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Ramucirumab for the treatment of gastroesophageal cancers

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Abstract

Introduction—In 2014, the U.S. Food and Drug Administration (FDA) approved ramucirumab for use in the second line setting of advanced or metastatic, gastric or gastroesophageal adenocarcinoma (GEAC) based on the result of Phase III clinical trials; REGARD and RAINBOW.

Areas covered—We briefly review the mechanisms of angiogenesis, anti-angiogenic therapy, and current status of advanced GEAC treatment then highlight the challenges and future prospects of novel molecular targeted agents.

Expert opinion—Although both the REGARD and RAINBOW trials met their primary endpoints of significantly prolonged overall survival (OS) and progression-free survival (PFS), the magnitude of the difference is still relatively modest. Given that ramucirumab alone has a marginal effect, a combination of paclitaxel and ramucirumab is strongly preferred as a second line therapy. To maximize the impact of ramucirumab in patients with GEAC, we can leverage the recent pharmacokinetics (PK) data of ramucirumab from the REGARD and RAINBOW trials. In addition, the quest for identifying biomarkers to select patients who are likely to benefit the most should continue. It is our firm belief that taxanes should no longer be added to the frontline regimens in most cases, given the success of the taxane/ramucirumab in the second line setting.

1. Introduction

In November of 2014, the U. S. Food and Drug Administration (FDA) approved ramucirumab (box 1) for use in combination with paclitaxel for second line treatment of patients with advanced gastric or gastroesophageal junction adenocarcinoma (GEAC)[1]. Prior to that, in April, 2014, ramucirumab was approved as a single agent for the treatment of patients with advanced GEAC with disease progression, during or following first-line therapy with fluoropyrimidine or platinum agents [2]. This is the first drug to be approved in

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the second line and these approvals were based on the results from the two Phase III clinical trials: RAINBOW and REGARD.

In spite of advances in diagnostic imaging, surgical techniques, and wide exploration of classical chemotherapy agents, outcome of stage 4 GEAC patients remains poor. Along with other solid organ malignancies, researchers have focused on deeper understanding of carcinogenesis and refining the molecular characterization of GEAC. The pioneer targeted therapy for advanced GEAC was trastuzumab against the extracellular domain of human epithelial growth factor receptor type 2 (HER2) and has resulted in moderate prolongation of OS in combination with chemotherapy in the setting of HER2 over-expressing advanced GEAC. Following trastuzumab, other clinical trials investigating targeted agents have been conducted, but most of their results have been disappointing. Ramucirumab has demonstrated modest but favorable results in two Phase III clinical trials in the second-line setting. Against this background, we review mechanisms of angiogenesis, molecular targeted therapy, and new trials.

1.1 Gastroesophageal adenocarcinoma

Although there is significant regional difference in incidence of GEAC with the highest found in eastern Asia and the lowest in North America and Africa [3], GEAC represents the fifth most common cancer across the globe and third leading cause of cancer mortality [4]. Currently, the standard of care for GEAC consists of combinations of surgery, chemotherapy, and radiotherapy. However, the outcome of patients with localized GEAC remains poor with 25%-35% 5-year survival rate [5-7] and median survival ranging from 9 to 14 months (often <11 months) with advanced disease [8, 9].

It has been shown that chemotherapy can prolong survival in the setting of advanced disease, and combination of fluoropyrimidine and platinum are commonly the first-line therapy. Currently, oxaliplatin and capecitabine have been shown to be as effective as cisplatin and fluorouracil, and S-1 is used in Asia as an oral fluoropyrimidine [10, 11]. As a result of the ToGA trial, it is standard to add trastuzumab to a platinum-fluoropyrimidine doublet in HER2 over-expressing advanced or metastatic GEAC [12].

In the second line, the choices have been either a taxane (i.e., docetaxel or paclitaxel) or irinotecan to reflect the findings of several trials that demonstrated prolonged OS with either of those drugs added to best supportive care (BSC) compared with BSC alone [13-16].

2. Angiogenesis and vascular endothelial growth factor (VEGF)-targeted therapies

Angiogenesis, the formation of new blood vessels, plays a key role in the growth, invasion, and metastasis of solid malignancies [17-21]. From a focus on the cancer treatment outcomes with conventional methods, researchers shifted their attention to better understanding of molecular biology of carcinogenesis and development of rationally designed drugs that would target specific molecular structure in signal transduction cascades. The result of this effort has been the FDA approval of nine antiangiogenic agents for various cancer treatments, including ramucirumab for GEAC.

VEGFs and their receptors, which have emerged as targets for the development of anticancer agents, are endothelial cell-specific mitogens and assume a key role of angiogenesis and development of vascular permeability. VEGF family consists of 7 ligands that bind in a specific manner to three different receptor tyrosine kinases: VEGF receptor (VEGFR)-1, VEGER-2, and VEGFR-3. In GEAC, correlation between VEGF expression and increased vascular involvement, lymph node metastasis, and poor prognosis were reported [22]. Bevacizumab is the first FDA approved antiangiogenic agent and specifically binds to VEGF-A, preventing its interaction with VEGFR-1 and VEGFR-2. Bevacizumab has shown benefits in patients with advanced colorectal cancer, renal cells carcinoma, ovarian cancer, glioblastoma and non-small cell lung cancer [23, 24]. In spite of encouraging Phase II trial results for bevacizumab [25], the Phase III AVAGAST trial did not meet its primary end point; overall survival (OS) [26]. The AVAGAST biomarkers analysis was also not helpful [27].

Other signaling pathways including epidermal growth factor receptor (EGFR) and mammalian target of rapamycin (mTOR) cascades are important in cancer progression and some agents targeting these mechanisms (i.e., cetuximab, panitumumab, and everolimus) are used in various malignancies. Despite the efficacy of molecular target therapy in GEAC demonstrated by ToGA trial, the trials of such agents in this cancer have failed to demonstrate any improvement in OS [9, 28-30].

Recently, apatinib, an oral tyrosine kinase inhibitor (TKI) targeting VEGFR-2 has shown good safety and efficacy in the treatment of patients with advanced GEAC refractory to second-line chemotherapy in clinical studies of Phase II [31] and Phase III [32]. A total of 273 patients were randomly assigned to oral apatinib 850 mg q.d. (28-day treatment cycles) or placebo at a ratio of 2:1. The study demonstrated improved OS, with a median of 195 days in patients in the apatinib group compared to 140 days in those in the placebo group (HR 0.71, 95% CI: 0.54-0.94; $P < 0.016$). PFS, studied as a secondary endpoint, was also prolonged with a median of 78 days in apatinib group and 53 days in placebo group (HR 0.44, 95% CI: 0.33-0.61; $P < 0.0001$). The tolerability was acceptable. About 60% of patients in treatment arm experienced grade 3 or higher adverse events including hypertension, hand-and-foot syndrome, proteinuria, fatigue, anorexia, elevated aminotransferase, which were manageable by dose interruptions or reductions. As this trial was conducted in Asia and the different immunity signatures of GEAC between Asian and non-Asian populations have been reported [33], in spite of its favorable findings, a globally designed study is needed to confirm the global impact of this novel oral drug.

3. Pharmacodynamics and pharmacokinetics

Ramucirumab (IMC-1121B) is a fully human IgG1 monoclonal antibody that binds with high affinity to the extracellular domain of VEGFR-2 (Figure 1), and was discovered from an antibody phage display library constructed from the pooled B lymphocytes of non-immunized healthy human donors [34]. Since ramucirumab has no activity against mouse VEGFR-2 receptor, its murine version (DC-101) was designed to conduct preclinical studies and demonstrated significant antitumor activity in several malignancies in animal models [35, 36]. Referring to preclinical *in vitro* studies, the binding affinity of ramucirumab to

VEGFR-2 demonstrated a half maximal effective concentration (EC_{50}) of approximately 0.15 nM, while VEGF-A, the primary native ligand for VEGFR-2 has an affinity to VEGFR of 0.77-0.88 nM [17, 37, 38]. The high affinity of ramucirumab with extracellular domain of VEGFR-2 was suggested by the post treatment VEGF-A elevation of 1.5 – 3-foldover the pretreatment level. A crystal structure analysis performed by Franklin *et al.* in 2011 demonstrated ramucirumab Fab binding to domain 3 of VEGFR-2 near the N-terminus [39]. It was also revealed that this action blocks VEGF cascade by both steric blocking of the ligand and changing the receptor conformation.

The pharmacokinetics of ramucirumab was studied in a Phase I trial which enrolled 37 patients with advanced malignancies. Patients were treated with doses ranging from 2 to 16 mg/kg infused weekly [40]. All patients demonstrated trough levels greater than 20 μg/mL, which was the target value, associated with anticancer activity. Among patients treated with 8 – 16 mg/kg doses, the half-life ranged from approximately 200 – 300 hours. These findings supported 8 mg/kg as ideal dose for treatment and this dose has been adopted in Phase II trials, Phase III trials, and clinical practice. In a Phase II trial with advanced hepatocellular carcinoma (HCC) patients, treatment with ramucirumab 8 mg/kg every 2 weeks demonstrated an increase in serum VEGF and placental growth factor (PlGF) and a transient decrease in soluble VEGFR-2 levels [41]. Also decreases in soluble VEGFR-1 levels were observed and appeared to have association with better outcomes. These findings might be a key milestone to reach specific biomarkers and overcome drug resistance.

At 2015 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, Tabernero *et al.* presented the findings about exposure-response relationship of ramucirumab in two Phase III clinical trials of patients with advanced GEAC where first-line therapy failed [42]. Pharmacokinetic samples of 321 patients (97.3%) in ramucirumab plus paclitaxel arm from RAINBOW trial and those of 72 patients (30.3%) in ramucirumab arm from REGARD trial were analyzed. Population pharmacokinetic-predicted exposure values were determined for ramucirumab patients using a nonlinear mixed-effect modeling approach and exposure-efficacy analysis. Finally an exposure-safety analysis was conducted. In these two trials, improved efficacy was observed with increasing levels of ramucirumab exposure and these beneficial changes remained significant after adjustment for baseline characteristics. Higher incidence of grade 3 or higher hypertension, neutropenia, and leukopenia was observed in the RAINBOW study without increase of febrile neutropenia and fatigue. In the REGARD study, they found no relationship between exposure and grade 3 or higher hypertension. With these findings about exposure-response relationship, the administration method of ramucirumab 8 mg/kg given intravenously on day 1 and 8 in combination with cytotoxic agents was adopted in the first-line trial (NCT02314117) which is currently ongoing[43]. Forays into this type of research are exciting because they would allow us to maximize the efficacy of currently available drugs.

4. Clinical trials of ramucirumab

In 2010, Spratlin *et al.* conducted the Phase I study with ramucirumab in 37 patients with advanced solid malignancies to evaluate the safety, maximum-tolerated dose (MTD), and preliminary anticancer activity [40]. Patients were treated with weekly administration of

ramucirumab starting at 2 mg/kg and up to 16 mg/kg. Since two patients developed dose-limiting hypertension and deep venous thrombosis (DVT) at 16 mg/kg, 13 mg/kg, the next lower dose was considered as MTD on a weekly schedule. 60% of patients experienced grade 3 to 5 adverse events including hypertension, abdominal pain, anorexia, vomiting, increased blood alkaline phosphatase, headache, proteinuria, dyspnea, and DVT. 15% of patients with measurable disease demonstrated a partial response, and 30% of patients had either a partial response or stable disease lasting at least 6 months across a range of doses.

The REGARD trial was an international, randomized, double-blind, placebo-controlled, Phase III study conducted in 355 patients with advanced GEAC and disease progression after first-line fluoropyrimidine or platinum-based therapy [44]. Patients were randomly assigned in a 2:1 ratio to receive best supportive care plus either ramucirumab 8 mg/kg or placebo, intravenously once every 2 weeks. The study demonstrated improved OS, a primary endpoint of this trial, with a median of 5.2 months in patients in the ramucirumab group compared to 3.8 months in those in the placebo group (hazard ratio (HR) 0.776, 95% CI: 0.603-0.998; P=0.047). This survival benefit remained significant after multivariable adjustment for other prognostic factors: performance status, location of the primary tumor, and presence of peritoneal metastases. PFS, studied as a secondary endpoint, was modestly but significantly prolonged with a median of 2.1 months in ramucirumab group and 1.3 months in placebo group respectively (HR 0.483, 95% CI: 0.376-0.620; $P < 0.05$). The duration of disease control was significantly longer in the study group (median 4.2 months) than in the placebo group (median 2.9 months), and the result of disease control rate (DCR) also had significant difference between with ramucirumab group (49%) and with placebo group (23%). Despite these favorable findings, there was no significant improvement in tumor symptoms and in quality of life. Regarding toxicity, 94% of patients in ramucirumab group and 88% of patients in placebo group had adverse events of any grade, and hypertension was more common in the ramucirumab group (16%) than in the placebo group (8%). Ramucirumab was not associated with increased rates of proteinuria, bleeding, venous thrombosis, or gastrointestinal perforation. Overall, the toxicity for patients in the ramucirumab group was low and considered to be acceptable.

The second Phase III trial of ramucirumab, the RAINBOW trial, is a randomized, placebo-controlled, double-blind study conducted between December 23, 2010 and September 23, 2012 in 27 countries all over the world [45]. 60% of whole trial populations were from Europe, Australia, or North America, and approximately one third of them were from East Asia. Patients with advanced GEAC and disease progression on or within 4 months after first-line treatment with a platinum-based chemotherapy were randomly assigned in a 1:1 ratio to paclitaxel 80 mg/m^2 alone (n=335) or in combination with intravenous ramucirumab 8 mg/kg once every 2 weeks (n=330). Paclitaxel was chosen for the combination based on the favorable findings of single-agent second-line trials which were conducted beforehand [46-48]. The primary endpoint was OS. Randomization was stratified by geographic regions, time to progression on first-line therapy (<6 months vs >6 months), and measurable versus nonmeasurable disease. Compared with placebo plus paclitaxel, ramucirumab plus paclitaxel significantly prolonged median OS from 7.4 months to 9.6 months, translating into a 19% reduction in the risk of death (HR 0.807, 95% CI: 0.678-0.962; P =0.017). Multivariate analysis using the stepwise Cox model identified seven significant independent survival

predictors: Asian origin, ECOG performance status 0, weight loss less 10%, up to two metastatic sites, absence of ascites, well-differentiated tumor histology, and previous gastrectomy. After adjusting for these factors, the HR for overall survival with ramucirumab plus paclitaxel compared with placebo plus paclitaxel was 0.745 (95% CI: 0.626-0.888; P =0.010). Patients enrolled in the ramucirumab plus paclitaxel arm also had an improvement in PFS (stratified HR 0.635, 95% CI: 0.536-0.752; P <0.0001) and a significant increase in DCR (80% vs 64% with placebo plus paclitaxel; P<0.0001). Large differences were shown between GEAC in the preplanned subgroup analyses of both PFS and OS. Overall, the incidence of grade 3 or higher treatment related adverse events was significantly increased in the ramucirumab plus paclitaxel group (82% vs 63%), with a higher incidence of grade 3 or 4 neutropenia (41% vs 19%), leucopenia (17% vs 7%), and hypertension (14% vs 2%), and fatigue (12% vs 5%). Although increased incidences of adverse events were found, these findings did not impact on treatment discontinuation. An analysis about quality of life (QoL) was also performed as one of the secondary endpoints, which showed that QoL in both treatment groups were similar [49]. Based on the results of this trial, the preferred second line therapy for metastatic GEAC should be taxanes combined with ramucirumab, with ramucirumab alone given only when chemotherapy is contraindicated. The findings from Phase III clinical trials with ramucirumab in GEAC and other solid malignancies are summarized in Table 1.

In contrast to two Phase III trials in second-line setting of GEAC treatment, FOLFOX which has demonstrated considerable efficacy and feasible toxicity for advanced gastric cancer with a number of Phase II studies [50-53], plus ramucirumab failed to show significant survival benefit in first-line setting. In a randomized, placebo-controlled, Phase II trial, 164 patients with previously untreated advanced GEAC were assigned to receive oxaliplatin, leucovorin, and 5-fluorouracil (modified FOLFOX) plus ramucirumab 8 mg/kg or modified FOLFOX plus placebo [54]. Although patient group with combination therapy had significantly improved DCR (85% vs 67%, p=0.008), this trial failed to show differences between two arms in PFS, its primary endpoint (6.44 months vs 6.74 months; HR 0.98; 95% CI 0.69-1.37), and OS (11.7 months vs 11.5 months; HR 1.08; 95% CI 0.73-1.58). Higher incidence of treatment discontinuation reported in ramucirumab plus modified FOLFOX arm caused by factors other than disease progression may have impacted this trial.

Currently, two clinical trials of ramucirumab in the patients with advanced GEAC, one in Phase II (NCT 02317991) and the another one in Phase III, are ongoing (NCT 02317117). The purpose of Phase II trial is to evaluate the efficacy of ramucirumab plus nab-Paclitaxel in the patients with metastatic GEAC and primary outcome of this trial is PFS. Ongoing Phase III trial is a randomized, double-blind, placebo-controlled study that purpose is to determine whether ramucirumab is effective when used in combination with capecitabine and cisplatin in patients with previously untreated metastatic GEAC.

5. Toxicity profile and Tolerability

Judging from the clinical trials currently available for ramucirumab, side effects of this drug are acceptable both if used as a single agent and in combination therapy. In the REGARD trial, in which ramucirumab was used as a single agent, although similar proportion of

patients had grade 3 or higher adverse events between the ramucirumab group (57%) and the placebo group (58%), more patients in the ramucirumab group had grade 3 hypertension than those in placebo group (8% vs 3% in ramucirumab group and placebo groups, respectively). This trial demonstrated no increased risk of bleeding, venous thrombosis, proteinuria, gastrointestinal perforation with ramucirumab monotherapy in GEAC treatment. In contrast, patients treated with ramucirumab in combination with other cytotoxic agents showed different toxicity profiles. In the RAINBOW study, patients in ramucirumab plus paclitaxel group had higher incidence of grade 3 or 4 adverse events including neutropenia (41% vs 19%), leucopenia (17% vs 7%), hypertension (14% vs 2%), fatigue (12% vs 5%), and abdominal pain (6% vs 3%). Despite of significantly higher incidence of neutropenia in the study arm, the incidence of grade 3 or higher febrile neutropenia was low in both groups (3% vs 2%). Both ramucirumab plus paclitaxel group and placebo plus paclitaxel group had 2% of patients whose adverse events lead to death with a causal relation to any study drug. In the Phase II study of ramucirumab plus modified FOLFOX for previously untreated gastroesophageal cancer, the most common grade 3 or higher adverse events were neutropenia (27% vs 36%), fatigue (18% vs 15%), and neuropathy (9% vs 11%), and the incidence of therapy cessation for non- progressive disease was more common in the study group (48% vs 16%). Based on clinical trials, the incidence of adverse events such as bleeding, thrombo-emboric events, fistula formation, and gastrointestinal perforation which are common in treatment with anti-VEGF agents were comparatively lower than expected. Although ramucirumab appeared to be tolerable when used in GEAC treatment with its specific binding ability to VEGFR-2, oncologists have to remain vigilant given that the toxicity data is still limited. The toxicities related to ramucirumab in gastric cancer clinical trial are summarized in Table 2.

6. Conclusion

Owing to its selective and high affinity binding to VEGFR-2, the toxicity profile of ramucirumab is tolerable both as a single agent and for use in combination with cytotoxic drugs. Although the primary endpoints of REGARD and RAINBOW trials are both statistically significant, and ramucirumab has become an important option for patients with advanced gastric cancer in the second-line treatment, the benefit of ramucirumab alone is marginal clinically with an OS improvement of only 6 weeks. For this reason, a combination of taxanes and ramucirumab should be used in the second line setting unless chemotherapy use is contraindicated. To maximize the efficacy of this new agent, further investigation into specific biomarkers, which predict response to therapy, is necessary. From here on, many trials will be conducted with ramucirumab in GEAC but also other malignancies. These trials should focus not only on clinical outcomes but also on cost-effectiveness of this drug.

7. Expert opinion

Ramucirumab is an agent targeting the VEGFR cascade that plays a key role in cancer development, progression, and metastases, and now in cancer treatment as well. The importance of antiangiogenic agents in GEAC therapy is more obvious following ramucirumab's FDA approval and utility in clinic. Recent study analyzing the data from the REGARD and RAINBOW trials supported ramucirumab use in elder patients (≥65 years

old) with similar improvements and similar toxicity profiles compared to the findings with those younger than 65 year-old [55]. These findings and moderate toxicity profiles have opened the door of GEAC treatment for those who were not eligible previously. Regarding GEAC treatment, the geographical difference in treatment outcomes between Western and Eastern remains a contentious matter. Referring to the findings of RAINBOW trial, not only patients in the ramucirumab plus paclitaxel group, but also those in the placebo plus paclitaxel group lived much longer after disease progression in Asia than in other regions. As the geographical difference in PFS was much smaller than that in OS, it is hard to attribute the difference in survival outcome to tumor biology difference or to the different site proportion of cancer occurrence. Wilke *et al.* speculated this regional difference might be due to the much higher use of post-study treatment in Asian region, which were supposed to be about 70% [45]. What can definitely be concluded currently is that ramucirumab alone has a relatively marginal benefit and should be used in combination with taxane in the second line setting unless chemotherapy is contraindicated. To take this a step further, we would recommend that taxanes no longer be used in the first line setting now that a viable second line option for their use exists.

Although ramucirumab improved the OS of advanced GEAC patients with tolerable toxic profiles, the overall outcome from therapy in these patients remain poor. Many questions still need to be answered. One of these questions is the cost efficacy profile of this new agent. Though achieving better outcome from cancer treatment is a critical issue, so is maximizing limited health care resources and taking account of financial strain on cancer patients caused by multimodality treatment and multiple line therapy including combination therapy with molecular targeted agents and cytotoxic anticancer agents. To address this issue, the ASCO published guidelines that can be used to assess the costs of high quality cancer treatment [56]. To further address this need, specific biomarker which predicts response to these agents should be established. Additionally we should continue to pursue the optimal administration method, in addition to optimal dosing interval as is suggested by the recent PK study about exposure-response relationship. Quest for specific biomarkers can throw light upon the other issues surrounding molecular targeted therapy; i.e. drug resistance. The eventually observed resistance after prolonged exposure to these agents is great obstacle for those engaged in cancer treatment. It is becoming increasingly apparent that many different pathways of resistance to angiogenic inhibitors exist such as direct selection of clonal cell populations with the capacity to upregulate alternative proangiogenic pathways, intrinsic resistance to hypoxia, and increased invasive capacity [57-59]. The combination of molecularly targeted therapies is another way to potentially circumvent resistance [60], however, there has been many challenges to moving this into clinical use. Research regarding ramucirumab is still ongoing, and more research needs to be done to maximize the utility of this drug.

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Box 1

Drug summary.

Drug name	**Ramucirumab (IMC-1121B)**
Phase	Launched
Indication	Advanced gastric or gastroesophageal junction adenocarcinoma, as a single agent or in combination with paclitaxel, after prior fluoropyrimidine- or platinum-containing chemotherapy.
Pharmacology description/ mechanism of action	Vascular endothelial growth factor receptor-2 antagonist
Route of administration	Intravenous infusion
Chemical structure	$C_{6374}H_{9864}N_{1692}O_{1996}S_{46}$
Pivotal trial(s)	REGARD trial [41], RAINBOW trial [42]

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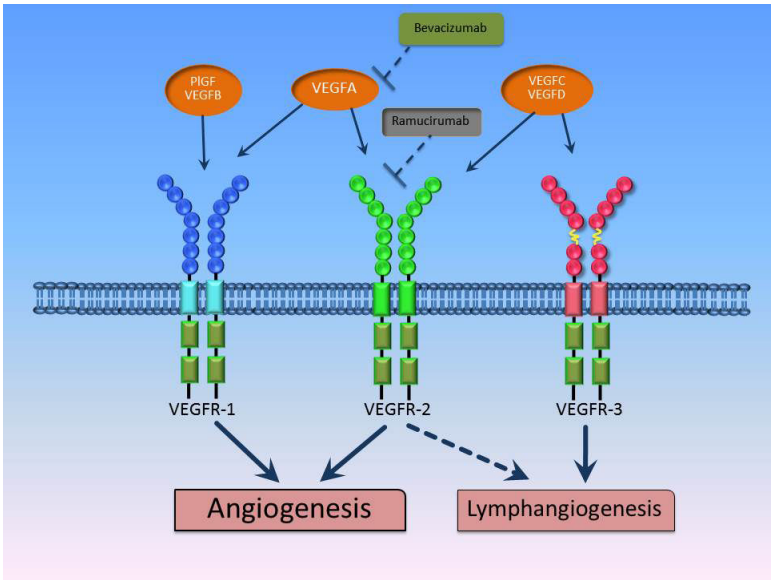

Figure 1.

Mechanism of action of ramucirumab. Ramucirumab binds specifically to the extracellular domain of VEGFR-2, while bevacizumab binds to circulating VEGF thus blocking downstream signaling.

Table 1

Summary of the Phase III trials with ramucirumab

Trial	Study population	Study arm(s)	Primary end point	Results (in months)	P-value
NCT00917384 REGARD [44]	Metastatic gastric or GEJ adenocarcinoma progressed during or following first-line plutinum- or fluoropyrimidine-based therapy	Ramucirumab + BSC vs Placebo + BSC	OS	5.2 vs 3.8	0.0473
NCT01170663 RAINBOW [45]	Metastatic gastric adenocarcinoma progressed or following first-line plutinum- or fluoropyrimidine-based therapy	Ramucirumab + paclitaxel vs placebo + paclitaxel	OS	9.6 vs 7.4	0.0169
NCT02314117 RAINFALL [43]	Previously untreated metastatic gastric or GEJ adenocarcinoma	Ramucirumab + CX vs placebo + CX	PFS	Ongoing	–
NCT007003326 ROSE [61]	HER2-negative, unresectable, locally recurrent or metastatic breast cancer	Ramucirumab + docetaxel vs placebo + docetaxel	PFS	9.5 vs 8.2	0.077
NCT01168973 REVEL [62]	metastatic NSCLC progressed during or following first-line platinum-based therapy	Ramucirumab + docetaxel vs placebo + docetaxel	OS	10.5 vs 9.1	0.02
NCT01183780 RAISE [63]	metastatic CRC progressed during or following first-line therapy with bevacizumab, oxaliplatin, and fluoropyrimidine	Ramucirumab + FOLFIRI vs placebo + FOLFIRI	OS	Ongoing	–
NCT01140347 REACH [64]	HCC progressed during or following sorafenib and with Child-Pugh score of A	Ramucirumab + BSC vs Placebo + BSC	OS	Ongoing	–

NCT, number of clinical trial; GEJ, Gastroesophageal junction; BSC, Best supportive care; OS, Overall survival; CX, Cisplatin plus capecitabine; HER2, Human epidermal growth factor receptor; PFS, Progression free survival; NSCLC, Non-small-cell lung cancer; CRC, Colorectal cancer; FOLFIRI, Follinic acid, 5-fluorouracil, and irinotecan; HCC, Hepatocellular carcinoma.

Table 2

Selected ≥ grade 3 toxicities of randomized clinical trial with ramucirumab

	REGARD [44]		RAINBOW [45]		FOLFOX [54]	
	Ramucirumab	**Placebo**	**Ramucirumab + paclitaxel**	**Paclitaxel**	**Ramucirumab + FOLFOX**	**FOLFOX**
Neutropenia			41%	19%		
Thrombocytopenia			2%	2%	6%	3%
Febrile neutropenia			3%	2%		
Proteinuria	<1%	0%	1%	0%		
Neuropathy			8%	5%	6%	9%
Vomiting	3%	3%	3%	4%		
Decreased appetite	3%	3%	3%	4%	6%	0%
Venous thromboembolism	1%	4%	2%	3%	4%	5%
Arterial thromboembolism	1%	0%	1%	1%	2%	0%
Hypertension	8%	3%	15%	3%	16%	4%
Hemorrhage	3%	3%	4%	2%	6%	6%
Gastrointestinal perforation	<1%	<1%	1%	0%		