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Gastrointestinal Cancer

Targeted Therapy in the Management of Advanced Gastric Cancer: Are We Making Progress in the Era of Personalized Medicine?

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the subset of advanced gastric cancer patients who might benefit from approved anti-HER2 therapy.
2. Explain the cellular signaling pathways and the biological rationale of novel targeted agents in the management of advanced gastric cancer.

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ABSTRACT

Background. **Gastric cancer is one of the leading causes of cancer death. With greater understanding of the molecular basis of carcinogenesis, targeted agents have led to a modest improvement in the outcome of advanced gastric cancer (AGC) patients.**

Methods and Results. **We conducted an overview of the published evidence regarding the use of targeted therapy in AGC patients. Thus far, the human epidermal growth factor receptor (HER) pathway, angiogenic pathway, and phosphatidylinositol-3-kinase (PI3K)–Akt–mammalian target of rapamycin pathway have emerged as potential avenues for targeted therapy in AGC patients. The promising efficacy results of the Trastuzumab for Gastric Cancer trial led to the approved use of trastuzumab-based therapy as first-line treatment for patients with HER-2$^+$ AGC. On the other hand, the Avastin® in Gastric Cancer trial evaluating bevacizumab in combination with chemotherapy did not meet its primary endpoint of a longer overall survival duration despite a significantly higher response rate and longer progression-free survival time in patients in the bevacizumab arm. Phase III data are awaited for other targeted agents, including cetuximab, panitumumab, lapatinib, and everolimus.**

Conclusion. **Recent progress in targeted therapy development for AGC has been modest. Further improvement**

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in the outcome of AGC patients will depend on the identification of biomarkers in different patient populations to facilitate the understanding of gastric carcinogenesis, combining different targeted agents with chemotherapy, and unraveling new molecular targets for therapeutic intervention. ***The Oncologist*** 2012;17:346–358

INTRODUCTION

Gastric cancer is one of the leading causes of cancer death [1]; although its global incidence is declining, it remains highly prevalent in Asian countries [2]. Conventional treatment modalities, including surgery, radiotherapy, and chemotherapy, play a role mainly in patients with early disease, for whom adjuvant chemotherapy and chemoirradiation have led to 20%–35% longer overall survival (OS) times [3, 4]. These modalities, however, have modest efficacy in treating patients with advanced gastric cancer (AGC), conferring a median survival time in the range of 6–11 months, with considerable treatment-related toxicities [5]. Despite the better response rates (RRs) and tolerability with various new-generation combination regimens using capecitabine, oxaliplatin, S1, docetaxel, and irinotecan [6–9], the OS outcome of AGC patients remains dismal.

With the greater understanding of the biology and underlying molecular basis of carcinogenesis, several targeted agents have led to better outcomes for advanced lung, colon, breast, and kidney cancer patients, leading to their approval and widespread use for these entities. In this respect, the development of targeted agents for AGC is apparently making rather slow progress. Unlike other solid tumors, which are predominantly addicted to a particular signaling pathway, such as human epidermal growth factor receptor (HER)-2^+ breast cancer, the molecular and genetic pathogenesis of gastric cancer may be more complex [10, 11]. Many pathways may play key roles in gastric tumor carcinogenesis whereas the predominant driving pathway is difficult to delineate.

Nevertheless, the release of the promising efficacy results of the Trastuzumab for Gastric Cancer (ToGA) trial [12, 13] marked the beginning of a new era. This pivotal trial led to the approval of trastuzumab as the first targeted agent in the first-line treatment of patients with HER-2^+ AGC. In addition, other signaling pathways have also emerged as potential avenues for future therapeutic interventions.

In this review, we outline the underlying molecular basis and summarize the current clinical evidence and ongoing trials supporting the use of targeted agents in the treatment of patients with AGC. We also explore future perspectives, including predictive biomarkers and novel signaling pathways, that may potentially be exploited as strategic targets of treatment.

THE HER FAMILY

The HER family consists of four members: HER-1 (epidermal growth factor receptor [EGFR]), HER-2, HER-3, and HER-4. HER-1, HER-3, and HER-4 are all activated by ligand binding, whereas HER-2 does not require a ligand for activation. Activation of these receptors leads to homo- or heterodimerization that in turn initiates phosphorylation cascades and subsequent activation of the phosphatidylinositol-3-kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) and Ras–Raf–mitogen-activated protein kinase/extracellular signal–related kinase (ERK) kinase (MEK)–ERK pathways, which are important in cancer cell proliferation and survival [14, 15] (Fig. 1).

Targeting HER-2

HER-2 overexpression is observed in 10%–38% of gastric cancer tumor samples [16–20], with a higher prevalence in intestinal-type and gastroesophageal junction (GEJ) tumors than in diffuse-type and gastric tumors [17–19]. The prognostic value of HER-2 overexpression in gastric cancer remains controversial; it is generally associated with a poorer outcome [21, 22] [23–25], although contradictory evidence exists [26, 27]. Notably, in the ToGA trial [13], HER-2^+ patients had a superior outcome in the control arm consisting of chemotherapy without trastuzumab, a humanized recombinant monoclonal antibody that selectively binds to the extracellular domain of HER-2, thereby blocking its downstream signaling (Fig. 1). Although this suggests against a negative prognostic role for HER-2, it may be confounded by factors such as second-line therapy or a better intrinsic prognosis associated with the intestinal subtype. On the other hand, HER-2 overexpression has been shown to predict response to trastuzumab [28].

Table 1 summarizes the results of first-line trastuzumab-based trials in AGC patients. Trastuzumab in combination with chemotherapy achieved an overall response rate (ORR) of 35%–44% [29, 30]. The ToGA trial is a large, phase III, randomized controlled multicenter trial [12, 13] wherein tumor samples from >3,800 patients with locally advanced, recurrent, or metastatic gastric or gastroesophageal adenocarcinoma were centrally tested for HER-2 overexpression. Subsequently, 594 (22%) patients with HER-2^+ disease, defined by an immunohistochemical (IHC) staining score of 3+ or positive fluorescence in situ hybridization (FISH) result, were randomized to receive chemotherapy with cisplatin and 5-fluorouracil (5-FU) or capecitabine for six cycles with or without trastuzumab until progression. The addition of trastuzumab to chemotherapy led to a significantly higher ORR, 47% versus 35% ($p = .0017$), significantly longer progression-free survival (PFS) interval, 6.7 months versus 5.5 months ($p = .0002$), and significantly longer OS duration, 13.8 months versus 11.1 months ($p = .0046$). The greatest benefit was seen in patients with higher levels of HER-2 expression, with either an IHC score of 3+ or 2+ plus FISH positivity; the OS time of those patients reached 16 months. The trastuzumab-containing regimen was generally well tolerated. Moreover, the addition of trastuzumab did not affect quality of life. To date, trastuzumab is the first and only targeted agent for gastric cancer approved by both the U.S. [31] and European [32] authorities. It is indicated in combination with cisplatin and capecitabine or 5-FU in the first-line treatment of HER-2–overexpressing AGC; strong HER-2 expression, with an IHC score of 3+ or 2+ plus FISH positivity, is required by the European guide-

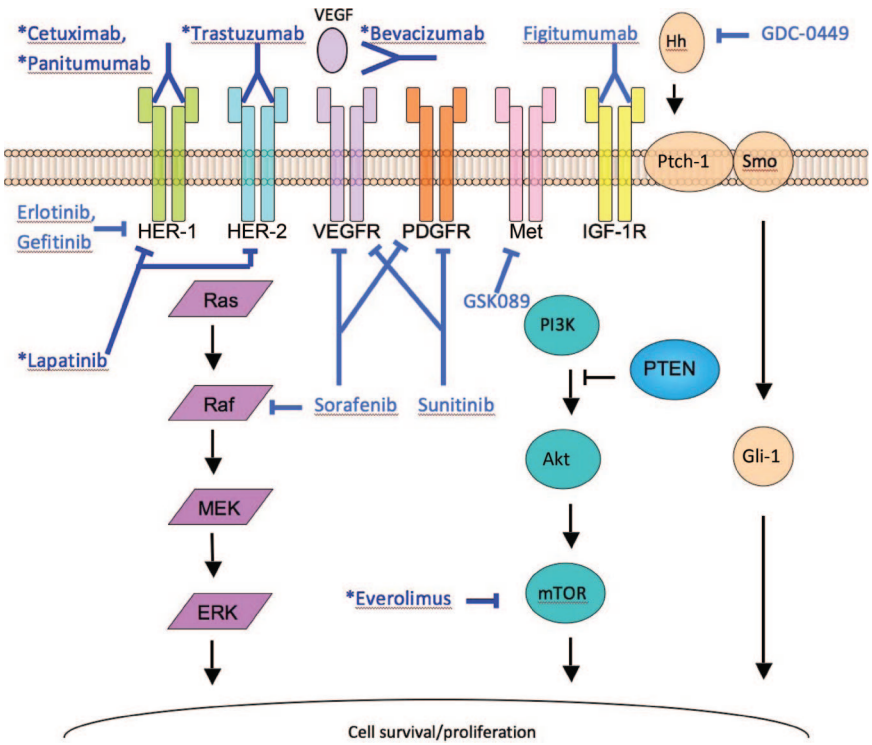

Figure 1. Schematic diagram of key signaling pathways in gastric cancer cells, and mechanisms and sites of action of various targeted agents that may play a role in advanced gastric cancer treatment. Agents that have been or are currently under phase III testing are marked with an asterisk.

Abbreviations: ERK, extracellular signal–related kinase; HER, human epidermal growth factor receptor; Hh, hedgehog; IGF-1R, insulin-like growth factor 1 receptor; MEK, mitogen-activated protein kinase/ERK kinase; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PI3K, phosphatidylinositol 3-kinase; Ptch-1, Patched 1; PTEN, phosphatase and tensin homologue deleted on chromosome ten; Smo, Smoothened; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

lines. Despite these exciting results, it is worthwhile to note that only a relatively small proportion of AGC patients have HER-2$^+$ disease after all.

In the second-line setting, after progression on platinum- or 5-FU–based chemotherapy, a trial studied single-agent trastuzumab in AGC patients, but it was limited by poor accrual [33].

Targeting EGFR

EGFR overexpression, observed in 27%–44% of gastric cancer cases, is generally reported to be a poor prognostic factor [34–36], despite contradictory evidence [37].

Cetuximab is a recombinant human–mouse chimeric monoclonal antibody against EGFR. In first-line phase II trials (Table 2), cetuximab was evaluated in combination with various chemotherapy regimens [38–48]. The most common side effects observed were neutropenia, diarrhea, and rash. The ORR was in the range of 40%–60%, the time to progression (TTP) was 5.5–8 months, and the OS time was 9.5–16 months. In particular, Enzinger et al. [48] reported on a recent three-arm randomized phase II study comparing cetuximab plus epirubicin, cisplatin, and 5-FU with irinotecan plus cisplatin) and with 5-FU, leucovorin and oxaliplatin. The trial was not designed to test the efficacy of cetuximab, but none of the treatment arms showed a better survival outcome than in historical controls. More recently, the preliminary results of a randomized, phase II study showed no clinically significant benefit when cetuximab was added to docetaxel plus oxaliplatin [49]. A randomized phase III trial, Erbitux® in Combination With Xeloda® and Cisplatin in Advanced Esophago-gastric Cancer [50], is ongoing to evaluate capecitabine and cisplatin with or without cetuximab as first-line treatment. In the pretreated setting, data are conflicting in the literature [51–53] (Table 2). Mature data from large-scale, randomized trials are needed to support the incorporation of cetuximab into the management of AGC patients.

In contrast to cetuximab, panitumumab is a fully humanized monoclonal antibody targeting EGFR. It showed activity in patients with advanced colorectal cancer after failure on 5-FU, irinotecan, and oxaliplatin [54]. Nonetheless, there is very limited experience with this agent in AGC patients. Recently, the Randomized ECF for Advanced and Locally Advanced Esophago-gastric Cancer 3 trial [55] was started to explore the role of panitumumab in combination with epirubicin, oxaliplatin, and capecitabine (EOC). The ORR of patients treated with the chemotherapy triplet plus panitumumab was 52% in the phase II section of the study [56]; phase III results are awaited. On the other hand, other EGFR monoclonal antibodies, namely matuzumab and nimotuzumab, achieved even a shorter PFS time in combination with chemotherapy than with chemotherapy alone, in randomized phase II studies [57, 58].

Table 1. Summary of phase II and III trastuzumab trials in first-line treatment of advanced gastric cancer

Trial	Phase	Line of treatment	*n* of patients	Treatment	ORR	OS	Toxicities (%)
Cortes-Funes et al. (2007) [29]*	II	First	21	Cisplatin and trastuzumab	35%	NA	No grade 4; grade 3 asthenia (18%), nausea/vomiting (18%), diarrhea (12%), hyporexia (12%), neutropenia (6%)
Nicholas et al. (2006) [30]*	II	First	9	Docetaxel, cisplatin, and trastuzumab	44%	NA	Grade 3 or 4 peripheral neuropathy (20%), neutropenia (20%), 1 patient died of an upper gastrointestinal bleed
Bang et al. (2011) [109][a]	III	First	594	Fluoropyrimidine, cisplatin and trastuzumab versus Fluoropyrimidine and cisplatin	47 versus 35% ($p = .0017$)	13.8 months versus 11.1 months ($p = .0046$)	Similar in both groups, including cardiac adverse events; no unexpected events

Data presented in abstract form are marked with an asterisk.
[a]Trastuzumab for Gastric Cancer (ToGA) trial.
Abbreviations: NA, not available; ORR, overall response rate; OS, overall survival.

The EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib were evaluated in phase II trials but produced disappointing results as monotherapy for AGC. Response occurred in GEJ but not gastric cancer patients in a phase II first-line trial [59]. Other studies demonstrated minimal efficacy, mainly in pretreated patients [60–62]. On the other hand, a recent phase II trial showed an ORR >50% with the combination of 5-FU, oxaliplatin, and erlotinib in patients with esophageal or GEJ cancer [63].

Although a randomized trial is needed to clarify the role of EGFR TKIs in combination with chemotherapy, and phase III data on EGFR antibodies are awaited, biomarkers predictive of response may still be of research interest. *EGFR* mutation, high *EGFR* copy number, *KRAS* mutation status, and the development of a skin rash have all been suggested to predict response to EGFR inhibitors, but study results are conflicting. For example, EGFR overexpression evaluated using IHC with low serum EGF and transforming growth factor α levels was associated with response to cetuximab [41], although another study showed no such correlation [42]. Moreover, the RR was significantly higher (76.5% versus 40.0%) and the TTP was longer (6.8 months versus 3.0 months) in patients with grade 2–3 skin rash than in those with a less severe rash [44]; although this phenomenon is also observed in colon and lung cancer, further validation is needed in AGC patients.

Dual Targeting of HER-2 and EGFR

Lapatinib is a dual TKI inhibiting both HER-2 and EGFR. In a phase II trial of 47 patients with metastatic gastric cancer, lapatinib achieved an ORR of 7% and a 20% rate of disease stabilization [64]. The median TTP was only 2 months. One patient had grade 4 cardiac toxicity, two patients had grade 4 fatigue, and one patient had grade 4 vomiting. In another cohort of 21 previously treated patients, lapatinib had limited single-agent activity, with only two patients having durable stable disease [65]. Notably, in those two trials, lapatinib was given to both HER-2^+ and HER-2^- patients; thus, these disappointing results were not unexpected.

Two phase III trials are ongoing: the Lapatinib Optimization Study in ErbB2 (HER-2) Positive Gastric Cancer (LoGIC) trial, investigating first-line treatment with capecitabine and oxaliplatin with or without lapatinib [66], and the Lapatinib (Tykerb) with paclitaxel (Taxol) in Asian ErbB2+ (HER2+) Gastric Cancer Study (TYTAN) trial, investigating second-line paclitaxel with or without lapatinib in Asian patients [67]. In sharp contrast to their precedent studies, the LoGIC and TYTAN trials only target AGC patients with HER-2^+ disease. The results from these trials will be instrumental in guiding the future role of lapatinib in treating AGC patients.

Intracellular Signaling Pathways

The PI3K–Akt–mTOR Pathway

mTOR is a key protein kinase that regulates cell growth and proliferation, cellular metabolism, and angiogenesis. It is mainly activated by PI3K through Akt (Fig. 1). mTOR activity is positively regulated by many receptors, including members of the EGFR and vascular endothelial growth factor receptor (VEGFR) families and their ligands, whereas phosphatase and tensin homologue deleted on chromosome ten (PTEN) is an example of a negative regulator. It is involved in the initiation of ribosomal translation of mRNA into proteins for cell growth, cell cycle progression, and cell metabolism [68].

As illustrated in Figure 2, the PI3K–Akt–mTOR pathway is frequently activated in gastric cancer, as suggested by the

Table 2. Summary of phase II trials of cetuximab in combination with various chemotherapy regimens

Trial	Phase	Line of treatment	*n* of evaluable patients	Chemotherapy in combination with cetuximab	ORR (%)	TTP/PFS (mos)	OS (mos)
Pinto et al. (2007) [38]	II	First	38	5-FU, LV, and irinotecan	44.1	8	16 (expected)
Kanzler et al. (2009) [39]*	II	First	49	5-FU, LV, and irinotecan	42	8.5	16.6
Moehler et al. (2010) [40]	II	First	49	5-FU, LV, and irinotecan	46	9.0	16.0
Han et al. (2009) [41]	II	First	38	5-FU, LV, and oxaliplatin	50	5.5	9.9
Lordick et al. (2010) [42]	II	First	46	5-FU, LV, and oxaliplatin	65	7.6	9.5
Yeh et al. (2009) [47]*	II	First	35	5-FU, LV, and cisplatin	68.6	11.0	14.5
Kim et al. (2011) [43]	II	First	44	Capecitabine and oxaliplatin	52.3	6.5	11.8
Zhang et al. (2009) [44]*	II	First	47	Capecitabine and cisplatin	48.1	5.2	NA
Woell et al. (2008) [45]*	II	First	35	Oxaliplatin and irinotecan	63	24.8	9.5
Pinto et al. (2009) [46]	II	First	72	Docetaxel and cisplatin	41.2	5	9
Enzinger et al. (2010) [48]*	II	First	245	Epirubicin, cisplatin, and 5-FU versus irinotecan and cisplatin versus oxaliplatin, 5-FU, and LV	58 versus 38 versus 51	5.6 versus 5.0 versus 5.7	10 versus 8.6 versus 10
Tebbutt et al. (2008) [51]*	II	Second	38	Docetaxel	6	2.1	5.3
Stein et al. (2007) [52]*	II	Second or later	13	Irinotecan	38	2.6	3.3
Li et al. (2010) [53]*	II	Second	49	5-FU, LV, and irinotecan	34.7	4.9	8.1

Data presented in abstract form are marked with an asterisk.
Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

prevalent expression of phospho-Akt (29%–86%) [69, 70] and phospho-mTOR (47%–64%) [69, 71, 72]. This can be mediated either by the overexpression of upstream receptors or by constitutively enhanced PI3K activity caused in turn by activating mutations of *PIK3CA* or PTEN loss. Whereas upstream receptors are overexpressed in only 20%–30% of gastric cancer cases, Akt is activated in >80% (Fig. 2). This observation suggests that the survival and proliferation of a significant proportion of gastric cancer cells are independent of the upstream receptors. In fact, *PIK3CA* activating mutation was reported in 4%–36% of gastric cancer cases [73, 74] and PTEN loss was reported in 20%–36% of cases [73, 75]. Specifically, for HER-2^+ gastric cancer, recent preliminary evidence suggested that PTEN was lost in the majority of cases [76]. These findings may explain resistance to receptor blockade, and suggest rational targets for treatment.

Inhibitors of the PI3K–Akt–mTOR pathway have been developed at multiple levels, such as PI3K–Akt inhibitors and mTOR inhibitors. In particular, everolimus is an mTOR inhibitor. In a multicenter phase II trial using everolimus as salvage therapy for pretreated AGC patients, the disease control rate was 55%, although no objective response was noted [77]. The median PFS and OS times were 2.7 months and 10.1 months, respectively. Subgroup analysis did not reveal a difference in PFS stratified by number of lines of chemotherapy. Putting these data into perspective, everolimus achieved similar, if not better, PFS and OS results to those seen in second-line chemotherapy trials [78–81]. Everolimus was generally well tolerated. Stomatitis (73.6%), anorexia (52.8%), and fatigue (50.9%) were the commonly encountered adverse events. Based on these provocative results, a phase III randomized trial is ongoing to compare everolimus with placebo plus best supportive care in patients with progressive disease after one or two prior lines of chemotherapy [82]. Given its second-line activity, its oral form of administration, and its good tolerability, the authors suggested that everolimus could also possibly be evaluated as maintenance therapy after induction of response by first-line systemic treatment for AGC.

The Ras–Raf–MEK–ERK Pathway

The Ras–Raf–MEK–ERK pathway is another key signaling pathway downstream of HER. For colon cancer, most evidence suggests that *KRAS* mutations are negative predictors of response to cetuximab and panitumumab [83, 84], but the predictive ability of *BRAF* mutations remains controversial. For gastric cancer, *KRAS* mutation was observed in 2%–20% of cases [85–90] and *BRAF* mutations was observed in 0%–2.7% of cases [85, 87]. The predictive ability of *KRAS* and *BRAF* has not been extensively studied, but small reports did not demonstrate such characteristics [42, 91].

Sorafenib is a multitargeted inhibitor of Raf and other pathways, in addition to its antiangiogenic properties. It was combined with docetaxel and cisplatin in a single-arm Eastern Cooperative Oncology Group phase II study [92]. Efficacy data were encouraging, with ORR of 41% in 44 evaluable chemotherapy-naive patients. The median PFS and OS times were 5.8 months and 13.6 months, respectively. Nevertheless, grade 3 neutropenia was common, and two patients possibly died as a result of treatment-related toxicities. In pretreated patients, single-agent sorafenib was studied in a phase II trial—preliminary analysis of 16 evaluable patients included one durable complete response and another case of protracted stable disease of >19 months [93]. More mature phase II–III data are needed to validate these results and, more importantly, to evaluate the long-term safety of the compound.

Tumor Angiogenesis

Misregulated angiogenesis is a key step in tumor growth and metastasis [94]. The VEGF family of proteins, as ligands, are important promoters of endothelial cell proliferation and new vessel formation by interacting with VEGFRs [95]. There are four VEGF members (VEGF-A through VEGF-D) and three VEGFRs (VEGFR-1 through VEGFR-3).

In gastric cancer, expression of VEGF and VEGFR was reported in ~40% [35, 96] and 36% [97] of cases, respectively. In particular, the expression of VEGF was associated with tumor vascularity, hematogenous metastases, and poor prognosis [35, 98]. Certain *VEGF* polymorphisms also affected cancer risk [99] and prognosis [100]. The occurrence of hypertension during bevacizumab treatment and *VEGF* gene polymorphisms were suggested to be associated with clinical outcomes in metastatic breast cancer patients [101]. In the case of gastric cancer, however, the occurrence of hypertension has not been reported to predict benefit from bevacizumab [102].

Targeting VEGF

Bevacizumab is a monoclonal antibody that binds to VEGF-1, also commonly known as VEGF (Fig. 1). Several phase II trials studied bevacizumab in addition to chemotherapy [103–106] (Table 3). An ORR of 42%–67% was achieved; when available, the median TTP was 6.6–12 months and the OS time was 8.9–16.2 months. Nevertheless, grade 3–4 thromboembolic events occurred in up to 25% of patients and gastric perforation occurred in ~8% of patients enrolled in phase II studies. Moreover, significant upper gastrointestinal bleeding

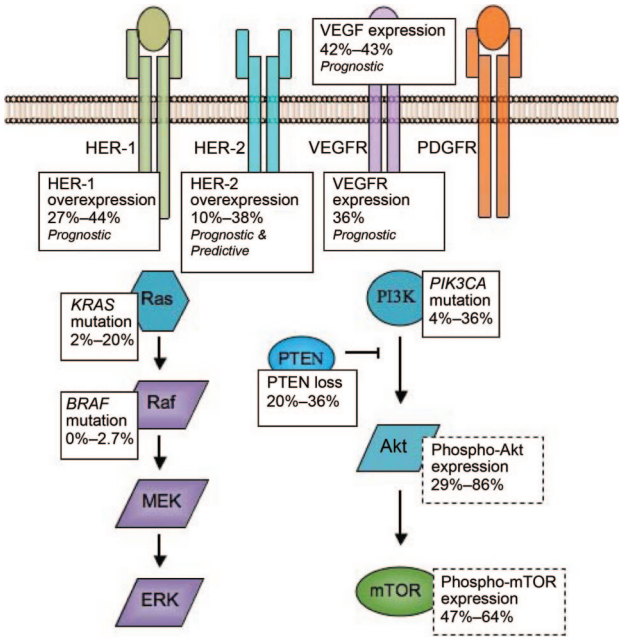

Figure 2. Summary of overexpression or mutation in the signaling pathways of gastric cancer cells. These studies are retrospective analyses of human gastric cancer cell lines and primary tumors. In general, overexpression was detected by immunohistochemistry, and mutations were detected by direct sequencing. Results specific for advanced gastric cancer, as opposed to early gastric cancer or cell lines, are summarized here if specified in the studies; otherwise, general results are quoted. HER-2 overexpression is established to be both predictive and prognostic. HER-1, VEGFR, and VEGF expression are generally regarded as prognostic, but the role of other gene mutations or protein overexpression is not well-defined.

Abbreviations: ERK, extracellular signal–related kinase; HER, human epidermal growth factor receptor; MEK, mitogen-activated protein kinase/ERK kinase; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue deleted on chromosome ten; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

was also noted in a minority of patients with unresected primary tumor.

In the phase III Avastin® in Gastric Cancer (AVAGAST) trial, 774 patients were randomized to receive capecitabine and cisplatin with or without bevacizumab [107, 108]. Cisplatin was given for six cycles; capecitabine and bevacizumab or placebo were given until progression or unmanageable toxicity. Although the study did not meet its primary endpoint of OS and was thus a negative trial for this endpoint, the ORR was significantly better in the bevacizumab arm (46% versus 37%; $p = .0315$) and the PFS interval was significantly longer, 6.7 months versus 5.3 months (hazard ratio, 0.8; $p = .0037$) [107, 108]. Interestingly, differences across geographical regions were reported. Survival was longer in patients in pan-America with the addition of bevacizumab, but not in Asians or Europeans despite the better prognosis of the latter. Differences in pa-

Table 3. Summary of clinical trials of bevacizumab in combination with various chemotherapy regimens

Trial	Phase	Line of treatment	*n* of evaluable patients	Treatment	ORR (%)	TTP (mos)	OS (mos)	Bevacizumab-related grade 3 or 4 toxicities
Shah et al. (2006) [103]	II	First	47	Irinotecan, cisplatin, and bevacizumab	65	8.3	12.3	Hypertension, 28% Gastric near perforation or perforation, 6%; myocardial infarction, 2%; thromboembolic events, 25%; upper GI bleed, $n = 1$
El-Rayes et al. (2010) [104]	II	First	38	Docetaxel, oxaliplatin, and bevacizumab	42	6.6 (PFS)	11.1	GI perforation, 8%
Kelsen et al. (2009) [105]*	II	First	44	Modified docetaxel, cisplatin, 5-FU, and bevacizumab	67	12 (PFS)	16.2	GI perforation, $n = 1$ Bleeding, $n = 1$
Cohenuram et al. (2008) [106]*	Retrospective review	First or prior chemotherapy ($n = 7$)	16	mFOLFOX6 and bevacizumab	63	7	8.9	No thromboembolic event, GI bleed, or perforation
Kang et al. (2010) [107][a]	III	First	774	Capecitabine, cisplatin, and bevacizumab versus capecitabine and cisplatin	46 versus 37 (p significant)	6.7 versus 5.3 (p significant)	10.1 versus 12.1 (p not significant)	Hypertension, 6.2%; hemorrhage 3.9%; GI perforation, 1.3%; arterial thromboembolic event, 6.5%; venous thromboembolic event, 3.1%

Data presented in abstract form are marked with an asterisk.
[a]Avastin® in Gastric Cancer (AVAGAST) trial.
Abbreviations: 5-FU, 5-fluorouracil; GI, gastrointestinal; mFOLFOX6, modified 5-FU, leucovorin, and oxaliplatin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

tient selection, clinical practice, population genetics, and second-line chemotherapy may explain the results, and biomarker studies are under way. The most commonly encountered grade 3–5 adverse events in both arms were neutropenia, anemia, and decreased appetite, the incidences of which were similar with or without bevacizumab. No new bevacizumab-related safety concerns were reported. Suffice it to say, it seems inappropriate to incorporate bevacizumab in the treatment algorithm of AGC patients now.

Targeting VEGFR and PDGFR

Multitargeted TKIs (MTIs), such as sorafenib and sunitinib, take another approach to suppress angiogenesis, by targeting VEGFR and other signaling pathways simultaneously. To date, most of these agents are in phase I/II of clinical development for treating AGC patients. Sunitinib inhibits PDGFR, Kit, REarranged during Transfection, and Flt-3 together with VEGFR. In a phase II study of single-agent sunitinib as second-line treatment for AGC patients treated with one prior chemotherapy regimen, 2.6% of the enrolled patients had a partial response and 25 patients (32.1%) had stable disease. The median PFS and OS times were 2.3 months and 6.8 months, respectively. Notably, grade ≥3 thrombocytopenia and neutropenia were reported in 34.6% and 29.4% of patients, respectively [109]. Another phase II study of pretreated AGC patients reported disease stabilization in five of 14 patients [110]. These data suggest that single-agent sunitinib has limited activity as salvage therapy for chemotherapy-refractory AGC patients. Moreover, it is rather unlikely that positive results will be yielded when sunitinib is tested in the first-line setting or in combination with chemotherapy because of the complete failure of sunitinib to change the survival outcome when combined with chemotherapy for other solid tumors, such as lung and colorectal cancers. Sunitinib is indeed very unlikely to be further developed in the AGC patient population.

Other MTIs are in early-phase clinical investigation. Telatinib in combination with capecitabine and cisplatin resulted in a preliminary ORR of 67% in a phase II first-line study [111]. Axitinib in combination with capecitabine and cisplatin is currently in phase I of clinical development [112]. In the third-line setting, single-agent apatinib produced an ORR on the order of 10% in another phase II trial [113].

Future Perspectives

The ToGA and AVAGAST trials have marked the beginning of a new era in AGC treatment. A number of other phase III clinical trials are ongoing (Table 4). Nevertheless, our current understanding of the biology of gastric cancer is very preliminary. It is possible that many key molecular pathways play equally pivotal roles in AGC; the predominant pathway that the tumor is addicted to, if any, has yet to be conclusively defined. Moreover, only a limited proportion of patients with known activated molecular targets can benefit from the currently available therapeutics, and the achieved clinical benefit is only modest. Further improvement in the outcome of AGC patients will depend on the following.

Table 4. Ongoing phase III trials of targeted agents in the systemic treatment of advanced gastric cancer

Clinical trial	Targeted agent	Chemotherapy	Line of treatment	Status
ToGA, Bang et al. (2011) [109]	Trastuzumab	FP or XP	First	Completed
AVAGAST, Kang et al. (2010) [107]	Bevacizumab	XP	First	Completed
EXPAND [50]	Cetuximab	XP	First	Ongoing
REAL-3 [55]	Panitumumab	EOX	First	Ongoing
LoGIC [66]	Lapatinib	OX	First	Ongoing
TYTAN, Satoh et al. (2010) [67]	Lapatinib	T	Second	Ongoing
GRANITE-1 [82]	Everolimus	–	Second or third	Ongoing

Abbreviations: AVAGAST, Avastin® in Gastric Cancer; E, epirubicin; EXPAND, Erbitux® in Combination With Xeloda® and Cisplatin in Advanced Esophago-gastric Cancer; F, 5-fluorouracil; GRANITE-1, Safety and Efficacy of RAD001 (Everolimus) Monotherapy plus Best Supportive Care in Patients with Advanced Gastric Cancer; LoGIC, Lapatinib Optimization Study in ErbB2 (HER-2) Positive Gastric Cancer; O, oxaliplatin, P, cisplatin; REAL-3, Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 3; T, paclitaxel; ToGA, Trastuzumab for Gastric Cancer; TYTAN, Lapatinib (Tykerb) with paclitaxel (Taxol) in Asian ErbB2+ (HER2+) Gastric Cancer Study; X, capecitabine.

Patient Selection for Targeted Therapy Trials

Gastric carcinoma is a heterogeneous disease that results from a complex interaction among bacterial, environmental, host-genetic, and molecular mechanisms. The overexpression and amplification of many molecular targets for treatment vary with different histological, anatomical, epidemiological, and molecular AGC subtypes [114, 115]. For example, it is overall suggested that gastric cancer can be classified into three main subtypes, with distinct epidemiology and possibly genetic profiles, namely, distal intestinal-type tumors, distal diffuse-type tumors, and GEJ tumors. More HER-2^+ disease is observed in intestinal-type and GEJ tumors than in diffuse-type and gastric tumors [17, 18]. Moreover, the prevalence of *PIK3CA* mutations is ~23% in western gastric cancer populations but is rarely seen in Asian populations [74]. This, together with the population-based difference in the benefit of targeted therapy suggested by the AVAGAST trial [107], underscores the importance of conducting clinical trials stratified by clinical gastric cancer subtypes and by ethnic subgroups because of potential differences in tumor biology and pharmacogenomics.

Development of Biomarkers

In the era of personalized medicine, given the financial implications and potential toxicities associated with targeted therapy, identification of predictive biomarkers is crucial to enable the effective use of targeted therapy in AGC patients. Prospective biomarker-driven clinical trials dedicated to specific patient populations enriched with rational molecular targets would potentially enhance the efficacy results, and also allow evaluation of targeted agents as monotherapy to provide insight on gastric cancer biology and the prevalence and mechanisms of primary and secondary resistance.

Various markers, including EGFR and VEGF overexpression, skin rash, and hypertension, have not been validated to be predictive in AGC patients, and HER-2 overexpression and *HER-2* amplification remain the only predictive biomarkers. It is imperative to refine and standardize techniques for HER-2 determination. Current IHC testing is associated with significant false-positive and false-negative results [116]. More accurate techniques, such as FISH, should be adopted and samples should be analyzed in a centralized laboratory. Notably, unlike breast cancer, the occurrence of basolateral membrane staining of glandular cells (resulting in incompletely stained membranes) and tumor heterogeneity in gastric cancer lead to discrepancies between IHC and FISH results. Modifications to the HercepTest™ (Dako, Glostrup, Denmark) score for gastric cancer [117] should be widely promoted. Further to the qualitative detection of HER-2 overexpression, the level of HER-2 may be associated with the magnitude of benefit [13].

Combination Strategies

The combination of targeted agents, the addition of chemotherapy to targeted agents, and the development of multitargeted agents may overcome resistance and improve clinical efficacy.

Primary and secondary resistance to targeted agents remain poorly defined problems. The addition of trastuzumab to chemotherapy results in only a 12% higher RR and 10% greater clinical benefit rate (complete responses plus partial responses) [13]. Although the prevalence of primary trastuzumab resistance in AGC cannot be clearly determined without first-line monotherapy trastuzumab trials, it can be inferred that this occurs in the majority of HER-2–overexpressing AGC patients, and all initially sensitive patients eventually become trastuzumab refractory. As discussed earlier, constitutive activation of the PI3K pathway through *PIK3CA* mutation or PTEN loss may play a role in resistance to receptor monoclonal antibodies, and they may represent rational targets irrespective of the upstream receptor expression status.

Resistance to targeted therapy may also be contributed to partly by intratumoral heterogeneity [118]. In initially sensitive disease, selection of a nonsensitive clone with continued targeted therapy may give rise to acquired resistance. Although intratumoral heterogeneity is better described for colon, breast, ovarian, and cervical cancers [119–122], it has also been demonstrated in gastric cancer [26, 123–125].

Multilevel blockade is therefore a promising strategy to tackle intratumor heterogeneity. For example, a preclinical study suggested that the combination of trastuzumab and lapatinib was synergistic in inhibiting cell growth in *HER-2*–amplified human upper gastrointestinal cell lines [126]; the combination lower rates of Akt and ERK activation, G_0–G_1 cell cycle arrest, and greater rates of apoptosis. These provocative data may provide a strong rationale for testing this interesting combination in early-phase clinical trials. Similarly, the combination of targeted therapy with chemotherapy was also shown to have a synergistic effect in gastric cancer cell lines [127]. More importantly, new-generation MTIs can target multiple molecular defects concurrently. The promising clinical activity of the pan-HER inhibitor neratinib in metastatic breast cancer patients serves as an example: neratinib resulted in an ORR of 56% [128], compared with the 23%–35% rates achieved by trastuzumab [129, 130] in HER-2–overexpressing disease, although definitive conclusions cannot be drawn from crosstrial comparisons.

Novel Molecular Targets

A few signaling pathways have attracted a lot of enthusiasm. First, the ubiquitin–proteosome pathway is involved in cell cycle control, through normal degradation of cellular proteins; disruption of this pathway contributes to tumor growth. Bortezomib, a proteosome inhibitor, was shown to induce apoptosis and suppress tumor growth in gastric cancer cell lines [131]. In a preliminary phase II study, bortezomib plus irinotecan led to an RR of 44% in chemotherapy-naive patients and an RR of 9% in pretreated patients when used as monotherapy [132]. Nevertheless, recent evidence showed disappointing results. Single-agent bortezomib did not achieve any objective response in 15 evaluable patients with advanced gastric or GEJ adenocarcinoma with up to one line of prior therapy [133]. Another trial evaluating bortezomib, paclitaxel, and carboplatin as first-line treatment for metastatic esophageal, gastric, and GEJ cancers showed a disappointing ORR of 23%, leading to premature termination of the study [134]. Thus, the initial enthusiasm in using bortezomib for AGC cannot be confirmed.

Second, the overexpression/activation of c-Met, a receptor for hepatocyte growth factor, leads to proliferation and antiapoptotic signals [135]. It was found to be activated both in vitro in human gastric cancer cell lines [136] and in vivo in human gastric cancer tissue [137], and this may result from the infection of gastric cells by *Helicobacter pylori* (HP) [138]. Amplification of *MET* predicts response to Met inhibition in vitro [139]. Interim results of a phase II study of GSK1363089 (GSK089, formerly XL880), a c-Met TKI, showed minimal activity in a cohort of metastatic gastric cancer patients unselected for c-Met but was well tolerated, with toxicities including liver function abnormalities, fatigue, and venous thromboembolism [140]. In another preliminary report, two of 10 gastroesophageal cancer patients with *MET* amplification had tumor shrinkage with the Met inhibitor crizotinib [141]. Notably, variable responses were noted in different Met-overexpressing esophageal cancer cell lines [142], suggesting that factors other than Met overexpression may play a role in predicting response. For example, a recent report showed that HER activation induced resistance to Met inhibition in Met-addicted gastric cancer cells in vitro and in vivo [143, 144]; this reiterates the importance of the development of predictive biomarkers.

The Hedgehog (Hh) pathway further complicates the complex signaling in gastric cancer cells [145]. The Hh protein family includes Sonic (Shh), Indian (Ihh), and Desert (Dhh) Hedgehogs. In gastric cancer, the aberrant activation of Shh, through binding Patched 1 receptor and subsequent disinhibition of Smoothened in turn activates the transcription factor Gli-1. Cyclopamine, an Hh inhibitor, induced gastric cancer cell apoptosis in vitro [145]. Clinical use of Hh inhibitors is currently only in early phases of development [146].

Inhibition of other biological pathways in AGC is in preclinical or early clinical evaluation. The expression of insulin-like growth factor 1 receptor (IGF-1R) is correlated with poor outcome in AGC patients [147], and the IGF-1R antibody figitumumab in combination with docetaxel was well tolerated in a phase I trial of patients with advanced solid tumors [148]. Fibroblast growth factor receptor (*FGFR*) mutations are associated with the development of gastric cancer [149], and FGFR inhibitors may play a role in AGC treatment [150]. Heat shock protein 90 (HSP90) regulates oncogenic protein stability, and an HSP90 inhibitor was shown to inhibit gastric cancer cell growth in vitro and in xenografts [151]. Histone deacetylase (HDAC) has an important role in cell cycle regulation; its expression was associated with tumor aggressiveness in gastric cancer [152]. A phase I trial demonstrated tolerability of the combination of the HDAC inhibitor vorinostat, irinotecan, and 5-FU in patients with upper gastrointestinal cancer [153]. Moreover, the expression of interleukin (IL)-6 is higher in HP-induced gastritis, and it has been implicated in carcinogenesis via activation of the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway [154]. Both IL-6–neutralizing antibody and AZD 1480, a selective JAK-2 inhibitor with potent activity in blocking STAT-3 signaling, are in the early phase of clinical testing.

Conclusion

In conclusion, recent progress in targeted therapy development for AGC has been modest. The ToGA trial was practice changing for patients with HER-2–overexpressing AGC, for which trastuzumab is approved in combination with chemotherapy in the first-line setting, whereas other agents require vetting in well-designed phase III trials. There is still an unmet need for researchers to unravel the molecular carcinogenic mechanisms underlying AGC, to rationally design targeted therapy or combinations of such, and to develop predictive biomarkers to aid patient selection.

Author Contributions

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