HEPANOVA: A phase II trial of Tumor Treating Fields concomitant with sorafenib for advanced hepatocellular carcinoma

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TTFIELDS AND HEPATOCELLULAR CARCINOMA

- Tumor Treating Fields (TTFields) are a non-invasive, loco-regional, anti-mitotic cancer treatment modality that continuously deliver low-intensity alternating electrical fields to tumor regions via a patient-operated, portable, home-use device
  - The efficacy and safety of TTFields in newly-diagnosed glioblastoma (GBM) has been demonstrated in a phase III trial
  - Recent National Comprehensive Cancer Network (NCCN) Guidelines recommend TTFields as Category 1 adjuvant therapy for newly diagnosed GBM

- Hepatocellular carcinoma (HCC) is the most common primary liver cancer. The only curative therapies for HCC are surgical resection, ablation or liver transplantation. Most patients are ineligible for these therapies due to the disease burden or the severity of their liver disease
  - Transarterial therapy and stereotactic body radiotherapy (SBRT) for unresectable, eligible patients has shown survival benefit
  - TTFields are a loco-regional therapy, which can be delivered to treat HCC when transarterial treatment options or SBRT are not feasible

- TTFields have demonstrated efficacy in in vitro models of HCC
  - TTFields (150 kHz) reduced both HepG2 and Huh-7D12 cell counts (53–64%) and clonogenic potential (>70%). The combined treatment of TTFields and sorafenib led to a significant reduction in the number of HepG2 and Huh-7D12 cells (p<0.001) vs. each treatment alone
  - TTFields are loco-regional and can be delivered to HCC-specific tumor areas, even when transarterial treatment options or SBRT are not feasible (Figure 1)

- Sorafenib, an inhibitor of VEGFR and PDGFR, has been reported to improve overall survival (OS) in HCC and improve the 1-year survival rate of HCC patients with well-preserved liver function

Figure 1. (A) The NovoTTF-100L(P) System is experimental for the treatment of HCC and has not been approved for this indication. (B, C) Transducer array placement for delivery of TTFields to the upper abdominal region for the treatment of HCC. Simulation studies demonstrate TTFields of sufficient intensity for clinical benefit are achieved within the abdomen for the depicted array layout

HEPANOVA PHASE II TRIAL

- The HEPANOVA Phase II trial is a prospective, single-arm study investigating the safety and efficacy of TTFields as a treatment option for advanced HCC in combination with sorafenib (Figure 2)

MAJOR_ELIGIBILITY CRITERIA

Inclusion criteria include:
- Unresectable HCC that is not amenable to any local treatment
- HCC diagnosed by biopsy, imaging criteria (CT/MRI), serum tumor marker alpha-fetoprotein (AFP) or mRECIST
- ≥18 years of age
- Barcelona Clinic Liver Cancer (BCLC) stage 0–C
- Child-Turcotte-Pugh (CTP) score of 5–8 points
- At least 4 weeks since major surgery
- ECOG performance status (PS) of 0–2
- Life expectancy of at least 12 weeks

Exclusion criteria include:
- Candidate for surgical resection or local treatment
- High levels of serum HBV DNA without anti-viral therapy
- Prior malignancy requiring anti-tumor treatment or concurrent malignancy
- Significant co-morbidities within 4 weeks prior to enrollment
- Implanted pacemaker, defibrillator, or electrical devices in the torso
- Known allergies to medical adhesives or hydrogel

Unresectable HCC not amenable to local treatment
Screening/baseline
Sorafenib + TTFields (150 kHz) applied to upper abdomen for ≥18 hours/day
Follow-up q4W + CT/MRI scan q12w
Post PD follow-up visit
Survival follow-up
HCC diagnosis by biopsy/imaging, AFP or mRECIST; BCLC 0–C, CTP score 5–8 points
TTFields and follow-up until PD in liver per RECIST
30 days after discontinuation
Every 8 weeks until death

Figure 2. HEPANOVA study schema

STUDY TREATMENTS

- TTFields: Continuous (≥18 hours/day) TTFields (150 kHz) using the NovoTTF-100L(P) System until disease progression in the liver per RECIST. Treatment start +/- 7 days from the beginning of sorafenib
- Sorafenib: Daily dose of sorafenib 400 mg (2 x 200 mg tablets) taken twice daily. Treatment should continue until the patient is no longer clinically benefiting from therapy (as determined by each investigator) or until unacceptable toxicity occurs
- Other treatments: Standard local therapy or additional systemic therapy per investigator’s decision when patient is no longer clinically benefiting from study therapy

STUDY OBJECTIVES

Primary objective:
- To determine if TTFields combined with sorafenib in patients with advanced HCC improved the overall response rate (ORR)

Secondary objectives:
- Progression-free survival rate at 12 month (FFS12) of TTFields in combination with sorafenib
- Overall survival rate at 1 year of TTFields combined with sorafenib
- The distant metastases-free survival rate at 1 year of TTFields in combination with sorafenib
- Toxicity of TTFields combined with sorafenib

STATISTICAL CONSIDERATIONS

- A sample size of 25 patients is required to achieve a power of 77% at a one-sided alpha level of 0.05 using one sample Exact test for proportion
- Sample size was based on ability to detect an ORR of 20% in TTFields-treated patients compared to the 4.5% overall response rate calculated from historical controls