \], where \( n_i = A_i + B_i + C_i + D_i \)

The weighted mean OR\(_{MH}\) is the sum of the products (effect size OR\(_i\) times weight W\(_i\)) divided by the sum of the weights. The study weights are assigned with the goal of minimizing the with-in study error; meaning that larger studies, which have smaller standard errors, are given more weight than smaller studies, which have larger standard errors.

MH Weight Equation

\[ W_i = \frac{1}{V_i} \]

MH Pooled Summary Odds Ratio Equation

\[ OR_{MH} = \frac{\sum_{i=1}^{k} W_i (OR)_i}{\sum_{i=1}^{k} W_i} \]

To determine the strength of this relationship, we can estimate the raw odds ratio across the 2 x 2 table. Although, the raw odds ratio indicates how much or worse, on average, the treatment group performed relative to the control group, its scale is asymmetric with a lower bound of zero and an upper bound of infinity figure 2 (Petscher & Schatschneider, 2013). Thus,
the comparison of the OR from each clinical trial is not feasible since they can have different scales.

Therefore, what is typically done with raw odds ratio is transformed to a scale symmetric about zero by taking the natural logarithm. The log transformation makes the scale symmetric: the log of 0 is minus infinity, the log of 1 is zero, and the log of infinity is infinity. This transformation yields the log odds ratio in which a value of one indicates no intervention effect figure 3 (Petscher & Schatschneider, 2013). Once, the log transformation is done the log OR can be compared and conclusions concerning the magnitude of the intervention effect can be analyzed. Graphical displays for meta-analysis performed on ratio scales usually use the log scales as well. This has the effect of making the confidence intervals appear symmetric, for the same reason (Higgins & Green, 2011).
The odds ratio is transformed from raw units to log units to compute the Z-score and confidence limits. The \( \ln(\text{OR}_{\text{MH}}) \) is computed by taking the natural log (ln) of \( \text{OR}_{\text{MH}} \).

\[
\ln \text{OR}_{\text{MH}} = \ln(\text{OR}_{\text{MH}})
\]

The MH approach required the following computed frequency values for each study to be calculated, which will be summed across all studies, and then used to compute the variance of the summary effect. For each study (i) calculate the following values (the variable name is not significant):

\[
R_i = \frac{A_i \times D_i}{n_i}
\]

\[
S_i = \frac{B_i \times C_i}{n_i}
\]

\[
E_i = \frac{(A_i + D_i)A_i \times D_i}{n_i^2}
\]
\[ F_i = \frac{(A_i + D_i)B_i * C_i}{n_i^2} \]
\[ G_i = \frac{(B_i + C_i)A_i * D_i}{n_i^2} \]
\[ H_i = \frac{(B_i + C_i)B_i * C_i}{n_i^2} \]

MH Pooled Variance of the Summary Effect, in log units

\[ V_{ln OR_{MH}} = 0.5 \left( \frac{\sum_{i=1}^{k} E_i}{\left( \sum_{i=1}^{k} R_i \right)^2} + \frac{\sum_{i=1}^{k} F_i + \sum_{i=1}^{k} G_i}{\sum_{i=1}^{k} R_i * \sum_{i=1}^{k} S_i} + \frac{\sum_{i=1}^{k} S_i}{\left( \sum_{i=1}^{k} S_i \right)^2} \right) \]

MH Pooled Standard Error Estimate

\[ SE_{ln OR_{MH}} = \sqrt{V_{ln OR_{MH}}} \]

MH 95 percent Confidence Interval for the Summary Effect, in log units:

\[ LowerLimit = \ln(OR_{MH}) - 1.96 * SE_{ln OR_{MH}} \]
\[ UpperLimit = \ln(OR_{MH}) + 1.96 * SE_{ln OR_{MH}} \]

MH Z Value

The calculation of the Z-value and the one-tailed test for the p-value are as follows where Φ (Z) is the standard normal cumulative distribution.
$$Z = \frac{\ln OR_{MH}}{SE_{\ln OR_{MH}}}$$

$$p = 1 - \Phi(\pm |Z|)$$

**Heterogeneity**

In meta-analysis, the usual way of assessing whether a set of single studies is homogeneous is by means of the Q statistic; however, the Q statistic only informs meta-analysts about the presence versus the absence of heterogeneity, but it does not report on the extent of such heterogeneity. The $I^2$ index is used to report the extent of heterogeneity. The principal advantage of $I^2$ index is that it can be calculated and compared across meta-analyses of different sizes, of different types of study, and using different types of outcome data (Higgins & Thompson, 2002).

**Q Statistic**

The Q statistic is useful in detecting the with-in study variation. The Q statistic has a chi-squared distribution with k-1 degrees of freedom where k is the number of studies utilized in the meta-analysis (Lipsey & Wilson, 2001). The Q statistic is testing the null hypothesis in that the studies are homogeneous in the combined analysis or $H_0$: $Q = 0$ implying the studies is evaluating the same effect versus the alternative hypothesis, $H_A$: $Q \neq 0$ implying the studies is not evaluating the same effect in the combined analysis.

The formula for the Q statistic:

$$Q = \sum W_i (\ln OR_i - \ln OR_{MH})$$

The Q statistic can produce inaccurate results in extreme situations. When there is only a few studies the Q statistic can give a false assumption of homogeneity. On the other hand, when
there are a large number of studies, the Q test has high power to detect even a small amount of heterogeneity that may be clinically unimportant. When the meta-analysis incorporates only a few studies, utilizing the random effect model is appropriate when there are concerns about homogeneity. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. The random-effects method and the fixed-effect method will give identical results when there is no heterogeneity among the studies.

I² Index

The I² index is also used in detecting heterogeneity between studies which can be interpreted as the percentage of variability in effect estimates that are due to heterogeneity rather than chance or sampling error. Between-study heterogeneity is estimated using the I² statistic; typically, values greater the 50 percent are considered large, 25 percent to 50 percent modest, and less than 25 percent low heterogeneity (Higgins & Green, 2011). The formula for the I² index:

\[ I^2 = \left( \frac{Q - df}{Q} \right) \times 100\% \]

In meta-analyses that include between 2 to 4 studies such a sample is not usually adequate to accurately estimate heterogeneity, leading to a false homogeneity assumption (Kontopantelis, Springate, & Reeves, 2013). These estimates can have large uncertainty, especially in the presence of few trials, and should be interpreted with caution.

Publication Bias

Publication bias is assessed using a funnel and forest plots. A funnel plot is a scatter plot of the effect estimates from individual studies against the measure of each study’s precision. A forest plot is a graphical representation of meta-analysis data.
In a funnel plot the y axis is the standard error of the effect estimate and the natural log of the odd ratio is the x axis. The diagonal lines indicate the triangular region within which 95 percent of studies are expected to lie in the absence of both biases and heterogeneity (Sterne et. al., 2011). The solid vertical line is the line of no intervention effect. A funnel plot places effect estimate for larger, more powerful studies are towards the top of the plot and estimates from smaller, less powerful studies should scatter more widely at the bottom.

In the absence of publication bias we would expect the studies to be distributed symmetrically about the combined effect size which is observed in the funnel plot. In the absence of bias and between study heterogeneity, the scatter will be due to sampling variation alone and the plot will resemble a symmetrical inverted funnel. If no bias is present then the fixed effect assumption that the true treatment effect is the same in each study is valid.

By contrast, in the presence of bias, we would expect that the bottom of the plot would show a higher concentration of studies on one side of the mean than the other. This would reflect the fact that smaller studies (which appear toward the bottom) are more likely to be published if they have larger than average effects, which makes them more likely to meet the criteria for statistical significance (Borenstein et al., 2009).

When assessing forest plots one should compare the point estimate for each study to all other studies included in the meta-analysis, and to the combined point estimate to assess publication bias. The point estimates should not be scattered across the graph, for example, if one point estimate favors the control and the other point estimate favors the treatment that could indicate that publication bias may be present in a meta-analysis. The assessment of a forest plot should be to evaluate the graph holistically. The graph portion should have the point estimate for each study that is grouped close together near the summary effect estimate. The point estimates
should not be scattered across the graph, for example if one point estimate favors the control and the others point estimates favor of the treatment that is an indication that bias may be present in the meta-analysis. The 95 percent CI should overlap similar portions and also overlap the summary effect estimate.

The forest plot provides the summary data entered for each study. In addition, it provides the weight for each study; the effect measure, method and the model used to perform the meta-analysis; the confidence intervals used; the effect estimate from each study, the overall effect estimate, and the statistical significance of the analysis. In a forest plot the vertical line which corresponds to the value one is the line of no intervention effect. If one is included in the 95 percent confidence intervals, it indicates that there is no statistical significant difference between the treatment and control at five percent significance level. If one is not included in the 95 percent confidence intervals, it indicated that there are statistically significant difference between the treatment and control at five percent significance level. This is applicable for effect estimates for the individual study level and for the overall estimate for the meta-analysis.
Chapter IV: RESULTS

The results of the systematic review resulted in only three eligible trials that met the defined search parameters. The key elements for the clinical trials are that patients had disease progression while on or after treatment that included an anthracycline, a taxane, and trastuzumab. Analysis was conducted using Comprehensive Meta-Analysis software (Version 3.3.070, Biostat, Englewood, NJ).

The studies randomized patients 1:1 to lapatinib plus capecitabine or capecitabine. The eligible trials identified 1,131 patients with HER2 positive breast cancer, 576 assigned to lapatinib plus capecitabine (LC) and 555 assigned to capecitabine (C). The data extracted from the clinical trials is detailed in table 3.

Table 3

Lapatinib plus Capecitabine versus Capecitabine Data Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Lapatinib + Capecitabine</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event</td>
<td>Non-Event</td>
</tr>
<tr>
<td>Cameron</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>Geyer</td>
<td>12</td>
<td>85</td>
</tr>
<tr>
<td>Kaufman</td>
<td>92</td>
<td>71</td>
</tr>
</tbody>
</table>

I used the number of events per arm to calculate odds ratio (OR) and their 95 percent confidence interval (CI). An event is defined as patient death, the spread of cancer to new locations within the body, or increased growth of a cancerous lesion. The combined ORs to calculate pooled point estimates with the corresponding CIs using the Mantel-Haenszel fixed effect method. I tested heterogeneity using the Q statistic and $I^2$ index. Publication bias is assessed using funnel and forest plots.
Mantel-Haenszel Odds Ratio

The summary the odds ratio is shown in Figure 4. Each study is shown by the point estimate of the odds ratio, lower and upper limits of the 95 percent confidence interval, p-value and forest plot. The forest plot the square black box indicates the relative weight assigned to each study and the 95 percent confidence interval is shown by the extending whiskers. The combined odds ratio estimate and the 95 percent confidence interval by MH fixed effect calculations are shown by the diamond at the bottom. The diamond is centered at the combined point estimate and the width of the diamond reflects the 95 percent confidence interval.

### Mantel - Haenszel Odds Ratio

<table>
<thead>
<tr>
<th>Model</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>MH odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MH odds ratio</td>
<td>Lower limit</td>
</tr>
<tr>
<td>Cameron</td>
<td>0.726</td>
<td>0.429</td>
<td>1.228</td>
</tr>
<tr>
<td>Geyer</td>
<td>0.757</td>
<td>0.504</td>
<td>1.136</td>
</tr>
<tr>
<td>Kaufman</td>
<td>0.710</td>
<td>0.454</td>
<td>1.111</td>
</tr>
<tr>
<td>Fixed</td>
<td>0.733</td>
<td>0.565</td>
<td>0.952</td>
</tr>
</tbody>
</table>

Figure 4

Mantel-Haenszel Odds Ratio

The analysis of the odds ratio shows that the Cameron study has a point estimate of 0.726, 95 percent CI of 0.429 to 1.228 and a p value of 0.233. Based on this result the Cameron study does not show a decrease in tumor progression because the 95 percent confidence interval of the study overlaps one the line of no intervention effect. So, there is no statistical significance at the study level.

The analysis of the odds ratio shows that the Geyer has a point estimate of 0.757, 95 percent CI of 0.504 to 1.136 and a p value of 0.179. Based on this result the Geyer study does not show
a decrease in tumor progression because the 95 percent confidence interval of the study overlaps one the line of no intervention effect. So, there is no statistical significance at the study level.

The analysis of the odds ratio shows that the Kaufman has a point estimate of 0.710, 95 percent CI of 0.454 to 1.111 and a p value of 0.134. Based on this result the Kaufman study does not show an a decrease in tumor progression because the 95 percent confidence interval of the study overlaps one the line of no intervention effect. So, there is no statistical significance at the study level.

The analysis of the odds ratio shows the combined meta-analysis has a point estimate of 0.733, 95 percent CI of .565 to .952 and a p value of 0.020. Based on this result the combined meta-analysis the 95 percent confidence interval combined effect estimate does not overlap one the line of no intervention effect. There is statistical significance at the meta-analysis level. The odds ratio point estimate of 0.733 represents an overall 26.7 percent a decrease in women experiencing tumor related events in the lapatinib plus capecitabine arm versus the capecitabine monotherapy. Even though the benefit is moderate it shows that there is statistical support to pursue new clinical trials utilizing lapatinib plus capecitabine as a new treatment option for women with metastatic breast cancer.

Heterogeneity

The test for heterogeneity utilizing the Q statistic and $I^2$ index are recorded in the figure 5.

<table>
<thead>
<tr>
<th>Model</th>
<th>Effect size and 95% interval</th>
<th>Test of null (Z-Test)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number Studies</td>
<td>Point estimate</td>
<td>Lower limit</td>
</tr>
<tr>
<td>Fixed</td>
<td>3</td>
<td>0.733</td>
<td>0.565</td>
</tr>
<tr>
<td>Random effects</td>
<td>3</td>
<td>0.733</td>
<td>0.565</td>
</tr>
</tbody>
</table>

Figure 5

Q statistic and $I^2$ index
The fixed and random effect models produce the same point estimate, Z-value, and p value meaning there is no heterogeneity among the studies. The fixed effect model is more conservative than the random effect model so I am reporting the results for the fixed effect model.

The $I^2$ index is the percentage of variability in effect estimates that are due to heterogeneity rather than chance or sampling error. The $I^2$ index has a value of 0.000 which suggest that there is low heterogeneity in this meta-analysis. Since, this meta-analysis includes only three clinical studies the sample size may not be adequate to accurately estimate heterogeneity resulting in an incorrect zero of the $I^2$ index. Potentially leading to a false homogeneity assumption and should be interpreted with caution. In general, meta-analyses which include between two to four studies are not usually adequate to accurately estimate heterogeneity, leading to a false homogeneity assumption (Kontopantelis, Springate, & Reeves, 2013). These estimates may have a large uncertainty due to the lack of published clinical trials available for examination and should be interpreted with caution.

**Publication Bias**

Publication bias is assessed with a funnel plot and a forest plot. The table 4 is the natural log (ln) of the odds ratio for each of the included studies.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>MH Odds Ratio</th>
<th>ln (MH odds ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameron</td>
<td>0.726</td>
<td>-0.320</td>
</tr>
<tr>
<td>Geyer</td>
<td>0.757</td>
<td>-0.278</td>
</tr>
<tr>
<td>Kaufman</td>
<td>0.710</td>
<td>-0.342</td>
</tr>
<tr>
<td>Combined</td>
<td>0.733</td>
<td>-0.311</td>
</tr>
</tbody>
</table>
In a funnel plot the standard error of the effect estimate is the y axis and the natural log of the odd ratio is the x axis. The vertical line represents the natural log of the combined estimate of 0.733 which has a value of -0.311. Comprehensive Meta-Analysis software uses the term log to represent the natural log. All the studies are represented by the open circles in figure 6.

![Funnel Plot of Standard Error by Log odds ratio](image)

**Figure 6**

Funnel Plot of Standard Error by Log Odds Ratio

Starting from the top of the graph the first circle corresponds to the Geyer study, the second circle corresponds to the Kaufman study and the final circle corresponds to Cameron study. The relative weight of each study is indicated by their location on the funnel plot. The Geyer study has largest relative weight, since it is located at the top of the graph. The Kaufman study has the second largest relative weight, since it is located between the Geyer and Cameron studies. The Cameron study has the smallest relative weight compared to Geyer and Kaufman. All the studies are close to the fixed estimate and closely grouped together which indicates the meta-analysis is not expressing publication bias. In the absence of publication bias we would expect
the studies to be distributed symmetrically about the combined effect estimate which is observed in the above funnel plot.

The second method of detecting publication bias is by a forest plot. The forest plot figure 7 includes the study name, MH odds ratio estimate, the lower and upper limits of the 95 percent CI, the p value, a line graph of the point estimate with extending whiskers representing 95 percent CI, and the relative weight assigned to each study.

<table>
<thead>
<tr>
<th>Model</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Events / Total</th>
<th>MH odds ratio and 95% CI</th>
<th>Weight (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MH odds ratio Lower limit</td>
<td>Lapatinib +</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Capectabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper limit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cameron</td>
<td>0.726</td>
<td>0.429 1.228</td>
<td>166 / 207</td>
<td>172 / 201</td>
<td>24.88</td>
</tr>
<tr>
<td>Geyer</td>
<td>0.757</td>
<td>0.504 1.136</td>
<td>121 / 200</td>
<td>120 / 193</td>
<td>40.02</td>
</tr>
<tr>
<td>Kaufman</td>
<td>0.710</td>
<td>0.454 1.111</td>
<td>92 / 163</td>
<td>104 / 161</td>
<td>34.49</td>
</tr>
<tr>
<td>Fixed</td>
<td>0.733</td>
<td>0.566 0.952</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 7
Forest Plot and Relative Weight Analysis

The first assessment of the forest plot is to assess the plot holistically. The graph portion shows that each study point estimate (vertical line) is either slightly above or below the combined point estimate. The 95 percent CI cover the same portion of the graph for each study as well as the summary effect estimate. All the study point estimates favor the treatment intervention of lapatinib plus capecitabine. Based on the funnel and forest plots this meta-analysis is not representing publication bias.

In assessing the relative weights of studies, a large study provides a good estimate of the common effect and is assigned a larger weight; a small study offers a less reliable estimate of that same effect, so it is assigned a smaller weight. The Cameron study point estimate is 0.726 with a relative weight of 24.88 percent; the Kaufman study point estimate is 0.710 with a relative
weight of 34.49 percent; the Geyer study point estimate in 0.757 with a relative weight of 40.62 percent. Under the fixed effect model these studies are all estimating the same effect with the Geyer study providing a more precise estimate of the effect. Consequently, the Geyer study is assigned 40.62 percent of the weight in the combined point estimate with the remaining 59.38 percent divided amongst the remaining studies. Since, the Geyer study is assigned a disproportionate amount of weight it is evident that the Geyer study is more significant, statistically, than the Kaufman and Cameron studies. The disproportionate weight given to the Geyer study has caused the combined point estimate to definitively shift in favor of the Geyer point estimate.

The study by Geyer has a point estimate of 0.757, a 95 percent CI of 0.504 to 1.136, a p value of 0.179, and a relative weight of 40.62 percent. Based on the above forest plot the Geyer study the 95 percent CI includes the value one which indicates there is no treatment difference between lapatinib and capecitabine versus capecitabine monotherapy. As a result, there is no statistical significance at the study level. The Geyer study has the smallest variance therefore the study has more relative weight than Cameron and Kaufman studies.

The study by Kaufman has a point estimate of 0.710, a 95 percent CI of 0.454 to 1.111, a p value of 0.134, and a relative weight of 34.49 percent. Based on the above forest plot the Kaufman study shows 95 percent CI includes the value one which indicates there is no treatment difference between lapatinib and capecitabine versus capecitabine monotherapy. As a result, there is no statistical significance at the study level. The Kaufman study has a slightly larger variance when compared to Geyer therefore the study has more relative weight than the Cameron study.
The study by Cameron has a point estimate of 0.726, a 95 percent CI of 0.429 to 1.228, a p value of 0.233, and a relative weight of 24.88 percent. Based on the above forest plot the Cameron study shows 95 percent CI includes the value one which indicates there is no treatment difference between lapatinib and capecitabine versus capecitabine monotherapy. As a result, there is no statistical significance at the study level. The Cameron study has the largest variance therefore the study has the least relative weight when compared to Geyer and Kaufman.

The combined meta-analysis result has a point estimate of 0.733, a 95 percent CI of .565 to .952, and a p value of 0.020. Based on the above forest plot the combined fixed point estimate, the 95 percent confidence interval (indicated by the left and right edges of the diamond) of the combined point estimate does not overlap value one which indicates there is a statistically significant treatment difference between lapatinib and capecitabine versus capecitabine monotherapy at five percent significance level. So, there is statistical significance at the meta-analysis level. New hypotheses can be evaluated in phase II or III clinical trials utilizing lapatinib plus capecitabine in the treatment of metastatic breast cancer.

Utilizing lapatinib plus capecitabine as first line therapy will provide a more accurate estimate of the survival benefit to women diagnosed with metastatic breast cancer then provided in this meta-analysis. The odds of an event occurring in the combination therapy group was reduced by 26.7 percent when compared to the monotherapy group. There is currently a clinical trial NCT00496366 Phase II Trial of Capecitabine (Xeloda) and Lapatinib (Tykerb) as First-line Therapy in Patients With HER2/Neu-Overexpressing Advanced or Metastatic Breast Cancer sponsored by Rutgers, The State University of New Jersey. The clinical study is ongoing and expected to be concluded in September of 2016 with survival and time to progression data.
The use of lapatinib plus capecitabine should also be considered for women who are older or have compromised cardiac function at time of initial diagnosis. Older women are at a 20 percent increased risk of developing congestive heart failure after finishing chemotherapy. The clinical trial NCT01262469 Phase II Study Evaluating the Toxicity and Activity of the Combination Lapatinib + Capecitabine in Elderly Patients Aged 70 and Over with Metastatic Breast Cancer over Expressing HER2 sponsored by UNICANCER has concluded, but the clinical results of this trial have not been published. This clinical study will give a more precise cardiac toxicity profile and survival benefit of lapatinib plus capecitabine in older patients.

The clinical trials mentioned above offer a new option for newly diagnosed HER 2 positive breast cancer patients. Current research is investigating the role of lapatinib in combination with other chemotherapy agents and in adjuvant therapy for early breast cancer progression or relapse. The common benefit for lapatinib plus capecitabine is the convenience of oral administration. No longer, will women have to take time out of their schedules for their weekly or monthly chemotherapy infusions thus improving quality of life.
Chapter V: CONCLUSION

The primary limitation of this meta-analysis is the small number of clinical trials used when interpreting the results. First, my approach was based on data abstracted from publications and not individual patient data; thus, results should be viewed as hypothesis generating, and not as definitive evidence. Second, using short term results from only three randomized trials may be a source of bias when calculating the combined point estimate. Additional limitations are the sources of heterogeneity not taken into account due to the limited number of available studies, such as: clinical differences among the patient populations, patient baseline disease severity or characteristics, study design, or other sources that are not easily detected.

The goal of chemotherapy or treatment is to maximize quality of life, prolong life, stabilize the disease, and manage or reduce symptoms. Lapatinib plus capecitabine indicated the event occurred 26.7 percent less frequently for women treated with combination lapatinib plus capecitabine in comparison to women treated with capecitabine monotherapy. Although the decreased odds of tumor advancement is moderate, it is significant when life expectancy is measured in weeks and not years.

The ultimate cure for breast cancer remains elusive, but there is still hope for a cure with our advancements in medical science, for instance earlier detection and targeted chemotherapy drugs. Also our enhanced understanding of genetics, such as testing for breast cancer susceptibility protein (BRCA) genes and other abnormal genes responsible for cancer development. The disease is so complex, diverse, and so subtly connected to genetics and environmental factors, such as hormone therapy after menopause and oral contraceptives, that finding a cure can often feel impossible. While a cure has not yet been found, public perception surrounding breast cancer has changed dramatically in the past few decades. Once a disease that
woman felt ashamed to discuss, breast cancer now has lost much of its stigma. The combined efforts of Susan G. Komen for the Cure ©, the Breast Health Global Initiative, the U.S. Centers for Disease Control and Prevention, and advances in medical science has greatly improved access to treatment and screening. Greater awareness has been brought to this disease and with increased funding for research and drug development we have seen an increased success rate in breast cancer treatment.
REFERENCES

References marked with an asterisk indicate studies included in the meta-analysis


doi:10.1371/journal.pone.0069930


[http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)
## APPENDIX

Data Table of the Seven Potentially Eligible Clinical Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Lapatinib + Capecitabine dosing schedule</th>
<th>Capecitabine dosing schedule</th>
<th>Included in Meta-analysis</th>
</tr>
</thead>
</table>
| Cameron | Lapatinib 1,250 mg/day of a 21 day cycle  
Capecitabine 2,000 mg/m² days 1-14 of a 21 day cycle | Capecitabine 2,500 mg/m² on days 1-14 of a 21 day cycle | Yes, final report for clinical trial EGF100151 |
| Cameron | Lapatinib 1,250 mg/day of a 21 day cycle  
Capecitabine 2,000 mg/m² days 1-14 of a 21 day cycle | Capecitabine 2,500 mg/m² on days 1-14 of a 21 day cycle | No, interim analysis for clinical trial EGF100151 |
| Gajria  | Lapatinib 1,250 mg/day of a 21 day cycle  
Capecitabine 2,000 mg/m² days 1-7 and 15-21. No capecitabine day 8-14 of a 21 day cycle | Capecitabine 2,500 mg/m² on days 1-14 of a 21 day cycle | No, treatment arm novel capecitabine dosing schedule 7 days on 7 days off |
| Geyer   | Lapatinib 1,250 mg/day of a 21 day cycle  
Capecitabine 2,000 mg/m² days 1-14 of a 21 day cycle | Capecitabine 2,500 mg/m² on days 1-14 of a 21 day cycle | Yes, final report for clinical trial NCT00078572 |
| Kaufman | Lapatinib 1,250 mg/day of a 21 day cycle  
Capecitabine 2,000 mg/m² days 1-14 of a 21 day cycle | Capecitabine 2,500 mg/m² on days 1-14 of a 21 day cycle | Yes, no clinical trial identified |
| Ryan    | Lapatinib 1,250 mg/day of a 21 day cycle  
Capecitabine 2,000 mg/m² days 1-14 of a 21 day cycle | Capecitabine 2,500 mg/m² on days 1-14 of a 21 day cycle | No, duplicate publication of clinical trial NCT00078572 |