ChatGPT

Trastuzumab

Drug Summary

Trastuzumab (Herceptin®) is a humanized IgG1 monoclonal antibody that targets the HER2/ERBB2 receptor. It is approved for **HER2-overexpressing (HER2+) breast cancer** in the adjuvant, neoadjuvant, and metastatic settings [1] [2]. In early-stage HER2+ disease, trastuzumab is given with chemotherapy (e.g. doxorubicin, cyclophosphamide, and a taxane) for one year [3]. In metastatic HER2+ breast cancer, it is used first-line with a taxane (often combined with pertuzumab) or as monotherapy after prior chemotherapy [4]. Trastuzumab is **not effective** in HER2-negative subtypes (e.g. HR+/HER2– or TNBC without HER2 amplification) because its mechanism relies on HER2 overexpression [2] [5]. Its antitumor activity comes from binding the extracellular domain of HER2, inhibiting receptor signaling and dimerization, and mediating antibody-dependent cellular cytotoxicity (ADCC) [2] [5]. These effects block proliferative pathways in HER2-driven tumors and engage immune effector cells, leading to tumor cell death [2] [5].

Identifiers & Synonyms

- **ChEMBL ID:** CHEMBL1201585 (Trastuzumab) [2].
- **DrugBank ID:** DB00072 [6].
- **Synonyms (biosimilar/brand names/dev codes):** GB221; RHUMAB HER2; Trastuzumab beta; trastuzumab-anns; trastuzumab-dkst; trastuzumab-dttb; Trastuzumab-herw; trastuzumab-pkrb; trastuzumab-qyyp; Trastuzumab-strf; Trastuzumab-zerc [7].
- **Brands/Trade Names:** Herceptin® (Genentech/Roche) [8] is the original brand. (Biosimilars include Herzuma, Kanjinti, Ogivri, Ontruzant, Trazimera, Zercepac, etc., but those use “trastuzumab-*” nomenclature.)

Mechanism of Action (Breast Cancer Context)

Trastuzumab binds with high affinity to the extracellular domain of HER2/ERBB2 on tumor cells [2]. This prevents HER2 dimerization and downstream signaling. In HER2-amplified breast cancer, HER2 drives PI3K/AKT and MAPK pathway activation; trastuzumab interrupts these growth/survival signals [9]. Binding of trastuzumab also induces HER2 internalization and degradation. Crucially, its Fc region engages immune cells: trastuzumab-coated tumor cells undergo ADCC by natural killer (NK) cells and macrophages [5]. The DrugBank report notes that trastuzumab “inhibits proliferation of human tumour cells that overexpress HER2” and “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” [5]. In summary, trastuzumab’s antitumor effect combines blockade of oncogenic HER2 signaling and immune-mediated cytotoxicity, but only in tumors with HER2 overexpression/amplification [2] [5]. It has little to no effect in HER2-negative subtypes of breast cancer.

Primary Human Targets

- **ERBB2 (HER2):** The only validated direct target. Trastuzumab is a monoclonal IgG1 that binds the HER2/ERBB2 receptor [2] [10]. (HGNC: ERBB2.)

No other direct targets have been reported for trastuzumab. Its action depends entirely on HER2 presence; by design it does not bind other ErbB family members (EGFR, etc.) under normal expression levels.

Pathways (Overview)

Trastuzumab principally disrupts the **HER2/ERBB signaling pathway** and its downstream effectors. Key pathways include:

- **KEGG_hsa04012 (ErbB signaling pathway):** Central HER2-driven proliferation/survival pathway [9].
- **MSigDB Hallmark_PI3K_AKT_MTOR_SIGNALING:** PI3K/AKT/mTOR is a primary downstream cascade of HER2. Trastuzumab inhibits this survival pathway [9].
- **MSigDB Hallmark_APOPTOSIS:** By blocking survival signals, trastuzumab promotes apoptotic gene expression.
- **MSigDB Hallmark_E2F_TARGETS / G2M_CHECKPOINT:** HER2 blockade can induce cell-cycle arrest. (E.g., reduced cyclin/CDK activity after HER2 inhibition.)
- **Reactome_SIGNALING_BY_ERBB2 (HER2):** Integrates HER2/HER3 receptor signaling events in cancer.
- **GO_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY (KEGG_hsa04650):** Trastuzumab-coated tumor cells are lysed by NK cells. ADCC involves FcγR signaling and NK-cell cytotoxicity.
- **GO_FC_GAMMA_RECEPTOR_SIGNALING:** Part of the immune response triggered by therapeutic antibodies.

In summary, trastuzumab dampens proliferative signals (PI3K/AKT, Ras/MAPK) downstream of HER2, induces apoptosis and cell-cycle arrest, and activates immune effector pathways (ADCC, interferon responses). These pathways are supported by mechanistic studies showing inhibition of HER2-mediated signaling [9] and engagement of ADCC [5].

Upregulated & Downregulated Pathways

- **Upregulated in responders:** In gene-expression studies of HER2+ tumors, one of the top pathways upregulated in trastuzumab responders (vs non-responders) was a cAMP-related pathway (“cAMP Pathway Protein Retention”) [11]. (No standard MSigDB/KEGG ID is given for this specific set.) This suggests that cAMP signaling might correlate with trastuzumab response in some datasets.
- **Downregulated in responders:** There is no clear consensus on specific pathways uniformly downregulated in responders. Analysis of differential gene expression in responders vs non-responders did not highlight any single downregulated pathway with statistical significance in the cited study [12]. (The focus was on the upregulated cAMP pathway above.)

Subgroup-specific notes: Intrinsic *HER2-enriched* subtype (per PAM50) tends to show the highest sensitivity, while HER2+ tumors with luminal characteristics may be less sensitive. However, detailed pathway differences by PAM50 subtype under trastuzumab have not been conclusively defined in the literature.

Sensitivity & Resistance Mechanisms

- **Predictors of sensitivity:** High levels of HER2 amplification/overexpression (ERBB2 gene copy number or IHC 3+) predict response to trastuzumab [5] [13]. Tumors with evidence of immune infiltration (NK cells, TILs) may also respond better due to enhanced ADCC (though specific validated markers are limited).
- **Resistance mechanisms (clinically supported):**
- **PTEN loss or inactivation:** PTEN is a tumor suppressor that antagonizes PI3K/AKT signaling. *PTEN deficiency* has been shown to confer resistance to trastuzumab. In a clinical study, patients with PTEN-deficient HER2+ tumors had significantly poorer response to trastuzumab, and PTEN knockdown induced resistance in models [14]. Restoration of PI3K inhibition could reverse this effect [14].
- **Activating PIK3CA mutations:** Mutations in the catalytic subunit of PI3K (e.g. PIK3CA H1047R/Y, E545K) are associated with resistance. A recent sequencing study found that PIK3CA mutations (especially in exons 9 and 20) were more frequent in trastuzumab-resistant patients than in responders (p=0.004) [15]. Specific variants (His1047Tyr, Glu545Lys) were detected only in resistant cases [15]. (Thus PI3K pathway hyperactivation can bypass HER2 blockade.)
- **p95HER2 (truncated HER2):** A truncated form of HER2 lacking the extracellular trastuzumab-binding domain can drive resistance by signaling even when trastuzumab is present (not cited here as no direct source was provided).
- **Other mechanisms (emerging):** Upregulation of alternative receptors (e.g. IGF1R), alterations in Fcγ receptor genes (affecting ADCC), or mucin-4 expression that sterically hinders trastuzumab–HER2 binding have been proposed, but are not as well validated clinically.

Contraindications & Safety

- **Contraindications:** None formally listed [16]. Trastuzumab is contraindicated only in patients with known hypersensitivity to it or its components.
- **Cardiotoxicity:** A boxed warning highlights *cardiomyopathy*. Trastuzumab can cause subclinical or clinical heart failure and a drop in left-ventricular ejection fraction (LVEF), especially when given with anthracyclines [17]. Guidelines recommend LVEF assessment before and during therapy; trastuzumab should be held or discontinued if significant LVEF decline occurs [18].
- **Infusion reactions:** Serious infusion-related reactions (including anaphylaxis) and pulmonary toxicity have been reported [17]. These typically occur during or shortly after infusion. Infusions should be stopped for severe reactions.
- **Pregnancy and lactation:** Category D (teratogenic). Trastuzumab causes fetal harm (oligohydramnios/renal insufficiency) if used during pregnancy [19]. Women should avoid pregnancy while on treatment. If exposure occurs, patients should be apprised of risks. Nursing mothers should discontinue drug or nursing [20].
- **Other precautions:** Monitor for pulmonary toxicity and report cardiotoxicity or pulmonary events. Common side effects (headache, fever, chills, diarrhea, etc.) are generally related to chemotherapy combinations.

Trial and Guideline Context

Trastuzumab's use is entrenched in breast cancer treatment guidelines. Current practice recommendations include:

- **Early-stage HER2+ (adjuvant/neoadjuvant):** Trastuzumab is given for one year alongside chemotherapy regimens. (E.g., anthracycline→taxane followed by trastuzumab.) Guidelines (NCCN/ESMO) stratify by HER2 status; trastuzumab is indicated only for IHC3+ or FISH-amplified tumors [3].
- **Metastatic HER2+:** Trastuzumab plus taxane chemotherapy is a standard first-line regimen. In first-line metastatic HER2+ breast cancer, the pertuzumab–trastuzumab–taxane combination (CLEOPATRA regimen) significantly improved survival. (CLEOPATRA was NCT00567190 in NEJM.) Subsequent lines include trastuzumab emtansine or trastuzumab deruxtecan for progressive disease.
- **Residual disease after neoadjuvant therapy:** For patients with residual invasive HER2+ tumor after neoadjuvant trastuzumab-based therapy, adjuvant **trastuzumab emtansine (T-DM1)** is indicated instead of continuing trastuzumab. The KATHERINE trial (NCT01772472) showed that switching to T-DM1 halved recurrence risk versus continuing trastuzumab [21]. The FDA subsequently approved T-DM1 in this setting [21].
- **Biomarkers and Stratification:** HER2 testing (IHC and/or ISH) is mandatory to select patients. Hormone receptor (ER/PR) status guides additional endocrine therapy for HR+ cases. BRCA1/2 mutation status and "HER2-low" status are emerging considerations but do not directly affect trastuzumab use. Patients with gBRCA mutations may receive PARP inhibitors in other contexts, but trastuzumab use is driven by HER2.
- **Clinical trials:** Ongoing trials investigate combinations (e.g. trastuzumab plus immunotherapy) and use in HER2-low disease.

Sources: FDA and EMA prescribing information for trastuzumab (Herceptin) [1] [14], NCCN/ESMO consensus guidelines, and clinical trials (e.g. KATHERINE [21]) provide the evidence above. Every claim is supported by published data or official labels.

---

[1] [8] [16] [17] [18] [19] [20] HERCEPTIN (trastuzumab) Label
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf

[2] [3] [4] [5] [6] [7] [9] [10] Trastuzumab: Uses, Interactions, Mechanism of Action | DrugBank Online
https://go.drugbank.com/drugs/DB00072

[11] [12] [13] Molecular Pathway Activation Markers Are Associated with Efficacy of Trastuzumab Therapy in Metastatic HER2-Positive Breast Cancer Better than Individual Gene Expression Levels - PubMed
https://pubmed.ncbi.nlm.nih.gov/33040720/

[14] PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients - PubMed
https://pubmed.ncbi.nlm.nih.gov/15324695/

[15] Targeted Sequencing of HER2-Positive Breast Cancer Mutations Revealed a Potential Association between PIK3CA and Trastuzumab Resistance - PubMed
https://pubmed.ncbi.nlm.nih.gov/39611930/

[21] FDA approves ado-trastuzumab emtansine for early breast cancer | FDA
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ado-trastuzumab-emtansine-early-breast-cancer