Overview

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Title: A Phase Ib Study of Safety and Pharmacokinetics of Ramucirumab in Combination With Paclitaxel in Patients With Advanced Gastric Adenocarcinomas

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Disclosures

Taroh Satoh: Eli Lilly and Company, Chugai Pharmaceutical, Merck-Serono (C/A), Eli Lilly and Company, Chugai Pharmaceutical, Merck-Serono, Bristol-Myers Squibb, Yakult Honsha (RF), Chugai Pharmaceutical, Merck-Serono, Bristol-Myers Squibb, Yakult Honsha (H); **Ling Gao:** Eli Lilly and Company (E). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background

This phase Ib study evaluated the tolerability and pharmacokinetics of ramucirumab, an anti-VEGFR-2 antibody, combined with paclitaxel as second-line therapy in Japanese patients with metastatic gastric or gastroesophageal junction adenocarcinoma after first-line therapy with fluoropyrimidines and/or platinum.

Methods

Patients received ramucirumab 8 mg/kg on days 1 and 15 and paclitaxel 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Safety analyses included all patients ($n = 6$).

Results

No dose-limiting toxicities occurred in the first cycle. All patients experienced ≥1 treatment-emergent adverse event (TEAE); 5 patients experienced grade ≥3 TEAEs. There were two deaths caused by disease progression. The best overall responses were stable disease ($n = 5$) and partial response ($n = 1$). Patients received ramucirumab and paclitaxel for a median of 12.5 weeks (range: 11.4–42.7 weeks) and 12.2 weeks (range: 11.0–41.0 weeks), respectively. Following a single dose of ramucirumab IV infusion 8 mg/kg, clearance was ~0.017 L/hour, half-life ($t_{1/2}$) was 138 to 225 hours, and steady-state volume of distribution (V_{ss}) was ~3 L.

Conclusion

The ramucirumab/paclitaxel combination appears to be well-tolerated in Japanese patients with advanced gastric adenocarcinomas. These results are in line with previous ramucirumab pharmacokinetic studies as anticipated.

Discussion

The primary objective of this study was to confirm the recommended dose of ramucirumab in combination with paclitaxel and assess pharmacokinetics (PK) of ramucirumab in Japanese patients with advanced gastric adenocarcinomas who failed standard therapy with fluoropyrimidines and/or platinum. Exploratory objectives included pharmacodynamics and antitumor activity. Ramucirumab is a recombinant human monoclonal antibody against human vascular endothelial growth factor receptor-2 (VEGFR-2) preventing ligand binding and receptor-mediated pathway activation in endothelial cells [1, 2]. Inhibition of VEGFR-2 in gastric cancer xenografts (thymidylate kinase-1 cell line) is associated with reduced tumor growth [1]. Weekly administration of paclitaxel (at a dose of 80 mg/m^2) has been extensively studied as second-line chemotherapy for gastric cancer and is considered standard care [3–10].

Ramucirumab plus paclitaxel is approved by the U.S. Food and Drug Administration (FDA) for second-line treatment in gastric cancer based on the 2.2-month overall survival advantage seen in the RAINBOW trial (trial was powered to detect a 2.3-month difference) [11]. In the current study, 8 mg/kg ramucirumab was administered on days 1 and 15 combined with 80 mg/m^2 paclitaxel on days 1, 8, and 15 in a 28-day cycle. Patients received ramucirumab and paclitaxel for a median of 12.5 weeks (range: 11.4–42.7 weeks) and 12.2 weeks (range: 11.0–41.0 weeks), respectively.

Safety analyses included all treated patients ($n = 6$) (Table 1). All patients ($n = 6$) experienced $\geq$1 treatment-emergent adverse event (TEAE) of any grade (grade $\geq$3 in 5 patients), ramucirumab-related TEAEs, and paclitaxel-related TEAEs. There were no ramucirumab- or paclitaxel-related grade $\geq$4 TEAEs. Five patients discontinued because of progressive disease (PD), and one patient discontinued because of a TEAE (meningism) not related to ramucirumab or paclitaxel. The two deaths reported were due to PD and were not study drug-related. Seven serious adverse events (SAEs) occurred in four patients. Ramucirumab- or paclitaxel-related SAEs included pneumonia in two patients and gastrointestinal hemorrhage in one patient.

Following a single IV infusion of 8 mg/kg ramucirumab, PK analysis indicated a half-life ranging from 138 to 225 hours. Following multiple doses of 8 mg/kg ramucirumab, steady state was approximately achieved on cycle 2, day 1, and the accumulation ratio calculated using area under the concentration-time curve (R_A, AUC) was approximately 1.5. Geometric mean of steady state C_{min} ranged from 44.2 μg/mL (% coefficient of variation [CV]: 21%) to 66.6 μg/mL (% CV: 25%) between cycle 2, day 1 and cycle 3, day 1. Trend plots for pharmacodynamic data revealed increasing levels of VEGF-D following the first ramucirumab infusion. No apparent trends were identified for VEGF-C, soluble neuropilin-1, or VEGFR-1.

No dose-limiting toxicities (DLTs) were observed within the first 28-day cycle, which was the DLT-observation period. Four patients experienced SAEs in later cycles, and predefined dose-modification strategies were used. Limitations of this study included the small sample size and uncontrolled design. Because of the small sample size, no efficacy conclusions could be drawn. In conclusion, the combination of ramucirumab and paclitaxel at the doses and schedule given did not result in any DLTs and appeared to be safe and well-tolerated in Japanese patients with advanced gastric adenocarcinomas.

Trial Information

Disease	Gastric cancer
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	1 prior regimen
Type of study - 1	Phase Ib
Type of study - 2	Rolling Six
Primary Endpoint	Safety
Primary Endpoint	Tolerability
Secondary Endpoint	Pharmacokinetic
Secondary Endpoint	Correlative Endpoint
Additional Details of Endpoints or Study Design	Preliminary assessment of the antitumor activity of ramucirumab/paclitaxel combination and assessment of effect of ramucirumab on pharmacodynamic biomarkers (VEGFR-1, VEGF-C, VEGF-D, and neuropilin-1)
Investigator's Analysis	Safe and should be pursued further

Drug Information

Drug 1 **Generic/Working name**	Ramucirumab
Trade name	Cyramza
Company name	Eli Lilly and Company
Drug type	Antibody
Drug class	VEGFR-2 antagonist
Dose	8 mg/kg
Route	IV
Schedule of Administration	Days 1 and 15 of a 28-day cycle
Drug 2 **Generic/Working name**	Paclitaxel
Trade name	Taxol
Company name	Bristol-Myers Squibb
Drug type	Small molecule
Drug class	Microtubule-targeting agent
Dose	80 mg/m^2
Route	IV
Schedule of Administration	Days 1, 8, and 15 of each cycle, 1 hour after completion of the ramucirumab infusion

Patient Characteristics

Number of patients, male	5	
Number of patients, female	1	
Stage	**M stage**	***n* (%)**
	M0	1 (16.7)
	M1	4 (66.7)
	MX	0
	Unknown	1 (16.7)
Age	Median (range): 56.9 years (range: 38.6–76.0 years)	
Number of prior systemic therapies	Median (range): Not Collected	
Performance Status:	ECOG • 0 — 4 • 1 — 2 • 2 — 0 • 3 — 0 • unknown — 0	
Other	Not Collected	
Cancer Types or Histologic Subtypes	Diffuse Type 1 Intestinal type 1 Unknown 4	

Adverse Events

Adverse events at all dose levels, cycle 1

Preferred term	NC/NA[a]	1	2	3	4	5	All grades
Epistaxis	67%	33%	0%	0%	0%	0%	33%
Rash	67%	33%	0%	0%	0%	0%	33%

Alopecia	50%	50%	0%	0%	0%	0%	50%
Neutropenia	33%	0%	50%	17%	0%	0%	67%
White blood cell decreased	67%	0%	17%	17%	0%	0%	33%
Diarrhea	67%	33%	0%	0%	0%	0%	33%

Adverse Events Legend
[a]No change from baseline/no adverse event.
Treatment-emergent adverse events reported in ≥2 patients in the dose-limiting toxicity population are reported.
Abbreviations: NA, not applicable; NC, not calculated.

Adverse events at all dose levels, all cycles

Preferred term	NC/NA[a]	1	2	3	4	5	All grades
Epistaxis	17%	83%	0%	0%	0%	0%	83%
Hemorrhoidal hemorrhage	67%	33%	0%	0%	0%	0%	33%
Hypertension	67%	0%	33%	0%	0%	0%	33%
Proteinuria	50%	33%	0%	17%	0%	0%	50%
Neutropenia[b]	17%	0%	50%	33%	0%	0%	83%
Rash[b]	33%	67%	0%	0%	0%	0%	67%
Leukopenia[b]	50%	0%	33%	17%	0%	0%	50%
Neuropathy[b]	50%	50%	0%	0%	0%	0%	50%
Anemia	67%	0%	33%	0%	0%	0%	33%
Thrombocytopenia[b]	67%	33%	0%	0%	0%	0%	33%
Diarrhea	67%	33%	0%	0%	0%	0%	33%
Nausea	50%	50%	0%	0%	0%	0%	50%
Vomiting	67%	33%	0%	0%	0%	0%	33%
Fatigue	67%	33%	0%	0%	0%	0%	33%
Pyrexia	50%	50%	0%	0%	0%	0%	50%
Pneumonia	67%	0%	0%	33%	0%	0%	33%
Alanine aminotransferase increased	67%	33%	0%	0%	0%	0%	33%
Aspartate aminotransferase increased	67%	17%	17%	0%	0%	0%	33%
Anorexia (decreased appetite)	50%	17%	17%	17%	0%	0%	50%
Hyperglycemia	67%	33%	0%	0%	0%	0%	33%
Hyponatremia	67%	0%	0%	33%	0%	0%	33%
Back pain	67%	17%	17%	0%	0%	0%	33%
Headache	67%	33%	0%	0%	0%	0%	33%
Alopecia	50%	50%	0%	0%	0%	0%	50%

Adverse Events Legend
[a]No change from baseline/no adverse event.
[b]Consolidated AE terms are comprised of synonymous MedDRA preferred terms: neutropenia includes neutrophil count decreased; neuropathy includes peripheral sensory neuropathy, neuropathy peripheral; leukopenia includes white blood cell decreased; rash includes rash maculo-papular; thrombocytopenia includes platelet count decreased.
Treatment-emergent adverse events reported in ≥2 patients in the safety population are reported.
Abbreviations: NA, not applicable; NC, not calculated.

Serious adverse events

Serious adverse event	Grade	Related
Pneumonia	3	Possible
Pneumonia	3	Possible
Anorexia (decreased appetite)	3	Unrelated
Gastrointestinal hemorrhage	2	Possible
Intestinal obstruction	3	Unrelated
Lymphangiosis carcinomatosa	3	Unrelated
Meningism	5	Unrelated

Pharmacokinetics/Pharmacodynamics

Noncompartmental pharmacokinetic parameters for ramucirumab following single and multiple 8 mg/kg intravenous infusions

Geometric mean (% CV)

Number of doses	Number of patients	C_{max} (μg/mL)	t_{max} (h)[a]	$AUC_{(0-\tau)}$ (μg·h/mL)[b]	$AUC_{(0-\infty)}$ (μg·h/mL)	$t_{1/2}$ (h)	CL or CL_{ss} (L/h)	V_{ss} (L)	R_A, AUC[c]
Single dose	6	171 (26)	4.00 (1.02–9.05)	18,300 (35)	34,100[d]	181 (138-225)[e]	0.0166[d]	3.27[d]	NA
Multiple doses	4[f]	282 (15)	1.82 (1.03–2.15)	41,300, 42,600[d]	NC	218[d]	0.0133, 0.0138[d]	NC	1.52, 1.53[d]

[a]Median (range: minimum to maximum)
[b]τ = 337 hours on cycle 1, day 1; τ = 336 hours for other occasions.
[c]R_A,AUC = $AUC_{(0-\tau)}$ cycle 2/$AUC_{(0-\tau)}$ cycle 1.
[d]Individual subject value(s) are given when $N = 1$ or 2.
[e]Geometric mean (range: minimum to maximum), $N = 4$.
[f]One patient had ramucirumab infusion delayed for 13 days. Another patient had ramucirumab infusion delayed for 6 days. Pharmacokinetic parameters were excluded from mean summary statistics.
Abbreviations: $AUC_{(0-\infty)}$, area under the concentration-time curve from zero to time infinity; $AUC_{(0-\tau)}$, area under the concentration-time curve over a dosing interval; CL, total body clearance; CL_{ss}, total body clearance at steady state; C_{max}, maximum observed serum concentration; CV, coefficient of variation; h, hours; NA, not applicable; NC, not calculated; R_A, AUC, accumulation ratio based on the area under the concentration-time curve; $t_{1/2}$, terminal half-life; t_{max}, time to maximum observed serum concentration; V_{ss}, volume of distribution at steady-state; V_z, volume of distribution during the terminal elimination phase.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Safe and should be pursued further

Discussion

This was a phase Ib study of ramucirumab with paclitaxel in Japanese patients with advanced gastric adenocarcinomas. The results demonstrate that ramucirumab (8 mg/kg) administered intravenously on days 1 and 15 in combination with paclitaxel (80 mg/m^2) administered intravenously on days 1, 8, and 15 of a 28-day cycle appears to be safe and well-tolerated in Japanese patients with advanced gastric adenocarcinomas.

Ramucirumab is a recombinant human monoclonal antibody directed against human VEGFR-2 [1, 2]. Adverse events observed in phase I studies of ramucirumab given as monotherapy (8–10 mg/kg every 2 weeks or every 3 weeks) were fatigue, headache, nausea, hypertension, and peripheral edema [2]. Paclitaxel has been extensively studied as second-line chemotherapy in Western and Asian populations [3–10]. Weekly paclitaxel (80 mg/m^2) is associated with a favorable safety profile in Japanese patients, with frequencies of 16% for grade 4 neutropenia and 8% for grade 3 thrombocytopenia. The frequency of grade 3 nonhematologic toxicities was less than 3% for nausea, anorexia, diarrhea, and neuromotor or neurosensory neuropathy [10]. The comparison of the safety profiles of ramucirumab and of weekly paclitaxel revealed no overlapping toxicities. The safety profile of the combination would likely consist of the side effects of both elements of the combination. Therefore, a study on six patients was deemed sufficient to confirm the feasibility of the combination in Japanese patients, which was a requirement by the Japanese Pharmaceuticals and Medical Devices Agency prior to conducting the global phase 3 trial RAINBOW in Japan [11].

The six patients in this study were treated and comprised the safety population; five (83.3%) were male, and all were Asian (Japanese), with a median age of 56.9 years (range: 38.6–76.0 years). The primary tumor location was gastric for four patients and gastroesophageal junction for two patients. All patients had metastatic disease, with metastases to one or more sites. All patients received prior chemotherapy. The median relative-dose intensity for paclitaxel across all cycles was 73.0% (range: 58.3%–97.3%) and 96.3% (range: 76.9%–105.0%) for ramucirumab.

The median duration of treatment for paclitaxel and ramucirumab was 12.2 weeks (range: 11.0–41.0 weeks) and 12.5 weeks (range: 11.4–42.7 weeks), respectively. All six treated patients were DLT-evaluable and comprised the DLT population, which was evaluated based on cycle 1 assessments. There were no DLTs in cycle 1 in this study.

The most frequently reported TEAEs by preferred term for all cycles, occurring in at least two patients, were epistaxis and neutropenia (n = 5 each); rash (n = 4); leukopenia, neuropathy, nausea, alopecia, pyrexia, decreased appetite, and proteinuria (n = 3 each); and anemia, thrombocytopenia, hemorrhoidal hemorrhage, diarrhea, fatigue, vomiting, pneumonia, hyperglycemia, hyponatremia, back pain, headache, hypertension, alanine aminotransferase increased, and aspartate aminotransferase increased (n = 2 each).

Adverse events of special interest (AESIs) that are commonly associated with antiangiogenic agents and therapeutic monoclonal antibodies were experienced by six patients. Grade 3 AESIs included: hematuria ($n = 1$) and proteinuria ($n = 1$). Both were judged as unrelated to ramucirumab or paclitaxel.

During the study, two patients had grade 3 pneumonia that was considered to be related to both ramucirumab and paclitaxel. Other grade 3 paclitaxel-related TEAEs included neutropenia, neutrophil count decreased, and white blood cell count decreased ($n = 1$ each). There were no ramucirumab- or paclitaxel-related grade 4 or 5 TEAEs. There were no study drug-related deaths. The two reported deaths were due to disease progression and occurred 20 and 42 days after last dose. SAEs occurred in 4 patients: pneumonia ($n = 2$) and gastrointestinal hemorrhage, intestinal obstruction, decreased appetite, lymphoangiosis carcinomatosa, and meningism ($n = 1$ each). There were three SAEs (pneumonia [$n = 2$] and gastrointestinal hemorrhage [$n = 1$]) in two patients that were considered to be related to both ramucirumab and paclitaxel by the investigator. One patient had a TEAE of meningism not considered to be related to ramucirumab or paclitaxel, which led to treatment discontinuation. There were no TEAEs that led to treatment discontinuation in the DLT population. No efficacy conclusions were drawn from this study.

Serum samples were analyzed for ramucirumab at Intertek (Intertek Pharmaceutical Services) Analytical Laboratory (San Diego, CA, http://www.intertek.com/pharmaceutical/) by a validated enzyme-linked immunosorbent assay method. Pharmacokinetic data were analyzed by noncompartmental analysis using WinNonlin 5.3 (Pharsight Corporation, Tokyo, Japan, http://www.pharsight.com).

The PK analysis following a single intravenous infusion of 8 mg/kg ramucirumab indicated that half-life ($t_{1/2}$) ranged from 138 to 225 hours. Following multiple doses every 2 weeks of 8 mg/kg ramucirumab, steady state was approximately achieved on cycle 2, day 1 (the third infusion), and accumulation based on area under the concentration-time curve (R_A, AUC) was approximately 1.5. The geometric mean of steady-state C_{min} of ramucirumab ranged from 44.2 μg/mL (% CV: 21%) to 66.6 μg/mL (% CV: 25%) between cycle 2, day 1 (the third infusion) and cycle 3, day 1 (the fifth infusion). The PK results here did not show significant differences when compared with PK from studies in countries other than Japan [12, 13].

Trend plots revealed that the levels of VEGF-D tend to increase following the first infusion. However, no apparent trends could be identified for VEGF-C. Trends could not be established for soluble neuropilin-1 and VEGFR-1. Immunogenicity data will be reported separately.

Antiangiogenic agents such as bevacizumab and aflibercept that target the VEGF pathway are on the market or being studied in clinical trials [14–16]. Ramucirumab is currently the only VEGFR-2 targeting monoclonal antibody approved by the FDA for metastatic gastric cancer and non-small cell lung cancer based on three pivotal phase 3 studies: REGARD, RAINBOW, and REVEL [11, 17, 18]. Future research should explore optimal timing of ramucirumab use, biomarkers for patient selection, and mechanisms of resistance. Currently, RAINFALL is the first randomized, global phase 3 study of ramucirumab with or without standard therapy aimed at improving overall survival of patients with metastatic gastric cancer in the first-line setting (clinicaltrials.gov NCT02314117). In conclusion, in this phase Ib study, the combination of ramucirumab and paclitaxel at the doses and schedule given did not result in any DLTs and appeared to be safe and well-tolerated in Japanese patients with advanced gastric adenocarcinomas.

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Figure and Tables

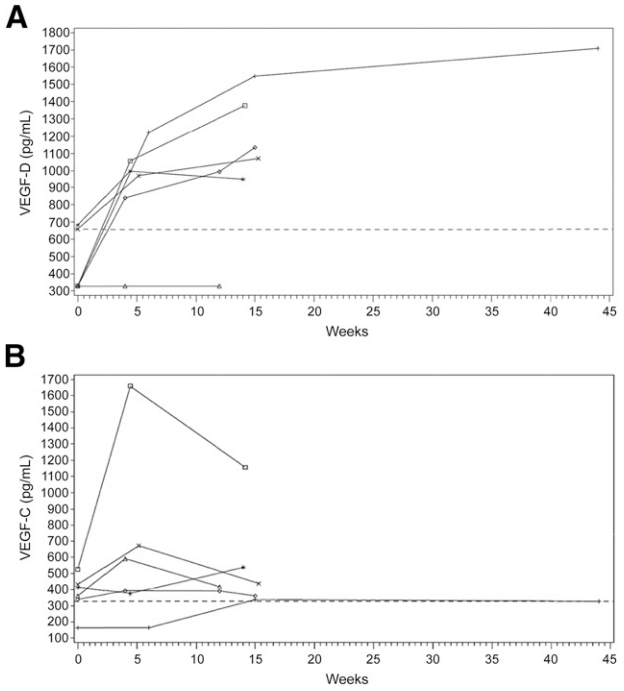

Figure 1. Change over time in VEGF-D **(A)** and VEGF-C **(B)** levels ($n = 6$).
Abbreviations: VEGF, vascular endothelial growth factor.

Table 1 Author Summary. Treatment-emergent adverse events (safety population, $N = 6$)

Adverse Events	***n* (%)**
Any DLT[a]	0
AE of any grade	6 (100.0)
Ramucirumab-related	6 (100.0)
Paclitaxel-related	6 (100.0)
Any SAE	4 (66.7)
Ramucirumab-related	2 (33.3)
Paclitaxel-related	2 (33.3)
AE $\geq$ grade 3	5 (83.3)
Ramucirumab-related	2 (33.3)
Paclitaxel-related	4 (66.7)
AE resulting in death[b]	0
Ramucirumab-related	0
Paclitaxel-related	0
AE resulting in ramucirumab delay/modification	4 (66.7)
AE resulting in paclitaxel delay/modification	4 (66.7)

AE resulting in ramucirumab discontinuation	1 (16.7)
AE resulting in paclitaxel discontinuation	1 (16.7)

[a]A DLT-evaluable patient (that is, a patient who is fully evaluable for determination of safety) was considered to be one who had either completed the first cycle of study medication or discontinued study medication because of a DLT during cycle 1. An AE meeting the definition of a DLT was only considered a DLT if it occurred during the first cycle (28 days).
[b]There were two deaths reported in this study. Both deaths were due to disease progression.
Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event.

Table 1. Patient demographics, characteristics, and disease status at baseline (safety population, $N = 6$)

Characteristics	**Value**
Age (years)	
Mean (SD)	57.6 (15.50)
Median	56.9
Sex, *n* (%)	
Male	5 (83.3)
Race, *n* (%)	
Asian	6 (100.0)
ECOG, *n* (%)	
0	4 (66.7)
1	2 (33.3)
≥ 2	0
Primary tumor location, *n* (%)	
Gastric	4 (66.7)
Gastroesophageal junction	2 (33.3)
Duration of disease (months)	
Mean (SD)	9.9 (8.81)
Median	9.0
Patients with any metastatic site, *n* (%)	6 (100.0)
Lung	1 (16.7)
Liver	4 (16.7)
Bone	1 (16.7)
Brain	0
Skin	0
Lymph nodes	5 (83.3)
Soft tissue	0
Other: esophagus	1 (16.7)
Other: abdominal wall	1 (16.7)
Prior disease-related therapy, *n* (%)	
Chemotherapy	6 (100.0)
Hormonal	0

Immunotherapy	0
Biologic	0
Other	0
Prior disease-related radiotherapy, *n* (%)	
Yes	0
No	6 (100.0)
Prior disease-related surgery, *n* (%)	
Yes	3 (50.0)
No	3 (50.0)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Best overall response (safety population, $N = 6$)

Response	***n* (%)**
CR	0
PR	1 (16.7)
SD	5 (83.3)
Progressive disease	0
Not evaluable	0
Objective response rate (CR + PR), % (95% CI)	16.7 (0.4–64.1)
Disease control rate (CR + PR + SD), % (95% CI)	100 (54.1–100.0)

Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

Table 3. Noncompartmental pharmacokinetic parameters for ramucirumab following single and multiple 8 mg/kg intravenous infusions

		Geometric mean (% CV)							
Number of doses	**Number of patients**	C_{max} (μg/mL)	t_{max} (h)[a]	$AUC_{(0-\tau)}$ (μg·h/mL)[b]	$AUC_{(0-\infty)}$ (μg·h/mL)	$t_{1/2}$ (h)	CL or CL_{ss} (L/h)	V_{ss} (L)	R_A, AUC[c]
Single dose	6	171 (26)	4.00 (1.02–9.05)	18,300 (35)	34,100[d]	181 (138–225)[e]	0.0166[d]	3.27[d]	NA
Multiple doses	4[f]	282 (15)	1.82 (1.03–2.15)	41,300, 42,600[d]	NC	218[d]	0.0133, 0.0138[d]	NC	1.52, 1.53[d]

[a]Median (range: minimum to maximum)
[b]$\tau = 337$ hours on cycle 1, day 1; $\tau = 336$ hours for other occasions.
[c]R_A,AUC = $AUC_{(0-\tau)}$ cycle 2/$AUC_{(0-\tau)}$ cycle 1.
[d]Individual subject value(s) are given when $N = 1$ or 2.
[e]Geometric mean (range: minimum to maximum), $N = 4$.
[f]One patient had ramucirumab infusion delayed for 13 days. Another patient had ramucirumab infusion delayed for 6 days. Pharmacokinetic parameters were excluded from mean summary statistics.
Abbreviations: $AUC_{(0-\infty)}$, area under the concentration-time curve from zero to time infinity; $AUC_{(0-\tau)}$, area under the concentration-time curve over a dosing interval; CL, total body clearance; CL_{ss}, total body clearance at steady state; C_{max}, maximum observed serum concentration; CV, coefficient of variation; h, hours; NA, not applicable; NC, not calculated; R_A, AUC, accumulation ratio based on the area under the concentration-time curve; $t_{1/2}$, terminal half-life; t_{max}, time to maximum observed serum concentration; V_{ss}, volume of distribution at steady-state; V_z, volume of distribution during the terminal elimination phase.

Table 4. Patient disposition, all enrolled patients

Patient disposition	*n* (%)
Enrolled	7 (100.0)
Treated	6 (85.7)
Safety population	6 (85.7)
DLT population	6 (85.7)
Completed cycle 1	6 (100.0)
Reasons for discontinuation	
Death	0
Adverse event	1 (16.7)
Progressive disease–objective tumor response	5 (83.3)
Progressive disease–symptomatic deterioration	0
Lost to follow-up	0
Withdrew consent	0
Completed therapy	0
Other	0

Abbreviation: DLT, dose-limiting toxicity.

Table 5. Treatment-emergent adverse events (safety population, $N = 6$)

Treatment-emergent adverse events	*n* (%)
Any DLT[a]	0
AE of any grade	6 (100.0)
Ramucirumab-related	6 (100.0)
Paclitaxel-related	6 (100.0)
Any SAE	4 (66.7)
Ramucirumab-related	2 (33.3)
Paclitaxel-related	2 (33.3)
AE $\geq$ grade 3	5 (83.3)
Ramucirumab-related	2 (33.3)
Paclitaxel-related	4 (66.7)
AE resulting in death[b]	0
Ramucirumab-related	0
Paclitaxel-related	0
AE resulting in ramucirumab delay/modification	4 (66.7)
AE resulting in paclitaxel delay/modification	4 (66.7)
AE resulting in ramucirumab discontinuation	1 (16.7)
AE resulting in paclitaxel discontinuation	1 (16.7)

[a]A DLT-evaluable patient (that is, fully evaluable for determination of safety) was considered to be one who had either completed the first cycle of study medication or discontinued study medication because of a DLT during cycle 1. An AE meeting the definition of a DLT was only considered a DLT if it occurred during the first cycle (28 days).
[b]There were two deaths reported in this study. Both deaths were due to disease progression.
Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event.

Table 6. Ramucirumab-related treatment-emergent adverse events reported in ≥2 patients (safety population, $N = 6$)

Preferred term	*n* (%)
Any grade	
Patients with ≥1 TEAE	6 (100.0)
Epistaxis	5 (83.3)
Rash	4 (66.7)
Proteinuria	3 (50.0)
Anemia	2 (33.3)
Decreased appetite	2 (33.3)
Hemorrhoidal hemorrhage	2 (33.3)
Nausea	2 (33.3)
Pneumonia[a]	2 (33.3)
Grade ≥3[b]	
Patients with TEAEs	2 (33.3)
Pneumonia	2 (33.3)

[a]Pneumonia was considered to be related to both ramucirumab and paclitaxel.
[b]No ramucirumab-related grade 4 or 5 TEAEs were observed.
Abbreviation: TEAE, treatment-emergent adverse event.

Table 7. Paclitaxel-related treatment-emergent adverse events reported in ≥2 patients (safety population, $N = 6$)

Preferred term	*n* (%)
Any grade	
Patients with ≥1 TEAE	6 (100.0)
Neutropenia	4 (66.7)
Alopecia	3 (50.0)
Epistaxis	3 (50.0)
Rash	3 (50.0)
Anemia	2 (33.3)
Decreased appetite	2 (33.3)
Nausea	2 (33.3)
Peripheral sensory neuropathy	2 (33.3)
Platelet count decreased	2 (33.3)
Pneumonia[a]	2 (33.3)
White blood cell count decreased	2 (33.3)
Grade ≥3[b]	
Patients with TEAEs	4 (66.7)
Pneumonia	2 (33.3)
Neutropenia	1 (16.7)
Neutrophil count decreased	1 (16.7)
White blood cell count decreased	1 (16.7)

[a]Pneumonia was considered to be related to both ramucirumab and paclitaxel.
[b]No paclitaxel-related grade 4 or 5 TEAEs were observed.
Abbreviation: TEAE, treatment-emergent adverse event.

Table 8. Serious adverse events (safety population, $N = 6$)

Serious adverse event	***n* (%)**
Patients with serious adverse events	4 (66.7)
Pneumonia	2 (33.3)[a]
Decreased appetite	1 (16.7)
Gastrointestinal hemorrhage	1 (16.7)[a]
Intestinal obstruction	1 (16.7)
Lymphangiosis carcinomatosa	1 (16.7)
Meningism	1 (16.7)

[a]Related to ramucirumab and paclitaxel.