The Oncologist®

Clinical Trial Results

Phase I Dose-Escalation Study of Ramucirumab in Chinese Patients with Advanced Solid Tumors

Junning Cao,[a] Dongmei Ji,[a] Zhiyu Chen,[a] Weina Shen,[a] Jin Wang,[b] Baoyue Li,[b] Haidong Chi,[b] Amanda Long,[c] Ling Gao,[d] Jin Li[a]

[a]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China; [b]Lilly China Drug Development and Medical Affairs Center, Shanghai, People's Republic of China; [c]Global Pharmacokinetics/Pharmacodynamics, Eli Lilly and Company, Indianapolis, Indiana, USA; [d]Global Pharmacokinetics/Pharmacodynamics, Eli Lilly and Company, Bridgewater, Massachusetts, USA

Trial Information

- **ClinicalTrials.gov Identifier**: NCT01682135
- **Sponsor(s)**: Eli Lilly and Company
- **Principal Investigator**: Jin Li
- **IRB Approved**: Yes

Lessons Learned

- Ramucirumab was well tolerated in Chinese patients with advanced solid tumors, and adverse events were manageable in this study.
- Pharmacokinetics characteristics in Chinese patients were similar to those in other populations. Immunogenicity was not detected.
- No efficacy conclusion could be drawn, and further randomized studies are warranted.

Abstract

Background. This single-arm, nonrandomized, open-label, dose-escalation, phase I study was designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of ramucirumab in Chinese patients with advanced solid tumors that were resistant to standard therapy or no standard therapy was available.

Methods. Dose escalation was a 3 + 3 design, with expansion in Cohorts 2 and 3 for PK. Ramucirumab was given intravenously at three different dosages: 6 mg/kg every 2 weeks, 10 mg/kg every 3 weeks, and 8 mg/kg every 2 weeks. Safety analyses included all patients. PK, immunogenicity, and antitumor activity were also assessed.

Results. Among 28 patients treated, 2 experienced dose-limiting toxicity, possibly related to ramucirumab. No maximum tolerated dose was determined. All patients experienced at least one treatment-emergent adverse event. Grade ≥3 adverse event was reported for 53.6% ($n = 15$) of patients. PK analyses indicated that ramucirumab had low clearance, small volume of distribution, and long half-life in Chinese patients, as in other populations. Immunogenicity was not detected. No patient had complete/partial response, and 64.3% ($n = 18$) had stable disease with a median duration of 5.55 months (95% confidence interval: 3.38−7.13 months).

Conclusion. Ramucirumab appeared to be well tolerated in Chinese patients with advanced solid tumors. PK characteristics in Chinese patients were similar to those in other populations.

The Oncologist 2017;22:638–e56

Discussion

Ramucirumab is a recombinant human IgG1 monoclonal antibody inhibiting vascular endothelial growth factor receptor-2 [1–3]. Its clinical benefit has been demonstrated in several phase III studies in patients with gastric cancer, non-small cell lung cancer, or colorectal cancer [4–7]. However, data among Chinese population were minimal.

In this study, eligible patients were enrolled sequentially into three cohorts and received ramucirumab intravenously at three different dosage levels, respectively. Dose selection and escalation were based on phase I trial results conducted globally [8, 9].

Two patients experienced dose-limiting toxicity (DLT), possibly related to ramucirumab: 1 in Cohort 1 (grade 3 proteinuria), 1 in Cohort 2 (grade 3 alanine aminotransferase (ALT) increased). No DLT was observed in Cohort 3 at the highest dose. All 28 treated patients experienced at least 1 treatment-emergent adverse event (TEAE). Study drug-related adverse events (AEs) that occurred in ≥20% of total patients included fatigue, hypertension, increased aspartate aminotransferase (AST), proteinuria, increased ALT, decreased appetite, sinus bradycardia, headache, decreased platelet count, mouth hemorrhage, and epistaxis. Related grade ≥3 AEs were reported in 35.7% ($n = 10$) of patients, and related grade ≥3 hypertension (25%, $n = 7$) was the only event ≥5%. Those grade ≥3

Correspondence: Jin Li, M.D., Ph.D., Department of Medical Oncology, Fudan University Shanghai Cancer Center, 270 Dong An Road, Shanghai, 200032 People's Republic of China. Telephone: 86-21-64433755; e-mail: fudanlijin@163.com Received December 22, 2016; accepted for publication February 17, 2017; published Online First on May 2, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0137

Adverse Events

Patients with AE *n* (%)	Cohort 1 (6 mg/kg/2w) *n* = 6	Cohort 2 (10 mg/kg/3w) *n* = 10	Cohort 3 (8 mg/kg/2w) *n* = 12	Total *n* = 28
Patients with DLT[a]	1 (16.7)	1 (10.0)	0 (0.0)	2 (7.1)
Ramucirumab-related	1 (16.7)	1 (10.0)	0 (0.0)	2 (7.1)
Patients with ≥1 TEAE	6 (100.0)	10 (100.0)	12 (100.0)	28 (100.0)
Ramucirumab-related	6 (100.0)	10 (100.0)	11 (91.7)	27 (96.4)
Patients with ≥1 CTCAE grade 3/4	3 (50.0)	8 (80.0)	4 (33.3)	15 (53.6)
Ramucirumab-related	2 (33.3)	6 (60.0)	2 (16.7)	10 (35.7)
Patients with ≥1 SAE[b]	1 (16.7)	2 (20.0)	1 (8.3)	4 (14.3)
Ramucirumab-related	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
AE leading to treatment delay or modification	0 (0.0)	2 (20.0)	1 (8.3)	3 (10.7)
Ramucirumab-related	0 (0.0)	2 (20.0)	1 (8.3)	3 (10.7)
AE leading to treatment discontinuation	1 (16.7)	1 (10.0)	1 (8.3)	3 (10.7)
Ramucirumab-related	1 (16.7)	1 (10.0)	0 (0.0)	2 (7.1)
AE leading to death[c]	0 (0.0)	0 (0.0)	1 (8.3)	1 (3.6)
Ramucirumab-related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]DLT: Grade 3 proteinuria (Cohort 1), grade 3 alanine aminotransferase increased (Cohort 2).
[b]SAE: Grade 3 fatigue (Cohort 1), grade 3 upper gastrointestinal hemorrhage (Cohort 2) and grade 4 blood bilirubin increased (Cohort 2), grade 4 impaired gastric emptying (Cohort 3). The only drug-related SAE was upper gastrointestinal hemorrhage in Cohort 2.
[c]Death: Impaired gastric emptying (Cohort 3), same patient as in SAE.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

hypertension events were all grade 3. No hypertension led to treatment discontinuation or study drug dose delay/modification. A total of four serious adverse events (SAEs) were reported, and one SAE (upper gastrointestinal hemorrhage) that occurred in a patient in Cohort 2 was considered to be related to study drug. Two patients died: one within 30 days of last dose due to study disease (fibrosarcoma) and one on treatment due to SAE (impaired gastric emptying) not related to ramucirumab.

The geometric mean values reported for single- and multiple-dose noncompartmental analysis (NCA)-derived PK parameters such as apparent terminal elimination half-life (6–10 days), total body clearance (13 to 19 mL/h), and volume of distribution at steady state (3–4 L) were consistent with those expected for an IgG-type monoclonal antibody and previously reported for ramucirumab [10–13]. Immunogenicity as anti-ramucirumab antibody was not detected in any of the patients.

Preliminary antitumor activity was demonstrated. No patient had complete/partial response; 64.3% ($n = 18$) had stable disease with a median duration of 5.55 months (95% confidence interval [CI]: 3.38–7.13 months). The median time to disease progression was 3.38 months (95% CI: 1.41–5.55 months). However, because of limited sample size and single-arm design, no efficacy conclusion can be drawn, and further randomized studies are warranted.

In conclusion, ramucirumab was well tolerated in Chinese patients. The safety profile, PK, and immunogenicity results observed are consistent with previous studies of ramucirumab. This supports further development of ramucirumab in Chinese cancer patients and could provide evidence to extrapolate global data to the Chinese population.

Trial Information	
Disease	Advanced cancer/solid tumor only
Stage of disease/treatment	Metastatic/advanced
Prior therapy	1 prior regimen
Type of study – 1	Phase I
Type of study – 2	Dose-escalation
Primary endpoint	Safety
Primary endpoint	Tolerability
Primary endpoint	Pharmacokinetics
Secondary endpoint	Efficacy
Secondary endpoint	Immunogenicity
Investigator's analysis	Drug Tolerable, Hints of Efficacy

Drug Information	
Drug 1	
Generic/working name	Ramucirumab
Trade name	Cyramza
Company name	Eli Lilly and Company
Drug type	Antibody
Drug class	VEGFR
Dose	Milligrams (mg) per kilogram (kg)
Route	IV
Schedule of administration	Cohort 1: 6 mg/kg/2w Cohort 2: 10 mg/kg/3w Cohort 3: 8 mg/kg/2w

Patient Characteristics	
Number of patients, male	14
Number of patients, female	14
Stage	Stage III: 6; Stage IV: 22
Age	Median (range): 57.0 (36.8–68.2)
Number of prior systemic therapies	Median (range): not collected
Performance Status: ECOG	0 — 3 1 — 25 2 — 3 — unknown —
Cancer types or histologic subtypes	Breast cancer: 6 Gastric cancer: 6 Colorectal cancer: 6 Head and neck cancer: 4 Other cancers: 6

Primary Assessment Method	
Control Arm: Total Patient Population	
Number of patients screened	40
Number of patients enrolled	28
Number of patients evaluable for toxicity	28
Number of patients evaluated for efficacy	28
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 0$ (0%)
Response assessment SD	$n = 18$ (64.3%)
Response assessment PD	$n = 9$ (32.1%)
Response assessment OTHER	$n = 1$ (3.6%)
(Median) duration assessments TTP	3.38 months, CI: 1.14–5.55

Adverse Events

All Dose Levels, All Cycles							
Name	NC/NA	1	2	3	4	5	All Grades
Aspartate aminotransferase increased	50%	43%	7%	0%	0%	0%	50%
Alanine aminotransferase increased	57%	25%	14%	4%	0%	0%	43%
Neutrophil count decreased	78%	7%	11%	0%	4%	0%	22%
Platelet count decreased	79%	14%	7%	0%	0%	0%	21%
Weight loss	79%	14%	7%	0%	0%	0%	21%
Vomiting	71%	14%	11%	4%	0%	0%	29%
Oral hemorrhage	79%	21%	0%	0%	0%	0%	21%
Epistaxis	75%	25%	0%	0%	0%	0%	25%
Back pain	79%	14%	7%	0%	0%	0%	21%
Hypertension	47%	7%	21%	25%	0%	0%	53%
Proteinuria	57%	32%	7%	4%	0%	0%	43%
Sinus bradycardia	75%	25%	0%	0%	0%	0%	25%
Dizziness	75%	25%	0%	0%	0%	0%	25%
Headache	75%	18%	7%	0%	0%	0%	25%
Anorexia	64%	25%	11%	0%	0%	0%	36%
Fatigue	31%	36%	29%	4%	0%	0%	69%
Non-cardiac chest pain	78%	18%	4%	0%	0%	0%	22%

Treatment-emergent adverse events reported in $\geq$20% patients.
Abbreviations: NA, no adverse event; NC, no change from baseline.

Serious Adverse Events

Name	Grade	Attribution
Fatigue	3	Unrelated
Upper gastrointestinal hemorrhage	3	Possible
Blood bilirubin increased	4	Unrelated
Impaired gastric emptying	4	Unrelated

Treatment-emergent adverse events reported in $\geq$ 20% patients.

Dose-Limiting Toxicities

Dose level	Dose of drug: ramucirumab	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting	Dose-limiting toxicity information
Cohort 1	6 mg/kg every 2 weeks	6	6	1	Grade 3 proteinuria
Cohort 2	10 mg/kg every 3 weeks	10	10	1	Grade 3 ALT increased
Cohort 3	8 mg/kg every 2 weeks	12	12	0	

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Drug Tolerable, Hints of Efficacy

Numerous evidence suggested that the interaction of vascular endothelial growth factor with vascular endothelial growth factor receptor-2 (VEGFR-2) plays an important role in tumor angiogenesis [1, 2]. Ramucirumab is a recombinant human IgG1 monoclonal antibody that specifically binds to the extracellular domain of VEGFR-2 with high affinity, inhibiting certain biological processes involved in tumor angiogenesis [3].

The safety and efficacy of ramucirumab have been demonstrated in four global, multicenter, double-blind, randomized phase III trials: REGARD, RAINBOW, REVEL, and RAISE [4–7]. Therefore, ramucirumab was approved by the U.S. Food and Drug Administration and in many other countries for the treatment of gastric or gastroesophageal junction adenocarcinoma, non-small cell lung cancer, and colorectal cancer.

We designed this single-arm, nonrandomized, open-label, dose-escalation, phase I study in Chinese patients with advanced solid tumors. Based on completed global phase I trial results [8, 9], ramucirumab was given intravenously at three dosage levels in three cohorts: 6 mg/kg every 2 weeks, 10 mg/kg every 3 weeks, and 8 mg/kg every 2 weeks. Dose escalation was based on a 3 + 3 design, with expansion in Cohort 2 and Cohort 3 for pharmacokinetics (PK) data if no maximum tolerated dose was determined after the first three to six patients. The primary objective of this study was to establish the safety profile and PK in Chinese patients. The secondary objectives included assessments of immunogenicity and antitumor activity.

A total of 28 patients were treated with ramucirumab in this study, and all patients completed at least one cycle of treatment. The median duration of treatment was 6.0 weeks (1 cycle) in Cohort 1, 12.0 weeks (2 cycles) in Cohort 2, and 15.5 weeks (2.5 cycles) in Cohort 3. The relative dose intensities were approximately 100% and similar across the three cohorts. Male and female each comprised 50% of the patients, with a median age of 57 years old (range 37–68).

One dose-limiting toxicity (DLT) happened in each of Cohort 1 (grade 3 proteinuria) and Cohort 2 (grade 3 ALT increased). No DLT was observed in Cohort 3 at the highest dose of this study. Therefore, no maximum tolerated dose was determined.

All 28 treated patients experienced at least 1 TEAE; 27 (96.4%) of them were considered to be study drug-related. The most frequent drug-related AEs reported were fatigue (64.3%; no grade $\geq$3 event), hypertension (53.6%; 25% grade 3, no grade 4), increased AST (42.9%; no grade $\geq$3), proteinuria (42.9%; 3.6% grade 3, no grade 4), increased ALT (39.3%; 3.6% grade 3, no grade 4), decreased appetite (28.6%; no grade $\geq$3), sinus bradycardia (25.0%; no grade $\geq$3), headache (25.0%; no grade $\geq$3), decreased platelet count (21.4%; no grade $\geq$3), mouth hemorrhage (21.4%; no grade $\geq$3), and epistaxis (21.4%; no grade $\geq$3). Hypertension is a common adverse event of special interest, potentially associated with antiangiogenic agents or therapeutic antibodies. Hypertension that occurred in this study can be controlled with antihypertensive therapy and did not lead to treatment discontinuation or to dose delay or modification. Grade 3 elevated ALT was resolved within 2 weeks, and the study treatment was resumed without dose reduction. Grade 3 proteinuria was resolved within 2 weeks, and the study treatment was discontinued. Three patients experienced AEs that lead to discontinuation of study drug: grade 1 proteinuria, grade 3 upper gastrointestinal hemorrhage, and grade 4 impaired gastric emptying.

A total of four SAEs were reported, and one SAE (upper gastrointestinal hemorrhage) was considered to be related to study drug. There were two deaths reported in this study: one within 30 days of last dose due to study disease (fibrosarcoma) and one on treatment due to SAE (impaired gastric emptying) not related to study drug.

Ramucirumab exposures were higher for the 8- and 10-mg/kg regimens as compared to the 6-mg/kg regimen. Greater accumulation was generally observed following the 2-week regimens as compared with the 3-week regimen. The geometric mean values reported for single- and multiple-dose NCA-derived PK parameters such as apparentterminal elimination half-life (6–10 days), total body clearance (13–19 mL/h), and volume of distribution at steady state (3–4 L) were consistent with those expected for an IgG-type monoclonal antibody and previously reported for ramucirumab in other ethnic populations [10–13]. Immunogenicity as anti-ramucirumab antibody was not detected in any of the patients treated with ramucirumab.

Ramucirumab was well tolerated in Chinese patients with advanced solid tumors in this study. The safety profile observed in this study is consistent with previous studies of ramucirumab. The safety profile, PK, and immunogenicity results observed are consistent with those from previous studies of ramucirumab. Results of this study support the further development of ramucirumab in Chinese cancer patients.

At the time of study completion, no patient showed complete/partial response. Eighteen patients had stable disease with a median duration of 5.55 months (95% CI: 3.38–7.13 months). The median time to disease progression was 3.38 months (95% CI: 1.41–5.55 months) in all 28 patients. RECIST were designed primarily for the evaluation of cytotoxic agents. Recent studies have shown a poor correlation between the objective response and survival benefit provided by antiangiogenic agents [14, 15]. As shown in REACH and REGARD studies, SD was often observed and resulted in the improvement of disease control rate (DCR) while ramucirumab was given as a single agent. In this study, preliminary antitumor activity was demonstrated. However, due to limited sample size and single-arm design, no efficacy conclusion can be drawn from this phase I study and further randomized studies are warranted.

Acknowledgments

The authors thank Sheng Yao (employee of Eli Lilly) for providing medical writing assistance.

Disclosures

Jin Wang: Eli Lilly (E, OI); **Baoyue Li:** Eli Lilly and Company (E); **Haidong Chi:** Eli Lilly (E, OI); **Ling Gao:** Eli Lilly (E, OI). The other author 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

References

1. Sullivan LA, Brekken RA. The VEGF family in cancer and antibody-based strategies for their inhibition. MAbs 2010;2:165–175.

2. Tugues S, Koch S, Gualandi L et al. Vascular endothelial growth factors and receptors: Anti-angiogenic therapy in the treatment of cancer. Mol Aspects Med 2011;32:88–111.

3. Lu D, Shen J, Vil MD et al. Tailoring in vitro selection for a picomolar affinity human antibody directed against vascular endothelial growth factor receptor 2 for enhanced neutralizing activity. J Biol Chem 2003;278:43496–43507.

4. Fuchs CS, Tomasek J, Yong CJ et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31–39.

5. Wilke H, Muro K, Van Cutsem E et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224–1235.

6. Garon EB, Ciuleanu TE, Arrieta O et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial. Lancet 2014;384:665–673.

7. Tabernero J, Yoshino T, Cohn AL et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): A randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 2015;16:499–508.

8. Spratlin JL, Cohen RB, Eadens M et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol 2010; 28:780–787.

9. Chiorean EG, Hurwitz HI, Cohen RB et al. Phase I study of every 2- or 3-week dosing of ramucirumab, a human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2 in patients with advanced solid tumors. Ann Oncol 2015;26:1230–1237.

10. Masuda N, Iwata H, Aogi K et al. Safety and pharmacokinetics of ramucirumab in combination with docetaxel in Japanese patients with locally advanced or metastatic breast cancer: A phase Ib study. Jpn J Clin Oncol 2016;46:1088–1094.

11. Ueda S, Satoh T, Gotoh M et al. A phase Ib study of safety and pharmacokinetics of ramucirumab in combination with paclitaxel in patients with advanced gastric adenocarcinomas. ***The Oncologist*** 2015;20:493–494.

12. Yoshino T, Yamazaki K, Gotoh M et al. Safety and pharmacokinetics of second-line ramucirumab plus FOLFIRI in Japanese patients with metastatic colorectal carcinoma. Anticancer Res 2015;35:4003–4007.

13. Chow LQ, Smith DC, Tan AR et al. Lack of pharmacokinetic drug-drug interaction between ramucirumab and paclitaxel in a phase II study of patients with advanced malignant solid tumors. Cancer Chemother Pharmacol 2016;78:433–441.

14. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.

15. Cheng AL, Kang YK, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.

Figures and Tables

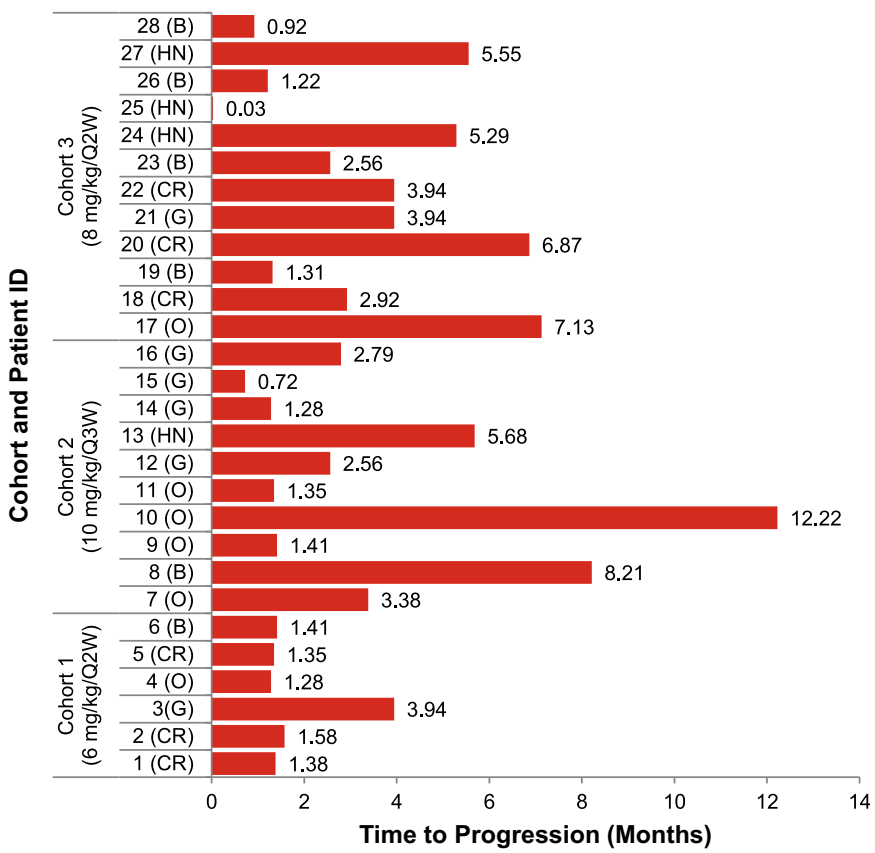

Figure 1. Time to progressive disease of individual patients.
Abbreviations: B, breast cancer; CR, colorectal cancer; G, gastric cancer; HN, head and neck cancer; ID, identification; O, other cancer.

Table 1. Patient demographics and baseline characteristics

Demographics and characteristics	Cohort 1 (6 mg/kg/Q2W) *n* = 6	Cohort 2 (10 mg/kg/Q3W) *n* = 10	Cohort 3 (8 mg/kg/Q2W) *n* = 12	Total *n* = 28
Age (years), mean (SD)	51.20 (9.06)	52.92 (9.51)	58.18 (9.44)	54.80 (9.54)
<65 years, *n* (%)	6 (100.0)	9 (90.0)	9 (75.0)	24 (85.7)
Gender, *n* (%)				
Female	4 (66.7)	3 (30.0)	7 (58.3)	14 (50.0)
BMI (kg/m^2), mean (SD)	24.74 (3.09)	22.17 (3.13)	22.86 (2.43)	23.02 (2.89)
Duration of disease (months)[a], mean (SD)	36.34 (27.95)	42.29 (30.95)	64.29 (52.12)	50.44 (41.53)
ECOG performance status score, *n* (%)				
0	2 (33.3)	1 (10.0)	0 (0.0)	3 (10.7)
1	4 (66.7)	9 (90.0)	12 (100.0)	25 (89.3)
Pathological diagnosis, *n* (%)				
Histopathological	6 (100.0)	10 (100.0)	12 (100.0)	28 (100.0)
Disease stage, *n* (%)				
Stage III	1 (16.7)	3 (30.0)	2 (16.7)	6 (21.4)
Stage IV	5 (83.3)	7 (70.0)	10 (83.3)	22 (78.6)

[a]Duration of disease is time from date of histology/cytologic confirmation of advanced solid tumor to date of first dose.
Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table 2. Ramucirumab-related treatment-emergent adverse events occurring in at least 20% patients in any cohort

	Number (%) of patients			
Preferred term[a]	Cohort 1 (6 mg/kg/2w) *n* = 6	Cohort 2 (10 mg/kg/3w) *n* = 10	Cohort 3 (8 mg/kg/2w) *n* = 12	Total *n* = 28
Patients with ≥1 TEAE	6 (100.0)	10 (100.0)	11 (91.7)	27 (96.4)
Fatigue	6 (100.0)	8 (80.0)	4 (33.3)	18 (64.3)
Hypertension	3 (50.0)	7 (70.0)	5 (41.7)	15 (53.6)
Aspartate aminotransferase increased	1 (16.7)	4 (40.0)	7 (58.3)	12 (42.9)
Proteinuria	3 (50.0)	3 (30.0)	6 (50.0)	12 (42.9)
Alanine aminotransferase increased	1 (16.7)	5 (50.0)	5 (41.7)	11 (39.3)
Decreased appetite	2 (33.3)	3 (30.0)	3 (25.0)	8 (28.6)
Sinus bradycardia	0 (0.0)	3 (30.0)	4 (33.3)	7 (25.0)
Headache	1 (16.7)	2 (20.0)	4 (33.3)	7 (25.0)
Platelet count decreased	1 (16.7)	4 (40.0)	1 (8.3)	6 (21.4)
Mouth hemorrhage	1 (16.7)	3 (30.0)	2 (16.7)	6 (21.4)
Epistaxis	2 (33.3)	3 (30.0)	1 (8.3)	6 (21.4)
Face edema	2 (33.3)	1 (10.0)	2 (16.7)	5 (17.9)
Dizziness	2 (33.3)	1 (10.0)	2 (16.7)	5 (17.9)
Neutrophil count decreased	0 (0.0)	3 (30.0)	1 (8.3)	4 (14.3)
Constipation	2 (33.3)	1 (10.0)	1 (8.3)	4 (14.3)
Diarrhea	1 (16.7)	0 (0.0)	3 (25.0)	4 (14.3)
Nausea	0 (0.0)	3 (30.0)	1 (8.3)	4 (14.3)
Stomatitis	2 (33.3)	2 (20.0)	0 (0.0)	4 (14.3)
Vomiting	1 (16.7)	2 (20.0)	1 (8.3)	4 (14.3)
Electrocardiogram T wave abnormal	0 (0.0)	3 (30.0)	0 (0.0)	3 (10.7)
White blood cell count decreased	1 (16.7)	2 (20.0)	0 (0.0)	3 (10.7)
Sinus tachycardia	0 (0.0)	3 (30.0)	0 (0.0)	3 (10.7)
Hemoptysis	0 (0.0)	2 (20.0)	1 (8.3)	3 (10.7)
Gingival pain	0 (0.0)	2 (20.0)	0 (0.0)	2 (7.1)
Arthralgia	2 (33.3)	0 (0.0)	0 (0.0)	2 (7.1)

[a]MedDRA Version 17.1.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Table 3. Ramucirumab-related grade ≥3 treatment-emergent adverse events

Preferred term[a]	Number (%) of patients			
	Cohort 1 (6 mg/kg/2w) *n* = 6	Cohort 2 (10 mg/kg/3w) *n* = 10	Cohort 3 (8 mg/kg/2w) *n* = 12	Total *n* = 28
Patients with grade ≥3 TEAE[b]	2 (33.3)	6 (60.0)	2 (16.7)	10 (35.7)
Hypertension	2 (33.3)	4 (40.0)	1 (8.3)	7 (25.0)
Alanine aminotransferase increased	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	1 (8.3)	1 (3.6)
Proteinuria	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.6)
Anemia	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Gastric hemorrhage	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Upper gastrointestinal hemorrhage	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)
Menstruation irregular	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.6)

[a]MedDRA Version 17.1.
[b]TEAEs were graded by CTCAE.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Table 4. Summary of single dose ramucirumab pharmacokinetic parameters for Chinese patients with solid tumors following administration ramucirumab as an IV infusion over approximately 1 hour

	Ramucirumab serum parameters (cycle 1) geometric mean (geometric CV%)		
	Cohort 1 6 mg/kg first dose (N_{PK} = 6[a])	Cohort 2 10 mg/kg first dose (N_{PK} = 9[b])	Cohort 3 8 mg/kg first dose (N_{PK} = 12[c])
C_{max} (μg/mL)	155 (13)	186 (22)	190 (39)
$t_{1/2}$ (day)	6.00 (31)	7.37 (44)	7.26 (25)
AUC (0-∞) (μg•day/mL)	870 (14)	1430 (31)	1350 (9)
CL (mL/hr)	18.5 (19)	18.5 (32)	14.7 (22)
V_{ss} (L)	3.42 (35)	4.27 (18)	3.15 (19)

[a]N_{PK} = 5 for AUC (0-∞), CL, and V_{ss}.
[b]N_{PK} = 7 for AUC (0-∞), CL, and V_{ss}.
[c]N_{PK} = 11 for $t_{1/2}$; N_{PK} = 7 for AUC (0-∞), CL, and V_{ss}.
Abbreviations: AUC, area under the concentration-time curve; $AUC_{(0-\infty)}$, AUC from time 0 extrapolated to infinity; CL, total body clearance of drug calculated after intravenous administration; C_{max}, maximum observed serum concentration; CV%, percent coefficient of variation; IV, intravenous; N_{PK}, number of subjects used in pharmacokinetic analysis; $t_{1/2}$, apparent terminal elimination half-life; t_{max}, time of C_{max}; V_{ss}, volume of distribution at steady state.

Table 5. Summary of multiple dose ramucirumab pharmacokinetic parameters for Chinese patients with solid tumors following administration of ramucirumab as an IV infusion over approximately 1 hour every 2 or 3 weeks

	Ramucirumab serum parameters (cycle 2) geometric mean (geometric CV%)		
	Cohort 1 6 mg/kg every 2 weeks fourth dose ($N_{PK} = 1$[b])	**Cohort 2[a] 10 mg/kg every 3 weeks third dose ($N_{PK} = 6$[c])**	**Cohort 3 8 mg/kg every 2 weeks fourth dose ($N_{PK} = 8$[d])**
$C_{max,ss}$ (μg/mL)	155	219 (22)	239 (19)
$t_{1/2}$ (day)	9.99	10.3 (52)	9.64 (28)
$AUC_{\tau,ss}$ (μg•day/mL)	892	1630 (32)	1540 (16)
CL_{ss} (mL/hr)	18.7	15.0 (32)	13.3 (22)
V_{ss} (L)	NC	4.46 (16)	3.62, 4.25
$R_{A,AUC}$	1.64	1.33 (21)	1.52 (24)

[a]The dosing interval from Dose 2 to Dose 3 was approximately 5 weeks for 1 patient in Cohort 2. Summary data excluding this patient are as follows: $C_{max,ss}$ 224 (23); $t_{max,ss}$ 2.00 (1.02–2.00); $t_{1/2}$ 12.4 (19); $AUC_{\tau,ss}$ 1830 (14); CL_{ss} 13.3 (10); V_{ss} 4.78 (10); $R_{A,Cmax}$ 1.27 (4); $R_{A,AUC}$ 1.42 (17).
[b]Individual data are presented.
[c]$N_{PK} = 4$ for V_{ss}; $N_{PK} = 5$ for $R_{A,Cmax}$ and $R_{A,AUC}$.
[d]$N_{PK} = 2$ for V_{ss}; individual values are presented.
Abbreviations: AUC, area under the concentration-time curve; $AUC_{\tau,ss}$, AUC over the dosing interval at steady state; CL, total body clearance of drug calculated after intravenous administration; CL_{ss}, clearance at steady state; C_{max}, maximum observed serum concentration; $C_{max,ss}$, maximum observed serum concentration at steady state; CV%, percent coefficient of variation; IV, intravenous; NC, not calculated; N_{PK}, number of subjects used in pharmacokinetic analysis; $R_{A,AUC}$, accumulation ratio based on AUC; $R_{A,Cmax}$, accumulation ratio based on C_{max}; $t_{1/2}$, apparent terminal elimination half-life; $t_{max,ss}$, time of $C_{max,ss}$; V_{ss}, volume of distribution at steady state.