

Safety and Pharmacokinetics of Second-line Ramucirumab plus FOLFIRI in Japanese Patients with Metastatic Colorectal Carcinoma

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Abstract. *Background:* This phase Ib study evaluated the pharmacokinetic profile and safety of ramucirumab, a recombinant human IgG1 neutralizing monoclonal antibody specific for vascular endothelial growth factor receptor 2, in combination with irinotecan, leovorinate and 5-fluorouracil (FOLFIRI) in Japanese patients with metastatic colorectal carcinoma (mCRC). *Patients and Methods:* Eligible patients had Eastern Cooperative Oncology Group performance status 0-1, and disease progression during or within 6 months following first-line therapy with bevacizumab, oxaliplatin and a fluoropyrimidine. Six enrolled patients received 8 mg/kg ramucirumab plus FOLFIRI every 2 weeks. *Results:* One out of six patients experienced a dose-limiting toxicity (grade 2 proteinuria and grade 4 neutropenia, resulting in a dose delay >2 weeks). All patients experienced at least one grade 3 or higher adverse event: neutropenia (five patients, 83%), proteinuria (two patients; 33%) and anemia, thrombocytopenia and hypertension (one patient each, 17%). There were no serious adverse events or deaths. *Conclusion:* Ramucirumab plus FOLFIRI was well-tolerated in Japanese patients with mCRC, warranting further investigation of this combination therapy.

Irinotecan plus 5-fluorouracil and leovorinate (FOLFIRI) is a standard regimen for metastatic colorectal carcinoma (mCRC) (1-3).

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Vascular endothelial growth factor (VEGF) is up-regulated in mCRC and VEGF receptor 2 (VEGFR2)-mediated signaling and angiogenesis are involved in mCRC pathogenesis (4). Anti-angiogenic agents have been successfully tested in various lines of mCRC treatment (5, 6). Ramucirumab, a recombinant human IgG1 neutralizing monoclonal antibody specific for VEGFR2, prevents ligand binding and receptor-mediated pathway activation in endothelial cells (7), and was recently shown to be efficacious in four phase III trials (in gastric, lung and colorectal cancer) (8-11). The phase III trial in mCRC (RAISE) evaluated ramucirumab in combination with FOLFIRI in patients with progression during or following first-line combination therapy with bevacizumab, oxaliplatin and a fluoropyrimidine (11).

Prior to participation in the RAISE trial, Japanese patients were enrolled in the present phase Ib study to evaluate safety and tolerability, and to confirm the recommended dose of ramucirumab in combination with FOLFIRI. In Japan, the most frequently used dose of irinotecan in the FOLFIRI regimen is 150 mg/m²; however, we used the global standard irinotecan dose of 180 mg/m² every 2 weeks (1, 3), which is in accordance with the RAISE trial.

Patients and Methods

Patient eligibility. Patients were required to be Japanese and aged 20 years or older, with histologically- or cytologically-confirmed mCRC (irrespective of Kirsten rat sarcoma viral oncogene homolog [KRAS] mutation status), Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and no more than two prior systemic chemotherapy regimens (one prior regimen for metastatic disease). Patients had to have a prior history of first-line combination therapy of bevacizumab, oxaliplatin and a fluoropyrimidine for metastatic disease, and had to have experienced disease progression during or within 6 months of the last dose of first-line therapy. This study was conducted in

Table I. TEAEs occurring in $\geq 30\%$ (≥ 2 patients) of patients in all grades regardless of causality. TEAEs were assessed using NCI-CTCAE v 4.03 on days 1 and 8 of cycles 1 and 2, and then on day 1 of each cycle thereafter.

TEAE	Patients with TEAE [†] , n (%)					
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Patients with any TEAE	6 (100.0)	0	0	3 (50.0)	3 (50.0)	0
Neutropenia	5 (83.3)	0	0	2 (33.3)	3 (50.0)	0
Diarrhea	5 (83.3)	3 (50.0)	2 (33.3)	0	0	0
Stomatitis	5 (83.3)	4 (66.7)	1 (16.7)	0	0	0
Thrombocytopenia	4 (66.7)	1 (16.7)	2 (33.3)	1 (16.7)	0	0
Vomiting	4 (66.7)	3 (50.0)	1 (16.7)	0	0	0
Decreased appetite	4 (66.7)	3 (50.0)	1 (16.7)	0	0	0
Epistaxis	3 (50.0)	2 (33.3)	1 (16.7)	0	0	0
Fatigue	3 (50.0)	3 (50.0)	0	0	0	0
Abdominal pain	2 (33.3)	2 (33.3)	0	0	0	0
Malaise	2 (33.3)	1 (16.7)	1 (16.7)	0	0	0
Peripheral edema	2 (33.3)	1 (16.7)	1 (16.7)	0	0	0
Nausea	3 (50.0)	2 (33.3)	1 (16.7)	0	0	0
Periodontal disease	2 (33.3)	2 (33.3)	0	0	0	0
Proteinuria	2 (33.3)	0	0	2 (33.3)	0	0

[†]Patients experiencing >1 TEAE within a prothrombin time or system organ class were only counted once for that prothrombin time or system organ class for the worst grade experienced by the patient.

accordance with Good Clinical Practices, the Declaration of Helsinki and approval by the medical institutions' Ethical Review Board (approval numbers K140, P22-26-22-1-2 and 10-1-45-0274). Patients provided written informed consent prior to inclusion. This trial was registered as ClinicalTrials.gov identifier: NCT01286818.

Treatment plan. This was a multi-center, open-label phase Ib study. Six patients were considered adequate to evaluate the safety of ramucirumab in combination with FOLFIRI among Japanese patients with mCRC. The actual sample size of the study was dependent on the number of dose-limiting toxicities (DLTs) observed during the DLT assessment period. Patients received ramucirumab (8 mg/kg) intravenously (*i.v.*) every 2 weeks plus FOLFIRI (*i.v.* infusion of 180 mg/m² irinotecan, *i.v.* infusion of 200 mg/m² leovorinate and 5-fluorouracil as a bolus of 400 mg/m², followed by a continuous infusion of 2400 mg/m²). DLTs were assessed from day 1 of cycle 1 to day 1 of cycle 3. If one patient or fewer out of six experienced DLT, the regimen was considered tolerable for Japanese patients.

Pharmacokinetics. On day 1 of cycles 1 and 5, blood samples were collected prior to the first ramucirumab infusion, immediately following the infusion, and after the infusion at 0.5, 1, 2 and 4 h. After day 1, during cycles 1 and 5, blood was sampled at 24, 48, 168 and 336 h after the infusion. Serum samples were analyzed for ramucirumab at Intertek Pharmaceutical Services (San Diego, CA, USA). The samples were analyzed using a modified validated enzyme-linked immunosorbent assay (ELISA) method. The serum ramucirumab concentration-time profiles were analyzed by standard non-compartmental methods of analysis using Phoenix[®] WinNonlin[®]

6.3 (Pharsight Corporation, Cary, NC, USA). Pharmacokinetic parameters of ramucirumab were determined following patients' first and fifth doses; however, only two patients had evaluable pharmacokinetic data in cycle 5.

Results

Baseline patient and disease characteristics. Six patients (two females and four males) with stage IV disease were included in the analyses. The median age was 62 years (range=48-71 years), with two patients aged 65 years or older. Patients had an ECOG performance status of 0 (n=3) or 1 (n=3). Patients were diagnosed with colon cancer (n=4) or rectal cancer (n=2). The median duration of disease at enrollment was 16.6 months (range=7.8-38.8 months). The most common sites of metastatic disease were the liver (4 patients, 66.7%), lung (3 patients, 50%) and lymph nodes (3 patients, 50%).

Safety. Out of the six patients who were evaluable for DLTs, one patient met the DLT criteria due to grade 2 proteinuria and grade 4 neutropenia that resulted in a delay of cycle 3, day 1 study medication beyond day 44. This patient received treatment on day 50 and was able to continue receiving treatment at a reduced dose of ramucirumab and FOLFIRI after completing the DLT assessment period.

All patients experienced at least one grade ≥ 3 treatment-emergent adverse event (TEAE), regardless of causality (Table I): neutropenia (five patients, 83%), proteinuria

Table II. Summary of ramucirumab pharmacokinetic parameters following administration of 8 mg/kg ramucirumab every 2 weeks in combination with FOLFIRI.

Parameter	Geometric mean [†] (geometric CV%)	
	Cycle 1 first dose (N _{PK} =6) [‡]	Cycle 5 fifth dose (N _{PK} =2) [§]
C _{max} or C _{max,ss} (µg/ml)	245 (6)	(247.00-288.50)
t _{max} or t _{max,ss} [†] (h)	1.15 (1.02-1.63)	(1.00-1.03)
t _{1/2} (day)	7.38 (19)	(8.41-8.70)
AUC _(0-∞) or AUC _{τ,ss} (µg* day/ml)	1600 [‡] (15)	(1300-2190)
CL or CL _{ss} (ml/h)	11.4 [‡] (26)	(6.96-15.4)
V _{ss} (l)	2.51 [‡] (25)	(2.12-4.43)
R _{A,Cmax}	--	(0.927-1.20)
R _{A,AUC}	--	1.25 [§]

AUC: Area under the concentration-time curve; AUC_(0-∞): AUC from time 0 extrapolated to infinity; AUC_{τ,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 serum concentration at steady-state; CV%: percent coefficient of variation; FOLFIRI: irinotecan, levofolinate and 5-fluorouracil; 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}: time of C_{max}; t_{max,ss}: time of C_{max} at steady-state; V_{ss}: volume of distribution at steady-state. [†]Median (minimum-maximum) shown for t_{max} and t_{max,ss}. [‡]N_{PK}=4 for cycle 1 AUC_(0-∞), CL and V_{ss}; [§](minimum-maximum) shown for cycle 5 as N_{PK}=2; value shown for R_{A,AUC} as N_{PK}=1.

(two patients; 33%) and anemia, thrombocytopenia and hypertension (one patient each, 17%).

Ramucirumab-related TEAEs of any grade reported in more than one patient were thrombocytopenia (n=3), epistaxis (n=3), proteinuria (n=2) and fatigue (n=2). The only grade 3 or 4 ramucirumab-related TEAE that occurred in more than one patient was proteinuria (n=2). The most common TEAE leading to study treatment dose modification was neutropenia (n=5). No serious AEs or deaths were reported during the study period.

Tumor response. Best overall response was evaluated as an exploratory analysis using RECIST version 1.1 (12); one patient had a partial response, four had stable disease and one had progressive disease. The median progression-free survival was 7.3 months (range=1.25-10.91 months; 95% confidence interval=1.2-10.9 months).

Pharmacokinetics. Figure 1 depicts the mean ramucirumab concentration-time profiles following patients' first and

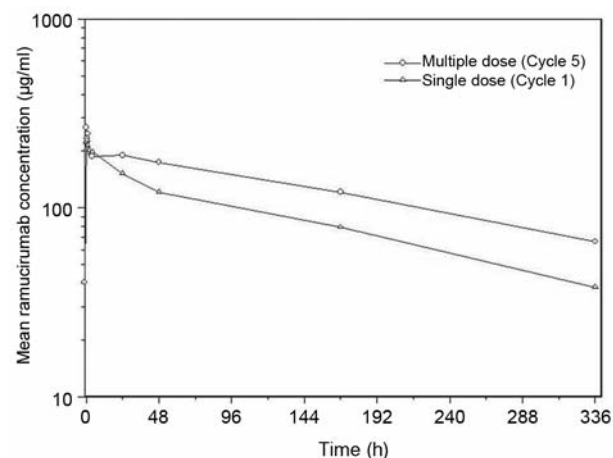


Figure 1. Mean ramucirumab concentration-time profiles following the first (Cycle 1) or fifth (Cycle 5) dose of ramucirumab in combination with FOLFIRI. n=2 for multiple dose profile.

fifth ramucirumab *i.v.* infusions in combination with FOLFIRI. Following a single dose of ramucirumab 8 mg/kg *i.v.* infusion, half-life (t_{1/2}), geometric mean clearance (CL) and volume of distribution at steady-state (V_{ss}) of ramucirumab were 7.38 days, 11.4 ml/h and 2.51 l, respectively (Table II), which is similar to those for other monoclonal IgG1 antibodies. Although pharmacokinetic parameters were only available from two patients following multiple doses, they appeared to be similar to those obtained from the single dose. Accumulation was observed after five doses of 8 mg/kg ramucirumab every 2 weeks. The accumulation ratio based on the area under the concentration-time curve was 1.25.

Discussion

This was the first study specifically evaluating the safety and tolerability of ramucirumab in Japanese patients with mCRC. The primary end-point was met, with one or fewer patients having a DLT. Findings in a subsequent phase II study demonstrated that ramucirumab may be given in combination with FOLFIRI without altering the pharmacokinetics of irinotecan or its metabolite, SN-38 (13). In the current study, the recommended dose of ramucirumab (8 mg/kg every 2 weeks) in combination with FOLFIRI with 180 mg/m² irinotecan was found to be safe and tolerable in Japanese patients, supporting their enrollment in the subsequent global phase III RAISE study (11). Ramucirumab exhibited low CL, small V_{ss} and long t_{1/2}, consistent with pharmacokinetic properties of other IgG1 monoclonal antibodies (14).

The types of TEAEs observed were largely consistent with the known or expected toxicity profiles of each of the study agents (1, 2, 7, 8, 15). No serious AEs or deaths were reported during the study.

With one or fewer DLTs and manageable grade 3 toxicities, this phase Ib study demonstrated that ramucirumab plus FOLFIRI used at the global standard irinotecan dose of 180 mg/m² is well-tolerated in Japanese patients with mCRC who were previously treated with bevacizumab, oxaliplatin and a fluoropyrimidine.

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Conflicts of Interest

TY received research funding from Eli Lilly and Company. KY received paid consulting fees from Yakult. MG and AO declare no conflict of interest. FN, LG and NY are employed by Eli Lilly and Company. The study was designed under the responsibility of Eli Lilly and Company, Bridgewater, NJ, U.S.A, in conjunction with the steering committee. Eli Lilly and Company collected and analyzed the data and contributed to the interpretation of the study. All Authors had full access to all of the data in the study and had final responsibility for the decision to submit this article for publication.

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