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Clinical Trial Results

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

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Author Summary

Lessons Learned

- The pharmacokinetic results of this phase Ib study of ramucirumab combined with paclitaxel as second-line therapy in Japanese patients with metastatic gastric or gastro-esophageal junction adenocarcinoma are in line with previous ramucirumab studies.
- This combination at the doses and schedule given did not result in any dose-limiting toxicities and appeared to be safe and well tolerated.

Abstract

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. ***The Oncologist*** 2015;20:493–494

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

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Table 1. 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 ≥ 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.

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 ≥1 treatment-emergent adverse event (TEAE) of any grade (grade ≥3 in 5 patients), ramucirumab-related TEAEs, and paclitaxel-related TEAEs. There were no ramucirumab- or paclitaxel-related grade ≥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.

Author disclosures and references available online.