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R&D INSIGHT REPORT

Ramucirumab: First Global Approval

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Abstract Ramucirumab (Cyramza™ [US]), a fully human immunoglobulin G1 (IgG1) monoclonal antibody that inhibits vascular endothelial growth factor receptor-2 (VEGFR-2), has been developed by Eli Lilly (formerly ImClone Systems) for the treatment of cancer. Ramucirumab has received its first global approval in the US for use as monotherapy in the treatment of advanced or metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma in patients who experience disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy. Ramucirumab is the first treatment to be approved by the US FDA for this setting. This article summarizes the milestones in the development of ramucirumab leading to this first approval for the treatment of gastric cancer and gastro-oesophageal junction adenocarcinoma.

This profile has been extracted and modified from the *Adis R&D Insight* drug pipeline database. *Adis R&D Insight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

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1 Introduction

Angiogenesis, the formation of new blood vessels, is critical for the growth, invasion and metastasis of solid tumours [1–5]. Vascular endothelial growth factor (VEGF) ligands and receptors play a key role in angiogenesis and have emerged as targets for the development of novel anticancer agents. Binding of the ligands VEGF-A, VEGF-C and VEGF-D to vascular endothelial growth factor receptor-2 (VEGFR-2 or kinase insert domain receptor [KDR]) on the endothelial cells of tumours initiates signalling cascades that lead to angiogenesis, endothelial cell proliferation and migration, and increased vascular permeability [6, 7]. Inhibition of VEGFR-2 activation by blocking the binding of these ligands is therefore expected to prevent the formation of new blood vessels and thereby limit the supply of nutrients to the tumour, thus causing the death of the tumour cells.

Expression of VEGF has been found to correlate with increased vascular involvement and lymph node and hepatic metastases, and hence poor prognosis, in gastric cancer [8]. VEGF is therefore an attractive target for the treatment of advanced or metastatic gastric cancer, for which treatment options are limited and overall survival durations short, particularly for patients who have disease progression on combination chemotherapy [6]. Bevacizumab, a monoclonal antibody targeting VEGF-A, was found to improve progression-free survival and response rate in patients with advanced gastric cancer in the first-line setting when added to chemotherapy in the phase III AVAGAST study; however, it did not significantly improve overall survival, the study's primary endpoint [9]. It has been suggested that targeting VEGFR-2 may be a more effective strategy, as this would also block the binding and pro-angiogenic activity of VEGF-C and VEGF-D [10].

Features and properties of ramucirumab

Alternative names	Anti-flk-1 monoclonal antibody – ImClone; Anti-KDR monoclonal antibody – ImClone; Anti-CEGFR 2 monoclonal antibody – ImClone; Cyramza™; IMC 1121; IMC 1121B; IMC 1C11 – ImClone; IMC-1121; IMC-1121 B: IMC-1121B; IMC-1C11 0 ImClone; IMC1121 B; IMC1121-B; IMC1121B; LY 3009806; LY-3009806; LY3009806
Class	Monoclonal antibodies
Mechanism of action	Vascular endothelial growth factor receptor-2 antagonist
Route of administration	IV infusion
Pharmacodynamics	Elevates serum VEGF concentrations following infusion; decreases tumour perfusion and vascularity
Immunogenicity	Anti-ramucirumab antibodies detected by ELISA in 7.4 % of patients in clinical trials, including neutralizing antibodies in 1 patient
Pharmacokinetics	C_{min} of 50 and 74 μg/mL, respectively, after 3 and 6 biweekly doses of 8 mg/kg; dose-dependent elimination and non-linear exposure; steady state $t_{1/2}$ of 200–300 h for doses of 8–16 mg/kg
Adverse events	
Most frequent[a]	Hypertension, diarrhoea, headache, hyponatremia, proteinuria
Occasional[b]	Neutropenia, epistaxis, rash, anaemia, severe haemorrhage, intestinal obstruction, arterial thromboembolic events
Rare	Gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome
ATC codes	
WHO ATC code	L01X-C (monoclonal antibodies)
EphMRA ATC code	L1X3 (Antineoplastic monoclonal antibodies)
Chemical name	Immunoglobulin G1, anti-(human vascular endothelial growth factor receptor type VEGFR-2 extracellular domain) (human monoclonal IMC-1121B γ-chain), disulfide with human monoclonal IMC-1121B κ-chain, dimer

[a] 5 % or more patients in REGARD and at least 2 % higher than placebo

[b] 1–5 % of patients in REGARD

Ramucirumab (Cyramza™ [US]), a fully human immunoglobulin G1 (IgG1) monoclonal antibody that inhibits the function of VEGFR-2, received its first global approval in the US on April 21 2014 for use as monotherapy in the treatment of advanced or metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma in patients who have experienced disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy [11]. The approved labelling carries a black box warning regarding the increased risk of haemorrhage in patients taking ramucirumab, including severe and sometimes fatal events [12].

Ramucirumab is approved for use as an 8 mg/kg intravenous (IV) infusion to be administered over 60 minutes every 2 weeks, and is available in single-dose vials containing either 100 mg/10 mL or 500 mg/50 mL (both 10 mg/mL) [12]. Treatment with ramucirumab should be continued until disease progression or unacceptable toxicity occurs. To prevent infusion-related reactions, all patients should receive an IV histamine H_1 antagonist such as diphenhydramine hydrochloride prior to each ramucirumab infusion. Patients who have experienced a grade 1 or 2 infusion reaction should also receive dexamethasone (or equivalent) and acetaminophen prior to each infusion and the infusion rate should be reduced by 50 % in these patients. Treatment interruption is required for patients who develop severe hypertension (until controlled with medical management) or proteinuria (urine protein levels of $\geq$2 g/24 h); for patients with proteinuria, ramucirumab can be restarted at a reduced dose of 6 mg/kg every 2 weeks after urine protein levels return to <2 g/24 h, with further reduction to 5 mg/kg every 2 weeks if proteinuria recurs. Treatment should also be interrupted prior to surgery due to the potential for wound healing complications, and should not be restarted until the wound is fully healed. Treatment with ramucirumab should be discontinued in patients who develop grade 3 or 4 infusion-related reactions, severe hypertension that cannot be controlled with antihypertensive agents, urine protein levels of >3 g/24 h or nephrotic syndrome, or arterial thromboembolism, gastrointestinal perforation or grade 3 or 4 haemorrhage.

The approval of ramucirumab in the US was based on results from the REGARD trial (NCT00917384; EudraCT2008-005964-15). This randomized, double-blind, phase III trial compared ramucirumab plus best supportive care (BSC) with placebo plus BSC in 355 patients with advanced gastric or gastro-oesophageal junction cancer with disease progression on or after platinum- or fluoropyrimidine-based chemotherapy in the US, Australia, Canada, Egypt, Europe, Latin America, New Zealand, South Africa, South-East Asia and India.

A regulatory application seeking approval for ramucirumab monotherapy in the treatment of advanced gastric cancer in patients with disease progression after initial chemotherapy has also been submitted in the EU [13]. Ramucirumab has been granted orphan drug status for the treatment of gastric cancer and hepatocellular carcinoma in the US and the EU [14–17].

Ramucirumab is also in development for a number of other solid tumour indications. It was in phase III development worldwide for metastatic breast cancer, but Eli Lilly decided not to submit regulatory applications for this indication after the phase III ROSE trial (NCT00703326, TRIO-012) failed to meet its primary endpoint [18].

1.1 Company Agreements

Ramucirumab is being developed by Eli Lilly (formerly ImClone Systems). ImClone Systems became a wholly-owned subsidiary of Eli Lilly in November 2008 [19], and has since merged and integrated into Eli Lilly.

In May 2014, Eli Lilly selected Biologics Inc's Oncology Pharmacy Services to be the exclusive specialty pharmacy provider of ramucirumab in the US [20].

In April 2003, ImClone and Dyax Corporation entered into an antibody library license agreement. Under the terms of the agreement, ImClone had a non-exclusive licence to Dyax's antibody phage display library and patent rights. In return, Dyax received an upfront licence fee and annual technology licence fee payments for up to 4 years. ImClone was to also pay Dyax clinical milestone payments and royalties on sales of any products arising from use of the library. Financial terms of the agreement were not disclosed [21, 22]. Cambridge Antibody Technology and Dyax have cross-patent licensing agreements in place.

2 Scientific Summary

2.1 Pharmacodynamics

Ramucirumab specifically binds VEGFR-2 and blocks the binding of VEGFR-A, VEGF-C and VEGF-D, thus inhibiting the VEGFR ligand-induced proliferation and migration of endothelial cells [12]. Analysis of the structure of ramucirumab showed that it directly blocks VEGF ligand binding at VEGFR-2 via binding at opposite ends of VEGFR-2 by two Fab fragments [23].

Ramucirumab doses of 2–16 mg/kg produced non-dose-dependent increases in VEGF-A and decreases in sVEGFR-1 and sVEGFR-2 in a study in 37 patients with advanced solid tumours [24]. Tumour perfusion and vascularity were decreased in 69 % of 13 evaluable patients, and was consistent across all target lesions in patients with multiple tumours assessed.

Treatment with ramucirumab 8 mg/kg every 2 weeks increased serum VEGF and placental growth factor levels and produced a rapid and transient decrease in soluble VEGFR-2 levels in patients with advanced hepatocellular carcinoma (HCC) in a phase II study [25]. A relationship between the change in sVEGFR-1 from baseline to day 8 and progression-free and overall survival was observed, with patients who had decreases in sVEGFR-1 appearing to have better outcomes.

2.2 Immunogenicity

Anti-ramucirumab antibodies were detected by enzyme-linked immunosorbent assay (ELISA) in 33 of 443 (7.4 %) of patients treatment with ramucirumab in clinical trials for whom post-baseline serum samples were available, with neutralizing antibodies in one patient [12]. It should be noted that this assay has limitations regarding the detection of anti-ramucirumab antibodies in the presence of ramucirumab.

2.3 Pharmacokinetics

In patients with advanced gastric or gastro-oesophageal cancer receiving ramucirumab 8 mg/kg every 2 weeks, geometric means of the minimum ramucirumab concentrations (C_{min}) after the third and sixth doses were 50 μg/mL and 74 μg/mL, respectively [12].

Non-compartmental pharmacokinetic analysis from a phase I trial of ramucirumab in 37 patients with advanced solid tumours showed dose-dependent elimination and non-linear exposure, consistent with saturable clearance, at doses of 2–16 mg/kg [24]. Target trough levels required for anti-tumour activity (≥20 μg/mL, determined from pre-clinical xenograft studies) were exceeded at all dose levels. After the first infusion in cycle 1, the mean half-life ($t_{1/2}$) ranged from 68.4–123 hours, mean C_{min} was 6.83–177 μg/mL, mean maximum plasma concentration (C_{max}) was 43.7–558 μg/mL and mean area under the plasma concentration-time curve ($AUC_{0-\infty}$) was 3,914–67,871 h · μg/mL. At steady state, the $t_{1/2}$ for doses of 8–16 mg/kg was approximately 200–300 hours. Minimal accumulation was observed over ≥32 cycles of treatment.

There have been no dedicated studies of the effects of renal or hepatic impairment on the pharmacokinetics of ramucirumab, nor have formal drug interaction studies been conducted [12].

Clinical trials of ramucirumab conducted by Eli Lilly

Drugs	Indication	Patient subgroup	Study phase	Status	Study location	Trial identifiers
Ramucirumab ± best supportive care (BSC)	Gastric cancer	Metastatic disease; monotherapy; second-line therapy or greater	III	Completed	US, Argentina, Australia, Bosnia & Herzegovina, Brazil, Canada, Chile, Colombia, Croatia, Czech Republic, Egypt, Guatemala, India, Indonesia, Italy, South Korea, Lebanon, Malta, Mexico, New Zealand, Philippines, Poland, Romania, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, UK	NCT00917384 (REGARD)
Paclitaxel ± ramucirumab	Gastric cancer	Metastatic disease; combination therapy; second-line therapy or greater	III	Enrolment completed	US, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Chile, Estonia, France, Germany, Hungary, Israel, Italy, Japan, South Korea, Lithuania, Mexico, Poland, Portugal, Romania, Russia, Singapore, Spain, Taiwan, UK	NCT01170663 (RAINBOW)
Ramucirumab + docetaxel	Breast cancer	First-line therapy; combination therapy; metastatic disease	III	Enrolment completed	US, Australia, Belgium, Brazil, Canada, Croatia, Czech Republic, Egypt, Germany, Ireland, Israel, South Korea, Lebanon, New Zealand, Peru, Poland, Russia, Serbia, Slovakia, South Africa, Spain, Taiwan, UK	NCT00703326 (ROSE)
Ramucirumab ± FOLFIRI (fluorouracil + folinic acid + irinotecan)	Colorectal cancer	Metastatic disease; combination therapy; second-line therapy or greater	III	Enrolment completed	US, Argentina, Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Greece, India, Italy, Japan, Puerto Rico, Romania, South Korea, Spain, Sweden, Taiwan	NCT01183780 (RAISE)
Ramucirumab ± best supportive care (BSC)	Hepatocellular carcinoma	Second-line therapy or greater	III	Enrolment completed	US, Austria, Australia, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Finland, France, Germany, Hong Kong, Hungary, Israel, Italy, Japan, Netherlands, Norway, Philippines, Portugal, Romania, Spain, Sweden, Switzerland, Taiwan, Thailand	NCT01140347 (REACH)
Ramucirumab + docetaxel	Non-small cell lung cancer	Second-line therapy or greater; combination therapy; late-stage disease	III	Enrolment completed	US, Argentina, Austria, Brazil, Canada, France, Germany, Greece, Hungary, India, Israel, Italy, Mexico, Netherlands, New Zealand, Norway, Poland, Puerto Rico, Romania, Russia, Spain, South Korea, Sweden, Switzerland, Taiwan, Turkey, UK	NCT01168973 (REVEL)
Ramucirumab + docetaxel or docetaxel ± icrucumab	Bladder cancer, (+pelvic cancer, renal cancer, urethral cancer)	Second-line therapy or greater	II	Enrolment completed	US, Canada	NCT01282463
Ramucirumab	Renal Cancer	Metastatic disease; monotherapy	II	Completed	US	NCT00515697

continued

Drugs	Indication	Patient subgroup	Study phase	Status	Study location	Trial identifiers
Ramucirumab	Gastric cancer (including gastro-oesophageal junction adenocarcinoma)	Metastatic disease; monotherapy; second-line therapy or greater	II	Recruiting	Japan	NCT01983878
Ramucirumab + mFOLFOX6 (oxaliplatin + folinic acid + fluorouracil)	Gastric cancer, Oesophageal cancer	Combination therapy	II	Enrolment completed	US	NCT01246960
Ramucirumab ± eribulin	Breast cancer	Combination therapy; second-line therapy or greater; late-stage disease	II	Enrolment completed	US	NCT01427933
Ramucirumab + capecitabine	Breast cancer	Combination therapy; second-line therapy or greater; late-stage disease	II	Enrolment completed	US	NCT1234402
Ramucirumab + mFOLFOX6	Colorectal cancer	First-line therapy; metastatic disease; combination therapy	II	Completed	Canada, Spain	NCT00862784
Ramucirumab + mFOLFOX6 Icrucumab + mFOLFOX6	Colorectal cancer	Second-line therapy; metastatic disease; combination therapy	II	Completed	US, Canada	NCT01111604
Ramucirumab ± dacarbazine	Malignant melanoma	First-line therapy; metastatic disease	II	Completed	US	NCT00533702
Ramucirumab + docetaxel	NSCLC	Second-line therapy or greater; combination therapy; late-stage disease	II	Recruiting	Japan	NCT01703091
Ramucirumab + pemetrexed + carboplatin + cisplatin OR Ramucirumab + gemcitabine + carboplatin + cisplatin	NSCLC	First-line therapy; combination therapy; late-stage disease	II	Enrolment completed	US, Belgium, Canada, Germany, Poland, UK	NCT01160744

continued

Drugs	Indication	Patient subgroup	Study phase	Status	Study location	Trial identifiers
Ramucirumab + paclitaxel + carboplatin	NSCLC	First-line therapy; combination therapy; late-stage disease	II	Completed	US, UK	NCT00735696
Ramucirumab	Ovarian cancer (+fallopian tube cancer, primary peritoneal carcinoma)	Second-line therapy or greater; monotherapy)	II	Enrolment completed	US, UK	NCT00721162
Ramucirumab + mitoxantrone + prednisone	Prostate cancer	Second-line therapy or greater; hormone refractory; metastatic disease	II	Completed	US	NCT00683475
Ramucirumab	Renal cancer	Monotherapy; metastatic disease; second-line therapy or greater	II	Completed	US	NCT00515697
Ramucirumab + FOLFIRI (irinotecan + folinic acid + fluorouracil)	Solid tumours	Combination therapy	II	Enrolment completed	US	NCT01634555
Ramucirumab + paclitaxel	Solid tumours	First-line therapy	II	Enrolment completed	US	NCT01515306
Ramucirumab	Solid tumours	Combination therapy	II	Enrolment completed	US	NCT01017731
Ramucirumab + docetaxel	Solid tumours	Combination therapy	II	Completed	US	NCT01567163

2.4 Therapeutic Trials

2.4.1 *Gastric Cancer and Gastro-Oesophageal Junction Adenocarcinoma*

Ramucirumab significantly prolonged overall survival in patients with advanced gastric or gastro-oesophageal junction cancer in the REGARD trial (NCT00917384) [26]. Patients in this study, all of whom had experienced disease progression after first-line platinum- or fluoropyrimidine-containing chemotherapy, were randomized to treatment with ramucirumab 8 mg/kg (n = 238) or placebo (n = 117) by IV infusion every 2 weeks, in addition to BSC. Median overall survival durations for the ramucirumab and placebo groups were 5.2 months and 3.8 months, respectively (hazard ratio [HR] 0.776, 95 % confidence interval [CI] 0.603–0.998; $P = 0.047$). The difference in overall survival remained significant after adjustment for other prognostic factors (HR 0.774, 95 %CI 0.605–0.991; $P = 0.042$). Estimated overall survival rates for ramucirumab versus placebo at 6 and 12 months were 41.8 % vs 31.6 % and 17.6 % vs 11.8 %, respectively. The median progression-free survival duration was also significantly increased with ramucirumab (2.1 vs 1.3 months; HR 0.483, 95 %CI 0.376–0.620; $P < 0.0001$). Disease control rates for ramucirumab and placebo were 49 % and 23 %, respectively ($P < 0.0001$). One patient (<1%) in the ramucirumab group had a complete response and seven (3 %) had partial responses, compared with three partial responses (3 %) in the placebo group; in addition, stable disease was achieved in 45 % and 21 % of patients in the ramucirumab and placebo groups, respectively. Quality of life (QOL) data were available at 6 weeks for 114 (48 %) patients in the ramucirumab group and 29 (25 %) placebo-treated patients; data were unavailable for the majority of patients due to treatment discontinuation. Stable or improved QOL was reported by 34 % of ramucirumab recipients, compared with 13 % of the placebo group ($P = 0.23$).

Combination therapy with ramucirumab plus paclitaxel significantly improved overall and progression-free survival in patients with gastric or gastro-oesophageal junction cancer who had disease progression on or within 4 months after platinum- or fluoropyrimidine-containing chemotherapy in the RAINBOW trial (NCT01170663) [27]. This phase III trial enrolled a total of 665 patients who were randomized to receive ramucirumab 8 mg/kg (n = 330) or placebo (n = 335) by IV infusion, every 2 weeks in addition to paclitaxel 80 mg/m^2 on days 1, 8 and 15 of a 4-week cycle. The median overall survival duration (primary endpoint) in the ramucirumab plus paclitaxel and placebo plus paclitaxel groups were 9.63 and 7.36 months, respectively (HR 0.807, 95 %CI 0.678–0.962; $P = 0.0169$). Median progression-free survival durations for the ramucirumab plus paclitaxel and placebo plus paclitaxel groups were 4.40 and 2.86 months, respectively (HR 0.635, 95 %CI 0.536–0.752; $P < 0.0001$), with median times to progression of 5.5 and 3.0 months, respectively ($P < 0.0001$). The objective response rate in the ramucirumab plus paclitaxel group was 28 %, compared with 16 % for placebo plus paclitaxel ($P = 0.0001$).

2.4.2 *Breast Cancer*

The addition of ramucirumab to first-line therapy with docetaxel did not achieve the primary endpoint of prolonging progression-free survival in patients with HER2-negative unresectable, locally recurrent or metastatic breast cancer in the phase III ROSE trial (NCT00703326) [28]. A total of 1,144 patients were randomized 2:1 to receive ramucirumab 10 mg/kg plus docetaxel 75 mg/m^2 (n = 759) or placebo plus docetaxel 75 mg/m^2 (n = 385), every 3 weeks until disease progression or unacceptable toxicity occurred. After a median follow-up duration of 16.2 months, progression-free survival durations in the ramucirumab and placebo arms were 9.5 months and 8.2 months, respectively (HR 0.88, 95 %CI 0.75–1.01; $P = 0.077$). There was also no significant difference in median overall survival between the ramucirumab and placebo groups (27.3 vs 27.2 months; HR 1.01, 95 %CI 0.83–1.23; $P = 0.915$). However, the median time to progression was significantly longer for ramucirumab versus placebo (9.7 vs 8.2 months; HR 0.78, 95 %CI 0.65–0.93; $P = 0.034$ and the objective response and disease control rates were higher for ramucirumab (44.7 % vs 37.9 %; $P = 0.027$ and 86.4 % vs 81.3 %; $P = 0.022$, respectively).

2.4.3 *Colorectal Cancer*

The combination of ramucirumab 8 mg/kg plus the modified FOLFOX-6 (folinic acid, fluorouracil, oxaliplatin) regimen, given every 2 weeks, was evaluated in an open-label phase II study in 48 patients with metastatic colorectal cancer (NCT00862784) [29, 30]. The median progression-free survival was 11.5 months (95 %CI 8.6–13.1 months), compared with an expected progression-free survival duration of 8 months. The median overall survival duration was 20.4 months (95 %CI 18.5–25.1 months). Objective response and disease control rates were 58.3 % and 93.8 %, respectively.

A phase Ib study (NCT01286818) evaluated the effects of ramucirumab 8 mg/kg every 2 weeks in combination with the FOLFIRI (fluorouracil, folinic acid, irinotecan) regimen in six Japanese patients with metastatic colorectal

cancer who had disease progression on or after first-line treatment with bevacizumab, oxaliplatin and a fluoropyrimidine [31]. The median progression-free survival duration was 7.3 months (95 %CI 1.2–10.9 months). One patient had a partial response and four had stable disease.

2.4.4 Hepatocellular Carcinoma

First-line treatment with ramucirumab (8 mg/kg every 2 weeks) as monotherapy produced a median progression-free survival duration of 4.0 months (95 %CI 2.6–5.7 months) in a phase II study in 42 patients with advanced HCC [25]. Partial responses were observed in four patients (9.5 %), with a median response duration of 14.1 months. Another 25 patients (59.5 %) had stable disease, giving a disease control rate of 69.0 %. The median overall survival duration was 12.0 months (95 %CI 6.1–19.7 months). Overall survival rates at 1 year and 2 years were 49.4 % and 23.4 %, respectively. Among patients with Barcelona Clinic Liver Cancer (BCLC) stage C disease, median overall survival durations for those with Child-Pugh A and B cirrhosis were 18.0 months (95 %CI 6.1–23.5 months) and 4.4 months (95 %CI 0.5–9.0 months), respectively; corresponding values for median progression-free survival were 4.2 months (95 %CI 2.6–6.7 months) and 2.6 months (95 %CI 0.5–6.2 months).

2.4.5 Lung Cancer

Combination therapy with ramucirumab plus first-line pemetrexed- and platinum-based chemotherapy demonstrated clinical activity in patients with non-small cell lung cancer (NSCLC) but did not achieve the primary endpoint of prolonging progression-free survival in a phase II study (NCT01160744) [32]. A total of 140 patients with non-squamous stage IIIb/IV NSCLC and no prior chemotherapy or anti-VEGF therapy were randomized to receive pemetrexed plus carboplatin or cisplatin either alone (arm A, n = 71) or in combination with ramucirumab 10 mg/kg (arm B, n = 69), every 3 weeks for 4–6 cycles; those without disease progression then received maintenance therapy with pemetrexed (arm A) or pemetrexed plus ramucirumab (arm B). Median progression-free survival durations for arms A and B were 5.6 months and 7.2 months, respectively (HR 0.75, 90 %CI 0.55–1.03; $P = 0.132$). Objective response rates in arms A and B were 38 % and 49.3 %, respectively ($P = 0.18$); this included one complete response in arm B. The disease control rate was significantly higher for patients treated with ramucirumab (86 % vs 70 % for arm A; $P = 0.031$). At the time of the final analysis for progression-free survival, the median overall survival duration was 10.4 months for arm A, compared with 13.9 months for arm B (HR 0.83, 90 %CI 0.56–1.22; $P = 0.43$).

The combination of ramucirumab plus paclitaxel and carboplatin was evaluated in another open-label phase II study in patients with advanced lung cancer [33]. Patients in this study received ramucirumab 10 mg/kg, paclitaxel 200 mg/m^2 and carboplatin AUC = 6 every 3 weeks for up to 6 cycles, followed by ramucirumab maintenance. An interim analysis of 15 patients showed an objective response rate of 67 % (one complete response and nine partial responses) and median progression-free survival of 5.7 months.

2.4.6 Melanoma

Ramucirumab, alone or in combination with dacarbazine, demonstrated modest activity in a randomized, open-label phase II study in chemotherapy-naïve patients with metastatic malignant melanoma (NCT00533702) [34]. A total of 102 patients were treated with ramucirumab 10 mg/kg every 3 weeks as monotherapy or in combination with dacarbazine 1000 mg/m^2 every 3 weeks. Median progression-free survival durations for the monotherapy and combination therapy arms were 1.7 and 2.6 months, respectively; however, the study was not powered to compare treatments. Partial response and stable disease rates for the monotherapy group were 4 % and 42 %, respectively; corresponding values for the combination therapy group were 17 % and 37 %.

2.4.7 Ovarian Cancer

Ramucirumab monotherapy was evaluated in an open-label phase II study in 60 patients with persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer [35]. Patients in this study, who had previously received platinum-based chemotherapy, received ramucirumab 8 mg/kg every 2 weeks. The 6-month progression-free survival rate was 34.2 % (95 %CI 21.7–47.0 %). Three patients (5 %) had a partial response (median duration 5.6 months) and 34 (57 %) had stable disease. Three patients (5 %) were not evaluable for response and 20 (33 %) had progressive disease. The median progression-free and overall survival durations were 3.5 months (95 %CI 2.3–5.3 months) and 11.1 months (95 %CI 8.3–17.0 months), respectively.

2.4.8 Prostate Cancer

Ramucirumab and cixutumumab, a fully human IgG1 monoclonal antibody targeting insulin-like growth factor, were evaluated in a phase II trial in patients with metastatic castration-resistant prostate cancer who had disease

progression on docetaxel-based therapy [36]. A total of 132 patients were randomized to receive IV ramucirumab 6 mg/kg (n = 66) or cixutumumab 6 mg/kg (n = 66), once weekly in addition to IV mitoxantrone 12 mg/m^2 every 3 weeks and oral prednisone 5 mg twice daily, for up to 12 cycles. Median follow-up durations for the ramucirumab and cixutumumab groups were 21.8 and 22.7 months, respectively. Median confirmed progression-free survival and overall survival durations were 6.7 months (95 %CI 4.5–8.3 months) and 13.0 months (95 %CI 9.5–16.0 months), respectively, for the ramucirumab group and 4.1 months (95 %CI 3.0–5.6 months) and 10.8 months (95 %CI 6.5–13.0 months), respectively, for the cixutumumab group. Prostate-specific antigen response rates in the ramucirumab and cixutumumab groups were 22.0 % and 18.4 %, respectively.

2.4.9 Renal Cancer

Ramucirumab demonstrated activity in tyrosine kinase inhibitor-refractory metastatic clear cell renal cell carcinoma in a multicentre phase II study [37]. Patients who had progressive disease or intolerance to prior sorafenib and/or sunitinib therapy (n = 40) received ramucirumab 8 mg/kg every 2 weeks. At an interim analysis there were two confirmed partial responses and 19 (49 %) patients had stable disease lasting >5 months; the median progression-free survival at the time of analysis was 6 months.

2.5 Adverse Events

Prescribing information for ramucirumab carries a black box warning regarding the risk of haemorrhagic events, including serious and sometimes fatal events [12]. It also contains warnings and precautions regarding the risks of arterial thromboembolic events, hypertension, infusion-related reactions, gastrointestinal perforations, impaired wound healing, reversible posterior leukoencephalopathy syndrome (RPLS) and clinical deterioration in patients with Child-Pugh B or C cirrhosis.

In the REGARD study, the most common adverse events of any grade occurring in >5 % of ramucirumab recipients with a difference of ≥2 % from the placebo group were hypertension (16 % vs 8 % for placebo; grade 3–4, 8 % vs 3 %), diarrhoea (14 % vs 9 %; grade 3–4, 1 % vs 2 %), headache (9 % vs 3 %; no grade 3–4 events) and hyponatremia (6 % vs 2 %; grade 3–4, 3 % vs 1 %) [12]. Clinically relevant adverse events occurring in 1–5 % of ramucirumab recipients were neutropenia (4.7 % vs 0.9 % for placebo), epistaxis (4.7 % vs 0.9 %), rash (4.2 % vs 1.7 %), intestinal obstruction (2.1 % vs 0 %) and arterial thromboembolic events (1.7 % vs 0 %). Proteinuria occurred in 8 % of ramucirumab recipients, compared with 3 % of patients in the placebo group, and two patients discontinued ramucirumab due to this event. Gastrointestinal perforation and infusion-related reactions occurred in 0.8 % and 0.4 % of patients, respectively. The most frequently reported serious adverse events in the ramucirumab group were anaemia (3.8 % and intestinal obstruction (2.1 %).

Overall rates of adverse events in the REGARD study were similar for ramucirumab versus placebo [26]. Grade 3–4 adverse events occurred in 57 % of patients in the ramucirumab group and 58 % in the placebo group. Although grade 3–4 arterial thromboembolic events were more frequent in the ramucirumab group (1 % vs 0 % for placebo), the difference was not statistically significant ($P = 0.55$). No increases in haemorrhage, venous thrombosis, proteinuria, infusion-related reactions, gastrointestinal perforation or fistula formation were seen with ramucirumab versus placebo. There were five deaths in the ramucirumab group (2 %) and two in the placebo group (2 %) that were considered to be related to study medication.

In the RAINBOW trial, grade 3 or higher adverse events occurring in >5 % of patients receiving ramucirumab in combination with paclitaxel were neutropenia (40.7 % of patients vs 18.8 % for placebo plus paclitaxel), leukopenia (17.4 % vs 6.7 %), hypertension (14.1 % vs 2.4), anaemia (9.2 % vs 10.3 %), fatigue (7.0 % vs 4.0 %), abdominal pain (5.5 % vs 3.3 %) and asthenia (5.5 % vs 3.3 %) [27]. Febrile neutropenia occurred in 3.1 % of patients treated with ramucirumab plus paclitaxel, compared with 2.4 % in the placebo plus paclitaxel group.

2.6 Ongoing Clinical Trials

There are several ongoing phase II and III trials of ramucirumab in different solid tumour indications:

- Randomized, double-blind, multinational phase III trial of ramucirumab versus placebo, in combination with paclitaxel, in patients with gastric cancer and gastro-oesophageal junction cancer who had disease progression on or within 4 months after platinum- or fluoropyrimidine-containing chemotherapy (RAINBOW; NCT01170663) [38]
- Randomized, double-blind, multinational phase III trial of ramucirumab plus docetaxel versus placebo plus docetaxel in patients with unresectable locally recurrent or metastatic breast cancer who have not received prior chemotherapy (ROSE; NCT00703326; TRIO-012) [39]
- Randomized, double-blind, multinational phase III trial of ramucirumab versus placebo, in combination with a FOLFIRI regimen, in patients with metastatic

colorectal cancer that has progressed after first-line therapy (RAISE; NCT01183780) [40]

- Randomized, double-blind, multinational phase III trial of second-line ramucirumab and BSC versus BSC alone in patients with HCC previously treated with sorafenib (REACH; NCT01140347) [41]
- Randomized, double-blind, multinational phase III trial of ramucirumab versus placebo, in combination with docetaxel, in patients with stage IV NSCLC with disease progression after one prior platinum-based regimen (REVEL; NCT01168973) [42]
- Randomized, open-label, multicentre phase II study of ramucirumab or icrucumab with docetaxel or docetaxel alone as second-line therapy for bladder, urethra, ureter or renal pelvis carcinoma (NCT01282463) [43]
- Open-label, single-arm, phase II trial of ramucirumab monotherapy in Japanese patients with metastatic gastric cancer or gastro-oesophageal junction cancer with disease progression after first-line platinum- or fluoropyrimidine-containing chemotherapy (NCT01983878) [44]
- Randomized, double-blind, phase II study of ramucirumab versus placebo, in combination with mFOLFOX6 regimen in patients with gastric, oesophageal and gastro-oesophageal cancer (NCT01246960) [45]
- Randomized, open-label, multicentre phase II trial of ramucirumab plus eribulin versus eribulin monotherapy in patients with unresectable, locally-recurrent or metastatic breast cancer who had previously been treated with anthracycline and taxane therapy (NCT01427933) [46]
- Randomized, open-label, phase II trial of ramucirumab or icrucumab in combination with oral capecitabine in patients with unresectable, locally advanced or metastatic breast cancer who had previously been treated with anthracycline and taxane therapy (NCT01234402) [47]
- Randomized, double-blind, phase II trial of ramucirumab plus docetaxel versus placebo plus docetaxel in Japanese patients with stage IV NSCLC who had disease progression after one prior platinum-based regimen (NCT01703091) [48]
- Randomized, multinational, open-label phase II trial of ramucirumab in combination with platinum-based chemotherapy as first-line treatment for recurrent or advanced NSCLC (NCT01160744) [49]
- Phase II non-randomized, open-label trial of ramucirumab in patients with persistent or recurrent ovarian cancer, fallopian tube cancer, and primary peritoneal carcinoma (NCT00721162) [50]
- Three phase II trials of ramucirumab in patients with solid tumours are also ongoing (NCT01634555, NCT01515306, NCT01017731) [51–53]

3 Current Status

Ramucirumab received its first global approval on April 21 2014 for use as monotherapy in the treatment of advanced or metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma who have experienced disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy in the US.

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References

1. Krupitskaya Y, Wakelee HA. Ramucirumab, a fully human mAb to the transmembrane signaling tyrosine kinase VEGFR-2 for the potential treatment of cancer. Curr Opin Investig Drugs. 2009;10(6):597–605.
2. Qiu M-Z, Xu R-H. The progress of targeted therapy in advanced gastric cancer. Biomark Res. 2013;1(1):32.
3. Frenette C, Gish R. Targeted systemic therapies for hepatocellular carcinoma: clinical perspectives, challenges and implications. World J Gastroenterol. 2012;18(6):498–506.
4. Hsu JY, Wakelee HA. Monoclonal antibodies targeting vascular endothelial growth factor: current status and future challenges in cancer therapy. BioDrugs. 2009;23(5):289–304.
5. Aprile G, Bonotto M, Ongaro E, et al. Critical appraisal of ramucirumab (IMC-1121B) for cancer treatment: from benchside to clinical use. Drugs. 2013;73(18):2003–15.
6. Meza-Junco J, Sawyer MB. Metastatic gastric cancer—focus on targeted therapies. Biologics. 2012;6:137–46.
7. Claesson-Welsh L, Welsh M. VEGFA and tumour angiogenesis. J Intern Med. 2013;273(2):114–27.
8. Maeda K, Chung YS, Ogawa Y, et al. Prognostic value of vascular endothelial growth factor expression in gastric carcinoma. Cancer. 1996;77(5):858–63.
9. Van Cutsem E, de Haas S, Kang YK, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. J Clin Oncol. 2012;30(17):2119–27.
10. Clarke JM, Hurwitz HI. Targeted inhibition of VEGF receptor 2: an update on ramucirumab. Expert Opin Biol Ther. 2013;13(8):1187–96.
11. US Food and Drug Administration. Ramucirumab. 2014. http://www.fdagov/drugs/informationondrugs/approveddrugs/ucm394260htm.
12. Eli Lilly and Company. Ramucirumab: Prescribing information. 2014. http://www.accessdatafdagov/drugsatfda_docs/label/2014/125477lblpdf.
13. Eli Lilly and Company. Lilly details progress on achieving strategic business goals and its advancing pipeline to investment community. Media Release. 2013.
14. European Commission. Community register of orphan medicinal products: Ramucirumab for the treatment of hepatocellular carcinoma. 2012. http://ec.europa.eu/health/documents/community-register/html/o1019.htm. Accessed.

15. European Commission. Community register of orphan medicinal products: Ramucirumab for the treatment of gastric cancer. 2012. http://ec.europa.eu/health/documents/community-register/html/o1004.htm. Accessed.
16. US Food and Drug Administration. Orphan drug designations: ramucirumab for hepatocellular carcinoma. 2011. http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=353911. Accessed.
17. US Food and Drug Administration. Orphan drug designations and approvals: ramucirumab for gastric cancer. 2012. http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=359711. Accessed.
18. Eli Lilly and Company. Lilly announces second positive ramucirumab phase III gastric cancer study meets primary endpoint; phase III Lilly/TRIO Breast Cancer Study Misses Primary Endpoint Media Release. 2013.
19. Eli Lilly and Company. Lilly completes acquisition of ImClone systems. Media Release. 2008.
20. Biologics Inc. Biologics, Inc. to be Exclusive Specialty Pharmacy Provider of Eli Lilly's CYRAMZA™ (ramucirumab).
21. Dyax Corp. Dyax enters into antibody library license agreement with ImClone systems incorporated. Media Release. 2003.
22. Dyax Corp. Dyax announces developments in licensing and funded research program. Media Release. 2009.
23. Franklin MC, Navarro EC, Wang Y, et al. The structural basis for the function of two anti-VEGF receptor 2 antibodies. Structure. 2011;19(8):1097–107.
24. Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol. 2010;28(5):780–7.
25. Zhu AX, Finn RS, Mulcahy M, et al. A phase II and biomarker study of ramucirumab, a human monoclonal antibody targeting the VEGF receptor-2, as first-line monotherapy in patients with advanced hepatocellular cancer. Clin Cancer Res. 2013;19(23):6614–23.
26. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31–9.
27. Wilke H, Van Cutsem E, Oh SC, et al. RAINBOW: a global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy rainbow IMCL CP12-0922 (I4T-IE-JVBE). J Clin Oncol Conf. 2014;32(3 Suppl):abstr. LBA7.
28. Mackey JR, Ramos-Vazquez M, Lipatov O, et al. Primary results of ROSE/TRIO-12, a randomized placebo controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. 36th Annual San Antonio Breast Cancer Symposium. 2013:abstr. S5-04.
29. Garcia-Carbonero R, Rivera F, Maurel J, et al. An open-label phase II study evaluating the safety and efficacy of ramucirumab combined with mFOLFOX-6 as first-line therapy for metastatic colorectal cancer. Oncologist. 2014;19(4):350–1.
30. Garcia-Carbonero R, Rivera F, Maurel J, et al. A phase II, open-label study evaluating the safety and efficacy of ramucirumab combined with mFOLFOX-6 as first-line therapy in patients (pts) with metastatic colorectal cancer (mCRC): CP12-0709/NCT00862784. J Clin Oncol Conf. 2012;30(4 Suppl):abstr. 533.
31. Yoshino T, Yamazaki K, Yoshida M, et al. A phase (Ph) Ib study of irinotecan (IRI), levofolinate (LV), and 5-fluorouracil (5-FU) (FOLFIRI) plus ramucirumab (RAM; IMC-1121B) drug product in Japanese (JP) patients (pts) with metastatic colorectal carcinoma (mCRC) progressive during or following first-line therapy with bevacizumab (BEV), oxaliplatin (OXALI), and a fluoropyrimidine (FP) (CP12-1029/NCT01286818). J Clin Oncol Conf. 2013;31(4 Suppl):abstr. 591.
32. Doebele RC, Spigel D, Tehfe M, et al. A phase 2 randomized open-label study of ramucirumab (IMC 1121B; RAM) in combination with first-line platinum-based chemotherapy in patients (pts) with recurrent or advanced non-small cell lung cancer (NSCLC): Final results from non-squamous (NSQ) pts (NCT01160744). J Thorac Oncol. 2013;8:S290.
33. Camidge DR, Ballas MS, Dubey S, et al. A phase II, open-label study of ramucirumab (IMC-1121B), an IgG1 fully human monoclonal antibody (MAb) targeting VEGFR-2, in combination with paclitaxel and carboplatin as first-line therapy in patients (pts) with stage IIIb/IV non-small cell lung cancer (NSCLC). J Clin Oncol Conf. 2010;28(15 Suppl 1):abstr. 7588.
34. Carvajal R, Thompson J, Gordon M, et al. A Phase 2 Randomized Study of Ramucirumab (Imc 1121B; Ram) with or Without Dacarbazine (Dtic) in Patients (Pts) with Metastatic Melanoma (Mm) (Cp12-0604/Nct00533702). 37th Congress of the European Society for Medical Oncology. 2012:abstr. 1115PD.
35. Penson RT, Moore KN, Fleming GF, et al. A phase II, open-label, multicenter study of IMC-1121B (ramucirumab; RAM) monotherapy in the treatment of persistent or recurrent epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) carcinoma (CP12-0711/NCT00721162). J Clin Oncol Conf. 2012;30(15 Suppl):abstr. 5012.
36. Hussain M, Rathkopf DE, Liu G, et al. A phase II randomized study of cixutumumab (IMC-A12: CIX) or ramucirumab (IMC-1121B: RAM) plus mitoxantrone (M) and prednisone (P) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) following disease progression (PD) on docetaxel (DCT) therapy. J Clin Oncol Conf. 2012;30(5 Suppl 1): abstr. 97
37. Garcia JA, Hudes GR, Choueiri TK, et al. Phase II study of IMC-1121B in patients with metastatic renal cancer (mRCC) following VEGFR-2 tyrosine kinase inhibitor (TKI) therapy (IMCL CP12-0605/ NCT00515697). Genitourin Cancers Symp. 2010:abstr. 326.
38. Eli Lilly and Company. A study of paclitaxel with or without ramucirumab in metastatic gastric adenocarcinoma (RAINBOW) [ClinicalTrials.gov identifier NCT01170663]. US National Institutes of Health, ClinicalTrialsgov 2010.
39. Eli Lilly and Company. Phase III study of docetaxel + ramucirumab or placebo in breast cancer [ClinicalTrials.gov identifier NCT00703326]. US National Institutes of Health, ClinicalTrialsgov. 2008.
40. Eli Lilly and Company. A study in second line metastatic colorectal cancer [ClinicalTrials.gov identifier NCT01183780]. US National Institutes of Health, ClinicalTrialsgov. 2010.
41. Eli Lilly and Company. A study of ramucirumab (IMC-1121B) drug product (DP) and best supportive care (BSC) versus placebo and BSC as 2nd-line treatment in patients with hepatocellular carcinoma after 1st-line therapy with sorafenib (REACH) [ClinicalTrials.gov identifier NCT01140347]. US National Institutes of Health, ClinicalTrialsgov. 2010.
42. Eli Lilly and Company. A study of chemotherapy and ramucirumab vs. chemotherapy alone in second line non-small cell lung cancer participants who received prior first line platinum based chemotherapy [ClinicalTrials.gov identifier NCT01168973]. US National Institutes of Health, ClinicalTrialsgov. 2010.
43. Eli Lilly and Company. Study of ramucirumab or IMC-18F1 with docetaxel or docetaxel alone as second-line therapy in participants with bladder, urethra, ureter, or renal pelvis carcinoma [ClinicalTrials.gov identifier NCT01282463]. US National Institutes of Health, ClinicalTrialsgov. 2011.

44. Eli Lilly and Company. A study of ramucirumab in treating japanese participants with metastatic gastric or gastroesophageal junction cancer [ClinicalTrials.gov identifier NCT01983878]. US National Institutes of Health, ClinicalTrialsgov. 2013.
45. Eli Lilly and Company. A study of ramucirumab in patients with gastric, esophageal and gastroesophageal cancer [ClinicalTrials.gov identifier NCT01246960]. US National Institutes of Health, ClinicalTrialsgov. 2010.
46. Eli Lilly and Company. a study of ramucirumab (IMC-1121B) in combination with eribulin versus eribulin alone in patients with breast cancer [ClinicalTrials.gov identifier NCT01427933]. US National Institutes of Health, ClinicalTrialsgov. 2011.
47. Eli Lilly and Company. Study of IMC-18F1 or ramucirumab DP in combination with capecitabine or capecitabine on previously treated breast cancer patients [ClinicalTrials.gov identifier NCT01234402]. US National Institutes of Health, ClinicalTrialsgov. 2010.
48. Eli Lilly and Company. A study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV Non-small cell lung cancer [ClinicalTrials.gov identifier NCT01703091]. US National Institutes of Health, ClinicalTrialsgov. 2012.
49. Eli Lilly and Company. A study of pemetrexed & carboplatin/cisplatin or gemcitabine & carboplatin/cisplatin with or without IMC-1121B in patients previously untreated with recurrent or advanced non-small cell lung cancer (NSCLC) [ClinicalTrials.gov identifier NCT01160744]. US National Institutes of Health, ClinicalTrialsgov. 2010.
50. Eli Lilly and Company. Study of ramucirumab in ovarian cancer [ClinicalTrials.gov identifier NCT00721162]. US National Institutes of Health, ClinicalTrialsgov. 2008.
51. Eli Lilly and Company. A study to assess the pharmacokinetics of ramucirumab in combination with FOLFIRI [ClinicalTrials.gov identifier NCT01634555]. US National Institutes of Health, ClinicalTrialsgov. 2012.
52. Eli Lilly and Company. A study of ramucirumab (IMC-1121B) and paclitaxel in participants with solid tumors [ClinicalTrials.gov identifier NCT01515306]. US National Institutes of Health, ClinicalTrialsgov. 2012.
53. Eli Lilly and Company. Study of ramucirumab (IMC-1121B) therapy and corrected QT (QTc) interval changes [ClinicalTrials.gov identifier NCT01017731]. US National Institutes of Health, ClinicalTrialsgov. 2009.