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Case Report

Long-Term Survival in Hepatocellular Carcinoma following Second-Line Tumor Treating Fields Therapy and Sorafenib: A Case Report

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Hepatocellular carcinoma · Tumor Treating Fields therapy · Case study

Abstract
Introduction: Hepatocellular carcinoma (HCC) is an aggressive solid tumor associated with high mortality. Surgery is the main treatment consideration for early disease, but patients who present with locally advanced or metastatic HCC at diagnosis have limited treatment options. There has been great progress in locoregional, immunotherapy, and targeted treatments for advanced HCC. Standard of care for HCC has changed due to results demonstrating safety and efficacy in phase 3 studies, namely, for atezolizumab concomitant with bevacizumab. Nonetheless, additional therapeutic approaches are still warranted to further increase overall survival in HCC. A first-in-class treatment option investigated in patients with HCC is Tumor Treating Fields (TTFields) therapy, which is delivered locoregionally to the tumor site from a portable medical device. TTFields are electric fields that interfere with critical cancer cell processes, hindering tumor progression. ***Case Presentation:*** Here, we report on a case study of a 62-year-old male patient with HCC receiving TTFields concomitant with sorafenib as second-line therapy. Although the patient experienced adverse events with previous nivolumab, they achieved a complete response and continued on treatment for 51 months until disease progression, which led to treatment cessation. We report that during 39 months of subsequent treatment with TTFields therapy and sorafenib, the patient experienced a good quality of life, low systemic

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toxicity, and stable disease following a partial response. ***Conclusions:*** These promising findings, along with those of the pilot phase 2 HEPANOVA clinical study, warrant further investigation of TTFields therapy in HCC.

Introduction

For patients with hepatocellular carcinoma (HCC), prognosis is very poor; the 5-year survival rate of patients with liver cancer is 21.7% in the USA [1]. Development of HCC is associated with chronic liver damage, for example, from cirrhosis, hepatitis B and C viruses, and alcoholic liver disease [2]. Treatment options depend on the site, size, and number of tumor lesions; Barcelona Clinic Liver Cancer (BCLC) stage; and degree of liver dysfunction [3]. For patients with early-stage disease (BCLC stages 0, A, and B), standard of care is resection, orthotopic liver transplant, thermal ablation, or transarterial chemoembolization (TACE) [3]. Standard of care for later stages of disease (BCLC stages C and D) comprises systemic therapy or, in cases where systemic treatment is not feasible, selective internal radiotherapy [3].

Although curative treatment options such as surgical resection, orthotopic liver transplant, radiofrequency ablation, and microwave ablation exist, they are often limited to patients with localized disease. Identifying patients that may benefit from these approaches can be difficult, given the late presentation of disease, and there are no randomized head-to-head trials comparing the efficacy of these treatments [4]. Furthermore, liver-specific therapies such as TACE can compromise hepatic blood flow, leading to acute deterioration of liver function [5].

Until recently, sorafenib was the only systemic treatment option for advanced HCC; however, given the results from a phase 3 study demonstrating efficacy and safety of atezolizumab concomitant with bevacizumab in patients with unresectable HCC, this combination has since become standard of care for BCLC stage C (advanced) disease [3, 6]. Other systemic treatment options include lenvatinib, regorafenib, cabozantinib, and ramucirumab [3]. Furthermore, recent data have demonstrated improved survival with durvalumab concomitant with tremelimumab (compared with sorafenib) in patients with advanced liver cancer [7]. While there has been great progress in treatments for advanced HCC, additional therapeutic approaches are still warranted to further increase overall survival in HCC.

Tumor Treating Fields (TTFields) therapy is a noninvasive and locoregional treatment that utilizes electric fields, delivered by a portable medical device to the tumor site via skin-placed arrays, which exert physical forces to disrupt cellular processes critical for cancer cell viability and tumor progression [8–11]. TTFields therapy is approved for the treatment of glioblastoma (GBM) as well as mesothelioma [12–14] and is being investigated in several solid tumors including HCC. The phase 2 HEPANOVA study (NCT03606590) assessed TTFields therapy (150 kHz) concomitant with sorafenib, and results demonstrated numerical improvements in outcomes versus historical controls [15]. Here, we present a case report of a 62-year-old male patient with HCC receiving second-line TTFields therapy concomitant with sorafenib, enrolled in the HEPANOVA study. The patient was followed for a period of 39 months, allowing for assessment of long-term outcomes. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539719).

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A full timeline of the patient's journey can be seen in online supplementary Figure 1. In June 2010, a 62-year-old male patient with a history of long-standing hypothyroidism and nonalcoholic hepatopathy (Child-Pugh class A) underwent emergency intervention for hemoperitoneum caused by a hepatic tumor rupture. The tumor was reported as a hepatic adenoma, so the patient continued normal follow-up until November 2011 when a computed tomography (CT) scan showed 4-cm and 3-cm masses in hepatic segment VIII (Fig. 1a, b). Serum alpha-fetoprotein (AFP) was normal at that time. After undergoing a TACE procedure, the patient started doxorubicin in March 2012.

In May 2015, a magnetic resonance imaging scan showed multiple hyper vascular hepatic lesions associated with multicentric HCC and several new hepatic metastatic lesions. The patient underwent a core needle biopsy which confirmed a differentiated HCC. AFP remained normal.

In June 2015, the patient was enrolled in a clinical trial and was treated with single-agent immunotherapy (nivolumab) [16]. After 6 cycles, a complete response was observed which continued through 83 cycles (last cycle: September 2019). The patient developed diabetes in 2017 through immune-mediated toxicity related to nivolumab and experienced a grade 4 adverse event (AE) of ketoacidosis. Despite the severity of the AE, the decision was made that the patient should continue the clinical study due to the long-term efficacy benefit.

In September 2019, a routine CT scan confirmed disease progression with the development of 1 lesion (10 mm) in hepatic segment V, 2 new hepatic lesions (10 mm and 7 mm) in hepatic segment VI, and 1 lesion (16 mm) in the mesenteric node (Fig. 1c–f). Nivolumab treatment was subsequently stopped, and the patient was enrolled into the phase 2 HEPANOVA clinical study (TTFields [150 kHz] therapy [≥18 h/day] concomitant with sorafenib [400 mg/12 h]) in October 2019. At the point of enrollment, the patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, Child-Pugh score of 7, and stage A disease per the BCLC staging system and had previously received first-line nivolumab. Serum levels of albumin, bilirubin, and AFP were 2.4 g/dL, 0.7 mg/dL, and 1.0 ng/mL, respectively.

The patient's transducer array layout was determined according to clinical practice guidelines developed to optimize array placement and achieve the recommended intensity of 1 V/cm. To evaluate the TTFields dose delivered to the patient, simulations developed by Novocure (Novocure Ltd, Haifa, Israel) were used to imitate the application of TTFields to the patient. A patient-specific model was segmented using the patient's CT scan, and virtual transducer arrays were placed on the model based on the prescribed array layout (Fig. 2a, b). The electric field intensity was estimated using Sim4Life v6.2 (ZMT, Zurich, Switzerland). To account for actual TTFields delivery, simulations were set such that the current output for each layout was based on analysis of the device log files.

Resulting average TTFields intensity delivered to the tumor was 2.36 V/cm peak to peak (2.52 V/cm in the anteroposterior direction and 2.18 V/cm in the lateral direction [Fig. 2c]). At the first evaluation in January 2020, the CT scan showed partial response with minimal residual disease (Fig. 3a–c). As of March 2023, the patient had received TTFields therapy for over 39 months. Mean TTFields therapy usage was 87%, with an average daily time on treatment of 21 h (Fig. 3d, e). The TTFields therapy usage was assessed as recommended by the sponsor.

The patient's disease remained stable while receiving TTFields therapy (39 months). Furthermore, the patient continues to experience a good quality of life (QoL) as per daily observations during consultations. TTFields device-related AEs included a grade 1 skin irritation caused by skin contact with the arrays, resulting in a treatment pause for 1 week. The AE was resolved after application of topical clobetasol cream (corticosteroid), which was continued for the remainder of TTFields therapy; no further dermatologic management was required.

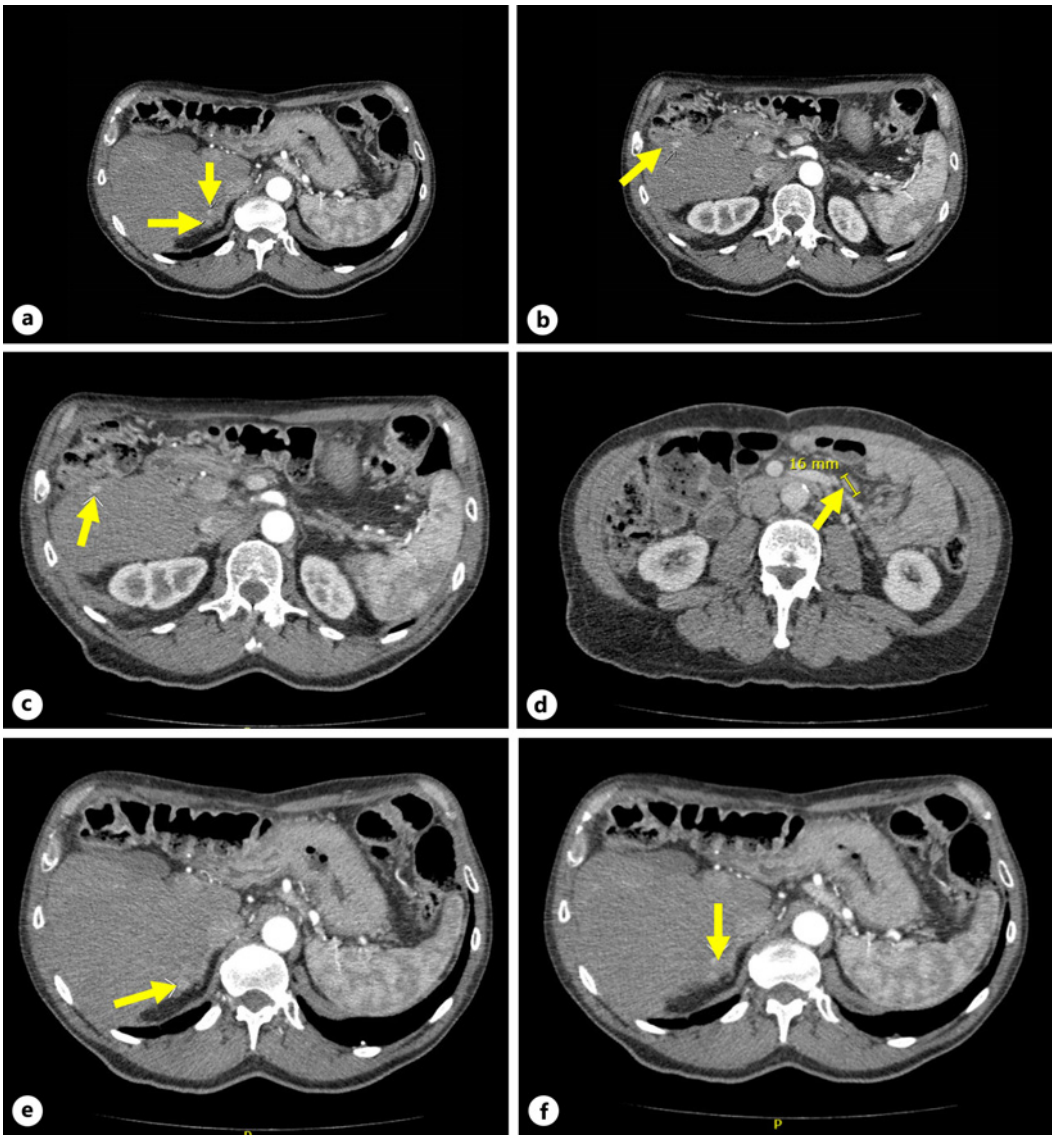

Fig. 1. a, **b** CT scans of the patient's abdomen at initial diagnosis (November 2011) with arrows indicating 4-cm and 3-cm masses in the hepatic segment VIII. **c–f** CT scans of the patient following disease progression after nivolumab treatment for 51 months (September 2019). **c** Arrow indicates the 10-mm lesion in the hepatic segment V. **d** Arrow indicates the 16-mm lesion in the mesenteric node. **e**, **f** Arrows indicate the 10-mm and 7-mm lesions in hepatic segment VI. Models courtesy of Novocure Ltd, Haifa, Israel.

Discussion

There have been notable advances in systemic treatment options for advanced HCC, which have undoubtably improved prognosis. Atezolizumab plus bevacizumab was the first combination to demonstrate a significant survival benefit compared with sorafenib, taking over from sorafenib as standard of care in first-line systemic therapy for HCC [3, 17]. More recently, it has been suggested that immunotherapeutic agents may help reduce the risk of recurrence and improve clinical outcomes for certain patients when used in the adjuvant setting [18]. In addition, recent studies combining locoregional approaches, such as TACE,

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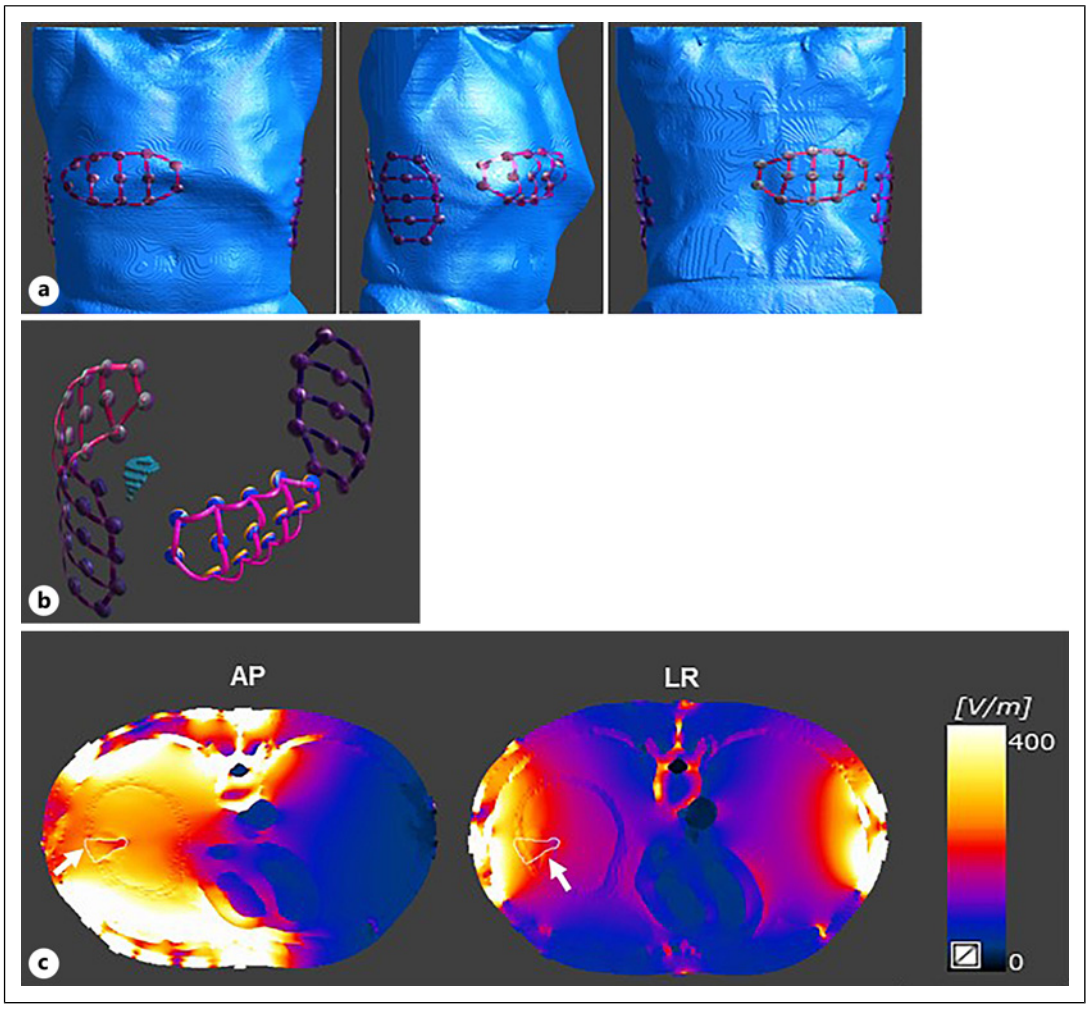

Fig. 2. a Patient-specific simulations for transducer array placement – arrays are paired in the anteroposterior (AP) and lateral (LR) directions, with the field active in each direction alternatively every 1 s. **b** Array placement relative to the tumor (in blue). **c** Axial slices of field intensity maps in both the AP and LR directions, with the tumor marked up in white (white arrow).

with newer systemic therapies have shown promising results; however, there is a need to use biomarkers or other predictors of success to identify patients who will respond best to these approaches [19]. Despite such advances, there remains an important unmet need for additional therapeutic approaches to improve outcomes in this patient population.

TTFields therapy may present an opportunity to extend survival in these patients, based on its demonstrated efficacy in GBM and mesothelioma and encouraging outcomes for HCC in the phase 2 HEPANOVA study [12–15]. The patient population of the HEPANOVA study had particularly poor prognosis, with over 50% of patients classified as Child-Turcotte-Pugh class B and more than 20% of patients with an ECOG performance status of 2 at baseline [15]. As such, duration of treatment with TTFields therapy was limited, and many patients died before the response rate analyses could be carried out [15]. Considering these limitations of HEPANOVA, the current case study provides valuable insight into the long-term use and tolerability of TTFields therapy in HCC when used over a longer period of time.

This patient demonstrated a partial response to TTFields therapy by the time of their first evaluation, within 3 months of enrollment in HEPANOVA. Through 39 months of treatment

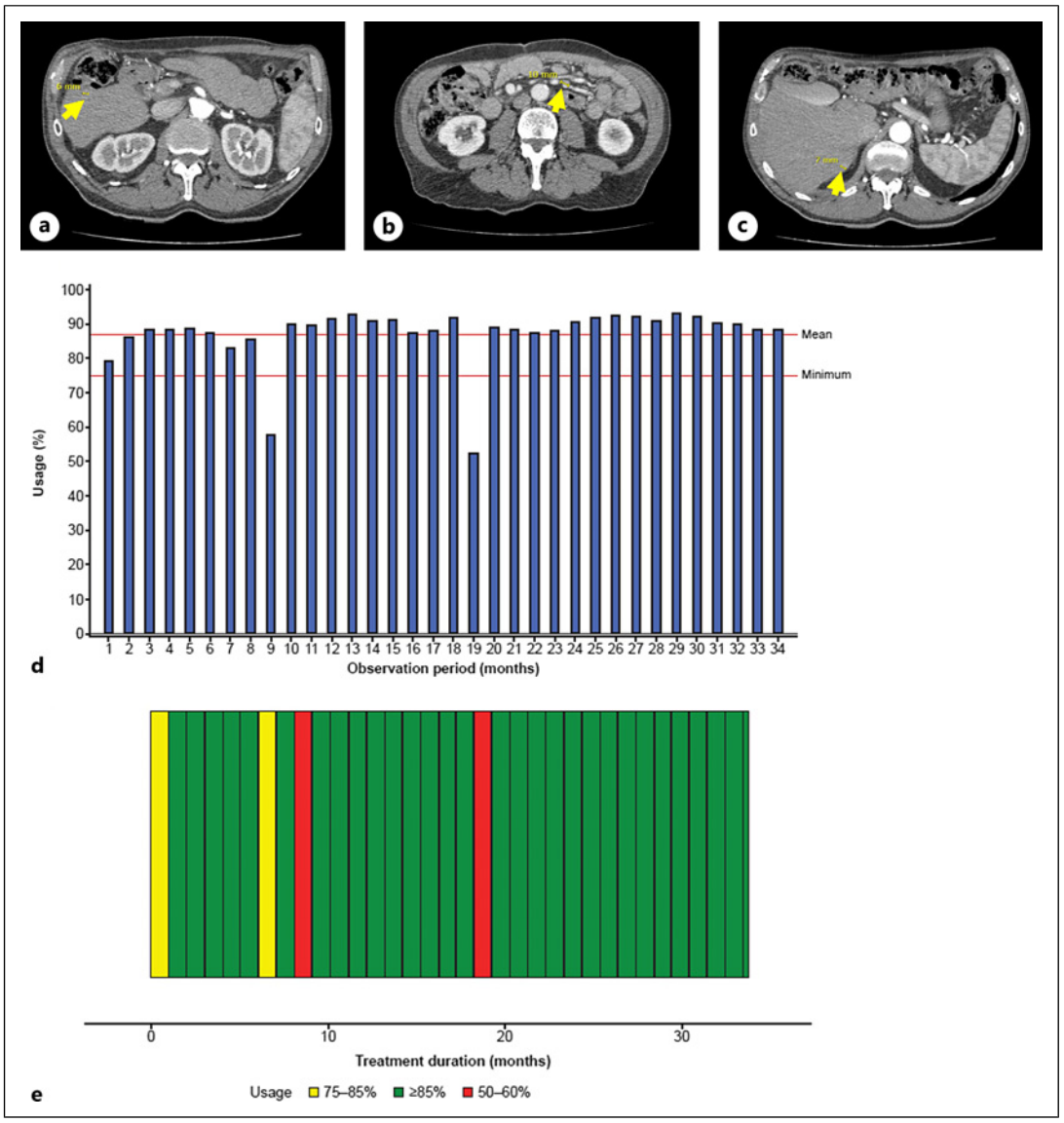

Fig. 3. a–c CT scans of the patient demonstrating stable disease after 1 year of TTFields therapy concomitant with sorafenib (January 2020); arrows indicate lesions. **d** Bar chart depicting rates of TTFields therapy usage throughout the treatment period – the red line indicates the minimum advised time as per label recommendations in approved indications, GBM and mesothelioma [12–14]. **e** Color-coded chart stratifying low usage (50–60%), medium usage (75–85%), and high usage (≥85%) throughout the treatment period. TTFields, Tumor Treating Fields.

with TTFields therapy, their disease has remained stable. Although QoL was not formally measured, the patient continued normal routines while using TTFields therapy including travelling 600 km to his summer house and working regularly in his large vegetable garden, demonstrating that QoL was good throughout treatment. This is remarkable considering the poor QoL associated with HCC; a 2022 systematic literature review of HCC QoL studies observed a profoundly negative impact of HCC on patient QoL, spanning various domains (e.g., physical, psychological, social, and spiritual) [20]. The current findings relating to favorable QoL with TTFields therapy are supported by a real-world study of patients with GBM in the USA and Europe, where disease progression and age were associated with poor QoL, whereas

duration on treatment with TTFields therapy was associated with QoL improvements including improved mobility and self-care [21].

In this case study, the patient experienced a low-grade skin irritation that was resolved within 1 week through use of corticosteroid treatment. As TTFields are delivered to the tumor via skin-adhered arrays, there is an inherent risk of skin reaction; however, such reactions are usually mild-to-moderate in intensity and can be effectively managed with timely interventions [22]. A recent single-center analysis of skin-related AEs among patients with mesothelioma enrolled in the STELLAR study demonstrated that a predefined multidisciplinary approach to skin event management was successful in preventing and managing mild-to-moderate AEs and preventing exacerbations [23]. It is important that healthcare professionals follow clinical practice guidelines related to the management of dermatologic AEs in patients receiving TTFields therapy in order to increase treatment duration and maximize patient clinical benefit and QoL [23].

In this case study, the patient's mean TTFields therapy usage over the entire period was 87%, thus meeting the ≥75% usage recommended per protocol in HEPANOVA [15]. Previous analyses of patients with GBM treated with TTFields therapy have shown correlation of survival benefit with both device usage rate and field intensity within the tumor bed [24–27]. Usage of TTFields therapy ≥18 h/day (equivalent to average monthly compliance of ≥75%) led to improved survival in both the EF-11 (recurrent GBM) and EF-14 (newly diagnosed GBM) pivotal studies [12, 14, 24, 27]. Based on these findings, a device usage rate of ≥75% is typically recommended for patients using TTFields therapy, regardless of tumor type. The interpretation of case studies is limited as they represent an individual patient's experience only and the findings may not be generalizable to broader patient populations. For example, this patient had previously received and experienced a strong response to nivolumab treatment, which may not be representative of most patients in this setting and may impact the subsequent efficacy of TTFields therapy. However, alongside the favorable outcomes of HEPANOVA, these promising findings support the continued investigation of TTFields therapy in HCC.

Conclusion

In this case report, the long-term results indicate that TTFields therapy concomitant with sorafenib shows clinical benefit with a low risk of systemic toxicity and is a potential treatment option for patients with HCC. Results from the phase 2 HEPANOVA clinical study and this case report support further investigation of TTFields therapy in this highly burdened patient population.

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Statement of Ethics

These patient data were collected as part of the HEPANOVA study (NCT03606590). The study protocol was reviewed and approved by the Central Institutional Ethics Committee on May 4, 2018, and the relevant Ministry of Health on May 14, 2018. All study procedures were

performed in accordance with relevant guidelines, such as the Declaration of Helsinki, as well as local regulations. Patients in HEPANOVA provided written informed consent for anonymized use of their clinical data. The patient referred to in this case study provided written informed consent for publication of the details of their medical case and any accompanying images. No identifiable images or data are included in this report.

Conflict of Interest Statement

All the authors have declared no conflicts of interest.

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The patient was enrolled in the single-arm phase 2 HEPANOVA study (NCT03606590), which was funded by Novocure Ltd.

Author Contributions

M.T.V., R.A.G., P.P., C.M.G., L.U., M.G.M., E.d.V.L., Y.Q., S.P., E.d.l.F., and A.C.G. (the authors) were involved in the development of the content, provided critical review/revision, and read and approved the final manuscript.

Data Availability Statement

The data generated and/or analyzed during the current study are available 3 years after the date of publication, upon reasonable request. Please contact Uri Weinberg, Chief Innovation Officer, Novocure Ltd (weinberg@novocure.com), to request access.

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