Abstract 4110

Single-agent HuMab-5B1 (MVT-5873), a monoclonal antibody targeting sLe^a, in patients with pancreatic cancer and other CA19-9 positive malignancies

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Abstract (updated)

Background: MVT-5873, a fully human IgG1 monoclonal antibody (mAb), targets sialyl Lewis A (sLe^a), an epitope on CA19-9. CA19-9 is expressed in pancreatic (PDAC) and other GI cancers, plays a role in tumor adhesion and metastasis, and is a marker of an aggressive tumor phenotype. MVT-5873 is active as a single agent and with chemotherapy in CA19-9+ murine xenografts.
Methods: MVT-5873 was given IV every other week (Q2W, Group 1) or weekly (QW, Group 2). Eligible patients had progressive, locally-advanced or metastatic PDAC or other CA19-9+ tumor and ECOG PS ≤1. Dose escalation followed a 3+3 design. Endpoints include safety, MTD, efficacy, and pharmacokinetics (PK), with changes in serum CA19-9 as an exploratory endpoint.
Results: As of May 24, 2017, data are available from n = 32 (Q2W, n = 9; QW, n = 23) at doses ranging from 1 to 3 mg/kg. The MTD was 1 mg/kg on both schedules, with dose-limiting toxicities (DLTs) of transient grade 3 elevations in AST, ALT, and total bilirubin. Liver function laboratory abnormalities typically emerged and resolved within a week of dosing without significant clinical sequelae. Of toxicities deemed possibly related, most were low grade and included GI toxicity (nausea/vomiting/abdominal pain/diarrhea), fatigue, and infusion reactions. Infusion reactions were mitigated by using pre-medications and decreasing the infusion rate. Best responses to date include 1 CR and 4 SD maintained for 3.25 to 9.75+ cycles. CA19-9 levels were measured pre- and post-dose. After Cycle 1 of treatment, 13/32 (41%) of patients exhibited ≥ 50% reduction in CA19-9, which was associated with a longer time (median 4 cycles) on treatment. Initial PK data demonstrate an initial (20 hours) and terminal $t_{1/2}$ (189 hours) comparable to other mAbs.[1]
Conclusions: Single agent MVT-5873 appears safe and tolerable at biologically active doses. DLTs included reversible serologic liver toxicity. The safety profile, efficacy, and reductions in serum CA19-9 levels over time support further development of MVT-5873 in this indication both as a single agent and in combination. **ClinicalTrials.gov Identifier: NCT02672917**

Study Design

- Phase 1, open-label, dose-escalation trial (3 + 3 design) with expansion (n = 10) at the recommended Phase 2 dose (RP2D)
- Evaluation of MVT-5873 as a single-agent with determination of MTD followed by combination with chemotherapy. Combination with chemotherapy not discussed in this presentation.

MTD established	Ongoing
Single Agent MVT-5873 Initial dose = 1 mg/kg Q2W Continuous 28-day cycle	**Combination MVT-5873** MVT-5873 at 1 level < MTD Gemcitabine 1000 mg/m^2 days 1, 8, 15 Nab-paclitaxel 125 mg/m^2 days 1, 8, 15

Key eligibility criteria

- Histologically confirmed progressive, locally advanced, or metastatic PDAC or other CA19-9+ tumor (PDAC only in combination phase)
- Evaluable disease by RECIST 1.1 during dose escalations
- ECOG performance status of 0 to 1
- Adequate hematologic, renal, and laboratory parameters

Primary Objectives

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

Secondary Objectives

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

Exploratory Outcomes

- Assess for presence of anti-MVT-5873 antibodies (ADA)
- Evaluate relationships between circulating CA19-9 levels and tumor response, MVT-5873 PK, and tumor sLe^a expression (IHC)

Results

Enrollment, Treatment and MTD for Single-Agent MVT-5873

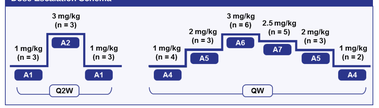
In this heavily pretreated population, 59% had received ≥ 3 prior systemic therapies, 52% had undergone surgery, and 28% radiation.

Demographics and Baseline Characteristics

Patients enrolled (n)	32
Male : Female	16 : 16
Median age, (range), yrs	65 (51-87)
ECOG PS 0 : 1, n (%)	7(22) : 25(78)
Prior Therapy:	
No. of systemic therapies	
1	8
2	5
3	11
4+	8
Radiation	9
Surgery	17
Primary tumor	16
Metastatic disease	2
Primary Disease Site (n)	
Pancreas	29
Head	17
Other	12
Colon/rectum	1
Other (unknown primary)	2
Stage at entry (n)	
IIIa	1
IIIb	1
IV	30

With the occurrence of DLTs at 3 mg/kg with Q2W dosing, a QW dosing schedule explored the effects of schedule on tolerability.

Dose Escalation Schema



Dose Cohorts, Cycles Administered, and Patient Disposition

	Baseline CA19-9 (U/mL)				Patient Disposition			
	< 2500		≥ 2500			Off Study		
Cohort	n	Median Cycles (range)	n	Median Cycles (range)	On Study	Toxicity	PD	Other
A1	1	4	5	1.25 (1-3)	0	0	5	1
A2	2	4.5 (4-5)	1	7.5	0	0	2	1
A4	4	4.75 (1-9.75)	2	1.125 (1-1.25)	3	0	3	0
A5	5	2 (1.5-3.5)	1	2	1	0	5	0
A6	0	-	6	1.375 (1-2)	0	0	6	0
A7	4	3.25 (0.25-4)	1	1	3	1	1	0
Total	16	3.25 (0.25-9.75)	16	1.25 (1-7.5)	7	1	22	2

Safety, Tolerability and Maximum Tolerated Dose

All Adverse Events, All Grades, in ≥ 30% of Patients

		At MTD		Exceeds MTD			
Cohort	Total* (n = 30)[#]	A1 (n = 6)	A4 (n = 4)	A2 (n = 3)	A5 (n = 6)	A6 (n = 6)	A7 (n = 5)
Preferred Term	n (%)						
↑ AST	27 (90)	-	6	-	5	5	11
↑ ALT	23 (77)	-	6	1	4	2	10
↑ Alkaline phosphatase	21 (70)	4	3	-	2	4	8
↑ Bilirubin	21 (70)	3	2	-	9	1	6
Fatigue	19 (63)	4	4	1	1	5	4
Nausea	13 (43)	3	1	2	5	-	2
Hypoalbuminemia	12 (40)	1	2	-	-	1	8
Hyperglycemia	11 (37)	4	3	-	2	-	2
Constipation	10 (33)	4	2	-	2	-	2
Vomiting	10 (33)	4	1	3	1	1	-
Back Pain	10 (33)	1	-	1	2	6	-
Anemia	9 (30)	1	1	-	-	-	7
All Treatment-Related Adverse Events ≥ Grade 3							
↑ ALT	9 (30)	-	-	1	2	1	5
↑ AST	8 (27)	-	-	-	2	2	4
↑ Alkaline phosphatase	5 (17)	-	1	-	1	-	3
↑ Bilirubin	4 (13)	1	-	-	3	-	-
↓ Lymphocyte count	2 (7)	-	-	-	1	-	1
↑ Lipase	1 (3)	-	-	-	1	-	-
Hyperbilirubinemia	1 (3)	-	-	1	-	-	-
Infusion reaction	1 (3)	1	-	-	-	-	-

*Total adverse events recorded in all patients across all cycles; [#]data form n = 30 as of 5/24/2017

Determination of MTD

The MTD was established at 1 mg/kg on both the Q2W (A1) and QW (A4) schedule.

Single-agent MVT-5873 was generally well tolerated, with dose-limiting toxicities consisting of transient elevations in ALT, AST and bilirubin that typically resolved within a week.

Infusion reactions were mitigated with premedication and extended infusion time.

Dose Limiting Toxicities

	Individual Patient Events (Cycle 1)				Treatment Disposition	
Cohort (n)	Day	Toxicity	CTCAE Grade	Duration (days)	Adjustment	Total Cycles
A1 (6)				none		
A2 (3)	3	↑ Bilirubin	3	12	↓ dose	4
	3	↑ ALT	3	2	↓ dose	5
A4 (6)				none		
A5 (6)	8	↑ Bilirubin	3	7	↓ dose	1.5
	3	↑ ALT,↑ AST	3, 3	3,3	↓ dose	1.25*
A6 (6)	5	↑ ALT,↑ AST	3, 3	3, 3	↓ dose (x2)	1.25
	3	↑ AST	3	6	↓ dose	1.5
A7 (5)	3	↑ ALT,↑ AST	3, 3	5,5	d/c	0.25[#]
	29	↑ ALT,↑ AST	3, 3	2,2	↓ dose	3.25*
	3	↑ ALT,↑ AST	3, 4	3,5	↓ dose	3*

*Continued on treatment; [#]discontinued (d/c) after 1st dose, resolution to grade 2 by day 5

Clinical Effects

Median time on therapy across all cohorts was in 1.25 cycles in patients with baseline CA19-9 levels ≥ 2500 U/L (n = 16) versus 3.25 cycles in patients CA19-9 levels < 2500 (n = 16).

Among evaluable patients (2 are too early), 12/30 were without disease progression by the time of the first RECIST evaluation.

To date, there has been 1 CR (2.25 cycles) and 4 patients have maintained stable disease for 3.25 to 9.75+ cycles.

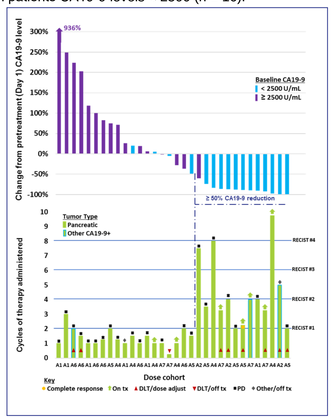
For individual patients (n = 32), relative change from baseline CA19-9 through cycle 1* (upper panel) are plotted relative to time on therapy (lower panel).

13/32 patients (41%) demonstrated a ≥ 50% reduction in CA19-9 (6 ≥ 90% reduction). All but one had a baseline CA19-9 level less than the median of 2500 U/mL.

Median CA19-9 levels in this population were comparable to those previously reported in a similar patient population.[2]

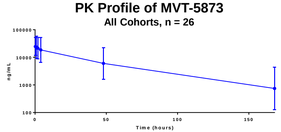
Median time on therapy in patients with a ≥ 50% reduction in CA19-9 was 4 cycles (range 2 to 9.75+).

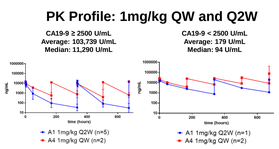
There has been no evidence of ADA induction in MVT-5873 treated patients.



* or at last measurement if treatment d/c < 1 cycle

Pharmacokinetics





MVT-5873 in patient sera was measured by ELISA and analyzed using compartmental methods.

Mean (SD) MVT-5873 concentrations from serial sampling following the first dose of MVT-5873 are depicted at left.

Mean (SD) PK parameters across all dose levels are: terminal $t_{½}$ = 189 ± 89 h; Cl = 220 ± 272.5 mL/h; Vd_{SS} = 17.3 ± 25.6 L.

There was no apparent accumulation with repeated dosing at all dose levels.

Preliminary PK comparison across dose groups at MTD suggest pre-dose CA19-9 levels affect PK parameters (1 mg/kg, MTD, data at left and below)

CA19-9 (U/mL)	Terminal $t_{½}$ (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

These data support QW dosing to mitigate fluctuations potentially caused by soluble antigen levels based on observed AUC, C_{min}, and C_{max} values.NAL

Discussion

This first-in-human clinical trial demonstrates that MVT-5873 can effectively target sLe^a in patients with CA19-9+ tumors. The MTD of single-agent MVT-5873 was recently established at 1 mg/kg with both Q2W and QW dosing regimens. As of May 24, 2017, there was 1 CR and 4 patients with prolonged SD lasting for 3.25 to 9.75+ cycles. All were among the patients with ≥ 50% reduction in CA19-9 levels after one cycle of treatment.

DLTs with single-agent MVT-5873 were reversible increases in liver function tests, which typically occurred early in Cycle 1 of therapy and resolved within a week. Most patients experiencing DLT events were able to continue therapy at a reduced dose. Infusion reactions were mitigated with the use of premedication and extended infusion times. To date, there has been no evidence that MVT-5873 induces ADA in treated patients.

Treatment with MVT-5873 resulted in a substantial decrease in circulating CA19-9 levels immediately following administration in all patients (data not shown). Over the course of treatment Cycle 1, 40% of patients had a sustained decrease in CA19-9 levels of ≥ 50%. Patients with a ≥ 50% reduction in CA19-9 levels continued on treatment for a median of 4 cycles (range 2 to 9.75+), compared to 1 cycle (range 0.25 to 3) for patients with < 50% decrease.

On average across all dose groups, MVT-5873 demonstrates a prolonged terminal half-life and an overall serum profile similar to other human mAbs. There was no apparent accumulation of MVT-5873 at the doses and schedules administered. Exploratory analyses suggest that clearance of MVT-5873 is influenced by circulating CA19-9 levels. Patients with a sustained decrease in CA19-9 of ≥ 50% had an approximate 8-fold increase in MVT-5873 exposure, as measured by AUC.

The safety profile, indications of efficacy, and reductions in serum CA19-9 levels over time support further development of MVT-5873 for treatment of CA19-9 positive malignancies, both as a single agent and in combination with chemotherapy.

- MVT-5873 weekly dosing appears well tolerated, primary toxicities are transient ↑LFTs
- These data support expansion of monotherapy to further explore safety and efficacy

HuMab-5B1 Clinical Development Platform

HuMab-5B1 represents 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

Radioimmunotherapy (MVT-1075)
^{177}Lu-CHX-A"-DTPA-HuMab-5B1 for targeted radiotherapy of PDAC/other CA19-9+ tumors
Phase 1 trial to be initiated June 2017
ClinicalTrials.gov NCT03118349

References

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2. Von Hoff DD, et al. N Engl J Med 2103;369:1691-703

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