

# Trastuzumab: A Milestone in Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer

## Abstract

Human epidermal growth factor receptor 2 (HER2) overexpression is seen in 25% of breast cancers. Patients with HER2-positive breast cancer have aggressive disease and inferior survival. HER2 overexpression is assessed by immunohistochemistry or fluorescent *in situ* hybridization-based methods. Trastuzumab has shown to improve survival in HER2-positive breast cancer. It is recommended in patients with  $\geq T1c$  for 1-year duration in adjuvant setting, preferably given concurrently with taxane.

**Keywords:** Breast cancer, human epidermal growth factor receptor 2-positive disease, trastuzumab

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## Introduction

Human epidermal growth factor receptor 2 (HER2) overexpression is seen in 25% of breast cancers.<sup>[1]</sup> Patients with HER2-positive breast cancer have aggressive disease, higher chance of metastasis, and inferior survival.<sup>[2]</sup> HER2 overexpression is assessed by immunohistochemistry (IHC) or fluorescent *in situ* hybridization (FISH)-based methods. Trastuzumab has shown to improve survival in HER2-positive breast cancer.

## Mechanism of Action

Trastuzumab is an IgG<sub>1</sub> kappa recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity to the extracellular domain of (HER2) protein and prevents the activation of intracellular tyrosine kinase. Other mechanisms include prevention of HER2 receptor dimerization, increased endocytic destruction of receptor, and antibody-dependent cell-mediated cytotoxicity.<sup>[3]</sup> There are a few differences in the mechanism of action between trastuzumab and newer anti-HER2 therapy. Pertuzumab binds to subdomain 2 of HER2 receptors and blocks its ligand-dependent heterodimerization with HER1, HER3, and HER4. Lapatinib binds to the intracellular domain of epidermal growth factor receptor and HER2 and prevents the downstream signaling.

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## Discovery

In 1979, Robert Weinberg identified that HER2 gene was involved in multiple cancer pathways. Many years later, Dennis Slamon (UCLA) collaborated with Axel Ullrich (Genentech) and showed that HER2 positivity was associated with poor prognosis and trastuzumab improved survival.<sup>[4]</sup>

## Approval

In 1998, trastuzumab was Food and Drug Administration (FDA) approved for the treatment of HER2-positive metastatic breast cancer. In 2006, trastuzumab was FDA approved for the treatment of HER2-positive breast cancer as an adjuvant therapy. In 2010, trastuzumab was FDA approved for the treatment of HER2-positive metastatic gastric cancer.

## Human Epidermal Growth Factor Receptor 2 Positivity (ASCO/CAP Guideline)

Breast cancer and gastroesophageal cancer – HER2 is positive when IHC for HER2 neu is 2+ and FISH for HER2 neu is positive or IHC 3+.

## Indication

The National Comprehensive Cancer Network and the European Society of Medical Oncology guidelines recommend trastuzumab for patients with  $\geq T1c$  HER2-positive

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**Table 1: Clinical trials with trastuzumab**

<b>Trial</b>	<b>n</b>	<b>Inclusion</b>	<b>Randomization</b>	<b>DFS/PFS</b>	<b>OS</b>
NSABP B31/NCCTG 9831 <sup>[5]</sup>	4064	HER2-positive operable breast cancer	Chemotherapy Chemotherapy + trastuzumab	10-year DFS 62% versus 74% (HR=0.60; CI=0.53-0.68; $P<0.001$ )	10-year OS 75% versus 84% (HR=0.63; CI=0.54-0.73; $P<0.001$ )
HERA <sup>[6]</sup>	5102	HER2-positive early-stage breast cancer	Chemotherapy Chemotherapy + trastuzumab (1 year)	10-year DFS 63% versus 69% (HR=0.76; CI=0.68-0.86)	HR=0.74; CI=0.64-0.86)
BCIRG 006 <sup>[7]</sup>	3222	HER2-positive early-stage breast cancer	Chemotherapy Chemotherapy + trastuzumab	5-year DFS 75% versus 84%	5-year OS 87% versus 92%
Slamon <i>et al.</i> <sup>[8]</sup>	469	HER2-positive advanced breast cancer	Chemotherapy Chemotherapy + trastuzumab	Median PFS 4.6 m versus 7.4 m ( $P=0.001$ )	Median OS 20 m versus 25 m ( $P=0.01$ )
Finher <sup>[9]</sup>	232	HER2-positive node-positive or node-negative high-risk breast cancer	Weekly trastuzumab for 9 weeks No trastuzumab	3-year RFS 89% versus 76% (HR=0.42; CI=0.21-0.83; $P=0.01$ )	-

HER2: Human epidermal growth factor receptor 2, DFS: Disease-free survival, HR: Hazard ratio, CI: Confidence interval, PFS: Progression-free survival, OS: Overall survival

breast cancer in adjuvant setting. Patients with pT1b can be considered for trastuzumab if the tumor is hormone negative or Grade 3. Trastuzumab is preferably given concurrently with a taxane. The key trials on trastuzumab in HER2-positive breast cancer are mentioned in Table 1.

### Other Indication

Trastuzumab-based chemotherapy is recommended in advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma. Addition of trastuzumab to chemotherapy in advanced gastric/gastroesophageal junction adenocarcinoma improves overall survival (OS) by 2 months.<sup>[10]</sup>

### Strength

Trastuzumab is available as 440 and 150 mg vial. The reconstituted vial can be used until 28 days when stored at 2°C–8°C.

### Dose and Administration

The 3 weekly dose is 8 mg/kg loading intravenous over 90 min followed by maintenance 6 mg/kg over 30 min. The weekly dose is 4 mg/kg loading intravenous over 90 min followed by 2 mg/kg maintenance over 30 min. Subcutaneous trastuzumab has also shown to be noninferior to intravenous trastuzumab.<sup>[11]</sup> The recommended dose is 600 mg trastuzumab with 10,000 units hyaluronidase Q 3 weekly subcutaneous over 2–5 min. Intrathecal trastuzumab 20–50 mg can be used in HER2-positive leptomeningeal disease.<sup>[12]</sup>

### Regimens in Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer

- <3 cm, node negative: weekly paclitaxel for 12 cycles along with trastuzumab (1 year)<sup>[13]</sup>

- Node positive and higher stage: TCH (docetaxel, carboplatin, and trastuzumab) or AC (adriamycin and cyclophosphamide) followed paclitaxel with trastuzumab<sup>[7]</sup>
- Advanced/metastatic: THP (docetaxel, trastuzumab, and pertuzumab).<sup>[14]</sup>

### Duration

Trastuzumab is continued lifelong for patients with metastatic disease and 1 year for patients with non-metastatic disease. Persephone trial in early-stage breast cancer from the UK has shown 6 months of trastuzumab to be non-inferior to 1-year duration.<sup>[15]</sup> Short-course trastuzumab (weekly for 9 weeks) has shown to improve survival as compared to no trastuzumab.<sup>[16,17]</sup>

### Toxicity

#### Cardiotoxicity

Clinical trials have shown that the incidence of clinically significant cardiotoxicity with chemotherapy and trastuzumab was about 2%.<sup>[7]</sup> The risk factors for trastuzumab-induced cardiotoxicity are prior anthracycline usage, coronary artery disease, baseline systolic dysfunction (left ventricular ejection fraction <50%), diabetes, hypertension, dyslipidemia, and atrial fibrillation. Cardiotoxicity is lesser in patients who received short duration trastuzumab (6 months: 4%) as compared to long duration (1 year: 6%).<sup>[15]</sup>

#### Monitoring

No blood investigations are necessary before administration of trastuzumab. Echocardiogram has to be done before starting trastuzumab, every 3 monthly while on trastuzumab, and 6 monthly for 2 years after completion of trastuzumab.

Patients who have received prior anthracycline need to be monitored for 5 years after completion of trastuzumab. Trastuzumab should be temporarily withheld if LVEF drop is >10% and permanently withheld if patients develop symptomatic heart failure or after 2 withholds.

### Biosimilar

Biosimilars are game-changers in oncology and have made cancer care affordable and cost-effective. In 2017, the FDA approved the first biosimilar trastuzumab (Mylan) based on the Heritage trial.<sup>[18]</sup> This was a phase 3 randomized controlled trial with 500 patients with HER2-positive metastatic breast cancer, where trastuzumab biosimilar showed equivalent response rate (69% for biosimilar and 64% for innovator) at 24 weeks. The OS was also similar in both groups.<sup>[19]</sup>

### Newer anti-HER2 therapy

FDA approved other anti-HER2 therapy includes lapatinib, trastuzumab emtansine, pertuzumab, neratinib, and trastuzumab deruxtecan.<sup>[20]</sup> Tucatinib<sup>[21]</sup> is a newer anti-HER2 therapy that has shown promise in heavily pretreated advanced breast cancer.

### Conclusion

Trastuzumab has significantly improved survival in early, locally advanced, and metastatic HER2-positive breast cancer. It can cause cardiotoxicity and needs periodic monitoring with echocardiogram.

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### Conflicts of interest

There are no conflicts of interest.

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