

# Optimizing treatment duration with ramucirumab and paclitaxel by managing chemotherapy-associated toxicity: Review of four cases

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Man Yee Merl<sup>1</sup>, Renee Moyer<sup>1</sup>, Anindya Chatterjee<sup>2</sup>   
and Kenyon D Ogburn<sup>2</sup> 

## Abstract

Gastric and gastroesophageal junction adenocarcinomas have poor prognoses. Ramucirumab is considered a second-line standard of care for patients with these cancers. Patients may develop chemotherapy-induced adverse events, and physicians may benefit from greater familiarity with treatment management in the setting of common adverse events. We report four cases of metastatic gastric or gastric and gastroesophageal junction adenocarcinoma treated with second-line ramucirumab plus paclitaxel. All patients developed chemotherapy-associated grade  $\geq 2$  neutropenia and/or neuropathy, and one experienced recurrence of neurotoxicity, during second-line therapy. These adverse events were successfully managed by withholding or reducing the paclitaxel dose, without modifying the ramucirumab dosage schedule, and allowed administration of additional therapy cycles. In all patients, second-line therapy was associated with a best overall response of complete or partial response ranging from 2.2 to 12.4 months. These four cases demonstrate that paclitaxel-associated adverse events can be managed with dose modifications, thereby allowing continued therapy and potential survival benefits.

## Keywords

Ramucirumab, chemotherapy, adverse event, gastric adenocarcinoma, gastroesophageal junction adenocarcinoma

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## Introduction

Gastric and gastroesophageal junction (GEJ) adenocarcinomas have poor prognoses, and most patients are diagnosed with inoperable, advanced, or metastatic disease.<sup>1</sup> Recurrence is common,<sup>2</sup> and effective treatment options are limited,<sup>3</sup> especially after progression or recurrence.

Ramucirumab is a human immunoglobulin G1 monoclonal antibody vascular endothelial growth factor (VEGF) receptor-2 antagonist approved by the US Food and Drug Administration (FDA) in 2014 as monotherapy or in combination with paclitaxel for the second-line treatment of advanced gastric or GEJ adenocarcinoma.

Two phase III clinical trials, REGARD (NCT00917384)<sup>4</sup> and RAINBOW (NCT01170663),<sup>5</sup> demonstrated survival benefits for ramucirumab in patients with advanced gastric or GEJ adenocarcinoma who progressed on first-line therapy. In REGARD, ramucirumab was administered as monotherapy after first-line fluoropyrimidine or platinum-based therapy (median overall survival was 5.2 months with

ramucirumab vs 3.8 months with placebo;  $p < 0.05$ ). The later RAINBOW trial also reported significant clinical benefits for ramucirumab in combination with paclitaxel after first-line platinum-based therapy (median overall survival: 9.6 months vs 7.4 months with placebo plus paclitaxel;  $p = 0.017$ ).<sup>5</sup> Objective (complete (CR) or partial (PR)) response rates for these treatments in RAINBOW were 28% versus 16% ( $p = 0.0001$ ); disease control rates were 80% versus 64% ( $p < 0.0001$ ).

In patients with gastric or GEJ adenocarcinoma, combinations of angiogenic inhibitors and chemotherapy agents have the potential to increase the efficacy of systemic

<sup>1</sup>Yale-New Haven Hospital, New Haven, CT, USA

<sup>2</sup>Global and US Medical Affairs Oncology, Eli Lilly and Company, Indianapolis, IN, USA

## Corresponding Author:

Anindya Chatterjee, Global and US Medical Affairs Oncology, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA.  
Email: chatterjee\_anindya@lilly.com



treatment with few overlapping toxicities.<sup>6,7</sup> Based on results of the RAINBOW and REGARD trials, ramucirumab is now considered a second-line standard of care option for patients with advanced gastric or GEJ adenocarcinoma.<sup>8,9</sup> In this setting, familiarity with managing ramucirumab treatment in combination with taxane-based chemotherapy following the development of chemotherapy-related adverse events (AEs) can be important.

The RAINBOW study evaluated ramucirumab in combination with paclitaxel in 665 patients with gastric cancer (80%) or GEJ adenocarcinoma (20%). As such, the extent to which paclitaxel-related AEs affected continued treatment can be assessed. At entry to the RAINBOW trial, patients were required to have resolution of previous treatment-related AEs to grade  $\leq 1$  according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 and an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0–1.

Herein, we report outcomes of four patients from this trial who successfully continued combined ramucirumab and paclitaxel therapy despite experiencing AEs during this therapy. Patients with human epidermal growth factor receptor-2 (HER-2)-positive tumors were also included to challenge the perception that these patients can only attain clinical benefit with trastuzumab.<sup>5</sup> Patients selected had either a CR or PR as their best overall response to ramucirumab plus paclitaxel. For all patients, second-line ramucirumab 8 mg/kg was administered on days 1 and 15 without any dose modification, and dose adjustments for paclitaxel 80 mg/m<sup>2</sup>, administered on days 1, 8, and 15 of a 28-day cycle, were made on a case-by-case basis.

## Case reports

### Case 1

A 64-year-old male presented with non-specific symptoms of low hemoglobin and lethargy and was diagnosed with HER-2-negative metastatic gastric adenocarcinoma. He did not undergo surgical resection. First-line therapy with epirubicin, cisplatin, and 5-fluorouracil resulted in a PR, but he progressed on therapy after 4 months.

After progression, the patient was enrolled in the RAINBOW trial. He had both measurable and non-measurable diseases at baseline: a solitary liver metastasis (19 mm) and peritoneal metastases (omental deposits), with ascites. At enrollment, he had mild paresthesia with no persistent AEs of grade  $\geq 1$  or higher from initial therapy.

The patient had a CR of the target lesion (liver metastasis) 6 weeks after initiation of second-line therapy. Seven months after starting second-line therapy, treatment was discontinued and progressive disease (PD) was recorded.

Due to grade 4 neutropenia in cycle 2 (duration 14 days), the day 15 dose of paclitaxel 80 mg/m<sup>2</sup> was not administered (Figure 1(a)). The full dosage of paclitaxel 80 mg/m<sup>2</sup> was administered for cycle 3 (days 1, 8, and 15). However in

cycle 4, grade 3 peripheral neuropathy necessitated paclitaxel dose reduction to 70 mg/m<sup>2</sup> on days 1 and 8, and grade 4 neutropenia led to the dose being withheld on day 15. Both neutropenic episodes were uncomplicated. Grade 3 peripheral neuropathy before the start of cycle 5 prompted an additional permanent paclitaxel dose reduction to 60 mg/m<sup>2</sup>, and the neuropathy improved. Ramucirumab was administered for all eight cycles with no interruptions. Thus, these dose modifications facilitated continuation of treatment with ramucirumab and paclitaxel for eight cycles in total, and the patient achieved a durable 6-month response.

### Case 2

A 49-year-old male presented with abdominal pain, anemia, hyperuricemia, grade 1 polyneuropathy and chronic renal failure, and was diagnosed with HER-2-positive metastatic gastric adenocarcinoma. The patient did not undergo surgical resection. First-line treatment with capecitabine, cisplatin, and trastuzumab led to stable disease (SD), but he progressed on therapy 9 months later.

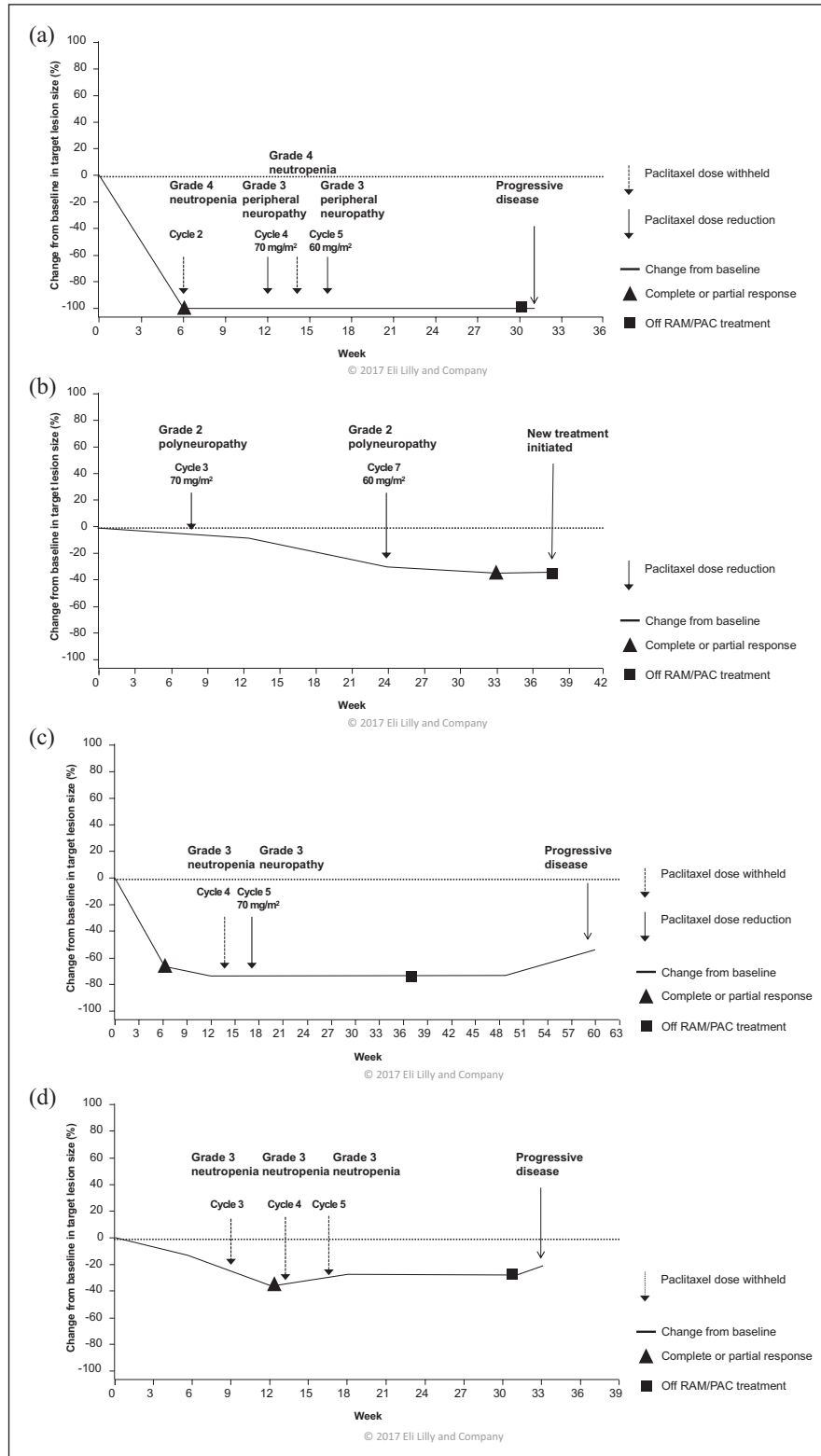
The patient was enrolled in the RAINBOW trial with both measurable and non-measurable diseases at baseline: multiple peritoneal (23 and 45 mm) and lymph node metastases (21 and 18 mm), a single pleural metastasis (17 mm), and ascites. Ongoing AEs from previous first-line chemotherapy included grade 1 polyneuropathy.

Second-line therapy resulted in SD for 8 months followed by a PR. Peritoneal metastases decreased to 15 and 31 mm, lymph node metastases to 10 and 11 mm, and the pleural metastasis to 15 mm. The patient discontinued study treatment due to PD approximately 9 months after randomization.

During cycles 2 and 6 of ramucirumab plus paclitaxel, the patient developed grade 2 polyneuropathy that was managed by a paclitaxel dose reduction to 70 mg/m<sup>2</sup> for cycles 3–6 and a second dose reduction to 60 mg/m<sup>2</sup> at cycle 7 (Figure 1(b)). This latter dose reduction allowed the patient to complete all cycle 7 doses of paclitaxel (and ramucirumab). The patient continued to receive ramucirumab alone for an additional 3 months, during which time a PR was achieved for approximately 2 months. The patient received a total of seven cycles of ramucirumab plus paclitaxel and then two cycles of ramucirumab alone before discontinuing treatment.

### Case 3

A 70-year-old male presented with symptoms suggestive of esophagitis, and was diagnosed with HER-2-negative metastatic gastric adenocarcinoma. The patient underwent a partial gastrectomy. First-line therapy with perioperative 5-fluorouracil, oxaliplatin, and leucovorin (FOLFOX) resulted in SD as the best response, and he progressed 10 months after the first dose.



**Figure 1.** Graphical representation of the paclitaxel dose-management strategy used to allow continued ramucirumab plus paclitaxel therapy for (a) case 1, (b) case 2, (c) case 3, and (d) case 4. Case 2 was censored for initiation of a new anti-cancer therapy and subsequently died 1 month later. The calculated duration of response was based on time from the date of response until death (without documented progression). PAC: paclitaxel; RAM: ramucirumab.

The patient was enrolled in the RAINBOW trial with measurable disease at baseline: a solitary peritoneal metastasis (15 mm) and jejunal mesenteric metastasis (15 mm). The time from last dose of FOLFOX to randomization was 4 months. Ongoing AEs from previous chemotherapy included mild gastrointestinal neurotoxicity.

The patient had a PR 6 weeks after initiation of second-line therapy, with the peritoneal metastasis reduced to 8 mm and jejunal mesenteric metastasis to 0 mm. At 9 months, the patient withdrew consent for treatment and remained under observation in the study until 14 months, when he discontinued due to PD at the jejunal mesentery.

Grade 3 neutropenia (duration 14 days) prompted a single paclitaxel dose omission on day 15 of cycle 4 (Figure 1(c)). Grade 3 neuropathy in cycle 5 (duration 28 days) was managed with a permanent paclitaxel dose reduction to 70 mg/m<sup>2</sup> from day 8 of the cycle. No additional paclitaxel dose reductions or omissions were required. All ramucirumab doses were administered without reduction, omission, or delay. The dose modifications facilitated continuation of treatment with ramucirumab and paclitaxel for a total of eight cycles, and the patient experienced a durable PR lasting for 12 months.

#### Case 4

A 34-year-old male presented with symptoms of anemia and hyperuricemia, and was diagnosed with HER-2-positive metastatic GEJ cancer. The patient underwent a total gastrectomy. First-line treatment with cisplatin, S-1, and trastuzumab resulted in a best response of PR; 16 months after the first dose, he progressed while on therapy.

The patient was enrolled in the RAINBOW trial with measurable and non-measurable diseases at baseline. The target lesion was a 14-mm solitary lung metastasis, although multiple non-measurable metastases were noted in the lungs and lymph nodes. No relevant AEs from first-line chemotherapy were noted for this patient. After initiation of second-line therapy, the patient had a PR of the target lesion (reduced to 10 mm) at 12 weeks and discontinued the study 8 months after randomization due to PD.

Grade 3 neutropenia in each of cycles 3, 4, and 5 (duration 7 days in each instance) led to omission of the paclitaxel dose on day 8 in each of those cycles (Figure 1(d)). All other paclitaxel doses were administered without modification. Ramucirumab was administered without dose reduction, omission, or delay. The dose modifications allowed the patient to continue with ramucirumab and paclitaxel for a total of seven treatment cycles. A durable PR was achieved that lasted for 5 months.

#### Discussion

Ramucirumab in combination with paclitaxel improves overall survival in patients with advanced gastric or GEJ adenocarcinoma who progress after first-line chemotherapy<sup>5</sup>

irrespective of HER-2 status.<sup>10</sup> The four cases reported here represent a relatively diverse group of patients treated with second-line ramucirumab plus paclitaxel. The selected patients were aged 34 to 70 years and half had HER-2-positive disease. Three patients had metastatic gastric adenocarcinoma, and one had metastatic GEJ adenocarcinoma; they had all progressed on platinum-based first-line therapy and most commonly had both measurable and non-measurable diseases.

The aim of reporting this patient case series was to demonstrate how chemotherapy-induced AEs can be managed during second-line ramucirumab plus paclitaxel therapy. As such, four patients who developed chemotherapy-associated grade  $\geq 2$  neutropenia and/or neuropathy during treatment with ramucirumab plus paclitaxel were selected, and three of these patients, who experienced neurotoxicity during second-line treatment, had this AE in a mild form after first-line chemotherapy. Neurotoxicity is a known AE of cisplatin- and oxaliplatin-based therapy,<sup>11</sup> and the use of these agents as well as the relatively longer duration of first-line therapy may have predisposed these patients to further nervous system damage. It is possible that the patients had experienced more severe neurotoxicity during first-line therapy, but to be eligible for enrollment in the RAINBOW trial,<sup>5</sup> previous treatment-related AEs were required to have resolved to grade  $\leq 1$ . Platinum-based therapy is also associated with neutropenia,<sup>11</sup> which may also have predisposed our patients to this event during second-line therapy. No other grade 3 or 4 paclitaxel-associated AEs were reported in these patients. These AEs tended to occur in earlier, rather than later, cycles and were successfully managed by withholding or reducing the dose of paclitaxel without the need for any modification of the ramucirumab dosage schedule, allowing additional cycles of therapy to be administered. Although allowed on an “as-needed” basis at the investigator’s discretion, no patient received granulocyte colony-stimulating factor therapy as prophylaxis for neutropenia or its management, and no patient was hospitalized because of these AEs. In all patients, second-line ramucirumab plus paclitaxel was associated with a best objective response lasting for 2.2–12.4 months. This compares with a median duration of response of 4.4 months in all evaluable ramucirumab plus paclitaxel-treated patients in RAINBOW.<sup>5</sup>

The strategies and supportive medications used to manage paclitaxel-associated neutropenia and neuropathy in the RAINBOW study are in general alignment with those used in real-world practice, although none of the four patients in this case series required these supportive treatments. In the authors’ experience, a dose of paclitaxel is reduced when these AEs are of grade 2 or lower severity and withheld if the AE is grade 3 or 4. The ramucirumab regimen is continued unchanged. However, when the AE has resolved, paclitaxel is continued at the reduced dosage, not reintroduced at full dosage. If a patient continues to experience neutropenia or neuropathy, the day 8 dose of paclitaxel in each cycle is dropped,

so the taxane is administered on days 1 and 15 every 28 days, and the ramucirumab dosing schedule continues unchanged. According to the US and EU paclitaxel labels, it is similarly recommended that a 20% paclitaxel dose reduction be initiated for patients with “severe” neuropathy (not defined) or neutropenia ( $<500$  cells/mm<sup>2</sup> for  $\geq 7$  days) and that the paclitaxel dose be withheld if the neutrophil count is  $<1500$  cells/mm<sup>2</sup> when the dose is due.<sup>12,13</sup> The alternative schedule of ramucirumab 8 mg/kg plus paclitaxel 110 mg/m<sup>2</sup> given once every 2 weeks has also been evaluated in a retrospective single-center database analysis.<sup>14</sup> The authors of that analysis considered that this amended dosage regimen did not compromise efficacy in the second-line setting (overall survival 9.46 months<sup>14</sup> vs 9.6 months in RAINBOW<sup>5</sup>), although dose delays, adjustments, and omissions were similar to those reported in the RAINBOW trial. Overall, 31% of patients receiving the alternative treatment regimen as second-line therapy, and 32.5% receiving this regimen as second-line or greater therapy, required a dose or schedule modification, most commonly because of neutropenia (44% of delays or adjustments in the total population), and occasionally neuropathy (3.6%).<sup>14</sup> In RAINBOW, 24% of patients randomized to ramucirumab plus paclitaxel had a paclitaxel dose reduction, and among this treatment group, 38%, 8%, 0%, and 0% experienced grades 1–2, 3 and 4, neuropathy, respectively, and 14%, 71%, and 62% experienced these grades of neutropenia, respectively.<sup>5</sup>

All four patients were able to continue on the full dose of ramucirumab despite the occurrence of these paclitaxel-associated AEs. Similarly, only 5% of patients in RAINBOW required ramucirumab dose reduction.<sup>5</sup> The AE profile of ramucirumab is similar to that of other angiogenic inhibitors and includes an increased risk of hypertension, proteinuria, low-grade (grade 1–2) bleeding, gastrointestinal perforation, and wound-healing complications compared with placebo.<sup>8</sup> However, rates of arterial thromboembolic events, venous thromboembolic events, high-grade bleeding, and high-grade gastrointestinal bleeding may be lower with ramucirumab than with other agents with a similar mechanism of action. In a meta-analysis of individual patient safety data from six randomized, placebo-controlled trials, no increase in relative risk of these AEs was observed in patients treated with ramucirumab compared with placebo.<sup>15</sup>

## Conclusion

Ramucirumab plus paclitaxel improves overall survival in patients with advanced gastric or GEJ adenocarcinoma who progress after first-line chemotherapy. The successful management of chemotherapy-associated neutropenia, neuropathy, or neurotoxicity suggests that ramucirumab in combination with paclitaxel should not be withheld in patients who experience chemotherapy-induced AEs, thereby allowing patients to achieve maximal potential survival benefits.

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## Data availability statement

Eli Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents—including the study protocol, statistical analysis plan, clinical study report, blank, or annotated case report forms—will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at [www.vivli.org](http://www.vivli.org).

## Declaration of conflicting interests

M.Y.M. and R.M. have nothing to disclose. A.C. and K.D.O. own stock in Eli Lilly and Company.

## Ethical approval

Ethical approval to report this case series was obtained from each center’s institutional review board or an independent ethics committee approved the study. The trial followed the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation.

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## Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

## ORCID iDs

Anindya Chatterjee  <https://orcid.org/0000-0003-4584-5990>

Kenyon D Ogburn  <https://orcid.org/0000-0002-2054-2662>

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