Therapeutics and Clinical Risk Management downloaded from https://www.dovepress.com/ For personal use only.

# Critical evaluation of ramucirumab in the treatment of advanced gastric and gastroesophageal cancers

#### Hesham ElHalawani Omar Abdel-Rahman

Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Abstract: Gastric (GC) and gastroesophageal junction (GEJ) cancers are two global health problems with a relatively high mortality, particularly in the advanced stage. Inhibition of angiogenesis is now contemplated as a classic treatment preference for myriad tumor types encompassing renal cell carcinoma, non-small cell lung cancer, colorectal cancer, glioblastoma, and ovarian cancer, among others. Bevacizumab and ramucirumab have been widely investigated in GC and GEJ cancer, with some controversy about their therapeutic role. Ramucirumab is a monoclonal antibody for vascular endothelial growth factor receptor-2, with demonstrated activity both as a monotherapy and as a part of combination strategy in the management of advanced GC/GEJ cancer. In this review article, we present a critical evaluation of the preclinical and clinical data underlying the use of this drug in this indication. Moreover, we provide a spotlight on the future perspectives in systemic therapy for advanced GC/GEJ cancer.

Keywords: ramucirumab, gastric cancer, gastroesophageal cancer

## Introduction

Gastric cancer (GC), in spite of the markedly declining incidence in the past decades, is still regarded as a global health problem, ranking as the fifth most common type of cancer, after malignancies of the lung, breast, colon, and prostate, and the third leading cause of cancer mortality globally, with around 952,000 new cases and 723,000 estimated deaths in 2012. Noteworthy, the decline in the incidence of GC was met by an opposing relative rise in the incidence of cancers of the gastroesophageal junction (GEJ) and gastric cardia.<sup>2</sup>

Given the heterogeneity of GC, several classifications and subclassifications of GC have been postulated based on tumor histology, degree of glandular differentiation, location, and molecular foundation. Histologically, the cardinal variants include three distinct subtypes, namely, proximal nondiffuse GC, distal nondiffuse GC, and diffuse GC.3

Proper staging of GC can be accomplished through an endoscopic ultrasound performed concomitantly with esophagoduodenoscopy. This confers high diagnostic accuracy for various GC stages. A preoperative laparoscopy can also be performed to improve staging diagnosis.4

An authentic preoperative staging of nodal involvement in GC is a must, given the fact that the extent of lymph node involvement is the most important prognostic factor according to the American Joint Committee on Cancer (AJCC) cancer staging manual.<sup>5</sup> Nevertheless, nodal sampling is technically rather challenging and the need for modern sentinel lymph node mapping technologies has driven many tests in this terrain.<sup>6</sup>

Multidetector computer tomography is currently used as the standard procedure for detecting distant metastases.<sup>7</sup> However, according to many consensus guidelines,



Correspondence: Omar Abdel-Rahman Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Lotfy Elsayed Street, Cairo 11665, Egypt Fax +20 3302 8656 Email omar.abdelrhman@med.asu.edu.eg positron emission tomography may be used additionally in GC staging, principally for describing distant spread or lymphatic deposits.<sup>8</sup>

#### Current state-of-the-art treatment of GC

Significant progress has been demonstrated in surgical and perioperative treatment modalities. Surgical resection carries the best odds for cure, with 5-year survival of 50%–70%, if paired with an early onset of diagnosis. Nonetheless, the prognosis of GC remains poor. The probability of tumor recurrence exceeds in 50% of patients with initially localized disease, especially in Western countries.<sup>9,10</sup>

Moreover, most newly diagnosed patients present with advanced and unresectable disease, and around 50% of cases present with synchronous metastasis with a very unfortunate corresponding relative 5-year survival rate of 4%–10%. 11,12

Of note, reports from Eastern countries have constantly revealed superior survival in GC patients, perhaps expressing geographical differences as regard epidemiology, pharmacogenomics, and molecular profiling.<sup>13,14</sup>

Cytotoxic chemotherapy represents the predominant treatment choice in the locally advanced and metastatic cohort of patients; notwithstanding, the median overall survival (OS) for advanced disease still continues to be below 1 year; while for best supportive care, it was 3–5 months. <sup>15,16</sup> There is no universal consensus about the standard combination for first-line chemotherapy. However, it is well established that combination chemotherapy (cisplatin/fluoropyrimidine) improves outcomes compared to fluoropyrimidine monotherapy. <sup>17</sup>

In recent years, the addition of trastuzumab to standard chemotherapy in patients with human epidermal growth factor receptor-2 (HER-2)-positive tumors has dramatically changed the management algorithm in this subset of patients. This has been established after achieving statistically significant increase in OS in the Trastuzumab for Gastric Cancer (ToGA) study (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.51–0.83), corresponding to median survival of 16 months versus 11.8 months. ToGA study was a randomized controlled trial that compared cisplatin and a fluoropyrimidine combination with the same combination in addition to trastuzumab.<sup>18</sup>

According to the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and other international consensus guidelines, treatment choices for HER-2-negative patients include two- and three-drug regimens in the first-line treatment setting, including 5-fluorouracil and cisplatin, in addition to irinotecan- or docetaxel-based regimens.<sup>7,19</sup> By the same

token, the evolving prescription of second-line therapies has led to an improved survival in selected patients.<sup>20,21</sup>

The recent data on the driving mechanisms of tumor progression and the tumor profiling based on molecular basis have led to the recognition of several alternative therapeutic targets. Distinctive spotlight was shed on vascular endothelial growth factor receptor (VEGFR) as a new target. Remarkably enough, VEGFR-2 is overexpressed in GC tissues compared with normal mucosa. VEGFR overexpression was also prominently observed in the case of lymph nodal metastases.<sup>22</sup>

Efficacy studies of recent trials disclosed progression-free survival (PFS) and OS benefit with the use of the monoclonal antibody (ramucirumab) or the tyrosine kinase inhibitor (apatinib) against the VEGFR-2, as second-line or even third-line therapies.<sup>23,24</sup>

#### VEGF pathway and cancer

In normal cells, there is a state of harmony between proand anti-angiogenic factors. Sustained angiogenesis is a fundamental process for the tumor growth and development and engages the interaction between tumor cells and stromal endothelial cells through multiple growth factors and membranous receptors that finally potentiate pro-angiogenic intracellular signaling pathways, hence providing nutritional supply to dividing cells through the formation of new blood vessels (neovascularization), with subsequent cancer progression and metastasis (Figure 1).<sup>25</sup>

Consequently, anti-angiogenesis has become a common therapeutic intervention for many clinical trials that proved improved survival by inhibiting angiogenesis, primarily the vascular endothelial growth factor (VEGF) axis, either by ligand inhibition, <sup>26</sup> receptor tyrosine kinase inhibition, or inhibition of intracellular signaling kinases<sup>27</sup> or combinations of these strategies. Anti-VEGF therapies have been associated with a survival benefit when these drugs were tested across different malignancies, including renal cell, non-small cell lung cancer, hepatocellular, and colorectal carcinomas.<sup>28</sup> Historically, angiogenesis has been studied as a fundamental contributor to diverse physiological processes, such as embryogenesis, normal tissue turnover, and wound healing.<sup>29</sup>

The mechanism of tumor angiogenesis was first depicted as early as in 1977 as a highly complex multifaceted program. The course of this process starts from the degradation of the basement membrane of a peritumoral capillary, recruitment of stromal cells and endothelial progenitor cells, development of a solid cord, remodeling of the extracellular matrix into an empty capillary with subsequent pro-angiogenic cytokine signaling, and activation of oncogenic signaling cascades.<sup>30</sup>

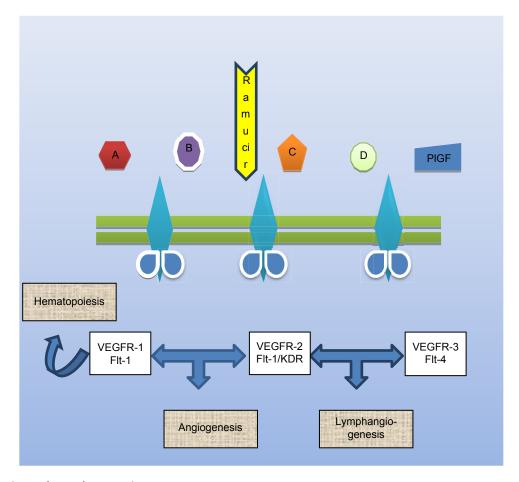


Figure I Basic mechanism of action of ramucirumab.

Note: A–D refer to different ligands for VEGFRs.

Abbreviations: VEGFR, vascular endothelial growth factor receptor; PIGF, placental growth factor; KDR: kinase insert domain receptor.

VEGF was isolated for the first time in 1989 as a diffusible heparin-binding polypeptide, which targets vascular endothelial cells.<sup>31</sup> The VEGF group of molecules includes VEGFA, VEGFB, VEGFC, VEGFD, VEGFE, and placental growth factor. These cytokines were consequently proved to be correlated with the mediation of tumor angiogenesis by interacting with different transmembrane tyrosine kinase receptors, such as VEGFR-1 (fins-like tyrosine kinase 1/Flt-1), VEGFR-2 (Flk-1/KDR), VEGFR-3 (Flt-4), along with two nonenzymatic coreceptors neuropilin-1 and -2 (NRP-1/2). NRP-1 is principally expressed in arterial endothelial cells, whereas NRP-2 exists in venous and lymphatic endothelium.<sup>32</sup>

VEGFR-1 shows high binding affinity for VEGFA, albeit it also shows weak phosphorylation activity, with a potentially negative modulator role on VEGF signaling. VEGFR-3 is primarily involved in lymphangiogenesis, while VEGFR-2 is by far nominated as the main receptor advocating angiogenesis.<sup>33</sup>

Logically, various malignancies exhibit upregulation of VEGFR-2 expression in the tumor vasculature.<sup>34</sup> The

pro-angiogenic downstream effects of VEGFR-2 signaling ultimately endorse the evolvement and maintenance of vastly haphazard and highly permeable neovascular network that promotes tumor growth and metastases.<sup>35</sup>

Engagement of VEGFs to VEGFR-2 launches receptor dimerization and booms intracellular autophosphorylation of various tyrosine residues with consequently activated pathways.<sup>36</sup> Two of the most significant activated pathways are the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3' kinase (PI3K) pathway, ultimately resulting in enhanced cell survival through AKT/PKB, cell migration, and vascular permeability through the expression of endothelial nitric oxide synthase.<sup>37</sup>

This compelling value of angiogenesis in the mechanisms of tumor growth, proliferation, and metastasis led to the rapid development and hence the widespread clinical use of angiogenic inhibitors.<sup>38</sup> It is also noteworthy to say that credits given to the anti-angiogenic inhibitors are not only attributed to the direct antitumoral effects mediated by the direct blockade of the process of new vessel formation, but also to the indirect antiproliferative effects

acquired from the normalization of the haphazard tumor vasculature, which in turn encourages intra-tumor delivery of cytotoxic drugs.<sup>39</sup>

## Pharmacology of ramucirumab

Ramucirumab is a fully humanized monoclonal antibody with a high binding affinity for the extracellular domain of VEGFR-2.<sup>40</sup> Preclinical studies showed that targeting of this VEGF family receptor was associated with inhibition of VEGF-mediated signaling, proliferation and migration of human endothelial cells, and antitumor activity in animal models.<sup>41–44</sup> Owing to species-specific differences in human VEGFR-2 and murine VEGFR-2 (Fk-1), the development of anti-VEGFR-2 antibodies required the production of immunoglobulins specific to both the human and murine forms of the receptor to specifically block ligand binding.

#### Pharmacodynamics and pharmacokinetics

A number of Phase I studies have evaluated different pharmacodynamic and pharmacokinetic aspects of ramucirumab; accordingly, they informed the selection of appropriate doses for Phase II and III studies.

In the initial Phase I study of ramucirumab monotherapy in GC, a total of 37 patients were treated with doses ranging from 2 to 16 mg/kg infused on a weekly basis. After one patient developed dose-limiting hypertension and deep venous thrombosis at 16 mg/kg, the next lower dose (13 mg/kg) was considered the maximum tolerated dose. A nonlinear effect of the ramucirumab dose was seen on the clearance rate, suggesting saturation of the clearance mechanism, which was likely to be largely receptor-mediated. However, minimal serum drug accumulation was evident over the course of the study.<sup>40</sup>

Following the earlier experience of weekly dosing of ramucirumab monotherapy, another Phase I study evaluated biweekly versus triweekly infusion of ramucirumab. A total of 25 patients were treated with ramucirumab: 13 with 6, 8, or 10 mg/kg Q2W and 12 with 15 or 20 mg/kg Q3W. Ramucirumab was well tolerated with no observed dose-limiting toxicities. Pharmacokinetic analyses showed low clearance and half-life of approximately 110–160 hours. Analysis of serum biomarkers also showed significant interpatient variability with trends toward increased VEGFA and a transient decrease in soluble VEGFR-2. This study was the proof behind the recommended doses of 8 mg/kg every 2 weeks and 10 mg/kg every 3 weeks in further studies.<sup>45</sup>

In another Phase Ib study of ramucirumab/paclitaxel combination (ramucirumab 8 mg/kg on days 1 and 15

and paclitaxel 80 mg/m² on days 1, 8, and 15 of a 28-day cycle), six patients were enrolled and all the patients experienced  $\geq 1$  treatment-emergent adverse event; five patients experienced grade  $\geq 3$  treatment-emergent adverse events. There were two deaths caused by disease progression. The best overall responses were stable disease (n=5) and partial response (n=1). Following a single dose of 8 mg/kg ramucirumab, infused intravenously (IV), clearance was  $\sim 0.017$  L/hour, half-life ( $t_{1/2}$ ) was 138–225 hours, and steady-state volume of distribution ( $V_{ss}$ ) was  $\sim 3$  L.<sup>46</sup>

Thus, the available Phase I data for ramucirumab both in monotherapy and in combination with paclitaxel settings suggested tolerability and encouraged further advancement of the drug in Phase II and III settings.

#### **Immunogenicity**

An additional characteristic phenomenon that has been observed with ramucirumab treatment is its immunogenicity. Anti-ramucirumab antibodies were detected by enzymelinked immunosorbent assay in 33 of 443 (7.4%) of patients treated with ramucirumab in clinical trials for whom post-baseline serum samples were available, with neutralizing antibodies detected in one patient only.<sup>47</sup> Moreover, anti-ramucirumab antibodies were not associated with infusion-related reactions in the majority of patients who developed antibodies against ramucirumab.

# Efficacy, safety, and tolerability studies

# Efficacy

The efficacy of ramucirumab in the second-line treatment of advanced gastric/gastroesophageal carcinomas has been proved by two randomized controlled studies (Table 1). The first one is the ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD) study, which was conducted to evaluate whether ramucirumab may improve survival in patients with advanced GC.<sup>24</sup> Patients with advanced gastric/GEJ adenocarcinoma after progressing on first-line chemotherapy (n=355) were randomized (2:1) to receive either ramucirumab 8 mg/kg (n=238) or a placebo (n=117), IV once every 2 weeks. In patients in the ramucirumab group, median OS was 5.2 months, while in patients in the placebo group it was 3.8 months (*P*=0.047).

The second study is the ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW) trial in which patients

Table I Summary of RCT addressing the role of ramucirumab in the treatment of advanced GC/GEJ

Study	Study	Assessment	Study Assessment Study end points	Number of patients (safety population)	Indication	SO	PFS	ORR (%)	Incidence
	type	tools		Treatment regimen		(months) (months)	(months)		of serious AEs
Fuchs et al <sup>24</sup>	Phase III RECIST RCT version	RECIST version 1.1	Primary: OS Arm A: r. Secondary: PFS, care (238 12-week PFS, ORR, Arm B: p duration of response, (117 pts) and ramucirumab	Arm A: ramucirumab 8 mg/kg plus best supportive Advanced gastric or GEJ care (238 pts)  Arm B: placebo plus best supportive care platinum-containing or fluoropyrimidine-contain chemotherapy	Advanced gastric or GEJ 5.2 vs 3.8 adenocarcinoma and disease (P=0.047) progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy	5.2 vs 3.8 (P=0.047)	2.1 vs 1.3 (P<0.0001)	2.1 vs 1.3 3% in either 109 (46.2%) (P<0.0001) arm (P=0.76) 51 (44.4%)	3% in either 109 (46.2%) vs arm (P=0.76) 51 (44.4%)
Wilke et al <sup>49</sup>		RECIST version I.1	Primary: OS Secondary: PFS, ORR, DCR, patient- reported outcomes, immunogenicity, and safety	Arm A: ramucirumab 8 mg/kg intravenously on days I and 15 plus paclitaxel 80 mg/m² intravenously on days I, 8, and 15 of a 28-day cycle (330 pts) Arm B: placebo intravenously on days I and 15 plus paclitaxel 80 mg/m² intravenously on days I, 8, and 15 of a 28-day cycle (335 pts)	Advanced gastric or GEJ adenocarcinoma, with progression after first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline)	-	4.4 vs 2.9 (P<0.0001)	4.4 vs 2.9 28% vs 16% (P<0.0001)	159 (48.6%) vs 144 (43.8%)
Yoon et al <sup>48</sup>	Phase II RCT	Phase II RECIST RCT version I.1	Primary: PFS Secondary: OS, RR, and DCR	Arm A: ramucirumab plus mFOLFOX6 (82 pts) Arm B: placebo plus mFOLFOX6 (80 pts)	Front-line therapy for advanced gastric or esophageal adenocarcinoma	(HR =1.08) (P=0.89)	6.4 vs 6.7 (P=0.89)	45.2% vs 46.4%	48 (58.5%) vs 32 (40%)
Abbreviation RCT, randomiz	s: AEs, adver	rse events; DCR d trial; RECIST, F	, disease control rate; GC, tesponse Evaluation Criteria	Abbreviations: AEs, adverse events; DCR, disease control rate; GC, gastric cancer; GEJ, gastroesophageal junction; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pts, patients; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria In Solid Tumors; REGARD, REbif vs Glatiramer Acetate in Relapsing MS Disease; RR, response rate.	ratio; ORR, overall response rat Relapsing MS Disease; RR, respon	te; OS, overall se rate.	survival; PFS, pr	rogression-free su	vival; pts, patient

(n=665) with advanced gastric/GEJ adenocarcinoma in the second-line setting were randomized to paclitaxel alone (80 mg/m² on days 1, 8, 15) or ramucirumab plus paclitaxel (8 mg/kg IV every 2 weeks) in 4-week cycles indefinitely. For patients receiving ramucirumab plus paclitaxel, median OS was 9.6 months, while it was 7.4 months for those receiving paclitaxel monotherapy (P=0.0169). Median PFS was 4.4 months in the combined treatment group and 2.9 months in the monotherapy group (P<0.0001).<sup>49</sup> Thus, the REGARD and the RAINBOW studies have shown that ramucirumab (both alone and in combination with paclitaxel) is an effective new standard for second-line treatment of advanced gastric/GEJ adenocarcinoma.

In accordance with the two studies mentioned earlier,

In accordance with the two studies mentioned earlier, the US Food and Drug Administration (FDA) has approved ramucirumab both as a monotherapy and in combination with paclitaxel as a second-line treatment of advanced gastric/gastroesophageal adenocarcinoma. However, in view of the very high cost of the drug, cost-effectiveness analyses versus other cheaper second-line alternatives such as irinotecan or docetaxel should be conducted.

## Safety and tolerability

Generally, the reported side effect profile in ramucirumabcontrolled clinical trials in solid tumors follows the traditional class effects of other anti-angiogenic agents including hypertension, proteinuria, stomatitis, gastrointestinal perforation, and fatigue. 50-54 The largest experience with safety and tolerability of ramucirumab monotherapy in gastric/gastroesophageal carcinomas was described by the REGARD trial.<sup>24</sup> In this study, approximately 10% of patients discontinued ramucirumab treatment due to adverse events compared with 6.0% receiving placebo. Grade 3 or higher adverse events with rates that were higher in the ramucirumab versus placebo arm included hypertension, abdominal pain, fatigue, and hyponatremia. VEGF class risks of special interest to ramucirumab were modestly increased compared to the control group and were generally in line with those seen with other VEGF inhibitors.55-57

Combination chemotherapy with ramucirumab from Phase II trials showed generally no significant unexpected toxicity. While dosing regimens varied between studies with weekly or every 2- to 3-week infusions, toxicity rates seemed independent of dose or frequency of administration. Further Phase III data with combination paclitaxel, docetaxel, or FOLFIRI (in gastric, lung, or colon cancer, respectively) have not revealed any unexpected toxicities. <sup>48,49</sup> In the RAINBOW study, grade ≥3 toxicities were higher in the combination

arm (ramucirumab/paclitaxel), including neutropenia, leukopenia, hypertension, anemia, fatigue, abdominal pain, and asthenia.<sup>49</sup>

# Comparison of the outcomes of bevacizumab and ramucirumab in the setting of advanced GC

Bevacizumab is a monoclonal antibody that binds VEGFA with subsequent restriction of its interaction with VEGFR-1 and VEGFR-2, thus exerting an anti-angiogenic impact. Bevacizumab was investigated in the setting of unresectable locally advanced or metastatic GC or GEJ adenocarcinomas in combination with cisplatin and capecitabine as a first-line therapy in a global randomized, placebo-controlled Phase III trial (the Avastin for Advanced Gastric Cancer trial [AVAGAST]).<sup>58</sup>

Unfortunately, unsatisfactory primary end point results were obtained, namely, nonstatistically significant OS benefit (12.1 vs 10.1 months; HR =0.87, 95% CI, 0.73–1.03, P=0.1002), coupled with statistically significant improved PFS (6.7 months vs 5.3 months; HR =0.80; P=0.0037), and response rate (46% vs 37.4%, P=0.0315). Further data extracted from the complementary Phase III AVATAR study contributed to better interpretation of the AVAGAST results in the right context.<sup>59</sup>

The inconsistent efficacy outcomes of anti-angiogenesis between bevacizumab in the AVAGAST trial and ramucirumab in the RAINBOW trial was so remarkable that it triggered many explanatory postulations. First of all, ramucirumab in the RAINBOW trial was investigated in the second-line setting, where angiogenesis is acknowledged for its pivotal role in cancer cell survival and proliferation as compared to less advanced disease. Not to mention, in the AVAGAST trial, bevacizumab was prescribed as 2.5 mg/kg/week, a dose inferior to the 5 mg/kg/week dose administered to the subjects in previous Phase II studies.60,61 Second, the impact of the chemotherapeutic agents opted in the design of each study cannot be undermined, especially pointing to the prominently established intrinsic anti-angiogenic activity of paclitaxel, which was solely utilized for the patients in the RAINBOW trial. This anti-angiogenic impact exerted by paclitaxel may be attributed to the restriction of either cell migration or tubule synthesis, along with impedance of the proliferation of the triggered endothelial lining cells.<sup>62</sup> As a consequence, the optimacy of platinum analog as the chemotherapeutic backbone, to which anti-angiogenic therapy should be combined, has been recently called into question.63

## **Future perspectives**

# Personalized anti-angiogenic treatment of GC

Despite the encouraging results for ramucirumab in secondline treatment of GC, questions still exist on how to improve and better select ramucirumab treatment as well as other anti-angiogenic therapies in GC. As it is quite remarkable to note that the majority of studies involving anti-angiogenic therapies in GC (except ramucirumab) were negative.<sup>64-67</sup>

This may be explained in the contest that GC is a heterogeneous disease, both biology-wise and genetics-wise. The inadequacy of the AJCC TNM staging algorithm in the prognostic assessment of GC necessitated the application of comprehensive genomic approaches to deepen the understanding of crucial cellular and molecular mechanisms of GC.<sup>68</sup>

Consequently, various prognostic and predictive biomarkers were explored in many studies, yet their utilization remains uncertain. Independent validation of possible prognostic and predictive biomarkers is a must before they can be routinely employed in clinical practice. It is also important to undertake retrospective studies evaluating the status of the most promising markers in GC samples integrated in specific clinical trials and correlating them with patient outcomes to test this postulation. <sup>69–72</sup> Detailed discussion of the candidate biomarkers may be outside the scope of this manuscript.

# Ongoing studies of ramucirumab in gastric/gastroesophageal carcinoma

A number of ongoing Phase II and III studies are evaluating different ramucirumab-based combinations in gastric/gastroesophageal carcinoma. The results of these studies are expected within the next 3 years (Table 2).

#### Conclusion

GC is a global health problem with a relatively high mortality, particularly in the advanced stage. Standard approach to the management of GC incorporates initial staging workup with appropriate laboratory, imaging, and endoscopic investigations. After assigning the patient to the appropriate anatomical stage, treatment recommendations will rely upon whether the disease is localized, locally advanced, or metastatic. For nonmetastatic disease, radical surgery is the cornerstone of treatment. This may be accompanied by perioperative chemoand/or radiotherapy according to the extent of the disease. For metastatic disease, systemic chemotherapy is the backbone of treatment. According to the biological characteristics of the tumor (HER-2-positive or HER-2-negative), this may be accompanied by anti-HER-2 therapies.

 Table 2 Ongoing studies of ramucirumab in advanced gastric and gastroesophageal cancers

participants A study of nametrumb in Phase II interventional, 31 japanes a participant and the manufactural by the participant and the manufactural participants and manufactural participants and manufactural participants and manufactural participants and manufactural participan	Clinical Trials.	Study status	Hypothesis	Study type	Estimated	Estimated	Treatment regimen	Current primary	Current secondary outcome
Organing bat A study of ramocramab in Phase II interventional 33 japanese parcipants with metastage participants and several control of the following desired participants with metastage participant of removerance and of restrictions participants and experimental participants with metastage gastric organization that and the following desired participants of removerance and of restrictions of the following desired participants with metastage gastric organization and countries of the following search participants and deplaces participants with metastage gastric organization and countries of the following gastric organization and desired and of the following gastric organization and countries of the following gastric organization and desired and of the following gastric organization and desired and of the following gastric organization and countries of the following gastric organization of the following gastric org	gov identifier				enrollment	completion date	0	outcome measures	measures
Organing that A study of interactional in Planet Interventional, 33 japanese participants with metastact gent correction with metastact gent correctional general participants and the study of interaction of first late of combination of combination						-			
recruining contenting or metastic gastric correcting barried participants and contenting or metastic gastric corrections greate progression on first-line and city-dependent and copied gastric corrections of the first-line progression on first-line and city-dependent or controlled phase III contained the participants and city-dependent or controlled phase III contained the past III contained the past III contained the past III contained the progression on first-line and city-dependent and city-dependent or controlled phase III contained the past	ACT01983878	Ongoing but	A study of ramucirumab in	Phase II interventional,	33 Japanese	September 2015	Ramucirumab 8 mg/kg administered IV	PFS rate at 12 weeks	PFS (estimated up to 12 months)
participans with reasonable genetic or main an expension of making genetic or main measurable genetic or main an expension of mits combination of page and p		not recruiting	treating lapanese participants	single arm, open-label			once every 2 weeks		ORR
Correctly for extension and frequency generated generate generate forms of frequency form				) <u>(</u>			•		900
grantesophyginal introduces are straightful agrees of the following disease propagation of the following disease present of interesting and state of the following disease participants with measured compared to expend the following and state of the following and th		pai ucipailes	With Inerastatic gasti ic of	רומו					2
combination therapy in patients and controlled place in a functionable in the single-grained controlled place in the single-grained controlled place in the single-arm controlled place in the single-arm controlled place in the single-arm controlled place in the single-grained in the single-arm controlled place in the single-arm co			gastroesophageal junction						ć
platinum containing containing progression on first-line platinum controlling continued containing containing containing containing containing containing containing containing containing platinum containing platinum containing containing platinum containing containing platinum containing platinum containi			cancer, following disease						Number of participants with
Inducerpy mideles-containing combination therapy in   Parameterization   Parameter containing   Parameter contai			progression on first-line						anti-ramucirumab antibodies
Currently participants containing combination blind, placebo— si 6 April 2018 8 ngglig cranucirumb given IV on day 1 PFS and 8 in combination with a participants of ramucirumb in complexed blind, placebo— si 6 mg/mi capecitable and ceptalnin corrolled phase III compared to expectable and ceptalnin corrolled phase III compared to corrolled to propried to corrolled to propried to corrolled to			platinum-containing or						
Sparinge patients   Paparinge patients   Paparing			fluoropyrimidine-containing						
Currently Protestates patients of ramacirumab given IV on days I PRS and Bin complication with a participants of ramacirumab in combination blind, placebo— participants of ramacirumab in complex blind, placebo— participants of ramacirumab in complex blind, placebo— cipitan alone as carefully and standy of patients and stagebase and capability of the cipital given IV on day I of each 21-day cycle (for up to 6 cycles) cipitan alone as carefully between a day on days I through I4.  First-line threapy in patients and capability of placebo— with meastate gastric of controlled place III of each 21-day cycle (for up to 6 cycles) currently participants and days and assist of participants who are unable to take on carefully placebol and a recommended and assist of the following participants with a fored and on meastate and doze angle for a ramacirumab administered IV on a stately gener part and control medical careforms and deconationman, leptocollular and control medical careforms and care			combination therapy in						
Currently projuncies puering the effectivements of the formation of the participants with captured puering the effectivements of the participants and an end-place in the participants with captured puering compared to capecitabline and citycles and city									
participants of rannertumb in combination blind placebo and participants with capacitable and cipalan correlled phase III and placebo and capacitor correlled phase III and placebo and capacitor compared to capacitable and cipalan correlled phase III and placebo and capacitable and cipalan correlled phase III and the capacitable and	71 CCO FO	(	Japanese parients		``	0.00		0	Č
recruiting of rannor transit in compared to capeciathier and cipplan controlled phase III compared to capeciathier and cipplan corrolled phase III compared to capeciathier and cipplan alone as compared to capeciathier and several transitions gaven compared to capeciathier and several compared to capeciathier and the capeciathier and dozen range for a capeciathier and dozen range for a cancer of any of the following cancer of any of the following capeciar advanced and on reaction and participants with a recommended and control and of the following capeciar advanced and on reaction and participants with a factor of any of the following capeciar and cancer of any of the following capeciar capeciar and capeciarity and any of the following capeciar capeciarity and any of the following capeciarity and capeciarit	VC102314117	Currently	lo evaluate the effectiveness		919	April 2018	8 mg/kg ramucirumab given IV on days I	- PFS	ŝ
participants with capectabline and cisplatin controlled plass III compared to capectabline and cisplatin and study capectabline and cisplatin alone as a study capectabline and study and 1,000 mg/m² capectabline given to compared to capectabline with measure gastror or gastrocarcinoma (RANI-RALL)  Currently Park Acos-ranging study and safety participants who are unable to take with interacting study capectabling and safety participants with a scenarior growth standing and safety participants with a recommended copen-label study per scalating and safety and		recruiting	of ramucirumab in combination				and 8 in combination with		ORR
compared to capecitabine and study as a study as a study of and 1,000 mg/m² capecidabine given and steep gastrosephageal luttorion and secondarion and steep		participants	with capecitabine and cisplatin	controlled phase III			80 mg/m² cisplatin given IV on day I		DCR
recruining Part Subscripting given with recruinment terrapy in patients open-label study participants who are unable to nake with meastatic gastro or agent are dose angle state of participants who participants who participants who participants to find a recommended participant with terrapy in patients and dose mage state of participants who participants to find a recommended participant to find a recommended open-label study for a find			compared to capecitabine and	study			of each 21-day cycle (for up to 6 cycles)		TTP
first-line therapy in patients with measuring grant or advanced page all unction and conscious grant or advanced page all unctions grant or advanced and/or measuring study participants with a recruiting and safety and conscious the page of participants with a recruiting and safety and participants with a recruiting and safety and participants with a recruiting and safety and page of participants with a recruiting and safety and page of participants with a recruiting and safety and safety and page of participants with a recruiting and safety and			risplation and a	•			and 1 000 mg/m² capacitahina giyan		800
first-line therapy in patients with meastactic gastric carred when the action of a participants who are unable to take adenocarcinoma. (AANIFALL)  Currently Part A dose-unage fluid ose adenocarcinoma (AANIFALL)  Part A dose-unage fluid ose adenocarcinoma (AANIFALL)  Part A dose-unage fluid ose scalation of the given 800 mg/m²/day 5-fluoroural (15-RJ) fluor days 1-5 of activities of participants who participants is steelled and dose ange for the activities of the activities of the advanced and/or metastatic cancer of any of the following open-label study advanced and/or metastatic cancer of any of the following astro-oscophageal junction and advanced and/or metastatic cancer of any of the following open-label study advanced and/or metastatic cancer of any of the following astro-oscophageal junction and advanced and/or metastatic cancer of any of the following astro-oscophageal junction and advanced and/or metastatic cancer of any of the following cancer of any of the following astro-oscophageal junction and advanced and/or metastatic cancer who used in a deficitive when used in a serflective when used in a service and municinumab open-label trial and 15 of every 28-day cycle (weekly for a combination of receasing patients with meastact and advanced on one days I and I sof the 28-day cycle of the 28-day c							13.19 cmbc/cmm20.11 cop(1.12)		
first-line therapy in patients with meastance gaster or gastroesophageal junction  And Acoser-ranging study participants to find a recommended and dose range for trace of any of the following participants to find a recommended open-label study advanced and/or metastatic cancer of any of the following pyper gasteric adenocarcinoma, hepatocellular cancer ranging luction and advanced and/or metastatic cancer ranging luction and advanced manufacturina by the following pacteriate when used in combination with a fixed dose of rannocinumab administered IV on days I and IS of every 28-day cycle or combination for treating and part of the following pacteriate when used in combination with a fixed dose of rannocinumab and pacteriate with metastatic combination for treating pacteriate with metastatic are effective when used in combination with a fixed dose of rannocinumab and pacteriate with metastatic are who seeks, with I week of rost of the 28-day cycle and patients with metastatic and have either pacteriated by the following patients with metastatic and participant are effective when used in combination of treating patients with metastatic and participant are effective when used in combination of the 28-day cycle or combination for treating patients with metastatic and participant are effective when used in combination of the 28-day cycle or combination for treating patients with metastatic and participant are effective with reasonate and participant and IS of the 28-day cycle or combination for treating patients with metastatic and participant and IS of the 28-day cycle or combination of the 28-day cycle or c							orally twice a day on days I through 14.		Time to deterioration
first-line therapy in patients with meastact grant correctional (RAINFALL)  Currently Part A cose-maging study exclaining and safety participants who participants who participants when participants when participants when participants when participant adenocarcinoma, help resolved the following cancer of any of the following cancer rectributing that the state of participant when transcribution and the following cancer rectributing that the following cancer rectributing that the following cancer of any of the following cancer relation for transition with a fixed dose of mon-small cell Lung cancer relations for tracting and ramucirumab participant when the rate of any of the following cancer of any of the following cancer of any of the following cancer relation for tracting participant and the following cancer of any of the following cancer relation for tracting participant and electron when used in combination for tracting participant partici									in ECOG PS
with meastatic gastric or adenocarcinoma (RAMINFAL)  Currently Part & dose-ranging study recruiting Part & safety/efficacy study escalating and safety part & dose-ranging study recruiting Part & safety/efficacy study participants with a recommendation of Part & dose-ranging study participants with a recommendation of Part & dose-ranging study participants with a recommendation of Part & dose-ranging study participants with a recommendation of Part & dose-ranging study participants with a recommendation of Part & dose-ranging study participants with a recommendation of Part & dose-ranging study participants with a recommendation of Part & dose-ranging study participants with a recommendation of Part & dose-ranging study participants with a recommendation of Part & dose-ranging study participants with metastatic and ramucirumab and participant progressed or recombination for treating patients with metastatic patients with recommendated to price the progressed or not patients with recommendated to price the pati			first-line therapy in patients				Participants who are unable to take		QoL
gastroesophageal junction  Annucirumal (ANINFALL)  Currently Part & dose-ranging study rectuting Part & dose-ranging study participants  Part & dose-ranging study participants  Tecruting Part & dose-ranging study participants with a may be a scalation of LY287358 when the dose of ramucirumal administered Port of the following participant with meast accompliation whether nab participant pactitaxel and ramucirumab participant pactitaxel progressed or roc combination for treating pactitaxel progressed or roc pactitation pactitaxel progressed prog			with metastatic gastric or				capecitabine will be given 800 mg/m <sup>2</sup> /day	>	Number of participants with
Search Service of the control of the							, 5 1 VI (III I)		
adenocarroma (AMINALL)  Currently Part A: dose-ranging study recruiting Part B: safety/efficacy study recruiting Part B: recommended Open-label study recruiting Part B: recommended LY287538B + ranucirumab administered IV on advanced and/or meastatic radenocarcinoma, repatocellular recruiting recruiting Part B: recomplication with a fixed dose of ranucirumab administered IV on advanced and/or meastatic radenocarcinoma, repatocellular recruiting recruiting patients with meastatic recruiting rare effective when used in combination for treating patients with meastatic recruiting rare effective when used in combination for treating patients with meastatic recruiting receive ranucirumab administered IV on days I: 8 and IS of the 28-day cycle (receivedly for responded to prior therapay).			gastroesopnageal Junction				5-fluorouracii (5-FU) IV on days 1—5 of		anti-ramucirumab antibodies
Currently Part A dose-ranging study Phase I bill dose 70 December 2015 Experimental L'Y2875358 + Part A rumber recruiting Part B stately given with recommended of pen-label study administered IV on days I and 15 every Part B: ORR Advanced and dose range for safely given with remarkation of pen-label study administered IV on days I and 15 every Part B: ORR Advanced and/or metastatic ancer of any of the following states of and or participants with a recommended to pen-label study administered IV on days I and 15 every Part B: ORR Advanced and/or metastatic ancer of any of the following states and and or pen-label study and I seem to day of the following states and or participants with a fored foreign and I seem to day of the following states and and ramucirumah and and ramucirumah or pen-label trial and I seem to day of the following acancer renal cell carcinoma, or advanced and armucirumah open-label trial and I seem to days I wad I seem to day seem to pen-label trial and I seem to day seem to pen-label trial and I seem to day I week of rest) Patients with metastatic combination for treating part pentlates and ramucirumah open-label trial and I seem to make I seem to day I week of rest) Patients with metastatic statement are effective when used in combination for treating participant pentlates and I seem to day I week of rest) Patients with metastatic statement and I seem to combination for treating the pentlates and I seem to combination for treating and I seem to combination			adenocarcinoma (RAINFALL)				each 21-day cycle		
recruiting to Part B. safety/efficacy study escalating and safety participants who participants to find a recommended open-label study and commended open-label study and commended open-label study and continuate that may be safety label study and commended observations with remaining that may be safety given to participants with remaining that may be safety given to participants with a safety given to participant given giv	JCT02082210	Currently	Part A: dose-ranging study	Phase 1b/11 dose-	70	December 2015	Experimental: LY2875358 +	Part A: number	DCR
participants to find a recommended open-label study shripting the part A: dose escalation of LY2875358 experienced DLTs schedule and dose range for ranucirumab that may be a range for ranucirumab that may be advanced and/or metastatic advanced and/or metastatic cancer of any of the following recommended the following propes gastro-esophageal junction advanced and/or metastatic cancer renal cell carcinoma, or non-small cell Lung cancer range celluses and are effective when used in combination of or treating patients with metastatic cancer renal cell cancer who combination for treating patients with metastatic combination for treating patients with metastatic cancer who days I and I5 of every 28-day cycle (weekly for cancer range clarameter may be add in the progressed or not asset in the progressed or not restraing complication or treating patients with metastatic pages asset or not cancer who cancer		recruiting	Part B: safety/efficacy study	escalating and safety			ramucirumab (Part A)	of participants who	PFS
schedule and dose range for the continuation with a fixed administered IV on days I and I S every Part B: ORR ramucirumab that may be safely given to participants with advanced and/or metastatic advanced and/or metastatic cancer of any of the following types: gastroesophageal junction adenocarcinoma, heaptocellular cancer, renal cell carcinoma, or non-small cell lung cancer renal cell lung cancer and ramucirumab administered IV on days I and I S of every 28-day cycle in combination with a fixed dose of ramucirumab administered IV on days I and I S of every 28-day cycle in combination with a fixed dose of ramucirumab and I soft every 28-day cycle in combination with a fixed dose of ramucirumab and I soft every 28-day cycle in combination with metastatic patents with metastatic are effective when used in combination for treating patients with metastatic patients with a combination of or treating patients with metastatic patients with a combination or proving the patients with metastatic patients with a combination or proving the patients with a combination with a patients with a combination with a patient proving the patients with a combination with a patient proving the patients with a de		participants	to find a recommended	open-label study			Part A: dose escalation of LY2875358	experienced DLTs	Number of participants with
LY287538 when given with a fixed advanced and/or meastatic cancer of any of the following participants with advanced and/or meastatic cancer of any of the following pypes; gastroesophageal junction adenocarcinoma, hepatocellular cancer, renal cell carcinoma, or non-small cell lung cancer are effective when used in combination for treating patients with metastatic combination for treating patients with metastatic combination for treating responded to prior theraby  LY2875388 when given to participants with a fixed of dose of representation adenocarcinoma, which a fixed of combination with a fixed dose of recurrent are effective when used in combination for treating patients with metastatic gastroesophageal cancer who patients with metastatic gastroesophageal cancer who responded to prior therapy.			schedule and dose range for				administered IV on days I and 15 every		anti-ramucirumab and
and cannot be a combination for the target and random when the range of participants with advanced and/or metastatic cancer of any of the following gratroesophageal junction adenocarcinoma, hepatocallular cancer renal cell carcinoma, or non-small cell lung cancer  Not yet open To determine whether nab- Phase II, single-arm, 65 December 2017 All patients with metastatic combination for treating patients with metastatic combination for prior theraps with metastatic cancer who open-label trial are effective who used in combination for treating patients with metastatic combination for prior theraps and random open-label trial responded to prior theraps and responded to prior theraps are responded to prior theraps and responded to prior theraps are responded to prior theraps.			1Y2875358 when given with				20 day over on the combination with a fixed	7	anti.1 Y2875358 antihodies
as a fel given to participants with a days I and I 5 of every 28-day cycle advanced and/or meastatic cancer roll any of the following cancer of any of the following cancer of any of the following cancer of any of the following types: gastric adenocarcinoma, and any of the following cancer real cell carcinoma, or non-small cell Lung cancer cancer, real cell Lung cancer cancer, cancer, real cell Lung cancer cancer, can			Lizovasa Wileli giveli With				20-day cycle III combination with a lixed		מונו-בו בפל סססס מונוססטופס
advanced and/or metastatic cancer of any of the following types: gastroesophageal junction adenocarcinoma, adenocarcinoma, adenocarcinoma, adenocarcinoma, or non-small cell Lung cancer mon-small cell Lung cancer more, read redictive when used in combination for treating patients with metastatic combination for treating patients with metastatic combination for treating patients with metastatic patients with metastatic combination for treating patients with metastatic patients with metastatic patients with responded to prior therapy responded to prior therapy			ramucirumab that may be				dose of ramucirumab administered IV or	Ę	
advanced and/or metastatic  cancer of any of the following  types; gastric adenocarcinoma,  gastroesophageal junction  adenocarcinoma, hepatocellular  cancer, renal cell carcinoma, or  non-small cell lung cancer  Not yet open  To determine whether nab- Phase II, single-arm, 65  Pert B. recommended LY28753S8 dose  from Part A to be administered IV on days I and IS of every 28-day cycle  in combination with a fixed dose of ramucirumab administered IV on days I and IS of every 28-day cycle  Not yet open  To determine whether nab- Phase II, single-arm, 65  December 2017  All patients will receive I2S mg/m² of PFS  nab-paclitaxel Von days I, 8, and IS of a region of combination for treating  patients with metastatic  gastroesophageal cancer who seither progressed or not responded to prior therapy  responded to prior therapy			safely given to participants with	_			days I and 15 of every 28-day cycle		
cancer of any of the following types: gastric adenocarcinoma, gastroesophageal junction adenocarcinoma, hepatocellular cancer, renal cell carcinoma, or non-small cell lung cancer non-small cell lung cancer are effective when there nab- recruitment are effective when used in combination for treating patients with metastatic gastroesophageal cancer who adenocarcinoma, or non-small cell lung cancer non-small cell lung cancer adenocarcinoma, or non-small cell lung cancer and 15 of every 28-day cycle ramucirumab administered IV on days I and 15 of every 28-day cycle ramucirumab administered IV on days I and 15 of every 28-day cycle ramucirumab administered IV on days I and 15 of every 28-day cycle ramucirumab administered IV on days I and 15 of every 28-day cycle ramucirumab and 15 of a and 15 of a 3 weeks, with I week of rest) Patients will receive ramucirumab 8 mg/ kg IV in combination with nab-paclitaxel on days I and 15 of the 28-day cycle or days I and 15 of the 28-day cycle or days I and 15 of the 28-day cycle			advanced and/or metastatic				Experimental: LY2875358 + ramucirumat	q	
ypes: gastric adenocarcinoma, gastroesophageal junction adenocarcinoma, hepatocellular cancer, renal cell carcinoma, or non-small cell lung cancer, renal cell carcinoma, or non-small cell lung cancer non-small cell lung cancer are effective when used in combination for treating patients with metastatic gastroesophageal cancer who have either progressed or not responded to prior therapy			cancer of any of the following				(Part B)		
gastroesophageal junction adenocarcinoma, hepatocellular cancer, renal cell carcinoma, or non-small cell lung cancer  Not yet open To determine whether nab- recruitment are effective when used in combination for treating patients with metastatic gastroesophageal cancer who have either progressed or not responded to prior therapy			types: gastric adenocarcinoma,				Part B: recommended LY2875358 dose		
adenocarcinoma, hepatocellular cancer, renal cell carcinoma, or non-small cell lung cancer  Not yet open To determine whether nab- recruitment are effective when used in combination for treating patients with metastatic gastroesophageal cancer who have either progressed or not responded to prior therapy			gastroesophageal junction				from Part A to be administered IV on		
cancer, renal cell carcinoma, or non-small cell lung cancer non-small cell			adenocarcinoma, hepatocellular	•			days I and 15 of every 28-day cycle		
non-small cell lung cancer  Not yet open To determine whether nab-Phase II, single-arm, 65 December 2017 All patients will receive 125 mg/m² of PFS recruitment are effective when used in combination for treating patients with metastratic gastroesophageal cancer who have either progressed or not responded to prior therapy			cancer, renal cell carcinoma, or				in combination with a fixed dose of		
Not yet open To determine whether nab- Phase II, single-arm, 65 December 2017 All patients will receive 125 mg/m² of PFS recruitment are effective when used in combination for treating patients with metastratic gastroesophageal cancer who have either progressed or not responded to prior therapy			non-small cell lung cancer				ramucirumab administered IV on days I		
Not yet open To determine whether nab- Phase II, single-arm, 65 December 2017 All pacificates of PFS for participant paclitaxel and ramucirumab open-label trial recruitment are effective when used in combination for treating patients with measurance gastroesophageal cancer who have either progressed or not responded to prior therapy			0				and 15 of every 28-day cycle		
paclitaxel and ramucirumab open-label trial nab-paclitaxel V on days 1, 8, and 15 of a are effective when used in combination for treating patients with metastatic gastroesophageal cancer who have either progressed or not responded to prior therapy	JCT02317991	Not yet open	To determine whether nab-	Phase II, single-arm,	65	December 2017	All patients will receive 125 mg/m² of	PFS	ORR
are effective when used in combination for treating a weekly for 3 weeks, with I week of rest)  patients with metastatic gastroesophageal cancer who kg IV in combination with nab-paclitaxel on days I and I5 of the 28-day cycle responded to prior therapy		for participant	paclitaxel and ramucirumab	open-label trial			nab-paclitaxel V on days 1, 8, and 15 of a	а	OS
		recruitment	are effective when used in				28-day cycle (weekly for		TT
			combination for treating				3 weeks, with I week of rest)		
			patients with metastatic				Patients will receive ramucirumab 8 mg/		
			gastroesophageal cancer who				kg IV in combination with nab-paclitaxel		
			have either progressed or not				on days I and 15 of the 28-day cycle		
			responded to prior therapy						

Abbreviations: 5-FU, fluorouracil 5-FU; DCR, disease control rate; DLTs, dose-limiting toxicities; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, progression.

Pathological angiogenesis has been considered one of the hallmarks of cancer and one of the fundamental pathological processes of almost all solid tumors. VEGF pathway has long been considered one of the principal pathways of both physiological and pathological angiogenesis. Accordingly, targeting VEGF pathway components has been considered an attractive therapeutic intervention for most solid tumors. This may be conducted either by targeting the VEGF itself or its receptors. VEGFR-2 has been found to be overexpressed by many solid tumors, and thus an enthusiastic research program has been launched to establish anti-VEGFR 2 treatments in these tumors. Ramucirumab, a monoclonal antibody against VEGFR-2, has been shown to have a significant antitumor activity against GC in preclinical and clinical studies. These efforts have been culminated in the publication of two randomized controlled studies of ramucirumab monotherapy and ramucirumab/paclitaxel combination in second-line treatment of advanced GC (REGARD and RAINBOW studies, respectively). These two studies have shown a statistically significant benefit for ramucirumab-based treatment versus control in the second-line treatment of advanced gastric/GEJ adenocarcinoma. Accordingly, both ramucirumab monotherapy and ramucirumab/paclitaxel combination have been approved by FDA in the second-line setting of advanced gastric/GEJ adenocarcinoma.

The toxicity profile of ramucirumab in these studies has been consistent with class effects from other VEGF pathwaytargeted agents. This includes risks of hypertension, gastrointestinal perforation, proteinuria, and neutropenia.

There is a considerable room for improving and personalizing ramucirumab treatment in advanced GC. This includes advancing the use of ramucirumab into first-line setting, utilizing newer ramucirumab-based combinations that may have extra advantages in terms of efficacy or toxicity, and using molecular biomarkers for improved selection of patients for ramucirumab treatment.

Finally, fine-tuning of the management of advanced gastric/gastroesophageal carcinoma is a challenging job. Appropriate incorporation of preclinical and clinical models into ongoing clinical trials may lead to improved results and impressive outcomes.

#### **Disclosure**

The authors report no conflicts of interest in this work.

#### References

 Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [webpage on the internet]. Lyon: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr/Default.aspx. Accessed March 19, 2015.

- Forman D, Burley V. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. Best Pract Res Clin Gastroenterol. 2006;20:633–649.
- Abdel-Rahman O. Targeting vascular endothelial growth factor (VEGF) pathway in gastric cancer: preclinical and clinical aspects. Crit Rev Oncol/Hematol. 2015;93(1):18–27.
- Mihaljevic AL, Friess H, Schuhmacher C, et al. Clinical trials in gastric cancer and the future. *J Surg Oncol*. 2013;107(3):289–297. doi:10.1002/Jso.23120.
- Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol. 2010;17(12):3077–3079. doi:10.1245/ s10434-010-1362-z.
- Kitagawa Y, Takeuchi H, Takagi Y, et al. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. *J Clin Oncol*. 2013;31(29):3704

  –3710. doi:10.1200/JCO.2013.50.3789.
- National Comprehensive Cancer Network. NCCN guidelines for gastric cancer. Fort Washington, PA: National Comprehensive Cancer Network; 2015. Available from: http://www.nccn.org/professionals/ physician\_gls/f\_guidelines.asp. Accessed March 19, 2015.
- Hopkins S, Yang GY. FDG PET imaging in the staging and management of gastric cancer. *J Gastrointest Oncol*. 2011;2(1):39–44. doi:10.3978/j.issn.2078-6891.2010.004.
- Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
- Van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012; 366:2074–2084.
- Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol*. 2006;24: 4901–4907
- Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358: 36–46
- Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol*. 2011; 29:4387–4393.
- Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol.* 2008;9:215–221.
- Cervantes A, Roda D, Tarazona N, Roselló S, Pérez-Fidalgo JA. Current questions for the treatment of advanced gastric cancer. *Cancer Treat Rev.* 2013;39(1):60–67. doi:10.1016/j.ctrv.2012.09.007.
- Oba K, Paoletti X, Bang YJ, et al; GASTRIC Group. Role of chemotherapy for advanced/recurrent gastric cancer: an individual-patient-data meta-analysis. *Eur J Cancer*. 2013;49(7):1565–1577. doi:10.1016/j.eica.012.12.016.
- Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2010;(3):CD004064.
- Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376:687–697.
- ESMO guidelines working group. European Society of Medical Oncology (ESMO) guidelines for Gastric Cancer. Available from: http://www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines/Gastrointestinal-Cancers/Gastric-Cancer. 2015 Accessed March 2015.
- Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol*. 2013;31:4438–4444.

- Kim HS, Kim HJ, Kim SY, et al. Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis. *Ann Oncol.* 2013;24:2850–2854.
- 22. Han FH, Li HM, Zheng DH, He YL, Zhan WH. The effect of the expression of vascular endothelial growth factor (VEGF)-C and VEGF receptor-3 on the clinical outcome in patients with gastric carcinoma. *Eur J Surg Oncol*. 2010;36:1172–1179.
- Li J, Qin S, Xu J, et al. Apatinib for chemotherapy refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel arm, phase II trial. *J Clin Oncol*. 2013;31:3219–3225.
- 24. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastrooesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2014;383:31–39.
- Abdel-Rahman O. Targeting vascular endothelial growth factor (VEGF) pathway in iodine-refractory differentiated thyroid carcinoma (DTC): from bench to bedside. Crit Rev Oncol/Hematol. 2014;94(1): 45–54.
- Ellis L, Hicklin D. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer. 2008;8(8):579–591.
- Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nat Rev Cancer. 2002;2(10):795–803.
- Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. Nat Rev Cancer. 2008;8(8):592

  –603.
- Burgos H. Angiogenic and growth factors in human amnio-chorion and placenta. Eur J Clin Invest. 1983;13:289–296.
- Ausprunk DH, Folkman J. Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumor angiogenesis. *Microvasc Res.* 1977;14:53–65.
- Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparinbinding growth factor specific for vascular endothelial cells. *Biochem Biophys Res Commun.* 1989;161:851–858.
- Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003;9(6):669–676.
- Abdel-Rahman O. Vascular endothelial growth factor (VEGF) pathway and neuroendocrine neoplasms (NENs): prognostic and therapeutic considerations. *Tumor Biol.* 2014;35(11):10615–10625.
- Giatromanolaki A, Koukourakis MI, Sivridis E, et al. Activated VEGFR2/KDR pathway in tumour cells and tumour associated vessels of colorectal cancer. Eur J Clin Invest. 2007;37(11):878–886.
- Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signalling in control of vascular function. *Nat Rev Mol Cell Biol*. 2006;7(5):359–371.
- Kerbel RS. Tumor angiogenesis. N Engl J Med. 2008;358: 2039–2049.
- Kowanetz M, Ferrara N. Vascular endothelial growth factor signaling pathways: therapeutic perspective. *Clin Cancer Res.* 2006;12(17): 5018–5022.
- Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of antitumour activity. Nat Rev Cancer. 2008;8:579

  –591.
- Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science*. 2005;307:58–62.
- Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol*. 2010;28:780–787.
- Lu D, Shen J, Vil MD, et al. Tailoring in vitro selection for a picomolar affinity human antibody directed against vascular endothelial growth factor receptor 2 for enhanced neutralizing activity. *J Biol Chem.* 2003; 278:43496–43507.
- Miao HQ, Hu K, Jimenez X, et al. Potent neutralization of VEGF biological activities with a fully human antibody Fab fragment directed against VEGF receptor 2. *Biochem Biophys Res Commun.* 2006;345: 438–445.
- 43. Jung YD, Mansfield PF, Akagi M, et al. Effects of combination anti-vascular endothelial growth factor receptor and anti-epidermal growth factor receptor therapies on the growth of gastric cancer in a nude mouse model. *Eur J Cancer*. 2002;38:1133–1140.

- Zhu Z, Hattori K, Zhang H, et al. Inhibition of human leukemia in an animal model with human antibodies directed against vascular endothelial growth factor receptor 2. Correlation between antibody affinity and biological activity. *Leukemia*. 2003;17:604–611.
- Chiorean EG, Hurwitz HI, Cohen RB, et al. Phase I study of every 2-or 3-week dosing of ramucirumab, a human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2 in patients with advanced solid tumors. *Ann Oncol*. 2015;26(6):1230–1237.
- Ueda S, Satoh T, Gotoh M, Gao L, Doi T. A phase Ib study of safety and pharmacokinetics of ramucirumab in combination with paclitaxel in patients with advanced gastric adenocarcinomas. *Oncologist*. 2015;20(5):493–494.
- Eli Lilly and Company. Ramucirumab: Prescribing Information; 2014.
   Available form: http://www.accessdatafdagov/drugsatfda\_docs/label/2014/125477lblpdf. March 19, 2015.
- 48. Yoon HH, Bendell JC, Braiteh FS, et al. Ramucirumab (RAM) plus FOL-FOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): randomized, double-blind, multicenter phase 2 trial. *J Clin Oncol*. 2014;32:5s. (Suppl; abstr 4004).
- Wilke H, Muro K, Van Cutsem EV, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014;15:1224–1235.
- Abdel-Rahman O, Fouad M. Risk of cardiovascular toxicities in patients with solid tumors treated with sunitinib, axitinib, cediranib or regorafenib: an updated systematic review and comparative meta-analysis. Crit Rev Oncol/Hematol. 2014;92(3):194–207.
- 51. Qi WX, Sun YJ, Tang LN, Shen Z, Yao Y. Risk of gastrointestinal perforation in cancer patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors: a systematic review and meta-analysis. Crit Rev Oncol/Hematol. 2014;89(3):394–403.
- Abdel-Rahman O, Fouad M. Risk of cardiovascular toxicities in patients with solid tumors treated with sorafenib: an updated systematic review and meta-analysis. *Future Oncol.* 2014;10(12):1981–1992.
- Santoni M, Conti A, Massari F, et al. Treatment-related fatigue with sorafenib, sunitinib and pazopanib in patients with advanced solid tumors: an up-to-date review and meta-analysis of clinical trials. *Int* J Cancer. 2015;136(1):1–10.
- Abdel-Rahman O, Fouad M. Risk of mucocutaneous toxicities in patients with solid tumors treated with sunitinib: a critical review and meta-analysis. Expert Rev Anticancer Ther. 2015;15(1):129–141.
- Full Prescribing Information: Stivarga. Available from: http:// www.accessdata.fda.gov/drugsatfda\_docs/label/2012/203085lbl.pdf. Accessed April 10, 2013.
- Full Prescribing Information: Avastin. Available from: http://www.accessdata.fda.gov/drugsatfda\_docs/label/2013/125085s267lbl.pdf. Accessed April 10, 2013.
- Full Prescribing Information: Zaltrap. Available from: http://www.accessdata.fda.gov/drugsatfda\_docs/label/2012/125418s000lbl.pdf. Accessed April 10, 2013.
- Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol*. 2011;29(30):3968–3976.
- 59. Shen L, Li J, Xu J, et al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). Gastric Cancer. 2015;18(1):168–176.
- Shah MA, Ramanathan RK, Ilson DH, et al. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol*. 2006;24(33):5201–5206.
- 61. Uronis HE, Bendell JC, Altomare I, et al. A phase II study of capecitabine, oxaliplatin, and bevacizumab in the treatment of metastatic esophagogastric adenocarcinomas. *Oncologist*. 2013;18(3):271–272.

- Pasquier E, Honore S, Pourroy B, et al. Antiangiogenic concentrations of paclitaxel induce an increase in microtubule dynamics in endothelial cells but not in cancer cells. *Cancer Res.* 2005;65(6):2433–2440.
- De Gramont A, Van Cutsem E, Schmoll HJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncol*. 2012;13:1225–1233.
- Moehler M, Mueller A, Hartmann JT, et al. An open-label, multicentre biomarker-oriented AIO phase II trial of sunitinib for patients with chemorefractory advanced gastric cancer. Eur J Cancer. 2011;47: 1511–1520.
- Bang YJ, Kang YK, Kang WK, et al. Phase II study of sunitinib as second-line treatment for advanced gastric cancer. *Invest New Drugs*. 2011;29:1449–1458.
- 66. Sun W, Powell M, O'Dwyer PJ, Catalano P, Ansari RH, Benson AB 3rd. Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. *J Clin Oncol*. 2010;28: 2947–2951.
- 67. Satoh T, Yamada Y, Muro K, et al. Phase I study of cediranib in combination with cisplatin plus fluoropyrimidine (S-1 or capecitabine) in Japanese patients with previously untreated advanced gastric cancer. *Cancer Chemother Pharmacol*. 2012;69:439–446.

- Potts SJ, Huff SE, Lange H, et al. Tissue pattern recognition error rates and tumor heterogeneity in gastric cancer. *Appl Immunohistochem Mol Morphol*. 2013;21(1):21–30. doi:10.1097/PAI.0b013e31825552a3.
- 69. Durães C, Almeida GM, Seruca R, et al. Biomarkers for gastric cancer: prognostic, predictive or targets of therapy? *Virchows Arch.* 2014;464(3):367–378. doi:10.1007/s00428-013-1533-y.
- Abdel-Rahman O. Targeting the hepatocyte growth factor/mesenchymal epithelial transition pathway in gastric cancer: biological rationale and clinical applications. *Expert Rev Anticancer Ther*. 2015; 15(2):235–245.
- Abdel-Rahman O. Insulin-like growth factor pathway aberrations and gastric cancer; evaluation of prognostic significance and assessment of therapeutic potentials. *Med Oncol.* 2015;32(1):431.
- 72. Abdel-Rahman O. Hedgehog pathway aberrations and gastric cancer; evaluation of prognostic impact and exploration of therapeutic potentials. *Tumor Biol.* 2015;36(3):1367–1374.

#### Therapeutics and Clinical Risk Management

## Publish your work in this journal

Therapeutics and Clinical Risk Management is an international, peerreviewed journal of clinical therapeutics and risk management, focusing on concise rapid reporting of clinical studies in all therapeutic areas, outcomes, safety, and programs for the effective, safe, and sustained use of medicines. This journal is indexed on PubMed Central, CAS, EMBase, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

 $\textbf{Submit your manuscript here:} \ \texttt{http://www.dovepress.com/therapeutics-and-clinical-risk-management-journal} \\$ 

