Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Long-term response to trastuzumab in patients with HER2-positive advanced gastric or gastroesophageal adenocarcinoma

Autor: Isabel Porth
Institut / Klinik: Pathologisches Institut
Doktorvater: Prof. Dr. T. Gaiser

Gastric cancer is the fifth most prevalent cancer type, with the fourth highest cancer-related mortality worldwide. Since 2010, the HER2-targeting agent trastuzumab has been approved as a first-line therapy in combination with chemotherapy for HER2-positive advanced/metastatic gastric or gastroesophageal junction cancer. However, despite improvement of overall survival through trastuzumab treatment, the median overall survival with 13.8 months remains poor. However, a subgroup of patients with long-term response to trastuzumab has been observed in small studies and case reports. Genetic alterations and the level of HER2 gene amplification have been proposed to identify patients with trastuzumab long-term response. Despite this, a biomarker for superior response - beyond conventional HER2 testing - to trastuzumab remains elusive.

This study aimed to identify a biomarker that could distinguish between HER2-positive gastric cancer patients with long-term and short-term response to trastuzumab plus chemotherapy.

FFPE tumor samples and follow-up data of 19 patients with HER2-positive advanced/metastatic gastric or gastroesophageal junction cancer who underwent trastuzumab-containing therapy were retrospectively collected from four German clinical centers. The patients were divided into long-term (n=7) and short-term responding groups (n=12) according to progression-free survival on trastuzumab-containing therapy (PFS≥12 months vs. PFS<12 months). A comprehensive genetic and gene expression analysis was performed. In addition, established biomarkers HER2, PD-L1 and MSI were analyzed.

An automated analysis pipeline was developed to detect genetic alterations such as somatic single nucleotide variants and copy number alterations. The copy number of the HER2 gene, *ERBB2*, could not distinguish between trastuzumab long-term and short-term response in gastric cancer patients. However, two somatic non-synonymous mutations were detected in *ERBB2,* and both mutations occurred in patients with long-term response to trastuzumab. Other genetic alterations and the tumor mutational burden were not correlated with response to trastuzumab. The HER2 protein expression pattern was also evaluated, and the results showed that patients with homogeneous HER2 expression pattern had improved progression-free survival on trastuzumab-containing therapy.

Evaluation of the biomarker PD-L1 revealed a higher PD-L1 combined positive score in long-term responding patients, and a positive correlation between PD-L1 combined positive score and PFS in the overall study population. PD-L1 positivity, defined as a combined positive score ≥1, was associated with improved PFS on trastuzumab-based treatment. Furthermore, using bioinformatics methods, increased PD-L1 combined positive scores could be associated with a higher level of CD4+ memory T-cells.

In conclusion, genetic alterations and the tumor mutational burden were not correlated with response to a trastuzumab-containing therapy, while a homogeneous HER2 protein expression pattern and PD-L1 combined positive score were identified as potential biomarkers for improved progression-free survival. The findings highlight the clinical relevance of PD-L1 for the treatment of HER2-positive advanced gastric and gastroesophageal adenocarcinoma.