Abstract
CTO26

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

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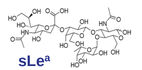
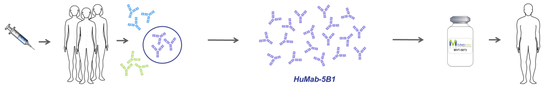
Background

HuMab-5B1 (MVT-5873) is a fully human IgG1/λ monoclonal antibody specifically targeting sialyl Lewis^a (sLe^a), a sialylated tetrasaccharide that is the immunodominant epitope on carbohydrate antigen CA19-9.[1-3]

Expression of sLe^a, a known ligand for E-selectin, is involved in cell adhesion and may influence tumor cell invasiveness and metastasis.



Antibody Discovery



Following repeated vaccinations with an sLe^a-KLH conjugate vaccine, high titers of anti-sLe^a antibodies are identified in blood samples from two patients with breast cancer.

Peripheral blood mononuclear cells are used to generate human antibody-expressing hybridoma cells.

Cross-reactivity and binding affinity studies lead to selection of antibody 5B1 (IgG1/λ), for subcloning. High anti-sLe^a antibody producing clones identified and expanded for monoclonal antibody (mAb) production.

Characterization studies of 5B1 affinity, in vitro cytotoxicity, and in vivo efficacy support investigation of clinical activity.

IND enabling studies completed in 2015.

First-in-human phase I trial of MVT-5873, a fully human IgG1/λ mAb targeting sLe^a, initiated in February 2016.

CA19-9 as an Immunotherapeutic Target

CA19-9 is a proteoglycan antigen defined by the murine monoclonal antibody 116-NS-19-9. It circulates as a high molecular weight mucin with a terminal serum $t_{½}$ of about 4 days.[4]

CA19-9 is frequently expressed in pancreatic ductal adenocarcinomas (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.

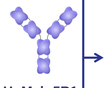
Proteoglycans, such as CA19-9, are established immunotherapy targets.[6]

HuMab-5B1 represents a novel antibody platform for the treatment of patients with CA 19-9 positive tumors.

CA19-9 expression rates[5]

Tumor type	Positivity (%)
Pancreas	92
Stomach	37
Endometrium	36
Uterus	30
Colon/rectum	29
Breast	24
Ovary	15
Other	3

HuMab-5B1 Clinical Development Platform



Therapeutic Antibody (MVT-5873)
Treatment of PDAC and other CA19-9 positive tumors
Phase I trial initiated February 2016

Immuno-PET Imaging (MVT-2163)
^{89}Zr-HuMab-5B1 for PET imaging of PDAC and other CA19-9 positive tumors[7]
Phase I trial to begin May 2016

Radioimmunotherapy
^{177}Lu/^{90}Y-DTPA-HuMab-5B1 for targeted radiotherapy of PDAC and other CA19-9 positive tumors
Phase I trial expected to begin 4Q 2016

Binding Specificity

Glycan Array Binding

Against a glycan array of 465 distinct carbohydrates, HuMab-5B1 binds with specificity to both major sLe^a isoforms:

- Neu5Ac-Le^a form, containing sialic acid N-acetylneuraminic acid (Ac)
- Mammalian variant Neu5Gc-Le^a, containing sialic acid N-glycolylneuraminic acid (Gc)

Importantly, no binding was seen against the structurally similar glycans sLe^x, Le^a, Le^x, and Le^y.

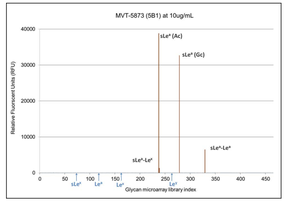
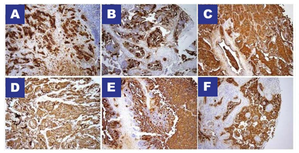


Chart number	Glycan structure	Average	SD	SEM	% CV
237	Neu5Aca2-3Galβ1-3(Fuca1-4)GlcNAcβ-Sp8	38851	2797	1399	7
278	Neu5Gca2-3Galβ1-3(Fuca1-4)GlcNAcβ-Sp0	32714	2624	1312	8
329	Neu5Aca2-3Galβ1-3(Fuca1-4)GlcNAcβ1-3Galβ1-3(Fuca1-4)GlcNAcβ-Sp0	6477	399	200	6
238	Neu5Aca2-3Galβ1-3(Fuca1-4)GlcNAcβ1-3Galβ1-4(Fuca1-3)GlcNAcβ-Sp0	1344	131	65	10

Tissue Binding

In tissue microarrays, binding was specific, differentially expressed, and restricted.

MVT-5873 tumor tissue staining (IHC)



- Typical tumor tissue reactivity by IHC shows diffuse cytoplasmic staining with some membrane staining.
- Most normal tissues lack reactivity.†

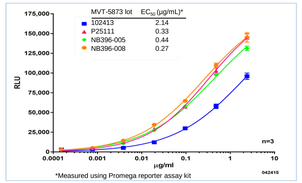
†staining of secretory epithelial structures were considered unlikely to be relevant as they are generally considered inaccessible to circulating antibodies

A) Pancreatic ductal adenocarcinoma
B) Colon carcinoma
C) Lung adenocarcinoma
D) Urinary bladder, mucinous adenocarcinoma
E) Colon metastatic to ovary
F) Breast carcinoma, lymph node

ADCC and CDC Activity

Antibody-dependent cellular cytotoxicity (ADCC)

Potent ADCC activity against the sLe^a positive BxPC3 human pancreatic cancer cell line.*



*Measured using Promega reporter assay kit

Complement-mediated cytotoxicity (CDC)

Potent CDC activity against the sLe^a positive DMS 79 human lung cancer cell line. Cell kill proportional to MVT-5873 concentration.**

MVT-5873 conc. (μg/mL)	% cell kill	
	Mean	SD
10.00	67.8	1.5
3.30	51.2	1.6
1.10	28.6	4.1
0.36	10.9	2.2
0.12	2.5	0.6

**Measured using Guava PCA-96 Cell Toxicity™ kit

Antitumor Efficacy and Pharmacokinetics

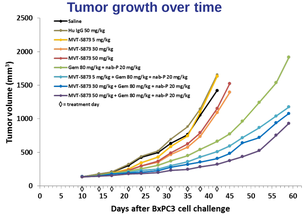
BxPC3 Human Pancreatic Cancer Xenograft Model

Efficacy of MVT-5873 evaluated as a single agent and in combination with gemcitabine (Gem)/nab-paclitaxel (nab-P) chemotherapy, a standard regimen for advanced or metastatic PDAC.

Dose-dependent inhibition of tumor growth observed with single-agent MVT-5873.

Potentiation of tumor growth inhibition and growth delay seen with co-administration of MVT-5873 and chemotherapy.

Tumor growth over time



Treatment group (n = 5)	Tumor growth inhibition index	Time to 50% tumor growth* (Days)	
		Median	Range
Human IgG 50 mg/kg (control)	-	32	32-41
Saline	15.2	35	33-38
MVT-5873 5 mg/kg	1.46	35	34-38
MVT-5873 30 mg/kg	36.8	37	35-49
MVT-5873 50 mg/kg	32.8	38	36-41
Gem 80 mg/kg + nab-P 20 mg/kg	65.5	46	42-51
MVT-5873 5 mg/kg Gem 80 mg/kg + nab-P 20 mg/kg	75.5	50	47-60+
MVT-5873 30 mg/kg Gem 80 mg/kg + nab-P 20 mg/kg	82.2	60	49-60+
MVT-5873 50 mg/kg Gem 80 mg/kg + nab-P 20 mg/kg	87.6	64	47-60+

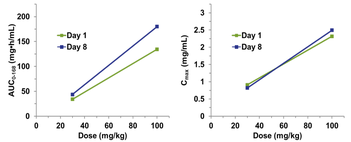
Methods

- Groups of SCID mice (n = 5) treated twice weekly for 5 weeks; tumor volumes assessed twice weekly
- Mice culled if mean group volume > 1,500 mm^3 or at Day 60 (end of experiment)
- Time to 50% tumor growth calculated relative to IgG control
- Mean tumor growth inhibition calculated on day 42, the time point at which the IgG control group reached maximum permitted tumor size:

$$\left(1 - \frac{\text{mean volume treated}^{(\text{Day 42})} - \text{mean volume treated}^{(\text{Day 0})}}{\text{mean volume control}^{(\text{Day 42})} - \text{mean volume control}^{(\text{Day 0})}}\right) x\ 100$$

Pharmacokinetics (PK) of MVT-5873 in Cynomolgus monkeys

MVT-5873 plasma exposure (AUC) and peak concentration (C_{max}) after Day 1 and Day 8 dosing



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 are above EC$_{50}$ for ADCC and CDC activity

MVT-5873 dose (mg/kg)	Concentration (μg/mL)	
	C$_{max}$	C$_{min}$
3	82	25
10	274	82
15	411	124

Methods

- IV administration of MVT-5873 at 30 and 100 mg/kg in Cynomolgus monkeys (n = 4)
- MVT-5873 quantified in serum using a target (sLe^a)-based capture ELISA

Phase I Trial Rationale and Design

Rationale

MVT-5873 is a fully human monoclonal antibody targeting sLe^a, an epitope on the proteoglycan antigen CA 19-9 that is expressed in greater than 90% of pancreatic cancers.

MVT-5873 binds with high specificity to sLe^a and demonstrates cytotoxicity by multiple mechanisms against sLe^a positive cell lines.

This first-in-human phase I trial evaluates MVT-5873 as a single agent and in combination with gemcitabine and nab-paclitaxel, a standard of care regimen for advanced PDAC.

Study Design

Single agent MVT-5873

Histologically confirmed progressive, locally advanced, or metastatic PDAC or other CA19-9 positive tumor

↓

Dose escalation (3 + 3 design)
MVT-5873 1, 3, 6, 10, 15 mg/kg
q 14 days, continuous 28-day cycle

↓

Dose expansion (n = 10)
at recommended Phase II dose

Combination MVT-5873 with gemcitabine/nab-paclitaxel

Histologically confirmed unresectable or metastatic PDAC

↓

Dose escalation (3 + 3 design)
MVT-5873 at 1 level < MTD, q14 days
gemcitabine 1000 mg/m^2 days 1, 8, 15
nab-paclitaxel 125 mg/m^2 days 1, 8, 15
continuous 28-day cycle

↓

Dose expansion (n = 10)
at recommended Phase II dose

Primary Objectives

- Determine the safety, pharmacokinetics, and MTD of MVT-5873 as a single agent and in combination with gemcitabine and nab-paclitaxel

Secondary Objectives

- Evaluate tumor response rate by RECIST 1.1
- Evaluate duration of response

Exploratory Outcomes

- Assess for presence of anti-5B1 antibodies
- Evaluate relationships between circulating CA19-9 levels and tumor response, MVT-5873 PK, and tumor sLe^a expression (IHC)
- Evaluate changes in circulating tumor cell (CTC) levels (dose expansion phase)

Key eligibility criteria

- Evaluable disease by RECIST 1.1 during dose escalations
- ECOG performance status of 0 to 1
- Adequate hematologic, renal, and laboratory parameters

ClinicalTrials.gov Identifier: NCT02672917

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