Published in final edited form as:
Expert Opin Biol Ther. 2013 August ; 13(8): 1187–1196. doi:10.1517/14712598.2013.810717.

Targeted inhibition of VEGF Receptor-2: An update on Ramucirumab

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Abstract

Introduction—Ramucirumab (IMC-1121B) is a fully humanized IgG1 monoclonal antibody targeting the extracellular domain of VEGF receptor 2 (VEGFR2). Numerous phase I-II trials with ramucirumab in various malignancies have shown promising clinical antitumor efficacy and tolerability. Most recently, the large phase III REGARD trial evaluated ramucirumab in patients with refractory metastatic gastric cancer. Patients receiving ramucirumab experienced a median overall survival of 5.2 months compared to 3.8 months on placebo.

Areas Covered—The purpose of this article is to review the preclinical motivation for VEGFR2 targeted therapies and survey recent data from clinical trials involving ramucirumab, as well as highlight ongoing studies.

Expert Opionion—Rational multi-target approaches to angiogenesis are needed to overcome resistance mechanisms. Predictive angiogenic biomarkers are also needed to optimize patient selection for novel anti-angiogenic agents.

Keywords

Ramucirumab; angiogenesis; cancer; VEGF; VEGFR2; monoclonal antibody; gastric cancer; adenocarcinoma; vascular endothelial growth factor

1.1 Introduction

Sustained angiogenesis is a hallmark of cancer; and targeted inhibition of blood vessel development is an established modality of antitumor therapy[1]. During the past decade, multiple clinical trials have demonstrated improved survival by inhibiting angiogenesis, principally the vascular endothelial growth factor (VEGF) axis, by one of two mechanisms: monoclonal antibody binding of VEGFA [VEGF] with bevacizumab and multi-target receptor tyrosine kinase (RTK) inhibitors with anti-angiogenic specificity. Anti-VEGF therapies have been associated with a survival benefit across multiple malignancies including colorectal, non-small cell lung (NSCLC), renal cell, and hepatocellular carcinomas, among others[2-5]. Accordingly, novel approaches resulting in greater blockade of VEGF signaling and inhibition of angiogenesis have generated substantial interest.

Ramucirumab (IMC-1121B) is a fully humanized IgG1 monoclonal antibody targeting the extracellular domain of VEGF receptor 2 (VEGFR2). VEGFR2 is largely considered the primary VEGF family receptor driving angiogenesis. While multiple lines of evidence support the preclinical efficacy of targeted VEGFR2 inhibition, within the past several

years, numerous phase I-II trials have showed promising clinical antitumor effect and tolerability. Most recently, the results of the large phase III REGARD trial of ramucirumab in patients with refractory metastatic gastric cancer were announced. The primary aim of this article is to review the preclinical motivation for VEGFR2 targeted therapies and survey recent data from clinical trials involving ramucirumab.

1.2 VEGF signaling and Tumor Angiogenesis

Tumor angiogenesis is a highly complex process dependent on a multi-faceted program of endothelial cell activation, stromal cell and endothelial-progenitor recruitment, extra-cellular matrix remodeling, pro-angiogenic cytokine signaling, and activation of oncogenic signaling cascades[6, 7]. A critical pillar of angiogenesis is the interaction of the VEGF family of pro-angiogenic cytokines and their respective receptors. The VEGF family includes VEGFA, VEGFB, VEGFC, VEGFD, VEGFE, and placental growth factor (PlGF) with three receptors: VEGFR1 (fms-like tyrosine kinase 1/Flt-1), VEGFR2 (Flk-1/KDR), and VEGFR3 (Flt-4) with associated co-reptors neuropillin 1 and 2 (NRP1/2)(see fig. 1)[8]. VEGFR2 expression is typically limited to vessel endothelial cells, while VEGFR1 can also be found on bone-marrow derived progenitors[9]. VEGFR1 classically binds to homodimers of VEGFA, VEGFB, and PlGF, while VEGFR2 binds VEGFA, VEGFE and processed forms of VEGFC and VEGFD[10]. While VEGFR3 is principally involved in lympangiogenesis, VEGFR2 is widely considered the main receptor driving angiogenesis. VEGFR1 exhibits high binding affinity for VEGFA, but weak phosphorylation activity possibly suggesting a negative modulatory role on VEGF signaling[9, 11]. Furthermore, both PlGF and VEGFB bind exclusively to VEGFR1, can form heterodimers with VEGFA, and affect tumor growth[12-16]. VEGFR1 is also implicated in monocyte chemotaxis, hematopoietic stem cell (HSC) survival, and inhibition of dendritic cell maturation[17-20], while soluble VEGFR1 plays a role in pre-eclampsia[21]. Upregulation of VEGFA mRNA is demonstrated across almost every type malignancy, including breast, lung, colorectal cancers, renal cell, ovarian, and glioblastoma[22]. Likewise, upregulation of VEGFR2 expression is seen in the tumor vasculature in a variety of malignancies as well [23-25].

The VEGFRs belong to the immunoglobulin subclass of the receptor tyrosine kinase (RTK) superfamily and have seven Ig-like extracellular domains with a single transmembrane helix with an intracellular kinase region[10, 26]. Following binding of VEGFA, VEGFR2 has the potential to form either a homodimer or heterodimer complex with VEGFR1, resulting in intracellular tyrosine phosphorylation[10, 26]. Ultimately, downstream effects of VEGFR2 signaling which culminate in angiogenesis, include a potent increase in vascular permeability and promotion of endothelial cell migration, proliferation, and survival[10]. Complicating the differential effects of VEGFA signaling and VEGFR2 activation, is the substantial crosstalk with other pro-angiogenic molecules and adhesion proteins, including multiple VEGF isoforms, angiopoetins, and integrins[6]. Ang/Tie, Dll4/Notch, and a_v integrin signaling pathways all intersect with the VEGF axis and modulate angiogenesis, lymph-angiogenesis, and metastasis (see fig. 1)[6, 27].

Binding of VEGFs to VEGFR2 initiates receptor dimerization and robust intracellular autophosphorylation of multiple tyrosine residues with numerous downstream

consequences. Specifically, phosphorylation of Y1175 allows docking of phospholipase C-gamma (PLC-γ) resulting in activation of the mitogen activated protein kinase (MAPK) pathway and promotion of endothelial cell proliferation[9, 10]. Furthermore, Y1175 mediates phosphatidylinositol 3′ kinase (PI3K) activity leading, ultimately, to increased cell survival through AKT/PKB, cell migration, and vascular permeability via expression of endothelial nitric oxide synthase. Phosphorylation of other critical residues include Y951 and Y1214, which also promote vascular permeability, actin remodeling, and cell migration by way of Src/TSAd and P38/MAPK pathways[9, 10].

Disruption of VEGFR2 signaling by currently FDA approved, anti-angiogenic agents occurs namely by either specific binding of circulating VEGF or small molecule inhibition of RTKs. Bevacizumab potently binds VEGFA reventing its docking with VEGFR1 and VEGFR2. Bevacizumab is widely used in mCRC, nonsmall cell lung, glioblastoma, and renal cell carcinomas. More recently, ziv-Afliberacept, a soluble VEGF receptor decoy with VEGFA, VEGFB, and placenta growth factor (PlGF) affinity, demonstrated efficacy in treatment refractory metastatic colorectal cancer (mCRC) patients, but not in NSCLC, prostate, or pancreatic adenocarcinoma [28-31]. The number of FDA approved small molecule RTK inhibitors with anti-angiogenic specificity has increased significantly within the past several years. Currently, there are seven FDA approved mutlikinase inhibitors that are known to target VEGF (alone or with other targets):sorafenib, sunitinib, axitinib, pazopanib, vandetinib, cabozantinib, and regorafenib. Many of these agents demonstrate VEGFR inhibition, along with blockade of other receptors, such as PDGF and cKit. However, off target promiscuity coupled with incomplete blockade of pro-angiogenic kinases can theoretically cause RTK inhibitors to be associated with toxicity and have suboptimal antitumor activity[32]. Thus, ramucirumab offers a novel mechanism for anti-angiogenic therapy with the potential for both high affinity and high specificity blockade of VEGFR2,

2. Introduction to Ramucirumab

2.1 Preclinical Evidence

Due to species-specific differences in human VEGFR2 (KDR) and murine VEGFR2 (flk-1), the development of anti-VEGFR2 antibodies has required the production of immunoglobulins specific to both the human and murine forms of the receptor to sterically block ligand binding. In 1998, Witte et al initially described the development anti-flk-1 (DC101) and anti-KDR (p1C11) high affinity monoclonal antibodies, which demonstrated *in vitro*potent inhibition of VEGF receptor binding, intracellular phosphorylation and signaling, and human umbilical vein endothelial cell (HUVEC) mitogenesis[33]. DC101 was later shown, by the same group, to suppress the growth of primary murine lung, mammary, melanoma *in vivo* and inhibited multiple other human tumor xenografts[34]. DC101 effects included tumor cell apoptosis, decreased vessel density, and reduced tumor cell proliferation.

In 2003, Lu et al used a large phage display library with tailored *in vitro*selection methods to identify a high affinity antibody, 1121, with a >30-fold higher binding affinity to KDR compared to other candidate VEGFR2 antibodies. 1121 blocked VEGFA/KDR interaction with an IC50 of 1 nM and potently inhibited VEGF-stimulated KDR phosphorylation[35].

More recently, Miao et al in 2006 reported the production of a humanized anti-KDR Fab fragment leading to the generation of Fab 1121B, which retained high affinity for KDR. Indeed, 1121B was subsequently shown to block VEGFA binding, neutralize VEGFA-stimulated phosphorylation of KDR, and inhibit HUVEC mitogenesis[36].

2.2 Chemistry

Ramucirumab is a fully humanized immunoglobulin G1 monoclonal antibody[37]. During initial preclinical development, a conserved variable heavy chain (VH) sequence was identified between multiple potential parent compounds, with reported greatest homology to the germline DP77 segment of the human VH3 family. This single VH was recombined with variable light chains (VL) using a phage display library with subsequent rounds of affinity maturation selection. The resulting consensus VH/VL combination was labeled as 1121, the amino acid sequence of which has been previously reported[35].

2.3 Pharmacodynamics and Pharmacokinetics

Based on preclinical *in vitro* data, the binding affinity of the 1121B Fab to KDR demonstrated an ED50 of approximately 0.1-0.15 nM. VEGFA, the primary native ligand for VEGFR2 has an affinity to VEGFR2 of .77-.88 nM, or approximately 8-9 fold weaker than the 1121B monoclonal antibody[35, 36]. 1121B effectively binds KDR both as a soluble protein and as a cell-surface based receptor, with an IC50 of 1-2 nM[36]. A detailed crystal structure analysis of the 1121B:KDR complex was performed by Franklin et al in 2011 showing that 1121B Fab binds to domain 3 of KDR near the N-terminus[38]. The epitope for 1121B binding consists of a B-hairpin with an adjacent B-strand, and domain 3 of the KDR receptor. Inhibition of VEGFA binding to KDR is likely mediated by both steric blocking of the ligand and induction of conformation change in the receptor when in contact with 1121B[38].

In the initial phase I study of ramucirumab, a total of 37 patients were treated with doses ranging from 2 to 16 mg/kg infused weekly[37]. Favorable pharmacokinetic data was obtained from the study, as all patients demonstrated trough levels greater than the target of 20 ug/mL, and the half-life at steady-state ranged at 200-300 hours for 8-16 mg/kg doses. 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. Despite large inter-patient variability, the findings were consistent with PK data from other anti-receptor antibodies[37].

Pharmacodynamic data from the phase I clinical trial incorporated serum measurement of VEGFA and soluble VEGFR1/2 at time points before and during each cycle of treatment[37]. Following the first infusion, an immediate increased in VEGF of 1.5-3 fold over the pretreatment level was measured, which lasted the duration of the treatment course. VEGFR1/2 levels immediately decreased after the initial infusion of ramucirumab, then returned to baseline levels. Neither the VEGF or VEGFR1/2 change was dose related, suggesting saturation of the receptor as also described by the PK data. Sequential DCE-MRI measurement did confirm reduced tumor vascularity in 69% of the patients. Importantly, no

anti-ramucirumab antibodies were detected at the conclusion of treatment in any of the patients[37].

3. Clinical Evidence using Ramucirumab

3.1 Phase I and II Trials

Two phase I studies with ramucirumab have been completed to date, however the results of only one trial have been fully published[37, 39]. Spratlin et al in 2010 reported the phase I results with ramucirumab in 37 patients with advanced solid malignancies. The majority of the patients had received prior chemotherapy, however less than 15% had reported prior exposure to anti-angiogenic therapies. A standard 3+3 dose escalation scheme was used with weekly administration of ramucirumab starting at 2 mg/kg. Patients were treated up to 16 mg/kg, however 2 patients developed dose-limiting hypertension and venous thrombosis, thus 13 mg/kg was determined to be the maximum tolerated dose. 60% of patients developed grade 3 or higher toxicity with fatigue, nausea/vomiting, proteinuria, and hypertension being noted. Promising efficacy was observed as 4 of 27 patients with measurable disease had a partial response. Partial response or stable disease was seen in 73% of patients, and 11 of 37 patients had a partial response or stable disease at 6 months follow up. A smaller study in 2007 also evaluated q2 week or q3 week dosing regimens with ramucirumab and demonstrated similar PK and safety data[39].

Given the promising phase I results, numerous phase II disease specific trials have been performed over the past five years. Beginning in 2010, results of combinations of ramucirumab with various chemotherapy regimens were reported in metastatic melanoma, metastatic renal cell carcinoma (RCC), NSCLC, and hepatocellular carcinoma (HCC). Many of these studies have been reviewed previously[40]. Insorafenib-naïve patients with advanced HCC, ramucirumab demonstrated a progression free survival of 4.3 months[41]. In advanced NSCLC patients, combination ramucirumab q3 weeks with carboplatin and paclitaxel demostrated an overall response rate of 67% with a progression free survival of 5. 7 months[42]. Additionally, in metastatic RCC patients with previous sorafenib/sunitinib exposure, ramucirumab showed a median progression free survival of 6 months with nearly 50% of patients having stable disease at >5 months. Finally, a randomized trial of patients with metastatic melanoma compared ramucirumab with or without dacarbazine. Although, treatment was relatively well tolerated, efficacy was poor with a progression free survival of 1.6 and 2.5 months, respectively, in each group[43].

Within the past year, additional phase II study results have been presented in ovarian, prostate, and colorectal cancers. Ramucirumab was evaluated in women with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma after previous platinum- based chemotherapy. Approximately one third of patients had progression free survival at 6 months, with a median progression free survival of 3.5 months and OS of 11.1 months[44]. Efficacy of ramucirumab in metastatic castrate resistant prostate cancer (CRPC) was studied in a randomized phase II study comparing mitoxantrone / prednisone with either ramucirumab or cixutumumab[45]. Patients were randomized between treatment arms. PSA response was seen in 22%, with a progression free survival and overall survival of 6.7 months and 13.0 months, respectively. In metastatic colorectal cancer, ramucirumab was

combined with FOLFOX chemotherapy; this regimen demonstrated a median progression free survival of 11.5 months, with an ORR of 67%, including 5 patients with complete response and 27 with a partial response[46].

Multiple studies are currently ongoing evaluating novel combinations of ramucirumab with chemotherapy. Vahdat et al are examining ramucirumab in a 3-arm trial in metastatic breast cancer patients previously treated with an anthracycline and taxane. Patients will be randomized to capecitabine alone or in combination with either IMC-18F1 (VEGFR1 inhibitor) or ramucirumab[47]. A similar 3 arm study is ongoing to evaluate ramucirumab or IMC-18F1 with docetaxel in advanced urothelial cell carcinoma following platinum-based chemotherapy[48]. Other studies evaluating ramucirumab with docetaxel in metastatic NSCLC and in combination with FOLFIRI in advanced solid tumors are also currently enrolling (NCT01703091, NCT01634555).

3.2 Phase III Trials

The results of the pivotal phase III randomized trial for ramucirumab in metastatic gastric cancer have now been presented in full detail, however publication is pending[49, 50]. The REGARD trial was an international, placebo-controlled, double-blind trial evaluating efficacy and safety of ramucirumab monotherapy in patients with metastatic gastric or gastroesophageal junction cancer following standard first line treatment with platinum or fluoropyrimidine based therapy. A total of 355 patients were randomized in a 2:1 fashion to 8 mg/kg or placebo every 2 weeks in combination with best supportive care. The study enrolled 355 patients from 30 countries at 120 different centers. The primary endpoint of the trial was overall survival, with secondary endpoints of progression free survival and quality of life. Following randomization, median age was 60 years with approximately 75% of patients with metastatic gastric cancer and 25% metastatic gastroesophageal junction cancer in each treatment arm. Patients were well matched with respect to number of sites of metastases, histologic subtype, presence of peritoneal disease, and response to prior therapy.

Patients receiving ramucirumab on average received 4 infusions over 8 weeks compared to 3 infusion over 6 weeks with placebo. Ramucirumab demonstrated improved overall survival (HR 0.78; p=0.047), with a median of 5.2 months compared to 3.8 months on placebo. Six-month and 12-month survival rates were 42% vs 32% and 18% vs 11%, respectively between ramucirumab and placebo arms. progression free survival was also significantly prolonged (HR=0.48), with median progression free survival of 1.3 months to 2.1 months with ramucirumab, as well as 12-week progression free survival (40% vs. 16%). While ORR was low between both arms (3.4% vs 2.6%), disease control rate (49% vs. 23%) was superior in the active treatment arm. Post-discontinuation treatment was performed in 31.5% of patients on ramucirumab compared with 39.3% on placebo. Sub-group analysis showed general consistent effects on overall survival and progression free survival independent of primary tumor location, preceding weight loss > 10%, geographic region, type of 1st line chemotherapy, and presence of peritoneal disease. Importantly, overall toxicity for patients in the ramucirumab arm was low (see Safety and Tolerability).

Given the favorable toxicity profile and survival benefit, ramucirumab is a potential new second line agent in metastatic gastric cancer. Prior to ramucirumab, antiangiogenic agents

including bevacizumab, sunitinib and sorafenib have shown limited efficacy in 1st and 2nd line settings in metastatic gastric cancer[51, 52]. For instance, the recent AVAGAST trial of combination bevacizumab with cisplatin and capecitabine in 774 patients showed an improvement in progression free survival and response rate, but failed to meet its primary endpoint of overall survival[53]. Two recent phase III clinical trials have demonstrated a survival benefit of chemotherapy alone in the 2nd and 3rd line setting for patients with metastatic gastric cancer. Irinotecan demonstrated improved overall survival compared with best supportive care (BSC), HR of 0.48 (p=0. 012) with median survival of 4.0 months compared to 2.4 months[54]. Treatment with either irinotecan or docetaxel following progression after one or two prior chemotherapy regimens, yielded increased survival versus best supportive care with a HR of 0.657 (p=.007) and median overall survival of 5.2 months vs 3.8 months[55]. Based upon the activity of taxanes in 2nd line gastric cancer, the RAINBOW phase III trial is evaluating paclitaxel with or without ramucirumab for patients with metastatic treatment refractory gastric cancer (NCT01170663). Approximately 600 patients will be recruited from 200 study centers in 30 countries and results of this trial are expected in the near future.

Several other phase III trials of ramucirumab are currently in progress. A large study of ramucirumab versus placebo in patients with HCC following treatment with sorafenib is also ongoing. The primary endpoint is overall survival with goal of 544 patients powered to detect an increase of 2 months[56]. Additionally, a multinational randomized trial of docetaxel with or without ramucirumab for treatment naïve, HER2 negative, metastatic breast cancer patients is ongoing with a primary endpoint of progression free survival. Finally, FOLFIRI with or without ramucirumab will be evaluated in patients with metastatic CRC who have experience progression during 1st line treatment, including bevacizumab (NCT01183780).

3.3 Safety and Tolerability

The largest experience with safety and tolerability of targeted VEGFR2 inhibition is described by the REGARD trial[50]. In general ramucirumab was very well tolerated. Approximately 10% of patients discontinued ramucirumab treatment due to adverse event compare with 6.0% receiving placebo. Grade 3 or higher adverse events with rates that were higher in the the ramucirumab vs 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 [57-59](see table 1). Combination chemotherapy with ramucirumab from phase II trials showed generally no significant unexpected toxicity. While dosing regimens varied between studies with either weekly or every 2-3 week infusions, toxicity rates seemed independent of dose or frequency of administration. Further phase III data with combination docetaxel or FOLFIRI, for example, will be helpful in delineating the toxicity profile with multi-drug regimens.

4. Conclusion

Ramucirumab is the first monoclonal antibody targeting VEGFR2 to be used in phase III clinical trials. The REGARD study demonstrated that ramucirumab is generally well tolerated and improves overall survival and progression free survival in refractory gastric

and gastro-esophogeal cancers. Numerous additional phase II and III trials are currently ongoing to examine combination therapy of ramucirumab with cytotoxic chemotherapy in multiple disease settings, including 2nd line and 1st line metastatic gastric and gastro-esophogeal cancer, metastatic breast, NSCLC, colorectal, and HCC.

5. Expert Opinion

The demonstration of efficacy with targeted inhibition of VEGFR2 in a phase III trial represents an important milestone in anti-angiogenic therapy. However, the modest survival benefit illustrates a recurrent difficulty with anti-VEGF agents in clinical use. One explanation for the frequently varied clinical response and relatively transient benefit, may lie in the understanding of angiogenic resistance mechanisms. While VEGFR2 is considered the major signaling pathway of physiologic and pathological angiogenesis, a number of other pro-angiogenic pathways are known to contribute to tumor blood vessel formation including PDGF, FGF, angiopoietin, Ephrin, Dll4/Notch, and PlGF, among others[60, 61]. Inhibition of VEGFR2 (or VEGFA) may have some impact on these elements given pathway crosstalk, but is likely insufficient to prevent all escape mechanisms from occurring.

Despite these potential mechanisms of resistance, ramucirumab may have distinct mechanistic advantages compared to other anti-angiogenic modalities. For example, proteolytic processing of VEGFC and VEGFD allow their binding to VEGFR2 and promotion of angiogenesis, theoretically bypassing the effects of bevacizumab[62]. Of interest, in patients with mCRC treated with FOLFIRI and bevacizumab, VEGFC levels increased at time of disease progression[63]. Plasma VEGFD levels in pancreatic cancer patients were found to predict for benefit from bevacizumab when this agent was added to gemcitabine in the phase III study CALGB80303[64]. In the phase III MAX trial, tissue levels of VEGFD predicted for benefit from bevacizumab in combination with capecitabine and mitomycin C[65]. VEGFC and VEGFD signaling through VEGFR2, which may play a possible role in resistance to VEGFA targeted therapies, would be blocked with ramucirumab. The long half-life of ramucirumab would be expected to provide optimal VEGFR2 coverage, even if these ligands are up-regulated. However, VEGFA effects mediated via VEGFR1, would be blocked by bevacizumab or ziv-aflibercept, but not by ramicumerab. VEGFA can stimulate monocyte chemotaxis and inhibit dendritic cell maturation[20, 66, 67]. VEGFA can also induce proliferation, migration, and invasion of some tumor cells, at least in vitro[16, 68]. These effects on myeloid cells and tumor cells appear to be mediated by VEGFR1. Treatment with bevacizumab has been shown to reverse defective DC maturation and increase mature DCs in circulation[67]. Therefore, up-regulation of VEGFA as a result of VEGFR2 blockade by ramucirumab, may have effects on the immune system and angiogenesis by altering monocyte and dendritic cell function, and potentially even direct effects on the tumor cell.

Rational multi-target approaches to angiogenesis are needed to overcome resistance. The specificity, tolerability, and long half-life of ramucirumab suggest this agent will be well suited for combination anti-angiogenesis strategies. Predictive angiogenic biomarkers are also urgently needed to optimize patient selection, toxicity, and efficacy for the growing

number of anti-angiogenic agents. Considerable data has been published and reviewed regarding the performance of various candidate predictive markers. Biomaker analyses, from REGARD and from other ramucirumab studies, are eagerly awaited.

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Drug Summary Box

Drug name (generic)

Ramucirumab

Phase (for indication under discussion)

Phase III

Indication (specific to discussion)

Metastatic gastric or gastroesophageal junction adenocarcinoma

Pharmacology description/mechanism of action

Vascular endothelial growth factor receptor-2 IgG1 monoclonal antibody

Route of administration

8 mg/kg intravenously every 2 weeks

Pivotal trial(s)

REGARD: A phase III, randomized, double-blinded trial of ramucirumab and best supportive care versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- and/or fluoropyrimidine-containing combination therapy.

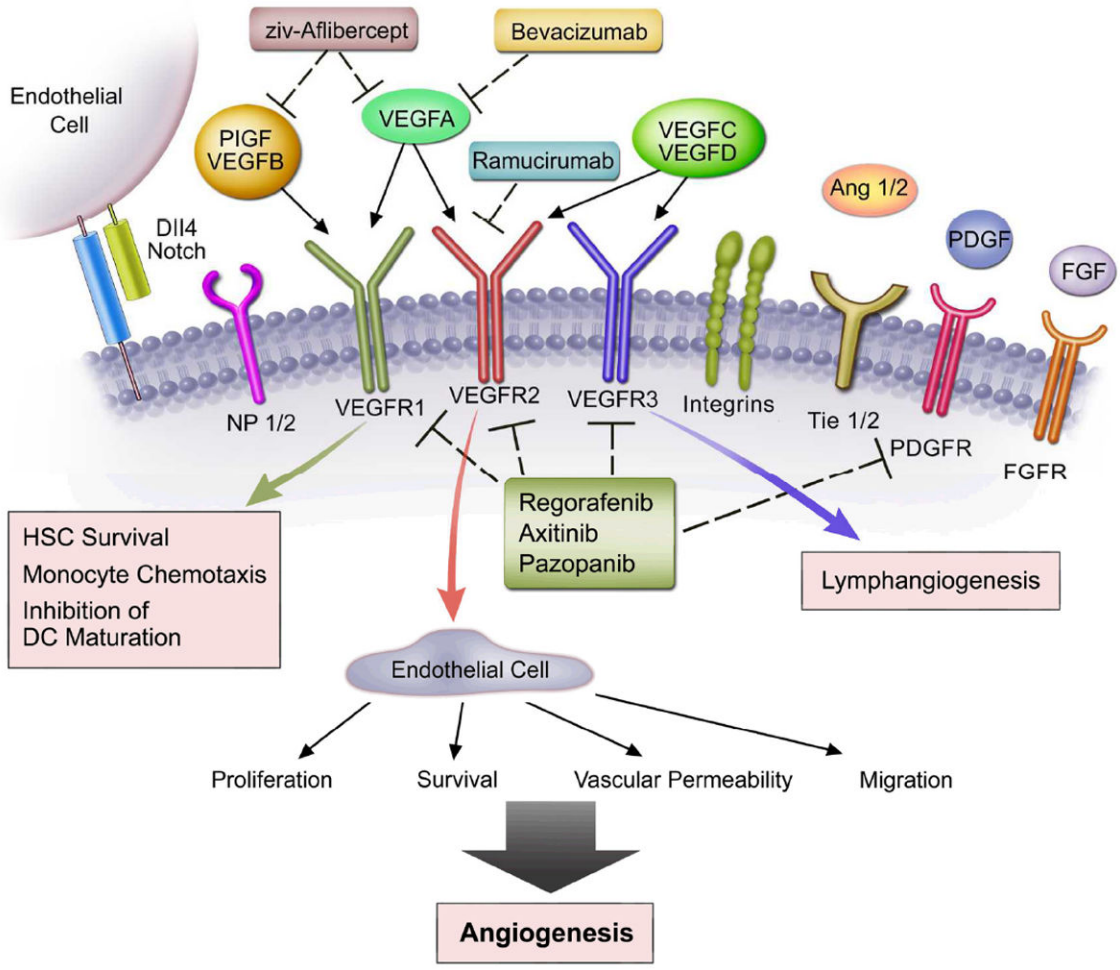

Figure 1.

Binding of VEGFR2 to its ligand results in intracellular transphosphorylation and activation of multiple downstream pathways including PLC-γ, MAPK, PI3K, Akt, and Src. Proangiogenic signals and VEGFR activity is modulated by several receptors including integrins, FGFR, PDGFR, Notch, and TIE2. Activation of VEGFR1 leads to downstream effects on HSC, DC maturation, and chemotaxis, while VEGFR3 promotes lymphangiogenesis. General drug targets are illustrated for aflibercept, bevacizumab, ramucirumab, and multiple RTK inhibitors.

Table 1

Comparison of therapies targeting VEGFR, with mechanism, and FDA approved indications.

Drug	Bevacizumab	ziv-Aflibercept	Regorafenib	Ramucirumab
Target(s)	VEGFA	VEGFA, VEGFB, PlGF	VEGFR1-3, BRAF, PDGFR, KIT, RET, TIE2	VEGFR2
Mechanism	Monoclonal antibody	Fusion protein of VEGFR1 and VEGFR2	Multikinase inhibitor	Monoclonal antibody
Dose	5-15 mg/kg IV Q2-3 weeks	4 mg/kg IV Q2 weeks	160 mg PO day 1-21 of 28 cycle	4-6 mg/kg Q2-3 weeks
FDA Approved indications	Metastatic CRC, NSCLC, metastatic RCC, Glioblastoma	Metastatic CRC	Metastatic CRC	NA

Table 2

Rates of selected adverse events observed in the REGARD trial, reported as percentages. Table adapted from Fuchs et al[50].

	Ramucirumab		Placebo	
Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Hypertension	16.1	7.6	7.8	2.6
Bleeding	12.7	3.4	11.3	2.6
Arterial thromboembolism	1.7	1.3	0	0
Venous thromboembolism	3.8	1.3	7	4.3
Proteinuria	3	0.4	2.6	0
GI perforation	0.8	0.8	0.9	0.9
Fistula	0.4	0.4	0.9	0.9
Infusion reaction	0.4	0	1.7	0
Heart Failure	0.4	0	0	0