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# Lenvatinib Rechallenge After Ramucirumab Treatment Failure for Hepatocellular Carcinoma

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**Abstract.** *Background/Aim: While there is increasing evidence supporting the role of several first- and second-line treatment regimens for advanced hepatocellular carcinomas (HCC), the clinical relevance of rechallenge treatment with previously administered drugs, however, remains to be explored. Patients and Methods: Five consecutive patients with advanced HCC who received lenvatinib rechallenge treatment after ramucirumab were assessed. Results: All patients were clinically diagnosed with failure after ramucirumab treatment, and the frequencies of ramucirumab administration before lenvatinib re-administration ranged from 3 to 11. The alfa-fetoprotein level in four of five patients decreased 1 month after the lenvatinib rechallenge. Radiological findings via the modified Response Evaluation Criteria in Solid Tumors showed stable diseases in four patients and a partial response in one. Conclusion: Rechallenge treatment with lenvatinib after ramucirumab can be effective, and may be a treatment option for HCC in cases wherein the disease progressed after an initial response to lenvatinib treatment.*

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer and remains one of the leading causes of cancer deaths worldwide (1, 2). Since HCC is rarely detected at an early stage, only a small number of patients are eligible for curative treatments, including hepatectomy, radiofrequency ablation, and liver transplantation (3, 4). The majority of patients are diagnosed with more advanced stage HCC, for which curative options are lacking. Sorafenib has long been the only available systemic treatment option for advanced-stage HCC (5, 6). However, several systemic treatment options have recently emerged, including treatment with the tyrosine kinase inhibitors (TKIs) lenvatinib, regorafenib, and cabozantinib, the vascular endothelial growth factor receptor (VEGFR)-2 inhibitor ramucirumab, and combined immunotherapy/vascular endothelial growth factor (VEGF) inhibition with atezolizumab and bevacizumab (7-11).

Lenvatinib is an oral multityrosine kinase inhibitor that acts on the VEGFR 1-3, fibroblast growth factor receptors (FGFR) 1-4, platelet-derived growth factor receptor (PDGFR)-α, RET, and KIT signaling networks (12-14). The REFLECT trial showed the overall survival noninferiority and statistically improved progression-free survival rate of lenvatinib, compared to sorafenib, for unresectable HCC (7).

Ramucirumab is a monoclonal antibody targeting the extracellular domain of VEGFR 2. Based on two phase 3 studies (REACH and REACH-2) (11, 15), ramucirumab has been approved as a second-line systematic treatment in patients with advanced HCC and baseline alfa-fetoprotein (AFP) levels ≥400 ng/ml.

Despite advances in systemic treatments, there is a paucity of effective second- and later-line treatments for advanced HCC. Rechallenging chemo-resistant tumors with previously administered treatments may be a potential life-prolonging option considering the limited chemotherapeutic treatment options for HCC. The present study aimed to investigate the clinical relevance of rechallenge treatment with lenvatinib after ramucirumab treatment.

## Patients and Methods

*Study design and population.* This study retrospectively evaluated patients with unresectable HCC who received rechallenge treatment

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*Key Words:* Hepatocellular carcinoma, lenvatinib, ramucirumab, rechallenge.

Table I. *Characteristics of all patients*.

| | No. of patients (n=5) |
|---|---|
| Age (years)* | 62.0 (48-71) |
| Gender, male:female | 5:0 |
| ECOG PS, 0:1 | 2:3 |
| Etiology, HBV:HCV:NBNC | 3:1:1 |
| BCLC classification, B:C | 0:5 |
| Child-Pugh score, 5A:6A | 4:1 |
| ALBI grade, I:II | 2:3 |
| mALBI grade, I:IIa:IIb | 2:2:1 |
| Extrahepatic metastasis, yes:no | 4:1 |
| Previous TKI history before 1st lenvatinib, yes:no | 1:4 |

Data are expressed as number of patients (%) unless specified. *Values are median (interquartile range). ECOG PS: Eastern cooperative Oncology Group performance status; HBV: hepatitis B virus; HCV: hepatitis C virus; NBNC: non B non C; BCLC: Barcelona Liver Clinic; ALBI: albumin-bilirubin; mALBI: modified albumin-bilirubin; TKI: tyrosine-kinase inhibitor.

with lenvatinib after ramucirumab treatment at Kobe University Hospital between October 2018 and December 2020.

The diagnosis of HCC was confirmed radiologically using computed tomography (CT) or magnetic resonance imaging (MRI) and also based on elevated levels of AFP or elevated levels of protein induced by vitamin K absence or antagonist II (PIVKAII). The Barcelona Clinic Liver Cancer (BCLC) classification was used to identify the tumor stage (16). Child-Pugh status, albumin-bilirubin (ALBI) grade (17), and the modified ALBI (mALBI) grade (18) were used as the standard of measures to assess liver impairment. Performance status was evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status guidelines. Patients were followed up until May 2021 or until death before May 2021. This study was conducted per the principles of the Declaration of Helsinki.

*Inclusion criteria and treatment details*. Inclusion criteria for lenvatinib and ramucirumab were as follows: 1) ECOG performance status of ≥2, 2) HCC with BCLC stage B or C who were not eligible for locoregional treatment, 3) Child-Pugh class A or B, and 4) serum AFP levels of ≥400 ng/ml (those only for ramucirumab patients). The lenvatinib dose was determined according to the patient's body weight: patients weighing <60 kg received 8 mg once daily, while those weighing ≥60 kg received 12 mg once daily. Ramucirumab was administered intravenously at a dose of 8 mg/kg once every 2 weeks.

The serum levels of AFP and PIVKAII were measured at baseline and every month after the treatment. CT or MRI was performed every 4-12 weeks, and the radiological response was determined by independent radiologists and classified according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) (19, 20). Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

*Statistical analyses*. All statistical analyses were performed using the JMP® 14 statistical package (SAS Institute, Cary, NC, USA). Continuous variables are expressed as the median (interquartile range), and categorical variables are expressed as percentages. The overall survival was defined as the period from the start of the initial lenvatinib treatment to the day of disease progression or death. The survival curve was described by the Kaplan–Meier method and compared using the log-rank test; $p<0.05$ was considered statistically significant.

## Results

*Patient baseline characteristics*. Five patients with advanced HCC who had been readministered lenvatinib as a rechallenge after ramucirumab treatment failure at Kobe University Hospital between January and December 2020 were assessed. All patients had finished sequential treatments with lenvatinib and ramucirumab and the re-administration of lenvatinib. Table I presents the patient's characteristics. All patients were male, and the median age was 62 years (range=48-71 years). The ECOG performance status score was 0 for two patients and 1 for the remaining three. The ALBI grade was 1 for two patients (40%) and 2 for three (60%). Four of the five (80%) patients had extrahepatic involvement (*i.e.*, nodal involvement or distant metastases) before treatment. Only one patient had a history of using other TKIs before the initial lenvatinib administration.

*Clinical course of the initial lenvatinib treatment*. Table II presents the data pertaining to the clinical course of all five patients following their initial treatment with lenvatinib. Lenvatinib was the first TKI for four of the five patients, whereas it was the third line treatment (following sorafenib and regorafenib) for one patient. The liver function was Child-Pugh class A5 in four patients and A6 in one. Similarly, the mALBI grade was I for four patients and IIb for the remaining one. The aggravation of the ALBI score 3 months after lenvatinib administration was noted in two patients (cases 2 and 4). The serum AFP levels decreased 1 month after treatment initiation in four patients, and the radiological findings defined by the mRECIST showed stable disease (SD) in two and partial response (PR) in three. At the final administration of lenvatinib, the AFP scores and the tumor size (radiological finding) had increased for all patients. The duration of the initial lenvatinib treatment ranged from 3.1-15.0 months, and no severe adverse events (grade ≥III) were noted.

*Clinical course of rechallenge with lenvatinib*. Data pertaining to the clinical course of all five cases during lenvatinib rechallenge treatment is shown in Table III. All five patients were readministered lenvatinib immediately after ramucirumab failure. The frequencies of ramucirumab administrations ranged from 3 to 11. The ratio of AFP levels (1 month after/before treatment) was 0.24-1.29, and four of five patients showed decreased AFP levels after the

Table II. *Clinical course of initial lenvatinib treatment.*

| Case, Age/Gender | Treatment course before 1st LEN (LEN line) | Child-Pugh grade | ALBI score before (m ALBI grade) | ALBI score 3 month after (mALBI grade) | AFP (ng/ml) | AFP 1month after (ng/ml) | Proportion of AFP, 1 month/before | Response by mRECIST | Duration of 1st LEN treatment |
|---|---|---|---|---|---|---|---|---|---|
| 1, 48/M | None (1st line) | A (5) | –2.735 (I) | –2.987 (I) | 6,234 | 4,290 | 0.69 | PR | 3.1 months |
| 2, 58/M | Sora, Rego (3rd line) | A (5) | –2.990 (I) | –2.688 (I) | 7,805 | 5,624 | 0.72 | SD | 4.8 months |
| 3, 64/M | None (1st line) | A (5) | –2.858 (I) | –3.041 (I) | 3 | 4 | 1.33 | SD | 10.6 months |
| 4, 69/M | None (1st line) | A (5) | –2.954 (I) | –2.274 (IIa) | 10,751 | 8,413 | 0.78 | PR | 4.4 months |
| 5, 71/M | None (1st line) | A (6) | –2.008 (IIb) | –2.820 (I) | 93 | 22 | 0.24 | PR | 15.0 months |

LEN: Lenvatinib; ALBI: albumin-bilirubin; mALBI: modified albumin-bilirubin; AFP: alpha-fetoprotein; mRECIST: modified Response Evaluation Criteria in Solid Tumors criteria; Sora: sorafenib; Rego: regorafenib; SD: stable disease; PR: partial response.

Table III. *Clinical course of lenvatinib rechallenge treatment.*

| Case, Age/Gender | Treatment line before rechallenge | | Child-Pugh grade | ALBI before (mALBI grade) | ALBI 3 month after (mALBI grade) | AFP (ng/ml) | AFP 1 month after (ng/ml) | AFP proportion 1 month/before | Response by mRECIST | Duration of 2nd LEN treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| 1, 48/M | LEN, RAM | 6 | A (5) | –2.48 (IIa) | –2.99 (I) | 20,910 | 17,577 | 0.84 | SD | 2.2 months |
| 2, 59/M | Sora, Rego, LEN, RAM | 5 | A (6) | –1.89 (IIb) | –2.22 (IIb) | 173,425 | 128,775 | 0.74 | SD | 3.2 months |
| 3, 66/M | LEN, RAM | 3 | A (5) | –2.73 (I) | –2.6 (I) | 418 | 542 | 1.29 | SD | 7.2 months |
| 4, 69/M | LEN, RAM | 4 | A (6) | –2.05 (IIb) | –1.2 (III) | 23,383 | 5,592 | 0.24 | PR | 12.2 months |
| 5, 73/M | LEN, RAM | 11 | A (5) | –2.76 (I) | –2.45 (IIa) | 4,881 | 3,727 | 0.76 | SD | 6.8 months |

LEN: Lenvatinib; RAM: ramucirumab; ALBI: albumin-bilirubin; mALBI: modified albumin-bilirubin; AFP: alpha-fetoprotein; mRECIST: modified Response Evaluation Criteria in Solid Tumors criteria; Sora: sorafenib; Rego: regorafenib; SD: stable disease; PR: partial response.

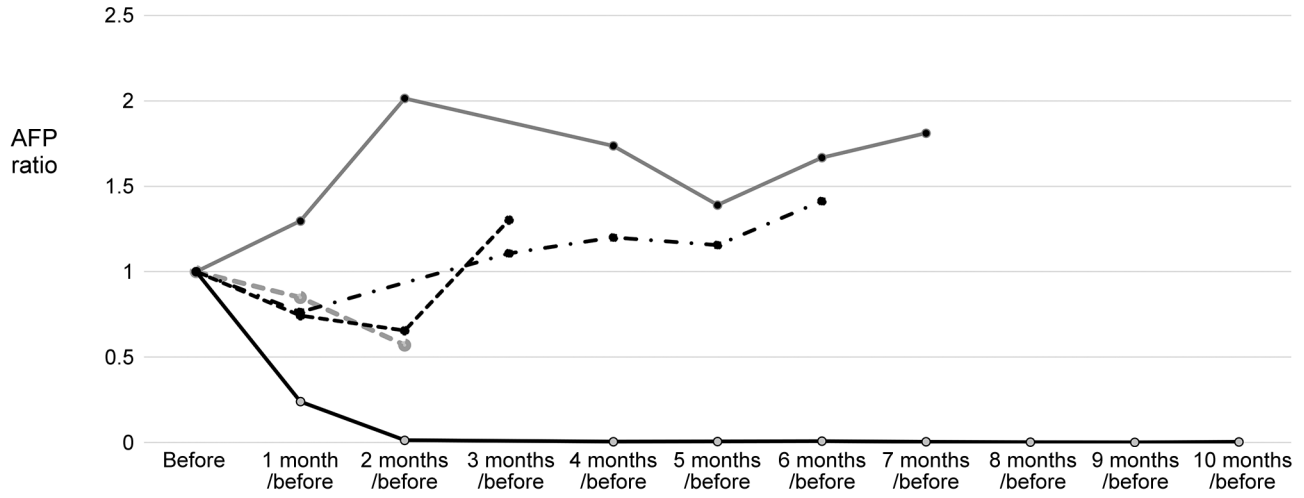


Figure 1. *Changes in serum alfa-fetoprotein levels in response to rechallenge lenvatinib treatment.*

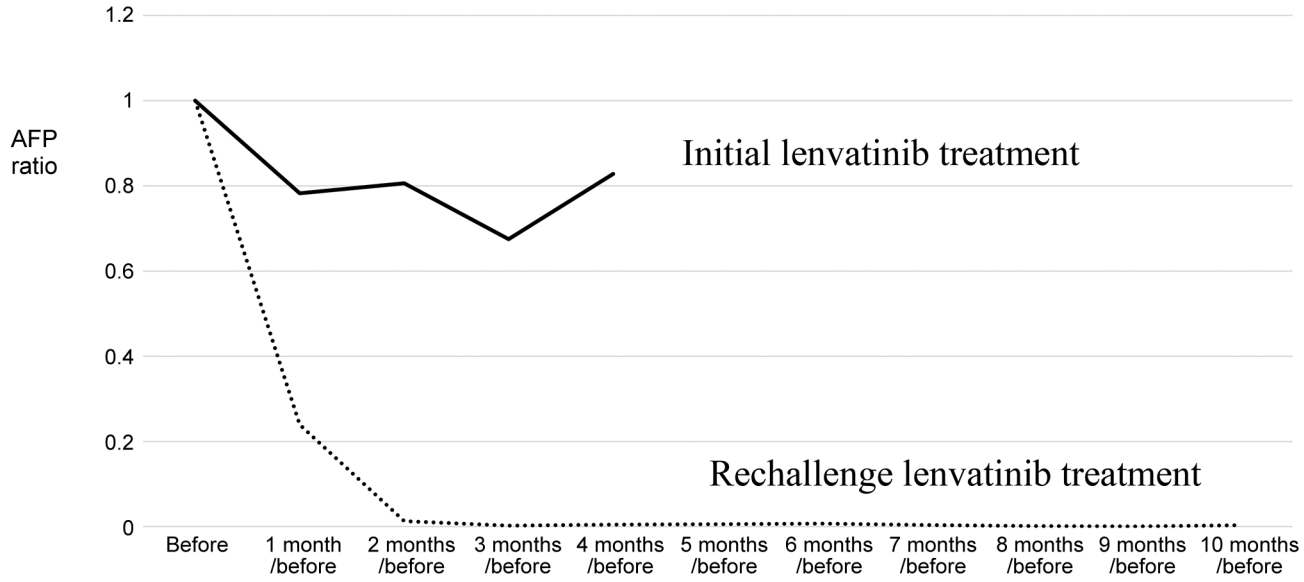


Figure 2. *Changes in serum alfa-fetoprotein level in case 4 during initial and rechallenge lenvatinib treatment.*

lenvatinib rechallenge. The changes in AFP levels after lenvatinib rechallenge treatment are shown in Figure 1. There was a trend of decreasing AFP levels until 2 months after the re-administration of lenvatinib with increased levels thereafter. In one patient (Case 3), the AFP levels increased for 2 months during rechallenge treatment and gradually decreased 3 months after lenvatinib administration. The radiological findings indicated that the disease was stable during rechallenge treatment, which lasted for 7.2 months. Severe adverse events (grade ≥III) did not occur in any of the five patients.

*Case presentation*. Only the Case 4 patient achieved PR after rechallenge treatment. The AFP levels decreased dramatically and achieved PR within 3 months of lenvatinib rechallenge treatment, as confirmed by radiological findings. The AFP levels were 23,383 ng/ml before the lenvatinib rechallenge, 5,592 ng/ml at 1 month of rechallenge treatment, 300 ng/ml at 2 months, 56 ng/ml at 3 months, 109 ng/ml at 4 months, 136 ng/ml at 5 months, 171 ng/ml at 6 months, 90 ng/ml at 7 months, 33 ng/ml at 8 months, and 16 ng/ml at 9 months. However, after 10 months, both the AFP levels and the tumor size gradually increased. This patient also achieved PR after

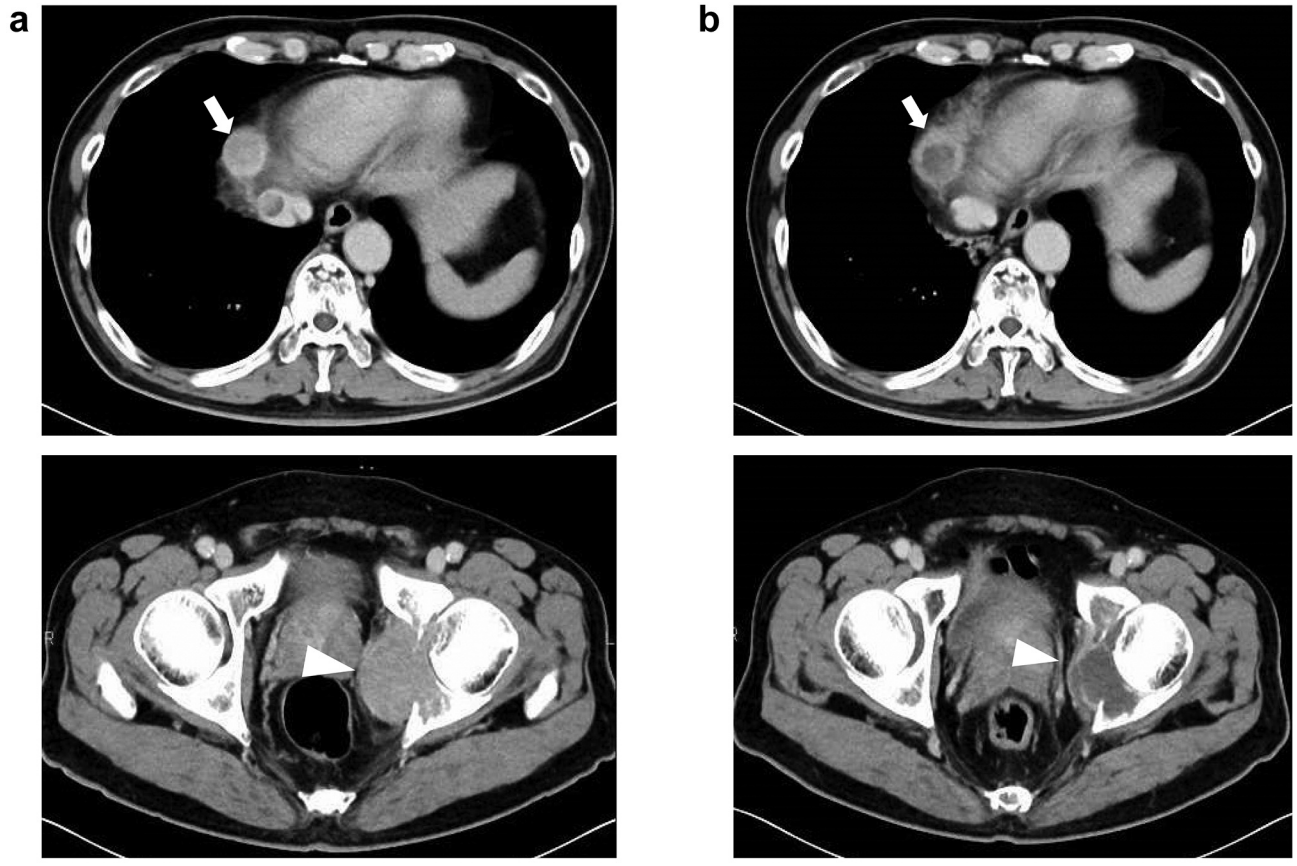


Figure 3. *Radiological findings of case 4 during initial lenvatinib treatment. The figure shows radiological images obtained (A) before treatment and (B) 3 months after lenvatinib administration. The tumor with peritoneal dissemination (arrow) and bone metastasis (arrowhead) decreased in size with diminishing contrast enhancement.*

the initial administration of lenvatinib; however, the change in AFP levels during the initial lenvatinib treatment was as follows: 10,751 ng/ml (before) to 8,413 ng/ml (1 month), 8,671 ng/ml (2 months), 7,262 ng/ml (3 months), and 8,902 ng/ml (4 months). Both the AFP levels and tumor size increased 4 months after the initial lenvatinib treatment. Figure 2 shows the changes in AFP levels in response to the initial and rechallenge treatment with lenvatinib in case 4. The decrease in AFP levels was significantly greater and lasted longer during rechallenge treatment than during initial treatment. The radiological findings of this case during the initial and rechallenge treatments are shown in Figure 3 and Figure 4, respectively. In both instances, tumor size reduction and diminishing contrast enhancement of both the peritoneal dissemination and bone metastases were observed.

## Discussion

The therapeutic landscape of later lines of HCC treatment has recently become more complex due to the availability of several drug options (8, 15). To the best of our knowledge, this is the first report evaluating potential treatment options involving rechallenge with lenvatinib for HCC patients after the development of refractoriness to initial treatment with lenvatinib and failure after ramucirumab treatment. This study discusses five cases wherein PR (n=1) and SD (n=4) were achieved with lenvatinib rechallenge treatment suggesting effectiveness of this treatment. The decrease in AFP levels in response to 1-month rechallenge treatment in four of five patients indicates a potentially effective antitumor effect exerted by this combination treatment. The radiology findings from the only patient that achieved PR indicate a significant decrease in tumor marker levels and considerable tumor shrinkage, highlighting the efficiency of this treatment. The difference in tumor marker transition between initial and second-time lenvatinib (Figure 2) has demonstrated the impact of lenvatinib rechallenge after ramucirumab treatment.

Tumor resensitization with rechallenge TKI treatment has been reported for other malignant tumors (21-25). The effectiveness of lenvatinib rechallenge after refractoriness to

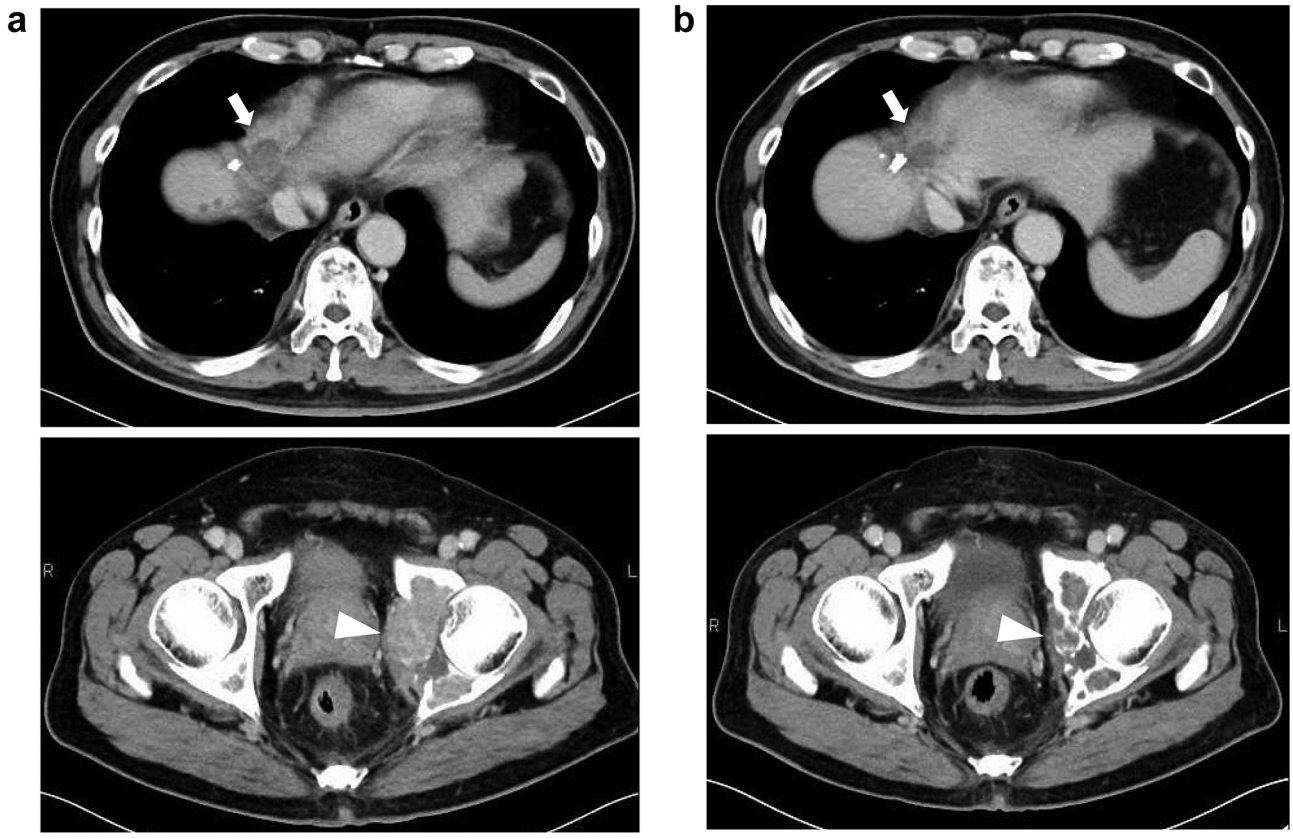


Figure 4. *Radiological findings of case 4 during rechallenge lenvatinib treatment. The figure shows radiological images obtained (A) before treatment and (B) 3 months after rechallenge treatment. The tumor with peritoneal dissemination (arrow) and bone metastasis (arrowhead) decreased in size with diminishing contrast enhancement compared to the initial readings.*

initial lenvatinib treatment followed by sorafenib in a patient with metastatic papillary thyroid carcinoma has been reported (26). Because both lenvatinib and sorafenib are multitargeted TKIs, the authors hypothesized that the differences in targeted signaling pathways between the two might play a role in resensitization to lenvatinib. The interaction between lenvatinib and ramucirumab as administered in this study has not previously been investigated. Lenvatinib is a multi-kinase inhibitor that predominantly inhibits signaling pathways *via* VEGFR 1-3, whereas ramucirumab binds explicitly to VEGFR-2, reducing endothelial cell permeability, migration, and proliferation. The mechanisms through which tumors are re-sensitized by rechallenge with lenvatinib are not fully understood. A potential hypothesis is that the specific inhibition of VEGFR-2 with ramucirumab may lead to the expression and activation of other VEGF ligands, such as VEGF-A, VEGF-B, and placental growth factor. The over-expression of these ligands might result in enhanced activation of VEGFR-1 due to inhibition of VEGFR-2 by ramucirumab. Subsequent rechallenge with lenvatinib might then inhibit binding of ligands to VEGFR-1, resulting in an antitumor effect. It can be hypothesized that these differences in targeted signaling pathways, and various genetic alterations, may play a role in resensitization. In addition, the cases of lenvatinib rechallenge described here had high AFP levels at baseline. Montal *et al*. reported that higher baseline AFP levels might correlate with the over-expression of VEGF ligands and VEGFR signaling in a human HCC (27). These findings might further strengthen the above hypothesis.

New chemotherapeutic options, including atezolizumab plus bevacizumab and cabozantinib, have become available (8, 9), and HCC chemotherapy is now entering a new era. However, second or later-line treatment options are not yet established, despite advances in the favorable response rate of new chemotherapy.

The present study has several limitations, such as retrospective design and small sample size. Despite these limitations, considering the lack of effective later-line treatment options for chemotherapeutic approaches in HCC treatment, this case series is clinically significant as it provides evidence supporting a potentially effective therapeutic option for dealing with resistance in sequential treatments.

In conclusion, HCC tumors refractory to prior lenvatinib treatment can be resensitized by rechallenge with lenvatinib after ramucirumab treatment. Therefore, rechallenge with lenvatinib after ramucirumab failure may be a viable treatment option for HCC patients with disease progression despite lenvatinib treatment. Further prospective studies are required to investigate the efficacy of rechallenge lenvatinib treatment.

## Conflicts of Interest

The Authors declare no conflicts of interest in relation to this manuscript.

## Authors' Contributions

Study design; Komatsu S, Yano Y. Data collection; Kido M, Kuramitsu K, Gon H, Fukushima K, Urade T, So S. Article preparation and review; Yanagimoto H, Toyama H, Kodama Y. Supervision; Fukumoto T.

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