COST UTILITY AND BUDGET IMPACT ANALYSIS OF EARLY TREAMENT INITIATION WITH TRASTUZUMAB IN THE TREATMENT OF HER2 POSITIVE BREAST CANCER PATIENTS IN KENYA

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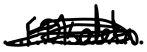
Signature  ..... Date.....16th October 16, 2023.....

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DEDICATION

To my Parents, Dr. Hemant Mandaliya and Mrs. Heera Mandaliya; You have sacrificed a lot for me to allow me to become who I am.

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LIST OF ABBREVIATIONS AND ACCRONYMS

AC-T	Doxorubicin, cyclophosphamide and paclitaxel
ASCO	American Society of Clinical Oncology
BMI	Body mass index
CDC	Center for disease control
CHF	Congestive heart failure
DFS	Disease free survival
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
HER2	Human epidermal growth factor receptor 2
HR	Hazard Ratio
ICER	Incremental Cost-Effectiveness Ratio
IgG	Immunoglobulin G
KNH	Kenyatta National Hospital
LLN	Lower limit of normal
LMIC	Low- to Middle-Income countries
LVEF	Left ventricular ejection fraction
LYG	Life years gained
MRI	Magnetic Resonance Imaging
NCD	Non Communicable Diseases
NHIF	National Health Insurance Fund
NICE	National Institute for Clinical Excellence
QALY	Quality adjusted life year
DALY	Disability adjusted life year
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
SEER	Surveillance, Epidemiology, and End Results
NCCN	National Comprehensive Cancer Network
TNM	Tumor, Nodes and Metastases
SOLD	Synergism or Long Duration

OPERATIONAL DEFINATIONS

Cost utility analysis	it is an economic evaluation that compares the cost and resulting outcome (in QALYs or DALYs) of a health-related intervention.
Budget impact analysis	It is an economic assessment that estimates the total cost of adopting a new intervention. It uses data from the cost effectiveness analysis.
Quality-Adjusted Life Year	It is a measure of disease burden, that takes into account both the quantity and quality of life lived. It is a product of utility and number of life years. In health economics it is a measure of the effectiveness of an intervention.
Incremental cost effectiveness ratio	It is the difference in cost between two interventions divided by the difference in their effect. It is a statistic that helps summarize the cost effectiveness of an intervention.
International Dollar	The international dollar also known as Geary–Khamis dollar, is a hypothetical unit of currency that has the same purchasing power parity that the U.S. dollar has in the United States at a given point in time.
Time horizon	The time period over which the costs of the clinical outcomes are being evaluated for.

ABSTRACT

Background

Breast cancer is the leading cancer in Kenya with a total of 5985 new cases in 2018. Approximately 15-30 percent of breast cancer cases overexpress human epidermal growth factor receptor 2 (HER2). The treatment regimen for HER2+ breast cancer as per the Kenyan National guidelines for cancer management 2013 recommends the use of trastuzumab for a period 52 weeks which consists of 18 cycles. The National Health Insurance Fund (NHIF) currently only pays for 4 cycles of treatment while the patient covers the cost of the remaining cycles. The cost-effectiveness of this treatment in most low and middle income countries such as Kenya is under debate. Trastuzumab based regimens can be given for 9-weeks and 6, 9, 12, 16 and 24-months. It remains uncertain which of these regimens is most cost-effective. The impact of adoption of any of these regimens on the five-year budget of the NHIF has not been accessed.

Objective

The objective of this study was to compare the cost effectiveness of early initiation of trastuzumab in the treatment of HER2+ breast cancer as well as to conduct a budget impact assessment of early initiation on the budgets of NHIF and Kenyatta National Hospital (KNH). This was done from the payers perspective

Methodology

The study was conducted in three different parts. The first part was a cost analysis done using a micro-ingredient/bottom-up approach with the aim of identifying direct medical costs associated with trastuzumab for the management of HER2+ breast cancer. The costing perspective was that of the payer. The second part was a cost utility analysis. Utilities and effectiveness data were obtained from literature. A Markov model was used to evaluate costs and benefits of treatment with trastuzumab over a 5-year time horizon. The cycle length was one month. A willingness to pay threshold for Kenya of US$ 919.11 / KSh 111,212.31 (1 USD was KSh 121 as of 9/10/2022) was used. Probabilistic sensitivity analysis was done to determine the impact of uncertainty of the data. The final part was the budget impact analysis. Modelling was done using base R software, a sensitivity analysis was done using *dampack* package and transition probabilities were computed using *heemod* package.

Results

The regimen with the lowest incremental cost effectiveness ratio (ICER) value of 5517148.58 KSh per QALY gained was the 9-week regimen and the 6-months' regimen had the highest ICER value of 7152616.73 KSh per QALY gained. The 9-, 12-, 16- and 24-month regimens had ICER values of 6640186.45, 6804768.23, 6873653.66 and 6874095.83 KSh per QALY gained respectively. Chemotherapy without trastuzumab was the cheapest but also the least effective option. The 9-week regimen would cost NHIF KSh 4198272901.11 for a period of 5 years for the projected 6100 new patients. The number of vials of trastuzumab consumed by a patient was the most sensitive parameter as per the sensitivity analysis and the effectiveness of the treatment also affected the ICER.

Conclusion

Based on the costing analysis, the 9-week regimen was cheapest trastuzumab containing regimen. With the current willingness to pay threshold for Kenya of US$ 919.11 / KSh 111,212.31 none of the trastuzumab containing regimens are affordable in the Kenyan context. In order to make any of the trastuzumab containing regimens affordable, the government would need to get significant discounts on trastuzumab and train health care workers on good dispensing practices to avoid wastage. Patients would also need to have good adherence to the treatment for better outcomes and in-turn this will improve the cost-effectiveness ratio. Further studies on the safety and treatment outcomes of trastuzumab are needed in the Kenyan setting.

CHAPTER ONE: INTRODUCTION

1.1 Background

In 2015 it was estimated that cancer was the second leading cause of deaths worldwide, with approximately 8.8 million deaths occurring worldwide. Lung cancer caused the highest number of deaths which totaled to nearly 1.7 million. (1) This was followed by liver cancer with about 787,000 deaths, then colorectal cancer with around 775,000 deaths, then stomach cancer with approximately 755,000 deaths, and breast cancer with nearly 571,000 deaths. (1) About 1 in 6 deaths are linked to cancer globally where approximately 70% of deaths occur in low- and middle-income countries. It is expected that in the next few years the number of new cases annually will increase by 70% to 14 million cases. (1) For women in Africa, more than 50% of the those suffering from breast cancer, die due to the disease. The percentage mortality is below 25% in more developed countries. The death rate of advance stage breast cancer is nearly 70% in low to middle income countries (LMICs). (2)

In Kenya, cancer ranks just after cardiovascular diseases in relation to all deaths. For deaths caused by non-communicable diseases, cancer ranked 2nd and accounted for nearly 7% of deaths in the country. (3)

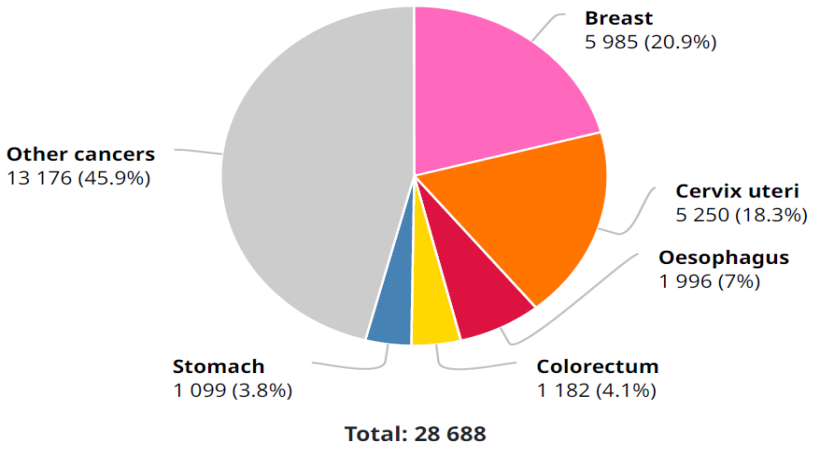

Figure 1: Number of new cancer cases in females in Kenya in 2018. (Source is Globocan 2018 (1))

There are around 37,000 new cases of cancer diagnosed every year in Kenya and the number of deaths amount to nearly 28,000 per year. Cancer of cervix uteri is the cancer with the highest incidence in women having an incidence of 40.1/100,000. (4) This is followed by breast cancer with 38.3/100,000 and esophageal cancer ranks in third place at 15.1/100,000. While for men, prostate cancer has the highest incidence of 31.6/100,000, followed by Kaposi's sarcoma with 16/100,000 and in third place esophageal cancer at 20.5/100,000. (4) As per the Kenya Cancer Screening Guidelines of 2018, "In 2018 the cancer with the highest number of new cases was breast cancer. There were a total of 5985 new cases reported" (2). This is shown in figure 1.

HER2 is a type of breast cancer where the human epidermal growth factor receptor type 2 is expressed at a higher than normal rate. Patients who test positive for HER2 tend to have a more aggressive form of the disease as compared to those that test negative. An analysis by Cronin et al found that the prevalence of HER2 positive (HER2+) breast cancer from twelve SEER registries for women aged 49 or below was of 19% and women aged 50 or above was 15%. (5)

The use of monoclonal antibodies in the treatment of HER2+ breast cancer is recommended by American Society of Clinical Oncology (ASCO) and US National Comprehensive Cancer Network. These monoclonal antibodies specifically target an antigen in patients that are HER2+. Trastuzumab is a monoclonal antibody used in the treatment of HER2+ breast cancer patients and in metastatic disease. Recently it has been used as the main therapy for HER2+ breast cancer. (6) Two large trials have shown the effectiveness of trastuzumab by demonstrating a reduction in the risk of local reoccurrence and death by up to 52% and 33% respectively, as compared to chemotherapy regimens that did not contain the drug. (7) Due to the growing number of available monoclonal antibodies and high cost of treatment, these drugs have a great impact on healthcare expenditure.

Newer molecules have now been added to regimens containing trastuzumab for the treatment of HER2+ breast cancer. NICE has recommended pertuzumab in combination with trastuzumab and a taxane in the treatment of HER2+ breast cancer. (8) Other tyrosine kinase inhibitors such as tucatinib and pyrotinib have shown improved survival in patients that have brain metastases with

HER2+ breast cancer. (9) Another molecule that has recently been approved by the FDA for early stage HER2+ breast cancer is ado-trastuzumab emtansine (T-DM1). (10) We did not consider these emerging treatment options as they were either no available in Kenya or were more expensive than treatment with trastuzumab.

Several studies have demonstrated the effectiveness of trastuzumab in treating HER2+ breast cancer which has resulted its extensive use for HER2+ breast cancer treatment. As a result, the number of patients eligible for trastuzumab has increased but due to the limited healthcare resources, currently it is used in combination therapy and cannot be used on its own.

As per the Kenyan National Cancer Treatment Guidelines the current therapy for HER2 positive breast cancers involves surgery, followed by chemotherapy. A combination of doxorubicin/ cyclophosphamide, and a taxane, either simultaneously or sequentially with trastuzumab for 12-month. The Kenyan treatment guidelines for breast cancer does not specify the stage for initiation for treatment with trastuzumab. (11)

The increase in survival rates and improved quality of life with the early initiation of monoclonal antibodies especially in earlier stages of breast cancer has been seen in developed countries. It is possible that early initiation of Trastuzumab may be a more cost-effective choice compared to not using it all in Kenya.

1.2 Problem statement

The treatment regimen for HER2+ breast cancer as per the Kenyan National guidelines for cancer management 2013 recommends the use of trastuzumab for a period 52 weeks which consists of 18 cycles. (12) NHIF currently only pays for 4 cycles at a maximum cost of Kenya shillings (KSh) 150,000 per cycle for treatment with trastuzumab per financial year; leaving the patient to cover the cost of the remaining cycles along with the costs of any tests or investigations that are to be done prior, during and after treatment. Majority of the patients cannot afford the cost for the remaining cycles thus leading to incomplete therapy. Optimum effectiveness of trastuzumab is seen when all 18 cycles are received by the patient.

No Health Technology Assessment (HTA) has been conducted for this drug to inform the Universal Health Care (UHC) Health Benefits Package advisory panel as to whether trastuzumab should be added to the oncology benefits package. Given that breast cancer was the most prevalent cancer in Kenya in 2018 and that trastuzumab is shown to be more effective than chemotherapy alone it deserves a consideration. (2,13) Thus data on local costs and cost effectiveness is missing, so clinicians are unable to justify inclusion of this drug in the oncology benefits package**.** This results in the need for a formal cost analysis of trastuzumab. Roche pharmaceuticals has sponsored treatment with this drug in the past, though this mode of financing is not sustainable as it is completely dependent on a third party. A long-term financing approach would be social insurance. A survey in Africa showed that even though the drug trastuzumab was available in 10 out of 19 health facilities only 5% of patients could afford treatment with the drug.(14) Breast cancer patients from lower-income countries have lower 5-year survival rates at every stage compared to those from high-income countries. (15)

There was a need for this study as the only study which has been done for sub-Saharan Africa had some gaps. The study by Gershon et al in 2019 evaluated the cost effectiveness of Trastuzumab in sub-Saharan Africa for early stage *HER2*-positive breast cancer. The gaps in this study were that the cost input used was a blanket $20,000 for all countries in the study. Given that the per capita gross domestic product - Purchasing Power Parity(PPP) varies greatly in Africa from international $29,835 in Seychelles to a low of international $708 in Burundi. (16) This was not appropriate as there are vast regional differences in costs which are generally context specific. It also did not include the costs for monitoring and diagnosis which are done prior to, during and post initiation of therapy with the drug. A budget impact analysis was not done in this study. (17)

This study filled these gaps by evaluating the cost effectiveness of various regimens containing trastuzumab in the Kenyan context.

1.3 Research questions

1. What were the direct cost to NHIF for treatment of patients with HER2+ breast cancer using Trastuzumab at an early stage?
2. Was initiation with Trastuzumab at an early stage in HER2+ breast cancer patients more cost effective than treatments without Trastuzumab?
3. Were any trastuzumab containing regimen affordable in the Kenyan context?
4. What was the impact of early treatment initiation with Trastuzumab on the NHIF and KNH budgets?

1.4 Objectives

Main objective

The main objective was to conduct a cost utility analysis on early initiation of trastuzumab in the treatment of HER2+ breast cancer as well as assess the impact on the budgets of Kenyatta National Hospital and National Health Insurance Fund.

Specific objectives

The specific objectives were to:

1. Estimate the total direct cost of the early initiation of trastuzumab using various regimens in HER2+ breast cancer.
2. Compare the cost utility various trastuzumab based regimens using chemotherapy only as the reference point.
3. Determine the most acceptable trastuzumab regimen using various values of willingness to pay thresholds.
4. Determine the impact of the early treatment initiation with trastuzumab on the NHIF and KNH budgets in the treatment of HER2+ breast cancer.

1.5 Significance of the study

The high mortality due to cancer in Africa can be attributed to low access to high-impact treatment, late-stage presentation and lack of screening programs. (18) These factors lower the rate of breast cancer survival. The problem of lack of access to high-impact treatments can be alleviated by inclusion of high cost anticancer drugs in health insurance oncology benefit packages. Given the high cost and benefits of the drug, NHIF needs cost effectiveness data to support the inclusion of the drug in the oncology benefits package.

The findings of this study can be used by NHIF and KNH as a source of data on the costs of all direct medical costs associated with the use of the trastuzumab, cost-effectiveness of the drug and number of patients that they would need to budget for. This study can also be used by the UHC Health Benefits Package advisory panel as evidence when considering to add the drug to the oncology benefits package. This study can be used to determine cost parameters that are most sensitive. These parameters can then be targeted in order to reduce the incremental cost effective ratio of the trastuzumab regimens hence making them more cost effective and affordable.

If the major financial burden of direct medical costs is assumed by NHIF, there will be improved treatment outcomes as the number of patients defaulting on the drug will reduce. This will lead to better treatment outcomes and decrease unnecessary hospitalizations, morbidity and mortality. This study can help policy makers justify the early initiation of trastuzumab and determine which trastuzumab containing regimen will be the most cost effective.

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of breast cancer in Kenya and the World

2.1.1 Incidence in Kenya

Cancer is going to kill more Kenyan women than men according to a report by the WHO's research agency. The Globocan 2018 data shows that there were 28688 new cancer cases in women compared to 19,199 in men. The risk of getting cancer under the age of 75 is also higher in women (20.1%) compared to men (16.7%) and deaths due to cancer in 2018 was 18,772 for women and 14,215 in males. (19) Since women are not the bread winners in many Kenyan households, the lack of access to funds leads to late diagnosis of the disease. This is due to lack of screening and high cost of the medication leading to the high death rate.

Breast cancer ranked 1st by accounting for 5,985(12.5%) of new cases in females and had the 3rd highest death rate of 2,553(7.7%). (19) A study done by Sayed et al showed that about 25.6% of the breast cancer patients were HER2+. (20)

2.1.2 Worldwide incidence

Cancer has been projected to overtake all other non-communicable diseases and become the leading cause of reduced life expectancy in the world. According to WHO 2015 data estimates, it will be the top 2 causes of death in people aged <70 years in 91 out of 172 countries and top 4 cause of death in 22 other countries(1) as seen in figure 2. The large number of deaths from cancer in Africa are a result of various factors like poor infrastructure, use of traditional therapy, diagnosis of the disease at an advance stage, lack of health-care workers, poor compliance, and reduced treatment options. (21)

The cancer with the highest prevalence in women in 140 of 184 countries worldwide is breast cancer. (19) As per Globocan 2018, breast cancer had an incidence of 2088849 cases in both sexes worldwide with a mortality of 626679 deaths. HER2 positive subtype of breast cancer is seen in about 15-20% of breast cancer cases.(22)

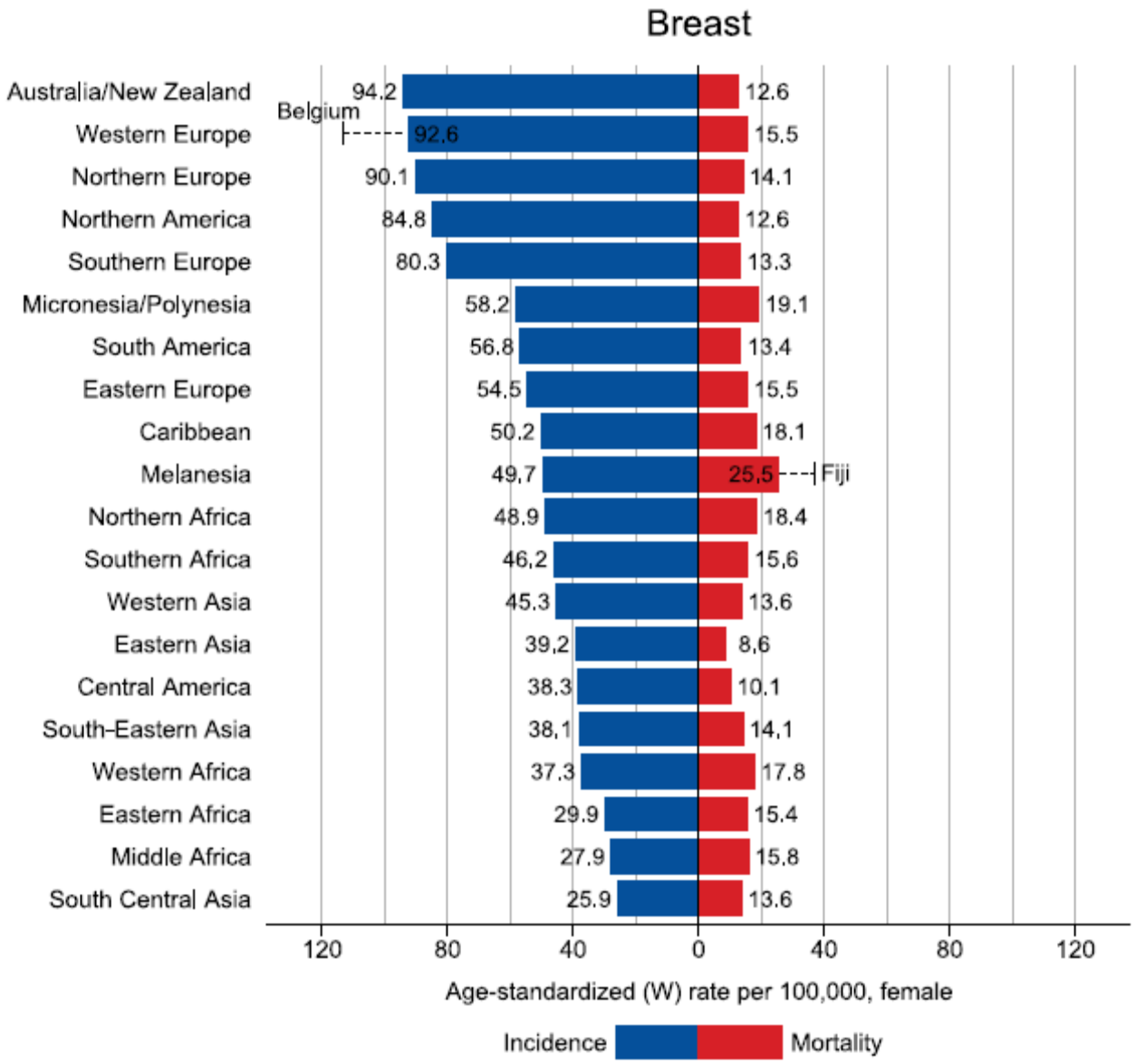

Figure 2: Regional incidence and mortality rates of breast cancer that have been age standardized. (Source is Globocan 2018 (1)**)**

2.2 Risk factors for Breast Cancer

The use of known risk factors when doing a risk assessment of women is important to help screen and diagnose breast cancer. A study done in the US showed the models based on traditional risk factors and use of mammographic density gave an accurate picture. (23) The risk factors are classified as either intrinsic/non-modifiable or extrinsic/modifiable.

2.2.1 Intrinsic/ Non-modifiable risk factors for breast cancer

Intrinsic risk factors are usually not under the control of an individual. In the case of breast cancer, they are age at menarche, race, age at which first child was born alive, age at menopause, benign breast cancer and history of breast cancer in the family.

Studies have shown that if a lady got her first period at a younger age and menopause at a later age then she was at a higher risk for breast cancer. First and last pregnancy at an older age increased the risk but as the number of children increase the risk reduces. (15) CDC data from 2017 showed that the incidence was higher in older people. (24)

SEER report showed that race in the US in 2016 was a determinant of prevalence of breast cancer. The incidence was higher in black females (48.4/100,000) as compared to white females (45.5/100,000) for women aged <50 years of age but for women >50 years' white females (366.8/100,000) had a higher incidence as compared to black females (348.5/100,000). However, the mortality rate was higher in black women for both age groups. (25)

Family history is an important risk factor as there is an association between BRCA gene mutation and breast cancer. Women that had an immediate relative with a history of breast cancer were at a higher risk and those with multiple first degree family members were at a greater risk. (26) This risk was seen to be higher in those women that were less than 40 (9%) years as compared to those that were aged above 40years (2%). (27)

A meta-analysis by Dyrstad et al found that proliferative benign breast disease increased the risk of breast cancer. Patients with atypical hyperplasia had a two- to four-fold increase in incidence of breast cancer when compared with those that were diagnosed with a non-proliferative type. (28)

2.2.2 Extrinsic/ Modifiable risk factors for breast cancer

Extrinsic risk factors that are under the control of an individual and they can be changed to reduce the risk. They include diet, body mass index (BMI), smoking, alcohol intake, contraceptive use and hormone replacement therapy.

A meta-analysis showed that for every increase of 5kg/m there was a corresponding 2% increase in the risk. However, in women who had not reached menopause, a higher BMI had a protective effect. (29) It was concluded that effects of being overweight on breast cancer prognosis was dependent on menopausal status. (20)

A series of cohort studies have shown that a healthy diet leads to risk reduction, especially in women that are post-menopausal. (30) A higher intake of fiber during adolescence and early adulthood reduced breast cancer incidence in women. (31) Having a diet rich in vegetables reduced the risk, whereas red meat increased the risk in postmenopausal women. (32) Studies concerned with fat in-take have shown a weak or no association. (33)

A study by Chelsea et al found an association between breast cancer risk and smoking. It showed that current smokers are at a higher risk for breast cancer than former smokers and the highest association was seen in women that smoked for 40 years or more. (34) Another meta-analysis of 86 studies came to the same conclusion. (35)

Alcohol intake increased the risk, though the mechanism is not very clear. It is thought that acetaldehyde being a byproduct of alcohol metabolism leads to an increase in androgen and estrogen levels in women which in turn increases the risk of breast cancer. A meta-analysis by Bagnardi et al showed a relative risk of 1.61 for women with high alcohol consumption as compared to those with no or low alcohol consumption. (36) Alcohol consumption has also been linked to increased breast density. (37)

Oral contraceptives use has been linked to an increased risk of breast cancer in women. The duration of oral contraceptive use has a positive association with risk, thought the type of oral contraceptive is not a major factor. (38) Current use of oral contraceptives increases the risk by 24% when compared to women who have never used them. (39)

2.3 Human Epidermal Growth Receptor type 2

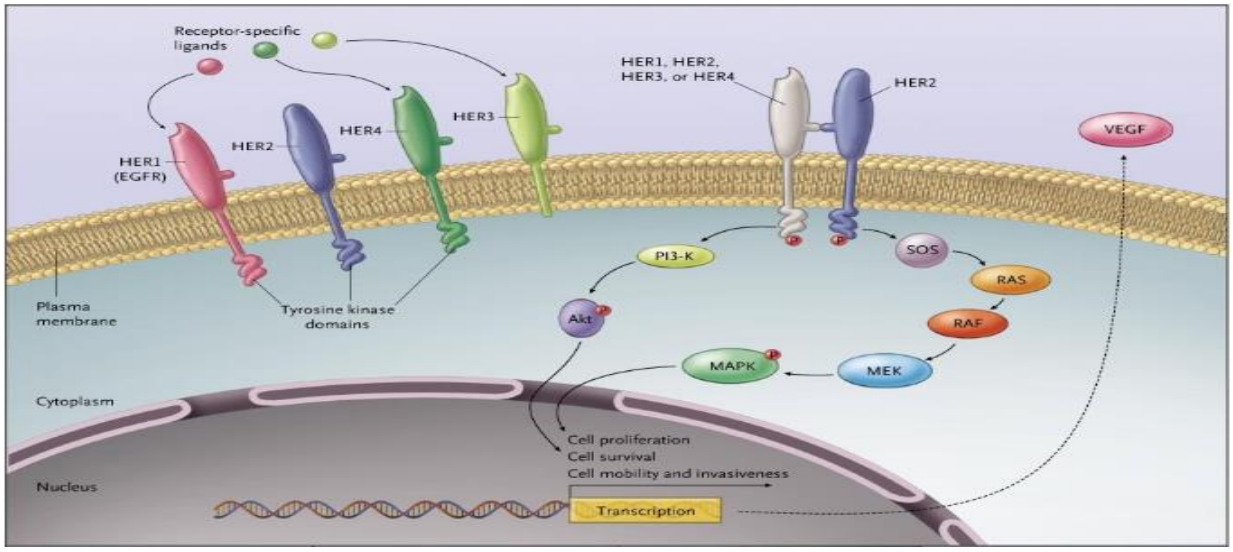

Figure 3: Different types of Human epidermal growth factor receptors (40)

The Human Epidermal Growth Factor receptor (HER) comprises of HER1, HER2, HER3, and HER4 receptor types and in found in cells all over the body. Each receptor type has a receptor specific ligand except for HER2. HER1, HER2 and HER4 have a tyrosine domain that gets activated by phosphorylation. This is done by homodimerization or heterodimerization which then leads to a chain of events as shown in Figure 3. These events result in both cell proliferation and survival signaling. A parallel system leads to cellular proliferation. Angiogenesis is caused by Vascular Endothelial Growth Factor (VEGF). (40)

2.4 Testing for HER2 using Immunohistochemistry (IHC) assay

Immunohistochemical staining is the cheapest and most common test done to determine HER2 status. The results are a score that ranges between 0-3. A score of 0 and 1+ means a negative result for HER2 protein, 2+ means it is borderline/equivocal and requires FISH test for confirmation and 3+ means its positive for HER2 protein. There are 2 commercially available assays that are approved by the USFDA, Dako HercepTest™ and Ventana Pathway™. (41)

2.4.1 In Situ Hybridization test for HER2+ breast cancer

Fluorescence In Situ Hybridization (FISH) is used to determine level of cell amplification as shown in figure 4. It is mainly used as a confirmatory test in case the IHC test showed a result of 2+. The three approved FISH assays by the FDA for HER2 amplification status are PathVysion™, INFORM and PHarmDX. (42,43)

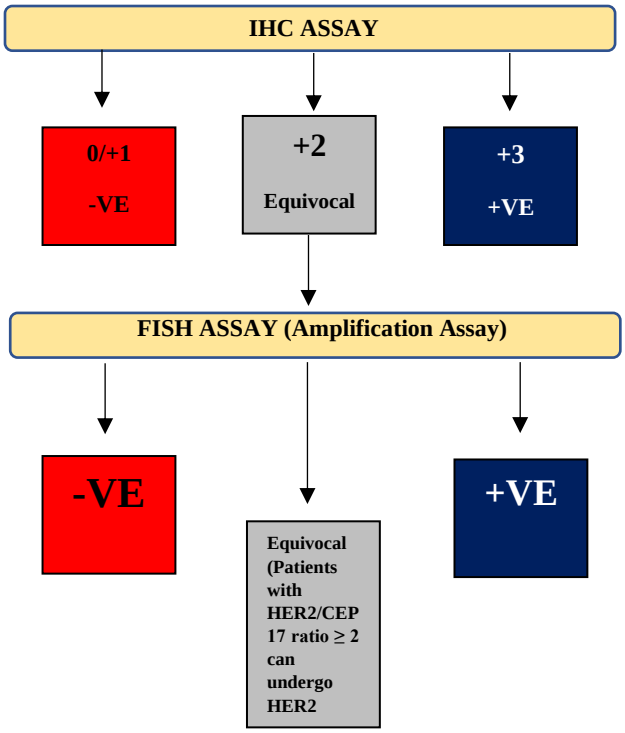

Figure 4: Algorithm for assessment of HER2 status

2.5 Chemotherapy for HER2+ breast cancer

2.5.1 Trastuzumab

Trastuzumab is a recombinant humanized IgG1 monoclonal antibody, presently one of the approved adjuvant treatments for patients with HER2-positive early stage breast cancer. It targets the extracellular domain of HER2 and inhibits its tyrosine kinase, but its exact antitumor activity is unknown. Some of the mechanisms by which it can decrease signaling are by cleaving the

extracellular half of HER2 and the membrane-bound phosphorylated p95 remains, which in-turn activates the signal-transduction pathways. Another mechanism is by binding of trastuzumab to the extracellular domain of HER2, thus preventing it from being cleaved off and does not allow activation of p95. This prevents homodimerization or heterodimerization and inhibits signaling. Nearby immune effectors cells are also activated, which results in an antibody dependent cytotoxic reaction. Receptor down-regulation also occurs. (40) These are shown in figure 5.

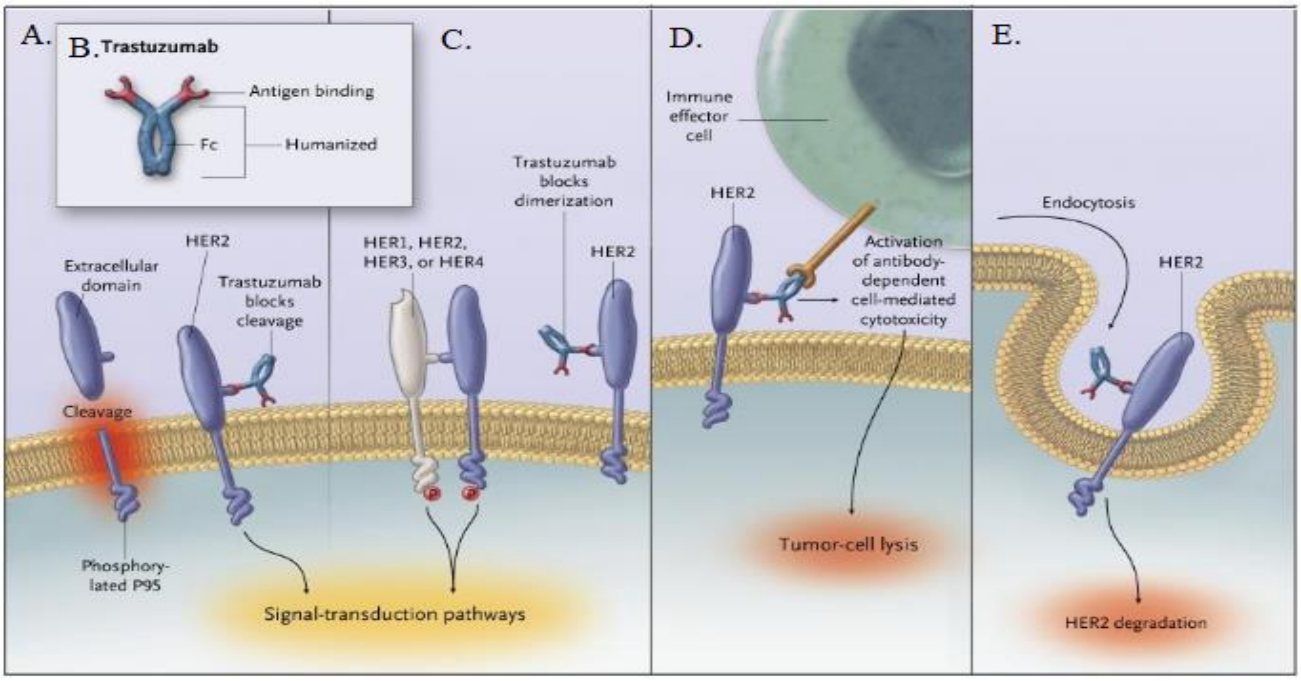

Figure 5: Mechanism of action of Trastuzumab (40)

2.5.2 Emerging treatments for HER2+ breast cancer

Newer molecules have now been added to regimens containing trastuzumab for the treatment of HER2+ breast cancer. NICE has recommended pertuzumab in combination with trastuzumab and a taxane in the treatment of HER2+ breast cancer. (8) A dual tyrosine kinase inhibitor called Lapatinib is used in metastatic HER2+ breast cancer (44). Other tyrosine kinase inhibitors such as tucatinib and pyrotinib have shown improved survival in patients that have brain metastases with HER2+ breast cancer. (9)

Another molecule that has recently been approved by the FDA for early stage HER2+ breast cancer is ado-trastuzumab emtansine (T-DM1). A study by Minckwitz et al showed that recurrence and death by breast cancer was reduced by 50% in the T-DM1 group as compared to the trastuzumab only group. (45) These molecules where not considered in this study as they are more expensive than trastuzumab.

2.5.3 Toxicity of Trastuzumab

The incidence of hypersensitivity like reaction is less than 10% in patients that have been started on trastuzumab. It can be prevented by using anti-inflammatory drugs, corticosteroids and antihistamines. Other adverse effects seen are myelosuppression, emesis and nausea. (46)

During clinical trials trastuzumab caused sporadic heart failure. It caused impairment of the left ventricular ejection fraction. (13) Another study showed that treatment of trastuzumab along with an anthracycline had a greater risk of reducing the LVEF. In the study the first group received trastuzumab with an anthracycline, the second group received trastuzumab and paclitaxel, and the final group received trastuzumab alone. The percentage of patients that experienced cardiotoxicity were 27%, 13% and 5% respectively. (47)

Cardiac dysfunction caused by trastuzumab is thought to be as a result of inhibition of HER2 signaling in cardiac myocytes, though it is a reversible process. (48) The manufacturer of Herceptin® recommend that a thorough cardiac assessment be done before starting the drug and then a baseline measurement of left ventricular ejection fraction (LVEF) by echogram be done immediately after initiation, every 3 months for the duration of the treatment and every 6 months for 2-years after completion. In case the drug is withheld for significant LVEF reduction then repeat LVEF measurements should be done every 4 weeks. (49)

NICE guidelines has recommended that trastuzumab should be used with caution in patients with less than 55% baseline left ventricular ejection fraction (LVEF), history of or currently suffering from congestive heart failure, myocardial infarction, angina pectoris, cardiomyopathy, cardiac arrhythmias, valvular heart disease, hemodynamic effective pericardial effusion and poorly controlled hypertension. (50)

2.5.4 Hold, re-initiation and discontinuation of Trastuzumab

When a patient's LVEF declines beyond a certain level, the treatment has to be put on hold and then reinitiated when it improves. The drug is put on hold when the LVEF is above the lower limit of normal (LLN) and there is ≥16% absolute decrease from baseline measurement and/or if the LVEF is below the LLN and ≥10% absolute decrease from baseline measurement. This is done for 4-8 weeks after which an echo scan is done.

Trastuzumab is reinitiated once the LVEF is above normal limits and there is ≤15% absolute decrease from baseline. The holding and reinitiating can be done up to 3 times during the course of treatment.

The drug is discontinued permanently if the patient presents with congestive heart failure and/or clinically significant asymptomatic decrease in LVEF and/or a persistent decrease in LVEF for a period of more than 8 weeks. If the drug has been held for more than 3 times due to cardiomyopathy, then the use of the drug is discontinued. (49)

2.5.5 Dosing of Trastuzumab

The serum half-life of trastuzumab is long which allows for infrequent dosing. It can be given in the following dosing schedules as shown in the figure 6:

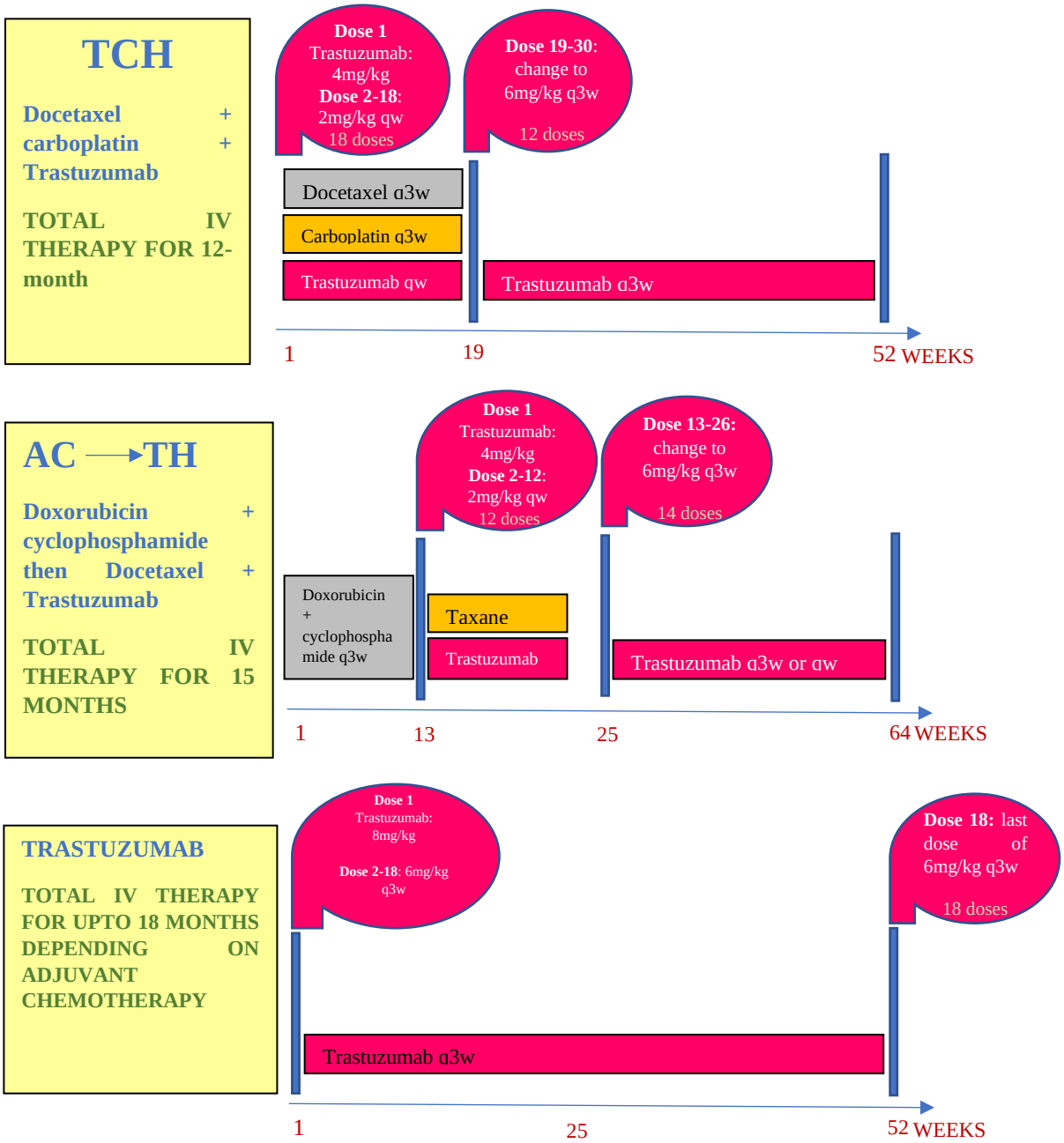

Figure 6: Recommended dosing of trastuzumab as per manufacture. (49) ***per week (qw) and once every 3 weeks(q3w)***

2.6 Breast cancer staging

The stage of breast cancer depends on the features of the cancer and these includes the size, location, if hormones are involved and if it has spread. Oncologist use diagnostic tests such as biopsy, mammography, MRI and ultrasound to determine the current stage. Cancer staging aids in determining the prognosis and outcome of the disease, devising the most effective treatment and see if any available clinical trials are an option. Breast cancer staging starts at stage 0, which is a non-invasive form of the cancer that does not spread from its origin, while stage IV is a highly invasive form that spreads from the breast to other parts of the body. (51)

American Joint Committee on Cancer oversees the TNM system which is the system used to stage breast cancer. It is characterized by three factors, which are the size of the tumor (T), lymph nodes involvement (N) and if the cancer has spread and become metastatic (M). These letters are then followed by numbers and or letters, which increase as the disease becomes more advanced. Combination of these factors give the different stages.

Table 1: Stage of breast cancer based on tumor characteristics. (52)

Tumors **(T)**	**T0/ Tis**	**T1**	**T2**	**T3**	**T4**
	No evidence of tumor in healthy cells	Tumor ≤ 20 mm	Tumor > 20 mm but ≤ 50mm	Tumor > 50 mm	Tumor has spread to the other parts of the body such as the skin and/or the wall of the chest.
Nodes **(N)**	**NX**	**N0**	**N1**	**N2**	**N3**
	Lymph nodes cannot be assessed	No metastases of the lymph nodes	Metastases in 1-3 axillary lymph nodes (level 1and2) **N1mi:** Lymph node tumor >2mm	Metastases in 4-9 axillary lymph nodes (level 1and2)	>10 axillary lymph nodes have metastases present or Metastases in ipsilateral infraclavicular (level 3)
Metastases **(M)**	**M0**	**cM0**	**M1**		
	No signs of metastases	Physical exam, x-ray and scans do not show metastases but lab test show spread to the bone marrow	Shows clear metastases		

Depending on the grade of the three factors as shown in table 1, breast cancer can be staged based on this. Stages of breast cancer are shown in table 2.

Table 2: Staging of breast cancer. (52)

		T	N	M
Stage 0		T_{IS}	N0	M0
Stage I	A	T1	N0	M0
	B	T0/T1	N1mi	M0
Stage II	A	T0/T1/T2	N0/N1	M0
	B	T1/T2/T3	N0/N1	M0
Stage III	A	T1/T2/T3	N1/N2	M0
	B	T4	N0/N1/N2	M0
	C	Any T	N3	M0
Stage IV		Any T	Any N	M1

The American Joint Committee on Cancer (AJCC) made a further update to this staging in 2018 that now added new factors shown in table 3.

Table 3: New factors added by AJCC in 2018 for staging breast cancer. (52)

Tumor grade:	**Estrogen and progesterone receptor status**	**HER2 status**	**Oncotype DX score**
How similar cancer and normal cells look.	Cancer cells have estrogen and or progesterone receptors.	Overexpression of HER2 protein.	Cancer cells are estrogen receptor +ve, HER2 -ve, and no cancer in the lymph nodes.

2.7 Effectiveness of trastuzumab

Clincal trials and studies demonstrate the efficacy of trastuzumab. These are shown in Table 4.

Table 4: Effectiveness of trastuzumab *FEC = Fluorouracil, Epirubicin and Cyclophosphamide.*

Study No.	Study Name	Number of patients and duration of the study	Arms of study	Disease free survival	Overall survival	Conclusion
1.	BCIRG006 Trial (53)	3222 women over 65months.	**AC-T:** Doxorubicin + Cyclophosphamide followed by docetaxel every 3 weeks	75%	87%	Both Trastuzumab arms had a superior disease-free survival (DFS) and overall survival (OS) rate. (Compute differences)
			AC-T plus trastuzumab: Same regimen above plus trastuzumab for 52weeks	84% Hazard Ratio when compared to AC-T Hazard Ratio **0.64** (P<0.001)	92% **0.63** (P<0.001)	
			TCH: Docetaxel + Carboplatin followed by trastuzumab for 52weeks	81% Hazard Ratio when compared to AC-T **0.75** (P=0.04)	91% **0.77** (P=0.04)	
2.	Joint Analysis of NSABP B-31 trial and NCCTG N9831 trial (54)	4046 women in total over a median time of 8.4 years.	**Control:** doxorubicin cyclophosphamide, followed by paclitaxel every 3 weeks or every week (depending on dosing) for 12 weeks	62.2%	75.2%	Addition of trastuzumab in both studies showed a better DFS and OS.
			T group: doxorubicin and cyclophosphamide, then paclitaxel (same as above) and trastuzumab every week for a year	73.3% Hazard Ratio compared to control of **0.60** (P<0.001)	84% Hazard Ratio compared to control of **0.63** (P<0.001)	
3.	HERA Trial (55)	5099 women over a median follow up time of 11years	**Observation:** Four cycles of standard chemotherapy	63%	73%	Addition of trastuzumab in showed a better disease-free and overall survival rate (fewer deaths in hormone-receptor positive women). 2-years of trastuzumab had no additional advantage.
			1year T: Four cycles of standard chemotherapy + Herceptin® Initial dose 8 mg/kg, maintenance dose 6 mg/kg every 3 weeks for 1 year	69% HR **0·76** (95% CI 0·68–0·86) compared observation	81% HR **0·81** (95% CI 0·65–1·00)	
			2-year T: Four cycles of standard chemotherapy + Herceptin® Initial dose 8 mg/kg, maintenance dose 6 mg/kg every 3 weeks for 2-years	69% HR **0·99** (95% CI 0·69–0·87) p=0.86 compared to 1 year T	81% HR **1.05** p=0.63 compared to 1year T	

Study No.	Study Name	Number of patients and duration of the study	Arms of study	Disease free survival	Overall survival	Conclusion
4.	FNCLCC-PACS 04 trial (56)	3010 women of which 528 were HER2 positive. Done over a median follow up time of 47 months.	**Observation** FEC (epirubicin 100 mg/m^2 + fluorouracil 500 mg/m^2 + cyclophosphamide 500 mg/m^2 (at day 1 of a 21-day cycle). **OR** ED75 regimen included docetaxel 75 mg/m^2 (day 1 day 21) + epirubicin 75 mg/m^2	78%	96%	Risk of relapse was not statistically different in the two groups. Though the sample size was small others. Also, of the 234 patients that received a loading dose of trastuzumab 58 (25%) of them dropped out before completion of 1 year mainly due to cardiac toxicity.
			T group: loading dose was 8 mg/kg. Maintenance dose was 6 mg/kg given every 3 weeks for 1 year.	81% Hazard Ratio **0.86** p=0.41	95% Hazard Ratio **1.27**	
5.	Fin Her Trial (57)	232 HER2 receptor positive women over a median period of 62months	**1)** Docetaxel/FEC/ No trastuzumab	74.1%	82%	Use of docetaxel gives a better overall survival as compared to vinorelbine. Also, addition of trastuzumab to both regimens showed a better disease-free survival and overall survival.
			2) Docetaxel/FEC/ trastuzumab for 9-week at either weekly dosing of 4mg/kg then 2mg/kg or 3 weekly dose of 600mg per dose.	92.5% Hazard Ratio **0.32** P = .029 compared to **1)**	94.4% Hazard Ratio **0.42** P = .14 compared to **1)**	
			3) Vinorelbine/FEC/ No trastuzumab	72%	82.8%	
			4) Vinorelbine/FEC/ trastzumab	75% Hazard Ratio **0.92** P = .82 compared to **3)**	88.4% Hazard Ratio **0.64** P = .35 compare to **3)**	
6.	PHARE trial (58)	3380 women over 3.5years of follow up	**1 year:** Primary treatment+12months trastuzumab	93·8%	N/A	12-month of treatment should remain the standard as the study showed that the 6-month group was inferior in comparison to the 1 year group.
			6-months: Primary treatment+6months trastuzumab	91·1% Hazard Ratio **1.28**	N/A	
7.	Deng et al. (59)	7949 women with HER2+ breast cancer	**1 year:** Primary treatment+12months trastuzumab	Hazard Ratio **1.10** P=0.09	Hazard Ratio **1.14** P=0.07	12 month of treatment was superior as compared to the 6 month regimen.
			6-months: Primary treatment+6months trastuzumab			
8.	El-Enbaby et al. (52)	60 women aged between 18-70 years and followed for 12 months	**1 year:** Primary treatment+12months trastuzumab	90% P=0.402	-	No statistically significant difference was found between the two with regards to effectiveness
			9-months: Primary treatment+9months trastuzumab	83.3% P=0.402	-	

Study No.	Study Name	Number of patients and duration of the study	Arms of study	Disease free survival	Overall survival	Conclusion
9.	ALLTO Trial (60)	8381 patients over a median follow up time of 4.5years	Patients were given either 1) neoadjuvant or adjuvant chemotherapy followed by anti-HER2 agent OR 2) anthracycline component of adjuvant chemotherapy with taxane and anti-HER2 agent OR 3) no anthracycline chemotherapy was given concomitantly with anti-HER2 agents			Addition of Lapatinib did not significantly improve DFS so 1 year of trastuzumab is still the recommended therapy
			Anti-HER2 agents: **T** trastuzumab 52weeks	86%	94%	
			L Lapatinib 52weeks	82% Hazard Ratio **1.34** p< .0005	93% Hazard Ratio **1.36** p= 0.007	
			T→L T 12weeks 6-week gap L 34weeks	87% Hazard Ratio **0.96** p= 0.61	95% Hazard Ratio **0.91** p= 0.433	
			L+T T 52 weeks L 52 weeks	88% Hazard Ratio **0.84** p= 0.048	95% Hazard Ratio **0.80** p= 0.078	
10.	SOLD Trial (61)	2174 women over a period of approximately 6 years	**2)** Docetaxel/FEC/ trastuzumab for 9-week at either IV weekly dosing of 4mg/kg then 2mg/kg or 3 weekly dosing of 8mg/kg then 6mg/kg or 3 weekly SC dose of 600mg per dose.	-	-	9-week of trastuzumab was not non-inferior to 1 year of trastuzumab when given with similar chemotherapy.
			2) Docetaxel/FEC/ trastuzumab for 1 year with dosing of 8mg/kg then 6mg/kg or 3 weekly.	Hazard Ratio **1.39** CI = 1.12-1.72	Hazard Ratio **1.36** CI = 0.98-1.98	

A systemic review by Moja et al that has a median follow-up period of 3 years showed a hazard ratio of 0.66 for overall and disease free survival in the group taking trastuzumab for 1 year as compared to the control group. (62)

Table 4 gives data from 10 randomized trials and studies that showed use of adjuvant therapy with trastuzumab for a year increased the disease-free survival in women with HER2-positive, and the overall survival in those trials that had a long enough duration. Investigators also allowed crossover of patients from the control group into the trastuzumab group in some of the trials. Some trials showed addition of drugs such as Lapatinib to the trastuzumab resulted in a minor improvement in treatment outcomes but had a larger incidence of adverse effects. (63)

In the SOLD trial patients were given trastuzumab along with docetaxel as either an intra-venous dose weekly or 3 weekly or as a sub cutaneous dose of 600mg regardless of weight every 3 weeks. The trial did not compare the efficacy of the different 9-week group regimens and assumed them to be of the same efficacy. This was a possible short coming of the study, given that the costs are drastically different for each of the 9-week regimens and they may differ with regards to effectiveness.

2.8 Treatment Guidelines for Breast Cancer

NCCN guidelines have added trastuzumab to all regimens used for treating HER2+ breast cancer. (64) The NICE guidelines recommend that the combination of trastuzumab and Pertuzumab should only be used in early HER2+ breast cancer therapy only if it is lymph node positive. This is because since the drug is relatively new, it is known how it affects the long-term survival. (65)

2.9 Evaluation of the cost-effectiveness of trastuzumab

Studies have been done is different countries on the cost-effectiveness of trastuzumab. The ICER values depend on the country the study has been done. Some of these studies are summarized in table 5.

Table 5: Cost-Effectiveness of trastuzumab (LYG = Life years gained, QALY = Quality adjusted life years and ICER = Incremental cost effectiveness ratio)

Study Name	**Groups**	**Treatment time**	**Incremental costs (Difference in total + follow up costs in both arms)**	**LYG**	**QALY gained**	**ICER/LYG**	**ICER/QALY**
Aboutorabi et al 2015 (66)	1-year trastuzumab + AC-T v/s AC-T (docetaxel 100 mg/m^2, doxorubicin 60 mg/m^2, cyclophosphamide 600mg/m^2 IV per session, 6 times every 3 weeks for 4 months)	Early stage	$44596	0.82	0.87	$54223	$51302
Ansarpour et al 2017 (67)	1-year trastuzumab + standard regimen v/s standard regimen (as per HERA trial)	Early stage	€18,619	1.40	1.14	€13,279	€16,695
Hedden et al 2012 (68)	1-year trastuzumab adjuvant treatment v/s standard treatment	Early stage	C$ 18,133	1.17	1.38	C$15,492	C$13,095
Lang et al 2016 (69)	1-year trastuzumab adjuvant treatment v/s standard treatment (combination of docetaxel/paclitaxel, doxorubicin and cyclophosphamide)	Early stage	$93,028	-	1.631	-	$51,863

Study Name	Groups	Treatment time	Incremental costs (Difference in total + follow up costs in both arms)	LYG	QALY gained	ICER/LYG	ICER/QALY
Leung et al 2016 (70)	1-year trastuzumab adjuvant treatment v/s standard treatment	Early stage	**25 to 44**: $47,941 **45 to 54**: $48,783 **55 to 64**: $49,558 **65 to 74**: $49,559 **75 to 84**: $46,108 **85≥**: $41,409	-	**25 to 44**: 1.55 **45 to 54**: 1.23 **55 to 64**: 1.24 **65 to 74**: 1.12 **75 to 84**: 0.65 **85≥**: 0.31	-	**25 to 44**: $30,921 **45 to 54**: $39,744 **55 to 64**: $39,982 **65 to 74**: $44,053 **75 to 84**: $70,949 **85≥**: $132,905
Seferina et al 2017 (71)	1-year trastuzumab adjuvant treatment v/s standard treatment	Early stage	**Real World:** € 3,560 **Guidelines:** € 5,495	-	**Real World:** 0.827 **Guidelines:** 0.861	-	**Real World:** €4,304 **Guidelines:** € 6,382
Puromen et al 2011 (72)	1-year trastuzumab adjuvant treatment v/s standard treatment (as per final 5 years of Fin-Her Trial)	Early stage	€ 7900	0.85	0.66	€9300	€12 000

The study by Leung et al 2016 (60) showed that as the age increases the ICER per QALY also increases. This can be attributed to the reduced quality of life at an older age as the incremental costs were similar across the different age groups.

2.10 A critical appraisal of studies done on the cost effectiveness of trastuzumab

There are very limited cost effectiveness studies done in the African context. A study by Gershon et al had a costing component, the methodology was unclear and the researchers used a fixed cost of US$20,000 for all countries. This ignores the fact that costs are highly context specific and can

vary from region to region. (17) Secondly none of the cost effectiveness studies evaluated the impact of shortening the duration of treatment. Out of 7 cost effectiveness analyses that have been summarized in Table 5, hidden costs such as treatment monitoring and management of adverse events were not included in some studies, whereas non-medical costs where included in some.

With regard to the utility values used, none maybe applicable in the African setting as no quality of life assessment amongst breast cancer patients in East Africa has been done.

A budget impact analysis is only done with regard to the budget of a given payer. Consequently, any budget impact analysis that have been reported in literature do not apply to the Kenyan context. Given that the costs are highly context specific, a Kenyan study was required to inform policy makers.

2.11 Theoretical and Conceptual framework

Markov modelling is used to predict future costs and outcomes. It models stochastic events which are events that are random. For the purpose of our study the recurrent events were the different health states, that is disease-free survival, metastasis, local recurrence and death. Markov modelling is based on the Markov chain principle which computes the probabilities of sequential events occurring. The main advantage is that it can handle both costs and outcomes at the same time. Though this model is said to be memoryless and hence does not take into consideration other events and this is called the Markovian assumption.

A transition matrix is used to predict the occurrence of the various recurrent states. It is generated from the know incidence/prevalence of events or they can be estimated if data on this is unavailable probabilities can be calculate using equation 1:

Equation 1: Formula for calculation of transition probabilities

$$tp_1 = 1 - (1 - tp_t)^{1/t}$$

Where transition probability per year is denoted tp_1 and tp_t is the total transition probability for a period t. (73) The markov cycle is defined as a time period where the patient can transit from one state to another. A time horizon of 5 years was used as this is the duration for most projects in the government and funding agencies need data for a minimum of this period. The length of a cycle will be one month.

A cost utility analysis compares costs of different interventions against their outcomes which have a "utility based" measure in units that relate to a person's level of wellbeing. Utility is defined as the measure of quality of life. It is a composite health outcome measure. Utility theory is a part of decision analysis that deals with models that describe and guide choice of behavior under uncertain conditions. (74) The different types of utilities are ordinal, cardinal, total and marginal utility. (75–77)The most common unit is the quality adjusted life year (QALY). QALYs are calculated by estimating the total life years gained from a procedure or intervention and attaching a weight for each year based on the quality of life in that year. (78)

In a markov model weights have to be attached to help in estimating the costs and outcomes. For outcomes a weight greater than zero is given to all health states in which the patient is alive, while a weight of zero is given to all the health states in which the patient is dead. The maximum weight is one and this represents perfect health. (79) The model is for a specified number of cycles and the sum of the weights across the cycles is used to calculate the mean life expectancy. If the length of a cycle in years is multiplied to this, then the life expectancy in years can be obtained. The same method can be used for costs, were the cost in each health state per cycle is obtained. Then the model is run for a large number of cycles and the total cost is obtained by getting the sum of all the cycles. The computed future costs were adjusted to their present value.

This was done using equation 2, which is the standard discounting formula:

Equation 2: Standard discounting formula

$$V_0 = \frac{V_t}{(1+r)^t}$$

The equivalent current value at time zero is denoted V_0, V_t is the value at time t and r is the discount rate. (73) The model that was used is 'cohort stimulation'. This is where a hypothetical cohort was assumed to start therapy in 2020 and future prognosis was simulated. The study has seven groups that are Group A that had patients on standard chemotherapy but without trastuzumab, while Group B – G had patients on standard chemotherapy with trastuzumab of varying durations as shown in figure 7.

A budget impact analysis is a part of a comprehensive economic assessment. It is based on the theory of budgeting which has origins in accounting. (80) Its purpose is to determine the financial resources needed to implement an intervention within the health-care setting. It helps predict how a change in the elements of a therapy or mix of drugs for a particular health condition will affect the resources needed to be allocated for the given health condition. It can be used for forecasting, impact of a health technology on insurance premiums and budget planning. (81)

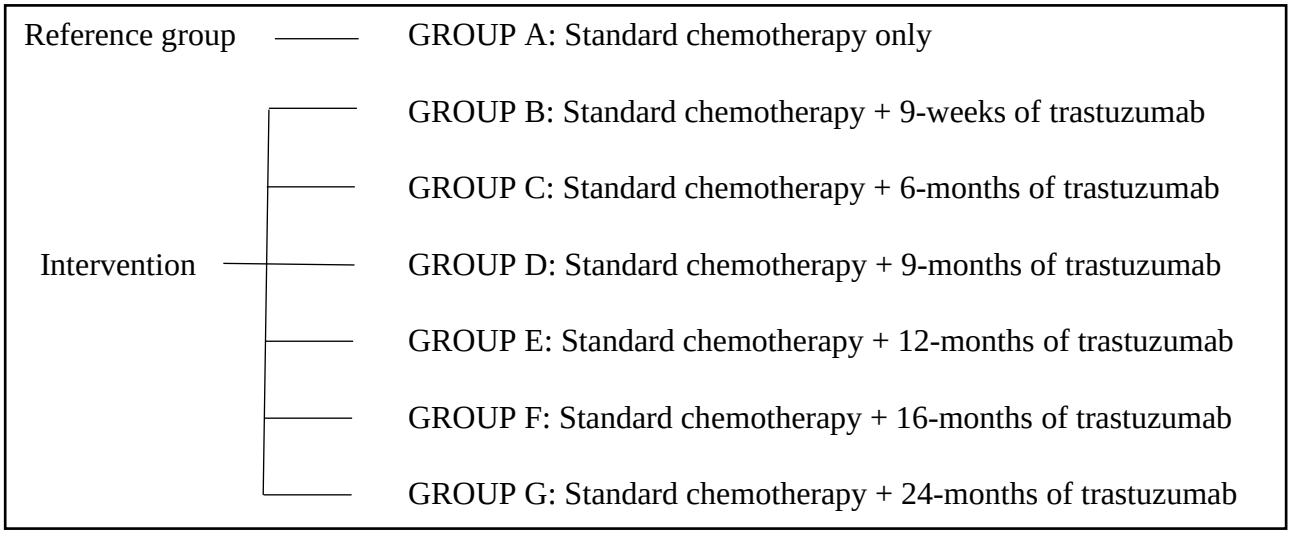

Figure 7: List of treatments groups that were compared in the cost-effectiveness analysis.

CHAPTER THREE: METHODOLOGY

The study was conducted in three parts. The first part was a cost analysis aimed at identifying costs associated with trastuzumab for management of HER2+ breast cancer. The second part was the pharma-economic cost utility analysis. The final part was the budget impact analysis.

3.1 Cost Analysis for management of HER2+ breast cancer at Kenyatta National Hospital

3.1.1 Study design and study site

The study design for the cost analysis was a cross-sectional survey. Face-to-face interviews were carried to get quantitative data on costs, quantity and probability of using the item as per the local setting. The study site for the face-to-face interview was Kenyatta National Hospital. KNH is the largest public tertiary referral hospital located in Nairobi and serves as the teaching hospital for the University of Nairobi. Patients from across Kenya and parts of East/Central Africa are seen at KNH as they offer specialty diagnostic, preventive and curative health services. They are also one of the largest public providers for cancer related services in the country.

A market price survey to obtain market prices for medicines and laboratory tests was conducted in Nairobi county, amongst established suppliers. Nairobi is the commercial capital of Kenya and a large majority of the established suppliers for both laboratory and pharmaceuticals have a branch/premise in the county.

3.1.2 Study Population for the Face-to-face Interview and market price survey

For the face-to-face interviews that were conducted, the study population included the key personnel who provided direct patient services in the cancer unit at the hospital. This included oncologists, radiotherapist, anesthetist, nurses, pharmacists, billing/procurement officers and laboratory personnel. The study population for the market price survey included individuals in the sales department of the established suppliers of pharmaceuticals.

3.1.3 Inclusion and Exclusion Criteria

For the face-to-face interview the inclusion criteria for participant selection were:

1. Involved in care of cancer patients at KNH,
2. Worked at KNH for a minimum of 2 years,
3. Gave informed consent to participate in the study.

Those who did not meet the inclusion criteria were excluded.

For the market price survey, the inclusion criteria were:

1. Worked in an establishment listed in Pharmfinder® and/or Kenya Medical Directory
2. They were willing to provide prices by telephone or in person

Those who do not meet the inclusion criteria were excluded.

3.1.4 Sample size determination

3.1.4.1 Sample size and sampling technique for the face-to-face interview

In this study, we did purposive sampling whereby individuals who are experts in their field are sought for. In purposive sampling the principle of saturation is used. As per the principle, sampling is terminated if no additional information is obtained by interviewing more respondents. (82) Therefore for some cadres only 2 respondents were sampled.

3.1.4.2 Sample size and sampling technique for the Market price survey

The principles used for sampling for market price surveys are described in the measuring medicine prices, availability, affordability and price components by World Health Organization and Health Action International. (83) Universal sampling was done for the market price survey. The minimum sample size was set as 3, but for certain items where only the originator brand was available, the sample size was one.

3.1.6 Participant recruitment

For the face-to-face interview two letters where given to the relevant head of departments at KNH for permission to interview the interviewees. The first was a letter of introduction was obtained from the School of Pharmacy, University of Nairobi and the second document was a letter of ethical approval from the University of Nairobi//Kenyatta National Hospital Ethics Review Committee (UON/KNH-ERC). A suitable date and time were arranged with the identified interviewees. The potential participant was invited to sign the informed consent form (Appendix B) after an explaining on the purpose of the study. Participants for the market price survey were contacted by phone or visited in person where telephone contact could not be established.

3.1.7 Data Collection

For the oral face-to-face interview closed ended questions on prices, quantities and probabilities along with a few open ended questions as presented in the interview guide (Appendix B) was used by the principal investigator. Each cadre had a different interview guide based on their area of expertise. A research assistant recorded the interview using a mobile phone and writing down information was done where necessary. Some interviews were done online due to the ongoing COVID-19 pandemic, but this did not affect the quality of the information that was obtained as compared to the in person interview. The audio recording was transcribed within 24 hours and destroyed/deleted.

The intention was to sample at least five establishments to get the prices of each pharmaceutical item, in some cases there were only three or less suppliers willing to give this information. Each of the suppliers were called by telephone and were asked for the lowest and highest priced generic and the originator brand. For the purpose of sensitivity analysis, we used the lowest price and highest prices from the market survey for each cost item. The base price used was obtained from the KNH 2020 procurement plan.

For the laboratory tests and imaging for cancer the sampling frame consisted of the four large laboratory service providers based in Nairobi. This included KNH, two large private hospitals and

one specialist laboratory service provider. The hospital-based charges such consultation fees, bed charges and other fees were obtained from face-to-face interviews of the healthcare workers.

The market price survey data from suppliers was collected using the Market price survey form (APPENDIX D) and then entered into MS Excel. The supplier was asked for the current unit price for the item/service.

3.1.8 Data Analysis

Data analysis was divided into 2 parts, that were computation of costs and discounting of the costs and utilities.

3.1.8.1 Analysis of quantitative data – Computation of costs

Costing was done from the payers perspective as the study was done for funding agencies such as NHIF and KNH which would not cover other non-medical cost. The time horizon for the study was 5 years as this is the minimum period that most funding agencies require data for. Direct medical costs were calculated from the payers' perspective using a micro-ingredient/bottom-up approach. This approach involved identification, quantification and valuation of resources. Cost categories were identified using the face-to-face interviews. Face-to-face interview, treatment guidelines and published literature were used to determine the quantity of each item. The average weight of the patient used in the study was 65.5 kgs and average height of 157.9 cm, which were taken from a study done by Gitonga et al. (84) The body surface area (BSA) was calculated for the weight and height using the formula presented in equation 3.

Equation 3: Formula for calculation of body surface area (85)

BSA = 1/6 (Weight in kilograms x Height in meters) x 0.5

The body surface area was needed for dosing of certain chemotherapeutic agents. The loading dose of trastuzumab was 8mg/kg, while that of the continuation phase was 6 mg/kg. Although we did not adjust for inflation the effects of price fluctuations were explored using sensitivity analysis.

Costing was done in the following sequence, firstly the prices for items such as chemotherapy, drug administration, laboratory items, imaging, surgical items, hospitalization and cost of

management of side effects were identified. The next step involved quantifying the number of units consumed for each cost item per patient. For the medication and laboratory investigations, quantification was done based on frequency and duration specified by the face-to-face interview and/or current treatment guidelines. The third step was to determine and assign a unit price to each of the cost items. These prices were obtained from the market survey or face to face interviews. Lastly the total cost per patient was obtained by multiplying the unit price of the cost item by the number of units consumed.

The cost of pre-medication and management of side effects due to standard chemotherapy were accounted. The cost of management of congestive heart failure, which is one of the more commonly documented side effect attributed to trastuzumab was ignored as the incidence was extremely low in the Kenyan setting as per the interviewees.

Non-medical costs such as transport, loss of productivity, care-giver time and insurance related costs were omitted. Overhead costs that are attributed to administration department and cleaning were ignored. Capital and maintenance cost of equipment were ignored.

3.1.8.3 Discounting of cost and utilities

Future prices after 2020 were adjusted for their present value. The base discount rate used was 6% for costs and 4% for utilities. Although it is recommended the rate of return on government bonds should be used for costs discounting, we ignored this because in the Kenyan context it is very high at between10-12% (86). We catered for this in the sensitivity analysis. In majority of economic evaluation studies the discount rate used is 3% but for LMIC a rate of 5-6% is preferred as recommended by Haacker et al. (87)

3.2 Cost Utility Analysis

3.2.1 Study design

A cost utility analysis was conducted by using a Markov model to estimate outcomes and predict costs over a 5-year period. It compared patients that were treated with trastuzumab for various

durations and those who did not receive trastuzumab. Data on utility and effectiveness were obtained from published literature.

3.2.2 Time Horizon and perspective of the study

A cycle length of one month was used in the study as treatments changed on a month-to-month basis and this led monthly changes in utility and costs. The time horizon of the study was 5 years as this is the duration of a strategic plan for most corporations. A payer's perspective was used as under universal health care only direct medical costs for cancer patients are provided by the National Health Insurance Fund through contracted facilities such as Kenyatta National Hospital

3.2.3 Markov Model for the cost utility analysis

A Markov model entails dividing a disease into different states and assigns probabilities for an individual to remain in a certain state or move to another state. Every state has a cost and transition probability attached to it. (73) The Markov model is typically used when a disease has prolonged outcomes and recurrent states. It was used to assess the cost-effectiveness of chemotherapy over the 5-year period. The model consisted of five key states that shows the progression of breast cancer. These states included disease free survival, local or regional reoccurrence, metastasis, all-cause mortality and death by breast cancer. Tunnel states where incorporated in to the model because costs and utilities tended to vary monthly depending on the type of treatment or procedures received. For instance, the 1st year of treatment was divided into 12 tunnel states as illustrated in table 6. The transition between states is shown in figure 8.

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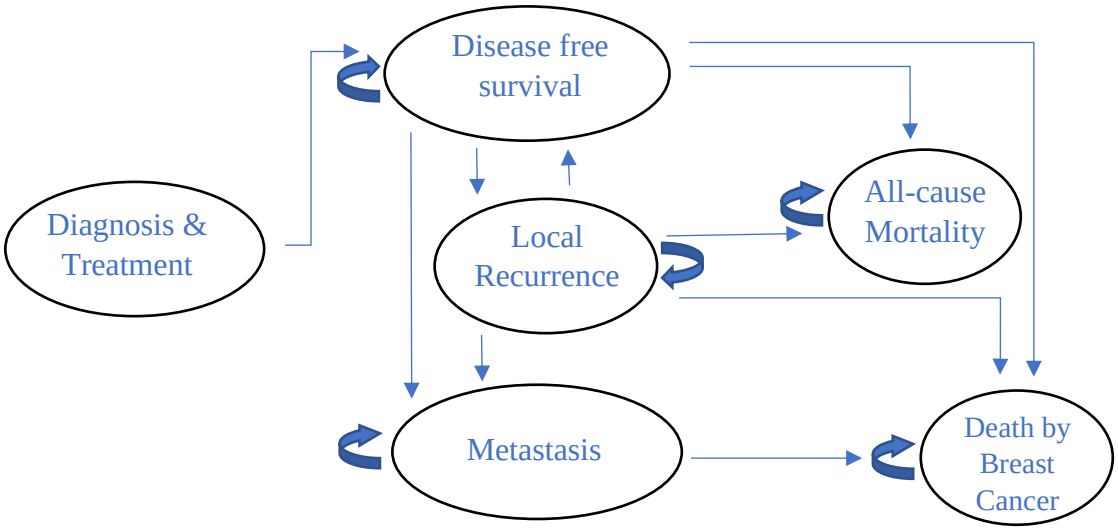


Figure 8: Markov transition states for breast cancer patients on chemotherapeutic regimens.

As per the Figure 8 in each cycle patients could move to any of the states. The absorbing states were all cause mortality and death by breast cancer. The model outputs were costs, QALYs and ICERs. Table 6 shows how patients would move from one state to the next for the 5-year period

Table 6: Summary of health states that patients in the chemotherapy alone and 12- month group would occupy at a given cycle.

Cycle	**0**	**1**	**2**	**3-6**	**7**	**8-10**	**11-22**	**23-34**	**35-46**	**47-59**
Chemo Only	Diag	Surgery	Radio	AC	Pac	Pac	DFSI	DFSI	DFSII	DFSII
12 Months	Diag	Surgery	Radio	AC	THLoad	THCont	EST	DFSI	DFSI	DFSII

Diag: Diagnosis, Radio: Radiotherapy, Pac: Treatment with paclitaxel, AC: Treatment with adriamycin and cyclophosphamide, THload: Loading dose of trastuzumab along with paclitaxel, THCont: Continuation dose of trastuzumab along with paclitaxel, EST: Trastuzumab only, DFSI: Hormonal treatment with anastrazole for the first two years and DFSII: Hormonal treatment for the following years.

Patients moved from diagnosis to surgery and this was followed by radiotherapy. After radiotherapy patients would receive their respective chemotherapy, followed by hormonal treatment for the remainder of the cycles. The choice of hormonal treatment depended on whether the patients were pre or post-menopausal, but in our study we took the cost of post-menopausal treatment as it was higher. Patients that got a local recurrence where changed from post-menopausal to pre-menopausal hormonal treatment after completing chemotherapy. For patients that got metastasis, they received palliative care on completion of chemotherapy. The detailed table for the other regimens, local recurrence and metastasis can be found in APPENDIX I.

A time varying transition matrix was used. The dimensions of the transition matrix with tunnel states was 182 by 182 with each state contributing 60 cells with exception of the absorbing states. Markov modelling was done using the cohort approach. The risk ratios that were used to populate the transition matrix were obtained from literature as shown table 8. The one and three-year cumulative risk were obtained from literature and these were converted to one-month transition probabilities using *"reshape_prob"* function in *Heemod* in R software. (88)

Table 7: Transition probabilities for early stage breast cancer

PARAMETER	**BASE VALUE (Per Month)**	**95% CI**	**SOURCE**
Chemotherapy + trastuzumab			
Year 1			
DFS > LR	0.0018	0.0015 - 0.0019	Gupta et al. (89)
DFS > Met	0.003	0.0026 – 0.0033	Gupta et al. (89)
DFS > DBC	0.0026	0.00078 – 0.0087	Ansaripour et al. (67)
DFS > DFS*			
LR > DFS*			
LR > LR**	0.000083	0.0000025 – 0.000083	Estimated
LR > Met	0.0085	0.0075 – 0.0095	Gupta et al. (89)

PARAMETER	BASE VALUE (Per Month)	95% CI	SOURCE
LR > DBC**	0.000008	0.000025 – 0.0017	Estimated
Met > DBC	0.0062	0.0018 – 0.10	Ioannou et al. (90)
Met > Met	0.0019	0.00092 – 0.0029	Ansaripour et al. (67)
Year 2			
DFS > LR	0.002193	0.0019 – 0.0024	Gupta et al. (89)
DFS > Met	0.003830	0.0033 – 0.0043	Gupta et al. (89)
DFS > DBC	0.002620	0.0017 – 0.0038	Ansaripour et al. (67)
DFS > DFS*			
LR > DFS*			
LR > LR	0.0128	0.00084 – 0.056	Ioannou et al. (90)
LR > Met	0.010878	0.0078 – 0.013	Gupta et al. (89)
LR > DBC**	0.031	0.01 – 0.05	Swain et al (91)
Met > DBC	0.0349	0.0274 – 0.0678	Hedden et al. (68)
Met > Met	0.036132	0.0087 – 0.095	Ioannou et al. (90)
Year 3-5			
DFS > LR	0.003137	0.002792 – 0.003483	Gupta et al. (89)
DFS > Met	0.005496	0.004879 – 0.006118	Gupta et al. (89)
DFS > DBC	0.0066	0.0034 - 0.0078	Elsisi et al. (92)
DFS > DFS*			
LR > DFS	0.099	0.00874 – 0.221	Ioannou et al. (90)
LR > LR	0.0128	0.0078 – 0.049	Ioannou et al. (90)
LR > Metastatic	0.016003	0.014034 – 0.018015	Gupta et al. (89)
LR > DBC	0.0066	0.0025 – 0.0087	Elsisi et al. (92)
Met > DBC	0.0349	0.0274 – 0.0678	Hedden et al. (68)
Met > Met	0.036132	0.0087 – 0.074	Ioannou et al. (90)

**For the following transition probabilities DFS > DFS, LR > DFS, was calculated as the difference between 1 and the row total of the probabilities that were provided.*

***For LR > LR, LR > DBC, we assigned a hypothetical value as the yearly transition probability, as no value could be traced from literature.*

****There is very limited literature on transitions for LR > Death therefore for this transition we used the transition probability for metastasis to death as reported in this study.*

The limited Kenyan data available in literature gave very low transition probabilities as a result of loss to follow up and hence data from Kenya was not used. (93)

Table 8: Risk ratios of different regimens when compared to 12-month of trastuzumab.

Name	Risk Ratio	Source
Chemotherapy Only		
Local Recurrence	1.248 (0.997-1.562)	Perez et al. (46)
Metastasis	1.604 (1.41- 1.824)	
Death by Breast Cancer	1.503 (1.276-1.77)	
9-week of trastuzumab		
Local Recurrence	1.35 (0.54-1.65)	Joensuu et al. (61)
Metastasis	1.16 (0.65-1.9)	
Death by Breast Cancer	1.034 (0.65-1.65)	
6-month of trastuzumab		
Local Recurrence	1.21 (0.54-1.51)	Deng et al. (59)
Metastasis	0.83 (0.65-1.1)	
Death by Breast Cancer	1.09 (0.8-1.5)	
9-month of trastuzumab		
Local Recurrence	1 (0.54-1.3)	El-Enbaby et al. (94)
Metastasis	0.9 (0.65-1.1)	
Death by Breast Cancer	1 (0.8-1.32)	
2-years of trastuzumab		
Local Recurrence	1.051 (0.842-1.312)	Cameron et al. (55)
Metastasis	0.998 (0.875-1.139)	
Death by Breast Cancer	1 (0.99-1.01)	

The risk ratios from Table 8 were used to get the transition probabilities of the various interventions and the 12-month group was used as the reference. The transition probabilities for the 16-month group were identical to the 12-month group as no study was found in literature for comparing the 16-month regimen with the 12-month regimen.

Data on costs was obtained from the cost analysis which was conducted in the first part of this study described in Section 3.1.

The transition probabilities for the 12-months trastuzumab arm were obtained first. They were taken from various studies and meta-analyses as shown in Table 7. Then using the risk ratios from various studies, we computed the transition probabilities for the other regimens. The first source was the Joint NSABP B-31 and NCCTG N9831 trial (54) which compared two anthracycline based regimens; one regimen had trastuzumab for 12-month and the other did not. This study was used to compute the risk ratio for the no trastuzumab arm (control) and it was selected because the primary regimens that is AC-T is the most widely used regimen in KNH for treatment of HER2+ breast cancer when trastuzumab is not used. Another trial that was used to get data was the HERA trial. (55) This was used to get the risk ratio to compare the 1 year trastuzumab arm with the 2-year trastuzumab arm. The risk ratio for comparison of the efficacy for the 9-week trastuzumab arm against 12-month was taken from a meta-analysis by Clarke et al. (95). The risk ratios used for the other intervention groups are presented in Table 8.

Data for the 9-week regimen was computed from the results of the SOLD trial (61), as it had a regimen of intra-venous trastuzumab to be given 3 weekly with dose of 6mg/kg as loading dose followed by two cycles of 4mg/kg. This was the cheapest 9-week regimen out of those described in the SOLD trial.

3.2.4 Comparator interventions

The reference group was an anthracycline containing regimen that is given with cyclophosphamide for 4 cycles, followed by 4 cycles with paclitaxel. This was chosen as it is currently the most affordable chemotherapeutic regimen for HER2+ breast cancer patients in Kenya. All patients in the comparator regimens had undergone the same initial chemotherapy regimen as the reference group of four cycles of doxorubicin with cyclophosphamide and four cycles of paclitaxel. Trastuzumab was initiated with paclitaxel in the comparator groups for the four cycles. This was then followed up with trastuzumab been given for varying durations on its own. The 9-week group was the only comparator group that did not follow this order. The groups are shown in Table 9.

Table 9: Drug regimen used by the different arms.

S.I.	Name	Regimen	Reference
GROUP A (REFERENCE)	Chemotherapy only	AC (4) + T (4)	Perez et al. (54)
GROUP B	9-week	T(3) + FEC (3) + H(3)	Joensuu et al. (61)
GROUP C	6-month	AC (4) + TH (4) + H(4)	Deng et al. (59)
GROUP D	9-month	AC (4) + TH (4) + H(8)	El-Enbaby et al. (94)
GROUP E	12-month	AC (4) + TH (4) + H(12)	Perez et al. (54)
GROUP F*	16-month	AC (4) + TH (4) + H(18)	Estimated*
GROUP G	24-month	AC (4) + TH (4) + H(28)	Cameron et al. (55)

( )= Number of cycles, AC=Doxorubicin & Cyclophosphamide, T= Paclitaxel, H =Trastuzumab and FEC =Fluorouracil, epirubicin and cyclophosphamide.
**There was no study with this regimen and hence the parameters for this group were estimated.*

The chemotherapeutic regimens that are used in KNH are doxorubicin, cyclophosphamide and paclitaxel (AC-T). The 16-month regimen was used to show if there was any advantage for patients that were given treatment for more than 12 months but less than 2 years.

3.2.5 Key assumptions

The following assumptions were made in the analysis:

1. As there is no study to show effectiveness in the 16-month trastuzumab arm, it was assumed that it was the same as the 12-month trastuzumab arm.

2. All patients that were under "disease free survival" were taking hormonal treatment for post-menopausal women. Only after local recurrence they would use drugs for pre-menopausal women. This is because from the interviews it was reported that majority of the patients were post-menopausal and the cost of treatment of post-menopausal women was higher.

3. Minor costs of various items were either added together and given a summary figure or omitted if insignificant.

4. Congestive heart failure due to trastuzumab costs approximately KSh 6000 to manage. There is a very low incidence in Kenya for the condition and hence it was excluded.

5. Recurrence of contralateral breast cancer was combined with local and regional recurrence.

6. Patients in local recurrence could transition to ‘distant recurrence’ while patients in the distant recurrence state remained in that state until death

7. It was assumed that the effectiveness of AC-T was equal to Docetaxel with FEC regimen from the FinHer trial for 9-week arm. (96)

8. Efficacy and cost of any regimen containing Docetaxel was replaced with that of Paclitaxel as they were assumed to be equal in effectiveness. (97)

9. The cost of being dead was assumed to be zero.

10. Effectiveness of the drugs are dependent on disease progression and not age.

3.2.6 Stimulated cohort for markov modelling

In this markov model, we assumed that 100 people joined the cohort every month with an initial cohort of 100 people. Therefore 1200 new people joined the cohort every year and after a period of 5 years the funder will treat 6100 individuals. This is the projected amount of people that were to be initiated on treatment over 5 years. We decided that 100 people would enter the cohort monthly, as there are about 6000 new cases of breast cancer diagnosed in 2018 in Kenya (1) and approximately 25% are HER+ (20). This translated to about 100 new cases monthly.

3.2.9 Data on utilities

The measures of health quality of life in breast cancer patients were taken from several studies as described in Table 10. The QALY value was determined by using the utility value associated with a given state of health and multiplying it with the number of years lived in that state. (98) Given that there were no Kenyan data on health-related quality of life in women from Kenya with breast cancer, sensitivity analysis was conducted to test the robustness of the assumption that the data obtained from these systemic reviews can be extrapolated to the local context.

Table 10: Health utility values for breast cancer

Parameter	Method used to measure utility	Base	Min.	Max.	Reference
Diagnosis (Core Biopsy)	Testing morbidity index (TMI)	0.84	0.63	0.93	Swan et al. (2015) (99)
Surgery (Breast Conservation Surgery)	Standard Gamble (SG)	0.76	0.683	0.827	Songtish et al.(2014) (100)
Radiotherapy	EuroQol – 5 Dimension (EQ-5D)	0.77	0.73	0.8	Prescott et al. (2007) (101)
Doxorubicin + Cyclophosphamide (AC)	EQ-5D	0.71	0.6	0.95	Garrison et al 2007 (102)
Paclitaxel + trastuzumab	EQ-5D	0.71	0.6	0.95	Garrison et al 2007 (102)
Trastuzumab only	Time trade off (TTO)	0.9	0.85	0.94	Lidgren et al 2007 (103)
Disease free survival (Anastrazole) in Year 1	EQ-5D	0.73	0.62	0.84	Seferina et al. (2017) (104)
Disease free survival (Anastrazole) in Year 2+	EQ-5D	0.805	0.65	0.93	Seferina et al. (2017) (104)
Diagnosis (Bone Metastasis)	TMI	0.84	0.63	0.93	Swan et al. (2015) (99)
Radiotherapy (Bone Metastasis)	TTO	0.41	0	0.86	Matza et al. (2013) (105)

Parameter	Method used to measure utility	Base	Min.	Max.	Reference
Chemotherapy (AC+Zolendronic Acid)	TTO	0.47	0.02	0.89	Matza et al. (2013) (105)
Chemotherapy (Zolendronic Acid + Palliative care)	TTO and SG	0.36	0.09	0.63	Bonomi et al. (2008) (106)
Modified Radical Mastectomy (Local recurrence)	SG	0.88	0.84	0.98	Hayman et al. (2005) (107)
Chemotherapy (Capecitabine + trastuzumab)	SG and TTO	0.7	0.5	0.8	Matter-Walstra et al. (2010) (108)
Radiotherapy (Local recurrence)	SG	0.61	0.35	0.87	Kim et al. (2017) (109)
Disease free survival (Tamoxifen)	SG	0.88	0.77	0.99	Mansel et al. (2007) (110)

TMI = Testing morbidity index, SG = Standard Gamble, EQ-5D = EuroQol – 5 Dimension and TTO = Time trade off.

3.2.10 Incremental cost effectiveness ratio (ICER)

The incremental cost effectiveness ratio was computed using the formulae presented:

Equation 4: Formula for computing the incremental cost effectiveness ratio (73).

$$ICER = \frac{Cost_{\text{intervention group}} - Cost_{\text{reference group}}}{Outcome_{\text{intervention group}} - Outcome_{\text{reference group}}}$$

The affordability of the regimen was determined by checking if the calculated ICER value was below or above the WTP threshold of US$ 919.11 (111) / KSh 111,212.31 (USD to KSh 121 as of 9/10/2022 (112)). If the ICER was above the WTP threshold than the intervention was deemed not affordable and vice versa.

3.2.11 Sensitivity Analysis

Sensitivity analysis was done to determine the robustness of the study results and to promote them applicability to the general population. One-way probabilistic sensitivity analysis was done using the *"dampack"* package in R (113). All the parameters that were used in the sensitivity analysis are listed in APPENDIX G with their corresponding minimum, maximum, base value, type of distribution, mean and standard deviation value. The results of the sensitivity analysis of the different cost parameters were presented in the form of tornado diagrams in the APPENDIX H

3.3 Budget impact analysis

Analysis was done to determine the total budget required for the various interventions over a 5-year period on eligible patients. It was obtained by multiplying the 5 year cost per patient for each regimen and multiplying it by the number of eligible patients. The number of eligible patients was determined by using the incidence and prevalence data for breast cancer in Kenya. The incidence was taken from the Globocan 2018 fact sheet (19) and prevalence of HER2+ breast cancer was taken from a study by Sayed et al. (20). The data was then used to calculate the expected number of patients with HER2+ breast cancer in Kenya. The 5 year cost per patient for the different regimens was determined using the Markov model. The resulting total 5 year cost for the total number of patients was divided by the total 5-year budget for NHIF and KNH separately. The resulting values were multiplied by 100 to determine the percentage of the 5-year budget that would be utilized for each intervention. The 5 year budget for NHIF was calculated using the Auditor general's report (114) and the 2018 financial report for KNH. (115) These values were inflated by 15% per year to cater for inflation.

3.4 Software

Microsoft excel was used to manage data. Transition probabilities were computed using the *Heemod* package for health economic evaluation for Markov chain models and *Dampack* package was used for the sensitivity analysis in R studio 1.2.1. The markov model analysis was done using base R as described by Filipovi et al. (116).

3.6 Ethical Consideration

Ethical approval was attained from University of Nairobi/ Kenyatta National Hospital Ethics and research Committee. Letter reference number P871/11/2019 (Appendix A). All information was handled with the uttermost confidentiality. The hard copies of documents and electronic information was only shared between the principal investigator and supervisors. Only information relevant to this study was extracted. No information that would identify an interviewee was taken and code numbers were used instead.

CHAPTER FOUR: RESULTS

4.1 Cost analysis for treatment HER2+ breast cancer patients

4.1.1 Cost of diagnosis of HER2+ breast cancer

The total for each cost parameter was calculated by multiplying the unit cost by the unit price of each individual item and then totaling the same. The cost of diagnosis is shown in table 11.

Table 11: Cost of diagnosis of HER2 breast cancer.

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	First Visit	1150	1	1	1150	2.5
2	Mammography	2500	1	0.5	1250	2.8
3	Breast Ultrasound	5000	1	0.5	2500	5.5
4	Chest CT scan	8000	1	1	8000	17.7
5	Abdominal Pelvic CT Scan	8000	1	1	8000	17.7
6	Biopsy	10000	1	1	10000	22.2
7	Histology	1100	1	1	1100	2.4
8	HER-2 test	2000	1	1	2000	4.4
9	Liver Function Test	900	1	1	900	2.0
10	UEC	700	1	1	700	1.6
11	Coagulation Profile	1000	1	1	1000	2.2
13	2D Echo	3000	1	1	3000	6.7
14	Ki67	5000	1	1	5000	11.1
15	Full Hemogram	500	1	1	500	1.1
16	Total Cost of Initial Diagnosis				45100	

UEC = Urea and creatinine test

The probability of incurring any of the cost items was estimated from the responses of the face to face interviews. The main drivers for the cost of diagnosis are chest CT scan, abdominal pelvic CT scan and biopsy. For patients 45 years and above a mammogram was done and breast ultrasound for those under 45 years.

4.1.2 Cost of Radiotherapy at an early stage for HER2+ breast cancer patients

Table 12: Cost of radiotherapy at an early stage

	Cost Category	Price	Quantity	Cost	Probability	Adjusted Cost	Percent
1	Repeat Visit	650	1	650	0.066667	43.33	0.9
2	Radiotherapy Session	3600	1	3600	1	3600.00	72.6
3	Radiotherapy Plan	10000	1	10000	0.066667	666.67	13.5
4	Radiotherapy Lab Total	1200	3	3600	0.066667	240.00	4.8
5	Nausea(Ondansetron oral)	8.86	6	53.16	0.7	37.21	0.8
6	Pneumonitis (Prednisolone)	10	15	150	0.01	1.50	0.0
7	Dermatitis (Hydrocortisone)	100	1	100	0.05	5.00	0.1
8	Mucocitis (Mouth Wash)	250	1	250	0.75	187.50	3.8
9	Mouth Ulcer (Mouth Wash)	250	1	250	0.7	175.00	3.5
10	Total Cost per session					4956.21	100
11	Total Cost of Early Radiotherapy	4956.21	15	74343.18	0.80	59474.54	

The percentage for each cost category shown in table 12 was calculated based on the total cost per session. The cost of repeat visits, radiotherapy planning and laboratory tests were divided equally based on the number of sessions, as each session did not incur the costs every time. The probability of getting a radiotherapy related toxicity was taken from the face to face interview. The probability of a patient to undergoing radiotherapy after surgery was 0.8 as per the face to face interview. The main drivers for the cost of radiotherapy were the cost per session of radiotherapy and the planning cost. Cost of treatment for the reference group, that was chemotherapy without trastuzumab are shown in table 13 and 14.

4.1.3 Cost of chemotherapeutic agents used in treatment of HER2+ breast cancer

Table 13: Cost of chemotherapy with doxorubicin and cyclophosphamide per cycle

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Chemo Administration	4500	1	1	4500	52.9
2	Doxorubicin	403	3	1	1209	14.2
3	Cyclophosphamide	191	3	1	573	6.7
4	Ondansetron	26.75	3	1	80.25	0.9
5	Dexamethasone	7.9	2	1	15.8	0.2
6	UEC	700	1	1	700	8.2
7	Full Hemogram	500	1	1	500	5.9
8	2D Echo	3000	1	0.25	750	8.8
9	Filgrastim	1150	1	0.1	115	0
10	Blood Transfusion	2000	1	0.025	50	0
11	FH for Blood Grouping	500	1	0.025	12.5	0
12	Blood Grouping	1000	0.25	0.025	6.25	0
13	Total Blood Side Effects				183.75	2.2
14	Total AC Chemo				8511.8	

The probabilities of getting a blood related side effect was got from the face to face interview. Patients would require to do the blood grouping only once every 4 cycles and hence the quantity was divided equally to each cycle. The main drivers for the total cost were the cost of chemo administration and the cost of the chemotherapeutic agents.

Table 14: Cost of paclitaxel per cycle

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Chemo Admin	4500	1	1	4500	39.53
2	Paclitaxel	1206.3	4	1	4825.2	42.39
3	Ondansetron	26.75	3	1	80.25	0.70
4	Dexamethasone	7.9	2	1	15.8	0.14
5	Chlorpheniramine	6	2	1	12	0.11
6	2D Echo	3000	0.25	1	750	6.59
7	UEC	700	1	1	700	6.15
8	Full Hemogram	500	1	1	500	4.39
9	Total Cost per Cycle	0	0	0	11383.25	100.00

The main cost drivers for were chemotherapy administration fee and the cost of the chemotherapeutic agents. The 2D echo is done once every four cycles, thus the cost was divided equally between the four cycles.

4.1.4 Cost of trastuzumab containing treatment cycles

Those patients that were on a regimen containing trastuzumab the, the cost are shown in table 15, 16 and 17.

Table 15: Cost of treatment with Paclitaxel and Trastuzumab (Cycle 1)

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Chemo Admin	4500	1	1	4500	2.38
2	Paclitaxel	1206.3	4	1	4825.2	2.55
3	Trastuzumab	88995	1	2	177990	93.99
4	Ondansetron	26.75	3	1	80.25	0.04
5	Dexamethasone	7.9	2	1	15.8	0.01
6	Chlorpheniramine	6	2	1	12	0.01
7	2D Echo	3000	0.25	1	750	0.40
8	UEC	700	1	1	700	0.37
9	Full Hemogram	500	1	1	500	0.26
10	Herceptin Loading Dose				189373.3	0

Table 16: Cost of treatment with Paclitaxel and Trastuzumab (Cycle 2-4)

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Chemo Admin	4500	1	1	4500	4.48
2	Paclitaxel	1206.3	4	1	4825.2	4.81
3	Trastuzumab	88995	1	1	88995	88.66
4	Ondansetron	26.75	3	1	80.25	0.08
5	Dexamethasone	7.9	2	1	15.8	0.02
6	Chlorpheniramine	6	2	1	12	0.01
7	2D Echo	3000	0.25	1	750	0.75
8	UEC	700	1	1	700	0.7
9	Full Hemogram	500	1	1	500	0.5
10	Trastuzumab + Paclitaxel Continuation Dose	0	0	0	100378.3	0
11	Total Cost per Cycle	0	0	0	100378.3	0

Table 17: Cost of treatment with trastuzumab only per cycle

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Chemo Admin	4500	1	1	4500	4.7
2	Trastuzumab	88995	1	1	88995	93.2
3	2D Echo	3000	0.25	1	750	0.8
4	UEC	700	1	1	700	0.7
5	Full Hemogram	500	1	1	500	0.5
6	Total Only Herceptin Cost per Cycle				95445	

For the regimens that contained trastuzumab the main cost driver was the price of trastuzumab.

4.1.5 Total costs of all parameters

The total cost of the various cost parameters was summarized and presented in Table 18. The remaining tables for the other cost parameters can be found in APPENDIX H.

Table 18: Totals of different cost parameters

Cost Description	Median cost per cycle (Kshs)	Range (Kshs)
Diagnosis	44137 [38976, 49636]	27389 - 68906
Early stage Radiotherapy (cost of 15 sessions)	47824 [37951, 66129]	18307 - 106536
Doxorubicin & cyclophosphamide cost per cycle	8373 [7265, 9626]	5568 - 11795
Paclitaxel cost per cycle	10144 [8067, 13214]	4567 - 23034
Paclitaxel & trastuzumab (loading dose) cost per cycle	195781 [152382,247564]	62865 - 536949
Paclitaxel & trastuzumab (continuation) cost per cycle	95114 [74186, 118786]	50012 - 187808
Trastuzumab cost per cycle	92714 [76715, 113407]	36860 - 181342
Fluorouracil, epirubicin & cyclophosphamide cost per cycle	14930 [13022, 17057]	9189 -29098
Disease free survival (Anastrazole) for the first 2-years cost per cycle	1469.2 [1120.9, 1974.9]	672.2 - 4119.8
Cost Description	**Median cost per cycle (KSh)**	**Range (KSh)**

Disease free survival (Anastrazole) for year 2-5 cost per cycle	638.8 [496.8, 771.4]	289.4 - 1786.2
Radiotherapy for Local recurrence/ bone metastasis (5 sessions)	29362 [23300, 38172]	14592 - 107923
Local recurrence overall cost (over 5 years)	967590 [856134, 1141139]	543786 - 1655629
Metastasis overall cost (over 5 years)	570510 [479588, 660041]	289058 - 1236612

[Inter quartile range]

The median value and range were obtained from the probabilistic sensitivity analysis for each cost parameter. As per the face-to-face interview there was an 80% chance that a patient would need to undergo fifteen sessions of radiotherapy after breast conservation surgery and for patients with local recurrence would undergo five sessions of radiotherapy after modified radical mastectomy. Patients with metastasis underwent five sessions of radiotherapy as well. The monthly costs for DFS reduced after the second year, because the frequency of mammograms, laboratory investigations and specialist visits reduced.

4.1.6 Yearly cost of the 12-month group

The yearly cost for those patients that were in the 12-month group is summarized in table 19 to show which years during treatment bare the majority of the costs.

Table 19: Yearly cost of treatment with trastuzumab in the 12-month group

	Cost Category	**Cost**	**Percent**
1	Year One	774297.3	41.1
2	Year Two	1051550	55.8
3	Year Three	19857.6	1.1
4	Year Four	19762.15	1.0
5	Year Five	18712.2	1.0
6	Total	1884179	100.0

The first two years had the main share of the costs as this was the period the patients had to undergo diagnosis, surgery, radiotherapy and chemotherapy. The second year was the most expensive as

the majority of this phase involved treatment with trastuzumab. On completion of chemotherapy the yearly costs reduced significantly.

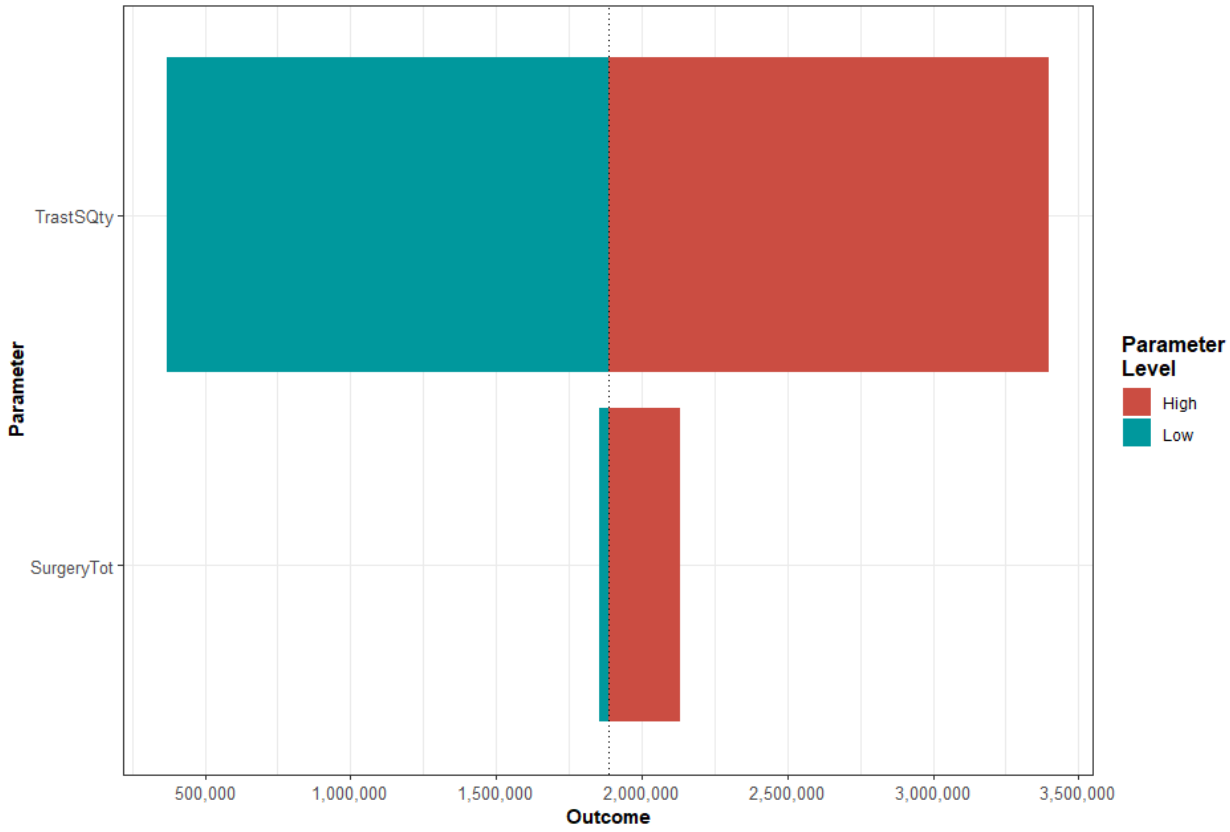


Figure 9: Tornado diagram for yearly costs.

The tornado diagram in figure 9 showed that the quantity of trastuzumab and cost of surgery were the main parameters that affected the total cost. If the quantity of trastuzumab was increased, then the total cost for treatment increased to above KSh 4,000,000 and reduced to below KSh 500,000 if minimal quantities of trastuzumab was used.

4.2 Cost Effectiveness analysis of different treatment regimens

As expected as the duration of treatment increased, the costs increased and this is shown in Figure 10. The 6-month regimen showed extended dominance, which meant that the increase in the cost was far above the expected increase in benefit. This was reflected by the fact that it had the highest ICER value as shown in Table 20.

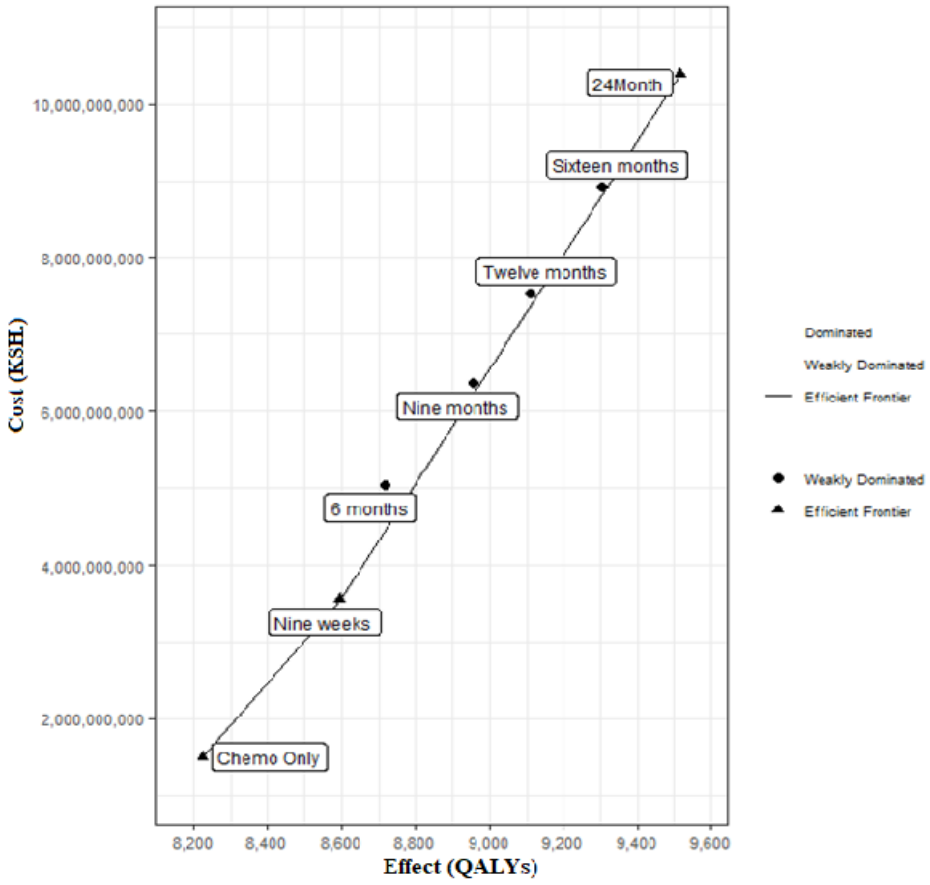


Figure 10**: Cost-effectiveness plane of the cost and effectiveness of trastuzumab based regimens in Kenya.**

The reference intervention was chemotherapy alone and it was the least costly and the least effective option.

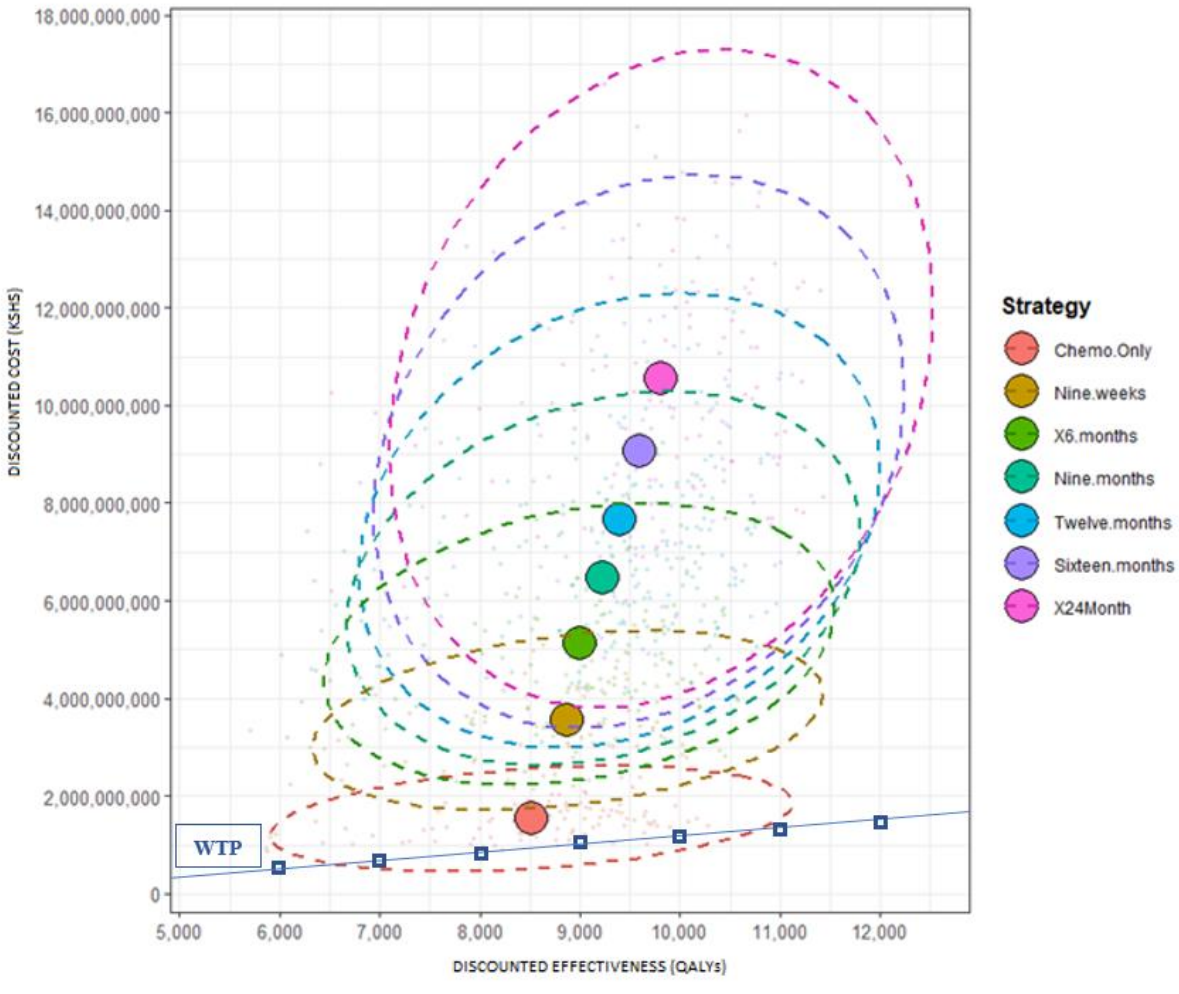
Table 20: Total costs and incremental cost effectiveness ratios (ICER)

Parameter	**Total Discounted Cost**	**Total Discounted QALYs**
Chemotherapy only	KSh1,501,511,708.97	8223.97
Nine weeks of trastuzumab	Ksh3,551,867,002.44	8595.60
6-month of trastuzumab	Ksh5,037,968,695.01	8718.40
Nine months of trastuzumab	Ksh6,359,775,032.30	8955.62
Twelve months of trastuzumab	Ksh7,532,863,840.32	9110.31
Sixteen months of trastuzumab	Ksh8,918,469,826.08	9303.01
Twenty four months of trastuzumab	Ksh10,383,541,479.20	9516.07
Differences	**Total Discounted Cost**	**Total Discounted QALYs**
Chemotherapy only	0.00	0.00
Nine weeks of trastuzumab	Ksh2,050,355,293.47	371.63
6-month of trastuzumab	Ksh3,536,456,986.04	494.43
Nine months of trastuzumab	Ksh4,858,263,323.33	731.65
Twelve months of trastuzumab	Ksh6,031,352,131.35	886.34
Sixteen months of trastuzumab	Ksh7,416,958,117.10	1079.04
Twenty four months of trastuzumab	Ksh8,882,029,770.23	1292.10
ICER	**ICER (KSh/QALY)**	
Chemotherapy only	-	
Nine weeks of trastuzumab	5,517,149	
6-month of trastuzumab	7,152,617	
Nine months of trastuzumab	6,640,186	
Twelve months of trastuzumab	6,804,768	
Sixteen months of trastuzumab	6,873,654	
Twenty four months of trastuzumab	6,874,096	

The regimen with lowest ICER was found to be nine weeks of trastuzumab at 5,517,149 KSh per QALY gained, which was closely followed by nine months of trastuzumab at 6,640,186 KSh per QALY gained. The 9, 12, 16 and 24-month regimens had ICER values of 6,640,186 KSH/QALY

gained, 6,804,768 KSh/QALY gained, 6,873,654 KSh/QALY gained and 6,874,096 KSh/QALY gained respectively.

4.3 Acceptability of the intervention on the basis of willing to pay threshold



The blue line represents a WTP threshold of Kenya of USD 919.11 (111) */ KSh 111212.31 (USD to KSh was 121 on (14/10/2022)*(112)*) The dotted lines represents the confidence elipse of the point estimates of the cost effectiveness ratios.*

Figure 11: ICER confidence elipse of trastuzumab based intervention

From figure 11, we saw that there was a very wide overlap in the confidence ellipse. This meant that even small changes in costs greatly affect which intervention is more cost effective. For instance, the confidence ellipse of the 24-month regimen overlapped nearly all other regimens. This meant that at sub-optimal combinations of cost inputs and treatment outcomes the 24-month regimen can be comparable to a 9-week regimen. With the current threshold of USD 919.11 / KSh 111212.31, none of the trastuzumab containing regimens are affordable.

4.4 Sensitivity analysis of the incremental cost effectiveness ratio

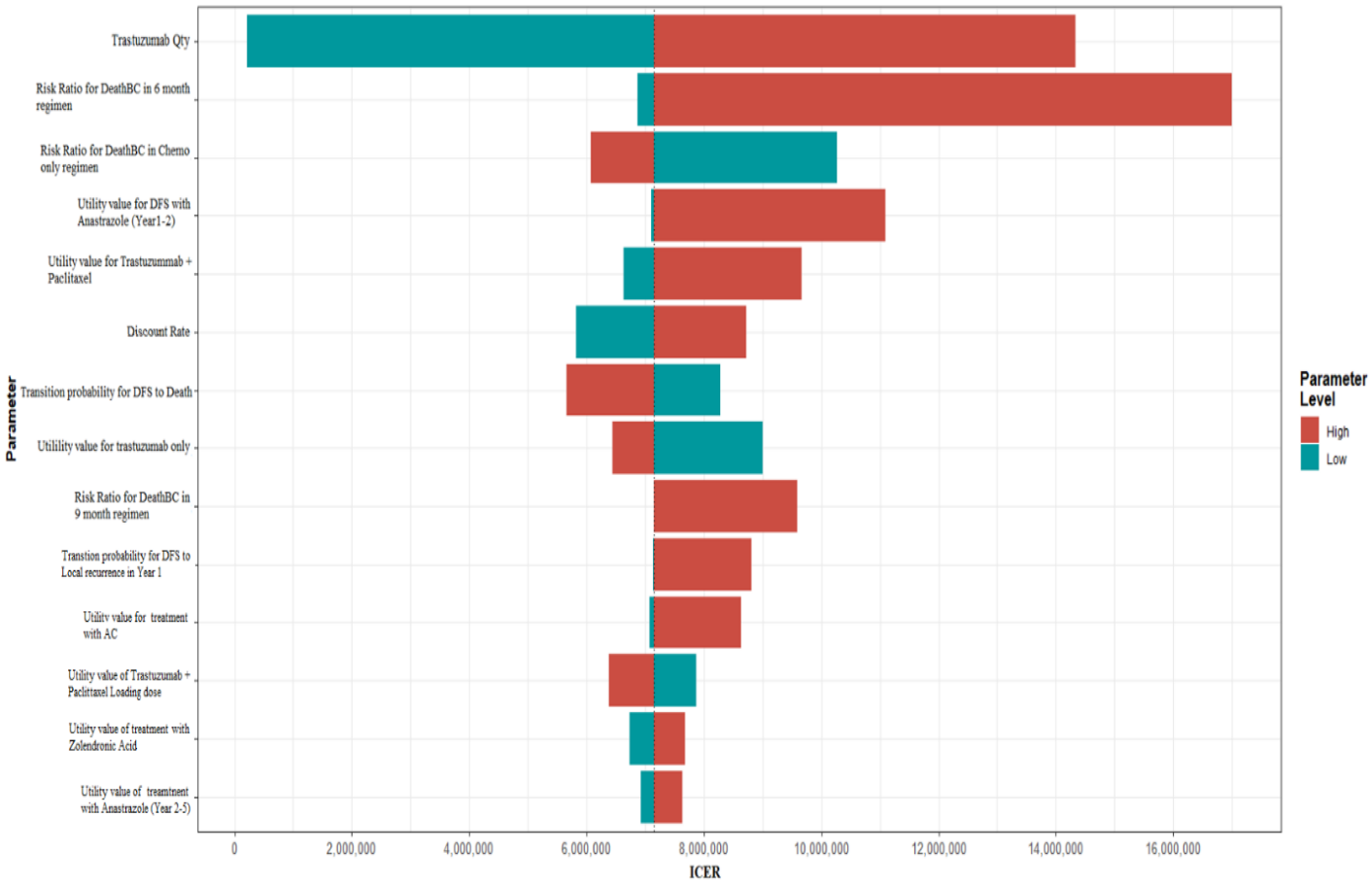


Figure 12: Tornado diagram for incremental cost effectiveness ratio

The sensitivity analysis showed that the main parameter that can drastically affect the ICER value is the quantity of trastuzumab used. It can reduce the ICER to less than 200,000 KSh/QALY gained

and increase it to above 14,000,000 KSh/QALY gained. Other parameters that affect the ICER value are risk ratio for death by breast cancer for the different regimens, utility value for disease free survival using anastrazole and discount rate.

4.5 Cost effectiveness acceptability curve

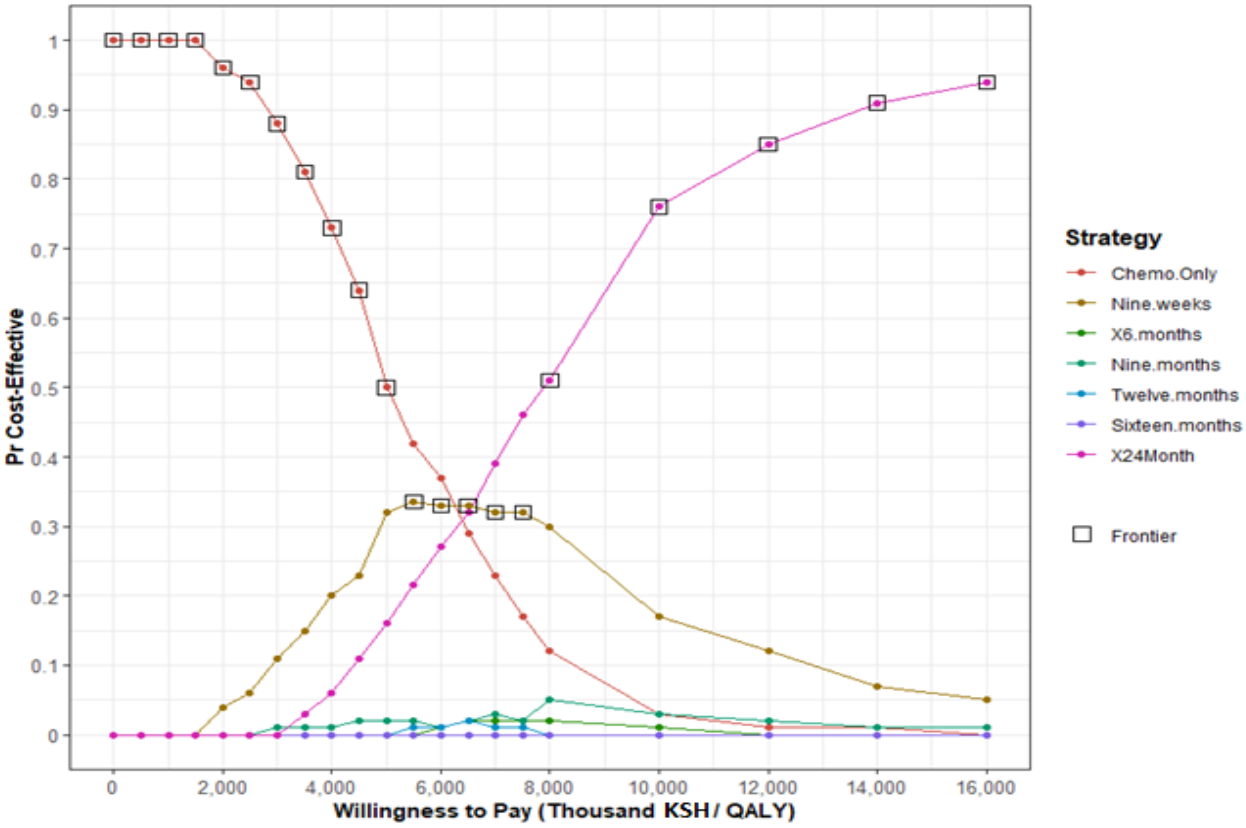


Figure 13: Cost effectiveness acceptability curve.

The curve shown in the figure 13, is used to show the most acceptable intervention for policy makers based on how much they are willing to pay for extra benefit. From the curve when the willingness to pay of Kenyan policy makers ranged between 0-1,750,000 KSh/QALY gained, the intervention of choice would be chemotherapy alone. Thus with the current WTP the regimen with the highest probability to be chosen is chemotherapy alone. It would remain the intervention of choice even though willingness to pay ranged from 1,750,000-6,250,000 KSh/QALY gained.

When the willingness to pay is approximately between 6,200,000-6,500,000 KSh/QALY gained the 9-week regimen has the highest probability to be accepted. Above a willingness to pay of 7,000,000 KSh/QALY, the 24-month regimen has the highest chance of being considered.

4.6 Projected survival and mortalities of patients in the 12-month trastuzumab group over a 5-year period

Table 21: A summary of projected individuals in each state. The 12-month regimen was selected as this is the standard recommended duration.

	DFS	LR	MET	DEATH BC	DEATH ACM	CUMULATIVE MORTALITY	TOTAL PATIENTS
YEAR 1	1247 (95.9%)	9 (0.7%)	15 (1.2%)	23 (1.8%)	6 (0.5%)	29 (2.2%)	1300
YEAR 2	2336 (93.4%)	22 (0.9%)	40 (1.6%)	81 (3.3%)	21 (0.8%)	102 (4.1%)	2500
YEAR 3	3300 (89.2%)	39 (1.1%)	72 (1.9%)	243 (6.6%)	45 (1.2%)	288 (7.8%)	3700
YEAR 4	4135 (84.4%)	55 (1.1%)	103 (2.1%)	530 (10.8%)	77 (1.6%)	607 (12.4%)	4900
YEAR 5	4863 (79.7%)	69 (1.1%)	131 (2.1%)	921 (15.1%)	115 (1.9%)	1036 (17.0%)	6100

DFS = Disease free survival, LR = Local recurrence, Met = Metastasis, BC = Breast cancer and ACM = All-cause mortality

The total number of patients that will require treatment in the first year will be 1300 and the projected mortality in this year is 29 patients, which is about 2%. The cumulative mortality will increase yearly and out of 6100 patients initiated with trastuzumab about 17% of them will die at the end of 5 years.

It is projected that the 0.7% patients will get a local recurrence in the first year and 1.1% of them will get a local recurrence at the end of five years. Another worsening outcome is metastasis and about 1.2% of patients will get metastasis in the first year. At the end of a 5-year period, about 2.1% of the totals patients will get metastasis.

In the first year nearly 96% of the patients will remain in disease free survival and the end of 5 years, 8 out of 10 patients will be living disease free.

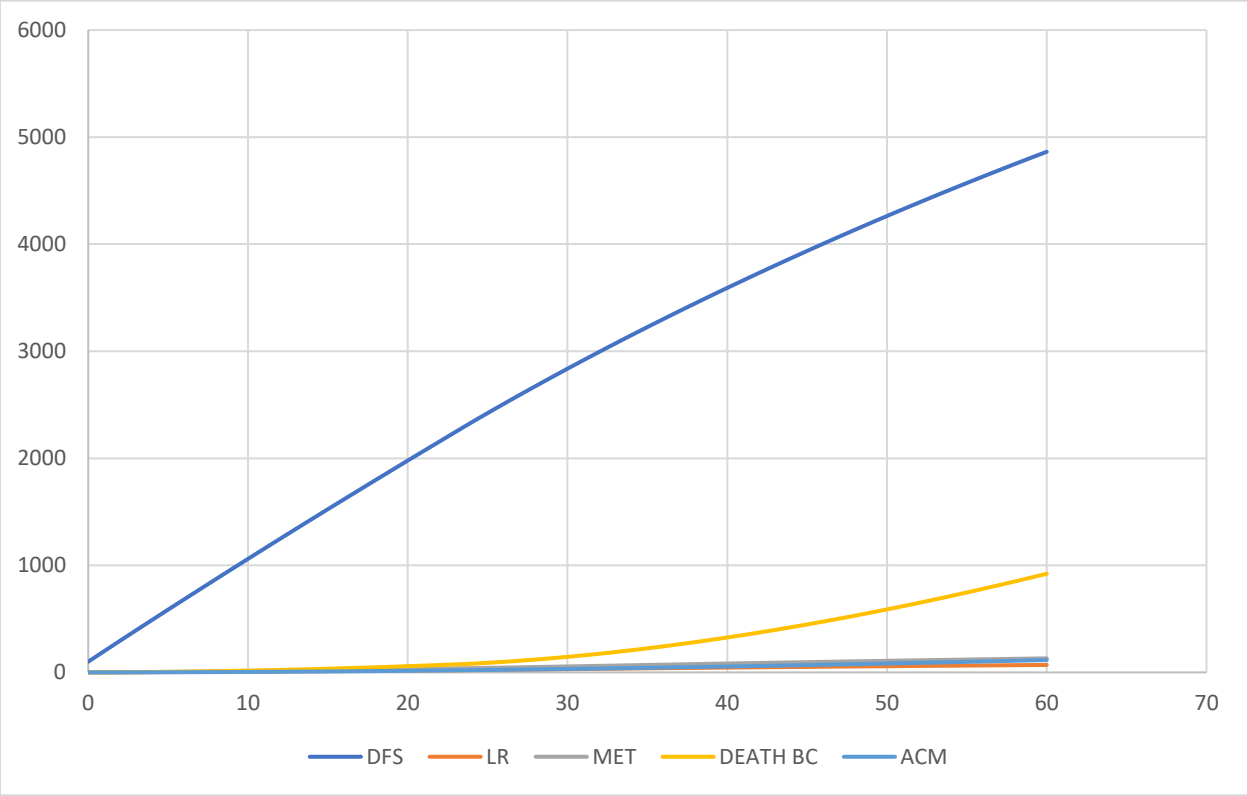


Figure 14: Number of people in each state at different time intervals

The graph shown in figure 14 is curvilinear. The graph shows that as time goes on the of patients that die due to breast cancer has an exponential increase.

4.7 Budget impact Analysis

4.7.1 Impact on the budget of National Health Insurance Fund

From the Table 22 we can see that the regimen for nine weeks will be the most feasible for NHIF at a total cost of KSh 4,198,272,901.11 for a period of 5 years for the projected 6100 patients in the given period. This will account for approximately 1.4% of the 5-year forecasted NHIF expenditure. In the year 2019, NHIF spent KSh 45,922,051,651 for claims as per the Auditor general's report (114). We inflated the value by 15% per year to cater for inflation and got a 5-year total of KSh 309,623,980,013 as the projected 5-year expenditure for claims for NHIF.

Table 22: Budget impact analysis for National Health Insurance Fund

Name	Total cost for 5 year period for 6100 patients	Percentage of forecasted 5-year NHIF expenditure utilized
Chemotherapy Only	KSh 1,787,067,938.17	0.6 %
Nine weeks	KSh 4,198,272,901.11	1.4 %
Six months	KSh 5,994,070,588.13	2.0 %
Nine months	KSh 7,591,414,624.26	2.5 %
Twelve months	KSh 9,025,372,690.93	3.0 %
Sixteen months	KSh 10,737,335,800.23	3.5 %
Twenty Four months	KSh 12,581,773,574.62	4.0 %

4.7.2 Impact on the budget of Kenyatta National Hospital

The number of new patients visiting Kenyatta National Hospital per month with a diagnosis of breast cancer was approximately 120 as per the face-to-face interview. This equated to about 30 new HER2+ patients per month. Therefore, over a period of 5 years KNH should see 1830 HER2+ breast cancer patients. From Table 20 we can deduce that the 9-week regimen is the cheapest trastuzumab containing regimen. The total cost for the 5-year period for the projected 1830 patients will be KSh 1,259,481,870.33 for KNH. As per the 2018 financial report for KNH, the total revenue in the financial year ended of 2018 was KSh 12,761,866,000 (115). We inflated the value

by 15% per year to cater for inflation and got a 5-year total of KSh 86,045,366,033.41 as the projected 5-year revenue.

Table 23: Budget impact analysis for Kenyatta National Hospital

Name	Total cost for 5 year period for 1830 patients	Percentage of forecasted 5-year KNH revenue utilized
Chemotherapy Only	KSh 536,120,381.45	0.6 %
Nine weeks	KSh 1,259,481,870.33	1.5 %
Six months	KSh 1,798,221,176.44	2.1 %
Nine months	KSh 2,277,424,387.28	2.7 %
Twelve months	KSh 2,707,611,807.28	3.2 %
Sixteen months	KSh 3,221,200,740.07	3.7 %
Twenty Four months	KSh 3,774,532,072.38	4.4 %

CHAPTER FIVE: DISCUSSION

5.1 Discussion of the findings

Patients with breast cancer that are HER2+ have an increased risk for mortality and progression to metastasis. In recent years the treatment of choice for patients with HER2+ breast cancer is trastuzumab. (117) Given the high cost of trastuzumab the policy makers in Kenya have limited it's use and the number of cycles covered to 4 per year. However, this may be associated with reduced treatment effectiveness. The important questions that needed to be answered for policy makers was whether the use of trastuzumab is cost-effective in Kenya, and if it is then what is the ideal duration of use, that is affordable and at the same time effective. In this study we compared the costs and effectiveness of different treatment protocols with trastuzumab against chemotherapy without trastuzumab. Using the WTP for Kenya of US$ 919.11 (111)/ KSh 111,212.31 (USD to KSh 121 as of 9/10/2022(112)) none of the trastuzumab containing regimens were affordable in the Kenyan context. This was expected as the cost of treatment with trastuzumab is currently very high as a single vial costs about KSh 90,000. Although we used the standard willingness to pay threshold, it is acceptable to vary the value based on the severity of illness as per the study by Schurer et al. (118)

From our study the projected overall survival associated with the 12-month regimen was 83% and the 5-year disease free survival is projected to be about 79.7%. A study by Slamon et al showed that the disease free survival for a five-year period was 84%. (53) A Canadian study showed that the overall survival for HER2+ breast cancer patients was 88.6% (77.4-94.4%) and disease free survival was 74.9% (64.1-82.9%) (119). Therefore, the projections for our study are within those found in literature. A study done by Tuwei et al. at Kenyatta National hospital showed the 4-year survival rate of HER2+ breast cancer patients as 62.5%. The low survival rate was attributed to lack of access to trastuzumab, treatment initiation at a late stage, lack of early screening and economic constraints. (120)

Our study found that the median cost of treatment with chemotherapy without trastuzumab over a five-year period was KSh 302,294 [266,966, 344,179]. It was the least costly option in Kenya, but

also the least effective regimen. Various studies including one done by Gitonga et al. (53–55,84) reported a lower cost for treatment with chemotherapy alone. Gitonga's study underestimated cost of diagnosis, radiotherapy, chemotherapy and duration of hormonal treatment. The cost of planning radiotherapy, treatment of side effects, number sessions were not adequately factored in. Also the cost of treatment with paclitaxel for 4 cycles was not considered and the cost of hormonal treatment was limited to only six months of therapy. Our study shows that chemotherapy alone is the least costly, least effective and the most affordable regimen in resource limited settings. The selection of sub optimal therapy is a reality in many African countries, whereby patients break-down emotionally when informed about trastuzumab based treatments. (121) In African countries chemotherapy is often paid out of pocket. Regimens that lack trastuzumab would not be considered by policy makers who might have a low willingness to pay.

Existing literature on the cost and effectiveness on various trastuzumab based regimens is inadequate in sub Saharan Africa. To date only one study compares the costs and effectiveness of trastuzumab based therapy has been done for patients in Africa. (17) However this study used a gross costing approach and a single standard cost for all sub-Saharan countries of USD 20,000 for the treatment with trastuzumab. Given that costs are highly context specific the findings of this study may not apply in the Kenyan context.

From our analysis we got a median cost for treatment with trastuzumab in the 12-month group as KSh 1,785,993 [1,509,328, 2,155,869] which at the current exchange rate of 1 USD = 121 KSh (112), gives a median cost of approximately USD. 14,760. This includes the cost of surgery, radiotherapy, chemotherapy with trastuzumab for one year and hormonal therapy for a period totaling 5 years. Majority of the cost in the first year of treatment is paid towards the diagnostic test, radiology and surgery. From the second year onwards the main cost driver is chemotherapeutic agents. For regimens containing trastuzumab, approximately half the cost is paid in the first year and the remain in the second year as the cost of trastuzumab greatly affects the overall cost. As per a study by Gitonga et al. (84) done at KNH, the total cost over a 5 year period with trastzumab was KSh 1,700,000. Although some of the costs were omitted in the study by

Gitonga et al as stated earlier, these costs had a minimal effect on the total cost of treatment with trastuzumab. Our cost analysis seemed to exactly match the findings by Gitonga et al. despite use of different costing methodologies. This validates our findings. The study by Gershon et al. (17) that showed a much higher cost of USD. 20,000 for treatment with trastuzumab in Kenya. The study did not evaluate changes in costs and effectiveness with varying duration of therapy. To the best of our knowledge our study is the first in the Kenyan context that used a micro-costing/bottom-up approach to estimate the costs of trastuzumab therapy for varying durations. Unlike many cost effectiveness studies (54,55,59,61,94) on trastuzumab, ours is probably the first that evaluated six different interventions containing trastuzumab. There is paucity of cost effectiveness research in Kenya and ours represents the limited basket of available studies.

Using the chemotherapy alone, 9-week and 12-month regimens as bench mark the median cost of treating a patient for the first year was KSh 221,324 [193,317, 259,062], KSh 554,230 [502,671, 645,316] and KSh 740,251 [669,637, 848,841] respectively. The majority of the cost (>75%) was incurred in the first year as all the diagnostic, radiotherapy and chemotherapy was done in the first year. The cost drastically reduces in the consecutive years. For the 12-month group the first year took up about 40% of total cost and the second year took up 56% of the total cost. This is because the treatment with trastuzumab was mainly done in the second year and it is the major cost driver as per the sensitivity analysis. Policy makers should target cost containment measures to the first year of therapy.

The cheapest trastuzumab containing intervention as per our study was the 9-week group, if adopted the incremental/added cost over chemotherapy alone is KSh 2,050,355,293.47 and incremental/ added benefit is an additional 371.63 QALYs gained. This gave an ICER value of 5,517,149 KSh/QALY gained. Even though the 9-week regimen is cheaper, but from literature (57,61,122) it is less effective, but still remains superior to chemotherapy alone. It is important to note that we costed for paclitaxel as opposed to docetaxel because as per the face-to-face interview it was the drug of choice of choice at KNH and was widely used in many clinical trials. We therefore assumed paclitaxel is equally as effective as docetaxel which was the drug of choice in

the Fin-HER, SOLD and Short-HER trial. In the SOLD trial it was noted that 9-week regimen was more effective with higher doses of docetaxel of 100mg/m2. If the 9-week regimen is adopted than the dose of Docetaxel should be increased to 100mg/m2 to achieve an efficacy that is similar to that of one year trastuzumab. Since the 9-week regimen had the lowest ICER, it would be ideal for Kenya. In Kenya patients are expected to undergo 1 year of treatment with trastuzumab where the National insurer only covers a fraction of the treatment. Policy makers could look at the 9-week treatment protocol as it has a duration of treatment with trastuzumab that is currently covered by the NHIF and is shown to be effective in clinical trials.

From literature it has been shown that the addition of trastuzumab to standard chemotherapy has shown to be more effective than standard chemotherapy on its own as shown in table 4. From the one-way sensitivity analysis, we managed to deduce that the quantity of trastuzumab used is the major factor that affects the overall cost of treatment with the drug. Another factor that affected the ICER was the mortality for the various durations of trastuzumab, which was seen in the study by Gershon et al. (17) Factors that increase the mortality should be controlled, such as timely treatment, early treatment initiation and more aggressive treatment such as radiotherapy and modified radical mastectomy. Pharmacists should be encouraged to use good dispensing practices and promote sharing of vials where applicable. The government needs to negotiate better prices for the drug and source for bio-similars.

In the cost effectiveness plane all trastuzumab based regimens with exception of the 6-month regimen were on the cost effectiveness frontier. This meant that the 6-month regimen was affected by extended dominance. This means that for all other regimens except the 6-month regimen, as the cost increased there was a linear increase in effectiveness. There two studies done that show conflicting data with regards to the effectiveness of the 6- month regimen vis-a-vie 12-month regimen. A study by Deng et al. (59) showed that the 1 year regimen is more effective than the 6-month regimen, while the study by Elsisi et al. (92) stated the contrary. At this point in time, there is not enough evidence to replace the 12-month regimen with the 6-month regimen as the gold standard, given the conflicting data on effectiveness. The 6-month regimen had an ICER of

7,152,616.73 which the largest of the interventions that were considered. Nonetheless from our findings it is more effective than the 9-week regimen.

From literature regimens that were longer than 12-month were not more effective. The HERA trial (55) showed that treatment for 2-years of trastuzumab is not more effective than treatment for one year. We found no other study in literature to show that treatments longer than one year would be more effective than the one-year regimen. Therefore, long treatment regimens should not be encouraged.

It is unlikely that in any resource limited country like Kenya any of the trastuzumab containing regimens would be included in the benefit package of a social health insurer. Given the cash constraints, these regimens are unlikely to be accepted by NHIF. Most African countries do not readily use trastuzumab for treatment due to the high cost of treatment. A study by Vanderpuye et al. (14) stated that out-of-pocket payment for trastuzumab is affordable for < 20% of patients in sub-Saharan Africa. Patients that cannot afford the 12-month regimen, the 9-week regimen can be recommended as a suitable alternative, and the 6-month regimen can also be considered based on ability to pay. The 12-month regimen remains the gold standard in terms of effectiveness.

As per literature, during treatment with trastuzumab there is a low chance of a decrease in LVEF in patients. These patients are required to do a baseline 2D echogram and treatment is delayed till the LVEF becomes normal again. As per our face-to-face interviews we found out that the incidence of cardiac events due to trastuzumab, is extremely low at KNH and in case of an event the cost associated with the event would be approximately between KSh 6000-10000. Therefore, given that the cost would be insignificant, the cost and utility associated to a cardiac event was omitted. This was omitted in the other known study that showed the cost effectiveness of trastuzumab in Sub-Saharan countries including Kenya by Gershon et al. (17)

As per the budget impact analysis the 9-week regimen would result in an increase in the 5-year expenditure by 1.4% if all patients diagnosed countrywide are put on treatment. A 1-2% increase in the budget can be absorbed by lobbying for higher premiums, by adding healthier people to the

scheme and more rational spending. The current policy direction with regards to social insurance by the government is to increase the premiums to be paid by the insured (123).

The ICER value for our study was higher than those found in literature. In other studies, the ICER was much lower, but this is expected as costs are context specific and the QALY values from our study were lower than other studies because we had a shorter time horizon, the size of the opening cohort was small with 100 patients and other studies generally used a single utility value for a single year, were as our study varied utilities monthly as shown in table 10. Our study also used transition probabilities from studies done in LMIC and not clinical trials, as a result the treatment outcomes were worse and therefore the benefit from treatment was lower. Risk ratios used in our study were also mainly from studies that were not RCTs. As per the study by Ioannou et al. (90) it shows that as the time horizon increase the ICER for a given intervention reduces. The ICER for our study was high as the time horizon was short.

Addition of trastuzumab to the oncology benefits package will also lead to better treatment outcomes. This will reduce the number of patients requiring surgery and hospitalization as the incidence of local recurrence and metastasis will reduce. This leads to cost saving, lesser strain on the healthcare workforce and increased availability of hospital beds. There is a reduction in morbidity and mortality, which leads a more productive population.

Policy makers should look into increasing targeted screening of breast cancer so as to detect the disease early and this would lead to better treatment outcomes. Another limitation of our study was that the data on effectiveness and utility of trastuzumab were based on studies majorly done outside Africa.

It is important to get a buy in from the NHIF & KNH board and increased budget allocation for oncology drugs. Implementation of this policy can be done in an incremental approach. It can be started with level 6 public health facilities and this can then be scaled up to all facilities in the country. Policy makers can use the initial time period for policy learning and diffusion. (124) To minimize wastage caps should be place on reimbursement based on reference prices.

5.2 Study Limitations

The health utility values were taken from systemic reviews as Kenyan data for the same is not available. Sensitivity analysis was done to cater for these assumptions. Nonetheless a quality of life survey still needs to be conducted in Kenya.

Patients that are hormone receptor negative are more prone to recurrence and death. We assumed that all patients are hormone receptor positive. Although there are some cohort studies done in Kenya (93,120) we could not use the findings to compute transition probabilities because the mortalities were very low and this reflected that the quality of the studies were affected by loss to follow-up, non- adherence to therapy and abscondment.

We assumed a coverage of 100% for interventions, yet during implementation coverage gradually increases. Hence for the budget impact analysis, the impact over the next 5 years is greater than maybe realized in a real life scenario.

Some of the quantities and prices of the costing parameters/items used for the sensitivity analysis were estimated from the face to face interview and these could have been affected by response bias. The probabilities used in the cost analysis were based on expert opinion.

Our study findings cannot be applied to the majority of breast cancer patients in Kenya, as most patients present at stage III & IV and most are not HER2 positive as per a studies by Sayed et al. (125) and Tuwei et al. (120)

CHAPTER SIX: CONCLUSION AND FUTURE RESEARCH

6.1 Conclusion

Our study shows that interventions containing trastuzumab are more expensive but also more effective. As per the current willingness to pay threshold for Kenya none of the trastuzumab containing regimens were affordable. In order to make any of the trastuzumab containing regimens cost effective, the government would need to get significant discounts on trastuzumab and train health care workers on good dispensing practices to avoid wastage, to make treatment with trastuzumab more affordable. Patients would also need to have good adherence to the treatment for better outcomes and in-turn this will improve the cost-effectiveness ratio. The current treatment guidelines state treatment of HER2+ positive breast cancer with the 12-month trastuzumab regimen, which cost about KSh 2.7 million. This amount is not affordable to a majority of the population. NHIF could consider paying for this as it would take up about 3% of their budget or opt for the 9-week regimen that would consume less than 2% of their budget. This would cushion the patients from the high costs and lead to better treatment outcomes.

6.2 Recommendations for policy makers

1. Policy makers should look into investing in screening for breast cancer as the treatment outcomes for early stage disease are better as compared to late stage.

2. The Kenyan government should negotiate prices for drugs such as trastuzumab with importers and look into manufacturing a bio-similar locally.

3. NHIF should cover the total cost of diagnosis in totality, for patients with breast cancer by adding the investigations into the oncology benefits package.

4. Better data capture on cancer patients should be available and accessible for future research. This can be done by improved documentation of patient outcomes by using software for electronic medical records. These records should be updated real time or at appropriate intervals in the National Cancer Registry.

5. The improved health outcomes from trastuzumab use can lead to lower incidence of local recurrence and metastasis, thus reducing patient hospitalization and workload on healthcare workers. This in turn may lead to cost savings, reduce hospital beds utilization and a more productive population.

6.3 Recommendations for practice

1. Good dispensing practices should be observed at all times when handling chemotherapeutic agents, so as to reduced wastage and spillage.

2. Direct procurement from manufacturers of chemotherapeutic agents and use of generics or bio-similars can reduce the overall cost of treatment.

3. To improve effectiveness, treatment delays should be avoided and patients should be counselled to improve adherence to treatment.

6.4 Future research

1. Given that there are different types of 9-week regimens, clinical trials are required to compare the efficacy amongst them to show which is the superior regimen.

2. Studies are also needed to compare the efficacy and safety of 9-week and 6-month regimen.

3. Cost effectiveness and utility studies are needed from the African setting to compare the cost effectiveness and utility values of trastuzumab and pertuzumab.

4. Given that in many African countries, majority of patients present at later stages, a cost benefit analysis demonstrating the benefit of targeted screening for breast cancer are needed to show the benefit to policy makers.

5. Costing studies from the patients point of view should be done for trastuzumab, for a more comprehensive assessment of affordability given that treatment is often paid out of pocket.

6. Larger studies in the Kenyan context are required to determine if 9-week of trastuzumab with high dose docetaxel is non-inferior to 1-year regimen.

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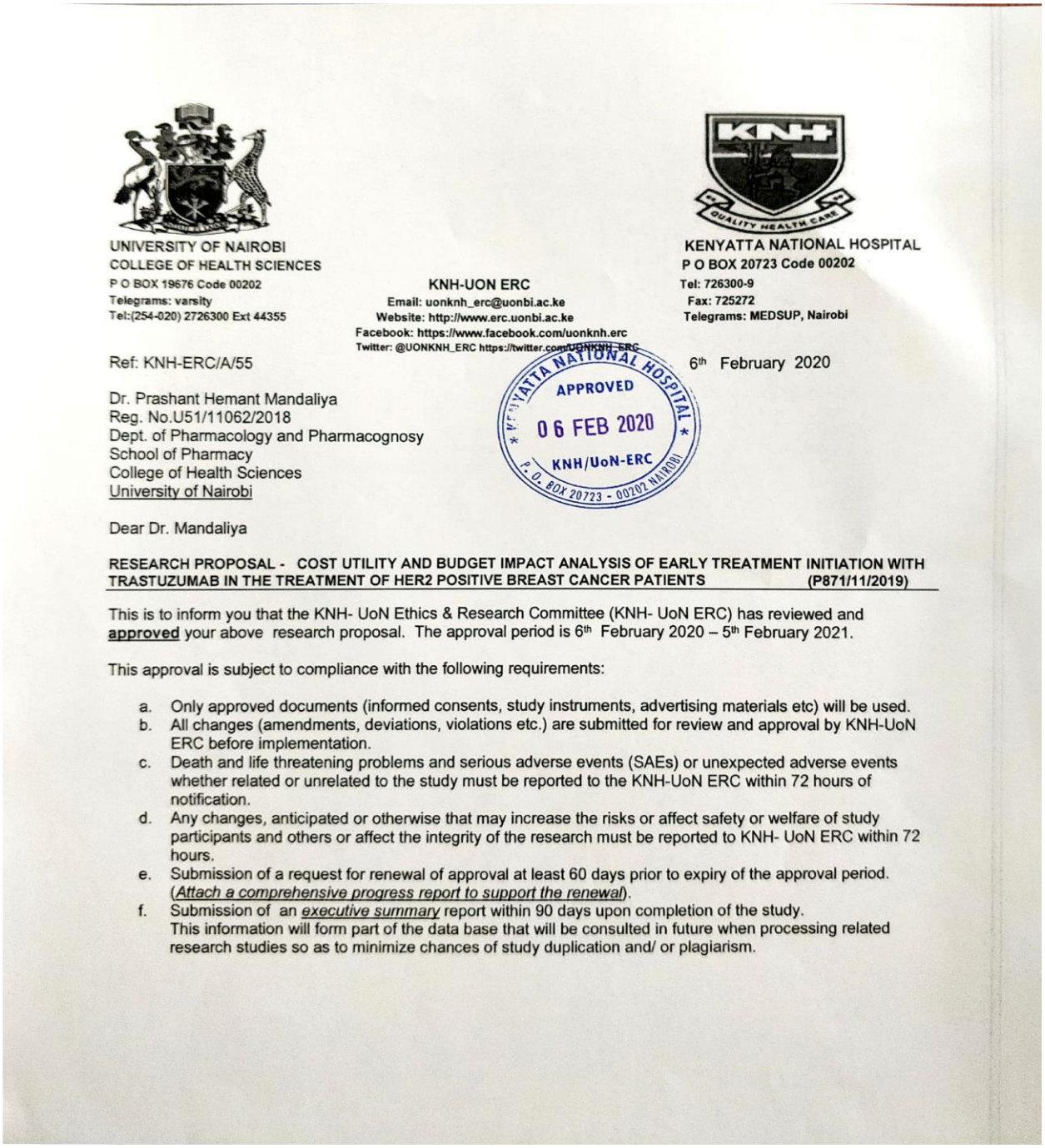
APPENDIX A:

A.1. KNH-UoN ERC Approval letter



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Ref: KNH-ERC/A/55

6th February 2020

KENYATTA NATIONAL HOSPITAL * APPROVED 06 FEB 2020 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI

Dr. Prashant Hemant Mandaliya
Reg. No.U51/11062/2018
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dr. Mandaliya

RESEARCH PROPOSAL - COST UTILITY AND BUDGET IMPACT ANALYSIS OF EARLY TREATMENT INITIATION WITH TRASTUZUMAB IN THE TREATMENT OF HER2 POSITIVE BREAST CANCER PATIENTS (P871/11/2019)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 6th February 2020 – 5th February 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmacology and Pharmacognosy, UoN
Supervisors: Prof. Faith A. Okalebo, Dept. of Pharmacology and Pharmacognosy, UoN
Dr. Edwin Barasa, KEMRI Wellcome Trust Research Programme
Dr. Dorothy Aywak, KNH

A.2. KNH-UoN ERC Renewal letter

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Ref. No.KNH/ERC/R/168

19th August , 2021

Prashant Hemant Mandaliya
Reg. No.U51/11062/2018
Dept. of pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Prashant

Re: Approval of Annual Renewal – Cost utility and budget impact analysis of early treatment initiation with Trastuzumab in the Treatment of HER2 positive breast cancer patients (P871/11/2019)

Refer to your communication dated 4th August 2021.

This is to acknowledge receipt of the study progress report and hereby grant annual extension of approval for ethical research protocol P871/11/2019 for data analysis only.

The approval dates are 6th February 2021 – 5th February 2022.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH- UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH- UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

Kindly adhere to study renewal timelines reflected in clause (e) above.

For more details, consult the KNH-UoN ERC website http://www.erc.uonbi.ac.ke

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UON ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director CS, KNH
The Chairperson, KNH-UoN ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmacology and Pharmacognosy, UoN
Supervisors: Prof. Faith A. Okalebo, Dept. of Pharmacology and Pharmacognosy, UoN
Dr. Edwin Barasa, KEMRI Wellcome Trust Research Programme
Dr. Dorothy Aywak, KNH

APPENDIX B: Face-to-face interview guide

***NB**: The spaces to answer questions have been removed from the guide to reduce total number of pages*

DATE: CODE NUMBER:

Introduction

My name is Prashant Hemant Mandaliya, currently studying my Masters in Pharmacy at University of Nairobi to specialize in pharmacovigilance and pharmacoepidemiology.

Purpose of the interview

The purpose of this interview is to obtain data for my study on the COST UTILITY AND BUDGET IMPACT ANALYSIS OF EARLY TREAMENT INITIATION WITH TRASTUZUMAB IN THE TREATMENT OF HER2 POSITIVE BREAST CANCER PATIENTS. I would request to get details relating to treatment modalities and laboratory tests done at different stages of breast cancer.

Eligibility check-list

Are you involved in direct medical care of patients with breast cancer? YES/NO

Have you worked for a minimum of 2-years at KNH? YES/NO

B.1. Questionnaire for Surgical oncologist and nurse

Q1) COST OF SURICAL INTERVENTIONS

RECOMMEND TYPE OF SURGICAL INTERVENTIONS AT VARIOUS STAGES

Stage 1:

Stage 2:

Stage 3:

Stage 4:

Bone:

Q2) What are the fixed charges that a patient pays for any of the afore mentioned procedures? Please state bed charges as well.

Q3) Is there a significant difference in the total costs for the surgical procedures mentioned above?

Q4) Preoperative costs:

a) Does a patient have to be admitted prior to surgery? If yes, please state the average number of days for hospitalization prior to surgery?

b) What routine laboratory tests are done prior to surgery?

c) Please fill the table below:

	QUANTITY OF RESOURCES CONSUMED	**COST PER ITEM**	**TOTAL**
Items used for Pre-operative care			

Q5) During Surgery

Please fill the table below:

	QUANTITY OF RESOURCES CONSUMED	**COST PER ITEM**	**TOTAL**
Items used for during an operation			

6) Post-Surgery

a) Please fill the table below:

	QUANTITY OF RESOURCES CONSUMED	**COST PER ITEM**	**TOTAL**
Items used for Post-operative care			

b) On average what are the number of days that a patient has to spend at the hospital post-surgery?

c) What tests are routinely done post-surgery in women with breast cancer?

d) What other items are used post-surgery?

Q7) What is the most common surgical procedure that a HER2+ breast cancer patient undergoes in your experience?

Q8) What percentage of HER2+ patients undergo radiotherapy post-surgery?

Q9) What surgical procedures do patients that present with local reoccurrence undergo?

Q10) What is the average total cost for the procedures mentioned above?

Q11) What surgical procedures do patients with metastasis undergo?

Q12) What is the average total cost for the procedures mentioned above?

Q13) What is interventions are given to patients with inoperable tumor?

Q14) Does the HER2 status influence the decision to undertake a surgical procedure?

Q15) Do patients use any prosthetic items post-surgery? If YES, please name the items and costs for the same.

Any other questions or comments?

2.B. Questionnaire for Radiotherapy oncologist and nurse

Q1: For patients that present with **EARLY STAGE** HER2+ breast cancer:

Hospital visits and diagnostic & laboratory Investigations.

a) What laboratory investigations are done prior, during and post radiotherapy?

	Mandatory at first visit	**Recommended Investigations during therapy (Number and frequency)**	**When deciding stopping therapy (Patient shows signs of remission)**
Chest X-Ray			
Chest CT scan			
Abdominal-Pelvic Ultrasound			
Abdominal-Pelvic CT scan			
Bone Scan			
Head CT scan			
2D Cardiac Echo			
ECG			
Core needle biopsy (blind)			
Core needle biopsy (U/S guided)			
Histology			
Biopsy gun			
HER2 IHC			
ER IHC			
PgR IHC			
Fine Needle aspirate			
FISH for IHC 2 equivocal HER2 tests			
Ki 67 testing			
Mammogram			
Full panel of Liver function tests			
Selected LFTs			
Urea and electrolytes			
Full Hemogram			
Cardiac function markers			

OTHERS INVESTIGATIONS THAT ARE NOT INCLUDED IN THIS LIST			

b) What is the consultation fee a patient has to pay on the first visit?

c) What is the consultation fee a patient has to pay on subsequent visits?

d) Do patients pay a separate fee for planning of their radiotherapy regimen?

e) What is the cost per session of radiotherapy?

f) Are there any other costs that are charged due to radiotherapy to the patient during a visit?

g) What % of HER2+ve patients undergo radio therapy post-surgery?

h) Can a patient that hasn't undergone surgery, undergo radiotherapy?

I) What is the average and maximum cost for planning and per session of radiotherapy at private facilities?

j) Do all patients that undergo neo-adjuvant therapy have to undergo radiotherapy? If the answer is NO, then what percentage of these patients undergo radiotherapy?

Radiotherapy

a)

	Recommended Number of Radiotherapy sessions		
	MIN	MAX	OTHER
Presents stage 1 (operable tumor)			
Presents stage 2 (inoperable tumor)			
Stage 3			
With auxiliary node involvement			
After total mastectomy			

b) Do patients routinely receive any drugs pre, during or post radiotherapy? If YES please state the names, dose and duration of therapy with the drugs.

Q2: For patients that present with **LOCAL REOCCURENCE**:

Hospital visits and diagnostic & laboratory Investigations.

a) What laboratory investigations are done prior, during and post radiotherapy?

	Mandatory at first visit	**Recommended Investigations during therapy (Number and frequency)**	**When deciding stopping therapy (Patient shows signs of remission)**
Chest X-Ray			
Chest CT scan			
Abdominal-Pelvic Ultrasound			
Abdominal-Pelvic CT scan			
Bone Scan			
Head CT scan			
2D Cardiac Echo			
ECG			
Core needle biopsy (blind)			
Core needle biopsy (U/S guided)			
Histology			
Biopsy gun			
HER2 IHC			
ER IHC			
PgR IHC			
Fine Needle aspirate			
FISH for IHC 2 equivocal HER2 tests			
Ki 67 testing			
Mammogram			
Full panel of Liver function tests			
Selected LFTs			
Urea and electrolytes			
Full Hemogram			
Cardiac function markers			
OTHERS INVESTIGATIONS THAT ARE NOT INCLUDED IN THIS LIST			

b) What is the consultation fee a patient has to pay on the first visit?

c) What is the consultation fee a patient has to pay on subsequent visits?

d) Do patients pay a separate fee for planning of their radiotherapy regimen?

e) What is the cost per session of radiotherapy?

f) Are there any other costs that are charged due to radiotherapy to the patient during a visit?

g) What percentage of patients with local recurrence undergo radiotherapy?

Radiotherapy

a)

	Recommended Number of Radiotherapy sessions		
	MIN	MAX	OTHER
Has a local recurrence			

b) Do patients routinely receive any drugs pre, during or post radiotherapy? If YES please state the names, dose and duration of therapy with the drugs.

Q3: For patients that present with METASTASIS:

Hospital visits and diagnostic & laboratory Investigations.

a) What laboratory investigations are done prior, during and post radiotherapy?

	Mandatory at first visit	**Recommended Investigations during therapy (Number and frequency)**	**When deciding stopping therapy (Patient shows signs of remission)**
Chest X-Ray			
Chest CT scan			
Abdominal-Pelvic Ultrasound			
Abdominal-Pelvic CT scan			
Bone Scan			
Head CT scan			
2D Cardiac Echo			
ECG			
Core needle biopsy (blind)			

Core needle biopsy (U/S guided)			
Histology			
Biopsy gun			
HER2 IHC			
ER IHC			
PgR IHC			
Fine Needle aspirate			
FISH for IHC 2 equivocal HER2 tests			
Ki 67 testing			
Mammogram			
Full panel of Liver function tests			
Selected LFTs			
Urea and electrolytes			
Full Hemogram			
Cardiac function markers			
OTHERS INVESTIGATIONS THAT ARE NOT INCLUDED IN THIS LIST			

b) What is the consultation fee a patient has to pay on the first visit?

c) What is the consultation fee a patient has to pay on subsequent visits?

d) Do patients pay a separate fee for planning of their radiotherapy regimen?

e) What is the cost per session of radiotherapy?

f) Are there any other costs that are charged due to radiotherapy to the patient during a visit?

g) What percentage of patients with METASTASIS undergo radiotherapy?

Radiotherapy

a)

	Recommended Number of Radiotherapy sessions		
	MIN	MAX	OTHER
Metastasized to the bone			

Metastasized to the brain			
Metastasized to the lung			

b) Do patients routinely receive any drugs pre, during or post radiotherapy? If YES please state the names, dose and duration of therapy with the drugs.

Q4) Chemotherapy

What neo-adjuvant therapy is commonly given to patients that have HER2+ breast cancer?

What alternative regimen is given?

What adjuvant therapy is commonly given to patients that have HER2+ breast cancer?

What alternative regimen is given?

What drugs are given for patients that are hormone receptor positive?

5) Post radiation toxicities

Toxicity	Estimated prevalence (very rare, rare, common, very common)	Medication	dose	Frequency
Nausea and vomiting				
Breast deformity				
(Hyperpigmentation)				
Radiation pneumonitis				
Mastodynia				

Cardiac toxicities (myocardial infarction, coronary artery disease, congestive heart failure, electrical abnormalities, pericarditis, valvular disease, cardiomyopathy),				
Closed rib fracture				
Dermatitis				
Mucocitis				
Mouth Ulcers				
Candid (mouth)				

Any other questions or comments?

B.2. Questionnaire for Clinical oncologist and nurse

Q1: For patients that present with **EARLY STAGE** HER2+ breast cancer:

Hospital visits and diagnostic & laboratory Investigations.

a)

	Mandatory at first visit	**Recommended Investigations during therapy (Number and frequency)**	**When deciding stopping therapy (Patient shows signs of remission)**
Chest X-Ray			
Chest CT scan			
Abdominal-Pelvic Ultrasound			
Abdominal-Pelvic CT scan			
Bone Scan			
Head CT scan			
2D Cardiac Echo			
ECG			
Core needle biopsy (blind)			
Core needle biopsy (U/S guided)			
Histology			
Biopsy gun			
HER2 IHC			
ER IHC			
PgR IHC			
Fine Needle aspirate			
FISH for IHC 2 equivocal HER2 tests			
Ki 67 testing			
Mammogram			
Full panel of Liver function tests			
Selected LFTs			

Urea and electrolytes			
Full Hemogram			
Cardiac function markers			
OTHERS INVESTIGATIONS THAT ARE NOT INCLUDED IN THIS LIST			

b) What is the consultation fee a patient has to pay on the first visit?

c) What is the consultation fee a patient has to pay on subsequent visits?

d) Do patients pay a separate fee for planning of their treatment regimen?

e) What charges other than those for pharmaceuticals do patients have to pay for during subsequent visits to receive drug therapy?

f) Do patients require to be hospitalized in order to receive their treatment?

g) IF the answer is YES, what is the average duration of hospitalization for a patient?

h) Do patients that are ER/PR +ve require special laboratory investigations during treatment? IF the answer is YES please state the name and frequency of these investigations.

I) How often do you do filgrastim boost, blood transfusion and give erythropoietin?

j) Does trastuzumab increase the chance of hospitalization in breast cancer patients?

Drug Regimens

a) What are the FIRST LINE treatment combinations for management of HER2 positive breast cancer patients? IF A DECISION IS MADE TO GIVE TRASTUZUMAB. Also give the % of patients that present with the given state.

Drug	Dose (per kg)	Duration	Co-administered drugs and quantity	% of patients
Stage one or two breast cancer (operable tumor)				

Stage one or two breast cancer (Inoperable tumor)				
Stage three breast cancer (Inoperable tumor) – without inflammation				
Stage three breast cancer (Inoperable tumor) – with inflammation				

B) What are the FIRST LINE treatment combinations for management of HER2 positive breast cancer patients? IF A DECISION IS MADE TO NOT GIVE TRASTUZUMAB. Also give the % of patients that present with the given state.

Drug	Dose (per kg)	Duration	Co-administered drugs and quantity	% of patients
Stage one or two breast cancer (operable tumor)				
Stage one or two breast cancer (Inoperable tumor)				
Stage three breast cancer (Inoperable tumor) – without inflammation				

Stage three breast cancer (Inoperable tumor) – with inflammation				

c) What are the SECOND LINE treatment combinations for management of HER2 positive breast cancer patients? IF A DECISION IS MADE TO GIVE TRASTUZUMAB. Also give the % of patients that present with the given state.

Drug	Dose (per kg)	Duration	Co-administered drugs and quantity	% of patients
Stage one or two breast cancer (operable tumor)				
Stage one or two breast cancer (Inoperable tumor)				
Stage three breast cancer (Inoperable tumor) – without inflammation				
Stage three breast cancer (Inoperable tumor) – with inflammation				

d) What are the SECOND LINE treatment combinations for management of HER2 positive breast cancer patients? IF A DECISION IS MADE TO NOT GIVE TRASTUZUMAB. Also give the % of patients that present with the given state.

Drug	Dose (per keg)	Duration	Co-administered drugs and quantity	% of patients
Stage one or two breast cancer (operable tumor)				

Stage one or two breast cancer (Inoperable tumor)				
Stage three breast cancer (Inoperable tumor) – without inflammation				
Stage three breast cancer (Inoperable tumor) – with inflammation				

e) When is a patient given neo-adjuvant therapy and what regimen is given? Please also state what % of patients undergo neo-adjuvant therapy?

f) How many times is a patient that is undergoing neo-adjuvant therapy reviewed in the treatment period? When reviewed what tests are done and is the patient charged a reviewing/consultation fee?

g) If a patient is ER/PR +ve are any drugs added to their regimen?

h) If the answer to the previous question is YES, please state the name, dose, duration of therapy and if any other drugs need to be administered? Please also state the frequency of hospital visits that the patient makes during this treatment regimen.

Q2: For patients that present with **LOCAL REOCCURENCE**:

Hospital visits and diagnostic & laboratory Investigations.

a)

	Mandatory at first visit	**Recommended Investigations during therapy (Number and frequency)**	**When deciding stopping therapy (Patient shows signs of remission)**

Chest X-Ray			
Chest CT scan			
Abdominal-Pelvic Ultrasound			
Abdominal-Pelvic CT scan			
Bone Scan			
Head CT scan			
2D Cardiac Echo			
ECG			
Core needle biopsy (blind)			
Core needle biopsy (U/S guided)			
Histology			
Biopsy gun			
HER2 IHC			
ER IHC			
PgR IHC			
Fine Needle aspirate			
FISH for IHC 2 equivocal HER2 tests			
Ki 67 testing			
Mammogram			
Full panel of Liver function tests			
Selected LFTs			
Urea and electrolytes			
Full Hemogram			
Cardiac function markers			
OTHERS INVESTIGATIONS THAT ARE NOT INCLUDED IN THIS LIST			

b) What is the consultation fee a patient has to pay on the first visit?

c) What is the consultation fee a patient has to pay on subsequent visits?

d) Do patients pay a separate fee for planning of their treatment regimen?

e) What charges other than those for pharmaceuticals do patients have to pay for during subsequent visits to receive drug therapy?

f) Do patients require to be hospitalized in order to receive their treatment?

g) IF the answer is YES, what is the average duration of hospitalization for a patient?

h) Do patients that are ER/PR +ve require special laboratory investigations during treatment? IF the answer is YES please state the name and frequency of these investigations.

Drug therapy

a) What is the FIRST LINE treatment option and any drugs that are co-administered to patients that have local reoccurrence and have been exposed previously to TRASTZUMAB? Also state % of patients that present as such.

b) What is the FIRST LINE treatment option and any drugs that are co-administered to patients that have local reoccurrence and have been NOT exposed previously to TRASTZUMAB? Also, state % of patients that present as such.

c) What is the SECOND LINE treatment option and any drugs that are co-administered to patients that have local reoccurrence and have been exposed previously to TRASTZUMAB? Also, state % of patients that present as such.

d) What is the SECOND LINE treatment option and any drugs that are co-administered to patients that have local reoccurrence and have been NOT exposed previously to TRASTZUMAB? Also, state % of patients that present as such.

e) What treatment option is available for patients that have been exposed to both trastuzumab and Tamoxifen/Aromatase Inhibitor? Also, state % of patients that present as such.

f) What drugs are given for hormonal manipulation? Please state name, dose and duration of treatment. Also state number of hospital visits and any special tests to be done during the above drug therapy.

Q3: For patients that present with **METASTASIS**:

Hospital visits and diagnostic & laboratory Investigations.

a)

	Mandatory at first visit	**Recommended Investigations during therapy (Number and frequency)**	**When deciding stopping therapy (Patient shows signs of remission)**
Chest X-Ray			
Chest CT scan			
Abdominal-Pelvic Ultrasound			
Abdominal-Pelvic CT scan			
Bone Scan			
Head CT scan			
2D Cardiac Echo			
ECG			
Core needle biopsy (blind)			
Core needle biopsy (U/S guided)			
Histology			
Biopsy gun			
HER2 IHC			
ER IHC			
PgR IHC			
Fine Needle aspirate			
FISH for IHC 2 equivocal HER2 tests			
Ki 67 testing			
Mammogram			
Full panel of Liver function tests			
Selected LFTs			
Urea and electrolytes			
Full Hemogram			
Cardiac function markers			

OTHERS INVESTIGATIONS THAT ARE NOT INCLUDED IN THIS LIST			

b) What is the consultation fee a patient has to pay on the first visit?

c) What is the consultation fee a patient has to pay on subsequent visits?

d) Do patients pay a separate fee for planning of their treatment regimen?

e) What charges other than those for pharmaceuticals do patients have to pay for during subsequent visits to receive drug therapy?

f) Do patients require to be hospitalized in order to receive their treatment?

g) IF the answer is YES, what is the average duration of hospitalization for a patient?

ii) Drug therapy

a) What treatment is given to patients with BONE metastasis? Please state name, dose and duration of therapy. Please state average number of hospital visits the patient has to make, routine laboratory investigations and any drugs that are co-administered with the specified treatment regimen.

b) What % of patients are that previously completed therapy with trastuzumab for HER2+ breast cancer, present with bone metastasis?

c) What treatment is given to patients with LUNG metastasis? Please state name, dose and duration of therapy. Please state average number of hospital visits the patient has to make, routine laboratory investigations and any drugs that are co-administered with the specified treatment regimen.

d) What % of patients are that previously completed therapy with trastuzumab for HER2+ breast cancer, present with lung metastasis?

e) What treatment is given to patients with BRAIN metastasis? Please state name, dose and duration of therapy. Please state average number of hospitals visits the patient has to make, routine laboratory investigations and any drugs that are co-administered with the specified treatment regimen.

f) What % of patients are that previously completed therapy with trastuzumab for HER2+ breast cancer, present with brain metastasis?

g) What drugs are used for ovarian ablation and what % of patients undergo this procedure?

Q4) **Adverse drug reactions**

What are the common ADRs have you seen due to trastuzumab? Please state percentages.

If a patient shows a reduced LVEF during therapy with trastuzumab, how is the treatment regimen altered?

What treatment regimen is given for trastuzumab induced congestive heart failure?

Please state treatment for any other common ADRs?

Any other questions or comments?

B.3. Questionnaire for Oncology Pharmacist

1. Which of the following types of trastuzumab do you stock?
2. Do you stock biosimilar? _____
3. What are the acquisitions prices of the bio-similars and the originator brands?
4. What strategies do you put into place to minimize costs to the patients?
5. What charges does a patient pay for when they come to receive a cycle of chemotherapy?
6. What drugs are co-administered with the various chemotherapeutic agents?
7. What are the hidden costs in management of breast cancer?
8. Have patients complained of any side effects related to trastuzumab?
9. What regimen is used for HER2+ patients as neo-adjuvant chemotherapy?
10. What items do you use to administer anticancer drugs in one single session?
11. Any other question that might be of importance?
12. What is the first line regimen for HER2+ (early stage) patients that undergo neo-adjuvant chemotherapy?
13. What is the first line regimen for HER2+ (early stage) patients that DO NOT undergo neo-adjuvant chemotherapy?
14. What is second line regimen for HER2+ breast cancer?
15. What % of HER2+ patients present as triple +ve? What drug regimen is given for them?
16. Incase trastuzumab is not given to a HER2+ patient, what treatment options are available?
17. Are any drugs added if the tumor is present with inflammation?
18. What is the first line regimen in case of local recurrence if trastzumab has been previously used?
19. What is the first line regimen in case of local recurrence if trastzumab has NOT been previously used?
20. What is the second line regimen in case of local recurrence?
21. What is the first line treatment for Bone Metastasis and dosage?

B.4. Questionnaire for Anesthetist and Theater nurse

The question is to determine the billable items used during a surgical procedure done on a breast cancer patient.

1. What are the drugs that are routinely used on a patient undergoing a form of breast conservation surgery? Please specify the average quantity used as well.

2. What are the drugs that are routinely used on a patient undergoing a form of Modified Radical Mastectomy? Please specify the average quantity used as well.

APPENDIX C: Informed consent for Face-to-face interview

TITLE OF THE STUDY: COST UTILITY AND BUDGET IMPACT ANALYSIS OF EARLY TREAMENT INITIATION WITH TRASTUZUMAB IN THE TREATMENT OF HER2 POSITIVE BREAST CANCER PATIENTS

Institution: Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi, P.O BOX 30197-00400, Nairobi

Investigator: Dr Prashant Hemant Mandaliya, P.O BOX, 81940-80100, Mombasa.

Supervisors:

Prof. F.A Okalebo,
Department of Pharmacology and Pharmacognosy.

Dr. E. Barasa
Nairobi Director, KWTRP.

Dr. D. Aywak
Assistant Chief Pharmacist, KNH.

Ethical Approval Kenyatta National Hospital/ University of Nairobi Ethical and Research Committee, P.O BOX 20723-00100, Nairobi. Tel 2726300/2716450 Ext 44102

INTRODUCTION in this study, am evaluating the costs and effectiveness of early initiation of trastuzumab for the treatment of HER2+ breast cancer. A cost utility analysis will be performed and will compare the treatment in simulated cohorts that have trastuzumab in their treatment regimen against those that do not have it. A budget impact analysis will also be done and data from this can be used by the purchaser that is NHIF to convince them to fully fund patients on treatment regimens containing trastuzumab for HER2+ breast cancer.

PURPOSE OF THE STUDY The purpose of the study is to perform a cost utility analysis on early initiation of trastuzumab in the treatment of HER2+ breast cancer as well as to produce a budget impact assessment of early initiation on the budgets of KNH and NHIF.

Permission is requested from you to participate in this study. You should understand the following general principles which apply to all participants in a medical research:

1. Your agreement to participate in this study is voluntary.
2. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal
3. After you have read the explanation, please feel free to ask any questions that will enable you to understand clearly the nature of the study.

PROCEDURE TO BE FOLLOWED

With your permission, I will engage you in a discussion relating to treatment modalities and laboratory tests done at different stages of breast cancer. I will take some notes using a pen and paper. All the information given will be handled with confidentiality and will only be used for the purpose of this study.

RISKS

There will be no risks involved in this study.

BENEFITS

There will be no direct benefits to you but the findings will be useful in informing KNH, NHIF and policy makers.

ASSURANCE OF CONFIDENTIALITY

All information obtained from you will be kept in confidence. At no point will your name be mentioned or used during data handling or in any resulting publications. Codes will be used instead.

CONTACTS

In case you need to contact me, my academic department or the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee concerning this study please feel free to use the contacts provided above. I request you to sign the consent form attached.

APPENDIX D: Consent form

COST UTILITY AND BUDGET IMPACT ANALYSIS OF EARLY TREAMENT INITIATION WITH TRASTUZUMAB IN THE TREATMENT OF HER2 POSITIVE BREAST CANCER PATIENTS

I, the undersigned, willingly agree to participate in this study, the nature and purpose of which have been fully explained to me by the investigator. I understand that the information gathered will be used for the purposes of this study only and maximum confidentiality will be maintained.

Respondent.....

Sign.....Date.....

Witness (Research assistant) .....

Sign.....Date.....

Investigators statement I, the undersigned, have explained to the participant in a language he/she understands the procedures to be followed in the study and the risks and benefits involved. Investigator.....

Sign..... Date.....

APPENDIX E: Market price survey form

DATE:

NAME OF SUPPLIER:

S.I.	ITEM/SERVICE NAME	UNITS	UNIT PRICE
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			

COMMENTS:_____

_____

APPENDIX F: R code for computation of Markov Model, Costs and ICER.

```
#RRdfsToLR
#RR dfsToDeath
#RRdfsToMet
#RRdfsToLR, RRdfsToMet, RRdfsToDeath
# The Markov Function
library(dampack)
library(heemod)
library(ggplot2)
library(dplyr)
prashant<-read.csv("C:/Users/pmand/OneDrive/Desktop/Uni/Thesis/Sensitivity Analysis/Sensitivity edited by Prashant all parameters.csv")
# ********** MAKING VECTORS THAT CAN BE USED BY DAMPAK"C:/Users/ADMIN/Documents/DOCS/Prashant/a.
aPrashantSept2022/Sensitivity edited by PrashantDAD.csv"
#my_params : vector of all the parameters
#my_distributions: vector of the type of distribution
#my_parametrization_type: eg. mean, standard deviation needed
#my_distribution_params: LIST OF VECTORS with values of the mean

my_params <- as.vector(prashant$Parameter)
my_dists <- as.vector(prashant$distribution)
my_parameterization_types <- as.vector(prashant$parameters)
my_dists_params <- lapply(1:nrow(prashant), function(I) c(prashant$mean[I], prashant$sd[I]))
# ****************************************************************
# CREATING A NAMED VECTOR THAT HAS THE BASE VALUES
my_params_basecase <- as.list(prashant$Base)
names(my_params_basecase) <- as.vector(prashant$Parameter)
# ****************************************************************
#*CREATING A DATA FRAME FOR DETERMINISTIC SENSITIVITY ANALYSIS
# Create a params_range
# data.frame with 3 columns in the following order: "pars", "min", and
# "max".
params_range <- subset(prashant, select=c("Parameter", "min", "max"))
names(params_range) <- c("pars", "min", "max")
l_params <- as.list(my_params)
# Creating the Markov function
markovmodel <- function (l_params) {
 for (I in 1:length(my_params)) {
  assign(names(my_params_basecase[I]), l_params[[I]])
 }
 #Chemotherapy for Bone Mets per cycle
 ChemoAdminTot=(ChemoAdminQty)* (ChemoAdminPrice)
 DoxTot=(DoxQty)* (DoxPrice)
 CycloTot=(CycloQty)* (CycloPrice)
 FHTot=(FHQty)* (FHPrice)
 OndTot=(OndQty)* (OndPrice)
 DexaTot=(DexaQty)* (DexaPrice)
 Tot2D=(Qty2D)*(Price2D)
 ZoldTot=(ZoldQty)*(ZoldPrice)
 CalsupTot=(CalsupQty)*(CalsupPrice)
 LFTTot=(LFTQty)*(LFTPrice)
 UECTot=(UECQty)*(UECPrice)
 SerCalTot=(SerCalQty)*(SerCalPrice)


 BoneMetChemoTot=ChemoAdminTot+DoxTot+FHTot+CycloTot+OndTot+DexaTot+(Tot2D*Prob2D)

 BoneMetZolTot= ZoldTot+ CalsupTot+ LFTTot+ UECTot+ SerCalTot
```

```
BoneMetChemoZolTot= BoneMetChemoTot+BoneMetZolTot

#Chemotherapy of Bone mets with Zol and Pal
ZoldTot=(ZoldQty)*(ZoldPrice)
CalsupTot=(CalsupQty)*(CalsupPrice)

LFTTot=(LFTQty)*(LFTPrice)

UECTot=(UECQty)*(UECPrice)

FHTot=(FHQty)*(FHPrice)

SerCalTot=(SerCalQty)*(SerCalPrice)
CaregiverTot=(CaregiverQty)*(CaregiverPrice)
  PalliativedrugsTot=(PalliativedrugsQty)*(PalliativedrugsPrice)

BoneMetZolTot= ZoldTot+ CalsupTot+ LFTTot+ UECTot+ FHTot+ SerCalTot
PalliativecareTot=CaregiverTot+PalliativedrugsTot

BoneMetZolPalTot= BoneMetZolTot +PalliativecareTot

# ****************************************************

#CHEMOEARLY STAGE BREAST CANCER - AC

# Chemotherapy for Early Stage A-C

ChemoAdminTot= (ChemoAdminQty)* (ChemoAdminPrice)
DoxTot=(DoxQty)*(DoxPrice)
CycloTot=(CycloQty)*(CycloPrice)
OndTot=(OndQty)*(OndPrice)
DexaTot=(DexaQty)*(DexaQty)
UECTot=(UECQty)*(UECPrice)
FHTot= (FHQty)*(FHPrice)
AC_2DTot=(AC_2DQty)*(AC_2DPrice)
CSFTot=(CSFQty)* (CSFPrice)
FHTot=(FHQty)* (FHPrice)
FilTot=(((CSFTot*0.5)+(FHTot*0.5))* (CSFProb))
BloodTTot=(BloodTQty)* (BloodTPrice)
FHTot=(FHQty)* (FHPrice)
GXRTot = (GXRQty) *(GXRPrice)
HemoSideEffect <- (FilTot +((BloodTTot*(BloodTProb))*0.25)+ ((FHTot*(BloodTProb))*0.25)+ ((GXRTot*(BloodTProb))*0.25))
ESACTot= ChemoAdminTot+DoxTot+CycloTot+OndTot+DexaTot+(AC_2DTot*AC_2DProb)+ FHTot + UECTot + HemoSideEffect
# Chemotherapy for EarlyStage T
ChemoAdminTot= (ChemoAdminQty)* (ChemoAdminPrice)
TrastSTot= (TrastSQty)*(TrastSPrice)
EST_2DTot = (EST_2DQty)*( EST_2DPrice)
UECTot=(UECQty)*(UECPrice)
FHTot= (FHQty)*(FHPrice)
ESTTot= ChemoAdminTot +TrastSTot + (EST_2DTot *( EST_2DProb))+ UECTot + FHTot
# Chemotherapy for Early Stage T-H
ChemoAdminTot= (ChemoAdminQty)* (ChemoAdminPrice)
PacTot=(PacQty)*(PacPrice)
TrastSTot=(TrastSQty)*(TrastSPrice)
OndTot=(OndQty)*(OndPrice)
DexaTot=(DexaQty)*(DexaQty)
ChlorphenTot=(ChlorphenQty)*(ChlorphenPrice)
ESTH_2DTot=(ESTH_2DQty)*(ESTH_2DPrice)
UECTot=(UECQty)*(UECPrice)
FHTot= (FHQty)*(FHPrice)
ESTHContTot=ChemoAdminTot+PacTot+(TrastSTot)+OndTot+DexaTot+ChlorphenTot+(ESTH_2DTot*(ESTH_2DProb))+ UECTot+FHTot
ESTHLoadTot=(ChemoAdminTot+PacTot+ (TrastSTot*2) +OndTot+DexaTot+ChlorphenTot+UECTot+FHTot)+
(ESTH_2DTot*(ESTH_2DProb))
```

```
# Cost related to DFS
#DFS I Pre per month
RepeatVisitTotal=(RepeatVisitQty)*(RepeatVisitPrice)
TamoxTot=(TamoxQty)*(TamoxPrice)
FHTot=(FHQty)*(FHPrice)
MamTot=(MamQty)*(MamPrice)
DFSIpretTot= TamoxTot +(RepeatVisitTotal*(RepeatVisitProb))+(FHTot*( ProbFHDFS))+(MamTot* (ProbMamoDFS))
#DFS I Post per month
AnasTot=(AnasQty)*(AnasPrice)
CalsupTot= (CalsupQty)*(CalsupPrice)
DFSIpostTot= AnasTot +(RepeatVisitTotal*(RepeatVisitProb))+(FHTot* (ProbFHDFS))+(MamTot*(ProbMamoDFS))+CalsupTot
#DFS II Pre per month
  RepeatVisitTotal=(RepeatVisitQty)*(RepeatVisitPrice)
TamoxTot=(TamoxQty)*(TamoxPrice)
FHTot=(FHQty)*(FHPrice)
MamTot=(MamQty)*(MamPrice)
ProbMamoDFS=0.083
RepeatVisitProb2=0.167
ProbFHDFS2=0.167
DFSIIpreTot <- TamoxTot+(RepeatVisitTotal*(RepeatVisitProb2))+(FHTot*(ProbFHDFS2))+(MamTot*(ProbMamoDFS))
#DFS II Post per month
RepeatVisitTotal=(RepeatVisitQty)*(RepeatVisitPrice)
AnasTot=(AnasQty)*(AnasPrice)
CalsupTot= (CalsupQty)*(CalsupPrice)
FHTot=(FHQty)*(FHPrice)
MamTot=(MamQty)*(MamPrice)
ProbMamoDFS=0.083
RepeatVisitProb2=0.167
ProbFHDFS2=0.167
DFSIIpostTot= AnasTot +(RepeatVisitTotal*(RepeatVisitProb2))+(FHTot*(ProbFHDFS2))+(MamTot*(ProbMamoDFS))+CalsupTot
### ****CODING FOR DIAGNOSIS
FeeFirstTot=(FeeFirstQuantity)*(FeeFirstPrice)
MamTot=(MamQty)*(MamPrice)
BreastUSTot=(BreastUSQty)*(BreastUSPrice)
CCTscanTot=(CCTscanQty)*(CCTscanPrice)
APCTTot=(APCTQty)*(APCTPrice)
BiopsyTot=(BiopsyQty)*(BiopsyPrice)
HistoTot=(HistoQty)*(HistoPrice)
HER2Tot=(HER2Qty)*(HER2Price)
LFTTot=(LFTQty)*(LFTPrice)
CoagTot=(CoagQty)*(CoagPrice)
GXRTot=(GXRQty)*(GXRPrice)
Diag_2DTot=(Diag_2DQty)*(Diag_2DPrice)
Ki67Tot=(Ki67Qty)*(Ki67Price)
FHTot=(FHQty)*(FHPrice)
# Diagnosis Bone Metastasis
BoneSTot= (BoneSQty)*(BoneSPrice)
MamTot=(MamQty)*(MamPrice)
BreastUSTot=(BreastUSQty)*(BreastUSPrice)
CCTscanTot=(CCTscanQty)*(CCTscanPrice)
APCTTot=(APCTQty)*(APCTPrice)
BoneBiopsyTot=(BoneBiopsyQty)*(BoneBiopsyPrice)
HistoTot=(HistoQty)*(HistoPrice)
HER2Tot=(HER2Qty)*(HER2Price)
LFTTot=(LFTQty)*(LFTPrice)
UECTot <- (UECQty) * (UECPrice)
CoagTot=(CoagQty)*(CoagPrice)
GXRTot=(GXRQty)*(GXRPrice)
Diag_2DTot=(Diag_2DQty)*(Diag_2DPrice)
FHTot=(FHQty)*(FHPrice)
DiagnosisTot = FeeFirstTot+(MamTot*0.5) +(BreastUSTot*0.5)+CCTscanTot+APCTTot+BiopsyTot+HistoTot+HER2Tot+LFTTot+
CoagTot+GXRTot+Diag_2DTot+Ki67Tot+UECTot+FHTot
```

```
BoneDiagnosisTot=BoneSTot+FeeFirstTot+(MamTot*0.5)+(BreastUSTot*0.5)+CCTscanTot+APCTTot+BoneBiopsyTot+HistoTot+HER2Tot+
LFTTot+CoagTot+GXRTot+Diag_2DTot+UECTot+FHTot
  # **** MANAGEMENT OF LOCAL RECURRENCE
  #Chemotherapy cycle 1
  ChemoAdminTot = (ChemoAdminQty)* (ChemoAdminPrice)
  CapecTot=(CapecQty)*(CapecPrice)
  TrastSTot=(TrastSQty)*(TrastSPrice)
  OndTot=(OndQty)*(OndPrice)
  DexaTot=(DexaQty)*(DexaQty)
  LR_2DTot=(LR_2DQty) * (LR_2DPrice)
  UECTot=(UECQty)*(UECPrice)
  FHTot= (FHQty)*(FHPrice)
  LFTTot=(LFTQty)*(LFTPrice)
LR1chemoloadTot=ChemoAdminTot+CapecTot+ (TrastSTot*2) +OndTot+DexaTot+ UECTot+FHTot+(LR_2DTot*(LR_2DProb))+LFTTot
  #Chemotherapy 2-5
  ChemoAdminTot = (ChemoAdminQty)* (ChemoAdminPrice)
  CapecTot=(CapecQty)*(CapecPrice)
  TrastSTot=(TrastSQty)* (TrastSPrice)
  OndTot=(OndQty)*(OndPrice)
  DexaTot=(DexaQty)*(DexaQty)
  EchoTot=(EchoQty) * (EchoPrice)
  UECTot=(UECQty)*(UECPrice)
  FHTot= (FHQty)*(FHPrice)
  LFTTot=(LFTQty)*(LFTPrice)
  EchoProb=0.33
  lr12chemocontTot=ChemoAdminTot+CapecTot+TrastSTot+OndTot+DexaTot+(EchoTot*EchoProb) + UECTot+FHTot+LFTTot
  #Chemotherapy 2 per cycle
  ChemoAdminTot = (ChemoAdminQty)* (ChemoAdminPrice)
  CapecTot=(CapecQty)*(CapecPrice)
  CarboTot=(CarboQty)*(CarboPrice)
  OndTot=(OndQty)*(OndPrice)
  DexaTot=(DexaQty)*(DexaQty)
  PyriTot=(PyriQty)*(PyriPrice)
  UECTot=(UECQty)*(UECPrice)
  FHTot= (FHQty)*(FHPrice)
  LFTTot=(LFTQty)*(LFTPrice)
  lr2chemoTot=ChemoAdminTot+CapecTot+CarboTot+OndTot+DexaTot+PyriTot+ UECTot+FHTot+LFTTot
  # Radiotherapy for Bone*******************************
  RepeatVisitTotal=(RepeatVisitQty)*(RepeatVisitPrice)
  Rad_OpTot=(Rad_OpQty)*(Rad_OpPrice)
  Rad_PlanTot=(Rad_PlanQty)*(Rad_PlanPrice)
  Rad_OpTotForAllBoneSes= (BoneQtyRadSes)*(Rad_OpPrice)
    UECTot=(UECQty)*(UECPrice)
    FHTot= (FHQty)*(FHPrice)
    RadLabTot=(UECTot+FHTot)
    OndoralTot= (OndoralQty)*(OndoralPrice)
    RadTox1Tot= OndoralTot*(RadTox1Prob)
    PredTot=(PredQty)*(PredPrice)
    RadTox2Tot= PredTot* (RadTox2Prob)
    HydroTot=(HydroQty)*(HydroPrice)
    RadTox3Tot= HydroTot*(RadTox3Prob)
    MWTot=(MWQty)*(MWPrice)
    RadTox4Tot= MWTot* (RadTox4Prob)
    MWTot=(MWQty)*(MWPrice)
    RadTox5Tot= MWTot*(RadTox5Prob)
    RadToxTot=RadTox1Tot+RadTox2Tot+RadTox3Tot+RadTox4Tot+RadTox5Tot
   BoneRadTot=(RepeatVisitTotal/(BoneQtyRadSes))+Rad_OpTot+(Rad_PlanTot/(BoneQtyRadSes))+RadToxTot+
(RadLabTot*((BoneQtyRadSes)/5))*(1/(BoneQtyRadSes))
   TotBoneRadCost= BoneRadTot* (BoneQtyRadSes)
  #Radiotherapy for Early Stage
  # Lab
 RepeatVisitTotal=(RepeatVisitQty)*(RepeatVisitPrice)
  Rad_OpTot=(Rad_OpQty)*(Rad_OpPrice)
```

```
 Rad_OpTotForAllSes= (QtyRadSes)*(Rad_OpPrice)
 Rad_PlanTot=(Rad_PlanQty)*(Rad_PlanPrice)
 UECTot=(UECQty)*(UECPrice)
 FHTot= (FHQty)*(FHPrice)
 RadLabTot=UECTot+FHTot
 RadLabperSession= (RadLabTot*((QtyRadSes)/5))*(1/(QtyRadSes))
 OndoralTot= (OndoralQty)*(OndoralPrice)
 RadTox1Tot= OndoralTot*(RadTox1Prob)
 PredTot=(PredQty)*(PredPrice)
 RadTox2Tot= PredTot*(RadTox2Prob)
 HydroTot=(HydroQty)*(HydroPrice)
 RadTox3Tot= HydroTot*(RadTox3Prob)
 MWTot=(MWQty)*(MWPrice)
 RadTox4Tot= MWTot* (RadTox4Prob)
 MWTot=(MWQty)*(MWPrice)
 RadTox5Tot= MWTot*(RadTox5Prob)
 RadToxTot=RadTox1Tot+RadTox2Tot+RadTox3Tot+RadTox4Tot+RadTox5Tot
RadESTot=(RepeatVisitTotal/(QtyRadSes))+Rad_OpTot+(Rad_PlanTot/(QtyRadSes))+RadToxTot+ RadLabperSession
TotRadCost= RadESTot* (QtyRadSes)
TotRadCostAdjusted= (Rad_OpProb)*(RadESTot* (QtyRadSes))
 # Chemotherapy for Early Stage with FEC
FuTot=FuQty*FuPrice
CycloTot=CycloQty*CycloPrice
EpiTot=EpiQty*EpiPrice
OmepTot=OmepQty*OmepPrice
ChemoAdminTot = ChemoAdminQty* ChemoAdminPrice
ESFECTot <-ChemoAdminTot+FuTot+CycloTot+EpiTot+OndTot+OmepTot+DexaTot+AC_2DTot+ FHTot + UECTot
PacTot=PacQty*PacPrice
ESTH_2DProb=0.25
 ESTaxTot=ChemoAdminTot+PacTot+OndTot+DexaTot+ChlorphenTot+(ESTH_2DTot*ESTH_2DProb)+ UECTot+FHTot
MetUtilities <- c(uBoneDiagnosisTot, uBoneRadTot, rep(uBoneMetChemoZolTot, 6), rep(uBoneMetZolPalTot, 15), rep(uFinal_MRMTot, 37))
LocalRecurrenceUtility <- c(uDiagnosisTot, uFinal_MRMTot, LR1chemoloadTot, rep(uLRFinalloadTot, 5),  uBoneRadTot, rep(uDFSIpretTot, 51))
####**********COST AND UTILIITY VECTORS
# SHARED UTILITIES
#Metastasis
Metcosts <- c(BoneDiagnosisTot, TotBoneRadCost, rep(BoneMetChemoZolTot, 6), rep(BoneMetZolPalTot, 15), rep(0, 38))
Metcosts60 <- c(BoneDiagnosisTot, TotBoneRadCost, rep(BoneMetChemoZolTot, 6), rep(BoneMetZolPalTot, 15), rep(0, 37))
MetUtilities <- c(uBoneDiagnosisTot, uBoneRadTot, rep(uBoneMetChemoZolTot, 6), rep(uBoneMetZolPalTot, 15), rep(uBoneMetZolPalTot, 37))
#Local reccurence
LocalRecurrenceCost <- c(DiagnosisTot, Final_MRMTot, LR1chemoloadTot, rep(lr12chemocontTot, 5),  TotBoneRadCost, rep(DFSIpretTot, 24), rep(DFSIIpreTot, 28))
LocalRecurrenceCost60 <- c(DiagnosisTot, Final_MRMTot, LR1chemoloadTot, rep(lr12chemocontTot, 5),  TotBoneRadCost, rep(DFSIpretTot, 24), rep(DFSIIpreTot, 27))
LocalRecurrenceUtility <- c(uDiagnosisTot, uFinal_MRMTot, rep(uLRFinalloadTot, 6),  uBoneRadTot, rep(uDFSIpretTot, 24), rep(uDFSIIpreTot,27))
ACMcosts <- rep(0, 61)
DeathBCcosts <- rep(0, 61)
Metcosts60 <- c(BoneDiagnosisTot, TotBoneRadCost, rep(BoneMetChemoZolTot, 6), rep(BoneMetZolPalTot, 15), rep(0, 37))
# 16-month OF TRANS
DFScosts16MonthTras <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 18), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 8))
DFScosts16MonthTras60 <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 18), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 7))
DFSUtilities16MonthTras60 <- c(uDiagnosisTot, uSurgeryTot,  uRadESTot, rep(uESACTot, 4), uESTHLoadTot, rep(uESTHContTot, 3), rep(uESTTot, 18), rep(uDFSIpostTot, 24), rep(uDFSIIpostTot, 7))
v_costs16months <- c(DFScosts16MonthTras60, LocalRecurrenceCost60, Metcosts60, 0, 0)
v_utilities16months <- c(DFSUtilities16MonthTras60, LocalRecurrenceUtility, MetUtilities, 0, 0)
m_Costs16months <-as.matrix(v_costs16months)
m_utilities16months <-as.matrix(v_utilities16months)
df_Costs_monthly16months = data.frame(DFScosts16MonthTras, LocalRecurrenceCost, Metcosts, ACMcosts, DeathBCcosts)
set16months = c(1, 1, 1, m_Costs16months,  m_utilities16months)
```

```
# 12-month OF TRAS
DFScostsTwelveMonths61 <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 12), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 14))
DFScostsTwelveMonths <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 12), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 13))
DFSUtilitiesTwelveMonths <- c(uDiagnosisTot, uSurgeryTot, uRadESTot, rep(uESACTot, 4), uESTHLoadTot, rep(uESTHContTot, 3), rep(uESTTot, 12), rep(uDFSIpostTot, 24), rep(uDFSIIpostTot, 13))
v_costsTwelveMonths <- c(DFScostsTwelveMonths, LocalRecurrenceCost60, Metcosts60, 0, 0)
v_utilitiesTwelveMonths <- c(DFSUtilitiesTwelveMonths, LocalRecurrenceUtility, MetUtilities, 0, 0)
m_CostsTwelveMonths <-as.matrix(v_costsTwelveMonths)
m_utilitiesTwelveMonths <-as.matrix(v_utilitiesTwelveMonths)
df_Costs_monthly24Months = data.frame(DFScostsTwelveMonths61, LocalRecurrenceCost, Metcosts, ACMcosts, DeathBCcosts)
setTwelveMonths = c(1, 1, 1, m_CostsTwelveMonths,  m_utilitiesTwelveMonths)
# NO TRASTUZUMAB AT ALL
DFScostsNoTras61 <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4),  rep(ESTaxTot, 4),  rep(DFSIpostTot, 24), rep(DFSIIpostTot, 26))
DFScostsNoTras <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4),  rep(ESTaxTot, 4),  rep(DFSIpostTot, 24), rep(DFSIIpostTot, 25))
DFSUtilityNoTras <- c(uDiagnosisTot, uSurgeryTot, uRadESTot, rep(uESACTot, 4), rep(uESTHContTot, 4), rep(uDFSIpostTot, 24), rep(uDFSIIpostTot, 25))
v_costsNoTras <-  c(DFScostsNoTras, LocalRecurrenceCost60, Metcosts60, 0, 0)
v_utilitiesNoTras <- c(DFSUtilityNoTras, LocalRecurrenceUtility, MetUtilities, 0, 0)
m_CostsNoTras  <-as.matrix(v_costsNoTras)
m_utilitiesNoTras  <-as.matrix(v_utilitiesNoTras)
df_Costs_monthlyNoTras = data.frame(DFScostsNoTras61, LocalRecurrenceCost, Metcosts, ACMcosts, DeathBCcosts)
SetNoTras = c(1, 1, 1, m_CostsNoTras,  m_utilitiesNoTras)
#6-month
DFScostsSixMonths61 <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 4), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 22))
DFScostsSixMonths <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 4), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 21))
DFSutilitySixMonth <- c(uDiagnosisTot, uSurgeryTot, uRadESTot, rep(uESACTot, 4), uESTHLoadTot, rep(uESTHContTot, 3), rep(uESTTot, 4), rep(uDFSIpostTot, 24), rep(uDFSIIpostTot, 21))
v_costsSixMonth <- c(DFScostsSixMonths, LocalRecurrenceCost60, Metcosts60, 0, 0)
v_utilitySixMonth <- c(DFSutilitySixMonth, LocalRecurrenceUtility, MetUtilities, 0, 0)
m_CostsSixMonth <-as.matrix(v_costsSixMonth)
m_utilitySixMonth <-as.matrix(v_utilitySixMonth)
df_Costs_monthlySixmonths = data.frame(DFScostsSixMonths61, LocalRecurrenceCost, Metcosts, ACMcosts, DeathBCcosts)
#NINE MONTHS
DFScostsNineMonths61 <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 8), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 18))
DFScostsNineMonths <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 8), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 17))
DFSUtilityNineMonths <- c(uDiagnosisTot, uSurgeryTot, uRadESTot, rep(uESACTot, 4), uESTHLoadTot, rep(uESTHContTot, 3), rep(uESTTot, 8), rep(uDFSIpostTot, 24), rep(uDFSIIpostTot, 17))
v_costsNineMonth <- c(DFScostsNineMonths, LocalRecurrenceCost60, Metcosts60, 0, 0)
v_utilityNineMonth <- c(DFSUtilityNineMonths, LocalRecurrenceUtility, MetUtilities, 0, 0)
m_CostsNineMonth <-as.matrix(v_costsNineMonth)
m_utilityNineMonth <-as.matrix(v_utilityNineMonth)
df_Costs_monthlyNineMonths = data.frame(DFScostsNineMonths61, LocalRecurrenceCost, Metcosts, ACMcosts, DeathBCcosts)
#TRASTU (9-week)
ESTTot6= ESTTot*6
DFScosts9Weeks61 <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, ESTHLoadTot, rep(ESTHContTot, 2), rep(ESFECTot, 3), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 28))
DFScosts9Weeks <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, ESTHLoadTot, rep(ESTHContTot, 2), rep(ESFECTot, 3), rep(DFSIpostTot, 24), rep(DFSIIpostTot, 27))
DFSUtilities9Weeks <- c(uDiagnosisTot, uSurgeryTot, uRadESTot, uESTHLoadTot, rep(uESTHContTot, 2), rep(uESACTot, 3), rep(uDFSIpostTot, 24), rep(uDFSIIpostTot, 27))
v_costs9Weeks <-  c(DFScosts9Weeks, LocalRecurrenceCost60, Metcosts60, 0, 0)
v_utilities9Weeks <- c( DFSUtilities9Weeks, LocalRecurrenceUtility, MetUtilities, 0, 0)
m_Costs9Weeks  <-as.matrix(v_costs9Weeks)
m_utilities9Weeks <-as.matrix(v_utilities9Weeks)
df_Costs_monthly9Weeks = data.frame(DFScosts9Weeks61, LocalRecurrenceCost, Metcosts, ACMcosts, DeathBCcosts)
```

```
#AS PER 24Month 24 CYCLES
DFScosts24Month61 <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 28), rep(DFSIpostTot, 22))
DFScosts24Month <- c(DiagnosisTot, SurgeryTot, TotRadCostAdjusted, rep(ESACTot, 4), ESTHLoadTot, rep(ESTHContTot, 3), rep(ESTTot, 28), rep(DFSIpostTot, 21))
DFSUtilities24Month <- c(uDiagnosisTot, uSurgeryTot, uRadESTot, rep(uESACTot, 4), uESTHLoadTot, rep(uESTHContTot, 3), rep(uESTTot, 28), rep(uDFSIpostTot, 21))
v_costs24Month <- c(DFScosts24Month, LocalRecurrenceCost60, Metcosts60, 0, 0)
v_utilities24Month <- c(DFSUtilities24Month, LocalRecurrenceUtility, MetUtilities, 0, 0)
m_CostsManufacture  <-as.matrix(v_costs24Month)
m_utilities24Month <-as.matrix(v_utilities24Month)
df_Costs_24Month = data.frame(DFScosts24Month61, LocalRecurrenceCost, Metcosts, ACMcosts, DeathBCcosts)
set24Month <- c(1, 1, 1, m_CostsManufacture,   m_utilities24Month)
#*****************************************
RR_NoTras = c(RRNoTras_LR, RRNoTras_Met, RRNoTras_DeathBC)
RR_9week <- c(RR9week_LR, RR9week_Met, RR9week_DeathBC)
RR_SixMonth <- c(RR6mon_LR,RR6mon_Met, RR6mon_DeathBC)
RR_NineMonth <- c(RR9mon_LR, RR9mon_Met, RR9mon_DeathBC)
RR_TwelveMonths = c(1, 1, 1)
RR_16months = c(1, 1, 1)
RR_set24Month <- c(RRManu_LR, RRManu_Met, RRManu_DeathBC)
v_RR <- list(RR_NoTras, RR_9week, RR_SixMonth, RR_NineMonth, RR_TwelveMonths, RR_16months, RR_set24Month)
l_Cost_Matrix <- list (m_CostsNoTras, m_Costs9Weeks, m_CostsSixMonth, m_CostsNineMonth, m_CostsTwelveMonths, m_Costs16months, m_CostsManufacture)
l_utilities_Matrix <- list(m_utilitiesNoTras, m_utilities9Weeks, m_utilitySixMonth, m_utilityNineMonth, m_utilitiesTwelveMonths, m_utilities16months, m_utilities24Month)
#List and vectors to loop through v_RR, #v_CostMatrix, v_utilities_Matrix
# VECTOR WITH ALL THE CONDITIONS TO USE IN LOOP
list_costinputs <- list(df_Costs_monthlyNoTras, df_Costs_monthly9Weeks, df_Costs_monthlySixmonths, df_Costs_monthlyNineMonths, df_Costs_monthly24Months, df_Costs_monthly16months, df_Costs_24Month)
v_durationTherapy = c("Chemo Only", "Nine weeks", "6-month", "Nine months", "Twelve months", "Sixteen months", "24Month")
names_m_M <- paste("m_M", v_durationTherapy, sep = "_")
names_PeopleTrace_df <- paste("df_PeopleTrace",  v_durationTherapy, sep = "_")
names_Cost_Utilities_df <- paste("df_Cost_Utilities",  v_durationTherapy, sep = "_")
#RRdfsToLR <- setcondition[[i]][1]
#RRdfsToMet <- setcondition[[i]][2]
#RRdfsToDeath <- setcondition[[i]][3]
#m_Costs <- setcondition[[i]][4]
#m_Utilities <- setcondition[[i]][5]
#*********************************************
# TRANSITION MATRIX – generating the trans probabilities
D <- c(1,1,1)
#Funct_m_M = function (RRdfsToLR, RRdfsToMet, RRdfsToDeath)
Funct_m_peopletrace = function (A)
{
prob_DFS_LR1 <- prob_DFS_LR1 * A[1]
prob_DFS_Met1 <- prob_DFS_Met1 * A[2]
prob_DFS_DeathBC1 <- prob_DFS_DeathBC1 * A[3]
prob_LR_DeathBC1 <- prob_LR_DeathBC1 * A[3]
prob_DFS_LR2 <- prob_DFS_LR2 * A[1]
prob_DFS_Met2 <- prob_DFS_Met2 * A[2]
prob_DFS_DeathBC2 <- prob_DFS_DeathBC2 * A[3]
prob_LR_DeathBC2 <- prob_LR_DeathBC2 * A[3]
prob_DFS_LR3 <- prob_DFS_LR3 * A[1]
prob_DFS_Met3 <- prob_DFS_Met3 *  A[2]
prob_DFS_DeathBC3 <- prob_DFS_DeathBC3 * A[3]
prob_LR_Met1 <- prob_LR_Met1 * A[2]
prob_LR_Met3 <- prob_LR_Met3 * A[2]
prob_LR_Met2 <- prob_LR_Met2 * A[2]
prob_LR_DeathBC3 <- prob_LR_DeathBC3 * A[3]
transprob_acm = rescale_prob(p = prob_acm, to = 1/12)
transprob_DFS_LR1 = rescale_prob(p = prob_DFS_LR1, to = 1/12)
transprob_DFS_Met1 = rescale_prob(p = prob_DFS_Met1, to = 1/12)
```

```
transprob_DFS_DeathBC1 = rescale_prob(p = prob_DFS_DeathBC1, to = 1/12)
C11 = 1- (transprob_DFS_LR1 + transprob_DFS_Met1 + transprob_DFS_DeathBC1 + transprob_acm)
transprob_LR_LR1 = rescale_prob(p = prob_LR_LR1 , to = 1/12)
transprob_LR_Met1 = rescale_prob(p = prob_LR_Met1, to = 1/12)
transprob_LR_DeathBC1 = rescale_prob(p = prob_LR_DeathBC1 , to = 1/12)
C21sum = transprob_LR_LR1 + transprob_LR_Met1  + transprob_LR_DeathBC1 + transprob_acm
C21 <- 1-   C21sum
#TRANSITION PROBABILITIES INVOLVING METASTASIS
transprob_Met_LR1 = rescale_prob(p = prob_Met_LR1 , to = 1/12)
transprob_Met_Met1 = rescale_prob(p = prob_Met_Met1, to = 1/12)
transprob_Met_DeathBC1 = rescale_prob(p = prob_Met_DeathBC1 , to = 1/12)
C31 = 1-( transprob_Met_LR1 + transprob_Met_Met1 + transprob_Met_DeathBC1 + transprob_acm)
YearOneRowThree = c(C31,  transprob_Met_LR1, transprob_Met_Met1, transprob_Met_DeathBC1,  transprob_acm)
#*******************************************************
###Common regardless of the year
YearOneRowFour <- c(transprob_DeathBC_DFS, transprob_DeathBC_LR, transprob_DeathBC_Met, transprob_DeathBC_DeathBC, transprob_DeathBC_ACM)
#*******************************************************
YearOneRowOne = c(C11, transprob_DFS_LR1, transprob_DFS_Met1, transprob_DFS_DeathBC1, transprob_acm)
YearOneRowTwo = c(C21, transprob_LR_LR1, transprob_LR_Met1, transprob_LR_DeathBC1, transprob_acm)
YearOneRowThree = c(C31,  transprob_Met_LR1, transprob_Met_Met1, transprob_Met_DeathBC1,  transprob_acm)
YearOneRowFour = c(transprob_DeathBC_DFS, transprob_DeathBC_LR, transprob_DeathBC_Met, transprob_DeathBC_DeathBC, transprob_DeathBC_ACM)
YearOneRowFive = c(transprob_ACM_DFS, transprob_ACM_LR, transprob_ACM_Met, transprob_ACM_DeathBC, transprob_ACM_ACM)
MatrixYearOne = rbind(YearOneRowOne, YearOneRowTwo, YearOneRowThree, YearOneRowFour, YearOneRowFive)
##*********************************************************************
transprob_acm = rescale_prob(p = prob_acm, to = 1/12)
transprob_DFS_LR2 = rescale_prob(p = prob_DFS_LR2, to = 1/12)
#Transition probability from DFS to metastasis
transprob_DFS_Met2 = rescale_prob(p = prob_DFS_Met2, to = 1/12)
transprob_DFS_DeathBC2 = rescale_prob(p = prob_DFS_DeathBC2, to = 1/12)
##Risk of death from any cause
C12 = 1-  (transprob_DFS_LR2 + transprob_DFS_Met2 + transprob_DFS_DeathBC2  + transprob_acm)
#TRANSITION PROBABILITIES REGARDING LOCAL RECURRENCE – row two
#Transition probability from LR2 to Death from Breast Cancer
transprob_LR_LR2 = rescale_prob(p = prob_LR_LR2 , to = 1/12)
transprob_LR_Met2 = rescale_prob(p = prob_LR_Met2, to = 1/12)
transprob_LR_DeathBC2 = rescale_prob(p = prob_LR_DeathBC2 , to = 1/12)
C22sum  = transprob_LR_LR2 + transprob_LR_Met2  + transprob_LR_DeathBC2 + transprob_acm
C22 <-  1-   C22sum
#TRANSITION PROBABILITIES INVOLVING METASTASIS
transprob_Met_LR2 = rescale_prob(p = prob_Met_LR2 , to = 1/12)
transprob_Met_Met2 = rescale_prob(p = prob_Met_Met2, to = 1/12)
transprob_Met_DeathBC2 = rescale_prob(p = prob_Met_DeathBC2 , from=3/12, to = 1/12)
C32 = 1-( transprob_Met_LR2 + transprob_Met_Met2 + transprob_Met_DeathBC2 + transprob_acm)
YearTwoRowThree = c(C32,  transprob_Met_LR2, transprob_Met_Met2, transprob_Met_DeathBC2,  transprob_acm)
#*******************************************************
###Common regardless of the year
YearOneRowFour <- c(transprob_DeathBC_DFS, transprob_DeathBC_LR, transprob_DeathBC_Met, transprob_DeathBC_DeathBC, transprob_DeathBC_ACM)
#*******************************************************
YearTwoRowOne = c(C12, transprob_DFS_LR2, transprob_DFS_Met2, transprob_DFS_DeathBC2, transprob_acm)
YearTwoRowTwo = c(C22, transprob_LR_LR2, transprob_LR_Met2, transprob_LR_DeathBC2, transprob_acm)
YearTwoRowThree = c(C32,  transprob_Met_LR2, transprob_Met_Met2, transprob_Met_DeathBC2,  transprob_acm)
YearTwoRowFour = c(transprob_DeathBC_DFS, transprob_DeathBC_LR, transprob_DeathBC_Met, transprob_DeathBC_DeathBC, transprob_DeathBC_ACM)
YearTwoRowFive = c(transprob_ACM_DFS, transprob_ACM_LR, transprob_ACM_Met, transprob_ACM_DeathBC, transprob_ACM_ACM)
MatrixYearTwo = rbind(YearTwoRowOne, YearTwoRowTwo, YearTwoRowThree, YearTwoRowFour, YearTwoRowFive)
MatrixYearTwo
#*********************************************************************
transprob_acm = rescale_prob(p = prob_acm, to = 1/12)
transprob_DFS_LR3 = rescale_prob(p = prob_DFS_LR3, to = 1/12)
transprob_DFS_Met3 = rescale_prob(p = prob_DFS_Met3, to = 1/12)
```

```
transprob_DFS_DeathBC3 = rescale_prob(p = prob_DFS_DeathBC3, from=6/12, to = 1/12)
C13 = 1-(transprob_DFS_LR3 + transprob_DFS_Met3 + transprob_DFS_DeathBC3  + transprob_acm  )
#TRANSITION PROBABILITIES REGARDING LOCAL RECURRENCE – row two
transprob_LR_LR3 = rescale_prob(p = prob_LR_LR3 , to = 1/12)
transprob_LR_Met3 = rescale_prob(p = prob_LR_Met3, to = 1/12)
transprob_LR_DeathBC3 = rescale_prob(p = prob_LR_DeathBC3 , from=3/12, to = 1/12)
C23sum  = transprob_LR_LR3 + transprob_LR_Met3  + transprob_LR_DeathBC3 + transprob_acm
C23 <-  1-   C23sum
#TRANSITION PROBABILITIES INVOLVING METASTASIS
transprob_Met_LR3 = rescale_prob(p = prob_Met_LR3 , to = 1/12)
transprob_Met_Met3 = rescale_prob(p = prob_Met_Met3, to = 1/12)
transprob_Met_DeathBC3 = rescale_prob(p = prob_Met_DeathBC3 , from=3/12, to = 1/12)
C33 = 1-( transprob_Met_LR3 + transprob_Met_Met3 + transprob_Met_DeathBC3 + transprob_acm)
#*****************************************************
#Create a tunnel state -                EXPANDED MATRIX
## Number of tunnels for each state
n_t=60
n_tunnel_size <- n_t
## Names for tunnel states DFS  state
v_DFS_tunnel <- paste("V1_", seq(1, n_tunnel_size), "Month", sep = "")
## Names for tunnel states of LR  state
v_LR_tunnel <- paste("LR_", seq(1, n_tunnel_size), "Month", sep = "")
## Names for tunnel states of Metastasis  state
v_Met_tunnel <- paste("Met_", seq(1, n_tunnel_size), "Month", sep = "")
v_names_states_tunnels <- c(v_DFS_tunnel , v_LR_tunnel , v_Met_tunnel,  "DeathBC", "DeathACM") # state names
#Next get the length
n_states_tunnels <- length(v_names_states_tunnels) # number of states
v_names_states_tunnels <- c(v_DFS_tunnel , v_LR_tunnel , v_Met_tunnel,  "DeathBC", "DeathACM") # state names
## Names for tunnel states DFS  state
v_DFS_tunnel <- paste("V1_", seq(1, n_tunnel_size), "Month", sep = "")
## Names for tunnel states of LR  state
v_LR_tunnel <- paste("LR_", seq(1, n_tunnel_size), "Month", sep = "")
## Names for tunnel states of Metastasis  state
v_Met_tunnel <- paste("Met_", seq(1, n_tunnel_size), "Month", sep = "")
#Next get the length
n_states_tunnels <- length(v_names_states_tunnels) # number of states
already_BC <- c(rep(100, 60), rep(4,60), rep(20, 60,), 0, 0) #
v_s_init_tunnels = c(100, rep(0, 181))
#Initialize the matrix
n_states_tunnels=length(v_s_init_tunnels)
m_tunnel_states <- matrix(0,  nrow = n_states_tunnels, ncol = n_states_tunnels,
dimnames = list(v_names_states_tunnels, v_names_states_tunnels))
#COMPLETING MATRIX FOR TUNNEL STATES
m_tunnel_states = matrix(0, n_states_tunnels, n_states_tunnels)
dim(m_tunnel_states)
m_tunnel_states[1:5, 1:5]
#All transition to DeathBC
v_DFS_DeathBC_tunnels <- c(rep(transprob_DFS_DeathBC1,12), rep(transprob_DFS_DeathBC2, 12),  rep(transprob_DFS_DeathBC3, 36))
v_LR_DeathBC_tunnels <- c(rep(transprob_LR_DeathBC1,12), rep(transprob_LR_DeathBC2, 12),  rep(transprob_LR_DeathBC3, 36))
v_Met_DeathBC_tunnels <- c(rep(transprob_Met_DeathBC1,12), rep(transprob_Met_DeathBC2, 12),  rep(transprob_Met_DeathBC3, 36))
m_tunnel_states[, 181] <- cbind(c(v_DFS_DeathBC_tunnels, v_LR_DeathBC_tunnels, v_LR_DeathBC_tunnels, 1, 0))
m_tunnel_states[1:10, 181]
##All transition to ACM
m_tunnel_states[, 182] <- cbind(c(rep(transprob_acm, 180), 0, 1))
m_tunnel_states[1:10, 182]
###PART FIVE: COSTS
#All transitions to Mets – column 121
v_DFS_Met_tunnels <- c(rep(transprob_DFS_Met1,12), rep(transprob_DFS_Met2, 12),  rep(transprob_DFS_Met3, 36))
v_LR_Met_tunnels <- c(rep(transprob_LR_Met1,12), rep(transprob_LR_Met2, 12),  rep(transprob_LR_Met3, 36))
v_Met_Met_tunnels <- c(rep(transprob_Met_Met1,12), rep(transprob_Met_Met2, 12),  rep(transprob_Met_Met3, 36))
m_tunnel_states[, 121] <- cbind(c(v_DFS_Met_tunnels, v_LR_Met_tunnels, v_LR_Met_tunnels, 0, 0))
m_tunnel_states[1:50, 121]
#All transitions to LRs – column 61
```

```
v_DFS_LR_tunnels <- c(rep(transprob_DFS_LR1,12), rep(transprob_DFS_LR2, 12),  rep(transprob_DFS_LR3, 36))
v_LR_LR_tunnels <- c(rep(transprob_LR_LR1,12), rep(transprob_LR_LR2, 12),  rep(transprob_LR_LR3, 36))
v_met_LR_tunnels <- c(rep(transprob_Met_LR1,12), rep(transprob_Met_LR2, 12),  rep(transprob_Met_LR3, 36))
m_tunnel_states[, 61] <- cbind(c(v_DFS_LR_tunnels, v_LR_LR_tunnels, v_met_LR_tunnels, 0, 0))
m_tunnel_states[1:50, 61]
#First column – get literature values
transprob_LR_DFS1<- rescale_prob(p=prob_LR_DFS1, from=12/12, to=1/12)
transprob_LR_DFS2<- rescale_prob(p=prob_LR_DFS2, from=12/12, to=1/12)
transprob_LR_DFS3<- rescale_prob(p=prob_LR_DFS3, from=12/12, to=1/12)
transprob_Met_DFS1<- rescale_prob(p=prob_Met_DFS1, from=12/12, to=1/12)
transprob_Met_DFS2<- rescale_prob(p=prob_Met_DFS2, from=12/12, to=1/12)
#LR to DFS First column
v_LR_DFS <- c(rep(transprob_LR_DFS1,12), rep(transprob_LR_DFS2,12),  rep(transprob_LR_DFS2,36))
#Met to DFS1
v_Met_DFS <- c(rep(transprob_Met_DFS1,12), rep(transprob_Met_DFS2,12),  rep(transprob_Met_DFS3,36))
m_tunnel_states[61:182, 1]<- cbind (c(v_LR_DFS, v_Met_DFS, 0, 0))
X= as.matrix(rowSums(m_tunnel_states))
#Remaining in DFS_DFS
for (t in 1:59)
 {m_tunnel_states[t, t+1] <- (1- X[t,1])}
m_tunnel_states[60, 60] <- (1- X[60,1])
#Remaining for LR to LR
for (t in 61:119)
 {m_tunnel_states[t, t+1] <- (1- X[t,1])}
m_tunnel_states[120, 120] <- (1- X[120,1])
#Remaining in Metastasis
for (t in 121:179)
 {m_tunnel_states[t, t+1] <- (1- X[t,1])}
m_tunnel_states[180, 180] <- (1- X[180,1])
#check row total for m_P (transition matrix is 1)
V_RowTotal_MP = as.matrix(rowSums(m_tunnel_states))
m_M <- matrix(NA,
nrow = (n_t + 1), ncol = n_states_tunnels,
dimnames = list(0:n_t, v_names_states_tunnels))
# Store the initial state vector in the first row of the cohort #trace
m_M[1, ] <-v_s_init_tunnels
m_n_enter = rbind(c(100, rep(0,181)))
#the run with people entering at each cycle
for (j in 1:n_t){
m_M[j+1,] <- (m_M[j,] + m_n_enter) %*% m_tunnel_states }
m_DFS = as.matrix(rowSums(m_M[, 1:60]))
m_LR = as.matrix(rowSums(m_M[, 61:120]))
m_Met = as.matrix(rowSums(m_M[, 121:180]))
m_TotalMortality = as.matrix(rowSums(m_M[, 181:182]))
Matrix_people = cbind(m_DFS, m_LR, m_Met, m_M[, 181], m_M[, 182], m_TotalMortality)
return(m_M)
}
#****************************************
#GENERATING PEOPLE TRACE MATRICES

list_m_M <- lapply(v_RR, Funct_m_peopletrace)

# ***********************************
#LIST OF VECTORS FOR DISCOUNTING
B<-seq(0,60)
#Create a DF vector for Costs
monthly_rate = discount_rate/12
Discount_factor <- function (x) {
P <- 1/(1+ monthly_rate)^x
return(P)}
v_DF_Cost = Discount_factor(B)
list_DF_Cost <- list(v_DF_Cost, v_DF_Cost, v_DF_Cost, v_DF_Cost, v_DF_Cost, v_DF_Cost, v_DF_Cost)
# ***************************************
```

```
#Create a DF vector for utility
monthly_rateA = discount_rate *ratio_discount /12
B<-seq(0,60)
Discount_factorA <- function (x) {
P <- 1/(1+ monthly_rateA)^x
return(P)}
v_DF_utility = Discount_factorA(B)
list_v_DF_utility<- list(v_DF_utility, v_DF_utility, v_DF_utility, v_DF_utility, v_DF_utility, v_DF_utility, v_DF_utility)
# ************************************************
# DISCOUNTING ****************************
#Create function getting the discounted cost
discountFunction <- function (vecA,vecB){
K<- length(vecA)
vecC <- rep(NA,times=K)
{for (x in 1:K){
vecC[x] <- vecA[x]* vecB[x]
}
return (vecC)}}
#************************************************
#Getting the total costs in a month and the utilities
list_v_TotCost_monthly <- Map(function(A,B) as.vector(A%*%B), list_m_M, l_Cost_Matrix)
list_v_TotUtils_monthly <- Map(function(A,B) as.vector(A%*%B), list_m_M, l_utilities_Matrix)
# DISCOUNTING OF THE MONTHLY COSTS AND UTILITES
list_v_discountCost_monthly <- Map(function(A,B) discountFunction(A,B), list_v_TotCost_monthly, list_DF_Cost)
list_v_discountUTILITY_monthly <- Map(function(A,B) discountFunction(A,B), list_v_TotUtils_monthly, list_v_DF_utility)
# FUCTION FOR DATAFRAME WITH KEY RESULTS
List_v_B <- list(B, B, B, B, B, B, B)
create_dataframe <- function (vec2,vec3, vec4,vec5,vec6,vec7){
df_all <- data.frame(
Mon_Cost = vec2,
DF_Cost = vec3,
Dis_Costs  = vec4,
Mon_Util = vec5,
DF_Util = vec6,
Dis_Utility = vec7)
return(df_all)}
list_df <- Map(function(A,B, C,D,E,F) create_dataframe(A,B,C,D,E,F), list_v_TotCost_monthly, list_DF_Cost, list_v_discountCost_monthly,
list_v_TotUtils_monthly, list_v_DF_utility, list_v_discountUTILITY_monthly)
# ************************************************
n_subcost <-length(1:7)
# ************************************************
A <- sapply(list_v_TotCost_monthly, function(num) sum(num))
B <- sapply(list_v_discountCost_monthly, function(num) sum(num))
C <- sapply(list_v_TotUtils_monthly, function(num) sum(num))
D <- sapply(list_v_discountUTILITY_monthly, function(num) sum(num))
df_ICER <- data.frame(
Duration_Tras = c("Chemo Only", "Nine weeks", "6-month", "Nine months", "Twelve months", "Sixteen months", "24Month"),
Costs_Tot = A,
Dis_Costs_Tot = B,
Utility_tot = C/12,
Dis_Util_tot = D/12)
#  ************************************************
v_names_incremental <-  c("Chemo Only","Nine weeks", "6-month", "Nine months", "Twelve months", "Sixteen months", "24Month")
   n_incremental <- length(v_names_incremental)
 df_Incremental <- data.frame(CostCategory=v_names_incremental,
                       Inc_Costs_Tot = numeric(n_incremental),
                       Inc_utils_Tot = numeric(n_incremental),
                       ICER = numeric(n_incremental),
                       stringsAsFactors = FALSE)

 Inc_Cost1= df_ICER[1, 3] - df_ICER[1,3]
 Inc_Cost2= df_ICER[2, 3] - df_ICER[1,3]
 Inc_Cost3= df_ICER[3, 3] - df_ICER[1,3]
```

```
 Inc_Cost4= df_ICER[4, 3] - df_ICER[1,3]
 Inc_Cost5= df_ICER[5, 3] - df_ICER[1,3]
 Inc_Cost6= df_ICER[6, 3] - df_ICER[1,3]
 Inc_Cost7= df_ICER[7, 3] - df_ICER[1,3]

 Inc_Utility1= df_ICER[1, 5] - df_ICER[1,5]
 Inc_Utility2= df_ICER[2, 5] - df_ICER[1,5]
 Inc_Utility3= df_ICER[3, 5] - df_ICER[1,5]
 Inc_Utility4= df_ICER[4, 5] - df_ICER[1,5]
 Inc_Utility5= df_ICER[5, 5] - df_ICER[1,5]
 Inc_Utility6= df_ICER[6, 5] - df_ICER[1,5]
 Inc_Utility7= df_ICER[7, 5] - df_ICER[1,5]


 df_Incremental [1,2] <- Inc_Cost1
 df_Incremental [2,2] <- Inc_Cost2
 df_Incremental [3,2] <- Inc_Cost3
 df_Incremental [4,2] <- Inc_Cost4
 df_Incremental [5,2] <- Inc_Cost5
 df_Incremental [6,2] <- Inc_Cost6
 df_Incremental [7,2] <- Inc_Cost7

 df_Incremental [1,3] <- Inc_Utility1
 df_Incremental [2,3] <- Inc_Utility2
 df_Incremental [3,3] <- Inc_Utility3
 df_Incremental [4,3] <- Inc_Utility4
 df_Incremental [5,3] <- Inc_Utility5
 df_Incremental [6,3] <- Inc_Utility6
 df_Incremental [7,3] <- Inc_Utility7

 ICER1= df_Incremental[1, 2] / df_Incremental[1,3]
 ICER2= df_Incremental[2, 2] / df_Incremental[2,3]
 ICER3= df_Incremental[3, 2] / df_Incremental[3,3]
 ICER4= df_Incremental[4, 2] / df_Incremental[4,3]
 ICER5= df_Incremental[5, 2] / df_Incremental[5,3]
 ICER6= df_Incremental[6, 2] / df_Incremental[6,3]
 ICER7= df_Incremental[7, 2] / df_Incremental[7,3]

 df_Incremental [1,4] <- 0
 df_Incremental [2,4] <- ICER2
 df_Incremental [3,4] <- ICER3
 df_Incremental [4,4] <- ICER4
 df_Incremental [5,4] <- ICER5
 df_Incremental [6,4] <- ICER6
 df_Incremental [7,4] <- ICER7

# dampack source: R/icers.R (rdrr.io)
# https://cran.microsoft.com/snapshot/2022-09-01/web/packages/dampack/vignettes/psa_analysis.html
#return (list_m_M)
#return (df_Incremental)
return (ICER)
}
# Testing the function
markovmodel (my_params_basecase)
A <- markovmodel (my_params_basecase)
class(A)
write.csv(A, file = "C:/Users/pmand/OneDrive/Desktop/Uni/Thesis/Sensitivity Analysis/27092022/SA for Incremental 270922.csv")
#output <- list(list_df, df_ICER)
#Costs_Tot Dis_Costs_Tot Utility_tot Dis_Util_tot
#*****************************************************
# use calculate_icers on basecase
df_ICER <- markovmodel(my_params_basecase)
hund_icers <- calculate_icers(df_ICER$Dis_Costs_Tot, df_ICER$Dis_Util_tot, df_ICER$Duration_Tras)
```

```
hund_icers
#interpret which is dominated, ED, ND
#Cost effectiveness plane
plot(hund_icers,
txtsize = 10,
label = c( "all"))
#output <- list(list_df, df_ICER)
df_ICER$Duration_Tras = v_durationTherapy
# CREATING THE DATAFRAME TO COMPUTE ICER
#Generating samples
#It  is a 3 step, first use gen_psa_samp
my_psa_params <- gen_psa_samp(params = my_params, dists = my_dists, parameterization_types = my_parameterization_types, dists_params =
my_dists_params, n = 100)
# Next use run_psa -since heemod is running use
dampack::run_psa()
run_psa <- dampack::run_psa

psa_output <- run_psa(
psa_samp = my_psa_params,
params_basecase = my_params_basecase,
FUN = markovmodel,
outcomes = c("Costs_Tot", "Dis_Costs_Tot", "Utility_tot", "Dis_Util_tot"),
strategies = c("Chemo Only", "Nine weeks", "6-month", "Nine months", "Twelve months", "Sixteen months", "24Month"),
currency="Kshs",
progress=FALSE)

# third step – make_psa_obj
cea_psa <- make_psa_obj(
  cost = psa_output$Costs_Tot$other_outcome,
  effect = psa_output$Utility_tot$other_outcome,
  parameters = psa_output$Costs_Tot$parameters,
  strategies = psa_output$Costs_Tot$strategies,
  currency = "Kshs")
cea_psa$strategies
head(cea_psa$cost)
head(cea_psa$effect)
# USE THE CODING IN
# https://cran.microsoft.com/snapshot/2022-09-01/web/packages/dampack/vignettes/psa_analysis.html

psa_obj <- make_psa_obj(cost = cea_psa$cost,
                        effectiveness = cea_psa$effect,
                        parameters = cea_psa$parameters,
                        strategies = cea_psa$strategies,
                        currency = "Kshs")

plot(psa_obj)

psa_sum <- summary(psa_obj, calc_sds = TRUE)
psa_sum
# COST EFFECTIVENESS ACCEPTABILITY CURVE

v_wtp <- c(0, 500000, 1000000, 1500000, 2000000, 2500000, 3000000, 3500000, 4000000, 4500000, 5000000, 5500000, 6000000, 6500000,
7000000, 7500000, 8000000,10000000,12000000,14000000,16000000)
ceac_obj <- ceac(wtp = v_wtp, psa = psa_obj)
head(ceac_obj)
plot(ceac_obj, frontier = TRUE, points = TRUE)
# Deterministic Sensitivity Analysis

names(params_range) <- c("pars", "min", "max")
l_owsa_det <- run_owsa_det(params_range = params_range,
                           params_basecase = my_params_basecase,
                           nsamp = 100,
                           FUN = markovmodel,
```

```
                    outcomes = c("ICER", "Inc_Costs_Tot", "Inc_utils_Tot"),
                    strategies  = c("Chemo Only", "Nine weeks", "6-month", "Nine months", "Twelve months", "Sixteen months", "24Month"))

owsa_tornado(
l_owsa_det$owsa_ICER,
  return = c("plot", "data"),
  txtsize = 12,
  min_rel_diff = 0.1,
  col = c("full", "bw"),
  n_y_ticks = 8,
  ylim = NULL,
  ybreaks = NULL
)
# dampack source: R/icers.R (rdrr.io)
  my_psa_params <- gen_psa_samp(params = my_params,
                          dists = my_dists,
                          parameterization_types =  my_parameterization_types,
                          dists_params = my_dists_params,
                          n = 100)
  #Turn off Heemod
  # run_psa
  psa_output <- run_psa(psa_samp = my_psa_params,
                    params_basecase = my_params_basecase,
                    FUN = markovmodel,
                    outcomes = c("Cost","Utility"),
                    strategies = c("Chemo Only", "Nine weeks", "6-month", "Nine months", "Twelve months", "Sixteen months", "24Month"))

summary( psa_output$Cost$Utility)
v_durationTherapy <- as.vector(psa_output$Cost$Utility[, 7])
```

APPENDIX G: Table with values and codes

Parameter	Base	min	max	distribution	parameters	mean	sd
RepeatVisitQty	1	0	3	gamma	mean, sd	1	0.5
DoxQty	3	2	6	gamma	mean, sd	3	0.333333
CycloQty	3	2	6	gamma	mean, sd	3	0.333333
FHQty	1	0	2	gamma	mean, sd	1	0.333333
OndQty	3	0	8	gamma	mean, sd	3	2.5
DexaQty	2	0	6	gamma	mean, sd	2	1.333333
Qty2D	1	0	3	gamma	mean, sd	1	0.833333
ZoldQty	1	0	2	gamma	mean, sd	1	0.666667
CalsupQty	30	0	60	gamma	mean, sd	30	0.666667
LFTQty	1	0	4	gamma	mean, sd	1	0.666667
UECQty	1	0	4	gamma	mean, sd	1	0.666667
SerCalQty	1	0	4	gamma	mean, sd	1	0.666667
ChemoAdminQty	1	0	1	gamma	mean, sd	1	0.666667
AC_2DQty	1	0	3	gamma	mean, sd	1	0.833333
CSFQty	1	0	3	gamma	mean, sd	0.5	0.5
BloodTQty	1	0	3	gamma	mean, sd	1	0.333333
GXRQty	0.25	0	0.5	gamma	mean, sd	0.25	0.5
TrastSQty	1	0	2	gamma	mean, sd	1	0.333333
EST_2DQty	1	0	2	gamma	mean, sd	1	0.333333
TamoxQty	30	15	60	gamma	mean, sd	30	7.5
MamQty	1	0	2	gamma	mean, sd	1	0.333333
AnasQty	30	15	60	gamma	mean, sd	30	7.5
CalsupQty	30	15	60	gamma	mean, sd	30	7.5
FeeFirstQuantity	1	0	1	gamma	mean, sd	1	0.333333
BreastUSQty	1	0	2	gamma	mean, sd	1	0.333333
CCTscanQty	1	0	2	gamma	mean, sd	1	0.333333
APCTQty	1	0	2	gamma	mean, sd	1	0.333333
BiopsyQty	1	0	2	gamma	mean, sd	1	0.333333
HistoQty	1	0	2	gamma	mean, sd	1	0.333333
HER2Qty	1	0	2	gamma	mean, sd	1	0.333333
CoagQty	1	0	2	gamma	mean, sd	1	0.333333
Diag_2DQty	1	0	2	gamma	mean, sd	1	0.333333
Ki67Qty	1	0	2	gamma	mean, sd	1	0.333333
BoneSQty	1	0	2	gamma	mean, sd	1	0.333333
ChemoAdminQty	1	0	1	gamma	mean, sd	1	0.1112
CapecQty	112	56	224	gamma	mean, sd	112	28
LR_2DQty	1	0	2	gamma	mean, sd	1	0.333333

CarboQty	2	0	4	gamma	mean, sd	2	0.666667
PyriQty	24	0	60	gamma	mean, sd	24	8
Rad_OpQty	1	1	1	constant	val	1	1
Rad_PlanQty	1	1	1	constant	val	1	1
OndoralQty	6	0	12	gamma	mean, sd	6	2
PredQty	15	0	30	gamma	mean, sd	15	5
HydroQty	1	0	2	gamma	mean, sd	1	0.833333
MWQty	1	0	2	gamma	mean, sd	1	0.833333
RadTox1Prob	0.7	0.3	1	beta	mean, sd	0.7	0.116667
RadTox2Prob	0.01	0.005	0.1	beta	mean, sd	0.01	0.008333
RadTox3Prob	0.05	0.025	0.1	beta	mean, sd	0.05	0.0125
RadTox4Prob	0.75	0.5	1	beta	mean, sd	0.75	0.083333
RadTox5Prob	0.7	0.3	1	beta	mean, sd	0.7	0.108333
aUECQty	3	1	4	gamma	mean, sd	3	0.5
aFHQty	3	1	4	gamma	mean, sd	3	0.5
RepeatVisitPrice	650	100	5000	gamma	mean, sd	650	816.6667
DoxPrice	403	403	2172	gamma	mean, sd	403	133.3333
CycloPrice	191	171	460	gamma	mean, sd	191	150
OndPrice	26.75	18	160	gamma	mean, sd	26.75	22.5
DexaPrice	7.9	4	35	gamma	mean, sd	7.9	3
Price2D	3000	2000	20000	gamma	mean, sd	3000	1000
ZoldPrice	1095	800	8550	gamma	mean, sd	1095	816.6667
CalsupPrice	5.2	3.5	50	gamma	mean, sd	5.2	8
LFTPrice	900	600	4000	gamma	mean, sd	900	650
SerCalPrice	1500	1000	3500	gamma	mean, sd	400	400
ChemoAdminPrice	4500	3000	7000	gamma	mean, sd	4500	1000
AC_2DPrice	3000	2000	10000	gamma	mean, sd	3000	1500
CSFPrice	1800	1000	5000	gamma	mean, sd	1800	783.3333
BloodTPrice	2000	800	4000	gamma	mean, sd	2000	583.3333
GXRPrice	1000	750	3500	gamma	mean, sd	1000	816.6667
TrastSPrice	88995	50000	280000	gamma	mean, sd	88995	28333.33
EST_2DPrice	3000	2000	20000	gamma	mean, sd	3000	916.6667
TamoxPrice	5.4	2	43	gamma	mean, sd	5.4	4.666667
MamPrice	2500	1500	7000	gamma	mean, sd	2500	1000
AnasPrice	33.46	10	165	gamma	mean, sd	33.46	23.33333
FeeFirstPrice	1150	800	7000	gamma	mean, sd	1150	1083.333
BreastUSPrice	5000	3000	15000	gamma	mean, sd	5000	2333.333
CCTscanPrice	8000	4000	20000	gamma	mean, sd	8000	2500
APCTPrice	8000	4000	20000	gamma	mean, sd	8000	3000

BiopsyPrice	10000	2000	20000	gamma	mean, sd	10000	3000
HistoPrice	1100	500	5000	gamma	mean, sd	1100	750
HER2Price	2000	1000	7000	gamma	mean, sd	2000	1500
CoagPrice	1000	500	2500	gamma	mean, sd	1000	750
Diag_2DPrice	3000	2000	20000	gamma	mean, sd	3000	1500
Ki67Price	5000	2500	10000	gamma	mean, sd	5000	3166.667
BoneSPrice	7500	2500	30000	gamma	mean, sd	7500	6333.333
CapecPrice	170.79	161	435	gamma	mean, sd	170.79	76.66667
LR_2DPrice	3000	2000	20000	gamma	mean, sd	3000	1500
CarboPrice	3589	2000	9000	gamma	mean, sd	3589	1500
PyriPrice	1	0.5	10	gamma	mean, sd	1	1.583333
Rad_OpPrice	3600	1000	10000	gamma	mean, sd	3600	1500
Rad_PlanPrice	10000	5000	15000	gamma	mean, sd	10000	2166.667
OndoralPrice	8.86	4	55	gamma	mean, sd	8.86	12.75
PredPrice	10	2	100	gamma	mean, sd	10	16.33333
HydroPrice	100	10	500	gamma	mean, sd	100	81.66667
MWPrice	250	180	1200	gamma	mean, sd	250	2333.333
Final_MRMTot	53938	20000	500000	gamma	mean, sd	53938	80000
SurgeryTot	49567	20000	300000	gamma	mean, sd	49567	46666.67
prob_acm	0.008033	0.00241	0.0099	beta	mean, sd	0.008033	0.000749
prob_DFS_LR1	0.021	0.0063	0.41	beta	mean, sd	0.021	0.03395
prob_DFS_Met1	0.035	0.0105	0.075	beta	mean, sd	0.035	0.056583
prob_DFS_DeathBC1	0.031	0.0093	0.1	beta	mean, sd	0.031	0.050117
prob_LR_LR1	0.0001	0.00003	0.001	beta	mean, sd	0.0001	0.000162
prob_LR_Met1	0.097	0.0291	0.1	beta	mean, sd	0.097	0.003545
prob_LR_DeathBC1	0.001	0.0003	0.02	beta	mean, sd	0.001	0.001617
prob_Met_LR1	0.0001	0.00003	0.001	beta	mean, sd	0.0001	0.000162
prob_Met_Met1	0.023	0.0069	0.23	beta	mean, sd	0.023	0.037183
prob_Met_DeathBC1	0.072	0.0216	0.72	beta	mean, sd	0.072	0.1164

transprob_DeathBC_DFS	0	0	0	constant	val	0	0
transprob_DeathBC_LR	0	0	0	constant	val	0	0
transprob_DeathBC_Met	0	0	0	constant	val	0	0
transprob_DeathBC_DeathBC	1	1	1	constant	val	1	0
transprob_DeathBC_ACM	0	0	0	constant	val	0	0
transprob_ACM_DFS	0	0	0	constant	val	0	0
transprob_ACM_LR	0	0	0	constant	val	0	0
transprob_ACM_Met	0	0	0	constant	val	0	0
transprob_ACM_DeathBC	0	0	0	constant	val	0	0
transprob_ACM_ACM	1	1	1	constant	val	1	0
prob_LR_DFS1	0.875	0.2625	0.95	beta	mean, sd	0.875	0.114583
prob_LR_DFS2	0.714	0.2142	0.95	beta	mean, sd	0.714	0.122633
prob_LR_DFS3	0.714	0.2142	0.95	beta	mean, sd	0.714	0.122633
prob_Met_DFS1	0.875	0.2625	0.95	beta	mean, sd	0.875	0.114583
prob_Met_DFS2	0.714	0.2142	0.95	beta	mean, sd	0.714	0.122633
transprob_Met_DFS3	0.047	0.0141	0.0705	beta	mean, sd	0.047	0.0094
UECPrice	700	200	2000	gamma	mean, sd	700	180
FilProb	0.1	0	1	beta	mean, sd	0.5	0.1111
AC_2DProb	0.25	0	1	beta	mean, sd	0.25	0.1111
CSFProb	0.1	0	0.3	beta	mean, sd	0.1	0.04
BloodTProb	0.1	0	0.3	beta	mean, sd	0.1	0.04
PacQty	4	0	8	gamma	mean, sd	4	0.5
PacPrice	1206.3	1000	7595	gamma	mean, sd	1206.3	800
TrastSPrice	88995	50000	280000	gamma	mean, sd	88995	23333.33

OndQty	3	1	6	gamma	mean, sd	3	0.833333
OndPrice	26.75	18	160	gamma	mean, sd	26.75	7.666667
DexaQty	2	0	6	gamma	mean, sd	2	1
DexaPrice	7.9	4	35	gamma	mean, sd	7.9	2.666667
ChlorphenQty	2	0	4	gamma	mean, sd	2	8.333333
ChlorphenPrice	6	2	20	gamma	mean, sd	6	3
ESTH_2DQty	1	0	3	gamma	mean, sd	1	0.5
ESTH_2DPrice	3000	2000	20000	gamma	mean, sd	3000	983.3333
ESTH_2DProb	0.25	0	0.4	gamma	mean, sd	0.25	0.066667
RepeatVisitPrice	650	200	5000	gamma	mean, sd	650	800
FHPrice	500	300	1500	gamma	mean, sd	500	216.6667
AnasQty	30	15	60	gamma	mean, sd	30	8.333333
VisitsPerYearDFS	4	1	8	gamma	mean, sd	4	0.833333
ProbMamoDFS	0.083	0	0.3	beta	mean, sd	0.083	0.05
MamQty	1	0	2	gamma	mean, sd	1	0.333333
ProbFHDFS	0.25	0	0.5	beta	mean, sd	0.25	0.083333
LR_2DProb	0.33	0	0.6	beta	mean, sd	0.33	0.1
prob_DFS_LR2	0.026	0.006	0.045	beta	mean, sd	0.026	0.0039
prob_DFS_Met2	0.045	0.02	0.065	beta	mean, sd	0.045	0.0045
prob_DFS_DeathBC2	0.031	0.02	0.045	beta	mean, sd	0.031	0.0025
prob_DFS_LR3	0.037	0.02	0.045	beta	mean, sd	0.037	0.0025
prob_DFS_Met3	0.064	0.04	0.09	beta	mean, sd	0.064	0.005
prob_DFS_DeathBC3	0.0762	0.04	0.09	beta	mean, sd	0.0762	0.005
prob_LR_LR2	0.053	0.02	0.08	beta	mean, sd	0.053	0.006
prob_LR_Met2	0.123	0.09	0.15	beta	mean, sd	0.123	0.006
prob_LR_DeathBC2	0.031	0.01	0.05	beta	mean, sd	0.031	0.004
prob_LR_LR3	0.143	0.09	0.45	beta	mean, sd	0.143	0.036
prob_LR_Met3	0.176	0.09	0.45	beta	mean, sd	0.176	0.036
prob_LR_DeathBC3	0.0762	0.03	0.1	beta	mean, sd	0.0762	0.007
prob_Met_LR2	0.0001	0.00005	0.0004	beta	mean, sd	0.0001	0.000035
prob_Met_Met2	0.357	0.1	0.7	beta	mean, sd	0.357	0.06
prob_Met_DeathBC2	0.1011	0.08	0.19	beta	mean, sd	0.1011	0.011
prob_Met_LR3	0.0001	0.00005	0.0003	beta	mean, sd	0.0001	0.000025

prob_Met_Met3	0.357	0.1	0.6	beta	mean, sd	0.357	0.05
prob_Met_Death BC3	0.1011	0.05	0.5	beta	mean, sd	0.1011	0.045
prob_LR_DFS1	0.875	0.1	0.95	beta	mean, sd	0.875	0.085
prob_LR_DFS2	0.714	0.1	0.95	beta	mean, sd	0.714	0.085
prob_LR_DFS3	0.714	0.1	0.95	beta	mean, sd	0.714	0.085
prob_Met_DFS1	0.875	0.1	0.95	beta	mean, sd	0.875	0.085
prob_Met_DFS2	0.714	0.1	0.95	beta	mean, sd	0.714	0.085
transprob_Met_DFS3	0.047	0.01	0.08	beta	mean, sd	0.047	0.007
FilPrice	2000	1050	4000	gamma	mean, sd	2000	708.3333
FilQty	1	0	4	gamma	mean, sd	1	0.666667
EchoQty	1	0	2	gamma	mean, sd	1	0.133
EchoPrice	3000	2000	20000	gamma	mean, sd	3000	1500
QtyRadSes	15	1	25	gamma	mean, sd	15	4.166667
Rad_OpProb	0.8	0.6	1	beta	mean, sd	0.8	0.033333
Prob2D	0.167	0	1	beta	mean, sd	0.167	0.1667
CaregiverPrice	20000	2000	40000	gamma	mean, sd	20000	6333.33
CaregiverQty	1	0	2	gamma	mean, sd	1	0.333333
PalliativedrugsPrice	7500	5000	25000	gamma	mean, sd	7500	3333.33
PalliativedrugsQty	1	0	2	gamma	mean, sd	1	0.333333
BoneBiopsyQty	1	0	2	gamma	mean, sd	1	0.333333
BoneBiopsyPrice	25000	15000	45000	gamma	mean, sd	25000	5000
BoneQtyRadSes	5	1	10	gamma	mean, sd	5	1.5
FHProb	0.8	0.6	1	beta	mean, sd	0.8	0.033333
EST_2DProb	0.25	0	1	beta	mean, sd	0.25	0.1667
RepeatVisitProb	0.25	0	1	beta	mean, sd	0.25	0.1667
RepeatVisitProb2	0.167	0	1	beta	mean, sd	0.167	0.1667
ProbFHDFS2	0.167	0	0.3	beta	mean, sd	0.167	0.05
discount_rate	0.06	0	0.12	beta	mean, sd	0.06	0.03
uDiagnosisTot	0.84	0.63	0.93	beta	mean, sd	0.84	0.05
uSurgeryTot	0.76	0.683	0.827	beta	mean, sd	0.76	0.024
uRadESTot	0.77	0.73	0.8	beta	mean, sd	0.77	0.011667
uESACTot	0.71	0.6	0.95	beta	mean, sd	0.71	0.058333
uESTHLoadTot	0.71	0.6	0.95	beta	mean, sd	0.71	0.058333
uESTHContTot	0.71	0.6	0.95	beta	mean, sd	0.71	0.058333
uESTTot	0.9	0.85	0.94	beta	mean, sd	0.9	0.015
uDFSIpostTot	0.73	0.62	0.84	beta	mean, sd	0.73	0.036667

uDFSIpostTotyear2	0.805	0.65	0.93	beta	mean, sd	0.805	0.046667
uDFSIIpostTot	0.805	0.65	0.93	beta	mean, sd	0.805	0.046667
uBoneDiagnosisTot	0.84	0.63	0.93	beta	mean, sd	0.84	0.05
uBoneRadTot	0.41	0	0.86	beta	mean, sd	0.41	0.143333
uBoneMetChemoZolTot	0.47	0.02	0.89	beta	mean, sd	0.47	0.145
uBoneMetZolPalTot	0.36	0.09	0.63	beta	mean, sd	0.36	0.09
uFinal_MRMTot	0.88	0.84	0.98	beta	mean, sd	0.88	0.023333
uLRFinalloadTot	0.7	0.5	0.8	normal	mean, sd	0.7	0.05
uLRFinalContTot	0.7	0.5	0.8	normal	mean, sd	0.7	0.05
uLRRadTot	0.61	0.35	0.87	beta	mean, sd	0.61	0.086667
uDFSIpreTot	0.88	0.77	0.99	beta	mean, sd	0.88	0.036667
uDFSIIpreTot	0.88	0.77	0.99	beta	mean, sd	0.88	0.036667
RR6mon_LR	1.21	0.54	1.51	normal	mean, sd	1.21	0.097
RR6mon_Met	0.83	0.65	1.1	normal	mean, sd	0.83	0.045
RR6mon_DeathBC	1.09	0.8	1.5	normal	mean, sd	1.09	0.07
RR9mon_LR	1	0.54	1.3	normal	mean, sd	1	0.076
RR9mon_Met	0.9	0.65	1.1	normal	mean, sd	0.9	0.045
RR9mon_DeathBC	1	0.8	1.32	normal	mean, sd	1	0.052
RR9week_LR	1.61	0.92	2.79	normal	mean, sd	1.35	0.187
RR9week_Met	1.18	0.9	1.56	normal	mean, sd	1.16	0.066
RR9week_DeathBC	1.03	0.65	1.66	normal	mean, sd	1.03	0.101
RRNoTras_DeathBC	1.503	1.276	1.77	normal	mean, sd	1.503	0.0494
RRNoTras_Met	1.604	1.41	1.824	normal	mean, sd	1.604	0.0414
RRNoTras_LR	1.248	0.997	1.562	normal	mean, sd	1.248	0.0565
RRManu_LR	1.051	0.842	1.312	normal	mean, sd	1.051	0.047
RRManu_Met	0.998	0.875	1.139	normal	mean, sd	0.998	0.0264
RRManu_DeathBC	1	0.99	1.01	normal	mean, sd	1	0.002
prob_DFS_LR1NoTras	0.049	0.0063	0.41	beta	mean, sd	0.049	0.03395
prob_DFS_Met1NoTras	0.084	0.0105	0.095	beta	mean, sd	0.084	0.0212

prob_DFS_DeathBC1NoTras	0.031	0.0093	0.1	beta	mean, sd	0.031	0.050117
prob_LR_LR1NoTras	0.0001	0.00003	0.001	beta	mean, sd	0.0001	0.000162
prob_LR_Met1NoTras	0.231	0.05	0.4	beta	mean, sd	0.231	0.156817
prob_LR_DeathBC1NoTras	0.001	0.0003	0.02	beta	mean, sd	0.001	0.001617
prob_LR_DFS1NoTras	0.875	0.2625	0.95	beta	mean, sd	0.875	0.114583
prob_LR_DFS2NoTras	0.714	0.2142	0.95	beta	mean, sd	0.714	0.122633
prob_LR_DFS3NoTras	0.714	0.2142	0.95	beta	mean, sd	0.714	0.122633
DoxPrice	403	403	2172	gamma	mean, sd	403	133.3333
CycloPrice	191	171	460	gamma	mean, sd	191	150
FuPrice	65	60	150	gamma	mean, sd	65	15
EpiPrice	2040	1890	2555	gamma	mean, sd	2040	110.8333
OmepPrice	220	73	954	gamma	mean, sd	220	146.8333
DoxQty	3	2	6	gamma	mean, sd	3	0.333333
CycloQty	3	2	6	gamma	mean, sd	3	0.333333
FuQty	4	2	8	gamma	mean, sd	4	1
EpiQty	3	2	6	gamma	mean, sd	3	0.666667
OmepQty	1	0	2	gamma	mean, sd	1	0.333333
ratio_discount	1	0	2	normal	mean, sd	1	0.333333
PacQty	4	0	8	gamma	mean, sd	4	0.5
uDFSIpretTot	0.88	0.77	0.99	beta	mean, sd	0.88	0.036667

APPENDIX H: Tables of cost parameters

H.1. Diagnosis of bone metastasis

	Cost Category	Price	Quantity	Cost	Percent
1	First Visit	1150	1	1150	1.8
2	Bone Scan	7500	1	7500	11.9
3	Mammography	2500	0.5	1250	2
4	Breast Ultrasound	5000	0.5	2500	4
5	Chest CT scan	8000	1	8000	12.7
6	Abdominal Pelvic CT Scan	8000	1	8000	12.7
7	Bone Biopsy	25000	1	25000	39.8
8	Histology	1100	1	1100	1.8
9	HER-2 test	2000	1	2000	3.2
10	Liver Function Test	900	1	900	1.4
11	UEC	700	1	700	1.1
12	Coagulation Profile	1000	1	1000	1.6
13	GXR	1000	0.25	250	0.4
14	2D Echo	3000	1	3000	4.8
15	Full Hemogram	500	1	500	0.8
16	Total Cost of Bone Diagnosis			62850	

H.2. Treatment of Bone Metastasis using Doxorubicin, Cyclophosphamide and Zolendronic acid regimen

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Chemo Administration	4500	1	1	4500	38.36
2	Doxorubicin	403	3	1	1209	10.31
3	Cyclophosphamide	191	3	1	573	4.88
4	Full Hemogram	500	1	1	500	4.26
5	Ondansetron	26.75	3	1	80.25	0.68
6	Dexamethasone	7.9	2	1	15.8	0.13
7	2D Echo	3000	1	0.167	501	4.27
8	Zolendronic Acid	1095	1	1	1095	9.33
9	Calcium Supplement	5.2	30	1	156	1.33
10	Liver Function Test	900	1	1	900	7.67
11	UEC	700	1	1	700	5.97

12	Serum Calcium Test	1500	1	1	1500	12.79
13	Total Met Chemo	0	0	0	7379.05	
14	Total Zolendronic	0	0	0	4351	
15	Total Chemo + Zol per cycle				11730.05	

H.3. Treatment of Bone Metastasis using Zolendronic acid only with palliative care

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Zolendronic Acid	1095	1	1	1095	3.38
2	Calcium Supplement	5.2	30	1	156	0.48
3	Liver Function Test	900	1	1	900	2.78
4	UEC	700	1	1	700	2.16
5	Full Hemogram	500	1	1	500	1.55
6	Serum Calcium Test	1500	1	1	1500	4.64
7	Caregiver	20000	1	1	20000	61.82
8	Palliative treatment	7500	1	1	7500	23.18
9	Total cost of Zolendronic Acid	0	0	0	4851	
10	Total cost of Palliative Care	0	0	0	27500	
11	Total cost per cycle				32351	

H.4. Disease free survival for the first two years for post-menopausal women

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Repeat visit	650	1	0.25	162.5	9.8
2	Anastrazole	33.46	30	1	1003.8	60.7
3	Calcium supplement	5.2	30	1	156	9.4
4	Full Hemogram	500	1	0.25	125	7.6
5	Mammogram	2500	1	0.083	207.5	12.5
6	Disease Free Survival				1654.8	

	Cost Category	Price	Quantity	Probability	Cost	Percent

1	Repeat visit	650	1	0.25	162.5	24.73
2	Tamoxifen	5.4	30	1	162	24.66
3	Full Hemogram	500	1	0.25	125	19.03
4	Mammogram	2500	1	0.083	207.5	31.58
5	Disease Free Survival				657	

H.5. Disease free survival for the first two years for pre-menopausal women

H.6. Disease free survival after two years for post-menopausal women

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Repeat visit	650	1	0.167	108.55	7.0
2	Anastrazole	33.46	30	1	1003.8	64.4
3	Calcium supplement	5.2	30	1	156	10.0
4	Full Hemogram	500	1	0.167	83.5	5.4
5	Mammogram	2500	1	0.083	207.5	13.3
6	Disease Free Survival				1559.35	

H.7. disease free survival after the first two years of treatment for pre-menopausal women

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Repeat visit	650	1	0.167	108.55	19.3
2	Tamoxifen	5.4	30	1	162	28.8
3	Full Hemogram	500	1	0.167	83.5	14.9
4	Mammogram	2500	1	0.083	207.5	37.0
5	Disease Free Survival				561.55	

H.8. Treatment using FEC regimen

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Chemo Administration	4500	1	1	4500	28.2
2	5-Fluorouracil	65	4	1	260	1.6
3	Cyclophosphamide	191	3	1	573	3.6
4	Epirubicin	2040	3	1	6120	38.3
5	Ondansetron	26.75	3	1	80.25	0.5
6	Omeprazole	220	1	1	220	1.4
7	Dexamethasone	7.9	2	1	15.8	0.1
8	UEC	700	1	1	700	4.4
9	Full Hemogram	500	1	1	500	3.1
10	2D Echo	3000	1	1	3000	18.8
11	Total FEC Chemo				15969.05	

H.9. Total cost of local recurrence for a five-year period

	Cost Category	Cost	Percent
1	Year One	916921.4	96.67502
2	Year Two	7884	0.831244
3	Year Three	7884	0.831244
4	Year Four	7884	0.831244
5	Year Five	7884	0.831244
6	Total	948457.4	100

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Chemo Admin	4500	1	1	4500	2.20

2	Capecitabine	170.79	112	1	19128.48	9.34
3	Trastuzumab	88995	2	1	177990	86.91
4	Ondansetron	26.75	3	1	80.25	0.04
5	Dexamethasone	7.9	2	1	15.8	0.01
6	2D Echo	3000	1	0.33	990	0.48
7	UEC	700	1	1	700	0.34
8	Full Hemogram	500	1	1	500	0.24
9	Liver function test	900	1	1	900	0.44
10	Herceptin Loading Dose				204804.5	

H.10. Local Recurrence treatment with Capecitabine and Trastuzumab (Cycle 1)

H.11. Treatment of local recurrence with Capecitabine from Cycle 2

	Cost Category	**Price**	**Quantity**	**Probability**	**Cost**	**Percent**
1	Chemo Admin	4500	1	1	4500	3.89
2	Capecitabine	170.79	112	1	19128.48	16.52
3	Trastuzumab	88995	1	1	88995	76.85
4	Ondansteron	26.75	3	1	80.25	0.07
5	Dexamethasone	7.9	2	1	15.8	0.01
6	2D Echo	3000	1	0.33	990	0.85
7	UEC	700	1	1	700	0.60
8	Full Hemogram	500	1	1	500	0.43
9	Liver function test	900	1	1	900	0.78
11	Total Cost per Cycle				115809.5	

H.12 Local recurrence treatment with Capecitabine and Carboplatin

	Cost Category	Price	Quantity	Probability	Cost	Percent
1	Chemo Admin	4500	1	1	4500	13.63
2	Capecitabine	170.79	112	1	19128.48	57.92
3	Carboplatin	3589	2	1	7178	21.73
4	Ondansetron	26.75	3	1	80.25	0.24
5	Dexamethasone	7.9	2	1	15.8	0.05
6	Pyridoxine	1	24	1	24	0.07
7	UEC	700	1	1	700	2.12
8	Full Hemogram	500	1	1	500	1.51
9	Liver function test	900	1	1	900	2.73
10	Total Cost per Cycle				33026.53	

H.13. Total cost of metastasis for a five-year period

	Cost Category	Cost	Percent
1	Year One	294515.4	45.28
2	Year Two	355861	54.72
3	Year Three	0	0
4	Year Four	0	0
5	Year Five	0	0
6	Total	650376.4	100

H.14. Radiotherapy for Bone metastasis

	Cost Category	Price	Quantity	Cost	Probability	Adjusted Cost	Percent
1	Repeat Visit	650	1	650	0.20	130	2.0
2	Radiotherapy Session	3600	1	3600	1	3600	56.5
3	Radiotherapy Plan	10000	1	10000	0.20	2000	31.4
4	Radiotherapy Lab Total	1200	1	1200	0.20	240	3.8
5	Nausea(Ondansetron oral)	8.86	6	53.16	0.70	37.21	0.6
6	Pneumonitis (Prednisolone)	10	15	150	0.01	1.50	0.0
7	Dermatitis (Hydrocortisone)	100	1	100	0.05	5	0.1
8	Mucocitis (Mouth Wash)	250	1	250	0.75	187.50	2.9
9	Mouth Ulcer (Mouth Wash)	250	1	250	0.70	175	2.7
10	Total Cost per session					6376.21	
11	Total Cost of Early Radiotherapy	6376.21	5		1	31881.06	

H.15. Diagnosis of bone metastasis

	Cost Category	Price	Quantity	Cost	Percent
1	First Visit	1150	1	1150	1.8
2	Bone Scan	7500	1	7500	11.9
3	Mammography	2500	0.5	1250	2
4	Breast Ultrasound	5000	0.5	2500	4
5	Chest CT scan	8000	1	8000	12.7
6	Abdominal Pelvic CT Scan	8000	1	8000	12.7
7	Bone Biopsy	25000	1	25000	39.8
8	Histology	1100	1	1100	1.8
9	HER-2 test	2000	1	2000	3.2
10	Liver Function Test	900	1	900	1.4
11	UEC	700	1	700	1.1
12	Coagulation Profile	1000	1	1000	1.6
13	GXR	1000	0.25	250	0.4
14	2D Echo	3000	1	3000	4.8
15	Full Hemogram	500	1	500	0.8
16	Total Cost of Bone Diagnosis	0	0	62850	0

H.16. Total cost of diagnosis and treatment followed by disease free survival for a five-year period

	Cost Category	Cost	Percent
1	Year One	774297.3	41.1
2	Year Two	1051550	55.8
3	Year Three	19857.6	1.1
4	Year Four	19762.15	1.0
5	Year Five	18712.2	1.0
6	Total	1884179	100.0

APPENDIX I: Summary of transition of patients through different health states.

Cycle	9 Weeks	6 Months	9 Months	16 Months	24 Months	Metastasis	Local Recurrence
0	Diagnosis	Diagnosis	Diagnosis	Diagnosis	Diagnosis	Diagnosis	Diagnosis
1	Surgery	Surgery	Surgery	Surgery	Surgery	Radio	Surgery
2	Radio	Radio	Radio	Radio	Radio	Zol	Load T+Cap
3	THLoad	ESACTot	ESACTot	ESACTot	ESACTot	Zol	Cont T+Cap
4	THCont	ESACTot	ESACTot	ESACTot	ESACTot	Zol	Cont T+Cap
5	THCont	ESACTot	ESACTot	ESACTot	ESACTot	Zol	Cont T+Cap
6	FEC	ESACTot	ESACTot	ESACTot	ESACTot	Zol	Cont T+Cap
7	FEC	THLoad	THLoad	THLoad	THLoad	Zol	Cont T+Cap
8	FEC	THCont	THCont	THCont	THCont	Zol + Pal	Radio
9	DFSIpost	THCont	THCont	THCont	THCont	Zol + Pal	DFSIpre
10	DFSIpost	THCont	THCont	THCont	THCont	Zol + Pal	DFSIpre
11	DFSIpost	ESTTot	ESTTot	ESTTot	ESTTot	Zol + Pal	DFSIpre
12	DFSIpost	ESTTot	ESTTot	ESTTot	ESTTot	Zol + Pal	DFSIpre
13	DFSIpost	ESTTot	ESTTot	ESTTot	ESTTot	Zol + Pal	DFSIpre
14	DFSIpost	ESTTot	ESTTot	ESTTot	ESTTot	Zol + Pal	DFSIpre
15	DFSIpost	ESTTot	ESTTot	ESTTot	ESTTot	Zol + Pal	DFSIpre
16	DFSIpost	DFSIpost	ESTTot	ESTTot	ESTTot	Zol + Pal	DFSIpre
17	DFSIpost	DFSIpost	ESTTot	ESTTot	ESTTot	Zol + Pal	DFSIpre
18	DFSIpost	DFSIpost	ESTTot	ESTTot	ESTTot	Zol + Pal	DFSIpre
19	DFSIpost	DFSIpost	DFSIpost	ESTTot	ESTTot	Zol + Pal	DFSIpre
20	DFSIpost	DFSIpost	DFSIpost	ESTTot	ESTTot	Zol + Pal	DFSIpre
21	DFSIpost	DFSIpost	DFSIpost	ESTTot	ESTTot	Zol + Pal	DFSIpre
22	DFSIpost	DFSIpost	DFSIpost	ESTTot	ESTTot	Zol + Pal	DFSIpre
23	DFSIpost	DFSIpost	DFSIpost	ESTTot	ESTTot	0	DFSIpre
24	DFSIpost	DFSIpost	DFSIpost	ESTTot	ESTTot	0	DFSIpre
25	DFSIpost	DFSIpost	DFSIpost	ESTTot	ESTTot	0	DFSIpre
26	DFSIpost	DFSIpost	DFSIpost	ESTTot	ESTTot	0	DFSIpre
27	DFSIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIpre
28	DFSIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIpre
29	DFSIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIpre
30	DFSIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIpre
31	DFSIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIpre
32	DFSIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIpre
33	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre
34	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre
35	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre

Cycle	9 Weeks	6 Months	9 Months	16 Months	24 Months	Metastasis	Local Recurrence
36	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre
37	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre
38	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre
39	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre
40	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre
41	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre
42	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	DFSIpost	0	DFSIIpre
43	DFSIIpost	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	0	DFSIIpre
44	DFSIIpost	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	0	DFSIIpre
45	DFSIIpost	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	0	DFSIIpre
46	DFSIIpost	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	0	DFSIIpre
47	DFSIIpost	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	0	DFSIIpre
48	DFSIIpost	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	0	DFSIIpre
49	DFSIIpost	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	0	DFSIIpre
50	DFSIIpost	DFSIIpost	DFSIIpost	DFSIpost	DFSIpost	0	DFSIIpre
51	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	0	DFSIIpre
52	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	0	DFSIIpre
53	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	0	DFSIIpre
54	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	0	DFSIIpre
55	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	0	DFSIIpre
56	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	0	DFSIIpre
57	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	0	DFSIIpre
58	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	0	DFSIIpre
59	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	DFSIIpost	0	DFSIIpre