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# Review on HER2 Positive Breast Cancers

**Divya R Mahyavanshi,* Poornima S Gudeballur *, Arindam Paul, Chirag Desai, Ankit Merai**

**Department of Pharmacology and Pharmacy Practice, Rofel Shri G.M. Bilakhia College of Pharmacy, Namdha-Vapi-396191, Gujarat, India.**

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***For Correspondence:***

**Mahyavanshi Divya R**

Department of Pharmacology and Pharmacy Practice, Rofel Shri G.M. Bilakhia College of Pharmacy, Namdha-Vapi-396191, Gujarat, India.

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## ABSTRACT:

Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor that belongs to the epidermal growth factor receptor family. Dimerization of the receptor causes auto-phosphorylation of tyrosine residues in the receptor cytoplasmic domain, triggering a range of signaling cascades that lead to cell proliferation and cancer. HER2 amplification or overexpression is found in 15–30% of breast cancers and 10–30% of gastric/gastroesophageal tumour, and it is used as a prognostic and predictive biomarker. Other malignancies with HER2 overexpression include the ovary, endometrial, bladder, lung, colon, and head and neck. The introduction of HER2-focused medicines has a significant impact on the outcomes of patients with HER2-positive breast and gastric/gastro esophageal cancers; however, the results in other HER2 overexpressing tumour have been dismal. This study examines the significance of HER2 in various malignancies and the therapy options for HER2.

**KEYWORDS:** HER2, cancer, HER2 probes.

## INTRODUCTION [1-10]

On chromosome 17q21, the HER2 (Human Epidermal growth factor receptor) proto oncogene encodes a transmembrane protein that belongs to the EGFR family of tyrosine kinases.[1,2] HER family consist of extracellular, transmembrane & tyrosine kinase domains and exist on the surface of the cell.[3] Signal transduction by HER family promotes proliferation, survival and invasiveness.[4] HER2 proteins are breast cell receptors produced by the HER2 gene under normal conditions, these receptors are necessary for healthy breast growth and for breast cell to divide and repair themselves. In 25% of breast cancers, the gene that encodes the HER2 receptor protein does not function properly and produces a high number of copies of itself, this phenomenon is known as amplification of the HER2 gene. [5]. Cytoplasmic portion of HER2 receptor is constitutively active when overexpressed. All the extra copies of this gene send the instruction to synthesize other HER2 receptors, that creating overexpression. As a result breast cells grow and divided uncontrollably causing the tumour to form. Immunohistochemistry (IHC), Fluorescence In Situ Hybridization (FISH), Bright Field In Situ Hybridization are the techniques use for the detection of HER gene in the cell. Herceptin monotherapy was effective as replacement to chemotherapy failed patients in phase 2 clinical trials. In 1998, Herceptin become FDA approval as metastatic breast cancer treatment. Anti- HER2 monoclonal antibody is a standard treatment for HER2 amplified in breast cancer and approved by the US FDA. [6] Other HER2 targeted agents have been approved for the treatment of HER2 positive cancer, Lapatinib plus capecitabine and neratinib. Lapatinib a small molecule tyrosine kinase inhibitors. The trial shows that, it blocks downstream signaling pathways of HER2 and EGFR through inhibition of auto phosphorylation site on the receptor. [7] Neratinib the phase 1 & 2 trials shows the patients previously treated with anthracyclines , taxanes & trastuzumab reported that up to 32 % of patient achieved an objective response and up to 44% of patient achieved a clinical benefit.[8]

WHAT IS BREAST CANCER

Breast cancer (BC) is the most frequent cancer among women. More than 1 million women worldwide are impacted by this condition, and 4, 00,000 people die each

year as a result of it. Over the last 5 years, mammography screening, improved adjuvant systemic treatment, and a decrease in the use of hormone replacement therapy have resulted in a decline in both BC incidence and death in industrialized countries. [9, 10]

Breast cancer occurs when healthy breast cells become abnormal grow out of control and form tumour. Breast cancer can developed inside the milk duct is called ductal carcinoma in situ (DCIS). When DCIS spread in surrounding tissue it is called invasive duct carcinoma (IDC). Abnormal cell can developed in the lobules in the breast called lobular carcinoma in situ (LCIS). When LCIS spread in surrounding tissue it is called invasive lobular carcinoma (ILC) [11]

The most frequent type of non-invasive breast cancer is ductal carcinoma in situ (DCIS) Lobular carcinoma in situ (LCIS) is a less common type of breast cancer that is thought to be a risk factor for the disease. [12] Cells that infiltrate the surrounding fatty and connective tissues of the breast after breaking through the duct and lobular walls. Cancer can be invasive without becoming metastatic (spreading to other organs or lymph nodes). [13, 14]

Inflammatory, tubular carcinoma, Colloid / Mutinous is a less common type of breast cancer.

TABLE 1: STAGES OF BREAST CANCER[15]

| | |
|---|---|
| Stage: 0 | The cancer has not spread to the breast's basal membrane (carcinoma in situ). |
| Stage:1 | Localize, No lymph node involvement, tumour size less than 2 cm. |
| Stage:2 | Early locally advance, with or without lymph node involvement, tumour size between 2-5 cm. |
| Stage:3 | Late locally advanced, with lymph node involvement, tumour size more than 5 cm. |
| Stage:4 | The tumour has spread to distant organs or tissues, such as the lungs or bones, or to lymph nodes outside the breast, regardless of its size. |

HER2 RECEPTOR

HER2 is member of ErbB (Erythroblastic oncogene B) family of receptors, a subfamily of four closely related receptors tyrosine kinase. EGFR (ErbB 1), HER 2(ErbB 2), HER 3(ErbB 3), HER 4(ErbB 4). HER2 have an external ligand binding domain, a transmembrane domain, and an intracellular domain that can interact with a wide range of signaling molecules and can function both ligand-dependent and ligand-independently. Notably, no HER2 ligands have yet been discovered.[16,17] Dimerization causes auto phosphorylation of tyrosine residues in the receptor's cytoplasmic domain, triggering a number of signaling cascades. HER proteins dimerize and Trans phosphorylate their intracellular domains in response to ligand binding to their extracellular domains. These phosphorylated tyrosine residues dock a variety of intracellular signaling molecules, activating a slew of downstream second messenger pathways and causing crosstalk with other Trans membrane signaling pathways, all of which result in a variety of biological effects. [18]

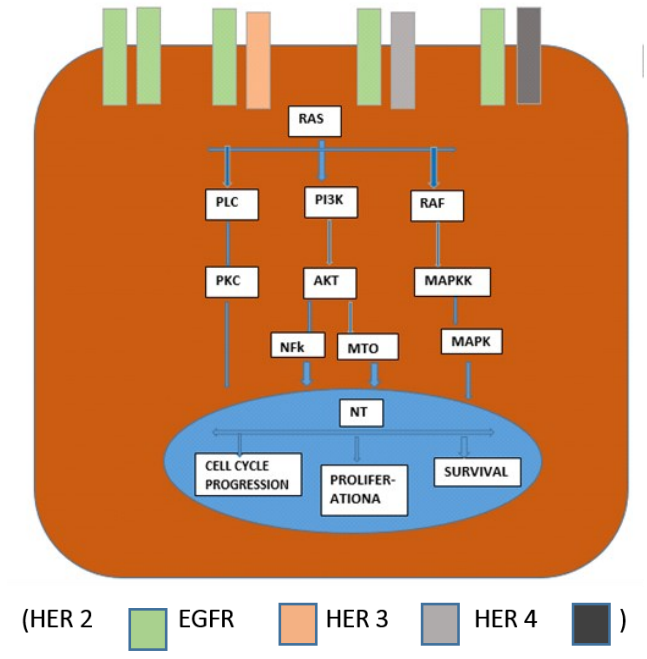
Signal transduction Edit HER2 activates the following signaling pathways: [19]

• Mitogen-activated protein kinase (MAPK) is a protein kinase that is triggered by (MAPK) PI3K/Akt (phosphoinositide 3-kinase).

• Signal transducers and activators of transcription (STAT)

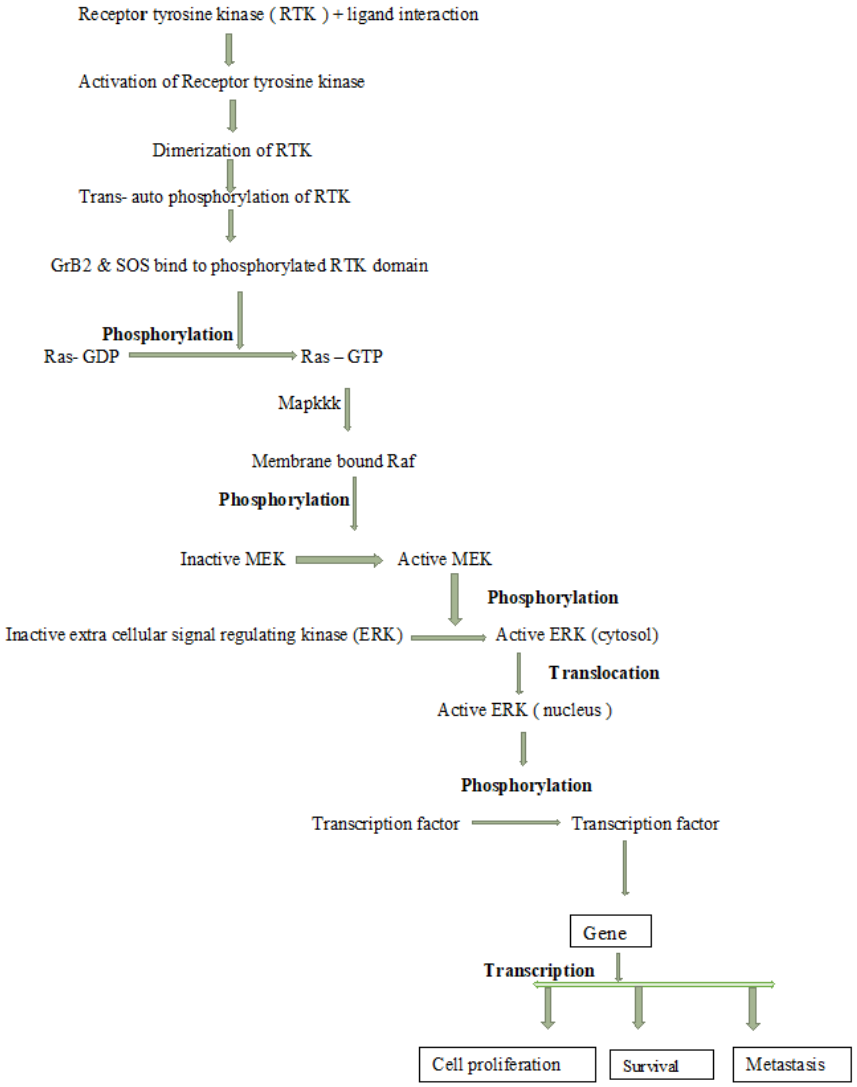
• protein kinase C phospholipase C (PKC)

In conclusion, signaling through the ErbB family of receptors promotes cell proliferation while inhibiting apoptosis, and so must be strictly regulated to prevent uncontrollable cell development. HER2 can impact a network of messages or signals, inside the cell that tell the cell to grow and divide to stay alive this network is called HER pathway. HER2 receptors are type of proteins exist on the surface of both normal and cancer cells. HER2 receptors are responsible for bringing signals from the outside of the cell to inside the cell. Although any ER receptor can potentially contribute to tumour growth and survival. The HER2 receptor plays most significant role in cancer. HER2 containing receptor pairs leads to strong signals into HER2 pathway.




[Figure: 1 HER 2 Signaling pathway.]

RAS – MAPK PATHWAY




[Figure 2: RAS- MAPK Pathway]

**PROTEIN MUTATION IN THE NORMAL HER2 SIGNALLING PATHWAY**

HER2 is a type of monomer transmembrane protein contains large end terminal extracellular module. Overexpression of HER2 which can increased the activation of Ras- MEK- ERK pathway.

- 40 -8 % in lung cancer
- 14 -19 % in non-small cell lung cancer
- 27 -77 % in colorectal cancer
- 30 - 50 % in pancreatic cancer. [19]

**RAS: Mutated Ras unable to hydrolyze GTP (ON) back to GDP (OFF)**

- Permanent activation of Ras protein.
- 3 Ras protein ( H,K,M )
- Mutation in codons 12,13,59,61.
- When H- Ras protein is mutated leads to bladder Tumour.
- When K- Ras protein is mutated leads to colon & pancreas Tumour.
- When M- Ras protein is mutated leads to hematopoietic Tumour.
- 90% in Pancreatic cancer
- 60% in Thyroid cancer
- 50% in colon cancer, endometrial cancer
- 30% in Lung adenocarcinomas
- 30% in myeloid leukemia.

**RAF: 3 RAF protein (A, B, C)**

- B- Raf constitutively active
- 70 % in Melanoma
- 50 % in Thyroid cancer10 % in colon cancer.

**PI3K/ AKT SIGNALLING PATHWAY**

Activation of PI3 kinase

PI3K/ AKT Pathway starts with activation of phosphotidyl Inositol 3 (PI3K) kinase. This activation can be accomplished by 3 different pathways. Depending on the receptor, different protein may bind to a phosphorylated domain. The insulin receptor substrate- 1 (IRS – 1) bind to the activated (IGF- 1) receptor. For simplification this receptor picked up as dimer. Receptor bound IRS – 1 serves as binding and activation site for the PI3K. In addition, PI3K may bind directly to phosphorylate receptor tyrosine kinase. Completely different mechanism of PI3K activation begins. The small membrane bound GTPase –Ras by binding to active bound GTPase - Ras, PI3K is activated.

Formation of the 2nd messenger phosphatidylinositol (3, 4, 5) triphosphate and activation of AKT

At the 2nd level of pathway the 2nd messenger PIP3 is formed. This results to the serine threonine kinase AKT activation. Active PI3K migrates to the inner side of the cell membrane, bind to the PIP2 which is the regular component of the membrane. PI3K is able to phosphorylate PIP2 to PIP3 can activate the kinase AKT which is also called protein kinase. AKT binds to apoptosis regulator BAX & hinder its ability to form holes in the outer membrane of mitochondria. In the absence of AKT these cause leads to apoptosis via caspase cascade.

Cascade begins with the activation of protein Rheb, which activates mTOR. It interact with and activates the translation factor S6Kby binding to the large cell unit of ribosomes. The translation of mRNA into protein is activated by S6K. AKT may lower the concentration of the protein FOXO is a substrate of the enzyme ubiquitin ligase. Which transfers ubiquitin peptides onto the protein. These peptides are symbolized as small black dots. In this way AKT prevents Tumour suppressor protein. [20, 21, 22]

**NF Kappa B SIGNALLING PATHWAY**

NFkB is not a single protein, it is a protein complex where the two different protein are combine together known as heterodimer. NFkB is nothing but transcription factor. This signaling pathway is always present in all the cell of the body. Whenever, the body is distress or any kind of outside stimuli enter into the body, the very first signaling pathway NFkB is activated that's why it is a unique pathway. The stimuli those can activate NFkB protein (transcription factor) are: Growth factor, viral infection, DNA damage.

There are 5 NFkB proteins: ReLA, ReLB, c-ReL, NFkB1, NFkB2 this protein form homodimers and heterodimers. Major IkB protein in mammals: IkBα, IkBβ, IkBε. In the absence of stimuli the NFkB protein bound to inhibitory protein (IkB). When stimulus TNFα bind to TNFα receptor present in the plasma membrane of the cell, it can signal the various protein results in activation of serine / threonine kinase.

**MUTATION IN NFkB GENE IN HUMAN CANCER**

NFkB has been shown to play a function in cancer in several animal models. For example, the transforming gene of an insect was discovered to be v-Rel, a viral homologue of c-Rel. A highly oncogenic avian retrovirus induces aggressive lymphomas and leukemia in chickens. [23] In addition, some viral oncoproteins may interact with the IKK complex and activate NFkB. The expression or activity of components of the NFkB signaling pathway may be altered in a wide range of hematopoietic proliferations. Chromosomal rearrangements or deletions affecting the NFkB2 locus on chromosome 10q24 result in the loss of p100 ankyrin repeats and the creation of constitutively active ankyrin repeats. The active p52 protein has been linked to B-cell and T-cell lymphoma. T-cell lymphomas and multiple myelomas are two types of lymphomas. [24, 25, 26] A t (14; 19) (q32; q13) translocation may be found in some B-cell lymphocytic leukemia. Bcl-3 is found on the human chromosome 19q13, close to the chromosomal breakpoint. [27] As a result of the translocation, there is an increase in Bcl-3 is a protein that is expressed in the body. Bcl-3 overexpression causes an increase in NFkB activity and up-regulation of its transcriptional targets such as cyclin D1 because it works as a transcriptional coactivator of p50 or p52 homodimers. [28, 29] The IkB family of proteins is one of the most important regulators of NFkB activation. Changes in these genes may impair the IkBs' ability to inhibit NFkB, resulting in NFkB inhibition. NFkB activity becomes constitutive. Mutations in IkB that cause a high level of constitutive nuclear activity. This implies that IkBs have a tumour-suppressing role. Non-small cell lung carcinoma and breast cancer have been discovered to have significant amounts of c-Rel in solid tumours. [30, 31]

TREATMENT [32, 33]

[Table: 1 Treatment of HER2 positive breast cancer]

| CLASSIFICATION | MECHANISM OF DRUG |
|---|---|
| | **Pertuzumab** |
| **HER2 dimerization inhibitor** | Monoclonal antibody that inhibits dimerization of HER2 |

| | |
|---|---|
| | **T- DM1** |
| **HER2 ADC** | Trastuzumab based ADC delivering cytotoxic drug for HER2 positive tumour cell |
| **PI3K inhibitors** | Small molecule selectively binding PI3K isoforms to inhibit the PI3K/AKT signaling pathway |
| | **Lapatinib** |
| **Tyrosine kinase inhibitors** | Reversible inhibitors of EGFR and HER2 tyrosine kinase |
| | **Neratinib** |
| | Irreversible inhibitors of EGFR,HER2 & HER 4 tyrosine kinase |
| | **Everolimus** |
| **mTOR inhibitors** | Small molecule inhibiting mTOR signal transduction |
| **HSP 90 inhibitors** | **Tanespimycin** |
| | Antineoplastic antibody inhibiting HSP 90 |
| | **Bevacizumab** |
| **VEGF receptor inhibitors** | Monoclonal antibody inhibiting VEGF |

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**CONCLUSION:**

In a minority of breast cancers, HER2 amplification is the predominant mechanism of HER2 receptor overexpression and is a prominent driver of tumour development and progression. The HER2 receptor, which is overexpressed in many cancers, is a promising therapeutic target. The goal of this Review is to explain HER2 biology, its importance in breast cancer, and current detection criteria. Potential therapeutic targets include receptors, protein tyrosine kinases, phosphatases, proteases, the PI3K/Akt signaling pathway and RAS- MAPK pathway.

**FUTURE SCOPE:**

For the treatment of breast cancer, several novel families of mechanism-based medicines have been devised and synthesized. Using genomic sequencing and posttranslational alterations, as well as rational drug design, researchers will gain a better knowledge of the pathophysiology of breast cancer and aid in the development of new therapeutic options. Oncomicro RNA suppression with antisense oligonucleotides, Restoration of tumour suppressors with micro RNA mimics and Chemical alteration of micro RNA are example of micro RNA based therapeutic methods.

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