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

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TRIAL INFORMATION

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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 (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

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

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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 |

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| 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<sup>a</sup> Ramucirumab-related | 1 (16.7) | 1 (10.0) | 0 (0.0) | 2 (7.1) |
| Patients with ≥1 TEAE Ramucirumab-related | 6 (100.0) | 10 (100.0) | 12 (100.0) | 28 (100.0) |
| Patients with ≥1 CTCAE grade 3/4 Ramucirumab-related | 3 (50.0) | 8 (80.0) | 4 (33.3) | 15 (53.6) |
| Patients with ≥1 SAE<sup>b</sup> Ramucirumab-related | 1 (16.7) | 2 (20.0) | 1 (8.3) | 4 (14.3) |
| AE leading to treatment delay or modification Ramucirumab-related | 0 (0.0) | 2 (20.0) | 1 (8.3) | 3 (10.7) |
| AE leading to treatment discontinuation Ramucirumab-related | 1 (16.7) | 1 (10.0) | 1 (8.3) | 3 (10.7) |
| AE leading to death<sup>c</sup> Ramucirumab-related | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

<sup>a</sup>DLT: Grade 3 proteinuria (Cohort 1), grade 3 alanine aminotransferase increased (Cohort 2).

<sup>b</sup>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.

<sup>c</sup>Death: Impaired gastric emptying (Cohort 3), same patient as in SAE.
### Drug Information

| Drug 1 | Ramucirumab |
|--------|-------------|
| 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<br>Cohort 2: 10 mg/kg/3w<br>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<br>1 — 25<br>2 — 3<br>unknown — |

| Cancer types or histologic subtypes | Breast cancer: 6<br>Gastric cancer: 6<br>Colorectal cancer: 6<br>Head and neck cancer: 4<br>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 |
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].

| 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 ≥20% patients.

| SERIOUS ADVERSE EVENTS |
|------------------------|
| Name                   |
| Fatigue                |
| Grade                  |
| Attribution            |
| 3                      |
| Unrelated              |
| Upper gastrointestinal hemorrhage |
| 3                      |
| Possible               |
| Blood bilirubin increased |
| 4                      |
| Unrelated              |
| Impaired gastric emptying |
| 4                      |
| Unrelated              |

Treatment-emergent adverse events reported in ≥20% patients.

| DOSE-LIMITING TOXICITIES |
|--------------------------|
| Dose level               |
| Number enrolled          |
| Number evaluable for toxicity |
| Number with a dose-limiting toxicity |
| 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   |
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 ≥3 event), hypertension (53.6%; 25% grade 3, no grade 4), increased AST (42.9%; no grade ≥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 ≥3), sinus bradycardia (25.0%; no grade ≥3), headache (25.0%; no grade ≥3), decreased platelet count (21.4%; no grade ≥3), mouth hemorrhage (21.4%; no grade ≥3), and epistaxis (21.4%; no grade ≥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 apparent terminal 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.

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[CA] Consulting/advisory relationship; [RF] Research funding; [E] Employment; [ET] Expert testimony; [H] Honoraria received; [OI] Ownership interests; [IP] Intellectual property rights/inventor/patient holder; [SAB] Scientific advisory board

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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/m²), 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)    |

*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

| Preferred term a | 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 |
|------------------|-------------------------------|---------------------------------|--------------------------------|--------------|
| 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)     |
| Hemoptyaxis      | 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)      |

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Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
Table 3. Ramucirumab-related grade ≥3 treatment-emergent adverse events

| Preferred term | Number (%) of patients | Number (%) of patients | Number (%) of patients | Total |
|----------------|------------------------|------------------------|------------------------|-------|
|                | Cohort 1 (6 mg/kg/2w)  | Cohort 2 (10 mg/kg/3w) | Cohort 3 (8 mg/kg/2w)  |       |
|                | n = 6                  | n = 10                 | n = 12                 | n = 28 |
| Patients with grade ≥3 TEAEs | 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) |

aMedDRA Version 17.1.  
bTEAEs 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) | Cohort 1 6 mg/kg first dose (Npk = 6a) | Cohort 2 10 mg/kg first dose (Npk = 9b) | Cohort 3 8 mg/kg first dose (Npk = 12c) |
|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| Cmax (µg/mL)                           | 155 (13)                               | 186 (22)                               | 190 (39)                               |
| t1/2 (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)                               |
| Vss (L)                                | 3.42 (35)                               | 4.27 (18)                               | 3.15 (19)                               |

aNpk = 5 for AUC (0-∞), CL, and Vss.  
bNpk = 7 for AUC (0-∞), CL, and Vss.  
cNpk = 11 for t1/2; Npk = 7 for AUC (0-∞), CL, and Vss.  
Abbreviations: AUC, area under the concentration-time curve; AUC(0,∞), AUC from time 0 extrapolated to infinity; CL, total body clearance of drug calculated after intravenous administration; Cmax, maximum observed serum concentration; CV%, percent coefficient of variation; IV, intravenous; Npk, number of subjects used in pharmacokinetic analysis; t1/2, apparent terminal elimination half-life; tmax, time of Cmax; Vss, 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) | Cohort 1 | Cohort 2 | Cohort 3 |
|---------------------------------------|----------|----------|----------|
|                                        | 6 mg/kg every 2 weeks | 10 mg/kg every 3 weeks | 8 mg/kg every 2 weeks |
|                                        | fourth dose | third dose | fourth dose |
|                                        | (NPK = 1\(^b\)) | (NPK = 6\(^c\)) | (NPK = 8\(^d\)) |
| \(C_{\text{max,ss}}\) (\(\mu\)g/mL) | 155 | 219 (22) | 239 (19) |
| \(t_{1/2}\) (day) | 9.99 | 10.3 (52) | 9.64 (28) |
| \(AUC_{\text{ss,ss}}\) (\(\mu\)g•day/mL) | 892 | 1630 (32) | 1540 (16) |
| \(\text{CL}_{\text{ss}}\) (mL/hr) | 18.7 | 15.0 (32) | 13.3 (22) |
| \(V_{\text{ss}}\) (L) | NC | 4.46 (16) | 3.62, 4.25 |
| \(R_{A,AUC}\) | 1.64 | 1.33 (21) | 1.52 (24) |

*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: \(C_{\text{max,ss}}\) 224 (23); \(C_{\text{max},\text{ss}}\) 2.00 (1.02–2.00); \(t_{1/2}\) 12.4 (19); \(AUC_{\text{ss,ss}}\) 1830 (14); \(\text{CL}_{\text{ss}}\) 13.3 (10); \(V_{\text{ss}}\) 4.78 (10); \(R_{A,C_{\text{max}}}\) 1.27 (4); \(R_{A,AUC}\) 1.42 (17).

*Individual data are presented.

\(^a\)NPK = 4 for \(V_{\text{ss}}\); NPK = 5 for \(R_{A,C_{\text{max}}}\) and \(R_{A,AUC}\).

\(^b\)NPK = 2 for \(V_{\text{ss}}\); individual values are presented.

Abbreviations: AUC, area under the concentration-time curve; \(AUC_{\text{ss,ss}}\), AUC over the dosing interval at steady state; \(\text{CL}_{\text{ss}}\), total body clearance of drug calculated after intravenous administration; \(\text{CL}_{\text{ss}}\), clearance at steady state; \(C_{\text{max}}\), maximum observed serum concentration; \(C_{\text{max},\text{ss}}\), maximum observed serum concentration at steady state; CV\%, percent coefficient of variation; IV, intravenous; NC, not calculated; NPK, number of subjects used in pharmacokinetic analysis; \(R_{A,AUC}\), accumulation ratio based on AUC; \(R_{A,C_{\text{max}}}\), accumulation ratio based on \(C_{\text{max}}\); \(t_{1/2}\), apparent terminal elimination half-life; \(t_{\text{max,ss}}\), time of \(C_{\text{max,ss}}\); \(V_{\text{ss}}\), volume of distribution at steady state.

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