

Abstract CT140

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Background

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.^{1,2} CA19-9 is frequently overexpressed in pancreatic ductal adenocarcinomas (PDACs) with overexpression also seen across other predominantly GI tumor types.³

To explore its potential as a targeted RIT agent, HuMab-5B1 was conjugated with the bifunctional chelator *p*-SCN-Bn-CHX-A"-DTPA and radiolabeled with Lutetium-177 (¹⁷⁷Lu) to form MVT-1075. ¹⁷⁷Lu is a low-energy β-emitter (max. energy, 0.5 MeV) with relatively short tissue penetration (max. 1.6 mm) that also emits γ-radiation (113 keV, 7%; 208 keV, 11%) suitable for scintigraphic imaging and dosimetry.

Phase I Trial Design

- First-in-human Phase 1 study: nonrandomized, open-label, dose-escalation (3+3 design) with cohort expansion of MVT-5873 / MVT-1075 in relapsed/refractory CA19-9+ PDAC or other CA19-9+ malignancies
- MVT-5873 blocking dose supported by immunoPET studies with MVT-2163 showing improved tumor targeting and decreased nonspecific tissue accumulation^{4,5}
- Fractionated dosing schedule coupled with image-based dosimetry permits treatment to be prescribed in terms of radiation absorbed dose to the bone marrow, anticipated to be the most sensitive organ

Treatment Overview

Day 1	MVT-5873: 70 mg blocking dose MVT-1075: 50% of amount predicted to result in cohort specified bone marrow dose
1-8	Dosimetry (gamma camera - planar and SPECT/CT scans)
15	MVT-5873: 70 mg blocking dose MVT-1075: remainder of amount predicted to result in cohort-specified bone marrow dose
Up to 3 additional cycles of therapy permitted, provided - Toxicities observed with prior cycle do not preclude additional therapy, as defined in protocol - Radiation dose 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 (PK) 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 PK
- 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

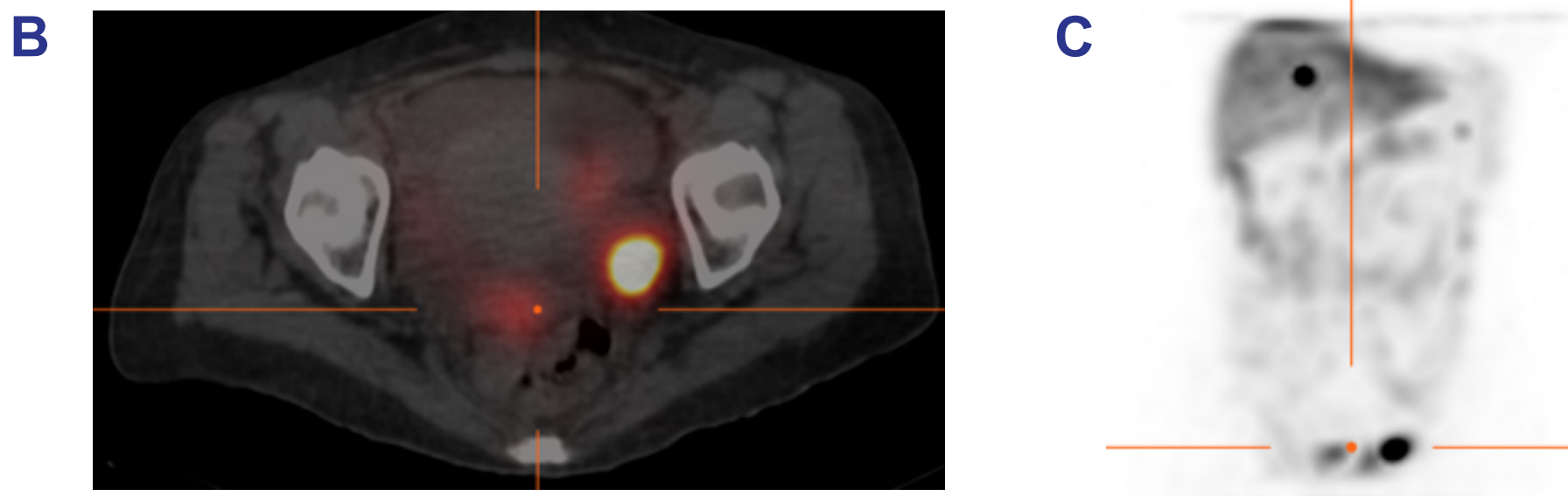
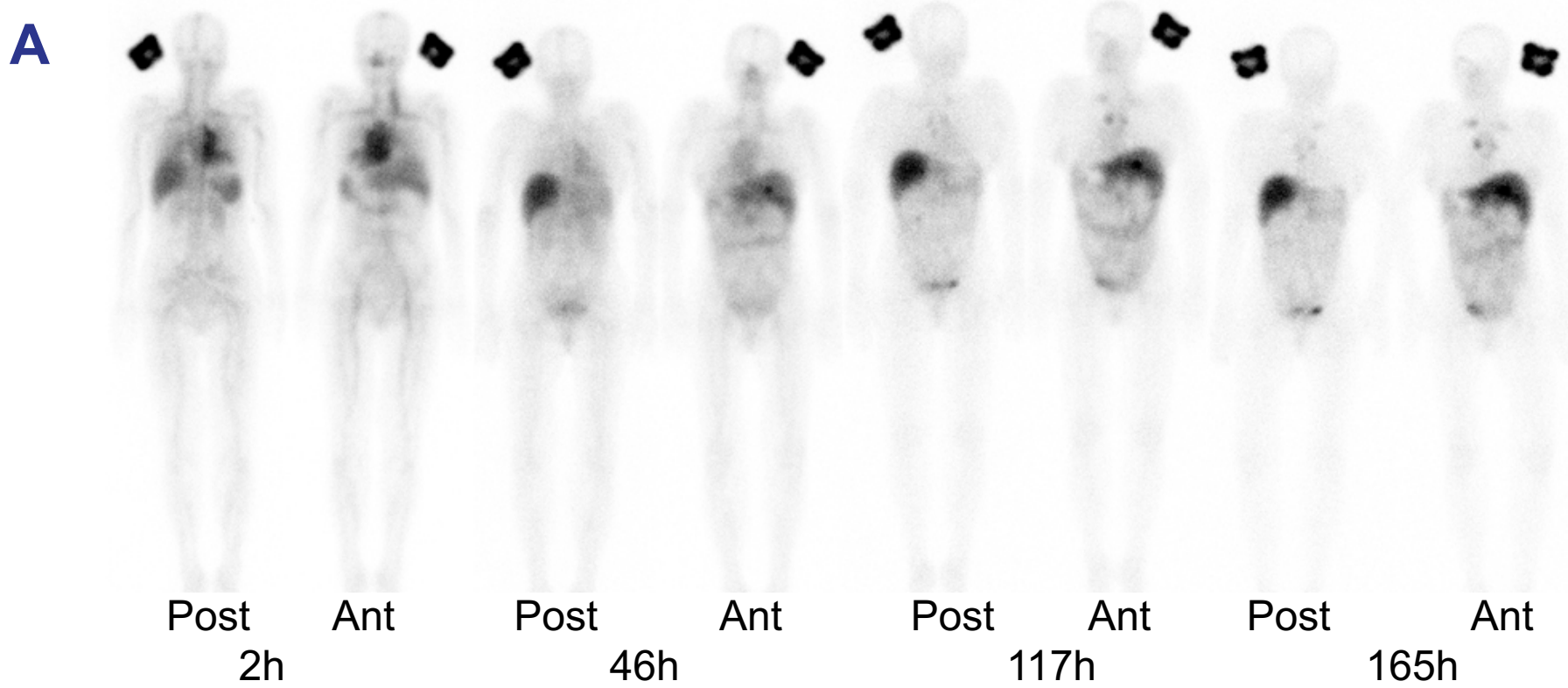
Enrollment and Treatment

Demographics and Baseline Characteristics – Cohort 1	
Subjects enrolled (n)	3
Male : Female	2 : 1
Median age, (range), yrs	60 (60 - 61)
ECOG PS 0 : 1	0 : 3
Prior Therapy: No. of systemic therapies	
1	0
2	0
3	2
4+	1
Radiation	0
Surgery	1
Primary Disease Site (n)	
Pancreas	3

As of 8-Apr-2018, 4 subjects, all with PDAC have been enrolled on study, with 3 subjects in Cohort 1 completing a full cycle of therapy and 1 subject in Cohort 2 currently undergoing treatment.

MVT-1075 Administered Doses			
Cohort 1: Target Red Marrow Exposure = 0.5 Gy (Initial estimated activity = 2220 MBq)			
Delivered Dose of MVT-1075 (MBq)			
Subject	Dose Fraction 1	Dose Fraction 2	Total Dose
S1	1067	1248	2315
M1	1120	2477	3597
M2	1120	760	1880

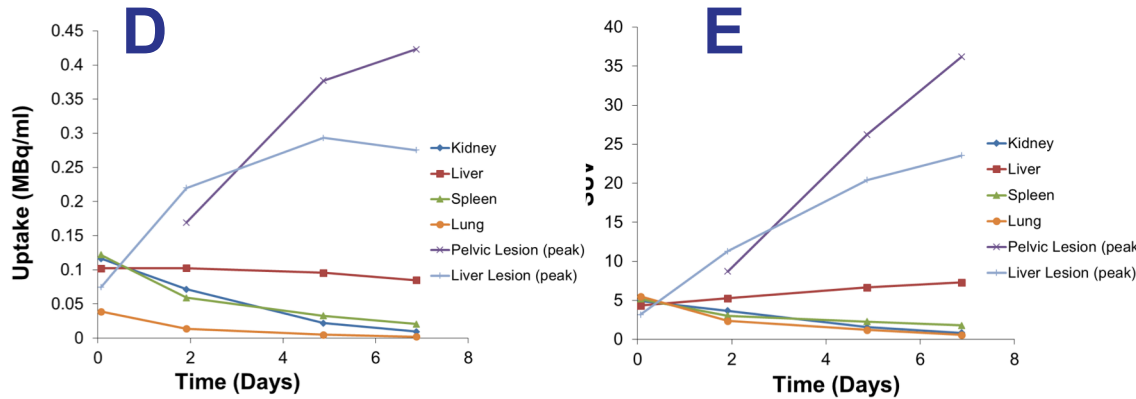
MVT-1075 Biodistribution



Serial planar imaging (A) of MVT-1075 in subject M2 shows the tissue with greatest uptake is liver. The 165h SPECT/CT image (B) shows focal uptake in a pelvic metastasis with SUV peak of 36. A liver metastasis is also visible in the MIP image (C) with SUV peak of 24.

Results

Uptake of MVT-1075

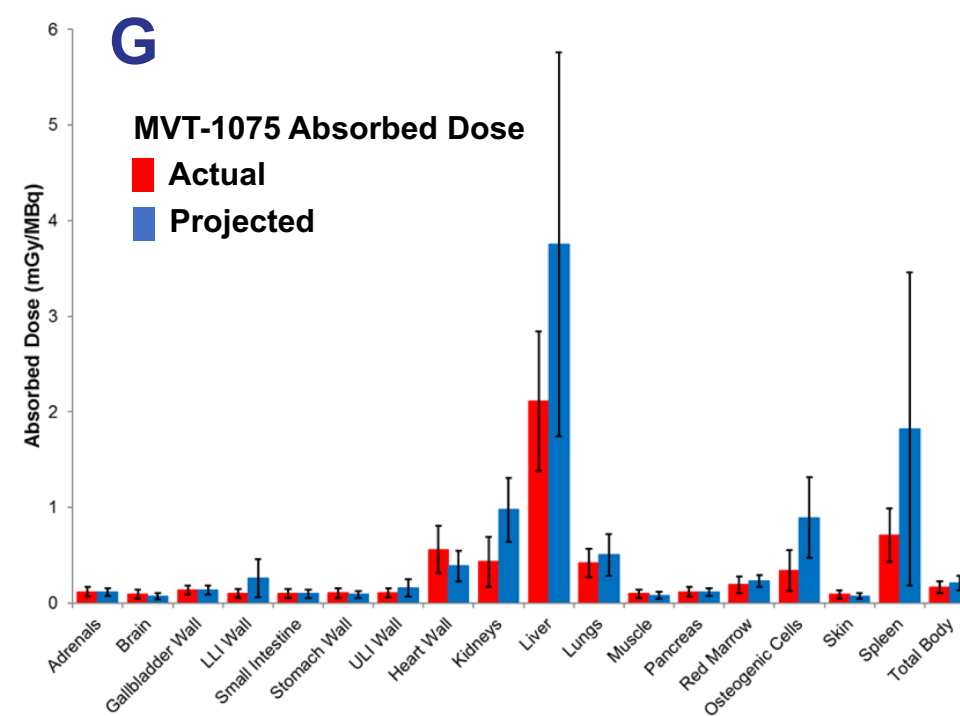


Time course of MVT-1075 uptake (D) and standardized uptake value (SUV) (E) from a representative subject indicating sustained accumulation on CA19-9+ lesions.

Predictive Biodistribution of MVT-1075 with MVT-2163

A previous PET/CT imaging study with MVT-2163 (⁸⁹Zr-DFO-HuMab-5B1) indicated significant CA19-9+ lesion targeting (F).

This study was used to generate absorbed dose projections for MVT-1075, suggesting an activity of 2220 MBq should deliver a radiation absorbed dose of 0.5 Gy to red marrow for an average patient.



Although MVT-1075 subject numbers are low, these projections seem to have been reasonable for red marrow (0.23 ± 0.06 vs 0.19 ± 0.09) mGy/MBq.

However for other tissues such as liver, spleen, kidney and bone, MVT-2163 uptake appears higher than has been seen so far with MVT-1075.

This is reflected in the comparison of absorbed doses (G) of MVT-1075 actual and projected from MVT-2163.

Safety and Outcomes

Treatment-related adverse events among the among Cohort 1 subjects (n = 3) following cycle 1 of therapy were as expected and manageable.

At the end of Cycle 1, there were 2 subjects with stable disease and 1 with disease progression. Treatment was discontinued in the stable disease subjects due to clinical indications of disease progression.

All MVT-1075 / MVT-5873 Related Adverse Events – Cohort 1 (n = 3)				
	CTCAE Grade (n)			
	1	2	3	4
Anemia	1	1		
Constipation	1			
Chills				
Fatigue		1		
↑ ALT		1		
↑ AST	3			
↑ Alkaline phosphatase	1			
↓ Lymphocyte count			1	
↓ Platelet count		1	1	
↓ White blood cell count	1			

Discussion

Preliminary results from this first-in-human Phase 1 study of MVT-5873 / MVT-1075 in patients with relapsed/refractory CA19-9+ PDAC are as follows:

- A fractionated dosing schedule of MVT-1075 combined with image-based dosimetry is a feasible RIT Phase 1 strategy, permitting within cycle dose adjustments to achieve a selected target red marrow exposure
- Early data indicate clear delineation of CA19-9+ lesions
- Data also suggest high uptake of MVT-1075 with a prolonged time course of residence and accumulation on target lesions
- Though the current data set is small, clinical biodistribution studies with the immunoPET imaging agent MVT-2163 appeared to predict the absorbed organ doses of MVT-1075, particularly red marrow, reasonably well
- The predominant treatment-related toxicities included expected and manageable (Grade 1-3) changes in hematologic and liver function parameters
- Study accrual is ongoing

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)

⁸⁹Zr-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)

¹⁷⁷Lu-CHX-A"-DTPA-HuMab-5B1 for targeted radiotherapy of PDAC and other CA19-9+ tumors
Phase I trial initiated June 2017
ClinicalTrials.gov Identifier: NCT03118349

References

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