EPIDEMIOLOGICAL TRENDS (2010-2021) AND ADVANCED DRUG THERAPIES FOR HER2-POSITIVE BREAST CANCER IN THE CURRENT US MARKET

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By

Kanika Mathur

Under the Supervision and Guidance of

Dr Arindam Das

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PharmaACE

Date: 28/06/2024

TO WHOMSOEVER IT MAY CONCERN

This is to certify that, **Kanika Mathur,** student of IIHMR University, Jaipur has completed her internship with **PharmaACE Analytics LLP** during the period of **April 01, 2024 to June 30, 2024.** During her internship she worked with the Competitive Intelligence department and has successfully worked on the project; **Epidemiological Trends (2010-2021) and Advanced Drug Therapies for HER2-Positive Breast Cancer in the Current US Market.**

We wish her every success in life.

Ashima Kumar

Ashima Kumar

Head – Training & Development and Corporate Communications

PharmaACE

DECLARATION

I hereby declare that this dissertation titled "**Epidemiological Trends (2010-2021) and Advanced Drug Therapies for HER2-Positive Breast Cancer in the Current US Market** "is the Bonafede record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

(Signature)

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Date: 6.07.24

CERTIFICATE BY FACULTY GUIDE

This is to certify that dissertation titled "**Epidemiological Trends (2010-2021) and Advanced Drug Therapies for HER2-Positive Breast Cancer in the Current US Market**" is a record of the research work undertaken by Dr Kanika Mathur in partial fulfilment of the requirements for the award of the degree of MBA (Hospital and Health Management from the IIHMR University, Jaipur under my guidance and supervision and her approach to the research study has been sincere, scientific, and analytical.

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Dr. Kanika Mathur

Date:

ABSTRACT

1. **Title:** Epidemiological Trends (2010-2021) and Advanced Drug Therapies for HER2-Positive Breast Cancer in the Current US Market
2. **Background:** The overexpression of the HER2 protein leads to this HER2 positive form of breast cancer. It represents about 20-30% of breast cancers. It is an aggressive form, leading to rapid cell growth and spread. Effective diagnosis and targeted treatments, such as HER2 inhibitors, have improved outcomes, yet it remains a significant cause of breast cancer mortality.
3. **Objective:**
    a. To analyze the epidemiological trends in age-adjusted incidence rates of HER2-positive breast cancer from 2010 to 2021 in the US.
    b. To examine the variations in incidence rates among different racial/ethnic groups.
    c. To evaluate the market dynamics of advanced HER2-targeted therapies, (Bi-specific antibodies, TKIs and ADCs)
4. **Methodology:**
    a. Study Design: Retrospective (data during 2010 to 2021)
    b. Study Setting: Organizational (PharmaAce Innovation LLP)
    c. Study Duration: 3 months.
    d. Data Collection Procedure: Data was collected from the SEER database for incidence rates and demographic information. Market data was sourced from industry reports, financial statements, and market research databases.
5. **Results:** From 2010 to 2021, HER2-positive breast cancer incidence in the US showed peaks in 2015-2016 and declined significantly in 2020, likely due to COVID-19. Non-Hispanic Black females had the highest rates of distant-stage cases. Five-year survival rates remained high across all racial groups, ranging from 91.37% to 91.91%. Advancements in targeted therapies, including bispecific antibodies, ADCs, and TKIs, have improved HER2-positive breast cancer treatment. Biosimilars have increased competition, reduced costs, and enhanced patient access. Reimbursement policies and patient assistance initiatives have further improved access to expensive therapies.
6. **Conclusion:** Despite challenges like resistance, brain metastases, and healthcare disparities, ongoing research aims to enhance personalized care for HER2-positive breast cancer patients in the US. By developing novel therapies, optimizing treatment sequencing, and utilizing artificial intelligence, future outcomes and quality of life are expected to improve.

7. **Keywords:** HER2 Positive breast cancer, Advanced breast cancer, HER2 + Breast cancer drugs, Metastatic breast cancer

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LIST OF ABBREVIATIONS

Abbreviation	Full form
HER	Human Epidermal Growth Factor Receptor
HR	Hormone Receptor
CBE	Clinical Breast Examination
BRCA	Breast Cancer Susceptibility Gene
PBLA	Peripheral Blood Lymphocyte Analysis
ASCO	American Society of Clinical Oncology
OS	Overall Survival
PFS	Progression-Free Survival
TTP	Time to Progression
ADC	Antibody-Drug Conjugate
TKI	Tyrosine Kinase Inhibitor
MAB	Monoclonal Antibody

CHAPTER 1: INTRODUCTION

1.1 BREAST CANCER: DISEASE OVERVIEW

A malignant tumor that starts in the breasts cells is called breast cancer. It happens when these cells start to grow out of control and form a lump or mass. Through the bloodstream and lymphatic system, it can spread to other areas of the body. (1) About one-fourth of all new cancer cases in women are breast cancer cases making it the most common cancer among women globally. Furthermore, it ranks second among women for cancer-related deaths, after lung cancer. Although rare breast cancer can also strike men although it primarily affects women. (1). Any one of the three primary breast regions can develop breast cancer (1,33).

- Lobules: milk producing glands (1,33)
- The ducts: Tubes that carry milk to the nipple. (1,33)
- Enveloping tissue. (1,33)

The World Health Organization estimates that the cells lining the ducts account for about 85% of breast cancer cases while the cells lining the lobules account for 15%. (33) Breast cancer is often asymptomatic and limited to the lobule or duct at stage 0 when the disease first appears. Afterwards adjacent breast tissue lymph nodes and other organs may be affected by breast cancer. Cancer of the breast may become lethal because of this metastasis. (1, 33)

Types of Breast Cancer

Breast cancer is categorized based on its molecular and histopathological characteristics. The primary types include:

- **Ductal carcinoma in situ:** It refers to a non-invasive cancer in which the aberrant cells are limited to the ducts. (33)
- **Invasive Ductal Carcinoma:** The most common type, where cancer cells spread beyond the ducts into surrounding breast tissue. (33)
- **Invasive Lobular Carcinoma**: It occurs in the lobules and tend to spread to adjacent tissues. (33)
- **Hormone Receptor-Positive:** Cancers that express estrogen and/or progesterone receptors, often treated with hormone therapies. (33)
- **HER2-Positive**: Cancers that overexpress the HER2 protein, treated with targeted therapies like trastuzumab. (33)
- **Triple-Negative Breast Cancer:** Cancer occurs due to lack of estrogen, progesterone, and HER2 receptors, often more aggressive and treated with chemotherapy. (33)

Signs and Symptoms

- Lumping or thickening found in either of the breasts. (2,3,4)
- Changes observed in the appearance or shape and size of the breast. (2,3,4)
- Dimpling, redness, or pitting of the breast skin. (2,3,4)
- Changes in the nipple, such as sores, discharge, or inversion. (2,4)
- Ongoing pain in the breast that is not related to the menstrual cycle. (4)

Diagnosis

Breast cancer screening tests are designed to detect breast cancer early, before symptoms appear, and when it is more treatable. The most common tests used for its screening are:

- Screening Mammogram: It's a low-dose X-ray. It is by far considered the best test to detect breast cancer in most women. (6,7)
- Clinical Breast Exam (CBE): A medical professional physical examination of the breasts. Regular CBEs may still be helpful in some circumstances such as for women who are more at risk than the average even though research has not indicated a clear benefit from them. (7,8)

Recommended Screening Schedule

- Average Risk Women: Must have mammogram once in a year after 40. (6,7)
- High Risk Women: Have a mammogram and breast MRI every year, typically starting at age 30. (7,8)

Follow-up Tests

- Diagnostic Mammogram: Used to detect abnormal findings particularly. (6,7)
- Breast Ultrasound: This test is performed following an abnormal mammography or CBE. (6,7)
- Breast MRI: This procedure which is frequently performed on high-risk or dense-breasted women creates images of the breast using magnetic fields. (6,7)
- Biopsy: Uses cell/ tissue specimen to confirm the diagnosis. (7)

Who is susceptible to breast cancer?

- Women: Females are more (approx. 99%) to breast cancers than males (0.5 – 1%). (1)
- Age: Increasing age is a significant risk factor, with the risk increasing after the age of 40.
- Obesity: Being overweight or obese can increase the risk of breast cancer. (1)
- Harmful Use of Alcohol: Excessive alcohol consumption can increase the risk of breast cancer.
- Family History: Genetic predisposition (BRCA/PBLA Mutations running in family) can pose a risk. (1)
- Reproductive History: Menarche, menopause, age at first pregnancy, and parity are additional factors that can affect the risk of developing breast cancer. (1)

Scope of the problem

In 2022, 2.5 million women were diagnosed with breast cancer, resulting in approximately 670,000 deaths globally. Breast cancer can affect women worldwide after puberty, with risk increasing with age. Incidence rates vary significantly based on the Human Development Index (HDI). For instance, in countries with a very high HDI, approximately 8% of women will receive a breast cancer diagnosis in their lifetime, with around 1.4% succumbing to the disease. In contrast, in nations with a low HDI, the figures are approximately 3.7% women diagnosed and 2.1% deaths due to breast cancer. (1)

Breast cancer scenario in USA

2020, the most recent year with available incidence data in the United States, Breast cancer incident cases were reported as 239,612. During the same period, 42,273 women succumbed to this disease. These staggering figures translate to an incidence rate of 119 new female breast cancer cases per 100,000 women and a mortality rate of 19 deaths per 100,000 women.

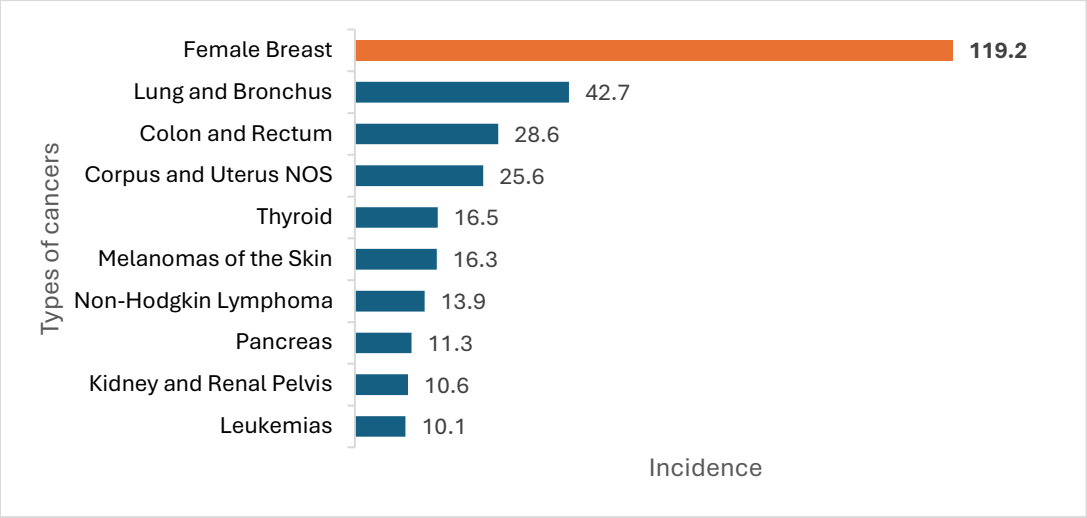

Figure 1.1 The top 10 cancers in the USA based on new cancer cases 2020(All race and ethnicities, women)
Rate per 100,000 women
Source - U.S. Cancer Statistics U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in November 2023.

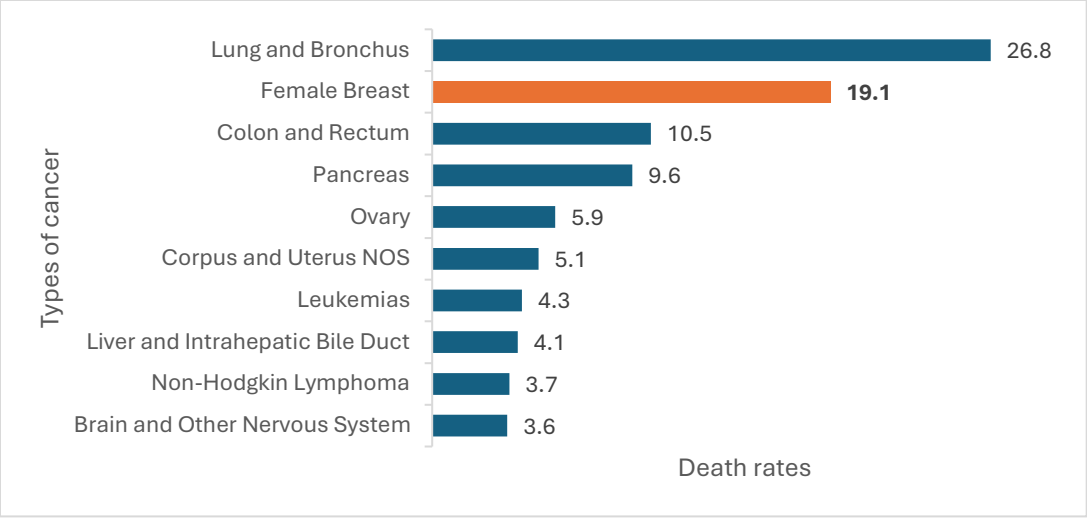

Figure:1.2 The top 10 cancers in the USA based on cancer-related death rates 2020 (All race and ethnicities, women)

Rate per 100,000 women
Source - U.S. Cancer Statistics U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in November 2023.

1.2 HER2 POSITIVE BREAST CANCER

Pathophysiology

The human epidermal growth factor receptor 2 (HER2) is found in higher amounts in about 20-30% of breast cancers. HER2 is one of four related proteins (along with HER1, HER3, and HER4) that help cells grow. Normally, HER2 helps with regular cell signaling, but when there is too much of it, cells can grow out of control, which is a sign of cancer. Unlike the other HER proteins, HER2 doesn't have a partner molecule to activate it. Instead, it pairs up with itself or with other HER proteins, especially HER3, to become active. This activation leads to a chain of signals that makes cells grow, move, spread, and survive. (9, 32)

Diagnosis

Diagnosis of HER2-positive breast cancer involves several tests to determine the presence and level of HER2 protein in breast cancer cells.

- **Immunohistochemistry (IHC)**: IHC is a widely used test to detect HER2 protein overexpression. It involves staining breast cancer tissue with antibodies that bind to HER2 protein. The results are categorized as 0, 1+, 2+, or 3+, with 3+ indicating high levels of HER2 protein. (10,11)
- **Fluorescence In Situ Hybridization (FISH):** FISH is a more sensitive test that detects HER2 gene amplification. It involves staining breast cancer cells with fluorescent probes that bind to the HER2 gene. The results are categorized as positive or negative, with positive indicating HER2 gene amplification. (10,11)

- **Inform Dual ISH:** This test combines IHC and FISH to detect both HER2 protein overexpression and gene amplification. It is used to confirm the results of IHC and FISH tests. (10,11)

Testing Strategy

The American Society of Clinical Oncology (ASCO) recommends a testing strategy that involves IHC as the initial test, followed by FISH confirmation for scores of 2+ or 3+. This strategy ensures accurate determination of HER2 status and reduces the risk of false-positive results. (10,11)

Prevalence treatment and prognosis

Poor patient outcomes and a more aggressive tumor biology have historically been linked to overproduction and expression of the HER2 protein in breast cancer. (32) **Approximately 20-30% of breast cancer patients** exhibit HER2 amplification and/or overexpression, a phenomenon linked to a poor prognosis and reduced overall survival. This highlights the significance of HER2 in breast cancer, as its overexpression can lead to uncontrolled cell growth and proliferation, ultimately impacting patient outcomes. (9) Since targeted therapies (e.g., trastuzumab, Pertuzumab, T-DM1), and hormone therapy (for hormone receptor-positive tumors) have been developed, treatment for HER2-positive breast cancer has greatly improved. Anti-HER2 medications and chemotherapy are common forms of treatment. For breast cancer that is HER2-positive the overall prognosis has improved, with 5-year survival rates ranging from **45% for distant metastatic disease to over 90% for localized disease**. (12)

HER2 Positive breast cancer scenario in USA

The prevalence of HER2-positive breast cancer in the United States had been a important concern due to its bad prognosis and heightened risk of metastasis. Historically, this subtype has been associated with an advanced liability of complaint progression and reduced survival rates. Yet recent statistics indicate a promising trend. According to the rearmost data, HER2-positive bone cancer now accounts for roughly 11- 12 of all bone cancer cases in the USA, a significant drop from former times.

This represents a significant decrease from previous years, indicating a positive trend in the management and treatment of this subtype.

CHAPTER 2: REVIEW OF LITERATURE

Table 2.1: Summary of literatures reviewed on HER2 + breast cancer

S.no	Year of publication	Title	Authors	Comments
1		Breast Cancer in the United States: A Cross-Sectional Overview	Emily C. and Nadeem Bilani rearrangement. Zabor Elizabeth B. Laurah Elson. Elimimian along with Zeina Nahle.	As the most common cancer in women to admit a opinion bone cancer varies greatly in terms of pathology clinical features and prognostic. In this study data from 2671549 cases with bone cancer who were diagnosed between 2004 and 2016 were examined retrospectively using the National Cancer Database. Results of the analysis showed that 75 ofnon-Hispanic White cases had a median age of 61 times at opinion. Ductal melanoma reckoned for 73 of the most common histology. Among the molecular subtypes were HR/ HER2-(58) HR/ HER2(26) HR-/ HER2-(10) and HR-/ HER2(6 point 4 percent). By subtype race and installation type overall survival(zilch's) varied significantly 83 percent of HR/ HER2 and 77 percent of HR-/ HER2 had an zilch's during a 5- time period. The rate of survival was smallest in community cancer programs and loftiest in academic centers. This study highlights the significance of taking race treatment installation and molecular and histologic subtypes into account in any unborn exploration on difference in cancer.
2	2022	Breast Cancer Statistics, 2022	Maria N. Giaquinto, Hyuna Sung, Kimberly D. Miller, Joan L. Kramer, Lisa A. Minihan, Ahmed in Jemal, Rebecca L. Newman, MD, MPH, Seigel.	Even so there was minimal increase (0.5%) in the incidence of breast cancer per year between 2010 and 2019 primarily due to cases that were localized-stage and HR-positive the mortality rate of the disease has been declining since 1989 declining by 43 percent by 2020 or 460000 fewer deaths. Black women have mortality rates that are 40% higher than White women especially for those under 50 despite having lower incidence rates. A better understanding of screening and treatment options is necessary to address the persistent racial disparities that black women experience as evidenced by their lower 5-year relative survival rates across all disease stages and molecular subtypes.
3	2021	Breast Cancer—Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies— An Updated Review	Sergiusz Łukasiewicz, Marcin Czeczelewski, Alicja Form, Jacek Baj, Robert Sitarz, Andrzej Stanisławek.	The review article offers a comprehensive analysis of breast cancer, particularly focusing on HER2-positive breast cancer. It likely includes statistics on the prevalence of HER2-positive tumors among breast cancer cases, which typically range from 15% to 20% of all breast cancer diagnoses. The paper would delve into the prognostic significance of HER2 amplification or overexpression, indicating a more aggressive disease course if left untreated. In terms of treatment, the review would discuss the efficacy of HER2-targeted therapies such as trastuzumab, which has shown to improve overall survival in HER2-positive breast cancer patients by approximately 30% when used in combination with chemotherapy. The introduction of Pertuzumab has further enhanced treatment outcomes, leading to reduced recurrence rates. Additionally, the review highlights ongoing research in the field, including the development of novel HER2-targeted agents and the exploration of biomarkers to identify patients who would benefit most from these therapies.

Table 2.1: Continued

S.no	Year of publication	Title	Authors	Comments
4	2019	Contrasting Epidemiology and Clinicopathology of Female Breast Cancer in Asians vs the US Population and The Asian Breast Cancer Cooperative Group	Chiun-Sheng Huang, Ching-Hung Lin, Fu-Chang Hu, Huiping Li, Kyung-Hun Lee, Roland Leung, Seock-Ah Im, Shu-Min Huang, Takayuki Ueno, Wonshik Han, Winnie Yeo, Yoichi Naito, Yoon Sim Yap, Ava Kwong, Benita Tan.	The article "Contrasting Epidemiology and Clinicopathology of Female Breast Cancer in Asians vs the US Population" by Lin et al. provides a detailed examination of HER2-positive breast cancer within the US population. It includes statistics on the prevalence of HER2-positive tumors among American women, highlighting any trends or changes over time. Based on age-adjusted incidence rates from 2010 to 2014, there is a notable probability of developing HER2-positive breast cancer among individuals aged 30 to 45, with estimates ranging from 20% to 40%. However, this probability decreases for older age groups. The data indicates a higher susceptibility to HER2-positive breast cancer in the younger age bracket, highlighting the importance of early detection and targeted screening strategies for this population.
5	2024	Reproductive characteristics, menopausal status, race and ethnicity, and risk of breast cancer subtypes defined by ER, PR and HER2 status: the Breast Cancer Etiology in Minorities	Jocelyn Koo, Amanda I. M., John Phipps, Teri A. Longacre, Allison W. Kurian, Anna H. Wu, Lisa M. Hines, and others.	The study examined correlations between 4579 African American Asian American or Hispanic controls and 2794 cases of breast cancer in California as well as harmonized data from these controls. The California Cancer Registry provided the tumors characteristics. A number of subtypes were identified including triple-negative and luminal A and HER2-enriched) cases. Subtype-specific connections with reproductive variables were set up using multivariable logistic retrogression models which also demonstrated subtle variations grounded on menopausal status and race/ race. For illustration, among African American premenopausal women advanced equality without breastfeeding was associated with an increased threat of luminal A and TN subtypes. harmonious odds rates were observed among all ethnical and ethnical groups for the premenopausal luminal. .
6	2019	HER2-positive breast cancer: new therapeutic frontiers and overcoming resistance	Sonia Pernas and Sara M. Tolaney	Both early-stage and advanced HER2-positive breast cancer patient survival rates have significantly improved since the introduction of anti-HER2 therapies. Even with these improvements the majority of HER2-positive metastatic patients eventually become resistant to these treatments. The main goals of research are to comprehend the mechanisms underlying this resistance as well as the functions of the microenvironment and tumor heterogeneity. The creation of sophisticated anti-HER2 treatments such as antibody-drug conjugates (ADCs) fresh anti-HER2 antibodies bispecific antibodies and unique tyrosine kinase inhibitors (TKIs) as well as dual-blockade tactics are examples of new tactics. While new TKIs like neratinib and tucatinib are being tested in combination with capecitabine promising ADCs like SYD985 & DS-8201a may replace T-DM1 or be used after progression on T-DM1. By addressing resistance and increasing treatment efficacy these developments hope to improve patients with HER2-positive breast cancers quality of life and chance of survival.

Table 2.1: Continued

S.no	Year of publication	Title	Authors	Comments
7	2019	Targeted therapeutic options and future perspectives for HER2-positive breast cancer	Jiani Wang1 and Binghe Xu1,2	Breast cancer is a heterogeneous disease, with HER2-positive subtypes comprising 20-25% of cases. This aggressive cancer poses challenges due to high recurrence rates and risk of metastasis. Anti-HER2 therapy, particularly with drugs like trastuzumab and Pertuzumab, is vital for both early and advanced stages. While one year of trastuzumab is standard, extending treatment offers no added benefit and increases cardiotoxicity risks. Despite advancements, one- fourth patients suffering from the early variants experience recurrence. Ongoing research focuses on improving treatment strategies, exploring new drugs, and refining HER2 detection techniques to enhance prognosis and survival rates. Future efforts aim to personalize treatment and achieve greater survival benefits through molecular biology research and predictive prognostic factors.
8	2020	HER2-positive Advanced Breast Cancer Treatment in 2020	Marcelle G Cesca1 , Lucas Vian1 , Sofia Cristóvão-Ferreira2, 3 , Noam Pondé1 , Evandro de Azambuja2	One particularly aggressive subtype of bone cancer was linked in the 1980s HER2-positive bone cancer. Case issues have greatly bettered since the development of HER2- targeted curatives. First- line binary leaguer with trastuzumab and Pertuzumab followed by the current standard of care i.e., T-DM1 (2012) as an alternate line. Third- line options are sour, but recent trials, presented in 2019, have introduced new medicines similar as tucatinib, neratinib, and trastuzumab-deruxtecan, raising questions about sequencing and treatmentpost-T-DM1 exposure. Other arising treatments include fresh antibody-medicine conjugates and bispecific antibodies. The introduction of putative biomarkers could revolutionize treatment selection and response evaluation. Despite the rapid FDA approval of these new third-line options, the trials face criticism for their design, providing limited data for decision-making. The authors suggest trastuzumab-deruxtecan as the likely third-line choice, with tucatinib for patients with severe lung comorbidities or CNS disease. The integration of biomarkers in clinical trials remains a crucial need to enhance personalized treatment strategies.
9	2020	Novel HER2–Targeted Therapies for HER2–Positive Metastatic Breast Cancer	Jame Abraham MD FACP Siddharth Kunte MBBS and Alberto J. Montero M. D. MBA	In approximately 20% of breast cancer cases HER2 is overexpressed. The prognosis for HER2-positive breast cancer was not good prior to the development of HER2-directed monoclonal antibodies. Many patients have been cured in the nonmetastatic setting thanks to treatments like trastuzumab Pertuzumab T-DM1 and trastuzumab deruxtecan which have significantly improved results. Resistance in cases where it spreads however continues to be difficult. An important change in treatment has occurred with the recent FDA approval of neratinib tucatinib and trastuzumab deruxtecan. It seems promising to incorporate novel drugs and optimize therapy sequencing. The success of novel therapies for lowering HER2 expression may be reflected in updated ASCO/CAP guidelines. In order to potentially treat HER2-positive metastatic breast cancer acquired resistance must be overcome.
10	2020	Systemic therapy for metastatic HER2-positive breast cancer	Philip Bredina , Janice M. Walshea , Neelima Denduluri	HER2 is overexpressed in 15-20% of breast cancers. HER2-targeted therapies like trastuzumab and pertuzumab, combined with chemotherapy, have considerably improved outcomes, extending median survival to over 57 months. However, metastatic HER2-positive breast cancer remains incurable, with challenges such as brain metastases and drug resistance. New treatments like tucatinib, neratinib, and trastuzumab deruxtecan offer hope. Despite advances, financial toxicity and access to therapies remain major global challenges, necessitating further research and improved infrastructure.

Table 2.1: Continued

S.no	Year of publication	Title	Authors	Comments
11	2020	The Changing Paradigm for the Treatment of HER2-Positive Breast Cancer	Aena Patel 1 , Nisha Unni 1,* and Yan Peng 2,	Compared to other breast cancer subtypes HER2-positive breast cancer was long linked to worse prognoses and greater death rates. Nonetheless the paradigm for treating HER2-positive breast cancer has undergone a significant shift since the introduction of trastuzumab (Herceptin). The array of treatment alternatives has been further broadened by the introduction of several HER2-targeted drugs including Pertuzumab (Perjeta). This review puts light on new developments in the treatment of HER2-positive bone cancer similar as immunotherapies and new HER2-targeted curatives that are witnessing clinical trials and are impacting standard care in the neoadjuvant adjuvant and metastatic settings. While numerous cases profit greatly from these treatments some develop resistance or relapse. Though the implicit advantages of incorporating new HER2- targeted specifics or immunotherapy are still unknown, a binary- targeted HER2 strategy is generally employed. Furthermore, many trials did not apply the 2018 ASCO/CAP updated guidelines for HER2 interpretation which reclassified cases with ambiguity as either HER2+ or HER2− thereby preventing overtreatment and lowering expenses.
12	2023	Targeting HER2-positive breast cancer: advances and future directions	Sandra M. Swain 1 , Mythili Shastry 2 & Erika Hamilton 2,	Treating aggressive HER2-positive breast cancer has advanced significantly since HER2 was discovered to be a viable and highly responsive therapeutic target. Nearly 25 years ago this accomplishment resulted in the approval of trastuzumab the first medication targeting the HER2 receptor. Following this there has been a noticeable acceleration of development with several trials using monoclonal antibodies targeting HER2 tyrosine kinase inhibitors and antibody-drug conjugates showing notable clinical efficacy. These successes have sparked significant initiatives to develop new platforms and more specialized treatments. In this review we examine the current treatment protocols for HER2-positive breast cancer the immune system manipulation agents' novel therapeutic strategies and the mechanisms underlying resistance to HER2-targeted therapies.

CHAPTER 3 – RESEARCH QUESTIONS, OBJECTIVES AND METHODOLOGY

1. Research question:

How have the epidemiological trends of HER2-positive breast cancer incidence in the US evolved from 2010 to 2021, and what are the current advanced drug therapies and market dynamics for HER2-positive breast cancer in the US?

2. Objectives:

- To analyze the epidemiological trends in age-adjusted incidence rates of HER2-positive breast cancer from 2010 to 2021 in the US.
- To examine the variations in incidence rates among different racial/ethnic groups.
- To evaluate the market dynamics of advanced HER2-targeted therapies, that includes antibody-drug conjugates, monoclonal antibodies, and tyrosine kinase inhibitors.

3. Materials and methods:

- **Study Design:** Retrospective study based on secondary data.
- **Study Setting:** Organizational (PharmaAce Innovation LLP)
- **Study Duration:** 3 months.
- **Data Collection Procedure**: Data was collected from the SEER database for incidence rates and demographic information. Market data was sourced from industry reports, financial statements, and market research databases.
- **Operational Definitions:**
  - HER2-positive breast cancer: A subtype of breast cancer with overexpression of the HER2 protein.
  - Age-adjusted incidence rates: Incidence rates standardized to eliminate the effect of age differences in population.
  - Advanced drug therapies: Targeted therapies including monoclonal antibodies, antibody-drug conjugates and tyrosine kinase inhibitors.

CHAPTER 4 – RESULTS AND DISCUSSION

4.1 EPIDEMIOLOGICAL TRENDS – INCIDENCE RATES OF HER2 + BREAST CANCER

The present study looks at the incidence rates of HER2+ breast cancer in female populations in the United States from 2010 to 2021 considering changes in SEER age-adjusted rates. Six different racial/ethnic groups are the subject of the study: non-Hispanic Black, non-Hispanic Whites, Black (including Hispanic), White (including Hispanic), Non-Hispanic American Indian/Alaska Native, and Non-Hispanic Asian/Pacific Islander. To find age-specific incidence patterns and trends the data is divided into different age groups. The four stages of breast cancer—localized regional distant and unknown—are also considered in the analysis to give a thorough picture of how the disease progresses across various demographic groups. The goal of this strategy is to draw attention to the differences and inequalities in the incidence rates of breast cancer which will facilitate the distribution of resources and support focused public health initiatives.

4.1.1 Yearly trends: Age adjusted incidence by Race (2010-21)

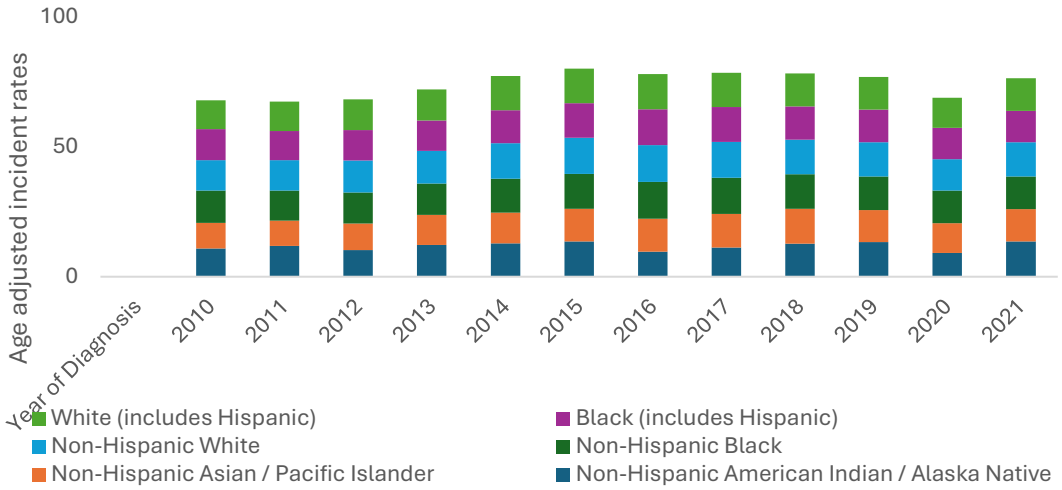

Figure: 4.1.1 Trends in Age-Adjusted Incidence Rates of HER2-Positive Breast Cancer by Race/Ethnicity (2010-2021)

The overall incidence rate of female HER2+ breast cancer has varied over time peaking at 80 points per 100000 cases in 2015 and falling to 67 points per 100000 cases in 2010. Figure 4 Point 1. 1 indicates a significant decline in the overall incidence rate in 2020 to 68. 9 cases per 100000 people. This decline may have been caused by the COVID-19 pandemics effects on cancer reporting and diagnoses. Non-Hispanic American Indian and Alaska Native female incidence rates varied reaching a high of 13 points six cases per 100000 in 2015 and a low of 9 points 6 cases per 100000 in 2016.

Females of non-Hispanic Asian and Pacific Island descent experienced rising rates overall in 2018 they peaked at 13. 4 cases per 100000 and they then remained comparatively stable. The rates of non-Hispanic Black females reached a peak in 2016 at 14. 2 cases per 100000 and then began to decline slightly in the subsequent years. White female non-Hispanics saw rates rise steadily reaching a peak of 14. 1 cases per 100000 in 2016 before slightly declining. Before 2016—when the rate of Black females including those of Hispanic descent reached 13 points eight cases per 100000—there was a growing trend with only small variations. The rates of white females including those of Hispanic descent peaked in 2015 at 13. 4 cases per 100000 people after which they began to slightly decline. In 2020 there was a significant decline in incidence rates for most groups possibly as a result of external factors such as the pandemic compared to the highest incidence rates recorded for most of them in 2015–2016**.**

4.1.2 Yearly trends: Age adjusted incidence by Stage (2010-21)

Breaking down the age-adjusted incidence rates by diagnosis stage there are several important trends to note in female HER2+ breast cancer cases. The incidence rate for localized cases grew from 6 points per 100000 in 2010 to a peak of 7.0 100000 in 2016. Thereafter there was a slight decline before another increase to 7.0 per 100000 in 2021. Regional cases likewise demonstrated an increasing trend starting in 2010 at 4 points per 100000 reaching a peak of 4 points per 100000 in 2014 and 2016 and then progressively falling to 4 points per 100000 in 2020 and 2021. The incidence of distant cases increased gradually over time from 0.8 per 100000 in 2010 4.1 per 100000 in 2015 2016 and 2021. Un-staged cases stayed mostly constant over the course of the time averaging 0 points per 100000 with the exception of a small rise in 2016. The COVID-19 pandemic is likely to have had an impact on the observed decline in incidence rates in 2020. Overall the highest incidence rates for localized and regional stages were noted between 2014 and 2016.

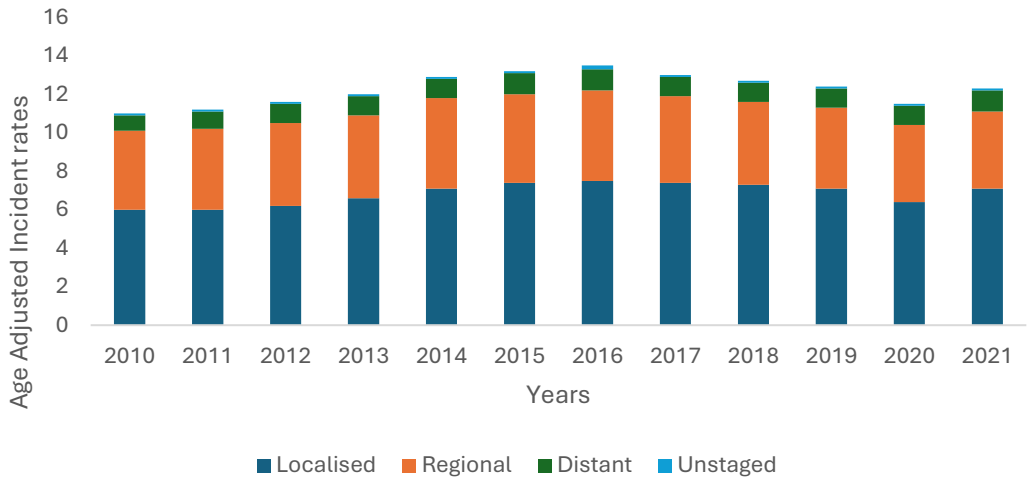

Figure: 4.1.2 Trends in Age-Adjusted Incidence Rates of HER2-Positive Breast Cancer by Stage at diagnosis (2010-2021)

4.1.3 Yearly trends: Age adjusted incidence by Age at diagnosis (2010-21)

The age-adjusted incidence rates of HER2+ breast cancer in women broken down by age group show a number of noteworthy patterns. With a slight decline to 6. 3 per 100000 in 2020—possibly as a result of fewer screenings during the COVID-19 pandemic—the incidence rate for females under 50 increased gradually from 5. 3 per 100000 in 2010 to a peak of 6. 6 per 100000 in 2016 and 2019. In 2021 the rate eventually returned to 6. 6 per 100000. The incidence rate in the 50–64 age group increased overall peaking at 30.7 per 100000 in 2016 after 25.1 per 100000 in 2010.

Following 2016 there was a minor decrease that resulted in 25. 4 per 100000 in 2020 and then another increase to 27. 9 per 100000 in 2021. The incidence rate for women 65 and older also generally increased reaching a peak of 33. 3 per 100000 in 2015 from 27. 1 per 100000 in 2010. Following 2015 there was a slow reduction that ended in 2020 at 26 points per 100000 and a small rise to 28 points per 100000 in 2021. All age groups saw a significant decline in incidence rates in 2020 possibly because of pandemic's effect on cancer diagnosis and reporting. Overall, the highest incidence rates were recorded for all age groups between 2014 and 2016.

4.1.4 Age and stage related disparities in HER2 + Breast cancer

The age- acclimated prevalence rates for HER2 bone cancer reveal distinct patterns across different age groups and ethnical/ ethnical orders. For ladies under 50, localized cases are most current (50.334 per 100,000), followed by indigenous(40.756 per 100,000), distant(7.928 per 100,000), and un-staged(0.983 per 100,000) cases.

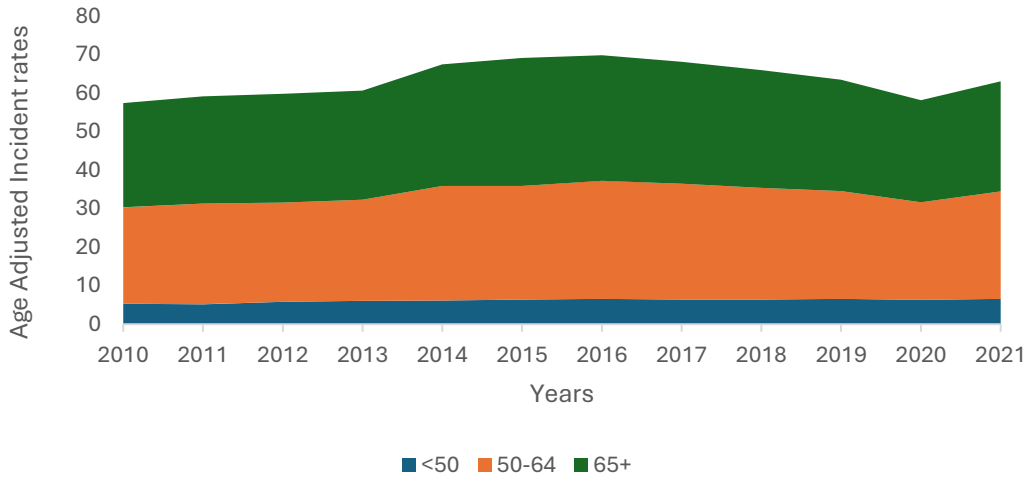

Figure: 4.1.3 Trends in Age-Adjusted Incidence Rates of HER2-Positive Breast Cancer by Age at diagnosis in years (2010-2021)

This trend is harmonious across aged age groups, with localized cases being most common57.453 per 100,000 for periods 50- 64 and61.179 per 100,000 for periods 65 and aged. Regional and distant cases drop with age, while un-staged cases remain low. Comparing ethnical/ ethnical groups, localized cases are loftiest among Non-Hispanic White females (59.312 per 100,000) and smallest among Non-Hispanic Black females (49.896 per 100,000). Regional cases are most common among Hispanic ladies (39.347 per 100,000) and least common among Non-Hispanic White females (31.772 per 100,000). Distant cases are specially advanced in Non-Hispanic Black females (11.335 per 100,000) compared to other groups, indicating a implicit difference in late-stage opinion or access to early discovery and treatment. Un-staged cases are low across all groups, with Hispanic ladies showing the loftiest rate(1.286 per 100,000) and Non-Hispanic American Indian/ Alaska Native ladies showing none.

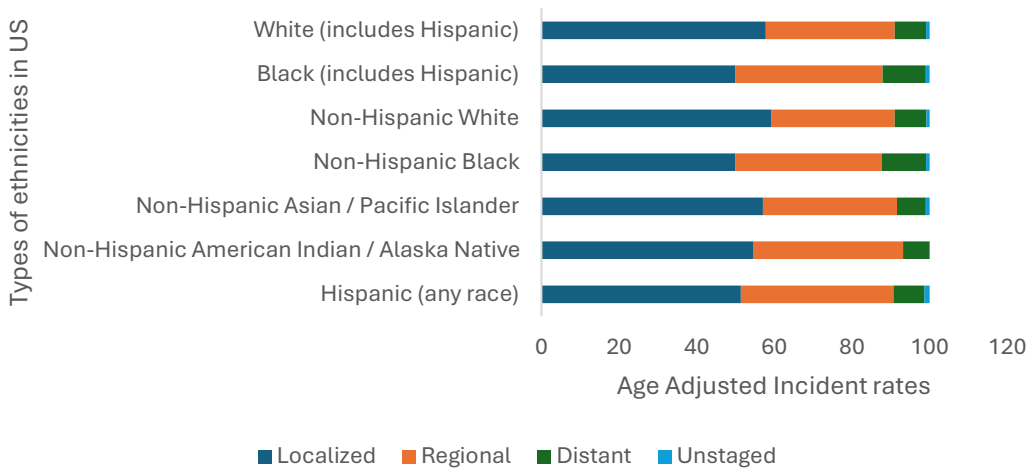

Figure: 4.1.4 Age-Adjusted Incidence Rates of HER2-Positive Breast Cancer by Race/Ethnicity and Stage of the disease (2010-2021)

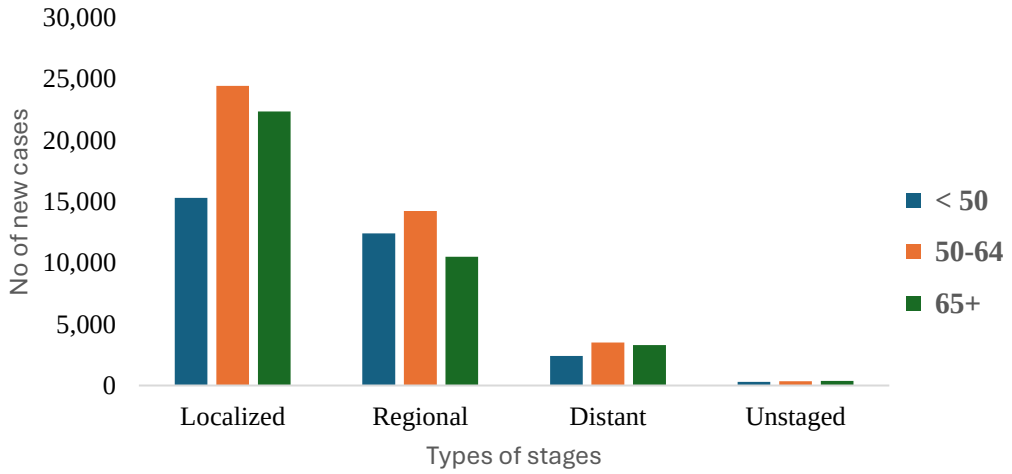

Figure: 4.1.5 Incident cases of HER2-Positive Breast Cancer by Stage and Age Group (2010-2021)

However, the greater frequency of distant cases in Black female non-Hispanic patients and the increasing incidence of distant cases with advancing age point to possible delays in diagnosis as well as disparities in healthcare access. The impact of external factors on cancer detection and reporting is highlighted by the noteworthy decline in overall incidence rates in 2020 which is probably related to the COVID-19 pandemic. All things considered the data point to the need for

significant work in addressing healthcare disparities and guaranteeing prompt diagnosis for all demographic groups even though early detection is successful.

4.2 EPIDEMIOLOGICAL TRENDS – RELATIVE 5-YEAR SURVIVAL RATES OF HER 2 + BREAST CANCER

Table 4.2.1: Five-year Relative survival rates (in percentages) for HER2 + Breast cancer (2017-21)

Year	All races	Blacks	Whites
2017	91.369	87.222	91.925
2018	91.508	87.629	92.035
2019	91.645	88.024	92.143
2020	91.78	88.407	92.25
2021	91.913	88.779	92.356

Figure 4.2.1 showcases the 5-year relative survival rates for HER2-positive breast cancer patients across different racial groups from 2017 to 2021. Throughout these years, the survival rates have remained consistently high, ranging from approximately 91.37% to 91.91%. This indicates a robust trend of survival, reflecting the effectiveness of treatments and healthcare strategies in prolonging the lives of HER2-positive breast cancer patients. Interestingly, there is a slight variation in survival rates between racial groups, with Whites showing slightly higher rates compared to Blacks, with a difference typically ranging between 0.6% to 0.8%. However, overall, both groups exhibit strong survival rates, suggesting that advancements in treatment approaches, early detection methods, and overall healthcare management have positively impacted the results for disease positive patients across racial backgrounds. This stability in survival rates over the years highlights the ongoing progress and success in managing HER2-positive breast cancer, contributing to improved patient outcomes and quality of life.

The 5-year relative survival rates for HER2-positive breast cancer patients, analysed by stage and racial groups from 2017 to 2021, reveal a consistent and positive trend in survival outcomes. Across all stages, including localized, regional, and distant cancers, survival rates remained notably high, ranging from approximately 98.5% to 99% for localized cancer, 88% to 89.5% for regional cancer, and 25% to 30% for distant cancer. While there were slight variations in survival rates between racial groups, with Whites generally showing slightly higher rates than Blacks, both groups exhibited significant improvements over the years.

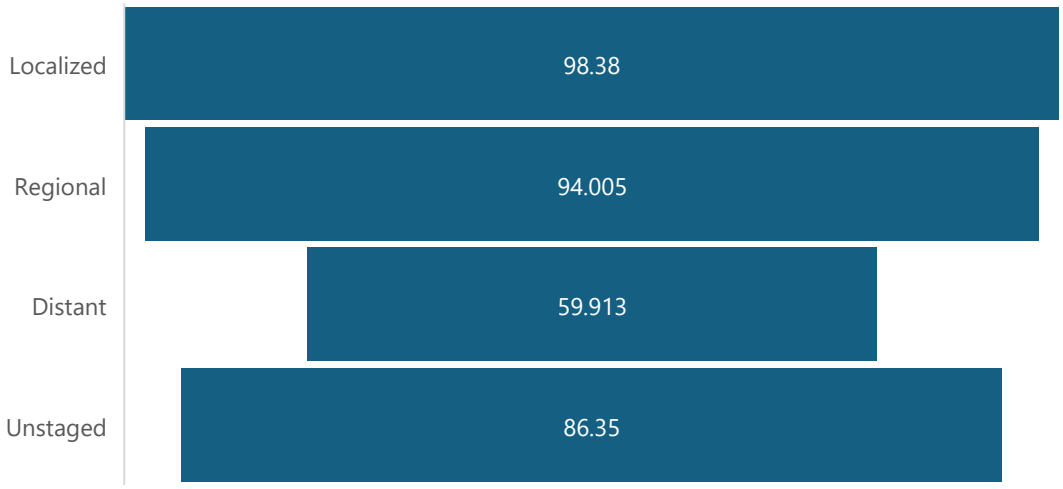

Figure: 4.2.1 Five-year Relative survivals percentages by stage for HER2 + Breast cancer

The 5-year relative survival rates for HER2-positive breast cancer patients, analysed by age groups from 2010 to 2016, demonstrate a consistently high level of survival across all age categories. For patients of all ages, the survival rates ranged from approximately 94.2% to 95.2%, indicating strong outcomes regardless of age.

Table 4.2.2: Five-year Relative survival percentages by age for HER2 + Breast cancer (2017-21)

	Relative Survival %			
Year of Diagnosis	All Ages	Ages < 50	Ages 50-64	Ages 65+
2010	94.2	92.7	94.1	95.2
2011	94.6	93.2	94	96.1
2012	94.2	92.9	94	95.1
2013	94.4	93.4	93.6	95.7
2014	94.8	93.8	94.4	95.8
2015	95.2	93.5	94.5	96.8
2016	95	93.4	94.6	96.1

Among specific age groups, those aged 50-64 consistently showed the highest survival rates, ranging from 94% to 94.6%. Patients aged 65 and above also exhibited high survival rates, ranging from 95.1% to 96.8%, showcasing the efficacy of treatments and healthcare strategies in older populations. Even among younger patients (<50 years old), survival rates remained robust, ranging from 92.7% to 93.8%. These results indicate that age is not a significant factor in the overall survival rates of patients with HER2-positive breast cancer but they do demonstrate the efficacy of treatment strategies for a variety of age groups.

4.3 PROPOSED THERAPEUTIC LANDSCAPE FOR HER2 POSITIVE BREAST CANCER

Table 4.3.1: Five-year Relative survival percentages by age for HER2 + Breast cancer (2017-21)

Line of therapy	Drug therapeutics	Conditions	
First	Taxane + Trastuzumab + Pertuzumab	Denovo metastasis/ Relapse after trastuzumab(>12mon)	
	Vinorelbine + Trastuzumab + Pertuzumab	Taxane is contraindicated/ Elderly	
	T-DM1	Relapse after trastuzumab (> 6 months)	
	Hormone therapy + Trastuzumab/Lapatinib	Non chemotherapy candidates	
Second	T-DM1	If T-DM1 not given in first line	
	T-DM1 Capecitabine + Lapatinib	In brain metastasis	
	Capecitabine + Trastuzumab/Lapatinib Trastuzumab/Lapatinib + Vinorelbine	Others	
	Hormone therapy + Trastuzumab/Lapatinib	HR +ve patients	
Third	Vinorelbine + Trastuzumab	Those administered by Trastuzumab + Pertuzumab and T-DM1	
	Capecitabine + Trastuzumab/Lapatinib		
	T-DM1	Never administered in earlier Lot	
	Trastuzumab+Lapatinib	Those administered by Trastuzumab + Pertuzumab	HR Negative
	Hormone therapy + Trastuzumab/Lapatinib		HR Positive

First Line of therapy:

As depicted in Fig. 4.3.1, The triplet of taxane + trastuzumab + pertuzumab is used as the first-line treatment for de novo metastasis which is defined as relapse following the first year of adjuvant

trastuzumab treatment. Progression-free survival (PFS) and overall survival (OS) have both risen to 56. Five months and eighteen. correspondingly after using this combination. If taxanes are contraindicated vinorelbine which has a median PFS of 11. 5 to 14. 4 months (14) can be used in their place. Elderly patients who are susceptible to Taxane toxicity can also benefit from this regimen. Since there is a higher risk of cardiotoxicity when combining anthracyclines with trastuzumab it is usually not recommended. T-DM1 whose median OS and PFS are 15. 2 and 29. If a patient relapses within six months of concluding trastuzumab adjuvant treatment the first-line treatment recommendation is 8 months respectively. In comparison to lapatinib plus capecitabine it also appears to be less toxic. For hormone receptor-positive cases that are not candidates for chemotherapy an endocrine therapy in addition to trastuzumab should be investigated. Based on the results of the Electra study which established a 14-month median time to progression (TTP) for this treatment this recommendation has been made. When combined with lapatinib hormone therapy also raises the clinical benefit rate (48 percent) and median PFS (eight months).

Second Line of therapy

For most patients who are not improving after receiving trastuzumab or Pertuzumab-based chemotherapy as their first line of treatment, T-DM1 monotherapy is the standard second-line therapy. T-DM1 is an antibody-drug conjugate (ADC) that combines the cytotoxic effects of microtubule inhibitor DM1 with the trastuzumab-targeted antitumor activities. T-DM1 as demonstrated by the EMILIA phase III trial with a median PFS (6.4 compared to 9.5) and overall survival (OS) (29.8 compared to 23.7) when compared to lapatinib plus capecitabine with a median OS of 29.4 . Furthermore T-DM1 demonstrated a greater overall response rate (ORR) and fewer severe adverse events. With a median PFS of 6 the TH3RESA phase III trial showed that T-DM1 performed better in the third line setting than the doctors prescribed trastuzumab and chemotherapy with OS of 22.7 months. As a result, T-DM1 was approved by the FDA and EMA in 2013. Although T-DM1 is generally recommended as a second-line treatment it has also shown promise in first-line settings and for particular patient subgroups such as those with brain metastases or those who relapsed early following anti-HER2 adjuvant therapy. Trastuzumab plus vinorelbine or capecitabine or lapatinib plus capecitabine are additional second-line options. (13,17) Patients who test positive for hormone receptors may benefit from combining hormone therapy with trastuzumab or lapatinib. (15).

Third Line of therapy

Options for third-line therapy rely on the previous regimens used. As vinorelbine has fewer side effects than docetaxel it is advised to combine trastuzumab with it if T-DM1 and trastuzumab have previously been administered to the patient along with Pertuzumab. Another option with good response is the combination of capecitabine and lapatinib (13,14,17,18). It is suggested that patients who have never used T-DM1 do so. (15,16) It has a 6.2 progression-free survival (PFS). Treatment benefit progression-free survival (PFS) and overall survival (OS) for patients with hormone receptor-negative tumours are improved by up to 14 months when trastuzumab plus lapatinib is used in place of lapatinib alone. In patients who have not previously received hormone therapy and whose cancer is hormone receptor-positive lapatinib or trastuzumab may be given in addition to hormone treatment. (15)

4.4 ADVANCED DRUG THERAPIES FOR THE TREATMENT OF HER2 POSITIVE BREAST CANCER

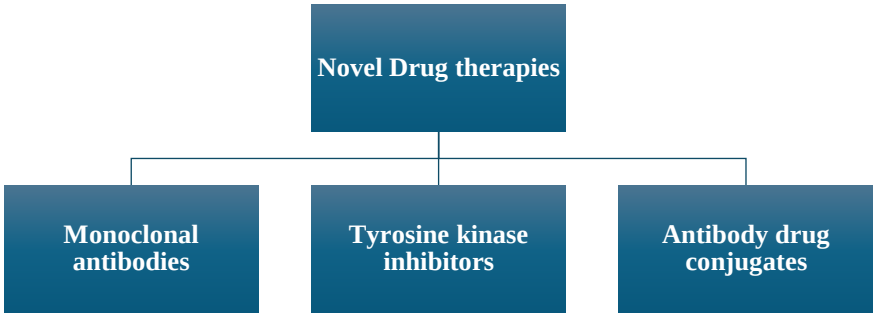

Figure 4.4.1: Major types of advanced drug therapeutics for HER2 + Breast cancer treatment

Twenty to thirty percent of patients receiving curative treatment for early-staged breast cancer will develop distant metastases in near future despite continuous advancements and the growing availability of adjuvant therapies that improve outcomes. Furthermore 5–10% of patients initially receive a diagnosis of metastatic disease. (9) The choice of treatment for advanced breast cancer is determined by the patients and the diseases characteristics such as the tumors phenotype particularly its oestrogen and progesterone receptor status tumor burden and prior treatments. Before the discovery of drugs that specifically target the HER2 pathway patients with advanced breast cancer had a very poor prognosis. Thanks to the development of highly effective anti-HER2 therapies which have significantly improved outcomes for this subgroup their prognosis is now comparable to or better than that of patients with HER2-negative disease. (9) The prognosis for HER2-positive advanced breast cancer has been improved even further by new treatments.

4.4.1 Bi-Specific antibodies

In order to bind to 2 separate antigens or 2 different epitopes on the same antigen an antibody has to have 2 different binding domains in order to be considered bispecific (BsAbs). This unique property allows BsAbs to target multiple antigens simultaneously, making them a promising therapeutic approach for various diseases, including cancer and autoimmune disorders. (9)

4.4.1.1 Monoclonal Antibodies

To address resistance and financial toxicity, several trastuzumab biosimilars and new HER2-targeted monoclonal antibodies have been developed. **Margetuximab**, for instance, has enhanced binding to CD16A, improving ADCC and showing better progression-free survival in clinical trials, although it did not improve overall survival compared to trastuzumab. Other emerging therapies include the **humanized monoclonal antibody 1E11** and the **HER2-targeted liposome MM-302**,(9) which have shown promise in preclinical models but need further testing in clinical settings.

A novel humanized monoclonal antibody, H2Mab-250, specifically targets HER2-positive breast cancer cells without binding to normal epithelial cells, unlike trastuzumab. H2Mab-250 showed antitumor activity in breast cancer xenograft models. (12)

As shown in table 4.4.1 (21) Below are the features of MAbs under clinical trials: -

Margetuximab: By improving ADCC and overcoming trastuzumab resistance, (MGAH22) a monoclonal anti-HER2 antibody exhibits a high affinity for CD16a. 66 patients with advanced HER2-overexpressing cancers participated in a phase 1 trial (NCT01148849) which demonstrated no MTD at different dosages. The SOPHIA phase 3 trial showed margetuximab plus chemotherapy improved PFS compared to trastuzumab plus chemotherapy in HER2-positive advanced breast cancer (NCT02492711). (18)

ZW25: ZW25 is a bispecific antibody showing activity in HER2-amplified cancers with varying expression levels. In a phase 1/2 trial (NCT02892123), ZW25 demonstrated a manageable safety profile and efficacy in heavily pretreated MBC patients, with partial responses and stable disease. The study is ongoing, exploring ZW25's potential in HER2-expressing cancers. (18)

PRS-343: In order to stimulate T cells to combat HER2-positive cancer cells PRS-343 is a bispecific anti-HER2 antibody that targets both HER2 and CD137. Studying PRS-343 atezolizumab (NCT03650348) it has demonstrated promise in advanced HER2-positive solid tumors as determined by phase 1 trials (NCT033 both independently and in concert with other

agents. 30561). As per ASCO/CAP guidelines patients with HER2-positive cancers are eligible for both trials. (18).

Table 4.4.1: Bi-specific Antibodies (Monoclonal antibodies) under clinical trial.

Type of Drug	Drug name	NCT Number	Target Population	Reference
HER2/HER2	MBS301	NCT03842085 (21)	Malignant HER2-expressing solid tumours	(21)
	Zanidatamab (ZW25)	NCT02892123 (21)	HER2-expressing solid tumours	(20)
		NCT05035836 (21)	Early HER2 BC	(20)
		NCT04224272 (21)	Advanced HER2 BC	(19, 20)
		NCT05027139 (21,23)	Anti-CD47 Solid HER2 tumours including the HER2-low breast cancer	(21)
	KN026	NCT04881929 (21)	HER2 breast cancer	(20)
		NCT04521179 (21) NCT04040699 (22)	Locally advanced HER2 solid tumours and HER2+ solid tumour	(21)
		NCT04778982 (25)	Advanced breast cancer	(21)
HER2/HER3	Zenocutuzumab (MCLA-128)	NCT03321981 (21)	HER2-low and metastatic breast cancer that progressed to T-DM1 treatment	(21)
	MM-111	NCT01097460 (21) NCT00911898 (25)	Advanced HER2 amplified and heregulin-positive breast cancer	(21)
HER2/CD137	PRS-343	NCT03330561 (21) NCT03650348 (25)	Advanced solid cancers that are HER2–positive	(21)

4.4.2 Tyrosine kinase inhibitors

In many cancers including breast cancer tyrosine kinase inhibitors or TKIs are prescribed. The only FDA-approved TKI for HER2-specificity before 2020 was lapatinib. Nevertheless, a number of additional novels TKIs are presently being studied in clinical settings. The FDA approved neratinib earlier this year and tucatinib is also being investigated as a treatment and preventive measure against the progression of HER2-positive breast cancer in the central nervous system (CNS).

As shown in table 4.4.2 (21) Below are the features of TKIs under clinical trials: -

Neratinib: Based on the phase III ExteNET study neratinib an irreversible pan-HER TKI was approved as an adjuvant treatment for early HER2-positive breast cancer. The NEfERT-T pilot study found that trastuzumab-paclitaxel was not better than neratinib-paclitaxel in untreated HER2-positive advanced breast cancer cases. (23,24) CNS recurrence risk was decreased by neratinib-paclitaxel. With neratinib-paclitaxel diarrhoea was more frequent (30.4 percent vs. 38%). Neratinib and capecitabine which is recommended by the NCCN decreased CNS lesions in 49% of patients with brain metastases in TBCRC 022.

Table 4.4.2: Tyrosine kinase inhibitors under current clinical trials. (21)

Type of Drug	Drug name	NCT Number	Target Population	Reference
Reversible HER2 inhibitor	Tucatinib	NCT04457596, (21) NCT03975647, (21) NCT01983501, (21) NCT05323955, (21) NCT04539938, (21) NCT04538742 (21)	HER2 breast cancer	(21)
Irreversible Pan HER2 inhibitor	Pyrotinib	NCT01937689 NCT02361112	HER2 +ve and metastatic breast cancer	(19,20)
	Poziotinib	NCT03429101	HER2 +ve breast cancer	(21)
	Neratinib	NCT00878709	Early stage HER2 +ve breast cancer	(21)
Selective HER2 inhibitor	DZD1516	NCT04509596	Metastatic HER2 +ve breast cancer	(22)

Tucatinib: Oral HER2-selective TKI tutakinib exhibits nanomolar potency and reduced EGFR-related toxicities. A 61 percent ORR and a median response duration of 10 months were observed in a phase Ib study combining tucatinib with either capecitabine or trastuzumab. The ORR was

42% among patients with detectable brain metastases. Tucatinib was granted Orphan Drug status by the US FDA for brain metastases that are positive for HER2.

Pyrotinib: Pyrotinib is an irreversible pan-HER TKI. It has shown promising activity in advanced HER2-positive breast cancer treated with at least two previous therapies. A phase II trial showed a 78.5% ORR for Pyrotinib/Capecitabine versus 57.1% for lapatinib/capecitabine (PFS: 18 vs. 7 months). A phase III trial (NCT03080805) is ongoing. (23,24)

Poziotinib: In a phase II study involving patients with heavily pretreated HER2 +ve and metastatic breast cancer, Poziotinib (an oral pan-HER kinase inhibitor) demonstrated a 75% disease control rate. PFS was 4 months on average. The two most common adverse effects were diarrhoea and stomatitis. (23-25)

DZD1516: DZD1516 is a novel, brain-penetrant HER2 inhibitor designed to treat HER2-positive breast cancer with central nervous system (CNS) metastases. In preclinical studies, DZD1516 demonstrated strong inhibition of HER2 signalling in the brain. DZD1516 was found to be well-tolerated with manageable side effects in a phase I study. Early clinical data indicated promising CNS activity, with reductions in brain metastases observed in several patients. Further clinical trials are ongoing to evaluate its efficacy and safety in larger patient populations**.** (23-25)

Antibody Drug Conjugates

ADCs use monoclonal antibodies delivery to transport cytotoxic drugs (minimises toxicity) directly to tumours for precise and effective medication. The creation of more recent HER2-targeting ADCs has been prompted by the success of T-DM1 which combines trastuzumab with a cytotoxic payload (DM1) via a indestructible linker. For T-DM1 to be effective it must internalize and cleave within lysosomes efficiently. Emerging ADCs feature more specific anti-HER2 antibodies, cleavable linkers, or cytotoxic payloads with unique mechanisms, enhancing therapeutic potential and reducing side effects.

Table 4.4.3: Antibody drug conjugates under clinical trials (21)

Type of Drug	Drug name	NCT Number	Target Population	References
topoisomerase I inhibitor	T-DXd	NCT04784715 NCT04538742 NCT04538742, NCT04539938 NCT04556773	HER2 low or advanced metastatic breast cancer	(21)
DNA alkylating agent	SYD-985	NCT03262935	HER2 (locally advanced/ metastatic)	(21, 22)
microtubule inhibitor	ARX788	NCT01042379	HER2 breast cancer	(20, 21)
		NCT04829604, NCT02512237	HER2 (metastatic)	(20, 21)
		NCT05018676	HER2 low breast cancer	(20, 21)
	RC-48	NCT05134519	HER2 breast cancer	(21)
		NCT04400695	(Locally advanced)HER2-low breast cancer	(21)
		NCT05331326	HER2 metastatic breast cancer (abnormal activation of PAM pathway)	(21)
		NCT03052634	Advanced breast cancer	(21)
	A166	NCT03602079	Relapsed/refractory amplified HER2 gene	(21)

	MRG-002	NCT05263869	HER2+ advanced breast cancer	(21)
	ZW-49	NCT03821233	Metastatic HER2 tumors	(21)
	ALT-P7	NCT03281824	HER2 breast cancer	(21)

As shown in table 4.4.3 (21) Below are the features of ADCs under clinical trials: -

T-DM1: The first ADC approved by the FDA for HER2+ breast cancer that did not respond to Trastuzumab and a Taxane was T-DM1. Emtansine a medication is combined with trastuzumab. When patients are unable to benefit from conventional treatments T-DM1 is typically used as a second-line therapy. T-DM1 is beneficial to patients with brain metastases according to clinical trials. It is not as effective for HER2-low breast cancer though. (23–25).

Trastuzumab-deruxtecan (T-DXd): T-DXd links trastuzumab with a drug called deruxtecan, which breaks DNA and kills cancer cells. T-DXd works better than T-DM1 in preclinical models because it is more effective at pemeating cancer cells.. It has shown strong results in patients previously treated with T-DM1 and received FDA approval in 2019. T-DXd is being tested in various cancers and combination therapies, showing promising results in HER2-low breast cancer. (23-25)

Trastuzumab-duocarmycine/SYD985: SYD985 combines trastuzumab with duocarmycine, a drug that targets DNA. Early studies showed positive results, leading to a phase 3 trial where SYD985 improved progression-free survival compared to chemotherapy. It is effective in the disease due to the bystander effect. (23,24)

ARX788: ARX788, a next-generation ADC, attaches a medication called Amberstatin 269 using a stable linker. It has shown effectiveness in variants that are low and moderately resistant to T-DM1. Clinical trials have shown low toxicity and promising results. (23,24)

Disitamab vedotin (RC48): RC48 links hertuzumab to vedotin, a drug already approved for lymphoma. It has exhibit great performance in HER2+ gastric, breast, and urothelial cancers and

offers a strong bystander effect. RC48 is being tested in multiple clinical trials for breast cancer and other cancers. (23,24)

A166: In early clinical trials patients with heavily treated breast cancer showed good tolerance and a promising antitumor effect when A166 was used in conjunction with duostatin-5. (23 24)

MRG002: MRG002 combines MMAE with a humanized anti-HER2 antibody. In HER2 low variants including those that are resistant to T-DM1 it has demonstrated tolerable toxicity and potent antitumor effects. Clinical trials are still going on. (2324).

Zanidatamab zovodotin (ZW49): Trastuzumab and pertuzumab combined with auristatin is known as ZW49. In brain metastases it exhibits antitumor activity. ZW49 has been investigated for metastatic HER2+ tumours in phase 1 of some clinical trials. (23,24)

ALT-P7: ALT-P7 is a new ADC with trastuzumab bio better HM2 linked to MMAE. Early results from clinical trials show good tolerability, leading to further development. (23,24)

4.5 CURRENT MARKET SCENARIO FOR HER2-POSITIVE BREAST CANCER DRUG THERAPIES

With a predicted value of USD 78. 61 billion by 2033 the global market for breast cancer drugs was estimated to be worth USD 32. 93 billion in 2023. The market is projected to grow at a CAGR of approximately 9 % for the forecast period of 2024 to 2033. With a 38. 61% revenue share in 2023 North America held a dominant position in the market. Key characteristics of HER2 + Breast cancer drug therapy market.

- North America dominated the market with a revenue share of 38.61% in 2023.
- The targeted therapy segment captured the largest share of 64.85% in 2023 and is expected to maintain dominance during the forecasted period.
- In 2023, the hormone receptor segment was a significant contributor to the global market. The segment accounted for the largest share of 66.97% in 2023.
- The hospital pharmacies segment held a significant revenue share of 66.61% in 2023.

4.5.1 FDA approved drugs in USA

Table 4.5.1: Therapeutic landscape for the drugs approved for HER2 + breast cancer in US Market

S.no	Drug name	Drug brand name	Drug class	Company	Drug dosage Form	FDA approval for HER2 Breast cancer Year	Annual sales (2023)	Region
1.	fam-trastuzumab deruxtecan	Enhertu (Pro)	ADC	AstraZeneca and Daiichi Sankyo Company, Limited	Injectable	2022, 2024	$2.5 billion	USA
2	Trastuzumab	Herceptin (Pro)	MCA	Genentech, Inc.	Injectable	2006	$1.7 billion	USA
3	tucatinib	Tukysa	TKI	Seattle Genetics, Inc.	Tablets	2020	$330 million	USA
4	pertuzumab, trastuzumab, and hyaluronidase-zzxf	Phesgo	MCA combination	Genentech, Inc.	Injectable	2020	$1.1 billion	USA

Table 4.5.1: Therapeutic landscape for the drugs approved for HER2 + breast cancer in US Market (Continued)

5	margetuximab-cmkb	Margenza	MCA	MacroGenics, Inc.	Injectable	2020	N/A	USA
6	ado-trastuzumab emtansine	Kadcyla	(ADC)	Genentech, Inc.	Injectable	2019	$1.3 billion	USA
7	trastuzumab and hyaluronidase-oysk	Herceptin Hylecta	MCA combination	Genentech, Inc.	Injectable	2019	$300 million	USA
8	rastuzumab-qyyp	Trazimera	MCA	Pfizer Inc.	Injectable	2019	N/A	USA
9.	neratinib	Nerlynx	TKI	Puma Biotechnology, Inc.	Tablets	2017	$100 million	USA
10	pertuzumab	Perjeta	MCA	Genentech	Injectable	2012	$1.5 billion	USA
11	lapatinib ditosylate	Tykerb	TKI	GlaxoSmith Kline	Tablets	2007, 2010	$100 million	USA

4.5.2 Top 5 market leaders

Table 4.5.2: Top 5 HER2-Positive Breast Cancer Drugs by US Market Share (2023)

S.no	Brand Name	Company	Annual sales 2023 (In $ million)
1	Enhertu (Pro)	AstraZeneca and Daiichi Sankyo Company, Limited	2500
2	Herceptin (Pro)	Genentech, Inc.	1700
3	Perjeta	Genentech	1500
4	Kadcyla	Genentech, Inc.	1300
5	Tukysa	Seattle Genetics, Inc.	330

The market for HER2-positive breast cancer drug therapies has seen significant advancements in recent years, with the introduction of targeted therapies, bispecific antibodies, and antibody-drug conjugates (ADCs). These novel treatments have significantly improved outcomes for patients with HER2-positive breast cancer, making their prognosis comparable to or even better than that of patients with no disease. (24)

The top market leaders in HER2 + breast cancer drug therapies include: (24)

1. Enhertu (fam-trastuzumab deruxtecan), an ADC developed by AstraZeneca and Daiichi Sankyo Company, with annual sales of $2.5 billion in 2023.

2. Herceptin (trastuzumab), a monoclonal antibody (MCA) from Genentech, Inc., with annual sales of $1.7 billion in 2023.

3. Tukysa (tucatinib), a tyrosine kinase inhibitor (TKI) from Seattle Genetics, Inc., with annual sales of $330 million in 2023.

4.5.3 Market share by drug class

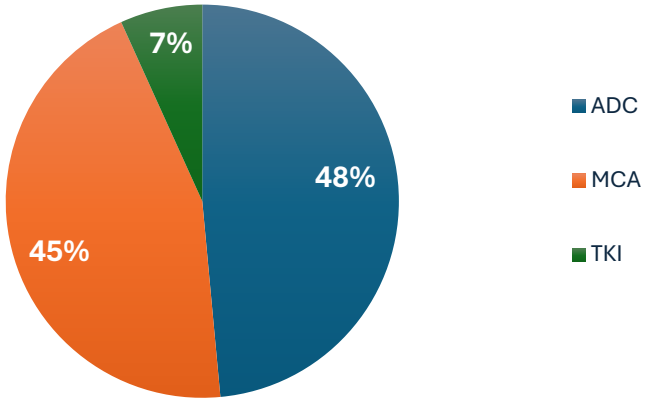

Figure 4.5.1: HER2 + Breast cancer drug class US market share (2023)

4.5.4 Impact of biosimilars on the market for HER2-positive breast cancer treatments

Pricing pressures: Branded HER2-targeted therapy prices have been driven down by the availability of less expensive biosimilars. In the event that the U. S. Herceptin's market share rapidly declined after its patent expired in 2019 as patients and insurers chose the less expensive biosimilar alternatives.

Enhanced competition: The market for treatments for HER2-positive breast cancer has become more competitive due to the introduction of numerous biosimilars. To capture market share producers of branded medications must now set themselves apart from the biosimilars by showcasing greater clinical benefit.

Difficulties facing novel therapies: Because patients and payers favour the less expensive biosimilars it is becoming more difficult for novel HER2-targeted therapies to obtain approval and market share in this fiercely competitive environment.

Potential for increased access: More patients may be able to obtain HER2-targeted therapies because of biosimilars lower costs particularly in healthcare systems with constrained funding. This is contingent upon the particular reimbursement and pricing guidelines in each nation.

4.5.5 Current pricing and reimbursement trends of breast cancer therapies.

Pricing: In Q2 2020 the originator medication Herceptin (trastuzumab) had a wholesale acquisition cost (WAC) of approximately $4364 per dose while the biosimilars had an average WAC of $3927 per dose. (24) Before rival biosimilars hit the market in 2019 the average sales price (ASP) of Herceptin reached a peak of $89706 in 2019. The price of Herceptin decreased by 29% to $63592 in 2022 with the launch of biosimilars. (25) With a mean unweighted treatment cost of $38173 the average cost of a biosimilar is currently 40% less than that of Herceptin. Compared to pre-biosimilar entry the average treatment cost decreased by 52% in 2022 or $45659. (25)

Reimbursement: Payback within the U. S. Medicare Part B which saw a 79% inflation-adjusted increase in biologics spending from 2011 to 2020 (25) is the primary payer for HER2-positive breast cancer therapies. By moving from the original Herceptin to a biosimilar Medicare beneficiary with a 20 percent coinsurance could save over $500 a month in out-of-pocket expenses. (25) To assist commercially insured patients in affording these costly therapies pharmaceutical companies frequently provide copay cards and patient assistance programs. (24) The US has several important aspects when it comes to reimbursement policies for herceptin (trastuzumab). Herceptin is mainly covered by Medicare Part B with a notable increase in biologics spending under this program between 2011 and 2020. Medicare enrolee's may experience a monthly savings of more than $500 when they convert from the original Herceptin to a biosimilar. Herceptin and other HER2-targeted treatments are also covered by private insurers although patient out-of-pocket expenses may still be substantial. Pharmaceutical companies address this by providing copay cards and patient assistance programs to help commercially insured patients afford these costly therapies. The cost of Herceptin has dropped dramatically since the introduction of biosimilar trastuzumab products which are 40–52% less expensive than the original product. This means that overall treatment costs will be 52% lower in 2022 compared to the pre-biosimilar era. Furthermore, although additional research is required to fully understand the programs impact the Oncology Care Model (OCM) program may encourage providers to use less expensive biosimilar options

4.4.5 Market Dynamics of HER 2 + Breast cancer

Driving Forces

The escalating incidence of breast cancer worldwide presents a significant market opportunity propelled by several key drivers. Currently, 1 in 8 women will develop this type of cancer in their lifetime, making it the most common cancer worldwide and among women in the United States specifically. Increased awareness and advancements in detection and treatment have significantly elevated survival rates. Approximately 90% of women now survive five years post-diagnosis. Factors such as globalization and economic development contribute to rising incidence rates, particularly in developing countries where rates are projected to increase by 64% to 95%, and in developed nations with an expected rise of 32% to 56%. Demographic shifts also play a role, with urban areas experiencing higher incidence rates among individuals aged 40–49, while rural areas see elevated rates in those aged 65–69. The need for early detection and cutting-edge treatment options coupled with these demographic shifts is what propels the market for breast cancer medications steady expansion. (26,27)

Challenges/Limitations

The limitations of HER2 targeted therapy pose challenges to its widespread usage in breast cancer treatment. Despite its promising efficacy, these drugs come with significant side effects, especially in specific patient groups. Pregnant individuals are advised against their use due to potential harm to the fetus, including fetal death. Monoclonal antibodies and antibody-drug conjugates used in HER2 targeted therapy can induce heart damage, leading to congestive heart failure, a serious complication. This risk is heightened when these drugs are combined with chemotherapy agents that also pose heart damage risks, such as doxorubicin and epirubicin. Additional risk factors include age over 50, obesity, pre-existing heart conditions, and concurrent use of medications for hypertension. These limitations and associated risks restrain the growth of the breast cancer drugs market, necessitating careful consideration of patient characteristics and potential adverse effects in treatment decisions. (28,29)

Opportunity

The integration of artificial intelligence (AI) in breast cancer treatment presents an opportunity for transformative advancements. AI's emergence has revolutionized patient management by offering more accurate and timely insights across the diagnostic spectrum, from screening to therapeutic response prediction. In radiology, AI applications in mammography, tomosynthesis, and risk prediction models enhance early detection efforts, while complementary imaging methods like magnetic resonance imaging and ultrasound benefit from AI-driven progress. Likewise, in pathology, AI facilitates pathologic diagnosis, biomarker evaluation, and predictions related to genetic alterations, treatment response, and prognosis. This comprehensive utilization of AI not only enhances patient outcomes but also creates synergistic opportunities for the breast cancer drugs market, as precision medicine approaches become more refined and targeted therapies gain traction in clinical practice. (30,31)

CHAPTER 5 CONCLUSION

The USs epidemiological trends for HER2-positive breast cancer incidence from 2010 to 2021 show variations peaking in 2015–2016 and then showing a significant decline in 2020 which was probably caused by the COVID-19 pandemics effect on cancer diagnoses and reporting. Different racial/ethnic groups had different incidence rates Non-Hispanic Black females demonstrated the highest incidence of distant stage cases indicating differences in timely diagnosis and access to healthcare. Notwithstanding these difficulties 5-year relative survival rates for patients with HER2-positive breast cancer stayed high ranging from 91. 37 percent to 91. 91 percent in all racial groups demonstrating improvements in treatment modalities and early detection techniques. Novel targeted therapies bispecific antibodies and antibody-drug conjugates (ADCs) have all contributed to a significant advancement in the US market for HER2-positive breast cancer therapies. Tyrosine kinase inhibitors such as Tukysa monoclonal antibodies Herceptin and Perjeta and the ADC Enhertu are among the top market leaders. With more biosimilars on the market competition has increased bringing down costs and possibly opening more patient access to these treatments. Resistance brain metastases and healthcare disparities are still issues that need to be addressed. Herceptins price has dropped by 29% because of biosimilar pricing pressure on average a biosimilar cost between 40% and 52% less than the brand-name medication. When comparing the current treatment costs to the pre-biosimilar era the difference is 52 percent. Improved access to these expensive therapies has also been aided by reimbursement policies like Medicare Part B coverage and patient assistance initiatives. Research is currently being conducted to develop new therapies optimize treatment sequencing and use artificial intelligence to improve personalized care for patients in the US with HER2-positive breast cancer. Priorities remain high for treating brain metastases including overcoming resistance to existing therapies and addressing unmet needs. Patients with HER2-positive breast cancer may experience even better results and a superior quality of life in the future due to the advancements in the treatment setting and the use of biomarkers.

CHAPTER 6 FUTURE DIRECTIONS

One of the most significant unmet needs in HER2-positive breast cancer is a therapeutic intervention to address brain metastasis, a substantial issue in this subtype. Nearly 20% of all breast cancers are HER2-positive. (24) Herceptin (trastuzumab), manufactured by Roche, has been the standard of care across nearly every HER2-positive breast cancer setting since its approval in 1998 as the first targeted treatment for this subtype. (25) However, the U.S. patent for Herceptin expired in 2019, introducing pricing pressures on the market with the availability of far cheaper biosimilars. Herceptin's market share has dropped rapidly, making it harder for novel therapies to gain approval in this market, as patients and insurers prefer the cheaper biosimilar options. (24)

To address this unmet need, future research should focus on developing innovative therapies that can effectively treat brain metastases in HER2-positive breast cancer patients. Antibody-drug conjugates (ADCs) like Enhertu (fam-trastuzumab deruxtecan), which was approved in 2022, have shown promising results in treating HER2-positive breast cancer, including in patients with brain metastases. (25) Continued research and development of ADCs and other novel targeted therapies may lead to more effective treatment options for HER2-positive breast cancer patients with brain metastases. Additionally, as biosimilars become more prevalent, it will be crucial for drug developers to focus on demonstrating the added clinical benefit of new therapies compared to the cheaper biosimilar options to gain regulatory approval and market access. Strategies like combining novel agents with existing therapies or developing therapies for specific patient subgroups may help differentiate new treatments in this increasingly competitive market.

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