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

1 Mr. Aditya A More, 1* Ms. Pooja S Murkute 2 Mr. Nakul P Kathar, 2 Dr. Gajanan. S. Sanap, 3 Mr. Rahul R Pawar

1 Research Scholar, Department of Pharmacognosy & Phytochemistry, LBYP College of D. Pharmacy (D. Pharm & B. Pharm), 1* Assistant professor, Department of Pharmacognosy & Phytochemistry, LBYP College of D. Pharmacy (D. Pharm & B. Pharm), 2 Assistant professor, Department of Pharmaceutics, LBYP College of D. Pharmacy (D.Pharm & B.Pharm), 2 Principal, Department of Pharmaceutics, LBYP College of D. Pharmacy (D.Pharm & B.Pharm), 3 Research Scholar, Department of Pharmacognosy & Phytochemistry, LBYP College of D. Pharmacy (D.Pharm & B.Pharm), 3* Assistant professor, Department of Pharmacognosy & Phytochemistry, LBYP College of D.Pharmacy (D.Pharm & B.Pharm),

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

1. 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 genes 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 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. Traditionally, 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.

**Figure 2. BRC A1 & BRC A2 Mechanism of action**
Doctors may use precision medication to assist them by following mentioned method:

II. BACKGROUND
The National Analysis Council discharged an agreement study report in 2011 entitled “Toward Precision Medication” [1]. Breast cancer, the foremost common cancer among girls worldwide, could be an extremely advanced heterogeneous and complex sickness. A 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 two 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].

“Illustration 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

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**Mechanism of action:**

Trastuzumab-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
Patients with HER2 overexpression develop disease by overexpressing a selected factor referred to as HER2. This factor makes a receptor on the surface of carcinoma cells and interferes with their ability to receive growth signals. By interfering with these signals, Herceptin works by attaching itself to the HER2 receptors of carcinoma cells. This causes them to start growing and multiplying excessively and too quickly. Carcinoma cells also collect signals that trigger their growth and repair. With HER2 overexpression, some carcinoma cells can create too many copies of HER2 receptors, leading to a large amount of growth. This process can lead to metastasis.

Mechanism of action:
Cancer cells grow in an uncontrolled fashion. Herceptin works on the surface of the somatic cell by interfering with the chemical signals that cause this uncontrolled growth. Genes are like instruction manuals that tell each cell of your body what to do. When these instructions are abnormal, cancer cells grow and multiply uncontrollably. Herceptin helps by attaching itself to HER2 receptors, interfering with the cancer cells' ability to receive these growth signals. This disruption slows or stops the expansion of the carcinoma. Additionally, Herceptin may facilitate the immune system's ability to destroy cancer cells.

Trastuzumab was the first available HER2-targeted therapy, offering promising response rates in the treatment of HER-2 positive metastatic breast cancer patients. The combination of trastuzumab and chemotherapy has demonstrated improved response rates, extended PFS, and improved PFS and OS. The survival benefit was also seen in patient subsets with HER2 positive breast cancer. Furthermore, trastuzumab has been shown to be effective in combination with other agents, including docetaxel, vinorelbine, and epirubicin/cyclophosphamide.
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.

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 degree Avastin (chemical name: bevacizumab) it's not an immune targeted medical care. Immune targeted therapies square measure versions of present antibodies that join with living proteins to 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.

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-naive 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].
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]

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. KNOWLEDGEMENT

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REFERENCES


