Initial experience with the combination of atezolizumab and bevacizumab in patients with unresectable hepatocellular carcinoma progressing after tyrosine kinase inhibitor therapy: A multicenter prospective observational study

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Research Article

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Abstract

Background

There is no evidence for the efficacy of atezolizumab plus bevacizumab treatment in patients with hepatocellular carcinoma previously treated with tyrosine kinase inhibitors (TKIs).

Methods

Twelve patients treated with atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma (HCC) and previously treated with TKIs were enrolled in the study.

Results

The treatment lines ranged from second line to sixth line. HCC staging was Barcelona Clinic Liver Cancer (BCLC) stage B in four cases and BCLC stage C in eight cases. The overall response rate and disease control rate according to the response evaluation criteria in solid tumors (RECIST) were 18.1% and 54.4%, respectively. Progression-free survival was 2.7 months, indicating that early response to treatment may differ depending on the type of previous therapy. The side effects profile also differed from that observed in IMbrave150, a phase 3 trial of atezolizumab plus bevacizumab, with many adverse events related to liver reserve.

Conclusions

The therapeutic effects and side effects differed from those previously reported during the treatment course of atezolizumab plus bevacizumab as first-line therapy.

Background

Several tyrosine kinase inhibitors (TKIs) have been developed for the treatment of unresectable hepatocellular carcinoma (HCC): sorafenib, lenvatinib, regorafenib, ramucirumab, and cabozantinib to date [1–5]. Atezolizumab plus bevacizumab is the first combination therapy incorporating a checkpoint inhibitor and a TKI for HCC, and showed significantly better overall survival (OS) and progression-free survival (PFS) than sorafenib for the treatment of unresectable HCC in a phase 3 trial, IMbrave150 [6]. However, this study was conducted in patients with no previous therapy [6], and there is no evidence that the same results can be achieved in patients who have already received treatment with TKIs. To examine this further, we conducted a multicenter observational study to determine the early outcomes and changes in liver reserve following treatment with atezolizumab plus bevacizumab in pretreated unresectable HCC. This study was approved by the ethics committee of Kyushu Cancer Center (2018-16) and was performed in compliance with the 1975 Declaration of Helsinki.

Methods

Patients

Two hundred twenty-nine patients who received TKI treatment for unresectable hepatocellular carcinoma at our hospital and related facilities from 2017 to November 2020 consented to this observational study (Iizuka Hospital, n = 68; Fukuoka City Hospital, n = 26; Fukuoka Higashi Medical Center, n = 14; Kyushu Cancer Center, n = 62; Kyushu Medical Center, n = 3; Kokura Medical Center, n = 16; Kyushu University Hospital, n = 16; Nakabaru Hospital, n = 1; Steel Memorial Yawata Hospital, n = 20; and Kyushu Rosai Hospital, n = 2). Twelve patients with advanced unresectable HCC previously treated with TKIs who received at least one TKI followed by atezolizumab plus bevacizumab between September 2020 and February 2021 were enrolled in this study. Clinical characteristics, prognostic factors associated with death or discontinuation of the combination of atezolizumab and bevacizumab, and treatment effects including PFS, tumor size, time to treatment failure, OS, adverse events, and tumor size were retrospectively analyzed. HCC from hepatitis B surface antigen-susceptible patients was diagnosed as hepatitis B virus-derived HCC and that from hepatitis C virus antibody-positive patients was diagnosed as hepatitis C-derived liver cancer.

Liver reserve assessment

Liver reserve was assessed using Child–Pugh scores [7] and albumin-bilirubin (ALBI) grade, the latter of which is calculated using albumin and bilirubin as follows [8]. [ALBI-score = (log10 bilirubin (μmol/L) × 0.66) + (albumin (g/L) × −0.085)]. ALBI grade is defined as follows: ≤−2.60, ALBI grade 1: >−2.60 to ≤ − 1.39, ALBI grade 2; and > − 1.39, ALBI grade 3. To further subdivide moderate liver damage, mALBI grades are classified as follows: ≤−2.60, ALBI grade 1; >−2.60 to ≤ − 2.270, ALBI grade 2a; >−2.270 to ≤ − 1.39, ALBI grade 2b; and > − 1.39, ALBI grade 3 [9, 10].

Diagnosis of HCC

HCC was diagnosed on the basis of dynamic computed tomography, magnetic resonance imaging, and/or pathological findings. Tumor node metastasis staging of liver cancer by the Liver Cancer Study Group of Japan (6th edition) [11] was used to evaluate tumor progression, in parallel with Barcelona Clinic Liver Cancer (BCLC) staging [12].

Determination of treatment efficacy

Antitumor efficacy was assessed using both the response evaluation criteria in solid tumors (RECIST) [13] and modified RECIST [14] (mRECIST). Four-phase (i.e., unenhanced, late arterial, portal, and equilibrium) contrast-enhanced computed tomography studies were performed at baseline and at every 3 to 9 weeks thereafter.

Adverse event assessment

Adverse events associated with atezolizumab plus bevacizumab treatment were determined on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The most serious grades of adverse events that occurred during the observation period were listed. When side effects occurred, appropriate therapeutic interventions such as discontinuation, dose reduction, and steroid administration were performed according to the guidelines for appropriate use [15].

Statistical analyses

Data are expressed as the mean and standard deviation. Statistical analyses were performed using Student's t-test, Fisher's exact test, Welch's t-test, Cox hazard analysis, the Kaplan–Meier method, and the log-rank test. A p-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using JMP Pro version 15.1.0 (SAS Institute Inc., Cary, NC, USA). Graphs were created using Prism version 9.1.0 (GraphPad Software, San Diego, CA, USA).

Results

Twelve patients were enrolled in this study. All patients are shown in Table 1.

Case	Age	Sex	BCLC	Treatment line	Previous treatment	mALBI Grade	Child–Pugh	Etiology	Time from initial TKI (months)
1	75	M	C	4	Reg	G2a	5	NASH	26
2	86	M	B	2	Len (with -drawal)	G2b	6	NASH	16
3	64	M	C	6	Len	G2b	7	NASH	24
4	74	M	C	5	Ram	G2b	6	NASH	22
5	66	F	C	3	Len	G2b	6	C	38
6	45	M	C	4	Reg	G1	5	B	19
7	76	F	C	3	Ram	G2a	5	NASH	15
8	66	M	B	4	Len	G2b	6	B	39
9	67	F	B	2	Len	G3	8	B	9
10	80	M	B	4	Reg	G2b	6	C	19
11	71	M	C	2	Len	G2a	5	ASH	10
12	73	M	C	3	Sor	G2a	5	ASH	12

The Child–Pugh score was Child–Pugh A in all patients in IMbrave150, but two patients with Child–Pugh B (7 and 8 points) were included in this study, reflecting real clinical practice. The median treatment line was 3.5 and ranged from second line to sixth line. The tumor status was BCLC B in four cases and BCLC C in eight cases. There was no significant change in ALBI grade during the treatment period from the start to the third course (week 9), and there was no deterioration in ALBI grade (Fig. 1).

Tumor size changes are shown in spider plots in Fig. 2a,2b.

One out of 12 patients had a partial response, two had no change, and four had tumor growth. Three patients had a partial response, six had stable disease, and three had progressive disease according to mRECIST (Table 2).

Cases	n = 12
Age	72 (45–86)
Gender (M / F)	10 (83%) / 2 (17%)
BCLC B / C	4 (33%) / 8 (66%)
up-to7 in /out	1 (25%) / 3 (75%)
Treatment line (2/3/4/5/6)	3 (25%) / 3 (25%) / 4 (33%) / 1 (8%) / 1 (8%)
mALBI grade (1/2a/2b/3)	1 (8%) / 4 (33%) / 6 (50%) / 1 (8%)
Child –Pugh (5/6/7/8) (score)	5 (42%) / 5 (42%) / 1 (8%) / 1 (8%)
Etiology (HBV HCV/NASH/ASH)	3 (25%) / 2 (17%) / 5 (42%) / 2 (17%)
Time from initial TKI (Month)	19 (9–39)

Among the eight cases in which we were able to measure the pretreatment growth rate and compare it with the post-treatment rate, one case had a tumor disappearance rate greater than or equal to two, which met the definition of hyperprogression [16]. In this case, the tumor markers decreased during the treatment, and the tumor began to shrink after further treatment (case 8; Fig.3a).

The change in tumor size in the early phase after the start of treatment varied considerably from case to case. In one case, there was a marked reduction in tumor size and the appearance of ascites immediately after the first course of treatment, but the tumor grew again immediately after the second course of treatment (Fig.3b).

The median PFS was 2.7 months, which was shorter than that in the IMbrave150 trial. In one case, the tumor was extremely large (28 cm) from the outset and rapidly grew before treatment, rupturing on day 7 of treatment (case 9). Analysis of spider plots by pretreatment showed that the treatment effect of atezolizumab plus bevacizumab tended to differ for each pretreatment (Fig.4a.b.c.d).

In the case of atezolizumab plus bevacizumab after treatment with lenvatinib, there was a rapid increase in tumor size followed by a decrease. However, for atezolizumab plus bevacizumab after treatment with regorafenib and sorafenib, all cases were almost SD. In patients with atezolizumab plus bevacizumab after treatment with ramucirumab, there was a rapid decrease in tumor size followed by an increase.

Treatment-related side effects were observed in many patients (Table 3).

n(%)	IMbrave150 (n=329)		LINKS (n=12)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hypertension	98 (29.8)	50 (15.2)	1 (8.3)	0
Fatigue	67 (20.4)	8 (2.4)	0	0
Proteinuria	66 (20.1)	10 (3.0)	4 (33.3)	3 (25)
AST increase	64 (19.5)	23(7.0)	2 (16.6)	2 (16.6)
Pruritus	64 (19.5)	0	0	
Diarrhea	62 (18.8)	6 (1.8)	0	0
Decreased appetite	58 (17.6)	4 (1.2)	0	0
Pyrexia	59 (17.9)	4 (1.2)	2 (16.6)	0
A□T increase	46 (16.0)	12 (3.6)	2 (16.6)	0
Constipation	44 (13.4)	0	0	
Blood bilirubin increase	43 (13.1)	8 (2.4)	4 (33.3)	2 (16.6)
Rash	41 (12.5)	0	0	
Abdominal pain	40 (12.2)	4 (1.2)	1 (8.3)	0
Weight decrease	37 (11.2)	8 (2.4)	0	
Asthenia	22 (6.7)	1 (0.3)	1 (8.3)	0
Infusion reaction	37 (11.2)	8 (2.4)	0	0
HFS	3 (0.9)	0	1 (8.3)	0
HCC Rupture	-	-	2 (16.6)	2 (16.6)
Hepatic encephalopathy	-	-	1 (8.3)	1 (8.3)
Ascites	-	-	2 (16.6)	2 (16.6)
Steven Johnson Syndrome	-	-	1 (8.3)	1 (8.3)

Compared with the IMbrave150 study without prior treatment, there were fewer side effects commonly seen with TKIs in general, such as fatigue, hypertension, anorexia, and abdominal pain. Conversely, the most common side effects, or those that were not observed in IMbrave150 but appeared in this study, were symptoms associated with liver function and liver cancer progression, such as ascites, encephalopathy, liver cancer rupture, and elevated bilirubin. Two patients who had large tumors before treatment initiation had HCC rupture immediately after treatment and at 5.5 months. Five out of 12 patients had their treatment discontinued. The reasons for discontinuation were progressive disease in

one case, liver cancer rupture in two cases, ascites jaundice in one case, and Stevens–Johnson syndrome in one case.

Discussion

Sorafenib, lenvatinib, regorafenib, ramucirumab, and cabozantinib [1–5] have been approved as molecular targeted therapy for unresectable advanced HCC. These inhibitors have considerably prolonged the prognosis of advanced HCC, and appropriate sequential treatment methods are being explored. Atezolizumab plus bevacizumab is the first combination therapy comprising an immune checkpoint inhibitor and a molecular targeted drug to show superiority over sorafenib [6] in terms of OS and PFS in the IMbrave150 trial. However, this study was conducted in patients who had not received prior therapy. Many patients with HCC are treated with TKIs, and there is no evidence that the same efficacy and safety of this regimen can be demonstrated in such patients. In this study, we retrospectively evaluated 12 patients treated with atezolizumab plus bevacizumab for advanced HCC who had previously been treated with TKIs. Both efficacy and PFS were not as good as that reported in the IMbrave150 trial, suggesting that the efficacy of second-line treatment may be worse than that of first-line treatment. In recent years, the concept of hyperprogression associated with immuno-oncology therapy has been proposed [16, 17]. In the present case, one case out of 12 met the definition of hyperprogression [18] at the first imaging examination within 3 months after the start of immuno-oncology therapy. There was also one case that did not meet the definition of hyperprogression but became progressive disease at an extremely early stage. In both cases, the treatment immediately before the switch was lenvatinib. Both patients continued treatment because their tumor markers had decreased and their side effects were mild. As a result, the tumors in both cases began to shrink at the time of imaging studies 1 or 2 months later.

TKIs have different inhibitory effects, with lenvatinib exhibiting strong antitumor activity by specifically inhibiting fibroblast growth factor (FGF) receptor (FGFR), vascular endothelial growth factor (VEGF) receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), KIT, and RET [19]. In contrast, bevacizumab is a monoclonal antibody against VEGF and has no inhibitory effects on FGFR or PDGFR [20]. In the final analysis of the REFLECT study, serum FGF19 and FGF23 were increased after lenvatinib treatment [21]. Furthermore, in another study, FGF19 at week 4 and FGF23 at week 8 of HCC treatment with lenvatinib were highly elevated, and this was associated with treatment response [22]. It was also reported that FGF23 was elevated in thyroid cancer treated with lenvatinib, and this was associated with long-term treatment response [23]. Therefore, it has been suggested that the use of molecular targeted drugs that cannot suppress the FGF pathway after lenvatinib treatment may have poor antitumor effects. In addition, there are reports of poor real-world outcomes of ramucirumab after lenvatinib treatment compared with trials conducted after sorafenib treatment, and poor outcomes of sorafenib after lenvatinib in terms of both OS and PFS [24, 25]. This transient acute exacerbation may be a response to the discontinuation of lenvatinib. Hyperprogression caused by immune checkpoint inhibitors (ICIs) has been reported in many cases and its pathogenesis is not clear, but it has been linked to tumor-associated macrophage reprogramming following treatment of non-small cell lung cancer with ICIs [26].

Hyperprogression is associated with extremely poor prognosis and rapid death [16–18, 26, 27]. However, these incidences were all caused by ICI monotherapy or ICI combination therapy, and none of them resulted from treatment with an ICI plus a TKI. It is possible that this is not reflective of true hyperprogression, considering that it takes a certain period for the effect of ICIs to appear. We believe that the judgment of treatment efficacy should be made carefully when atezolizumab plus bevacizumab treatment is administered after second-line treatment. However, there also are cases of rapid growth, and caution should be exercised when the tumor is too large, as in case 9. Liver reserve improved with drug withdrawal, although there were cases of temporary deterioration. After improvement, the reserve was maintained, and it was thought that safe treatment was possible even after second-line treatment.

There were many side effects that differed from those that occurred during the first-line treatment. The relatively low incidence of side effects such as hypertension and fatigue was likely due to the fact that the side effects had already been controlled by previous TKI treatment. However, side effects related to liver reserve, such as ascites and hepatic encephalopathy, which were not observed in the IMbrave150 study, were relatively common, and in some cases, ascites jaundice appeared after the start of treatment even though the Child–Pugh score at the start of atezolizumab plus bevacizumab was 5 points. All patients with a history of urinary protein or ascites during their previous treatment relapsed. It is known that liver reserve gradually declines with TKI treatment [28]. In these cases, even though the liver reserve seemed to have improved at the start of atezolizumab plus bevacizumab treatment, it is possible that the reserve had declined.

This study has some limitations, including its retrospective nature. In addition, the number of cases analyzed was too few to obtain concrete conclusions. In addition, the observation period was short, and thus the long-term prognosis and side effects are not yet known. Nevertheless, this study suggests that the treatment course of atezolizumab plus bevacizumab therapy in the second and subsequent lines may differ from that in the first line.

Conclusions

We reported our initial experience with atezolizumab plus bevacizumab therapy for HCC after TKI treatment. The therapeutic effects and side effects differed from those previously reported during the course of atezolizumab plus bevacizumab as first-line therapy.

Abbreviations

ALBI: albumin-bilirubin

BCLC: Barcelona Clinic Liver Cancer

FGF: fibroblast growth factor

FGFR: fibroblast growth factor receptor

HCC: hepatocellular carcinoma

ICI: immune checkpoint inhibitor

OS: overall survival

PDGFR: platelet-derived growth factor receptor

PFS: progression-free survival

RECIST: response evaluation criteria in solid tumors

TKI: tyrosine kinase inhibitors

VEGF: vascular endothelial growth factor

VEGFR: vascular endothelial growth factor receptor

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Kyushu Cancer Center (2018-16) and was performed in compliance with the 1975 Declaration of Helsinki. Written and verbal informed consent was obtained from all the patients.

Consent for publication

Written informed consent was obtained from all subjects for publication of this study and accompanying images. A copy of written consent is available for review upon request.

Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

RS and KM declares that he has competing interests with Eisai Co. The other authors declare that they have no competing interests.

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Authors' contributions

RS participated in the design of this study, measured and analyzed RECIST and mRECIST, performed the formal analysis, and drafted the manuscript. TS and AU participated in the data curation and review. TS and YT participated in the conceptualization and data curation. SY, TK, TK, NH, TN, MT, AO, KU, MK, ST, and YA participated in the data curation. KM and MK participated in the conceptualization and review.

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Figures

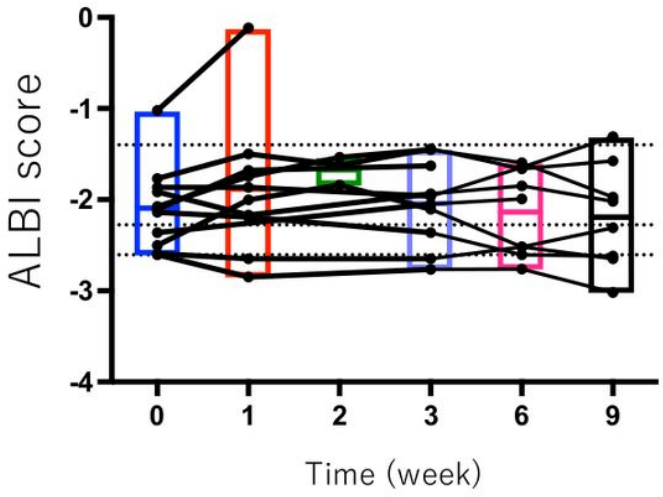

Figure 1

Changes in ALBI grade from the start of treatment to week 9.

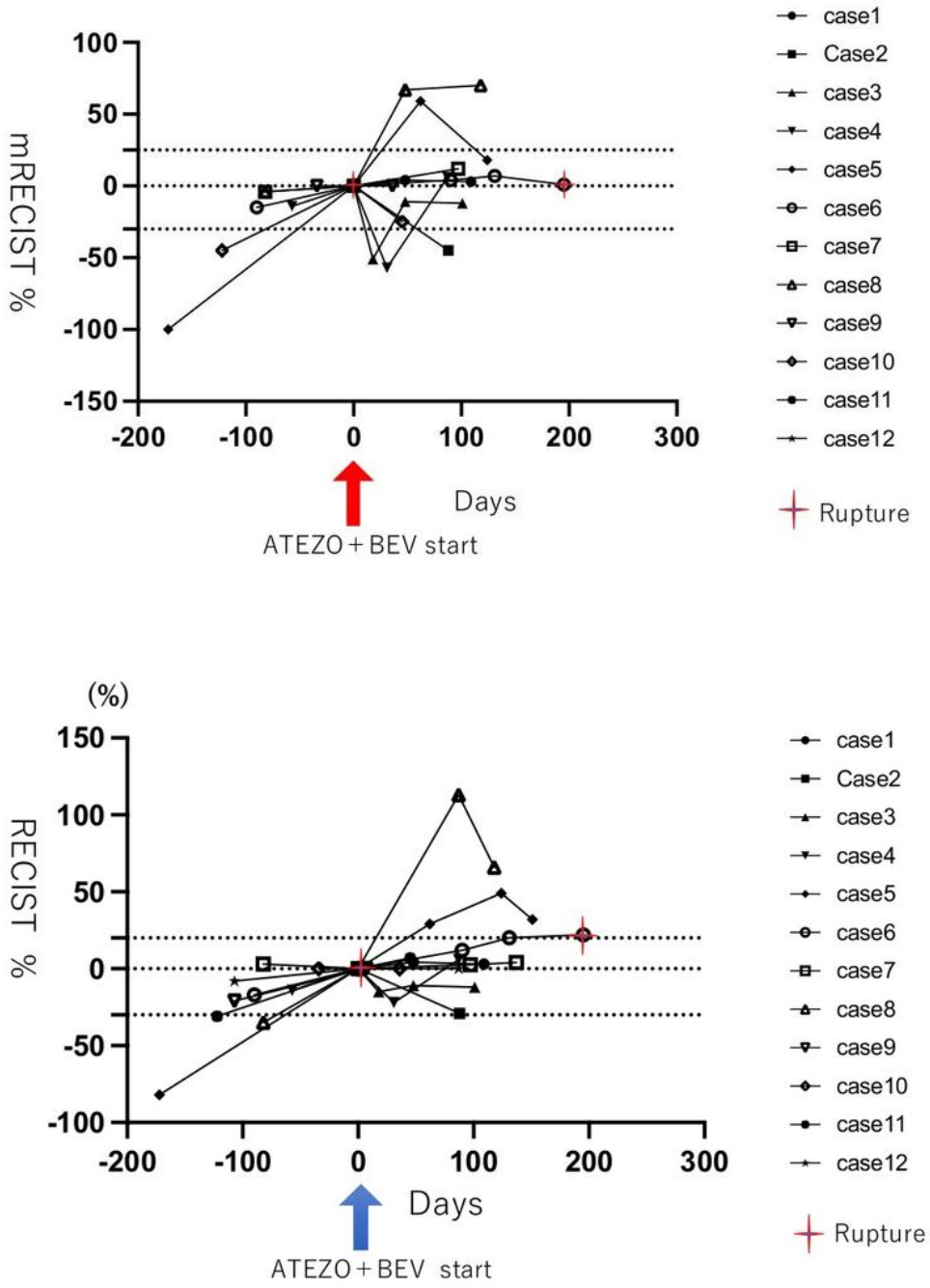

Figure 2

Changes in tumor size from pretreatment to start of treatment and after start of treatment. a. RECIST. b. mRECIST.

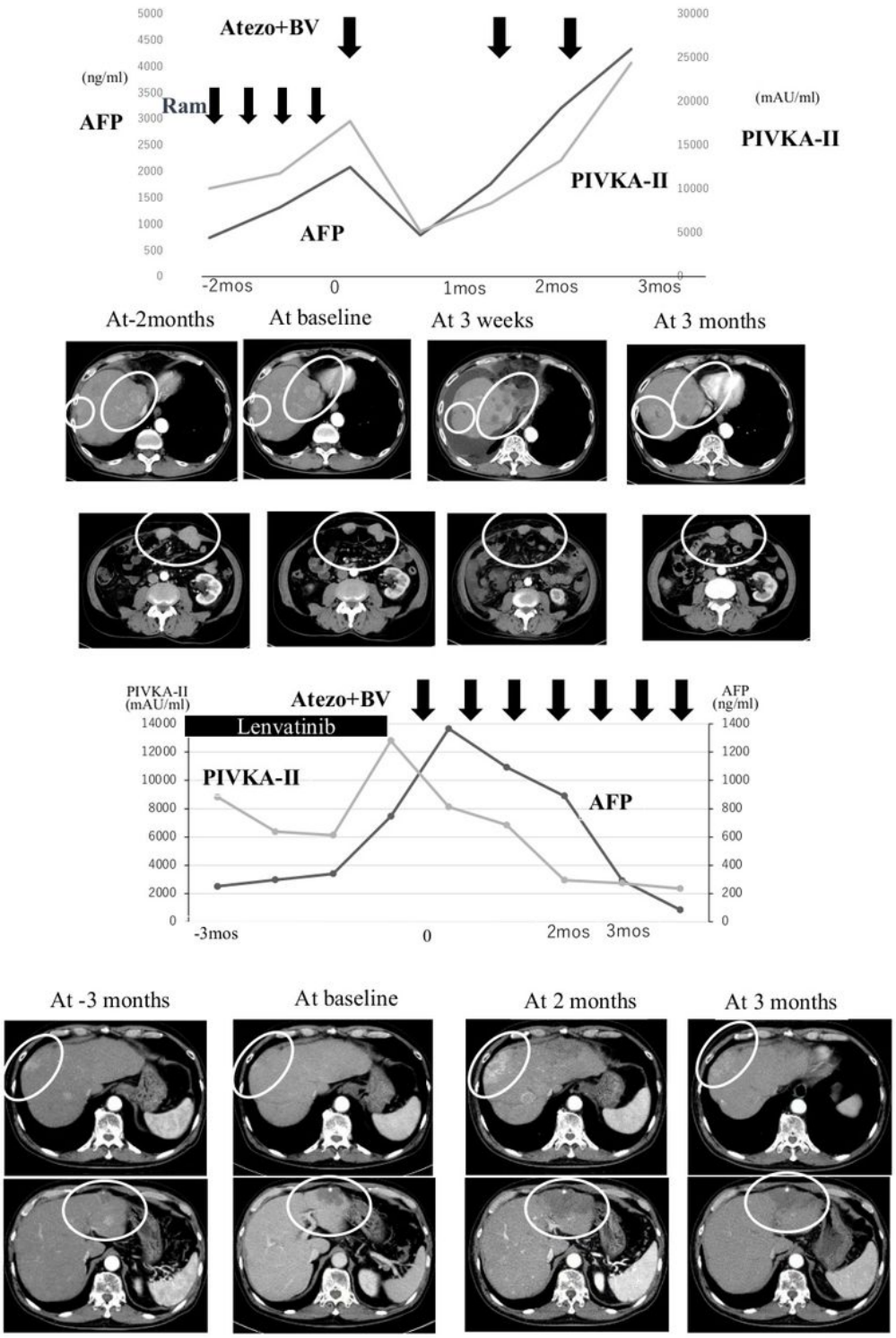

Figure 3

Contrast-enhanced CT images and tumor markers in characteristic cases according to previous treatment (AFP, PIVKA-II). a. Case 8. Pretreatment was lenvatinib. The tumor markers decreased after the start of treatment, but tumor size according to both RECIST and mRECIST was increased. However, the size decreased with continued treatment. b. Case 7. Pretreatment was ramucirumab. Early after the start of treatment, tumor size according to both RECIST and mRECIST was decreased and tumor markers were

also decreased, but liver atrophy occurred and ascites appeared. The patient improved after one course of withdrawal, but tumor markers and tumor size then both increased.

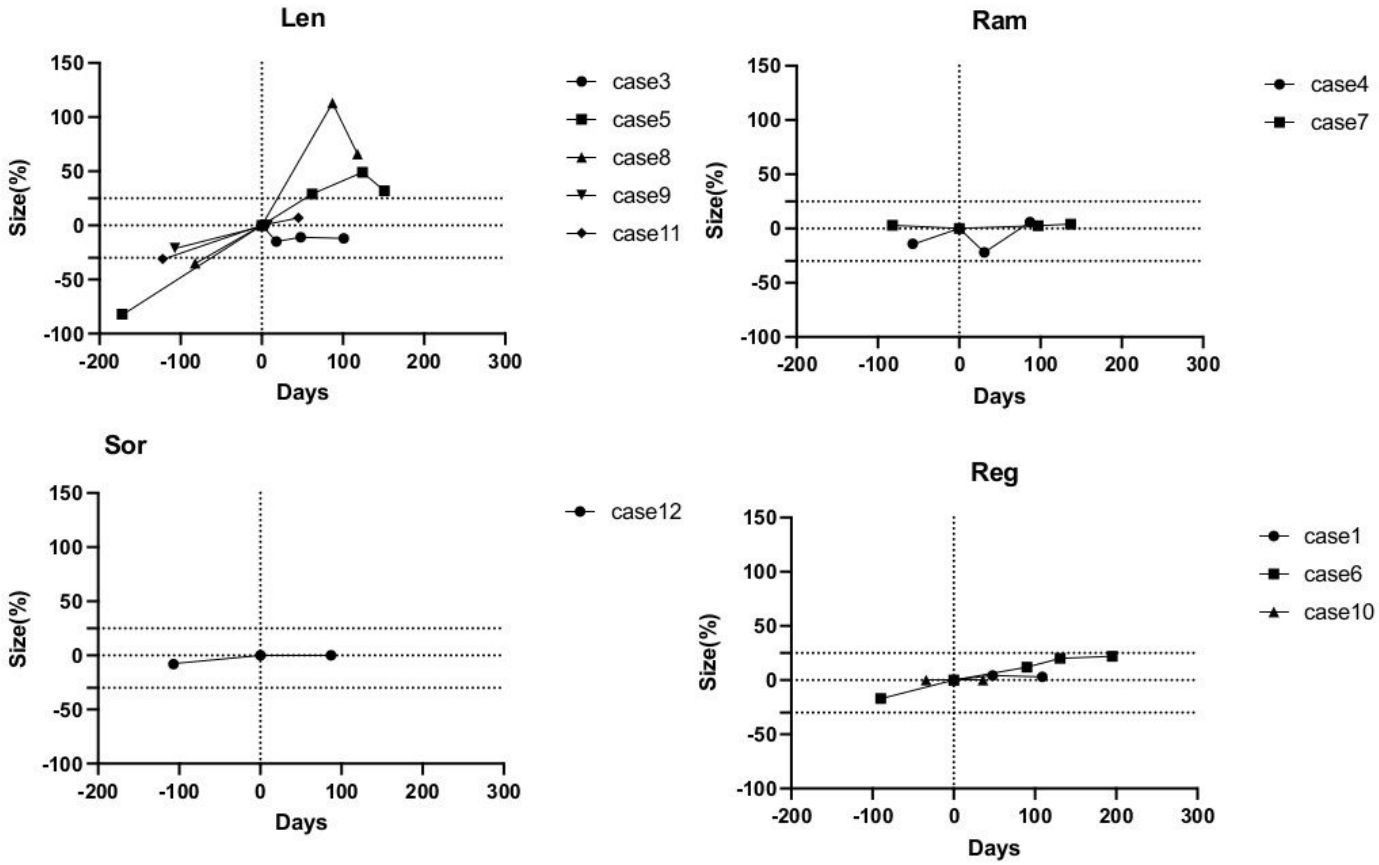

Figure 4

Changes in tumor size from pretreatment to during and after commencement of each previous treatment. a. Lenvatinib. b. Ramucirumab. c. Sorafenib. d. Regorafenib.