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# TRASTUZUMAB AS MONOCLONAL ANTIBODY; INHIBITOR OF HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 PROTEIN KINASE FOR BREAST CANCER

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## ABSTRACT

Trastuzumab is a targeted (biological) therapy. Targeted therapies block the growth and spread of cancer. They target and interfere with processes in the cells that help cancer grow. It is a biologic agent primarily used to treat HER2-positive breast cancer and may be used as adjuvant therapy for localized disease or as first-line treatment for metastatic disease. The inhibition of the hyperactive HER2 protein kinase receptor by trastuzumab in HER2+ breast cancer cells can be partly considered an immunotherapy strategy, since the monoclonal antibody (mAb) mechanism of action includes an immune-mediated component. HER2-positive breast cancer is a breast cancer that tests positive for a protein called human epidermal growth factor receptor 2 (HER2). This protein promotes the growth of cancer cells.

**KEYWORDS:** HER2 Receptor, monoclonal antibody, trastuzumab, breast cancer.

## INTRODUCTION

Trastuzumab is a type of targeted cancer drug called a monoclonal antibody. Targeted cancer drugs work by 'targeting' those differences that help a cancer cell to survive and grow. It is a treatment for cancers that have large amounts of a protein called human epidermal growth factor receptor 2 (HER2). It is a targeted (biological) therapy. Targeted therapies block the growth and spread of cancer. They target and interfere with processes in the cells that help cancer grow. It is a biologic agent primarily used to treat HER2-positive breast cancer and may be used as adjuvant therapy for localized disease or as first-line treatment for metastatic disease. It is sold under the brand name Herceptin among others, is a monoclonal antibody used to treat breast cancer and stomach cancer. It is specifically used for cancer that is HER2 receptor positive. It may be used by itself or together with other chemotherapy medication. It is given by slow injection into a vein [IV] and injection just under the skin [SC].[1-6]

Dennis Joseph Slamon (born August 6, 1948), is an American oncologist and chief of the division of Hematology-Oncology at UCLA. He is best known for his work identifying the HER2/neu oncogene that is amplified in 25–33% of breast cancer patients and the resulting treatment trastuzumab.

**Figure 1: Trastuzumab inventor [Dennis Joseph Slamon].**

### Classification

Kingdom: Organic Compounds
Super Class: Organic Acids
Class: Carboxylic Acids and Derivatives
Sub Class: Amino Acids, Peptides, and Analogues
Direct Parent: Peptides

**Common side effects:** It include fever, infection, cough, headache, trouble sleeping, and rash. Other severe side effects include heart failure, allergic reactions, and lung disease. Use during pregnancy may harm the baby. Trastuzumab works by binding to the HER2 receptor and slowing down cell replication. The safety and efficacy of trastuzumab-containing combination therapies (with chemotherapy, hormone blockers, or lapatinib) for the treatment of metastatic breast cancer. The overall hazard

ratios (HR) for overall survival and progression free survival were 0.82 and 0.61, respectively. It was difficult to accurately ascertain the true impact of trastuzumab on survival, as in three of the seven trials, over half of the patients in the control arm were allowed to cross-over and receive trastuzumab after their cancer began to progress. Thus, this analysis likely underestimates the true survival benefit associated with trastuzumab treatment in this population.

In early-stage HER2-positive breast cancer, trastuzumab-containing regimens improved overall survival (Hazard ratio (HR) = 0.66) and disease-free survival (HR = 0.60). Increased risk of heart failure (RR = 5.11) and decline in left ventricular ejection fraction (relative risk RR = 1.83) were seen in these trials as well. Two trials involving shorter term treatment with trastuzumab did not differ in efficacy from longer trials, but produced less cardiac toxicity.

**Background:** Produced in CHO cell cultures, trastuzumab is a recombinant IgG1 kappa, humanized monoclonal antibody 6 that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor protein (HER2). It is used as a treatment of human epidermal growth factor receptor (HER)-2+ metastatic breast cancer, where there is a proven amplification of the HER-2 oncogene or over-expression of the HER-2 protein in tumours. It is suggested that the overexpression or gene amplification of HER2 has been found in about 20–30% of breast cancers and elevated activation of HER2 triggers multiple downstream pathways leading to abnormal proliferation of cancer cells. Trastuzumab binds to HER2 and suppresses cancer cell growth, proliferation, and survival directly and indirectly. In December 2017, FDA approved OGIVRI (trastuzumab-dkst) as a biosimilar to Herceptin (trastuzumab) for the treatment of patients with breast or metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma) whose tumors overexpress the HER2 gene (HER2+). It displays biosimilar properties as Herceptin according to clinical data. While Ogivri is the first biosimilar approved in the U.S. for the treatment of breast cancer or stomach cancer, it is the second biosimilar approved in the U.S. for the treatment of cancer. Herzuma (trastuzumab-pkrb) is a biosimilar drug approved in December 2018 for the treatment of HER2-overexpressing breast cancer. KANJINTI (trastuzumab-anns) is another biosimilar approved by the FDA in June 2019.16 ONTRUZANT, another biosimilar of Herceptin, was approved by Health Canada in February 2022.22,23 In November 2023, trastuzumab was also approved by the EMA under the brand name Herwenda.[7-11]

**Monoclonal antibody (mAb) Protein Structure**

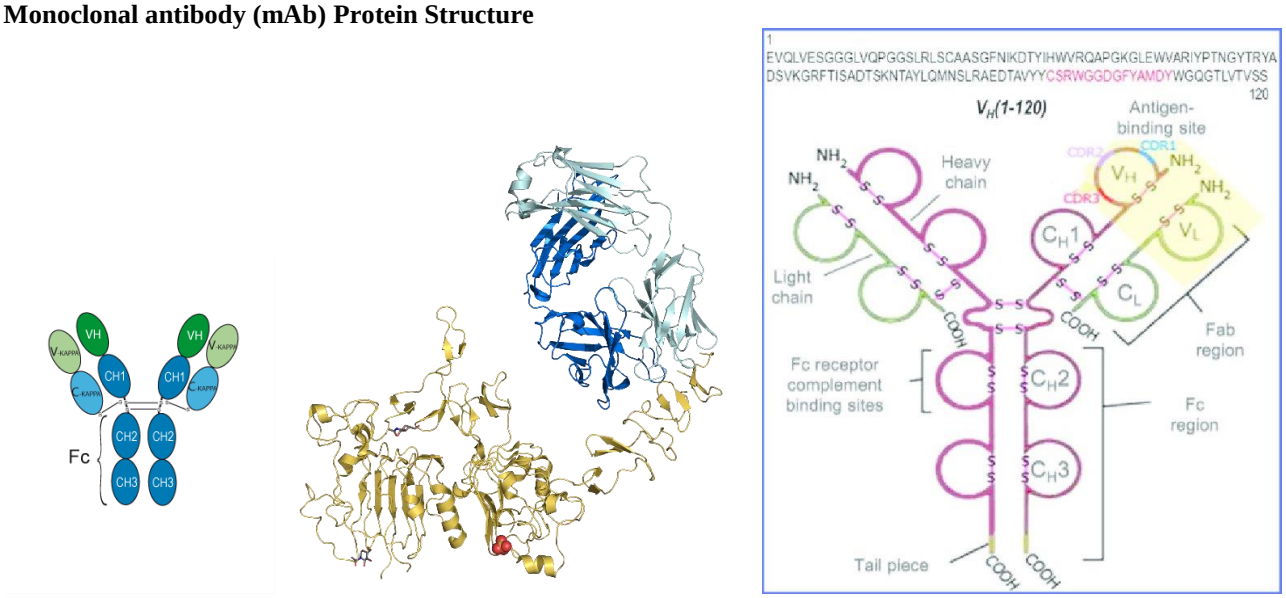


**Figure 2: Peptide structure of Trastuzumab.**

**Protein Chemical Formula:** $C_{6470}H_{10012}N_{1726}O_{2013}S_{42}$; Protein Average Weight: 145531.5 Da
**Sequences:** Anti-HER2 Light chain (1 and 2)
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT
ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW
KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Anti-HER2 Heavy chain (1 and 2)
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA
LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT

KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK

**Pharmacodynamics:** Trastuzumab exerts an antitumour activity and is used in the treatment of HER2-positive breast cancer. HER2 protein overexpression is observed in 20%-30% of primary breast cancers thus HER2 presents as a useful therapeutic target for the treatment of breast cancers. Trastuzumab has been shown, in both *in-vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. It works as a mediator of antibody-dependent cellular cytotoxicity, where it binds as an antibody to cells over-expressing HER2, leading to preferential cell death. Trastuzumab was also shown to inhibit angiogenesis of tumor cells *in-vivo*. Higher doses and longer dosing intervals show no significant benefit over standard dose schedules. In patients with HER2 positive solid tumours, trastuzumab did not exert any clinically significant QTc interval duration.

**Mechanism of action:** Trastuzumab binds to the extracellular ligand-binding domain and blocks the cleavage of the extracellular domain of HER-2 to induce its antibody-induced receptor downmodulation 4, and subsequently inhibits HER-2-mediated intracellular signaling cascades. Trastuzumab is a recombinant humanized IgG1 monoclonal antibody against the HER-2 receptor, a member of the epidermal growth factor receptors which is a photo-oncogene. Over-expressed in breast tumour cells, HER-2 overamplifies the signal provided by other receptors of the HER family by forming heterodimers. The HER-2 receptor is a transmembrane tyrosine kinase receptor that consists of an extracellular ligand-binding domain, a transmembrane region, and an intracellular or cytoplasmic tyrosine kinase domain. It is activated by the formation of homodimers or heterodimers with other EGFR proteins, leading to dimerization and autophosphorylation and/or transphosphorylation of specific tyrosine residues in EGFR intracellular domains. Further downstream molecular signaling cascades are activated, such as the Ras/Raf/mitogen-activated protein kinase (MAPK), the phosphoinositide 3-kinase/Akt, and the phospholipase Cγ (PLCγ)/protein kinase C (PKC) pathways that promote cell growth and survival and cell cycle progression. Due to upregulation of HER-2 in tumour cells, hyperactivation of these signaling pathways and abnormal cell proliferation is observed. Trastuzumab binds to the extracellular ligand-binding domain and blocks the cleavage of the extracellular domain of HER-2 to induce its antibody-induced receptor downmodulation, and subsequently inhibits HER-2-mediated intracellular signaling cascades.[12-17]

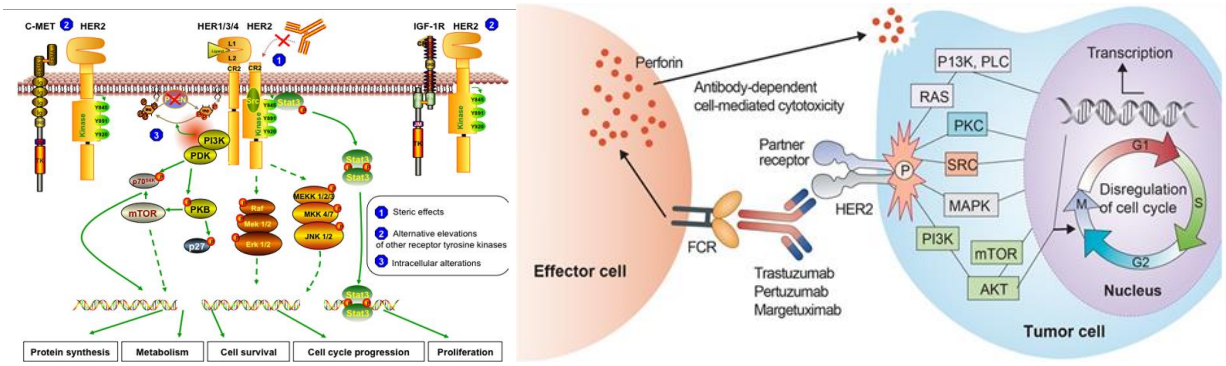


**Figure 3: Mode of action Trastuzumab.**

Inhibition of MAPK and PI3K/Akt pathways lead to an increase in cell cycle arrest, and the suppression of cell growth and proliferation. Trastuzumab also mediates the activation of antibody-dependent cell-mediated cytotoxicity (ADCC) 6 by attracting the immune cells, such as natural killer (NK) cells, to tumor sites that overexpress HER-2. While the drug alone has a minimal potential to induce complement-dependent cytotoxicity (CDC), one study demonstrated increased therapeutic effectiveness and a synergistic effect on uterine serous carcinoma cells *in-vitro* when used in combination with pertuzumab, which also has minor effects on CDC alone. This study showed that only the combination of both cell-bound antibodies would be sufficient to bind and activate the complement component 1q (C1q) required to initiate the complement cascade reaction. Intrinsic trastuzumab resistance has been noted for some patients with HER-2 positive breast cancer. Mechanisms involving trastuzumab resistance include deficiency of phosphatase and tensin homologue and activation of phosphoinositide 3-kinase, and the overexpression of other surface receptors, such as insulin-like growth factor.[18-22]


**Figure 4: Trastuzumab Medication.**

**Target:** Receptor tyrosine-protein kinase erbB-2.

**Absorption:** Peak and trough plasma concentrations at steady state (between weeks 16 and 32) were approximately 123 and 79 mcg/mL, respectively. At the highest weekly dose studied (500 mg), mean peak serum concentration was 377 mcg/mL.

**Metabolism:** After it binds to HER2, trastuzumab is metabolized intracellularly into smaller peptides and amino acids.

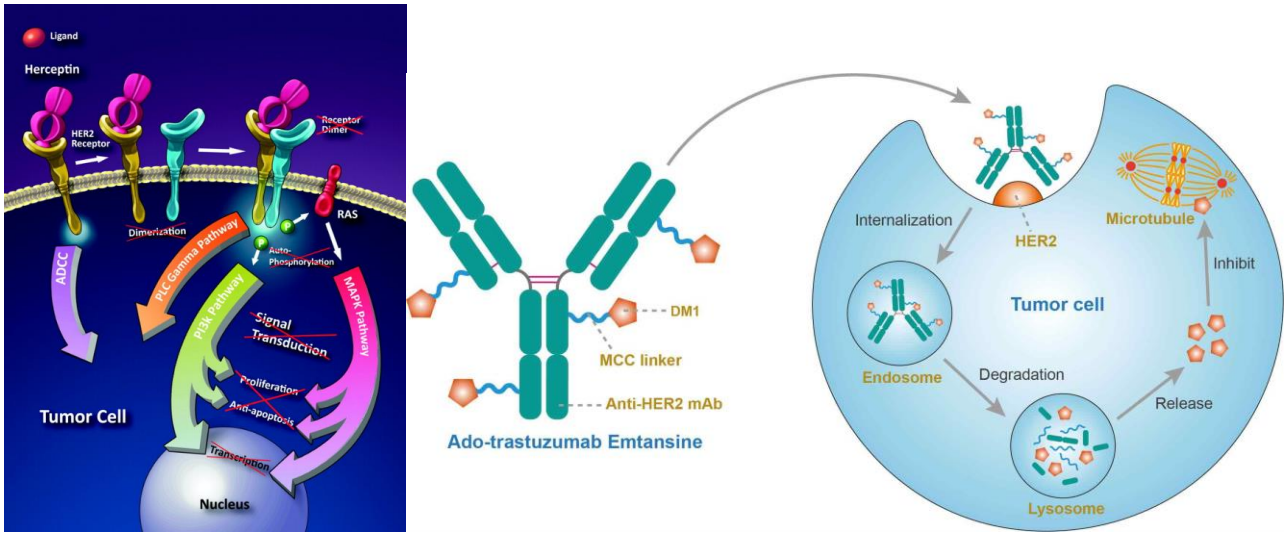


**Figure 5: Schematic diagram of monoclonal antibody plays a drastic role *in-vivo*.**

**Route of elimination:** Following metabolism, the complex elimination of trastuzumab in humans is mediated by epithelial cells in a dose-dependent (nonlinear) fashion. The renal excretion of trastuzumab is very low.

**Half-life:** The terminal half-life is approximately 28 days, but may decrease with lower doses - at the 10mg and 500mg doses, half-lives averaged approximately 1.7 and 12 days, respectively. Multiple-dose feature of vials may support efficiency and reduce waste, as it allows fewer vials to be used and disposed of. Unused product can be stored for future use. Store reconstituted TRAZIMERA multiple-dose vial in the refrigerator at 2 to 8°C (36 to 46°F); discard unused TRAZIMERA after 28 days. Trastuzumab needs to be kept in the fridge. The pharmacy team or chemotherapy day unit team gives you a special cool box to take the medicine home. Please bring a leakproof, tight-fitting plastic storage container with a lid (for example, Tupperware® or something similar) to collect your medicine.[23-28]

**Clearance:** The predicted steady-state clearance of trastuzumab is 0.173 - 0.337 L/day, dependent primarily on the dosing regimen. The clearance rate for subcutaneously administered trastuzumab, formulated with hyaluronidase for improved subcutaneous absorption, is 0.11 L/day.

**Toxicity:** There is no experience with overdosage of trastuzumab in clinical trials - single doses >8 mg/kg have not been tested in humans. Trastuzumab can contribute to the development of ventricular dysfunction and congestive heart failure, particularly when used in combination (or temporally adjacent) to other cardiotoxic chemotherapies such as anthracyclines.

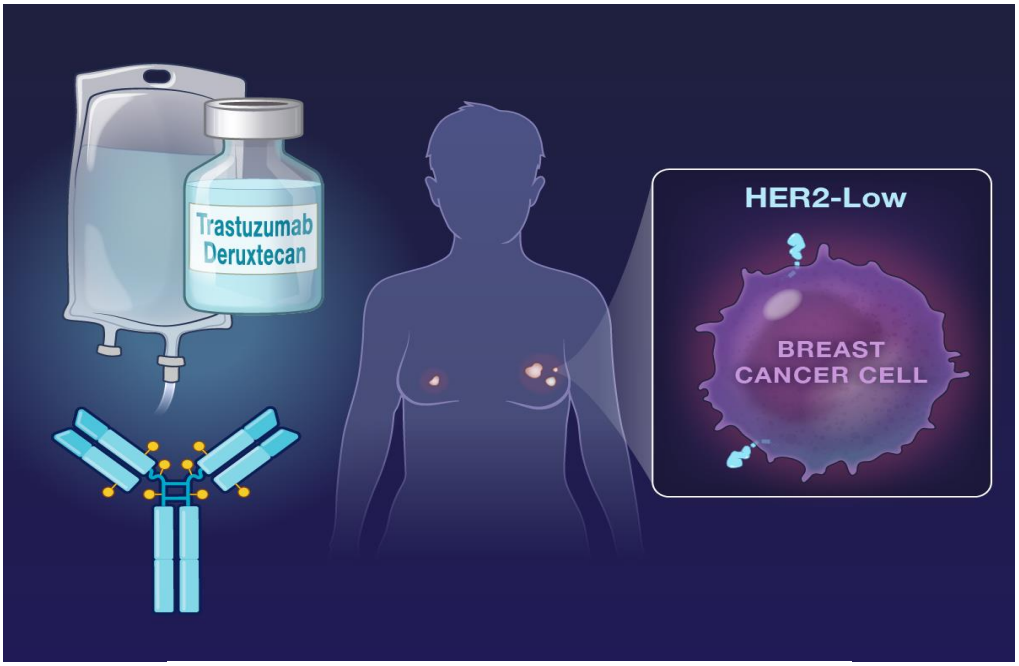


**Figure-6: Breast Cancer treatment by monoclonal antibody.**

## CONCLUSION

Herceptin was the first HER2-targeted therapy for breast cancer. It is a monoclonal antibody that binds to HER2 receptors present on the surface of HER2-positive tumour cells, blocking them from receiving growth signals and flagging them for destruction by the immune system. Herceptin (trastuzumab) is a human monoclonal antibody that interferes with the HER2 receptor. It is currently the only FDA-approved therapeutic antibody for HER2-positive breast cancer. This article will present the mechanism at action as well as the clinical role at this monoclonal antibody. Trastuzumab (Herceptin) is humanized monoclonal antibody that interferes with the HER2 receptor. It is currently the only FDA-approved therapeutic antibody for HER2-positive breast cancer. The targeting of HER overexpression was considered a major innovation to the concept of "personalized medicine."

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