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Targeted Therapy in Advanced Gastric Cancer: An Updated Review

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Abstract

Despite great efforts over the years, adenocarcinoma of the stomach remains a difficult disease to manage. It is the second leading cause of cancer death and is the fifth most common cancer worldwide. If diagnosed early, surgical resection can offer definitive therapy. However, disease is often advanced or metastatic at the time of diagnosis and chemotherapy becomes the only option. With increased understanding of the molecular pathways that are responsible for tumor development and proliferation, targeted therapies have become an important part of cancer treatment in the setting of advanced or metastatic disease. Trastuzumab is widely used in HER2-positive breast cancer. Similarly, the ToGA trial established its role in gastric cancer that overexpresses HER2 by demonstrating an overall survival benefit in that cohort. Based on these results, HER2 testing should be performed routinely in patients with metastatic gastric cancer in order to identify patients who can benefit from this biologic agent. Ramucirumab also improves survival either as a single agent or when combined with chemotherapy after disease progression using standard first-line therapy. Unfortunately, these favorable responses are not seen with many other targeted agents in gastric cancer. This review aims to outline and summarize currently available knowledge and clinical data for some of the most common signaling targets and their respective therapeutic trials.

Introduction

Adenocarcinoma of the stomach is the fifth most common malignancy worldwide, affecting 952,000 new individuals in 2012 alone according to the World Health Organization [1]. It is also the second leading cause of cancer mortality internationally [2]. With currently available treatment strategies, the median survival in advanced or metastatic gastric cancer is only about 1 year [3]. Though the survival outcome is poor overall, there is a great disparity between Asian and Western patients. In fact, the 5-year survival in Japanese patients with gastric cancer was more than 70% in 2008 but only about 20% worldwide. The reasons for this difference may be multifactorial. For example, Japanese patients are screened routinely for gastric cancer given its high incidence whereas American patients are not owing to cost ineffectiveness [4]. Asian countries also tend to offer second-line chemotherapy more frequently than their Western counterparts [5,6].

Currently, curative resection is the definitive therapy for early-stage disease. The standard of care for resectable gastric cancer also includes either adjuvant chemoradiation according to data presented in the INT-0116 [7] or the ARTIST trials [8] (favored in Asian countries) or perioperative chemotherapy based on the MAGIC trial [9]. For unresectable or metastatic disease, treatment usually includes the use of cytotoxic chemotherapy such as a platinum with a fluoropyrimidine and an anthracycline [3]. With the advent of targeted therapy and increased understanding of biological pathways that fuel tumor growth, numerous targeted agents have been studied in gastric cancer as well. Specifically, trastuzumab and ramucirumab were shown in phase III clinical trials to prolong overall survival in the unresectable or metastatic setting. This review aims to summarize currently available data on various targeted agents as well as examples of ongoing clinical trials.

HER2 Expression and Biologic Agents

It has been well established that the human epidermal growth factor receptor 2 (HER2) plays an important role in cell proliferation and differentiation. It is part of a family of transmembrane human epidermal growth factor receptors (EGFRs) consisting of 4 homologous receptors, HER1/EGFR, HER2, HER3 and HER4. HER2 has no known functional ligand. Instead, its tyrosine kinase functions via heterodimerization with other HER family members and autophosphorylation by having an extracellular domain that is always in the open conformation. Its overexpression causes increased growth, differentiation, migration, adhesion, and ultimately survival of the affected cell, leading to the final aggressiveness of the tumor [10,11]. However, despite this role in promoting tumor growth, its prognostic value in gastric adenocarcinoma is still controversial. Some investigators found that its amplification may not necessarily portend a poor prognosis [15-18] while others found it to be an independent adverse prognostic factor [19-21].

In gastric cancer, HER2 is estimated to be overexpressed or amplified in 7-34% of cases [10-15]. The rate of HER2 positive cancers (14.4% IHC3+ or FISH+) reported in the MAGIC trial [9] was lower than reported in advanced disease as seen both in the screening study for the ToGA trial (22.1%) [22] and an international collaborative biomarker study (20.6%) [23]. A biomarker analysis of the ACTS-GC study in early gastric cancer revealed that 13.6% of 829 resected gastric cancers were HER2 positive, defined by IHC3+ or IHC2+ and FISH+ [24]. A large European study reported HER2 expression in <10% of gastric cancers evaluated, albeit using breast cancer HER2 scoring [25]. The differences observed suggest that HER2 over-expression/ HER2 gene amplification may be more frequent in advanced than early disease.

Studies have shown that early onset gastric cancer has a different molecular expression profile than late onset gastric cancer [26,27]

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which is consistent with the finding that these cancers show a different (lower) HER2 overexpression and amplification frequency than late onset gastric cancer. Other studies using whole slides also have reported lower frequencies of overexpression [28-30].

There is significant heterogeneity in the detection of amplification and overexpression of HER2 according to the origin and location of the primary tumor as well, which may explain the difference in the literature regarding its prognostic value. In those arising from the gastroesophageal junction (GEJ), HER2 expression is amplified in 24-33% of cases but only increased in 12-20% of tumors in the stomach. It is also more commonly seen in intestinal type than diffuse or mixed cancers [18,20,22,31]. Increased HER2 expression also correlates with increased nodal involvement [31,34]. Furthermore, HER2 is often detected only focally in tissue samples as a result of the glandular cells having incomplete basolateral or lateral staining patterns [18,33]. These factors make assessment of HER2 positivity problematic in gastric adenocarcinoma. Currently, though low or high HER2 expressions (defined as 0 or 1+ for low expression and 3+ for high expression) can be readily interpreted based on immunohistochemical (IHC) testing, equivocal staining at 2+ should be followed by fluorescence *in situ* hybridization (FISH) testing for confirmation [34-36]. These methods of detection of HER2 contribution in the pathophysiology of gastric cancer have become the standard of practice and references in both trial design and clinical practice.

Despite these difficulties, HER2 targeting therapy in gastric cancer has been established and remains an active area of research.

Trastuzumab

Trastuzumab is a recombinant humanized monoclonal antibody targeting HER2 [37]. After binding to HER2, trastuzumab causes an internalization and degradation of the receptor. It inhibits downstream signaling and subsequent cleavage of the extracellular domain and prevents the formation of p95HER2, its active form. Tumor angiogenesis and DNA damage repair are thus inhibited [11,38]. It also induces antibody-dependent cellular cytotoxicity [13]. Its use in advanced or metastatic gastric cancer was approved in 2010 based on the pivotal Trastuzumab for Gastric Cancer (ToGA) trial, which showed an improvement in median survival of about 2 months when used with chemotherapy.

The ToGA trial was a phase III, multicenter, randomized controlled trial designed to evaluate the utility of adding trastuzumab to a chemotherapy backbone in patients with HER2-positive inoperable locally advanced, recurrent, metastatic gastric or GEJ cancer in the first-line setting. A total of 594 patients were randomly assigned to receive either capecitabine or fluorouracil with cisplatin alone or chemotherapy with trastuzumab. The primary endpoint was overall survival. After an initial median follow-up of about 18 months, median overall survival was 13.8 months (95% CI, 12 to 16 months) in those assigned to trastuzumab with chemotherapy compared to 11.1 months (95% CI, 10 to 13 months) in those who received chemotherapy alone (HR 0.74; 95% CI, 0.60 to 0.91; p=0.0046). This difference corresponded to a 26% reduction in rate of death. Median progression-free survival was 6.7 months (95% CI, 6 to 8 months) in those who received trastuzumab compared to 5.5 months (95% CI, 5 to 6 months) in those who did not (HR 0.71; 95% CI, 0.59 to 0.85; p=0.0002). Time to progression was 7.1 months with trastuzumab and 5.6 months without. Second-line therapy after disease progression was provided to 122 (42%) patients in the study arm compared to 131 (45%) patients in the control arm. In addition, overall tumor response rate, duration of response, and time to progression were all improved with use of trastuzumab.

The ToGA trial included patients with HER2 protein expression by IHC and gene amplification by FISH ranging from 0 to 3+ and negative to positive, respectively. According to pre-planned analysis, overall survival was increased in patients with higher HER2 protein expression and gene amplification. A post-hoc analysis found a median overall survival of 11.8 months (95% CI, 10 to 13 months) in the group with lower HER2 protein expression. Conversely, those with higher levels of HER2 expression had a median overall survival of 16 months (95% CI, 15 to 19 months). The hazard ratio was 0.65 (95% CI, 0.51 to 0.83). Furthermore, there was a significant interaction test between the use of trastuzumab and the two subgroups of HER2 expression (p=0.036), demonstrating that trastuzumab provided more benefit to those patients with a higher HER2 level of expression [13]. This was later validated in a study by Gomez-Martin et al. which demonstrated the predictive value of the level of HER2 gene amplification in regards to overall survival and sensitivity to trastuzumab [39].

The ToGA trial also showed that the rates of grade 3 and 4 toxicities did not differ between the two groups. Nausea, vomiting, neutropenia and anorexia were the most common adverse events. Frequencies of cardiac events were similar between the two arms [13].

In a subset analysis of the ToGA trial aimed to evaluate response to the addition of trastuzumab in Japanese patients, Sawaki et al. found an overall survival of 17.7 months (95% CI, 12 to 24 months) compared to 15.9 months (95% CI, 12 to 25 months) in the control arm (HR 1.00; 95% CI, 0.59 to 1.69). After adjusting for variables, the hazard ratio for overall survival was 0.68 (95% CI, 0.36 to 1.27). This increase in benefit for Japanese patients compared to Western patients correlated with previous data. The authors postulated that one reason could be that Japanese patients received second-line therapy after progression more often than their counterparts [40]. It should be noted also that the hazard ratio was similar in the isolated Japanese cohort compared to that found in the entire study population. This suggests that the relative effect of trastuzumab on overall survival remains consistent within a particular cohort.

More recently, an updated survival analysis was done after 227 deaths had occurred in patients receiving trastuzumab with chemotherapy and 221 deaths had occurred in patients receiving chemotherapy alone. This update showed a median survival of 13.1 months in those who were treated with trastuzumab with chemotherapy compared to 11.7 months in patients who received chemotherapy alone (HR 0.8, 95 percent CI 0.67, 0.97.) Subgroup analyses according to HER2 protein expression as defined by IHC levels confirmed that trastuzumab had the greatest overall survival impact in those patients whose tumors had a high expression of the protein. The overall survival hazard ratios in 294 patients with HER2 IHC 3+ and 160 patients with HER2 IHC 2+ tumors were 0.66 (95% CI, 0.50 to 0.87) and 0.78 (95% CI, 0.55 to 1.10), respectively. The addition of trastuzumab to chemotherapy was not found to be effective in tumors that did not overexpress HER2 as defined by IHC 1+ or 0 (HR 1.33, 95% CI, 0.92 to 1.92) [41]. Based on these updated

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results, trastuzumab should only be used in those patients whose tumor demonstrated overexpression or gene amplification of HER2.

Similarly promising data combining trastuzumab with S-1, an oral fluoropyrimidine, and cisplatin in advanced gastric adenocarcinoma in Asia has been found. In a phase II study known as the HERBIS-1 trial, response rate was 67.9% (95% CI, 53.7 to 80.1%) with a median overall survival of 16 months (95% CI, 13.3 months to not applicable). Median progression-free survival was found to be 7.8 months (95 CI, 6.0 to 8.8 months) [42]. Another phase II trial known as the HERBIS-5 study is currently ongoing, looking at the efficacy and safety profile of trastuzumab with irinotecan in the second-line setting [43]. A phase II trial adding trastuzumab to a backbone of docetaxel and capecitabine as first-line therapy (NCT02004769) and a phase II/III trial of trastuzumab versus taxane in the second-line setting (NCT01641939) are currently recruiting patients as well.

There are also ongoing efforts to assess the efficacy and safety of using trastuzumab in the peri-operative and adjuvant setting. A phase II open-label study has been completed in patients with resectable gastric cancer using capecitabine and oxaliplatin (XELOX) with trastuzumab peri-operatively followed by 1 year of trastuzumab maintenance. Results from this trial are not yet available (NCT01130337). Another example is the TOXAG trial, which is a phase II study using XELOX, trastuzumab, and radiotherapy in an adjuvant setting. It is currently recruiting patients for participation (NCT01748773).

Despite the improved overall survival seen when trastuzumab was added to chemotherapy in advanced gastric adenocarcinoma, patients still eventually developed resistance resulting in progression of disease. The activation of another receptor tyrosine kinase that bypasses the inhibited action of HER2 and EGFR has been proposed as one mechanism of resistance. For instance, c-MET (mesenchymal epithelial transition factor) is another such molecule that when bound by its ligand the hepatocyte growth factor (HGF), it causes an activation of mitogen-activated protein kinase (MAPK) and AKT, both also downstream targets of the EGFR pathway. It is overexpressed in gastric adenocarcinoma, up to 24.9% by one report, and is associated with worse outcomes [14,15,44-46]. In metastatic breast cancer, the presence of both c-MET and HGF were found to be associated with higher risk of failure and shorter duration to progression [47]. In fact, breast cancer cells with overexpression of HER2 can up-regulate MET expression after exposure to trastuzumab, thus creating its own resistance [48].

Another possible molecule responsible for trastuzumab resistance may be the phosphatase and tensin homolog (PTEN). It is a tumor-suppressor that usually inhibits the HER2 receptor-bound Src molecule and regulates the phosphoinositide 3-kinase (PI3K)-AKT activities. The loss of PTEN may be involved in the pathogenesis of gastric cancer and predictive of early resistance. Furthermore, overexpression of microRNA-21 (miR-21) decreased expression of PTEN, thus leading to enhanced trastuzumab resistance [49,50].

Efforts are being made to try and overcome this resistance. Using a trastuzumab-resistant cell line, Zheng et al. were able to demonstrate antitumor effect when trastuzumab was combined with cetuximab [51]. Others have also shown that combining trastuzumab with VEGF-Trap agent greatly inhibited tumor proliferation and survival [52]. A phase II study using one such antibody, ziv-aflibercept, in addition to mFOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) in the first-line setting is currently ongoing in gastric and esophagogastric cancer (NCT01747551).

Lapatinib

Following the success of trastuzumab in gastric cancer, investigators began to look to other agents that target the HER2 pathway. Additionally, an overall response rate to trastuzumab of 47% and the duration of response of only about 6.9 months [13] prompted a search for another strategy that could offer improved and more durable results. Lapatinib is a tyrosine kinase inhibitor that targets EGFR (HER1) and HER2 receptors. In preclinical data, lapatinib inhibited the proliferation of upper gastrointestinal cancer cell lines and decreased the phosphorylation of EGFR and HER2. It also induced G0-G1 arrest and apoptosis in HER2-overexpressed cell lines. These results were intensified when lapatinib was used in combination with trastuzumab [10].

Despite preclinical results and phase II data [53], however, phase III trials did not show survival benefit when lapatinib was added to chemotherapy. The LOGiC trial was a randomized, double-blinded phase III trial designed to investigate lapatinib's efficacy in the first-line setting when combined with XELOX in advanced or metastatic HER2 amplified upper gastrointestinal adenocarcinomas. The primary endpoint of overall survival was not yet reached at the time of data presentation at the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting. Median overall survival was 12.2 months in the lapatinib arm compared to 10.5 months in the control arm, with a hazard ratio of 0.91 (95% CI, 0.73 to 1.12, p=0.35). Progression-free survival did not reach statistical significance. Of note, pre-specified subgroup analyses showed improvements in Asian patients (HR 0.68) and younger patients (under 60 years of age, HR 0.69). Though this study included patients with gastric, esophageal, and gastroesophageal adenocarcinoma, the presented data did not specify whether any difference in response was seen from the addition of lapatinib among the different cancer types [54].

The TyTAN trial was a randomized, open-label, phase III trial in Asia that aimed to define lapatinib's role in the second-line treatment of advanced gastric cancer. Patients with HER2 overexpression were randomized to receive paclitaxel with lapatinib or paclitaxel alone. Median overall survival was 11 months with lapatinib and paclitaxel compared to 8.9 months with paclitaxel alone (p=0.1044). Median progression-free survival was 5.5 months and 4.4 months in the study and control arms, respectively. Neither endpoints were found to be statistically significant [55].

The lack of clinical response in lapatinib despite preclinical data suggests a mechanism of resistance. Similar to the scenario seen with trastuzumab resistance, Chen et al. showed that after inhibition of the HER2 pathway and signal transduction by lapatinib, c-MET activation was rescued by the addition of HGF, promoting cell cycle and proliferation once again. More importantly, this rescue phenomenon was curbed once more by the addition of a c-MET inhibitor, PHA-665752 [44]. Other tyrosine kinase receptors such as HER3 and insulin-like growth factor 1 receptor (IGF-1R) have also been implicated as a bypass mechanism resulting in lapatinib resistance [56]. The cytokine heregulin was also implicated in lapatinib

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resistance by activating HER3 and AKT [57]. The identification of these pathways is crucial for finding potential targets in the future.

Other HER Inhibitors

Trastuzumab has been conjugated with DM1, which is a cytotoxic molecular derivative of maytansine 1, into an antibody-drug conjugate (trastuzumab emtansine, or T-DM1) that has been shown to be effective in HER2-positive breast cancer. The conjugate uses the receptor-mediated endocytosis mechanism in HER2-overexpressing cells to deliver the cytotoxic molecule intracellularly. Once intracellular, DM1 inhibits microtubule assembly and subsequently induces cell death [58-60]. In HER2-positive gastric cancer cell lines, T-DM1 was shown to induce apoptotic cell death [60]. Currently, several clinical trials are investigating the use of T-DM1 in advanced gastric cancer.

The unsatisfactory results of lapatinib despite trastuzumab's efficacy prompted investigations of other agents that augment the HER pathways. Pertuzumab is an antibody directed against the domain II of HER2, which functions in dimerization. It was shown to have a significant effect in HER2-positive breast cancer when combined with trastuzumab and docetaxel [61]. Currently, data on the utility of pertuzumab with trastuzumab is scarce. One study using a xenograft model showed increased antitumor effects when pertuzumab was used with trastuzumab [62]. Another showed synergistic effect when pertuzumab was used in combination with T-DM1 in gastric cancer cell lines [63]. Early clinical data suggest that pertuzumab and trastuzumab given in combination with cisplatin and capecitabine are effective [64]. A subsequent phase III randomized trial investigating the combination of pertuzumab, trastuzumab, cisplatin and fluorouracil in recurrent or metastatic gastric or GEJ cancer is currently active (NCT01774786). A phase II study known as INNOVATION is being conducted in the peri-operative setting using trastuzumab or trastuzumab/pertuzumab against a cytotoxic backbone of cisplatin and fluorouracil (NCT00205047). The exploration of pertuzumab's effect in HER2-positive gastric cancer remains a very active area of research at this time.

Dacomitinib is another irreversible pan-HER tyrosine kinase inhibitor. It has been associated with antitumor effects in breast cancer cell lines that were resistant to trastuzumab and lapatinib [65]. It was also found to offer improved progression-free survival compared to erlotinib in advanced non-small cell lung cancer (NSCLC) [66]. There appears to be a synergistic effect with dacomitinib when combined with trastuzumab or other inhibitors of downstream signaling pathways [67]. A similar finding was noted from poziotinib, also a pan-HER inhibitor [68]. For instance, a phase I-II trial is currently recruiting patients using poziotinib with paclitaxel and trastuzumab in gastric adenocarcinoma (NCT01746771).

EGFR (HER1) Inhibitors

Epidermal growth factor receptor (EGFR), also known as HER1, signaling pathway is important in the proliferation and survival of tumor cells. While it is expressed in 70% of gastric cancers [69], it is overexpressed in 18-23% of cases [14,70] and may be associated with a poor prognosis [71,72] though this is controversial [73]. It is a biologic target in various forms of malignancies with promising results. However, its efficacy in gastric cancer remains equivocal.

One commonly used agent is erlotinib, an oral reversible inhibitor of the adenosine triphosphate (ATP) binding site of EGFR tyrosine kinase. In a phase II study, 25 patients with gastric cancer and 43 patients with cancer of the GEJ were enrolled and treated. Erlotinib provided an overall response rate of 9%. However, this response was only noted in patients with GEJ adenocarcinoma, not in patients with gastric cancer. In fact, the stomach adenocarcinoma arm was closed early because of this negative result. The authors suggested that this difference in response might be related to the intrinsically different biologies of the two malignancies [69].

Gefitinib is another EGFR tyrosine kinase inhibitor that has been approved for use in non-small cell lung cancer [74,75]. Its use in gastric cancer, however, has not been promising. A phase II study in patients who failed previous therapy found sufficient biological inhibition of EGFR expression and tumor growth. However, this did not translate into a clinical benefit [76].

Cetuximab is a recombinant monoclonal EGFR antibody. Phase II studies found no added benefit when cetuximab was added to docetaxel and oxaliplatin [77] or when used alone [78]. The phase III EXPAND trial was not able to show a benefit in progression-free survival or overall survival from cetuximab when added to capecitabine and cisplatin in the first-line setting [79].

Panitumumab is a human monoclonal antibody targeting EGFR. It has been shown to be useful in advanced colorectal cancer in the PRIME, ASPECCT, and PEAK trials [80-82]. In gastric cancer, it has not been shown to provide any overall survival benefit when added to epirubicin, oxaliplatin, and capecitabine (EOX) in the REAL3 trial [83].

Nimotuzumab is a recombinant humanized monoclonal antibody against EGFR. A phase II study found no survival benefit in patients with advanced gastric cancer who failed prior fluorouracil-based therapy. However, a subgroup analysis found significant improvement in efficacy in patients with EGFR 2+/3+ by IHC with a response rate of 33.3% in the treatment group (irinotecan and nimotuzumab) compared to 0% in the control group (irinotecan alone). The median progression-free survivals were 118.5 days (95% CI, 87 to not estimated days) for the nimotuzumab arm and 59 days (95% CI, 24 to 113 days) for the placebo arm. However, the hazard ratio was not found to be statistically significant for this. Median overall survival improved by over 100 days. Disease control rate also improved from 33.3% to 83.3% with the addition of nimotuzumab to irinotecan [84]. These findings suggest that nimotuzumab has a role in the treatment of gastric cancer that strongly overexpresses EGFR. A phase II study combining nimotuzumab, capecitabine, and radiotherapy for unresectable or recurrent gastric adenocarcinoma is currently recruiting patients (NCT01180166). A follow-up phase III trial investigating the safety and efficacy of nimotuzumab with irinotecan in patients with advanced disease in the second-line setting after disease progression on fluorouracil and platinum-based therapy is also enrolling patients (NCT01713253) in Japan and Korea. The inclusion criteria in this study mandate EGFR overexpression of 2+ or 3+ by IHC. Given the observed phase II data of a trend towards improved survival, nimotuzumab may be proven useful in a carefully-selected patient population.

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VEGF and Antiangiogenic Therapy

Vascular endothelial growth factor (VEGF) and the tyrosine kinase receptor VEGF receptor-2 (VEGFR-2) are important players in the angiogenesis pathway. When VEGFR-2 is bound by its ligand VEGF-A, a signaling cascade results in angiogenesis as well as increased endothelial cell survival, proliferation, and permeability [85]. When the receptor VEGFR-2 is inhibited in animal models, tumor growth and vascularity are reduced. In gastric cancer, high expressions of VEGF were found to correlate with tumor aggressiveness and poor outcomes. It was also noted to be an independent prognostic factor for decreased overall survival [86-89]. The overall role of anti-VEGF agents in advanced gastric cancer was found to be important, especially in those who progressed after other first-line therapies. There was a reduction of risk of progression of disease by 39% and risk of death by 58%. In addition, apatinib and ramucirumab were found to have the greatest antitumor effect [90]. In fact, ramucirumab is approved for use in advanced gastric cancer either aas a single agent or with paclitaxel in the second-line setting. This effect, however, cannot be generalized across all classes of VEGF inhibitors.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that is designed to block VEGF receptor binding. It has an established role when combined with chemotherapy in metastatic colorectal cancer as well as non-small cell lung cancer [91,92]. However, it was found to offer no improvement in overall survival when compared to placebo in the AVAGAST and AVATAR studies.

The AVAGAST study was a phase III randomized, placebo-controlled trial aimed to define the role of bevacizumab when added to capecitabine and cisplatin in the first line treatment of advanced gastric cancer. Median overall survival was 12.1 months with the addition of bevacizumab and 10.1 months without. This difference, though, was not found to be statistically significant (HR 0.87; 95% CI, 0.73 to 1.03; p=0.1002) and the study did not meet its primary endpoint. Despite this, the estimated 1-year overall survival rate was better when bevacizumab was added to chemotherapy at 50.2%, compared to 42.3% with placebo (p=0.0301). Median overall response rate was improved with bevacizumab at 46% compared to 37.4% with placebo (p=0.0315). Median progression-free survival also improved from 5.3 months to 6.7 months (HR 0.80; 95% CI, 0.68 to 0.93; p=0.0037). Additionally, the AVAGAST study identified regional subgroups that may benefit more from the addition of bevacizumab in preplanned analyses. Patients enrolled in North American and Latin America seemed to benefit most from the VEGF inhibitor with a median survival of 11.5 months compared to 6.8 months in those without. On the other hand, European patients received mixed benefits while Asian patients did not receive any. This difference in benefit may be relative but nonetheless important. The study found that Asian patients had the best median overall survival of 12.1 months whereas Pan-American patients had an overall survival of 6.8 months in the placebo arm [93]. It is possible to suggest that bevacizumab was able to improve a known poor outcome for Western patients to at least that of Asian patients, who historically fare better for reasons described earlier.

The Chinese conducted a phase III randomized study similar in design to the AVAGAST trial, known as the AVATAR trial, to investigate if the addition of bevacizumab to capecitabine and cisplatin would benefit their specific population given the regional differences observed by the former study. Again, there was no difference in overall survival with a hazard ratio of 1.11 (95% CI, 0.79 to 1.56; p=0.55670). Median progression-free survival was also similar in both arms at 6.3 months and 6.0 months with and without bevacizumab, respectively [94].

Ramucirumab

Ramucirumab is a fully human monoclonal IgG antibody against the extracellular domain of VEGFR-2. The phase III REGARD trial demonstrated a survival benefit for ramucirumab when used as a single agent compared to placebo. Patients recruited had gastric or GEJ adenocarcinoma who failed first-line platinum- or fluoropyrimidine-containing chemotherapy. Median overall survival was 5.2 months in patients who received ramucirumab compared to 3.8 months in the placebo group (HR 0.776; 95% CI, 0.603 to 0.998; p=0.047). Its use was associated with a 52% reduction in the risk of progression of disease or death with a median progression-free survival of 2.1 months and 1.3 months in the study and control groups, respectively. Hypertension was more commonly seen in the ramucirumab group (16%) compared to the control group (8%). Other adverse effects were similar between groups [86]. Although the noted benefits were modest and only in terms of months, ramucirumab offered an option when other targeted therapies have failed. This trial led to the approval of the drug for use in the second-line setting in the United States.

A similar study known as the RAINBOW trial presented its results in the 2014 Gastrointestinal Cancers Symposium and the ASCO Annual Meeting. It was a phase III randomized trial studying the efficacy of ramucirumab in combination with paclitaxel versus paclitaxel alone. Median overall survival was 9.63 months for the ramucirumab arm compared to 7.36 months in the control arm (HR 0.807; 95% CI, 0.678 to 0.962; p=0.0169). Median progression-free survival was 4.4 months and 2.86 months in the study group and the control group, respectively (HR 0.635; 95% CI, 0.536 to 0.752; p<0.0001). Median time to progression was also prolonged with the addition of ramucirumab from 3 months to 5.5 months. Furthermore, results were similar when Japanese and Western patients were analyzed individually except for overall survival, where there was no difference between the study and control arms in the Japanese cohort. The authors postulated that this lack of difference may be related to the use of "post-discontinuation treatment" [95,96].

Apatinib

A recently developed VEGFR inhibitor apatinib has gained much attention in the treatment of gastric adenocarcinoma. Apatinib is an oral small tyrosine kinase inhibitor that has been derived from valatinib. It selectively binds to VEGFR-2, thereby inhibiting subsequent endothelial migration and proliferation. It can also lead to decreased tumor microvascular density as a result [97]. It was shown to increase progression-free survival and overall survival in patients with metastatic gastric cancer after failure of 2 or more lines of therapy [98]. Much anticipated phase III data was presented at the 2014 ASCO Annual Meeting, which confirmed apatinib's efficacy and safety. Patients were randomized to receive apatinib or placebo.

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Median overall survival was 195 days in the apatinib group compared to 140 days in the control group (HR 0.71; 95% CI, 0.54 to 0.94; p<0.016). Median progression-free survival was also improved from 53 days in the placebo arm to 78 days in the study arm (HR 0.44; 95% CI, 0.33 to 0.61; p<0.0001) [99]. Though data from this clinical trial were measured in days, it introduces apatinib as a promising molecular agent for patients who have been heavily treated and progressed beyond second-line therapy, who otherwise have limited options.

Other VEGF Inhibitors

Other VEGF targeted therapies are currently being studied. There are limited phase I and II data involving the multitargeted tyrosine kinase inhibitor sorafenib in combination with S-1/cisplatin, docetaxel/cisplatin, and oxaliplatin [100-102]. Sunitinib, another multitargeted agent has also been studied in combination with chemotherapy [103,104]. However, the definitive roles of both agents are still in question. Pazopanib is an inhibitor of the VEGF receptor, platelet-derived growth factor receptor, and c-kit. It was found to be active in metastatic renal cell cancer [105]. There is limited data on its efficacy in gastric cancer and a phase II trial is ongoing using this agent in combination with FOLFOX in advanced disease in the first-line setting (NCT01503372). The variation in responses to different VEGF targeted agents may be due to subtle characteristics in the tumor biology that is not yet known. It may be an important goal of future studies to attempt to better identify patient groups or biomarkers that will more likely benefit from these biologic agents.

mTOR Pathway and its Inhibitor

The mTOR (mammalian Target of Rapamycin) pathway is a cell signaling pathway that has been successfully targeted in breast cancer and renal cell carcinoma using everolimus [106-108]. Its expression is associated with a poor prognosis in gastric adenocarcinoma [109]. When mTOR is activated, it leads to the translation of several proteins known to play important roles in tumor growth, including cyclin D1 and VEGF. Everolimus targets the mTOR complex 1 (mTORC1) by inhibiting its serine/threonine kinase activity, subsequently inducing cell death. It also decreases VEGF production by tumor cells [110,111]. This particular property to lower VEGF secretion has been found to enhance sunitinib's antitumor activity by counteracting sunitinib's VEGF induction [111]. It was also shown to have synergistic effects when combined with cyclophosphamide in preclinical studies [110,112].

Despite promising preclinical data, however, everolimus was not shown to provide survival benefit in the phase III GRANITE-1 trial when compared to best supportive care. Patients enrolled were those with advanced gastric cancer who progressed with previous chemotherapy. Median overall survival with everolimus was 5.4 months versus 4.3 months with placebo (HR 0.90; 95% CI, 0.75 to 1.08; p=0.124) [113]. Nonetheless, its efficacy in gastric cancer has not been investigated in clinical trials in combination with chemotherapy. The AIO-STO-0111 trial, a phase III randomized, double-blind study, aims to define its role when used with paclitaxel in patients who progressed after prior chemotherapy (NCT01248403).

c-MET Tyrosine Kinase and Hepatocyte Growth Factor Targeted Agents

As mentioned earlier, the c-MET pathway was implicated in trastuzumab and lapatinib resistance and associated with a worse clinical outcome. When bound to its ligand hepatocyte growth factor, the c-MET tyrosine kinase undergoes dimerization and phosphorylation, thus activating downstream pathways leading to cell proliferation.

New agents have been shown to exhibit effects on this pathway and inhibit cell survival in gastric cancer. A phase II study using foretinib, a MET/VEGFR inhibitor in 67 patients with metastatic gastric cancer found only a best response of stable disease in about 20% of patients and a median duration of 3.2 months. It should be noted that only 3 patients in those with tissue sample available expressed MET [114]. A phase I study using AMG337, a highly selective oral MET kinase inhibitor, was described at the 2014 ASCO Annual Meeting. It was found to result in 45 patients 1 complete response, 4 partial response, 28 stable disease, and 12 progressive disease responses, 8 of whom had known MET overexpression [115]. This study was conducted in patients with advanced solid tumors and not limited to gastric cancers; it is still too early to determine its specific effects on gastric adenocarcinomas. Nonetheless, this new agent showed much promise as a specific and oral targeted agent.

Other agents have shown promise in controlling gastric cancer by targeting this pathway as well. The c-MET inhibitor crizotinib was able to induce tumor regression in a PDGCX mouse model [116]. Volitinib, an inhibitor of c-MET, and saracatinib (AZD0530), an inhibitor of c-MET's downstream target Src, also showed anti-tumor effects in gastric cancer-derived xenograft models [117-119]. Onartuzumab, or MetMAb, is a monovalent monoclonal antibody that binds to the MET receptor, thus preventing HGF binding and its downstream signaling. A phase III randomized placebo-controlled trial, MetGastric, aims to evaluate the safety and efficacy of onartuzumab with mFOLFOX6 in metastatic HER2-negative, MET-positive metastatic gastric and GEJ adenocarcinoma (NCT01662869).

Recently, rilotumumab attracted much attention when it was shown to increase median progression-free survival in a phase Ib/II randomized trial when combined with epirubicine, cisplatin, and capecitabine (ECX). It is a fully human, monoclonal antibody that blocks binding of hepatocyte growth factor. When combined with chemotherapy, rilotumumab offered a median progression-free survival of up to 6.8 months (95% CI, 4.5 to 7.5 months) compared to 4.2 months (95% CI, 2.9 to 4.9 months) in placebo and chemotherapy, respectively.

Additionally and perhaps more importantly, this study confirmed MET's role as a negative prognostic marker while demonstrating the necessity of defining MET-positivity when using biologic agents such as rilotumumab. The study defined MET-positivity in two ways: at least 25% or 50% tumor staining by IHC. Results of tumor response to rilotumumab were similar in both definitions. In the placebo group, those with MET-positive tumors (defined as greater than 25% tumor staining) had a shorter median overall survival than those without increased MET expression (5.7 months compared to 11.5 months). Median overall survivals in the MET-positive groups were longer when rilotumumab was used whereas there was no difference in

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Table 1: Summary of key HER2 targeted agents.

Trial	Drug	Overall response rate (%)	Median Overall survival (months)	Progression-free survival (months)
HERBIS-1; Phase II	S-1 + *Trastuzumab* [42]	68 (95% CI, 54-80)	16 (95% CI, 13.3-NA)	7.8 (95% CI, 6-8.8)
ToGA; Phase III	5-FU/cisplatin ± *Trastuzumab* [13]	47 vs 35, p=0.002	13.8 vs 11.1 (HR 0.74; 95% CI, 0.60-0.91)	6.7 vs 5.5 (HR 0.71; 95% CI, 0.59-0.85)
LOGiC; Phase III	XELOX ± *lapatinib* [54]	53 vs 40	12.2 vs 10.5 (HR 0.91; 95% CI, 0.73-1.12; p=0.35	6.4 vs 5.4 (HR 0.86; 95% CI, 0.71-1.04; p=0.10)
TyTAN; phase III	Paclitaxel ± *lapatinib* [55]	27 vs 9	11 vs 8.9 (HR 0.84; 95% CI, 0.64-1.11; p=0.10)	5.5 vs 4.4 (HR 0.80; 95% CI, 0.59-1.08; p=0.13)

NA, not applicable.

Table 2: Summary of key EGFR targeted agents.

Trial	Drug	Overall response (%)	Median Overall survival (months)	Median Progression-free survival (months)
SWOG 0127; Phase II	*Erlotinib* [69]	Not reported	3.5	2
Phase II	Irinotecan ± *nimotuzumab* [84]	33.3 vs 0	358.5 days vs 229.5 days (HR 0.369; 95% CI, 0.11-1.242; p=0.0944)	118.5 days vs 59 days (HR 0.341; 95% CI, 0.08-1.457; p=0.1293)
EXPAND; phase III	Capecitabine, cisplatin ± *cetuximab* [79]	30 (95% CI, 26-34)	9.4 vs 10.7 (HR 1.00; 95% CI, 0.87-1.17; p=0.95)	4.4 vs 5.6 (HR 1.09; 95% CI, 0.92-1.29; p=0.32)
REAL3; phase III	EOX ± *panitumumab* [83]	46 vs 42	8.8 vs 11.3 (HR 1.37; 95% CI, 1.07-1.76; p=0.01)	6 vs 7.4 (HR 1.22; 95% CI, 0.98-1.52; p=0.07)

EOX, epirubicin, oxaliplatin, capecitabinz

Table 3: Summary of key VEGF targeted agents.

Trial	Drug	Overall response (%)	Median Overall survival (months)	Median Progression-free survival (months)
Phase I	S1, cisplatin, *sorafenib* [100]	38.5 (95% CI, 13.9-68.4)	Not reported	Not reported
Phase I	S-1, cisplatin, *sunitinib* [103]	37.5 (95% CI, 15.2-64.6)	Not reported	12.5 (95% CI, 6.4-16.5)
ECOG 5203; phase II	Docetaxel, cisplatin, *sorafenib* [101]	41 (90% CI, 28-54)	13.6 (90% CI, 8.6-16.1)	5.8 (90% CI, 5.4-7.4)
GEMCAD; phase II	Oxaliplatin, *sorafenib* [102]	50	6.5 (95% CI, 5.2-9.6)	3 (95% CI, 2.3-4.1)
Phase II	*Sunitinib* [104]	Not yet met	6.8 (95% CI, 4.4-9.6)	2.3 (95% CI, 1.6-2.6)
AVAGAST; Phase III	Capecitabine, cisplatin ± *Bevacizumab* [93]	46 vs 37.4 (p=0.03)	12.1 vs 10.1 (HR 0.87; 95% CI, 0.73 to 1.03; p=0.10)	6.7 vs 5.3 (HR 0.80; 95% CI, 0.68 to 0.93; p=0.004)
AVATAR; phase III	Capecitabine, cisplatin ± *Bevacizumab* [94]	40.7 vs 33.7 (p=0.35)	10.5 vs 11.4 (HR 1.11; 95% CI, 0.79-1.56; p=0.56)	6.3 vs 6 (HR 0.89; 95% CI, 0.66-1.21; p=0.47)
REGARD; phase III	*Ramucirumab* [96]	49 vs 23 (p<0.0001)	5.2 vs 3.8 (HR 0.776; 95% CI, 0.603-0.998; p=0.047)	2.1 vs 1.3 (HR 1.22; 95% CI, 0.98-1.52; p=0.07)
RAINBOW; phase III	Paclitaxel ± *Ramucirumab* [95,96]	28 vs 16 (p=0.0001)	9.63 vs 7.36 (HR 0.807; 95% CI, 0.678 to 0.962; p=0.0169)	4.4 vs 2.86 (HR 0.635; 95% CI, 0.536 to 0.752; p<0.0001)
Phase III	*Apatinib* [99]	2.84 vs 0	195 days vs 140 days (HR 0.71; 95% CI, 0.54 to 0.94; p<0.016)	78 days vs 53 days (HR 0.44; 95% CI, 0.33 to 0.61; p<0.0001)

FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin

survival between the study and control arms in the MET-negative groups. Similar results were seen in progression-free survival and response rates [120]. This study emphasized the need for MET overexpression or gene amplification testing to identify appropriate patients for the use of rilotumumab or other similar targeted agents. Two phase III trials known as RILOMET-1 and RILOMET-2 using rilotumumab with ECX and rilotumumab with cisplatin and capecitabine, respectively, are currently recruiting patients with cMET-positive gastric and GEJ adenocarcinoma in the first-line setting (NCT01697072; NCT02137343).

Hedgehog Inhibitor

The hedgehog (Hh) pathway plays an important role in gastric cancer. In normal embryonic and postnatal growth, it is responsible for the development of fingers and motor neurons. It is also responsible for the differentiation of gastric glands. When it is activated under abnormal conditions, its signaling cascade activation results in the growth of new tumors and acceleration of growth in existing tumors. In preclinical studies, the Hh antagonist cyclopamine was shown to be able to dampen gastric cancer cell proliferation and induce apoptosis [121-124]. Its overexpression may also be a marker of good prognosis in those with gastric cancer [125].

In 2012, the Hh inhibitor vismodegib was approved for the treatment of basal-cell carcinoma in the United States [126]. However, a randomized phase II study using vismodegib with FOLFOX compared to FOLFOX alone in patients with advanced or metastatic gastric and GEJ carcinoma in the first-line setting did not improve survival. Median progression-free survival was 11.5 months (95% CI,

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8.5 to 14.4 months) in the vismodegib arm versus 9.3 months (95% CI, 6.7 to 11.9 months) in the placebo arm with a p-value of 0.34. Median overall survival was 12.2 months in the treatment arm compared to 13.9 months in the placebo arm. Unfortunately, this difference was also not found to be statistically significant (p=0.48) [127]. Currently, there is no planned clinical trial studying this agent in gastric cancer.

FGFR Inhibitor

Fibroblasts growth factor receptors (FGFR) are also important under normal physiologic conditions for angiogenesis and wound repair. When activated, the ligand-receptor complex induces kinase activation and autophosphorylation, resulting in downstream activation of the (PI3K)-AKT and mitogen-activated protein kinase-extracellular signal-regulated kinase (MAPK-ERK) pathways [128]. Aberrant activations of FGFRs have been associated with various carcinomas, including bladder, ovarian, and breast [128,129]. In gastric cancer, it has been noted to be a gene amplification in 2-30% of cases and portends a poor prognosis [15,130]. However, of the 4 receptors in the family, it is unclear which is fueling the growth of the cancer. Using IHC techniques, FGFR1, FGFR2, and FGFR4 overexpression are associated with more aggressive tumor progression. Moreover, the coexpression of all three FGFRs was found to be an independent prognostic factor for worse outcome [131]. Using real-time PCR and FISH, however, only FGFR2 amplification was found in gastric adenocarcinoma samples [129]. Nonetheless, it is a target that has much potential in the treatment of gastric cancer.

Limited new drugs have been identified as promising FGFR2 targeting agents in gastric cancer. The multitargeted tyrosine kinase inhibitor ponatinib may also function as a pan-FGFR inhibitor. In preclinical data, it showed tumor inhibition both *in vitro* and *in vivo* [132]. The tyrosine kinase inhibitor dovitinib was also found to be effective in various solid tumors in early clinical trials though toxicities may be too severe when combined with cytotoxic chemotherapy [133-136]. A phase I/II study using dovitinib with docetaxel in the second-line setting (NCT01921673) and a phase II monotherapy trial in the first- and second-line settings (NCT01719549) are currently recruiting patients.

Other drugs in development such as AZD2171 and AZD4547, which are tyrosine kinase inhibitor of FGFR2 and inhibitor of FGFR1, FGFR2, and FGFR3, respectively, appear to have promising tumor growth inhibition effects *in vitro* and *in vivo*, especially when combined with cytotoxic chemotherapy [128,137]. Currently active clinical trials include the SHINE study, which is a phase II trial using AZD4547 as monotherapy compared to paclitaxel in recurrent or newly diagnosed advanced gastric or GEJ cancer (NCT01457846).

Immune Evasion Inhibitors

The programmed cell death-1 receptor and programmed cell death-1 ligand (PD-1 and PD-L1) pathway has recently been described to play an important role in tumor survival. PD-L1 is expressed exclusively on tumor cells and within the tumor milieu when confronted with an inflammatory stimulus. When this pathway is activated in tumor cells, the cytotoxic effects of T cells are blocked and tumors proliferate by escaping this immune response [138]. PD-L1 expression was also found to correlate with tumor differentiation and nodal metastasis [139]. This pathway's selective presence in tumor cells makes it a very promising target.

Until recently, antibodies targeting PD-L1 or its associated pathway have limited use in gastric cancer to date. Brahmer et al. conducted a phase I trial and found no objective response from BMS-936559 in enrolled patients with gastric cancer [138]. However, at the 2014 European Society for Medical Oncology (ESMO) Congress, Muro et al. found pembrolizumab to be well tolerated and efficacious in gastric or GEJ adenocarcinoma in a phase I study, KEYNOTE-012. Pembrolizumab is a selective and humanized monoclonal antibody that acts by inhibiting the interactions between PD-1 and its ligands PD-L1 and PD-L2. A total of 39 PD-L1-positive patients with recurrent or metastatic gastric or GEJ cancer were enrolled. Overall response rates were 32% in those patients in the Asian-Pacific region and 30% in the remainder of the world. Median response duration had not been met at the time of presentation with a range of 8 to 20 weeks [140]. As a result of this promising data, a phase II clinical trial is planned to start enrollment in 2015 (KEYNOTE-059) according to some reports. Additional clinical trials studying other PD-L1 targeted agents are ongoing as well (NCT01772004, NCT01375842).

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is another molecule known to provide a negative feedback on T cell activation and proliferation. It is, as a result, a potent facilitator of cancer growth by way of inhibiting immune response [141]. A phase II study using tremelimumab in the second-line setting found minimal response in gastric and esophageal cancer. Of 18 patients enrolled, 4 had stable disease and 1 had partial response [142]. Additional trials are actively recruiting patients with solid tumors, though most studies are enrolling patients with melanoma and mesothelioma at this point (NCT00610857, NCT01740401, NCT01655888).

Conclusion and Future Directions

Gastric cancer is a prevalent disease worldwide that is also difficult to treat, especially in the advanced or metastatic setting. Currently, surgical resection is the only option for cure while chemotherapy is the standard of care for unresectable disease. Nonetheless, prognosis is poor. With increased understanding of the molecular pathways that

Table 4: Summary of key features of gastric adenocarcinoma subtypes.

Chromosomal unstable	EBV infection associated	Microsatellite instability associated	Genomically stable
Intestinal histology	*PIK3CA* mutation	Hypermutation	Diffuse histology
TP53 mutation	*PD-L1/2* overexpression	Gastric-CIMP	*CDH1*, *RHOA* mutations
RTK-RAS activation	EBV-CIMP	*MLH1* silencing	*CLDN18-ARHGAP* fusion
	CDKN2A silencing	Mitotic pathways	Cell adhesion
	Immune cell signaling		

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promote tumor growth in recent years, there has been a rapid surge in the use of targeted therapy and a move towards a personalized approach to therapy.

An important change in the treatment of gastric cancer came with the ToGA trial, which showed that the use of trastuzumab in HER2-positive gastric cancer improved overall survival when combined with chemotherapy. Ramucirumab and apatinib, both VEGF receptor inhibitors, also provided a survival benefit. A myriad of other targeted agents have been engineered and studied in gastric adenocarcinoma. However, most have not been found to be active. Bevacizumab was not shown to be beneficial in gastric cancer; though it may be inferred to have minor improvements in survival parameters in Western patients given that these patients fared worse than their European and Asian counterparts.

The promise of targeted therapy continues to inspire extensive research. It remains imperative to be able to better characterize the molecular changes responsible for pathogenesis and tumor propagation in such an aggressive disease such as gastric cancer. The variations in results from targeted agents of the same class suggest that there may be more subtle differences yet to be defined. In a very comprehensive study published by the Cancer Genome Atlas Research Network, 4 molecular subtypes of gastric cancer were identified. These include EBV-infected tumors, tumors with microsatellite instability (MSI), genomically stable tumors, and chromosomally unstable tumors. Each of these subtypes has its own distinct genomic and histologic features. For example, tumors associated with EBV infection are more likely associated with PD-L1 and PD-L2 overexpression whereas tumors with MSI are associated with mitotic pathways. The locations from which the primary tumor arises also have unique features. Cancers arising from the GEJ are predominantly of the chromosomally unstable subtype. This subtype decreases to about 50% towards the distal stomach and genomically stable tumors become more prominent [143]. Table 4 summarizes the salient findings. This study is greatly important in directing future studies.

There are numerous active clinical trials aimed to identify new treatments for gastric cancer. For instance, an ambitious and promising study known as the PANGEA-IMBBP trial (Personalized Antibodies for Gastro-Esophageal Adenocarcinoma – A 1st Pilot Metastatic Trial of Biologics Beyond Progression) is being planned. It aims to utilize the concept of personalized medicine by screening for specific molecular profiles in tumor tissues and applying the corresponding targeted agents in therapy. Currently, oncogenic driver targets include EGFR, HER2, MET, FGFR2, and VEGFR2 and recruitment is planned to start in 2014 (NCT02213289). As more information becomes available and technology continues to advance, the potential of this unique and evolving set of therapeutic options will be limitless.

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