

Safety and Preliminary Efficacy of Ramucirumab in Combination with FOLFOX4 in Patients with Advanced Hepatocellular Carcinoma: A Nonrandomized, Open-Label, Phase Ib Study

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT02069041
- **Sponsor:** Eli Lilly and Company
- **Principal Investigators:** Chia-Chi Lin, Tsai-Sheng Yang, Chia-Jui Yen
- **IRB Approved:** Yes

LESSONS LEARNED

- The combination of ramucirumab (8 mg/kg intravenous, day 1 every 2 weeks) and FOLFOX4 as first-line treatment in patients with advanced hepatocellular carcinoma (HCC) was not sufficiently tolerated.
- Preliminary efficacy data suggest that the combination may provide clinical benefit to patients with HCC.
- Dose modification and patient selection should be considered for the future development of ramucirumab plus FOLFOX chemotherapy for advanced HCC.

ABSTRACT

Background. The objective of this study was to investigate the safety, preliminary efficacy, pharmacokinetics, and immunogenicity of ramucirumab plus FOLFOX4 as first-line treatment in patients with advanced hepatocellular carcinoma (HCC).

Methods. Patients received ramucirumab (8 mg/kg) intravenously (IV) on day 1, followed by FOLFOX4 (oxaliplatin 85 mg/m² IV on day 1, folinic acid 200 mg/m² IV, bolus fluorouracil [5-FU] 400 mg/m², and a continuous infusion of 5-FU 600 mg/m² over 22 hours, on days 1 and 2) every 2 weeks. The primary endpoint was to assess the safety and tolerability of the combination therapy.

Results. Eight patients (6 men, 2 women) were treated; all eight patients experienced at least one treatment-emergent adverse event (TEAE) of grade ≥3. Dose-limiting toxicities occurred in three patients (37.5%): hepatic hemorrhage (grade 4), blood bilirubin increased (grade 3), and febrile neutropenia (grade 3). Two patients discontinued study

because of hepatic hemorrhage (grade 4) and blood bilirubin increase (grade 3). Six deaths occurred due to progressive disease, and no deaths due to TEAEs.

Conclusion. There were no unexpected safety findings with ramucirumab plus FOLFOX4 based on the known safety and toxicity of this regimen. The combination was not sufficiently tolerated in patients with advanced HCC at the specified dose and schedule. *The Oncologist* 2020;25:e1921–e1929

DISCUSSION

Ramucirumab is a recombinant human receptor-targeted monoclonal antibody that specifically binds vascular endothelial growth factor receptor-2. Previously, in the REACH and REACH-2 trials, ramucirumab was demonstrated to be well tolerated, with a safety profile consistent with its established profile in patients with HCC [1, 2]. The EACH study has demonstrated the clinical benefits of FOLFOX 4 as a systemic chemotherapy regimen [3]. Consequently, the

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Chinese society guidelines have acknowledged the use of FOLFOX4 as one of the standard systemic therapies for advanced HCC. Based on published literature, it was hypothesized that antiangiogenic therapy in combination with oxaliplatin-containing systemic chemotherapy could provide additional benefit in patients with advanced HCC than with oxaliplatin-based therapy alone [3]. An acceptable safety profile for ramucirumab plus FOLFOX in patients with advanced solid tumors has been previously demonstrated [4]. However, the safety of ramucirumab plus FOLFOX4 has not been evaluated in patients with advanced HCC. Therefore, we investigated the safety and tolerability of ramucirumab (8 mg/kg IV, day 1 every 2 weeks) plus FOLFOX4 in patients ($n = 8$) with advanced HCC. All eight patients experienced at least one treatment-emergent adverse event (TEAE) of grade ≥ 3 (Table 1). For the HCC study population, some adverse events (AEs) are reasonably anticipated because underlying malignancy and liver disease. The combination as first-line treatment in patients with advanced HCC was not sufficiently tolerated because of the occurrence of grade ≥ 3 dose-limiting toxicity (DLT) events in three (37.5%) patients, which was higher than the expected DLT rate of 15.0% to 20.0% [4]. Two patients with treatment-related DLTs (grade 4 hepatic tumor hemorrhage and grade 3 blood bilirubin increased) had a medical history of chronic hepatitis B and liver cirrhosis. The underlying liver disease may have confounded the conclusion of the causality. Also, the majority of patients had bulky tumor, extrahepatic metastasis, or portal vein invasion (Fig. 1). Grade 3 febrile neutropenia in one patient resolved after antibiotic treatment (cefepime), and the patient received study treatment at a reduced dose after recovery. The grade 3 febrile neutropenia was related to FOLFOX4 and not due to ramucirumab, as assessed by the investigator. Other common TEAEs were consistent with those reported in previous clinical trials of ramucirumab plus FOLFOX/FOLFIRI in

Table 1. Study drug-related treatment emergent adverse events of grade ≥ 3

Preferred term	All treated patients ($n = 8$), n (%)
Patients with ≥ 1 study drug-related TEAE of grade ≥ 3	8 (100)
Neutrophil count decreased	4 (50)
White blood cell count decreased	2 (25)
Neutropenia	1 (12.5)
Diarrhea	1 (12.5)
Fatigue	1 (12.5)
Hepatic hemorrhage	1 (12.5)
Wound complication	1 (12.5)
Aspartate aminotransferase increased	1 (12.5)
Blood bilirubin increased	1 (12.5)
Gamma-glutamyl transferase increased	1 (12.5)
Febrile neutropenia	1 (12.5)

Abbreviation: TEAE, treatment-emergent adverse event.

patients with solid tumors [1, 3, 4]. No unexpected AEs were observed.

The disease control rate (DCR) (62.5%) and overall response rate (25.0%) were higher as compared with previous studies [2, 3]. However, no firm efficacy conclusions can be drawn. Single-dose pharmacokinetics (PK) parameters of ramucirumab plus FOLFOX4 were consistent with other ramucirumab studies [5]. In conclusion, dose modification and patient selection should be considered for the future development of FOLFOX chemotherapy plus ramucirumab for advanced HCC.

TRIAL INFORMATION

Disease	Hepatocellular carcinoma
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study	Phase Ib, multicenter, open-label, single-arm
Primary Endpoints	Safety, tolerability
Secondary Endpoints	Preliminary efficacy, pharmacokinetics, immunogenicity
Investigator's Analysis	The combination was not tolerated at tested dose and schedule

DRUG INFORMATION

Generic/Working Name	LY3009806
Company Name	Eli Lilly and Company
Drug Type	Biological
Drug Class	Protein-based therapies (monoclonal antibody)
Dose	Ramucirumab 8 mg/kg; FOLFOX4 (85 mg/m ² oxaliplatin, 200 mg/m ² FA, 400 mg/m ² 5-FU bolus, and 600 mg/m ² 5-FU continuous infusion) mg/kg
Route	IV

Schedule of Administration	8 mg/kg ramucirumab given intravenously on day 1 followed by FOLFOX4 given IV on day 1 of every 2 week cycles: 85 mg/m ² oxaliplatin IV on day 1; 200 mg/m ² FA IV on days 1 and 2; 400 mg/m ² 5-FU bolus on days 1 and 2; 600 mg/m ² 5-FU 22-h continuous infusion on days 1 and 2.
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PATIENT CHARACTERISTICS

Number of Patients, Male	6
Number of Patients, Female	2
Stage	Advanced, BCLC stage B/C
Age	Median (range): 55.56
Number of Prior Systemic Therapies	Median (range): 0
Performance Status: ECOG	0 — 4 (50%) 1 — 4 (50%) 2 — 0 3 — 0 Unknown — 0

Other	See Table 2 for detailed patient characteristics.
Cancer Types or Histologic Subtypes	Hepatocellular carcinoma, 8

PRIMARY ASSESSMENT METHOD

Number of Patients Screened	8
Number of Patients Enrolled	8
Number of Patients Evaluable for Toxicity	8
Number of Patients Evaluated for Efficacy	8
Evaluation Method	RECIST 1.1
Response Assessment CR	<i>n</i> = 0 (0%)
Response Assessment PR	<i>n</i> = 2 (25%)
Response Assessment SD	<i>n</i> = 3 (37.5%)
Response Assessment PD	<i>n</i> = 1 (12.5%)
(Median) Duration Assessments Response Duration	5.52 months
Outcome Notes	See Table 3 for detailed response data. Table 4 outlines treatment exposure.

ADVERSE EVENTS

Table 1 summarizes adverse events.

PHARMACOKINETICS

Table 5 summarizes the PK results.

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion	Study completed
Investigator's Assessment	The combination was not tolerated at tested dose and schedule

This is the first phase Ib study to evaluate the safety and tolerability of ramucirumab in combination with

FOLFOX4 in patients with advanced hepatocellular carcinoma (HCC). Results of the present study demonstrated

that ramucirumab (8 mg/kg intravenously [IV], day 1 every 2 weeks) plus FOLFOX4 as first-line treatment in patients with advanced HCC was not sufficiently tolerated because of the occurrence of grade ≥ 3 dose-limiting toxicity (DLT) events in three (37.5%) patients, which was higher than the expected DLT rate of 15.0% to 20.0% [4, 6] for the ramucirumab and FOLFOX4 combination.

For the HCC study population, some adverse events (AEs) are reasonably anticipated because of underlying malignancy and liver diseases, such as asthenic conditions, pain, abdominal distention, and liver dysfunction [7, 8]. In the REACH-2 study, the safety profile of single-agent ramucirumab was generally acceptable in advanced HCC, consistent with the prior REACH trial [1, 2]. The common grade ≥ 3 treatment-emergent AEs (TEAEs), which occurred at a higher frequency in ramucirumab versus placebo, were hypertension (13% vs. 5%), hyponatraemia (6% vs. 0%), and increased aspartate aminotransferase (3% vs. 5%) [3]. The noted safety profile of the placebo group was consistent with advanced HCC and underlying liver disease. In our study, two patients who experienced treatment-related DLTs (grade 4 hepatic tumor hemorrhage and grade 3 blood bilirubin increased) each had a medical history of chronic hepatitis B and liver cirrhosis. The underlying liver disease may have confounded the conclusion of the causality. Of note, the majority of enrolled patients in this study had a bulky tumor, extrahepatic metastasis, or portal vein invasion (Fig. 1). HCC is a heterogeneous disease, and Child-Pugh score alone may not be sufficient to avoid masking treatment outcomes by quick deterioration of liver function or death due to the nature of the disease. Lessons learned from recent HCC studies underscore the importance of proper patient selection in designing studies for systemic therapy of HCC. For instance, the REFLECT study, (a phase III study demonstrating noninferiority of lenvatinib compared with sorafenib) excluded patients with 50% or higher liver occupation, obvious invasion of the bile duct, or invasion at the main portal vein [9].

In this study, grade 3 febrile neutropenia in one patient was resolved after antibiotic treatment (cefepime), and the patient received study treatment at a reduced dose level after recovery. In the EACH study [3], neutropenia was the most-common hematological TEAE, with 68.85% of all grade and 30.60% of grade ≥ 3 in patients with HCC receiving FOLFOX4. The reported DLT of grade 3 febrile neutropenia was related to FOLFOX4 and not due to ramucirumab, as assessed by the investigator. Grade 3 or greater neutropenia also occurred in 30% to 40% of patients with other gastrointestinal cancers who underwent ramucirumab plus FOLFOX or FOLFIRI chemotherapy [4, 6, 10]. Also, some TEAEs are common in patients with HCC because of underlying malignancy and liver disease. Other common TEAEs observed in this study were consistent with those reported in previous clinical trials of ramucirumab plus FOLFOX/FOLFIRI in patients with solid tumors [1, 3, 4, 6]. No unexpected AEs were observed in this study.

Despite the low sample size of the study, antitumor activity of ramucirumab plus FOLFOX4 was preliminarily

evaluated. In this study, ramucirumab plus FOLFOX4 appears to have antitumor activity in the treatment of patients with HCC (Table 3; Figs. 2-4). The overall response rate (ORR) (25.0%) and DCR (62.5%) reported in our study were higher as compared with the EACH study [3], which reported an ORR of 8.2% and DCR of 52.2% after treatment with FOLFOX4 as first-line treatment in patients with HCC. Similarly, the ORR and DCR in our study were higher when compared with the pooled analysis of REACH/REACH-2 study, with an ORR of 5.4% and DCR of 56.3% in patients treated with ramucirumab [2]. Also, when compared with pooled data in Asian (ORR, 4.2%; DCR, 53.6%) and non-Asian (ORR, 6.8%; DCR, 59.5%) patients from REACH/REACH-2, the ORR and DCR [11] were higher in our study. Because of the small sample size, serum α -fetoprotein (AFP) level in relation with tumor response was not assessed (Fig. 5). This study enrolled the patients with poor-prognosis disease, as the majority of the patients had a Barcelona Clinic Liver Cancer classification of stage C disease. The expected median survival for this class of patients is about 6 months [12] if these patients are left untreated. Hence, the patient selection should be carefully considered in future development with this regimen.

Our study results are still encouraging and suggested that ramucirumab may improve the efficacy of FOLFOX4 in patients with advanced HCC. However, no firm efficacy conclusions can be drawn. Single-dose PK parameters ($t_{1/2}$, total body clearance of drug calculated after IV, and volume of distribution at steady state) after administration of ramucirumab (8 mg/kg, every 2 weeks) plus FOLFOX4 were consistent with ramucirumab studies in which different regimens and cancer types were being studied (Table 5) [5].

The positions of molecular-targeted therapy or cytotoxic chemotherapy for HCC management may change rapidly with the emergence of immune checkpoint inhibitors. Proangiogenic factors induce tumor growth and metastasis, not only by promoting angiogenesis but also by favoring immunosuppressive microenvironments [13]. Several lines of clinical evidences have shown that immune-based therapy can improve outcomes for patients with HCC [14–17]. Furthermore, clinical studies showed that the combination therapies with vascular endothelial growth factor receptor and checkpoint inhibitors have synergistic effects achieving improved response rates in solid tumors [17]. A better knowledge of a potentially synergistic interaction between antiangiogenesis and immune system may lead to new therapeutic strategies combining these two therapeutic modalities for patients with HCC.

The recent advent of several new agents for the treatment of unresectable HCC has enhanced the therapeutic armamentarium for this disease. This is the first study to test ramucirumab in a first-line setting in patients with advanced HCC, revealing that there were no unexpected safety findings based on the known safety and toxicity profile for this regimen. Combination therapy was not sufficiently tolerated. Ramucirumab may enhance the efficacy of FOLFOX4 in patients with HCC. However, no efficacy conclusions can be drawn because of limited sample size, but it merits further investigation with adjustment in dose of cytotoxic agents or patient selection.

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The authors state that they obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human

investigations. In addition, informed consent was obtained from all study participants prior to any study procedures being performed.

DISCLOSURES

Chia-Chi Lin: Boehringer-Ingelheim, Daiichi Sankyo, Novartis (C/A), Bristol-Myers Squibb, Novartis, Roche, Eli Lilly and Company (H), BeiGene, Eli Lilly and Company (Other); **Rebecca Cheng:** Eli Lilly and Company (E), **Junjun Liu:** Eli Lilly and Company (E); **Chiun Hsu:** Bristol-Myers Squibb/ONO, IPSEN, Roche (RF), AstraZeneca, Bayer, Bristol-Myers Squibb/ONO, Eli Lilly, Merck Sharpe & Dohme, Novartis, Roche (H). The other authors 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

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FIGURES AND TABLES

Table 2. Demographic and baseline characteristics of patients

Characteristics	All treated patients (n = 8)
Age, mean (SD), yr	55.56 (11.06)
Sex, n (%)	
Male	6 (75.0)
Female	2 (25.0)
Initial pathological diagnosis, n (%)	
Histopathological	3 (37.5)
Cytological	1 (12.5)
Biochemical assay and imaging	2 (25.0)
Missing	2 (25.0)
ECOG performance status, n (%)	
0	4 (50.0)
1	4 (50.0)
Duration of disease (months), median (range)	0.345 (0.23–0.66)
BCLC classification, n (%)	
Stage B	1 (12.5)
Stage C	7 (87.5)
Extrahepatic spread, n (%)	5 (62.5)
Macroscopic portal vein invasion, n (%)	2 (25.0)
Viral hepatitis B test positive, n (%)	8 (100.0)
α -fetoprotein (ng/mL),	
Median (range)	22,342.2 (8.9–43,094)
AFP >400 n (%)	4 (50)
AFP <400 n (%)	2 (25)

Abbreviations: AFP, α -fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group.

Table 3. Summary of tumor response

Tumor response	All treated patients (n = 8)
Best overall tumor response, n (%)	
CR	0 (0.0)
PR	2 (25.0)
SD	3 (37.5)
PD	1 (12.5)
Not evaluable	2 (25.0)
Disease control rate (CR+PR+SD), n (%)	5 (62.5)
Overall response rate (CR+PR), n (%)	2 (25.0)
Duration of response for 2 PR patients, month	5.91, 2.79
Duration of stable disease for 3 SD patients, month	2.76, 5.52, 5.52

Note: Response criteria used was RECIST version 1.1.

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4. Treatment exposure

Exposure	Ramucirumab (n = 8)	Oxaliplatin (n = 8)	Folinic acid (n = 8)	5-fluorouracil bolus (n = 8)	5-fluorouracil drip (n = 8)
Patients completing ≥6 cycles, n (%)	4 (50.0)	2 (25.0)	2 (25.0)	0 (0.0)	2 (25.0)
Number of infusions					
Mean (SD)	6.4 (4.0)	5.0 (3.1)	10.0 (6.2)	5.8 (4.3)	10.0 (6.2)
Median (range)	7 (1–11)	5.0 (1–10)	10.0 (2–20)	4.0 (2–12)	10.0 (2–20)
Cumulative Dose, mg/m ²	48.8 ^a (30.5)	392.5	2000.0	2,300.0	5,575.0
Mean (SD)		(242.7)	(1,246.7)	(1,733.7)	(3,474.7)
Dose intensity, mg/m ² /week	3.492 ^a	31.834	152.416	215.098	423.696
Mean (SD)	(0.646)	(11.873)	(48.495)	(129.850)	(137.587)
Relative dose					
Intensity, %	93.9	83.3	89.5	60.2	84.1
Median (range)	(59.9–100.7)	(31.4–100.0)	(38.7–97.7)	(7.7–93.3)	(33.3–87.5)

^aThe dose unit of ramucirumab is mg/kg per wk.

Table 5. Summary of ramucirumab pharmacokinetic parameters for Chinese patients with hepatocellular carcinoma, following 8 mg/kg of ramucirumab administered as an intravenous infusion over approximately 1 hour every 2 weeks in combination with FOLFOX4

Parameter	Ramucirumab serum parameters, geometric mean (geometric CV%)	
	Cycle 1, first dose (n _{PK} = 8) ^a	Cycle 3 third dose (n _{PK} = 3)
C _{max} or C _{max,ss} (μg/mL)	155 (25)	190 (29)
t _{1/2} (day)	6.06 ^a (28)	8.85 (7)
AUC(0–∞) or AUC _{τ,ss} (μg•day/mL)	940 ^a (24)	1,190 (25)
CL or CL _{ss} (mL/h)	24.0 ^a (31)	17.3 (22)
V _{ss} (L)	4.56 ^a (20)	b
R _{A,Cmax}		1.35 (14)
R _{A,AUC}		1.50 (14)

^an_{PK} = 7 for t_{1/2}; n_{PK} = 6 for AUC(0–∞), CL, and V_{ss}

^bV_{ss} not reported as AUC extrapolated from t_{last} to ∞ was >30%.

Abbreviations: 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 observed serum concentration at steady state; CV%, percentage coefficient of variation; n_{PK}, number of pharmacokinetic observations; 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; V_{ss}, volume of distribution at steady state.

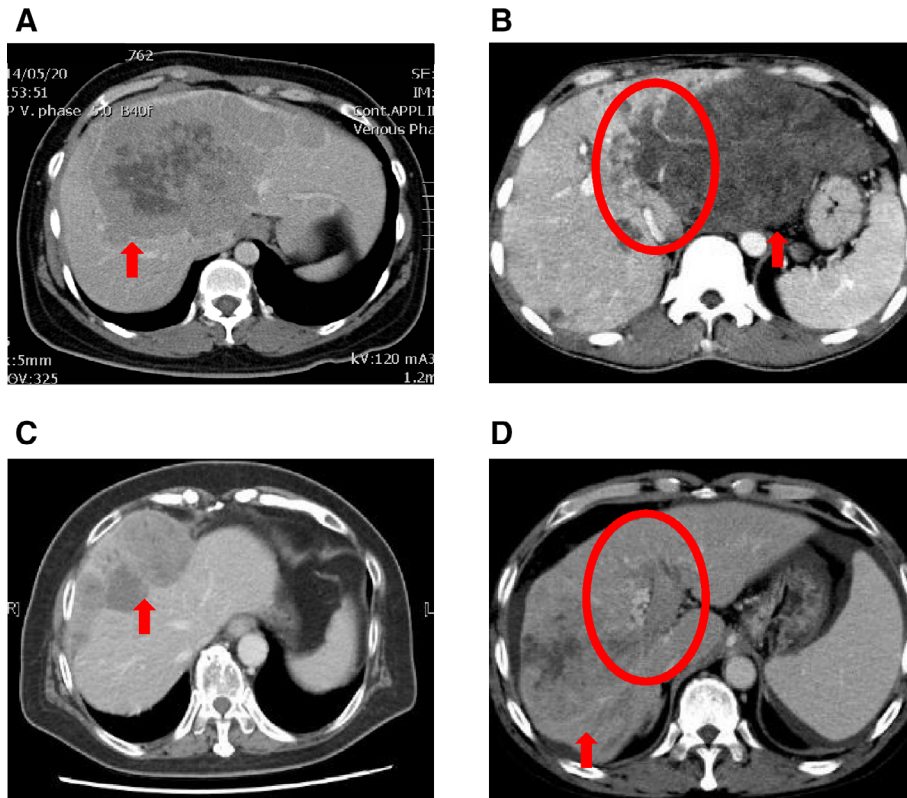


Figure 1. Pretherapy computed tomography images reveal bulky hepatic tumors (A, C) or extensive portal vein invasions (B, D) in patients with hepatocellular carcinoma.

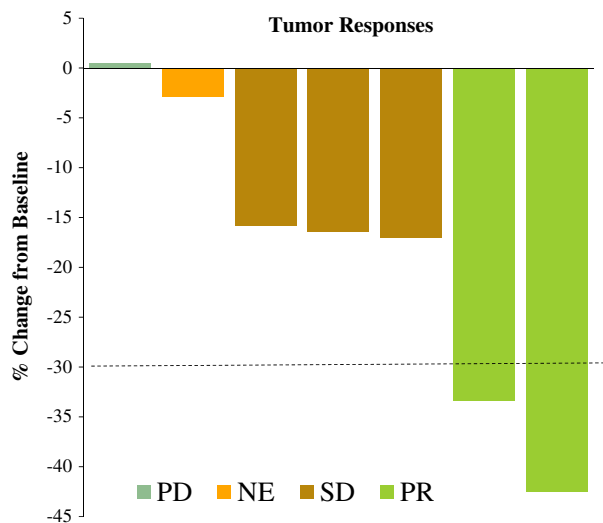


Figure 2. Maximum change from baseline in tumor size for patients who had baseline and at least one postbaseline tumor size assessment. Tumor size of the measurable lesions measured using RECIST version 1.1. The dashed line represents the 30% cutoff for radiographic response.

Abbreviations: NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

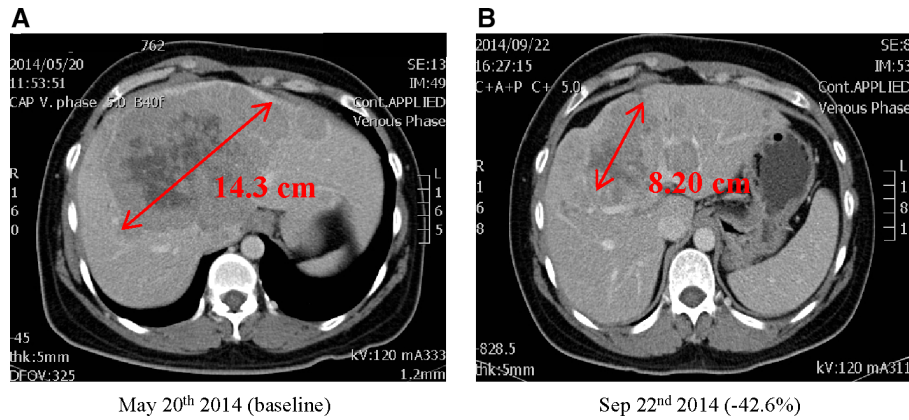


Figure 3. Imaging characteristics of one patient with hepatocellular carcinoma (HCC) with partial response to ramucirumab-FOLFOX4 at baseline (A) and mid-treatment (B). 44-year-old female patient with HCC with hepatitis B virus carrier state, Barcelona Clinic Liver Cancer stage C, and Child-Pugh A disease achieved partial response (with 42.6% shrinkage of tumor dimension) after 4 months of treatment with ramucirumab-FOLFOX4.

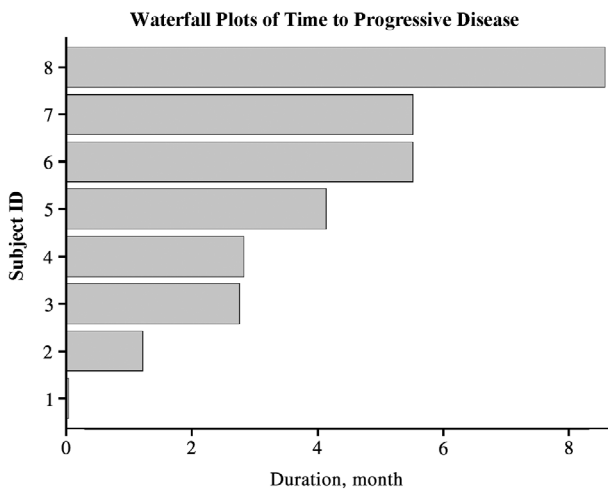


Figure 4. Waterfall plot of time-to-progressive disease. The plot consists of all treated patients. Abbreviation: ID, identification.

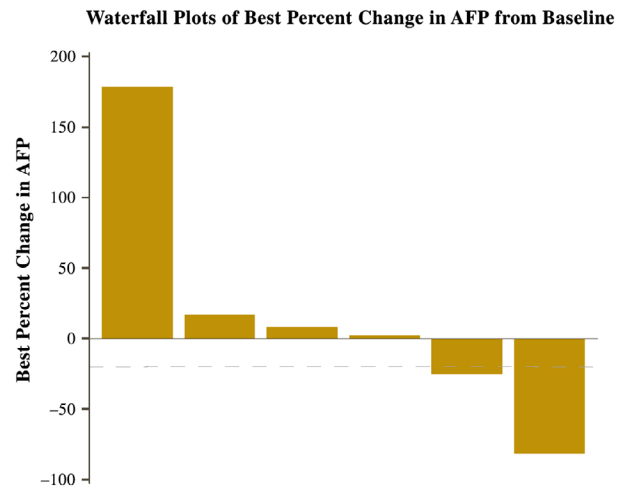


Figure 5. Waterfall plot of best percent change in AFP response from baseline. The plot includes patients with baseline and at least one postbaseline AFP measurement. The dashed line represents the 20% cutoff for AFP response. Abbreviation: AFP, α -fetoprotein.

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