Biodistribution and Radiation Dose Estimates for ^{89}Zr-DFO-HuMab-5B1 (MVT-2163) in CA19-9 Positive Pancreatic Cancer: First-in-Human Results

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Introduction

^{89}Zr-DFO-HuMab-5B1 (MVT-2163) was generated as a targeted PET imaging agent for CA19-9 positive malignancies. Here we report on the biodistribution and radiation dose estimates for MVT-2163 in 12 patients with CA19-9 positive cancer either when administered alone or with a cold version (MVT-5873) of the antibody used as a blocking dose. MVT-5873 is a fully human IgG1 monoclonal antibody (mAb) that targets sialyl Lewis A (sLe^a), an epitope on CA19-9, and is currently in phase 1 investigation as a therapeutic agent for patients with pancreatic cancer (PDAC) and other CA19-9 positive tumors. CA19-9 is expressed in over 90% of PDAC and in other disease including small cell lung and GI cancers. CA19-9 plays a role in tumor adhesion and metastasis, and is a marker of an aggressive phenotype. CA19-9 serum levels are considered a valuable adjunct in the diagnosis, prognosis and treatment monitoring of PDAC. We find that a blocking dose of cold antibody and a time delay between administrations of cold and labeled antibodies improves distribution and lesion uptake in patients with advanced PDAC.

Study Molecules

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

Therapeutic Antibody (MVT-5873)
Treatment of PDAC/other CA19-9+ tumors
Phase 1 trial initiated February 2016; ClinicalTrials.gov NCT02672917

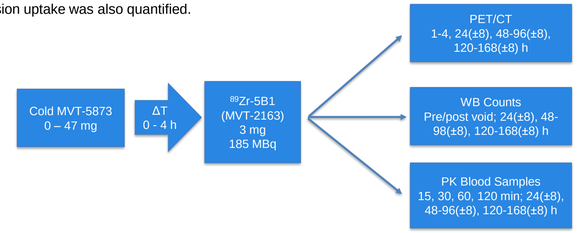
Immuno-PET Imaging (MVT-2163)
^{89}Zr-DFO-HuMab-5B1 for PET imaging of PDAC/other CA19-9+ tumors
Phase 1 trial initiated May 2016; ClinicalTrials.gov NCT02687230

Study Design

Twelve patients in 3 cohorts (3, 3, 6 pts per cohort) were administered 169 (SD 7) MBq of MVT-2163 (3mg) together with escalating masses (0, 17, 47 mg) of unlabeled MVT-5873. Unlabeled antibody, if administered, was always given prior to radiolabeled antibody. Data collected were:

1. Four whole-body PET/CT scans acquired at 1-4, 24(±8), 48-96(±8), 120-168(±8) h post-MVT-2163 administration.
2. Whole-body (WB) counts acquired using a NaI(Tl) scintillation detector immediately before and after first void and at the times of PET scanning.
3. Serial blood samples at approximately 15, 30, 60 120 min post-MVT-2163 administration and at the times of subsequent PET scans.

PET/CT images, WB and serum counts were analyzed to derive residence times for liver, kidney, spleen, lung, bone, red marrow, heart contents and remainder of body. These were used as input for OLINDA/EXM to generate normal tissue radiation dose estimates.
Lesion uptake was also quantified.

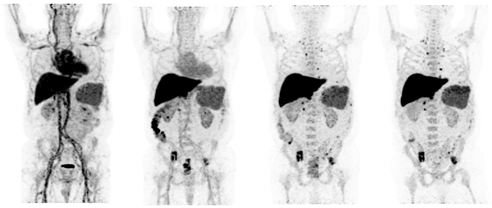


Results

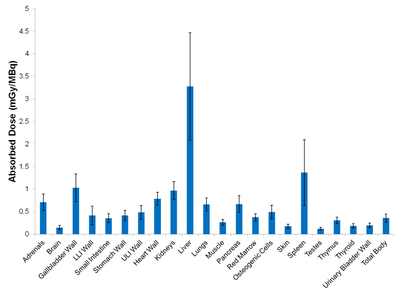
Patient Cohort Information

Cohort	1	2	3A	3B	3C
Patients (n)	3	3	2	2	2
MVT-2163 (mg)	3	3	3	3	3
Delay btw cold and hot mAb (min)	n/a	15	15	>120	>240
MVT-5873 (mg)	0	17	47		
Total mAb (mg)	3	20	50		

MVT-2163 Biodistribution



A representative time-course is shown above from a patient in Cohort 2. In general, MVT-2163 left the blood and accumulated in tumor sites, liver and, to a lesser extent, spleen. No significant urinary excretion was observed and renal uptake was relatively low. Maximal gut uptake was typically seen at 24h and was on average 3.9 (SD 3.3) % of the total administration. Low level diffuse bone uptake was also typical, becoming more apparent at later times.

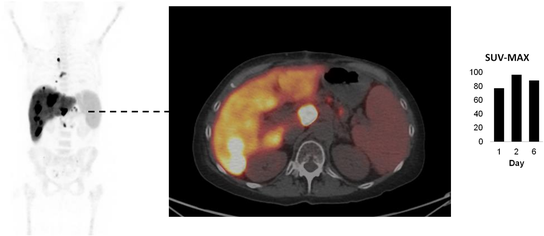


Overall, average of all patients demonstrate that normal organs with the highest absorbed doses (mGy/MBq) were liver, (3.3; SD 1.2), spleen (1.4; SD 0.7) and kidneys (0.97; SD 0.20). The average effective dose was 0.51 (SD 0.13) mSv/MBq.

Lesion Uptake

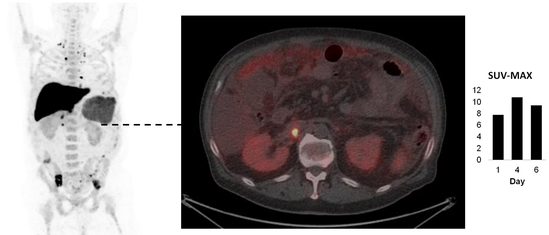
Both bone and soft tissue disease were visualized. Lesion uptake was variable but typically high. In one patient, uptake reached as high as SUV_{MAX} = 97 ($SUV_{LBM\text{-}MAX}$ = 67) by 44 h post-administration in an abdominal node (Example A). This is amongst the highest lesion uptake we have ever seen for a radiolabeled antibody. High focal uptake was frequently seen in chest/abdominal/pelvic nodes. In several instances, CT did not indicate any corresponding abnormality (Example B). We plan to include image-guided biopsy in future studies to examine this issue in more detail.

Example A – 2 h delay



MIP shows multiple sites of high uptake in the liver and abdomen with SUV_{MAX} in the range 50-100. There are also multiple small nodal sites with high focal uptake in the chest and abdomen (SUV_{MAX} 15-30). Transverse image indicates a large abdominal node (SUV_{MAX} 97) with MVT-2163 uptake maintained over 6 days of imaging.

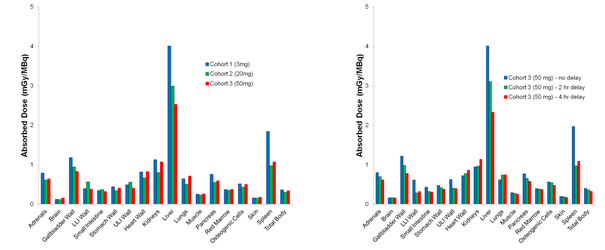
Example B – 15 min delay



MIP shows uptake in bi-lateral pelvic bone disease together with multiple small high intensity foci throughout the chest/abdomen/pelvis. Transverse image indicates a small abdominal nodal focus (SUV_{MAX} ~ 9) with no corresponding abnormality on CT and maintained uptake of MVT-2163 over 6 days of imaging.

Effect of Pre-administration of Cold MVT-5873

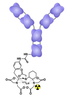
Observed differences between cohorts indicate a trend for lower liver uptake with higher antibody mass doses. In cohort 3 (47 + 3 mg) there was a trend for lower liver uptake with longer times between cold MVT-5873 and radiolabeled MVT-2163 administrations. Absorbed dose estimates shown below:



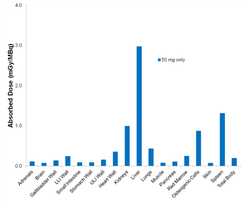
Conclusions and Next Steps

- Cold antibody pre-dose with 2-4 h delay between cold and hot mAb administrations appears to reduce liver and spleen accumulation.
- Effect of antibody mass dose and scheduling on MVT-2163 biodistribution will be further explored with the aim of maximizing lesion to normal tissue ratios.
- Image-guided biopsy will be performed to confirm CT + and CT – lesions.

Translation to Radioimmunotherapy



Radioimmunotherapy (MVT-1075)
^{177}Lu-CHX-A″-DTPA-HuMab-5B1 for targeted radiotherapy of PDAC and other CA19-9 positive tumors including small cell lung and colorectal cancer.
Phase 1 trial active June 2017; ClinicalTrials.gov NCT03118349
Normal tissue dose projections were generated for MVT-1075 assuming identical biodistribution and pharmacokinetics to MVT-2163.



Key Organs	Dose (mGy/MBq)	Dose Limit (Gy)	Max activity (GBq)	Max activity (mCi)
Red Marrow	0.25	1.5	5.98	162
Liver	2.98	32	10.8	291
Kidneys	1.00	23	23.1	623

- Red marrow likely to be dose-limiting for single administrations of ^{177}Lu-5B1 with liver likely to be dose-limiting for multiple administrations.
- The projected dose to kidney is relatively low and is unlikely to be limiting.

Acknowledgements

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