PERTUZUMAB AS AN ANTAGOINST ON HER2 DIMERIZATION:

(Soumya Bandi[1], Medical content writer, Jodas Expoim Pvt. Ltd)

ABSTRACT:

Breast cancer is a highly prevalent and serious condition that affects many women annually in both developed and developing nations.

Targeting the human epidermal growth factor receptor 2 (HER2), the monoclonal antibody Pertuzuzmab (PERJETA) is a HER2 receptor antagonist that is used in conjunction with trastuzumab and docetaxel to treat patients with HER2-positive metastatic breast cancer who have not previously undergone anti-HER2 therapy or chemotherapy for metastatic disease.[1] It is also administered as a whole therapy regimen's neoadjuvant to patients with HER2-positive, locally progressed, inflammatory, or early stage breast cancer and adjuvant treatment for patients at high risk of recurrence.[1] The article aims to emphasize the mechanism of pertuzumab in patients with early-stage HER2-positive breast cancer receiving neoadjuvant treatment. This review intends to present the current development of Pertuzumab. The prospects of Pertuzumab targeting the PI3K/AKT and RAS/MEK/ERK pathway for therapeutic intervention in HER2 positive breast cancer will be summarized.

New monoclonal antibodies targeting HER2 have been developed, enhancing immune response and binding to epitopes. Petruzumab, an anti-HER2 humanized antibody, is shown to improve overall and progression-free survival rates in patients with HER2-positive metastatic breast cancer. It inhibits ligand-dependent HER2 dimer formation and HER2 receptor domain II.

KEY WORDS: Pertuzumab, biosimilar, breast cancer, monoclonal antibodies, HER2 dimerization, trastuzumab

1. INTRODUCTION:

Breast cancer usually develops from benign ductal or lobular breast tissue through a series of genetic abnormalities that build up in one cell, causing it to multiply clonally and uncontrollably.[2]

For the treatment of patients with metastatic breast cancer who have not had chemotherapy or anti-HER2 therapy before, pertuzumab is used with trastuzumab and docetaxel. In individuals with a high risk of recurrence, it is also used as an adjuvant and neoadjuvant therapy for early-stage breast cancer.[1]

According to the global cancer statistics for 2023, there would be 43700 new breast cancer deaths out of 300,590 new predicted cases.[3] Genetic and environmental factors are frequently linked to the

development of breast cancer. Normal cells are protected from cell suicide by the PI3K/AKT pathway and the RAS/MEK/ERK pathway.

Cancer develops as a result of mutations in the genes responsible for encoding these protective processes, which prevents cells from killing themselves when they are no longer needed.[4] Trastuzumab and pertuzumab are monoclonal antibodies that are selective and have minimal side effects. They restrict cell development and increase cancer cell death by targeting the extracellular domain of HER2. Pertuzumab, a humanized monoclonal antibody, binds to the HER2 dimerization domain that prevents HER2-HER3 coupling.

2. TARGETING PATHWAYS OF PERTUZUMAB:

2.1.1 PI3K/AKT signaling pathway:

The 3-hydroxyl group of the inositol ring of phosphatidylinositol lipids in the plasma membrane is phosphorylated to activate PI3K, a member of the lipid kinases family.[5] In physiological settings, extracellular signals often trigger the activation of PI3K. Two main mechanisms of activation involve interacting with a factor receptor that carries a phosphorylated tyrosine residue to cause heterodimer structural changes and activation.[6] Several triggers have been shown to activate PI3K, including growth factors, cytokines, and hormones.

Specifically, the transmembrane receptor tyrosine kinase (RTK) region of the N-terminal extracellular domain is bound by epidermal growth factor (EGF), platelet-derived growth factor, and insulin-like growth factor. This leads to the auto phosphorylation of tyrosine residues in the cytoplasmic region of the RTK and the linker molecule.[7]The PI3K downstream cascade generates signals that are received by a number of polymerization targets, but the serine/threonine kinase AKT is the primary mediator. AKT is a significant member in the whole PI3K pathway's signal transduction.[8]

One of the most significant signal transduction pathways, PI3K/AKT serves a crucial role in the emergence and progression of tumors and is involved in apoptosis, cell proliferation, cell cycle regulation, and other pertinent pathophysiological processes.[8] As a result, it's possible to utilize appropriate pharmacological molecules to suppress or block the PI3K/AKT signaling pathway in order to make it easier to identify anti-tumor targets.[9]

2.1.2 Ras/Raf/MEK/ERK pathway:

The Ras/Raf/MEK/ERK cascade in tumour cells can be activated by a number of mechanisms, including: chromosomal ectopes, like BCR-ABL; cytokine mutations, like Flt-3, Fms, and Kit; and overexpression

of mutant receptors, like EGFR. The apoptosis process is influenced by the Ras/Raf/MEK/ERK cascade, which phosphorylates a number of apoptosis regulatory proteins, including the contested Bcl-2, Mcl-1, Bim, Bad, and caspase-9.[10] Mutations in upstream membrane receptors, Ras, and B-Raf, along with genes in other pathways (such PI3K, PTEN, and Akt), which control Raf activity, cause abnormal stimulation of this pathway in human cancer.[11]

Raf/MEK/ERK and/or PI3K/Akt signalling are frequently increased in transformed cells, and these pathways are essential for both promoting proliferation and preventing apoptosis. Ras has the ability to control both routes.[12] Additionally, in some cell types, Akt adversely regulates Raf activity, suggesting that there is communication between the two pathways. Both pathways play a part in the control of proliferation and survival of cells and may lead to the phosphorylation of several downstream targets.[11]

3. SYNERGISTIC RATIONALE OF TRASTUZUMAB WITH PERTUZUMAB:

Monoclonal antibodies are highly selective medicines with minimal side effects. Monoclonal antibodies, in addition to directly promoting cancer cell death, also cause immunological activation, which results in tumor cell toxicity.[13]Trastuzumab and pertuzumab are HER2-directed mAbs, targeting the extracellular domain of HER2 to inhibit cell growth. Their antitumor efficacy is attributed to their direct inhibitory action, with interactions with the immune system causing antibody-dependent cellular cytotoxicity.[14]

Pertuzumab is a humanized monoclonal antibody that binds to the HER2 dimerization domain, preventing the coupling of the most powerful HER signaling dimer, HER2-HER3. It has the ability to stimulate immunological effector actions such as antibody-dependent cell-mediated cytotoxicity. Trastuzumab and pertuzumab bind to separate epitopes on the HER2 protein and have complementary mechanisms of action. Trastuzumab inhibits ligand-independent HER2 signaling, blocks HER2 activation by extracellular domain shedding, and marks cells for immune system destruction.[15] It binds to the HER2 domain IV area near the HER2 juxtamembrane.[16]

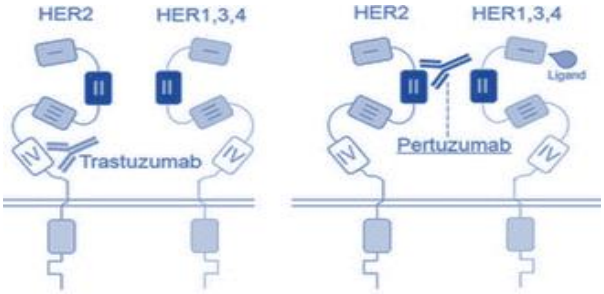

Fig: Inhibiting ligand-dependent HER2 heterodimerization.

pertuzumab binds to the HER2 receptor at domain II.[17]

Trastuzumab is the first FDA-approved HER2-targeted medication for the treatment of metastatic breast cancer. It cannot, however, block ligand-activated HER2/HER3 or HER2/HER1 heterodimerization, which is a possible tumor cell escape strategy.[15] Trastuzumab and pertuzumab reduce the survival of HER2-overexpressing breast cancer cells in a synergistic manner, enhancing the anticancer impact in HER2-overexpressing breast cancer.[18]

3.3 Pertuzumab on HER2 positive breast cancer:

3.3.1 HER family receptors:

Human epidermal growth factor receptor 2 (HER2) protein/oncogene overexpression and the presence of transmembrane receptors, specifically progesterone and estrogen, are used to classify breast cancer clinically.[19] Tumor-associated antigen (TAA) HER2 is overexpressed or amplified in approximately 25% of patients with breast cancer. Inadequate treatment with HER2-targeted treatments is associated with poor clinical outcomes.[20]

Three domains are present in HER receptors: an intracellular tyrosine kinase domain, a transmembrane domain, and an extracellular ligand-binding domain. The process of ligand binding to the HER proteins causes these receptors to homodimerize or heterodimerize, which activates downstream signaling pathways that encourage cell division and expansion while suppressing apoptosis.[21] In addition to enhanced signaling through ligand-dependent heterodimerization, HER2 overexpression or amplification causes ligand-independent dimerization and aberrant signalling.[21]

Patients with HER2-positive (HER2+) metastatic breast cancer (MBC) have improved clinical outcomes from passive immunotherapy with HER2-directed monoclonal antibodies (mAbs) like pertuzumab and trastuzumab in combination with chemotherapy, as these agents have been shown to improve median overall survival (OS) to as much as 57 months.[22]The HER family receptors (HER1, HER2, HER3, and HER4) are expressed in a specific cell type, have homologous extracellular ligand-binding and intracellular kinase domains, and are phosphorylated by hetero-dimerization events triggered by particular ligands.[23]

3.3.2 Pertuzumab mode of action on HER2 dimerization:

The HER2 heterodimer, which binds to the PI3K (Phosphoinositide 3-Kinases) p85 subunit, is the most potent activator of the PI3K/AKT (Protein Kinase B, PKB) signaling cascade.[24] Both HER2 and HER3 lack a ligand and tyrosine kinase activity.[25] Receptor dimerization, which can happen between two molecules of the same receptor (homodimerization) or between two distinct HER members (heterodimerization), is an

essential requirement for HER activity. As each receptor phosphorylates during dimerization, the tyrosine kinase domains of the dimer moiety are trans-activated. While other homomeric and heteromeric complexes exist, the most powerful signaling pair responsible for promoting cell proliferation in HER2-positive malignancy is thought to be the HER2–HER3 heterodimer.[26] As soon as the ligand attaches itself to HER3, HER2 dimerizes with HER3, trans-phosphorylates HER3, and the vital phosphoinositide 3-kinase pathway is triggered. As pertuzumab suppresses HER2 dimerization, it also restricts HER2-HER3 signalling.[27]

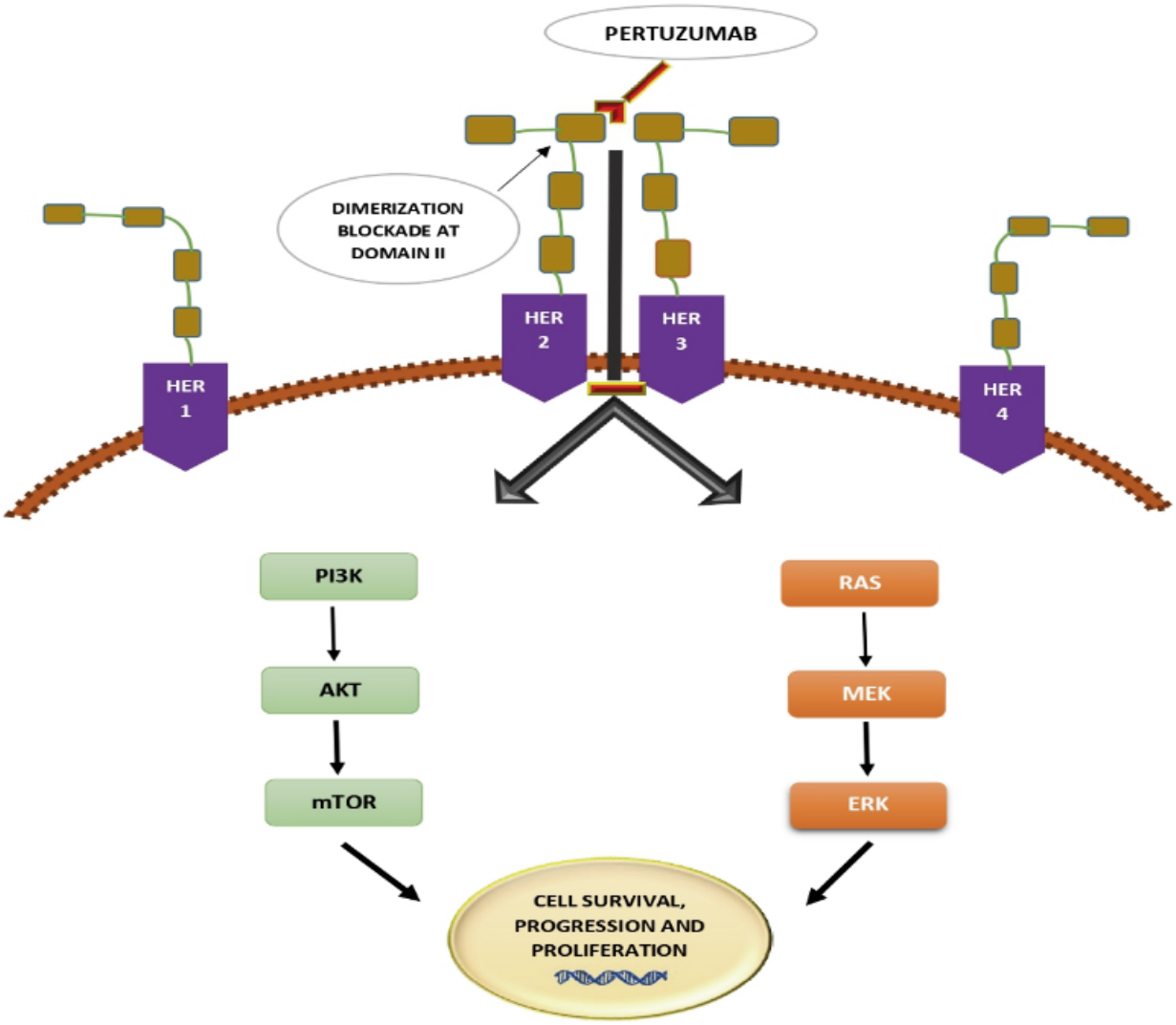

Fig: By binding to the HER2 receptor at domain II, pertuzumab prevents the PI3k and Ras pathways that are essential for cell survival and growth.

4. DISCUSSION:

Several new monoclonal antibodies that target HER2 have been developed; these antibodies have the capacity to connect to more epitopes to enhance activity or to trigger a stronger immune response, or they have a more selective binding to the HER2 receptor.[28] Patients with HER2-positive metastatic breast cancer who get treatment with the anti-HER2 humanized monoclonal antibody petruzumab in addition to chemotherapy have a much better overall and progression-free survival rate than those who receive chemotherapy alone. The PI3K/AKT signaling system is important in tumor development and progression, regulating apoptosis, cell proliferation, and cell cycle control. Raf activity is controlled by mutations in upstream membrane receptors, Ras, and B-Raf, as well as genes from other pathways, resulting in abnormal activation of this pathway in breast cancer.

The review demonstrates the therapeutic significance of pertuzumab in inhibiting ligand-dependent HER2 dimer formation to maximally suppress HER2 signaling and hence target HER2-positive breast tumors. In addition to blocking ligand-dependent dimerization, pertuzumab binds to the HER2 receptor's domain II and completely inhibits HER2 signaling.[29] Trastuzumab and pertuzumab are monoclonal antibodies that are selective and have minimal side effects. They induce cancer cell death and immune activation, resulting in tumor cell toxicity. Their anticancer activity relies from their direct inhibitory action, which results in antibody-dependent cellular cytotoxicity. Trastuzumab and pertuzumab bind to different epitopes on the HER2 protein and function in complementary ways.

CONCLUSION:

Since the advent of anti-HER2 therapy, patients with HER2-positive breast cancer have experienced markedly better clinical results, and HER2 is now most frequently targeted in breast cancer treatment. Pertuzumab is a humanized monoclonal antibody that targets the extracellular dimerization domain of HER2, preventing its dimerization with other HER family members. This inhibits downstream signaling and cell survival pathways, making it a complementary therapy to trastuzumab. Patients with HER2-positive breast cancer who receive pertuzumab in addition to chemotherapy have better overall survival rates.

Pertuzumab, targets the human epidermal growth factor receptor 2 (HER2), is used to treat patients with HER2-positive metastatic breast cancer in conjunction with trastuzumab and docetaxel. The mechanism of action of pertuzumab is based on the HER2 family receptors, which are overexpressed or amplified in around 25% of breast cancer patients.

The antibody specifically targets the PI3K/AKT and RAS/MEK/ERK pathways, which protect normal cells from suicide. Pertuzumab binds to the HER2 dimerization domain, blocking the most potent HER signaling dimer, HER2-HER3, from coupling. It can activate immunological effector mechanisms such as antibody-dependent cell-mediated cytotoxicity. Trastuzumab and pertuzumab work synergistically to diminish the survival of HER2-overexpressing breast cancer cells, improving the anticancer impact on HER2-overexpressing breast cancer.

5. REFERENCES:

1. PERJETA® (pertuzumab) injection, for intravenous use. Published online 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf

2. MD LAH, Ozge Gumusay MD, Dame Idossa MD, Hope S. Rugo MD. Systemic therapy for hormone receptor-positive/human epidermal growth factor receptor 2-negative early stage and metastatic breast cancer. *Cancer J Clin*. 2023;73(5):480-515. doi:10.3322/caac.21777

3. Rebecca L. Siegel MPH KDMM, Nikita Sandeep Wagle MBBS, MHA, PhD, Ahmedin Jemal DVM, PhD. Cancer statistics, 2023. *ACS J*. 2023;73(1):17-48. doi:10.3322/caac.21763

4. Muhammad Akram, Mehwish Iqbal, Muhammad Daniyal, Asmat Ullah Khan. Awareness and current knowledge of breast cancer. *Biol Res*. 2017;50(33):1-23. doi:10.1186/s40659-017-0140-9

5. Fruman DA, Meyers RE, Cantley LC. Phosphoinositide kinases. *Annu Rev Biochem*. 1998;67:481-507. doi:10.1146/annurev.biochem.67.1.481

6. Osaki M, Oshimura M, Ito H. PI3K-Akt pathway: its functions and alterations in human cancer. *Apoptosis Int J Program Cell Death*. 2004;9(6):667-676. doi:10.1023/B:APPT.0000045801.15585.dd

7. Ruderman NB, Kapeller R, White MF, Cantley LC. Activation of phosphatidylinositol 3-kinase by insulin. *Proc Natl Acad Sci U S A*. 1990;87(4):1411-1415. doi:10.1073/pnas.87.4.1411

8. Lawlor MA, Alessi DR. PKB/Akt: a key mediator of cell proliferation, survival and insulin responses? *J Cell Sci*. 2001;114(Pt 16):2903-2910. doi:10.1242/jcs.114.16.2903

9. XIANG SH XZ. Research progress on the PI3K/AKT signaling pathway in gynecological cancer. Published online 2019:4529-4535.

10. Li L, Zhao GD, Shi Z, Qi LL, Zhou LY, Fu ZX. The Ras/Raf/MEK/ERK signaling pathway and its role in the occurrence and development of HCC. *Oncol Lett*. 2016;12(5):3045-3050. doi:10.3892/ol.2016.5110

11. McCubrey JA, Steelman LS, Chappell WH, et al. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. *Biochim Biophys Acta*. 2007;1773(8):1263-1284. doi:10.1016/j.bbamcr.2006.10.001

12. Steelman LS, Chappell WH, Abrams SL, et al. Roles of the Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR pathways in controlling growth and sensitivity to therapy-implications for cancer and aging. *Aging*. 2011;3(3):192-222. doi:10.18632/aging.100296

13. Esteva FJ. Monoclonal antibodies, small molecules, and vaccines in the treatment of breast cancer. *The Oncologist*. 2004;9 Suppl 3:4-9. doi:10.1634/theoncologist.9-suppl_3-4

14. Ricardo L. B. Costa, Brian J. Czerniecki. Clinical development of immunotherapies for HER2+ breast cancer: a review of HER2-directed monoclonal antibodies and beyond. *Npj Breast Cancer*. Published online March 2020. doi:10.1038/s41523-020-0153-3

15. Harbeck N, Beckmann MW, Rody A, et al. HER2 Dimerization Inhibitor Pertuzumab - Mode of Action and Clinical Data in Breast Cancer. *Breast Care Basel Switz*. 2013;8(1):49-55. doi:10.1159/000346837

16. Nami B, Maadi H, Wang Z. Mechanisms Underlying the Action and Synergism of Trastuzumab and Pertuzumab in Targeting HER2-Positive Breast Cancer. *Cancers*. 2018;10(10):342. doi:10.3390/cancers10100342

17. Ishii K, Morii N, Yamashiro H. Pertuzumab in the treatment of HER2-positive breast cancer: an evidence-based review of its safety, efficacy, and place in therapy. *Core Evid*. 2019;14:51-70. doi:10.2147/CE.S217848

18. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Res*. 2004;64(7):2343-2346. doi:10.1158/0008-5472.can-03-3856

19. Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2010;28(16):2784-2795. doi:10.1200/JCO.2009.25.6529

20. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235(4785):177-182. doi:10.1126/science.3798106

21. Niall Tebbutt, Mikkel W. Pedersen, Terrance G. Johns. Targeting the ERBB family in cancer: couples therapy. *Nat Rev Cancer*. 2013;13:663-673. doi:10.1038/nrc3559

22. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783-792. doi:10.1056/NEJM200103153441101

23. Seshacharyulu P, Ponnusamy MP, Haridas D, Jain M, Ganti AK, Batra SK. Targeting the EGFR signaling pathway in cancer therapy. *Expert Opin Ther Targets*. 2012;16(1):15-31. doi:10.1517/14728222.2011.648617

24. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch Pathol Lab Med*. 2018;142(11):1364-1382. doi:10.5858/arpa.2018-0902-SA

25. Lee-Hoeflich ST, Crocker L, Yao E, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. *Cancer Res*. 2008;68(14):5878-5887. doi:10.1158/0008-5472.CAN-08-0380

26. Agus DB, Akita RW, Fox WD, et al. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell*. 2002;2(2):127-137. doi:10.1016/s1535-6108(02)00097-1

27. Sliwkowski MX, Schaefer G, Akita RW, et al. Coexpression of erbB2 and erbB3 proteins reconstitutes a high affinity receptor for heregulin. *J Biol Chem*. 1994;269(20):14661-14665.

28. Siddharth Kunte MBBS, Jame Abraham MD, FACP, Alberto J. Montero MD, MBA, FirAlberto J. Montero MD, MBA. Novel HER2–targeted therapies for HER2–positive metastatic breast cancer. *ACS J*. 2020;126(19):4278-4288. doi:10.1002/cncr.33102

29. Adams CW, Allison DE, Flagella K, et al. Humanization of a recombinant monoclonal antibody to produce a therapeutic HER dimerization inhibitor, pertuzumab. *Cancer Immunol Immunother CII*. 2006;55(6):717-727. doi:10.1007/s00262-005-0058-x