Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9701-22
Intern Med 62: 539-543, 2023
http://internmed.jp

【 CASE REPORT 】

Hepatocellular Carcinoma Pseudoprogression Involving the Main Portal Vein, Right Ventricular Invasion, and Exacerbation of Lung Metastases in a Patient on Atezolizumab Plus Bevacizumab

Ryuta Shigefuku, Kyoko Yoshikawa, Mone Tsukimoto, Hirono Owa, Yasuyuki Tamai, Masahiko Tameda, Suguru Ogura, Ryosuke Sugimoto, Hideaki Tanaka, Akiko Eguchi, Kazushi Sugimoto, Hiroshi Hasegawa, Motoh Iwasa and Hayato Nakagawa

Abstract:

A 70-year-old man was diagnosed with hepatocellular carcinoma (HCC) with portal vein invasion and lung metastases, for which atezolizumab plus bevacizumab (ATZ/BEV) was initiated. After two months, computed tomography revealed tumor growth accompanied by ascites, right ventricular invasion, exacerbation of the lung metastases, and main portal vein invasion. However, continuation of ATZ/BEV caused remarkable size reductions in all lesions, finally resulting in the disappearance of the vascular invasion and lung metastases after nine cycles of treatment. The tumor growth was considered to reflect pseudoprogression, which is difficult to distinguish from hyperprogression. We herein report a remarkable HCC case of pseudoprogression on ATZ/BEV.

Key words: hepatocellular carcinoma, atezolizumab plus bevacizumab, pseudoprogression, case report

(Intern Med 62: 539-543, 2023)
(DOI: 10.2169/internalmedicine.9701-22)

Introduction

Immune checkpoint inhibitors (ICIs) are being used increasingly frequently to treat several types of cancer, and they are effective against hepatocellular carcinoma (HCC). The IMbrave150 trial showed that atezolizumab plus bevacizumab notably increased the progression-free and overall survival (compared with sorafenib) in patients with advanced metastatic or unresectable HCC (1). Thereafter, the first-line systemic therapy for advanced HCC shifted from tyrosine kinase inhibitors (such as sorafenib and lenvatinib) to atezolizumab plus bevacizumab (2).

Unlike conventional anticancer drugs, ICIs may be associated with atypical responses, including pseudoprogression (where the tumor shrinks only after transient growth or the appearance of a new lesion) (3). Pseudoprogression is thought to be caused by infiltration of immune cells as a response to the immunotherapy. (3)

We herein report an impressive case of pseudoprogression (multiple lung metastases and portal and right hepatic vein invasion) followed by a dramatic response to atezolizumab plus bevacizumab in an HCC patient.

Case Report

A 70-year-old Japanese man was referred to our hospital with a liver segment 7 tumor and multiple lung metastases diagnosed by dynamic computed tomography (CT) and magnetic resonance imaging (MRI). His history included liver cirrhosis-related hepatitis virus C (HCV) infection, diabetes mellitus, and hypertension. He had taken repaglinide, empagliflozin, alogliptin, metformin hydrochloride and telmisartan amlodipine besilate. He was a social drinker. The HCV had not yet been eradicated, and the serum HCV-RNA level was 6.7 LogIU/mL. His body height was 162 cm, and

Department of Gastroenterology and Hepatology, Mie University Graduate School of Medicine, Japan
Received: March 3, 2022; Accepted: May 9, 2022; Advance Publication by J-STAGE: June 21, 2022
Correspondence to Dr. Hayato Nakagawa, nakagawah@med.mie-u.ac.jp

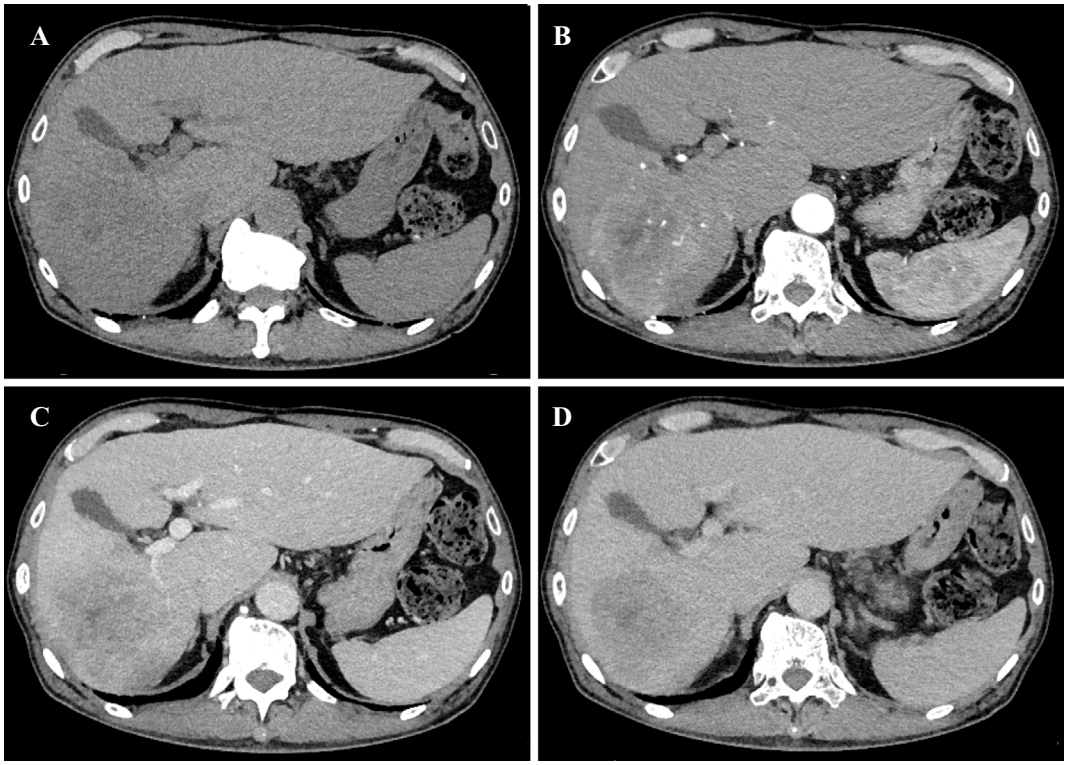

Figure 1. **Dynamic CT findings of the liver tumor. Plain CT revealed (A) a low-density tumor (75 mm in diameter) in segment 7 of the liver. The tumor was (B) enhanced in the arterial phase and (C and D) washed out in the portal and equilibrium phases. CT: computed tomography**

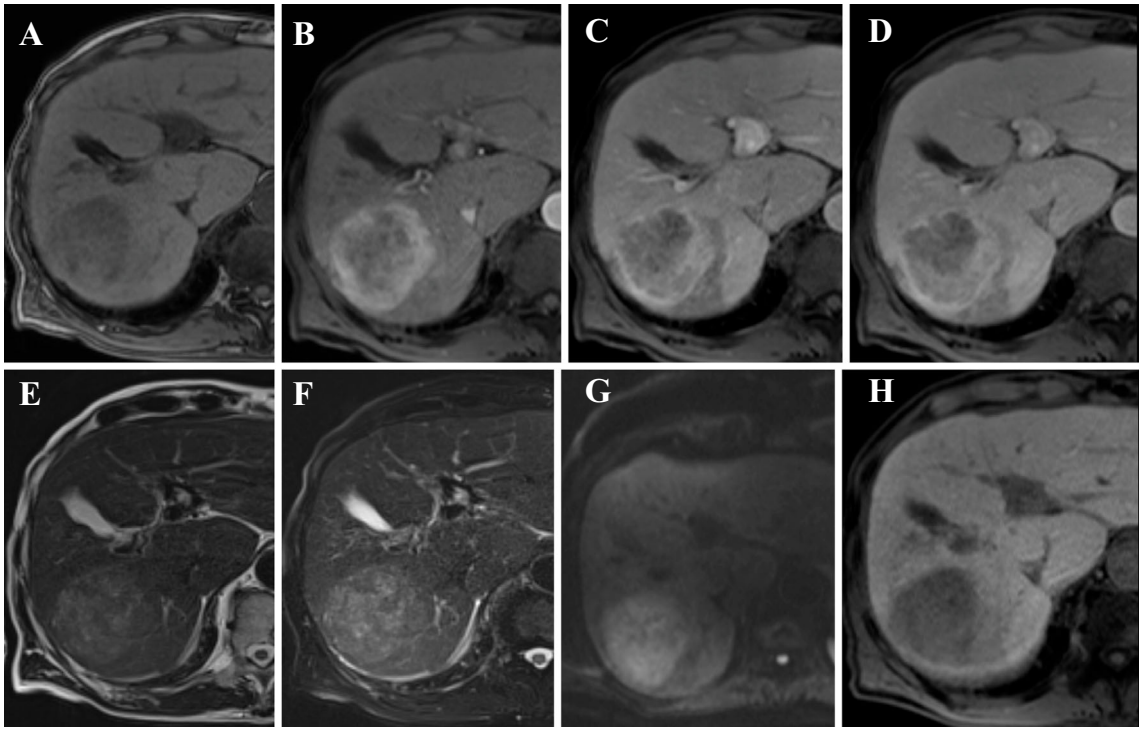

Figure 2. **MRI findings of the liver tumor. MRI contrasted with Gd-EOB-DTPA shows the tumor in the posterior lobe [T1-weighted imaging (A), arterial phase (B), portal phase (C), delayed phase (D), T2-weighted imaging (T2WI) (E), fat suppression image (F), diffusion-weighted imaging (DWI) (G) and hepatobiliary phase (H)]. The tumor was enhanced in the arterial phase (B) and washed out in the portal venous (C) and delayed phases (D). The tumor showed high intensity in T2WI (E) and DWI (G) and low intensity in the hepatobiliary phase (H). MRI: magnetic resonance imaging, Gd-EOB-DTPA: gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid**

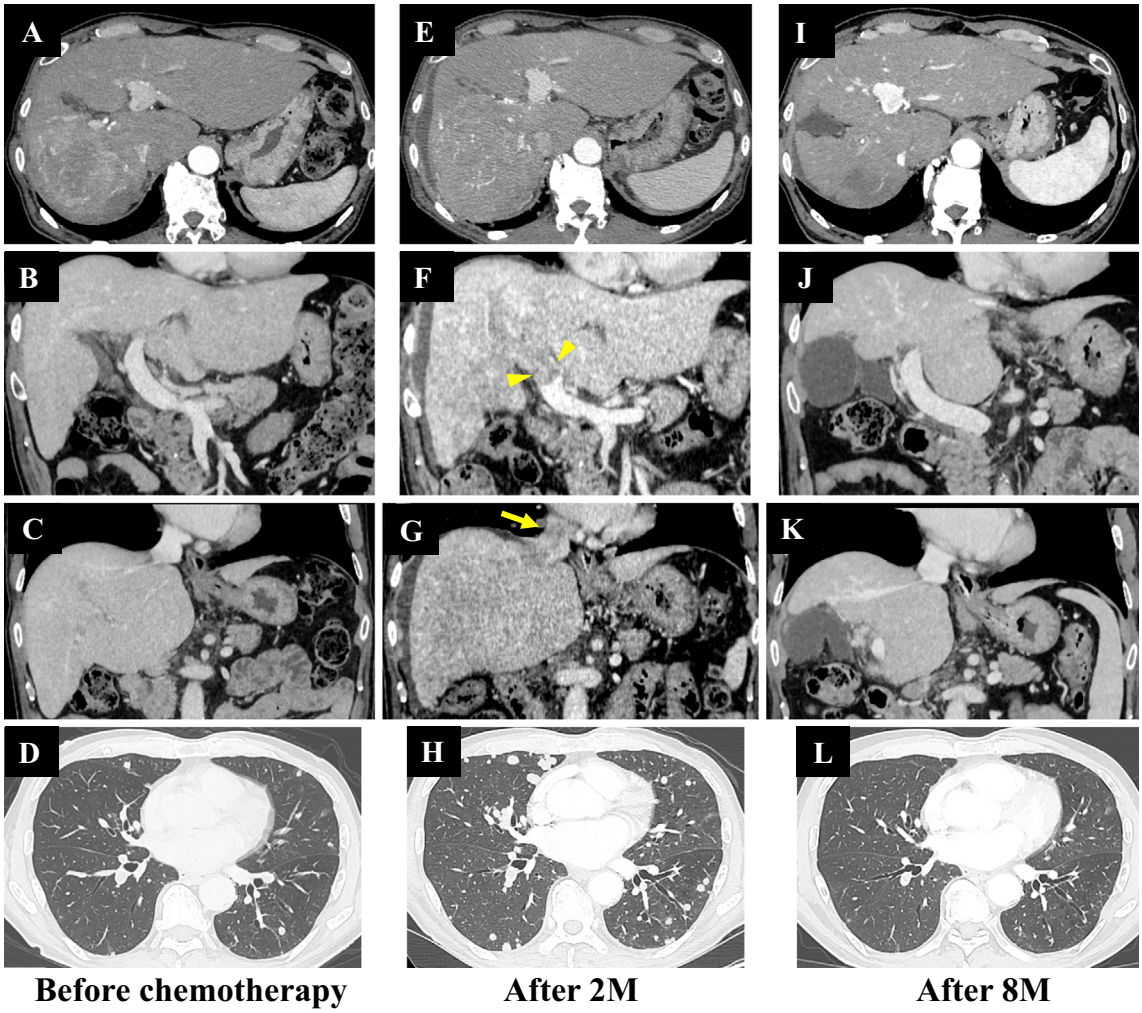

Figure 3. **CT findings over the course of treatment with atezolizumab plus bevacizumab. Dynamic CT findings before chemotherapy. (A) Liver tumor in the posterior segment. (B) Portal invasion (Vp2). (C) Right hepatic vein invasion (Vv2). (D) Multiple lung metastases. Dynamic CT findings after two months (after the second course was completed). (E) Liver tumor growth in the posterior segment and the appearance of ascites. (F) Main portal vein invasion (Vp4) (arrowhead). (G) Right ventricular invasion via the right hepatic vein (arrow). (H) Increased number of lung metastases. Dynamic CT findings after eight months (after the ninth course was complete). (I) Reduced tumor size in the posterior segment and the disappearance of ascites. (J) Disappearance of the main portal vein invasion. (K) Disappearance of the right ventricular invasion. (L) Disappearance of the multiple lung metastases. CT: computed tomography**

his body weight was 57 kg. The serum albumin level was 4.0 g/dL, the total bilirubin level 0.6 mg/dL, the platelet count 16.3×10^4/μL, and the Child-Pugh grade A. The serum levels of α-fetoprotein and protein induced by the vitamin K absence/antagonist II (PIVKA II) were 8,416 ng/mL and 938 mAU/mL, respectively.

Dynamic abdominal CT revealed a round hypodense liver segment 7 tumor 75 mm in diameter that was palely enhanced in the arterial phase and washed out in the portal venous and delayed phases (Fig. 1). On gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI, the liver tumor was hypointense in the hepatobiliary phase of T1-weighted imaging (Fig. 2). Thus, the patient was diagnosed with classical HCC and multiple lung metastases, portal vein invasion (Vp2) and right hepatic vein invasion (Fig. 3A-D).

Atezolizumab (1,200 mg daily) plus bevacizumab (1.5 mg/kg) was initiated as the first-line treatment. CT performed after the second course of treatment revealed prominent growth of the posterior segment lesion, main portal vein tumor thrombus (Vp4), right ventricular invasion via the right hepatic vein, and multiple lung metastases (Fig. 3E-H). Furthermore, ascites was evident around the liver (Fig. 3E-G), and new lesions were found in the lungs, indicating progressive disease according to the Response Evaluation Criteria in Solid Tumors. A high alpha-fetoprotein level and a dramatic increase in the PIVKA II level were also observed (Fig. 4). Although we considered a

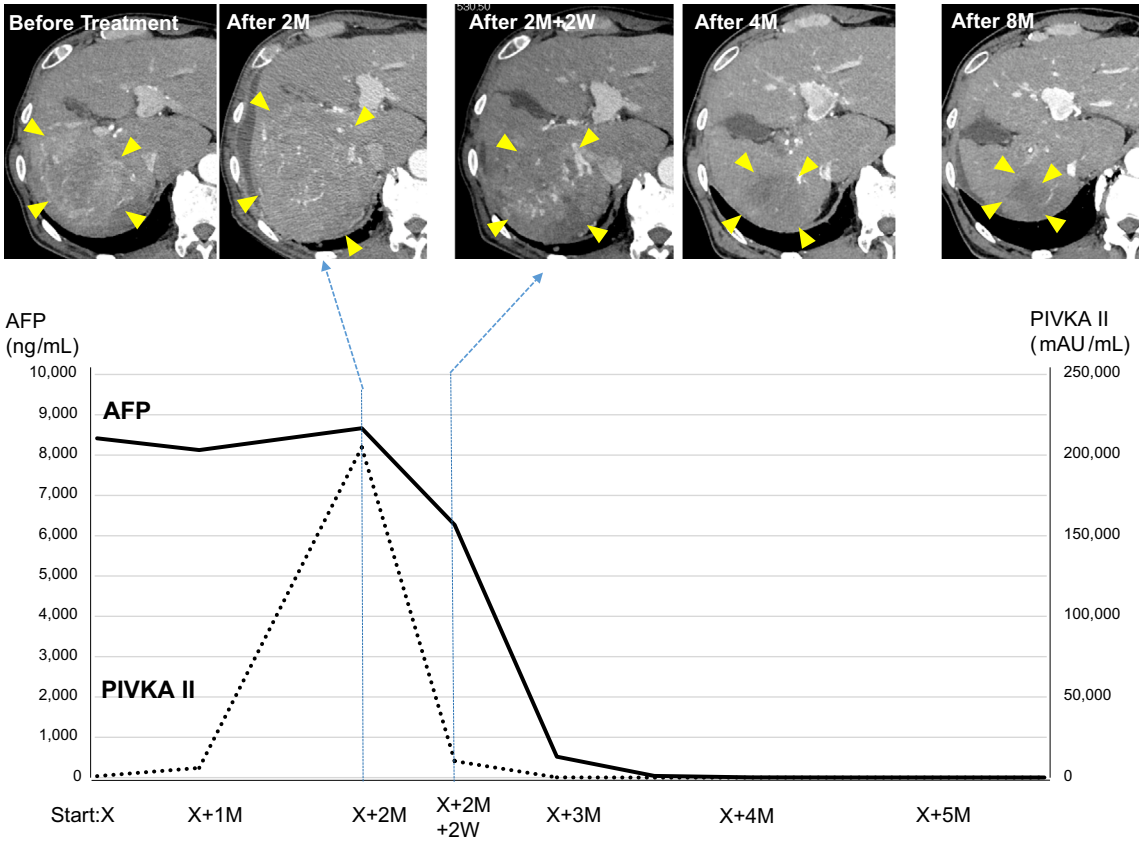

Figure 4. **Clinical course of treatment with atezolizumab plus bevacizumab. After the second course of atezolizumab plus bevacizumab, the PIVKA II level was elevated, and the HCC had grown in size. Although a change in treatment was considered, the PIVKA II level and liver tumor size decreased after two weeks, so the initial treatment was continued. After eight months of atezolizumab plus bevacizumab, CT revealed tumor shrinkage.**

change from atezolizumab plus bevacizumab to lenvatinib at this time, the dramatic reduction in the PIVKA II level and modest reduction in the AFP level over the following two weeks (Fig. 4) prompted to us continue the original treatment despite the (apparent) progressive disease.

CT revealed gradual decreases in the diameters of the main tumor and the metastatic lesions, and the main portal vein tumor thrombus, right ventricular invasion and metastatic lung tumors all disappeared after nine cycles of treatment (Fig. 3I-L). The main hepatic tumor shrank markedly, now presenting as a small hypovascular lesion (Fig. 4). The patient remains on atezolizumab plus bevacizumab and has not experienced any major adverse events.

Discussion

ICI anticancer agents exert antitumor effects by modulating the immune function and offer unique advantages in terms of both efficacy and side effects. Conventional anticancer drugs are deemed ineffective when the tumor grows to a certain extent, but ICIs may trigger "pseudoprogression" (where a tumor grows before it shrinks) in patients with various cancers (4). A systematic review and meta-analysis reported that the overall incidence of pseudoprogression was 6.0% in clinical trials of cancer patients on ICIs (5). However, HCC pseudoprogression is rare (6); indeed, to our knowledge, there have only been two previous reports (7, 8).

This is the first report of pseudoprogression of an HCC accompanied by main portal vein and right ventricular invasion followed by a dramatic response in a patient on atezolizumab plus bevacizumab. The tumor progression occurred very early, and we initially diagnosed the patient with hyperprogressive disease. However, frequent tumor marker tests and CT yielded the correct diagnosis of pseudoprogression. Of note, hyperprogressive disease (i.e. tumor growth acceleration on ICI treatment) was observed in 9 of 88 HCC patients (10.2%) on atezolizumab plus bevacizumab and was associated with a significantly reduced overall survival (median 4.3 months vs. not reached; $p<0.001$) (9). In clinical practice, it is difficult to distinguish between true progression and pseudoprogression using only one instance of diagnostic imaging. If an error is made, effective ICI treatment may be discontinued, compromising the prognosis. As ICIs are well-tolerated and not highly toxic, Oxnard et al. recommended continuous immunotherapy for patients exhibiting locally progressive disease, asymptomatic patients, and for patients with slow-growing tumors (10). Biomarkers that

distinguish true progression from pseudoprogression are urgently needed. Although the usefulness of the neutrophil-to-lymphocyte ratio and circulating tumor DNA has been reported in lung cancer (11), there have been no reports of serum markers in HCC. This case suggests that the frequent evaluation of tumor markers, AFP and PIVKA II, may aid in distinguishing between true progression and pseudoprogression.

The responses to immunotherapy were recently reported to be better in patients with hepatitis B virus- or HCV-induced HCC than in those with non-viral HCC (12). This is considered to reflect a difference in the hepatic immune microenvironment. Notably, although recent direct-acting antivirals have substantially improved HCV cure rates, HCV had not yet been eradicated in our patient. As HCV-induced activation of an intrahepatic immune response may contribute to anti-tumor immunity (13), active HCV infection might enhance the response to immunotherapy. Further studies are required.

The clinical features of pseudoprogression have been suggested to include no decline in the general condition or performance status despite tumor growth evident on imaging, no deterioration in tumor marker levels, and sustained infiltration of immune cells as revealed by a tissue biopsy (3, 14). However, no consensus has yet emerged. In our case, pseudoprogression was observed early (two months after initiation of treatment) and was associated with elevations in tumor marker levels. More cases are required to determine the characteristics of pseudoprogression after prescription of atezolizumab plus bevacizumab to treat HCC.

In conclusion, we encountered an impressive case of pseudoprogression in an HCC patient treated with atezolizumab plus bevacizumab; our findings are significant in terms of ICI treatment.

The authors state that they have no Conflict of Interest (COI).

References

1. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med **382**: 1894-1905, 2020.

2. Liu X, Lu Y, Qin S. Atezolizumab and bevacizumab for hepatocellular carcinoma: mechanism, pharmacokinetics and future treatment strategies. Future Oncol **17**: 2243-2256, 2021.

3. West HJ. JAMA oncology patient page. Immune checkpoint inhibitors. JAMA Oncol **1**: 115, 2015.

4. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med **375**: 1856-1867, 2016.

5. Park HJ, Kim KW, Pyo J, et al. Incidence of pseudoprogression during immune checkpoint inhibitor therapy for solid tumors: a systematic review and meta-analysis. Radiology **297**: 87-96, 2020.

6. Lee DH, Hwang S, Koh YH, et al. Outcome of initial progression during nivolumab treatment for hepatocellular carcinoma: should we use iRECIST? Front Med (Lausanne) **8**: 771887, 2021.

7. Watanabe Y, Ogawa M, Tamura Y, et al. A case of pseudoprogression in hepatocellular carcinoma treated with atezolizumab plus bevacizumab. J Investig Med High Impact Case Rep **9**: 23247096211058489, 2021.

8. Mamdani H, Wu H, O'Neil BH, et al. Excellent response to anti-PD-1 therapy in a patient with hepatocellular carcinoma: case report and review of literature. Discov Med **23**: 331-336, 2017.

9. Maesaka K, Sakamori R, Yamada R, et al. Hyperprogressive disease in patients with unresectable hepatocellular carcinoma receiving atezolizumab plus bevacizumab therapy. Hepatol Res **52**: 298-307, 2021.

10. Oxnard GR, Morris MJ, Hodi FS, et al. When progressive disease does not mean treatment failure: reconsidering the criteria for progression. J Natl Cancer Inst **104**: 1534-1541, 2012.

11. Zhou L, Zhang M, Li R, et al. Pseudoprogression and hyperprogression in lung cancer: a comprehensive review of literature. J Cancer Res Clin Oncol **146**: 3269-3279, 2020.

12. Pfister D, Nunez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature **592**: 450-456, 2021.

13. Llovet JM, Villanueva A. Liver cancer: effect of HCV clearance with direct-acting antiviral agents on HCC. Nat Rev Gastroenterol Hepatol **13**: 561-562, 2016.

14. Grierson P, Crites D, Ruzinova MB, et al. Distinct clinical and magnetic resonance features of metastatic hepatocellular carcinoma treated with pembrolizumab: a case report of late response after pseudoprogression. Hepatol Commun **2**: 148-151, 2018.