Precision Medicines and Its Targeted activity in multiple types of Breast Cancer

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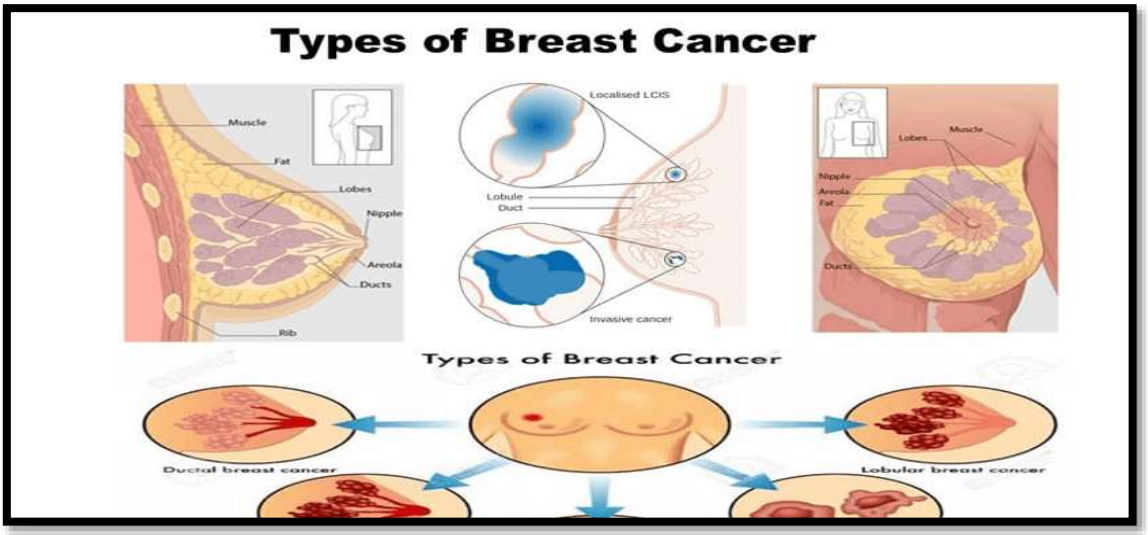
***Abstract*: Precision medicine is a medicine advance to the genotypic and phenotypic feature of an individual. It has host of destination including gene and their transcript protein and metabolite. Precision medicine and targeted therapies have long record in treatment of breast cancer. Breast cancer is the most common cancer among women is a highly complex, heterogeneous and multifactorial disease. It is cancer that start in breast when cells begin to grow out of control. Breast cancer have demonstrated prediction and support advantage thanks to the discovery of targeted therapies the advent of these new approaches marked the rise of precision medicine, which lead to improve the diagnosis, prediction and treatment of cancer. This article describes the important of precision medicine and targeted therapies in breast cancer.**

***Keywords*: Breast Cancer, Precision Medicine, Triple-Negative Breast Cancer, BRC A1, BRC A2, HER2 targeted medicine, Pertuzumab, Trastuzumab-DM1, Neratinib, Trastuzumab**

I. INTRODUCTION

Breast cancer is that most common malignancy poignant ladies with over 230,000 new cases diagnosed annually within the USA alone, poignant one in eight ladies [1]. Breast cancer is uncontrolled growth of cell. There are many types of breast cancer such as [1].

- Ductal carcinoma in situ (DCIS)
- Invasive breast cancer (ILC or IDC)
- Triple-negative breast cancer
- Inflammatory breast cancer
- Paget disease of the breast
- Angiosarcoma
- Phyllodes cancer



"Figure 1. Type of Breast cancer"

There are different ways trusted Source to stage breast cancer. One includes stages 0–4 with subcategories at each stage. Below, we describe each of these main stages. Sub-stages can indicate specific characteristics of a tumor, such as its HER2 receptor status.

Stage 0: This is also called ductal carcinoma in situ. The cancerous cells are only within the ducts and have not spread to surrounding tissues.

Stage 1: At this stage, the tumor measures up to 2 centimeters (cm) across. It has not affected any lymph nodes, or there are small groups of cancer cells in lymph nodes.

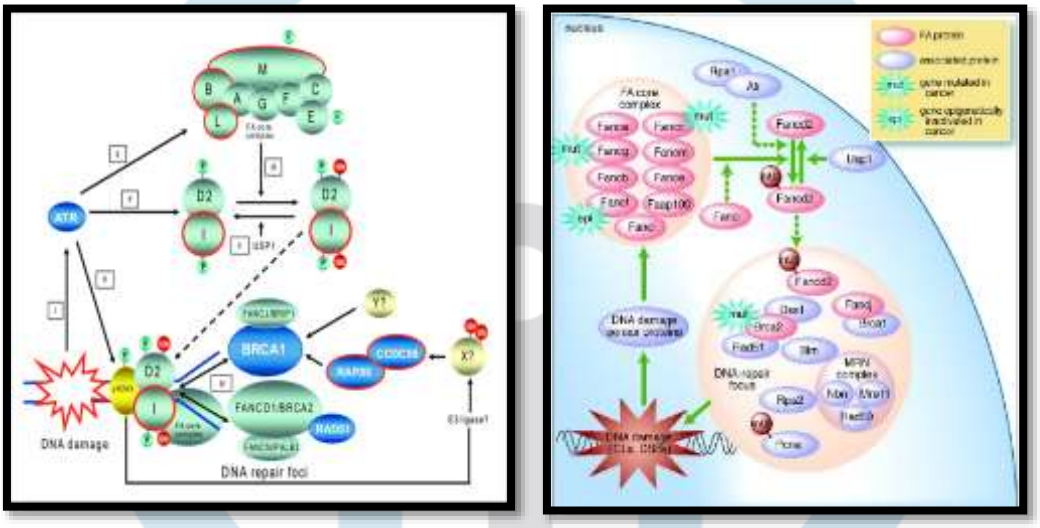
Stage 2: The tumor is 2 cm across and has started to spread to nearby nodes, or it is 2–5 cm across and has not spread to the lymph nodes.

Stage 3: The tumor is up to 5 cm across and has spread to several lymph nodes, or the tumor is larger than 5 cm and has spread to a few lymph nodes.

Stage 4: The cancer has spread to distant organs, most often the bones, liver, brain, or lungs.

II. TWO GENES ARE MAINLY RESPONSIBLE FOR BREAST CANCER (BRCA1 & BRCA2)

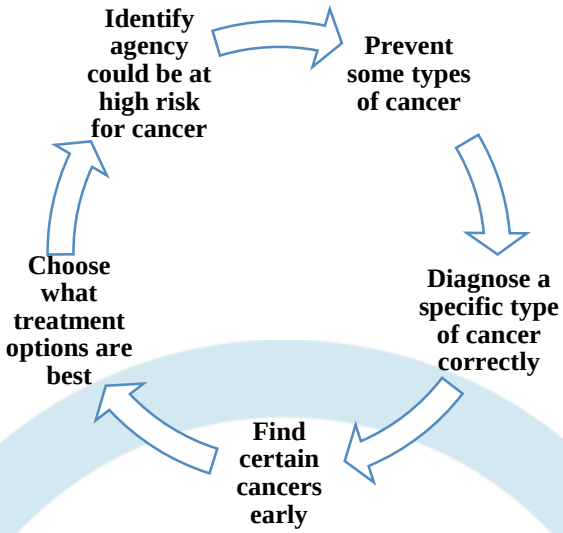
BRCA1 (Breast Cancer gene 1) and BRCA2 (Breast Cancer gene 2) are genes that produce protein that help repair damaged DNA. Everyone has two copies of each of these genes one copy inherited from each parent. BRCA1 and BRCA2 are sometimes called tumor suppressor gene because when they have certain changes, called harmful (or pathogenic) variants (or mutation), cancer can develop. About 5% to 10% of breast cancer cases are thought to be hereditary**.** One of the key challenges in carcinoma treatment stems from the fact that it is a heterogeneous sickness comprising at least 5 subtypes [2]. It's become evident that 20–25% of breast cancers are classified as human epidemic protein receptor 2 (HER2)-positive, that denotes associate aggressive composition leading to disease-free and overall survival compared with alternative carcinoma subtypes [2,3]. The term is outlined by the National Institutes of Health as "a rising approach for sickness treatment and that takes under consideration individual variability in genes, environment, and lifestyle for every person [6]. Precision drug aims to supply data- driven treatments



"Figure 2. BRC A1 & BRC A2 Mechanism of action"

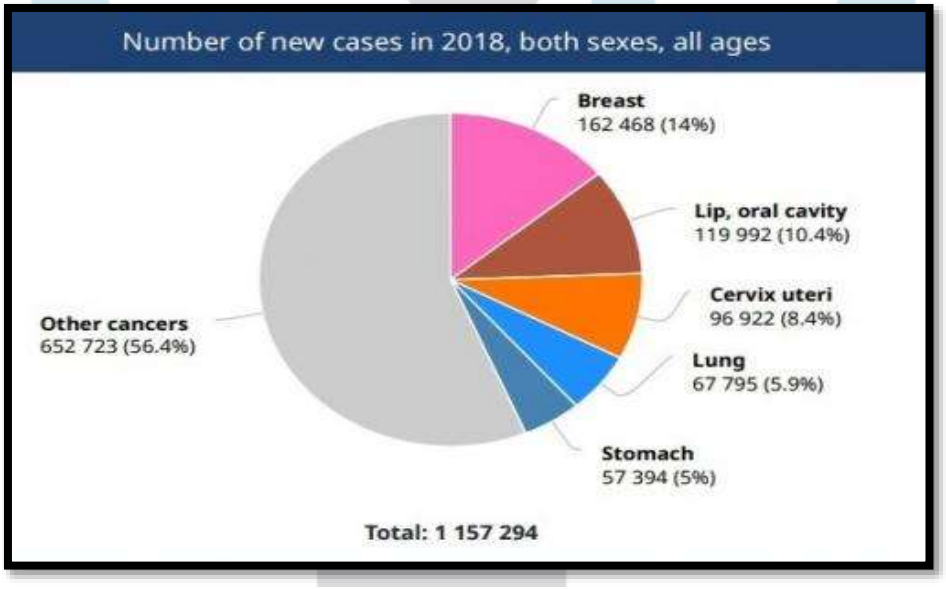
suited to the genetic, setting, associated lifestyle factors known to contribute to the individuality of an individual's body [6,7]. To date, precision medication has chiefly been in forced in oncology [8], via tumor-specific medication in, breast [9,10], brain cancer [11,12] the launch of the Precision Medicine Initiative in the U.S and initiatives worldwide [13,14,15] it is expected that this approach can a pace expand into several areas of health care and refine patient care. Breast cancer is that most often diagnosed cancer and 1 in every of the key causes of mortality in females worldwide. Breast cancer is additionally one in every of the four most investigated diseases and its management has progressed a pace into the molecular era. The present therapies have incorporated clinical, pathological and molecular understanding to boost outcomes, leading in a decrease in mortality. Precision drug may be strategy for sickness treatment and bar that considers individual variability in genes, environment, and lifestyle. Tradionally, breast cancer has been treated in keeping with biomarkers like as estrogen receptor and HER2 status. Precision medicine is being used for certain cancers to help know what tests and treatment are best.

Doctors may use precision medication to assist them by following mentioned method:



III.BACKGROUND

The National Analysis Council discharge an agreement study report in 2011 entitled "Toward Precision Medication [1] Breast cancer, the foremost common cancer among girl worldwide, could be an extremely advanced heterogeneous and complex sickness. variety of recognized risk factors contribute to develop carcinoma , together with internal secretion copy age, obesity, alcohol, radiation, benign breast sickness and lack of exercise [4]. Precision medication includes 2 different approaches, namely, stratified and personalized medication. The primary consists of testing a drug during a cohort of patients outlined by a particular molecular alteration, whereas the personalized medication determines whether the idea of individualized treatment improves outcomes in all together population [5].



"Figure 3. Background showing no of cancer affected people"

Precision drug encompasses an awfully broad spectrum of clinical and basic science disciplines. True personalization of treatment will account for the individual patient's genetics science and predispositions, the composition of their breast tissue, the omics profile of their cancer and sequent biological propensities, tissue micro-environment, lifestyle, affected person preference, and great of life. Precision drug enters the scene even before the cancer conclusion, within the arenas of prevention. After investigation, precision medication needs an elemental shift within the historic approaches to clinical trial style, as ever smaller bins of molecularly staged patients receiving novel targeted agents won't offer the statistical power to find significance for outcome endpoints like native management or overall survival beneath historic definitions.

IV. TARGETED DRUG THERAPIES FOR BREAST CANCER

1.Pertuzumab

Preclinical data showing increase antitumor activity for the combination of pertuzumab plus trastuzumab [16] have led investigators to focus on future clinical studies of pertuzumab in combination with trastuzumab. In a phase 2 trial evaluate the mixture of pertuzumab and trastuzumab, a 24.2% RR and a 50% clinical gain rate in 66 patients with HER2-positive MBC that advancement after trastuzumab-based therapy was reported. Pertuzumab has been approved by the US Food and Drug Administration in the first-line treatment of HER2-positive MBC [17]. In a phase II unarranged study of neo adjuvant setting, this dual-targeted drug

combination plus docetaxel resulted in a statistically significant increase in PCR as compared with trastuzumab or pertuzumab plus docetaxel (45.8 vs. 29.0 or 24.0%), and a PCR rate of 16.8% in patients with targeted therapy only (no chemotherapy) [18] Recent findings suggest the addition of pertuzumab to trastuzumab in HER2-positive breast cancer is a therapeutic option in the neo adjuvant setting [19]. A just now published clinical study also authenticated that the combination of pertuzumab plus trastuzumab plus docetaxel did not increase cardiac toxic effects [20]. In general, the combination of pertuzumab and trastuzumab was well permitted. However, the data on cardiac safety with pertuzumab should be clarification with caution as the trials were conducted in carefully selected patients.

Mechanism of action:

Pertuzumab is a humanized monoclonal antibody that binds to the extracellular domain II of HER2. Its mechanism of action is complementary to trastuzumab, inhibiting ligand-dependent HER2–HER3 dimerization and reducing signaling via intracellular pathways such as phosphatidylinositol 3-kinase (PI3K/Akt).Refer fig no. 4

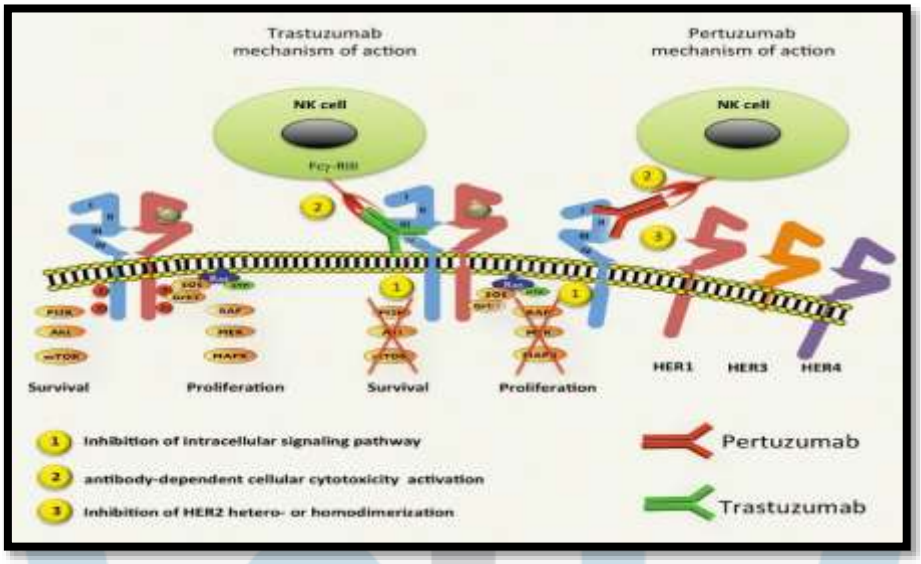


Figure 4. Pertuzumab MOA

2. Trastuzumab-DM1

The Food and Drug Administration (FDA) has expanded the accredited use of the drug ado-trastuzumab emtansine (Kadcyla) to treat some women with HER2-positive breast cancer.T-DM1, was initially accredited by FDA more than 6 years ago to treat women with metastatic HER2-positive breast cancer. In a phase II study of 110 patients with heavily pretreated HER2-positive MBC, trastuzumab-DM1 demonstrated that single-agent activity capitulate a RR of 41.3% and PFS of 7.3 months in patients with HER2-positive MBC who had previously received the two HER2-directed therapies and many chemotherapeutic agents [21].A unsystematic phase II trial of trastuzumab-DM1 vs. trastuzumab/docetaxel in 1st line, HER2-positive MBC demonstrated significant improve in RR (47.8 vs. 41.4%) and PFS (14.2 vs. 9.2 months) with trastuzumab-DM1 contrast with the control arm, respectively [22,23].Toxicities of trastuzumab-DM1 were mild and amendable, and included thrombocytopenia, elevated transaminases, nausea, and anemia [24]. No dose-limiting cardiotoxicity was observed [21].

Mechanism of action:

T-DM1 has multiple mechanisms of action, from the selective delivery of DM1 to HER2-positive tumor cells through to trastuzumab-mediated inhibition of HER2 signaling, inhibition of HER2 extracellular domain shedding and induction of antibody-dependent cell-mediated cytotoxicity [49]. Refer fig no.5

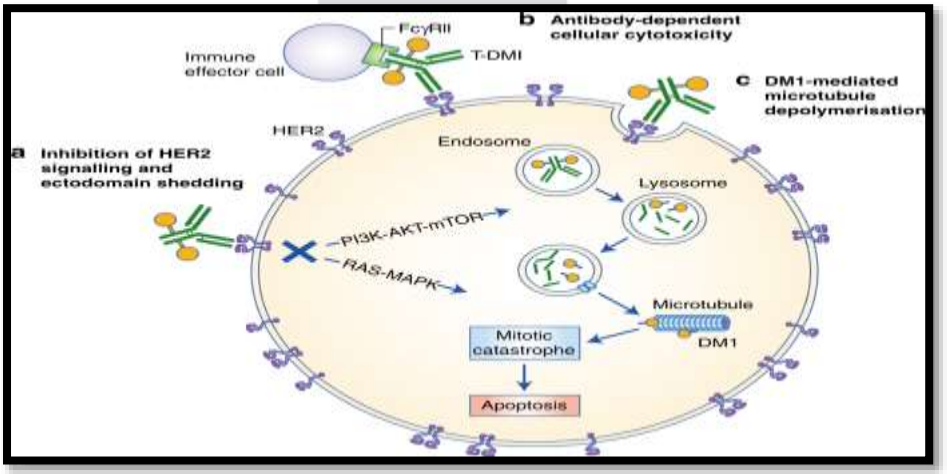


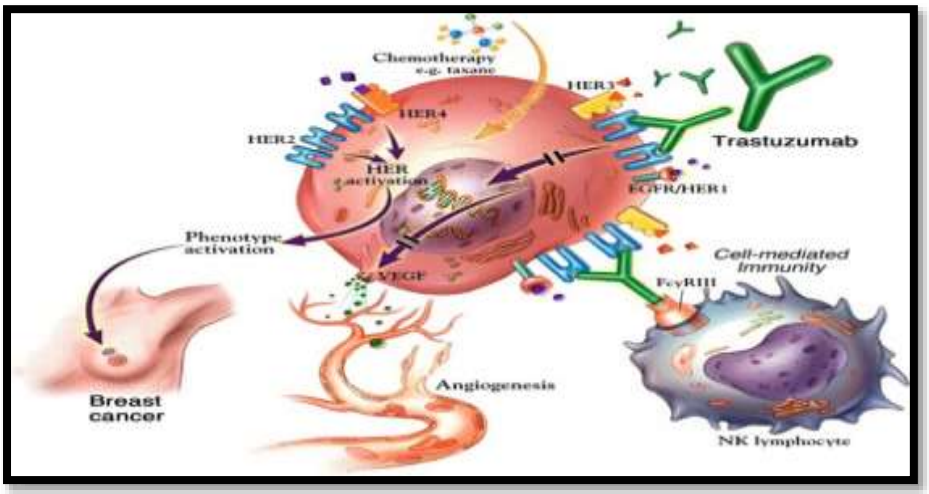
Figure 5. Trastuzumab-DM1 MOA

3. Trastuzumab

Herceptin was the first name for trastuzumab, however many similar versions (called biosimilar) square measure currently on the market furthermore, as well as Ogivri, Herzuma, Ontruzant, Trazimera, and Kanjinti. Another style of trastuzumab, known as trastuzumab and spreading factor injection (Herceptin Hylecta), is additionally on the market. it's given as a body covering (under the skin) shot over a number of minutes Trastuzumab (Herceptin^{TM}, Genetech/Roche, South San Francisco, CA) is the first approved anti-HER-2 targeted agent to show a highly promising response rate in the treatment of HER-2 positive metastatic breast cancer patients [25], as well as in combination with or after standard adjuvant chemotherapy of HER-2 positive breast cancer patients [26].The 1 st available HER2-targeted therapy, is a humanized murine IgG monoclonal antibody that binds to the HER2 extracellular domain. Its antitumor activity has not been completely ascertained, however, it is thought to result from a combination of antibody-dependent cell-mediated cytotoxicity, inhibition of cleavage of the extracellular domain of the HER2 [27] , reduced intracellular signal transduction and anti-angiogenic effects [28,29].Adding trastuzumab to chemotherapy in the 1st-line treatment of HER2-positive metastatic breast cancer (MBC) was based on the pivotal phase III trial in which 469 women with HER2-positive MBC were randomized to receive standard chemotherapy (paclitaxel or anthracycline/cyclophosphamide) with or without trastuzumab. The combination improved response rates (RRs; 50 vs. 32%), extended time to progression (TTP; 7.4 vs. 4.6 months) and median overall survival (OS; 25 vs. 20 months) [30] .Subsequently, results of two randomized trials demonstrated the profit of adding trastuzumab to chemotherapy in the treatment of HER2-positive MBC, as well as significant improvements in TTP and OS [31,32] Besides paclitaxel and docetaxel, other combination regimens of trastuzumab with chemotherapy drugs such as vinorelbine, capecitabine, platinum salts and gemcitabine, have also shown clinical benefit in patients with HER2-positive MBC [33,34,35,36,37]. Single agent trastuzumab has also been evaluated, however, it yielded lower RRs compared with the combination of chemotherapy and trastuzumab [38]. Thus, it appears applicable to inflict trastuzumab monotherapy for senior or frail patients whose performance standing permits administration of trastuzumab however not therapy. On the premise of obtainable knowledge on the employment of trastuzumab within the adjuvant setting, cardiotoxicity appears to be treatable and principally reversible and also the risk of severe internal organ pathology ranges from zero.6 to 3.9% [39].Marked improvement has been observed in patients with HER2-positive breast cancer since the widespread use of trastuzumab; however, approximately 10% of patients develop a distant recurrence following adjuvant trastuzumab-based chemotherapy and all patients with MBC eventually develop disease progression [40]. Furthermore, the chance of cardiotoxicity presently precludes sure patients from trastuzumab treatment, limiting the selection of agents which will be used at the same time with trastuzumab. Therefore, the event of novel targeted agents to be used in HER2-positive carcinoma remains clinically vital. In a massive clinical test, it absolutely was rumored that trastuzumab is mostly well tolerated despite.

Mechanism of action:

Cancer cells grow in associate degree uncontrolled fashion. Herceptin works on the surface of the somatic cell by interference the chemical signals which can trigger this uncontrolled growth. Genes are like instruction manuals that tell every cell of your body the way to grow, what quite cell to become, and the way to behave. Genes try this by ordering the cell to form special proteins that cause an exact activity — like cell growth, rest, or repair. Some cancer cells have abnormalities in genes that tell the cell what quantity and the way quick to grow. generally, the cancer cells have too several copies of those genes with abnormalities. once there are too several copies of those genes, doctors visit it as "overexpression." With some styles of factor overexpression, cancer cells can create too several of the proteins that management cell growth and division, inflicting the cancer to grow and unfold. Some carcinoma cells create too several copies of (overexpress) a selected factor referred to as HER2. The HER2 factor makes a super molecule referred to as a HER2 receptor. HER2 receptors are like ears, or antennae, on the surface of all cells. These HER2 receptors collect signals that trigger the cell to grow and increase. however, will cells with too several HER2 receptors can devour too several growth signals. This causes them to start out growing and multiplying an excessive amount of and too quick. carcinoma cells that overexpress the HER2 factor are aforementioned to be HER2-positive. Herceptin works by attaching itself to the HER2 receptors on the surface of carcinoma cells and interference them from receiving growth signals. By interference the signals, Herceptin will slow or stop the expansion of the carcinoma. Herceptin is associate degree example of associate degree immune targeted medical care. additionally, to interference HER2 receptors, Herceptin may also facilitate fight carcinoma by alerting the system to destroy cancer cells onto that it's connected. Refer fig. no 6



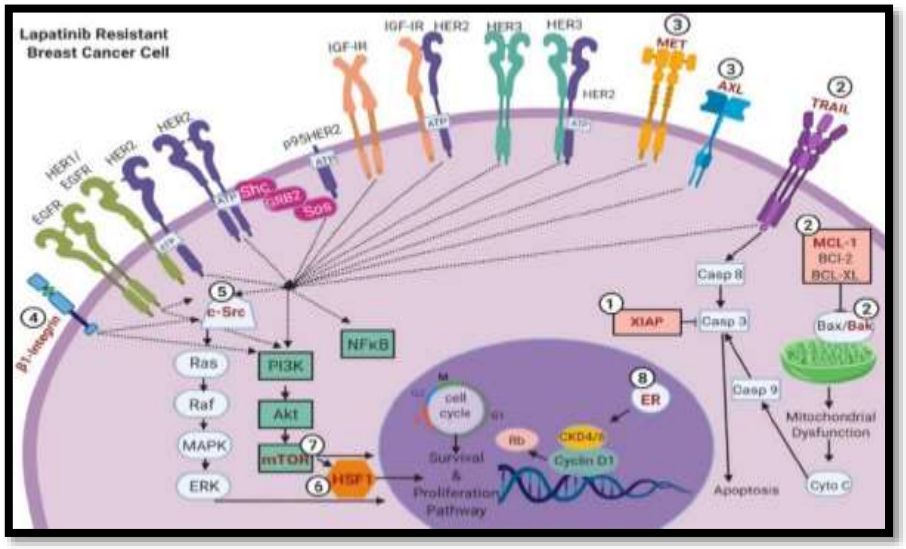
"Figure 6. Trastuzumab MOA"

4. Tyrosine kinase inhibitor: Lapatinib

Lapatinib could be a twin tyrosine kinase inhibitor matter that binds to the intracellular ATP-binding pocket of the macromolecule enzyme domain of HER2. By binding, lapatinib prevents auto phosphorylation of the protoplasm domain and thereby downstream communication and growth cell growth [41,42,43]. Lapatinib was approved together with capecitabine for the treatment of advanced or pathological process HER2-positive carcinoma supported the polar phase III trial within which 324 patients pretreated with associate degree anthracycline, taxane and trastuzumab were randomised to receive capecitabine and lapatinib or capecitabine alone. This trial showed that the addition of lapatinib to capecitabine considerably redoubled TTP (8.4 vs. 4.4 months) vs. capecitabine alone [44] The general analysis of lapatinib incontestable that it's well tolerated with manageable harmful effects [45]. Cancer cells grow in associate degree uncontrolled fashion. TYKERB works within the neoplastic cell by busy with sure proteins, known as kinases, that may stimulate this uncontrolled growth. Genes square measure like instruction manuals that tell every cell within the body a way to grow, what reasonably cell become, and the way to behave. they are doing this by ordering the cell to form special proteins that cause a definite activity - such cell growth, rest, or repair. Some cancer cells have abnormalities in genes that tell the cell what proportion and the way quick to grow. typically, the cancer cells have too several copies of those genes with abnormalities. once their square measure too several copies of those genes, doctors confer with it as "overexpression." With some varieties of sequence overexpression, cancer cells can build too several of the proteins that management cell growth and division, inflicting the cancer to grow and unfold. Some carcinoma cells build (overexpress) too several copies of a specific sequence referred to as HER2 (human cuticular receptor 2). The HER2 sequence makes a macromolecule known as referred to as a HER2 receptor. HER2 receptors square measure like ears, or antennae, on the surface of all cells. carcinoma cells that overexpress the HER2 sequence build too several HER2 receptor proteins and square measure aforesaid to be HER2-positive. HER2 receptors use macromolecule signals, known as kinases, to manage what proportion energy the cells have to be compelled to grow and multiply. Cells that overexpress HER2 can have an excessive amount of enzyme activity, that the cancer cells grow an excessive amount.

Mechanism of action:

TYKERB (lapatinib) could be a HER2 matter that works by busy with HER2-related kinases within the cell, limiting the number of energy carcinoma cells have to be compelled to grow and multiply. By limiting the number of energy, TYKERB will slow or stop the expansion of carcinoma. TYKERB could be a targeted medical care, however in contrast to Herceptin associate degreed Avastin (chemical name: bevacizumab) it's not an immune targeted medical care. Immune targeted therapies square measure versions of present antibodies that job just like the antibodies created by our immune systems. TYKERB could be a matter, not associate degree protein. TYKERB works otherwise than Herceptin and Perjeta (chemical name: pertuzumab), that are HER2 inhibitors. Herceptin and Perjeta block the HER2 macromolecule on the surface of carcinoma cells. Perjeta targets a distinct space on the HER2 receptor than Herceptin will, therefore it's believed to figure during a manner that's complementary to Herceptin. TYKERB blocks the HER2 macromolecule within the cell. It's attributable to this completely different mechanism that TYKERB is also effective against HER2-positive cancers that have stopped responding to Herceptin.



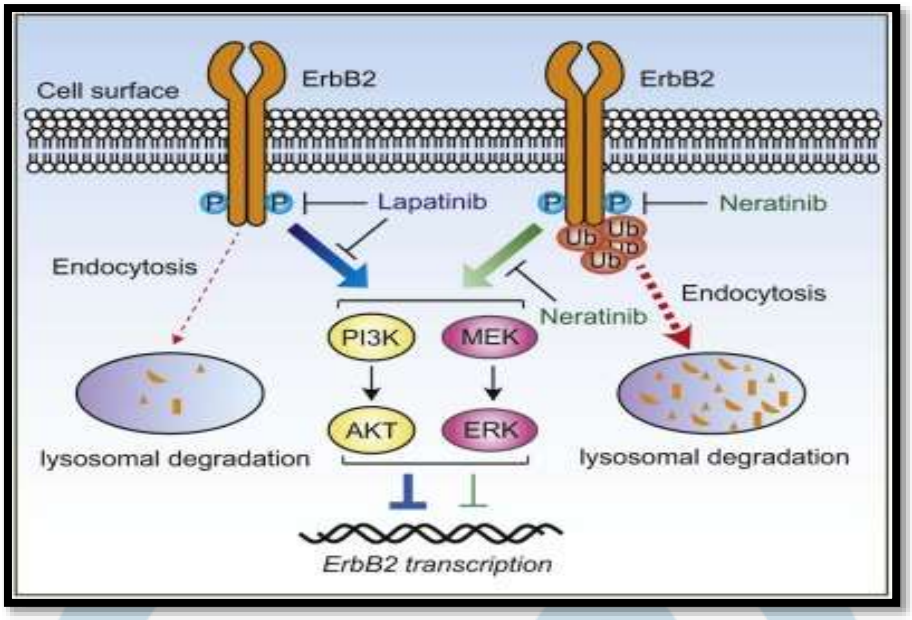
"Figure 7. Lapatinib MOA"

5. Neratinib

Neratinib is an irreversible, orally administered small molecule TKI of HER1, HER2 and HER4 that covalently binds to the cysteine residues of the ATP-binding portion of the HER TKs [46]. An open-label, phase 2 multicenter test of single-agent neratinib in 136 affected person with HER2-positive MBC showed a RR of 24% in patients earlier treated with trastuzumab, and a RR of 56% in trastuzumab-naïve patients. PFS at 16 weeks was 59 and 78%, respectively [47].

Mechanism of action:

Neratinib irreversibly binds to the intercellular signaling domain of HER1, HER2, HER3, and epithelial growth factor receptor, and inhibits phosphorylation and several HER downstream signaling pathways. The result is decreased proliferation and increased cell death [51].



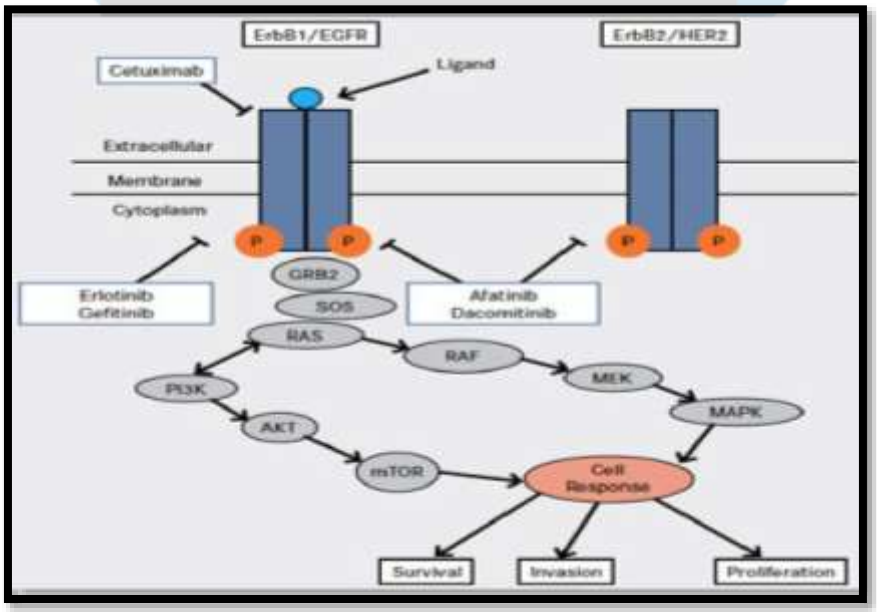
"Figure 8. Neratinib MOA"

6. Afatinib

Afatinib (BIBW 2992; Boehringer Ingelheim, Ingelheim, Germany) is a novel, oral, small-molecule TKI that covalently binds and irreversibly blocks all kinase-competent HER family members [48] Like lapatinib and neratinib, afatinib could be a supermolecule enzyme substance that conjointly irreversibly inhibits human epidermic protein receptor a pair of (Her2) and epidermic protein receptor (EGFR) kinases. Afatinib isn't solely active against EGFR mutations targeted by 1st generation tyrosine-kinase inhibitors (TKIs) like erlotinib or gefitinib, however conjointly against less common mutations that square measure proof against these medications. However, it is not active against the T790M mutation which generally requires third generation drugs like osimertinib [48]. Because of its additional activity against Her2, it is being investigated for breast cancer as well as other EGFR and Her2 driven cancers [49].

Mechanism of action:

Afatinib is a second-generation anilinoquinazoline that irreversibly binds to an intracellular tyrosine kinase domain, subsequently inhibiting members of the ErbB receptor family Most specifically, afatinib inhibits EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) receptors. [52]



"Figure 9. Afatinib MOA"

V.SIDE EFFECTS OF TARGETED THERAPY DRUGS

The facet effects of HER2 targeted medicine are typically delicate, however some will be serious. Discuss what you'll be able to expect together with your doctor. The being antibodies and antibody-drug conjugates will typically cause heart injury throughout or once treatment. this could result in symptom failure. for many (but not all) girls, this result lasts a brief time and gets higher once the drug is stopped. the danger of heart issues is higher once these medicine are given with bound chemo medicine that can also

cause heart injury, like antibiotic (Adriamycin) and epirubicin (Ellence) as a result of these medicine will cause heart injury, doctors typically check your heart operate (with AN sonogram or a MUGA scan) before treatment, and often whereas you're taking the drug. Let your doctor grasp if you develop symptoms like shortness of breath, leg swelling, and severe fatigue. Lapatinib, neratinib, tucatinib, and therefore the combination of pertuzumab with trastuzumab will cause severe diarrhea, thus it's vital to let your health care team understand any changes in intestine habits as presently as they happen. Lapatinib and tucatinib also can cause hand-foot syndrome, during which the hands and feet become sore and red, and should blister and peel [38,41].

VI.CONCLUSION

Precision medicine holds the promise of truly personalized treatment which provides every individual breast cancer patient with the most appropriate diagnostics and targeted therapies based on the specific cancer's genetic profile as determined by a panel of gene assays and other predictive and prognostic tests.

VII.AKNOWLEDGEMENT

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