PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ramucirumab (Cyramza) for Gastric Cancer

October 29, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effectiveness and safety of ramucirumab, as monotherapy and as part of combination therapy, for the treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma after prior chemotherapy.

Ramucirumab is a human monoclonal antibody that binds to vascular endothelial growth factor receptor-2 (VEGFR2) thereby inhibiting angiogenesis and metastasis.[1] The recommended dose is 8 mg/kg administered intravenously every two weeks as a one-hour infusion.[1,2] The Health Canada indication for ramucirumab is limited to those patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma with disease progression on or after prior platinum and fluoropyrimidine chemotherapy.[2]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two randomized controlled trials met the criteria for inclusion in the pCODR systematic review: REGARD[3] and RAINBOW.[4] Both REGARD (n=355) and RAINBOW (n=665) were randomized, double-blind, multi-national, parallel-arm, placebo-controlled, phase 3 industry sponsored trials. Enrolment in both trials was limited to patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Only the REGARD trial included patients from Canada.[5]

In the RAINBOW trial, 665 patients were randomized 1:1 to receive either ramucirumab (n=330) or placebo (n=335), each added to paclitaxel. Enrolled patients were predominantly white (61%), with 35% being Asian. Approximately, 71% were male, 61% had an ECOG performance status of one, and the median age was 61 years.

In the REGARD trial, 355 patients were randomized 2:1 to receive either ramucirumab (n=238) or placebo (n=117), each added to best supportive care. Enrolled patients were predominantly white (77%), with 16% being Asian. Approximately 70% were male, 72% had an ECOG performance status of one, and the median age was 60 years.

Potential limitations and sources of bias in both studies included the lack of inclusion of patients with an ECOG performance status of 2 or greater, which may limit the generalizability of the trial results to Canadian clinical practice as some patients may present with a performance status of 2 or greater. The use of a placebo comparator in the REGARD trial for patients with an ECOG performance status of 0 was considered inappropriate by the pCODR Clinical Guidance Panel (CGP), since these patients would generally receive chemotherapy in Canadian clinical practice. In the REGARD trial there were baseline imbalances between treatment groups in the number of metastatic sites, progression-free interval after previous treatment and presence of peritoneal metastases that may have favoured the ramucirumab group. Additionally, the sample size of the REGARD trial was modified three times due to difficulties with accrual. The final sample size was approximately half that originally planned. Although it was reported to have power of 80%, it was likely to be less due to the smaller than anticipated difference in overall survival observed between treatment groups, which would increase the uncertainty around the estimate.[3,6,7] The RAINBOW trial had an imbalance between treatment groups

for the diffuse histological subtype which might have favoured the ramucirumab-treated group and in ECOG performance status, number of metastatic sites, and ascites that might have favoured the paclitaxel plus placebo group.

Efficacy

In the RAINBOW trial, median overall survival was statistically significantly longer in the ramucirumab plus paclitaxel group (9.6 months) compared with the placebo plus paclitaxel group (7.4 months); hazard ratio (HR) 0.81, 95% confidence interval (CI), 0.68 to 0.96, p<0.017.[7,8] Estimated rates of OS at six months were 72% in the RAM+PAC group and 57% in the PBO+PAC group and one-year OS rates were 40% and 30%.[4] Median progression-free survival was also statistically significantly longer in those who received ramucirumab plus paclitaxel compared with those who received placebo plus paclitaxel (4.4 months versus [vs.] 2.9 months; HR 0.64; 95% CI 0.54 to 0.75; p<0.0001).[7,8] Health-related quality of life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Questionnaire (EORTC-QLQ-C30) and the European Quality of Life Questionnaire-5 Dimension (EQ-5D) Index Score. Significant differences in time to deterioration in the emotional functioning (HR 0.64; 95% CI 0.49 to 0.84) and the nausea and vomiting (HR 0.75; 95% CI 0.57 to 0.97) scales of the EORTC-QLQ-C30 in favour of the ramucirumab plus paclitaxel group, and in the diarrhea symptom scale in favour of the paclitaxel plus placebo group were reported.[9] No significant differences between groups were noted for the remaining scales.[9]

Similarly, in the REGARD trial, median overall survival was statistically significantly longer in the ramucirumab group (5.2 months) compared with the placebo group (3.8 months); HR 0.78, 95% CI 0.60 to 1.0, p<0.047.[3,7] Estimated rates of OS at six months were 41.8% in the ramucirumab-treated group and 31.6% in those receiving placebo and one-year OS rates were 17.6% and 11.8%.[3] Median progression-free survival was also statistically significantly longer in those who received ramucirumab (2.1 months) compared with those who received placebo (1.3 months; HR 0.48; 95% CI 0.38 to 0.62; p<0.0001).[3,7] HRQoL was assessed in the REGARD trial using the EORTC-QLQ-C30; however, due to a lack of post-baseline data for a majority of patients in the trial, no data on time-to-deterioration were available.[10]

Harms

In the RAINBOW trial, 99.1% of patients in the ramucirumab plus paclitaxel group experienced an adverse event compared with 97.9% of patients in the placebo plus paclitaxel group.[7] In the REGARD trial, 94.5% of patients who received ramucirumab experienced an adverse event compared with 87.8% of patients who received placebo.[7] In both trials, the proportion of patients who experienced a serious adverse event was similar between the group of patients who received ramucirumab compared with those who received placebo (RAINBOW, 46.8% vs. 42.2%; REGARD, 44.9% vs. 44.3%).[7] Grade 3 or higher adverse events occurred in more patients in the ramucirumab plus paclitaxel group (81.7%) than in the placebo plus paclitaxel group (62.6%) in the RAINBOW trial, whereas they occurred in a similar proportion of patients in both treatment groups in the REGARD trial (ramucirumab, 56.8%; placebo, 58.3%).[7] In REGARD, the proportion of patients who discontinued treatment due to adverse events was higher in the ramucirumab plus best supportive care arm than in the placebo plus best supportive care arm (ramucirumab, 10.5%; placebo, 6.0%). For the RAINBOW study, discrepant values for the proportion of patients who discontinued treatment due to adverse events were reported within the European Medicine Agency's Committee for Medicinal Products for Human Use (EMA CHMP) assessment report for ramucirumab[7] and by Wilke et al.[4] The EMA CHMP reported that the proportion of patients who discontinued due to adverse events was higher in the ramucirumab plus paclitaxel arm (31.2%) compared with placebo plus paclitaxel (24.3%),

but also reported, similarly to Wilke et al[4], that the proportions of patients who discontinued due to an adverse event were 12% for ramucirumab plus paclitaxel and 11% for placebo plus paclitaxel.

1.2.2 Additional Evidence

pCODR did not receive input on ramucirumab for advanced or metastatic gastric cancer or GEJ adenocarcinoma from any patient advocacy group; therefore, pCODR conducted a formal literature search and grey literature search to inform pERC's deliberation on patient values as part of its deliberative framework. Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of ramucirumab and is discussed as supporting information:

- *Critical appraisal of a network meta-analysis (NMA) of ramucirumab and paclitaxel combination therapy and other second-line treatments for adult patients with advanced or metastatic gastric cancer or GEJ cancer.*

  The manufacturer-submitted NMA of ramucirumab and paclitaxel combination therapy versus other second-line treatments of adult patients with advanced or metastatic GC or GEJC was summarized and critically appraised. The methodology used for the NMA and indirect comparisons were not reported in detail. Due to the limited number of studies informing the networks, the assumptions that were made to connect the network for PFS, and the poor quality of the data from included studies, results were not presented from this NMA.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Stomach cancers (gastric and GEJ) are the 9th and 10th leading causes of cancer-related mortality in men and women, respectively. Assuming 3,000 new cases of advanced esophago-gastric adenocarcinoma in Canada annually and assuming that 80% would receive first-line therapy with a 60% drop-off after first-line therapy, roughly 1,500 Canadians would be considered eligible for second-line therapy. There is no defined standard of care for patients after failure of first-line therapy. For patients who maintain an ECOG performance status of 0 to 2, a modest survival benefit with taxanes (docetaxel, paclitaxel) and irinotecan-based chemotherapy has been demonstrated when compared with best supportive care. Currently, there are no novel biologic therapies available for patients in this setting. Better therapies are needed.

Effectiveness

The pCODR Clinical Guidance Panel considered that the 2.2 month difference in median overall survival and HR of 0.81 in favour of ramucirumab plus paclitaxel compared with paclitaxel plus placebo, demonstrated in the RAINBOW trial, was clinical meaningful in this second-line population of patients with advanced or metastatic gastric or GEJ adenocarcinoma, who had progressed after prior fluoropyrimidine/platinum chemotherapy. The results of the secondary endpoints of progression-free survival and objective response were also in favour of ramucirumab plus paclitaxel. Statistically significant differences in time to deterioration in the emotional functioning and nausea and vomiting scales of the EORTC-QLQ-C30 were noted in favour of the ramucirumab plus paclitaxel arm. No differences in the remaining 13 scales were noted. The findings of the RAINBOW trial are generalizable to the Canadian second-line population of patients with gastric or GEJ adenocarcinoma.

The results of the REGARD trial demonstrated a statistically significant and clinically modest improvement in overall survival in favour of ramucirumab compared with best supportive care. However, best supportive care is not a clinically relevant comparator in Canadian patients with an ECOG performance status of 0 or 1 as chemotherapy is the currently accepted standard of care.

While the RAINBOW study specified that prior chemotherapy be a fluoropyrimidine and platinum combination and the REGARD study specified that prior chemotherapy be a fluoropyrimidine and/or platinum combination, the pCODR Clinical Guidance Panel felt that patients with a non-platinum first-line regimen (such as FOLFIRI) would still be considered eligible for treatment with ramucirumab plus paclitaxel or ramucirumab alone. Furthermore, both studies restricted the entry criteria to gastric or GEJ adenocarcinoma and ECOG performance status of 0 or 1. Therefore, the results of the trials are not readily generalizable to patients with distal esophageal adenocarcinoma or to patients with an ECOG performance status of 2 or higher.

Safety

In the RAINBOW trial, a similar proportion of patients in both treatment arms experienced a serious adverse event. Grade 3 or higher neutropenia, hypertension and fatigue occurred more commonly in the ramucirumab plus paclitaxel arm than in the paclitaxel plus placebo arm. In addition, a higher proportion of patients in the ramucirumab plus paclitaxel arm discontinued treatment due to an adverse event than in the paclitaxel plus placebo arm. In the REGARD trial, grade 3 or higher hypertension and abdominal pain occurred more frequently in the ramucirumab alone arm than in the placebo arm. In addition, a higher proportion of patients in the ramucirumab alone arm discontinued treatment due to an adverse event than in the placebo arm. The pCODR Clinical Guidance panel noted that the toxicities of treatment with ramucirumab would be considered acceptable and manageable in this patient population.

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit with the use of ramucirumab in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with an ECOG performance status of 0-1, after prior chemotherapy.

The Clinical Guidance Panel concludes that there may be a net overall clinical benefit with the use of ramucirumab monotherapy for the treatment of patients with advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with an ECOG performance status of 0-1, after prior chemotherapy. The uncertainty of the CGP's conclusion for ramucirumab monotherapy is due to the difficulty in interpreting the clinical relevance of the modest OS benefit observed in the REGARD trial given that the comparator arm of best supportive care in this good performance status patient population does not reflect current Canadian practice.

In making this conclusion, the Clinical Guidance Panel considered:

- **Effectiveness:** The efficacy of ramucirumab in combination with paclitaxel was demonstrated in the RAINBOW global randomized controlled trial, with a statistically significant and clinical meaningful improvement in OS, when compared with paclitaxel alone. RAINBOW is considered generalizable to Canadian patients with pre-treated advanced gastric or GEJ adenocarcinoma with a performance status of 0-1.

The efficacy of ramucirumab monotherapy was demonstrated in the REGARD global randomized controlled trial, with a consistent, statistically significant but more modest median OS improvement when compared to best supportive care only.

There was no evidence of quality of life impairment associated with ramucirumab use in both trials, although data were limited in the REGARD study.

- **Safety:** The use of ramucirumab in combination with paclitaxel or as monotherapy was associated with an acceptable and manageable toxicity profile.

- **Need and Burden of disease:** While chemotherapy is now recommended over best supportive care in the second-line setting, there is no defined standard of care. There are currently no biologics available for use in this setting. As better therapies are needed, ramucirumab addresses an unmet need in this patient population.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding ramucirumab for advanced gastric cancer or gastro-esophageal junction adenocarcinoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.cadth.ca/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding ramucirumab conducted by the gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ramucirumab and a summary of submitted Provincial Advisory Group Input on ramucirumab are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Ramucirumab received a Notice of Compliance from Health Canada on July 16th, 2015 for the following indication: as a single agent or in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma with disease progression on or after prior platinum and fluoropyrimidine chemotherapy.[2] Ramucirumab is a human monoclonal antibody that binds to vascular endothelial growth factor receptor-2 (VEGFR2) thereby inhibiting angiogenesis and metastasis.[1]The recommended dose is 8 mg/kg administered intravenously every two weeks as a one-hour infusion.[1,2] There are currently no monoclonal antibody drugs with a Health Canada indication for the second-line treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma. For the assessment of monotherapy in the second-line setting, the CGP considered docetaxel, irinotecan, paclitaxel, and best supportive care as the most relevant comparators while FOLFIRI was considered the most relevant comparator in the assessment of combination therapy. Input from both the CGP and PAG confirmed the lack of standardization in second-line treatment of advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma. No patient input was submitted for this review.

2.1.2 Objectives and Scope of pCODR Review

The primary objective of this review was to evaluate the beneficial and harmful effects of ramucirumab compared with appropriate comparators in both the monotherapy and combination therapy settings in patients with advanced metastatic gastric cancer or gastroesophageal junction adenocarcinoma after prior chemotherapy.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

Background

Two trials meeting the criteria for the systematic review were identified from the literature: REGARD[3] and RAINBOW.[4] Both REGARD (n=355) and RAINBOW (n=665) were randomized, double-blind, multi-national, parallel-arm, placebo-controlled, phase 3, industry-sponsored trials that enrolled patients with advanced or metastatic gastric or GEJ adenocarcinoma whose disease had progressed during or within 4 months of first-line chemotherapy for metastatic disease, or within 6 months of adjuvant chemotherapy (REGARD only). Only REGARD included patients from Canada.[5] REGARD was designed to test the superiority of ramucirumab (RAM) 8 mg/kg i.v. every two weeks added to best supportive care (BSC) compared with BSC alone.[3] RAINBOW was designed to test the superiority of RAM 8 mg/kg i.v. given on days 1 and 15 in combination with paclitaxel (PAC) 80 mg/m^2 i.v. on days 1, 8, and 15 of a 28-day cycle compared with PAC (same regimen) alone.[4]

In REGARD, randomization (2:1) was stratified by weight loss, geographic region, and location of primary tumor.[3] REGARD originally planned to enroll 651 patients, but difficulties with recruitment led to three revisions and a final sample size of 348 with 80% power to detect a hazard ratio of 0.690 (median OS: 7.25 months in RAM+BSC group versus 5 months in PBO+BSC group) at a two-sided alpha of 0.05.[3,6]

In RAINBOW, randomization (1:1) was stratified by geographic region, time to progression after first dose of first-line therapy, and disease measurability.[4] RAINBOW originally planned to enroll 663 patients and ended up recruiting 665; the planned sample size provided 90% power to detect a hazard ratio of 0.75 (median OS: 9.33 months in RAM+PAC group versus 7.0 months in PBO+PAC group) at a one-sided alpha of 0.025.[7] No amendments were filed that affected the design of the trial.[7]

In both REGARD and RAINBOW, efficacy analyses were performed on the intention-to-treat (ITT) population. The primary efficacy outcome for each trial was overall survival (OS), which was analyzed by the Kaplan-Meier method for time-to-event and used a log-rank test for between-group comparisons; a similar analytic approach was used for secondary analyses of progression-free survival (PFS), the key secondary outcome for each trial.[3,4] Other than randomization strata, there was no further covariate adjustment for either primary or secondary efficacy analyses in REGARD or RAINBOW.[7]

In REGARD, patients were randomized to either ramucirumab (RAM; n=238) or placebo (PBO; n=117), each added to best supportive care (BSC). Enrolled patients were predominantly white (77%) and male (70%) with a median age of 60 years (range: 24 to 87 years). About 72% of patients had an ECOG performance score of one. Asians, who are disproportionately affected by gastric cancer, were underrepresented (16%) in the trial. Gastric carcinoma was the primary tumor in 3/4 of patients.

In RAINBOW, patients were randomized to either RAM (n=330) or PBO (n=335), each added to paclitaxel (PAC). Similar to REGARD, enrolled patients were predominantly white (61%) and male (71%) with a median age of 61 years (range: 24 to 84 years). About 61% of patients had an ECOG performance score of one. Asians were better represented in RAINBOW than they were in REGARD (35% versus 16%). Gastric carcinoma was the primary tumor in almost 80% of patients.

Main Results

Efficacy

In REGARD, the median OS was 5.2 months (95% CI, 4.4 to 5.7) in ramucirumab-treated patients compared with 3.8 months (95% CI, 2.8 to 4.7) in patients receiving placebo, which corresponded to a hazard ratio (HR) of 0.78 (95% CI, 0.60 to 1.0; $P < 0.047$).[3,7] Estimated rates of OS at six months were 41.8% in the ramucirumab-treated group and 31.6% in those receiving placebo and one-year OS rates were 17.6% and 11.8%.[3] Median PFS was 2.1 months (95% CI, 1.5 to 2.7) in ramucirumab-treated patients compared with 1.3 months (95% CI, 1.3 to 1.4) in patients receiving placebo; this corresponded to a HR of 0.48 (95% CI, 0.38 to 0.62; $P < 0.0001$).[3,7] (Table 1)

In RAINBOW, the median OS was 9.6 months (95% CI, 8.5 to 10.8) in RAM+PAC-treated patients compared with 7.4 months (95% CI, 6.3 to 8.4), which corresponded to a HR of 0.81 (95% CI, 0.68 to 0.96; $P = 0.017$).[4,7] Estimated rates of OS at six months were 72% in the RAM+PAC group and 57% in the PBO+PAC group and one-year OS rates were 40% and 30%.[4] Median PFS was 4.4 months (95% CI, 4.2 to 5.3) in RAM+PAC-treated patients compared with 2.9 months (95% CI, 2.8 to 3.0) in patients receiving PBO+PAC; this corresponded to a HR of 0.64 (95% CI, 0.54 to 0.75; $P < 0.0001$).[4,7] (Table 1)

Table 1: Summary of Key Efficacy Outcomes

Outcome	REGARD[3,11]		RAINBOW[4,7]	
	RAM+BSC (n=238)	PBO+BSC (n=117)	RAM+PAC (n=330)	PBO+PAC (n=335)
Overall Survival (months)				
Median (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)	9.6 (8.5, 10.8)	7.4 (6.3, 8.4)
Log-rank p-value (2-sided), stratified[a,b]	0.047		0.017	
HR (95% CI), stratified[a,b,c]	0.776 (0.603, 0.998)		0.807 (0.678, 0.962)	
Progression-Free Survival (months)				
Median (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)	4.4 (4.2, 5.3)	2.9 (2.8, 3.0)
Log-rank p-value (2-sided), stratified[a,c,d]	<0.0001		<0.0001	
HR (95% CI), stratified[a,c,d]	0.483 (0.376, 0.620)		0.635 (0.536, 0.752)	

BSC= best supportive care; CI= confidence interval; HR= hazard ratio; PAC= paclitaxel; PBO= placebo; RAM= ramucirumab

ITT set

Refer to (Table 7) for additional efficacy outcomes.

Quality of Life

Health-related quality of life (HRQoL) in the RAINBOW trial was assessed using the European Organization for Research and Treatment of Cancer Questionnaire (EORTC-QLQ-C30) and the European Quality of Life Questionnaire-5 Dimension (EQ-5D) Index Score.

Significant differences in time to deterioration in the emotional functioning (HR 0.64; 95% CI 0.49 to 0.84) and the nausea and vomiting (HR 0.75; 95% CI 0.57 to 0.97) scales of the EORTC-QLQ-C30 in favour of the ramucirumab plus paclitaxel group, and in the diarrhea symptom scale in favour of the paclitaxel plus placebo group were reported.[9] No significant differences between groups were noted for the remaining scales.[9]

HRQoL was assessed in the REGARD trial using the EORTC-QLQ-C30; however, due to a lack of post-baseline data for a majority of patients in the trial, no data on time-to-deterioration were available.[10]

Harms

The proportion of patients experiencing serious adverse events (SAEs) was similar between RAM+BSC and PBO+BSC in REGARD (44.9% versus 44.3%) and between RAM+PAC and PBO+PAC in RAINBOW (46.8% versus 42.2%).[7] In REGARD, the proportion of patients experiencing any adverse event (AE) regardless of severity grade was higher in the RAM+BSC group (94.5%) compared with the PBO+BSC group (87.8%).[7] In RAINBOW, the distribution of AEs was similar between the RAM+PAC group (99.1%) and the PBO+PAC group (97.9%).[7] AEs of grade ≥3 severity occurred at a similar frequency between groups in REGARD (56.8% versus 58.3%, respectively), but at a higher frequency in the RAM+PAC group (81.7%) than in the PBO+PAC group (62.6%) in RAINBOW.[7] In REGARD, the proportion of patients who discontinued treatment due to adverse events was higher in the ramucirumab plus best supportive care arm than in the placebo plus best supportive care arm (ramucirumab, 10.5%; placebo, 6.0%). For the RAINBOW study, discrepant values for the proportion of patients who discontinued treatment due to adverse events were reported within the European Medicine Agency's Committee for Medicinal Products for Human Use (EMA CHMP) assessment report for ramucirumab[7] and by Wilke et al.[4] The EMA CHMP reported that the proportion of patients who discontinued due to adverse events was higher in the ramucirumab plus paclitaxel arm (31.2%) compared with placebo plus paclitaxel (24.3%), but also reported, similarly to Wilke et al[4], that the proportions of patients who discontinued due to an adverse event were 12% for ramucirumab plus paclitaxel and 11% for placebo plus paclitaxel.

In REGARD,[7] diarrhea and headache (both of any severity), and hypertension (any severity and grade ≥3) were more common with RAM treatment than control.

In RAINBOW,[7] any severity of diarrhea, epistaxis, peripheral edema, stomatitis, proteinuria, thrombocytopenia, and hypoalbuminemia were all more common with RAM+PAC treatment than control. In addition, fatigue, neutropenia, leukopenia, and hypertension were all more common with RAM+PAC treatment than control, both as adverse events of any severity and of those of grade ≥3 severity.

Limitations

Major limitations and sources of bias in the trials included the following:

- Sample size was revised three times in REGARD, resulting in a final sample size that was almost half the size of the original (348 versus 651).[3,6,7] Sample size recalculation is typically seen in 'adaptive' trial designs; this was not the design of the REGARD trial. It is also notable that the observed difference between treatment arms in OS (5.2 months versus 3.8 months) was actually much smaller than the expected magnitude of difference (7.25 months versus 5 months) used in the final sample size calculation. A large reduction in sample size would reduce the precision of the estimate for various study outcomes, including the primary outcome of OS. Although the final sample size was said to have 80% power, the

trial's actual power is likely to have been even less than 80% as a consequence of the smaller than anticipated difference observed between groups in OS (1.4 months versus the projected 2.5 months), which would have increased the uncertainty around the estimate.

- Using a placebo comparator in REGARD for patients (28%) with a baseline ECOG PS of 0 was felt by the CGP to be inappropriate. Instead, the CGP indicated that the most appropriate comparator for these patients would have been chemotherapy. This suggests, from a Canadian point of view, that patients with an ECOG PS of 0 assigned to the control group were undertreated compared to usual clinical practice. Thus, the findings from this subgroup of patients may not be generalizable to Canadian clinical practice.
- Asian patients accounted for 35% of randomized patients in RAINBOW compared with 16% in REGARD. In RAINBOW, almost 97% of Asian patients enrolled were living in countries in East Asia;[12] such demographic information was not reported for REGARD. Given that the majority of Asian patients studied in the pivotal trial (RAINBOW) were from non-Western countries, it is unclear to what extent the findings are generalizable to Asians living in Western countries such as Canada.
- A few imbalances between groups were noted that potentially advantaged treatment with RAM:
    - REGARD: number of metastatic sites ('≥3' more prevalent in PBO+BSC group), progression-free interval after previous treatment ('< 6 months' more prevalent in PBO+BSC group), and peritoneal metastases (present more often in PBO+BSC group)
    - RAINBOW: histological subtype ('diffuse' more prevalent in PBO+PAC group)
        - Note: There were imbalances between arms in ECOG performance status, number of metastatic sites, and ascites that may have potentially advantaged treatment with paclitaxel plus placebo.
- Eligibility criteria for the RAINBOW trial included first-line chemotherapy with a platinum + fluoropyrimidine doublet-based regimen and an ECOG PS of 0 or 1. Eligibility criteria for the REGARD trial included first-line chemotherapy with a platinum- and/or fluoropyrimidine-containing regimen and an ECOG PS of 0 or 1. According to the CGP, these criteria should have been broader to include first-line chemotherapy with FOLFIRI and an ECOG PS of ≤2, which would have increased the generalizability of the findings to Canadian clinical practice.
- In RAINBOW, regional differences were observed in a sub-analysis of OS, in which, unlike western countries (region 1), Asian countries (region 3) did not show a statistically significant benefit of RAM treatment. Practice variation between the regions in the use of post-discontinuation chemotherapy (PDT) was posited as a potential explanation for this inconsistent finding. The increased overall use of PDT in Asian countries compared with western countries (67% versus 37%) was thought to have contributed to the observed increase in median OS in the control group in region 3 compared with that observed in region 1 (10.5 months versus 5.6 months, respectively),[4,7] potentially erasing any small differences between the treatment and control groups in region 3.
- Neither trial investigated for potential differences in clinical response to treatment based on the expression of biomarkers such as HER2 or VEGFR2 in tumor tissue, exposing an evidence gap for characterizing which patients may benefit most from RAM treatment.[7]

- Only REGARD included patients from Canada, which potentially limits the generalizability of the findings from RAINBOW.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

Critical appraisal of a NMA of ramucirumab and paclitaxel combination therapy and other second-line treatments for adult patients with advanced or metastatic gastric cancer or GEJ cancer

The manufacturer-submitted NMA of ramucirumab and paclitaxel combination therapy versus other second-line treatments of adult patients with advanced or metastatic gastric cancer or GEJ cancer was summarized and critically appraised. The methodology used for the NMA and indirect comparisons were not reported in detail. Due to the limited number of studies informing the networks, the assumptions that were made to connect the network for PFS, and the poor quality of the data from included studies, results were not presented from this NMA.

See section 7.1 for more information.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

No patient input was submitted for this review. Therefore, pCODR conducted a formal literature search and grey literature search to inform pERC's deliberation on patient values as part of its deliberative framework.

PAG Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of ramucirumab for gastric cancer and gastro-esophageal cancer:

Clinical factors:

- The relative benefits of monotherapy versus in combination with paclitaxel

Economic factors:

- Drug wastage
- If combination therapy, the additional costs of administering paclitaxel

2.2 Interpretation and Guidance

Ramucirumab is a human monoclonal antibody (IgG1) that binds the vascular endothelial growth factor receptor 2 (VEGFR2) and acts as a receptor antagonist by blocking the

binding of vascular endothelial growth factor (VEGF) to VEGFR2. VEGFR2 is understood to mediate the majority of the downstream effects of VEGF in angiogenesis. This submission is considering a funding indication for ramucirumab as a single agent or in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric or GEJ adenocarcinoma, after prior chemotherapy.

Effectiveness

As summarized in the Systematic review, ramucirumab has been studied in two international randomized trials – RAINBOW and REGARD.

The RAINBOW study is a global, randomized (1:1) double-blind study that compared ramucirumab in combination with paclitaxel (RAM+PAC, n=330) with placebo in combination with paclitaxel (PBO+PAC, n=335) for the treatment of patients with advanced (metastatic or advanced and unresectable) gastric cancer or GEJ adenocarcinoma whose disease had progressed after prior fluoropyrimidine/platinum chemotherapy. The enrolled population was 71% male with a median age of 61 years, 35% Asian, approximately 80% gastric and 61% with an ECOG PS of 1. The RAM+PAC arm was superior for the primary efficacy endpoint of OS (median 9.6 months vs 7.4 months, HR 0.81, p=0.017). The overall median survival improvement of 2.2 months (HR 0.81) would be considered clinically meaningful and relevant in this patient population, particularly given that the median survival for patients with advanced gastric and GEJ cancers is less than one year.

The secondary endpoints of PFS (4.4 months vs 2.9 months, HR 0.64, p <0.0001) and objective response rate (ORR) (28% vs 9%, p=00001) also favoured RAM+PAC. In a pre-planned subgroup analysis by geographic region, the survival efficacy of ramucirumab versus placebo was not significantly improved in Asian countries (HR 0.986, 95% CI 0.73-1.33) vs non-Asian countries (HR 0.732, 95%CI 0.59-0.91).

The REGARD study is a global, randomized (2:1), double-blinded trial of ramucirumab (RAM, n=238) and best supportive care (BSC) versus placebo and BSC (PBO, n=117) in the treatment of metastatic gastric or GEJ adenocarcinoma following disease progression on first-line platinum- and/or fluoropyrimidine-containing combination therapy. The enrolled population was 70% male with a median age of 60 years, only 16% Asian, 75% gastric and 72% with an ECOG PS of 1. RAM was superior for the primary endpoint of OS (5.2 months vs 3.8 months, HR 0.78, p=0.047). The overall median survival improvement of 1.4 months (HR 0.78) would be considered to be modest in this patient population. The secondary endpoints of PFS (2.1 months vs 1.3 months, HR 0.48, p<0.0001). ORR were similar (3.4% vs 2.6%) but disease control rates were higher with RAM (48.7% vs 23.1%, p<0.0001). The CGP feels that the BSC arm is not a clinically relevant comparator in an ECOG PS 0-1 patient population as chemotherapy currently represents the more commonly accepted standard of care.

With respect to QoL in RAINBOW, a significant difference in time to deterioration favouring RAM+PAC was observed in 2 of the 15 scales from the EORTC-QLQ-30: emotional functioning and nausea and vomiting. A statistically significant difference in time to deterioration in the diarrhea symptom scale in favour of the paclitaxel plus placebo arm was also observed. No differences were observed for the remaining scales. EQ-5D index scores were similar at baseline and decreased similarly between RAM+PAC and PBO+PAC. In REGARD, no published time to deterioration analysis was available as post baseline-data was not available for the majority of patients.

Of note, several limitations were identified in a manufacturer-submitted network meta-analysis to estimate the efficacy of RAM+PAC versus other second-line treatments. As such, this analysis was not used by the CGP to inform this opinion.

In the opinion of the CGP, the findings of the RAINBOW trial are considered meaningful and generalizable to the Canadian second-line population of gastric or GEJ adenocarcinoma. The absence of Canadian participation in the RAINBOW study and the fact that second-line paclitaxel is not currently uniformly available across Canada does not limit its generalizability to the Canadian population. While paclitaxel is sometimes delivered on a less resource-intensive schedule of every 3 weeks, the 3 weeks out of 4 schedule used in RAINBOW is generally more tolerable. As such, the safety of using ramucirumab in combination with q3weekly paclitaxel cannot be readily extrapolated from the available data. In addition, as ramucirumab is still given every 2 weeks, the incremental resource advantage of using q3weekly paclitaxel will be modest as patients would still need to come in for day 1 and day 15 visits every 4 weeks.

Regional differences were observed in the RAINBOW analysis and it is noted that, among the Asian patients enrolled in this study, the vast majority (96.5%) were treated in East Asia. However, the subgroup findings are interpreted as hypothesis-generating and would not presently limit the generalizability of the RAINBOW results to Asian patients treated in Canada. While both studies specified prior chemotherapy to be a fluoropyrimidine and/or platinum combination, the CGP feels that patients treated with a non-platinum first line regimen (such as FOLFIRI) would still be considered eligible for RAM+PAC or RAM. There are presently no known predictive biomarkers for ramucirumab.

While the defined population specifies prior treatment with a platinum and/or fluoropyrimidine, patients treated with a first-line fluoropyrimidine-irinotecan combination (FOLFIRI) and patients with HER2 positive disease treated with first-line trastuzumab therapy may also be considered to be candidates for 2nd line ramucirumab therapy.

Both studies restricted eligibility to gastric or GEJ adenocarcinoma and ECOG PS 0-1, hence these results are not readily generalizable to patients with distal esophageal adenocarcinoma or to patients with an ECOG PS of 2 or higher.

Safety

In RAINBOW, the proportion of patients experiencing serious adverse events was similar between both arms. While the pattern of toxicity was also similar, increased grade 3+ toxicities in the RAM+PAC arm included neutropenia (41% vs 19%), hypertension (15% vs 3%), and fatigue (12% vs 6%), with a higher proportion of patients discontinuing treatment due to adverse events (31.2% vs 24.3%) based on data reported in the EMA CHMP assessment report for ramucirumab. Of note, Wilke et al, as well as the EMA, reported that the proportion of patients who discontinued treatment due to adverse events was 12% in ramucirumab plus paclitaxel arm and 11% in the paclitaxel plus placebo arm. In REGARD, RAM was well-tolerated with a similar proportion of patients experiencing any adverse event in both treatment arms. The only increased Grade 3+ toxicities compared to PBO were noted to be hypertension (8% vs 3%) and abdominal pain (6% vs 3%) and a similar proportion of patients discontinued treatment due to adverse events in both arms (10.5% vs 6%).

This pattern of toxicity would be considered acceptable and manageable in this patient population.

Need and Burden of Illness

Stomach cancers (gastric and GEJ) are the 9th and 10th leading causes of cancer-related mortality in men and women, respectively. Assuming 3,000 new cases of advanced esophago-gastric adenocarcinoma in Canada annually and assuming that 80% would receive first-line therapy with a 60% drop-off after first-line therapy, roughly 1,500 Canadians would be considered eligible for second-line therapy. As highlighted in section 3, there is no defined standard of care for patients after failure of first-line therapy. For patients

who maintain an ECOG PS <=2, a modest survival benefit with taxanes (docetaxel, paclitaxel) and irinotecan-based chemotherapy has been demonstrated when compared with best supportive care. Currently, there are no novel biologic therapies available for patients in this setting. Better therapies are needed.

No patient advocacy group input was provided for this review. This may be due, in part, to the absence of an established patient advocacy presence for stomach cancers in Canada, which is probable consequence of the limited survivorship in this disease.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit with the use of ramucirumab in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with an ECOG performance status of 0-1, after prior chemotherapy.

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit with the use of ramucirumab monotherapy for the treatment of patients with advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with an ECOG performance status of 0-1, after prior chemotherapy. The uncertainty of the CGP's conclusion for ramucirumab monotherapy is due to the difficulty in interpreting the clinical relevance of the modest OS benefit observed in the REGARD trial given that the comparator arm of BSC in this good performance status patient population does not reflect current Canadian practice.

In making this conclusion, the Clinical Guidance Panel considered:

- **Effectiveness:** The efficacy of ramucirumab in combination with paclitaxel was demonstrated in the RAINBOW global randomized controlled trial, with a statistically significant and clinical meaningful improvement in OS, when compared with paclitaxel alone. RAINBOW is considered generalizable to Canadian patients with pre-treated advanced gastric or GEJ adenocarcinoma with a performance status of 0-1.

  The efficacy of ramucirumab monotherapy was demonstrated in the REGARD global randomized controlled trial, with a consistent, statistically significant but more modest median OS improvement when compared to BSC only.

  There was no evidence of quality of life impairment associated with ramucirumab use in both trials, although data were limited in the REGARD study.

- **Safety:** The use of ramucirumab in combination with paclitaxel or as monotherapy was associated with an acceptable and manageable toxicity profile.

- **Need and Burden of disease:** While chemotherapy is now recommended over BSC in the second-line setting, there is no defined standard of care. There are currently no biologics available for use in this setting. As better therapies are needed, ramucirumab addresses an unmet need in this patient population.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

The Canadian Cancer Society estimates that, for 2014, 3,300 Canadians were diagnosed with gastric cancer and another 2,100 Canadians were diagnosed with esophageal cancer with at least half(or 1,100 cases) attributable to distal esophageal or gastroesophageal junction (GEJ) adenocarcinomas.[13,14] Among these estimated 4,400 new cases of esophago-gastric adenocarcinoma, two-thirds (or approximately 3,000) are expected to present with advanced, unresectable disease.[15] As such, the burden of advanced gastric/GEJ cancers is a concern and the need for improved treatments remains significant.

3.2 Accepted Clinical Practice

In the unresectable setting of locally advanced and/or metastatic disease, gastric and GEJ adenocarcinomas are treated similarly. Adenocarcinomas represent over 90% of gastric and gastroesophageal cancers. Gastric cancers may be further histologically subdivided by Lauren classification to intestinal or diffuse. While this classification may have prognostic value, it does not inform systemic therapy decisions. Approximately 20% of gastric/GEJ adenocarcinomas overexpress the HER2 protein (a member of the EGFR family).

The therapeutic goals for patients with advanced gastric and GEJ cancers is palliative – to reduce symptoms related to disease, improve quality of life and extend survival. The median survival for patients treated with best supportive care is less than 6 months[16] while patients treated with contemporary chemotherapies may be expected to reach a median survival of 9-11 months.[17] While selected patients may benefit from palliative radiation or surgery to relieve obstruction and/or bleeding, the primary treatment modality in this setting is chemotherapy which is considered suitable for patients with an ECOG PS of 2 or better. In Canada, the most commonly used regimens contain a combination of a fluoropyrimidine (5-fluorouracil or capecitabine) and a platinum (cisplatin or oxaliplatin). The addition of epirubicin (an anthracycline) is also a commonly employed option.[18] Other active agents include irinotecan (a topoisomerase 1 inhibitor) and taxanes (docetaxel or paclitaxel). These latter two classes are more commonly considered in the second-line setting but may be considered in first-line particularly for patients unsuitable for platinum therapy. Indeed, there is recent evidence to support the use of 5FU and irinotecan (FOLFIRI) in first-line with similar survival when compared to epirubicin, cisplatin and capecitabine but with a better time to treatment failure (5.1 months vs 4.2 months, p=0.008) and reduced grade 3+ toxicity (69% vs 84%, p<0.001).[19] Given its more favourable toxicity profile, the use of FOLFIRI in the first-line setting may be expected to increase. For patients with HER2 positive disease, the addition of trastuzumab to first-line 5FU/platinum chemotherapy significantly extends survival and is current accepted practice.[20]

There is no defined standard of care for patients after failure of first-line therapy. For patients who maintain an ECOG PS <=2, a modest survival benefit with taxanes (docetaxel,

paclitaxel) and irinotecan chemotherapy has been demonstrated when compared to BSC (Table 1)

Table 1. Second-line randomized trials in advanced esophago-gastric cancers

Trial	Sample Size	ECOG PS	Comparators	Median Survival
COUGAR-02[21]	168	0-2	Docetaxel 75mg/m2 q3w vs BSC	5.2m vs 3.6m (p=0.01)
Thuss-Patience etal[22]	40	0-2	Irinotecan 250mg/m2 IV q3w vs BSC	4.0 vs 2.4m (p=0.012)
Kang et al.[23]	202	0-1	Irinotecan 150mg/m2 IV q2w OR docetaxel 60mg/m2 IV q3w vs BSC	5.3m vs 3.8 m (p =0.007)
Hironaka et al.[24]	223	0-2	Paclitaxel 80mg/m2 IV d1,8,15 q4w vs Irinotecan 150mg/m2 IV q2w	9.5m vs 8.4m, p-0.38

Ramucirumab is a human monoclonal antibody (IgG1) that binds to the vascular endothelial growth factor receptor 2 (VEGFR2) and acts as a receptor antagonist by blocking the binding of vascular endothelial growth factor (VEGF) to VEGFR2. It has now been evaluated in patients with pre-treated advanced gastric/GEJ adenocarcinoma in two international randomized phase III trials.

RAINBOW is a global, placebo-controlled phase III trial which randomized 665 patients with advanced gastric or GEJ adenocarcinoma previously treated with platinum/fluoropyrimidine therapy and an ECOG PS of 0-1, to ramucirumab 8mg/kg or placebo given IV on days 1 and 15 with paclitaxel 80mg/m2 IV day 1, 8 and 15 of a 28 day cycle.[4] The primary endpoint of overall survival (OS) significantly favoured the ramucirumab arm (median 9.6 months vs 7.4 months, HR 0.807, p=0.017). Secondary efficacy endpoints of progression-free survival (PFS) (4.4 months vs 2.9 months, HR 0.63, p <0.0001) and objective response rate (ORR) (28% vs 9%, p=00001) also favoured the ramucirumab combination arm. Increased grade 3+ toxicities included neutropenia (41% vs 19%), hypertension (14% vs 2%), fatigue (12% vs 5%) and abdominal pain (6% vs 3%). Approximately 35% of patients in RAINBOW were Asian (Japan, South Korea, Singapore and Taiwan) with the remainder from the US, Europe, Israel, Australia and South America. In a pre-planned subgroup analysis by geographic region, the survival efficacy of ramucirumab versus placebo was not significantly improved in Asians (HR 0.986, 95% CI 0.73-1.33) vs non-Asians (HR 0.732, 95%CI 0.59-0.91). With respect to Quality of Life (QoL) in RAINBOW, more patients in the RAM+PAC arm reported stable or improved QoL at 18 weeks (24% vs 16%) and time to deterioration in their EORTIC QLQ-C30 scores were similar or better with RAM+PAC in 14 of 15 QoL parameters.

REGARD is the second global, placebo-controlled phase III trial in a similar population which randomized 335 patients in a 2:1 fashion to 2nd line ramucirumab monotherapy versus placebo.[3] About 16% of patients were Asian. The primary endpoint of OS significantly favoured ramucirumab (5.2 months vs 3.8 months, HR 0.776, p=0.047). PFS also favoured ramucirumab (2.1 months vs 1.3 months, HR 0.620, p<0.0001). ORR were similar (3.4% vs 2.6%) but disease control rates were higher with ramucirumab (48.7% vs 23.1%, p<0.0001). Ramucirumab was well-tolerated with the only increased Grade 3+ toxicities compared to placebo noted to be hypertension (8% vs 3%) and abdominal pain (6% vs 3%). While recognizing that there was limited completion of post-baseline QoL

assessment (48% in ramucirumab arm and 25% in placebo), ramucirumab appeared to be associated with a longer time to ECOG deterioration (to PS >=2) (5.1 months vs 2.4 months).

The use of ramucirumab as monotherapy or in combination with paclitaxel in the 2nd line setting is currently endorsed in the guidelines of the National Comprehensive Cancer Network (NCCN) as a Category 1 recommendation ("based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[25]

3.3 Evidence-Based Considerations for a Funding Population

Based upon the REGARD and RAINBOW trial eligibility criteria, the population under consideration is patients with advanced gastric or gastroesophageal adenocarcinoma, previously treated with platinum and fluoropyrimidine based chemotherapy with an ECOG PS of 0 to 1.

Assuming 3,000 new cases of advanced esophago-gastric adenocarcinoma in Canada and assuming that 80% would receive first-line therapy with a 60% drop-off after first-line therapy, roughly 1,500 Canadians would be considered eligible for treatment with ramucirumab annually.

Currently, there are no biomarkers that predict for a response to ramucirumab. Patients with a histologic subtype of squamous carcinoma would not be considered eligible. In terms of the chemotherapy partner to be combined with ramucirumab, paclitaxel is the only agent which has been investigated as per the RAINBOW study. While ramucirumab in combination with FOLFIRI has been associated with a tolerable safety profile and improved survival in the 2nd line setting of MCRC in the phase 3 RAISE trial,[26] the benefit of ramucirumab with irinotecan in 2L gastric cancer is unknown. With respect to earlier lines of therapy, a randomized phase II trial presented at ASCO 2014 failed to demonstrate a benefit with the addition of ramucirumab to FOLFOX chemotherapy in the first-line setting.[27] There is presently no evidence on the role of ramucirumab in the adjuvant setting.

3.4 Other Patient Populations in Whom the Drug May Be Used

While REGARD excluded patients with PS of 2, ramucirumab monotherapy may be a reasonable consideration in patients with an ECOG PS of 2. In addition, while advanced distal esophageal adenocarcinomas were not included, it may be reasonable to extrapolate the benefit of ramucirumab to this patient population as well.

While the defined population specifies prior treatment with a platinum and/or fluoropyrimidine, patients treated with a first-line fluoropyrimidine-irinotecan combination (FOLFIRI) and patients with HER2 positive disease treated with first-line trastuzumab therapy may also be considered to be candidates for 2nd line ramucirumab therapy.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

By the deadline of April 29, 2015, no patient advocacy group input on ramucirumab (Cyramza) for advanced gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma was received by the pan-Canadian Oncology Drug Review (pCODR). As such, a formal literature search through Medline (see Appendix A) was undertaken by the pCODR secretariat and CADTH's Information Specialists (IS) in an effort to inform pERC's deliberation on patient values as part of its deliberative framework. This was supplemented by a grey literature search of national and international patient advocacy group websites and cancer forums. The formal literature search did not identify any relevant publications; however, relevant information was identified from grey literature sources through non-formal sampling methods by a single reviewer. The intent of this process was not to conduct an exhaustive systematic review of patient experiences, but to compile information to help illustrate some of the patient experiences and perspectives on gastric or GEJ adenocarcinoma and ramucirumab.

According to the Canadian Cancer Society, gastric cancer incidence rates in 2015 are estimated to be 2.3% in males and 1.3% in females.[13] Some of the key symptoms of gastric and/or GEJ adenocarcinoma reported by patients included indigestion, abdominal and chest pain, nausea, vomiting and weight loss. Some patients also noted the late diagnosis often associated with this cancer thus causing limited treatment options by the time of diagnosis.

pCODR found personal accounts from five individual patients on their experiences with ramucirumab for the treatment of gastric or GEJ adenocarcinoma as well as one caregiver's experience in caring for a patient with gastric cancer. From the information gathered, patients treated with ramucirumab expressed side effects such as fatigue, weakness, hoarseness and dizziness. However, some patients reported better tolerability with ramucirumab compared to other treatments. Unfortunately, one patient noted progression despite treatment with ramucirumab. Patients who were placed on ramucirumab after their chemotherapy had become ineffective hoped that it could lead to remission. However, some patients were also aware of its palliative intention and expected the treatment to stabilize the cancer in order to have a better quality of life with fewer side effects and regain the ability to resume to normal daily activities.

Please see below for a detailed summary of patient experiences with gastric cancer/GEJ adenocarcinoma and ramucirumab. Quotes are reproduced as they appeared from comments of personal accounts with no modifications made for spelling, punctuation or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Gastric Cancer and/or Gastro-Esophageal Junction Adenocarcinoma

Patients and caregivers alike noted the huge amount of burden on the daily living of patients with gastric and/or GEJ cancer. One of the most commonly reported symptoms of the disease is difficulty swallowing (i.e. dysphagia). Some patients reported having an inflamed esophagus while others described food being stuck in their throat or chest as if they were choking. In an attempt to alleviate this symptom, some patients modified their diet to compose primarily of soft foods being consumed in smaller amounts. Some also incorporated liquid nutritional supplements (e.g. Boost and Ensure) to supply adequate nutrition. However, even with these measures, some patients still reported having difficulties swallowing where even ingesting liquids posed a challenge. Below are comments from two patients to help illustrate these difficulties.

One patient noted: "*When I eat the food doesn't go down anymore. It just sits there. If I lay down, I wake suddenly, like I am about to throw up. I also have heartburn like you wouldn't believe. It is awful.*

(Source: MedicineNet, Inc. Patient Comments: Stomach Cancer – Describe your experience [Internet]. San Clemente, CA: MedicineNet, Inc. c1996-2015 [cited 2015 Jul 07]. Available from: *http://www.medicinenet.com/stomach_cancer/patient-comments-56-page4.htm*)

Another patient indicated that: "*…The biggest danger, other than choking, obviously, is loss of weight. At one point it was 3 cans of Ensure and whatever else I could get down. I did have a script for a lidocane slurry. That negated the pain but did nothing for the stricture. Eventually at week 5 I was dilated and again at week 9 as well. So far so good!*

(Source: Cancer Society Network. Esophageal cancer: Choking and food getting stuck [Internet]. [place unknown]: Cancer Society Network. c2010-2015 [cited 2015 Jul 07]. Available from: http://csn.cancer.org/node/262895)

Frequent vomiting was also reported by patients as a major concern. It was noted that, most of the time, it was not food which was expelled but instead, bile and mucous. Some patients also reported frequent occurrence of heartburn, stomach ache, bloating, diarrhea and constipation. These are illustrated in the following comment: *[My husband] can't keep anything down, not broth, not even water. It burns like heck on the way down and then he says his stomach feels like someone is crushing it. Even when he doesn't eat, he gets pains and then throws up bile. Soooo, he will have to have a G or J tube put in but his white blood cell count is too low (neutrophils at 1.0) for them to do it.*

(Source: Cancer Society Network. Esophageal cancer: Extreme stomach pain and nausea – had to stop chemo/radiation [Internet]. [place unknown]: Cancer Society Network. c2010-2015 [cited 2015 Jul 07]. Available from: *http://csn.cancer.org/node/293070*)

Due to the above symptoms, some patients reported having very little to no appetite or experienced early satiety which ultimately resulted in significant weight loss. Consequently, they felt constant debilitating fatigue and weakness. With such dramatic weight loss, some patients needed a feeding tube inserted (GJ- or J-tube) while others required total parenteral nutrition (TPN) to deliver necessary nutrition.

4.1.2 Patients' Experiences with Current Therapy for Advanced Gastric Cancer

Some patients referred to gastric cancer as a "silent and sinister killer" due to the difficulties they experienced with the diagnosis and the grave consequences resulting from a late diagnosis. Currently, the only potentially curative treatment for gastric cancer is through surgical resection (Cancer Care Ontario, 2015). However, with some patients already having advanced or metastatic gastric/GEJ cancer by the time of diagnosis, surgery is oftentimes not an option by the time their diagnosis is confirmed. As a result, they are often referred to chemotherapy and/or radiation instead of surgical treatment.

(Sources: June. Oesophageal cancer – silent and sinister [Internet]. Victoria, AU: Cancer Council Victoria; 2015 Jan 20 [cited 2015 Jul 07]. Available from: http://www.cancervic.org.au/tell_your_cancer_story/story_2015-01-15_01.html

CancerCompass. Anyone with stomach cancer [Internet]. [place unknown: Rising Tide – Cancer Treatment Centers of America, Inc. 2008 May 19 [cited 2015 Jul 07]. Available from: http://www.cancercompass.com/message-board/message/all,790,6.htm)

Due to a variety of chemotherapeutic agents available for gastric cancer and the heterogeneity of the disease, there is currently a lack of standard regimen that is clinically used. Patients reported having received trastuzumab, paclitaxel, docetaxel, cisplatin, epirubicin among many others. According to an evidence-based clinical practice guideline developed by the Cancer Care Ontario Program in Evidence-Based Care (PEBC),[28] the current standard of care practiced in Ontario is the combination of epirubicin, cisplatin and 5FU (ECF). However, they also noted that epirubicin, oxaliplatin and capecitabine (EOX) is an acceptable alternative and may be chosen based on patient preference.

The following are selected accounts of patient experiences with current treatment for gastric and/or GEJ cancer.

Patient Experience #1

The ECF worked very well the firt time round. I had 6 sessions in total, which is the maximum, I had plenty of side effects, put weight on; tiredness; sickness; but felt better after the first week. The 5 FU on this occasion was in form of tablets - Xeloda; than after a laparoscopy showed that there is still plenty cancer in the peritonium, although less in the stomach itself, I had 6 sessions of Irinotekan and Taxotere, which was dreadfull, constant diaria and pains and dont feel it did anything at all, as 2 months after stopping the sessions, the cancer had got worst and spread to the bowels and plenty of it, blocking and not allowing food in. Scans do not really show the disease much, just a layer of tickness, I normally have a laparoscopy under general anaesthetic, which allows a good look. Scans have shown changes but only when it has been too late... By God's miracle I am here today and feeling excellent, eating full portions now, lookling well, having energy. Thats after the 6 more sessions of the latest chemo, that time I received the chemo via tube and line, as could not swallow tablets. Immunotherapy so far no problem, but some side effects may appear at any time during the 3 months period in between infusions.

(Source: CancerCompass. Anyone with stomach cancer [Internet]. [place unknown: Rising Tide – Cancer Treatment Centers of America, Inc. 2006 Dec 01 [cited 2015 Jul 07]. Available from: *http://www.cancercompass.com/message-board/message/all,5661,5.htm*)

Patient Experience #2

My son was diagnosed with Cancer of the GE junction in 3/04 after loosing almost 50# and being treated for back strain @ back pain. I took him to the Ireland Cancer Center when his local Dr. had done an endoscopy & found a tumor in his stomach & across his esophagus… He was started on a clinical trial of Xeloda, Oxaliplatin, & Irinotecan… He handled the chemo on the clinical trial with no problems. Anyways, he ended up in our local hospital for dehydration, in the emergency room of the Cleveland hospital for dehydration, and then a week later they put him on a mild chemo (stating he no longer qualified for the trial as they feel his cancer "progressed" while on the study) - still weak and not eating. After 2 treatments he ended up in the Cleveland hospital for pain & dehydration... BUT - now the Dr. said since he ended up in the hospital after the mild chemo - they plan no further treatment - saying he can't handle any...not taking into consideration his condition caused from the radiation.

(Source: CancerCompass. Esophageal/Stomach Cancer [Internet]. [place unknown: Rising Tide – Cancer Treatment Centers of America, Inc. 2004 Aug 28 [cited 2015 Jul 07]. Available from: *http://www.cancercompass.com/message-board/message/all,1051,1.htm*)

Patient Experience #3

My husband is one year and 5 months away from the surgeries for his complete gastrectomy. He has had a variety of side affects, the worst being nausea and exhaustion/weakness. He did have sensitivity to cold for awhile, but nothing that affected his breathing. Currently, he is working on gaining back the weight that he lost during radiation/chemo treatment that ended in August of 2011. He has gained a little over 13 pounds since then, eating 5 small meals that for him don't start until around 3pm when he begins to get hungry. He does not drink any beverage with his meal as he has experienced the dumping syndrome which is not comfortable for him at all.

(Source: Cancer Society Network. Stomach cancer: Stomach cancer warriors and caregiver family [Internet]. [place unknown]: Cancer Society Network. c2010-2015 [cited 2015 Jul 07]. Available from: *http://csn.cancer.org/node/234210*)

Patient Experience #4

I am 42 and suffering with [linitis plastica], it came just out of the blue as for most of us it seems. I am still around since Janu this year diagnoses. I have gone under European regimen - 5fu - tabs; cisplatin and Epirubicin, every 3 weeks. This made my stomach very stretchy and I have been eating v well, in fact put 2 stone on. I hsve been on 24 aeroplane journeys in between chemos, travelling the world and just enjoying my life.

(Source: CancerCompass. Anyone with stomach cancer [Internet]. [place unknown: Rising Tide – Cancer Treatment Centers of America, Inc. 2005 Aug 23 [cited 2015 Jul 07]. Available from: http://www.cancercompass.com/message-board/message/all,790,2.htm)

Patient Experience #5

My 54 year old husband, Rickie, was diagnosed with stage IV EC October 8th. He is being treated at MD Anderson in Houston. When he was first diagnosed we were told the tumor was quite large encompassing his whole esophagus. From the reports is says that it "starts at 20 cms and involves the entire length of the esophagus from 20 cms to 40 cms and extends distally into the stomach for about 4 cms to 44cms". There is metastatic involvement of multiple lymph nodes as well as a few "hot spots" on his spine and sternum. Not being a candidate for surgery, the doctors decided to treat with palliative chemotherapy. No other organs are involved that we know of at this time. From what I have read and researched it seems that a tumor this large in unusual. I was wondering if anyone else has experienced this. Although he has lost 90 lbs, he presently weighs around 185 lbs and [the doctor] does not think a feeding tube is necessary. He received the first round of chemo, which he tolerated well except for constipation. The chemo gave somewhat mixed results, and so we elected to join a clinical trial for IMC-1121B ramucirumab. In 2 weeks we will have finished 6 weeks on the trial and will have a CT scan to see how he is progressing. If it is getting worse we will discontinue it and try something else. We know that this is not curable, but we hope and pray for time.

(Source: Cancer Society Network. Esophageal cancer: Looking for advice [Internet]. [place unknown]: Cancer Society Network. c2010-2015 [cited 2015 Jul 07]. Available from: *http://csn.cancer.org/node/212345*)

4.1.3 Impact of Gastric Cancer and Current Therapy on Caregivers

Caregivers of gastric cancer patients reported the large impact on their day-to-day lives as they care for the patients' needs. These range from accommodating new diets to

becoming informed about potential treatments while attending to their own personal duties, such as work and family responsibilities, all at the same time. Many have also expressed the great emotional and financial burden of a loved one's cancer diagnosis.

The following is an excerpt that encapsulates the different aspects of a caregiver's experience while caring for a patient with gastric cancer.

My husband is dying. No, that's not quite accurate; he's been dying for years…

This isn't about his diabetes, or multiple medical problems. This is about the diagnosis that threw us all for a loop. He was diagnosed with advanced gastric cancer a month ago. My first reaction was "are you freakin kidding me?" I've watched the decline over the last decade, but CANCER…NO, the diabetes is supposed to be the reason he dies, not cancer. I know what to do for the diabetes, the heart disease, the depression, I don't know what to do with cancer! I can regulate the sugar, I can stop the angina, I can give the drugs, I can do the wound care, I can be the physical therapist….but cancer with no effective treatment, I don't know what to do with that!

…He couldn't eat solid foods, tolerated small amounts of liquids, voided less and less but I continued to search for the liquid that would provide the nutrition that I felt was so important. Over the next few days the deterioration was not to be denied. I was carrying him to the wheelchair, instead of him transferring, the weight loss was staggering and he was becoming more and more confused.

And then the reality hit. I couldn't fix this one. I couldn't make this better. I was going to lose my best friend and there was nothing I could do about it. My epiphany had hit. This wasn't about providing good nursing care, this was about dying… This diagnosis that I couldn't accept a month ago, had given us all the freedom to breathe again… I was no longer his nurse, I was his wife who was going to be there for him, to make him comfortable and ease his journey. It was time to put away the technology and get back to basics.

…The strangest part of this was how life just moves on. You still have to go to the grocery store, do laundry and pay bills. We entered into 4 weeks of normal daily activities, except that Bill was in bed. Each week brought a new decline. Drastic weight loss was now very noticeable, his fluid intake was decreasing, hallucinating, and talking to people who I couldn't see, but then we had days where he would drink everything he was offered without a problem and he would converse with a friend about details of his old job. What a roller coaster of emotions. I know that he is dying, yet I am able to watch a favorite television show as if nothing was wrong. This "normalcy "of day to day continued until today. It's been 4 weeks since we got the diagnosis. I was beginning to think he was going to live forever like this. This morning signaled the change that this journey was coming to an end. He can no longer swallow liquids and complains of chest pain. His speech is slurred and breathing is more difficult. He's doing that "puffing lips" thing that I've seen in so many past patients of mine. He has a fever and despite insulin, his blood sugar is all over the place. Now is when I have to hold it together and keep the promise that I made so many years ago. I give morphine and ativan freely which calms him, but at the same time removes him from us. This is a whole lot harder than I expected it to be.

(Source: Laurie Y. Husband advanced gastric cancer diabetes heart [Internet]. [place unknown]: Don't Lose Heart – Caregivers caring for caregivers. c2013 [cited 2015 Jul 07]. Available from: http://dontloseheart.org/stories/a-new-story-laurie-y/)

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Ramucirumab

Due to the novelty of ramucirumab and its very recent approval by the FDA and European Medicines Agency (EMA) for gastric cancer in late 2014, there is scarce information on patient experience with the drug. From the small sample of collected patient input from a cancer drug forum, most patients reported having experienced side effects such as fatigue, weakness and dizziness. As some patients are often referred to ramucirumab after ineffective chemotherapy, patients and their caregivers alike are wishful of positive results with the drug. While some expressed favourable outcomes with ramucirumab, some reported the opposite. One respondent noted progression of the disease despite being treated with ramucirumab. These are described in the following excerpts of patient experiences with ramucirumab.

Patient Experience with Ramucirumab #1
12 Jun 2014
My fiance will be taking his second round tomorrow. It keeps him weak but it didn't make him as sick as all the other chemotherapy treatments.

(Source: Drugs.com. Cyramza – Is there anybody starting to use ramucirumab for stomach cancer? [Internet]. [place unknown]: Drugs.com. 12 Jun 2014 [cited 07 Jul 2015]. Available from: *http://www.drugs.com/answers/cyramza-starting-ramucirumab-stomach-cancer-1095420.html)*

Patient Experience with Ramucirumab #2
25 Jul 2014
My fiance took his 6th treatment today. He stay very tired. He be a little hoarse after every treatment but only on the day of treatment. Its really getting to me how weak he have become since he started this medicine. We go for our ct scan on the 29th. I pray every day and night that he have had some success with this medicine. All the other chemotherapy failed every time we went for a ct scan the mass was just getting bigger.My husband just received his first treatment a week ago. He is experiencing dizziness and hoarseness. He is also very tired.

2 Aug 2014
… Unfortunately the mass is still growing and the found new mass appearing in other spots. They said there is nothing else they can do for him.

(Source: Drugs.com. Cyramza – Is there anybody starting to use ramucirumab for stomach cancer? [Internet]. [place unknown]: Drugs.com. [cited 07 Jul 2015]. Available from: *http://www.drugs.com/answers/cyramza-starting-ramucirumab-stomach-cancer-1095420.html)*

Patient Experience with Ramucirumab #3
20 Sep 2014
I started on ceramza two weeks ago. I had my second dose yesterday. I have no stomach as it was removed Dec. 2012 after lots of chemo and radiation. My cancer stared at the top of my stomach. I finally got through all the treatments and had a good pet scan. In April this year I was told I had a sheet cancer wrapped around my small intestine. I could not eat or drink for 7 weeks. I was on tpn and it kept me alive until they stared chemo again and within 10 days my intestines opened up and was able to eat and drink again. The chemo was really working me over and the Oncologist decided to put me on ceramza. So

far I have not had real side effects except some high blood pressure readings. I am hoping for some good results from the new drug.

2 Oct 2014
Yesterday I was given a lesser amount of chemo to go with the cyramza. The Dr. wanted to help the antibody in attacking the cancer. I have no real side affects from cyramza except being a little tired for a few days after

6 Oct 2014
At this point I'm not sure if they will stop the chemo. They gave me a smaller dose to help shrink the cancer that is wrapped around my small intestine. Hopefully the cryamza will do the job in the long run. Right now I think that it is slower acting than I was hoping for. The Dr. tells me to be patient. I guess with a new drug you have to be

(Source: Drugs.com. Cyramza – Is there anybody starting to use ramucirumab for stomach cancer? [Internet]. [place unknown]: Drugs.com. [cited 07 Jul 2015]. Available from: *http://www.drugs.com/answers/cyramza-starting-ramucirumab-stomach-cancer-1095420.html)*

Patient Experience with Ramucirumab #4
15 Jan 2015
My sister began Cyramza yesterday in addition to Taxol. She has metastatic esophageal junction/stomach adenocarcinoma. She has had chemo, radiation, surgery, and now begins second round. Was told she will be receiving palliative treatment as long as effective. I am hopeful that Cyramza will be a mircle drug.

24 Feb 2015
My sister is doing very well with Cyramza. She has Cyramza every other week, with Taxol every week. No side effects except fatigue. She is even going to the gym every day. She will have her PET scan in a few weeks. Prayers said that the metastatic liver lymph nodes will be GONE.

(Source: Drugs.com. Cyramza – Is there anybody starting to use ramucirumab for stomach cancer? [Internet]. [place unknown]: Drugs.com. [cited 07 Jul 2015]. Available from: *http://www.drugs.com/answers/cyramza-starting-ramucirumab-stomach-cancer-1095420.html)*

Patient Experience with Ramucirumab #5
10 Mar 2015
…husband was diagnosed stage 4 in 2010 has had 2 surgeries many rounds of different types of chemo and has had radiation as well we keep on fighting right now this so far seems to be keeping the cancer at bay we are having chemo every other friday we had been doing it every friday with no breaks and he could barely do anything it was kicking his rear end this regiment seems to be working better for him he is back at work we will have more chemo and scan again in may we have been at this taxol cyramza since beginning of November…

(Source: CancerCompass. Esophageal cancer: cyramza taxol [Internet]. [place unknown: Rising Tide – Cancer Treatment Centers of America, Inc. 2015 Mar 10 [cited 2015 Jul 07]. Available from: *http://www.cancercompass.com/message-board/message/all,83255,0.htm?mid=608524)*

4.3 Additional Information

No additional comments were received.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of ramucirumab for gastric cancer and gastro-esophageal cancer:

Clinical factors:

- The relative benefits of monotherapy versus in combination with paclitaxel

Economic factors:

- Drug wastage
- If combination therapy, the additional costs of administering paclitaxel

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that there is no standard of care and there is variability in the chemotherapy drugs and regimens used. Chemotherapeutic drugs used include 5-fluorouracil (5-FU), capecitabine, cisplatin, epirubicin, docetaxel, and irinotecan. Best supportive care is also an option for these patients. The treatment of choice is determined by disease-related factors, patient factors and patient preferences as assessed by the medical oncologist.

5.2 Factors Related to Patient Population

PAG noted that ramucirumab provides an option for patients who are fit enough to receive chemotherapy and fills the treatment gap where best supportive care would be the alternate option.

As ramucirumab would be an additional line of therapy, PAG is seeking guidance from tumour groups for a national treatment algorithm for metastatic gastric cancer and metastatic gastroesophageal junction cancer and the appropriate place in therapy for ramucirumab.

PAG is seeking information on the generalizability of the trial results to patients who have received other chemotherapy agents in the first-line, including patients who have received radiation therapy with chemotherapy.

5.3 Factors Related to Dosing

PAG is seeking information on the relative benefits of ramucirumab as a single agent compared to ramucirumab in combination with paclitaxel, as this could impact cost-effectiveness.

5.4 Factors Related to Implementation Costs

PAG has concerns for incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult because there would be only one patient in the day. As dose is based on weight and there are two vial sizes (100mg and 500mg), a dose of 560mg (8mg/kg x 70kg) would result in 40mg wastage given that any unused portion would be discarded as the vials are single-use vials.

Ramucirumab is a new anti-VEGF drug and health care professionals would need to become familiar with the preparation, administration and monitoring. PAG noted that resources may be required to monitor and treat infusion related reaction and serious adverse events. In addition, ramucirumab is a 60 minute infusion administered every two weeks and PAG noted that this may be a challenge to scheduling chair time and for resources required to prepare, administer and monitor the infusion for patients who would have previously received best supportive care.

In provinces where paclitaxel is not funded for second-line treatment of gastric and gastroesophageal junction cancers, paclitaxel would need to be added if ramucirumab is to be given in combination with paclitaxel.

5.5 Factors Related to Health System

Ramucirumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded (i.e. no co-payments for patients) in all jurisdictions for eligible patients, which is an enabler for patients.

As ramucirumab is a high cost drug and requires monitoring of immune-mediated reactions post-infusion and serious adverse events that includes hemorrhages, PAG noted that smaller outpatient cancer centres may not have the expertise and resources to administer ramucirumab. This is a barrier for those patients who will need to travel to larger cancer centres that have the expertise and resources and expertise to administer ramucirumab.

5.6 Factors Related to Manufacturer

The high cost of ramucirumab would be a barrier to implementation.

PAG identified that the availability of two different vial sizes and the availability of ramucirumab as a solution are enablers to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this review was to evaluate the beneficial and harmful effects of ramucirumab compared with appropriate comparators in both the monotherapy and combination therapy settings in patients with advanced metastatic gastric cancer or gastroesophageal junction adenocarcinoma after prior chemotherapy.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of a network meta-analysis of ramucirumab and paclitaxel combination therapy and other second-line treatments for adult patients with advanced or metastatic gastric cancer or GEJ cancer

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. (Table 2) Studies were chosen for inclusion in the review based on the criteria in the table below. No patient advocacy group input was received on which considerations could be made on outcomes that are most relevant to patients.

Table 2. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators[a]	Outcomes
Published and unpublished RCT	Patients with advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy	Ramucirumab (i.v.) as monotherapy or in combination with paclitaxel at the recommended dose[b]	*Monotherapy:* • Docetaxel • Irinotecan • Paclitaxel • Best supportive care[c] *Combination therapy:* • FOLFIRI	• OS • PFS • HRQoL • Objective tumor response • Disease response • SAEs • AEs (i.e., overall, Grade ≥3; special interest[d]) • WDAEs

AE=adverse event; **FOLFIRI**=folinic acid+5-fluorouracil+irinotecan; **HRQoL**=health-related quality of life; **i.v.**=intravenously; **OS**= overall survival; **PFS**= progression-free survival; **RCT**=randomized controlled trial; **SAE**=serious adverse event; **WDAE**=withdrawal due to adverse event

[a]Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

[b]8 mg/kg i.v. every 2 weeks

[c]According to this review's Clinical Guidance Panel, in Canada, best supportive care is defined as palliative (e.g., palliative radiation, blood transfusions). No active chemotherapy is administered.

[d]Adverse events of special interest were related to toxicity arising from anti-vascular endothelial growth factor (VEGF) activity and included hypertension, bleeding, and thromboembolic events.

6.2.2 Literature Search Methods

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2015, Issue 3) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Cyramza (ramucirumab).

No methodological filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language.

The initial search was completed on April 17, 2015. Regular alerts were established to update the search until the completion of the final report on August 6, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies, health technology assessment agencies, clinical trial registries and professional associations. Google and other Internet search engines were used to search for additional web-based materials, including conference abstracts. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

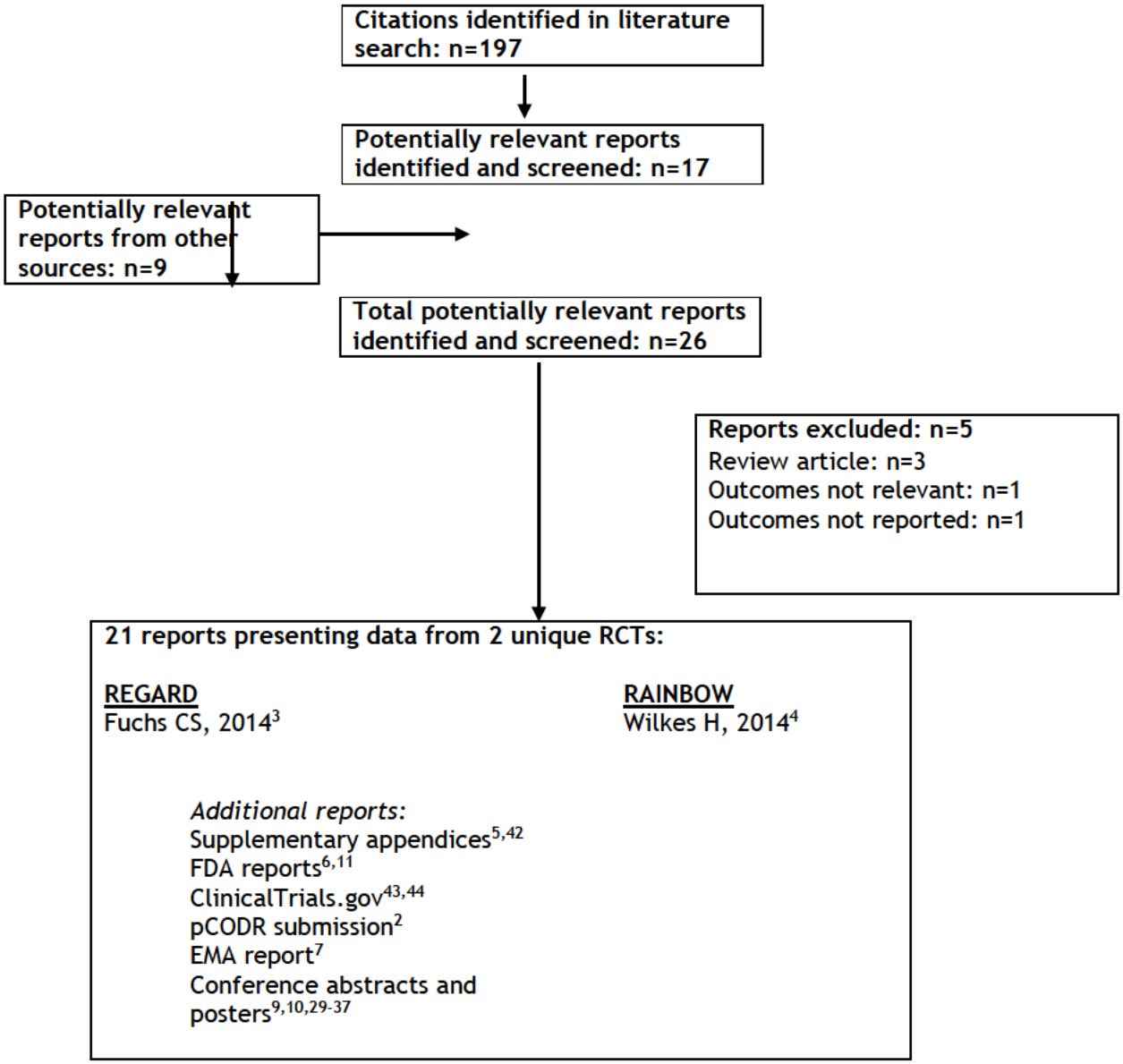
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 17 potentially relevant reports identified, 12 reports[3,4,10,29-37] representing two unique RCTs[3,4] were included in the pCODR systematic review. Five reports were excluded for the following reasons: publication was a review article,[1,38,39] outcomes were either not relevant[40] or not reported.[41]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

Provide a brief statement summarizing the number and type of included studies.

6.3.2.1 Detailed Trial Characteristics

Two trials were included in this systematic review: REGARD[3] and RAINBOW[4] - both randomized, double-blind, placebo-controlled trials. Each trial was multi-centre, multi-national, and industry-sponsored.[5,42] Only REGARD included two Canadian centres.[5] Detailed trial characteristics for REGARD and RAINBOW are summarized below in (Table 3) and (Table 4).

Table 3. Summary of Trial characteristics of REGARD[3,5,43]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
REGARD 119 centres in 29 countries in North America (including Canada), Central and South America, Europe, Asia, Australia, and Africa October 2009 to July 2012[a] Randomized (2:1), double-blind, parallel-arm, placebo-controlled, phase 3 trial stratified for weight loss, geographic region, and location of primary tumor n=355 (randomized) n=355 (ITT set) n=351 (Safety set) Funded by:	• Age ≥18 years • ECOG PS ≤1 • Histologically or cytologically confirmed diagnosis of gastric carcinoma, including gastric or GEJ adenocarcinoma • Metastatic disease or locally recurrent, unresectable disease with measurable lymph node metastases • Measurable and/or evaluable disease • Progressed disease: either during or within 4 months after last dose of first-line therapy for metastatic disease, or during or within 6 months after the last dose of adjuvant therapy • Disease not amenable to potentially curative resection • First-line combination chemotherapy regimens that included platinum or fluoropyrimidine components • Life expectancy ≥ 12 weeks • Resolution to Grade ≤ 1 (or Grade ≤ 2 in case of neuropathy) by NCI-CTCAE (Version 3.0), of	RAM+BSC versus PBO+BSC	Primary: OS Secondary: PFS, 12-week PFS, objective tumor response, duration of response, QoL, safety, immunogenicity of RAM

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Eli Lilly	all clinically significant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy (exception: alopecia) • Adequate hepatic, renal, hematologic, coagulation function • Urinary protein ≤ 1+ on dipstick or routine urinalysis, or < 1000 mg/24 hours **Exclusion criteria:** • Documented and/or symptomatic brain or leptomeningeal metastases • Any Grade 3-4 GI bleeding ≤ 3 months prior to randomization • Any arterial thromboembolic event ≤ 6 months prior to randomization • Uncontrolled or poorly controlled hypertension • Major surgery ≤ 28 days or s.c. venous access device placement ≤ 7 days prior to randomization, **or** elective or planned major surgery during the course of the trial • Chronic NSAID or anti-platelet therapy, or ASA > 325 mg/day		

ASA= acetylsalicylic acid; BSC= best supportive care; CR= complete response; DB= double-blind; ECOG PS= Eastern Cooperative Oncology Group performance status; GEJ= gastroesophageal junction; GI= gastrointestinal; ITT = intention-to-treat; NCI-CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID= non-steroidal anti-inflammatory drug; OS= overall survival; PBO= placebo; PC= placebo controlled; PFS= progression-free survival; PR= partial response; QoL= quality of life; RAM= ramucirumab; RECIST= Response Evaluation Criteria in Solid Tumours; RCT= randomized controlled trial; s.c.= subcutaneous

[a]Final data collection date for primary outcome measure[43]

Table 4. Summary of Trial characteristics of RAINBOW[4,42,44]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
RAINBOW 170 centres in 27 countries in North and South America (excluding Canada), Europe, Asia, and Australia December 2010 to July 2013[a] Randomized (1:1), double-blind, parallel-arm, placebo-controlled, phase 3 trial stratified for geographic region, time to progression after first dose of first-line therapy, and disease measurability n=665 (randomized) n=665 (ITT set) n=656 (Safety set) Funded by: Eli Lilly	• Age ≥18 years • ECOG PS ≤1 • Histologically or cytologically confirmed diagnosis of gastric or GEJ adenocarcinoma • Metastatic or locally advanced, unresectable disease • Documented objective radiographic or clinical disease progression during first-line therapy or ≤ 4 months after last dose of first-line therapy • Resolution to Grade ≤ 1 by NCI-CTCAE of all clinically significant toxic effects of previous therapy • Adequate organ function • Urinary protein ≤ 1+ on dipstick or routine urinalysis, or < 1000 mg/24 hours **Exclusion criteria:** • Squamous cell or undifferentiated gastric cancer • Major surgery ≤ 28 days or central venous access device placement ≤ 7 days prior to randomization • First-line chemotherapy other than platinum + fluoropyrimidine +/- anthracycline • History of DVT, PE, or any other significant thromboembolism ≤ 3 months prior to randomization • Therapeutic anticoagulation with	RAM+PAC versus PBO+PAC	Primary: OS Secondary: PFS, objective tumor response, disease control, PROs, immunogenicity of RAM

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
	warfarin, LMWH, or similar agents • Chronic NSAID or anti-platelet therapy, or ASA > 325 mg/day • Significant bleeding disorders, vasculitis, or a GI bleed ≤ 3 months prior to study entry • History of GI perforation and/or fistulae ≤ 6 months prior to randomization • CHF (NYHA II-IV) or symptomatic or poorly controlled cardiac arrhythmia • Arterial thrombotic event ≤ 6 months prior to randomization • Uncontrolled hypertension ≥150/≥90 mm Hg • Serious or non-healing wound or peptic ulcer or bone fracture • Bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection, Crohn's disease, ulcerative colitis, or chronic diarrhea • History or evidence of known CNS metastases		

ASA= acetylsalicylic acid; CHF= congestive heart failure; CNS= central nervous system; CR= complete response; DB= double-blind; DVT= deep vein thrombosis; ECOG PS= Eastern Cooperative Oncology Group performance status; GEJ= gastroesophageal junction; GI= gastrointestinal; ITT= intention-to-treat; LMWH= low-molecular weight heparin; NCI-CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID= non-steroidal anti-inflammatory drug; NYHA= New York Heart Association; OS= overall survival; PAC= paclitaxel; PBO= placebo PC= placebo controlled; PE= pulmonary embolism; PFS= progression-free survival; PR= partial response; PRO= patient reported outcome; RAM= ramucirumab; RECIST= Response Evaluation Criteria in Solid Tumours; RCT= randomized controlled trial; VEGF= vascular endothelial growth factor; VEGFR= vascular endothelial growth factor receptor

[a]Final data collection date for primary outcome measure[44]

a) Trials

Two trials, both sponsored by the Submitter, were identified for inclusion into the systematic review: REGARD[3] and RAINBOW.[4] Both REGARD (n=355) and RAINBOW (n=665) were randomized, double-blind, parallel-arm, placebo-controlled, phase 3 trials. REGARD was conducted in 119 centres in 29 countries (including Canada) while RAINBOW was performed in 170 centres in 27 countries (excluding Canada). REGARD was designed to test the superiority of ramucirumab (RAM) 8 mg/kg i.v. every two weeks added to best supportive care (BSC) compared with BSC alone. RAINBOW was designed to test the superiority of RAM 8 mg/kg i.v. given on days 1 and 15 in combination with paclitaxel (PAC) 80 mg/m^2 i.v. on days 1, 8, and 15 of a 28-day cycle compared with PAC (same regimen) alone.

In REGARD, randomization (2:1) was stratified by weight loss (≥10% versus <10% in previous 3 months), geographic region (North America, Europe, Australia, and Zealand [region 1] versus South and Central America, India, South Africa, and Middle East [region 2] versus Asia [region 3]), and location of primary tumor (gastric versus GEJ).[3] In RAINBOW, randomization (1:1) was stratified by geographic region (Europe, Israel, Australia, and US [region1] versus Argentina, Brazil, Chile, and Mexico [region 2] versus Japan, South Korea, Hong Kong, Singapore, and Taiwan [region 3]), time to progression after first dose of first-line therapy (<6 months versus ≥ 6 months), and disease measurability (measurable versus non-measurable).[4]

REGARD originally planned to enroll 651 patients based on a projected 531 OS events occurring with an associated hazard ratio (HR) of 0.752 (median OS: 6.65 months in RAM+BSC group versus 5 months in PBO+BSC group).[6] This sample size was subsequently amended to 615 patients with a projected 459 OS events and 90% power to detect a hazard ratio (HR) of 0.714 (median OS: 7 months in RAM+BSC group versus 5 months in PBO+BSC group) at a two-sided alpha of 0.05.[3,6] However, two years into recruitment and difficulties with accrual, the sample size was almost cut in half to 315 patients with a projected 256 OS events and 80% power to detect a HR of 0.690 (median OS: 7.25 months in RAM+BSC group versus 5 months in PBO+BSC group);[3,6] follow-up for OS was also reduced from 1.5 years to 1 year.[7] Almost one year later, the sample size was slightly increased to 348 patients with a projected 268 OS events. Thirty months were allocated for accrual and a 10% drop-out was assumed.[7] The sample size in REGARD was amended a total of three times,[6] presumably because of persistent problems recruiting patients. The FDA did not review the statistics associated with these repeated sample size revisions, however.[6]

RAINBOW originally planned to enroll 663 patients based on a projected 510 OS events, an accrual rate of 30 patients per month (including 5% drop-out), and 90% power to detect a HR of 0.75 (median OS: 9.33 months in RAM+PAC group versus 7.0 months in PBO+PAC group) at a one-sided alpha of 0.025.[7] There were three amendments made to the protocol; no patients were enrolled subsequent to these amendments and no amendment affected the design of the trial.[7]

In both REGARD and RAINBOW, efficacy analyses were performed on the intention-to-treat (ITT) population. The primary efficacy outcome for both trials was OS.[3,4] OS and PFS were analyzed by the Kaplan-Meier method for time-to-event. The primary efficacy analysis compared OS between groups and used a stratified log-rank test for the between-group comparison; a similar approach was used for secondary analyses of PFS. Objective tumor response used RECIST Version 1.0 criteria, which was compared between groups using the Cochran-Mantel-Haenszel

test to adjust for randomization strata.[3-5] Scores from disease-specific quality of life (i.e., EORTC-QLQ-C30) were analyzed both descriptively and by the Kaplan Meier method for time to deterioration (i.e., ≥10% deterioration from baseline).[3-5] Other than randomization strata, there was no further covariate adjustment for either primary or secondary efficacy analyses in REGARD or RAINBOW.[7]

b) Populations

REGARD

REGARD randomized a total of 355 patients to either ramucirumab (RAM; n=238) or placebo (PBO; n=117), each added to best supportive care (BSC). Enrolled patients were predominantly white (77%) and male (70%) with a median age of 60 years (range: 24 to 87 years). About 72% of patients had an ECOG performance score of one. Asians, who are disproportionately affected by gastric cancer, were underrepresented (16%) in the trial. Gastric carcinoma was the primary tumor in 3/4 of patients. A few imbalances were noted between groups, notably in histological subtype ('intestinal' more prevalent in PBO+BSC group), number of metastatic sites ('≥3' more prevalent in PBO+BSC group), progression-free interval after previous treatment ('< 6 months' more prevalent in PBO+BSC group), and peritoneal metastases (present more often in PBO+BSC group); with the exception of intestinal subtype, these imbalances potentially advantaged treatment with ramucirumab. (Table 5)

RAINBOW

RAINBOW randomized a total of 665 patients to either ramucirumab (RAM; n=330) or placebo (PBO; n=335), each added to paclitaxel (PAC). Enrolled patients were predominantly white (61%) and male (71%) with a median age of 61 years (range: 24 to 84 years). About 61% of patients had an ECOG performance score of one. Asians were better represented in RAINBOW than they were in REGARD (35% versus 16%). Gastric carcinoma was the primary tumor in almost 80% of patients. A few imbalances were noted between groups, notably in histological subtype ('diffuse' more prevalent in PBO+PAC group), number of metastatic sites ('≥3' more prevalent in RAM+PAC group), and in the ECOG performance score ('1' more prevalent in RAM+PAC group); of the imbalances noted, only diffuse histological subtype potentially advantaged treatment with ramucirumab. (Table 5)

Table 5. Baseline characteristics

Variable	REGARD[3,11]		RAINBOW[4,7]	
	RAM+BSC (n=238)	PBO+BSC (n=117)	RAM+PAC (n=330)	PBO+PAC (n=335)
Age, years				
Median (range)	60.0 (30 to 86)	60.0 (24 to 87)	61 (25 to 83)	61 (24 to 84)
≥ 65 years, n (%)	82 (34.5)	46 (39.3)	126 (38.2)	123 (36.7)

Variable	REGARD[3,11]		RAINBOW[4,7]	
	RAM+BSC (n=238)	PBO+BSC (n=117)	RAM+PAC (n=330)	PBO+PAC (n=335)
Sex, n (%)				
Male	169 (71.0)	79 (67.5)	229 (69.4)	243 (72.5)
Race, n (%)				
White	181 (76.1)	91 (77.8)	208 (63.0)	199 (59.4)
Asian	39 (16.4)	17 (14.5)	110 (33.3)	121 (36.1)
Other	18 (7.6)	9 (7.7)	12 (3.6)	15 (4.5)
Geographic region, n (%)				
North America, Europe, Australia, New Zealand	165 (69)	80 (68)	---	---
Asia	18 (8)	8 (7)	---	---
South and Central America, India, South Africa, Middle East	55 (23)	29 (25)	---	---
Europe, Israel, Australia, USA	---	---	198 (60)	200 (60)
Argentina, Brazil, Chile, Mexico	---	---	23 (7)	21 (6)
Japan, South Korea, Hong Kong, Singapore, Taiwan	---	---	109 (33)	114 (34)
Location of primary tumor, n (%)				
Gastric	178 (75)	87 (74)	264 (80)	264 (79)
GEJ	60 (25)	30 (26)	66 (20)	71 (21)
Histological subtype, n (%)				
Intestinal	52 (22)	35 (30)	145 (44)	135 (40)
Diffuse	96 (40)	44 (38)	115 (35)	133 (40)
Mixed	---	---	21 (6)	14 (4)
Unknown or not applicable/available	90 (38)	38 (32)	49 (15)	53 (16)
ECOG performance status, n (%)				
0	67 (28)	31 (26)	117 (35)	144 (43)
1	171 (72)	85 (73)	213 (65)	191 (57)
2	0	1 (1)	0	0
Primary tumor presence				

Variable	REGARD[3,11]		RAINBOW[4,7]	
	RAM+BSC (n=238)	PBO+BSC (n=117)	RAM+PAC (n=330)	PBO+PAC (n=335)
Yes, n (%)	174 (73)	86 (74)	209 (63)	209 (62)
Number of metastatic sites, n (%)				
0-2	163 (68)	71 (61)	209 (63)	232 (69)
≥3	75 (32)	46 (39)	121 (37)	103 (31)
Progression-free interval after previous treatment				
< 6 months	154 (65)	83 (71)	250 (76)	256 (76)
≥ 6 months	81 (34)	34 (29)	80 (24)	79 (24)
Measurable disease				
Yes, n (%)	218 (92)	106 (91)	267 (81)	273 (81)
Peritoneal metastases				
Yes, n (%)	64 (27)	45 (38)	163 (49)	152 (45)
Previous anti-cancer treatment, n (%)				
Fluoropyrimidine + platinum + anthracycline	---	---	76 (23)	87 (26)
Fluoropyrimidine + platinum	200 (84)	88 (75)	253 (77)	246 (73)
Fluoropyrimidine + other systemic drug	13 (5)	17 (15)	---	---
Fluoropyrimidine alone	16 (7)	7 (6)	---	---
Platinum + other systemic drug	9 (4)	5 (4)	---	---
HER2, EGFR, or other	---	---	31 (9)	26 (8)

BSC= best supportive care; ECOG= Eastern Cooperative Oncology Group; EGFR= epidermal growth factor receptor; GEJ= gastroesophageal junction; HER2= human epidermal growth factor receptor 2; PAC= paclitaxel; PBO= placebo; RAM= ramucirumab; SD= standard deviation

[a]Months from first diagnosis of cancer to randomization

ITT set

c) Interventions

For comparisons of monotherapy, the following comparators were specified in the systematic review protocol: docetaxel, irinotecan, paclitaxel, and best supportive care. Only the REGARD trial[3] was identified from the literature search, which compared ramucirumab against best supportive care; there were no trials directly comparing ramucirumab against docetaxel, irinotecan, or paclitaxel. According to the experts on the Clinical Guidance Panel (CGP) for this review, best supportive care in Canada is palliative, in which no active treatment (i.e., chemotherapy) is

administered. In Canada, palliative care for gastric cancer may include palliative radiation and blood transfusions, among other support strategies. For comparisons of combination therapy, FOLFIRI was specified as the only appropriate comparator in Canadian clinical practice by the CGP; however, no trials directly comparing ramucirumab against FOLFIRI were identified. Only the RAINBOW trial[4] was identified from the literature search, which compared ramucirumab in combination with paclitaxel against placebo plus paclitaxel; there were no trials directly comparing ramucirumab plus paclitaxel against FOLFIRI. The dosing of ramucirumab was the same in both REGARD and RAINBOW, that is 8 mg/kg by i.v. infusion every two weeks on days 1 and 15 of a 28-day cycle.[3,4] In RAINBOW, the dosing of paclitaxel was 80 mg/m^2 by i.v. infusion on days 1, 8, and 15 of a 28-day cycle.[4] Patients in each trial were continued on their study drug(s) until disease progression, unacceptable toxicity, or withdrawal of consent occurred. Standardized protocols for adjusting dosing in case of toxicity were used in each trial.[5,42] No cross-over between treatment groups was permitted in either trial.[3,4] Concomitant therapies meant to be palliative or supportive were allowed during REGARD and RAINBOW.[5,7]

d) Patient Disposition

In REGARD,[3] a total of 459 patients were screened, of which 355 (77.3%) were randomized. The intention-to-treat (ITT) set consisted of all patients randomized while the safety set consisted of all randomized patients who received at least one dose of study drug (i.e., ramucirumab or placebo).[7] The ITT set therefore consisted of 355 patients: 238 in the RAM+BSC group and 117 in the PBO+BSC group. The safety set consisted of 351 patients: 236 in the RAM+BSC group and 115 in the PBO+BSC group; four patients from the ITT set (two from each group) did not receive any study drug. (Table 6)

In RAINBOW,[4] a total of 794 patients were screened, of which 665 (83.8%) were randomized. Definitions for the ITT and safety sets were the same as those used in REGARD.[7] The ITT set consisted of 665 patients: 330 in the RAM+PAC group and 335 in the PBO+PAC group. The safety set consisted of 656 patients: 327 in the RAM+PAC group and 329 in the PBO+PAC group; one patient who was randomized to the PBO+PAC group received one dose of ramucirumab in error; thus, this patient was included in the safety set under RAM+PAC exposure.[4] (Table 6)

Table 6: Patient Disposition

	REGARD[3]		RAINBOW[4]	
	RAM+BSC	PBO+BSC	RAM+PAC	PBO+PAC
Screened, n	459		794	
Randomized, n (%)	355 (77.3)		665 (83.8)	
	238	117	330	335
ITT analysis set	238	117	330	335
Safety analysis set	236	115	327[a]	329[a]
Discontinued, n (%)	222 (93.3)	114 (97.4)	313 (94.8)	323 (96.4)

	REGARD[3]		RAINBOW[4]	
	RAM+BSC	PBO+BSC	RAM+PAC	PBO+PAC
Reasons for discontinuing treatment:				
• Progressive disease[b], n (%)	167 (70.2)	89 (76.1)	236 (71.5)	255 (76.1)
• Adverse events, n (%)	25 (10.5)	7 (6.0)	39 (11.8)	38 (11.3)
• Died	20 (8.4)	13 (11.1)	12 (3.6)	13 (3.9)
• Withdrew consent, n (%)	7 (2.9)	3 (2.6)	23 (7.0)	13 (3.9)
• Other, n (%)	3 (1.3)	2 (1.7)	3 (0.9)	3 (0.9)
• Lost to follow-up	---	---	---	1 (0.3)

BSC= best supportive care; ITT= intention-to-treat; PAC= paclitaxel; PBO= placebo; PP= per-protocol; RAM= ramucirumab

[a]One patient was randomly assigned to the placebo group, but received one dose of ramucirumab.

[b]Radiographic progression or symptomatic deterioration

e) Limitations/Sources of Bias

Both trials

Blinding and allocation concealment were considered adequate for each trial. Although inclusion and exclusion criteria were comparable between REGARD and RAINBOW, it is interesting to note the different randomization stratification factors - other than geographic region - that were used in REGARD (i.e., weight loss, location of primary tumor) and RAINBOW (i.e., time to progression after first dose of first-line therapy, disease measurability). It is unclear why the strata used in REGARD were not also used in RAINBOW. Participating countries numbered 27 and 29 in REGARD and RAINBOW, respectively; however, overlap between trials only occurred with 13 countries. Asian patients accounted for 35% of randomized patients in RAINBOW compared with 16% in REGARD. In RAINBOW, almost 97% of Asian patients enrolled were living in countries in East Asia;[12] such demographic information was not reported for REGARD. Given that the majority of Asian patients studied in the pivotal trial (RAINBOW) were from non-Western countries, it is unclear to what extent the findings are generalizable to Asians living in Western countries such as Canada.

In the REGARD trial, patients were eligible to participate if their first-line chemotherapy had been a platinum- and/or fluoropyrimidine-containing regimen. In the RAINBOW trial, patients were eligible to participate if their first-line chemotherapy had been a platinum + fluoropyrimidine doublet-based regimen. However, the CGP indicated that it would have been additionally informative if patients treated first-line with a FOLFIRI regimen had also been included in both trials since the CGP felt these patients would have also been potential candidates for second-line therapy with ramucirumab.

As is often the case in clinical trials, the CGP felt the study population for each trial was highly selected, representing about one-third of the type of patients with gastric or GEJ cancer that they would expect to treat in their practice. Patients with an ECOG PS of 2 were not studied in either trial; however, the CGP felt this was a missed opportunity since they believed that these patients would also have been potential candidates for this treatment.

Sample size and accrual rate projections appeared better in RAINBOW than REGARD based on the absence of amendments related to sample size revisions in RAINBOW compared with three sample size revisions-related amendments in REGARD. Commensurately, RAINBOW had closer alignment between predicted and observed median OS than REGARD.

Best supportive care (BSC, REGARD) or supportive care (RAINBOW) guidance was similar between trials. BSC was to be delivered according to guidance provided in the protocol, which included but was not limited to the use of antiemetics, analgesics, appetite stimulants, and hematopoietic growth factors (e.g., G-CSF, erythropoietin).[5] The extent to which participating sites around the globe would have employed these supportive strategies is likely variable, potentially influencing tolerability of study treatment(s). However, the direction of potential bias would be difficult to predict.

No cross-over was permitted in either REGARD or RAINBOW, which removes a frequently encountered impediment to making 'clean' treatment comparisons within trials.

Neither trial investigated for potential differences in clinical response to treatment based on the expression of biomarkers such as HER2 or VEGFR2 in tumor tissue,[7] exposing an evidence gap for characterizing which patients may benefit most from RAM treatment.

REGARD

- Sample size was revised three times, resulting in a final sample size that was almost half the size of the original (348 versus 651).[3,6,7] Persistent difficulties with recruitment were implied, but the specific challenges encountered by the trialists were not described. Drop-out was originally set at 5%, which might have been overly optimistic, but was increased to 10% in the final version of the protocol.[3] It is not clear to what extent 'peeks' at the accumulating data may have driven sample size revisions. Sample size recalculation is typically seen in 'adaptive' trial designs; this was not the design of the REGARD trial. It is also notable that the observed difference between treatment arms in OS (5.2 months versus 3.8 months) was actually much smaller than the expected magnitude of difference (7.25 months versus 5 months) used in the final sample size calculation. A large reduction in sample size would reduce the precision of the estimate for various study outcomes, including the primary outcome of OS. Although the final sample size was said to have 80% power, the trial's actual power is likely to have been even less than 80% as a consequence of the smaller than anticipated difference observed between groups in OS (1.4 months versus the projected 2.5 months), which would have increased the uncertainty around the estimate.
- Progression-free survival, a secondary efficacy endpoint, was analyzed according to a gate-keeping/hierarchical method.[5] However, analyses of other secondary efficacy endpoints (including objective tumor response, quality of

life) were not similarly adjusted to minimize the type I error rate,[6] potentially raising the risk of spurious interpretations of these analyses.

- HRQoL: No data were reported for EORTC-QLQ-C30. This was because post-baseline data were not available for a majority of patients (50% in RAM+BSC and 75% in PBO+BSC), which prevented time-to-deterioration analyses from being performed.[10]
- Underrepresentation of Asian patients: Although balanced in number between groups, Asian patients as a whole were understudied in REGARD. Because gastric cancer is a particular public health concern among Asian people, it is not clear why more resources were not invested into recruiting more people of Asian descent to enable appropriately-powered subgroup analyses.
- A few imbalances between groups in baseline characteristics could have introduced bias favoring treatment with ramucirumab. These included: number of metastatic sites ('≥3' more prevalent in PBO+BSC group), progression-free interval after previous treatment ('< 6 months' more prevalent in PBO+BSC group), and peritoneal metastases (present more often in PBO+BSC group).
- For patients with a baseline ECOG=0 (28%), the CGP indicated that from the perspective of Canadian clinical practice, the most appropriate comparator would have been chemotherapy, not placebo or BSC as in the trial. This implies that, from a Canadian point of view, patients with an ECOG PS of 0 assigned to the control group were undertreated compared to usual clinical practice. Thus, for this subgroup of patients, the trial's results may not be generalizable to Canadian clinical practice.
- Exposure to treatment was considered brief at 8 weeks, which does not provide much time to assess treatment-related toxicity.

RAINBOW

- Baseline characteristics were generally well balanced between groups in RAINBOW. Only one imbalance was noted - histological subtype ('diffuse' more prevalent in PBO+PAC group) - which could have introduced bias favoring treatment with ramucirumab. Three imbalances were noted that could have introduced bias favouring treatment with paclitaxel plus placebo: ECOG performance status, number of metastatic sites, and ascites.
- Regional differences were observed in a sub-analysis of overall survival (OS), in which, unlike western countries (region 1), Asian countries (region 3) did not show a statistically significant benefit of ramucirumab treatment. Practice variation between the regions in the use of post-discontinuation chemotherapy (PDT) was suspected as a potential explanation to this subgroup finding. In RAINBOW, the increased overall use of PDT in Asian countries compared with western countries (67% versus 37%) was thought to have contributed to the observed increase in median OS in the control group in region 3 compared with that observed in region 1 (10.5 months versus 5.6 months, respectively).[4,7] In other words, small differences between the treatment and control groups in region 3 may have been made undetectable with aggressive implementation of PDT.
- Although Canada was a participating country in REGARD, no Canadian sites participated in RAINBOW. The findings from RAINBOW, therefore, may not be entirely generalizable to Canadian clinical practice.

- HRQoL: The availability of post-baseline quality of life data steadily declined over time,[7] likely due to the rapidly progressing nature of the disease. In one analysis of global health status in the EORTC-QLQ-C30, end-of-treatment data were available for only 62% of patients.[4] This was similarly the case for EQ-5D data.[4] Despite comparable data losses and scores in each group, such marked attrition complicates the generalizability of the findings, leading one to question whether the remaining patients still reflect the original sample.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Overall Survival

Overall survival (OS) was the primary outcome in both REGARD and RAINBOW. It was defined as the interval covering the time from randomization to death from any cause.[3,4]

In REGARD, 278 (78%) patients had died at the time of data cut-off: 179 (75%) from the ramucirumab group and 99 (85%) from the placebo group. The median OS was 5.2 months (95% CI, 4.4 to 5.7) in ramucirumab-treated patients compared with 3.8 months (95% CI, 2.8 to 4.7) in patients receiving placebo, which corresponded to a hazard ratio (HR) of 0.78 (95% CI, 0.60 to 1.0; $P < 0.047$).[3,7] Estimated rates of OS at six months were 41.8% in the ramucirumab-treated group and 31.6% in those receiving placebo and one-year OS rates were 17.6% and 11.8%.[3]

In RAINBOW, 516 (78%) patients had died at the time of data cut-off: 256 (78%) from the RAM+PAC group and 260 (78%) from the PBO+PAC group. The median OS was 9.6 months (95% CI, 8.5 to 10.8) in RAM+PAC-treated patients compared with 7.4 months (95% CI, 6.3 to 8.4) in patients receiving PBO+PAC, which corresponded to a HR of 0.81 (95% CI, 0.68 to 0.96; $P = 0.017$).[4,7] (Table 7) Estimated rates of OS at six months were 72% in the RAM+PAC group and 57% in the PBO+PAC group and one-year OS rates were 40% and 30%.[4]

Progression-free Survival

Progression-free survival (PFS) was a secondary outcome in both REGARD and RAINBOW. In REGARD, PFS was defined as the interval covering the time from randomization to either disease progression or death from any cause – whichever occurred first.[3] In RAINBOW, PFS was defined as the interval covering the time from randomization to radiographic progression or death.[4]

In REGARD, median PFS was 2.1 months (95% CI, 1.5 to 2.7) in ramucirumab-treated patients compared with 1.3 months (95% CI, 1.3 to 1.4) in patients receiving placebo. This corresponded to a HR of 0.48 (95% CI, 0.38 to 0.62; $P < 0.0001$).[3,7]

In RAINBOW, median PFS was 4.4 months (95% CI, 4.2 to 5.3) in RAM+PAC-treated patients compared with 2.9 months (95% CI, 2.8 to 3.0) in patients receiving PBO+PAC. This corresponded to a HR of 0.64 (95% CI, 0.54 to 0.75; $P < 0.0001$).[4,7] (Table 7)

Table 7: Summary of Efficacy Outcomes

Outcome	REGARD[3,11]		RAINBOW[4,7]	
	RAM+BSC (n=238)	PBO+BSC (n=117)	RAM+PAC (n=330)	PBO+PAC (n=335)
Overall Survival (months)				
Median (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)	9.6 (8.5, 10.8)	7.4 (6.3, 8.4)
Log-rank p-value (2-sided), stratified[a,b]	0.047		0.017	
HR (95% CI), stratified[a,b,c]	0.776 (0.603, 0.998)		0.807 (0.678, 0.962)	
Progression-Free Survival (months)				
Median (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)	4.4 (4.2, 5.3)	2.9 (2.8, 3.0)
Log-rank p-value (2-sided), stratified[a,c,d]	<0.0001		<0.0001	
HR (95% CI), stratified[a,c,d]	0.483 (0.376, 0.620)		0.635 (0.536, 0.752)	
Objective Tumor Response (%)				
CR+PR (95% CI)[e,f]	3.4 (NR)	2.6 (NR)	27.9 (23.3, 33.0)	16.1 (12.6, 20.4)
p-value[g,h]	0.76		0.0001	
OR (95% CI)	NR		2.14 (1.50, 3.16)	
Disease Control (%)				
CR+PR+SD (95% CI)[e,f]	49 (NR)	23 (NR)	80 (75, 84)	64 (58, 69)
p-value[g,h]	<0.0001		<0.0001	
OR (95% CI)	NR		NR	

BSC= best supportive care; CI= confidence interval; CR= complete response; HR= hazard ratio; ITT= intention-to-treat; NR= not reported; OR= odds ratio; PAC= paclitaxel; PBO= placebo; PR= partial response; RAM= ramucirumab; SD= stable disease

ITT set

Heath-related Quality of Life

Health-related quality of life (HRQoL) was a secondary outcome in both REGARD and RAINBOW. In REGARD, HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Questionnaire (EORTC-QLQ-C30) while RAINBOW used both the EORTC-QLQ-C30 and the European Quality of Life Questionnaire-5 Dimension (EQ-5D) Index Score.[43,44]

In REGARD, no published raw, untransformed quality of life data could be located in the public domain for the EORTC-QLQ-C30. This was likely because post-baseline data were not available for a majority of patients (50% in RAM+BSC and 75% in PBO+BSC), which prevented time-to-deterioration analyses from being performed.[10]

In RAINBOW, only two scales of the 15 scales from the EORTC-QLQ-C30 - emotional functioning (HR: 0.64; 95% CI, 0.49 to 0.84) and nausea and vomiting (HR: 0.75; 95% CI, 0.57 to 0.97) - showed a statistically significant difference in time to deterioration which favoured RAM+PAC treatment.[9] Only the diarrhea symptom scale demonstrated a statistically significant difference in time to deterioration which favoured treatment with PBO+PAC. Time to deterioration did not differ between groups for any of the remaining scales.[9] (

Table 8) A separate analysis of global health status within the EORTC-QLQ-C30 was also performed.[3] (Scores for this scale could range from 0 to 100, where the higher the score, the better the better the quality of life.[3]) Baseline scores for global health status were available for 98% of patients in each group compared with 64% and 61% at end-of-treatment in RAM+PAC and PBO+PAC groups, respectively.[3] This corresponded to baseline global health status scores of 61.5 ± 22.0 points and 58.0 ± 22.0 points in RAM+PAC and PBO+PAC groups, respectively, compared with similarly reduced end-of-treatment scores of 49.0 ± 23.0 and 48.3 ± 23.9.[4] The EQ-5D was used to measure general health status, in which scoring is based on a scale ranging from -0.59 to 1, with 1 representing perfect health.[4] As with the EORTC-QLQ-C30, the same proportions of patients in each group completed the EQ-5D at baseline and at end-of-treatment.[4] EQ-5D index scores were similar between RAM+PAC (0.75 ± 0.22) and PBO+PAC groups (0.75 ± 0.24) at baseline and decreased similarly between groups at end-of-treatment (0.61 ± 0.32 versus 0.60 ± 0.35, respectively).[4]

Table 8. Quality of Life: EORTC-QLQ-C30 - RAINBOW

EORTC-QLQ-C-30: RAINBOW[9]	Time to Deterioration			
	HR	95% CI	RAM+PAC n	PBO+PAC n
Global Health Status				
Score	0.93	0.73, 1.18	161	136
Functional domain score				
Physical	0.83	0.66, 1.05	173	148
Role	0.87	0.70, 1.07	190	171
Cognitive	0.80	0.63, 1.02	150	132
Emotional	0.64	0.49, 0.84	112	117
Social	0.93	0.74, 1.18	167	140
Symptom score				
Fatigue	0.82	0.67, 1.02	194	174
Pain	0.81	0.64, 1.03	149	137
Nausea and Vomiting	0.75	0.57, 0.97	121	121
Dyspnea	0.99	0.77, 1.29	133	110
Appetite loss	0.81	0.63, 1.05	133	121
Insomnia	0.81	0.62, 1.06	118	107
Constipation	0.98	0.74, 1.29	124	93
Diarrhea	1.33	1.01, 1.76	138	83
Financial difficulties				

EORTC-QLQ-C-30: RAINBOW[9]	Time to Deterioration			
	HR	95% CI	RAM+PAC n	PBO+PAC n
Score	0.97	0.72, 1.31	102	81

BSC= best supportive care; **CI**= confidence interval; **HR**= hazard ratio; **PAC**= paclitaxel; **PBO**= placebo; **RAM**= ramucirumab

Objective Tumor Response

Objective tumor response was defined as the proportion of patients achieving a best overall response of complete (CR) or partial response (PR).[7]

In REGARD, the objective tumor response (CR+PR) did not differ between RAM+BSC (3.4%) and PBO+BSC (2.6%) groups (*P* =0.76).[7]

In RAINBOW, the objective tumor response was statistically significantly better in the RAM+PAC group than the PBO+PAC group (27.9% versus 16.1%; odds ratio: 2.140, 95% CI: 1.499 to 3.160; *P* =0.0001).[7] (Table 7)

Disease Control

Disease control was defined as the proportion of patients achieving a best overall response of complete (CR), partial (PR), or stable disease (SD).[3,4]

In REGARD, disease control (CR+PR+SD) was statistically significantly better in the RAM+BSC group than the PBO+BSC group (49% versus 23%, *P*<0.0001).[3]

In RAINBOW, disease control was statistically better in the RAM+PAC group (80%; 95% CI, 75 to 84) than the PBO+PAC group (64%; 95% CI, 58 to 69), *P*<0.0001.[4] (Table 7)

Harms Outcomes

Study Drug Exposure

In REGARD, the mean duration of therapy was 12.7 (11.7) weeks in the RAM+BSC group, corresponding to a mean of 6.1 (5.6) cycles received at a mean dose intensity of 3.9 (0.3) mg/kg/week. By comparison, the mean duration of therapy in the PBO+BSC group was 7.9 (7.7) weeks, corresponding to a mean of 3.9 (3.8) cycles received at a mean dose intensity of 3.9 (0.3) mg/kg/week.[7] (Table 9)

In RAINBOW, the mean duration of RAM and PAC in the RAM+PAC group was 23.0 (18.5) and 21.7 (16.7) weeks, respectively, compared with 16.4 (13.8) and 16.5 (14.4) weeks for PBO and PAC, respectively, in the PBO+PAC group. The mean number of cycles received was 5.7 (4.3) and 5.4 (3.9) for RAM and PAC, respectively, in the RAM+PAC group and 4.2 (3.3) and 4.2 (3.4) for PBO and PAC, respectively, in the PBO+PAC group. Mean dose intensity was 3.9 (0.3) mg/kg/week and 50.2 (8.9) mg/m^2/week for RAM and PAC, respectively, in the RAM+PAC group and 3.9 (0.2) mg/kg/week and 53.7 (7.2) mg/m^2/week for PBO and PAC, respectively, in the PBO+PAC group.[7,42] (Table 9)

Table 9. Study Drug Exposure

	REGARD[7]		RAINBOW[7]			
	RAM+BSC (n=236)	PBO+BSC (n=115)	RAM+PAC (n=327)		PBO+PAC (n=329)	
	RAM	PBO	RAM[a]	PAC[b]	PBO[a]	PAC[b]
Duration of therapy (weeks)						
Mean (SD)	12.7 (11.7)	7.9 (7.7)	23.0 (18.5)	21.7 (16.7)	16.4 (13.8)	16.5 (14.4)
Total number of cycles received[c]						
Mean (SD)	6.1 (5.6)	3.9 (3.8)	5.7 (4.3)	5.4 (3.9)	4.2 (3.3)	4.2 (3.4)
Dose intensity (mg/kg/week or mg/m^2/week)[d]						
Mean (SD)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	50.2 (8.9)	3.9 (0.3)	53.7 (7.2)

BSC= best supportive care; PAC= paclitaxel; PBO= placebo; RAM= ramucirumab; SD= standard deviation
[a]Based on last available weight prior to each infusion.
[b]Based on last available body surface area prior to each infusion.
[c]RAINBOW: Number of cycles received: Patients counted only once using the maximum number of cycles received.
[d]Ramucirumab: mg/kg/week; paclitaxel: mg/m^2/week
Safety set

Dose Modifications

Dose reductions were infrequent overall (<2%) in REGARD.[7] In RAINBOW,[4] dose reductions were more common in the RAM+PAC group than in the PBO+PAC group. For the RAM/PBO component, dose reductions occurred in 4.9% of patients in the RAM+PAC group and 0.9% in the PBO+PAC group; for the PAC component, dose reductions occurred in 23.9% in the RAM+PAC group and 7.3% in the PBO+PAC group.(Table 10)

Dose omissions in REGARD were more frequent in the RAM+BSC group (20.3%) than the PBO+BSC group (10.4%). In RAINBOW, dose omissions were more common in the RAM+PAC group (50.2%) than in the PBO+PAC group (32.8%); no data reporting on the individual components of the treatment arms were publically available. (Table 10)

Table 10. Summary of Patients Experiencing Dose Modifications

	REGARD[7]		RAINBOW[4,7]			
	RAM+BSC (n=236)	PBO+BSC (n=115)	RAM+PAC (n=327)		PBO+PAC (n=329)	
			RAM/PBO	PAC	RAM/PBO	PAC
Any dose reductions, n (%)						
Any	3 (1.3)	1 (0.9)	16 (4.9)	78 (23.9)	3 (0.9)	24 (7.3)
Dose Held (omitted)						
n (%)	48[a] (20.3)	12[a] (10.4)	50.2[b]		32.8[b]	

BSC= best supportive care; PAC= paclitaxel; PBO= placebo; RAM= ramucirumab
[a]pCODR-calculated
[b]Data for individual components of the treatment arm not available in the public domain; alternatively, percentages reflect dose omissions for the given treatment arm regimen.[7] Safety set

Post-Discontinuation Treatments

The prevalence of post-discontinuation treatments (PDTs) - most often, chemotherapy - was reported for each trial according to treatment group for the whole study population and by region stratum. It should be noted that the constituent countries for a given region stratum differed between REGARD and RAINBOW, particularly for region 2.

In REGARD,[7] 'any systemic PDT' was more frequently provided to patients in the RAM+BSC group (30.3%) compared with patients in the PBO+BSC group (37.6%). A sub-analysis by region revealed a similar pattern of distribution for regions 1 (32.1% versus 45.0%) and 3 (27.8% versus 37.5%), but the opposite distribution for region 2, in which more patients in the RAM+BSC group received any systemic PDT compared with the PBO+BSC group (25.5% versus 17.2%). (Table 11)

In RAINBOW,[42] any systemic PDT was provided at similar frequency to patients, whether assigned to the RAM+PAC group (48%) or PBO+PAC group (46%). Likewise, similar proportions of patients regardless of treatment group received any systemic PDT when analyzed by region (region 1: 38% versus 36%; region 2: 30% versus 33%; region 3: 69% versus 66%); however, the overall frequency of PDT treatment was notably higher in region 3 compared with regions 1 and 2. (Table 11)

Table 11: Post-Discontinuation Treatments

	REGARD[7]	
	RAM+BSC	PBO+BSC
All regions, n (%)		
n	238	117
Any systemic PDT	72 (30.3)	44 (37.6)
Chemotherapy	69 (29.0)	44 (37.6)
Irinotecan	36 (15.1)	26 (22.2)

	REGARD[7]	
	RAM+BSC	RAM+BSC
Taxanes	23 (9.7)	18 (15.4)
Region 1 (North America, Europe, Australia, New Zealand), n (%)		
n	165	80
Any systemic PDT	53 (32.1)	36 (45.0)
Chemotherapy	50 (30.3)	36 (45.0)
Irinotecan	28 (17.0)	21 (26.3)
Taxanes	15 (9.1)	14 (17.5)
Region 2 (South and Central America, India, South Africa, Jordan, Egypt, Saudi Arabia, Lebanon), n (%)		
n	55	29
Any systemic PDT	14 (25.5)	5 (17.2)
Chemotherapy	14 (25.5)	5 (17.2)
Irinotecan	5 (9.1)	2 (6.9)
Taxanes	5 (9.1)	1 (3.4)
Region 3 (Asia), n (%)		
n	18	8
Any systemic PDT	5 (27.8)	3 (37.5)
Chemotherapy	5 (27.8)	3 (37.5)
Irinotecan	3 (16.7)	3 (37.5)
Taxanes	3 (16.7)	3 (37.5)
	RAINBOW[42]	
	RAM+PAC	PBO+PAC
All patients, n (%)		
n	330	335
Any treatment	158 (48)	154 (46)
Biologic	23 (7)	18 (5)
Chemotherapy[a]	158 (48)	152 (45)
Irinotecan	124 (38)	117 (35)
Fluorouracil	83 (25)	74 (22)
Other[b]	125 (38)	113 (34)
Other	1 (<1)	7 (2)

	RAINBOW[42]	
	RAM+PAC	RAM+PAC
Region 1 (Europe, Israel, Australia, US), n (%)		
n	198	200
Any treatment	76 (38)	72 (36)
Biologic	9 (5)	5 (3)
Chemotherapy[a]	76 (38)	71 (36)
Irinotecan	57 (29)	48 (24)
Fluorouracil	55 (28)	47 (24)
Other[b]	60 (30)	50 (25)
Other	0	1 (<1)
Region 2 (Argentina, Brazil, Chile, and Mexico), n (%)		
n	23	21
Any treatment	7 (30)	7 (33)
Biologic	0	1 (5)
Chemotherapy[a]	7 (30)	7 (33)
Irinotecan	6 (26)	7 (33)
Fluorouracil	2 (9)	4 (19)
Other[b]	4 (17)	3 (14)
Other	0	0
Region 3 (Japan, South Korea, Hong Kong, Singapore, and Taiwan), n (%)		
n	109	114
Any treatment	75 (69)	75 (66)
Biologic	14 (13)	12 (11)
Chemotherapy	75 (69)	74 (65)
Irinotecan	61 (56)	62 (54)
Fluorouracil	26 (24)	23 (20)
Other[b]	61 (56)	60 (53)
Other	1 (<1)	6 (5)

BSC= best supportive care; PAC= paclitaxel; PBO= placebo; RAM= ramucirumab
[a]Patients may be in more than one category.
[b]Other chemotherapies include anthracyclines, antineoplastic agents, folic acid analogues, nitrogen mustard analogues, non-steroids, cytotoxic antibiotics, platinum compounds, podophyllotoxin derivatives, pyrimidine analogues, and taxanes.

Serious Adverse Events

The proportion of patients experiencing serious adverse events (SAEs) was similar between RAM+BSC and PBO+BSC in REGARD (44.9% versus 44.3%) and between RAM+PAC and PBO+PAC in RAINBOW (46.8% versus 42.2%).[7] SAEs by preferred term were not publically available by severity grading for REGARD; such data were, however, available for RAINBOW.[7] The frequency distribution of individual SAEs was similar between treatment arms for each trial, regardless of severity grade. (Table 12)

Table 12. Serious Adverse Events

Serious adverse events[a]	REGARD[7]				RAINBOW[7]			
	RAM+BSC (n=236)		PBO+BSC (n=115)		RAM+PAC (n=327)		PBO+PAC (n=329)	
n, (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any SAE	106 (44.9)	---	51 (44.3)	---	153 (46.8)	---	139 (42.2)	---
Malignant neoplasm progression[b]	10 (4.2)	---	7 (6.1)	---	40 (12.2)	39 (11.9)	45 (13.7)	45 (13.7)
Abdominal pain	10 (4.2)	---	3 (2.6)	---	8 (2.4)	7 (2.1)	10 (3.0)	7 (2.1)
Anemia	9 (3.8)	---	2 (1.7)	---	7 (2.1)	6 (1.8)	6 (1.8)	5 (1.5)
Neutropenia	---	---	---	---	12 (3.7)	12 (3.7)	3 (0.9)	3 (0.9)
Medication error[c]	7 (3.0)	---	1 (0.9)	---	---	---	---	---
Ascites	6 (2.5)	---	3 (2.6)	---	---	---	---	---
Multi-organ failure	6 (2.5)	---	1 (0.9)	---	---	---	---	---
Vomiting	6 (2.5)	---	5 (4.3)	---	7 (2.1)	4 (1.2)	9 (2.7)	8 (2.4)
Febrile neutropenia	---	---	---	---	8 (2.4)	8 (2.4)	4 (1.2)	4 (1.2)
General physical health deterioration	---	---	---	---	8 (2.4)	7 (2.1)	9 (2.7)	7 (2.1)
Dysphagia	5 (2.1)	---	3 (2.6)	---	---	---	---	---
Intestinal obstruction	5 (2.1)	---	0	---	---	---	---	---
Pyrexia	---	---	---	---	7 (2.1)	2 (0.6)	6 (1.8)	0

BSC= best supportive care; PAC= paclitaxel; PBO= placebo; RAM= ramucirumab; SAE= serious adverse event

[a]≥2% of patients in RAM+BSC (REGARD) and RAM+PAC (RAINBOW), respectively

[b]Referred to as 'disease progression' in REGARD.

[c]Medication errors were reported per the protocol procedures. No safety issues were associated with medication errors.[2]

Safety set

Adverse Events

In REGARD, the proportion of patients experiencing any adverse event (AE) regardless of severity grade was higher in the RAM+BSC group (94.5%) compared with the PBO+BSC group (87.8%).[7] In RAINBOW, the distribution of AEs was similar between the RAM+PAC group (99.1%) and the PBO+PAC group (97.9%).[7] AEs of grade ≥3 severity occurred at a similar frequency between groups in REGARD (56.8% versus 58.3%, respectively), but at a higher frequency in the RAM+PAC group (81.7%) than in the PBO+PAC group (62.6%) in RAINBOW.[7] In REGARD, the proportion of patients who discontinued treatment due to adverse events was higher in the RAM+BSC arm (10.5%) than in the PBO+BSC arm (6.0%). For the RAINBOW study, discrepant values for the proportion of patients who discontinued treatment due to adverse events were reported within the European Medicine Agency's Committee for Medicinal Products for Human Use (EMA CHMP) assessment report for ramucirumab[7] and by Wilke et al.[4] The EMA CHMP reported that the proportion of patients who discontinued due to adverse events was higher in the RAM+PAC arm (31.2%) compared with PBO+PAC (24.3%) (Table 13), but also reported, similarly to Wilke et al[4], that the proportions of patients who discontinued due to an adverse event were 12% for RAM+PAC and 11% for PBO+PAC. No data on withdrawals due to adverse events could be located in the publically available literature.

In REGARD,[7] diarrhea (14.4% versus 8.7%) and headache (9.3% versus 3.5%) of any severity, and hypertension of both any severity (16.1% versus 7.8%) and grade ≥3 severity (7.6% versus 2.6%) were more prevalent in the RAM+BSC group compared with the PBO+BSC group. In RAINBOW,[7] diarrhea (32.4% versus 23.1%), epistaxis (30.6% versus 7.0%), peripheral edema (25.1% versus 13.7%), stomatitis (19.6% versus 7.3%), proteinuria (16.8% versus 6.1%), thrombocytopenia (13.1% versus 6.1%), and hypoalbuminemia (11.0% versus 4.9%) of any severity were more prevalent in the RAM+PAC group compared with the PBO+PAC group. Fatigue (56.9% versus 43.8% and 11.9% versus 5.5%), neutropenia (54.4% versus 31.0% and 40.7% versus 18.8%), leukopenia (33.9% versus 21.0% and 17.4% versus 6.7%), and hypertension (25.1% versus 5.8% and 14.7% versus 2.7%) were more common in the RAM+PAC group compared with the PBO+PAC group, in both adverse events classified as being of any severity and in those of grade ≥3 severity, respectively. (Table 13)

Table 13. Adverse Events

Adverse events[a]	REGARD[7]		RAINBOW[7]	
	RAM+BSC (n=236)	PBO+BSC (n=115)	RAM+PAC (n=327)	PBO+PAC (n=329)
n, (%)				
Any AE	223 (94.5)	101 (87.8)	324 (99.1)	322 (97.9)
AE Grade ≥ 3	134 (56.8)	67 (58.3)	267 (81.7)	206 (62.6)
SAE	106 (44.9)	51 (44.3)	153 (46.8)	139 (42.2)
AE leading to discontinuation of any study drug:	25 (10.5)	7 (6.0)	102 (31.2)	80 (24.3)
RAM/PBO	---	---	68 (20.8)	68 (20.7)
PAC	---	---	91 (27.8)	76 (23.1)

Adverse events[a]	REGARD[7]				RAINBOW[7]			
	RAM+BSC (n=236)		PBO+BSC (n=115)		RAM+PAC (n=327)		PBO+PAC (n=329)	
WDAEs	NR		NR		NR		NR	
%	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatigue	---	---	---	---	56.9	11.9	43.8	5.5
Neutropenia[b]	---	---	---	---	54.4	40.7	31.0	18.8
Leukopenia[c]	---	---	---	---	33.9	17.4	21.0	6.7
Diarrhea	14.4	0.8	8.7	1.7	32.4	3.7	23.1	1.5
Epistaxis	---	---	---	---	30.6	0	7.0	0
Abdominal pain[d]	28.8	5.9	27.8	2.6	---	---	---	---
Hypertension[e]	16.1	7.6	7.8	2.6	25.1	14.7	5.8	2.7
Peripheral edema	---	---	---	---	25.1	1.5	13.7	0.6
Stomatitis	---	---	---	---	19.6	0.6	7.3	0.6
Proteinuria	---	---	---	---	16.8	1.2	6.1	0
Thrombocytopenia	---	---	---	---	13.1	1.5	6.1	1.8
Hypoalbuminemia	---	---	---	---	11.0	1.2	4.9	0.9
Gastrointestinal hemorrhage events[f]	---	---	---	---	10.1	3.7	6.1	1.5
Headache	9.3	0	3.5	0	---	---	---	---
Hypokalemia[g]	5.9	2.1	5.2	0.9	---	---	---	---
Hyponatremia	5.5	3.4	1.7	0.9	---	---	---	---

BSC= best supportive care; NR= not reported; RAM= ramucirumab; PAC= paclitaxel; PBO= placebo
[a]≥5% of patients in RAM+BSC (REGARD) and RAM+PAC (RAINBOW), respectively
[b]Includes neutropenia and neutrophil count decreased.
[c]Includes leukopenia and white blood cell count decreased.
[d]Includes abdominal pain, abdominal pain lower, abdominal pain upper, and hepatic pain.
[e]Includes blood pressure increased and hypertension.
[f]Includes anal hemorrhage, diarrhea hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, Mallory-Weiss syndrome, melena, esophageal hemorrhage, rectal hemorrhage, and upper gastrointestinal hemorrhage.
[g]Includes blood potassium decreased and hypokalemia.
Safety set

Adverse Events of Special Interest

Of the adverse events of special interest reported,[3,4] a higher proportion of patients experienced hypertension regardless of severity in both REGARD and RAINBOW whether receiving RAM with (RAINBOW) or without (REGARD) PAC. (TABLE 14) [Data also presented previously in ***Adverse Events***.] Bleeding or hemorrhage (42% versus 18%), proteinuria (17% versus 6%), and liver injury or failure (17%

versus 12%) – all of any severity - were more prevalent in RAINBOW among patients receiving RAM+PAC than among those receiving PBO+PAC, respectively. (TABLE 14)

Table 14. Adverse Events of Special Interest

Adverse events of special interest	REGARD[3]				RAINBOW[4]			
	RAM+BSC (n=236)		PBO+BSC (n=115)		RAM+PAC (n=327)		PBO+PAC (n=329)	
n, (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade[a]	Grade ≥3[a]	Any grade[a]	Grade ≥3[a]
Bleeding or hemorrhage[b]	30 (13)	8 (3)	13 (11)	3 (3)	137 (42)	14 (4)	59 (18)	8 (2)
Proteinuria	7 (3)	1 (<1)	3 (3)	0	55 (17)	4 (1)	20 (6)	0
Liver injury or failure	---	---	---	---	54 (17)	15 (5)	41 (12)	13 (4)
Hypertension[c]	38 (16)	18 (8)	9 (8)	3 (3)	82 (25)	48 (15)	19 (6)	9 (3)
Gastrointestinal hemorrhage[d]	---	---	---	---	33 (10)	12 (4)	20 (6)	5 (2)
Infusion-related reaction	1 (<1)	0	2 (2)	0	19 (6)	2 (<1)	12 (4)	0
Renal failure	---	---	---	---	22 (7)	6 (2)	14 (4)	3 (<1)
Cardiac/Congestive heart failure	1 (<1)	0	0	0	8 (2)	2 (<1)	4 (1)	2 (<1)
Venous thromboembolic events[e]	9 (4)	3 (1)	8 (7)	5 (4)	13 (4)	8 (2)	18 (5)	11 (3)
Arterial thromboembolic events[f]	4 (2)	3 (1)	0	0	6 (2)	3 (<1)	5 (2)	3 (<1)
Gastrointestinal perforation	2 (<1)	2 (<1)	1 (<1)	1 (<1)	4 (1)	4 (1)	1 (<1)	0
Fistula formation	1 (<1)	1 (<1)	1 (<1)	1(<1)	---	---	---	---

BSC= best supportive care; PAC= paclitaxel; PBO= placebo; RAM= ramucirumab

[a]Calculated by pCODR

[b]REGARD: Includes epistaxis, gastric hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hematoma, hematuria, hemoptysis, hemorrhage, hemorrhoidal hemorrhage, melena, nail-bed bleeding, petechiae, rectal hemorrhage, and upper gastrointestinal hemorrhage.

[c]REGARD: Includes increased blood pressure.

[d]RAINBOW: Events pooled as gastrointestinal hemorrhage are also pooled as bleeding or hemorrhage.

[e]REGARD: Includes pulmonary embolism, deep vein thrombosis, thrombosis, and venous thrombosis in a limb.

[f]REGARD: Includes angina pectoris, cardiac arrest, cerebral ischemia, cerebrovascular accident, myocardial infarction, and myocardial ischemia.

6.4 Ongoing Trials

No additional on-going and/or unreported trials were identified that would have been included had they been completed.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of ramucirumab for advanced or metastatic gastric cancer or GEJ cancer:

- Critical appraisal of a network meta-analysis of ramucirumab and paclitaxel combination therapy and other second-line treatments for adult patients with advanced or metastatic gastric cancer or GEJ cancer

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical appraisal of a network meta-analysis of ramucirumab and paclitaxel combination therapy and other second-line treatments for adult patients with advanced or metastatic gastric cancer or GEJ cancer

7.1.1 Objective

To summarize and critically appraise the methods and findings of the manufacturer-submitted network meta-analysis (NMA) of ramucirumab and paclitaxel combination therapy and other second-line treatments of adult patients with advanced or metastatic gastric cancer or GEJ cancer.

7.1.2 Findings

The manufacturer provided a network meta-analysis (NMA) to estimate the efficacy of ramucirumab and paclitaxel combination therapy versus other treatments used in the second-line treatment of adult patients with advanced or metastatic gastric cancer or GEJ cancer to inform the pharmacoeconomic model. According to the manufacturer, a NMA was not performed for ramucirumab monotherapy as the only appropriate comparator would be best supportive care, as patients indicated to receive ramucirumab monotherapy would likely not receive a second-line chemotherapy due to prior toxicities or personal preference.

The comparators identified from a targeted review were docetaxel, paclitaxel, irinotecan-based regimens, 5-fluorouracil (5-FU)-based regimens, and best supportive care (BSC). A systematic review of the efficacy and safety of ramucirumab and these comparators was conducted to identify the network of relevant RCTs. Nine phase II and phase III RCTs assessing second-line therapies in patients with advanced or metastatic gastric cancer or GEJ cancer were included in the evidence networks for PFS and OS. Study characteristics are listed in Table 15.

Table 15: Summary of studies used in the NMA

Trial, Publications	Study design	Patient population	Intervention and comparator used in NMA	Outcomes
RAINBOW Wilke et al. 2014[4]	Multinational, Multicenter, Phase III, DB RCT	665 patients with advanced GC or GEJC and disease progression on or within 4m after first-line chemotherapy (platinum-plus-fluoropyrimidine with or without an anthracycline)	Ramucirumab 8 mg/kg IV (days 1 and 15) + paclitaxel (days 1, 8 and 15) 80 mg/m^2 of a 28d cycle (n = 330) Placebo + Paclitaxel 80 mg/m^2 (days 1, 8 and 15) 80 mg/m^2 of a 28d cycle (n = 335)	Primary: OS Secondary: PFS, ORR, PROs
REGARD Fuchs et al. 2014[3]	Multinational, Multicenter, Phase III, DB RCT	355 patients with advanced GC or GEJC and disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy	Ramucirumab 8 mg/kg IV every 2 weeks + BSC (n = 238) Placebo + BSC (n = 117)	Primary: OS Secondary: PFS, ORR, duration of response, QoL
COUGAR-02 Ford et al. 2014[21]	Multicenter (UK sites), Phase III, OL RCT	168 patients with advanced esophageal cancer or GEJC and disease progression on or within 6m after first-line platinum-containing or fluoropyrimidine-containing chemotherapy	Docetaxel 75 mg/m^2 IV over 1 h every 3 weeks up to 6 cycles + active symptom control (n = 84) Active symptom control – community and hospice care (n = 84)	Primary: OS Secondary: Time to disease progression, QoL
Roy et al. 2013[45]	Multinational, Multicenter, Phase II, OL RCT	135 patients with advanced GC or GEJC who have failed one prior systemic chemotherapy	Irinotecan 300 mg/m2 IV over 90 min every 3 weeks (n = 44) Docetaxel 75 mg/m^2 over 1 h every 3 weeks (n = 44) PEP-02 (n = 44)	Primary: ORR Secondary: PFS, OS
AIO Investigator Initiated Trial Thuss-Patience et al. 2011[22]	Investigator-initiated, Multicenter, Phase III, OL RCT	40 patients with metastatic GC or GEJC and disease progression on or within 6m after first-line chemotherapy	Irinotecan 250 mg/m^2 over 30 min every 3 weeks, increased to 350 mg/m^2 after one cycle (n = 21) BSC (n = 19)	Primary: OS Secondary: ORR, TTP

WJOG 4007 Trial Hironaka et al. 2013[24]	Multicenter (Japan sites), Phase III, OL RCT	223 patients with metastatic or recurrent GC with disease progression on or within 6m after treatment with platinum-plus-fluoropyrimidine chemotherapy	Paclitaxel 80 mg/m^2 IV (days 1, 8 and 15) every 4 weeks (n = 111) Irinotecan 150 mg/m^2 IV (days 1 and 15) every 4 weeks (n = 108)	Primary: OS Secondary: PFS, ORR
TCOG GI-0801/BIRIP Trial Higuchi et al. 2014[46]	Multicenter, Phase III, OL RCT	130 patients with advanced GC who are refractory to S-1-based first-line chemotherapy (tegafur, gimestat, and otatat potassium)	Irinotecan 60 mg/m^2 IV over 1 h + cisplatin 30 mg/m^2 IV over 90 min every 2 weeks (n = 64) Irinotecan 150 mg/m^2 IV over 90 min every 2 weeks (n = 66)	Primary: PFS Secondary: OS, time to treatment failure, tumour response
Tamura et al. 2013[47]	Phase III, OL RCT	168 patients with metastatic GC who are resistant to S-1-based first-line chemotherapy	Irinotecan 60 mg/m^2 IV over 1 h + cisplatin 30 mg/m^2 IV over 90 min every 2 weeks (n = 84) Irinotecan 150 mg/m^2 IV over 90 min every 2 weeks (n = 84)	Primary: OS Secondary: PFS, ORR, time to treatment failure
Sym et al. 2013[48]	Single center, Phase II, OL RCT	59 patients with metastatic GC or GEJC with disease projection during or within 6m after platinum-, fluoropyrimidine- or taxane-based first-line chemotherapy	Irinotecan 150 mg/m^2 IV over 90 min every 2 weeks (n = 29) mFOLFIRI: irinotecan 150 mg/m^2 over 90 min, leucovorin 20 mg/m^2 over 5 min, 5-FU 1,000 mg/m^2 IV over 2 days every 2 weeks (n = 30)	Primary: ORR Secondary: PFS, OS
BSC = best supportive care; DB = double-blind; GC = gastric cancer; GEJC = gastroesophageal junction cancer; IV = intravenous; OL = open label; ORR = objective response rate; OS = overall survival; PRO = patient-reported outcome; PFS = progression-free survival; QoL = quality of life; RCT = randomized controlled trial; TTP = time to tumour progression				

The network of RCTs for PFS was disconnected, as two trials[21,22] did not include PFS as an outcome and one trial[45] did not report a hazard ratio for PFS. Based on the similarities of the Kaplan-Meier estimates from the first three months from the REGARD trial of ramucirumab and from the trial by Roy et al. of irinotecan and docetaxel, the manufacturer assumed hazard ratios (HRs) of one for the comparison between each of these agents.

Standard errors of 0.01 were assigned (lowest acceptable level of error required to run analysis in WinBUGS), with the rationale that the objective of assigning HRs of one between these agents was to constrain the hazards of progression for ramucirumab, irinotecan, and docetaxel. The impact of differing levels of uncertainty on the point estimates of PFS HRs was explored using two methods. First, a standard error of 0.287 were assigned to all HRs assumed to be one using a Cox analysis of the Roy et al. Kaplan-Meier data. Secondly, a standard error of zero (no uncertainty) was assigned to all HRs assumed to be one using the Bucher method, which is an adjusted indirect comparison approach.

The network for OS was not disconnected as per PFS, so it was not necessary to make assumptions in order to build a complete network. However, the manufacturer noted that the Kaplan-Meier OS curves for the comparators indicated a potential violation of the proportional hazard assumption, but proportional hazards was still assumed to hold in order to be able to analyze the available data.

Due to the uncertainty in the methods used to assign hazard ratios and standard errors to the treatment comparisons, results from this network meta-analysis are not presented.

Limitations

There are several limitations in the conduct of the NMA. The network for PFS was incomplete, and the assumptions that were made based on a visual inspection of Kaplan-Meier curves may not be appropriate. In addition, the methods used to assign levels of uncertainty to the point estimates of the NMA and the indirect comparison may also not be appropriate.

There was a lack of studies to inform the networks for both PFS and OS, and two of the studies enrolled a small number of patients (< 60), which increases uncertainty in the results. The patient population enrolled appears to be generally homogeneous between studies, but not all of the dosing regimens would be used in Canadian clinical practice. The dosing of irinotecan typical used in clinical practice is 150 mg/m^2 every two weeks, as it is better tolerated than the higher doses used in the study by Thuss-Patience et al. and Roy et al.[22,45] In addition, the doses of irinotecan, leucovorin, and 5-FU used in the FOLFIRI regimen may vary to what was used in the study by Sym et al. according to the clinical guidance panel, but this was the only study included in the network that used FOLFIRI.[48]

The manufacturer noted that the analyses for OS may not have been appropriate given the possible violation of the proportional hazards assumption based on a visual inspection of the Kaplan-Meier curves in the included studies. There was no in-depth reporting of the methods used for the NMAs for both PFS and OS. Due to the uncertainty associated with this analysis, the RAINBOW within-trial analysis was presented as the base case cost-effectiveness analysis and scenario analyses were conducted to explore the impact of including other therapies.

The quality of the manufacturer-submitted indirect comparison was assessed according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[49] Details and commentary for each of the relevant items identified by the ISPOR group are provided in (Table 16)

Table 16. Appraisal of the indirect comparison analyses using ISPOR criteria[49]

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting a network meta-analysis and the study objectives were stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility for the RCTs was stated and included second-line treatments in adult patients with advanced or metastatic GC/GEJC • No information was provided on the information sources, search strategy, study selection process, the data extraction, or the validity of the individual studies.
3.	Are the outcome measures described?	• Outcome assessed in the NMA (included overall survival, OS and progression free survival, PFS) were stated.

ISPOR Checklist Item		Details and Comments
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• The Bucher method was used for the indirect comparisons between ramucirumab and paclitaxel combination therapy and other second-line therapies. There was no description of the methodologies used for the NMA.
5.	Are sensitivity analyses presented?	• No sensitivity analyses were presented
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• The selection process of included studies was not reported. • No table summarizing patient characteristics of the studies used for the indirect comparisons was provided; only a brief description highlighting their similarities. • Brief trial characteristics were provided in table form. • A figure showing the network of studies was provided.
7.	Does the study describe an assessment of model fit? Are competing models being compared?	• No in-depth description of the assessment of the model fit was provided.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were not clearly reported or complete.

7.1.3 Summary

The manufacturer-submitted NMA of ramucirumab and paclitaxel combination therapy versus other second-line treatments of adult patients with advanced or metastatic gastric cancer or GEJ cancer was summarized and critically appraised. The methodology used for the NMA and indirect comparisons were not reported in detail. Due to the limited number of studies informing the networks, the assumptions that were made to connect the network for PFS, and the poor quality of the data from included studies, results were not presented from this NMA.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on ramucirumab for advanced gastric cancer or gastro-esophageal junction adenocarcinoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Gastrointestinal Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

Search Strategy for Patient Values

See section 4 for more details on literature search methods.

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	(Cyramza* or IMC 1121B or IMC1121B or ly 3009806 or ly3009806 or Ramucirumab* or UNII-D99YVK4L0X or 947687-13-0).ti,ot,ab,sh,hw,rn,nm,kw.	133
2	Stomach Neoplasms/	76842
3	(Metastatic adj4 (Stomach or gastric) adj4 (Cancer* or Neoplasm*)).ti,ab.	1140
4	Esophageal Neoplasms/	39933
5	(Esophageal or Esophagus).ti,ab.	95522
6	Adenocarcinoma.hw.	146161
7	(Adenocarcinoma* or Malignant Adenoma*).ti,ab.	104388
8	((Granular Cell or Tubular) adj3 Carcinoma*).ti,ab.	820
9	(4 or 5) and (6 or 7 or 8)	11751
10	1 or 2 or 3 or 9	86515
11	exp patient acceptance of health care/ or exp patient participation/ or exp patient preference/ or exp patient satisfaction/ or caregivers/ or exp consumer participation/	208773
12	patient-reported outcome*.ti,ab.	4812
13	patient*.jw.	11251
14	((patient or patients or care giver* or caregiver* or carer or carers or family or families or consumer or consumers or public or layman or laymen or lay-man or lay-men or lay-person* or layperson* or user*) adj3 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or "day-to-day" or participat* or acceptance or symptom or symptoms or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or engage* or involvement)).ti.	50361
15	((patient or patients or care giver* or caregiver* or carer or carers or family or families or consumer or consumers or public or layman or laymen or lay-man or lay-men or lay-person* or layperson* or user*) adj3 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or "day-to-day" or participat* or acceptance or symptom or symptoms or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or engage* or involvement)).ab. /freq=2	59189
16	11 or 12 or 13 or 14 or 15	290481
17	10 and 16	472
18	limit 17 to (english language and yr="2010 -Current")	119

Search Strategy for Systematic Review

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials March 2015, Embase 1974 to 2015 April 17, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	(Cyramza* or IMC 1121B or IMC1121B or ly 3009806 or ly3009806 or Ramucirumab* or UNII-D99YVK4L0X or 947687-13-0).ti,ot,ab,sh,hw,rn,nm,kw. use pmez	132
2	*ramucirumab/	100
3	(Cyramza* or IMC 1121B or IMC1121B or IMC 1121 B or IMC1121 B or ly 3009806 or ly3009806 or Ramucirumab*).ti,ab. use oemezd	180
4	2 or 3	187
5	(Cyramza* or IMC 1121B or IMC1121B or IMC 1121 B or IMC1121 B or ly 3009806 or ly3009806 or Ramucirumab*).ti,ab. use cctr	11
6	1 or 4 or 5	330
7	exp animals/	38438539
8	exp animal experimentation/ or exp animal experiment/	1850121
9	exp models animal/	1258410
10	nonhuman/	4489158
11	exp vertebrate/ or exp vertebrates/	37374595
12	animal.po.	0
13	or/7-12	39764919
14	exp humans/	30086423
15	exp human experimentation/ or exp human experiment/	347687
16	human.po.	0
17	or/14-16	30088513
18	13 not 17	9678002
19	6 not 18	330
20	limit 19 to english language	315
21	remove duplicates from 20	199

2. Literature search via PubMed

Search	Query	Items found
#1	Search **(Cyramza OR IMC 1121B OR IMC1121B OR ly 3009806[tiab] OR ly3009806[tiab] OR Ramucirumab) AND publisher[sb]**	11

3. Cochrane Central Register of Controlled Trials (Central)

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See Ovid strategy above.

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: **Cyramza OR IMC 1121B OR ly 3009806 OR Ramucirumab**

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: **Cyramza OR ramucirumab**

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

Search terms: Cyramza OR IMC 1121B OR ly 3009806 OR Ramucirumab / last 5 years

European Society for Medical Oncology (ESMO)

http://www.esmo.org/

Search terms: Cyramza OR IMC 1121B OR ly 3009806 OR Ramucirumab / last 5 years

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