LETTER

Using dual checkpoint blockade to treat fibrolamellar hepatocellular carcinoma

We have read with interest the paper by Gerbes *et al*,[1] which highlights the current developments in the treatment of hepatocellular carcinoma (HCC). Fibrolamellar HCC (FL-HCC) is, in contrast to HCC,[2] an infrequent tumour, most often occurring in adolescents or young adults without underlying liver disease.[3] Chemotherapy-based regimens are typically used to treat FL-HCC based on studies in small patients' cohorts and case series.[3] Despite anecdotal reports of response to systemic treatment, the prognosis of advanced FL-HCC is poor.[4]

The development of immune checkpoint inhibitors (ICP) is drastically changing the approach to the treatment of HCC. In particular, recent trials showed that immunoncological treatment can be potentiated if ICP are used in combination.[5 6] This is exemplified by the use of nivolumab/ipilimumab,[7] and by the results of the phase III IMBRAVE 150 trial, which recently marked a breakthrough in the front-line treatment of HCC.[8]

Despite the fact that FL-HCC and HCC are distinct entities,[4] many have raised the question of whether ICP may be as effective in the treatment of FL-HCC as in the treatment of HCC. Preliminary data to this regard were, unfortunately, disappointing: although one case of response to nivolumab was described,[3] lack of response to single-agent anti-PD1/PDL-1 therapy was reported in three further cases of FL-HCC.[9]

We were recently confronted with the case of a heavily pretreated 22-year-old woman with progressive metastatic FL-HCC (table 1). On treatment with gemcitabine/oxaliplatin a radiological progression was observed, with metastases disseminated in the lungs, peritoneum, lymph nodes and pelvis. The decision was thus taken to initiate treatment with combined nivolumab/ipilimumab, in analogy to the Checkmate-040 trial for advanced HCC, whose results had recently been released.[7]

After four cycles of treatment, a near-complete response of all tumour lesions was observed as shown in figure 1. Retrospectively evaluated pathological specimens were negative for PDL-1 and microsatellite instability (MSI) and showed a low mutational burden.

Table 1 Time course of the patient's multimodal treatment since diagnosis

Time after diagnosis (months)	Treatment
0	Extended right hemihepatectomy and lymphadenectomy pT1b (12.4 cm), pN1 (4/12), L0, V0, Pn0, G2, R0
4	Hilary lymph node recurrence, irradiation of perihepatic lymphatic pathways (45 Gy) followed by lymph node dissection
11	Bilateral pulmonary metastases, atypical resection
18	Hepatic recurrence with pulmonary metastasis, pelvic lymph node metastasis and peritoneal carcinosis
18–21	Six cycles of biweekly gemcitabine (1000 mg/m^2) and oxaliplatin (85 mg/m^2). Progressive disease
21	Initiation of treatment with nivolumab (240 mg, one cycle) followed by three cycles of nivolumab (1 mg/kg) and ipilimumab (3 mg/kg)
23	Immunogenic hyperthyroidism, self-limiting
24	Near-complete response. Temporary discontinuation of nivolumab/ipilimumab due to immunogenic hepatitis

On day 79 after treatment initiation, laboratory examination showed signs of liver failure with increased liver enzymes and bilirubin and decreased blood coagulation. However, after treatment with prednisolone (2 mg/kg) and mycophenolate (1.5 g two times per day) transaminases fell rapidly and blood coagulation returned to normal values. The performance status of the patient and her daily activities remained uncompromised throughout the treatment.

In three out of four previously reported cases of FL-HCC known to us, single-agent anti-PD1/PDL1 treatment failed to provide clinical benefit. Although the case illustrated here is to our knowledge the first and only report on combined ICP-treatment for this entity, the profound and rapid response seen by us might mirror the highly increased potency of combination treatment versus the use of ICP as monotherapy observed in recent HCC trials. The observed severe liver toxicity was not entirely unexpected, as grade 3/4 elevation of liver enzymes is seen in up to 20% of cases of combined treatment with nivolumab/ipilimumab.[10]

We suggest that dual-ICP-blockade should be attempted in patients with FL-HCC in the presence of non-resectable disease regardless of PDL-1 status, MSI or mutational burden. The profound response observed by us suggests that combination therapy could also be beneficial as neoadjuvant treatment for primarily inoperable tumours. This will have to be assessed in clinical trials or, due to the rarity of this tumour, by national registries.

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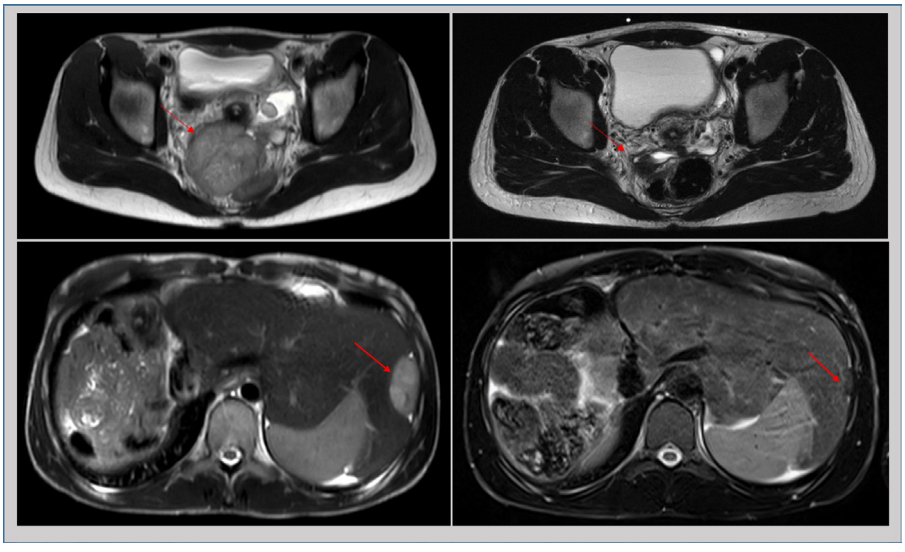

Figure 1 Representative figures of MRI scans at baseline (left panels) and after four cycles of immunotherapy (right panels) exemplarily showing the regression of the pelvic and a peritoneal lesions indicated by the arrows.

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Contributors ENDT and DR conceived and drafted the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests ENDT has served as a paid consultant for AstraZeneca, Bayer, BMS, EISAI, Eli Lilly & Co, Pfizer, IPSEN and Roche. He has received reimbursement of meeting attendance fees and travel expenses from Arqule, BMS, Bayer, Celsion and Roche, and lecture honoraria from BMS and Falk. He has received third-party funding for scientific research from Arqule, AstraZeneca, BMS, Bayer, Eli Lilly and Roche. DR has received reimbursement of meeting attendance fees and travel expenses from Celsion and IPSEN.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite De Toni EN, Roessler D. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2020-320604

Received 4 January 2020
Revised 16 January 2020
Accepted 1 February 2020

Gut 2020;**0**:1–2. doi:10.1136/gutjnl-2020-320604

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