Preliminary phase 1 data comparing HuMab-5B1 (MVT-5873), a monoclonal antibody targeting sLe^a, as a single agent and in combination with first-line nab-paclitaxel and gemcitabine in patients with CA19-9 positive pancreatic cancer

Poster LB-25

Eileen Mary O'Reilly[1], Judy Sing-Zan Wang[2], Kenneth H. Yu[1], Maeve Aine Lowery[1], Anna M. Varghese[1], Johanna C. Bendell[3], Erkut Hasan Borazanci[4], Hayley Estrella[1], Kimberly Fowler[5], Mariella Hoskin[5], Stephanie Bussen[5], Teresa J. Melink[6], Christine M. Kearns[6], H. Toni Jun[5], Paul W. Maffuid[5], John C. Gutheil[6], Todd Michael Bauer[3]

[1]Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Florida Cancer Specialists & Research Institute, Sarasota, FL; [3]Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; [4]HonorHealth Research Institute, Scottsdale, AZ, [5]MabVax Therapeutics Holdings, Inc., San Diego, CA; [6]SciQuus Oncology, La Jolla, CA

Abstract (updated)

Introduction: 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 in combination with nab-paclitaxel (nab-P) and gemcitabine (gem) in murine xenografts.

Methods: Single agent: For each 28-day treatment cycle, MVT-5873 was given IV every second week (Group 1) or weekly (Group 2) at doses ranging from 1 to 3 mg/kg. Combination with nab-P and gem: For each 28-day treatment cycle, MVT-5873 was administered IV weekly (1.0mg/kg or 0.125mg/kg) followed by IV infusion of 125 mg/m^2 of nab-P and then 1000mg/m^2 gem, on day 1, 8 and 15 (Group 3). Eligible patients had recurrent progressive (single agent) or newly diagnosed (combination), locally advanced or metastatic PDAC or other CA19-9+ malignancy and ECOG PS ≤1. Dose escalation followed a standard 3+3 design with a 10-patient expansion at the maximally tolerated dose (MTD). Trial endpoints include safety, MTD, dose limiting toxicities (DLT), pharmacokinetics (PK) and efficacy. Exploratory endpoints include changes in serum CA19-9 levels.

Results: As of 24-October-2017, data are available for single agent N=32 in Groups 1 (N=9) and 2 (N=23) at 1, 2, 2.5 and 3 mg/kg and combination Group 3 (N=7) at 1.0 and 0.125mg/kg. DLTs of transient grade 3 elevations in AST, ALT, and total bilirubin were encountered in the single agent groups at 2, 2.5 and 3mg/kg in both single agent groups and in the combination group at 1mg/kg. Single agent liver function laboratory abnormalities typically emerged and resolved within a week of dosing although they were more persistent in the combination treated patients. Other toxicities associated with all groups included low grade GI toxicity (abdominal pain/cramps/diarrhea/nausea) and infusion reactions. Infusion reactions were mitigated with premedications and an increase in the infusion time. Combination MVT-5873 DLTs at 1mg/kg were persistent ALT and bilirubin elevations and resulted in significant dose de-escalation. Combination MVT-5873 dosed at 0.125 mg/kg was generally well tolerated with peripheral neuropathy and delayed (8wk) pneumonitis observed. Single agent activity included SD of >6 months in 5 of 32 of patients with an MTD established at 1 mg/kg. Combination MVT-5873 activity at 0.125 mg/kg with nab-P/gem included 2 PRs and 1 SD in 3 patients. Interestingly, sustained suppression below ULN of CA19-9 levels was observed in 3 of the 6 patients in the combination arm and substantial CA19-9 reduction at the 0.125mg/kg combination dose. Accrual at 0.125mg/kg is in progress.

Conclusions: Single agent MVT-5873 appears safe and tolerable at biologically active doses. DLTs included reversible liver function abnormalities. Determination of the MTD in combination with first line nab-P/gem is underway and preliminary response data are encouraging. Overall, 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.

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.

MTD established — **Single Agent MVT-5873**
Initial dose = 1 mg/kg Q2W
Continuous 28-day cycle

Ongoing — **Combination MVT-5873**
MVT-5873 at 0.125 mg/kg QW
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

ClinicalTrials.gov Identifier: NCT02672917

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

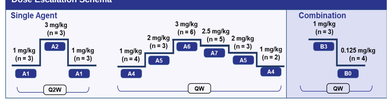
- Assess for presence of anti-MVT-5873 antibodies
- Evaluate relationships between circulating CA19-9 levels and tumor response, MVT-5873 PK, and tumor sLe^a expression (IHC)

Results

Demographics/Baseline Characteristics:

	Single Agent	Combination
Patients enrolled (n)	32	7
Male : Female	16 : 16	4 : 3
Median age, (range), years	65 (51-87)	62 (43-78)
ECOG PS 0 : 1, n (%)	7(22) : 25(78)	4(57) : 3(43)
Prior Therapy:		
No. of systemic therapies		
1	8	No prior therapy
2	5	
3	11	
4+	8	
Radiation	9	
Surgery	17	
Primary tumor	16	
Metastatic disease	2	
Primary Disease Site (n)		
Pancreas	29	7
Colon/rectum	1	
Other (unknown primary)	2	
Stage at entry (n)		
III	2	2
IV	30	5

Dose Escalation Schema



Dose Cohorts, Cycles Administered, and Patient Disposition

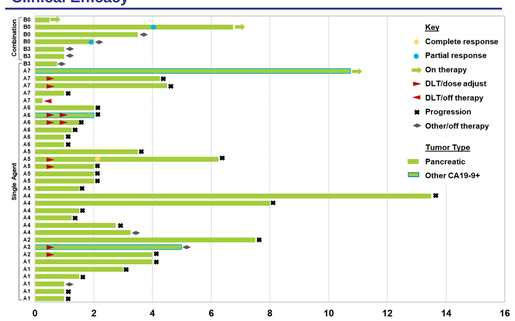
		Baseline CA19-9 (U/mL)				Patient Disposition			
		< 2500		≥ 2500			Off Study		
Cohort	n	Median Cycles (range)	n	Median Cycles (range)	On Study	Toxicity	PD	Other
A1	1	4	5	1.25 (1-3)	0	0	5	1
A2	2	4.5 (4-5)	1	7.5	0	0	2	1
A4	4	5.625 (1.5-13.5)	2	2 (1.25-2.75)	0	0	5	1
A5	5	2 (1.5-6.25)	1	2	0	0	6	0
A6	0	-	6	1.375 (1-2)	0	0	6	0
A7	4	4.375 (0.25-10.75)	1	1	1	1	3	0
Total	16	4 (0.25-10.75)	16	1.375 (1-7.5)	1	1	27	3
B3	2	0.875 (0.75 – 1.0)	1	1	0	0	1	2
B0	3	2.0 (0.5-6.75)	1	3.5	2	0	1	1
Total	5	1 (0.5-6.75)	2	2.25 (1-3.5)	2	0	2	3

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

	Single Agent							Combination		
		At MTD		Exceeds MTD						
Cohort	Total* (n = 32)	A1 (n = 6)	A4 (n = 6)	A2 (n = 3)	A5 (n = 6)	A6 (n = 6)	A7 (n = 5)	Total* (n = 7)	B3 (n = 3)	B0 (n = 4)
Preferred Term	n (%)							n (%)		
↑ AST	23 (72)	-	2	-	5	5	11	2 (29)	-	2
↑ ALT	18 (56)	-	1	1	4	2	10	1 (14)	-	1
↑ Alkaline phosphatase	22 (69)	4	4	-	2	4	8	2 (29)	2	-
↑ Bilirubin	20 (63)	3	1	-	9	1	6	7 (100)	7	-
Fatigue	19 (59)	4	4	1	1	5	4	3 (42)	2	1
Nausea	13 (41)	3	1	2	5	-	2	2 (29)	2	-
Hypoalbuminemia	12 (38)	1	2	-	-	1	8	-	-	-
Hyperglycemia	10 (31)	4	2	-	2	-	2	5 (71)	2	3
Vomiting	10 (31)	4	1	3	1	1	-	2 (29)	2	-
Back Pain	10 (31)	1	-	1	2	6	-	-	-	-
Anemia	10 (31)	1	2	-	-	-	7	7 (100)	4	3
Pneumonitis	-	-	-	-	-	-	-	2 (29)	-	2
All Treatment-Related Adverse Events ≥ Grade 3										
↑ ALT	9 (30)	-	-	1	2	1	5	1 (14)	1	-
↑ AST	8 (27)	-	-	-	2	2	4	1 (14)	1	-
↑ Alkaline phosphatase	5 (17)	-	1	-	1	-	3	-	-	-
↑ Bilirubin	4 (13)	1	-	-	3	-	-	2 (29)	2	-
Pneumonitis	-	-	-	-	-	-	-	2 (29)	-	2
↓ Lymphocyte count	2 (7)	-	-	-	1	-	1	-	-	-
↑ Lipase	1 (3)	-	-	-	1	-	-	-	-	-
Hyperbilirubinemia	1 (3)	-	-	1	-	-	-	1 (14)	1	-
Infusion reaction	1 (3)	1	-	-	-	-	-	-	-	-

*Total adverse events recorded in all patients across all cycles; ♦data as of 08/30/2017

Clinical Efficacy



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*
B3 (3)	8	↑ ALT	3	7	delay	0.75
	3	↑ Bilirubin	3	5	delay	1

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

DLTs and Adverse Events

Single Agent MVT-5873

- MTD established at 1 mg/kg on both the Q2W (A1) and QW (A4) schedules
- Single-agent MVT-5873 was generally well tolerated; DLTs consisted of transient elevations in ALT, AST and bilirubin that typically resolved within a week.
- Infusion reactions were mitigated with premedication and extended infusion time.

Combination MVT-5873 and nab-paclitaxel/gemcitabine

- At B3 dose level (MVT-5873 1 mg/kg QW), 2/3 patients had grade 3 elevations in ALT or bilirubin
- At B3, in contrast to findings with single-agent therapy, LFT elevations with combination therapy were more persistent and associated with treatment delays
- Out of an abundance of caution, the dose of MVT-5873 was significantly de-escalated 8-fold to cohort B0 (0.125 mg/kg QW)
- Among first 3 patients treated at B0, there were no increases in LFTs
- However, 2 patients experienced delayed-onset pneumonitis at week 8 (attributed to chemotherapy)
- Cohort B0 was expanded to 6 patients, with 4th patient currently on-study

Duration of Therapy and Response

Single Agent MVT-5873

- Disease control of ≥ 6 cycles in 5/32 patients, with 1 patient remaining on treatment for >10 cycles

Combination MVT-5873 and nab-paclitaxel/gemcitabine

- B3 Cohort (3 patients) RECIST1.1 at EOT (2 SD, 1 not evaluated)
- B0 Cohort (3 patients), 2 PR, and 1 SD, 1 patient remaining on therapy for > 6 cycles
- Substantial (>50%) reduction of CA19-9 levels observed for patients in B0

Discussion

This first-in-human clinical trial demonstrates that MVT-5873 can effectively target sLe^a in patients with CA19-9+ tumors as a single agent and in combination with nab-P/gem. The single-agent MVT-5873 MTD was established at 1 mg/kg in Q2W and QW dosing regimens. The combination MVT-5873 dose escalation is currently enrolling patients at 0.125 mg/kg QW.

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. DLTs in the initial combination MVT-5873 cohort (B3) included more persistent increases in liver function tests resulting in a substantial dose de-escalation. Combination MVT-5873 cohort (B0) is generally well tolerated with delayed (8wk) pneumonitis observed. Pneumonitis was not observed with single-agent MVT-5873 (32 patients). To date, there has been no evidence that MVT-5873 induces ADA in treated patients in both study arms.

As of October 24, 2017, there were 5 patients treated with single-agent MVT-5873 with prolonged SD lasting from 6.25 to 13.5 cycles. All were patients with ≥ 50% reduction in CA19-9 levels after one cycle of treatment. With combination MVT-5873 (B0), the first three patients were on treatment lasting from 2 to 6.75+ cycles. Preliminary response is promising and includes 2 PRs and 1 SD. Patients had substantial (>50%) reduction in CA19-9 levels at this dose.

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.

In single-agent MVT-5873 weekly dosing appears well tolerated, primary toxicities are transient ↑LFTs. Patients (5/32) with substantial CA19-9 reduction have prolonged SD (median 8 cycles)

In combination MVT-5873, the low dose regimen (0.125 mg/kg) appears well tolerated, primary toxicities are transient ↑LFTs and delayed (8wk) pneumonitis observed. Patients (2/3) with substantial CA19-9 reduction had PR (2 to 6.75+ cycles)

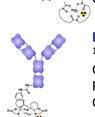
Cohort B0 expansion on-going to obtain additional safety and response data

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

2017 AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Conference Philadelphia, PA Oct 26 - 30

Contact: Paul Maffuid, PhD, Exec VP, Research and Development, MabVax Therapeutics Holdings, Inc. pmaffuid@mabvax.com

Funding: NIH grants P30 CA08748, F32CA180452-01A1, 5R25CA096945-09, 2R42CA128362 and HHSN261201300060C