A phase I/IIa study to evaluate the safety and tolerability, activity and pharmacokinetics of a potential novel CNTN4-targeted checkpoint inhibitor, EP0089, in patients with advanced solid tumors

TPS2688

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BACKGROUND

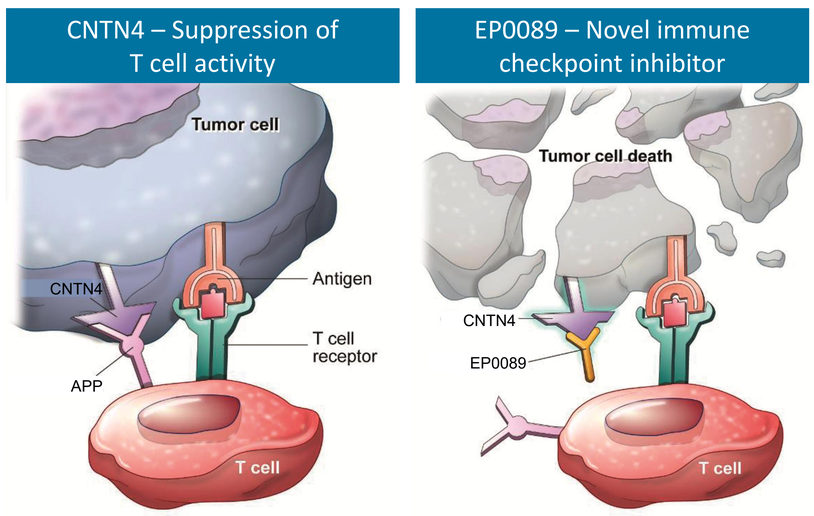
CNTN4 as a novel target

- Contactin 4 (CNTN4; alias BIG-2) is a glycosylphosphatidylinositol-anchored neuronal membrane protein that plays a pivotal role in maintaining the mechanical integrity and signaling properties of the synapse, as well as in the formation of axon connections in the developing nervous system[1]
- Recently, CNTN4 has also been identified as a novel immunomodulatory protein and has been shown to negatively regulate T cell activity through binding with the T cell transmembrane protein amyloid precursor protein (APP), and it may bind to other APP family members in the absence of APP[1–3]
  - The interaction between CNTN4 on the surface of tumor cells and APP diminishes T cell receptor signaling cascades, thus inhibiting the activity and proliferation of CD4+ and CD8+ T cells[4–7]
- Both APP and CNTN4, whilst serving important physiological functions, are also implicated in various neurodevelopmental and neurodegenerative diseases, such as Autism Spectrum Disorder and Alzheimer's Disease, but the exact mechanism behind this is currently unclear[1–3]
- CNTN4 is highly expressed on multiple tumor types including gastrointestinal, genitourinary, melanoma, breast and lung[8]
- Preliminary data show that there is an inverse relationship between CNTN4 and programmed cell death ligand-1 (PD-L1)[9]
- Tumor upregulation of CNTN4 may facilitate tumor immune evasion, and elevated CNTN4 levels have been associated with poorer outcomes for patients treated with programmed cell death-1 checkpoint inhibitors[10]

EP0089

- EP0089 is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that specifically binds CNTN4 and inhibits the interaction between CNTN4 and APP, thereby triggering an immune response within the tumor microenvironment
- *In vitro* and *in vivo* studies demonstrated that EP0089 neutralized CNTN4-mediated suppression of T cell activation and promoted killing of tumors overexpressing CNTN4 (**Figure 1**)
- Therapeutic agents that block the interaction of CNTN4 with APP may have the potential to address significant unmet medical need across a range of tumor types

Figure 1. Proposed mechanism of action for EP0089

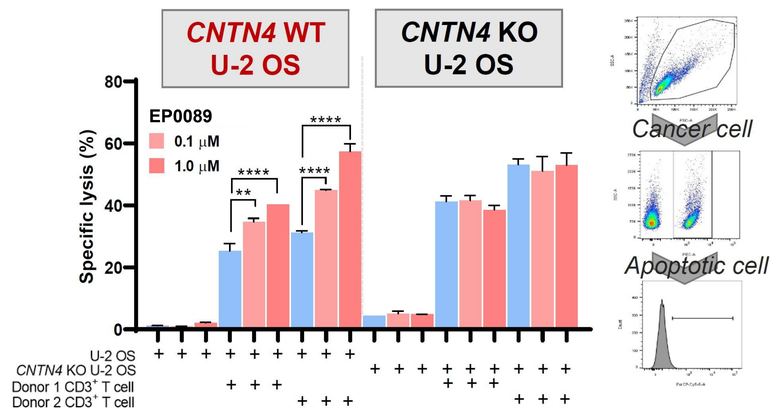


APP, amyloid precursor protein; CNTN4, contactin 4

In vitro and in vivo activity

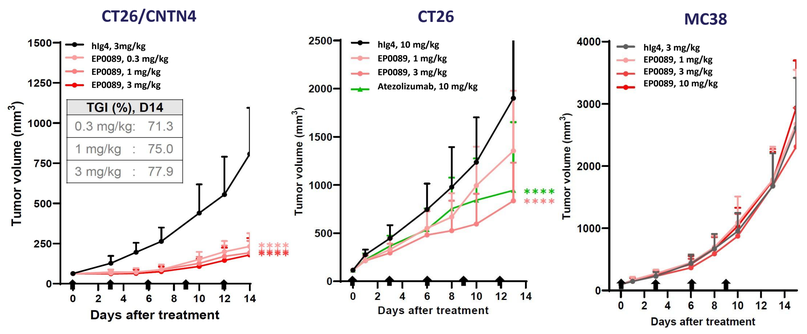
- EP0089 inhibited the interaction between CNTN4 and APP, which increased T cell mediated cytotoxicity when CNTN4-expressing U-2 OS cancer cells were co-cultured with T cells (**Figure 2**)[10]
- Treatment with EP0089 showed significant antitumor activity in the CT26/CNTN4 overexpression model (**Figure 3**)[11]

Figure 2. Cytotoxicity of human CD3+ T cells against U-2 OS or CNTN4 KO U-2 OS human cancer cells with or without EP0089[10]



Flow cytometric profiles for quantification of apoptotic human cancer cells after incubation with human CD3+ T cells in the absence or presence of EP0089. U-2 OS pulsed human CD3+ T cells were cultured with CMFDA-stained U-2 OS or CNTN4 KO U-2 OS human cancer cells in the presence or absence of EP0089 (0.1 or 1 μM) at 24 hours. Apoptotic human cancer cells were determined by flow cytometry (**, P<0.01; ***, P<0.005; ****, P<0.001)
KO, knockout; WT, wild type

Figure 3. *In vivo* antitumor activity of EP0089[11]

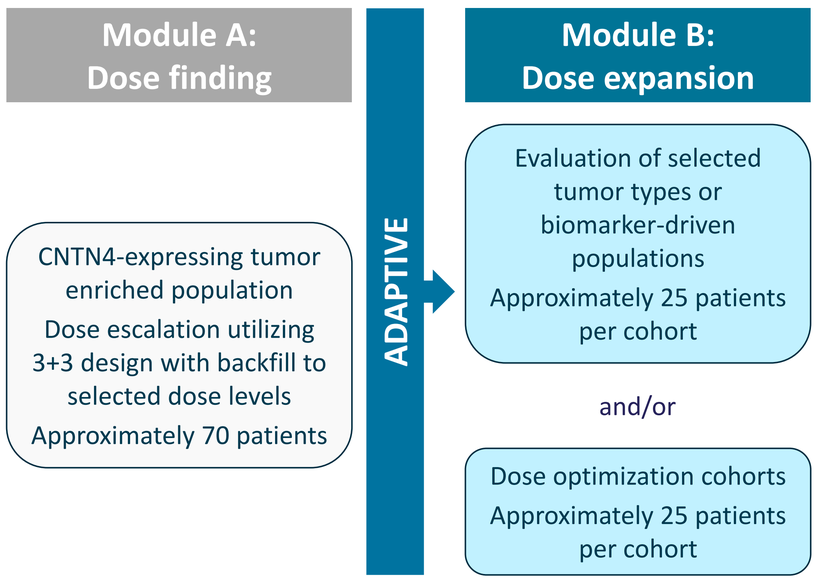


Treatment with EP0089 demonstrated significantly higher antitumor activity in CNTN4 expressing models. CNTN4 expression was confirmed by western blot and flow cytometry (data not shown). Data are displayed as mean ± SD versus control group (hIg4) by multiple comparison two-way ANOVA (***, P<0.001; ****, P<0.001)
ANOVA, analysis of variance; D, day; SD, standard deviation; TGI, tumor growth inhibition

STUDY DESIGN

- EP0089-101 (NCT07030478) is a first-in-human, open-label, phase I/IIa study (**Figure 4**)
- The study is being conducted in the Republic of Korea and Australia, and will later open in the United States and Europe
- Target enrolment is approximately 190 patients
- Doses evaluated may include 1, 3, 10, 15 and 20 mg/kg or other doses subject to Safety Monitoring Committee review

Figure 4. EP0089-101 study design



Primary objective

- To determine the maximum tolerated dose and recommended phase II dose of EP0089

Secondary objectives

- To characterize the PK and immunogenicity profile of EP0089
- To assess preliminary antitumor activity of EP0089

Exploratory objectives

- To explore predictive biomarkers and biomarkers of response, including impact of CNTN4 expression

Key eligibility criteria

- A confirmed diagnosis of an unresectable, recurrent, or metastatic advanced solid tumor with no available standard therapy or for whom standard therapy has failed
  - The population will be enriched for tumor types known to express CNTN4, including gastric, gastro-esophageal, esophageal adenocarcinoma, hepatocellular, bladder, gallbladder, endometrial, melanoma, and prostate
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Life expectancy >3 months
- Measurable disease per RECIST v1.1 (or disease-specific guidelines, e.g., Prostate Cancer Working Group 3)
- No primary CNS disease or known CNS metastases

Study procedures

- Patients will initially receive EP0089 by intravenous infusion once every 2 weeks, subject to ongoing Safety Monitoring Committee review throughout dose escalation. Patients may continue to receive EP0089 until disease progression, unacceptable toxicity or withdrawal of consent
- Adverse event and safety assessments will be performed throughout
- Blood samples will be collected for evaluation of pharmacokinetics (PK), anti-drug antibodies and neutralizing antibodies
- Tumor imaging will be performed every 8 weeks for 24 weeks and then every 12 weeks thereafter
- Blood and tissue samples will be collected for safety and exploratory biomarker analyses, which may include the relationship between antigen expression (e.g., CNTN4, PD-L1) and antitumor activity, target engagement, proof of mechanism (e.g., immune-modulation) and evidence of efficacy (e.g., circulating tumor DNA)

SUMMARY

- CNTN4, a novel immunomodulatory protein, has been shown to negatively regulate T cell activity through binding with APP on T cells, making it a newly identified target for cancer therapy; particularly as it is highly expressed on multiple tumor types including gastrointestinal, genitourinary, melanoma, breast and lung
- EP0089 is a humanized IgG4 monoclonal antibody that specifically binds CNTN4 and inhibits the interaction between CNTN4 and APP
- EP0089-101 (NCT07030478) is a first-in-human, open-label, phase I/IIa study evaluating the safety and efficacy of EP0089 in patients with unresectable, recurrent, or metastatic advanced solid tumors for whom no standard therapy exists or for whom standard therapy has failed

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