

# Overview on Gastric Cancer

## Chapter 4

# HER-2: A Therapeutic Target in Gastric Cancer

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## 1. Introduction

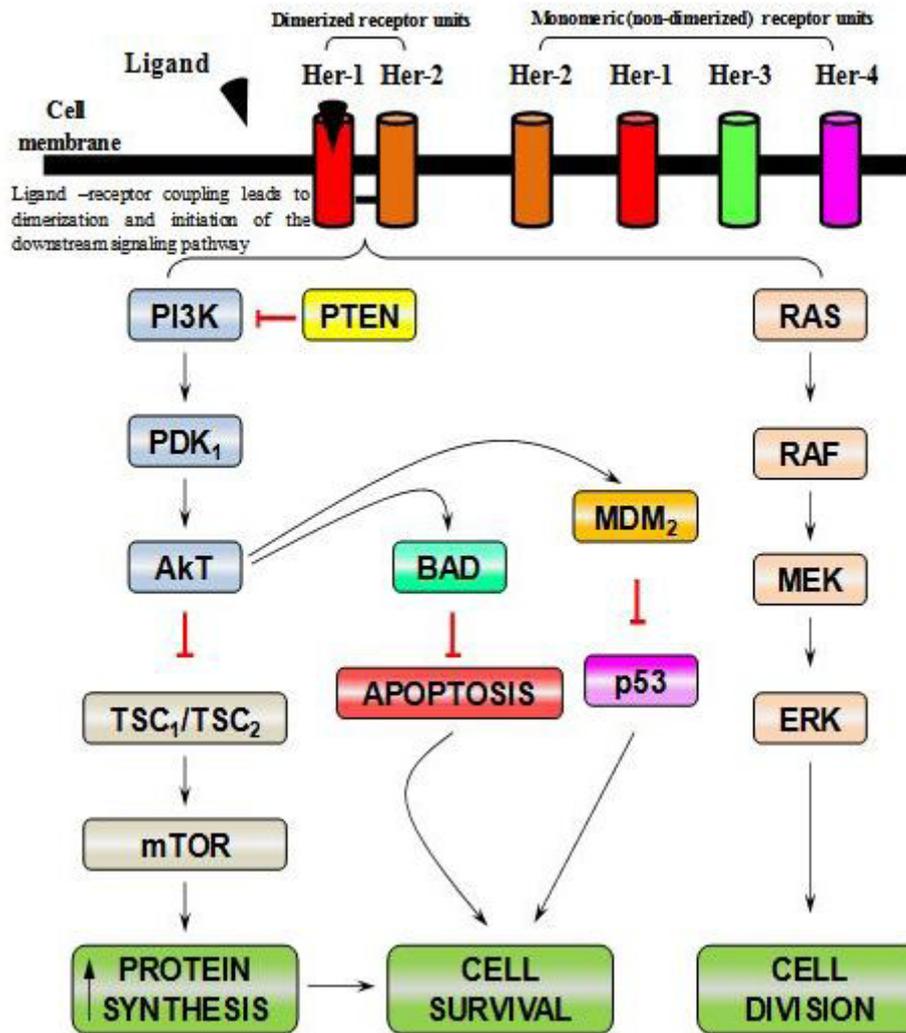
Globally, gastric cancer ranks to be the 5<sup>th</sup> most common cancer & 3<sup>rd</sup> leading cause of death [1]. As the disease presents with non specific early symptoms, it is often diagnosed in the advanced stages. In un-resectable cases, chemotherapy remains alternative line of treatment which might follow in recurrence of the disease. Recent advances assures us newer targeted therapies for better survival of gastric cancer patients. One such molecular target in limelight is Human Epidermal Growth Factor Receptor.

## 2. Cell Signaling

Her-2 is a protein encoded by proto-oncogene *C-erbB2*, located on chromosome 17q21. It belongs to Her family and is associated with cell growth (**Figure 1**). Over expression of Her-2 supports abnormal cell growth, cell survival and hence promotes malignant transformation.

## 3. Scoring of Her-2 Expression in Gastric Adenocarcinomas

Various techniques including immunohistochemistry (IHC) and Fluorescent in situ hybridization (FISH) is being used to study Her-2 expression. Researchers observed a vast variability of Her-2 expression in gastric adenocarcinomas. Hence, in order to reduce intra observer variability & to achieve consistency in results, Hofmann Validation Scoring is proposed which is based on IHC (**Table 1**) [4]. This scoring is assimilated by College of American Pathologist (CAP) & Food and Drug administration (FDA) [5].



**Figure 1:** Her family of proteins consists of four structurally related receptors Her-1, Her-2, Her-3 and Her-4. When a ligand (usually a growth factor) binds with these receptors, they dimerize with each other resulting in phosphorylation of intracellular portion of these receptors and activate different pathways. PI3K/AKT a pro-survival pathway, BAD an antiapoptotic protein and MAPK through RAF, RAS, and MAP2K/MEK & ERK leads to survival & proliferation of cells [2, 3]. Her=Human epidermal growth factor; PI3K/AKT=Phosphoinositide 3-kinase; PDK1=Pyruvate dehydrogenase kinase; TSC=Tuberous sclerosis; mTOR=Mammalian target of rapamycin; PTEN= Phosphatase & tensin homolog; BAD=Bcl2 associated death promoter protein; MDM2=Mouse double minute 2 homolog; p53=Tumor suppressor gene; RAS=Rat sarcoma; RAF= Rapidly accelerated fibrosarcoma; MEK=Mitogen activated protein kinase; ERK=Extracellular signal regulated kinases.

**Table 1:** Hofmann Validation Scoring [4]

Pattern of staining	% of tumor cells stained	Score
No staining	< 10% / <5%	0 / -ve
Faint/barely perceptible basolateral membrane stainin	>10% / >5%	1+ / -ve
Weak to moderate complete membrane/basolateral membrane staining	>10% / >5%	2+/equivocal
Strong complete membrane/ Basolateral membrane staining	>10% / >5%	3+ / +

#### 4. Use of trastuzumab in Her-2 positive gastric adenocarcinomas

Trastuzumab is a humanized monoclonal antibody which has affinity and specificity for Her-2. Its mechanism of action includes various modalities including arresting the growth of tumor cells at G<sub>1</sub> phase of the growth cycle and down regulation of Her-2 by down streaming the PI3K cascade pathway [6]. Antibody dependent cellular cytotoxicity (ADCC) is another mechanism by which trastuzumab acts by attracting the immune cells towards the tumor sites [7]. It has shown promising results as a targeted therapy in Her-2 positive breast carcinomas. In order to investigate if trastuzumab can also be used in Her-2 positive gastric adenocarcinomas, a randomized controlled phase 3 trial, the ToGA trial (Trastuzumab with chemotherapy in Her-2 positive gastric cancer) was conducted at 122 centres in 24 countries amongst 3803 gastric adenocarcinoma and gastroesophageal junctional adenocarcinoma patients. Of these patients, 810 patients (22%) were Her-2 positive. The Her-2 positive patients were divided into 2 groups: patients in group I were treated with chemotherapy and trastuzumab while patients in group II were treated with chemotherapy alone. The median survival of the patients for group I was 13.8 months while that for group II was 11.1 months. This corresponded to 26% reduction in death rate of patients treated with trastuzumab and 36% reduction in death rate of patients treated with trastuzumab who expressed high Her-2 receptor. Based on the results obtained from the ToGA trial, trastuzumab has been approved in Japan, USA and Europe for those metastatic gastric adenocarcinomas which show over-expression of Her-2 at a score of 3+ in IHC and a positive score at FISH [8]. Favorable outcomes of trastuzumab with chemotherapy have been stated by few of the case reports. [9,10] More clinical trials are underway to develop and introduce other  $\alpha$ -Her-2 drugs to be used in clinical practice for Her-2 positive gastric cancer patients[11].

#### 5. References

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