Trastuzumab & Pertuzumab in the Fight Against Breast Cancer: Mechanisms, Significance, & Future Aspects

By

Janifa Ferdous Joya
18346035

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

School of Pharmacy
Brac University
September 2023

Declaration

1. It is hereby declared that
2. The thesis submitted is my/our own original work while completing degree at Brac University.
3. The thesis does not contain material previously pblished or written by a third party, except where this is appropriately cited through full & accurate referencing.
4. The thesis does not contain material which has been accepted, or submitted, foraany other degree or diploma at a university or other institution.
5. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Janifa Ferdous Joya

18346035

Approval

The thesis/project titled "Trastuzumab & Pertuzumab in the Fight Against Breast Cancer: Mechanisms, Significance, & Future Aspects" submitted by Janifa Ferdous Joya (18346035) of Summer 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on [Date-of-Defense].

Examining Committee:

Supervisor:
(Member)

_____

Dr. Shahana Sharmin
Assistant Professor, School of Pharmacy
BracUniversity

Program Coordinator:
(Member)

_____

Dr. Hasina Yasmin
Professor, Assistant Dean & Program Director, School of Pharmacy
Brac University

Departmental Head:
(Chair)

_____

Dr. Eva Rahman Kabir
Professor & Dean, School of Pharmacy
Brac University

Ethics Statement

I, Janifa Ferdous Joya, hereby certify that the following criteria are fulfilled for the manuscript 'Trastuzumab & Pertuzumab in the Fight Against Breast Cancer: Mechanisms, Significance, & Future Aspects'.

1. This material is my own original material of review that has never been published before-hand.

2. The study does not include any animal or human trial.

3. All the sources utilized are correctly credited (correct citation) along with a proper & justified reference.

Abstract

Cancer is a dangerous disease that has plagued humanity for centuries, ranking as the second leading cause of global mortality. In 2020, nearly 20 million lives were lost to cancer, with breast cancer (BC) being the most common type. Understanding the risk factors for developing BC, such as family history, is crucial for improving survival rates. There are various treatment methods available for BC, including the use of docetaxel with monoclonal antibodies Pertuzumab & Trastuzumab, which target the overexpressed the human epidermal growth factor receptor 2 (HER2) gene in HER2-positive breast tumors. These antibodies have significantly changed the therapeutic strategy for the human epidermal growth factor receptor 2(HER2)-positive breast cancer. However, while patient results have improved, the number of people benefiting from this medication. This paper aims to explore all available BC treatments & propose a model of the synergistic effects of trastuzumab & pertuzumab, critically analyzing findings & hypotheses related to their combined activity.

Keywords: Trastuzumab; Breast Cancer; Pertuzumab; HER2; Synergism; HER Family Receptors; Mechanisms.

Dedication

Dedicated to my beloved parents & my instructors.

Acknowledgement

First of all, I would like to express my sincere gratitude to almighty Allah for granting me countless blessings & opportunity to be able to complete this project.

Besides, I'd like to express my heartiest gratitude to my project supervisor Dr. Shahana Sharmin (Assistant Professor, School of Pharmacy, BRAC University) for providing me with the excellent opportunity to work on this fantastic project, which also allowed me to perform a lot of research & learn a lot of new things. I will be grateful to her for being so patient & sharing all those expert, valuable & sincere guidance throughout the entire phase which allowed me to accomplish this study.

I would also like to express my cordial gratitude to all the faculty members of school of Pharmacy for being a constant source of knowledge & inspiration throughout this whole four years which will definitely help me in the future while pursuing my dream.

Finally, the guidance & support received from my parents & my friends helped me a lot in finishing this project.

Table of Contents

List of Tables

List of Figures

List of Acronyms

AFAB	Assigned Female at Birth
AMAB	Assigned Male at Birth
PD-L1	Programmed Death-Lig& 1
TRAM	Transverse Rectus Abdominis Myocutaneous Flap
BRCA	Breast Cancer gene
TNM	Tumor, Node, Metastasis
TNBC	Triple Negative Breast Cancer
HER2	Human Epidermal Growth Factor Receptor 2
ADCC	Antibody-Dependent Cellular Cytotoxicity
PI3K	Phosphoinositol 3-kinase
MAPK	Mitogen-Activated Protein Kinase
WHO	World Health Organization
NPC	Nasopharyngeal Carcinoma
PFS	Progression-Free Survival
RTG	Renal Threshold for Glucose
FDA	Food & Drug Administration

Chapter 1

Introduction

1.1 General Background

Cancer refers to any of the many diseases that are characterized by the development of abnormal cells that divide uncontrollably, have the ability to infiltrate, & cause the destruction of healthy bodily tissue. It's typical for cancer to spread all over your body. Cancer is the second-leading global cause of death. However, thanks to improvements in cancer detection, treatment, & prevention, survival rates for many cancer types are increasing. (‘Cancer’, 2022b)

Throughout recorded history, both humans & other animals have experienced cancer. It should come as no surprise that humans have written about cancer from the dawn of history. Human mummies from ancient Egypt, fossilized bone tumors, & old texts all include some of the oldest proof of cancer. Mummies have developed growths that may be osteosarcoma, a bone cancer. Additionally, bone skull degradation similar to that observed in head & neck cancer has been discovered. Despite the absence of the word "cancer," the first known account of the disease was found in Egypt & dated to around 3000 BC. A portion of an ancient Egyptian manual on trauma surgery is replicated in the Edwin Smith Papyrus. The surgical removal of eight breast tumors as well as ulcers by cauterization with a tool termed a fire drill is reported. The sickness is described as having no known cure in the writing.

The Greek physician Hippocrates, known as the "Father of Medicine," is credited with creating the word "cancer." Hippocrates lived from 460 to 370 BC. Hippocrates used the words carcinos & carcinoma to refer to tumors that do not cause ulcers & those that do. These names, which translate from Greek to mean "crab," were probably chosen to characterize the condition because expanding projections from a cancer that resembled the shells of crabs were similar to

fingers. Celsus, a Roman physician who lived from 25 BC to 50 AD, later translated the Greek phrase into the Latin term for crab, cancer. Tumors were called oncos (Greek for swelling) by another Greek doctor, Galen (130–200 AD). Even if the crab analogy from Hippocrates & Celsus is still used to describe malignant tumors, Galen's term is still part of the term for cancer specialists: oncologists.

Beginning in the 15th century, scientists improved their knowledge of the human body during the Renaissance. The scientific approach, which was later applied to research disease, was first utilized by scientists like Galileo & Newton. Harvey (1628) performed autopsies, which helped to shed light on the hitherto mysterious blood circulation through the heart & body. The practice of doing autopsy to connect the patient's disease to postmortem pathologic findings was pioneered in 1761 by Giovanni Morgagni of Padua. This served as the cornerstone for the study of cancer in science. John Hunter (1728–1793), a renowned Scottish surgeon, proposed that some malignancies may be treated surgically & explained how the surgeon might choose which tumors to operate on. There is no improperness in removing the tumor if it has not infiltrated neighboring tissue & is "moveable," the doctor stated. A century later, the invention of anesthesia enabled surgery to advance & the creation of traditional cancer procedures like the radical mastectomy.

By using the new microscope to analyses sick tissues, scientific oncology emerged in the 19th century. The contemporary pathologic study of cancer was founded on the scientific principles developed by Rudolf Virchow, who is sometimes referred to as the father of cellular pathology. Virchow established a connection between microscopic pathology & disease, much like Morgagni had done with autopsy findings visible to the unaided eye & the clinical course of sickness. This approach helped the development of cancer surgery as well as a greater understanding of the harm that cancer had caused. An accurate diagnosis could now be established using the body tissues that the surgeon had taken for examination. If the malignancy had been

entirely eliminated by the surgery, the pathologist might also inform the surgeon. (‘Understanding What Cancer Is: Ancient Times to Present’, 2018)

Simply said, cancer is a collection of more than 100 disorders that appear gradually over time & entail unchecked cell division. Although practically every tissue in the body can acquire cancer, & each kind of cancer has its own distinctive characteristics, the fundamental mechanisms that cause cancer are relatively similar in all cancer types.

When a cell rebels against the usual constraints on cell division & starts to proliferate according to its own plan, cancer develops. All of the cells created by the division of this initial, primordial cell & its offspring exhibit unsuitable proliferation. These aberrant cells can form a tumor, or clump of cells, which can either stay inside the tissue from which it started (a condition known as in situ cancer) or start to invade surrounding tissues (a disease known as invasive cancer). If a tumor is invasive & prone to spread across different bodily areas by cells secreted into the lymphatic or blood vessels, it is classified as malignant. When a tumor's development affects vital tissues & organs, it poses a threat to a person's life. (‘Understanding Cancer’, 2007)

A mass of aberrant cells, or tumors, is created as mutant cells—those with mistakes in their genetic blueprint—grow & divide. These cells can form a distinct lump in some situations, whereas in other situations, like leukemia, the body has aberrant blood cells. Cancer cells can be transported to other parts of the body & away from the mass (or tumor) by the lymphatic or circulatory systems. These cells have the capacity to metastasize, or spread throughout the body, & grow into a second cancer. Because these secondary malignancies prevent certain biological functions, cancer might result in early death. (‘What Is Cancer?’, n.d.)

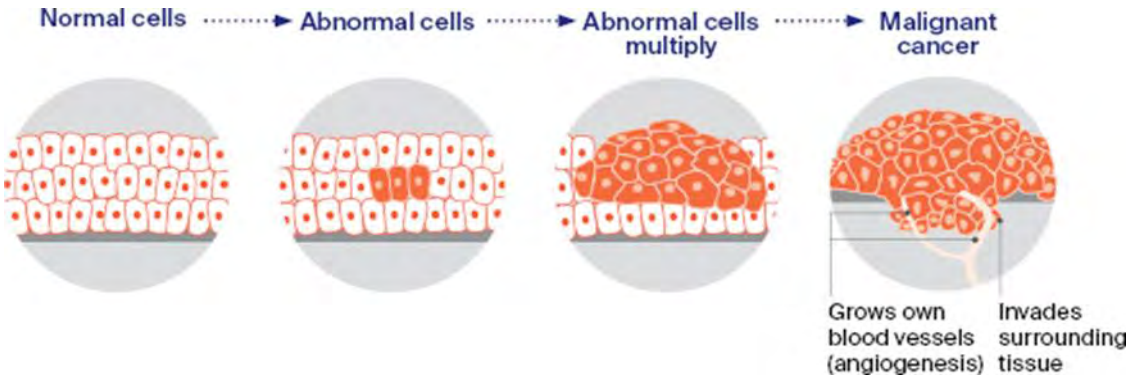

Figure 1: Development of Cancer Cell

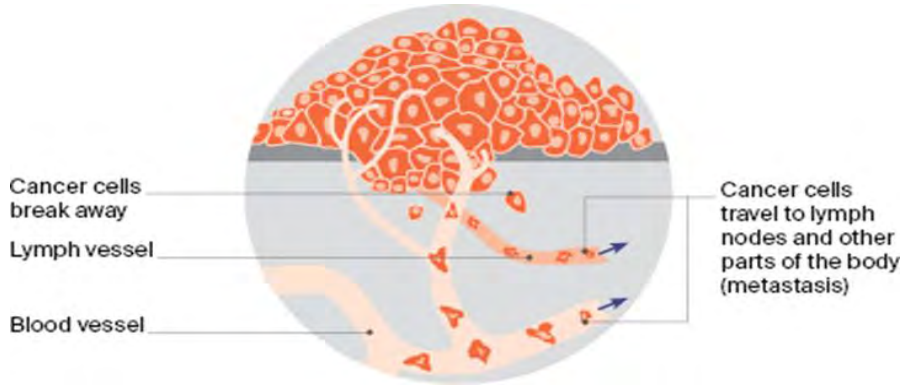

Figure 2: Development of Secondary Cancer

Table 1: Differences between cancer & normal cells

Characteristic	Cancer Cells	Normal Cells
Growth Signals	Grow without external signals	Require signals to grow
Signal Response	Ignore signals to stop dividing or undergo apoptosis	Respond to signals to stop dividing or undergo apoptosis
Invasion & spread	Invade nearbyareas, spread to other body parts	Stop growing upon contact, stay in place
Blood Vessel Interaction	Induce blood vessels to grow toward tumors	No influence on blood vessel growth
Interaction with Immune System	Hide from the immune system	Normally eliminated by the immune system
Immune System Manipulation	Trick immune cells to support cancer growth	Immune cells target & eliminate abnormal cells
Chromosomal Changes	Accumulate multiple changes in chromosomes	Maintain typical chromosome structure
Nutrient Usage & Energy Production	Rely on different nutrients & energy production	Follow standard nutrient usage &energy production
Growth Rate	Grow rapidly due to altered energy production	Grow at a controlled rate

Five important moments (diagnosis, treatment, recovery, living with treatable but incurable cancer, & end of life) have been highlighted by Macmillan as those when there is a very high degree of unmet need. These phases in people's cancer journeys have been recognized by Macmillan as those where experiences are often shared.

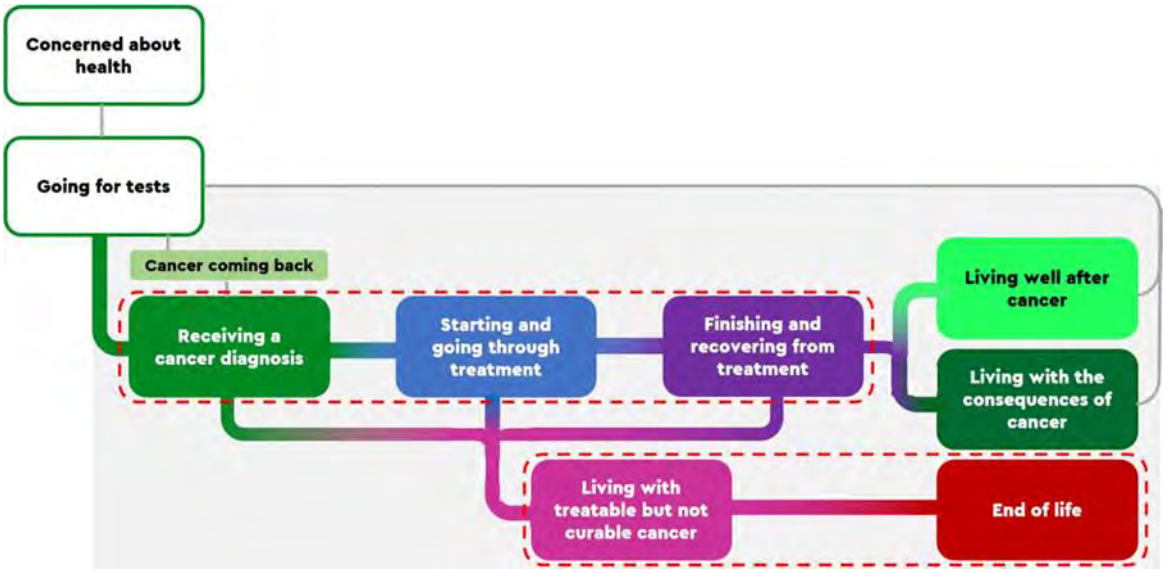

Figure 3: The cancer journey ('Statistics Fact Sheet', 2022)

One of the diseases that is spreading quickly is cancer. The biggest number of disease-related fatalities occurred in Canada in 2019 owing to cancer.

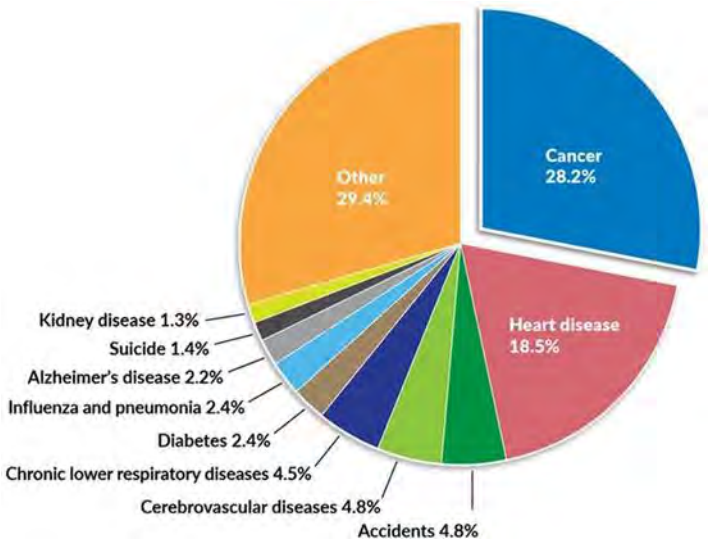

Figure 4: Proportion of deaths due to cancer & other causes in Canada, 2019 ('Cancer Statistics at a Glance', 2022)

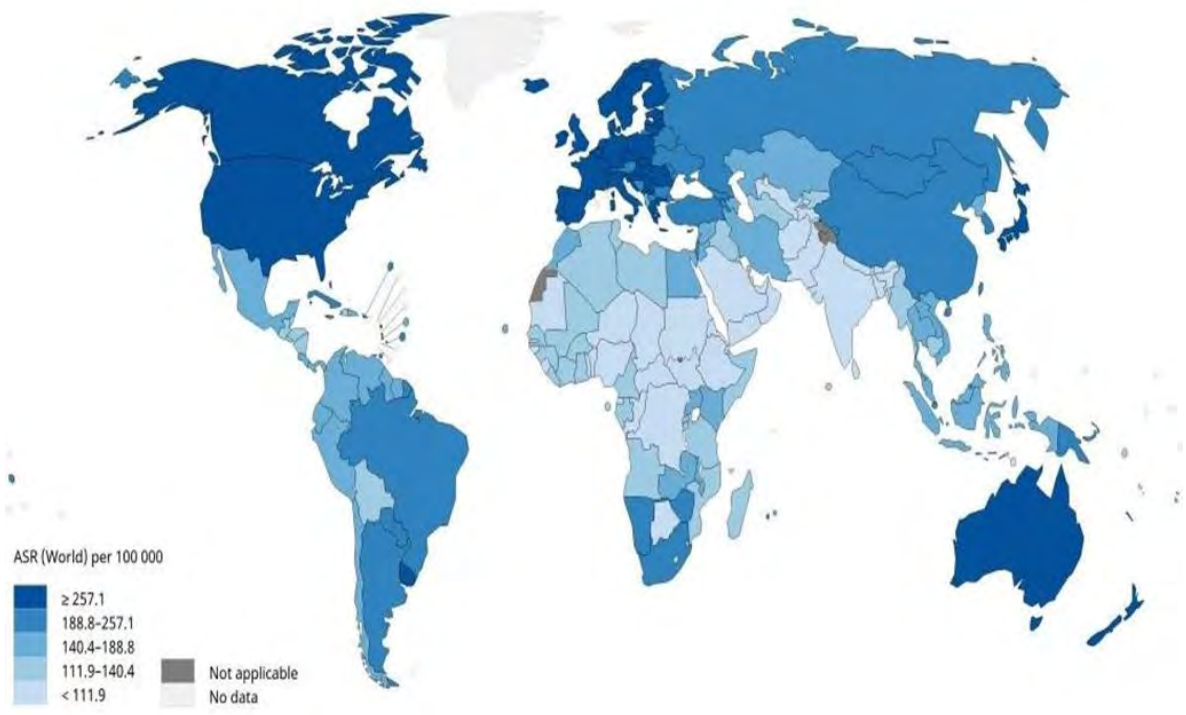

Figure 5: Estimated age-standard incidence rates in 2020, all cancers, both sexes, all ages ('GLOBOCAN 2020: New Global Cancer Data', 2020)

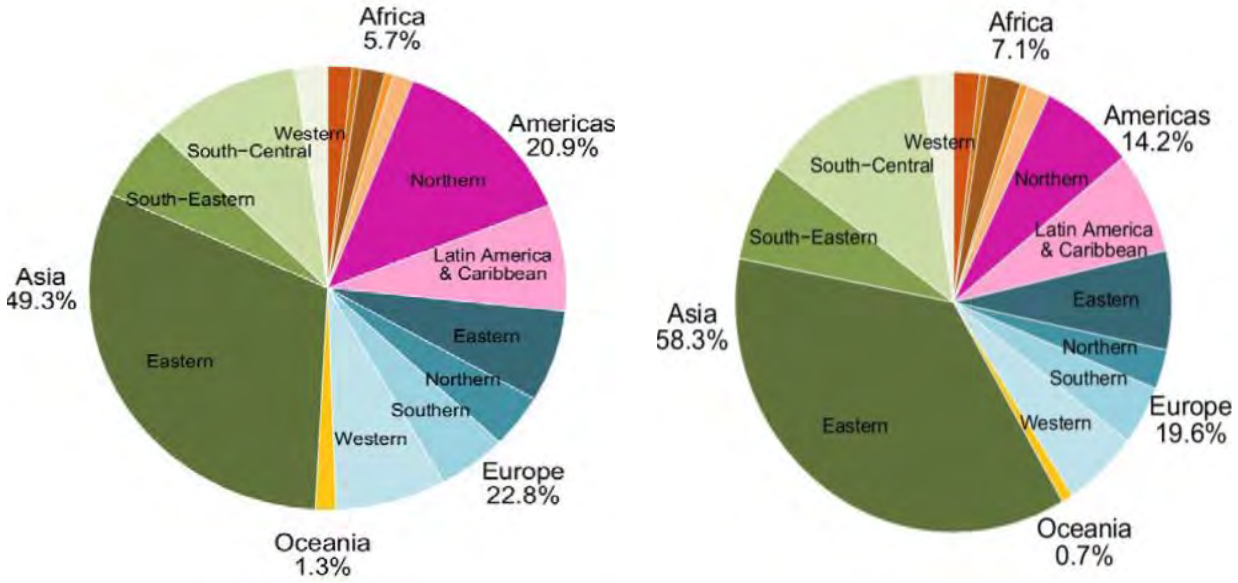

Figure 6. Region-wise percentage share of cancer incidences & deaths in 2022(Bhupender S. Chhikara & Key-kavous Parang, 2022)

Table 2: Data between cancer figures in different countries in 2020(Zia Sherrell, 2021)

Country	Mortality rate (Age standardized)	Incidence rate (Age standardized)	5-Year survivors
China	129.4	204.8	9,294,006
United States	86.3	362.2	8,432,938
India	63.1	97.1	2,720,251
Brazil	91.2	215.4	1,563,761
Mexico	63.2	140.4	530,602
Russia	113.7	234.3	1,580,383
Germany	102.3	313.2	2,188,176
Japan	81.5	285.1	2,710,728
Greece	107.2	264.7	179,828
France	107.9	341.9	1,501,881
United Kingdom	100.5	319.9	1,514,320
Italy	91.1	292.6	1,230,693

Table 3: Global cancer incidence in men in 2020 ('Worldwide Cancer Data', 2022)

Sl. No	Cancer	Percentage of all cancers	New cases in 2020
	All cancers*		9,342,957
1	Lung	15.4	1,435,943
2	Colorectal	11.4	1,065,960
3	Prostate	15.1	1,414,259
4	Liver	6.8	632,320
5	Stomach	7.7	719,523
6	Esophagus	4.5	418,350
7	Bladder	4.7	440,864
8	Kidney	2.9	271,249
9	Non-Hodgkin lymphoma	3.3	304,151
10	Lip, oral cavity	2.8	264,211
11	Leukemia	2.9	269,503
12	Melanoma of skin	1.9	173,844
13	Pancreas	2.8	262,865
14	Larynx	1.7	160,265
15	Brain, central nervous system	1.8	168,346
16	Multiple melanoma	1.1	98,613

17	Thyroid	1.5	137,287
18	Oropharynx	0.8	79,045
19	Nasopharynx	1.0	96,371
20	Hypopharynx	0.8	70,254
21	Testis	0.8	74,458
22	Gallbladder	0.4	41,062
23	Hodgkin lymphoma	0.5	48,981
24	Salivary glands	0.3	29,694
25	Penis	0.4	36,068
26	Mesothelioma	0.2	21,560
27	Kaposi sarcoma	0.3	23,413

There are about 200 distinct types of cancer, & we can classify them according to where in the body they initially manifest, for example, lung or breast cancer.

Additionally, we may classify cancers based on the sort of cell they first appear in. Five primary groupings are present. As follows:

Carcinoma: This particular kind of cancer begins in the dermis as well as the tissues around or proximal to internal organs. Adenocarcinoma, squamous cell carcinoma, basal cell carcinoma, & transitional cell carcinoma are among the subtypes.

Sarcoma: This type of cancer begins in the supporting or connective tissues, including the blood vessels, cartilage, fat, bone, & muscle.

Leukemia: This white blood cell cancer is what it is. It originates in the bone marrow & other organs that produce blood cells.

Myeloma & Lymphoma: Cancers that start in immune system cells.

Cancer of the spinal cord & brain: They are known as malignancies of the central nervous system. (‘Types of Cancer’, 2020)

Worldwide, the most common types of cancer are:

Breast cancer: This type of cancer is the most common. People who identify as AFAB & women are the ones who are most affected. However, about 1% of all cases of breast cancer are male and/or associated with AMAB.

Lung cancer: It is the cancer type that grows the second fastest. There are two types of lung cancer: small cell lung cancer & non-small cell lung cancer.

Prostate cancer: AMAB & 1 in 9 males are afflicted by the disease.

Colorectal cancer: Your digestive tract is affected differently by colon & rectal cancer.

Blood cancers: Leukemia & lymphoma are the two most prevalent blood cancers. ('Cancer', 2022a) Based on statistical data, breast cancer is among the deadliest type of cancer that has been identified over time.

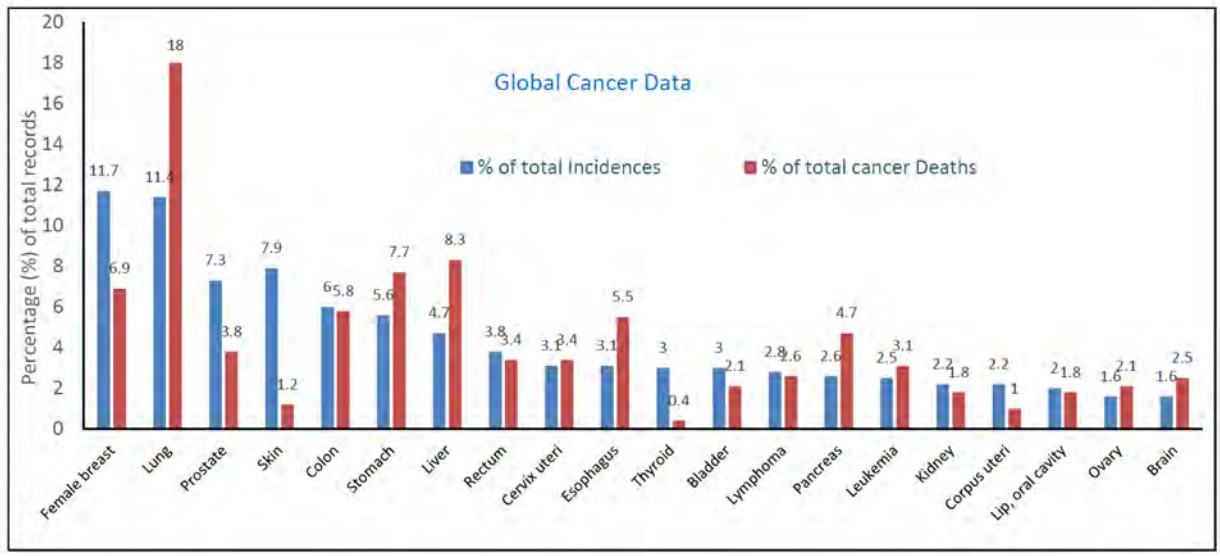

Figure 7. Comparative representation as a fraction of all cancer-related incidences (19.3 million) & deaths (10 million) in 2022. (Bhupender S. Chhikara & Keykavous Parang, 2022)

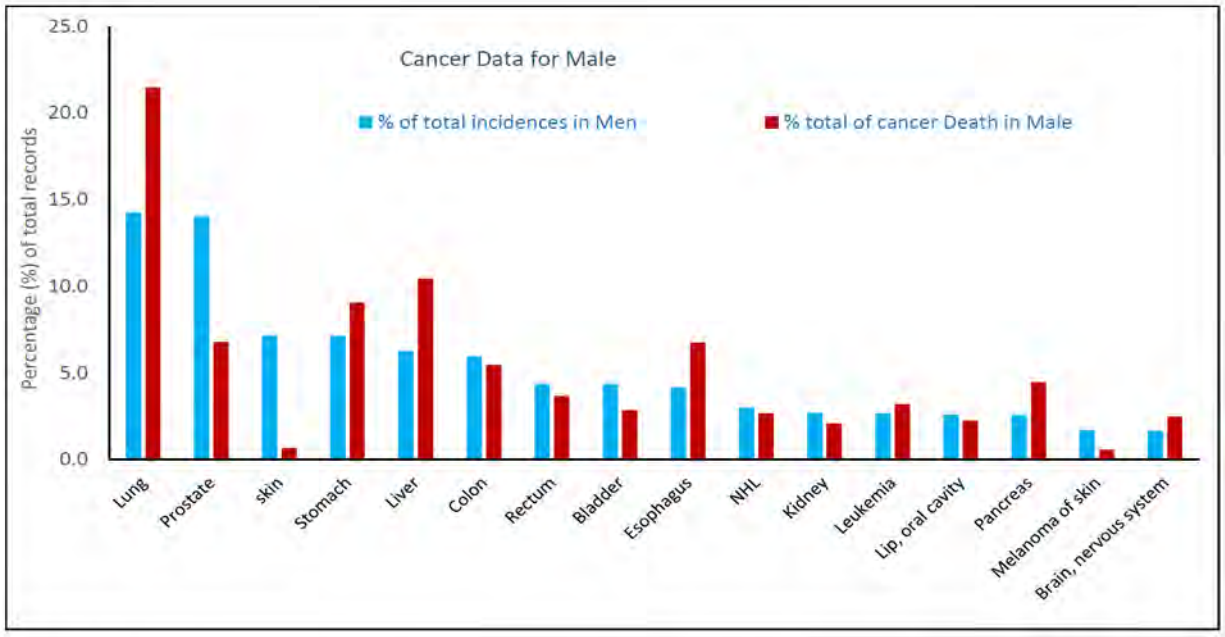

Figure 8. Ratio of selected main cancer types to total male cancer incidences (10.1 million) & total male cancer deaths (5.5 million) in men in 2022. (Bhupender S. Chhikara & Keykavous Parang, 2022)

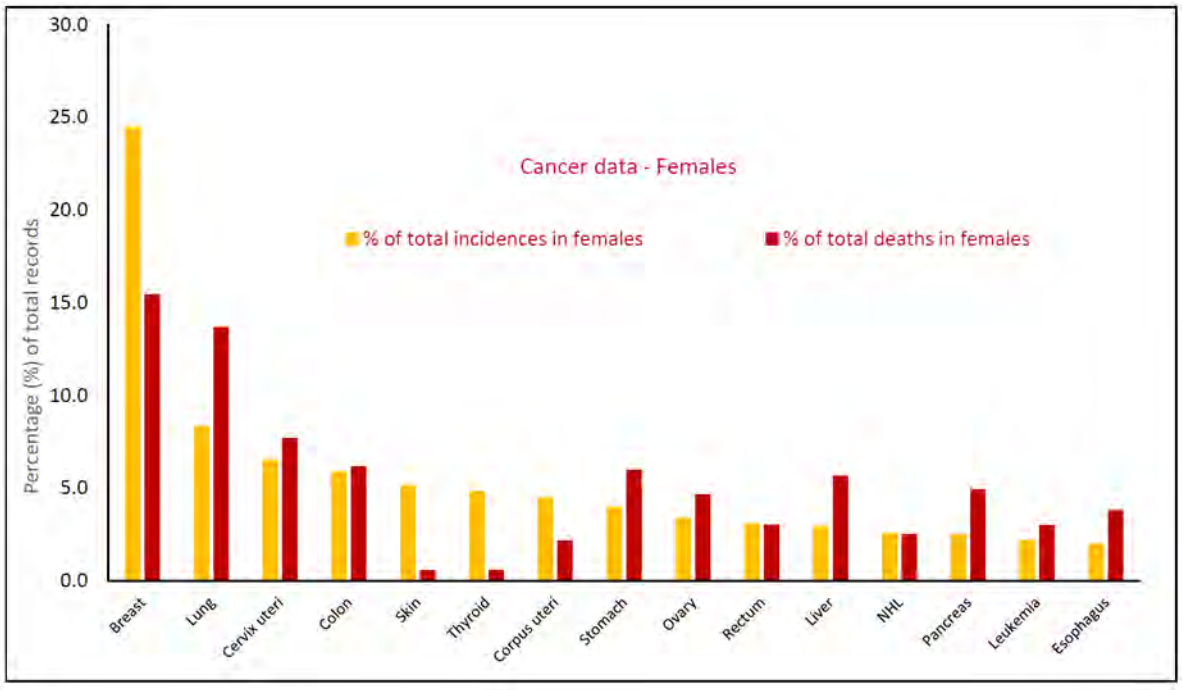

Figure 9. Proportional representation of specific major cancer types in percentage terms of all female cancer cases (9.2 million) & all female cancer deaths (4.4 million) in 2022. (Bhupender S. Chhikara & Keykavous Parang, 2022)

Table 4: New Cases & Deaths for 36 Cancers in 2020(Hyuna Sung et al., 2021)

Cancer site	No. Of New Cases (% Of All Sites)		No. Of New Deaths (% Of All Sites)	
Female breast	(11.7)	2,261,419	(6.9)	684,996
Prostate	(7.3)	1,414,259	(3.8)	375,304
Lung	(11.4)	2,206,771	(18.0)	1,796,144
Colon	(6.0)	1,148,515	(5.8)	576,858
Nonmelanoma of skin	(6.2)	1,198,073	(0.6)	63,731
Liver	(4.7)	905,677	(8.3)	830,180
Stomach	(5.6)	1,089,103	(7.7)	768,793
Cervix uteri	(3.1)	604,127	(3.4)	341,831
Rectum	(3.8)	732,210	(3.4)	339,022
Thyroid	(3.0)	586,202	(0.4)	43,646
Esophagus	(3.1)	604,100	(5.5)	544,076
Non-Hodgkin lymphoma	(2.8)	544,352	(2.6)	259,793
Bladder	(3.0)	573,278	(2.1)	212,536
Leukemia	(2.5)	474,519	(3.1)	311,594
Pancreas	(2.6)	495,773	(4.7)	466,003
Corpus uteri	(2.2)	417,367	(1.0)	97,370
Kidney	(2.2)	431,288	(1.8)	179,368
Melanoma of skin	(1.7)	324,635	(0.6)	57,043
Lip, oral cavity	(2.0)	377,713	(1.8)	177,757
Brain, nervous system	(1.6)	308,102	(2.5)	251,329
Ovary	(1.6)	313,959	(2.1)	207,252
Multiple myeloma	(0.9)	176,404	(1.2)	117,077
Larynx	(1.0)	184,615	(1.0)	99,840
Gallbladder	(0.6)	115,949	(0.9)	84,695
Nasopharynx	(0.7)	133,354	(0.8)	80,008
Hypopharynx	(0.4)	84,254	(0.4)	38,599
Oropharynx	(0.5)	98,412	(0.5)	48,143
Testis	(0.4)	74,458	(0.1)	9,334
Hodgkin lymphoma	(0.4)	83,087	(0.2)	23,376
Anus	(0.3)	50,865	(0.2)	19,293
Salivary glands	(0.3)	53,583	(0.2)	22,778
Vagina	(0.1)	17,908	(0.1)	7,995
Vulva	(0.2)	45,240	(0.2)	17,427
Mesothelioma	(0.2)	30,870	(0.3)	26,278
Kaposi sarcoma	(0.2)	34,270	(0.2)	15,086

Penis	(0.2)	36,068	(0.1)	13,211
All sites excluding non-melanoma skin		18,094,716		9,894,402
All sites		19,292,789		9,958,133

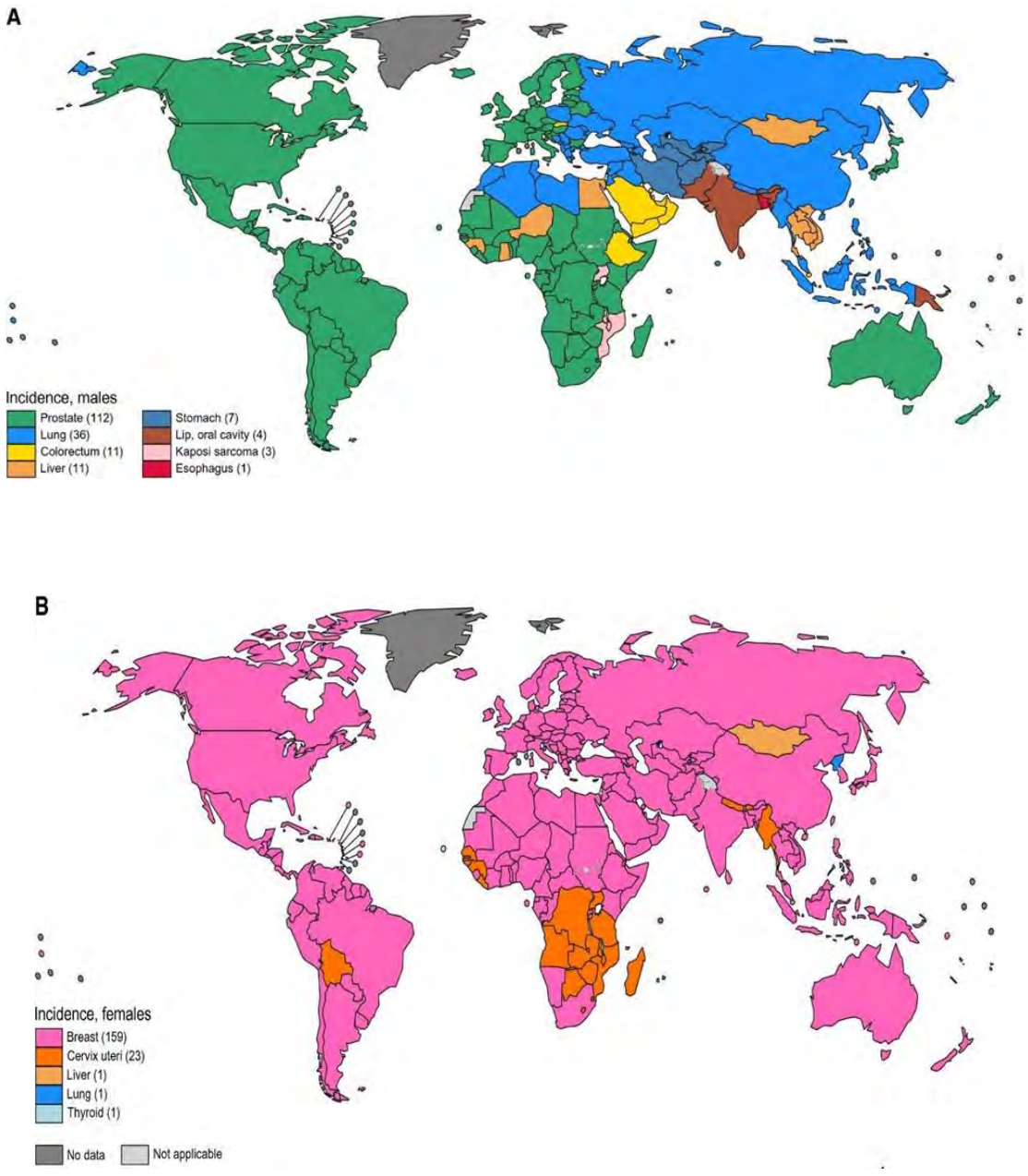

Figure 10: The most prevalent kind of cancer among (A) men & (B) women in each country in 2020. (Hyuna Sung et al., 2021)

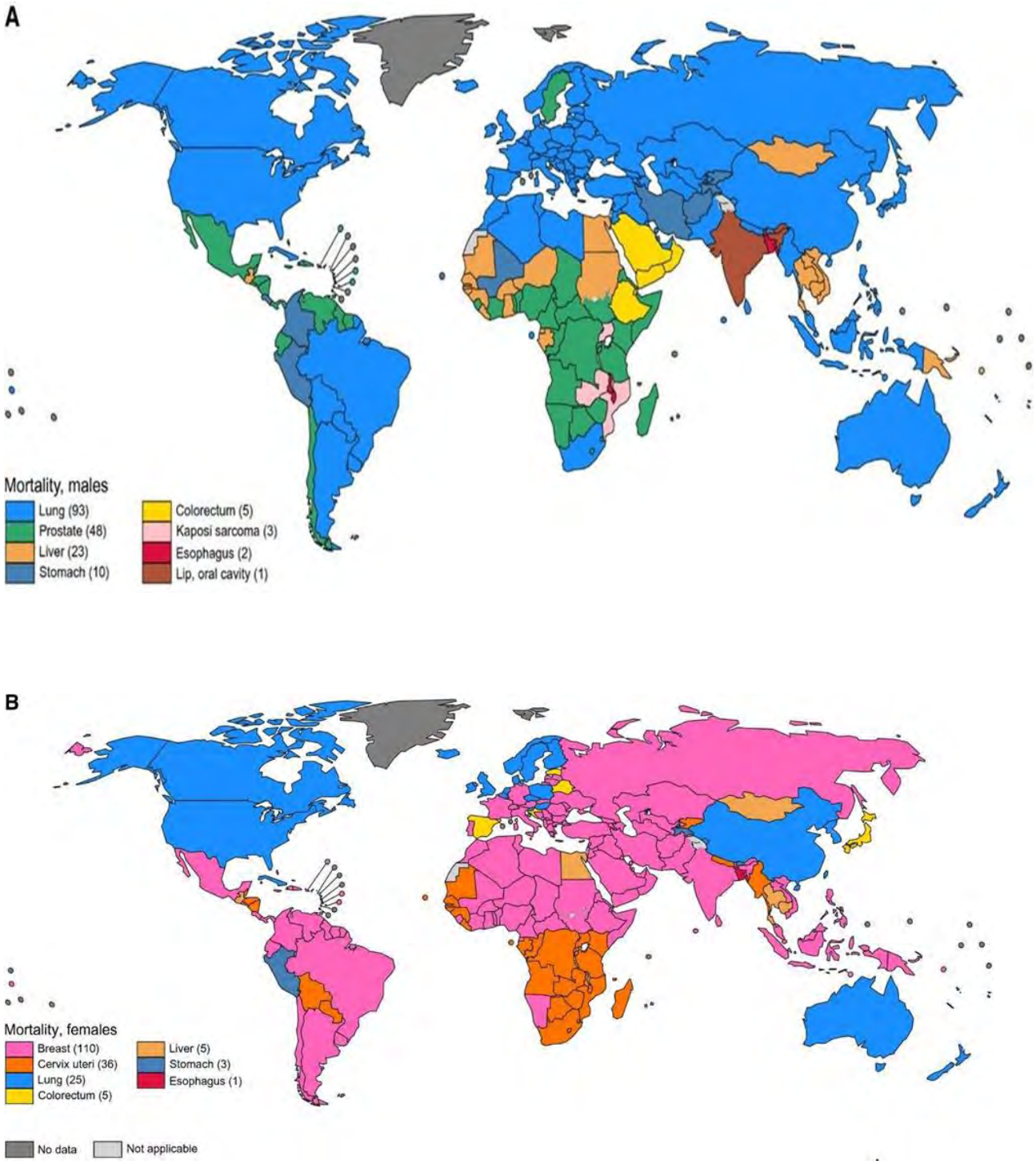

Figure 11: Most Common Type of Cancer Mortality by Country in 2020 Among (A) Men & (B) Women (Hyuna Sung et al., 2021)

Table 5: Cancer incidence worldwide: both sexes in 2020 ('Worldwide Cancer Data', 2022)

Sl. No.	Cancer	Percentage of all cancers	New cases in 2020
	All cancers*		18,094,716
1	Breast	12.5	2,261,419
2	Colorectal**	10.7	1,931,590
3	Lung	12.2	2,206,771
4	Stomach	6.0	1,089,103
5	Prostate	7.8	1,414,259
6	Cervix uteri	3.3	604,127
7	Liver	5.0	905,677
8	Thyroid	3.2	586,202
9	Esophagus	3.3	604,100
10	Non-Hodgkin lymphoma	3.0	544,352
11	Bladder	3.2	573,278
12	Leukemia	2.6	474,519
13	Pancreas	2.7	495,773
14	Corpus uteri	2.3	417,367
15	Kidney	2.4	431,288
16	Melanoma of skin	1.8	324,635
17	Lip, oral cavity	2.1	377,713
18	Brain, central nervous system	1.7	308,102
19	Ovary	1.7	313,959
20	Multiple myeloma	1.0	176,404
21	Larynx	1.0	184,615
22	Gallbladder	0.6	115,949
23	Nasopharynx	0.7	133,354
24	Hypopharynx	0.5	84,254
25	Oropharynx	0.5	98,412
26	Testis	0.4	74,458
27	Hodgkin lymphoma	0.5	83,087
28	Vulva	0.3	45,240
29	Salivary glands	0.3	53,583
30	Kaposi sarcoma	0.2	34,270
31	Penis	0.2	36,068
32	Vagina	0.1	17,908
33	Mesothelioma	0.2	30,870

Table 6: Cancer incidence worldwide in women in 2020 ('Worldwide Cancer Data', 2022)

Rank	Cancer	Percentage of all cancers	New cases in 2020
	All cancers*		8,751,759
1	Breast	25.8	2,261,419
2	Lung	8.8	770,828
3	Colorectal	9.9	865,630
4	Thyroid	5.1	448,915
5	Cervix uteri	6.9	604,127
6	Stomach	4.2	369,580
7	Corpus uteri	4.8	417,367
8	Liver	3.1	273,357
9	Ovary	3.6	313,959
10	Pancreas	2.7	232,908
11	Non-Hodgkin lymphoma	2.7	240,201
12	Esophagus	2.1	185,750
13	Leukemia	2.3	205,016
14	Melanoma of skin	1.7	150,791
15	Kidney	1.8	160,039
16	Bladder	1.5	132,414
17	Brain, central nervous system	1.6	139,756
18	Multiple myeloma	0.9	77,791
19	Lip, oral cavity	1.3	113,502
20	Vulva	0.5	45,240
21	Gallbladder	0.9	74,887
22	Hodgkin lymphoma	0.4	34,106
23	Nasopharynx	0.4	36,983
24	Salivary glands	0.3	23,889
25	Larynx	0.3	24,350
26	Vagina	0.2	17,908
27	Oropharynx	0.2	19,367
28	Kaposi sarcoma	0.1	10,857
29	Hypopharynx	0.2	14,000
30	Mesothelioma	0.1	9,310

The information indicates that breast cancer remains among the deadliest & rapidly progressing kind of cancer. To solve this urgent situation, immediate actions must be taken. Anti-breast cancer medications can be important in this area. Despite their shortcomings, these medications are extremely important & offer a promising path in the battle against breast cancer. They have the ability to influence how this condition will be treated in the future.

1.2 Scope of the Study

The most prevalent & dangerous type of disease, particularly for women, is breast cancer. It has surpassed lung cancer as being the most commonly diagnosed disease globally, resulting in one out of every eight cancer diagnoses & 2.3 million new instances in total in both sexes. With nearly one quarter of all female cases of cancer, it was by far the most common cancer diagnosed in 2020 & its prevalence has been rising globally, particularly in developing countries. According to estimates, 685,000 women will have passed away from breast cancer in 2020, accounting for 16% or 6 out of every 100 female cancer fatalities. In the preceding five years, 7.8 million women had received a diagnosis. Though the incidence rates climb with age, breast cancer affects women in all nations in the world after puberty. The Worldwide Breast Cancer Initiative was started by the World Health Organization (WHO) in reaction to the public health community's prior lackluster reaction to this development. The WHO & partners seek to lower breast cancer mortality by promoting early detection, appropriate treatment, & patient care, as well as through involving international partners & coordinating sustainable efforts to improve outcomes. A solid understanding of worldwide trends & variance in the illness burden is essential as the cornerstone for these efforts. (Melina Arnold et al., 2022)

From the 1930s through the 1970s, when surgery alone was the main form of treatment (radical mastectomy), the death rate for breast cancer did not significantly alter. As early detection programs for breast cancer were connected to thorough treatment plans that included efficient medicinal medicines, survival rates started to rise in the 1990s.

The primary cause of this rising death rate is the lack of early diagnosis of the illness. This problem is a direct result of decreased breast cancer awareness that has been seen in most developing nations. Understanding breast cancer is essential for early detection, prevention, & treatment of this illness. Since breast cancer is present, it is important to have a proper grasp of its signs & symptoms, threat factors, prevention, treatment options, & facilities. Women who have adequate knowledge of breast cancer will be able to recognize warning signs before the disease progresses & seek medical attention early. Women who are also knowledgeable about the causes & risk factors of cancer will be better equipped to take preventive actions & make the necessary lifestyle changes to help prevent the disease. The most effective methods to reduce mortality are often cancer prevention by prompt, stepped-forward detection & treatment & subsequent screening applications. (AKOR UGWU, 2020)

1.3 Purpose of the work

- To provide an overview of anti-breast cancer drugs specially- Trastuzumab & Pertuzumab
- To focus on mechanism of action,
- To provide clinical significance
- Limitations
- Future Aspects

Chapter 2

Methodology

Several keywords, including HER-2, trastuzumab, & pertuzumab, were used in a structured literature search on PubMed & Google Scholar. 5360 records were uncovered during the search. The number fell to 1200 after deduplication & preliminary screening. We utilized articles on trastuzumab, pertuzumab, & breast cancer. The reference management of choice was Mendeley.

Figure 12 displays the full procedure together with the inclusion & exclusion standards.

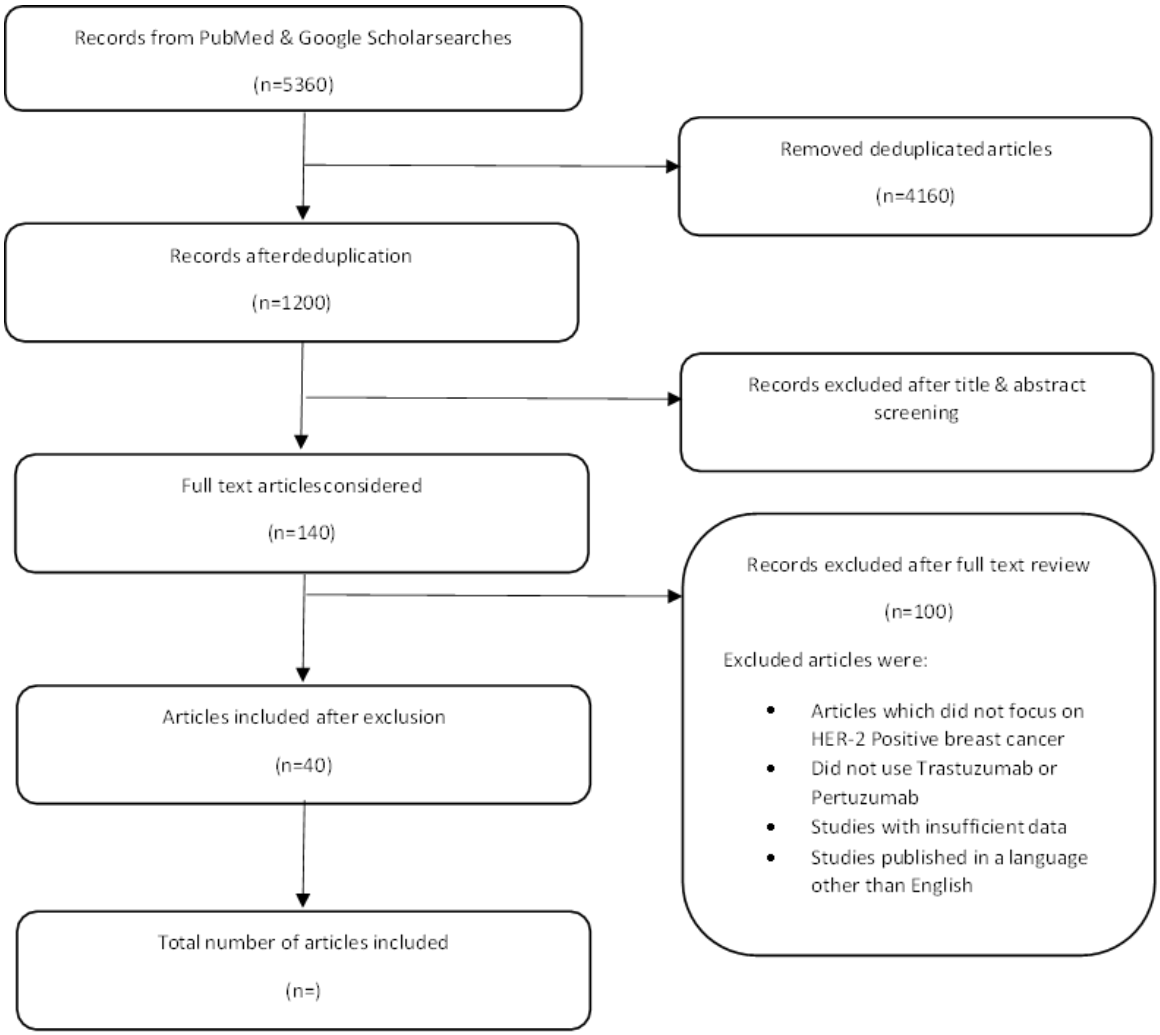

Figure 12. Methodology

Chapter 3

Breast Cancer

Cells are the minuscule building units that make up the human body. Your body produces them, replacing the ones that perish with fresh ones. Normally, the body develops sound, regular cells that carry out their intended functions. This comprises the tissue in the breasts, the two spherical portions on the front of the chest. However, if a cell transforms into an aberrant, occasionally deadly form, it may rapidly replicate again without dying, producing countless copies of itself. When this occurs, a tumor, which is a collection of abnormal body cells that resembles a mass or lump, can form & develop. One kind of tumor that develops in the cells of the breast is called breast cancer. You might believe that breast cancer exclusively affects women, but since everyone has breast tissue, it is possible for males to have the disease as well, although it is quite uncommon. If someone has breast cancer, there may only be cancerous cells in one area of the breast, which can be felt as a lump. One or both breasts may be affected by the cancer's spread. Breast cancer can occasionally migrate to the liver, bones, or other organs. (Steven Dowshen, 2017)

Breast cancer begins in the breast tissue. Breast cells that mutate (change) & proliferate uncontrollably result in a lump of tissue known as a tumor. Like other cancers, breast cancer has the potential to grow & spread through the tissue that surrounds your breast. It may also grow new tumors & spread to other parts of your body. In medicine, this is called metastasis. (‘Breast Cancer’, 2022a)

Overall, Breast cancer is a disease that occurs when the breast's cells proliferate out of control. There are several types of breast cancer. What breast cells develop into cancer determines the kind of breast cancer. (‘What Is Breast Cancer?’, 2023)

3.1 History of breast cancer

Since the organ's location made breast cancer simple to identify, it is not unexpected that literary accounts & depictions of the disease date back to ancient times. The Edwin Smith Surgical Papyrus, dating from 3,000–2,500 B.C., is believed to have been written by the Egyptian physician-architect Imhotep & contains true accounts of breast cancer. When the illness was "cool to the feel it, sagging, & expanded throughout the breast," it was deemed irreversible. Breast votive offerings at Greek temples dedicated to the lord of medicine, Asclepius, demonstrate that in ancient Greece, a deity was favored for curing breast ailments. Hellen-istic literature is the source of the phrase's scirrhous (hard, Greek skirros), carcinoma (also known as karkinoma), & cacoethes (malignant sickness, Greek kakoethes). Hippocrates' theory, which dates back to approximately 400 B.C., that disease results from an imbalance of humors (blood, phlegm, yellow & black bile), together with his well-known accounts of how breast cancer develops, are among the earliest hypotheses regarding the cause of cancer.

In the first century A.D., Leonides of Alexandria openly & deftly described his method of incision & cautery while upholding Greek customs. His requirement that a broad margin of excision be left & that only tumors with a small extent be removed foreshadows the oncological principles of modern surgical treatment. About 200 AD, Galen concluded that black bile accumulation in the bloodstream was the cause of breast cancer, which constituted a systemic sickness. These old doctors thought that there was a link between cancer & the end of menstruation; in fact, the link was probably related to the relationship between cancer & advanced age. Galen didn't think ligatures should be used & instead advocated for surgical wounds to be left open to drain the black bile. The dilation of the veins originating from the tumour led him to coin the word "crab" to characterize cancer.

Between 476 & 1500 A.D., religious philosophy & medical advancement were intricately linked. Early Christian beliefs preferred miracles & spiritual healing over surgery, which they viewed as barbarous. Greek medicine was revitalized by Islam, & through careful translations, medical knowledge was preserved for future generations. Three prominent Arab physicians, Maimonides from Spain in the 12th century, Avicenna from Persia (Ibn Sina), & Albucasis from Spain (Abu Al-Qasim Al-Zahrawi) in the 10th century, served as role models whose medical acumen extended beyond the boundaries of the expanding Islamic conquests. Albucasis was an ardent advocate of cautery during surgery. The rationale for the current use of chemotherapy for large breast tumors is similar to that of the past, when the tumor was removed & rendered operational by caustic pastes. To speed up the removal of breast tumors, Henri de Mondeville (the "father" of French surgery), Albucasis, & Guy de Chauliac (France, 14th century) all developed specialized tools.

In addition to fostering artistic innovation, the 16th to 18th century were also a golden period for the development of surgery. The surgical profession was once associated with barbering, but thanks to Andreas Vesalius' extensive anatomical study of human anatomy during 16th-century Belgium, the surgical profession was freed. The 18th century discoveries of Sappey's subareolar plexus of lymphatics & the Cooper's namesake ligaments of the breast in England & France, respectively, led to a reexamination of the origins & course of breast cancer. Around the same time, lymph rather than "black bile" was suggested as the true cause of breast cancer by the Scottish "father" of investigatory surgery, John Hunter. Numerous theories have been added to the fire of carcinogenesis, such as inhaled milk, trauma, type of personality, exposure to air, & infection. Naturally, the disease's occurrence in families was linked to infection. Medical records are made more interesting by tales of daring operations, ranging from straightforward lumpectomies to complete excision of the pectoralis. They become even more vivid & admirable when one remembers that, in the days before anesthesia, a successful surgeon could

only possess quickness & ability. It serves as a somber reminder that surgery was the only treatment that offered an anecdotal chance of success. Conservative comrades chose to strangle the tumors with ligatures or lead plates instead of undergoing the gruesome breast amputation.

The foundation of a wave of discoveries that made surgery safer & improved patient outcomes allowed it to exp& quickly. The first significant events were the usage of sterile gloves, sterilization, & disinfection. The ease of the surgeon (& in fact, the patient!) was revolutionized by general anesthesia. Even though James Blundell tried blood transfusion in 1818 during a postpartum hemorrhage, safe transfusions would not be achievable until the early 1900s, when Karl Landsteiner discovered blood types. In light of this, from Hooke in the 17th century in England through Müller & Virchow in the 19th century in Germany, microscopic differences among malignant & normal cells were essential in expanding our understanding of cancer. By claiming that malignancies are made up of live cells & arguing that metastasis is caused by the spread of these cells, Müller disapproved of the humoral theory regarding the genesis of cancer. A number of excision procedures were built on the evidence that breast cancer propagated from the lymphatics to the guardian axillary nodes. A different strategy to treatment would be required for the distinct modes of dissemination that result in Paget's disease & the clinical signs of peau d'orange or carcinoma en cuirasse.

The mid-19th century celebrated the recently achieved surgical independence with bold & daring treatments. Charles Moore's en bloc resection in London10 & Kuster & Volkmann's in Germany proceeded in tandem. William Banks carried out 11 axillary lymph node dissections in Liverpool, United Kingdom, in 1882 as part of his annihilation philosophy. Even though they can seem particularly mutilating in retrospect, they offered a rare chance to examine how the illness propagated. The man credited with pioneering breast cancer surgery at the beginning of the century was William S. Halstead, a professor of surgeon at Johns Hopkins Hospital in Baltimore, USA. His radical mastectomy (first reported in 1894) became the unquestionable

course that many surgeons scrupulously followed for years, with an emphasis on removing tissues in one piece to prevent spread & deleting the pectoralis major to pre-empt recurrence. "The suspicious tissues ought to be removed in a single component, (1) to stop the incision from propagating to other organs or lymph vessels from carrying cells from cancer, & (2) since shreds or bits of malignant tissue are likely to be ignored in the sequential extirpation."

These strict rules regarding non-violation of the location of the tumor prohibited a preoperative test to ascertain whether the patient indeed had cancer, demonstrating the strength of an expert clinical diagnosis! Another long-standing custom that was abandoned was allowing the surgical wound from an excision to granulate. Due to reduced infection rates, the usage of ligatures has now improved wound healing.

Since breast cancer strikes younger women more frequently, the idea that hormones play a part in the disease was first proposed. Beatson started the era of endocrine surgery in 190615, preceding Jensen's 196716 discovery of estrogen receptors & the widespread use of oophorectomy & adrenalectomy (to achieve castration). These extremely harsh methods were gradually superseded by estrogen receptors modulators, lute-inizing hormone-releasing agents, & aromatase inhibitors.

For a period, Halstead's legacy was sustained by Milanese surgeons Margottini & Veronesi, who removed internal mammary nodes as well. Other surgeons who extended the application of "radicality" to supraclavicular & mediastinal cells also contributed to this. But in the late 19th & early 20th centuries, the adage saying "big surgeons create enormous incisions"—& hence undertake enormous surgeries—gradually faded. A movement-initiated doctors Londoners Patey & Handley & the New Yorker Auchin-closs Jr. preserved the pectoralis major & "modified" the radical mastectomy. Rapid developments in medical radiation therapy for cancer cells & novel forms of chemotherapy that accomplished the same result while also targeting

mutant tumor receptors or achieving medical castration forced a reevaluation of cancer management strategies. These were combined with the expanding understanding of breast cancer's biochemical behavior & the less-than-certain effectiveness of surgery alone. Mammography's ability to detect cancer early in tiny lesions has given surgical management a fresh perspective.

The call to refocus towards restricted surgery came from the surgical fraternity. Bernard Fisher, a University of Pittsburgh surgery professor, revived Galen's outmoded notion that cancer of the breast is a systemic disease. Large-scale randomized controlled clinical trials, such as the 1989-published National Surgical Adjuvant Breast & Bowel Project (NSABP), provided scientific support. It is ironic that the development of trials, the adoption of neoadjuvant therapy, & the downfall of the radical Halstedian system were all facilitated by a surgeon! Veronesi, an Italian surgeon, & many others backed the idea of restricted surgery combined with adjuvants. Surgery underwent a revolution in order to collaborate with the other disciplines. Breast conservation & reconstruction have been popular since the turn of the 20th century, oftentimes in conjunction with sentinel node dissection. If only a few "sentinel" nodes (those to which the tumor had advanced) were removed, the swollen lymphedematous arm, an important consequence of axillary lymph node dissections, would be relegated to surgical history.

French surgeon Verneuil took tentative moves in 1887 to restore cosmesis by autologous tissue transplantation using the functional breast to the ill one. Surgeons had previously led the movement toward minimizing extirpation. This opened the door for a wide range of inventive autologous & synthetic materials that might potentially outdo nature's original design in terms of restored form. Natural possibilities included omentum, lipomas, myocutaneous flaps, & muscle. Since its first description by Holmstrom in 1979, the transverse rectus abdominis myocutaneous flap (TRAM) has experienced several modifications. Artificial & prosthetic options, such as silicone, glass beads, rubber, ivory, & polyvinyl alcohol sponge, brought business & industry into the mix.

Breast cancer has been treated mostly with surgery since the first documented cases in medical literature. The reports of surgery performed without anesthesia as a physically & mentally torturous therapeutic alternative have long been interesting & terrifying, balancing the promise for a cure provided by the abrupt excision of a sick organ. Surgery continues to be the cornerstone of care in a multimodality context, although being far from its nadir. Now, instead of eradicating the breast cancer survivor, it provides support, striking a balance between cure & cosmesis. (Ritu Lakhtakia, 2014)

3.2 Percentage of people are affected by breast cancer worldwide

Table 7 displays the number of cases of breast cancer in women globally in 2020. The two nations with the greatest rates of breast cancer among women in 2020 were Belgium & the Netherlands. ('Breast Cancer Statistics', 2022)

Table 7: Global breast cancer incidence rate for women in 2020

Sl. No.	Country	ASR/100,000	Number
	World	47.8	2,261,419
1	Belgium	113.2	11,734
2	Luxembourg	99.8	497
3	The Netherlands	100.9	15,725
4	France, New Caledonia	99.0	185
5	France	99.1	58,083
6	Australia	96.0	19,617
7	Denmark	98.4	5,083
8	Finland	92.4	5,228
9	New Zealand	93.0	3,660
10	US	90.3	253,465

This table 8 displays the global breast cancer death rate for women in 2020. Fiji & Barbados were the two nations with the highest rates of female cancer of the breast deaths in 2020. (‘Breast Cancer Statistics’, 2022)

Table 8: Global breast cancer death rate for women in 2020

Sl. No.	Country	ASR/ 100,000	Number
	World	13.6	684,996
1	Barbados	42.2	111
2	Jamaica	34.1	637
3	Fiji	41.0	184
4	Papua New Guinea	27.7	847
5	Bahamas	31.0	80
6	Mali	26.6	1,425
7	Somalia	27.2	1,189
8	Syria	26.2	1,946
9	Dominican Republic	26.4	1,577
10	Samoa	25.6	21

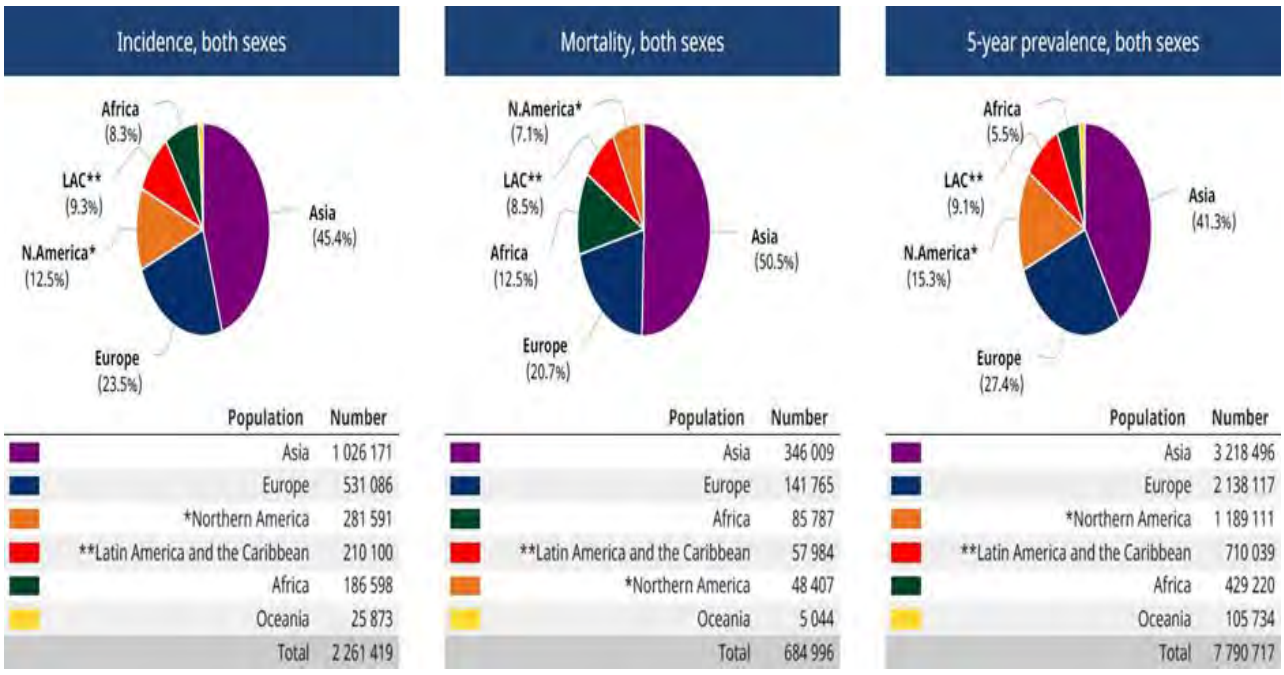

Figure 13. Incidence, mortality, & prevalence of breast cancer in both sexes globally in 2020(‘Breast’, 2020)

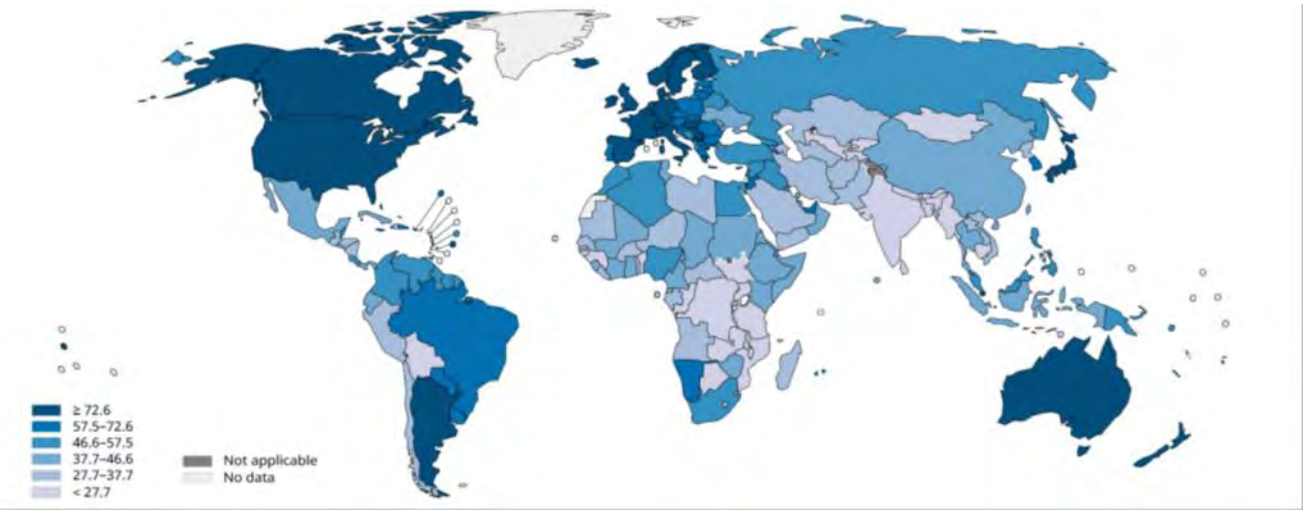

Figure 14. All ages, breast, age-standardized incidence rates ('Breast', 2020)

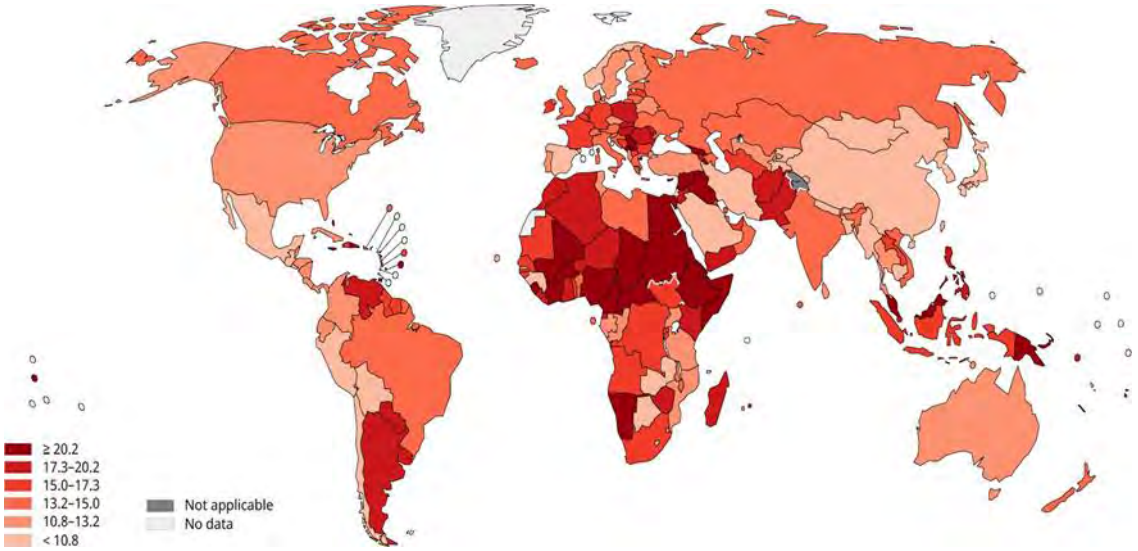

Figure 15. Age standardized mortality rates, breast, all ages('Breast', 2020)

3.3 Causes of breast cancer

According to medical professionals, breast cancer is caused by the abnormal development of certain breast cells. A bulk or lump is created as a result of these cells continued faster division & multiplication than that of healthy cells. Cells may travel through your breast to spread (metastasise) to the lymph nodes as well as other parts of your body.

Cells in the milk-producing ducts are usually the first to develop into aggressive ductal carcinoma, which is a type of breast cancer. Invasive Lobular carcinoma is a type of breast cancer that can originate from other cells or tissues within the breast, such as the glandular tissue called lobules.

Research suggests that hormonal, behavioral, & environmental variables may raise the possibility of breast cancer. It is unknown, nonetheless, why some persons with warning signs never develop cancer while others do. Breast cancer most likely originates from a complex interaction between genetic makeup & environment.

The majority of breast cancers, between 5 & 10 percent, are thought to be caused by gene abnormalities that have been passed down through a family.

A number of inherited mutant genes can increase the likelihood of breast cancer. The genes that significantly increase the risk of developing breast & ovarian cancer are the most well-known ones, BRCA1 & BRCA2.

In order to discover specific mutations in BRCA or other genes which are being passed down through your family, your doctor can suggest a biopsy if you've got a lengthy family record of breast cancer or related cancers.

Think about asking your doctor to recommend a genetic counselor who can go through your family's medical history. In order to help you with shared decision-making, a genetic counselor can also go over the advantages, hazards, & limits of genetic testing.

A breast cancer risk indicator is anything that raises your likelihood of getting the disease. Nevertheless, the presence of one or more risk factors for breast cancer does not ensure that you will get the illness. Many women who develop breast cancer are just women & do not have any other known risk factors.

Several factors have been associated with an increased risk of breast cancer, including:

- Being female: Compared to men, women are significantly more likely to get breast cancer.
- Increasing age: Your risk of breast cancer increases with age.
- A personal history of breast conditions: If a breast biopsy shows atypical hyperplasia or lobular carcinoma in situ (LCIS), you have an increased risk of developing breast cancer.
- A personal history of breast cancer: If you have previously had breast cancer in one breast, your chances of developing it in the other breast are increased.
- A family history of breast cancer: If any of your mother's sisters, daughters, or uncles had breast cancer, especially while they were young, your chances of getting it increased. A large percentage of breast cancer patients, however, are without a family history of the disease.
- Inherited genes that increase cancer risk: Certain genetic alterations that increase the chance of breast cancer can be inherited from one's parents. The most well-known mutations in the genes are those in BRCA1 & BRCA2. Breast cancer & other cancers can be considerably increased by these genes; however, they do not ensure that you will get any of them.
- Radiation exposure: If you received chest radiation treatments as a child or young adult, your risk of breast cancer is increased.
- Obesity: Being overweight increases your risk of breast cancer.
- Beginning your period at a younger age: If you begin menstruation before the age of twelve, your risk of breast cancer increases.
- Beginning menopause at an older age: Among women who went through menopause later in life, breast cancer is more common.

- Having your first child at an older age: Women who wait until after turning 30 to conceive their first child may be at increased risk of breast cancer.
- Having never been pregnant: Women who never gave birth have a greater risk of acquiring breast cancer than those who have given birth one or more times.
- Postmenopausal hormone therapy: Women who use oestrogen & progesterone-containing hormone therapy medications to treat menopausal symptoms & indications are more likely to develop breast cancer. Women who stop using these medications have a decreased risk of breast cancer.
- Drinking alcohol: Drinking alcohol increases the risk of breast cancer.('Breast Cancer', 2022b)

3.4 Symptoms of breast cancer

Breast cancer symptoms frequently include:

1. Changes to the skin's texture: Breast cancer can alter skin cells & inflame them, changing the texture of the skin as a result. Examples of these textural changes include skin thickening in any area of the breast & scaly skin around the nipple & areola that appears burnt or excessively dry. Although it is uncommon, these alterations may also produce the itching that is frequently linked to breast cancer. These skin abnormalities might indicate Paget's disease, an uncommon form of breast cancer. Texture changes can also come from benign skin disorders like eczema & dermatitis.
2. Nipple discharge: A person may notice nipple discharge, which can be clear, milky, yellow, green, or red in color & can be thick or thin. One nipple is usually the source of the discharge. However, if both breasts are malignant, it may originate from both nipples. A milky discharge from the nipples is typical in nursing individuals, but it is essential to see a doctor if there is any other type of nipple discharge. Nipple discharge

is often non-cancerous, but in some people, it may be an indication of breast cancer. Birth control, certain drugs, & some diseases are additional potential causes of nipple discharge.

3. Dimpling: Skin dimpling may occasionally be a symptom of severe inflammatory breast cancer. Lymph fluid can accumulate in the breast due to cancer cells, which can result in swelling, dimpling, or pitted skin. Anyone who finds skin dimpling must consult a doctor right away. Because of the dimpled skin's resemblance to an orange's surface, doctors refer to this alteration in the skin's look as "peau d'orange" in French.
4. Lymph node changes: Immune system organs known as lymph nodes are tiny, spherical clusters that filter fluid & engulf potentially dangerous cells. These include cancer cells, germs, & viruses. The underarm lymph node area on the same side as the afflicted breast is often where a cancer cell goes initially after leaving the breast. This may cause edema in the region. Swollen lymph nodes can be seen around the collarbone in addition to the armpits. They often feel sensitive to the touch & might be tiny, hard, swollen lumps. Lymph tissue, however, can also alter as a result of breast infections or other, unrelated disorders. To determine a likely reason of these changes, a patient should discuss them with a doctor.
5. Breast or nipple pain: Breast pain, tenderness, & discomfort can result from changes in skin cells brought on by breast cancer. A bump that is present is not uncomfortable. Despite the fact that breast cancer is frequently painless, it is crucial to pay attention to any signs or symptoms that can be related to the disease. Some folks might say the pain feels sensitive & searing.
6. Nipple retraction or inversion: Cell alterations behind the nipple can be brought on by breast cancer. The nipple may flip & reverse inside the breast as a result of these alterations, or it may alter in terms of size. People should see a doctor if they notice any new

nipple alterations since the shape of the nipples can frequently change during ovulation or other phases of the menstrual cycle.

7. Skin color changes: Skin changes brought on by breast cancer may make it seem irritated or pigmented. On skin that is white or pale, this may seem red. The skin tone of persons of color may seem brownish or reddish-brown. A person should see a doctor if these changes cannot be explained by recent trauma to the breast. Even if trauma was the cause of breast discoloration, it is crucial to seek medical care if it persists.
8. Swelling: The entire breast or a portion of the breast may enlarge as a result of breast cancer. After this swelling, there might not be a clear lump, but the breast might be bigger than the other breast. Even while it is conceivable for people to have somewhat different-sized breasts all the time, this swelling would produce a deviation from their typical breast size. Due to the swelling, the skin could also feel constrictive.

Changes in breast size: It's common for people to have breasts that are different sizes from one another. On the other hand, an unexplained rise in the size of one breast might indicate breast cancer. A quick rise in breast size, according to the National Cancer Institute, may be a sign of inflammatory breast cancer even though changes in breast size can be a sign of any form of breast cancer. This is an uncommon & severe kind of breast cancer. Someone might think about calling a doctor if they discover that one or both of their breasts have grown in size.(Teresa Hagan Thomas et al., 2022)

3.5 Stages of breast cancer

- A number from 0 & IV is frequently used to indicate the cancer's stage once it has been determined:
- Stage 0 pertains to "pre-invasive" breast tumors, like ductal carcinoma in situ (DCIS). In cases of DCIS & lobular carcinoma in situ (LCIS), respectively, this suggests the

presence of aberrant cells that are confined, within the milk duct or inside the lobules (milk-producing glands).

- Stages I & II of breast cancer are considered early cases. It is referred to as invasive breast cancer when cancer cells from the lobules or milk duct expand to nearby tissue. The disease's early stage is invasive & only affecting the breast. It's possible that the spread hasn't reached the lymph nodes under the armpit or in the breast. Even though they are invisible, some cancer cells can have spread outside of the breast & underarm area.
    - Locally advanced breast cancer is defined as having reached stage III. This kind of invasive breast cancer has any or all of the following traits:
    - Possibly significant (often more than 5 cm) & able to extend to several nodes in the axillary region in the underarm area or to other areas around the breast
    - It might have extended to the breast & other adjacent tissues like the skin, muscles, or ribs.
- Stage IV refers to metastatic or advanced breast cancer. The cancer has now moved outside of the breast to other bodily areas. Bones, the liver, the lungs, & the brain are common sites where breast cancer spreads. Breast cancer can, however, potentially spread to other organs.

Table 9: Breast cancer stages

Breast cancer stage	**Size of cancer**	**Have cancer cells been found in...**	
		...lymph nodes?	...other parts of the body?
0	Size not used for stage 0	No	No
I	<2 cm	No	No
IIA	<2 cm	Yes (Category 1)	No
	2–5 cm	No	No
	No cancer found in breast	Yes (Category 1)	No

IIB	2–5 cm	Yes (Category 1)	No
	>5 cm	No	No
IIIA	<2 cm	Yes (Category 2)	No
	2–5 cm	Yes (Category 2)	No
	>5 cm	Yes (Category 1)	No
	>5 cm	Yes (Category 2)	No
	No cancer found in breast	Yes (Category 2)	No
IIIB	Any size but the cancer has spread to nearby muscles & skin	Any (Can be yes or no)	No
IIIC	Any size	Yes (Category 3)	No
IV	Any size	Any (Can be yes or no)	Yes

The TNM method is sometimes used by clinicians to stage breast cancer. In this approach, descriptions are made using both letters & numbers:

- The tumor's size (the letter T stands for tumor)
- The quantity of afflicted lymph nodes (where N stands for nodes)
- Whether the disease has metastatically spread to other regions of the body

T, N, & M are followed by numbers or letters that give further information about each of these traits. The more advanced the malignancy, the higher the number or later the letter after each TNM component in the diagnosis.

The following information was added to the TNM staging system in 2018 to help in cancer classification:

- What is the condition of the estrogen & progesterone receptors? Are there hormone receptors on the cancer cells?
- Are cancer cells producing an excessive amount of the HER2 protein?
- The degree to which cancer cells resemble normal cells is known as the tumor grade.

- Oncotype DX score (if relevant) - Some malignancies that are estrogen-receptor positive, HER2-negative, & have not progressed to the lymph nodes may be staged using the oncotype DX score.

3.6 Categories of Breast cancer

The following criteria can also be used to classify breast cancer if it has been discovered in the lymph nodes:

- Category 1: One to three armpit lymph nodes have been reported to contain breast cancer cells.
- Category 2: Cells of breast cancer have been discovered in:
  - 4–9 lymph nodes between the armpits that are swollen and/or joined to other lymph nodes or adjacent tissue; or
  - Not in any lymph nodes in the armpit, but 1 or more lymph nodes under the breastbone.
- Category 3: Cells of breast cancer have been discovered in:
  - 10 or more armpit lymph nodes; or
  - a lymph node or nodes above or below the collarbone; or
  - at least one lymph node in each armpit & at least one lymph node under the breastbone.

3.7 Grading for breast cancer

The tumor's grade indicates the activity of the cells & the likelihood of its growth rate. To determine the cancer grade, a pathologist will use a microscope to analyses the tumor tissue removed during a biopsy.

Grade 1 (Low grade): Normal cells & cancer cells have slightly distinct appearances. These tumors often develop slowly.

Grade 2 (intermediate grade): According to, cancer cells don't look like healthy ones. They frequently progress faster compared to grade 1 cells with cancer.

Grade 3 (High grade): Normal cells & cells with cancer have drastically diverse appearances. They frequently spread & exp& quickly.

The grade of your breast cancer is used to assist forecast your prognosis & identify the therapies that are most likely to be successful. (Dr. Sunil Lakhani, n.d.)

3.8 Types of breast cancer

There are several types of breast cancer, such as:

• Infiltrating (invasive) ductal carcinoma: the type of breast cancer starts in the milk ducts, pierces the duct wall, & then spreads to the surrounding breast tissue. With over 80% of cases being of this kind, it is the most common type of breast cancer.

• Ductal carcinoma in situ: Also referred to as Stage 0 breast cancer, this condition is considered precancerous by some due to the fact that the cells have not progressed past your milk ducts. It is astonishingly treatable. Treatment for cancer must begin right away in order to prevent it from growing more aggressive & from spreading to other tissues.

• Infiltrating (invasive) lobular carcinoma: This cancer started in the lobules of your breast, wherein breast milk is generated, & it has subsequently spread to neighboring breast tissue. It is the cause of 10–15% of breast cancer cases.

• Lobular carcinoma in situ: This precancerous illness is characterized by abnormal cells in the breast lobules. This is not a true cancer, but it might indicate a potential subsequent possibility

of breast cancer. As a result, it's critical that women who have lobular carcinoma in situ get routine clinical breast exams & mammograms.

• Triple negative breast cancer (TNBC): One of the most difficult types of breast cancer to treat, triple negative breast cancer accounts for 15% of all cases. Triple negative breast cancer is so named because it does not exhibit three of the indicators associated with other forms of breast cancer. This complicates therapy & diagnosis.

• Inflammatory breast cancer: This type of cancer seems infectious & is rare as well as severe. Inflammatory breast cancer is commonly characterized by redness, swelling, pitting, & dimpling of the breast skin. It is caused by cancerous cells that clog the lymphatic vessels beneath their skin.

• Paget's disease of the breast: This cancer affects both the skin around your nipple, or areola, & the skin itself. (‘Breast Cancer’, 2022a)

3.9 Treatments of breast cancer

For breast cancer, there are five basic therapy options. The immunohistochemical profile, stage, & general health of the patient will all be taken into consideration while determining the treatment plan.

1. Surgery: The two primary surgical procedures are mastectomy & lumpectomy. Full mastectomies are less frequent today than they were twenty years ago due to improvements in surgical methods. Reconstruction becomes more important in ensuring that patients have the highest possible quality of life as more & more individuals survive breast cancer. Using the patient's own tissue or implants, reconstruction might be immediate or delayed. To guarantee they get the best outcome, the oncoplastic surgeon will go over their alternatives with the patient.

2. Radiotherapy: Radiation is often used to eradicate any cancerous cells that may remain following surgery. Patients with breast cancer often take radiation therapy well, with minimal side effects such as mild skin reactions, lymphoedema, pain, & swelling. With professional assistance, these adverse effects may be managed, & they frequently have short durations. The long-term danger of radiation includes cardiac tissue damage, which can lead to heart issues in women years after radiotherapy treatment. To minimize cardiac damage, new methods, such holding one's breath, have been devised.

3. Chemotherapy: Chemotherapy medications are frequently administered in combination to some individuals with breast cancer. Chemotherapy is more likely to be used to treat cancers that don't respond to hormone therapy.

4. Targeted therapy: By interfering with certain chemicals on the cell surface, targeted therapies prevent the growth & spread of cancer. One of the most well-known targeted medicines, Herceptin, can be used to treat cancers that test positive for the HER2 receptor. Out of all breast cancers, only 15% are HER2 positive. Three doses of Herceptin are given annually, & potential adverse effects include diarrhea, hot flushes, tiredness, & infection. Herceptin may have certain related contraindications for patients with cardiac conditions.

5. Hormone therapy: Hormone therapy either reduces or blocks the effects of estrogen & progesterone. For the treatment to be successful, the tumor has to be ER+, or have estrogen receptors upon the cell surface. About 70% of cases of breast cancer fall into this category.

Tamoxifen & aromatase inhibitors are the two most used hormone therapies. They are usually used for a lengthy amount of period (five years or longer) in order to treat the tumor & reduce the possibility of recurrence. Menopause-like side effects include hot flashes, nausea, mood changes, tiredness, & vaginal dryness/discharge. (‘Breast Cancer: Treatment & Follow-Up’, n.d.)

Chapter 4

Drug to Combat Breast Cancer

4.1 Trastuzumab

Trastuzumab is an active anti-HER2 drug that is available as an intravenous (IV) or subcutaneous (subcutaneous) formulation. Its safety profile & effectiveness are similar to those of other anti-HER2 medications. Considering its well-established safety & effectiveness profile, trastuzumab is still the preferred choice for treating both advanced & early cases of chronic hepatitis B (CBT) when used alone or in conjunction with other therapies. (Gabriel Tinoco et al., 2013)

4.1.1 Mechanism of action:

Although trastuzumab exhibits a considerable affinity for the extracellular domain of HER2, the overall process behind the therapeutic action remains unclear. The fact that it is the result of several acts working together is well acknowledged. (Pradip De et al., 2013) (Karly P Garnock-Jones et al., 2011) (Thuy Vu & Francois X. Claret, 2012)

De et al. recently studied the process of action of trastuzumab & hypothesized that it operates directly on three levels:

• By blocking the HER2-HER3 heterodimerization that occurs when HER2 is overexpressed, which is ligand-independent. (Thuy Vu & Francois X. Claret, 2012)

• By impeding the p95HER2 fragment's growth & the HER2 extracellular domain's proteolytic cleavage (Thuy Vu & Francois X. Claret, 2012)

• HER2-positive tumours through antibody-dependent cellular cytotoxicity (ADCC), which is induced by immune effector cells' interactions with Fc receptors. (Thuy Vu & Francois X. Claret, 2012)

The activities lead to the downregulation of the phosphoribosyl 3-kinase (PI3K), protein kinase B (Akt), & MAPK (mitogen-activated protein kinase) signaling pathways. As a result, nuclear

import is enhanced, the CDK inhibitor p27 is stabilized, angiogenic factor release is reduced, & the DNA damage response is hampered. (Thuy Vu & Francois X. Claret, 2012)

These processes are therefore thought to be behind the clinical effectiveness of trastuzumab, according to various reviews. Trastuzumab's capacity to target immune cells in tumor locations that overexpress HER2 has also been documented in multiple investigations. (Pradip De et al., 2013) (Thuy Vu & Francois X. Claret, 2012) (Anna Emde et al., 2012)

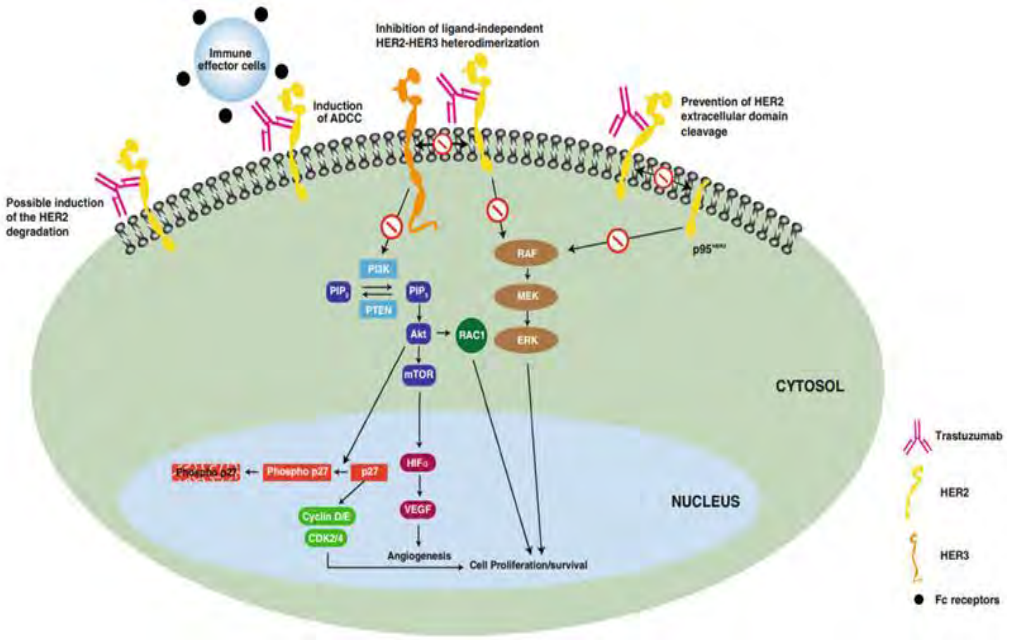

Figure 16: Mechanism of Action of Trastuzumab

Figure 16 illustrates the mechanism of action of trastuzumab. The direct & indirect effects outlined above have a dual effect: they induce cell cycle arrest & death while suppressing cell proliferation & angiogenesis. (Anna Emde et al., 2012) (Ana Catarina Pinto et al., 2013)

4.1.2 Pharmacokinetic Properties:

Numerous research on the pharmacokinetic properties of intravenous trastuzumab has been carried out, & most lately the development of the subcutaneous version has prompted a comparison of these two administration methods. ('Summary of Product Characteristics:Herceptin.', 2016) (J-R Azanza et al., 2015) (Dominique Levêque et al., 2008) Trastuzumab's pharmacokinetic characteristics are listed in Table 10 along with a comparison of its intravenous & subcutaneous routes of administration in Table 11.

Body weight-adjusted intravenous doses of trastuzumab are administered each week alternatively every three weeks (Table 10). The mean steady state concentrations for the once-weekly therapy & the three-weekly procedure are 60 mg/mL & 65.47 mg/mL, respectively, as reported by Garnock-Jones et al. (Pradip De et al., 2013). The latter group's mean highest concentration (Cmax) & mean lowest concentration (Cmin) were around 70% & 20% lower, respectively, suggesting a higher blood drug concentration fluctuation index. The average exposure across the two dosing regimens was found to be similar at any point during the trastuzumab treatment, though. (Pradip De et al., 2013)

Table 10: Pharmacokinetic Parameters (Pradip De et al.,2013) (J-R Azanza et al.,2015) (Dominique Leveque et al.,2008)

	Administration route	
	SC	**IV**
Maintenance dose	Fixed dose of 600 mg every 3 weeks	3-Weekly schedule: 6 mg/kg Weekly schedule: 2 mg/kg
Time of administration	2–5 min	Loading dose: 90 min Following doses: 30 min
Loading dose	Not required	3-Weekly schedule: 8 mg/kg Weekly schedule: 4 mg/kg
Efficacy & safety profile	N/A	Similar
Pharmacokinetic profile	N/A	Bioequivalent

Trastuzumab has a small range of distribution (Table 10; low distribution volume), & very little of the medication gets into the CSF fluid. This is in line with the brain metastases that were seen to occur in individuals who received the antibody. (Pradip De et al., 2013) (J-R Azanza et al., 2015) (Dominique Levêque et al., 2008)

There are no known trastuzumab elimination mechanisms. However, unlike with conventional medications, it does not appear that its clearance happens through excretion & hepatic metabolism but rather through an analogous process linked to the homeostatic control of endogenous immunoglobulin G. (Gabriel Tinoco et al., 2013)

Table 11. Intravenous vs Subcutaneous (J-R Azanza et al.,2015) (Dominique Leveque et al.,2008)

Pharmacokinetic Parameter	Value
Subcutaneous absorption	84%
Distribution volume	3.02 & 2.68 L
Half-life	28-38 days
Steady state	6-37 weeks
Washout period	>27 weeks
Clearance	0.241 L/day

4.2 Pertuzumab

The humanized recombinant monoclonal antibody pertuzumab targets an extracellular a dimerization domain (subdomain II) of the human form of the receptor for epidermal growth factor 2 protein (HER2). It has two heavy chains & two light chains, with 448 & 214 residues, respectively. It was first approved by the FDA in 2012 for use in conjunction with docetaxel & trastuzumab, additional HER2-targeted monoclonal antibody, for the therapy of metastatic HER2-positive breast cancer. Subsequently, its expanded indications now include the therapy of HER2-positive breast cancers with an elevated likelihood of recurrence. This covers use as an adjuvant & neoadjuvant treatment.

4.2.1 Mechanism of action of Pertuzumab

Human epidermal growth factor receptor-2 (HER2) is a tyrosine kinase receptor that is essential for cell proliferation, differentiation, & survival. When HER2 dimers with the HER2 receptor, another HER protein family member (such as HER3), or interacts with a ligand, it becomes active. This dimer then phosphorylates & activates a variety of intracellular signaling proteins, initiating signal transduction via pathways that include the Ras/mitogen-activated protein kinase route, the phosphatidylinositol 3' kinase (PI3K)/Akt path, & finally Janus kinases/signal transducer & activator transcription pathways. (Stephanie J Malenfant et al., 2014)

The prognosis for HER2-positive breast cancers is often poorer than that of HER2-negative breast cancers. Approximately 20% of breast tumors are HER2-positive, meaning they are overexpressed or gene-amplified. (Stephanie J Malenfant et al., 2014)

Pertuzumab impacts the additional dimerization domain (subdomain II) of HER2 by obstructing intracellular signalling initiated by ligands through the MAP kinase & PI3K pathways. (Product Synopsis) Characteristics:PERJETA, 2019)

When these routes are blocked, cell growth is inhibited & apoptosis begins, respectively. Additionally, pertuzumab seems to be involved in the cytotoxicity of antibody-dependent cells. (Summary of Product Characteristics: PERJETA, 2019) ('Pertuzumab', 2022)

4.2.2 Pharmacokinetics

In Arms B, C, & D, the mean observed serum Ctrough for pertuzumab Cycle 2 was 70 g/mL, with 98% (130 of 133) of the participants achieving the PK objective serum Ctrough of > 20 g/mL, a PK target first set based on non-clinical data. The projected mean Ctrough for each individual model at Cycle 2 was 60 g/mL, & 97% of the patients (130 out of 134) achieved a predicted Ctrough serum levels greater than 20 g/mL. The PK results in NeoSphere participants are similar to PK data previously seen among people with different metastatic solid tumors, according to the VPC & NPC's evaluation of the covariate-adjusted population PK model simulations versus the observed pertuzumab serum concentrations in NeoSphere. The pharmacokinetic properties of pertuzumab differ between patients based on their treatment groups, as demonstrated by Online Resource 1. NeoSphere patients must be taken into account when comparing the PK since they differed considerably from the population used to develop the pertuzumab population PK model in terms of median LBW (44.6 vs. 49.2 kg) & mean blood albumin (4.4 vs. 3.9 g/dL). The VPC results are presented in Figure 16, where for each treatment arm, the measured pertuzumab data (circles) in NeoSphere fall within the simulated pertuzumab values for the historical population (thin lines). All things considered, NPC asserts that the observed NeoSphere PK percentiles match the model's projected historical data per-

centiles (95.7, 79.1, 39.9, 14.3, 5.0% for the 95, 75, 50, 25, 5th projected percentile).One reason for the small NPC divergence is the moderate 0 20 40 60 80 0 100 200 300 400 500 B. 0 100 200 300 400 500 C; 0 20 40 60 80 0 100 200 300 400 500 D; 0 20 40 60 80 Pertuzumab concentration during the day (g/mL) Figure 16 shows the pertuzumab serum concentrations by treatment group in comparison to those obtained from simulation. The dashed lines represent the 97.5th & 2.5th percentiles based on population PK model simulations, as well as the observed distributions of lean body mass & albumin in NeoSphere. The solid lines show projections using the public's PK model for an individual whose lean body weight & albumin medians are for each treatment group. For NeoSphere patients, the empty circles match the Ctrough serum concentrations. Restrictions may apply. Content provided courtesy of Springer Nature. Rights reserved. 2017; 79:353–361;357–1-3 sample size for chemotherapy pharmaceuticals for cancer. The robust connection between an individual's projected & observed serum C trough concentrations supports the adoption of the model-predicted C trough for DDI & ER assessment. The PK DDIs between pertuzumab & trastuzumab as well as the effect of docetaxel on pertuzumab were assessed by comparing model-predicted Ctrough serum concentrations at Cycles 2 & 4 as properly as specific model-predicted pertuzumab PK variables for NeoSphere recipients across the various treatment groups. An ANOVA at either Cycle 2 ($p = 0.232$) or Cycle 4 ($p = 0.039$) confirmed the consistency of the model-predicted Ctrough values across treatment groups, as shown in Figure 16. The same study yielded consistent results when assessed Ctrough concentrations (Cycle 2, $p = 0.458$; Cycle 4, $p = 0.033$), according to Online Source 2. As seen in Fig. 16, the model's predictions for certain pertuzumab PK characteristics did not seem to vary based on whether the patient got trastuzumab. An analysis of variance using ANOVA revealed that the pertuzumab C_L & Vc values were similar for patients getting trastuzumab or not ($p = 0.264$ for CL & $p = 0.956$ for Vc, comparing Arms B & D) & docetaxel or not ($p = 0.016$ for CL & $p = 0.823$ for Vc, contrasting Arms B & C). Transtuzumab on pertuzumab PK or trastuzumab on pertuzumab PK was not shown to have a DDI effect by docetaxel overall, according to the research.

Chapter 5

Challenges

For those suffering from HER2+ breast cancer, trastuzumab combined with chemotherapy has come to be considered standard treatment. Trastuzumab access, however, may be constrained by the expense of treatment in regions with insufficient funding for treatment reimbursement. Through a physician survey, this study assessed the availability of trastuzumab & highlighted potential obstacles to its usage in the Mexico, United States, Russia, Turkey, & Brazil. The study also looked into whether easier access to & greater usage of HER2 monoclonal antibody therapy might result from the development of a biosimilar to trastuzumab. A subgroup of oncologists from all nations mentioned obstacles to using trastuzumab as a neoadjuvant, adjuvant, or metastatic treatment. Trastuzumab usage was frequently hampered by problems with insurance coverage, medication supply, & patient expense. Oncologists responded that if a less expensive biosimilar to trastuzumab was available, they would employ HER2 monoclonal antibody treatment more frequently in all therapeutic situations. Almost fifty percent of oncologists agreed. We draw the conclusion that the availability of a trastuzumab biosimilar might reduce financial obstacles to care & broaden patients access to HER2-directed treatment across all the nations we have looked at. (Philip Lammers et al., 2014)

The best way to use chemotherapy or additional HER2-targeted medications in conjunction with pertuzumab, the order of treatment of pertuzumab-based treatments with other HER2-targeted methods (see Figure 17), & the right length of pertuzumab therapy, particularly in the neoadjuvant setting, are all challenges that must be overcome. Research on these unanswered concerns is now being conducted using both FDA-approved medications (such as T-DM1 &

lapatinib) & more recent small-molecule inhibitors of tyrosine kinase (such as afatinib, neratinib, & everolimus). When choosing the best regimens for certain patients, taking the adverse effect profiles of medication combinations into account may prove useful. (Ciara C. O'Sullivan & Roisin M. Connolly, 2014)

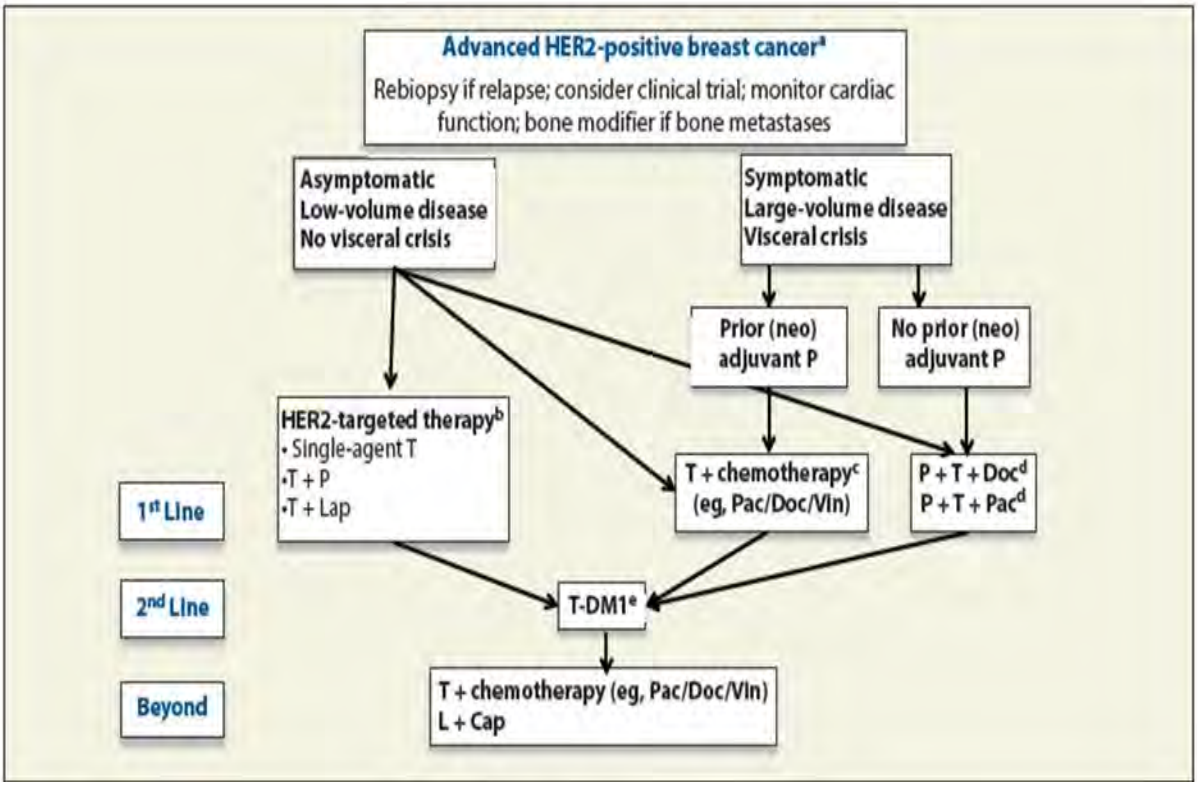

Figure 17. Proposed Treatment Sequence for HER2-Positive Advanced Breast Cancer

Al = aromatase inhibitor; Cap = capecitabine; Doc = docetaxel DM1 = emtansine: ECOG = Eastern Cooperative Oncology Group; HR = hormone receptor; Lap = lapatinib; P = pertuzumab; Pac = paclitaxel; T = trastuzumab; Vin = vinorelbine.

a Consider ECOS performance status & comorbidities' when making treatment decisions.

b Consider endocrine therapy combinations if HR-positive (Al + T, letrozole + Lap).

c Combination chemotherapy may be considered if visceral crisis.

d if no prior P; after 6 cycles, consider maintenance P + T until progression.

e If trastuzumab-exposed

Chapter 6

Conclusion

One of the top three malignancies globally by prevalence is breast cancer. It is thought that early breast cancer may be treatable. Both locoregional & systemic therapy have advanced significantly in recent years with a decrease in therapeutic intensity; a primary emphasis now is on avoiding both overtreatment & undertreatment. Therapy approaches must be chosen in a multidisciplinary environment with a curative objective, considering the tumor's molecular subtype & locoregional burden. Primary conventional surgery is no longer the best option for all patients. Neoadjuvant treatment has gained popularity in early breast cancer that is triple-negative & HER2-positive. Endocrine treatment, anti-HER2 targeting, & chemotherapy are the mainstays of therapeutic approaches based on the clinical tumor subtype. The goals of treatment for individuals with advanced breast cancer are aimed at prolong survival & maintain quality of life. Thanks to advancements in endocrine drugs & combinations, HER2 targeting, & the promise of new targeted therapies, long-term therapy for metastatic breast cancer is starting to seem more feasible.

6.1 Future direction

In the case of metastatic illness, chemotherapy treatment is typically used up until the disease progresses, after which another medication is added. Trastuzumab clinical trials used a similar strategy. Trastuzumab is a molecularly focused medicine, thus there could be more efficient methods to use it in therapeutic settings. As will be discussed below, there is evidence from anecdotal clinical & preclinical data that trastuzumab may benefit beyond the course of the illness; nevertheless, it has been challenging to confirm this notion in randomized trials conducted within the United States (US). Even yet, many patients in clinical practice receive

trastuzumab even in the absence of any symptoms of the illness. Furthermore, for HER2-positive illnesses progressing on first-line trastuzumab-based regimens, the latest National Comprehensive Cancer Network (NCCN) Practise Rules recommend main-training HER2 blockade. This can be achieved by using either a trastuzumab-based regimen, lapatinib alongside capecitabine, or trastuzumab + lapatinib. (M. Pegram & J. Liao, 2012)

Pertuzumab is now undergoing clinical studies to treat breast cancer. In many trials, pertuzumab was coupled with a monoclonal antibody targeting PD-L1, which prolonged PFS for patients with advanced triple negative breast cancer. (Peter Schmid et al., 2018) Connolly et al. showed that early changes in tumour maximum standardised uptake amounts modified for the quantity for lean body mass measured on (18F) fluorodeoxyglucose positron emission tomography/computed tomography anticipated response in patients with breast cancer who had oestrogen receptor-negative, HER2-positive disease & received four cycles of pertuzumab & trastuzumab therapy. (Roisin M. Connolly et al., 2019) The outcomes of these clinical studies will provide more practical applications & efficient methods for choosing patients for regimens that include pertuzumab. (Kei Ishii et al., 2019)

References

1. AKOR UGWU. (2020). Breast Cancer Classification Using Machine Learning. An Empirical Study. https://www.grin.com/document/1012996

2. Ana Catarina Pinto, Felipe Ades, Evandro de Azambuja, & Martine Piccart-Gebhart. (2013). Trastuzumab for patients with HER2 positive breast cancer: Delivery, duration and combination therapies. National Library of Medicine, 22. https://doi.org/10.1016/j.breast.2013.07.029

3. Anna Emde, Wolfgang J Köstler, & Yosef Yarden. (2012). Therapeutic strategies and mechanisms of tumorigenesis of HER2-overexpressing breast cancer. National Library of Medicine, 84, 49–57. https://doi.org/10.1016/j.critrevonc.2010.09.002

4. Bhupender S. Chhikara & Keykavous Parang. (2022). Global Cancer Statistics 2022: The trends projection analysis. 10(1), 451.

5. Breast. (2020, December). The Global Cancer Observatory. https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf

6. Breast Cancer. (2022a, January). Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/3986-breast-cancer

7. Breast cancer. (2022b, December 14). Mayo Clicnic. https://www.mayoclinic.org/diseases-conditions/breast-cancer/symptoms-causes/syc-20352470

8. Breast cancer statistics. (2022, March 23). World Cancer Research Fund International. https://www.wcrf.org/cancer-trends/breast-cancer-statistics/

9. Breast cancer: Treatment and follow-up. (n.d.). The Royal Marsden. https://www.royalmarsden.nhs.uk/information-gps/gp-resources/breast-cancer/breast-cancer-treatment-and-follow

10. Cancer. (2022a, August 11). Cleveland Clinic.

11. Cancer. (2022b, December 7). [Medical Education and Research]. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588

12. Cancer statistics at a glance. (2022). Canadian Cancer Society. https://cancer.ca/en/research/cancer-statistics/cancer-statistics-at-a-glance

13. Ciara C. O'Sullivan & Roisin M. Connolly. (2014). Pertuzumab and Its Accelerated Approval: Evolving Treatment Paradigms and New Challenges in the Management of HER2-Positive Breast Cancer. Cancer Network, 28(3). https://www.cancernetwork.com/view/pertuzumab-and-its-accelerated-approval-evolving-treatment-paradigms-and-new-challenges-management

14. Dominique Levêque, Luc Gigou, Jean Pierre Bergerat, & Jean Pierre Bergerat. (2008). Clinical pharmacology of trastuzumab. National Library of Medicine, 3(1), 51–55. https://doi.org/10.2174/157488408783329931

15. Dr. Sunil Lakhani. (n.d.). Stages & Types of Breast Cancer. National Breast Cancer Foundation. https://nbcf.org.au/about-breast-cancer/diagnosis/stages-of-breast-cancer/

16. Gabriel Tinoco, Sean Warsch, Stefan Glück, Kiran Avancha, & Alberto J. Montero. (2013). Treating breast cancer in the 21st century: Emerging biological therapies. National Library of Medicine, 4(2), 117–132. https://doi.org/10.7150/jca.4925

17. GLOBOCAN 2020: New Global Cancer Data. (2020, December 17). Union for International Cancer Control. https://www.uicc.org/news/globocan-2020-new-global-cancer-data

18. Hyuna Sung, Jacques Ferlay, Rebecca L. Siegel, Mathieu Laversanne, Isabelle Soerjomataram, Ahmedin Jemal, & Freddie Bray. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. 71(3), 209–249. https://doi.org/10.3322/caac.21660

19. J-R Azanza, B Sádaba, & A Gómez-Guiu. (2015). Monoclonal antibodies: Pharmacokinetics as a basis for new dosage regimens? National Library of Medicine, 21(5), 370–376. https://doi.org/10.1177/1078155214538085

20. Karly P Garnock-Jones, Gillian M Keating, & Lesley J Scott. (2011). Trastuzumab: A review of its use as adjuvant treatment in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. National Library of Medicine, 71(12). https://doi.org/10.2165/11203700-000000000-00000

21. Kei Ishii, Nao Morii, & Hiroyasu Yamashiro. (2019). Pertuzumab in the treatment of HER2-positive breast cancer: An evidence-based review of its safety, efficacy, and place in therapy. National Library of Medicine, 2019(14), 51–70. https://doi.org/10.2147/CE.S217848

22. M. Pegram & J. Liao. (2012). Trastuzumab Treatment in Multiple Lines: Current Data and Future Directions. Clinical Breast Cancer, 12(1), 10–18. https://doi.org/10.1016/j.clbc.2011.07.003

23. Melina Arnold, Eileen Morgan, Harriet Rumgay, Allini Mafra, Deependra Singh, Mathieu Laversanne, Jerome Vignat, Julie R. Gralow, Fatima Cardoso, Sabine Siesling, & Isabelle Soerjomataram. (2022). Current and future burden of breast cancer: Global statistics for 2020 and 2040. Elsevier, 66, 15–23. https://doi.org/10.1016/j.breast.2022.08.010

24. Pertuzumab. (2022). DrugBank Online. https://go.drugbank.com/drugs/DB06366

25. Peter Schmid, Sylvia Adams, Hope S. Rugo, Andreas Schneeweiss, Carlos H. Barrios, Hiroji Iwata, Véronique Diéras, Roberto Hegg, Seock-Ah Im, Gail Shaw Wright, Volkmar Henschel, Luciana Molinero, Stephen Y. Chui, Roel Funke, Amreen Husain, Eric P. Winer, Sherene Loi, & Leisha A. Emens. (2018). Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. The New England Journal of Medicine, 379(22). https://doi.org/10.1056/NEJMoa1809615

26. Philip Lammers, Carmen Criscitiello, Giuseppe Curigliano, & Ira Jacobs. (2014). Barriers to the Use of Trastuzumab for HER2+ Breast Cancer and the Potential Impact of Biosimilars: A Physician Survey in the United States and Emerging Markets. National Library of Medicine, 7(9), 943–953. https://doi.org/10.3390/ph7090943

27. Pradip De, Max Hasmann, & Brian Leyland-Jones. (2013). Molecular determinants of trastuzumab efficacy: What is their clinical relevance? National Library of Medicine, 38(8), 925–934. https://doi.org/10.1016/j.ctrv.2013.02.006

28. Ritu Lakhtakia. (2014). A Brief History of Breast Cancer. 14(2), 166–169.

29. Roisin M. Connolly, Jeffrey P. Leal, Lilja Solnes, Chiung-Yu Huang, Ashley Carpenter, Katy Gaffney, Vandana Abramson, Lisa A. Carey, Minetta C. Liu, Mothaffar Rimawi, Jennifer Specht, Anna Maria Storniolo, Vicente Valero, Christos Vaklavas, Ian E. Krop, Eric P. Winer, Melissa Camp, Robert S. Miller, Antonio C. Wolff, … Vered Stearns. (2019). TBCRC026: Phase II Trial Correlating Standardized Uptake Value With Pathologic Complete Response to Pertuzumab and Trastuzumab in Breast Cancer. Journal of Clinical Oncology, 37(9), 714–722. https://doi.org/10.1200/JCO.2018.78.7986

30. Statistics fact sheet. (2022, October). Macmillan Cancer Support. https://www.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/9468-10061/2022-cancer-statistics-factsheet

31. Stephanie J Malenfant, Karen R Eckmann, & Chad M Barnett. (2014). Pertuzumab: A new targeted therapy for HER2-positive metastatic breast cancer. National Library of Medicine, 34(1), 60–71. https://doi.org/10.1002/phar.1338

32. Steven Dowshen. (2017, November). Breast Cancer. Nemours Children's Health. https://kidshealth.org/en/kids/breast-cancer.html

33. Summary of product characteristics:Herceptin. (2016). European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000278/WC500074922.pdf. Accessed 9 Feb 2016

34. Summary of product characteristics:PERJETA. (2019). https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf

35. Teresa Hagan Thomas, Rachel Nall, & Hana Ames. (2022, June 30). What signs of breast cancer are there other than a lump? Medical News Today. https://www.medicalnewstoday.com/articles/322832

36. Thuy Vu & Francois X. Claret. (2012). Trastuzumab: Updated Mechanisms of Action and Resistance in Breast Cancer. National Library of Medicine, 2, 62. https://doi.org/10.3389/fonc.2012.00062

37. Types of cancer. (2020). Cancer Research UK. https://www.cancerresearchuk.org/what-is-cancer/how-cancer-starts/types-of-cancer

38. Understanding Cancer. (2007). National Libary of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK20362/

39. Understanding What Cancer Is: Ancient Times to Present. (2018, January 4). American Cancer Society. https://www.cancer.org/cancer/understanding-cancer/history-of-cancer/what-is-cancer.html

40. What Is Breast Cancer? (2023, July 25). Centers for Disease Control and Prevention. https://www.cdc.gov/cancer/breast/basic_info/what-is-breast-cancer.htm#:~:text=Breast%20cancer%20is%20a%20disease,the%20breast%20turn%20into%20cancer.

41. What is cancer? (n.d.). Cancer Council. https://www.cancer.org.au/cancer-information/what-is-cancer

42. Worldwide cancer data. (2022, March 23). World Cancer Research Fund International. https://www.wcrf.org/cancer-trends/worldwide-cancer-data/#:~:text=Find%20information%20about%20world%20cancer,and%208.8%20million%20in%20women.

43. Zia Sherrell. (2021, July 29). What to know about cancer survival, incidence, and death rates. Medical News Today. https://www.medicalnewstoday.com/articles/cancer-rates-by-country