Molecular Targeted Therapy of Gastric Adenocarcinoma

Subjects: Oncology

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Gastric cancer is characterized by poor survival despite surgery and chemotherapy. Current research focusses on biomarkers to improve diagnosis, prognosis and to enable targeted treatment strategies. The aim of our review was to give an overview over the wide range of novel biomarkers in gastric cancer. These biomarkers are targets of a specitif treatment, like antibodies against human epidermal growth factor receptor 2. Other promising biomarkers for targeted therapies that have shown relevance in clinical trials are vascular endothelial growth factor, programmed cell death protein 1 and Claudin 18.2.

Keywords: gastric cancer ; targeted therapy ; biomarkers

1. Human Epidermal Growth Factor Receptor 2

Human epidermal growth factor receptor 2 (HER2), also called ERBB2, is a receptor tyrosine-protein kinase. It is an important biomarker and key driver of tumorigenesis in GC [1]. HER2-positive tumors show *HER2* gene amplification that is generally, although not always, associated with protein overexpression, leading to tumorigenesis [2]. *HER2* acts as an oncogene, mainly because high-level amplification of the gene induces protein overexpression in the cellular membrane and subsequent acquisition of advantageous properties for a malignant cell [3]. *HER2* gene amplification can be detected by fluorescence in situ hybridization (ISH), whereas overexpression of HER2 protein is commonly assessed by immunohistochemistry (IHC). Concordance between positive gene amplification and protein overexpression has been observed in 96% of GC, whereby positive *HER2* amplification was defined as a *HER2*/chromosome 17 centromere (CEP17) ratio ≥ 2.0 [4].

HER2-positivity rates by IHC in GC range between 10.9 and 27% [4][5][6][7][8][9]. HER2-positivity rates are higher in papillary and tubular adenocarcinoma compared to poorly differentiated adenocarcinoma or signet-ring cell carcinoma [6]. For clinical use, it has been proposed to test the HER2 status in all adenocarcinoma of the stomach and carcinomas of the GEJ by IHC first. In inconclusive cases, *HER2* amplification status needs to be assessed with ISH [10].

HER2-targeted therapy has dramatically improved outcomes for HER2-positive gastric cancer. Trastuzumab is a monoclonal antibody targeting the HER2-receptor, causing downregulation of HER2. The Trastuzumab for Gastric Cancer (ToGA) trial showed improved overall survival (OS) of patients treated with trastuzumab in combination with cisplatin and a fluoropyrimidine compared to chemotherapy alone in patients with HER2-overexpressing advanced gastric or GEJ cancer (13.8 vs. 11.1 months, $p = 0.005$) [1]. A subgroup analysis of Japanese patients confirmed the benefit of adding trastuzumab to chemotherapy [11]. Trastuzumab in combination with chemotherapy is the standard of care when treating HER2-positive metastatic gastric and GEJ cancers. Furthermore, it is the first molecular targeted agent approved as standard treatment in gastric cancer.

A retrospective analysis compared OS in advanced GC patients according to HER2 status and exposure to trastuzumab. It showed longer OS of HER2-positive patients treated with trastuzumab than HER2-negative patients (24.7 vs. 13.9 months, $p = 0.03$), with trastuzumab having a significant impact on OS. Interestingly, HER2-positive patients not treated with trastuzumab showed similar OS as HER-negative patients (13.5 vs. 13.9 months, $p = 0.91$). The authors concluded that trastuzumab improved prognosis of HER2-positive beyond that of HER2-negative AGC patients, but HER2 status itself without targeted therapy might have a small impact on survival in advanced GC [12].

2. Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) overexpression is reported in 27–55% of GC, and it is associated with shortened overall survival by multivariate analysis [13].

Lapatinib is a dual tyrosine kinase inhibitor that blocks both the HER2 and epidermal growth factor receptor (EGFR) pathways. In a phase 2 trial, lapatinib was tested as first-line single therapy in metastatic GC and showed only modest activity, with a PFS of 1.9 months and an ORR of 9% [14]. Addition of lapatinib has not proven to be superior to conventional chemotherapy in terms of OS and PFS, neither in first- nor in second-line treatment of advanced GC [15][16][17][18]. In a phase 2 trial with lapatinib and capecitabine as first-line treatment, lapatinib induced no changes in gene expression, and no associations between single nucleotide polymorphisms and treatment outcome were found [19].

Panitumumab, a monoclonal antibody to EGFR, has shown no advantage in terms of histological response, OS, and PFS in patients with untreated advanced esophageal, gastric, or GEJ cancer when added to conventional first-line chemotherapy, compared to chemotherapy alone [13][20].

Similarly, nimotuzumab, also a monoclonal antibody to EGFR, in combination with irinotecan has shown no superiority in PFS compared to irinotecan alone as second-line therapy in advanced GC. Interestingly, there was a trend toward better response rate, OS, and PFS with nimotuzumab in the subgroup with high EGFR expression levels [21].

Cetuximab, another monoclonal antibody directed against EGFR, is primarily known as a treatment in metastatic colorectal cancer. Several nonrandomized phase 2 trials without a control group have investigated cetuximab in combination with conventional chemotherapy. As a first-line treatment, overall response rates (ORR) between 45 and 65%, PFS between 5 and 9 months, and OS between 9 and 17 months have been reported [22][23][24]. In the randomized EXPAND trial, cetuximab was tested in combination with capecitabine and cisplatin compared to chemotherapy alone in previously untreated advanced GC without any survival benefit [25]. As a second-line therapy, addition of cetuximab to conventional chemotherapy has shown more limited treatment response [26].

Studies analyzing the impact of EGFR expression on survival and treatment response showed inconsistent results. EGFR expression was associated with better OS and a higher response rate in advanced GC under EGFR-directed therapy [23][27], while other studies showed no impact of EGFR expression on survival and treatment response [24][26]. Taken together, it remains unclear if EGFR is a prognostic or predictive biomarker.

3. Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) plays a role in pathogenesis and progression of GC.

Ramucirumab, a monoclonal antibody that binds to VEGF receptor-2, was tested in the RAINBOW trial in combination with paclitaxel. This was a randomized placebo-controlled and double-blind study of 665 patients with advanced gastric or GEJ cancer with disease progression on or after first-line chemotherapy. Compared to paclitaxel alone, overall survival was significantly longer with ramucirumab [28].

Bevacizumab, a monoclonal antibody to VEGF, was tested in the AVAGAST study in untreated patients with advanced GC. Adding bevacizumab to chemotherapy did not improve OS, but led to a longer PFS and higher ORR compared to chemotherapy alone [29]. Meulendijks et al. investigated the efficacy of bevacizumab in combination with chemotherapy in untreated advanced gastric and GEJ cancer in two phase 2 trials without a control group. In HER2-negative patients PFS was 8.3 months and OS was 12 months, while in HER2-positive patients, a combination of trastuzumab and bevacizumab led to a PFS of 10.8 months and an OS of 17.9 months [30][31].

Sunitinib, a tyrosine kinase inhibitor targeting platelet-derived growth factor (PDGF) receptor and VEGFR, was tested as monotherapy in pretreated patients with advanced GC. It was associated with very limited tumor response [32]. Sunitinib did not improve PFS or response as an adjunct to FOLFIRI compared to FOLFIRI alone in chemotherapy-resistant GC [33].

Foretinib, another multikinase inhibitor targeting MET and VEGFR-2, lacked efficacy in metastatic GC [34].

Several studies have analyzed the impact of VEGF on survival in advanced GC. They consistently showed a negative association between VEGF levels and survival, indicating that VEGF is a negative prognostic biomarker [26][32][33][35]. In a biomarker study from the RAINBOW trial, all analyzed biomarkers including VEGF were not predictive for ramucirumab efficacy [36].

4. Fibroblast Growth Factor Receptor

Won et al. tested the efficacy of a combined inhibition of VEGF receptors 1–3, PDGF receptor, and fibroblast growth factor receptor (FGFR) 1–3 with the tyrosine-kinase inhibitor nintedanip. In patients with metastatic esophageal or GEJ adenocarcinoma and disease progression on first-line chemotherapy, treatment with nintedanip showed no partial or complete response [37].

The selective FGFR 1–3 tyrosine kinase inhibitor AZD4547 was tested as a second-line therapy in patients with advanced GC in the randomized controlled SHINE study, and did not improve PFS compared to paclitaxel [38].

The prognostic value of FGFR was analyzed in advanced GC treated with multikinase inhibitors. FGFR2 expression was a significant prognostic factor for PFS with pazopanib, while there was only a trend to better PFS with nintedanip [37][39].

5. Hepatocyte Growth Factor Receptor

Hepatocyte growth factor receptor (HGFR), also called c-Mesenchymal-Epithelial Transition (MET), is a tyrosine kinase receptor. MET overexpression is highly heterogenous and uncommon in GC by immunohistochemistry [40].

The MET signaling pathway plays an integral role in GC. An aberrant, overactivated MET pathway promotes disease progression, and serves as a common mechanism of resistance to *HER*-targeted therapy. Beyond anti-HER2 therapy, the MET pathway seems to be a culprit of cancer invasiveness, with MET-overexpressing tumors having poorer prognosis [41].

Rilotumumab, a monoclonal antibody to MET, was tested against placebo in combination with chemotherapy in advanced or metastatic gastric or GEJ adenocarcinoma without testing MET status. PFS was longer with rilotumumab [42]. Zhu and colleagues found that high rilotumumab exposure was associated with better PFS compared to low exposure and placebo among patients with MET-positive tumors [43]. A randomized phase 3 trial testing rilotumumab against placebo in combination with chemotherapy was stopped early due to higher mortality in the rilotumumab group [44]. MET positivity was defined in both trials as 25% or more of membranous staining of tumor cells in IHC.

Several other tyrosine kinase inhibitors targeting the HGF/MET pathway were studied in MET-positive gastric cancer, but no substantial benefit was proven [45]. Thus, onartuzumab was tested in a phase 3 trial against placebo in combination with chemotherapy in HER2-negative, MET-positive gastroesophageal cancer and showed no improvement in survival or response rates [46].

MET expression has been shown to be a prognostic factor in locally advanced gastric and GEJ cancer treated with chemotherapy and panitumumab, as it was associated with shorter PFS and OS [20]. Resistance to the kinase inhibitor afatinib was associated with MET amplification in advanced GC [47]. Hence, MET might be predictive for decreased treatment response.

6. Claudin 18.2

In normal tissue, the tight junction molecule Claudin 18.2 is only expressed on the membrane of differentiated epithelial cells of the gastric mucosa. Its expression is activated in primary and GC and GC metastases, but also in malignancies of the pancreas, esophagus, ovaries, and the lung [45]. Claudin 18.2 expression is found in 77–87% of primary GC, and in 51–80% of lymph node metastasis [45][48]. The exclusive expression of Claudin 18.2 in differentiated gastric cells, in combination with the fact that transient gastrointestinal toxicity is a frequent and manageable adverse event, makes this molecule highly attractive as a target for the development of safe and potent drugs [45].

The monoclonal antibody zolbetuximab targets Claudin 18.2. In the FAST trial, patients with advanced gastric, GEJ, or esophageal adenocarcinoma and with moderate-to-strong Claudin 18.2 expression in ≥40% of tumor cells received chemotherapy with or without zolbetuximab. Patients treated with zolbetuximab had significantly higher PFS and OS, with an even more pronounced difference in the subpopulation with very high Claudin 18.2 expression [49]. The ongoing SPOTLIGHT study compares the effect of zolbetuximab against placebo in combination with chemotherapy as a first-line therapy in Claudin-18.2-positive and HER-2-negative advanced gastric or GEJ cancer [50].

7. Ataxia Teleangiectasia Mutated

Ataxia telangiectasia mutated (ATM) is a key activator of DNA damage response. GC cell lines with low levels of ATM are sensitive to the poly ADP ribose polymerase (PARP) inhibitor olaparib, which prevents tumor cells from repairing DNA

damage from chemotherapy. Olaparib was tested against placebo in combination with paclitaxel in patients with metastatic GC and showed improved OS in both the overall population and the population with low ATM levels, but no difference in PFS or response rates [51].

8. AKT

Ipatasertib is a small molecule inhibitor of AKT, a key component of the PI3K/AKT pathway. When tested in a randomized controlled trial in combination with FOLFOX6 against placebo, it did not improve PFS. No benefit was observed in biomarker-selected patients (PTEN-low, PI3K/AKT-activated tumors) [52].

9. Histone Deacetylase

Vorinostat, an inhibitor of histone deacetylase (HDAC), was investigated in combination with capecitabine and cisplatin as a first-line chemotherapy in advanced GC, and showed an ORR of 42% and a 6-month PFS rate of 44%. As in a previous phase 3 study with capecitabine and cisplatin with a 6-month PFS rate of 40%, the addition of vorinostat was not likely to enhance efficacy. A biomarker analysis using Western blotting included plasma levels of atecyl-H3, HDAC2, and p21. None of these three biomarkers correlated with PFS, but high baseline acetyl-H3 and p21 were significantly associated with worse OS [53].

10. Matrix Metalloproteinase-9

Matrix metalloproteinases are proteases involved in degradation and remodeling of the extracellular matrix and basement membranes. Matrix metalloproteinase-9 (MMP9), which is expressed heterogeneously by tumor epithelia and infiltrating inflammatory cells, has been associated with loss-of-tumor suppression activity, as well as oncogenic activity [54].

Andecaliximab, a monoclonal antibody targeting MMP9, showed encouraging results in a phase 2 trial, but failed to show improved OS in the ensuing randomized GAMMA-1 trial [55].

11. Immunotherapy

Programmed cell death protein 1 (PD-1) is located at the surface of immune cells, and functions as an immune checkpoint by regulating the immune response. Programmed cell death ligand 1 (PD-L1) binds to PD-1 and inhibits the immune response through inhibition of T-cell receptor-mediated lymphocyte proliferation and cytokine secretion, among other mechanisms [56]. PD-L1 expression is measured with IHC, and PD-L1 positivity is defined as a combined positivity score (CPS) ≥ 1, where CPS is the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100 [57].

In the molecular evaluation of gastric adenocarcinoma as part of the TCGA project, PD-L1/2 expression was elevated in EBV-positive tumors, suggesting that PD-L1/2 antagonists should be tested in this subgroup [58]. This was confirmed by Liu and colleagues, who found PD-L1 expression significantly associated with MSI, EBV-positive, and H. pylori status. There was a greater proportion of PD-L1 CPS ≥ 1 tumors among MSI-H versus microsatellite stable (MSS), EBV-positive versus EBV-negative, and H. pylori-positive as compared to H. pylori-negative tumors. PD-L1 CPS ≥ 1 was observed in 49.7% of EBV-negative and MSS tumors [57].

Pembrolizumab, a monoclonal antibody to PD-1, was tested in the phase 1b KEYNOTE-012 trial in patients with PD-L1-positive recurrent or metastatic gastric or GEJ adenocarcinoma, and showed an objective response rate of 22% and a rate of grade 3–4 treatment-related adverse events of 13% [59]. In the following phase 2 KEYNOTE-059 trial, pembrolizumab was tested in 259 patients with disease progression after two or more lines of chemotherapy. PD-L1 expression was assessed in tumor biopsy samples by immunohistochemistry. Tumors were considered PD-L1 positive if the combined positive score (number of PD-L1-positive cells including tumor cells, macrophages, and lymphocytes divided by the total number of tumor cells, multiplied by 100) was 1 or greater. Response to pembrolizumab treatment was observed in both PD-L1-positive and -negative tumors, but was higher in patients with PD-L1-positive compared to PD-L1-negative tumors (15.5 vs. 6.4%, $p = 0.02$). There was no difference in OS between patients with PD-L1-positive and PD-L1-negative tumors (5.8 vs. 4.9 months) [60].

Kim et al. observed very high ORR with pembrolizumab in patients with MSI-high (85.7%) and EBV-positive (100%) metastatic GC [61]. These results were in line with higher immunogenicity of MSI or virally induced tumors in other localizations, such as gynecologic malignancies [62].

More recently Kawazoe et al. tested pembrolizumab in combination with the oral fluorouracil derivate S-1 plus oxaliplatin as a first-line treatment in patients with PD-L1-positive and HER2-negative advanced gastric or GEJ cancer, and observed high ORR [63].

A recent single-arm phase 2 trial investigated the combination of pembrolizumab with a HER2-targeting antibody as a proof of concept of synergistic antitumor activity. Janjigian et al. tested trastuzumab and pembrolizumab plus conventional chemotherapy as a first-line therapy in HER2-positive metastatic gastric or GEJ cancer. The PFS at 6 months was 70% [64]. The combination of pembrolizumab and trastuzumab is currently being further tested in the ongoing KEYNOTE-811 randomized controlled trial [65].

Margetuximab, a novel anti-HER2 monoclonal antibody, was evaluated in a single-arm phase 1b-2 trial in combination with pembrolizumab in HER2-positive, PD-L1-unselected gastric or GEJ cancer on progression after chemotherapy with trastuzumab. This phase 1b/2 trial showed a considerable ORR of 18.5%. This study confirmed that combined targeting of HER2 and PD-1/PD-L1 could yield antitumor activity greater than that with either approach alone [66].

The anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab were tested alone or in combination in patients with chemotherapy-refractory gastric or GEJ cancer. ORR and PFS were low and did not differ between treatment arms [67].

Toripalimab, a monoclonal antibody to PD-1, was given as monotherapy in a group of patients with chemo-refractory GC, and in combination with chemotherapy in a group of chemotherapy-naïve patients. With toripalimab, monotherapy ORR was 12.1%, while in combination with chemotherapy, the ORR was 66.7% [68].

In the ATTRACTION-2 trial, the PD-1 antibody nivolumab was tested against placebo in patients with advanced gastric or GEJ cancer refractory to two or more regimens of chemotherapy. OS was significantly longer with nivolumab compared to placebo at 2-year follow-up. The authors concluded that nivolumab might be a new treatment option for heavily pretreated patients with advanced gastric or GEJ cancer [69].

The CheckMate 577 trial showed that Nivolumab was efficient as an adjuvant treatment in patients with resected esophageal or GEJ cancer who had received neoadjuvant chemoradiotherapy and had residual pathological disease. Disease-free survival was 22.4 months with nivolumab compared to 11 months with placebo ($p < 0.001$) [70].

The JAVELIN Gastric 100 trial, which tested the PD-L1 antibody avelumab against chemotherapy maintenance after first-line induction chemotherapy in locally advanced or metastatic gastric or GEJ cancer, showed no superior OS with avelumab, both in an overall and PD-L1-positive population [71].

The anti-PD-1 antibody SHR-1210 was tested as a second-line treatment in advanced GC, and showed an ORR of 26.7% [72].

There was no association of PD-L1 expression with treatment outcome in advanced GC treated with toripalimab and SHR-1210 [68][72].

In conclusion, PD-L1 is a prognostic biomarker and predictive for response to pembrolizumab therapy. Based on the results of the KEYNOTE-059 trial, pembrolizumab was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with recurrent, locally advanced, or metastatic gastric or GEJ adenocarcinoma with disease progression on or after two or more systemic therapies, and whose tumors express PD-L1 [60][73]. As mentioned above, there might be a role of combined targeting of HER2 and PD-1/PD-L1. The recently published CheckMate 577 trial showed that nivolumab is also highly efficient as an adjuvant treatment in patients at risk for recurrence, regardless of PD-L1 expression [70]. Therefore, the main role of immunotherapy may be to prevent recurrence, rather than to treat metastatic or advanced disease in the future.

Adjuvant immunotherapy with autologous cytokine-induced killer cells has been assessed in a nonrandomized study for patients after gastrectomy and subsequent chemotherapy for locally advanced GC. Compared to a control group without immunotherapy, patients treated with cytokine-induced killer cells had longer 5-year disease-free survival. For patients with intestinal-type tumors, OS and disease-free survival were significantly higher for patients with immunotherapy. Subgroup analysis of patients with diffuse or mixed-type tumors showed no survival benefit from adjuvant immunotherapy [74].

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