International Journal of Gastroenterology Sciences
Online ISSN: 2664-9217, Print ISSN: 2664-9209
Received: 03-04-2019; Accepted: 04-05-2019; Published: 03-06-2019
www.gastroenterologyjournals.com
Volume 1; Issue 1; 2019; Page No. 11-20

Targeted therapy in gastric cancer: Review of literature

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Abstract
Gastric cancer (GC) is the second leading cause of cancer-related death, and despite having improved treatment modalities over the last decade, for most patients, only modest improvements have been seen in overall survival. Conventional chemotherapy and radiation have shown limited efficacy for advanced gastric cancer, showing an overall survival (OS) rate of ~10 months. Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2), is the first approved molecularly targeted agent for HER2-overexpressing gastric cancer, which was found to prolong the OS and the progression free survival (PFS) of patients. Angiogenesis is a vital process in the progression and metastasis of solids tumors including gastric adenocarcinoma. Monoclonal antibodies, soluble receptors, and small molecule tyrosine kinase inhibitors have been developed to inhibit tumor angiogenesis: The recent REGARD trial RAINBOW trial for advanced pretreated gastric cancer confirmed the survival advantage of this anti-angiogenic agent in gastric cancer.

Keywords: gastric, HER2, trastuzumab, bevacizumab, target, therapie

1. Introduction
Gastric cancer is one of the most commonly diagnosed cancers worldwide. Around 700,000 people die due to gastric cancer every year. This makes gastric cancer the second most common cause of cancer related death in the world [1]. Western countries report a lower incidence of gastric cancer, patients, however, have a higher mortality due to advanced stages of disease at the time of diagnosis [2]. a 5-year overall survival (OS) under 10 % and a median OS under 12 months remains the poor outcome for patients with metastatic disease [3], Chemotherapy is the most common therapy for advanced gastric cancer, but efficacy is limited. Targeted therapy, as a new strategy, may improve the survival of advanced gastric cancer patients. Here, we review the clinical trials related to targeted therapies for gastric cancer, such as anti-EGFR signaling including anti-human epidermal growth factor receptor 2 (HER2) and anti-EGFR1, anti-VEGF signaling, anti-mTOR, tyrosine kinase inhibitors (TKIs) and anti-MET.

Material and methods
An analytical and comparative PubMed research for targeted therapy in gastric cancer was executed. Results were implemented into a critical analysis and discussion of the state of the art-targeted therapy of gastric cancer.

Results
Anti-EGFR signaling
The epidermal growth factor receptor (EGFR/HER1) belongs to a receptor tyrosine kinase protein family that includes HER2/neu, HER3 and HER4 (4). The EGFR is a transmembrane glycoprotein receptor for the EGF family of extracellular protein ligands [5] that is overexpressed in several gastrointestinal malignancies. It is activated by specific ligands, such as epidermal growth factor (EGF), Transforming growth factor-α, amphiregulin, heparinbinding EGF, betacelulin, epiregulin, and neuregulin 2-α. Ligand binding can induce homodimerization or heterodimerization with consequent tyrosine kinase auto phosphorylation and activation [6]. Overexpression of EGFR occurs in 30–50% of GC and has been associated with older age, more aggressive histology, and advanced stage [7, 8]. With regards to KRAS, it has been reported that a very low percentage of patients with GC are found to have the mutation, suggesting that, based on the colon-rectal clinical treatment lessons, the anti-EGFR-antibodies would not be an optimal treatment in GC [9]. EGFR pathway and relative target of mAbs are reported in Fig. 1.

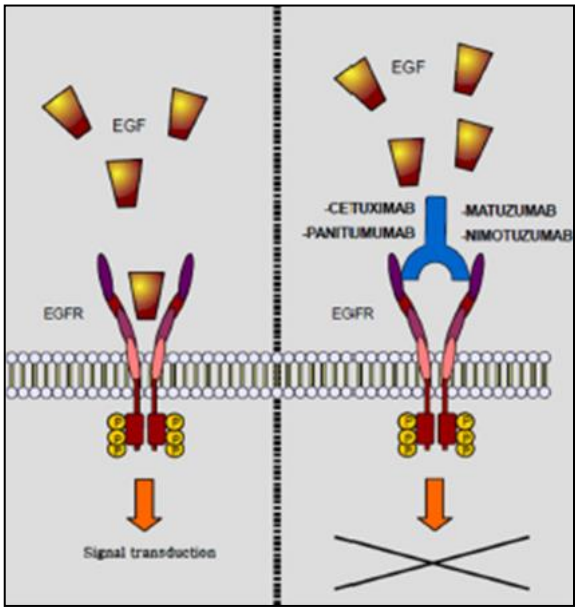

Fig 1: Monoclonal antibodies targeting EGFR pathway

Therapies anti EGFR

In most clinical trials the patients are not selected according to EGFR expression status. Several phase III clinical trials studied the effect of antibodies targeting EGFR in advanced gastric or gastroesophageal junction cancer (Table 1). Cetuximab, a mouse/ human chimeric monoclonal antibody targeting the extracellular domain I of EGFR and thereby preventing EGFR from binding with its endogenous ligands, was used in the randomized open-label phase III EXPAND trial in a first line setting in addition to capecitabine and cisplatin (10). No difference in progression-free survival (4.4 vs 5.6 months; HR 1.09; 95% CI: 0.92 to 1.29), overall survival (9.4 vs 10.7 months; HR 1.00; 95% CI: 0.87 to 1.17) or overall response (29% vs 30%) was seen when chemotherapy plus cetuximab vs chemotherapy alone group were compared (10). In the REAL3 randomized open-label phase III trial the human monoclonal antibody panitumumab, which binds to the extracellular domain III of the EGFR and prevents its ligand-induced activation, was used in combination with chemotherapeutic agents. Unexpectedly, the addition of panitumumab to standard therapy did reduce the overall survival (8.8 vs 11.3 months; HR 1.37; 95% CI: 9.6 to 13.0) and is thus not recommended for use in an unselected population [11]. No phase III trials with EGFR tyrosine kinase inhibitors (TKIs) gefitinib or erlotinib are ongoing, due to only modest benefits as monotherapy or in combination with chemotherapy in gastric cancer, as observed in phase II trials (12–13). Another phase II trial (SPIGA) is evaluating the efficacy and safety of panitumumab in combination with docetaxel and cisplatin in patients with untreated GC carcinoma [14]. This study is ongoing, but not recruiting participants. According to the published results, the addition of panitumumab does not seem to be a beneficial therapeutic option for advanced GC.

HER2 targeting agents

Overexpression of HER2 in patients with gastric cancer ranges from 6% to 23% [15, 16]. Depending on the location of the primary tumor, rates of HER2 amplification varies. Recent studies report a less common finding in distal gastric cancers, whereas overexpression of HER2 is more common in cancers of the gastroesophageal [17, 18, 19]. HER2 amplification was predominantly seen in intestinal type (32%) than in diffuse (6%) or mixed type gastric cancers (20%). In gastric cancer, the expression of HER2 is primarily determined by using immunohistochemistry (IHC) and/or by detecting HER2 gene amplification by in situ hybridization (ISH) as described previously by Hofmann *et al*. in 2008. Rüschoff *et al*. reassessed this method in 2010 [20, 21]; Fig 2.

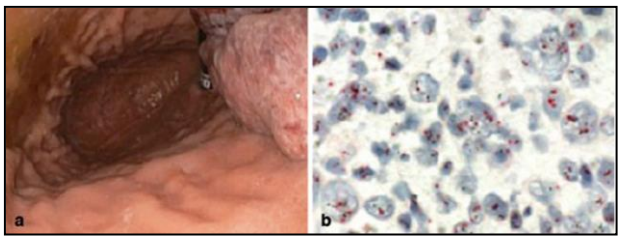

Fig 2: a Esophagogastroduodenoscopy showing a gastric adenocarcinoma in the fundus ventriculi. b Dual-color in situ hybridization: *red* centromere chromosome 17, *black* the HER-2 gene. Note that the ratio of HER-2 gene copies/ centromere 17 is < 2 in the majority of cells. Original magnification x600

Although the overexpression of HER2 was considered to be a negative prognostic factor in breast cancer associated with a worse OS, to date, the association between HER2 status and the prognosis of GC patients remains controversial. Nevertheless, inhibition of the HER2 pathway in HER2-positive GC patients demonstrated clinical benefits. HER2 pathway and relative target of mAbs are reported in Fig. 3.

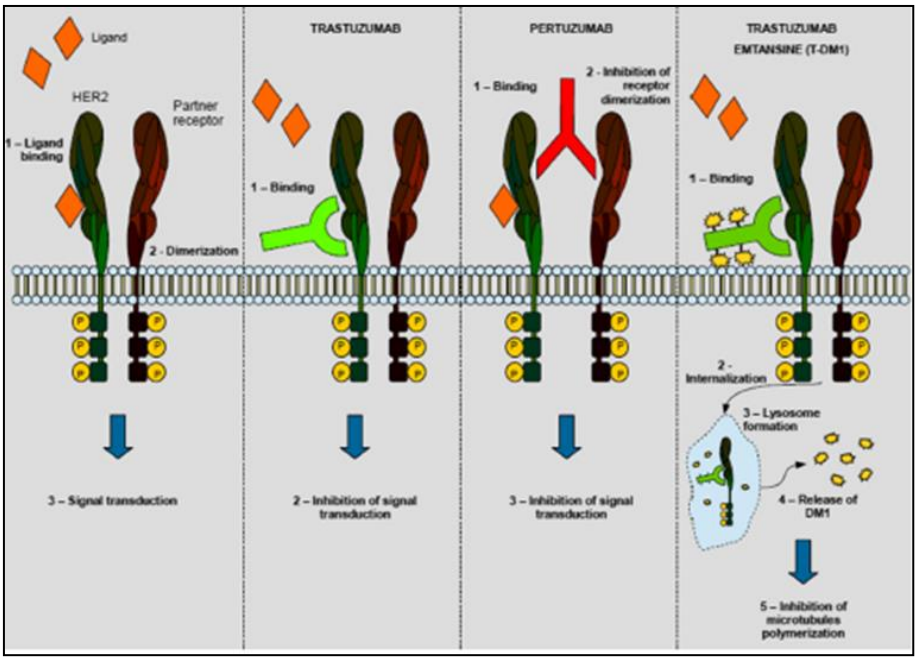

Fig 3: Monoclonal antibodies targeting HER2 pathway

Trastuzumab in gastric cancer

Trastuzumab is the first molecular targeted agent, approved as standard therapy in gastric cancer [17, 22]. Trastuzumab induces antibody dependent cellular cytotoxicity. In addition, trastuzumab inhibits HER2 mediated signaling and prevents cleavage of the extracellular domain for HER2. An

addition of trastuzumab to conventional cytotoxic chemotherapy in patients with HER2 positive advanced gastric cancer was investigated in the Trastuzumab for Gastric Cancer (ToGA) trial [17]. In terms of tumor response, the ToGA trial showed a clinical benefit in the chemotherapy plus trastuzumab group. Patients receiving chemotherapy and trastuzumab had a significantly better OS. In a reassessment of HER2 expression levels, IHC +++ patients showed the greatest benefit from additional trastuzumab [17]. As a result of this reassessment, the European Medicine Agency (EMA) restricted approval of trastuzumab to patients suffering from IHC +++ or ++/FISH + metastatic gastric or gastro-esophageal junction adenocarcinoma. The National Institute for Clinical Excellence limited its recommendation for trastuzumab to patients showing IHC +++ disease only in the United Kingdom based on this reassessment. Beside these restrictions in Europe, in the United States, the Food and Drug Administration (FDA) has ratified trastuzumab therapy for patients with HER2 overexpression without any further specification. Due to these limited results the development of new combined therapy schemes are necessary to overcome these therapeutic insufficiencies. Promising data came from the Japanese multicenter phase II study HERBIS-1. In this trial patients with advanced, HER2 positive gastric cancer received S1 on day 1-14, cisplatin on day one and trastuzumab on day one of a cycle of 21 days. The response rate, taken from the RECIST trial was 68% (95% CI 0.54-0.80) and the disease control rate was 94% (95% CI 0.84-0.99). The median overall survival (OS), the progression free survival (PFS) and the time to treatment failure (TTF) were estimated at 16.0, 7.8 and 5.7 month, respectively [23].

New approaches targeting HER2

Pertuzumab

Pertuzumab is a new humanized anti-HER2 antibody that exerts its anti-tumor activity through binding to the HER2 domain II, the region of dimer formation; inhibiting the dimerization of HER2 with other HER family proteins; and preventing ligand-dependent HER2 signaling. Pertuzumab is distinct and complementary to trastuzumab [24]. Similar to trastuzumab, pertuzumab activates antibody-dependent cellular cytotoxicity, with equivalent efficacy, leading to cancer cell death [25]. The combination of trastuzumab plus pertuzumab has been reported to be synergistic in breast cancer with a dramatic increase of OS [26]. In GC, a phase II study of first-line pertuzumab in combination with trastuzumab, capecitabine, and cisplatin in patients with HER2-positive advanced GC was carried out [27]. Patients were divided into two arms: pertuzumab and trastuzumab vs. pertuzumab alone. Partial responses were achieved in 86 and 55 % of patients, respectively. Based on these results, the JACOB phase III study (a study of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2- positive metastatic GC) randomized patients with metastatic or locally advanced unresectable disease to first-line cisplatin, fluoropyrimidine, and trastuzumab with or without pertuzumab [28].

Trastuzuma Emtansine

Trastuzumab-DM1) is a conjugate of cytotoxic drug maytansine derivate DM1 and trastuzumab. Likewise vinca Alkaloids do, DM1 binds microtubules and inhibits their assembly and blocks mitosis. In vitro, using gastric cancer models, trastuzumab-DM1 shows more aggressive tumor activity than single trastuzumab [29]. Patients with HER2 positive advanced gastric cancer after progression after first-line treatment are currently recruited for a multicenter phase III study of trastuzumab-DM1 [30]. In GATSBY, we examined the efficacy and tolerability of trastuzumab emtansine in patients previously treated for HER2-positive advanced gastric cancer (unresectable, locally advanced, or metastatic gastric cancer, including adenocarcinoma of the gastro-oesophageal junction).but the Trastuzumab emtansine was not superior to taxane in patients with previously treated, HER2-positive advanced gastric cancer. There is still an unmet need in this patient group and therapeutic options remain limited [31].

Lapatinib

Lapatinib is an oral tyrosine kinase inhibitor (TKI) that has reversible inhibitory effects on HER-2 and EGFR (Table 1). This drug showed modest single agent activity in non-selected metastatic gastric cancer patients in a phase II study [32]. However, in two phase III studies no significant effect on overall survival and progression-free survival for advanced gastric or gastroesophageal adenocarcinoma patients was reported [33, 34]. The LOGIC multicenter placebo controlled study showed that addition of lapatinib to oxaliplatin and capecitabine did not result in improved median overall survival of HER-2-positive patients, which was 12.2 months with lapatinib and 10.5 months with standard treatment only (n = 545; HR 0.91; 95% CI: 0.73 to 1.12). Improvements of lapatinib addition on overall survival were only seen in two subgroups, those of patients under 60 years (HR 0.69) and in Asian patients (HR0.68) [33]. The open-label randomized Tytan study compared second- line treatment of 261 Asian patients with advanced HER-2-positive gastric cancer with either paclitaxel alone or in combination with lapatinib. No significant improvement of median overall survival was found between the lapatinib plus paclitaxel group (11.0 months) vs paclitaxel alone group (8.9 months; HR 0.84; p = 0.2) [34].

Table 1: Overview of targeted therapy trials in gastric cancer

Target	Drug/Treatment	Type	Clinical trial phase	References
HER-2	Trastuzumab	Antibody	II, III	(12), (14), (15)
HER-2	Lapatinib	Inhibitor	II, III	(16), (17), (18)
HER-2	Pertuzumab	Antibody	III	(19)
EGFR	Cetuximab	Antibody	III	(26)
EGFR	Panitumumab	Antibody	III	(27)
EGFR	Gefitinib	Inhibitor	II	(28), (29)
EGFR	Erlotinib	Inhibitor	II	(30), (31)
VEGFR-2	Ramucirumab	Antibody	II, III	(35), (36), (37)
VEGFR-2	Apatinib	Inhibitor	II	(38)
VEGF-A	Bevacizumab	Antibody	III	(39)
mTOR	Everolimus	Inhibitor	II, III	(45), (46), (47)
HGF	Rilotumumab	Antibody	II, III	(53), (54), (55)
c-MET	Crizotinib	Inhibitor	II	(52)
c-MET	Onartuzumab	Antibody	III	(56)

HER-2, epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; VEGFR-2, vascular endothelial growth factor receptor 2; VEGF-A, vascular endothelial growth factor; mtor, mammalian target of rapamycin; HGF, hepatocyte growth factor; c-MET, mesenchymal-epithelial transition factor receptor.

Strategies to overcome trastuzumab-resistance

Beside improved outcome in patients with HER2 positive gastric cancer due to trastuzumab, the median duration of response remains moderate. A multitude of patients, suffering from HER2-positive gastric cancer develop secondary resistance to trastuzumab [35]. Thus, a better understanding of the molecular mechanisms in the development of resistance to trastuzumab is urgently needed beside others, alterations of the HER2 structure or its surroundings, dysregulation of HER2 downstream signal effectors and interaction of HER2 with membrane receptors, are responsible for the development of resistance in targeted therapy. Afatinib is an irreversible inhibitor of EGFR, HER2, and HER4. Afatinib are potentially active against receptors with secondary mutations, resistant to first-generation inhibitors. A phase II study in metastatic HER2-positive trastuzumab refractory esophageal and gastric cancer Single agent provs that afatinib shows clinical efficacy in patients with trastuzumab refractory EG cancer. The study has been expanded to accrue additional patients. Efforts to elucidate the mechanisms of trastuzumab resistance in EG cancer are ongoing. Updated molecular and clinical data will be presented [36]. The PI3K/Akt/mTOR pathway plays a cruitial role in trastuzumab resistance, dysregulating the HER2 downstream signal [37]. The mTOR inhibitor everolimus inhibits the mTOR/S6K signal, and therefore improves fluorouracil-induced apoptosis in gastric cancer cells with HER2 amplification. A concordant therapy using HER2-targeted agents and everolimus might lead to an improvement in therapy of HER2-positive gastric cancer.

Angiogenesis in gastric cancer

Angiogenesis is today universally considered as a cancer hallmark because it is one of the main processes for tumor progression. The increase of tumor size and the functional abnormalities of the tumor vasculature lead to tissue hypoxia that induces neoangiogenesis [38, 39]. The primary proangiogenic driver of this process is vascular endothelial growth factor (VEGF), also known as VEGF-A. The family of VEGF molecules also includes VEGF-B, VEGFC, VEGF-D, VEGF-E, and placental growth factor (PGF). Each component of this family can bind to several VEGF receptors (VEGFR), known as VEGFR1 (fms-like tyrosine kinase 1/Flt-1), VEGFR2 (Flk-1/KDR), and VEGFR3 (Flt-4), and 2 co-receptors, neuropilin 1 and 2 (NRP1/2). In particular, VEGF-A binds to VEGFR-1 and VEGFR-2, VEGF-B and PGF to VEGFR-1, and VEGF-C and -D to VEGFR-2 and -3 [39, 40]. The most important receptor is VEGFR-2 [41], which regulates the proliferation of endothelial cells through a number of different mechanisms [39, 42]. The expression of VEGFR2 in intestinal-type GC was found to correlate with the vessel count and the stage of disease [43]. In addition, in patients with GC, several studies have investigated the clinical and prognostic significance of circulating VEGF levels [43, 44]. Other proteins, such as hypoxia inducible factor (HIF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), angiopoietin (Ang), and Notch, play important roles in angiogenesis [45, 46]. VEGF/VEGFR pathway and relative target of mAbs are reported in Fig. 4.

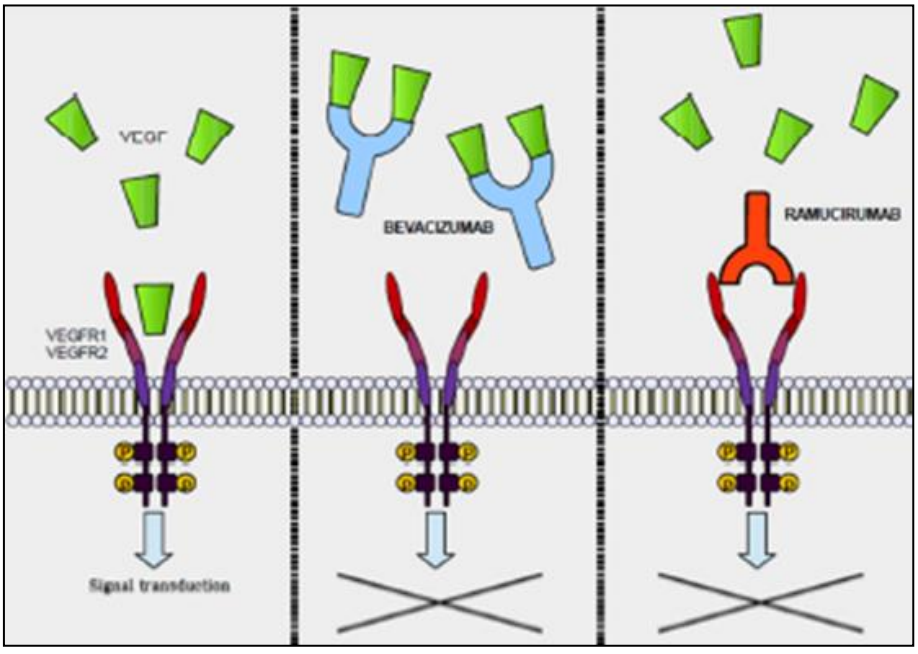

Fig 4: Monoclonal antibodiestargeting VEGF/VEGFR pathway

Monoclonal Antibodies

Bevacizumab

Bevacizumab is a humanized monoclonal antibody blocking the binding of VEGF to its receptors. AVAGAST, a global, randomized, phase III trial, investigated chemotherapy with capecitabine xeloda/cisplatin versus chemotherapy with capecitabine xeloda/cisplatin plus bevacizumab. Beside PFS and overall response rate (ORR) showed significant improvements, the primary endpoint median OS was not reached (HR = 0.87; p = 0.1002) [47]. The AVATAR study, a Chinese, randomized, phase III trial, using the same study design, found no significant improvement in survival as well [48]. Bevacizumab was also evaluated in a small phase II study in the second-line treatment of esophagogastric cancer. An encouraging RR of 27% was reported in combination with weekly docetaxel in the 20 evaluable patients, and the final results of the study are awaited [49]. These results are summarized in Table 2.

Table 2: Phase II/III trials of antiangiogenic drugs in advanced esophagogastric cancer

Trial	Eligible patients	Treatment	*n* of patients	Response rate	Median PFS (95% CI), mos	Median OS (95% CI), mos
First line						
Phase II, Sun et al. (2010) [75]	Locally advanced or metastatic gastric or EGJ adenocarcinoma	Docetaxel (75 mg/m^2) + cisplatin (75 mg/m^2) on day 1 + sorafenib (400 mg) twice daily days 1–21 every 21 days	44	41%	5.8 (5.4–7.4)	13.6 (8.6–16.1)
Phase II, Shah et al. (2006) [64]	Metastatic or unresectable gastric or EGJ adenocarcinoma	Irinotecan (65 mg/m^2), cisplatin (30 mg/m^2) on days 1 and 8 + bevacizumab (15 mg/kg) on day 1 every 21 days	47	65%	8.3 (5.5–9.9)	12.3 (11.3–17.2)
Phase II, Enzinger et al. (2008) [62]	Metastatic esophagogastric cancer	Docetaxel (30 mg/m^2) + cisplatin (25 mg/m^2) + irinotecan (50 mg/m^2) on days 1 and 8 + bevacizumab (10 mg/kg) every 21 days	26	68%	Not reported	Not reported
Phase II, Shah et al. (2011) [63]	Metastatic gastric or EGJ adenocarcinoma	Docetaxel (40 mg/m^2) on day 1, 5-FU (400 mg/m^2 on day 1 + 2,000 mg/m^2 over 48 hrs) + leucovorin (400 mg/m^2) on day 1, cisplatin (40 mg/m^2) on day 3 + bevacizumab (10 mg/kg) on day 1 every 14 days	44	67%	12 (8.8–18.2)	16.8 (12.1–26.1)
Phase II, El-Rayes et al. (2010) [65]	Locally advanced or metastatic gastric or EGJ adenocarcinoma	Oxaliplatin (75 mg/m^2), docetaxel (70 mg/m^2) + bevacizumab (7.5 mg/kg) on day 1 every 21 days	38	42%	6.6 (4.4–10.5)	11.1 (8.2–15.3)
Phase III, AVAGAST, Kang et al. (2010) [66]	Metastatic or inoperable locally advanced gastric or EGJ adenocarcinoma	Cisplatin (80 mg/m^2) on day 1, capecitabine (2,000 mg/m^2 per day) on days 1–14 + placebo on day1 every 21 days versus cisplatin (80 mg/m^2) on day 1, capecitabine (2,000 mg/m^2 per day) on days 1–14 + bevacizumab (7.5 mg/kg) on day 1 every 21 days	387 versus 387	37% versus 46% (p = .032)	5.3 versus 6.7; HR, 0.80; CI, 0.68–0.93 (p = .004)	10.1 versus 12.1; HR, 0.87; CI, 0.73–1.03 (p = .100)

Ramucirumab

Ramucirumab, a humanized IgG1 monoclonal antibody against VEGFR-2, prevents ligand binding and receptormediated pathway activation in endothelial cells [50]. Preclinical studies have shown that targeting VEGF receptors with ramucirumab was associated with the inhibition of VEGF mediated signaling along with the inhibition of proliferation and migration of endothelial cells exerting simultaneously an anti-tumor activity [50, 51]. The REGARD trial, a global, randomized, double-blind, phase III trial of 355 patients with progressive disease, investigated the addition of ramucirumab to standard chemotherapy. This addition brought a significantly prolonged median OS (3.8 to 5.2 month, p = 0.0473) [52]. The RAINBOW trial investigated ramucirumab as second-line treatment in patients with advanced gastric or gastro-esophageal junction cancer and disease progression after first-line chemotherapy, showing a significantly better OS in the ramucirumab plus chemotherapy group (median 9.6 vs. 7.4 month, p = 0.017) [53]. Due to these results, the FDA has approved ramucirumab in April 2014.

Tyrosine kinase inhibitors

Sorafenib

Sorafenib is a multitarget inhibitor of BRAF, VEGF, PDGFR and the Ras/Raf/MERK/ERK pathway. Docetaxel and cisplatin are both active in gastric cancer. ECOG 5203: phase II study evaluated the efficacy and toxicity of the combination of sorafenib with docetaxel and cisplatin in the first-line treatment of 44 metastatic or advanced gastric and GEJ adenocarcinoma patients [54]. The primary endpoint was RR for the combination. Toxicity, OS and PFS were assessed as secondary endpoints. The PR rate was 41% (90% CI, 28-54).

The median PFS was 5.8 months (90% CI, 5.4-7.4 months). The median OS was 13.6 months (90% CI, 8.6-16.1 months). The major toxicity was neutropenia; 64% of the patients presented with grade 3-4 neutropenia. One patient experienced hemorrhage at the tumor site. Although the combination of sorafenib, docetaxel and cisplatin has an encouraging efficacy profile with tolerable toxicity, large scale studies of sorafenib with chemotherapy are needed in gastric cancer. The efficacy and tolerability of sorafenib as second-line treatment in patients with advanced or metastatic gastric cancer who failed from first-line chemotherapy of ECF regimen were studied. The study has been terminated due to low RR, no evidence of PFS or OS improvement (NCT00595985).

Sunitinib

Sunitinib has been found to suppress PDGFR, kit, rearranged during transfection (RET), Flt-3 and VEGFR. A phase II, open-label, multicenter study assessed the efficacy and toxicity of sunitinib as a second-line treatment for patients with advanced gastric or GEJ adenocarcinoma [55]. Seventy‑eight patients received sunitinib 50 mg/day on a schedule 4/2 (4 weeks on treatment, followed by 2 weeks off treatment). The trial did not meet the primary endpoint

ORR. The rate of partial response (PR) was 2.6% (2/78), and the best response of SD for ≥6 weeks was 32.1% (25/78). Median PFS and OS were 2.3 months (95% CI, 1.6-2.6 months) and 6.8 months (95% CI, 4.4-9.6 months). Patients (34.6 and 29.4%) presented with grade ≥3 thrombocytopenia and neutropenia, respectively. The most common non-hematologic AEs were fatigue, anorexia, nausea, diarrhea and stomatitis. The present study suggested that single-agent sunitinib has insufficient clinical value as second line treatment for advanced gastric cancer. Further studies were conducted to research the role of
sunitinib in combination with chemotherapy for gastric cancer.

Apatinib

Apatinib is a small-molecule TKI targeting VEGFR-2. Results from a multicenter, randomized, double-blind, placebo-controlled phase III trial of apatinib was reported in 2014 at the ASCO meeting [56]. Median OS and median PFS were prolonged in the apatinib group compared with the placebo group (195 vs. 140 days, HR=0.71; 95% CI, 0.54-0.94; p<0.016) and (78 vs. 53 days, HR=0.44; 95% CI, 0.33-0.61; p<0.0001) respectively. The ORR of the apatinib and placebo groups were 2.84 and 0.00%, respectively. Concerning safety, treatment of the apatinib group was generally well tolerated. Grade 3/4 adverse reactions that occurred in >2% of patients were hypertension, hand-and-foot syndrome, proteinuria, fatigue, anorexia and elevated aminotransferase. Thus, the efficacy and safety of apatinib in patients with advanced gastric cancer were then further confirmed. The recommended dose for clinical use is 850 mg once daily.

MTOR inhibitors

Everolimus is an inhibitor of mTOR, which is regulated by PI3K-Akt-pathway. MTOR protein kinase regulates cell growth and cellular metabolism [57]. MTOR has been shown to be upregulated in gastric cancer [58]. Everolimus has been shown to be active in preclinical setting [57, 59] and in a phase I study of gastric cancer [60]. In theGRAniTE-1 randomized phase III study 633 patients with advanced gastric cancer were treated second- or third-line with best supportive care plus everolimus or placebo (Table 3) (61). No significant improvement of median overall survival was found, which was 5.4 months with everolimus vs 4.3 months with placebo (HR 0.90; 95% CI: 0.75 to 1.08). The median progression-free survival was 1.7 months with everolimus vs 1.4 months with placebo (HR 0.60; 95% CI: 0, 56 to 0.78), and the safety profile of the treatment as reported in other cancers [61].

Table 3: Results of completed phase III studies with targeted therapy in gastric cancer

Target	Trila name	Treatment	OS (months)	PFS (months)	Reference
			p-Value	p-value	
HER-2	ToGA	Cisplatin, capecitabine or FU f trastuzumab	13.8 vs 11.1	6.7 vs 5.5	(12)
			0.0046	0.0002	
HER-2	LOGIC	Capecitabine, oxaliplatin f lapatinib	12.2 vs 10.5	6.0 vs 5.4	(17)
			0.35	0.10	
HER-2	TyTAN	Paclitaxel f lapatinib	11.0 vs 8.9	5.4 vs 4.4	(18)
			0.2088	0.2411	
EGFR	EXPAND	Cisplatin, capecitabine f cetuximab	9.4 vs 10.7	4.4 vs 5.6	(26)
			0.95	0.32	
EGFR	REAL3	Epirubicin, oxaliplatin, capecitabine	8.8 vs 11.3	6.0 vs 7.4	(27)
		panitumumab	0.013	0.068	
VEGFR-2	REGARD	BSC ± ramucirumab	5.2 vs 3.8	2.1 vs 1.3	(35)
			0.047	<0.0001	
VEGFR-2	RAINBOW	Paclitaxel f ramucirumab	9.63 vs 7.36	4.40 vs 2.86	(36)
			0.0169	<0.0001	
VEGF-A	AVAGAST	Cisplatin, capecitabine or FU f bevacizumab	12.1 vs 10.1	6.7 vs 5.3	(39)
			0.1002	0.0037	
mTOR	GRANITE-1	BSC ± everolimus	5.4 vs 4.3	1.7 vs 1.4	(46)

0.124 <0.001, BSC, best supportive care; FU, fluorouracil.

Anti-MET pathway

C-MET, the mesenchymal-epithelial transition factor receptor is activated by hepatocyte growth factor (HGF). The c-MET receptor is expressed in epithelial cells and its activation leads to pleiotropic biological responses that are pro-migratory, mitogenic and anti-apoptotic (62). C-MET overexpression is a marker of poor prognosis in gastric cancer (63). Additionally, c-MET amplification seemed to associate to sensitivity to crizotinib, a small molecular inhibitor of c-MET and ALK (64). Crizotinib as monotherapy is currently investigated in a phase II clinical trial, where gastric cancers with c-MET amplification are treated among other metastatic or advanced tumors (Table 1). Rilotumumab is a human monoclonal antibody that binds to and neutralizes HGF, preventing the binding of HGF to c-MET. In The RILOMET-1 phase III randomized trial, the addition of rilotumumab to epirubicin, cisplatin, and capecitabine in a first-line setting will be evaluated in 450 c-MET-positive advanced gastric or gastroesophageal cancer patients (65). The RILOMET-2 phase III randomized trial has a similar setup as RILOMET-1; however, in the chemotherapy arm cisplatin and capecitabine will be used plus rilotumumab or placebo (66). Onartuzumab is a monoclonal antibody against c-MET that prevents binding of HGF. Onartuzumab is currently tested in the MetGastric phase III randomized clinical study, in which 800 patients with HER-2 negative, c-MET-positive gastric or gastroesophageal junction adenocarcinomas will receive chemotherapy (FOLFOX6) plus onartuzumab or placebo (67). Fig. 5 shows the agents that act on the various targets discussed.

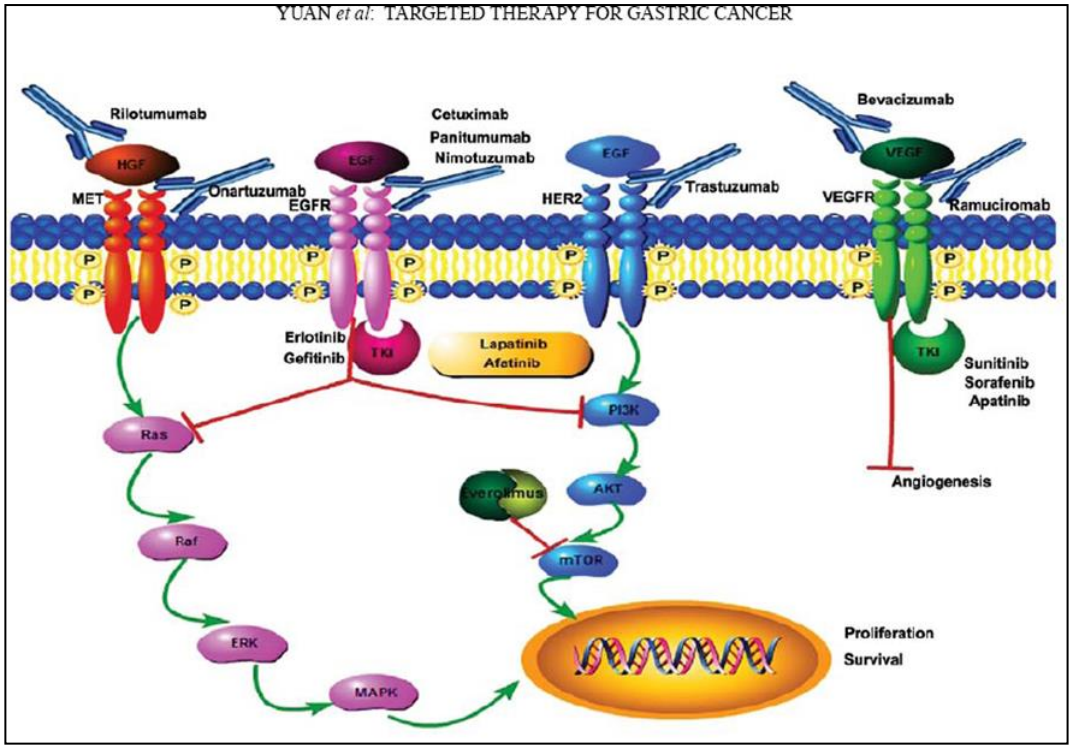

Fig 5: Agents that act on various molecular targets in gastric cancer

Discussion

The role of targeted therapy in gastric cancer emerged over the last few years. HER2 status and angiogenesis, both associated with disease aggressiveness were recognized and established as prognostic markers. As shown and described in this study, preclinical as well as clinical trials have proved the importance of combining conventional chemotherapy and targeted therapy in gastric cancer. These scientists proposed a molecular classification of GC into four subtypes: tumors positive for Epstein-Barr virus, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability. This characterization of the molecular profile of GC offers the possibility for the development of target agents such as the mAbs. However, the selection of patients based on the identification of specific predictive biomarkers appears as a very crucial point. In this context, the first main step may be considered to be the TOGA trial. In this study [17], patients with GC tumors who showed HER2 overexpression by IHC or gene amplification via FISH were eligible for trastuzumab. This trial successfully identified a key molecular driver, such as HER2, and a subsequent target therapy using the mAb trastuzumab as the first biologic therapy to have activity in advanced GC. In particular, this study highlights the important issue of the selection of patients based on the identification of specific predictive biomarkers. Indeed, the greatest benefit was seen in patients with high levels of HER2 expression (IHC score of 3 or 2 with FISH positivity) in whom the OS can exceed 15 months. Currently a number of promising molecules, showing synergistic effects in concomitant use with trastuzumab to overcome secondary resistance are under investigation. In the therapeutic field of angiogenic inhibitors, ramucirumab and apatinib, both VEGFR-2 inhibitors, remain the only two promising agents until now. As in HER2-directed targeted therapy, mechanisms for intrinsic or secondary resistance to antiangiogenic therapy need to be unmasked. Combined targeting of HER2 and VEGF showed encouraging inhibition rates in breast cancer. Due to these findings, further studies and trials, combining HER2 and VEGF-targeted therapies in gastric cancer are necessary.

Acknowledgements

I‘m very grateful to our patient for providing his informed consent for publication of this review and I am indebted to my families for their continuous support and encouragement.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. The authors presented all the necessary information about their review in the manuscript. However, about the literature review, all used literature was referenced appropriately in the “References” section.

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