Abstract
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Preclinical development of MVT-1075 as radioimmunotherapy for pancreatic cancer and other CA19-9 positive malignancies

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Background

CA19-9 as a Therapeutic Target

CA19-9 cellular expression, typically in high copy numbers, occurs in up to 94% of pancreatic cancers, with high rates also seen across other predominantly GI tumor types[1]

HuMab-5B1 (MVT-5873) is a fully human IgG1/λ monoclonal antibody that binds with high affinity to sialyl Lewis^a (sLe^a), the immunodominant epitope of CA19-9, and is highly internalized in CA19-9 expressing tumor cells.[2,3]

Studies with the immuno-PET conjugate ^{89}Zr-DFO-HuMab-5B1 (MVT-2163) show clear tumor delineation and prolonged cellular retention in CA19-9+ pancreatic cancer models.[4]

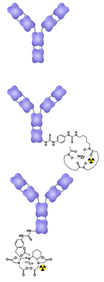
HuMab-5B1 based Radioimmunotherapy (RIT)

To explore its potential as a targeted radioimmunotherapeutic, HuMab-5B1 was conjugated with the bifunctional chelator *p*-SCN-Bn-CHX-A"-DTPA (DTPA) and then radiolabeled with Lutetium-177 (^{177}Lu) to form MVT-1075[5] or Yttrium-90 (^{90}Y) to form MVT-1916.

Property	Key Attributes		
	^{90}Y	^{177}Lu	MVT-1075 Product (^{177}Lu-DTPA-HuMab-5B1)
Emission	β 2.3 MeV (max)	β 0.5 MeV (max)	^{177}Lu is a relatively low energy β-emitter compared to ^{90}Y
		γ 113 keV, 208 keV	γ-emissions from ^{177}Lu useful for scintigraphic imaging and to dosimetry to assess target organ exposure
Maximum range	11-12 mm	1-2 mm	Shorter path length of ^{177}Lu may afford less bystander toxicity to non-targeted cells
Half-life	2.7 days	6.7 days	Half-life of ^{177}Lu pairs well with approximate 20 day half-life of human monoclonal antibodies[6]
Internalization		✓	Internalization of HuMab-5B1 in sLe^a expressing cells potentially sequesters ^{177}Lu within tumor cells, with longer half-life providing extended therapeutic radiation exposure[7]
Tumor binding		✓	Dense expression of sLe^a epitope on tumor cells potentially enhances therapeutic radiation exposure[8]

HuMab-5B1 Clinical Development Platform

HuMab-5B1 represents a novel antibody platform for the development of therapeutic and diagnostic agents targeting CA 19-9 positive tumors.



Therapeutic Antibody (MVT-5873)
Treatment of pancreatic ductal adenocarcinoma (PDAC) and other CA19-9+ tumors
Phase I trial initiated February 2016
ClinicalTrials.gov Identifier: NCT02672917

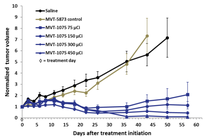
Immuno-PET Imaging (MVT-2163)
^{89}Zr-DFO-HuMab-5B1 for PET imaging of PDAC and other CA19-9+ tumors
Phase I trial initiated May 2016
ClinicalTrials.gov Identifier: NCT02687230

Radioimmunotherapy (MVT-1075)
^{177}Lu-CHX-A"-DTPA-HuMab-5B1 for targeted radiotherapy of PDAC and other CA19-9 positive tumors
FDA authorization to proceed, first-in-human phase I trial planned early 2017

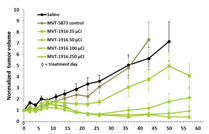
RIT Efficacy and Dose Selection

Single Dose RIT Studies in a BxPC3 Human Pancreatic Cancer Xenograft Model

MVT-1075 (^{177}Lu-DTPA-HuMab-5B1)



MVT-1916 (^{90}Y-DTPA-HuMab-5B1)



Escalating doses of MVT-1075 or MVT-1916 were given as a single administration (Day 1) to groups of athymic nude mice (n = 7 or 8) with established subcutaneous BxPC3 xenografts (mean volume ~150 mm^3). An equivalent antibody mass was given in all treatment arms.

Tumor growth was measured by caliper over the 57-day study period, with measurements normalized to individual starting volumes. Data were censored when ≥ 25% of group exceeded the maximum allowed tumor volume of 1,500 mm^3.

Both MVT-1075 and MVT-1916 were well tolerated and provided effective and sustained tumor growth inhibition throughout the observation period.

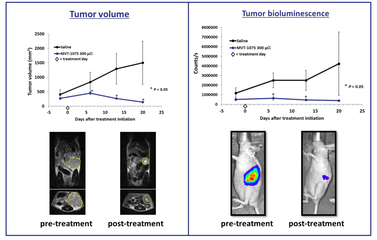
Given the clinically favorable properties of ^{177}Lu, MVT-1075 was selected for further development.

Efficacy in an Orthotopic BxPC3 Tumor Model

Groups of athymic nude mice (n = 6 or 8) with established orthotopic BxPC3-Luc tumors (mean volume ~300 mm^3) were treated with a single 300 µCi dose of MVT-1075.

Tumor growth was measured by both MRI and bioluminescence imaging (BLI) throughout the 20-day study period, at which point the saline exceeded the maximum allowed tumor volume of 1,500 mm^3.

- Treatment with MVT-1075 significantly inhibited tumor growth compared to the saline control.
- MVT-1075 treated group regressed to approximately 50% of the pretreatment volume by Day 20
- Mean tumor volume in the saline control group increased 4-fold from the pretreatment volume



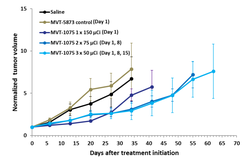
RIT Dose Fractionation

Effect of Dose Fractionation in a BxPC3 Human Pancreatic Cancer Xenograft Model

Delivery of RIT on a fractionated dose schedule may permit delivery of a higher total dose of therapy while maintaining acceptable tolerability levels.[9]

Three dose fractionation schedules of MVT-1075, (total dose = 150 µCi) were evaluated in groups of athymic nude mice (n = 8) with established subcutaneous BxPC3 xenografts (mean volume ~250 mm^3). Data were censored when ≥ 50% of group exceeded the maximum allowed tumor volume of 1,500 mm^3.

MVT-1075 (^{177}Lu-DTPA-HuMab-5B1)



MVT-1075 administered at dose of 150 µCi as either a single dose or on a fractionated schedule effectively inhibited tumor growth compared to controls. Though preliminary, these data also suggest a potential for benefit to delay tumor growth with the fractionated schedules.

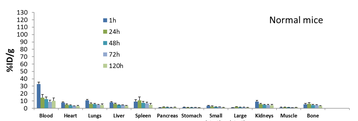
The findings are supportive of the use of a fractionated schedule in the phase I clinical trial.

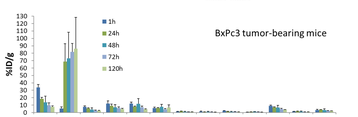
MVT-1075 Biodistribution

The biodistribution of MVT-1075, assessed by gamma counting of tissues, was evaluated in groups (n = 5 per timepoint) of normal athymic nude mice and in mice bearing subcutaneous BxPC3 xenografts (mean volume ~ 200 mm^3) over a period of 120 hours.

In normal mice, there was an expected gradually decreasing activity in blood, heart, and lungs, with low uptake in normal pancreas.

Biodistribution in tumor-bearing mice showed rapid uptake in tumor tissue, reaching 69% ID/g by 24 h and 86% ID/g by 120 h. Otherwise, the biodistribution pattern paralleled that of normal mice, with relative %ID/g values within about ± 25% of those seen in normal mice across all time points for blood, heart, lungs, kidneys, and pancreas. with slightly higher uptake in liver and slightly lower uptake in spleen.





The biodistribution of MVT-1075 in normal mice was used to estimate normal organ radiation doses in the 70-kg Standard Adult anatomic model (OLINDA program) and inform the starting dose level of MVT-1075 for the phase I trial.

Phase I Trial Rationale and Design

Overview

MVT-1075 RIT combines HuMab-5B1's properties of highly specific sLe^a binding and high degree of cancer cell internalization with the favorable radionuclide properties of ^{177}Lu to selectivity target CA19-9 expressing tumor cells and potentiate cell killing.

The first-in-human phase I study is a nonrandomized, open-label, dose-escalation (3+3 design) with cohort expansion study of MVT-5873 / MVT-1075 in patients with previously treated CA19-9+ PDAC or other CA19-9+ malignancies.

Use of a blocking dose of MVT-5873 is supported by improved tumor targeting and decreased nonspecific tissue accumulation of the immunoPET agent MVT-2163 seen with pre-administration of MVT-5873.[10]

The fractionated dosing schedule coupled with dosimetry permits precise evaluation of dosimetry and bone marrow radiation exposure, anticipated to be the most sensitive organ.

Study Design

Day 1	MVT-5873: 70 mg blocking dose MVT-1075: 50% of dose predicted to result in cohort specified exposure
1-8	Dosimetry (gamma camera + SPECT/CT scans)
15	MVT-5873: 70 mg blocking dose MVT-1075: remainder of dose predicted to result in cohort specified exposure

Up to 3 additional cycles of therapy permitted, provided
- Toxicities observed with prior cycle do not preclude additional therapy, as defined in protocol
- Exposure limits to specified organs are not exceeded
- All laboratory-based initial entry criteria are met (with the exception of serum CA19-9 levels)
- No evidence of disease progression
- At least 6 weeks and no more than 12 weeks elapsed from Day 1 of prior cycle of therapy

Primary Objectives
- Determine the MTD and safety profile of MVT-5873 / MVT-1075

Secondary Objectives
- Determine the dosimetry and pharmacokinetics of MVT-1075
- Evaluate tumor response rate (RECIST 1.1) and duration of response

Exploratory Outcomes
- Evaluate relationships between circulating CA19-9 levels and tumor response and MVT-1075 pharmacokinetics
- Evaluate formation of anti-drug antibodies

Key eligibility criteria
- Histologically or cytologically confirmed previously treated CA19-9+ PDAC or other CA19-9+ malignancies
- Evaluable disease by RECIST 1.1
- ECOG performance status of 0 or 1
- Adequate hematologic, renal, and laboratory parameters

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