

Clinical utility of ramucirumab in advanced gastric cancer

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Abstract: Gastric cancer is currently the third most common cause of cancer deaths worldwide. Prognosis remains poor with most patients presenting with advanced or metastatic disease. A better understanding of angiogenesis has led to the investigation of drugs that inhibit the vascular endothelial growth factor (VEGF) pathway including anti-VEGF antibody therapy (eg, bevacizumab), inhibitors of angiogenic receptor tyrosine kinases (eg, sunitinib, sorafenib, apatinib, regorafenib), and inhibitors of vascular endothelial growth factor receptors (VEGFRs) (eg, ramucirumab). Ramucirumab, a VEGFR-2 inhibitor, is the first anti-angiogenic agent approved by the US Food and Drug Administration for use in the treatment of advanced gastric cancers. This review will focus on the clinical utility and potential use of ramucirumab in advanced gastric cancer.

Keywords: ramucirumab, IMC-1121B, gastric cancer, vascular endothelial growth factor receptor-2, angiogenesis, targeted therapy

Introduction

Gastric cancer is currently the fifth most common cancer and the third most common cause of cancer deaths worldwide, accounting for almost 9% of all deaths from cancer.¹ Cure is possible for patients presenting with early stage disease, where surgical resection can be combined with adjuvant chemotherapy with or without radiotherapy. In this setting, improved outcomes have been demonstrated with the addition of perioperative chemotherapy,² post-operative chemotherapy,³⁻⁵ or post-operative combination chemotherapy with radiotherapy⁶ to radical surgery. However, almost two-thirds of patients will have locally advanced or metastatic disease at presentation which is currently considered incurable, and many of those who initially present with early disease will develop loco-regional or distant relapse sometime during the course of their illness. Despite incremental improvements in systemic chemotherapy over many years, the prognosis of patients with advanced gastric cancer remains poor, and until recently, little progress has been made in the development of new chemotherapeutic agents or molecularly targeted therapies that provide a meaningful impact on survival. This review will focus on the clinical utility and potential use of ramucirumab, a monoclonal antibody that blocks vascular endothelial growth factor receptor-2 (VEGFR-2), in advanced gastric cancer.

Advanced gastric cancer Prognosis

The prognosis of patients with advanced or metastatic gastric cancer is poor with a median survival of approximately 3–4 months with supportive care alone.⁷

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Systemic therapies are the mainstay of treatment with radiotherapy reserved for the management of symptomatic local problems. Traditional cytotoxic chemotherapies remain the backbone of treatment with increasing evidence for incorporation of targeted therapies, including human epidermal growth factor receptor-2 (HER-2) inhibitors and anti-angiogenic agents, in certain settings.

Management

First-line therapy

In the advanced disease setting, first-line treatment using combination palliative chemotherapy with a platinum (cisplatin or oxaliplatin) and fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine or S-1 [Taiho Pharmaceutical Co., Ltd, Tokyo, Japan]) doublet, or a triplet regimen with the addition of epirubicin or docetaxel, provides a survival benefit and improved quality of life. There is some regional variation in practice with recommended regimens varying between guidelines, although, final selection of a validated doublet or triplet regimen will depend on performance status, co-morbidities, organ function, access to drugs, and local practice. However, outcomes remain poor with a median overall survival (OS) of approximately 9–14 months in patients who receive first-line systemic chemotherapy.^{7–16} In the subset of patients with HER-2 positive advanced gastric cancer, the Phase III Trastuzumab in Gastric Cancer (ToGA) trial has shown that the anti-HER-2 monoclonal antibody, trastuzumab (Herceptin; Hoffman-La Roche Ltd., Basel, Switzerland), has a modest survival benefit in the HER-2

positive population when used in combination with platinum and fluoropyrimidine chemotherapy, when compared with the same chemotherapy alone.¹⁷

Second-line therapy

Patients with good Eastern Co-operative Group Performance Status (ECOG PS 0–1) and who develop disease progression following platinum and fluoropyrimidine-based chemotherapy should be offered second-line therapy based on evidence from three randomized, Phase III trials, demonstrating a modest survival benefit for docetaxel or irinotecan monotherapy, as compared with best supportive care.^{18–20} Summaries of these trials are shown in Table 1. A meta-analysis of these trials showed a significant reduction in the risk of death associated with the use of salvage chemotherapy in the second-line setting when compared with supportive care (hazard ratio [HR]: 0.64, 95% CI: 0.52–0.79, $P < 0.0001$).²¹ The optimal second-line regimen is unclear because there have been few trials that have directly compared the efficacy and safety of different second-line treatments. A Japanese trial that compared weekly paclitaxel (80 mg/m² on Day [D] 1, D8, and D15 and then every [q] 28 days [d]) versus irinotecan (150 mg/m² on D1 and D15 and then q28d) showed neither superiority for efficacy nor safety for paclitaxel.²² For patients who developed disease progression on S-1-based first-line chemotherapy, the TCOG GI-0801/BIRIP trial randomized 130 patients to combination cisplatin (30 mg/m² on D1 and then q14d) plus irinotecan (60 mg/m² on D1 and then q14d) or irinotecan alone (150 mg/m² on D1 and then q14d). This

Table 1 Summary of Phase III trials investigating second-line chemotherapy for advanced gastric cancer

Trial reference	Country	n	Regimens	Results			
				ORR (%)	DCR (%)	mPFS (months)	mOS (months)
Post-combination platinum and fluoropyrimidine-based chemotherapy							
Thuss-Patience et al ²⁰	Germany	40	BSC ± irinotecan (250 mg/m ² on D1 and then q21d, increasing to 350 mg/m ² C2 if tolerated)	0	53	2.5	4.0 vs 2.4; HR: 0.48, P=0.012
Kang et al ¹⁸	Korea	202	BSC ± chemotherapy (irinotecan 150 mg/m ² on D1 and then q14d or docetaxel 60 mg/m ² on D1 and then q21d)	NA	NA	NA	5.3 vs 3.8; HR: 0.657, P=0.007
Ford et al ¹⁹	UK	168	BSC ± docetaxel (75 mg/m ² on D1 and then q21d)	7	53	2.8	5.2 vs 3.6; HR: 0.67, P=0.01
Hironaka et al ²²	Japan	223	Weekly paclitaxel (80 mg/m ² on D1, D8, and D15 and then q28d) vs biweekly irinotecan (150 mg/m ² on D1 and D15 and then q28d)	20.9 vs 13.6 (P=0.24)	NA	3.6 vs 2.3; HR: 1.14, P=0.33	9.5 vs 8.4; HR: 1.13, P=0.38
Post-S-1-based chemotherapy							
Higuchi et al ²³	Japan	130	Irinotecan (60 mg/m ²) + cisplatin (30 mg/m ²) q2w vs irinotecan (150 mg/m ² q2w)	22 vs 16 (P=0.4975)	75 vs 54 (P=0.0162)	3.8 vs 2.8; HR: 0.68, P=0.0398	10.7 vs 10.1; HR: 1.00, P=0.9823

Abbreviations: BSC, best supportive care; C, cycle; d, days; D, day; DCR, disease control rate; HR, hazard ratio; mOS, median overall survival; mPFS, median progression free survival; NA, not available; ORR, overall response rate; q, every.

showed that cisplatin and irinotecan improved progression free survival (PFS) (3.8 vs 2.8 months; HR: 0.68, $P=0.0398$) but not OS (10.7 vs 10.1 months; HR: 1.00, $P=0.9823$).²³

Molecularly targeted treatments

A number of molecularly targeted therapies have been tested in advanced gastric cancer including epidermal growth factor receptor (EGFR) inhibitors, cetuximab (Erbix; Merck Serono, Darmstadt, Germany)²⁴ and panitumumab (Vectibix; Amgen Inc., Thousand Oaks, CA, USA),²⁵ and the mTOR inhibitor, everolimus (Afinitor; Novartis International AG, Basel, Switzerland),²⁶ none of which demonstrated a survival benefit in Phase III trials. A second-line Japanese/Korean study of irinotecan with or without nimotuzumab is ongoing (NCT01813253). An OS advantage was also not demonstrated in the TyTAN study, which is a second-line, Phase III trial of the HER-2 tyrosine kinase inhibitor, lapatinib (Tykerb; Glaxo-SmithKline plc, London, UK), in combination with paclitaxel.²⁷ Phase III trials investigating trastuzumab emtansine (Kadcyla TDM-1; Hoffman-La Roche Ltd) in the GATSBY trial and pertuzumab (Perjeta; Hoffman-La Roche Ltd) in the JACOB trial are ongoing.²⁸ Trials investigating mesenchymal epithelial transition factor (MET) pathway inhibitors, rilotumumab (AMG102; Amgen), have been halted due to an excess number of deaths related to the study drug and a randomized Phase II trial of mFOLFOX6 (oxaliplatin 85 mg/m² D1, leucovorin 400 mg/m² D1, 5-FU bolus 400 mg/m² D1, and 5-FU infusion 2,400 mg/m² over 48 hours, and then q14d) with or without onartuzumab (MetMab; Hoffman-La Roche Ltd) did not improve PFS.²⁹ A Phase III study investigating a poly ADP ribose polymerase inhibitor olaparib in combination with paclitaxel chemotherapy is ongoing (NCT01924533) following Phase II data in the second-line which showed an OS benefit in the olaparib group.³⁰

Two studies that examined the role of bevacizumab (Avastin; Hoffman-La Roche Ltd) directed against the vascular endothelial growth factor (VEGF) did not demonstrate a survival benefit when used in combination with first-line chemotherapy.^{31,32} However, there is evidence from two Phase III studies of the VEGFR-2 inhibitor, ramucirumab,^{33,34} and one Phase III study of the VEGFR-2 tyrosine kinase inhibitor, apatinib,³⁵ to suggest that VEGFR-2 is an important, clinically relevant target in advanced gastric cancer.

Anti-angiogenesis therapy

Tumor angiogenesis and the VEGF pathway

Inducing angiogenesis to support the tumor-associated neovasculature is considered a key hallmark of cancer.³⁶

The VEGFs that mediate these proangiogenic effects are homodimeric glycoproteins that include VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor.^{37,38} The angiogenic process is complex and involves the interaction between VEGF and its receptors including VEGF-1, VEGF-2, and VEGF-3. VEGFR-2 is a type II cell surface transmembrane kinase receptor that is mainly expressed on vascular endothelial cells.³⁹ Binding of VEGF to VEGFR-2 results in phosphorylation and activation of multiple downstream pathways, activating a signaling cascade which promotes tumor angiogenesis.⁴⁰ Despite a tenfold lower binding affinity of VEGF-A to VEGFR-2 compared to VEGFR-1, VEGFR-2 is considered to be the main driver of angiogenesis because the phosphorylated downstream targets are more potent signaling intermediaries.^{39,41} Therefore, it has been a key target for drug development. The VEGF pathway has also been closely investigated to help identify potential therapeutic strategies that may inhibit angiogenesis and tumor growth in order to develop new treatments. Strategies developed to inhibit the VEGF pathway are shown in Figure 1 and include anti-VEGF antibody therapy (eg, bevacizumab), inhibitors of angiogenic receptor tyrosine kinases (eg, sunitinib, pazopanib, sorafenib, regorafenib), inhibitors of VEGFR-2 tyrosine kinases (eg, apatinib), and anti-VEGFR antibody therapy (eg, ramucirumab). Currently approved anti-angiogenic agents for various tumor types including lung, renal, and colon cancers include bevacizumab, sunitinib, pazopanib, and sorafenib. Increased expression of VEGF in tumor and serum has been shown in gastric cancer which is associated with poor prognosis and more aggressive disease.^{42,43} This suggests that angiogenesis may be an important target for gastric cancer and that inhibitors of the VEGF pathway may be a useful anti-tumor strategy.

Anti-VEGF antibody (bevacizumab)

The Avastin in Gastric Cancer (AVAGAST) study³¹ was a large (n=774), multicenter, international, Phase III trial of capecitabine and cisplatin chemotherapy with (n=387) or without (n=387) bevacizumab (Avastin; Hoffman-La Roche Ltd). This study showed a better response rate (46% vs 37%; $P=0.0315$) and longer PFS (6.7 vs 5.3 months; HR: 0.8, 95% CI: 0.68–0.93, $P=0.0037$) in the bevacizumab group. However, this study did not meet its primary endpoint of improved OS (12.1 vs 10.1 months; HR: 0.87, 95% CI: 0.73–1.03, $P=0.1002$). Interestingly, on subgroup analysis there were differences in efficacy across the geographic regions involved in the trial (Asia, Europe, and Pan-America) with superior efficacy in Pan-America compared to Asia. However, it is unclear whether these differences are due to

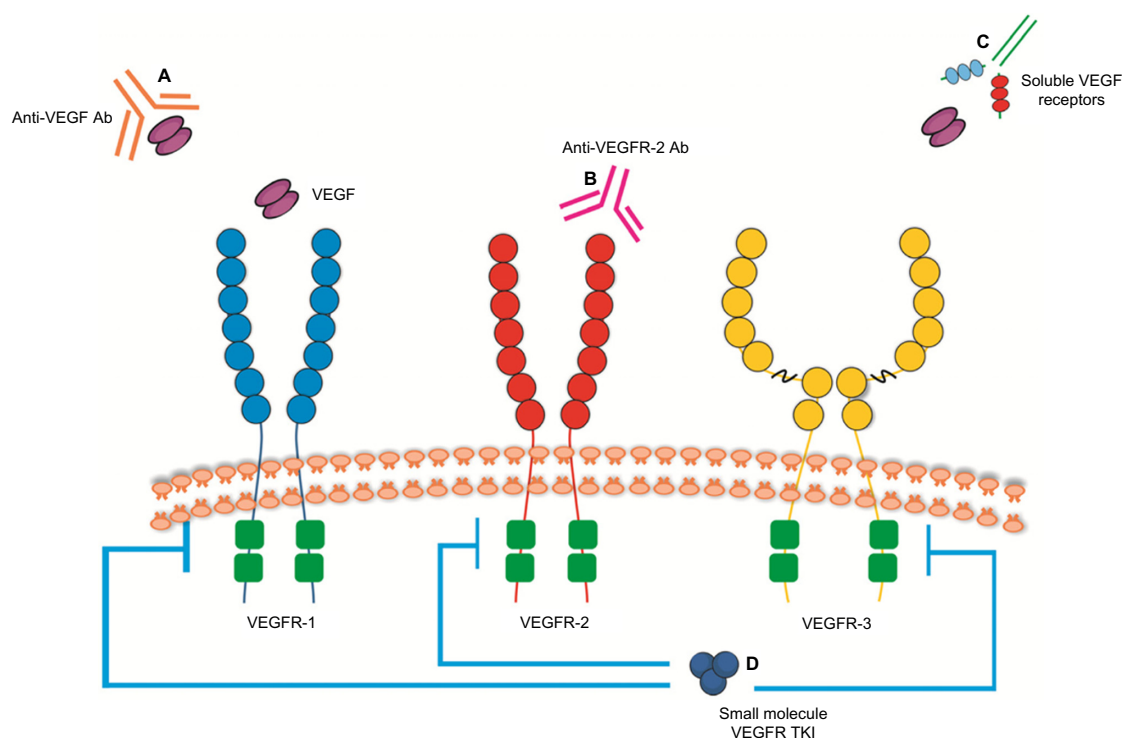


Figure 1 Strategies to inhibit VEGF pathway signaling.

Notes: (A) anti-VEGF antibody (eg, bevacizumab); (B) anti-VEGFR-2 antibody (eg, ramucirumab); (C) soluble VEGF receptors (eg, aflibercept); and (D) VEGF receptor tyrosine kinase inhibitors (eg, sunitinib, sorafenib, regorafenib, apatinib [anti-VEGFR-2 TKI]).

Abbreviations: Ab, antibody; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

pharmacogenetics or variations in clinical practice such as the use of subsequent lines of chemotherapy after initial progression on first-line therapy. This trial was followed by the AVATAR study, which was a randomized, Phase III trial of similar design, in Chinese patients, which did not show any improvement in OS (10.5 vs 11.4 months; HR: 1.11, $P=0.56$) nor PFS (6.3 vs 6.0 months; HR: 0.89, $P=0.47$).³² Based on the results of these studies, there is currently no role for anti-VEGF monoclonal antibodies such as bevacizumab in advanced gastric cancer outside of clinical trials.

Angiogenic receptor tyrosine kinases (sunitinib, sorafenib)

Sunitinib (Sutent; Pfizer Inc., New York, NY, USA) and sorafenib (Nexavar; Bayer AG, Leverkusen, Germany) are small molecule, multi-targeted, tyrosine kinase inhibitors that inhibit VEGF-1, 2, and 3. A second-line Phase II trial, for advanced gastric cancer, randomized patients to docetaxel (60 mg/m² D1 and then q21d), with or without sunitinib (37.5 mg oral daily). This showed a higher objective response rate but the differences in median time to progression (3.9 vs 2.6 months, $P=0.206$) and median OS (8.0 vs 6.6 months, $P=0.802$) were not statistically significant.⁴⁴ Sorafenib (400 mg oral twice daily) has been studied in combination with docetaxel (75 mg/m² D1 and then q21d) and cisplatin

(75 mg/m² D1 and then q21d) in a first-line, Phase II study, in advanced gastric cancer. This study showed a median survival of 13.6 months, objective tumor response was seen in 41%, with the main grade 3/4 adverse event being neutropenia.⁴⁵ Regorafenib (160 mg po D1-21 and then q28d) has shown sufficient activity and safety in a randomized, placebo controlled, Phase II trial (INTEGRATE), with a longer PFS (11.1 vs 3.9 weeks; HR: 0.41, $P<0.0001$) demonstrated to warrant consideration for Phase III evaluation.⁴⁶

Anti-VEGFR-2 receptor tyrosine kinases (apatinib)

Apatinib is a small molecule tyrosine kinase inhibitor that targets VEGFR-2. Phase II studies of advanced gastric cancer in chemotherapy refractory patients showed promising activity with improvements in PFS and OS⁴⁷ which have been confirmed in a recently completed Phase III study, presented in abstract form, demonstrating an improvement in median OS (195 vs 140 d; HR: 0.71, 95% CI: 0.54–0.94, $P<0.016$).³⁵ The full manuscript is keenly awaited.

Anti-VEGFR-2 antibody (ramucirumab)

Ramucirumab (Cyramza™; Eli Lilly and Company, Indianapolis, IN, USA, IMC-1121B, LY30009806) is a novel,

fully humanized, IgG1 monoclonal antibody that binds to the extracellular domain of VEGFR-2.⁴¹ This specifically and potentially blocks with high affinity the binding of VEGFR-2 to its ligands including VEGF-A, VEGF-C, and VEGF-D thus inhibiting receptor activation of downstream VEGF signaling pathways resulting in reduced tumor neovascularization and growth.⁴¹ Ramucirumab is the first monoclonal antibody that targets angiogenesis to show a survival benefit in advanced gastric cancer. It has also been shown to improve OS and PFS in Phase III trials of non-small-cell lung cancer (NSCLC) and colorectal cancer but not of breast cancer or hepatocellular carcinoma (HCC) (Table 2).^{48–51}

Pharmacology

Ramucirumab is administered intravenously with dosing based on body weight. It is mixed with normal saline for administration. At the standard recommended dose of 8 mg/kg administered by intravenous infusion over 60 minutes q2 weeks, the pharmacokinetic profile of ramucirumab at steady state is characterized by a half-life of 200–300 hours.⁵²

Preclinical studies

The development of anti-VEGFR-2 antibodies specific for murine (fetal liver kinase 1, Flk-1) and human (kinase-insert domain receptor, KDR) forms of the VEGFR-2 was required due to species-specific differences. DC101, a mouse-specific anti-Flk-1 monoclonal antibody, was shown to potentially block VEGF receptor binding to its ligands in vitro interfering with VEGF pathway signaling.⁵³ DC-101 was then shown in mouse xenograft models to inhibit tumor growth in vivo supporting the therapeutic strategy of using an anti-VEGFR-2 antibody to suppress tumor-induced neovascularization in angiogenesis-dependent tumors.⁵⁴ A phage display library and standard hybridoma technology were used to develop a high-affinity anti-KDR antibody which was shown to block the VEGF–KDR interaction thus inhibiting receptor activation and associated downstream signaling pathways.^{55,56} A minimum trough level of 20 µg/mL was determined in xenograft models to have sufficient anti-tumor activity for use as a target for subsequent clinical trials.⁵⁷

Phase I/II studies

An initial Phase I safety and dose-finding study was conducted in 37 patients with advanced solid malignancies including patients with gastric cancer who were refractory to treatment and did not have any standard treatment options (Table 3).⁵² Using a standard 3+3 dose escalation trial design, after evaluating seven dose levels between 2 mg/kg and 16 mg/kg, this study found a maximum tolerated dose of 13 mg/kg weekly although pharmacokinetic studies demonstrated that clearance was saturated at 8 mg/kg. The predefined C_{min} (20 µg/mL) based on preclinical xenograft data was met in all patients. This study showed a safety profile that was similar to bevacizumab with grade 3 adverse events that included hypertension, deep venous thrombosis, vomiting, and proteinuria. Of the 27 patients who had measurable disease, four patients had partial responses lasting at least 12 weeks including one patient with gastric cancer and 23 patients who had stable disease as their best response. No patient had a complete response. Another Phase I study of 14 patients that examined 2-weekly dosing at 6–10 mg/kg showed that the target trough level of 20 µg/mL was met.⁵⁸ Based on these studies, ramucirumab was evaluated at the 8 mg/kg dose q2 weeks in ongoing studies.

Phase II studies of ramucirumab in combination with paclitaxel and docetaxel in patients with gastric cancer have been published in abstract form.^{59,60} These studies showed that co-administration of ramucirumab with paclitaxel or docetaxel chemotherapy does not affect the pharmacokinetics of the chemotherapy agents and the side effects reported were consistent with the safety profiles of the individual drugs.

A Phase II study of mFOLFOX6 (oxaliplatin 85 mg/m² D1, leucovorin 400 mg/m² D1, 5-FU bolus 400 mg/m² D1, and 5-FU infusion 2,400 mg/m² over 48 hours, and then q14d) plus ramucirumab (8 mg/kg q14d) versus mFOLFOX6 plus placebo in first-line treatment of advanced gastric and esophageal cancer accrued 168 patients and showed a median PFS of 6.4 versus 6.7 months (HR: 0.98, $P=0.89$) and median OS of 11.7 versus 11.5 months (HR: 1.08).⁶¹ Disease control rate was better in the ramucirumab group (85% vs 67%). Subgroup analysis by tumor site showed that for patients with gastric cancer, the median PFS was 8.7 versus 7.1 months

Table 2 Summary of Phase III trials of ramucirumab in other tumor types

Trial ID	Tumor	Line	n	Regimens	Status
NCT01168973 ⁴⁸	NSCLC	Second	1,253	Ramucirumab + docetaxel vs placebo + docetaxel	Improved OS and PFS
NCT01183780 ⁵⁰	Colon	Second	1,050	Ramucirumab + FOLFIRI vs placebo + FOLFIRI	Improved OS
NCT01140347 ⁵¹	HCC	Second	565	Ramucirumab + BSC vs placebo + BSC	Did not meet primary end point OS
NCT00703326 ⁴⁹	Breast	First	1,144	Ramucirumab + docetaxel vs placebo + docetaxel	Did not meet primary end point PFS

Abbreviations: BSC, best supportive care; FOLFIRI, fluorouracil and irinotecan; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression free survival.

Table 3 Summary of trials investigating ramucirumab for advanced gastric cancer

Trial ID	Phase	Line	Indication	n	Regimens	Results			
						ORR (%)	DCR (%)	mPFS (months)	mOS (months)
NCT00793975 ⁵²	I	Last	Solid tumors	37	Ramucirumab	NA	73	NA	NA
NCT00786383	I	Last	Solid tumors	25	Ramucirumab	NA	NA	NA	NA
NCT01005355	I	Last	Solid tumors	17	Ramucirumab	NA	NA	NA	NA
NCT01253525	I	Last	Gastric	6	Ramucirumab + paclitaxel	NA	NA	NA	NA
NCT01515306	I	Last	Solid tumors	40	Ramucirumab + paclitaxel	NA	NA	NA	NA
NCT01567163	I	Last	Solid tumors	22	Ramucirumab + docetaxel	NA	NA	NA	NA
NCT01634555	I	Last	Solid tumors	29	Ramucirumab + FOLFIRI	NA	NA	NA	NA
NCT01246960 ⁶¹	II	First	Esophageal + gastric	168	Ramucirumab + FOLFOX	45 vs 46	85 vs 67	6.4 vs 6.7; HR: 0.98, <i>P</i> =0.89	11.7 vs 11.5; HR: 1.08
NCT00917384 (REGARD) ³³	III	Second	Gastric	355	Ramucirumab + BSC (n=238) vs placebo + BSC (n=117)	3 vs 3	49 vs 23	2.1 vs 1.3; HR: 0.48, <i>P</i> <0.0001	5.2 vs 3.8; HR: 0.78, <i>P</i> =0.047
NCT01170663 (RAINBOW) ³⁴	III	Second	Gastric	665	Ramucirumab + paclitaxel (n=330) vs placebo + paclitaxel (n=335)	28 vs 16	80 vs 64	4.4 vs 2.9; HR: 0.634, <i>P</i> <0.0001	9.6 vs 7.4; HR: 0.807, <i>P</i> =0.0169

Abbreviations: BSC, best supportive care; FOLFIRI, fluorouracil and irinotecan; FOLFOX, fluorouracil and oxaliplatin; ORR, overall response rate; DCR, disease control rate; mPFS, median progression free survival; HR, hazard ratio; mOS, median overall survival; NA, not available.

(HR: 0.77, *P*=0.28) and OS 14.6 versus 12.5 months. These data suggest that mFOLFOX6 may be worth examining in a Phase III trial as first-line treatment for patients with advanced gastric cancer only.

Efficacy studies, including any combinational studies

Phase III studies

There have been six Phase III trials of ramucirumab completed to date including studies in breast cancer, hepatocellular cancer, colorectal cancer, NSCLC, as well as two in advanced gastric cancer (Table 2).

The landmark REGARD trial (NCT00917384) of ramucirumab was the first study of an anti-angiogenic targeted drug to demonstrate a survival benefit in patients with advanced gastric cancer.³³ This was a large, multicenter, randomized, Phase III trial designed to evaluate the efficacy of second-line ramucirumab monotherapy for advanced gastric cancer (Table 3). Patients who were ECOG PS 0–1 were required to have disease progression within 4 months of first-line metastatic treatment or 6 months of adjuvant treatment with platinum or fluoropyrimidine-based chemotherapy. Three hundred and fifty-five patients received best supportive care and were randomized 2:1 to receive either ramucirumab (8 mg/kg intravenous infusion q2 weeks) or placebo until disease progression or unacceptable toxicity. No treatment cross-over was permitted. Intention to treat analysis was used. The median treatment duration was 8 weeks in the ramucirumab group and 6 weeks in the placebo group. There was an improvement

in PFS in the ramucirumab treated group (HR: 0.483, 95% CI: 0.376–0.620, *P*<0.0001) with median PFS of 2.1 months for ramucirumab and 1.3 months for placebo. There was an improvement in OS in the ramucirumab treated group (HR: 0.776, 95% CI: 0.603–0.998, *P*=0.047) with a median OS of 5.2 months for the ramucirumab and 3.8 months for the placebo treated groups, respectively. The objective response rate based on investigator-determined RECIST (Response Evaluation Criteria in Solid Tumors) criteria was 3% in both groups. However, the disease control rate was higher for ramucirumab (49%) than placebo (23%). The authors concluded that VEGFR-2 is an important target in gastric cancer given the benefits in OS seen in patients with advanced gastric cancer who have progressed after first-line treatment with platinum or fluoropyrimidine-based chemotherapy.

The RAINBOW trial (NCT01170663) was a large, international, multicenter, randomized, double-blind, placebo-controlled, Phase III trial designed to evaluate the use of paclitaxel with or without ramucirumab in patients with previously treated advanced gastric cancer.³⁴ Patients were required to have disease progression within 4 months of completing first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline). Six hundred and sixty-five patients received paclitaxel (80 mg/m² on D1, D8, D15, and then q28d) and were randomized to receive either ramucirumab, 8 mg/kg D1 and then q2 weeks (n=330), or placebo (n=335) until disease progression, unacceptable toxicity, or withdrawal of consent. No treatment cross-over was permitted. Intention to treat analysis

was used. The median treatment duration was 18.0 weeks in the paclitaxel plus ramucirumab group and 12.0 weeks in the paclitaxel plus placebo group. The median PFS was 4.4 months for the paclitaxel plus ramucirumab and 2.9 months for the paclitaxel plus placebo groups (HR: 0.635, 95% CI: 0.536–0.752, $P<0.0001$). The median OS was 9.6 months for paclitaxel plus ramucirumab and 7.4 months for paclitaxel plus placebo arms of the study (HR: 0.807, 95% CI: 0.678–0.962, $P=0.017$). The objective response rate (28% vs 16%, $P=0.0001$) and the disease control rate (80% vs 64%, $P<0.001$), based on investigator-determined RECIST assessments, were both better in the paclitaxel plus ramucirumab group.

The RAINBOW trial is the largest trial of second-line therapy in gastric cancer to date. Although the median OS of patients treated with paclitaxel plus ramucirumab in the RAINBOW trial was higher than the median OS of patients treated with ramucirumab monotherapy in the REGARD trial, the REGARD trial included more heavily pretreated patients and did not include any concurrent chemotherapy. As these trials are not directly comparable, the additional benefit of adding chemotherapy to ramucirumab as second-line therapy is not known and the optimal treatment strategy remains uncertain. However, these studies compare favorably with second-line studies of chemotherapy alone. Ongoing trials investigating ramucirumab in advanced gastric cancer, outlined in Table 4, include an international, multicenter, Phase III trial of cisplatin plus capecitabine with, or without, ramucirumab as first-line treatment for gastric cancer (NCT02314117).

A summary of Phase III trials of ramucirumab in other tumor types are summarized in Table 2. A survival benefit was demonstrated for NSCLC and colon cancer but not for HCC or breast cancer.^{48–51} Interestingly, the subset of patients with elevated baseline alpha-fetoprotein who received treatment with ramucirumab for advanced HCC did show a

survival benefit making this a promising potential predictive biomarker for these patients. It is not clear if the absence of a survival benefit seen in HER-2 negative metastatic breast cancer, when ramucirumab was added to first-line docetaxel chemotherapy, is due to the choice of chemotherapy partner or a more general lack of efficacy of anti-angiogenic strategies for this tumor type.

Safety and tolerability Toxicity

Overall, ramucirumab is well tolerated (Tables 5 and 6). In the REGARD trial of ramucirumab versus placebo, the most frequent grade 3 or above adverse events were hypertension (8% vs 3%), abdominal pain (6% vs 3%), and arterial thromboembolism (1% vs 0%). There was no increased risk of grade 3 fatigue (6% vs 10%), decreased appetite (3% vs 3%), vomiting (3% vs 4%), anemia (6% vs 8%), bleeding (3% vs 3%), venous thrombosis (1% vs 4%), proteinuria (<1% vs 0%), gastrointestinal perforation (<1% vs <1%), fistula formation (<1% vs <1%), or infusion-related reactions (0% vs 0%) associated with ramucirumab use. More patients had to discontinue the drug due to an adverse event in the ramucirumab group compared to placebo (10% vs 6%). In the RAINBOW trial of paclitaxel plus ramucirumab versus paclitaxel, the most frequent grade 3 or above adverse events were neutropenia (41% vs 19%), leucopenia (17% vs 7%), hypertension (14% vs 2%), abdominal pain (6% vs 4%), and fatigue (12% vs 5%). The rate of febrile neutropenia was similar between the two treatment groups (3% vs 2%). There was no increased rate of treatment discontinuation or treatment-related death in the paclitaxel plus ramucirumab group. Further safety and efficacy data based on the real world use of ramucirumab would be informative as this treatment has only a modest survival benefit. In particular, safety issues such as the use of ramucirumab in patients with the primary tumor in-situ ought to be examined given the risks

Table 4 Ongoing clinical trials investigating ramucirumab for advanced gastric cancer

Trial ID	Phase	Line	Intervention and schedule	Recruitment	Projected accrual	Country
NCT01682135	I	Last line	Ramucirumab	Closed to recruitment	26	Chinese study
NCT02082210	Ib/II	Advanced cancers	Ramucirumab + LY2875358	Recruiting	70	US study
NCT01983878	II	Second line	Ramucirumab	Closed to recruitment	33	Japanese study
NCT02359058	I	First line	Ramucirumab + other anti-cancer drugs ^a	Not yet open	18	Japanese study
NCT02317991	II	Second line	Ramucirumab + nab-paclitaxel	Not yet open	65	US study
NCT02314117	III	First line	Cisplatin + capecitabine ± ramucirumab	Recruiting	616	International study

Notes: ^aGroup 1: capecitabine + cisplatin, group 2: S-1 + cisplatin, group 3: S-1 + oxaliplatin.

Table 5 Adverse events, according to grade

	Ramucirumab (n=236)		Placebo (n=115)	
	Any event	Grade ≥ 3	Any event	Grade ≥ 3
Fatigue*	84 (36%)	15 (6%)	46 (40%)	11 (10%)
Abdominal pain†	68 (29%)	14 (6%)	32 (28%)	3 (3%)
Decreased appetite	57 (24%)	8 (3%)	26 (23%)	4 (3%)
Vomiting	47 (20%)	6 (3%)	29 (25%)	5 (4%)
Constipation	36 (15%)	1 (<1%)	26 (23%)	3 (3%)
Anaemia‡	35 (15%)	15 (6%)	17 (15%)	9 (8%)
Dysphagia	25 (11%)	5 (2%)	12 (10%)	5 (4%)
Dyspnoea	22 (9%)	4 (2%)	15 (13%)	7 (6%)
Adverse events of special interest				
Hypertension [§]	38 (16%)	18 (8%)	9 (8%)	3 (3%)
Bleeding or haemorrhage	30 (13%)	8 (3%)	13 (11%)	3 (3%)
Arterial thromboembolism [¶]	4 (2%)	3 (1%)	0	0
Venous thromboembolism ^{**}	9 (4%)	3 (1%)	8 (7%)	5 (4%)
Proteinuria	7 (3%)	1 (<1%)	3 (3%)	0
Gastrointestinal perforation	2 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
Fistula formation	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Infusion-related reaction	1 (<1%)	0	2 (2%)	0
Cardiac failure	1 (<1%)	0	0	0

Notes: Data are n (%), unless otherwise indicated. *Includes asthenia. †includes upper or lower abdominal pain and hepatic pain. ‡Includes decreased haematocrit and red blood-cell count. §Includes increased blood pressure. ||Includes epistaxis, gastric haemorrhage, gastrointestinal haemorrhage, gingival bleeding, haematemesis, haematoma, haemorrhage, and upper gastrointestinal haemorrhage. ¶Includes angina pectoris, cardiac arrest, cerebral ischaemia, cerebrovascular accident, myocardial infarction, and myocardial ischaemia. **Includes pulmonary embolism, deep vein thrombosis, thrombosis and venous thrombosis in a limb. Reprinted from The Lancet, volume 283, Fuchs CS, Tomasek J, Yong CJ, et al, Ramucirumab monotherapy for previously treated advanced gastric cancer or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multi-centre, placebo-controlled, phase 3 trial, pages 31–39, Copyright © 2014, with permission from Elsevier.³³

of bowel perforation with some of the other anti-angiogenic drugs like bevacizumab.

Patient reported outcomes

Quality of life was examined as a secondary outcome in the REGARD study.³³ The European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire C30 (QLQ-C30 version 3.0) was completed by patients at baseline, 6, 12, and 18 weeks of treatment. Although 97% of patients in the best supportive care (BSC) plus ramucirumab group and 94% of patients in the BSC plus placebo group had baseline quality of life data, only 48% of patients receiving ramucirumab and 25% of patients receiving placebo had quality of life data obtained at week 6 because of treatment discontinuation mostly due to disease progression. Although there was a greater proportion of patients who reported stable or improved global quality of life in the ramucirumab group, this was not statistically significant when compared with the placebo treated group ($P=0.23$). Patients in the ramucirumab group maintained ECOG PS longer than the placebo group (5.1 vs 2.4 months, HR: 0.59, $P=0.002$). Given the poor prognosis of patients with advanced gastric cancer, patient reported outcomes may need to be collected more frequently.

There were only preliminary quality of life results reported within the primary manuscript of the RAINBOW

study which was a secondary outcome measure of the study.³⁴

The EORTC QLQ-C30 version 3.0 and the EuroQoL five-dimensional, three-level health status questionnaire (EQ-5D-3L) were completed by patients at baseline, q42d while on study and at study discontinuation. Ninety-eight percent of patients in both groups had baseline quality of life data and 64% of patients receiving ramucirumab plus paclitaxel and 61% of patients receiving placebo plus paclitaxel had end of treatment quality of life data. The baseline and end of treatment quality of life scores from the EORTC QLQ-C30 were similar in both treatment groups and we await further details to be published in a subsequent manuscript.

Potential place in therapy

There has been no universally accepted approach for second-line treatment of advanced gastric cancer. However, recent Phase III studies and meta-analyses of chemotherapy as well as Phase III studies of ramucirumab would suggest that appropriate patients with good performance status should be considered and that they do benefit from treatment with active systemic therapy, after progression on standard first-line chemotherapy.^{18–21,33,34} Based on the results of the REGARD study, the US Food and Drug Administration approved ramucirumab, in April 2014, as monotherapy, in patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who have progressed following treatment

Table 6 Treatment related side effects occurring in at least 10% of patients on ramucirumab plus paclitaxel, irrespective of causality

	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Any patients with a treatment-emergent adverse event	57 (17%)	155 (47%)	73 (22%)	39 (12%)	116 (35%)	128 (39%)	27 (8%)	51 (16%)
Non-haematological adverse events								
Fatigue*	147 (45%)	39 (12%)	0	0	126 (38%)	18 (5%)	0	0
Neuropathy*	123 (38%)	27 (8%)	0	0	104 (32%)	15 (5%)	0	0
Decreased appetite	121 (37%)	10 (3%)	0	0	92 (28%)	13 (4%)	0	0
Abdominal pain*	98 (30%)	20 (6%)	0	0	87 (26%)	10 (3%)	1 (<1%)	0
Nausea	109 (33%)	5 (2%)	1 (<1%)	0	100 (30%)	8 (2%)	0	0
Alopecia	107 (33%)	0	0	0	126 (38%)	1 (<1%)	0	0
Diarrhoea	94 (29%)	12 (4%)	0	0	71 (22%)	4 (1%)	1 (<1%)	0
Epistaxis	100 (31%)	0	0	0	23 (7%)	0	0	0
Vomiting	78 (24%)	9 (3%)	1 (<1%)	0	56 (17%)	12 (4%)	0	0
Peripheral oedema	77 (24%)	5 (2%)	0	0	43 (13%)	2 (<1%)	0	0
Hypertension	32 (10%)	46 (14%)	0	0	8 (2%)	8 (2%)	0	0
Constipation	70 (21%)	0	0	0	69 (21%)	2 (<1%)	0	0
Stomatitis	62 (19%)	2 (<1%)	0	0	22 (7%)	2 (<1%)	0	0
Pyrexia	56 (17%)	3 (<1%)	0	0	36 (11%)	1 (<1%)	0	0
Proteinuria	50 (15%)	4 (1%)	0	0	20 (6%)	0	0	0
Malignant neoplasm progression	5 (2%)	16 (5%)	4 (1%)	27 (8%)	1 (<1%)	24 (7%)	1 (<1%)	34 (10%)
Weight decreased	39 (12%)	6 (2%)	0	0	45 (14%)	4 (1%)	0	0
Dyspnoea	34 (10%)	8 (2%)	0	0	29 (9%)	2 (<1%)	0	0
Rash*	42 (13%)	0	0	0	31 (9%)	0	0	0
Cough	40 (12%)	0	0	0	25 (8%)	0	0	0
Back pain	35 (11%)	4 (1%)	0	0	35 (11%)	5 (2%)	0	0
Hypoalbuminaemia*	32 (10%)	4 (1%)	0	0	13 (4%)	2 (<1%)	0	1 (<1%)
Myalgia	34 (10%)	0	0	0	32 (10%)	1 (<1%)	0	0
Ascites	21 (6%)	11 (3%)	1 (<1%)	0	14 (4%)	13 (4%)	0	0
Headache	32 (10%)	0	0	0	21 (6%)	1 (<1%)	0	0
Haematological adverse events								
Neutropenia*	45 (14%)	71 (22%)	62 (19%)	0	40 (12%)	51 (16%)	11 (3%)	0
Anaemia*	84 (26%)	30 (9%)	0	0	85 (26%)	31 (9%)	3 (<1%)	0
Leucopenia*	54 (17%)	52 (16%)	5 (2%)	0	47 (14%)	19 (6%)	3 (<1%)	0
Thrombocytopenia*	38 (12%)	5 (2%)	0	0	14 (4%)	6 (2%)	0	0

Notes: Data are number (%), unless otherwise stated. *Consolidated adverse event category comprising synonymous MedDRA preferred terms. Reprinted from The Lancet Oncology, volume 15, Wilke H, Muro K, Van Cutsem E, 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. pages 1224–1235, Copyright © 2014, with permission from Elsevier.³⁴

with fluoropyrimidine or platinum-based chemotherapy. Its approval was subsequently extended to ramucirumab in combination with paclitaxel chemotherapy in November 2014 based on the results of the RAINBOW study.⁶² In the absence of comparative studies, ramucirumab alone or in combination with paclitaxel provides an alternative treatment option to docetaxel or irinotecan chemotherapy in the second-line setting given the similar modest survival benefits and potentially a more favorable side effect profile. However, there have been no comparative trials of ramucirumab versus chemotherapy and its routine use may be limited by access when compared with the availability of inexpensive chemotherapy options such as the taxanes or irinotecan, particularly in health systems with resource constraints or where cost effectiveness

is an important consideration for reimbursement. Given that patients included in the REGARD study had a good performance status (ECOG PS 0–1) and organ function, the more meaningful clinical benefit seen with using ramucirumab in combination with paclitaxel chemotherapy in the second-line setting as shown in the RAINBOW study makes this the more preferred approach for patients suitable for combination therapy who are willing to accept the possibility of more treatment-related side effects. However, this has also not been examined in a head-to-head comparative trial.

It remains unclear what percentage of patients who fail first-line therapy will be suitable for and benefit from ramucirumab, given that poor performance status and declining clinical status are common in patients with advanced

gastric cancer and that all patients included in the trials were very carefully selected populations with good performance status. Quality of life is a particularly important consideration when evaluating suitability of second-line treatment given the poor overall prognosis in these patients with advanced gastric cancer.

Second-line chemotherapy using a taxane or irinotecan may be considered for patients with good ECOG PS who have advanced gastric cancer where ramucirumab is not available.^{18–20} There is currently a lack of data to show that combination chemotherapy would be more effective than monotherapy in this setting.²² The optimal second-line approach for patients with HER-2 over-expressing advanced gastric cancers who have disease progression following trastuzumab containing chemotherapy regimens remains unclear although clinical trials with other HER-2 targeting agents are ongoing. Identification of predictive biomarkers in the future may help better identify those who would benefit most from treatment with ramucirumab.

Biomarkers

It is becoming increasingly evident that the identification of predictive biomarkers in order to best identify those patients who will benefit most from molecularly targeted therapies is very important. However, in patients with gastrointestinal cancers, a validated predictive biomarker to select patients for anti-angiogenic therapy has not been identified to date despite extensive preclinical and clinical research. The AVAGAST trial in advanced gastric cancer showed that baseline plasma VEGF-A and tumor expression of neuropilin were potential predictive markers of efficacy for bevacizumab.⁶³ However, a comprehensive evaluation of baseline VEGF-A levels in several Phase III trials of colorectal, lung, and renal cancers showed a trend toward an adverse prognostic effect with higher VEGF-A levels but showed no predictive value for treatment with bevacizumab.⁶⁴ We eagerly await biomarker analysis from the studies of ramucirumab. We consider that

mandating tissue and plasma collection within clinical trials to aid biomarker discovery is an essential part of conducting clinical trials.

Future considerations

The benefits shown with the VEGFR-2 inhibitor, ramucirumab, and the VEGFR-2 tyrosine kinase inhibitor, apatinib, represent important milestones in the development of anti-angiogenic drugs in advanced gastric cancer. Future considerations may include investigating the use of ramucirumab in the first-line setting, in combination with other chemotherapeutic or molecularly targeted agents, its use in maintenance therapy, and sequencing with other active treatments. In particular, the chemotherapy partner appears to be important and warrants further investigation given the positive OS data when combined with paclitaxel that was not seen when ramucirumab was combined with mFOLFOX6. Therefore, the Phase III trial of ramucirumab in combination with cisplatin and capecitabine in first line is eagerly awaited. Dosage and dose intensity are additional issues that may be examined as well as the ramucirumab exposure-survival and ramucirumab exposure-safety relationship. Further post registration studies may provide further safety and efficacy data based on the real world use of ramucirumab that may not have been identified in the Phase III studies given the modest improvement in survival. Given the increasing costs of cancer care, cost-effectiveness analysis should be incorporated into future clinical trials of this agent. Ongoing clinical trials of targeted therapies are outlined in Table 7. Despite promising recent advances in therapeutic treatment options for advanced gastric cancer, which now includes treatments with molecularly targeted agents against VEGFR-2 and HER-2, prognosis remains poor and further research is needed.

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Table 7 Ongoing studies of targeted therapies in gastric cancer

Trial ID	Clinical trial	Phase	Line	Intervention and schedule	Projected accrual
Angiogenesis inhibitors (Phase II/III)					
ACTRN12612000239864	INTEGRATE	II	Second	Regorafenib vs BSC	150
Other targeted therapies (Phase III)					
NCT01774786	JACOB	III	First	XP-T with or without pertuzumab	780
NCT01450696	HELOISE	III	First	XP-T (standard) vs XP-T (high dose)	400
NCT01641939	GATSBY	III	Second	TDM-I vs taxane	412
NCT01813253		III	Second	Irinotecan ± nimotuzumab	400
NCT01924533		III	Second	Paclitaxel ± olaparib	500

Abbreviations: BSC, best supportive care; XP, cisplatin and capecitabine; T, trastuzumab; TDM-I, trastuzumab emtansine.

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