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A Phase II and Biomarker Study of Ramucirumab, a Human Monoclonal Antibody Targeting the VEGF Receptor-2, as First-Line Monotherapy in Patients with Advanced Hepatocellular Cancer

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Disclosure of Potential Conflicts of Interest

J.D. Schwartz is employed as a study sponsor (other than primary affiliation; e.g., consulting) and is vice president in Eli Lilly and Company. (ImClone). A. Joshi is employed as a research scientist, Statistics (other than primary affiliation; e.g., consulting) in Eli Lilly and Company. R.R. Hozak is employed as a senior research scientist (other than primary affiliation; e.g., consulting) and Eli Lilly has ownership interest (including patents) in Eli Lilly stock. R.K. Jain has a commercial research grant from Dyax, MedImmune, and Roche, has ownership interest (including patents) in Enlight, SynDevRx, and XTuit, is a consultant/advisory board member of Enlight, Noxxon, Zyngenia, and is on the Board of Directors of XTuit and Board of Trustees of H&Q Healthcare Investors Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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Abstract

Purpose—To assess the efficacy and safety of the anti-VEGF receptor-2 (VEGFR-2) antibody ramucirumab as first-line therapy in patients with advanced hepatocellular carcinoma and explore potential circulating biomarkers.

Experimental Design—Adults with advanced hepatocellular carcinoma and no prior systemic treatment received ramucirumab 8 mg/kg every two weeks until disease progression or limiting toxicity. The primary endpoint was progression-free survival (PFS); secondary endpoints included objective response rate (ORR) and overall survival (OS). Circulating biomarkers were evaluated before and after ramucirumab treatment in a subset of patients.

Results—Forty-two patients received ramucirumab. Median PFS was 4.0 months [95% confidence interval (CI), 2.6–5.7], ORR was 9.5% (95% CI, 2.7–22.6; 4/42 patients had apartial response), and median OS was 12.0 months (95% CI, 6.1–19.7). For patients with Barcelona Clinic Liver Cancer (BCLC) stage C disease, median OS was 4.4 months (95% CI, 0.5–9.0) for patients with Child-Pugh B cirrhosis versus 18.0 months (95% CI, 6.1–23.5) for patients with Child-Pugh A cirrhosis. Treatment-related grade 3 toxicities included hypertension (14%), gastrointestinal hemorrhage and infusion-related reactions (7% each), and fatigue (5%). There was one treatment-related death (gastrointestinal hemorrhage). After treatment with ramucirumab, there was an increase in serum VEGF and placental growth factor (PlGF) and a transient decrease in soluble VEGFR-2.

Conclusion—Ramucirumab monotherapy may confer anticancer activity in advanced hepatocellular carcinoma with an acceptable safety profile. Exploratory biomarker studies showed changes in circulating VEGF, PlGF, and sVEGFR-2 that are consistent with those seen with other anti-VEGF agents.

Introduction

Treatment options for advanced hepatocellular carcinoma remain limited. Sorafenib, a multi-targeted tyrosine kinase inhibitor whose targets include VEGF receptor-2 (VEGFR-2), was the first systemic therapy that prolonged overall survival (OS) in advanced hepatocellular carcinoma (1, 2). However, sorafenib-induced disease control is generally modest and transient, with median survival less than one year.

Angiogenesis contributes to cancer growth and metastasis (3) and is regulated by interactions between multiple VEGF ligands and receptors (VEGFR; ref. 4). VEGF-A (hereafter referred to as VEGF) is a central regulator of endothelial cell proliferation and survival, tumor angiogenesis, and vascular permeability, which is thought to be primarily due to VEGFR-2 activation (4). Overexpression of VEGFR-2 in hepatocellular carcinoma has been correlated with rapid disease progression (5). Antibody-mediated inhibition of VEGFR-2 also reduces hepatocellular carcinoma growth in animal models (6).

Ramucirumab [IMC-1121B (LY3009806)] is a human IgG1 monoclonal antibody that specifically binds with high affinity to the extracellular domain of the human VEGFR-2. Ramucirumab blocks the interaction of VEGFR-2 and its ligands and inhibits endothelial proliferation and migration (7). Inhibition of VEGFR-2 by DC101, a murine analogue to ramucirumab, confers antitumor activity in multiple murine models involving human cancer xenografts (7, 8).

In two phase I studies, ramucirumab was evaluated at doses ranging from 2 mg/kg/week to 20 mg/kg/3 weeks (9). Disease control more than 5 months was observed in 40% of patients with diverse and largely treatment-resistant malignancies (including two patients with advanced hepatocellular carcinoma who had disease control approaching and exceeding 1 year, respectively). Dose-limiting toxicities were observed infrequently and consisted of hypertension and deep vein thrombosis. A phase II dose of 8 mg/kg every 2 weeks was selected because it was associated with minimum drug concentrations that exceeded levels associated with tumor growth inhibition in preclinical models and with pharmacokinetic profiles suggesting receptor saturation, and because preliminary efficacy was observed across a range of phase I doses and schedules. The selected dose was substantially lower than the maximum tolerated dose (13 mg/kg/wk) identified in phase I evaluation. We conducted a phase II and biomarker study of ramucirumab in patients with advanced hepatocellular carcinoma who had not received prior systemic anticancer therapy.

Materials and Methods

Eligibility criteria

Eligibility criteria included histologically confirmed, advanced hepatocellular carcinoma; measurable target lesion(s) as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.0); age ≥ 18 years; life expectancy ≥ 12 weeks; Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1; Cancer of the Liver Italian Programme (CLIP) score 0–3 (10) and Child-Pugh Cirrhosis A or B (11, 12). Adequate organ function was required, including hepatic [bilirubin ≤ 3.0 mg/dL, aspartate transaminase and alanine transaminase ≤ 5 times upper limit of normal (ULN)], renal (serum creatinine ≤ 2.0 mg/dL, protein 1+ on urinalysis or urinary protein <1,000 mg/24 hours if 2+ on urinalysis), hematologic [absolute neutrophil count ≥ 1.0×10^9 /L, hemoglobin ≥ 10 g/dL (to minimize potential accrual of patients with subacute hemorrhagic sequelae of their hepatocellular carcinoma/cirrhosis), platelets ≥ 75×10^9 /L], and coagulation (International Normalized Ratio ≤ 1.5 and partial thromboplastin time ≤ 5 seconds above ULN) function. Patients with prior liver transplantation were allowed to participate.

Exclusion criteria included prior systemic anticancer therapy, locoregional therapy, or surgery within 28 days before study entry; gastric varices not amenable to ablative therapy; ascites or encephalopathy refractory to medical management; bleeding from esophageal or gastric varices during 3 months before study participation; acute hepatitis; fibrolamellar hepatocellular carcinoma; central nervous system metastases; poorly controlled hypertension or other poorly controlled medical conditions. Endoscopic evaluation was required for patients with a history of varices, or with evidence of esophageal varices on CT/MRI evaluation before study entry.

This study was approved by the institutional review board (IRB) at each study site and conducted in accordance with ethical principles in the Declaration of Helsinki and Good Clinical Practice guidelines. Patients provided informed consent via IRB-approved consent documents before enrollment.

Treatment plan

Patients received ramucirumab 8 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. Dose modifications were permitted for non-life-threatening, reversible grade 3/4 adverse events (AE; e.g., fever) that resolved to grade 1 within 2 weeks and in the setting of resolved, non-life-threatening hypertension and proteinuria. Ramucirumab was discontinued for grade 3/4 infusion reactions, arterial or venous thromboembolic or bleeding events; grade 4 or poorly controlled hypertension; or proteinuria exceeding 3 g/24 hours or recurrent proteinuria >2 g/24 hours.

Efficacy and safety assessments

Evaluations done at baseline and each cycle included physical examination, vital signs, ECOG PS, and hematology and chemistry profiles. AEs were categorized and graded at each cycle according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3 (NCI-CTCAE v 3.0). Chest CT and contrast-enhanced, triple-phase abdominal CT (or MRI) were performed every 6 weeks. Serum alpha-fetoprotein (AFP) was assessed at baseline, every 6 weeks, and at end of therapy.

Circulating biomarker evaluations

Peripheral blood was obtained from 9 patients for pharmacodynamic and correlative studies before and after therapy in cycle 1 (immediately, and 1 hour following the end of infusion, and on day 8), and in cycles 2, 3, 4, and 7 (before infusion and 1 hour following the end of infusion). Serum samples were analyzed at Massachusetts General Hospital (MGH; Steele Laboratory) using Meso-Scale Discovery Multiplex assays for circulating VEGF, soluble (s) VEGFR-1, placental growth factor (PIGF), basic fibroblast growth factor (bFGF), interleukin (IL)-1 β , IL-6, IL-8, and TNF- α ; and using ELISA kits for sVEGFR-2 and stromal-derived factor (SDF)-1 α (R&D Systems) and for collagen IV (Exocell), as described (13). For VEGF, sVEGFR-1, and sVEGFR-2, independent measurements were obtained at the ImClone clinical pharmacology laboratory using ELISA kits from R&D Systems. All samples for each biomarker were run simultaneously.

Immunogenicity evaluations

Immunogenicity data were assessed from serum samples from 20 patients. Samples for analysis of anti-drug antibody (ADA) for ramucirumab were collected pretreatment, before cycles 4 and 7 (approximately 6 and 12 weeks after first dose), and at a 30-day follow-up visit. Analytic methods, results, and potential significance are described in the Supplementary Note.

Statistical analyses

The primary endpoint was progression-free survival (PFS). Secondary endpoints included time to progression (TTP), OS, overall response rate (ORR), duration of response, safety, and immunogenicity. In addition, we explored potentially relevant biomarkers of ramucirumab activity. The planned enrollment of 40 patients was calculated assuming a median PFS of 5 months for ramucirumab as compared with a median PFS of 3 months for no or ineffective therapy. These assumptions, using a two-sided 95% confidence interval (CI), yielded 81% power to detect a difference in median PFS for ramucirumab as compared with no or ineffective therapy.

All patients who received ramucirumab were included in efficacy and safety analyses. The Kaplan–Meier method was applied to time-to-event endpoints to estimate the medians with corresponding 95% CIs. Exploratory analyses of PFS and OS were performed in patient subgroups using baseline measurements of Barcelona Clinic Liver Cancer (BCLC) stage, Child-Pugh score, normotensive/prehypertensive at baseline and based on measurements of blood pressure during study evaluations classified by the Joint National Committee (JNC) 7 hypertension stage or by hypertension reported as an AE (14). Analyses of biomarkers were performed separately for each laboratory and marker. Time-trend plots and summary statistics of fold changes (medians and interquartile ranges) were generated to assess the change from baseline levels; changes from baseline were also tested with the exact Wilcoxon signed rank test. Biomarker baseline levels and day 8 changes were correlated with PFS and OS in exploratory Cox regression models and nonparametric Spearman rank tests. All data were analyzed using SAS version 8.2 or later (SAS Institute).

Results

Patient characteristics and treatment administration

Of 43 patients enrolled, 42 received ramucirumab. Table 1 lists baseline and disease characteristics. The median age was 63 years. Most patients were male (81%) and had Child-Pugh A cirrhosis (74%), a CLIP score of 1–2 (71%), and BCLC stage C (86%). Hepatitis C (HCV) accounted for 50% of the underlying etiologies. The mean cumulative ramucirumab dose/patient was 63 mg/kg (SD = 58.6) and mean relative dose intensity was 91.1% (SD = 15.25%, range 41.1%–104.2%).

Efficacy

Median PFS was 4.0 months (95% CI, 2.6–5.7; Fig. 1A). Median TTP was 4.2 months (95% CI, 2.8–8.4). Median OS was 12.0 months (95% CI, 6.1–19.7; Fig. 1B). The 1-year and 2-year OS rates were 49.4% (95% CI, 33.1–63.7) and 23.4% (95% CI, 11.6–37.5), respectively. For patients with BCLC stage C disease and Child-Pugh A cirrhosis, median PFS was 4.2 months (95% CI, 2.6–6.7) and median OS was 18.0 months (95% CI, 6.1–23.5); versus a median PFS of 2.6 months (95% CI, 0.5–6.2) and median OS of 4.4 months (95% CI, 0.5–9.0) for those with BCLC Stage C and Child-Pugh B cirrhosis (Fig. 1C and D). In patients who developed clinical AE of hypertension, median PFS was 4.2 months (95% CI, 2.6–8.4) and median OS was 23.1 months (95% CI, 10.3–N/A) versus a median PFS of 3.1 months (95% CI, 1.3–6.2) and a median OS of 6.1 months (95% CI, 3.3–12.0).

for those who did not develop hypertension (Fig. 2A and B). PFS and OS were similar for patients who received angiotensin converting enzyme inhibitors and angiotensin receptor blockers versus other antihypertensive or no antihypertensive treatment (Supplementary Fig. S1). In addition, median PFS was 4.1 months (95% CI, 2.8–6.7) for patients with underlying HCV versus 2.6 months (95% CI, 1.2–8.4) for those with other etiologies of liver disease. Median PFS was shorter in patients with extrahepatic metastases and in those with macrovascular invasion (data not shown).

Of the 42 patients, 4 had partial responses [ORR: 9.5% (95% CI, 2.7–22.6)] with a median duration of 14.1 months (95% CI, 4.3–14.1), 25 (59.5%) had stable disease, and 9 (21.4%) had progressive disease. The disease control rate (partial response + stable disease) was 69.0% (95% CI, 52.9–82.4). Figure 3 shows waterfall plots of best overall percent change from baseline of target lesion measurements by Child-Pugh status. Best response AFP data are presented in Supplementary Fig. S2.

Subsequent anticancer therapy

Following discontinuation, 19 patients (45.2%) received subsequent therapy, defined as any anticancer therapy administered after ramucirumab: 7 (17%) received systemic therapy with sorafenib, 8 (19%) with chemotherapy, 2 (5%) with bevacizumab, and 1 (2%) with everolimus; 2 (5%) had locoregional Y-90 radioembolization.

Toxicity and dose modification

AEs considered possibly, probably or definitely related to ramucirumab are shown in Table 2. Treatment-related grade 3–5 AEs were observed in 14 patients (33%). The most common treatment-related grade 3 AEs included hypertension (6 patients, 14%), gastrointestinal hemorrhage and infusion-related reactions (3 patients, 7%, each), and fatigue (2 patients, 5%). One treatment-related death (grade 5, 2%) occurred from gastrointestinal hemorrhage (esophageal varices).

Three patients required dose reductions for toxicity (hypertension: 2 patients; musculoskeletal chest/back pain: 1 patient). Six patients discontinued for drug-related AEs of infusion-related reaction and gastrointestinal hemorrhage (2 patients each), and hypertension and musculoskeletal chest/back pain. Nine patients had 1 serious AEs considered related to ramucirumab—most frequently gastrointestinal hemorrhage (3 patients), hypertension (3 patients) and infusion-related reaction (2 patients). Gastrointestinal hemorrhage was the most frequently reported liver-related AE. Other liver-related AEs were largely considered to be related to underlying disease by the investigators.

Circulating biomarker analysis

Following VEGFR-2 blockade patients demonstrated persistent elevation in circulating levels of serum VEGF and PIGF (Fig. 4 and Supplementary Fig. S3 and Supplementary Table S1). Patients also experienced a rapid decrease in serum sVEGFR-2 immediately and 1 hour following the end of infusion (Fig. 4 and Supplementary Fig. S3 and Supplementary Table S1). There were no consistent changes in other circulating serum markers. The changes in VEGF and sVEGFR-2 were independently confirmed at ImClone

(Supplementary Table S2). In an exploratory analysis of relationships between biomarkers and efficacy, there was an association between relative change in sVEGFR-1 (between baseline and day 8) with both PFS and OS. Patients with decreases in sVEGFR-1 appeared to have better outcomes (MGH assays; unadjusted Spearman rank P values of 0.0009 and 0.047, respectively, and Cox regression P values of 0.049 and 0.28, respectively).

Discussion

Antiangiogenic therapy is efficacious in the treatment of some but not all advanced malignancies. The first antiangiogenic drug approved by health authorities was the monoclonal antibody bevacizumab which neutralizes the proangiogenic factor VEGF-A. Another approach is blocking the receptor that is thought to be primarily responsible for proangiogenic signals in endothelial cells (VEGFR-2) using the monoclonal antibody ramucirumab (IMC-1121B, LY3009806; ref. 7). While both of these agents block the VEGF/VEGFR-2 interaction, their biologic effects might differ since VEGF binds other receptors (VEGFR-1, NRP1) while VEGFR-2 is a receptor for other ligands (VEGF-C and VEGF-D; ref. 7). Ramucirumab is currently being tested in six pivotal phase III trials (15–19). The first one to be reported, a phase III study in gastric cancer following initial platinum- or fluoropyrimidine-based chemotherapy, showed increased OS with ramucirumab monotherapy (17). There have been extensive correlative biomarker investigations of bevacizumab and other antiangiogenic agents in cancer settings. Biomarker studies of ramucirumab are warranted to delineate overlapping or differential activities of this promising agent relative to approved antiangiogenic therapies.

In hepatocellular carcinoma, antiangiogenic agents have produced mixed results. While sorafenib, a tyrosine kinase inhibitor (TKI) of all VEGF receptors, is the worldwide standard of care, other agents, including bevacizumab, have not demonstrated comparable efficacy. This manuscript presents the results of the first phase II study of ramucirumab in advanced hepatocellular carcinoma including exploratory correlative studies. This study was initiated before the approval of sorafenib and study accrual occurred during the year following approval of sorafenib in the United States, and was considered appropriate given the known biology of hepatocellular carcinoma, the preliminary efficacy and safety observed with ramucirumab in phase I evaluation, and the limited experience of sorafenib at that time. Despite the inherent limitations of a single-arm trial, we provide the first data on potential correlations between hypertension and outcome with ramucirumab. Moreover, we conducted the first biomarker studies of ramucirumab using data from a patient subset. These exploratory studies provide initial insights into this agent's mechanisms of action.

Ramucirumab was associated with an ORR of 9.5%, a median PFS of 4.0 months, a median TTP of 4.2 months, and a median OS of 12.0 months in advanced hepatocellular carcinoma. In the pivotal SHARP study, sorafenib conferred a 2% ORR, a median TTP of 5.5 months and a median OS of 10.7 months. In an earlier phase II study in which (like the present trial) approximately 25% of patients had Child-Pugh B cirrhosis—sorafenib conferred a 2.2% ORR, a median TTP of 4.2 months, and a median OS of 9.2 months. In several randomized phase III trials, other multi-targeted tyrosine kinase inhibitors have not conferred survival benefits in either first-line versus sorafenib (sunitinib, linifanib, brivanib; refs. 20–22) or

second-line (brivanib; ref. 23) treatment of advanced hepatocellular carcinoma. Similarly, a recently completed second-line phase III trial of the mTOR inhibitor everolimus was also reportedly negative per sponsor communication. Although our observed PFS was lower than the 5-month target used to estimate sample size, the ORR of 9.5% and median OS of 12.0 months indicate potential anticancer activity of ramucirumab in hepatocellular carcinoma, particularly in patients with BCLC stage C cancer and Child-Pugh A cirrhosis.

Drug-related serious AEs occurred in 9 patients and there was 1 drug-related death from gastrointestinal hemorrhage. Grade 3–5 hemorrhagic events observed in this study emphasize the need for more extensive requirements for screening endoscopy in subsequent studies evaluating ramucirumab in hepatocellular carcinoma, and more consistent restrictions on the use of antiplatelet or anticoagulant agents. These observations informed the design of the currently ongoing second-line phase III study evaluating ramucirumab in hepatocellular carcinoma. Other frequent AEs included infusion-related reaction, hypertension, and fatigue. Three patients required dose reductions and 6 patients discontinued due to toxicity. The safety profile of ramucirumab in advanced hepatocellular carcinoma was generally acceptable and compared favorably to multi-targeted agents. With the exception of bleeding, the overall incidence of liver-related AEs was within an expected range for this cirrhotic study population. No specific safety concerns were identified in the subset of 11 patients with Child-Pugh B cirrhosis, although median PFS and OS were shorter in this population. However, larger studies are warranted to establish the safety of ramucirumab in Child-Pugh B patients.

As seen in studies evaluating other antiangiogenic agents in other malignancies, patients who developed the AE of hypertension after angiogenic blockade had longer PFS and OS (22, 24, 25). The AE of hypertension has been proposed as a predictive biomarker of antiangiogenic therapy (26). However, the analyses investigating associations between hypertension and efficacy were exploratory and interpretation is limited both by the lack of an appropriate control and the small sample size (27). These associations require additional confirmation.

Consistent with data from blood biomarker studies of anti-VEGFR-2 TKIs in hepatocellular carcinoma and other cancers (13, 28, 29), antibody blockade of VEGFR-2 with ramucirumab appeared to increase the circulating levels of VEGF and PlGF in hepatocellular carcinoma patients. These potential pharmacodynamic biomarkers may be upregulated via hypoxia-mediated feedback mechanisms in response to specific VEGFR-2 blockade (30). Increases in circulating VEGF could also be due to antibody-mediated receptor blockade, which prevents VEGF binding. In addition, in contrast to anti-VEGFR-2 TKIs (which continually decrease circulating sVEGFR-2 levels) and bevacizumab (which does not decrease or even increase circulating sVEGFR-2 levels) (31), ramucirumab only transiently decreased sVEGFR-2 levels in circulation. This may potentially indicate a difference in mechanism of action between ramucirumab versus other anti-VEGF agents. An exploratory analysis also suggested a potential correlation between reduction (from baseline to day 8) in the levels of sVEGFR-1, an endogenous blocker of VEGF and PlGF not directly affected by ramucirumab, and longer PFS and OS. This result is consistent with biomarker data from studies of sunitinib and cediranib in advanced hepatocellular carcinoma (13, 32).

However, these data should be considered hypothesis-generating and should be confirmed in larger, prospective, randomized trials to establish if these biomarkers are prognostic, or have pharmacodynamic or predictive value for ramucirumab treatment.

Study limitations include the single-arm design, modest sample size, enrollment of patients with both Child-Pugh A and B cirrhosis, inclusion of patients with prior liver transplant, correlative assessments performed in a subset of the population and absence of data enabling determination of modified RECIST response. We employed PFS as a primary endpoint as this study was designed before the published expert panel recommendations. As stated in the minority viewpoint in the panel statement, PFS enables capture of drug-induced safety signals (33). It is worth noting that in our study, PFS and TTP were comparable. Subsequent sorafenib use in 7 of the 42 patients on this study may have contributed to the relatively favorable median OS of 12 months.

In conclusion, ramucirumab conferred preliminary evidence of anticancer activity and an acceptable toxicity profile in advanced hepatocellular carcinoma. A phase III trial of ramucirumab monotherapy in a second-line setting (post-sorafenib) for advanced hepatocellular carcinoma is ongoing (NCT01140347).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Translational Relevance

Multiple signaling processes have been implicated in the development and progression of hepatocellular carcinoma. Sorafenib, a multi-targeted tyrosine kinase inhibitor whose targets include VEGFR-2, remains the standard treatment for advanced hepatocellular carcinoma. Ramucirumab is a human IgG1 monoclonal antibody that specifically binds with high affinity to the extracellular domain of the human VEGFR-2. Ramucirumab blocks the binding of ligands to VEGFR-2 that inhibits endothelial proliferation and migration. Inhibition of VEGFR-2 by DC101, a murine analogue to ramucirumab, confers antitumor activity in multiple murine models involving human cancer xenografts. The present study shows that ramucirumab may confer anticancer activity in patients with advanced hepatocellular carcinoma, providing evidence for the role of specific VEGFR-2 inhibition in this disease.

Figure 1. Kaplan-Meier survival distributions of (A) PFS ($N = 42$); (B) OS ($N = 42$); (C) PFS for BCLC Stage C by Child-Pugh A ($N = 26$) and B ($N = 10$); and (D) OS for BCLC Stage C by Child-Pugh A ($N = 26$) and B ($N = 10$).

Figure 2. Kaplan–Meier survival distributions for patients with clinical AE of hypertension ($N = 18$) and those without ($N = 24$) for (A) PFS and (B) OS (27).

Figure 3.
Waterfall plot of best response by Child-Pugh A and B ($N = 38$).

Figure 4.

Fold changes in biomarker levels relative to baseline following ramucirumab infusion. Each line indicates values for a single patient. Abbreviations: C, cycle; inf, infusion.

Table 1Baseline patient and disease characteristics ($N = 42$)

Variable	<i>N</i> (%)
Sex	
Male	34 (81.0)
Female	8 (19.0)
Age, y	
Median	63
Range	29–88
ECOG performance status	
0	18 (42.9)
1	23 (54.8)
2	1 (2.4)
Etiology of liver disease	
Hepatitis-C infection	21 (50.0)
Hepatitis-B infection ^a	5 (11.9)
Significant alcohol use ^b	13 (31.0)
Hepatitis-C/B co-infection	2 (4.8)
Hepatitis-C + significant alcohol use ^b	10 (23.8)
Other ^c	13 (31.0)
Child-Pugh score	
A	31 (73.8)
B	11 (26.2)
CLIP score	
0	5 (11.9)
1	13 (31.0)
2	17 (40.5)
3	7 (16.7)
BCLC stage	
A	2 (4.8)
B	4 (9.5)
C	36 (85.7)
Macrovascular invasion	
Present	7 (16.7)
Absent	32 (76.2)
N/A or missing	3 (7.1)
Extrahepatic tumor metastasis	
Present	32 (76.2)
Absent	10 (23.8)
Extent of disease ^d	
Liver	38 (90.5)

Variable	N (%)
Lymph nodes	23 (54.8)
Lung	15 (35.7)
Bone	8 (19.0)
Soft tissue	7 (16.7)
Prior therapy	
No prior locoregional therapy	25 (59.5)
Locoregional therapy ^e	17 (40.5)
Surgery	12 (28.6)
Radiofrequency ablation	8 (19.0)
TACE/chemoembolization	6 (14.3)
Liver transplant	5 (11.9)
Radioembolization/Y90	2 (4.8)

^aTwo patients had hepatitis-B status missing and 35 were hepatitis-B negative.

^bSignificant alcohol use was defined as >14 drinks per week (past or present).

^cPatients who were hepatitis-C and -B negative and had no significant alcohol use.

^dOther sites of disease reported in 3 patients were adrenal, pleural, peritoneal, and other.

^ePatients may have had more than one locoregional therapy.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; N/A, not available; TACE, transcatheter arterial chemoembolization.

Table 2

Adverse events possibly, probably, or definitely related to ramucirumab and specific liver-related adverse events (treatment-emergent)

Event ^a	Any Grade, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Fatigue	20 (47.6)	9 (21.4)	9 (21.4)	2 (4.8)	0 (0.0)	0 (0.0)
Hypertension	17 (40.5)	4 (9.5)	7 (16.7)	5 (11.9)	1 (2.4)	0 (0.0)
Headache	15 (35.7)	11 (26.2)	3 (7.1)	1 (2.4)	0 (0.0)	0 (0.0)
Nausea	13 (31.0)	13 (31.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	6 (14.3)	2 (4.8)	4 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)
Infusion-related reaction	6 (14.3)	2 (4.8)	1 (2.4)	3 (7.1)	0 (0.0)	0 (0.0)
Anorexia	4 (9.5)	3 (7.1)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal hemorrhage	3 (7.1)	0 (0.0)	0 (0.0)	2 (4.8)	0 (0.0)	1 (2.4)
Hypomagnesemia	3 (7.1)	2 (4.8)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	1 (2.4)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Hyponatremia	1 (2.4)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Hospitalization ^b	1 (2.4)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Liver related (treatment-emergent)						
Ascites ^c	6 (14.3)	2 (4.8)	1 (2.4)	3 (7.1)	0 (0.0)	0 (0.0)
Gastrointestinal hemorrhage	3 (7.1)	0 (0.0)	0 (0.0)	2 (4.8)	0 (0.0)	1 (2.4)
Hyperbilirubinemia	2 (4.8)	1 (2.4)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Hepatic failure ^c	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Hepatorenal syndrome ^c	1 (2.4)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Escherichia bacteremia ^c	1 (2.4)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Encephalopathy ^c	3 (7.1)	0 (0.0)	2 (4.8)	1 (2.4)	0 (0.0)	0 (0.0)
Hepatic encephalopathy ^c	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)

^a Includes any grade 3–5 event reported and any grade events affecting 5% of patients.

^b Reason for hospitalization was unknown as the patient was lost to follow-up; thus, the event term was reported as grade 3 hospitalization.

^c The 3 gastrointestinal hemorrhage events and one event of hyperbilirubinemia were considered by investigators to be possibly related to study therapy; the other liver related adverse events were considered unlikely related to study therapy.