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# Effectiveness of fourth-line dual immunotherapy in hepatocellular carcinoma with simultaneous steroid administration for immune-related hepatitis

Kristina Lowes, Johanna Reinecke, Marius Brunner, Matthias Scholz, Julia Kitz, Beate Michels, Ardian Mekolli, Jochen Gaedcke, Ali Seif Amir Hosseini, Philipp Ströbel, Michael Ghadimi, Volker Ellenrieder, Alexander Koenig and Ute Koenig

***Abstract*:** Medical therapy of advanced hepatocellular carcinoma (HCC) remains an emerging subject, but therapeutic sequences together with toxicity management are rarely described. Herein, we report the case of a therapeutic sequence and toxicity management in a 72-year old White male with advanced non-cirrhotic HCC. The HCC of this patient was refractory against treatment with several tyrosine kinase inhibitors, including lenvatinib and cabozantinib or immune combination of pembrolizumab and lenvatinib. Double immune combination of nivolumab and ipilimumab was effective in fourth-line treatment but resulted in immunotherapy-related grade 4 hepatitis. This toxicity responded well to high doses of corticosteroids, and reinduction of dual immune combination remained effective despite continuation of high-dose corticosteroids in a non-cirrhotic HCC. This case demonstrated the efficacy of double immune therapy in higher treatment lines in advanced non-cirrhotic HCC even if the patient was treated with other immune modulatory therapies earlier. Moreover, it can remain effective under concomitant administration of high-dose corticosteroids.

***Keywords:*** combination immunotherapy, hepatocellular carcinoma, immune-related adverse events, immune-related hepatitis, immunotherapy

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Correspondence to:
**Alexander Koenig**
Department of Gastroenterology and Gastrointestinal Oncology, University Medical Center Goettingen, Robert Koch Strasse 40, 37075 Goettingen, Germany.
alexander.koenig@med.uni-goettingen.de

**Kristina Lowes**
**Johanna Reinecke**
**Marius Brunner**
**Beate Michels**
**Ardian Mekolli**
**Volker Ellenrieder**
**Ute Koenig**
Department of Gastroenterology and Gastrointestinal Oncology, University Medical Center Goettingen, Goettingen, Germany

**Matthias Scholz**
**Ali Seif Amir Hosseini**
Department of Diagnostic and Interventional Radiology, University Medical Center Goettingen, Goettingen, Germany

**Julia Kitz**
**Philipp Ströbel**
Department of Pathology, University Medical Center Goettingen, Goettingen, Germany

**Jochen Gaedcke**
**Michael Ghadimi**
Department of General, Visceral, and Pediatric Surgery, University Medical Center Goettingen, Goettingen, Germany

## Case

A 72-year-old man without a history of liver cirrhosis or viral hepatitis was diagnosed with AFP-negative hepatocellular carcinoma (HCC) of the right liver in October 2017. The liver tumor was identified in a staging computed tomography (CT) during follow-up of a human papillomavirus (HPV)-negative squamous cell carcinoma of the soft palate, which was first diagnosed in 2014 and resected by laser surgery and neck dissection. In 2015, a recurrence of the squamous cell carcinoma occurred, which was again treated by laser surgery and subsequent radiochemotherapy of the tumor region and the locoregional lymph nodes up to a maximum of 64 Gy accompanied by four cycles of cisplatin (40 mg/m$^2$ weekly) from November 2015 to January 2016.

CT examinations in October and November 2017 showed a right hepatic carcinoma with suspected occlusion of the right hepatic vein and infiltration of the right portal vein (Figure 1(a)). Histopathological findings confirmed the diagnosis of HCC without signs of cirrhosis (Figure 1(b)). Immunohistochemistry showed positivity for CD34 with clearly increased pathological vascular pattern, positivity for glypican and CD10, as well as a significant overexpression of HSP70 and negativity for CK7. The performed tests for viral hepatitis were negative.

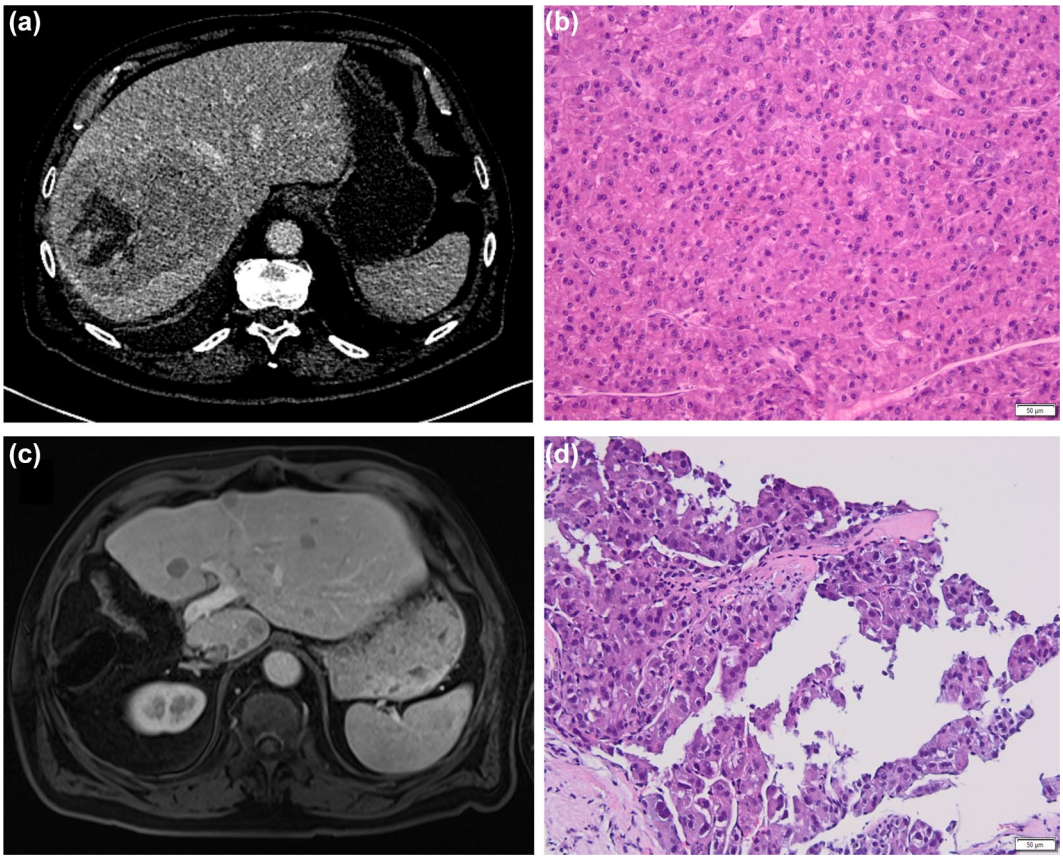


**Figure 1.** (a) October 2017: CT scan at first diagnosis, hepatic mass of 9.6 × 11.9 cm with arterial enhancement and central hypodensities, in the sense of tumor necrosis, the lesion extends from segment VIII to VI; (b) histological findings at first diagnosis (hemihepatectomy); (c) August 2018: MRI scan, recurrence of HCC, disseminated disease with more than 30 lesions in all liver segments; and (d) histological confirmation of recurrence of the HCC.

The patient is a retired electrician and postal worker. Until 1999, there had been a history of alcohol abuse, and he was a former smoker until 14 years ago (40 packyears). One possible factor that could have contributed to the development of HCC is the application of cisplatin as part of radiochemotherapy. Without a history of hepatitis, non-alcoholic fatty liver disease or liver cirrhosis due to the abuse of alcohol, the cause of the HCC remains unknown. Liver function tests were normal. According to the recommendations of the interdisciplinary tumor conference, he underwent extended right hemihepatectomy with simultaneous cholecystectomy in November 2017.

Nine months after R0 tumor resection, the patient developed recurrent cancer detected by magnetic resonance imaging (MRI) scan in August 2018. Instead of a single tumor as presented at primary diagnosis, the scan showed disseminated metastases with more than 30 lesions in all remaining liver segments without an option for surgical resection (Figures 1(c) and 2(a)). The diagnosis was again histologically confirmed (Figure 1(d)).

According to the valid guidelines at the time, medical therapy with the tyrosine-kinase-inhibitor lenvatinib was started. Staging after 4 months of treatment showed a tumor progression in all segments of the liver without detection of extrahepatic manifestations (Figure 2(b)). Following guidelines, we started a second line treatment with cabozantinib (reduced to 40 mg per day), another tyrosine-kinase-inhibitor, at the end of December 2018. The patient developed grade 3 mucositis and dysphagia while undergoing therapy with cabozantinib, thus necessitating a discontinuation of therapy in March 2019. Furthermore, MRI scans indicated further progressive disease after 3 months of treatment with cabozantinib (Figure 2(c)).

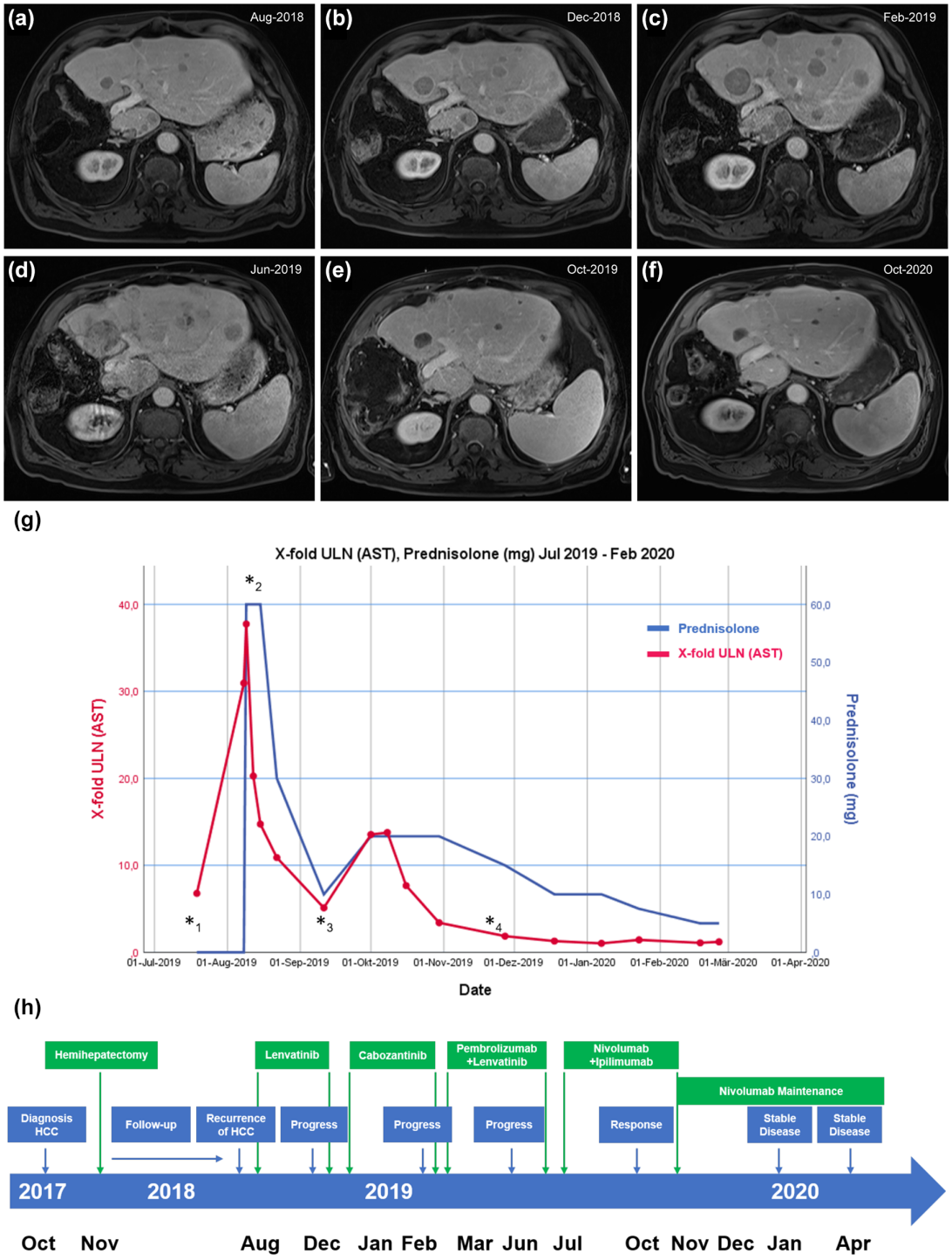


**Figure 2.** MRI scans August 2018–October 2020: (a) August 2018: recurrence of HCC, disseminated disease with more than 30 lesions in all liver segments; (b) December 2018: tumor progression in all segments of the liver after receiving lenvatinib from August 2018 to December 2018 (12 mg per day in August 2018, reduced to 8 mg per day September–December 2018 due to mucositis grade 2); (c) February 2019: progression after 3 months of cabozantinib (reduced dose to 40 mg per day due to mucositis); (d) June 2019: progression after receiving pembrolizumab (200 mg every 3 weeks) and lenvatinib (4 mg day 1–7 due to mucositis) from March 2019 to June 2019; (e) October 2019: objective tumor response to nivolumab-plus-ipilimumab with devascularization of the lesions and size reduction of defined target lesions greater than 30% which corresponds to partial remission (nivolumab 1 mg/kg + ipilimumab 3 mg/kg); (f) October 2020: stable disease; (g) June 2019–February 2020: time course of AST (x-fold ULN) and prednisolone, *1: nivolumab-plus-ipilimumab, *2: starting with prednisolone, *3: continuation nivolumab-plus-ipilimumab, *4: maintenance therapy with nivolumab; and (h) timeline from October 2018–April 2020.

Due to persistent tumor progression and good patient conditions (ECOG 1), we changed therapy to a combination of pembrolizumab (200 mg every 3 weeks) and lenvatinib (4 mg day 1–7 due to mucositis) which was shown to be effective in palliative HCC patients following progression under TKI (tyrosine-kinase-inhibitor) treatment.[1] Unfortunately, radiological controls again revealed a progression of the multifocal HCC 3 months later (Figure 2(d)) together with worsening of the clinical situation (ECOG (Eastern Cooperative Oncology Group) 1–2).

Due to another ineffective response to therapy, a dual immunotherapy with nivolumab and ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg every 2 weeks) was initiated in July 2019, in analogy to recently published results from CheckMate 040.[2] Ten days after receiving the first dose of nivolumab-plus-ipilimumab, his general practitioner noticed increased liver enzymes. In August, 3 weeks after the start of treatment, he consulted our medical department, presenting symptoms such as fatigue, dizziness, itching, epigastric pain, and an increasing abdominal girth. Laboratory-chemical examinations showed in particular elevated liver enzymes as well as an increased total bilirubin value reaching a maximum 3 days after admission to the hospital (serum aspartate aminotransferase (AST) 1321 U/l (range ⩽ 45 U/l, x-fold ULN 38), alanine aminotransferase (ALT) 724 U/l (range ⩽ 35 U/l, x-fold ULN 16) and bilirubin 3.8 mg/dl (range 0.3–1.2 U/l, x-fold ULN 3.2) (Figure 2(g)). After sonographic and laboratory exclusion of other reasons, immunotherapy associated hepatitis grade 4 was diagnosed and an immunosuppressive therapy with prednisolone 60 mg per day was initiated, leading to a sufficient decrease of elevated liver enzymes (Figure 2(g)).

According to the current guidelines and prescribing information, therapy should be permanently discontinued in case of 3- to 4-degree immune-related hepatitis.[3] Due to the lack of other promising therapeutic options, relatively good patient conditions (ECOG 1–2) and strong patient's decision, a cautious continuation of the specific tumor therapy was discussed with the patient and re-induced in September 2019. Because of a renewed increase in transaminases and bilirubin, the administration of the dual immunotherapy was split up into different weeks under continued steroid treatment of 20 mg prednisolone per day. This steroid dose was maintained until the combination therapy of nivolumab and ipilimumab was accomplished in November 2019. In the further course of treatment, the liver enzymes continued to decline, thus a cautious dose reduction of prednisolone over time to 5 mg (February 2020) was possible. MRI examination at the beginning of October 2019 already showed a partial response to therapy (PR according to RECIST 1.1) with size-regressive, mostly necrotic HCC metastases, so a maintenance monotherapy with nivolumab (flat dose 240 mg every 2 weeks) was continued (Figure 2(e)).

Further staging MRI scans in January, April, July, and October 2020 (Figure 2(f)) showed stable disease under immunotherapy with simultaneously stable liver enzymes and total bilirubin. At the same time, there was an improvement in the patient's performance status under immunotherapy (ECOG 0 in April 2020 compared with an ECOG 1–2 before initiation of double immune therapy). In May 2020, prednisolone was discontinued, resulting in no changes of liver enzymes or bilirubin levels under ongoing therapy with nivolumab which is planned to be continued for another 6 months. The patient gave his written informed consent to any therapy as well as to the publication of the case. The report received exemption from ethics approval from the ethics committee.

## Discussion

This patient shows a long-term response to dual immunotherapy after failing multiple pre-therapies including tyrosine-kinase-inhibitors or combination of PD-1 inhibition with vascular endothelial growth factor (VEGF)-sensitive-TKI. At the same time, the case questions the recommendations of current guidelines on discontinuation of therapy for grade 3–4 adverse events in patients undergoing immunotherapy and demonstrates a clinically relevant efficacy of double immune therapy under simultaneous immunosuppression with high-dose steroids.

In recent years, further systemic therapy options for HCC have been established for patients who are not eligible for surgery or local ablative/locoregional therapies. Since 2008, the tyrosine-kinase-inhibitor sorafenib has been a therapeutic option for advanced HCC showing survival benefit compared with placebo.[4] Ten years later, the

multi-tyrosine kinase inhibitor lenvatinib was shown to not be inferior to sorafenib and represents a further option in the first-line therapy of HCC.[5] Due to better patient-related tolerability, we chose lenvatinib for first-line therapy. For second-line therapy, the patient received the tyrosine kinase inhibitor cabozantinib, which displayed efficacy in the treatment of patients with progression after sorafenib and can be considered in second-line therapy of advanced HCC.[6] We did not choose regorafenib due to previous extensive mucositis while on other tyrosine kinase inhibitors. Ramucirumab was not evaluated because of AFP-negativity.

After the promising approach of immunotherapy with pembrolizumab monotherapy was shown to not lead to a significant benefit in a phase 3 trial,[7] combination therapies became the focus of further investigations. In our case, the patient received a combination therapy with lenvatinib and pembrolizumab based on preliminary results from a phase 1b trial.[1] With further tumor progress clinically and on MRI scan, we decided to implement a dual immunotherapy with nivolumab and ipilimumab based on the encouraging published results from CheckMate 040, showing a response rate of 31%.[2] As presented at the ESMO Congress in Asia 2019, the IMbrave150 trial showed stunning results of a phase 3 study for a combination therapy of atezolizumab and bevacizumab[8] and is now standard of care in first-line therapy. These and other combinations are currently the subject of further investigations and are necessary to provide useful recommendations for therapy sequences for patients with HCC in the future. Interestingly, combined inhibition of CTLA4 and the PD1/PDL1 system were found to be effective even after failure of preceding immune modulatory therapies.

Autoimmune-mediated hepatitis is defined as an increase in transaminases and bilirubin, graded using NCI Common Terminology Criteria for Adverse Events (CTCAE). The occurrence of hepatotoxicity is common, especially in patients treated with dual immunotherapy. In addition, there appears to be an overall increase of grade 3–4 toxicity in combination immunotherapy.[9] Current guidelines recommend discontinuation of treatment in case of grade 3 or 4 toxicity. However, continuation of treatment is possible in case of grade 1 or 2 toxicity. Laboratory tests should be performed more frequently and an immunosuppressive therapy with 0.5–1.0 mg/kg/day methylprednisolone equivalent is possible, in case of persistent symptoms or altered laboratory results.[3]

Due to the failure of all previous therapies and the associated lack of other promising treatment options while the patient remained in reasonable condition, in this case we decided to continue the therapy with simultaneous administration of a higher dose of daily steroids despite grade 4 toxicity. In the context of immunosuppression with steroids, there is concern about an inferior response to immunotherapy. Molecular mechanisms underlying immunosuppressive activity of corticosteroids are multilayered and can differentially influence the activity of a given individual's T-cells. The use of steroids in patients with immune-related adverse events (irAEs) and their effect on T-cell activation and proliferation may theoretically oppose the efficacy of immunotherapy, which mainly works by regulating T-cell function.

It is believed that immunotherapy leads to abnormal activation of T-cells, and the irAEs are mainly due to the immune attack by these activated T-cells, which has been confirmed by biopsy in various types of irAEs, including myocarditis, pneumonitis, and skin toxicities.[10]

There is preclinical evidence that corticosteroids can influence T-cell proliferation, differentiation, and activation,[11,12] suggesting an altered tumor immunity and reduced response to immunotherapy as well as clinical evidence of an inferior response to immune checkpoint inhibition with simultaneous use of corticosteroids.[13] There appears to be a negative impact of steroid use in adjuvant patients.[14] At the same time, observations indicate a good response to immunotherapy despite daily use of oral corticosteroids.[15,16] The indication of steroid use also seems important for the outcome of patients receiving immunotherapy. A recently published meta-analysis by Petrelli *et al.*[17] showed there was no negative effect in OS (Overall Survival) of patients receiving steroids for irAE in comparison with patients receiving steroids for tumor-related issues.

The question of whether an even better result could have been achieved without corticosteroid administration remains unanswered. Without the continuation of the treatment, which was made

possible by the continuous administration of steroids, the disease would presumably have progressed further to the present day.

Taken together, this case demonstrates impressively a potential therapeutic sequence in patients with advanced HCC. It shows that double immune therapy is effective even after failure of earlier immune therapy or under concomitant administration of high dose of prednisolone. And finally, it demonstrates that safe reinduction of double immune therapy is possible even after severe grade 3 or 4 toxicity.

## Author contributions

KL, AK and UK were involved in the treatment of the patient, compiled all relevant information about the case, did the literature research and wrote the manuscript with input from all authors. JR, MB, AM and BM were involved in diagnostic procedures and treatment of the patient and provided critical feedback. JG and MG were reponsible for the operative treatment of the patient and provided critical feedback. MS and AH provided the images of mri and ct scans and contributed to the figure legends. JK and PS covered histopathological findings and provided the images of histological findings. VE as head of department supervised all actions taken; all authors read the article and provided critical feedback.

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## ORCID iD

Kristina Lowes https://orcid.org/0000-0002-2455-8194

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