Phase I study of HFB200301, a first-in-class TNFR2 agonist monoclonal antibody in patients with solid tumors selected via Drug Intelligent Science (DIS).

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Background: Tumor necrosis factor receptor-2 (TNFR2) is expressed on effector CD8+ T cells, CD4+ T cells, T regulatory cells, natural killer cells, and myeloid cells. Targeting TNFR2 is anticipated to yield effective anti-tumor immunity by stimulating T-cell and NK-cell activation and proliferation in the tumor microenvironment. HFB200301 is a first-in-class anti-TNFR2 agonistic monoclonal antibody that triggers both innate and adaptive immune stimulation by binding to a specific epitope on TNFR2. HFB200301 has demonstrated dose-dependent anti-tumor activity in human TNFR2 knock-in mice bearing MC38 and Hepa1-6 syngeneic tumors. **Methods:** HFB200301 is being evaluated in a first-in-human, open-label, multi-center, dose escalation and expansion study in adult patients with advanced solid tumors. A single-cell immune profiling platform, DIS, was deployed to identify unique tumor-infiltrating T cell signatures that could help optimize patient selection for HFB200301 treatment. It is hypothesized that the presence of an effector T cell subpopulation that express both TNFR2 and CD8A in solid tumors may represent a tumor microenvironment favorable to TNFR2 agonism. The following cancer indications have been identified based on the prevalence of a TNFR2 high/CD8 high signature: Epstein-Barr Virus positive (EBV+) gastric cancer, clear cell renal cell carcinoma (ccRCC), cutaneous melanoma, testicular germ cell tumor (TGCT), soft tissue sarcoma (STS), and PD-L1+ cancers: cervical cancer, pleural mesothelioma, lung adenocarcinoma, and head and neck squamous cell carcinoma (HNSCC). The escalation portion of the study explores increasing doses in cohorts of up to six patients, utilizing mTPI-2 design to determine recommended dose(s) for expansion (RDE(s)). Based on pharmacokinetic modeling to maximize HFB200301 activity, 60-minute intravenous infusions of HFB200301 are administered every 4 weeks. Once RDE(s) is determined, expansion into three indication-specific cohorts is planned to determine the recommended phase 2 dose (RP2D). Key eligibility criteria include histologically documented advanced or metastatic solid tumors in the above listed indications. Patient enrollment opened in February 2022 in the USA, with plans for additional clinical sites in Spain and China. The primary objective is to identify the RDE, characterize safety and tolerability of HFB200301, and determine RP2D. Secondary objectives include pharmacokinetic parameters, preliminary evidence of anti-tumor efficacy (e.g., ORR, DCR, DOR) and pharmacodynamic evaluation (e.g., T cell subsets) in the blood and in the tumor. Furthermore, a potential predictive biomarker signature derived based on the DIS single-cell immune profiling approach will be investigated retrospectively. Clinical trial information: NCT05238883. Research Sponsor: HiFiBiO Inc.