Using CA19-9 as a translational biomarker for sLe^a targeted agents MVT-5873 and MVT-1075 in CA19-9 positive cancer

Poster 62

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Abstract

Background: Sialyl Lewis A (sLe^a) modification occurs on transmembrane and secreted proteins in pancreatic ductal adenocarcinoma (PDAC) and other GI cancers, leading to a high level of expression on cancer cells compared to normal tissue. sLe^a, also known as CA19-9, can be detected in patient serum using a CA19-9 diagnostic assay, which detects shed or secreted sLe^a modified proteins. MVT-5873, a fully human antibody that specifically targets the sLe^a antigen, is in a phase 1 clinical trial for the treatment of CA19-9 positive disease as a monotherapy/combination with chemotherapy, as an imaging agent (MVT-2163) and as a radioimmunotherapy (MVT-1075).
Methods: To understand the relevance of CA19-9 as a stratification marker, both annotated primary as well as patient derived xenograft (PDX) tissue microarrays (TMAs) were stained with MVT-5873. To evaluate sLe^a as a response biomarker, serum samples from patients in the MVT-5873 phase 1 clinical trial were analyzed for CA19-9 levels using the diagnostic assay, and compared to their MVT-5873 PK profile. Available samples were also characterized by ELISA assay to determine the representation of sLe^a modification on MUC family proteins.
Results: For the human colorectal (CRC) TMA, >75% of tumor cores displayed moderate to high levels of positive staining. In the PDX array, 21% of non small cell lung cancer (NSCLC), 50% of small cell lung cancer (SCLC), and 69% of CRC cores stained positive. Overall, staining was observed with similar frequency regardless of mutational status of the tumor, suggesting that CA19-9 expression is independent of KRAS, BRAF, PIK3CA, or MMR pathway mutations. Staining was also relatively unchanged in lung PDX cancer tumor cores that were rendered chemo-resistant compared to their chemo-sensitive precursor.
The serum CA19-9 analysis of PDAC patients treated with MVT-5873 demonstrated that detectable CA19-9 is inversely proportional to MVT-5873 drug levels when CA19-9 levels are >~1000 U/mL. CA19-9 is not detected after MVT-5873 treatment when CA19-9 levels are <~1000 U/mL, suggesting that MVT-5873 can fully occupy all serum CA19-9 at those levels. Taken together, these data indicate that the CA19-9 diagnostic assay may be used as a measure for target engagement, and imaging data from the MVT-2163 phase 1 trial confirmed that the drug can efficiently accumulate at tumor sites in a time-dependent manner in patients. When pancreatic cancer patient serum was analyzed for protein scaffold composition, Muc1 and Muc16 were found to be present.
Conclusions: These data support the use of sLe^a targeted therapeutics such as MVT-5873 and MVT-1075 in CRC and lung cancer, including for patients with KRAS or other genetic mutations. Additionally, for patients treated with MVT-5873, data suggest that the serum CA19-9 assay is a potential measure of target occupancy and is worthy of further investigation.

Clinical Programs

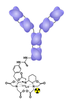
Targeting sLe^a as a cancer therapy and as a companion diagnostic

Therapeutic Antibody (MVT-5873)
Fully human HuMab-5B1 for the treatment of PDAC & other CA19-9+ tumors
Phase 1 trial initiated February 2016
ClinicalTrials.gov NCT02672917

- Single agent phase complete, combination with chemotherapy ongoing
- Exploratory objective included evaluation of relationships between circulating CA19-9 levels, tumor response, and MVT-5873 PK

Radioimmunotherapy (MVT-1075)
^{177}Lu-CHX-A″-DTPA-HuMab-5B1 a targeted radiotherapy of PDAC & CA19-9+ tumors
Phase 1 trial initiated June 2017
ClinicalTrials.gov NCT03118349

- Uses the 5B1 antibody for targeted delivery ^{177}Lu & beta radiation to tumor cells
- Phase I design guided by MVT-2163 ImmunoPET safety, biodistribution and clinically demonstrated accumulation on tumor
- Patient enrollment ongoing



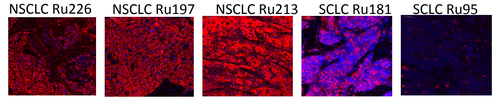
ImmunoPET Imaging (MVT-2163)
^{89}Zr-DFO-HuMab-5B1 for PET imaging of PDAC/other CA19-9+ tumors
Phase 1 trial initiated May 2016
ClinicalTrials.gov NCT02687230

- Uses the 5B1 antibody for a targeted delivery of ^{89}Zr to tumor cells
- Evaluated in combination with MVT-5873 and established that uptake to liver and spleen are reduced by pre-dosing with the cold parental antibody
- Potential to aid in the selection and staging of patients for surgical resection

MVT-5873 to Select for CA19-9 Expression: Lung Cancer and CRC

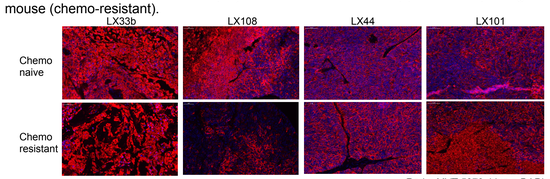
sLe^a is expressed in both non-small cell and small cell lung cancer

- Serum CA19-9 reported to be elevated in lung cancer as well as benign diseases of the lung[1]
- 10% of NSCLC patients have elevated serum CA19-9[2]



- Across a survey of PDX cores from non-small cell lung cancer (NSCLC) tumors, small cell lung cancer (SCLC) tumors, mesothelioma (MESO) tumors, and mixed phenotype tumors
  - 16/30 NSCLC and 4/9 SCLC tumors showed sLe^a expression based on IHC staining – more frequent sLe^a expression observed with direct staining than expected based on serum CA19-9
  - No MESO or mixed phenotype tumors were positive for MVT-5873 staining

- sLe^a expression evaluated in lung cancer PDX tumors prior to chemotherapy treatment (chemo-naïve) and in tumors induced to display resistance to chemotherapy via in vivo passage in the mouse (chemo-resistant).

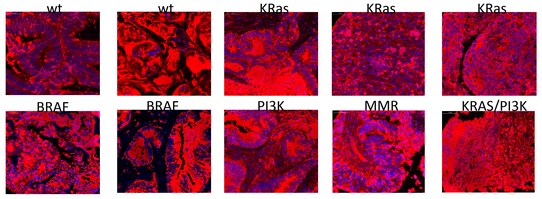


Red = MVT-5873, blue = DAPI

- sLe^a positive lung cancer PDX tumors retain sLe^a expression after acquiring chemo-resistance

sLe^a is expressed in all subsets of colorectal cancer

- CA19-9 originally identified in serum of CRC and pancreatic cancer patients[3]
- Elevated in CRC patient sera (41-54%)[4] and tissue (71-85%)[5]



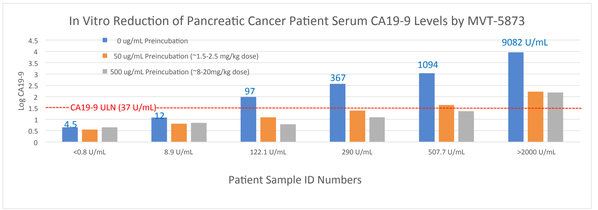
Mutation	High CA19-9	Med CA19-9	Low CA19-9	No CA19-9
wt	11/35 (31.4%)	12/35 (34.3%)	11/35 (31.4%)	1/35 (2.8%)
KRAS	20/41 (48.8%)	14/41 (34.1%)	6/41 (14.6%)	1/41 (2.4%)
BRAF	5/12 (41.7%)	2/12 (16.7%)	5/12 (41.7%)	0
PI3K	7/19 (36.8%)	7/19 (36.8%)	5/19 (26.3%)	0
MMR	3/7 (42.9%)	1/7 (14.3%)	3/7 (42.9%)	0

- Primary patient CRC cores demonstrated high expression levels in wt, KRAS, PI3K, BRAF, NRAS, and MMR loss mutant populations.
- High expression levels also observed in both metastatic and non-metastatic disease (data not shown)

Exploring the Relationship Between MVT-5873 PK and Serum CA19-9

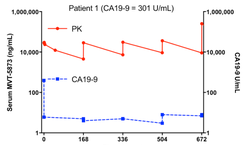
In vitro characterization of the effects of MVT-5873 on the CA19-9 assay

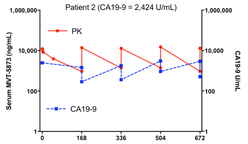
- Evaluation of sera from pancreatic cancer patients with low, mid-range, and high levels of CA19-9
- Serum samples were either untreated or spiked with 50 or 500 µg/mL MVT-5873 for 1 hour that represents MVT-5873 sera level after a ~2 mg/kg and ~10 mg/kg dose (see legend)
- Samples were then refrozen and submitted for analysis using clinical diagnostic assay
- 50 µg/mL of MVT-5873 spiked into serum can occupy >95% of serum CA19-9
- Data support that MVT-5873 binding to CA19-9 renders the circulating antigen non-detectable

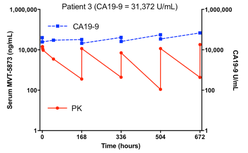


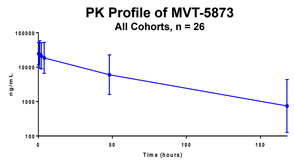
Preliminary analysis of select patient serum PK and CA19-9 levels

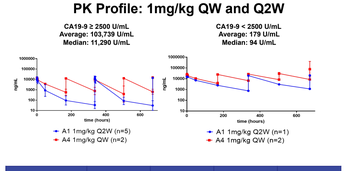
- MVT-5873 phase 1 study included analysis of PK and CA19-9 levels throughout treatment
- Data were analyzed for select patients to assess relationship between MVT-5873 serum levels and CA19-9 detection
- Patients with detectable starting CA19-9 levels (dotted line) demonstrated a marked reduction in CA19-9 levels (measured by diagnostic assay) that correlate with drug levels (solid line)
- Cycle 1 Day 1 CA19-9 level at time of administration is noted









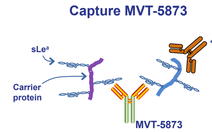


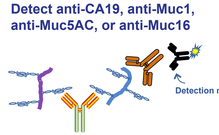
CA19-9 (U/mL)	Terminal $t_{1/2}$ (h)	AUC$_{0-\infty}$ (ng*hr/mL)	Vd (L)	Cl (mL/h)
≥ 2500 (n = 7)	190	449113	22.6	304
< 2500 (n = 3)	832	3158460	13.1	30

- MVT-5873 serum levels reflect the presence and magnitude of soluble CA19-9 antigen
- Patients with reduced CA19-9 levels have greater exposure measured by AUC have a longer duration on study (4 months average versus 1 month average)[6]
- In vitro data trend with clinical findings and further studies are required to establish a formal relationship

Characterization of CA19-9 protein carriers in patient sera

Assay development

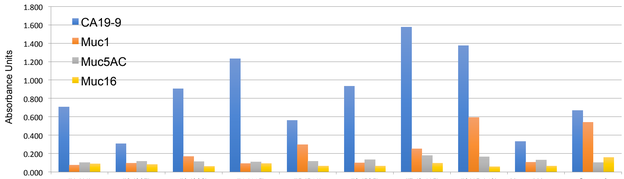




- Studies identifying CA19-9 carrier proteins in cancer patient sera have identified a number of candidates, including mucin and apolipoprotein family members[7]
- ELISA assays using MVT-5873 capture and various antibodies known to detect CA19-9 or carrier proteins were developed and validated in human serum and plasma matrices
- Supernatants from cell lines known to be CA19-9 positive were used to test sensitivity and specificity of the assays

Patient sera analysis

- Patient sera were analyzed by ELISA assay using MVT-5873, anti-CA19-9, anti-Muc1, anti-Muc5AC and anti-Muc16 (shown in legend) to detect sera CA19-9 and Mucin carrier proteins
- Muc1 was the most commonly observed protein carrier in patient sera analyzed to date
- Presence of multiple scaffold proteins confirmed in pancreatic cancer patient plasma, including Muc1, Muc5AC, and Muc16



Summary and Next Steps

Indication Selection
- Strong supporting evidence of a therapeutic opportunity for MVT-5873 in NSCLC (chemo-naïve and resistant), SCLC, and CRC
- sLe^a expression maintained in CRC patients with KRAS, BRAF, PI3K, or MMR mutations, suggesting potential for sLe^a targeted therapy

CA19-9 / PK Relationship
- MVT-5873 complexes with CA19-9 and is a potential surrogate for a receptor occupancy assay
- Suppression of CA19-9 levels below baseline is observed in some subjects and associated with longer times on treatment
- Additional data analyses are ongoing as subject data are accrued

Analysis of CA19-9 carrier protein content
- Assays compatible with human plasma were developed to identify CA19-9 carrier protein content
- Muc1 was the most commonly observed protein carrier in pancreatic cancer patient sera
- Additional data being analyzed as clinical trials progress

References

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