HuMab-5B1 (MVT-5873) is a fully human monoclonal antibody targeting sLea, a sialylated tetrasaccharide that is the immunodominant epitope on CA19-9 positive tumors. CA19-9 is frequently expressed in pancreatic ductal adenocarcinoma (PDAC), gastrointestinal cancers, and other epithelial cell tumors. Serum CA19-9 levels are an informative biomarker for assessing the aggressiveness and metastatic potential of PDAC and other CA19-9 expressing tumors. PDAC is a highly lethal cancer with high specificity for sLea and demonstrates cytotoxicity by multiple mechanisms against sLea positive cell lines. This first-in-human phase I trial evaluates HuMab-5B1 as a single agent and in combination with gemcitabine and nab-paclitaxel, a standard of care regimen for advanced PDAC.

Abstract

Background

Tumor type

- Pancreas
- Colorectal
- Uterus
- Ovary
- Other

CA19-9 expression rates

- Pancreatic ductal adenocarcinoma 84%
- Colon/rectum 36%
- Uterus 15%
- Ovary 29%
- Other 30%

Table 1: CA19-9 expression rates.

Table 2: Tissue binding.

In tissue microarrays, binding was specific, differentially expressed, and restricted. Tumor tissue reactivity by IHC shows diffuse cytoplasmic staining with some membranous staining. Normal tissue lacks reactivity. 6

Binding Specificity

- Against a glycan array of 465 distinct carbohydrates, HuMab-5B1 binds with specificity to both major sLea isoforms: Neu5Ac-Ler-form containing sialic acid N-acetylhexosaminidase-acid (Ac); Mammalian variant Neu5Gc-Ler-form containing sialic acid N-glycolylhexosaminidase-acid (Ac).

- Importantly, no binding was seen against the structurally similar glycans SLn, Lea, and Le.

Glycan Array Binding

Against a glycan array of 465 distinct carbohydrates, HuMab-5B1 binds with specificity to both major sLea isoforms: Neu5Ac-Ler-form containing sialic acid N-acetylhexosaminidase-acid (Ac); Mammalian variant Neu5Gc-Ler-form containing sialic acid N-glycolylhexosaminidase-acid (Ac).

Table 1: Tissue binding.

- CA19-9 is a proteoglycan antigen defined by the murine monoclonal antibody N1645S-19-9. It circulates as a high molecular weight mucin with a terminal serum t½ of about 4 days.

Antibody Discovery

- CA19-9 is frequently expressed in pancreatic ductal adenocarcinoma (PDAC), gastrointestinal cancers, and other epithelial cell tumors. Serum CA19-9 levels are an informative biomarker for assessing the aggressiveness and metastatic potential of PDAC and other CA19-9 expressing tumors.

- HuMab-5B1 is a fully human monoclonal antibody targeting sLea, an epitope on the CA19-9 positive tumor cell line. It is being developed for the treatment of CA19-9 positive tumors.

- Phase I trial of HuMab-5B1 (MVT-5873), a novel monoclonal antibody targeting sLea, in patients with advanced pancreatic cancer and other CA19-9 positive malignancies.

- Study Design
  - Single agent MVT-5873
  - Histologically confirmed progressive, locally advanced, or metastatic PDAC or other CA19-9 positive tumor

- Primary Objectives
  - Efficacy of MVT-5873 evaluated as a single agent and in combination with gemcitabine and nab-paclitaxel.
  - Safety and tolerability of MVT-5873.

- Secondary Objectives
  - Evaluate tumor response rate by RECIST 1.1.
  - Evaluate duration of response.

- Radioligand binding to sLea in PET-CT imaging.

- Phase I trial initiated in February 2016.

- Phase I trial is expected to begin 4Q 2016.

- Immunopharmacology
  - Relative human tumor cell killing is > 50% for a 6-week tumor volume assay.
  - Mice were euthanized after mean tumor volume reached 1500 mm³.

- Pharmacology (PK) of MVT-5873 in Cynomolgus monkeys.

- Pharmacokinetics (PK) of MVT-5873 in Cynomolgus monkeys.

- PK profile is typical for a monoclonal antibody and supportive of an every 2 week dosing strategy in humans.

- Predicted human steady-state plasma concentrations of MVT-5873 given every 2 weeks at clinical dose levels and above EC50 for ADCC and CDC activity.

- Efficacy of MVT-5873 evaluated as a single agent and in combination with gemcitabine and nab-paclitaxel.

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