Ramucirumab for advanced gastric cancer or gastro-oesophageal junction adenocarcinoma

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Abstract: Ramucirumab, a fully humanized monoclonal antibody directed against vascular endothelial growth factor receptor 2, is the first targeted agent to have demonstrated an improvement in survival, as a single agent or in combination, in a molecularly unselected population in gastro-oesophageal cancer. Now that second-line treatment is routinely considered for patients with advanced gastro-oesophageal cancer, ramucirumab, with its favourable toxicity profile compared with cytotoxic treatment, provides a valuable additional treatment option.

Keywords: angiogenesis, gastric cancer, gastro-oesophageal cancer, ramucirumab, vascular endothelial growth factor, vascular endothelial growth factor receptor 2

Introduction

Gastric and gastro-oesophageal cancer represent a significant global health burden. In 2012 there were just fewer than 1.5 million new cases and 1.1 million deaths from gastro-oesophageal cancer worldwide, making gastric cancer (GC) the third leading cause of cancer death in both men and women. The prevalence of gastro-oesophageal cancer varies widely with geography, with more than 70% of cases occurring in the developing world, the highest incidence being found in Eastern Asia, mainly in China [Ferlay *et al.* 2014].

Whilst in recent decades there has been a decline in the overall incidence of GC worldwide, the proportion of tumours of the gastric cardia, consisting of the proximal stomach and the gastro-oesophageal junction (GOJ), has increased. This is thought to be due to a combination of factors, including eradication treatment for *Helicobacter pylori* and improving diet and sanitation reducing the number of noncardia tumours, and the increase in obesity-associated gastro-oesophageal reflux disease leading to a rise in Barrett's oesophagus and a subsequent increase in the number of cardia tumours [Shah and Kelsen, 2010].

Over the last 40 years, the 5-year relative survival rates for GC have tripled, but the actual survival

rate remains low, with less than one in five patients surviving for more than 5 years. For advanced disease the prognosis is particularly bleak, with a median overall survival (OS) of only 3 months with best supportive care, and approximately 12 months with first-line combination chemotherapy.

Current standard of care

The first-line standard of care for metastatic or inoperable locally advanced gastro-oesophageal cancer consists of a doublet of a platinum and a fluoropyrimidine, or a triplet with the addition of epirubicin or a taxane. In 2010 the practice changing ToGA trial led to the addition of trastuzumab to the standard doublet for those patients who are Human Epidermal Growth Factor Receptor 2 (HER2) positive, approximately 20% of patients with advanced gastro-oesophageal cancer [Bang *et al.* 2010]. The addition of trastuzumab in this study resulted in a median OS of 16 months for the subgroup of HER2-positive patients with HER2 3+ on immunohistochemistry (IHC) testing or HER2 2+ on IHC with positive HER2 on fluorescence *in situ* hybridization testing. As yet, however, there is no standard targeted first-line treatment for HER2-negative patients.

There is less international consensus regarding second-line treatment, but irinotecan, docetaxel

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Figure 1. Overall survival with second-/subsequent-line chemotherapy in advanced gastric cancer.

*Hironaka *et al.* [2013]: paclitaxel *versus* irinotecan.

\$Ford *et al.* [2014]: docetaxel *versus* best supportive care (BSC).

*Kang *et al.* [2012]: docetaxel or irinotecan *versus* BSC.

\$Thuss-Patience *et al.* [2011]: irinotecan *versus* BSC.

†Fuchs *et al.* [2014]: ramucirumab *versus* placebo.

**Wilke *et al.* [2014]: paclitaxel and ramucirumab *versus* paclitaxel.

and weekly paclitaxel are all used in this situation [Kang *et al.* 2012; Thuss-Patience *et al.* 2011; Ford *et al.* 2014; Hironaka *et al.* 2013]. Across the studies performed in this setting the OS with best supportive care has ranged from 2.4 to 3.8 months, whereas the OS with single-agent chemotherapy has been between 4 and 9.5 months. However, it must be noted that the upper limit of survival quoted here is from the Japanese study of paclitaxel *versus* irinotecan where approximately 80% of patients went on to have third-line chemotherapy. In the other studies, OS was between 4 and 5.3 months (Figure 1).

This benefit with second-line chemotherapy was further supported by a meta-analysis conducted in 2013 of over 400 patients treated with second-line docetaxel or irinotecan, in which a significant reduction in the risk of death was observed with salvage chemotherapy [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.52–0.79; $p < 0.0001$] [Kim *et al.* 2013].

However, this benefit associated with second-line cytotoxic treatment is short lived, highlighting the need for improved treatment in this setting. Furthermore, for patients with progressive disease following first-line treatment for advanced gastro-oesophageal cancer, quality of life and maintaining performance status are key therapeutic goals and the toxicity of chemotherapy must not be overlooked. In these studies of second-line or subsequent chemotherapy, treatment toxicity was significant, particularly gastrointestinal symp-

toms, which are known to adversely impact quality of life [Al-Batran *et al.* 2015] (Table 1).

Targeted therapies

In recent years, the elucidation of various molecular pathways involved in the development of GC has led to a multitude of studies of targeted therapies. There is, as yet, no single clear molecular driver for gastro-oesophageal cancer, but following the success of the ToGA trial discussed above, agents targeting the vascular endothelial growth factor (VEGF) angiogenesis pathway, the hepatocyte growth factor pathway (MET), the phosphoinositide 3 kinase inhibitor/mammalian target of rapamycin (PI3K/mTOR) pathway and other agents targeting the epidermal growth factor receptor family (EGFR) have all been investigated (Table 2).

So far, these trials of targeted agents have been disappointing, with only trastuzumab in the first-line setting and ramucirumab in the second-line setting demonstrating a significant survival benefit. This may be, in part, due to the lack of predictive biomarkers for the majority of agents, with trastuzumab being a notable exception. In addition, the heterogeneity in molecular alterations seen in gastro-oesophageal cancer worldwide, add further complexity to the results from these large multi-centre studies.

A number of recent publications have clearly demonstrated that there is a range of distinct

Table 1. Grades 3–4 adverse events in second or subsequent line chemotherapy for advanced gastro-oesophageal cancer.

Trial	WJOG4007*		COUGAR-02\$		Korean†		AIO§	
Chemo	Paclitaxel	Irinotecan	Docetaxel	BSC	Irinotecan	Docetaxel	BSC	Irinotecan
No. patients	108	111	81	74	60	66	62	21
Toxicities								
Neutropenia	28%	39.1%	15%	0%	18%	15%	2%	21%
Febrile neutropenia	2.8%	9.1%	7%	0%	2%¶	2%¶	0%	16%
Anaemia	21.3%	30%	6%	5%	32%	30%	23%	11%
Thrombocytopenia	0.9%	1.8%	NR	NR	3%	2%	0%	0%
Infection	NR	NR	15%	3%	NR	NR	NR	NR
Diarrhoea	0.9%	4.5%	26%**	24%**	8%	3%	5%	26%
Nausea	1.9%	4.5%	26%**	24%**	3%	5%	6%	5%
Vomiting	2.8%	0.9%	26%**	24%**	NR	NR	NR	5%

*Hironaka *et al.* [2013]: paclitaxel *versus* irinotecan.
 \$Ford *et al.* [2014]: docetaxel *versus* BSC.
 †Kang *et al.* [2012]: docetaxel or irinotecan *versus* BSC.
 §Thuss-Patience *et al.* [2011]: irinotecan *versus* BSC.
 ¶Six episodes of febrile neutropenia in both irinotecan and docetaxel arms.
 **COUGAR-02 reported all gastrointestinal toxicities as a composite endpoint. In the COUGAR-02 study, 21% had at least one grade 4 toxicity with docetaxel compared with 4% in BSC.
 BSC, best supportive care; NR, not reported.

Table 2. Phase III studies of targeted therapies in GC and GOJC.

Trial	Patient population	Target (family)	Treatment	No. patients	Median PFS (months)	Median OS (months)
Completed: first line						
ToGA	HER2-positive advanced GC/GOJC	HER2 (EGFR)	CF/X +/- trastuzumab	594	5.5 6.7	11.1 13.8
LOGiC	HER2-positive advanced GC/GOJC/oesophageal cancer	HER2 (EGFR)	Oxaliplatin and capecitabine +/- lapatinib	545	5.4 6.0	10.5 12.2
REAL-3	Metastatic or inoperable locally advanced GC/GOJC/lower oesophageal adenocarcinoma/undifferentiated carcinoma	(EGFR)	EOX +/- panitumumab	553	6.0 7.4	8.8 11.3
EXPAND	Metastatic or inoperable locally advanced GC/GOJ adenocarcinoma	(EGFR)	XP +/- cetuximab	904	4.4 5.6	9.4 10.7
AVAGAST	Metastatic or inoperable locally advanced GC/GOJ adenocarcinoma	VEGF/angiogenesis	First-line chemo +/- bevacizumab	774	6.7 5.3	12.1 10.1
Completed: second or subsequent line						
TyTAN	Previously treated HER2-positive advanced GC	HER2 (EGFR)	Paclitaxel +/- lapatinib	261	4.4 5.4	8.9 11.0
REGARD	Previously treated advanced GC/GOJC	VEGF/angiogenesis	Ramucirumab <i>versus</i> BSC	355	2.1 1.3	5.2 3.8
GRANITE	Previously treated advanced GC	mTOR	Everolimus <i>versus</i> BSC	656	5.4 4.3	1.7 1.4
RAINBOW	Previously treated advanced GC/GOJC	VEGF/angiogenesis	Paclitaxel +/- ramucirumab	665	4.4 2.9	9.6 7.4
In progress: first line						
METGASTRIC	HER2-negative and MET-positive metastatic GEC	MET	FOLFOX +/- onartuzumab	800		
JACOB	HER2-positive advanced GC/GOJC	(EGFR)	XP-T +/- pertuzumab	780		
HELOISE	HER2-positive advanced GC/GOJC	(EGFR)	XP-T standard <i>versus</i> high dose	400		
RILOMET	MET-positive advanced GC/GOJC	MET	ECX +/- rilotumumab	450		
In progress: second or subsequent line						
GATSBY	Previously treated advanced GC/GOJC	(EGFR)	TDM1 <i>versus</i> taxane	412		
INTEGRATE (phase II)	Previously treated advanced GC/GOJC	VEGF/angiogenesis	Regorafenib <i>versus</i> BSC	150		
BSC, best supportive care; CF/X, cisplatin, 5FU/capecitabine; EGFR, epidermal growth factor receptor; EOX, epirubicin, oxaliplatin and capecitabine; FOLFOX, 5FU, folinic acid, oxaliplatin; ECX, epirubicin, cisplatin and capecitabine; GC, gastric cancer; GEC, GOJ, gastro-oesophageal junction; GOJC, gastro-oesophageal junction cancer; HER2, Human Epidermal Growth Factor Receptor 2; MET, hepatocyte growth factor pathway; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3 kinase inhibitor; OS, overall survival; PFS, progression-free survival; TDM1, trastuzumab emtansine; VEGF, vascular endothelial growth factor; XP, capecitabine and platinum; XP-T, capecitabine, platinum and trastuzumab.						

subsets of GC and gastro-oesophageal cancers according to genomic alterations [Deng *et al.* 2012; Bass *et al.* 2014]. Such research may allow

patients to be stratified in future trials of targeted agents, until better predictive biomarkers are elucidated.

Targeting angiogenesis and ramucirumab

Sustained angiogenesis is one of the hallmarks of cancer and is an attractive target in many cancers, GC being no exception. The interaction between VEGFs and their receptors (VEGFRs) is one of the key drivers of angiogenesis. This family consists of three receptors, VEGFR1–3, and six growth factors, VEGFA–E, and placental growth factor.

To date, the principal methods of inhibiting angiogenesis have been with the monoclonal antibody to VEGFA, bevacizumab, with the recombinant fusion protein to VEGF, aflibercept, and with various multitargeted tyrosine kinase inhibitors (TKIs) such as sunitinib, sorafenib, axitinib, regorafenib, vandetanib, cabozantinib and pazopanib. Following positive studies, bevacizumab, aflibercept and regorafenib are all US Food and Drug Administration (FDA) approved for metastatic colorectal cancer treatment and in addition bevacizumab is approved for non-small cell lung cancer, ovarian cancer metastatic renal cell carcinoma (RCC) and glioblastoma. The TKIs have varied indications, including the treatment of metastatic RCC, hepatocellular cancer, medullary thyroid cancer and sarcoma. However, the TKIs have not demonstrated activity in luminal gastrointestinal malignancies to date.

The main angiogenic response to VEGF is mediated *via* VEGFR2, a transmembrane tyrosine kinase receptor. VEGFR2 is expressed on vessel endothelial cells and binds VEGFA, VEGFE and processed VEGFC and VEGFD. On binding VEGFs, VEGFR2 either forms heterodimers with VEGFR1 or homodimers, causing tyrosine phosphorylation within the cell. This phosphorylation results in a signalling cascade, causing increased cell proliferation and survival, cell migration, increased vascular permeability, invasion and endothelial inflammation [Claesson-Welsh and Welsh, 2013]. Approximately 50% of GCs express VEGF, and VEGFA and D overexpression in GC is associated with a poor prognosis [Lieto *et al.* 2008; Peng *et al.* 2012], making VEGF2 an attractive target in this setting.

ImClone Systems (New York) developed ramucirumab as a fully humanized monoclonal antibody, directed against VEGFR2. The compound was initially isolated from a naïve human antibody phage display library. A subsequent *in vitro* selection process, using an additional specific

phage display library, selected a high affinity variant for further development [Lu *et al.* 2003]. This variant, clone 1121B, ramucirumab, binds to domain 3, close to the N terminus, and inhibits VEGF-induced signalling by altering the conformation of the receptor, preventing VEGF binding [Franklin *et al.* 2011]. By specifically binding VEGF2, ramucirumab prevents all known VEGFs binding to VEGF2 and therefore could lead to more complete inhibition of angiogenesis than agents directly binding a single VEGF.

Early studies

Ramucirumab has been extensively investigated in the preclinical setting, with murine studies demonstrating proof of principle [Prewett *et al.* 1999]. *In vitro* data have shown that ramucirumab has an 8–9-fold stronger affinity for VEGFR2 than the nascent ligand VEGFA [Lu *et al.* 2003] and binds VEGFR2 with an IC₅₀ (half maximal inhibitory concentration) of 1–2 nM [Miao *et al.* 2006].

Three phase I studies with ramucirumab have been completed [ClinicalTrials.gov identifier: NCT00793975, NCT00786383 and NCT01005355], although only one of these has been published [Spratlin *et al.* 2010]. This study recruited 37 patients with a range of advanced solid malignancies, including four with GC or oesophageal cancer, and treated them with escalating doses of once-weekly ramucirumab, between 2 and 16 mg/kg. Following dose-limiting toxicities of hypertension and deep vein thrombosis, the maximum tolerated weekly dose was set at 13 mg/kg. Other toxicities seen were nausea, vomiting, headache, fatigue and proteinuria.

Fifteen percent (4 of 27) of the patients with measurable disease had a partial response (PR) and the disease control rate (PR + stable disease) was 73% for all patients (27 of 37). Furthermore, 30% (11 of 37) of all patients had either a PR or stable disease lasting for 6 months or longer. Based on this tolerable safety profile and signal of anticancer activity, further phase II and III studies of ramucirumab were undertaken. There has only been one phase II study in gastro-oesophageal cancer, which followed on from the large phase III second-line studies discussed below.

Advanced studies

Efficacy data for second-line treatment

The two large phase III studies of ramucirumab in gastro-oesophageal cancer have been in the second-line setting. The first of these was the REGARD study, an international, randomized, multicentre, placebo-controlled trial of ramucirumab monotherapy conducted between 2009 and 2012 [Fuchs *et al.* 2014].

A total of 355 patients with advanced GC or GOJ cancer were randomized (2:1) to best supportive care plus ramucirumab 8 mg/kg intravenously or placebo 2 weekly, following disease progression on first-line chemotherapy. There was no crossover at progression and the primary endpoint was OS.

The treatment arms were well balanced, with over 75% of patients having gastric tumours, 70% of patients having a performance status of 1 and 69% of patients being recruited from Western populations (Europe, North America and the Antipodes).

Response rates were only 4% with ramucirumab treatment, but the rate of stable disease was considerably higher than in the placebo arm (45% *versus* 21%), resulting in a significantly greater disease control rate of 45% *versus* 23%. However, the median duration of treatment was only 8 weeks [interquartile range (IQR) 6–16] in the ramucirumab arm and 6 weeks (IQR 4–8) in the placebo arm.

Median OS was increased in the ramucirumab arm to 5.2 months compared with 3.8 months in the placebo arm (HR 0.776, 95% CI 0.603–0.998, $p = 0.047$). This benefit remained significant after multivariable adjustment for prognostic factors such as performance status, presence of peritoneal disease and site of primary disease. This is the first randomized trial to demonstrate such a survival advantage for a single-agent antiangiogenic monoclonal antibody in a solid tumour. Progression-free survival (PFS) at 6 months was also improved to 42% with ramucirumab *versus* 32% with placebo. These results are comparable with those seen using standard second-line chemotherapy in this setting, with less toxicity.

Based on these results the FDA granted ramucirumab a priority review and subsequently approved it for the treatment of GC and GOJ cancer on 14 April 2014.

The RAINBOW study recruited 665 patients with advanced GC or GOJ adenocarcinoma between December 2010 and September 2012 [Wilke *et al.* 2014]. They were randomized to treatment with either paclitaxel and ramucirumab or paclitaxel and placebo, following disease progression on or within 4 months of first-line chemotherapy. The study was double blind and multicentre, involving 27 countries, with a primary endpoint of OS.

Baseline characteristics between the two treatment groups were generally well balanced. Approximately two-thirds of the patients had progressive disease on first-line chemotherapy, 80% of patients had a gastric primary, roughly 60% of patients had performance status of 1 and 60% were from Europe, Israel, Australia and America, with 33% from Asia and 7% from South America.

OS was significantly longer in the paclitaxel plus ramucirumab arm (9.6 months, 95% CI 8.5–10.8 months, *versus* 7.4 months, 95% CI 6.3–8.4 months; HR 0.807, 95% CI 0.678–0.962, $p = 0.017$) and median PFS was improved to 4.4 months *versus* 2.9 months with placebo with a stratified HR of 0.635 (95% CI 0.536–0.752, $p < 0.0001$). Ramucirumab also improved the objective response rate (28% *versus* 16% with placebo) and achieved a disease control rate of 80% *versus* 64% with placebo.

The survival data in RAINBOW were analysed according to geographic region, comparing Asian and non-Asian patients. The OS benefit was not significant for Asian patients, although PFS remained significantly improved. The HRs for survival were 0.73 and 0.99 for non-Asian and Asian patients respectively for OS, and 0.64 and 0.63 for non-Asian and Asian patients for PFS. It was suggested that this difference could be explained by the higher use of third-line therapy following study discontinuation in Asian patients compared with non-Asian patients (almost 70% *versus* almost 40%).

A subsequent efficacy analysis was carried out contrasting Japanese and Western (European, American and Australian) patients in RAINBOW and found that in the Japanese population a benefit was seen in PFS, ORR (overall response rate) and OS at 6 months. Again post discontinuation therapy rates were much higher in the Japanese patients at 75% than in the Western patients at 37% and it was postulated that this masked the potential OS benefit [Hironaka *et al.* 2014].

Based on the data from the RAINBOW study in September 2014, the European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion for the use of ramucirumab, in combination with paclitaxel, or as a single agent if combination is not appropriate, for the treatment of advanced GC or GOJ adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. The FDA also extended the license for ramucirumab in November 2014 to include its use in combination with paclitaxel in the treatment of GC and GOJ adenocarcinoma, following failure of first-line treatment.

Toxicity data for second-line treatment

In REGARD adverse event rates were similar between the two treatment arms, other than hypertension, which was significantly higher in the ramucirumab arm at 16% *versus* 8%, as would be expected. Rates of bleeding and haemorrhage, venous thromboembolic events, fistula formation and perforation, in particular, were similar in both arms. There were more arterial thromboembolic events in the ramucirumab arm (2% *versus* 0%) but only four patients were affected across all grades.

Quality of life data were collected in REGARD but the percentage of patients providing this at the first 6-week assessment was very low, due to treatment discontinuation. Of these patients, a larger number in the ramucirumab group reported stable or improved global quality of life, but this was not significant. Time to deterioration in performance status to 2 or worse was also measured and was significantly better in the ramucirumab group at 5.1 months (IQR 1.9–16.8) *versus* 2.4 months (IQR 1.3–not reached) in the placebo group (HR 0.586, 95% CI 0.414–0.829, $p = 0.002$).

In the RAINBOW study grade 3 adverse events were seen in 47% of patients in the ramucirumab arm and 39% of patients in the placebo arm. Hypertension (35% *versus* 6%), proteinuria (17% *versus* 6%), bleeding (mainly low-grade epistaxis) or haemorrhage (43% *versus* 18%) and gastrointestinal perforations (four patients, including one death, *versus* one patient) were more commonly seen in the ramucirumab plus paclitaxel arm, as expected with antiangiogenic treatment. Grade 3 or 4 neutropenia, leucopenia, abdominal pain, fatigue and neuropathy (associated with a higher cumulative paclitaxel dose) were also all more

common in the ramucirumab plus paclitaxel arm. Febrile neutropenia was similar in both groups (3% *versus* 2%). However, importantly, the higher frequency of grade 3 and 4 adverse events in the ramucirumab plus paclitaxel arm did not result in more patients discontinuing treatment or in a higher number of treatment-related deaths (2% in each group).

Quality of life data were also collected here, with no impairment of global quality of life from QLQ-C30 (EORTC questionnaire) or index scores from EQ-5D-3L (health outcome instrument) with the addition of ramucirumab to paclitaxel. Furthermore, quality of life was maintained for longer, with more patients reporting stable or improved scores with ramucirumab [Al-Batran *et al.* 2014]. Deterioration in performance status was measured again but here the HR of 0.798 was not significant (95% CI 0.612–1.040, $p = 0.0941$).

Based on these two large phase III studies, ramucirumab therefore has a favourable side-effect profile compared with cytotoxic drugs. Specifically the addition of ramucirumab to paclitaxel did not increase the incidence of side effects in a clinically meaningful fashion. In these studies ramucirumab treatment helped to maintain quality of life and as a single agent prolonged the time to deterioration of performance status, both important therapeutic goals.

Advanced studies

First-line treatment

In a recent randomized, double-blind, placebo-controlled phase II study, ramucirumab was used first line in combination with FOLFOX in advanced GC or oesophageal adenocarcinoma [Yoon *et al.* 2014]. A total of 168 patients were enrolled across 47 sites in America to receive FOLFOX (5FU, folinic acid, oxaliplatin) plus ramucirumab (8 mg/kg intravenously) or placebo, 2 weekly.

The study did not meet the primary endpoint of improved median PFS, with a PFS of 6.4 months in the ramucirumab arm and 6.7 months in the placebo arm (HR 0.98, 95% CI 0.69–1.37, $p = 0.89$). The PFS rate was higher at 3 months in the ramucirumab arm (89% *versus* 75%, $p = 0.02$), but not at any other time point. OS was 11.7 months in the ramucirumab arm and 11.5 months in the placebo

arm. Response rate was not improved by ramucirumab (45% *versus* 46%), although disease control rate (made up of stable disease, complete response and PR) was higher in the ramucirumab arm (85% *versus* 67%, $p = 0.008$).

Approximately 50% of the patients in the study had oesophageal cancer and 50% had GC/GOJ cancer, well distributed between the treatment groups. Overall the patients with GC and GOJ cancer appeared to derive more benefit from the ramucirumab. In the GC/GOJ cancer subgroup analysis, OS was 14.6 months in the ramucirumab arm and 12.5 months in the placebo arm. In exploratory analyses, when PFS was censored at treatment discontinuation for nonprogressive disease, HR for PFS favoured the ramucirumab arm (PFS 9.3 months *versus* 7.6 months; HR 0.53, 95% CI 0.29–0.97, $p = 0.036$).

The treatment was fairly well tolerated with the expected grade 3 adverse events of neutropenia, fatigue, neuropathy and hypertension. However, treatment discontinuation for nonprogressive disease was more common in the ramucirumab arm and although both groups received a similar number of oxaliplatin cycles (8.5 *versus* 9.5), patients in the ramucirumab arm received fewer cycles of 5-fluorouracil (5FU) (9 *versus* 11) and ramucirumab/placebo (9 *versus* 11). The investigators suggested that this higher discontinuation rate and lower drug exposure might have impacted upon the PFS assessment.

It is difficult to establish why a differential effect was seen with ramucirumab treatment and oesophageal cancer *versus* GC and GOJ cancer. There could be intrinsic biological differences in how the tumour types respond to antiangiogenic treatment, or in the importance of completing 5FU treatment, but this could also simply be a chance finding from a subgroup analysis.

Discussion and future

A treatment milestone

Without doubt the improvement in OS with single agent ramucirumab in the REGARD study represents an important milestone in antiangiogenic treatment, as the first single agent antiangiogenic antibody to demonstrate a survival advantage in a solid tumour. Moreover, ramucirumab is the first targeted agent to improve survival, as a single agent or in combination, in a

molecularly unselected population with GC and GOJ cancer.

Treatment is generally well tolerated, with the toxicities expected for an antiangiogenic agent. Although these toxicities cannot be described as trivial, it should be noted that the number of treatment-related deaths were low and in the RAINBOW study, treatment-related deaths were equal in both the treatment and placebo groups, at only 2%.

As with the majority of studies, the patients selected in RAINBOW and REGARD were younger and fitter than some patients with second-line GC or gastro-oesophageal cancer may be and whether toxicity in the real world becomes more of an issue remains to be seen. However, in these trials, quality of life was not impaired and in fact the addition of ramucirumab maintained a stable or improved quality of life for longer than placebo. A potential chemotherapy-free option in patients in this setting, who may have residual toxicity from chemotherapy or simply be fed up with chemotherapy, is a very welcome addition to the treatments available, especially when maintaining quality of life is of utmost importance.

Geographical variability

In contrast to the AVAGAST study of bevacizumab in combination with first line chemotherapy in gastric and gastro-oesophageal cancer [Ohtsu *et al.* 2011], the REGARD study showed a similar survival benefit in Asian and non-Asian patients. In AVAGAST a survival benefit and improved response rate were only seen on subset analysis in the non-Asian patients. Even in RAINBOW where OS was not improved in Asian patients, response rate and PFS were. It is possible that disease biology varies across the globe such that geographical region may act as a surrogate marker for sensitivity to a particular antiangiogenic agent. The mechanistic advantage of ramucirumab, binding VEGF2 and its long half life, may also better bevacizumab. Interestingly the recent phase III study of apatinib, an oral small molecule VEGFR2 TKI, in advanced GC in Chinese patients demonstrated a prolonged median OS in the apatinib arm of 195 days *versus* 140 days in the placebo arm (HR 0.71, 95% CI 0.54–0.94, $p < 0.0001$) [Qin, 2014]. Finally, the success of antiangiogenic therapy may also vary in the first- and second-line setting, as supported by the first-line study of ramucirumab in

combination with FOLFOX failing to meet its primary endpoint.

Biomarkers

For ramucirumab, alongside other antiangiogenic agents, or indeed targeted treatments generally, the lack of predictive biomarkers in patients with GC is frustrating. Biomarker-driven patient selection may have changed the outcome of the first-line phase II study of ramucirumab in combination with FOLFOX. There are as yet limited data on potential biomarkers for GC and GOJ cancer. In the AVAGAST study high levels of circulating VEGFA and increased neuropilin 1 expression were associated with worse survival in the placebo arm and benefit from bevacizumab in the treatment arm [Van Cutsem *et al.* 2012]. Of particular note, the effect associated with circulating VEGFA levels was only seen in patients from non-Asian-Pacific regions. Asian patients tended to have lower overall VEGFA levels, but even those with higher levels did not benefit from bevacizumab treatment. These results were potentially biased by geographic variations in tissue acquisition and processing and are as such hypothesis generating. The translational work from the RAINBOW and REGARD studies will hopefully add to this body of work and may yield new potential predictive biomarkers to enable better patient selection for antiangiogenic treatment.

If such a biomarker is developed, ramucirumab could be trialled in the perioperative, adjuvant or even maintenance setting. Rational drug combinations, perhaps with other antiangiogenic agents to overcome possible resistance mechanisms, could also be very interesting.

Further trials are already planned in gastro-oesophageal cancer, combining ramucirumab with capecitabine and cisplatin in the first-line setting (RAINFALL) [ClinicalTrials.gov identifier: NCT02314117], combining ramucirumab with nab-paclitaxel in the second-line setting [ClinicalTrials.gov identifier: NCT02317991] and studying different doses and schedules as a single agent in the second-line setting.

At present, although ramucirumab has been approved by the FDA and has been granted orphan designation by the European Commission, there have been questions raised over its cost

effectiveness. With an appropriate predictive biomarker to enable better patient selection it would be easier to answer such concerns.

It is to be hoped that with the increasing accessibility of high throughput techniques and the large blood and tissue banks from these sizeable multinational studies that progress in the development of a predictive biomarker for ramucirumab treatment will be made in the near future, which could significantly widen the potential use of this drug.

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Conflict of interest statement

Dr Young and Dr Smyth declare no conflicts of interest. Dr Chau's conflicts are as follows: advisory board and consultancy for Bristol Myers Squibb, Roche, Sanofi Oncology, Merck Serono, Eli-Lilly, Novartis and Gilead Science; honorarium from Sanofi-Oncology, Eli-Lilly and Taiho; research funding from Sanofi Oncology, Roche, Novartis and Merck-Serono.

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