1. Publishable summary

PROBLEM: Hepatocellular carcinoma - HCC is a disease with high unmet medical need. Indeed, it accounts for about **6% of all new cancer cases diagnosed worldwide (nearly 750,000 new cases/year)**, and is the **third and the fifth leading cause of death from cancer globally in men and women**, respectively. Given the current lack of available effective treatments, the overall prognosis for patients with HCC is poor with a **dismal 5-year survival rate of approximately 5-6%.** In such a framework, development of innovative and novel therapies for HCC is mandatory and immunotherapeutic interventions, including cancer vaccines, may represent a valuable strategy**.**

***AIM*:** The main objective of HepaVac is to develop **a novel cancer vaccine approach for HCC based on epitopes naturally processed and presented by HLA class I and class II molecule (HLA-ligandome), to elicit both CD4+ T helper and CD8+ CTL tumor-specific effector and memory responses.** Such an approach aims at improving clinical outcome in adjuvant HCC patients after standard treatment. Feasibility, safety and immunogenicity will be evaluated in a randomized, controlled European multi-centre phase I/II clinical trial.

EXPERIMENTAL APPROACH: The experimental approach undertaken by the HepaVac Consortium is based on development of an **"off-the-shelf" vaccine** comprising multiple newly identified tumor-associated peptides (**TUMAPs**) naturally presented on the surface of primary HCC cells. Upon immunological validation of HCC-specific TUMAPs, a peptide cocktail made of up to 40 HLA class I and II restricted epitopes will be designed for a multi-epitope and multi-HLA allele strategy, aiming at inducing both tumor-specific CD4+ T helper cell and cytotoxic CD8+ lymphocyte effector and memory immune responses. Furthermore, a sub-set of patients will be boosted with newly identified patient-specific HCC-associated mutated epitopes in an **actively personalized vaccine (APVAC) approach**. The "off-the-shelf" as well as personalized vaccine will be combined with a **novel and potent RNA-based immunomodulator (RNAdjuvant®)**. Safety, feasibility and immunogenicity of the suggested approach will be tested in a randomised, controlled European phase I/II multi-centre clinical trial. A **comprehensive T-cell immunomonitoring and biomarker program** will be implemented to assess in detail the mechanism-of-action (MoA), identify immunological prediction markers of responsiveness and support further clinical development.

This will be one of the very few vaccine trials for HCC and the first multi-epitope, multi-target and multi-HLA allele therapeutic cancer vaccine for such a frequent and aggressive disease. Targeting the tumor with such a wide range of naturally occurring antigens will minimize the likelihood for tumor escape in vaccinated patients.