



Case Report

Remarkable Response to Immune Checkpoint Inhibitor Therapy in Advanced-Stage Hepatocellular Carcinoma: A Case Report

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Abstract

Advanced hepatocellular carcinoma (HCC) with extrahepatic metastases has a poor prognosis. Immune checkpoint inhibitors have recently become an important treatment option for certain types of cancer. A 58-year-old Kyrgyz male patient with a history of hepatitis B virus (HBV)-related liver cirrhosis for five years was referred to our hospital for liver transplant evaluation. However, a PET-CT (positron emission tomography-computed tomography) scan performed prior to evaluation revealed metastases in the lungs and lymph nodes in different parts of the body. Dynamic liver MRI (magnetic resonance imaging) was consistent with multicentric hepatocellular carcinoma (HCC). The patient had no history of variceal bleeding, hepatic encephalopathy, or ascites. Liver function tests were not elevated, and the baseline AFP (alpha-fetoprotein) level was 463 ng/mL, with a Child-Pugh score of 6 (A). Due to the presence of extrahepatic disease, the patient was not eligible for liver transplantation, and systemic treatment was planned. Systemic treatment was initiated with nivolumab 3 mg/kg + ipilimumab 1 mg/kg at 21-day intervals. These doses were started due to toxicity concerns. The first response evaluation showed an 80% reduction in intrahepatic disease burden and a marked reduction in the size and activity of other metastatic lesions. No side effects beyond grade 1 were observed in the patient. Thus, treatment was continued. In the second treatment response evaluation, although there was an increase in the metabolic activity of some extrahepatic lesions, the reduction in liver lesions was 50% less than the previous one. The patient's general condition was good, and he had no symptoms. The dual therapy started in July 2025 was continued in January 2026 with nivolumab 240 mg every two weeks. This case highlights an extraordinary response to dual immune checkpoint inhibition in metastatic HCC and demonstrates the potential of immunotherapy without compromising efficacy, with some dose adjustments to account for toxicity in selected patients with advanced disease.

Keywords: Case report, Hepatocellular carcinoma, Immunotherapy, Ipilimumab, Nivolumab

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The most common form of primary liver cancer is hepatocellular carcinoma (HCC), which accounts for 90% of primary liver cancer cases. HCC is the sixth most common form of cancer diagnosed worldwide and the third leading cause of cancer-related mortality. Liver cancer can also present as cholangiocarcinoma, which is a form of cancer that occurs in the bile duct.^[1] HCC predominantly affects individuals with pre-existing underlying conditions of chronic liver diseases and cirrhosis. Furthermore, the incidence of HCC is considerably higher in males compared to females. There are several risk factors that are considered critical in the development of hepatocellular carcinoma. These include viral infections, metabolic syndrome, toxic substances, and immune-related disorders. In addition, hepatocellular carcinoma is also resistant to chemotherapy and radiotherapy. The Barcelona Clinic Liver Cancer (BCLC) classification is universally accepted and used for the staging and management of HCC. Based on this algorithm, curative therapies such as surgical resection, local ablation, and liver transplantation are the first choice for the treatment of early-stage HCC. For the treatment of advanced-stage HCC, locoregional therapies such as radiofrequency ablation and transarterial chemoembolization are the first choice. For those who cannot be treated with locoregional therapies, systemic therapies are recommended. Finally, for the treatment of terminal-stage HCC, the best supportive care is recommended.^[2]

Until 2008, there was no systemic therapy that demonstrated a clear overall survival benefit in advanced hepatocellular carcinoma (HCC). The multi-target tyrosine kinase inhibitor sorafenib was the first systemic agent to show a survival advantage in patients with advanced HCC in randomized phase III trials, leading to its approval for use in this setting. Subsequently, in 2018, another tyrosine kinase inhibitor, lenvatinib, was demonstrated in the phase III REFLECT trial to be non-inferior to sorafenib for overall survival in first-line treatment of unresectable HCC, thereby establishing lenvatinib as another first-line systemic therapy option.^[3] Until the advent of these immune checkpoint inhibitor-based therapies, the median overall survival (OS) with first-line systemic therapies for advanced hepatocellular carcinoma (HCC) was generally in the range of 12-14 months with tyrosine kinase inhibitors. With the advent of these immunotherapy-based combinations, significant improvements in survival were demonstrated. In 2020, the combination of atezolizumab and bevacizumab was approved as a first-line therapy for unresectable HCC, showing that median OS can be extended up to 19.2 months with these therapies, as demonstrated in clinical trials, compared with previous therapies. In 2022, the combination of tremelimumab and durvalumab was approved as a first-line therapy for unre-

sectable HCC, showing that median OS can be extended up to 16.4 months with these therapies, as demonstrated in clinical trials, compared with previous therapies. These immunotherapy-based combinations have been established as first-line therapy options with median OS ranging from 16-19 months.^[4,5]

Nivolumab, a PD-1 inhibitor, in combination with CTLA-4 inhibitor ipilimumab, has demonstrated a significant OS advantage over lenvatinib or sorafenib in unresectable HCC in previously untreated patients. Moreover, this drug combination has demonstrated one of the best results in terms of ORR in this patient population, as demonstrated in the phase III CheckMate-9DW clinical trial, where the nivolumab + ipilimumab regimen demonstrated a median OS of 23.7 months compared with 20.6 months with lenvatinib or sorafenib, along with an ORR of 36% compared with 13% with tyrosine kinase inhibitors.^[6] The nivolumab + ipilimumab regimen has been approved by the Food and Drug Administration (FDA) as a first-line therapy for adult patients with unresectable or metastatic hepatocellular carcinoma and has been increasingly used as a new standard of care for this patient population.

Case Report

A 58-year-old male patient of Kyrgyz origin was referred to our center for evaluation for liver transplantation. The patient had been followed at an outside institution for the past five years due to hepatitis B virus (HBV)-related chronic liver disease. Dynamic contrast-enhanced computed tomography (CT) of the liver demonstrated lobulated hepatic contours consistent with chronic liver disease. Multiple space-occupying lesions compatible with hepatocellular carcinoma (HCC) were observed, the largest measuring up to 12.5 cm in diameter and almost completely occupying the right hepatic lobe. These lesions showed arterial phase hyperenhancement with venous phase washout and contained cystic and necrotic components.

¹⁸F-FDG PET-CT revealed multiple metabolically active metastatic lymph nodes predominantly in the perihepatic and intra-abdominal regions, including the costophrenic angle and midclavicular line, as well as contrast-enhancing lesions in the lungs consistent with metastatic disease. Given the extent of the disease, the patient was not considered suitable for local ablative therapies or liver transplantation. As the radiological findings were typical for HCC, histopathological confirmation was not deemed necessary.

Baseline laboratory evaluation revealed an alpha-fetoprotein (AFP) level of 463 ng/mL. HBV DNA level was 21,395 copies/mL. Other laboratory parameters were as follows: total bilirubin 1.5 mg/dL, direct bilirubin 0.43 mg/dL, albu-

min 2.7 g/dL, prothrombin time international normalized ratio (INR) 1.0, AST 70 U/L, ALT 32 U/L, hemoglobin 12.2 g/dL, platelet count $234 \times 10^3/\mu\text{L}$, and white blood cell count $14.2 \times 10^3/\mu\text{L}$. The patient had a Child–Pugh score of 6 (class A) and an ALBI grade of 3. There was no prior history of hepatic encephalopathy or variceal bleeding. Physical examination revealed no evidence of ascites. The Eastern Cooperative Oncology Group (ECOG) performance status was 0. Apart from chronic hepatitis B infection, there was no significant comorbidity in the patient's medical history.

On July 10, 2025, combination immunotherapy with nivolumab at a dose of 3 mg/kg and ipilimumab at a dose of 1 mg/kg, administered every 21 days, was initiated. Approximately 2.5 months after treatment initiation, an FDG PET-CT performed on September 24, 2025, demonstrated an approximately 80% reduction in viable tumor burden, consistent with a marked partial response according to RECIST criteria (Fig. 1). At the same time, AFP had dropped to 10.5 ng/mL at the first interim evaluation. Combination therapy was therefore continued.

In the follow-up FDG PET-CT scan performed on January 22, 2026, increased metabolic activity was detected in some mediastinal lymph nodes. However, a marked reduction in the intrahepatic tumor burden persisted. The current AFP level had dropped to 6.3 ng/mL. This increase in activity in the mediastinal lymph nodes was interpreted as pseudoprogression. It was planned to continue treatment with nivolumab monotherapy at a dose of 240 mg every two weeks. No immune-related adverse events beyond grade 1 were observed during treatment. The patient received nivolumab 240 mg on January 31, 2026, without any complications (Fig. 1).

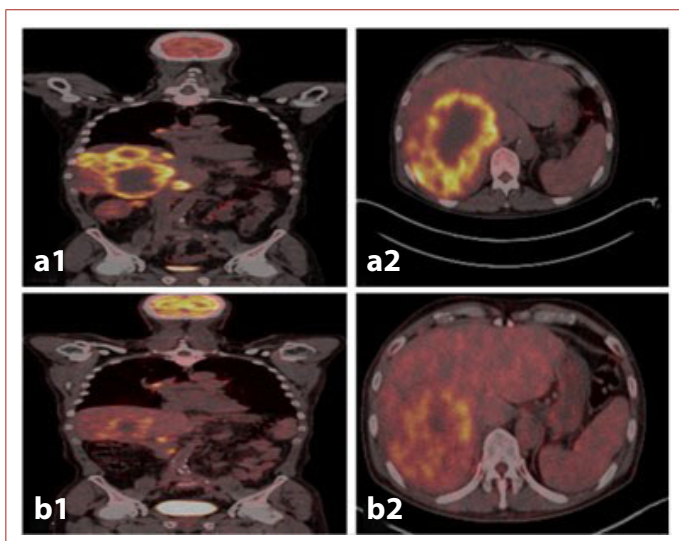


Figure 1. (a1, a2) Pre-treatment PET-CT image of the patient. (b1, b2) PET-CT image obtained 2,5 months after treatment.

Discussion

HCC is often asymptomatic during the early stages; therefore, the majority of cases are diagnosed at an advanced stage. Although the incidence is lower compared to other cancers, HCC ranks third among the cancers responsible for mortality worldwide. HBV infection is a major cause of HCC. Although the effectiveness of the HBV vaccine in preventing HBV-related HCC has been shown, especially in HBV-endemic areas such as East Asia, HBV remains a major cause of HCC worldwide. The management of hepatocellular carcinoma is considered challenging due to the innate drug resistance observed. Tyrosine kinase inhibitors were considered the standard treatment for patients with advanced-stage hepatocellular carcinoma until the early 2020s. However, recent treatment regimens targeting the immune system, either as monotherapy or in combination, have been established and are now considered the standard treatment regimens for the management of advanced-stage HCC. The immune system is considered an important regulator in controlling tumor progression. Liver cancer, like other cancers, uses natural physiological immune regulatory mechanisms to avoid an anti-tumor immune response by expressing immunosuppressive ligands on tumor and stromal cells. Multiple immune checkpoint pathways have been identified in this process, most notably programmed cell death protein 1 (PD-1) and its ligand PD-L1, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte activation gene-3 (LAG-3), and several others. Dysregulation of these pathways contributes to immune tolerance within the tumor microenvironment and promotes tumor growth and progression.^[7] In addition, a number of therapeutic agents targeting these immune checkpoints are currently in development. Against this background, combination immunotherapy with nivolumab, a PD-1 inhibitor, and ipilimumab, a CTLA-4 inhibitor, was initiated for our patient. This combination immunotherapy was granted regulatory approval in 2025 based on efficacy data from the CheckMate 9DW clinical trial.

In the CheckMate 9DW study, nivolumab was administered at a dose of 1 mg/kg in combination with ipilimumab at a dose of 3 mg/kg for four cycles. In the absence of disease progression, treatment was continued with nivolumab monotherapy at a fixed dose of 480 mg every four weeks. However, the incidence of treatment-related grade 3 or 4 adverse events was significantly higher in the nivolumab plus ipilimumab arm compared with the control arm, which consisted of sorafenib or lenvatinib.

The increase in toxicity among patients in the combination arm could also be explained by the increase in the dosage of ipilimumab, which is 3 mg/kg. It is worth noting that this

approach was previously tested in metastatic malignant melanoma and was included in treatment guidelines as a standard therapeutic approach. Previous studies have shown that ipilimumab is linked with low tolerability compared to nivolumab, supporting the claim that ipilimumab is a key contributor to toxicity.^[8,9] In the CheckMate 9DW trial, the rationale for selecting nivolumab at a dose of 1 mg/kg in combination with ipilimumab at a dose of 3 mg/kg was based on results from a previously conducted multi-arm, multi-cohort phase II study, in which this regimen demonstrated the greatest improvement in overall survival. However, in the same study, objective response rates were found to be comparable between the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg arm and the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg arm.^[10] Considering the toxicity profile, the treatment of the patient was initiated with nivolumab at a dose of 3 mg/kg combined with ipilimumab at a dose of 1 mg/kg administered every three weeks. After a period of six months with combination therapy, treatment with nivolumab monotherapy at a dose of 240 mg administered every two weeks was continued.

In fact, in the phase III CheckMate 9DW study, which led to this regimen being included as one of the standard treatment options, it was noted that the clinical benefits were more pronounced in patients who did not experience any disease progression or death during the initial six months of treatment. It is also important to note that there was an improvement in survival benefits, especially in those patients who experienced complete or partial responses. This is in line with our patient, who experienced a positive response within the initial six months, a response that has been ongoing. Importantly, there were no adverse effects associated with treatment, which led to its discontinuation or reduction in dosage.

One of the other key points to highlight in this case we are presenting is the ALBI and CHILD-PUGH scores. The ALBI score is an objective prognostic tool that predicts liver reserve in patients with HCC, calculated using albumin and bilirubin levels. The CHILD-PUGH score, on the other hand, is a prognostic scoring tool that combines both laboratory parameters and clinical findings. This scoring did not influence the dose selection we used in treatment. At the time of diagnosis, liver reserve was poor due to the excessive tumor burden in the liver, and the ALBI score was calculated as Grade 3. Consequently, a discordance may have arisen between the ALBI and CHILD-PUGH scores in this particular patient. In clinical practice, both scoring tools are utilized. The score changed following a good response to treatment. Initially an ALBI Grade 3, it had improved to Grade 2 at the first interim assessment. Our case demonstrates that this treatment is effective even in a patient with poor liver reserve.

Conclusion

In conclusion, the combination of nivolumab and ipilimumab represents an effective first-line systemic treatment option for selected patients with advanced-stage HCC. Moreover, individualized modifications to treatment scheduling and dosing, when applied within a reasonable clinical framework, may help preserve therapeutic efficacy while minimizing treatment-limiting toxicities, thereby improving overall treatment tolerability.

Disclosures

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