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Title: Perioperative MVT-5873, a Fully Human Monoclonal Antibody Against a CA 19-9 Epitope, for Operable CA 19-9 Producing Pancreatic Cancers, Cholangiocarcinomas, and Metastatic Colorectal Cancers

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Investigational Agents:

Drug Name:	HuMab-5B1 (MVT-5873)
IND Number:	144112
Sponsor:	NCI Center for Cancer Research
Manufacturer:	AAIPharma

Commercial Agents: None

PRÉCIS

Background:

- Resections to remove tumors in the liver, bile ducts and pancreas are rarely curative, and patients frequently succumb to disease recurrence in the ensuing months to year(s) after the operation.
- Standard adjuvant therapies, which typically begin 6-12 weeks after surgery, offer little demonstrable decreases in the rates of tumor recurrence.
- The concept and implementation of immediate perioperative therapy has not been evaluated given the serious concerns related to healing and recovery with standard cytotoxic chemotherapy and newer targeted agents.
- A significant percentage of metastatic colorectal cancers, and primary tumors of the pancreas and bile ducts express Sialyl Lewis^a, an epitope on the well-established tumor marker, CA 19-9.
- MVT-5873, a fully human antibody against Sialyl Lewis^a, has displayed ADCC and CDC *in vitro*, potentiated chemotherapeutic efficacy in mouse models and demonstrated efficacy in Phase 1 trials of patients with advanced inoperable HPB cancers.
- MVT-5873 is well tolerated as a single agent; moderate elevations in AST/ALT appear to be dose-limiting.
- Patients with resectable Sialyl Lewis^a-expressing cancers represent an ideal population to explore the use of perioperative MVT-5873 given moderate level of CA 19-9 elevations, and the potential for extension of recurrence-free survival.

Objectives:

- Document the safety of perioperative MVT-5873 in patients undergoing pancreas and liver resections.
- Determine if perioperative MVT-5873 can decrease 1-year recurrence rates for patients with operable CA 19-9-producing cancers.

Eligibility:

- Histologically or cytologically confirmed adenocarcinoma of the
    - Colon (metastatic to liver)
    - Pancreas
    - Bile Ducts (Cholangiocarcinoma)
- Serum CA 19-9 levels greater than the upper limit of normal, but less than 2500.
- Disease amenable to complete surgical extirpation.

Design:

- Pre-operative one-time treatment with MVT-5873, resection to remove all demonstrable disease in the liver, bile ducts and pancreas, and continuing MVT-5873 mono-therapy until off treatment criteria are met.

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1.1.1 Primary Objectives

- Document the safety of perioperative MVT-5873 in patients undergoing pancreas and liver resections.
- Determine if perioperative MVT-5873 can decrease 1-year recurrence rates for subjects with operable CA 19-9 producing cancers.

1.1.2 Secondary Objective

- Define disease free survival (DFS) for subjects treated with preoperative MVT-5873.

1.1.3 Exploratory Objectives

- Define overall survival (OS) for subjects treated with preoperative MVT-5873.
- Determine the mechanism(s) of liver function test abnormalities associated with MVT-5873 administration.
- Determine the tumor penetration of MVT-5873 in primary tumors of the pancreas and bile ducts, and in metastatic colorectal cancers to the liver.
- Evaluate the impact of MVT-5873 therapy on circulating tumor cells.
- Develop *ex vivo* models for pancreatic cancer, cholangiocarcinoma, and metastatic colorectal cancer.
- Evaluate chemotherapeutic and immunotherapeutic agent effects in tumors from patients undergoing pancreas and liver resections after pre-operative MVT-5873 therapy using a novel *ex vivo* platform, the SMART System.

1.2 BACKGROUND AND RATIONALE

1.2.1 HPB Cancers

Cancers of the pancreas, liver (primary and metastatic) and bile ducts represent some of the most recalcitrant diseases encountered by the practicing oncologist. When identified early, these cancers can be removed with technically challenging operations. Fortunately, experience has decreased the perioperative complications associated with these operations. However, the ability to prevent disease recurrence following the procedure has not yet come to fruition. Although resection remains the only hope for cure, this end-point is achieved by very few. Analysis of randomized prospective trial data and single institution series strongly suggests that nearly half of all patients undergoing resections for pancreatic cancer, cholangiocarcinoma and metastatic colorectal cancer to the liver will experience a recurrence of disease in the first 12-15 months following removal of tumor(s).[1-3] In other words, these patients underwent an operation for likely abbreviated benefit in terms of survival. The recently reported, not yet published, data on the BILCAP (cholangiocarcinoma) is very similar to these outcomes below. It has been postulated for some time that the operation itself may hasten demise for some patients by inciting an inflammatory milieu and triggering an angiogenic switch in remote dormant tumor cells. Substantial data exist

in mice[4] supporting this concept but data in humans is admittedly lacking. We do however know that surgery is associated with increases in circulating tumor cell numbers, likely secondary to manipulation during the procedure.[5] It would be ideal to give a perioperative agent with efficacy against the tumor cells at the time of resection. Unfortunately, chemotherapy has deleterious effects on wound healing that would make resection an extremely-risky endeavor. However, a well-tolerated monoclonal antibody targeting a tumor cell epitope may hold promise in mitigating those early recurrences and thereby increasing the efficacy of resection for cancers of the pancreas, liver and bile ducts. This concept of immediate perioperative therapy is unique and additive to what is generally undertaken with high-risk cancers. For example, patients could receive standard neo-adjuvant and/or adjuvant therapies in addition to immediate perioperative therapy without altering the standard regimens. Moreover, antibody penetration and binding to tumor cells would be directly assessed on resected specimens, as would the effects on circulating tumor cell populations (which have been demonstrated to be prognostic[6-8]), which could be used to stratify patients for combination antibody/chemotherapy should disease recur. In short, the employment of immediate perioperative therapy, if demonstrated to be safe, could add an additional tool in the oncologist's armamentarium for resectable high-risk cancers.

1.2.2 Sialyl Lewis A Antigen - CA19-9

The Sialyl Lewis A (sLe^a) antigen is an epitope present on Carbohydrate Antigen 19-9 (CA 19-9), defined by the mouse monoclonal antibody 116-NS-19-9, shown to be overexpressed on epithelial cell tumors.[9, 10] SLe^a is an oligosaccharide expressed primarily as a proteoglycan that is secreted and circulates as a mucin form, and also as a less well studied glycolipid form.[10, 11] The sLe^a antigen is predominantly expressed on cancer cells.[12] As a ligand for E selectin, sLe^a facilitates tumor adhesion and extravasation, key events for tumor metastasis, and is thus a marker of an aggressive tumor phenotype.[13] Glycolipids, such as sLe^a, are established targets for cancer immunotherapies.[14] The monoclonal antibody MVT-5873 (also referred to as HuMab-5B1 or 5B1), the investigational agent in this study, specifically targets the sLe^a antigen.

CA 19-9 is widely expressed on tumors of the gastrointestinal tract, with up to 94% of pancreatic cancers positive for CA 19-9 expression and high expression rates also seen in bile duct carcinomas and transitional cell carcinomas.[15, 16] Additionally, expression of CA 19-9 is frequently seen in ovarian, colon, stomach, and distal esophagus/stomach cancers. Circulating serum levels of CA 19-9 have been validated as a biomarker for assessing the metastatic potential of pancreatic ductal adenocarcinomas (PDAC)[17, 18] and have been used to evaluate the aggressiveness of other epithelial cell cancers.[19, 20] As a known ligand for endothelial leukocyte adhesion molecules, CA 19-9 expression is associated with increased metastatic potential in colon cancer[13, 21, 22] and pancreatic adenocarcinoma.[23]

Serum CA 19-9 levels have also been found to be informative with respect to prognosis and treatment effect in patients with pancreatic cancer, with several studies correlating increasingly higher serum levels with poorer survival outcomes.[17, 18, 24] In a Phase I/II clinical trial of nab-paclitaxel and gemcitabine in patients with advanced pancreatic cancer, decreases in CA 19-9 levels correlated with tumor response, PFS, and OS.[25] In a Phase II study of 5-fluorouracil-based chemoradiotherapy in patients with locally advanced pancreatic cancer, a greater than 90% reduction in CA 19-9 levels from baseline was associated with significantly improved median survival time, with a multivariate analysis finding a-post therapy CA 19-9 level of less than 85.5 U/mL to be an independent prognostic factor for survival.[26]

On normal cells, expression of CA 19-9 is restricted to the apical brush border, a relatively inaccessible location due to the basement membrane and the tight junctions of mature and polarized ductal epithelium.[27] In patients with CA 19-9 positive tumors, about 5% are negative for circulating levels of CA 19-9, and this appears to be related to poor secretion or release of CA 19-9 into the blood stream, not necessarily to expression of the CA 19-9 antigen by the tumor cell.[28-30] Because CA 19-9 has a high expression rate in patients with pancreatic cancer, this antigen was identified as a target for antibody-based biopharmaceuticals, and specifically this investigation of MVT-5873 in patients with PDAC.

1.2.3 MVT-5873

MVT-5873 (HuMab-5B1) is a fully human IgG1 lambda antibody discovered by MabVax in collaboration with investigators at Memorial Sloan Kettering Cancer Center (MSKCC). MVT-5873 was identified from blood lymphocytes from a breast cancer patient following immunization with a sLe^a-KLH vaccine.[31] This vaccine has been shown to induce high titers of both IgG and IgM antibodies against sLe^a in mice and humans without cross-reactivity to other similar blood group carbohydrate antigens.[31] Two human monoclonal antibodies (5B1 and 7E3) with high-affinity for sLe^a were identified, subsequently expressed as a recombinant antibodies, and further characterized.[32]

Evaluation of the specificity of MVT-5873 demonstrated cell surface binding in sLe^a positive colon cancer (HT29 and Colo205), ovarian cancer (SW626), small cell lung cancer (DMS79), and pancreatic cancer (BxPC3) cell lines, but not to a sLe^a negative melanoma (SK-MEL28) cell line.[32] Importantly, MVT-5873 did not bind to Le^a, sLe^x, Le^y, or other related carbohydrates when evaluated by enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance.[32] In addition, an independent binding analysis conducted by the Consortium on Functional Glycomics Core H group using a glycan array with 465 distinct carbohydrates revealed that MVT-5873 had exquisite specificity for the carbohydrate epitope of the sLe^a antigen.

MVT-5873 has been shown to be potent in complement-dependent cytotoxicity (CDC) assays and antibody-dependent cell mediated cytotoxicity (ADCC) assays (see below). Both of these mechanisms are consistent with antitumor activity. Based on these findings, MVT-5873 was selected for further development as a potential therapy for patients with CA 19-9 expressing tumor types.

1.2.4 Preclinical Studies

1.2.4.1 Tissue Specificity

MVT-5873 binding to tumor TMA appeared to be specific, differentially expressed, and restricted, with most normal tissues lacking reactivity. Expression of sLe^a was present on several adenocarcinomas, including pancreatic cancers, a finding consistent with literature reports of sLe^a expression identified by CA 19-9 antibody binding (**Figure 1**). Most of the human specimens evaluated in the TMA analysis were negative for staining. However, expression of sLe^a antigen was found on mucous glands of the small intestine, colon (goblet cells), and rectum. There was also expression in exocrine pancreas, germinal center of lymph node, gallbladder, breast (ductal cells), and uterine cervix of normal human tissue. The observed binding pattern is consistent with expression in tissues producing exocrine secretions, i.e. mucins that carry the sLe^a antigen.

Strong positive staining was seen in 23/34 colon adenocarcinomas (68%), 34/58 adenocarcinoma metastases to the ovary (59%), and 7/9 pancreatic ductal cancers (62%) at various stages. As shown in the figure below, typical reactivity shows as diffuse cytoplasmic staining, with some tumor cells clearly showing distinct staining at the cell membrane level. In addition, signet ring-metastatic to ovaries, some lung (i.e. bronchioalveolar, mucoepidermoid) and metastatic breast cancer lymph node biopsy cores were found to be strongly positive, albeit at lower frequencies. In contrast, only 2/43 prostate cancer samples (5%) and 0/51 gastrointestinal stromal tumors (GIST) specimens were positive (data not shown).

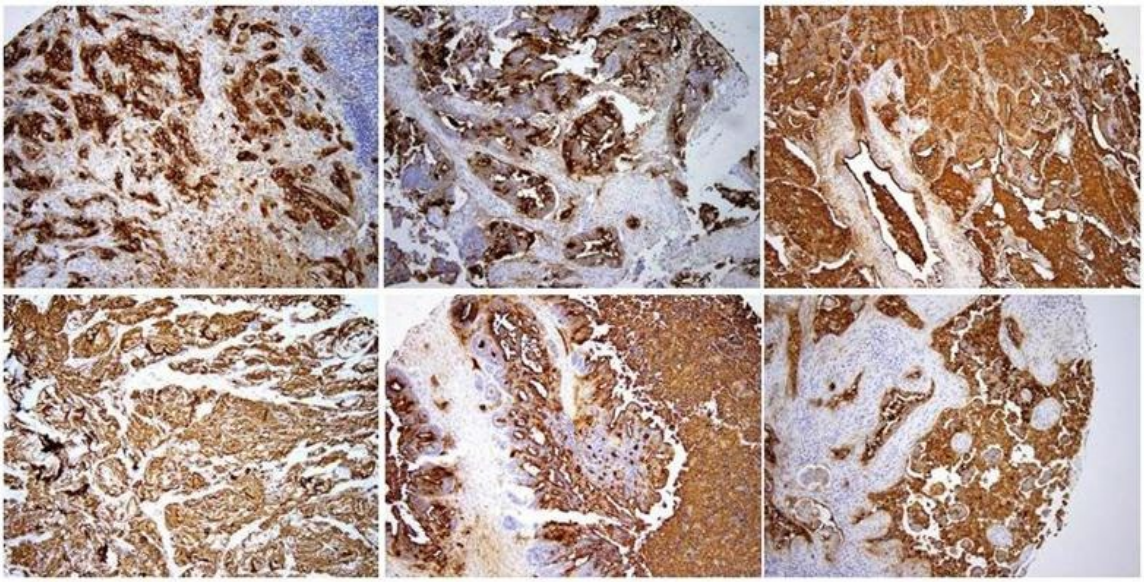


Figure 1: **Top left: pancreas, ductal adenocarcinoma, stage III**

Top center: sigmoid colon, carcinoma stage IIIB
Top right: lung adenocarcinoma, stage IB
Bottom left: urinary bladder, mucinous adenocarcinoma, stage IV
Bottom center: ovary, metastatic carcinoma from colon
Bottom right: lymph node, breast carcinoma, stage IIIA

1.2.4.2 Evaluation of MVT-5873 in Murine Xenograft Models

In an early exploratory study, the antitumor potential of MVT-5873 was assessed using a Colo205-luc xenograft model of metastatic colon cancer in SCID mice.[32] Across two experiments, groups of 5 mice were given either 4 doses of MVT-5873 at 5 mg/kg (20 mg/kg total dose) or 6 doses of MVT-5873 at 5 mg/kg (30 mg/kg total) intraperitoneally, each over the course of 21 days, while animals in the control groups received injections of phosphate buffered saline (PBS). Across all the control animals, the average median survival was 102 days and all died within 155 days. Treatment improved survival significantly; median survival in animals that received 4 doses of MVT-5875 was 207 days ($p < 0.05$; HR = 3.46), and in the animals that received 6 doses of MVT-5873, median survival had not yet been reached at day 301, the termination of the experiment ($p < 0.01$; HR =6.375).

To further evaluate the antitumor activity of MVT-5873, a series of *in vivo* studies were conducted utilizing human pancreatic cancer (BxPC3) xenograft models.

The combination of MVT-5873, both a single agent and in combination with gemcitabine and nab-paclitaxel in mice bearing BxPC3 tumor xenografts was evaluated. In this study MVT-5873 was administered as doses of 5, 15, and 30 mg/kg, blood samples for PK analysis were collected from all study groups, and tumor tissues were harvested at the end of study for IHC staining.

As had been observed in the previous BxPC3 xenograft experiments, single-agent MVT-5873 demonstrated tumor growth inhibition and growth delay at all dose levels compared to controls (**Figure 2**).

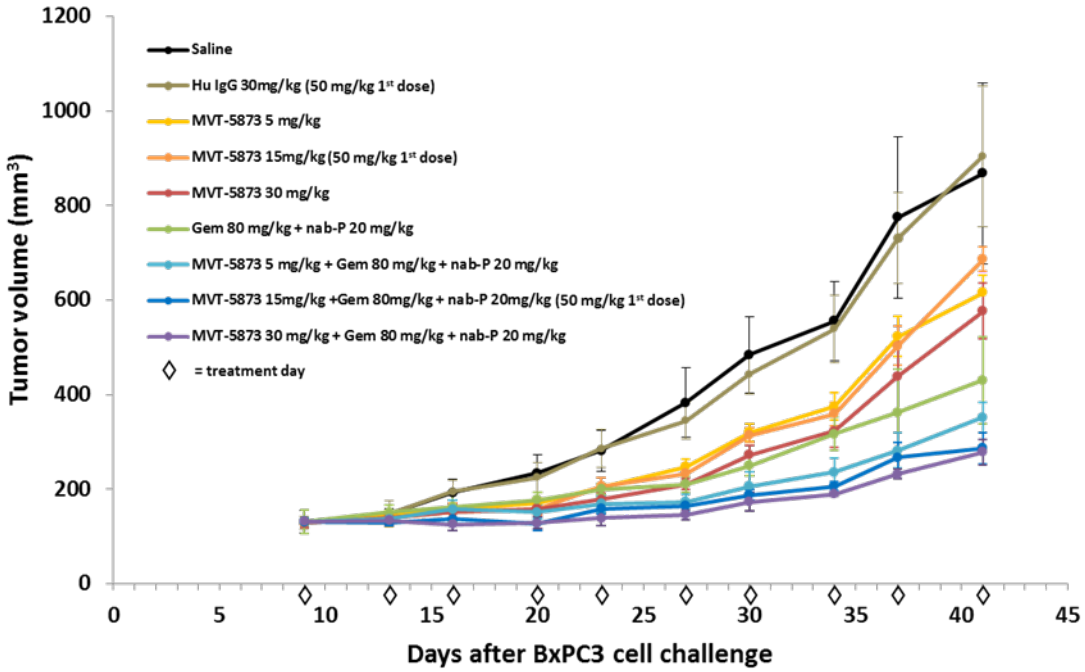


Figure 2: Tumor Growth Over Time – BxPC3 Xenograft Model with MVT-5873 Doses of 5, 15, and 30 mg/kg as a Single Agent and in Combination with Gemcitabine/nab-paclitaxel

Tumor tissue samples taken at the end of treatment were sectioned and stained for the presence of the sLe^a target using MVT-5873 as a probe **Figure 3**. Human IgG using goat anti-human IgG antibody was used as a probe for residual MVT-5873 bound to tumor post administration. Representative tissue staining samples are depicted. IHC staining signal intensities, recorded as optical densities, across the two panels are shown in the **Figure 3** below.

In the **Figure 3**, top panel, staining the presence of the sLe^a was high and similar in all samples, indicating a relative abundance of the sLe^a target in these tissues. These data provide evidence that upon treatment of gemcitabine plus nab-paclitaxel there is no change in expression of the target epitope. In the bottom panel, when stained with human IgG that lacks binding to the target epitope, the presence of residual MVT-5873 in tumor tissue was observed across all MVT-5873 treatment groups, with staining density correlating with response. The complete lack of staining in the chemotherapy alone group serves as a negative control.

As shown in the **Figure 3**, signal intensities of IgG staining across all MVT-5873 treatment groups were higher than that of the human IgG control, indicating binding selectivity of MVT-5873 in tumor tissue. There was a significant difference in signal intensity between the MVT-5873 5 mg/kg + chemotherapy group and the MVT-5873 15 mg/kg + chemotherapy group ($P < 0.05$), suggesting dose-dependent binding of MVT-5873 to tumor tissues.

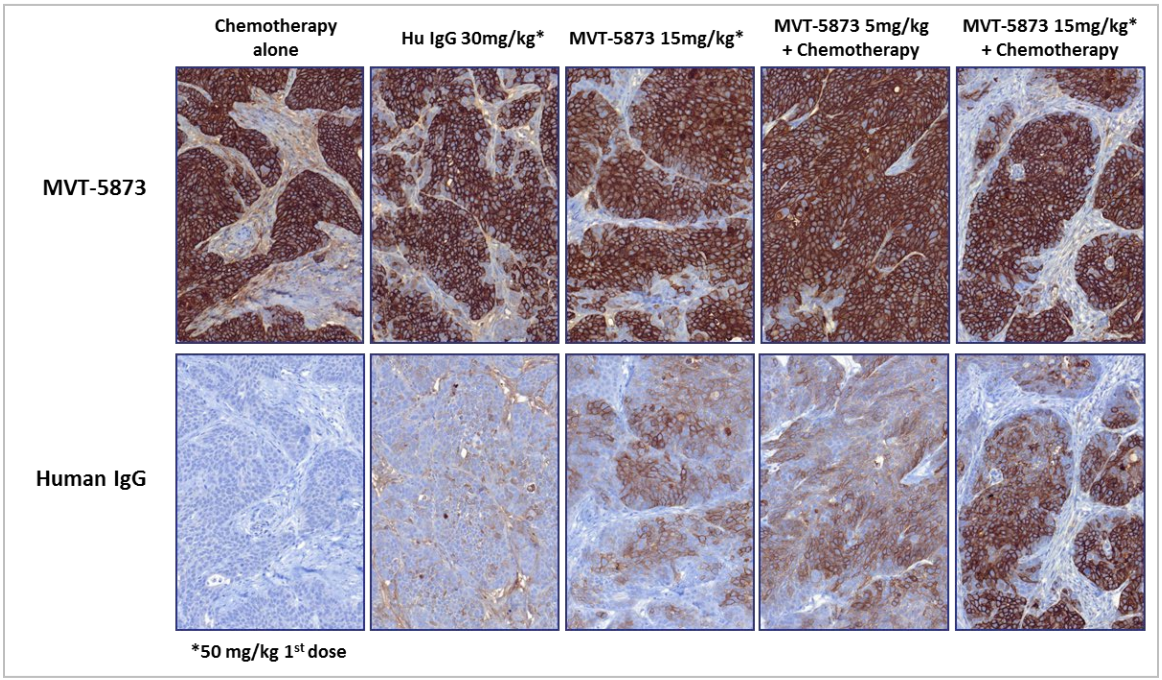


Figure 3: Immunohistochemical Staining of BxPC3 Tumor Tissue Samples at 20X Magnification; MVT-5873 (top panel) and Human IgG (bottom panel)

These xenograft studies indicate that MVT-5873 has activity in the known sLe^a-bearing tumor models.

Analysis of MVT-5873 binding to tumor tissue by IHC revealed an apparent dose-dependent uptake of MVT-5873 in tumor tissue.

Serum concentrations were measured. Further analysis of these data shown in **Figure 4** and **Figure 5** indicate an inverse relationship between MVT-5873 serum concentrations and tumor volume. This suggests that the presence or expansion of the sLe^a target, either on tumor tissue or in circulation, decreases the amount of free MVT-5873 in the serum and contributes to the systemic clearance of MVT-5873.

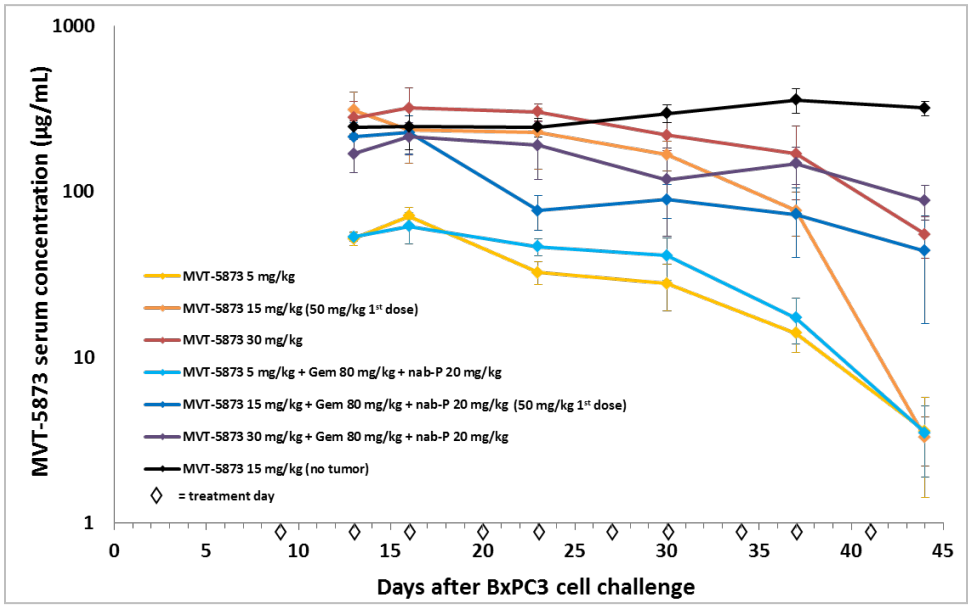


Figure 4: Mean MVT-5873 Serum Concentrations Over Time in BxPC3 Tumor-Bearing Mice and Nontumor-Bearing Mice

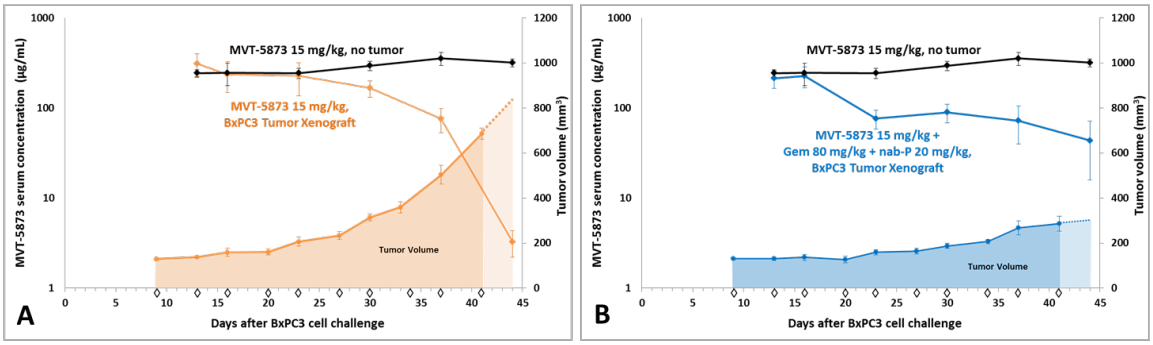


Figure 5: MVT-5873 Serum Concentration and BxPC3 Tumor Volume Versus Time

These studies support the clinical evaluation of MVT-5873, as a single agent and in combination with chemotherapy, in subjects with pancreatic cancer and other sLe[a] positive tumor types.

1.2.4.3 Pharmacokinetics

1.2.4.4 Single-Dose Pharmacokinetics

In a single-dose IV PK study in cynomolgus monkeys (non-GLP Study 20068188), MVT-5873 serum levels were determined over a one-month period using an ELISA procedure. MVT-5873 exhibited a low clearance from serum (0.384 to 0.503 mL/min/kg) and a low volume of distribution (40.9 to 83.0 mL/kg), with a resultant long half-life (65.2 to 217 hours) at dose levels of 10, 30 or 100 mg/kg MVT-5873 (**Table 1**).

Table 1: Pharmacokinetic Parameters for MVT-5873 Following Single Intravenous Doses of 10, 30, and 100 mg/kg of MVT-5873 to Cynomolgus Monkeys

Dose (mg/kg)	Sex	T_{max} (h)	C_{max} (µg/mL)	AUC_{0-t} (µg·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	V_d (mL/kg)
10	Female	0.250	141	12,800	NC	NC	NC
	Male	0.250	254	22,900	65.2	0.424	40.9
30	Female	0.280	499	41,900	NC	NC	NC
	Male	0.250	736	64,700	217	0.384	120
100	Female	0.750	1780	169,000	103	0.503	74.9
	Male	0.750	2190	213,000	126	0.456	83.0

Abbreviation: NC=Not Calculated (coefficient of determination less than 0.800 or the extrapolation of the AUC to infinity represented more than 20% of the total area)

The low serum clearance seen with MVT-5873 is typical of monoclonal antibodies, where the main route of elimination is generally thought to be by receptor binding and internalization and/or protein catabolism. The low volume of distribution is typical for a monoclonal antibody, since it is similar to the volume of plasma for the cynomolgus monkey and suggests limited distribution into tissue.

1.2.4.5 Repeat-Dose Pharmacokinetics

A multiple-dose toxicity study in cynomolgus monkeys (non-GLP Study 20068122) evaluated the effects of MVT-5873 (30 or 100 mg/kg) administered IV once a week for 2 weeks (2 doses). The toxicokinetic evaluations were conducted over each dosing interval on Days 1-7 and Days 8-15, revealing that exposure, measured by AUC_{0-168}, was approximately dose-proportional and similar across the dosing interval for both sexes, ranging from 26,600 to 146,00 µg•hr/mL for dose levels of 30 and 100 mg/kg, respectively (**Table 2**, **Figure 6**). There was minor MVT-5873 plasma accumulation when administered once weekly. Similarly, in a GLP 4-week once weekly (4 doses) IV toxicity study, trough plasma levels measured weekly were either similar to or greater than Week 1 indicating good exposure to MVT-5873 over the 4-week dosing period.

Table 2: Pharmacokinetic Parameters for MVT-5873 Following Intravenous Administration of 30 mg/kg and 100 mg/kg of MVT-5873 to Cynomolgus Monkeys on Day 1 and Day 8

Day	Dose (mg/kg)	Sex	C_{max} (µg/mL)	AUC_{0-168} (µg•h/mL)
1	30	Female	843	33,300
	30	Male	977	34,800
	30	Mean (M&F)	910	34,050
	100	Female	2260	151,000
	100	Male	2380	118,000
	100	Mean (M&F)	2320	134,500
8	30	Female	760	38,400
	30	Male	881	48,900
	30	Mean (M&F)	821	43,650
	100	Female	2540	212,000
	100	Male	2450	148,000
	100	Mean (M&F)	2495	180,000

Day	Dose (mg/kg)	Sex	C_{max} (µg/mL)	AUC_{0-168} (µg•h/mL)
M= Male; F = Female				

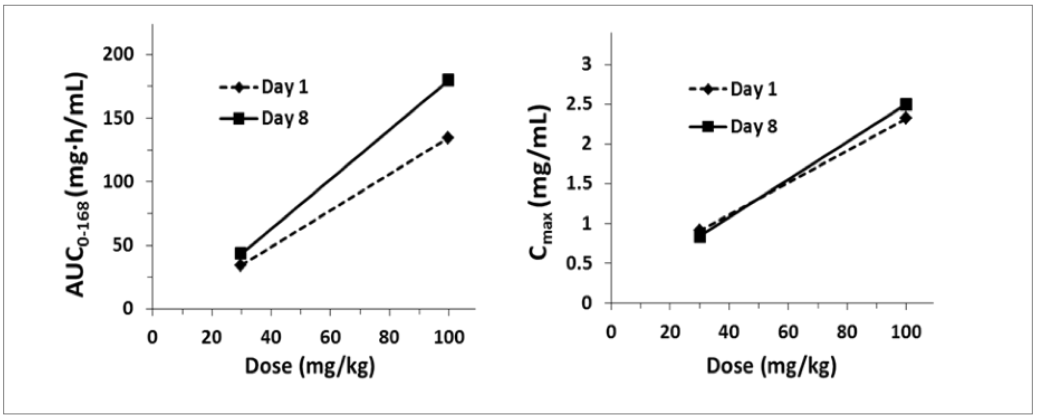


Figure 6: Serum Levels (AUC_{0-168} and C_{max}) of MVT-5873 after Repeated Intravenous Dosing in Cynomolgus Monkeys (Males and Females Combined) on Day 1 and Day 8

In addition to assessing PK in cynomolgus monkeys, serum levels of MVT-5873 were measured at various times during a multiple dose PK study in both nontumor- and tumor-bearing SCID mice. After intraperitoneal administration, MVT-5873 serum levels were maintained at an average of 46.1 µg/mL in nontumor-bearing mice. Mice with established CA 19-9 expressing tumor xenografts demonstrated lower serum levels, indicating a relatively higher clearance compared to nontumor-bearing mice.

Further information on the pharmacokinetics of MVT-5873 in mice the presence and absence of tumor was collected as part of the second BxPC3 xenograft study described above, which evaluated MVT-5873 as a single agent at doses of 5, 15, and 30 mg/kg as a single agent and in combination with 80 mg/kg of gemcitabine plus 20 mg of nab-paclitaxel. This study included an additional treatment group of nontumor-bearing mice that were treated with MVT-5873 15 mg/kg.

Serial pre-dose (C_{min}) concentrations of MVT-5873 were collected on Days 13, 16, 23, 30, and 37, with an additional sample collected 1 week later, on Day 44. As shown in the figure below, in the absence of tumor, serial C_{min} MVT-5873 concentrations (15 mg/kg dose level) appeared to slightly accumulate throughout treatment. However, in all tumor-bearing animals, serial C_{min} values declined over time, as had been observed previously.

1.2.4.6 Preclinical Safety

The preclinical studies conducted to determine the safety of MVT-5873 are summarized in the table below. Several toxicology studies have been conducted with MVT-5873 in cynomolgus monkeys and included a 4-week (4 dose) GLP safety study, a 2-week (2 dose) exploratory non-GLP toxicology study, and a single dose tolerability study. All studies were conducted at Charles River Laboratories (Reno, NV).

To support the cynomolgus monkey as an appropriate model for MVT-5873 toxicology studies, pivotal (GLP) tissue cross-reactivity studies were conducted to assess the binding of MVT-5873 to cryosections (or to fixed blood) of normal human tissues (GLP Study 20067038) and normal

cynomolgus monkey tissues (GLP Study 20074271); these studies were conducted at Charles River Laboratories (Pathology Associates, Frederick, MD).

Study Type and Duration	**Route / Mode of Administration**	**Species**	**Doses**	**Study No. Compliance**
Single dose				
Single-dose tolerability and pharmacokinetics with 4 week postdose observation/blood sampling period	IV slow bolus (1-3 min) or 30-min infusion via a saphenous vein	Monkey/ Cynomolgus	0, 10, 30 mg/kg (slow bolus) 100 mg/kg (30-min infusion)	20068188 Non-GLP
Repeat-dose studies				
Once weekly (2 doses) toxicity and toxicokinetic study with terminal sacrifice 2 weeks after the last dose	IV slow bolus (1-3 min) or 30-min infusion via a saphenous vein	Monkey/ Cynomolgus	0, 30 mg/kg (slow bolus) 100 mg/kg (30-min infusion)	20068122 Non-GLP
Once weekly (4 doses) toxicity and toxicokinetic study with terminal sacrifice 1 week after the last dose and with a 4-week recovery	IV slow bolus (1-3 min) or 30-min infusion via a saphenous vein	Monkey/ Cynomolgus	10, 30 mg/kg (slow bolus) 0, 100 mg/kg (30-min infusion) Recovery (0, 30, 100 mg/kg)	20068123 GLP
Other toxicity studies				
Tissue cross-reactivity (40 tissues from 3 donors)	In vitro (cyrosectioned tissue)	Monkey/ Cynomolgus	2 and 10 µg/mL	20067038 GLP
Tissue cross-reactivity (40 tissues from 3 donors)	In vitro (cyrosectioned tissue)	Human	2 and 10 µg/mL	20074271 GLP
Blood compatibility (hemolysis and erythrocyte clumping)	In vitro heparinized blood from Lewis A positive phenotype on red blood cells	Human	Final blood concentrations: 57.5 – 384 µg/mL	323966

1.2.4.7 Species Selection

The cynomolgus monkey is considered a relevant biological species for evaluating the safety of MVT-5873, since this species, like humans, expresses the gene (*FUT3*) responsible for expression of the pharmacologic target sLe^a. In contrast, both mice and rats lack a functional *FUT3* and do not express sLe^a. To establish the tissue expression of the sLe^a target in standard toxicology animal models, binding of MVT-5873 to tissue microarrays obtained from cynomolgus monkey, mouse, and rat was studied. As expected from the literature and from previous studies with MVT-5873 using normal human tissue, binding of MVT-5873 to cynomolgus monkey tissue was seen in mucus secreting epithelium in the gastrointestinal tract, as well as in other related tissues (e.g., salivary glands). Unlike cynomolgus monkey tissue microarrays, the tissue microarrays from mouse and rat showed no specific binding for MVT-5873. These results confirm literature reports that rodents do not express sLe^a and thus are not appropriate for nonclinical safety testing, and that

cynomolgus monkeys do express the pharmacologic target and are appropriate for toxicity testing with MVT-5873.

1.2.4.8 Repeat Dose Toxicity

1.2.4.8.1 MVT-5873: 2-Week Once Weekly (2 Doses) Toxicity Study

In a pilot toxicity study in cynomolgus monkeys (nonGLP Study 20068122), MVT-5873 was administered IV as a slow bolus dose at 0 and 30 mg/kg or as a 30-min infusion at 100 mg/kg on study Days 1 and 8. The vehicle was 25 mM histidine, 150 mM sucrose, 55 mM sodium chloride, 0.02% Tween 80 at pH 6.0. Observations were recorded during the study. Samples for hematology, coagulation, urinalysis and clinical chemistry were collected for all animals once prestudy and on Day 23 or, for urinalysis, on Day 25. Animals were necropsied on Day 25, organs weighed and tissue collected for histopathological examination.

Toxicokinetic samples were drawn for all animals on Days 1 and 8 at 0.25, 6, 12, 24, 72, and 168 hours post dose. Samples were also collected on Day 23 prior to sacrifice (see Section **1.2.4.8.2** for discussion of repeat-dose toxicokinetics).

There was no mortality, no changes in clinical observations, no changes in food consumption, or adverse reactions to MVT-5873. There were no MVT-5873-related changes in hematology, serum chemistry, urinalysis or coagulation parameters, and no MVT-5873-related macroscopic findings noted at terminal necropsy.

Non-adverse microscopic findings considered related to MVT-5873 were noted at 100 mg/kg in the gallbladder (minimal eosinophilic infiltration) in both the male and female monkeys and in the liver (mild Kupffer cell hypertrophy) in the male. Mild mononuclear cell infiltrates noted in the kidney of the female at 100 mg/kg was of uncertain relationship to the test article. These histological changes were not seen in the pivotal GLP 4-week study.

1.2.4.8.2 MVT-5873: 4-Week Once Weekly (4 Doses) Toxicity Study

In the pivotal GLP 4-week toxicity study in cynomolgus monkeys (GLP Study 20068123), MVT-5873 was administered IV as a 30-minute infusion at 0 and 100 mg/kg and as a slow bolus dose at 10 and 30 mg/kg on study Days 1, 8, 15 and 22. The vehicle was the same as the clinical formulation and consisted of 25 mM histidine, 150 mM sucrose, 55 mM sodium chloride, 0.02% Tween 80, pH 6.0. Observations were recorded during the study. Ophthalmic examinations were conducted predose and during Weeks 4 and 8. Electrocardiograms, heart rate, and waveform intervals (PR, QRS, RR, QT, and QTc Bazett's) were recorded predose and during Weeks 4 and 8. Samples for hematology, coagulation, and clinical chemistry were collected for all animals once predose, on Day 30, and at the end of the 4-week reversal period (Day 58). Samples for assessment of anti-MVT-5873 antibodies were drawn predose, on Day 29, and near the end of the 4-week reversal period (Day 57). Animals were necropsied, organs weighed and tissue collected for histopathological examination on Day 30 for the main sacrifice groups (3/sex/group) and on Day 58 for the reversal groups (2/sex at 0, 30 and 100 mg/kg).

Toxicokinetic samples were drawn at various times over a one-week period following the first dose administration, at weekly intervals until the main sacrifice, and then again at the end of the 4-week reversal period.

There was no mortality and no MVT-5873 related changes in clinical observations, body weight, food consumption, ophthalmic exams, or cardiac parameters. There were no MVT-5873 related changes in hematology, serum chemistry, or coagulation parameters and no MVT-5873 related macroscopic findings noted at the main necropsy or at the reversal necropsy. In contrast to the previous cynomolgus monkey toxicity study, no MVT-5873 related microscopic findings were observed in this GLP study.

The toxicokinetics of MVT-5873 in female and male cynomolgus monkey serum demonstrated similar systemic exposure as in the previous toxicity study, with mean weekly trough values over the 4-week study period being similar to, or greater than, those observed during Week 1. Although MVT-5873, a fully human monoclonal antibody, generated anti-MVT-5873 antibodies in most animals at all dose groups, the presence of these antibodies had no apparent effect on serum levels of MVT-5873 and was not associated with any microscopic changes. Two monkeys tested positive for anti-MVT-5873 antibodies prior to treatment with MVT-5873 and also demonstrated higher serum clearance of MVT-5873 on Day 1 versus monkeys with no predose antibodies; these results indicate that the positive results prestudy were likely cross-reactive antibodies. Development of antibodies during the study was expected following administration of a human monoclonal antibody to cynomolgus monkeys.

In summary, intravenous administration of MVT-5873 up to 100 mg/kg once weekly for 4 weeks generated no adverse toxicological effects. The dose of 100 mg/kg is near the maximum feasible dose based on maximum formulation concentration and maximum acceptable dose volume in monkeys. An expected immune reaction was induced in cynomolgus monkeys after treatment with MVT-5873, but had no apparent effect on serum levels of MVT-5873, which generally remained constant throughout the 4-week study period.

1.2.4.9 Tissue Cross-Reactivity Studies

The objective of this study was to determine the potential cross-reactivity of MVT-5873, a monoclonal human IgG antibody directed against Sialyl Lewis (a), with cryosections of human tissues. Sialyl Lewis (a) is a carbohydrate antigen present on O-glycans on the surfaces of cells and is often associated with high grade tumors from various tissues.[12, 33] Sialyl Lewis (a) has been reported to be expressed in a number of normal tissues as well.[34-37]

Pivotal (GLP) tissue cross-reactivity studies of MVT-5873 with cryosections (or with fixed blood) of normal human tissues (GLP Study 20067038) and normal cynomolgus monkey tissues (Study 20074271) were conducted using 41 different tissue types from typically 3 donors/tissue. In addition, positive control (cryosections of human DMS 79 cells), negative control (cryosections of human Jurkat cells), and ancillary control (cryosections of human colon which was previously shown to cross react with MVT-5873) tissues were used to ensure integrity of the staining. As a further control to ensure adequacy of the tissue sample, sections were immunostained for β_2-microglobulin, a relatively ubiquitous epitope. To ensure specificity of the MVT-5873 antibody, all tissue sections were concurrently stained with a negative control human IgG1 kappa antibody.

The optimal concentration of MVT-5873 was determined by finding the lowest concentration of test article that produced the maximum (plateau) binding to the target antigen (2 µg/mL). This concentration and a 5-fold increase (10 µg/mL), which did not incur excessive nonspecific staining of control samples and/or test tissues, were used for the definitive tissue cross-reactivity studies.

MVT-5873 produced moderate to intense membrane, cytoplasm, and cytoplasmic granule staining of the positive control material (cryosections of human DMS 79 cells) at both staining concentrations. MVT-5873 did not specifically react with the negative control material (cryosections of human Jurkat cells) at either staining concentration. The control article, HuIgG1, did not specifically react with either the positive or negative control materials or with the any of the tissue slides. There also was no staining of the assay control slides. MVT-5873 produced moderate to intense staining of membrane, membrane granules, cytoplasm, and cytoplasmic granules in frequent mucosal epithelial cells and weak to strong staining of occasional extracellular material with morphology and location expected for mucus in the ancillary control material (cryosections of human colon) at both staining concentrations. There was no staining of any human colon tissue elements from the ancillary control material with either concentration of HuIgG1 or in the respective assay control slide. The excellent specific reactions of MVT-5873with the positive control material and the lack of specific reactivity with the negative control material, as well as the lack of reactivity of the control article, indicated that the assay was sensitive, specific, and reproducible.

The results of human tissue staining with MVT-5873 at 10 and 2 µg/mL and with the control article, HuIgG1, at 10 and 2 µg/mL are presented in GLP Study 20067038 and summarized below.

Epithelium

MVT-5873 variably stained membrane, membrane granules, cytoplasm, and/or cytoplasmic granules in epithelium in a variety of human tissues including bladder (transitional), breast, colon (mucosa), eye (conjunctiva), Fallopian tube (mucosa), gallbladder (mucosa), esophagus (squamous, submucosal glands), small intestine (mucosa), stomach (mucosa), kidney (tubular), liver (bile duct), lung (bronchial, bronchiolar), ovary (surface, follicle), pancreas (acinar, ductal), pituitary (adenohypophysis), prostate (glandular, ductal), rectum (mucosa), salivary gland (acinar, ductal), skin (sweat gland, hair follicle, epidermis), testis (seminiferous tubules), thymus, tonsil (squamous, surface, crypt), ureter (transitional), cervix (external ostium [squamous], internal ostium, endocervical glands), and uterus (endometrium, surface, glandular). This staining was equivalent, reduced in intensity and/or frequency, or absent at the lower staining concentration. Sialyl Lewis (a) background expression has been reported in a variety of tissues including pancreas, gallbladder, stomach, colon, bronchial tree, endometrium, salivary glands, kidney and prostate. Based on the wide range of Sialyl Lewis (a) background expression, the observed staining of epithelium in the human tissues was judged expected.[34-37]

Mononuclear cells

MVT-5873 weakly to moderately stained cytoplasm and cytoplasmic granules in rare to occasional resident, migrating, and/or infiltrating mononuclear cells in lymph node at the higher staining concentration. This staining was reduced in frequency to rare at the lower staining concentration. No literature was available describing Sialyl Lewis (a) expression by mononuclear cells; thus, the observed staining of this cell type was judged unexpected.

Extracellular material

MVT-5873 variably stained extracellular material in a number of tissues including bladder, colon, eye, Fallopian tube, gall bladder, esophagus, small intestine, stomach, kidney, lung, ovary, pancreas, pituitary, placenta, prostate, rectum, salivary gland, testis, thymus, thyroid, tonsil, ureter, cervix, and uterus. This staining was generally equivalent at both staining concentrations. MVT-

5873 stained extracellular material generally had morphology and location consistent with that expected for mucus, serum components, colloid, lens protein, and/or serum components. Sialyl Lewis[a] is reported to be secreted into the serum in the form of high-molecular mucin-like glycoproteins; thus, the observed staining of extracellular material was judged expected.[12, 33]

Mesothelium

In one testis sample, MVT-5873 weakly to moderately stained the cytoplasm of occasional mesothelial cells at both staining concentrations. No literature was available describing Sialyl Lewis (a) expression by mesothelium; thus, the observed staining of this cell type was judged unexpected.

Summary

Consistent with the literature for expression of sLe[a], MVT-5873 stained a variety of epithelial cell types and related extracellular mucus-like material in both human and cynomolgus monkey tissues, all consistent with epithelial cell secretions. The structures stained included mucosal/secretory epithelium of the bladder, breast, eye (conjunctiva), Fallopian tube, gastrointestinal tract, kidney tubules, liver (bile duct), lung (bronchial, bronchiolar) ovary, pancreas (acinar ducts), pituitary (adenohypophysis), prostate (ducts), salivary gland (ducts), skin (sweat gland, hair follicle, epidermis), testis (seminiferous tubules), thymus, tonsils, ureter, cervix, and uterus. These epithelial cells were similarly stained in both human and cynomolgus monkey tissues, except for the ovary and testes, which were only stained in human tissue; however, extracellular mucus material in cynomolgus monkey testes did stain positive.

Additional staining was seen intracellularly in lymph node of one human and one cynomolgus monkey donor tissue and in the mesothelium of one human teste. Staining of these tissues is considered to be of little-to-no toxicologic relevance as the cytoplasmic compartment is generally thought to be inaccessible to monoclonal antibodies when administered intravenously to animals. The lack of toxicological significance of the epithelial secretory cell staining is supported by the lack of toxicology findings at doses up to 100 mg/kg/week in the GLP 4-week MVT-5873 toxicology study in cynomolgus monkeys.

1.2.5 Effects in Humans

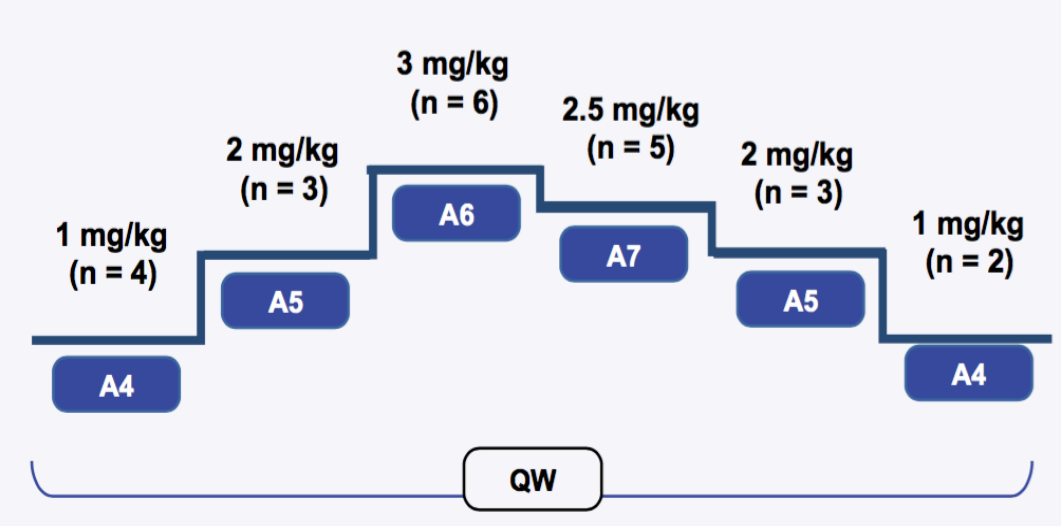
MVT-5873 is currently being evaluated in a Phase I/II study both as a single agent and in combination with gemcitabine/nab-paclitaxel. Trial MV-0715-CP-001.01 is a Phase 1 Safety and Tolerability Study of Human Monoclonal Antibody 5B1 (MVT-5873) as Monotherapy and with Chemotherapy in Subjects with Pancreatic Cancer or Other CA 19-9 Positive Malignancies. The primary objective for this trail is to determine the safety and maximum tolerated dose of MVT-5873 administered as monotherapy, determine safety and maximum tolerated dose of MVT-5873 administered in combination with nab-paclitaxel plus gemcitabine and to determine the pharmacokinetics of MVT-5873. Secondary objectives are to evaluate tumor response rate (based on RECIST 1.1) to MVT-5873 and evaluate the duration of response This study is currently ongoing in the dose escalation phase for both the monotherapy arm and the combination chemotherapy arm is being evaluated in an expansion cohort at an MVT-5873 dose of 0.125 mg/kg.

Trial MV-0715-CP-001.01 enrolled the first subject on 17-Feb 2016 and as of 15-Dec 2017 had accrued 32 subjects with pancreatic adenocarcinoma or other CA 19-9 positive malignancies in

the single agent study as summarized below. The population of this study consists of adults (males and females), 18 years of age and older who have locally advanced or metastatic pancreatic ductal adenocarcinoma or other CA 19-9 positive malignancies.

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

MVT-5873 was administered on an every-other-week schedule (Q2W) (Cohorts A1 and A2) and then modified to a weekly schedule (QW) based dose limiting toxicity at 3 mg/kg and on initial PK data. The QW dose escalation schema is shown below and further summarized in the subsequent table.



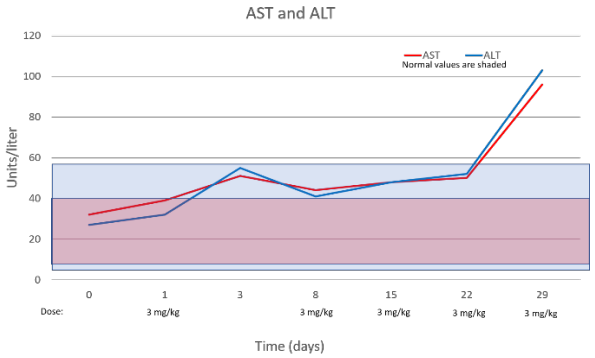
Parameter	Cohort Identifier					
	A1	**A2**	**A4**	**A5**	**A6**	**A7**
Number of subjects	6	3	4	3	6	4
Dose (mg/kg)	1	3	1	2	3	2.5
Schedule	Q2W	Q2W	QW	QW	QW	QW
Dose intensity (weekly mg/kg equivalent)	0.5	1.5	1	2	3	2.5

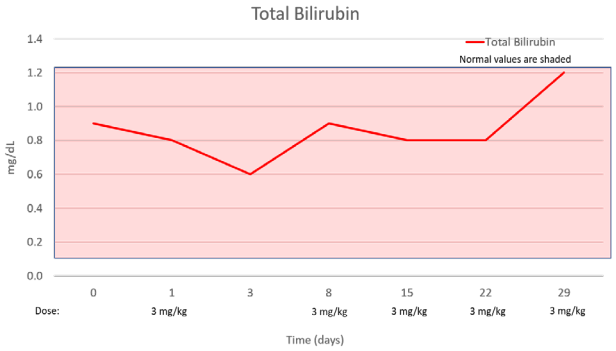
1.2.5.1 Summary of Safety Information

As of December 15, 2017, the single agent MTD for every other week (Q2W) and weekly (QW) schedules were defined as 1 mg/kg with dose limiting liver toxicity observed at 3 mg/kg for Q2W and 2 mg/kg for QW. The single agent weekly schedule has explored MVT-5873 doses ranging from 1 to 3.0 mg/kg (1.0, 2.0, 2.5 and 3.0 mg/kg). Based on the occurrence of dose limiting liver toxicity characterized by increased transaminases (AST/ALT) and blood bilirubin (Grade 3 and single Grade 4), MVT-5873 doses ≥ 2.0 mg/kg were considered to have exceeded the maximum tolerated dose (MTD).

The MTD for single agent MVT-5873 was determined to be 1 mg/kg. However, based on clinical data single-agent MVT-5873 at a dose of 3 mg/kg appears to demonstrate dose limiting toxicity with increases in liver transaminases and blood bilirubin. When seen, these abnormalities occurred within a few days of drug administration, were self-limited and resolved spontaneously within eight days and resulted in no permanent liver abnormalities. Moreover, dosing >1.0 mg/kg appeared to be a more effective dose in terms of RECIST responses than 1.0 mg/kg, and subjects on doses >1.0 mg/kg received more doses before PD was documented. A secondary aim of Trial MV-0715-CP-001.01 was to determine the mechanism(s) of this DLT, which may be related to Kupffer cell activation and not necessarily any direct injury related to the antibody. Non-human primate data support this hypothesis.

Patient #1





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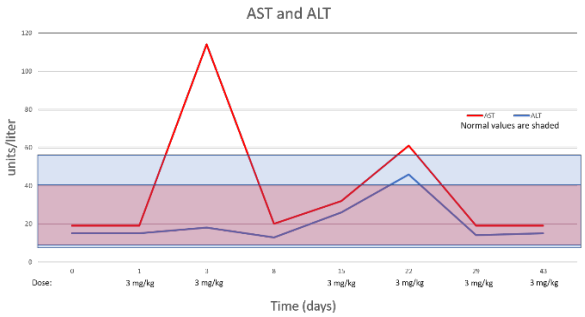

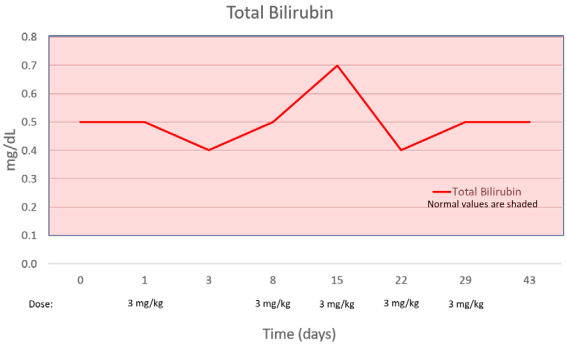

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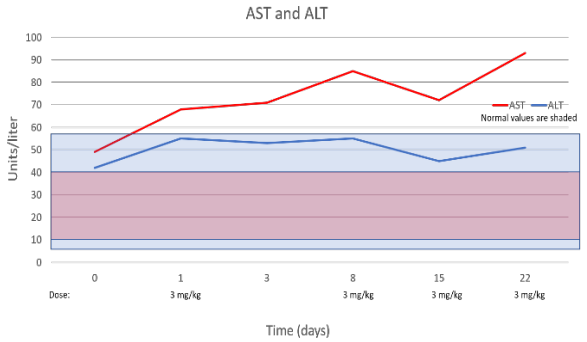

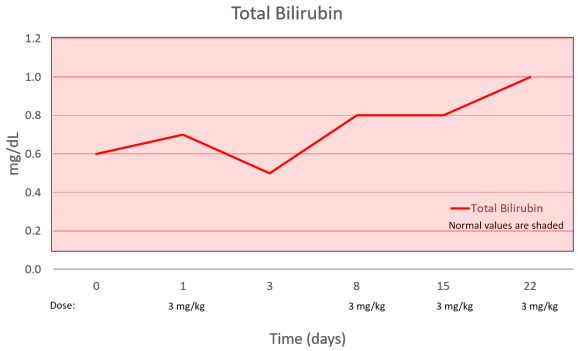

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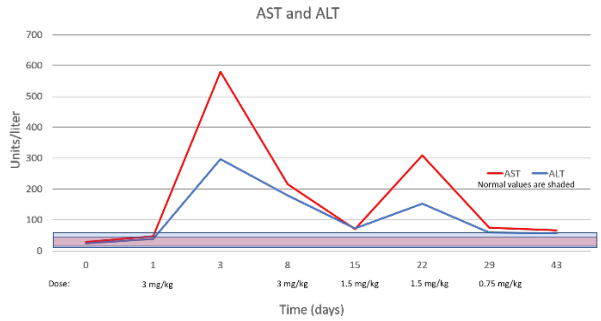

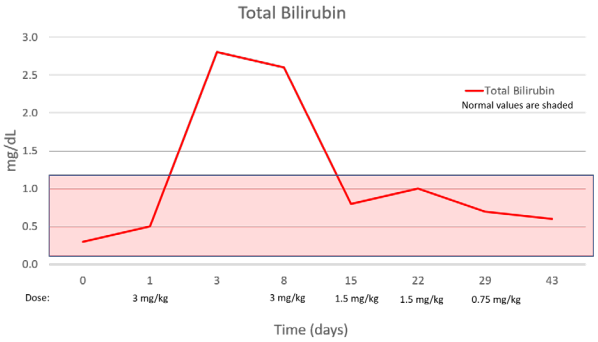

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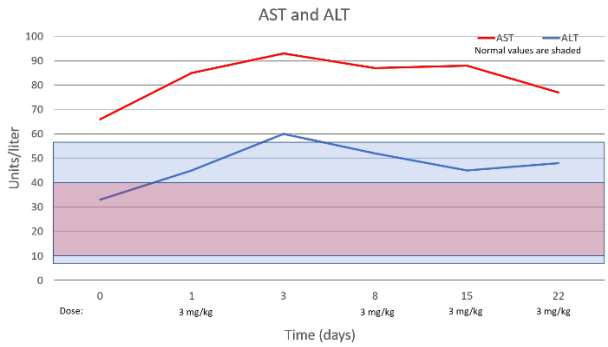

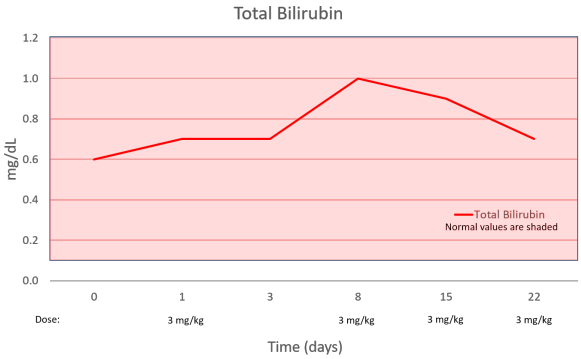

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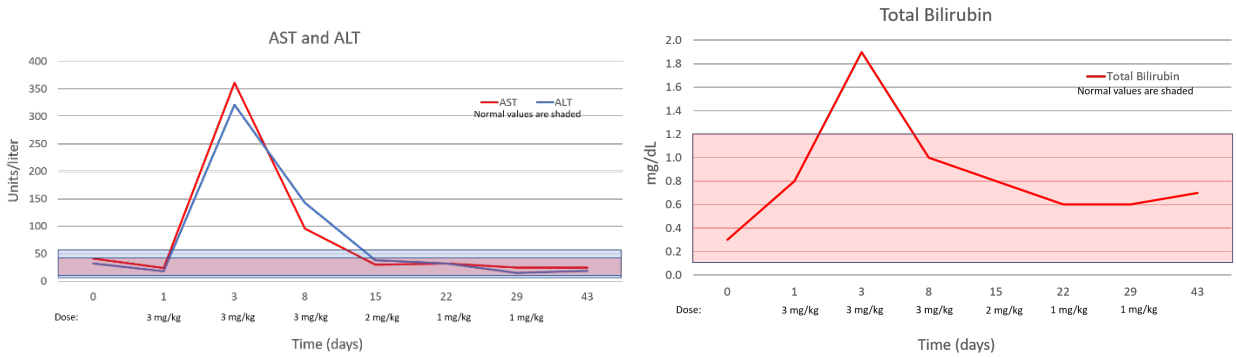

Figure 7: Liver Function Test with 3mg/kg Weekly Dosing of MVT-5873 from Six Subjects

As a single agent, severe (Grade 3+) toxicities considered related to MVT-5873 have predominately included reversible liver function abnormalities (manifest as increased transaminases and blood bilirubin), and infusion reactions. Infusion reactions decreased in frequency and severity following initiation of a prophylactic regimen (slower infusion rate and IV steroids). Low-grade (Grades 1 and 2) treatment-related toxicities consist predominately of toxicities related to immune activation (chills, fever, malaise, pruritus, rash, and skin induration). No significant related hematologic toxicity has been observed.

To date, no significant EKG changes (e.g., increases in QTcF) have been observed.

In summary, the predominate toxicity of MVT-5873 as a single agent and/or in combination with gemcitabine/nab-paclitaxel is dose limiting liver function test abnormalities. Increases in liver function tests are generally seen early (Day 3) and are reversible. Infusion reactions, when seen, generally appear during the infusion or shortly thereafter and appear less likely with slower infusion rates or with the use of steroid premedication.

A summary of the safety profile and adverse events are summarized below.

Table 3: Dose Cohorts, Cycles Administered and Patient Disposition

Cohort	**Baseline CA19-9 (U/mL)**				**Patient Disposition**			
	< 2500		**≥ 2500**		**On Study**	**Off Study**		
	n	Median Cycles (range)	n	Median Cycles (range)		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

Table 4: Summary of MVT-5873 Dose Limiting Toxicities and Treatment Disposition

Cohort (n)	**Individual Patient Events (Cycle 1)**				**Treatment Disposition**	
	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 1[st] dose, resolution to Grade 2 by Day 5						

The adverse event experience for MVT-5873 as a single agent is listed in the **Appendix B** and summarized below in the accompanying **Table 5** and **Table 6**.

Table 5: All Adverse Events, All Grades, in ≥ 30% of Subjects

Preferred Term	**n (%)**	**Cohort At MTD**		**Cohort Exceeds MTD**			
		A1 (n = 6)	**A4 (n = 6)**	**A2 (n = 3)**	**A5 (n = 6)**	**A6 (n = 6)**	**A7 (n = 5)**
↑ AST	23 (72)	-	2	-	5	5	11
↑ ALT	18 (56)	-	1	1	4	2	10
↑ Alkaline phosphatase	22 (69)	4	4	-	2	4	8
↑ Bilirubin	20 (63)	3	1	-	9	1	6
Fatigue	19 (59)	4	4	1	1	5	4
Nausea	13 (41)	3	1	2	5	-	2
Hypoalbuminemia	12 (38)	1	2	-	-	1	8
Hyperglycemia	10 (31)	4	2	-	2	-	2
Vomiting	10 (31)	4	1	3	1	1	-
Back Pain	10 (31)	1	-	1	2	6	-
Anemia	10 (31)	1	2	-	-	-	7
Pneumonitis	-	-	-	-	-	-	-

Total* (n = 32)

Table 6: All Treatment-Related Adverse Events ≥ Grade 3

Preferred Term	n (%)	Cohort At MTD		Cohort Exceeds MTD			
		A1 (n = 6)	A4 (n = 6)	A2 (n = 3)	A5 (n = 6)	A6 (n = 6)	A7 (n = 5)
↑ 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	-	-
Pneumonitis	-	-	-	-	-	-	-
↓ 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 subjects across all cycles; #data as of 08/30/2017							

1.2.6 Pharmacokinetics

MVT-5873 displays a half-life of 117.6 ± 33.4 h, clearance of 279.6 ± 313.0 mL/h, and volume of distribution at steady-state of 17.7 ± 21.0 L. These data demonstrate that MVT-5873 displays properties that are in the typical range for monoclonal antibodies. These initial PK values for the two different schedules of administration using a two-compartment model are summarized in the **Table 7**.

Table 7: MVT-5873 Human Pharmacokinetics

Regimen	Subject	Initial t1/2 (h)	Terminal t1/2 (h)	$AUC_{0-\infty}$ (ng•h/mL)	V_{ss} (mL)	Cl (ml/h)
Q2W	Mean	20.8	193.0	2339353	17147	226.3
	SD	9.5	93.4	3256439	27582	290.1
QW	Mean	37.3	833.1	2812486	14922	65.1
	SD	14.1	1164.4	3247729	12999	68.9

1.2.7 Reductions in Serum CA19-9 Levels

In study MV-0715-CP-001.01, serum CA 19-9 levels are assessed both pre- and post-MVT-5873 administration. Data on serum CA 19-9 levels indicate that serum CA 19-9 levels are uniformly reduced in all subjects regardless of dose. However, the probability of a CA 19-9 level within

normal limits (i.e., < 37 U/mL) post MVT-5873 appears to be related to dose. As shown in the table below, at a dose of 1 mg/kg, MVT-5873 appears to normalize an elevated CA 19-9 level in about 50% of subjects on Cycle 1 Day 1 and in about 20% of subjects across all administration days. In contrast, doses of 2 mg/kg or higher normalize CA 19-9 levels in essentially all subjects.

Table 8: Normalization (< 37U/mL) of CA 19-9 Levels Following Adminstration of MVT-5873

Dose MVT-5873 (mg/kg)	# Normal Post C1D1 *	Percent	# Normal Post All Days**	Percent
1	3/6	50%	4/20	20%
2	3/3	100%	10/10	100%
3	1/1	100%	12/13	92%
TOTAL	**7/10**	**70%**	**26/43**	**60%**

*Number of subjects with CA 19-9 level > 37U/mL pre MVT-5873 that was reduced to < 37U/mL post MVT-5873 on Cycle 1 Day 1 only.

**Number of subjects with CA 19-9 level > 37U/mL pre MVT-5873 that was reduced to < 37U/mL post MVT-5873 for all administration days.

1.2.8 Responses to Therapy

Upon review of the single agent dosing cohorts, dosing > 1 mg/kg appears to be a more effective dose based on RECIST responses than 1 mg/kg. Moreover, subjects on doses > 1 mg/kg remained on therapy longer before PD was documented indicating longer duration of response. Most importantly however the data clearly indicate efficacy for MVT-5873 when given as a single agent, and the subjects that experienced the most efficacy were those with CA 19-9 values less than 2,500 U/ml (**Figure 8**).

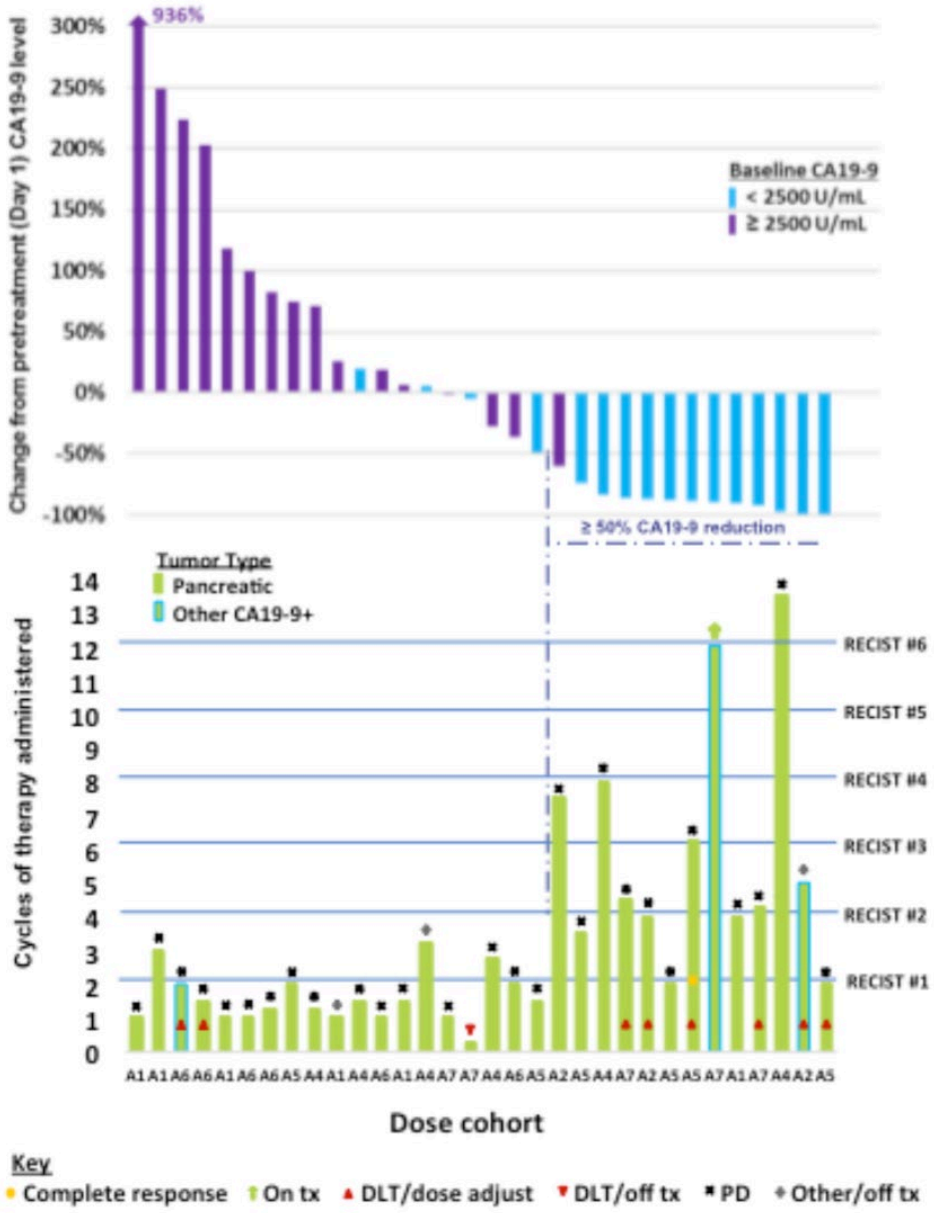

Figure 8: Efficacy for MVT-5873

The preliminary response data for MVT-5873 in combination with a standard of care chemotherapy are promising with 5 PR and 1 SD as best response. **Figure 9** illustrates the percent change in target lesion for the first six subjects at a dose of 0.125 mg/kg (Cohort B3).

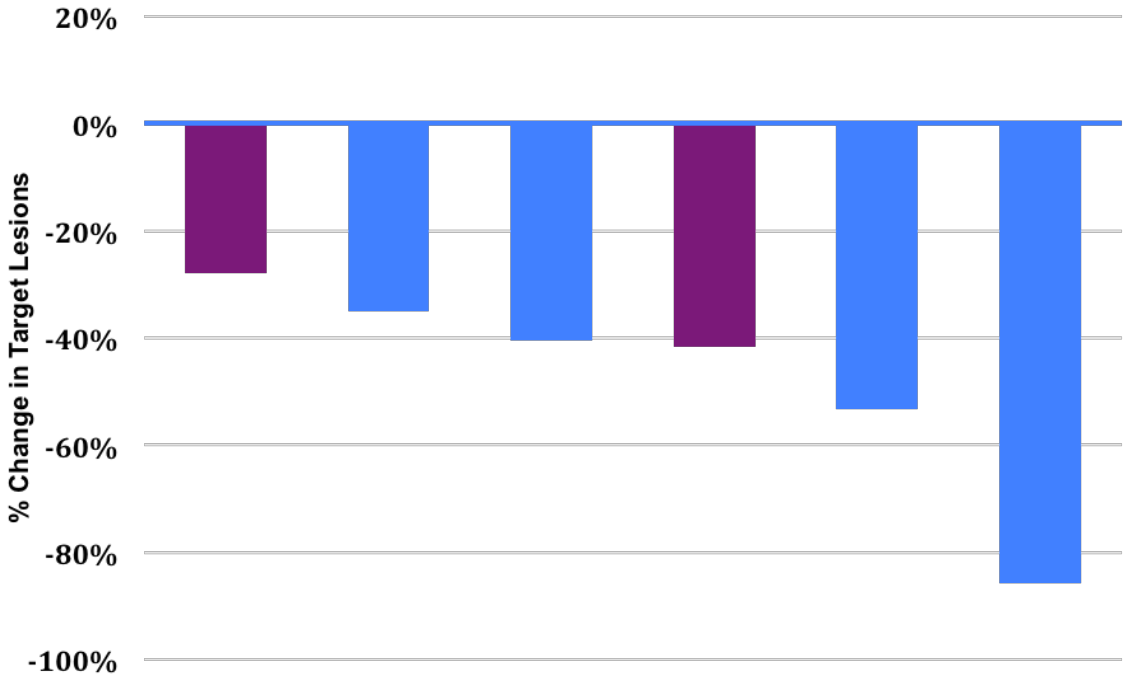

Figure 9: Percent Change in Target Lesions in Cohort B3 (0.125 mg/kg MVT-5873)

1.2.9 Rationale

In this study we are planning to give subjects a pre-operative, one-time infusion of 1 mg/kg of MVT-5873 at Day -3 before surgery, perform the resection and continue treatment with MVT-5873 at the dose of 1 mg/kg. We believe that peri-operative use of MVT-5873 adds "systemic" treatment during a time when none is given, despite the fact that the resection is associated with large increases in circulating tumors cells, and an inflammatory milieu believed to be, at least in part, responsible for the early recurrences observed in a substantial number of subjects. We believe peri-operative MVT-5873 will decrease early recurrence rates and increase DFS for subjects with CA 19-9 producing cancers included in this study.

To assess safety of the combination of treatment with MVT-5873 and surgery, we are planning to start with enrollment into safety lead-in cohorts and carefully monitor status of the subjects during 10 days after initial treatment and surgery. We will continue enrollment into the study only if treatment in the safety lead-in cohorts are proven to be safe.

If safety is documented with the safety-lead in cohorts at 1 mg/kg, we will dose escalate the single pre-operative dose of MVT-5873 to 3 mg/kg. We want to explore this higher dose for pre-operative treatment because we consider the drug to be more effective at this dose, and we

believe the days following the operation are the most critical time to for the reasons outlined above. We do not believe there will be undo risk as subjects will receive the 3 mg/kg dose once.

1.2.10 Metastasis Assays Using *Ex Vivo* Perfusion of Omentum

A major goal of Dr. Hernandez's lab is to understand how tumor cells adapt to and co-opt the liver microenvironment for eventual metastatic outgrowth. With tumor cells labelled and observable throughout week-long time courses, many downstream applications will be possible, including (but not limited to) interrogation of the tumor cells at various time-points and at various stages of the metastatic cascade, with and without forced over-expression of various genes of interest. In order to accomplish this, cholangiocarcinoma and pancreatic cancer tissue removed during pancreatic resections will be submitted to Dr. Hernandez's laboratory. Tumor cells will be immediately dissociated into single cells using the Miltenyi Tumor Dissociator and labelled using fluorescent protein tags (Cell tracking Dyes). Labelled single tumor cells will then be injected back into the perfusate to simulate the metastatic process. The cells will be tracked using specialized camera/detector system in combination with our multi-photon microscope.

1.2.11 *Ex Vivo* Hepatic Perfusion Model

This study is an important step toward our goal of implementing an ideal tumor model system. The ability to recapitulate the complexities of solid human tumors for the purposes of drug development and testing has been, and remains, a major obstacle in the progress of cancer care. Despite great efforts expended on pre-clinical optimization using existing validation models, most drugs simply fail to demonstrate efficacy when subjected to Phase III clinical trial scrutiny.

Our interpretation is that the currently available model systems lack the appropriate clinical predictive power. The reasons for the inadequacies of these model systems, which are largely based upon cell lines, mouse models or patient-derived xenografts, are myriad but are almost certainly related to the absence of the human stromal component and its intricate relationship with tumor cells. Indeed, modeling the multi-faceted interactions between human cancer cells and the multitude of various stromal components, including activated fibroblasts, immune cell infiltrate and the abnormal vasculature is, at present, an impossibility. The advent of a model system capable of accurately reproducing human tumors *ex vivo* carries broad implications across many fields of investigational medicine and brings with it the potential to fundamentally alter the translational research landscape. Moreover, if it were possible to represent a given patient's tumor in that model system, the benefits of personalized medicine could leap from generating lists of potentially useful drugs to designation of efficacious agents.

We intend to satisfy all the requirements of an ideal tumor model system by utilizing resected segments of tumor-containing liver and repurposing the Liver-Assist perfusion device for prolonged *ex vivo* animation via native blood vessel perfusion. This is entirely novel and has not been attempted elsewhere in the world. Moreover, the expertise required to accomplish this make it unlikely to be successful anywhere other than the clinical center. This study expands our CRC patient population and importantly expands it to include subjects with intrahepatic cholangiocarcinoma.

We will start the model with optimization of perfusion conditions for maintenance of both tumor and normal liver with serial evaluation to include the following:

1) Ultrasonographic evaluation to document preservation of tumor echogenic properties.

2) Core needle biopsy to document histopathologic preservation of the microscopic architecture and cellular viability. Sufficient tissue will be obtained for any necessary staining.

3) Transcriptomic profiling will be undertaken using snap-frozen biopsies. Samples from a given tumor will be run together to minimize variability. Standard HiSeq RNA platform with a read depth of 30-40 million will be employed.

4) Metabolomic profiling will be undertaken using snap-frozen biopsies. Samples from a given tumor will be run together to minimize variability.

We've chosen strategically to use Genomic Expression's OneRNA platform in the present protocol (refer to Section **5.2.2**). This technology is designated to quickly sequence 20K genes and provide lists of potentially usable drugs in addition to the sequencing data from tumor and normal liver. The platform will be of use to us as we move forward with our *ex vivo* tumor model, as we anticipate patterns will emerge among tumors such that likely drug combinations can be estimated for use in our *ex vivo* model. We will facilitate transfer of material from any pre-operative biopsies/tumor removal to genomic expressions for evaluation. This will allow us to utilize various agents predicted by OneRNA as efficacious. This model system will enable us to evaluate drug delivery, cell based therapies, etc. given the unlimited use of repeat biopsies. The perfusate is also the ideal medium for biomarker discovery, which can be related to actual changes demonstrable in the tumor. Although we will not be able to use efficacious drugs in the model to treat subjects, we believe the information will be of immediate value in guiding subjects toward subsequent trials should they recur.

Finally, we will be able to conduct metastases assays using the *ex viv*o tumor containing liver as the target organ and the tumor dissociator as above (see Section **1.2.10**).

1.2.12 Simulated Metastasis Assay with Relevant Tissue (SMART) Chamber

Dr. Hernandez's laboratory in the Surgical Oncology Program is also developing a novel tumor modeling system, referred to as the Simulated Metastasis Assay with Relevant Tissue (SMART) Chamber. Correlative studies in proteogenomic characterization of primary and metastatic cancers and *ex vivo* tumor tissue modeling of peritoneal metastasis will be added to this study, utilizing the SMART Chamber. In conjunction with ongoing laboratory work, segments of the peritoneum are removed from patients with peritoneal carcinomatosis at the time of operation. This peritoneal tissue is utilized in the SMART Chamber system to imitate conditions of metastasis within the abdominal cavity. This *ex vivo* tissue model system allows for observation of peritoneal metastasis, real-time cellular imaging, and manipulation of tumor-environment interactions.

1.2.13 The SMART System

The SMART System is an important step toward our goal of realizing personalized translational cancer care. The ability to recapitulate the complexities of solid human tumors for the purposes of drug development and testing has been, and remains, a major obstacle in the progress of cancer therapy. Despite great efforts expended on pre-clinical optimization using existing validation models, most drugs simply fail to demonstrate efficacy when subjected to Phase III clinical trial scrutiny. Our interpretation is that the currently available model systems lack the appropriate clinical predictive power. The reasons for the inadequacies of these model systems, which are

largely based upon cell lines, mouse models or patient-derived xenografts, are myriad but are almost certainly related to the absence of the human stromal component and its intricate relationship with tumor cells.

There has been a sizable expansion of oncologic pharmaceuticals that have targeted and/or immunomodulatory effects. However, the predictive accuracy of drug testing is predicated on models that accurately represent the architectural/cellular organization of the tumor and faithfully reflect the *in vivo* biology. We have satisfied many of the requirements of an ideal tumor model utilizing resected mesothelial metastases to create the SMART (**S**ample **M**icroenvironment of **R**esected **M**etastatic **T**umor) System. Multiple solid tumors commonly manifest with metastatic disease to the mesothelial surface (peritoneum, pleura, liver capsule) and some are candidates for metastasectomy. During these operations, resected tumor-bearing mesothelial tissue is affixed to a specialized platform and perfused in a sterile, oxygenated circuit at 37^0C to maintain normal physiologic parameters (**Figure 10**). Circulating oxygenated perfusate within the system is comprised of human plasma (from the patient), DMEM media, antibiotics, insulin (slow infusion).

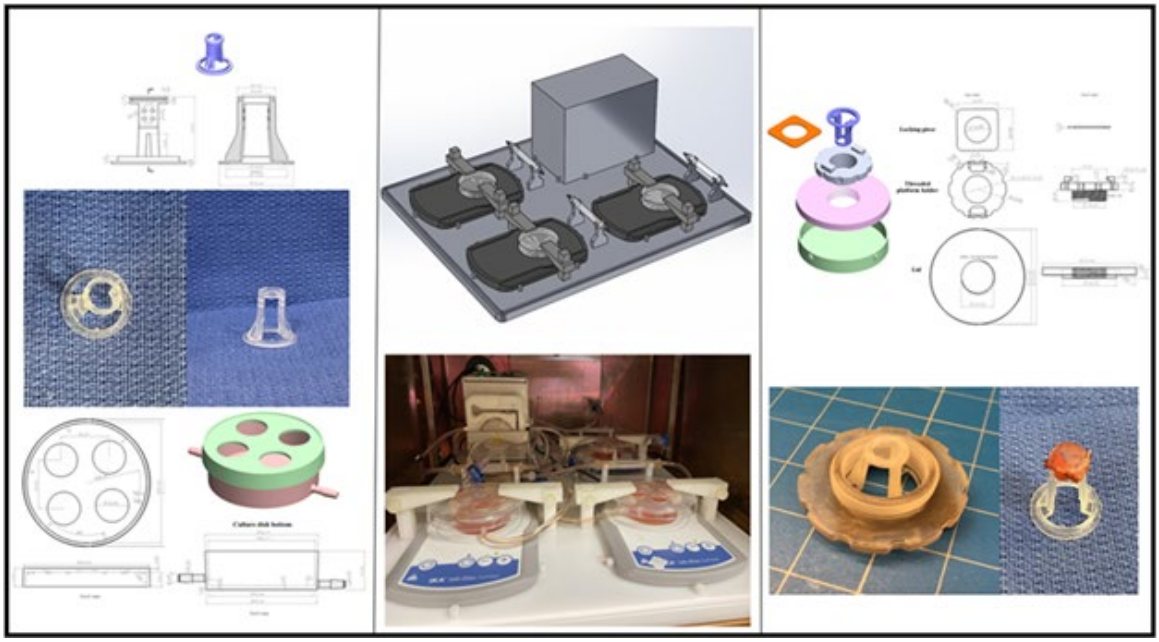

Figure 10: The SMART System Consisting of SMART Platform

The SMART platform (Top Left) is designed to mount the human mesothelial tissue containing tumor and be suspended in the reservoir of perfusate (Bottom Left), the SMART chamber. The chambers suspend maximum of 4 SMART platforms and placed on stir plate in the incubator (Middle). The SMART system boasts a physiologic oxygenated perfusion circuit that is suitable to keep tissue viable for up to four days. The Right Panel demonstrates the customized holder for each SMART platform that is imaged using complex imaging techniques.

We have evaluated gastric adenocarcinoma, pancreatic adenocarcinoma, gastrointestinal stromal tumor, and breast adenocarcinoma in the SMART system and documented *ex vivo* viability at 4 days with expected immune cell populations, intact architecture, and expected mitotic activity (**Figure 11A**). RNA sequencing was performed as well to compare transcriptomics between Day

0 and Day 4. Genes associated with hypoxia, oncogenes/tumor suppressor, cancer stem cells, metabolism, and epithelial-mesenchymal transition were isolated from the sequencing data and demonstrated conservation of transcriptomics (**Figure 11B**). These results ultimately demonstrate that tumor nodules in their native, functional microenvironment can be preserved *ex vivo* for 4 days with fidelity.

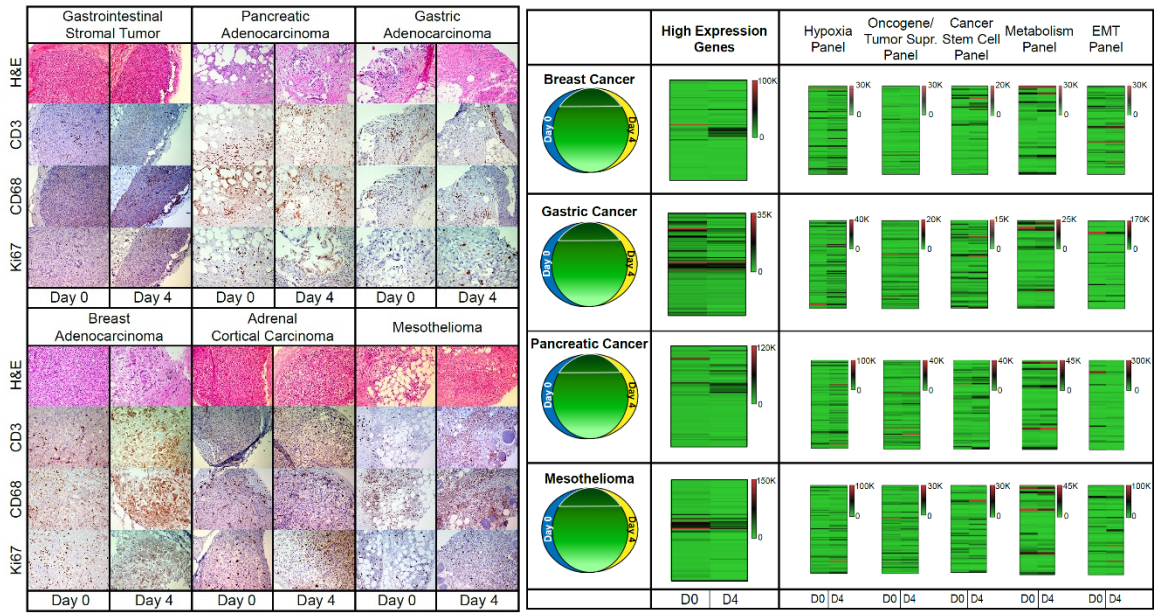

Figure 11: Ex Vivo Normal and Tumor Preservation in the SMART System

A (Left): Demonstration of various histologies on H&E, CD3, CD68 and Ki67 stains on Day 0 and Day 4.
B (Right): Conservation of transcriptomics in hypoxic panel, oncogene/tumor suppressor, cancer stem cell, metabolism and EMT panels over breast, gastric, pancreatic and mesothelioma histology.

Due to the translucent nature of the mesothelial tissue, the system is readily amenable to dynamic interrogation with confocal, two photon and light sheet microscopy. This avenue of investigation is supported by a research collaborative agreement (RCA) with BioLegend and our affiliation with CAT-I to develop fluorescently labelled Fab fragment for live cell labelling. For example, with the increasing use of checkpoint inhibitors like Pembrolizumab in solid tumors, we decided to evaluate the drug in the SMART system using tumor from a patient with gastric adenocarcinoma and a patient with colorectal adenocarcinoma. We demonstrated immune cell engagement with tumors cells for both gastric and colorectal adenocarcinoma, and captured tumor cell lysis with the latter (**Figure 12**). Such responses at the cellular level are key to understanding why some cells respond to the immune system while others are ostensibly resistant.

As the only currently known platform that has an intact, immunocompetent tumor microenvironment, the SMART System allows for the analysis of agents utilizing real controls to increase current understandings of the tumor microenvironment. Analyses can be readily imaged (taking video up to an hour) to obtain tangible visualizations of the tested agent effects (see **Figure 12**).

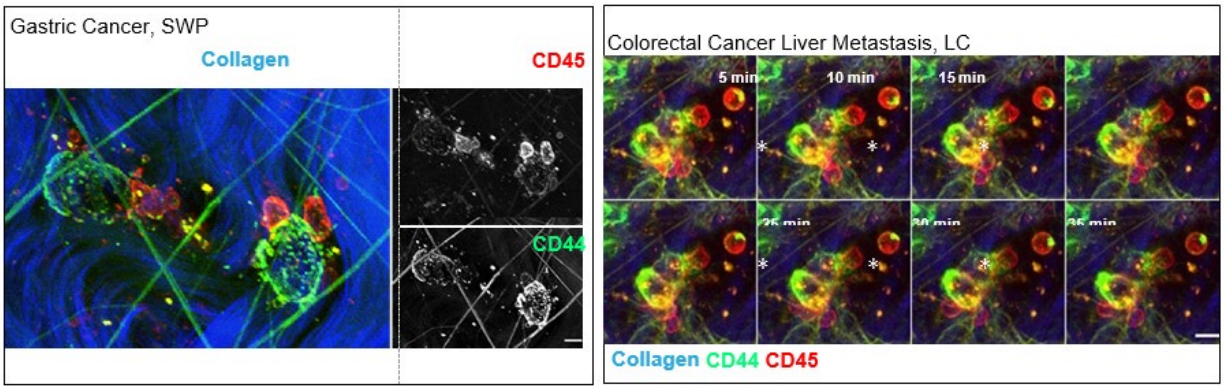

Figure 12: SMART Platforms are Valuable Tools for Drug Evaluations Such as Pembrolizumab

Left: SMART platforms with peritoneum from a patient with gastric cancer incubated with immune checkpoint inhibitor Pembrolizumab for 2 days followed by Alexa488CD44/ Alexa594CD45 antibodies. Maximum projections of 2-photon images illustrate the intimate contact between CD45-positive cells and the cancer cells.
Right: Timeseries montage taken from liver capsule tissue mounted on SMART platforms from a colorectal cancer patient with liver metastases incubated with 5 g/mL pembrolizumab for 4 hours. CD45-positive cells bound to CD44-positive cancer cell undergoing apoptosis.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Subjects must have histologically or cytologically confirmed diagnoses of adenocarcinoma in one of the following scenarios:

- Primary tumors of the pancreas
- Primary tumors of the bile duct and ampulla
- Metastatic colorectal cancers to the liver

2.1.1.2 Subjects must have disease resectable with a standard pancreatectomy (pancreaticoduodenectomy or distal pancreatectomy) or liver resection.

2.1.1.3 Subjects may have received prior therapy, including neoadjuvant regimens.

2.1.1.4 Subjects must have serum CA 19-9 elevations greater than the upper limit of normal but less than 2500 U/mL.

2.1.1.5 Age ≥ 18 years.

2.1.1.6 ECOG performance status ≤ 1 (**Appendix A**).

2.1.1.7 Subjects must have adequate organ and marrow function as defined below:

- leukocytes > 3,000/mcL

- absolute neutrophil count > 1,500/mcL
- platelets > 90,000/mcL

2.1.1.8 For subjects with Periampullary cancers that require a pancreaticoduodenectomy for complete tumor extirpation:

- total bilirubin < 10 ULN*
- AST(SGOT)/ALT(SGPT) < 5 X institutional upper limit of normal
- creatinine < 1.5 X institutional upper limit of normal

*Subjects with periampullary cancers typically present with biliary obstruction resulting in significant abnormalities in liver function tests that do not reflect liver dysfunction. These values normalize after tumor removal. They can be normalized pre-operatively with biliary stenting but several large studies have demonstrated an increase in infectious complications with drainage. As such, a practice standard has been to avoid stenting until bilirubin level rises above 10 X ULN.

2.1.1.9 For subjects with liver tumors (cholangiocarcinoma or metastatic colorectal cancer) requiring a hepatectomy for complete tumor extirpation:

- total bilirubin < 2.5 X institutional upper limit of normal*
- AST(SGOT)/ALT(SGPT) < 5 X institutional upper limit of normal*
- creatinine < 1.5 X institutional upper limit of normal

*Liver abnormalities in this range are consistent with parenchymal destruction from the tumor.

2.1.1.10 For subjects with pancreas tumors that require a distal pancreatectomy for extirpation:

- total bilirubin < 1.5 X institutional upper limit of normal*
- AST(SGOT)/ALT(SGPT) < 2 X institutional upper limit of normal*
- creatinine < 1.5 X institutional upper limit of normal

*Liver abnormalities in this range are consistent with pancreas cancer destruction from the tumor.

2.1.1.11 The effects of MVT-5873 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and for 3 months after completion of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.12 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.13 Subjects must agree to co-enrollment on the tissue collection protocol 13C0176, “Tumor, Normal Tissue and Specimens from Patients Undergoing Evaluation or Surgical Resection of Solid Tumors”.

2.1.2 Exclusion Criteria

2.1.2.1 Presence of disease outside the confines of a standard operation for subjects with peri-ampullary cancers (pancreatic and cholangiocarcinoma).

2.1.2.2 Presence of disease outside the liver for subjects with intrahepatic/hilar cholangiocarcinoma or metastatic colorectal cancer, other than a primary tumor for subjects with metastatic colorectal cancer.

2.1.2.3 Subjects who are receiving any other investigational agents.

2.1.2.4 Fewer than 28 days (or 5 half-lives for systemic agents, whichever is shorter) from the last day of prior anticancer therapy, including chemotherapy, hormonal, investigational, and or biological therapies and irradiation.

2.1.2.5 Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.6 Active concurrent malignancies within the last five years other than the primary tumor in subjects with metastatic colorectal cancer, basal or squamous cell skin carcinoma or non- medullary thyroid carcinoma.

2.1.2.7 Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects of the MVT-5873. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued if the mother is treated. These potential risks may also apply to other agents used in this study.

2.1.2.8 Subjects with active, Hepatitis B or C infection because of the potential for increased liver toxicity given the damaging effects of the virus.

2.1.2.9 Allergic to chimeric, humanized or human antibodies.

2.1.2.10 Received live vaccine within 4 weeks prior to the first date of study intervention.

2.1.2.11 Infection requiring hospitalization or herpes zoster treatment within 2 weeks prior to the first date of study intervention.

2.1.2.12 Long-term infectious diseases (tuberculosis, fungal infections) active within 2 years prior to the first date of study intervention.

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms. This study will also be listed on available websites (e.g., www.clinicaltrials.gov) and participants will be recruited from the current patient population at NIH. Participants may also be recruited through self-referrals and physician referrals. Dr. Hernandez is a member of the clinical trials committee of America's HepatoPancreatoBiliary Association and will also solicit eligible subjects through the organization.

Advertisements approved under this protocol may be distributed in local media (electronic and print) with recruitment efforts focused on, but not limited to, NIH and the greater Washington DC area; some recruitment efforts may take place nationwide.

2.2 SCREENING EVALUATION

2.2.1 Screening Activities Performed Prior to Obtaining Informed Consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of existing photographs or videos.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

A waiver of consent for these activities has been requested in Section **12.5.1**.

2.2.2 Screening Activities Performed After a Consent for Screening Has Been Signed

The following activities will be performed only after the subject has signed the study consent OR the consent for study 01C0129 (provided the procedure is permitted on that study) on which screening activities may also be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

Studies should be done within 6 weeks prior to being registered for treatment, unless otherwise noted below:

- History and Physical Examination:
  - Complete medical history and physical examination (including height, weight, vital signs, EKG and ECOG performance status).
- Laboratory Evaluation:
  - CA 19-9 levels
  - Hematological profile: CBC with differential and platelet count.
  - Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, calcium, phosphorus, albumin, magnesium, amylase.
  - Hep B and C
  - Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy), performed within 7 days prior to treatment.
- CT of chest, abdomen and pelvis. (Note: This scan does not need to be repeated at NIH if it has already been done at an external institute within 6 weeks prior to treatment ***and*** the investigator determines that the scan is of sufficient detail for study diagnostics.)
- Histologic confirmation by the Laboratory of Pathology, NIH (at any time point prior to enrollment). If there is no available tumor sample, biopsy will be performed to confirm the diagnosis.

- MRI (for subjects with liver disease). (Note: This scan does not need to be repeated at NIH if it has already been done at an external institute within 6 weeks prior to treatment ***and*** the investigator determines that the scan is of sufficient detail for study diagnostics.)

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2: CCR Participant Registration & Status Updates found here.

2.3.1 Treatment Assignment and Randomization/Stratification Procedures

2.3.1.1 Cohorts

Number	Name	Description
1	Cohort 1	Subjects with pancreatic cancer, cholangiocarcinoma or metastatic to the liver colorectal cancer, having low elevated LFTs (AST/ALT ≤ 2 X ULN and/or bilirubin ≤ 1.5 X ULN), enrolled into pre-operative MVT-5873 escalation dose levels.
2	Cohort 2	Subjects with pancreatic cancer, cholangiocarcinoma or metastatic to the liver colorectal cancer, having moderate elevated LFTs (LFTs above what is required for Cohort 1 AND AST/ALT < 5 X ULN and/or bilirubin ≤ 3 X ULN), enrolled into pre-operative MVT-5873 escalation dose levels.
3	Cohort 3	Subjects with pancreatic cancer enrolled at the pre-operative recommended dose (RD) of MVT-5873.
4	Cohort 4	Subjects with cholangiocarcinoma enrolled at the pre-operative recommended dose (RD) of MVT-5873.
5	Cohort 5	Subjects with metastatic to the liver colorectal cancer enrolled at the pre-operative recommended dose (RD) of MVT-5873.

2.3.1.2 Arms

Number	Name	Description
1	Arm 1	Pre-operative escalation doses of MVT-5873, pancreatectomy or hepatectomy and post-operative MVT-5873 treatment.
2	Arm 2	Pre-operative RD of MVT-5873, pancreatectomy or hepatectomy and post-operative MVT-5873 treatment.

2.3.1.3 Arm Assignment

Subjects in Cohorts 1 and 2 will be directly assigned to Arm 1.

Subjects in Cohorts 3-5 will be directly assigned to Arm 2.

2.4 BASELINE EVALUATION

Tests listed below that were performed within the appropriate timeframe at screening need not be repeated.

Within 3 weeks prior to study intervention unless otherwise indicated:

- Complete physical examination (including weight, vital signs, EKG and ECOG performance status).
- Laboratory Evaluation:
  - CA 19-9 levels
  - Hematological profile: CBC with differential and platelet count.
  - Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, calcium, phosphorus, albumin, magnesium, amylase.
  - PT/PTT/INR
  - Serum or urine pregnancy test for female participants of potential childbearing age (in the absence of prior hysterectomy), performed within 3 days prior to resection.
- CT of chest, abdomen and pelvis
- MRI (for subjects with liver disease)
- Concomitant medications
- Baseline adverse events

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a trial designed to determine if perioperative MVT-5873 is safe and effective for subjects with operable cancers of the pancreas and liver.

Eligible candidates will receive one dose of MVT-5873 (1 mg/kg (DL1) or 3 mg/kg (DL2) 3 days prior to resection (Day -3) as part of the safety lead-in cohorts (Cohorts 1 and 2). See **Table 9** below for expected course.

Once the pre-operative safe dose of MVT-5873 is identified, additional subjects will be evaluated within the treatment cohorts (Cohorts 3-5) at that MTD.

Resection will be undertaken to remove all demonstrable disease in the liver, bile ducts and pancreas on Day 0. The operation may be delayed for up to 4 days until any AST/ALT elevations are ≤ 10 X ULN, and Bilirubin is ≤ 2 X the baseline value or < 3 X ULN. All subjects will start post-operative infusions of MVT-5873 (1 mg/kg) in cycles consisting of 21 days. During Cycle 1, subjects will receive 2 weekly infusions of MVT-5873 (on Day 1 and Day 8). During Cycle 2, subjects will receive an infusion of MVT-5873 every 2 weeks (Day 1 and Day 15). Evaluations will be performed on C1D1, C1D8, C2D1 and C2D15 (+/- 48 hours) as indicated in Section **3.4**.

Cycle 1 Day 1 will be on any day between Day 4 and Day 10 after surgery, when AST/ALT elevations ≤ 10 X ULN and decreasing for 2 consecutive days, and Bilirubin ≤ 2 X ULN or

decreasing for 2 consecutive days. If LFTs do not decrease as described within 14 days after surgery, patient will be taken off treatment.

Treatment with MVT-5873 will continue until off treatment criteria are met.

Table 9: Safety Lead-In Study Design

Pre-operative Dose		**Operation**	**Weekly dosing**	**Q2 Weekly dosing**
Day -3		**Day 0**	**Cycle 1:** **Days 1 and 8**	**Cycle 2:** **Days 1 and 15**
DL1	MVT-5873 1 mg/kg	Pancreatectomy or Hepatectomy	1 mg/kg MVT-5873*	1 mg/kg MVT-5873*
DL2	MVT-5873 3 mg/kg			
* Post-operative infusions of MVT-5873 will consist of 1 mg/kg in all cycles. MVT-5873 dose variability is only within the single pre-operative dose.				

3.1.1 Dose Limiting Toxicity

The DLT period is 10 days after pre-operative MVT-5873 treatment.

Any Grade ≥ 3 adverse event (AE), occurring during the DLT evaluation period, possibly or definitely attributed to MVT-5873 with the exception of:

- Bilirubin < 6X ULN if resolved to < 3 or ≤ 2X the baseline in 7 days after first MVT-5873 treatment.
- AST/ALT ≤ 20X ULN if resolved to ≤ 10X ULN in 7 days after first MVT-5873 treatment.

Resection will be undertaken to remove all demonstrable-disease in the liver, pancreas or bile ducts on Day 0.

Note: The operation may be delayed until AST/ALT elevations are ≤ 10X ULN, and Bilirubin is ≤ 2X the baseline value or < 3X ULN. If the operation is delayed for more than 4 days due to failure of LFT to fall within the values outlined above, this will be considered DLT.

3.1.2 Safety Lead-In Cohorts

In order to minimize patient risk, we will initially accrue six (6) subjects sequentially in two safety lead-in cohorts based upon AST/ALT/Bili abnormalities and irrespective of tumor histology.

For each safety lead-in cohort we will evaluate two dose levels, 1 mg/kg and 3 mg/kg as summarized in **Table 10** below.

The safety lead-in continues until at least two subjects among the cohort of six subjects experience dose-limiting toxicities (ie, ≥33% of subjects with a dose-limiting toxicity at that dose level).

If none (0) or one (1) of the six subjects at 1 mg/kg experiences a dose-limiting toxicity, then escalation to 3 mg/kg may proceed within each safety lead-in cohort and 1 mg/kg is deemed safe.

If none (0) or one (1) of the six subjects experiences a dose-limiting toxicity at 3 mg/kg within each safety lead-in cohort, then 3 mg/kg is deemed safe at the respective safety lead in cohort. Dose esclation maximum will be 3 mg/kg.

Table 10: Safety Lead-In Cohorts

LFT	**Safety Lead-In Cohort 1 (Low elevated LFTs) N=6**	**Safety Lead-In Cohort 2* (Moderate elevated LFTs) N=6**
AST/ALT	≤ 2X ULN, and/or	< 5X ULN, and/or
Bilirubin	≤ 1.5X ULN	≤ 3X ULN
*LFTs above what is required for Cohort 1 AND AST/ALT < 5X ULN and/or bilirubin ≤ 3X ULN. Note: LFTs determined at screening for cohort assignment.		

Every subject of each safety lead-in cohort will be observed for at least 10 days after first dose of MVT-5873 before the subsequent subject can be treated.

Subjects who do not complete the DLT observation period for reasons other than a DLT will be replaced and will not be included in the response evaluation.

Intra-patient dose de-escalation is not permitted for subjects enrolled in the safety lead-in cohorts. Subjects will receive assigned dose and in case of DLT will be taken off protocol. Every subject enrolled onto safety lead-in cohorts will be part of the DLT evaluation of its respective dose level.

Subjects who experience DLT after pre-operative dose of MVT-5873 may have surgery when DLT is resolved and will be taken off MVT-5873 treatment after operation (see Section **3.5** for surgical guidelines and post-operative care).

Safety Lead-In Cohort 1 (Low Elevated LFTs)

Cohort 1 Dose Level 1 (1 mg/kg)

Six (6) subjects will be enrolled at Dose Level 1, treated with MVT-5873 (**1 mg/kg on Day -3**) and have surgery on Day 0.

If two (2) subjects experience a DLT during DLT period at dose level DL1, no further attempts at completing the safety run-in of MVT-5873 in combination with surgery will be conducted, and the trial will be closed to accrual.

If < 2 of 6 subjects experience DLT during DLT period, DL1 will be considered to be safe to use in subjects with low elevated LFTs and enrollment into Cohort 2 will begin at DL1. Concurrently, enrollment into Cohort 1 Dose Level 2 will begin.

Cohort 1 Dose Level 2 (3 mg/kg)

Six (6) subjects will be enrolled at Dose Level 2, treated with MVT-5873 (**3 mg/kg on Day -3**) and have surgery on Day 0.

If two (2) subjects experience a DLT during DLT period at dose level DL2, no further attempts at completing the safety run-in at DL2 will be conducted at trial will continue with DL1 only.

If < 2 of 6 subjects experience DLT during DLT period, DL2 will be considered to be safe to use in subjects with low elevated LFTs.

Safety Lead-In Cohort 2 (Moderate elevated LFTs)

Cohort 2 Dose Level 1 (1 mg/kg)

If DL1 is proved to be safe in Cohort 1 Dose Level 1, 6 subjects will be enrolled in Cohort 2 Dose Level 1. Subjects will be treated with MVT-5873 (**1 mg/kg on Day -3**) and have surgery on Day 0.

If two (2) subjects experience a DLT during DLT period at dose level DL1, no further attempts at completing the safety run-in of MVT-5873 in combination with surgery in subjects with moderate elevated LFTs will be conducted.

If <_2 of 6 subjects experience DLT during DLT period, DL1 will be considered to be safe to use in subjects with moderate elevated LFTs.

If DL1 is safe to use in subjects with moderate elevated LFTs, 6 subjects will be enrolled at Dose Level 2 in Cohort 2.

Cohort 2 Dose Level 2 (3 mg/kg)

Six (6) subjects will be treated with MVT-5873 (**3 mg/kg on Day -3**) and have surgery on Day 0.

If two (2) subjects experience a DLT during DLT period at dose level DL2, no further attempts at completing the safety run-in at DL2 will be conducted at trial will continue with DL1 only.

If < 2 out of 6 experience DLT during DLT period, DL2 will be considered to be safe to use in subjects with moderate elevated LFTs.

3.1.3 Treatment Cohorts

3.1.3.1 Treatment Cohorts at Pre-Operative MTD

Once the pre-operative safe dose of MVT-5873 and allowed elevated level of LFTs is estimated, additional subjects will be evaluated at that MTD (see **Table 11**) within Cohorts 3-5.

Treatment subjects will be accrued with the following histologies:

- Metastatic Colorectal Cancer (n=24)
- Cholangiocarcinoma (n= 24)
- Pancreatic Cancer (n=23)

Note: Subjects treated during the safety lead-in (Cohorts 1 and 2) will complete the study as indicated in Sections **3.1.2** and **3.5**.

Table 11: Treatment Study Design

Pre-operative Dose	**Operation**	**Weekly dosing**	**Q2 Weekly dosing**
Day -3	**Day 0**	**Cycle 1:** **Days 1 and 8**	**Cycle 2:** **Days 1 and 15**
MVT-5873 at MTD	Pancreatectomy or Hepatectomy	1 mg/kg MVT-5873*	1 mg/kg MVT-5873*

3.1.3.2 Treatment Cohorts at Two Different Pre-Operative MTDs by LFT Elevation are Determined from Safety Lead-In

If two different pre-operative safe doses of MVT-5873 are determined from the safety lead-in due to the difference of LFT elevation, subjects within the treatment cohorts will each be treated by their elevated level of LFTs as identified at screening (refer to **Table 12** and

Table 13).

Table 12: Treatment Guidelines (If Two Different Pre-Operative MTDs by LFT Elevation are Determined from Safety Lead-In)

Treatment **Cohorts**	**Low elevated LFTs** (AST/ALT ≤ 2X ULN and/or bilirubin ≤ 1.5X ULN)	**Moderate elevated LFTs** (LFTs above what is required for Cohort 1 AND AST/ALT < 5X ULN and/or bilirubin ≤ 3X ULN)
Cohorts 3-5	MVT-5873 at Low elevated LFTs MTD	MVT-5873 at Moderate elevated LFTs MTD
Note: LFTs determined at screening. * Baseline LFTs for a subject may be used if the subject's screening and baseline LFTs are different and the change is determined by the PI to be clinically indicated.		

Table 13:Treatment Study Design (If Two Different Pre-Operative MTDs by LFT Elevation are Determined from Safety Lead-In)

Pre-operative Dose		**Operation**	**Weekly dosing**	**Q2 Weekly dosing**
Day -3		**Day 0**	**Cycle 1:** **Days 1 and 8**	**Cycle 2:** **Days 1 and 15**
Low elevated LFTs	MVT-5873 at Low elevated LFTs MTD	Pancreatectomy or Hepatectomy	1 mg/kg MVT-5873*	1 mg/kg MVT-5873*
Moderate elevated LFTs	MVT-5873 at Moderate elevated LFTs MTD			
* Post-operative infusions of MVT-5873 will consist of 1 mg/kg in all cycles. MVT-5873 dose variability is only within the single pre-operative dose.				

3.2 STUDY DRUG ADMINISTRATION

3.2.1 Preparation and Administration of MVT-5873

MVT-5873 is provided as a single-use vial containing 3.0 mL of sterile solution at 10 mg/mL in a buffer at pH 6.0, containing 25 mM histidine, 150 mM sucrose, 55 mM sodium chloride, and 0.02% polysorbate 80.

Prior to infusion, MVT-5873 is diluted in normal saline to obtain a final concentration of less than 5 mg/mL. The administration apparatus must include a 0.2-micron inline filter.

3.2.2 Stability of MVT-5873 Following Preparation

MVT-5873 should be administered within 24 hours of preparation.

3.2.3 Upper Limit to Administered Dose in Obese Subjects

In subjects who weigh more than 100 kg (220 pounds), the administered dose should be calculated based on a theoretical weight of 100 kg.

3.2.4 Infusion Rate of MVT-5873

The first dose of MVT-5873 for each subject will be administered as an intravenous infusion over at least 120 minutes. In subjects who tolerate an initial infusion without difficulty, subsequent infusions may be reduced by 30 minutes to a minimum infusion duration of 60 minutes (i.e., a 120-minute infusion during the first infusion, a 90-minute infusion during the second infusion, a 60-minute infusion during the third and subsequent infusions). The duration of infusion for MVT-5873 should never be less than 60 minutes.

Vital signs will be taken pre-and post-MVT-5873 administration.

3.2.5 Treatment Guidelines for MVT-5873-Related Infusion Reaction

Please refer to table, **Treatment Guidelines for MVT-5873-Related Infusion Reaction,** for guidance on managing infusion related reactions during MVT-5873 administration.

Treatment Guidelines for MVT-5873-Related Infusion Reaction

Grade (CTCAEv4)	Definition	Treatment Guideline
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Monitor for at least 2 hours (120 minutes) after end of infusion; provide patient instructions and prophylactic medications at discharge as appropriate
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment	Infusion may be restarted once following a minimal 60-minute delay. A second infusion interruption requires discontinuation of MVT-5873 administration. Administration of medications (e.g., anti-histamines, steroids, NSAIDS and IV fluids etc.) as appropriate; monitor in clinic for at least 2 hours (120 minutes) after completion of infusion; provide prophylactic medications as appropriate for subsequent MVT-5873 doses
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	Administration of medications (e.g., anti-histamines, steroids, NSAIDS and IV fluids etc.) as appropriate; hospitalization for medical care and observation; Discontinue MVT-5873 permanently
4	Life-threatening consequences; urgent intervention indicated	Hospitalization for urgent medical treatment; Discontinue MVT-5873 permanently

3.2.6 Premedication

Subjects should receive their initial dose of MVT-5873 in the absence of premedication. In subjects who experience infusion reactions that are manageable and allow for additional administration of MVT-5873, premedication may be administered for subsequent doses consistent with institutional guidelines.

Starting in February 2017 (as documented in the MabVax 0715 Clinical Study Note to File dated 13-Feb 2017), the Safety Committee allowed for the use of prophylactic medications for the control of infusion reactions. The recommended dose was 12 – 20 mg of decadron IV at least 30 minutes prior and 4 mg BID PO of decadron for two days following each MVT-5873 administration. The investigator was free to manage the taper of decadron in those subjects who did not demonstrate infusion reactions.

3.3 DOSE MODIFICATIONS

Adverse Events: All adverse events in this trial will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 - a complete listing is available at the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Dose adjustments for pre-operative MVT-5873 are explained in Section **3.1.2**.

Summary of dose holding/interruptions for MVT-5873 in case of MVT-5873-related adverse events (graded according to NCI-CTCAE v5.0).

General Adverse Events	**Action**
Non-hematological, Grade 1 or 2	Continue MVT-5873 therapy at full dose prescribed. Apply maximum supportive care recommendations. If prolonged duration of Grade 2 adverse event (≥ 7 days) is affecting quality of life, consider discontinuation of the drug.
Non-hematological, Grade 3 or 4 (excluding cardiac and hepatobiliary events)	Apply maximum supportive care recommendations. Hold MVT-5873 therapy until recovery to Grade ≤ 1 (up to 14 days). For Grade 3 or 4 interstitial pneumonitis or Grade 3 or 4 rash manifested as toxic epidermal necrolysis (e.g. Stevens-Johnson Syndrome etc.) MVT-5873 must be discontinued. If recurrence of adverse event after drug hold/ interruptions is observed, and maximum supportive care measures applied, hold drug once again until recovery to Grade ≤ 1 (up to 14 days). If no recovery, consider discontinuation of the drug.
Non-hematological, Grade 3 or 4 adverse events NOT resolved to Grade ≤ 1 within a maximum of 2 weeks from last planned administration	Action (discontinue or resume MVT-5873 therapy) in individual cases after discussions with the Sponsor.

General Adverse Events	**Action**
Cardiac Adverse Events	
Cardiac (Severity corresponding to NYHA criteria)	MVT-5873 therapy to be discontinued permanently in case of symptomatic NYHA class III and IV CHF. MVT-5873 therapy to be held, continued, or resumed accordingly for subjects with NYHA class I or II CHF.
Hepatobiliary Adverse Events	
Grade 1-2 bilirubin or Grade 1-2 AST/ALT	Continue MVT-5873 therapy at full dose prescribed. Apply maximum supportive care recommendations.
Grade 3 bilirubin or Grade 3 AST/ALT	Apply maximum supportive care recommendations. Hold MVT-5873 therapy until recovery to Grade $\leq$ 1 If not resolved for 14 days, discontinue treatment.
Grade 2 bilirubin *and* Grade 3 AST/ALT Grade 4 events	*Discontinue MVT-5873
*Unless Surgery-related cause **Note:** In case of multiple short interruptions of dose due to either adverse events or drug supply or other reasons the sum of days without MVT-5873 treatment should not exceed 28 days between two treatments or in any 90-day treatment period.	

3.4 STUDY CALENDAR

	Screening[1]	**Baseline**[1]	**D-3**	**D0**[1]	**Cycle 1**		**Cycle 2**		**EOT**[2]	**Safety FU**[3]	**Long Term FU**[4]
					D1[5]	**D8**	**D1**	**D15**			
MVT-5873			X		X	X	X	X			
Surgery				X							
Informed Consent	X										
Medical History	X										
Concomitant Medications		X	X		X	X	X	X	X	X	
Adverse Event Evaluation		X	X		X	X	X	X	X	X	
Physical Exam	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	
Height	X										
EKG	X	X									
Weight	X	X	X	X	X	X	X	X	X	X	
Performance Status	X	X	X	X	X	X	X	X	X	X	
CBC w/Differential, Platelets	X	X	X	X	X	X	X	X	X	X	
PT, INR, PTT		X	X	X	X	X	X	X	X	X	
Serum Chemistry[6]	X	X	X	X	X	X	X	X	X	X	
CA 19-9[7]	X	X	X[7]	X	X[7]	X[7]	X[7]	X[7]	X	X	X

	Screening[1]	**Baseline**[1]	**D-3**	**D0**[1]	**Cycle 1**		**Cycle 2**		**EOT**[2]	**Safety FU**[3]	**Long Term FU**[4]
					D1[5]	**D8**	**D1**	**D15**			
Hepatitis B and C Serology and/or Viral Load	X										
Radiologic Evaluation[8]	X	X			X	X	X	X	X		
Serum or Urine Pregnancy Test	X	X									
Confirmation of dx by NCI LP	X										
Tissue Collection for Research				X							
Research Blood Collection (see Section **5.1**)			X	X	X				X		
Annual Telephone or Other NIH Approved Remote Platforms Contact											X

[1] Day 0 operation may be delayed for 4 days until AST/ALT elevations are ≤ 10X ULN, and Bilirubin is ≤ 2X the baseline value or < 3X ULN.

[2] Day 7 (+/-7 days) after treatment discontinuation. If patient is taken off treatment on the day of regular visit to Clinical Center, this day will be EOT visit.

[3] Safety Follow Up visits/labs will occur if patient is agreeable to coming back and physically able to return for the visit. This visit should occur around Day 28 post the last dose of study drug. If toxicities cause discontinuation of therapy, subjects will be followed until resolution of toxicity to at least Grade 1. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs from a local physician or laboratory (as these are routine, standardized laboratory tests, interlaboratory variability is not a concern). If this is not possible, subjects may be assessed by telephone or other NIH approved remote platforms for symptoms.

[4] Follow-up will be telephone or other NIH approved remote platforms contact of patient or medical oncologist every 4 months (+/- 2 weeks) to assess disease and survival status. Medical records from visits done with the home physician may be securely sent to the study team per CC policy and procedures.

[5] Cycle 1 Day 1 will be on any day between Day 4 and Day 10 after surgery, when AST/ALT elevations ≤ 10 X ULN and decreasing for 2 consecutive days, and Bilirubin ≤ 2 X ULN OR decreasing for 2 consecutive days.

[6] Electrolytes, BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, calcium, phosphorus, albumin, magnesium, amylase.

[7] Serum CA19-9 collection pre-dose and 2 hours post dose (+30 minutes) as noted in treatment cycles.

[8] Evaluations will be performed on C1D1, C1D8, C2D1 and C2D15 (+/- 48 hours) and EOT. CT scan of chest, abdomen and pelvis in all subjects. MRI with contrast for subjects with liver disease. Note: Exceptions for the use of contrast during this MRI may be made using the best clinical judgement of the investigator.

3.5 SURGICAL GUIDELINES

Pancreas tumors will be extirpated according to standard practice. Resections involving the pancreas may require either a pancreaticoduodenectomy or distal pancreatectomy, with or without splenectomy. Liver operations will be undertaken according to practice norms.

3.5.1 Preoperative Patient Management

Subjects will receive standard preoperative care as appropriate to the planned surgical intervention and the patient's underlying health status. This will include:

- Clear liquid-diet the evening prior to operation, without additional bowel preparation.
- Hibiclens shower the night before operation.
- CA 19-9 levels will be drawn the morning of the procedure.
- 20 mL of peripheral blood will be drawn prior to induction of anesthesia for circulating tumor cell acquisition and analysis (see Section **5.2.6**).
- Preoperative IV antibiotics administered in pre-op holding.
- Subcutaneous heparin administration for venous thromboembolism prophylaxis just prior to operation start.
- Sequential compression devices will be placed on the lower extremities prior to induction of general anesthesia.

3.5.2 Patient Management in the Operating Room

3.5.2.1 At Operation:

- Subjects will undergo a midline line or sub-costal incision. A thorough examination of the abdomen will ensue to rule-out occult metastatic disease on the peritoneal surfaces, or unrecognized suspicious lymphadenopathy. The operation will then be carried out according to standard practice.
- Prior to tumor extirpation, a 24-gage needle will be used to draw 20 mL of blood from the portal vein OR suprahepatic vena cava.
- Normal liver core biopsies and excisional biopsies will take place for exploratory endpoints but will not exceed 100 grams.

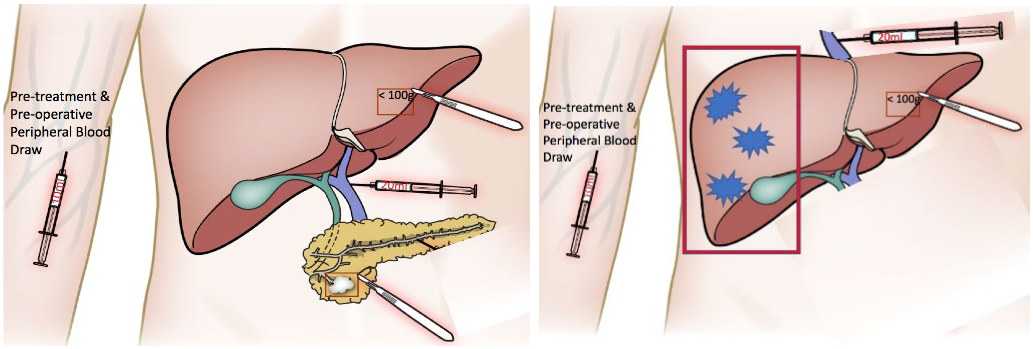

Figure 13: Operating Room Workflow

3.5.3 Postoperative Care

3.5.3.1 Patient Monitoring

- The subjects will be monitored in the ICU or on the surgical ward per routine.
- On the ward, vital signs (blood pressure, temperature, pulse, respirations) will be taken per routine (every 2-6 hours and as clinically indicated).
- Subjects will receive routine post-operative care; early ambulation will be encouraged. Note: Other standard of care may be performed as deemed clinically necessary by the PI.
- Laboratory evaluations will include:
    - CBC, platelets, acute care, mineral and hepatic panel on post-operative Days 1 through 7, and then as clinically indicated until discharge.
    - Subjects will be transfused as appropriate to maintain a hemoglobin greater than or equal to 8 g/dl.

3.5.4 Discharge

- Total hospitalization may be approximately 7-14 days.

  Subjects who are discharged within this time frame should be able to tolerate an oral diet with or without dietary supplements.

3.6 PATHOLOGICAL EVALUATION

The histopathologic evaluation, in addition to standard practice of lymph nodes, margin status, etc, will involve an evaluation by a third party laboratory for antibody/tumor cell binding (**Figure 14** top image) and a detailed evaluation of the liver parenchyma under the supervision of Dr. David Kleiner (**Figure 14** bottom image). The liver parenchyma evaluation will include standard immunohistochemical agents as well as any special evaluative measures as deemed necessary by Dr. Kleiner.

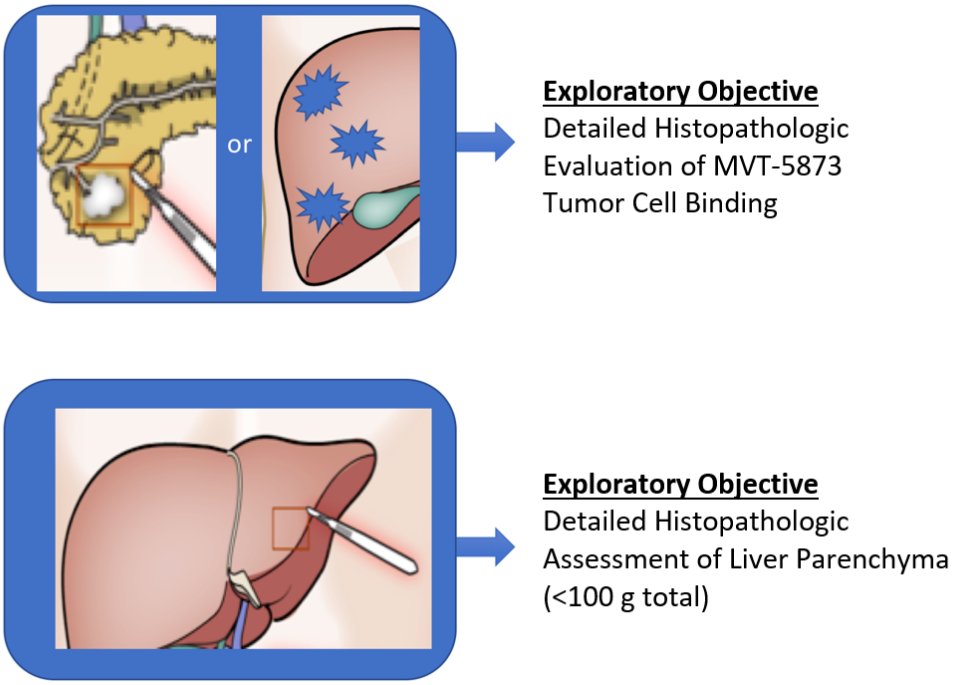

Figure 14: Pathologic Evaluation of Tumor and Liver Tissue Removed at the Time of Surgery

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 28 days following the last dose of study therapy.

3.7.1 Criteria for Removal from Protocol Therapy

- Excessive toxicity (see Sections **3.1.1** and **3.3**).
- Completion of 2 cycles of post-operative MVT-5873 treatment.
- Recurrent disease.
- CA 19-9 level > 2 X the lowest recorded post-operative dose ***AND*** > ULN.
- Participant requests to be withdrawn from active therapy.
- Investigator discretion.
- Positive pregnancy test.
- Start of standard adjuvant chemotherapy (per medical oncologist decision). **Note:** Patients need to be removed from therapy so that MVT-5873 will not be given within 2 weeks of the planned start date for adjuvant chemotherapy.
- Elapse of > 84 days from the start of Day 1, Cycle 1.

3.7.2 Off-Study Criteria

- Participant requests to be withdrawn from study.
- Death.
- Investigator discretion.
- Loss of follow up.
- PI decision to end the study.
- Screen failure.

4 CONCOMITANT MEDICATIONS/MEASURES

During the post-operative period, subjects will receive all standard of care supportive measures, including possible nasogastric tube drainage and bowel rest for ileus, pulmonary toilet teaching and incentive spirometry to prevent atelectasis, transfusions, and antibiotics as indicated. During receipt of study drug, standard adjunctive medications inclusive of anti-emetic, anti-nausea and bowel function therapy will be employed.

5 BIOSPECIMEN COLLECTION

5.1 SPECIMEN COLLECTION TABLE

Test/Assay	**Volume Blood (approx.)**	**Type of Tube**	**Collection Points** (+/-48hrs)	**Location of Specimen Processing/ Storage**	**Location of Specimen Analysis**
Circulating Tumor Cell Analysis	20 mL	CellSave Preservation Tubes	D-3, D0 & C1D1	(Delivered by study team to) Trepel Lab	Trepel Lab
Monocyte Phagocyte System (MPS) Profiling	17 mL	SST	D-3 & D0	Hernandez Lab for storage until shipment	Zamboni Lab at UNC Chapel Hill
Biomarker Studies	10 mL	EDTA (Lavender)	D-3, D0, C1D1 & EOT	Hernandez Lab (Blood Processing Core (BPC) as necessary, see Section 5.2.1)	Hernandez Lab

Metastasis Assays Using Ex Vivo Perfusion of Omentum	Omentum	N/A	D0 (at time of surgery)	(***Immediately*** to) Hernandez Lab	Hernandez Lab
Ex Vivo Hepatic Perfusion Models	Tumor tissue	N/A	D0 (at time of surgery)	(***Immediately***, when necessary) Hernandez Lab	Hernandez Lab
Proteogenomic Analysis	Tumor tissue with mesothelial metastases	N/A	D0 (at time of surgery)	Hernandez Lab (Blood Processing Core (BPC) as necessary, see Section **5.2.1**)	Hernandez Lab
Drug Penetration Analysis	Tumor tissue	N/A	D0 (at time of surgery)	Hernandez Lab (Blood Processing Core (BPC) as necessary, see Section **5.2.1**)	Hernandez Lab
RNA Analysis	10 mL	EDTA (Lavender)	D0	Hernandez Lab for storage until shipment (by study team)	Genomic Expression
RNA-Seq	Tumor tissue (and normal tissue, as available)	N/A	D0 (at time of surgery)	Hernandez Lab for storage until shipment (by study team)	Genomic Expression

5.2 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

5.2.1 Tumor and Tissue Collection

Tumor and normal tissue samples will be collected at the time of surgery. Tissue will only be taken for research purposes after it is removed as part of the standard operation, as viable tissue that will otherwise be removed as part of the operation, or as core needle biopsies of normal liver for subjects undergoing pancreatectomies. The total amount of normal liver tissue removed for research purposes will not exceed 100 grams.

Some of the samples will be immediately used in the Dr. Hernandez's lab (see Section **5.3.4** below), and the rest will be sent for barcoding and initial storage to Blood Processing Core (BPC) as necessary per PI instruction.

RNA-Seq data will be analyzed for correlation with recurrence patterns. The analysis will utilize logistic regression and corrections for false discovery (5%). The analysis will be undertaken in conjunction with the Branch's bioinformatics specialist.

5.2.2 RNA Evaluation

Tumor and normal tissue samples (coded-linked) will be sent to Genomic Expression for RNA analysis under MTA (Section **11.1**):

Gitte Pedersen, CEO
Genomic Expression, Inc.
100 Cummings Center, Suite 451C
Beverly, MA 01915
Phone: 203-812-0690
Email: glp@genomicexpression.com

Samples sent to Genomic Expressions for RNA analysis will be coded before shipment.

Genomic Expression has reengineered quantitative RNA sequencing for clinical applications, with the goal of enabling oncologists to routinely use tumor gene expression profiles to help select the best treatment options for their subjects. OneRNA, the proprietary platform from Genomic Expression, uses a novel approach to prepare sequencing libraries from tumor messenger RNA. The OneRNA library preparation technology, generates a library of nucleic acid tags from the 3' ends of mRNA molecules. These tag libraries can be "read out," meaning sequenced and counted, on next generation sequencers. This method reduces the number of reads to detect weakly expressed genes by 5- to 10-fold and simplifies the generation of a global expression profile from the sequencing data. OneRNA proprietary sample prep is integrated with proprietary analytics. After correcting for PCR duplicates, the sequenced tags are mapped to the human genome and/or transcriptome and compiled into gene expression profiles. Tumor expression profiles are normalized alongside normal tissue expression profiles to put them on a common scale. Using outlier detection methods, over and under expressed genes are identified by comparing the expression level of each gene in the tumor to the distribution of expression levels for that same gene in normal tissue(s).

5.2.3 Metastasis Assays Using *Ex Vivo* Perfusion of Omentum

For instances in which a standard Whipple procedure is done, omentum obtained from the operating room (as part of the standard Whipple procedure) will be immediately transported to Dr. Hernandez's lab. The gastroepiploic arterial arcade will be cannulated and the omentum kept viable using Dr. Hernandez's Liver Assist Device (**Figure 4** bottom).

5.2.4 *Ex Vivo* Hepatic Perfusion Model

Resected tumor-bearing liver and pancreas will be perfused through native blood vessels in order to develop *ex vivo* models for pancreatic cancer, cholangiocarcinoma, and metastatic colorectal cancer as indicated in Section **1.2.11**.

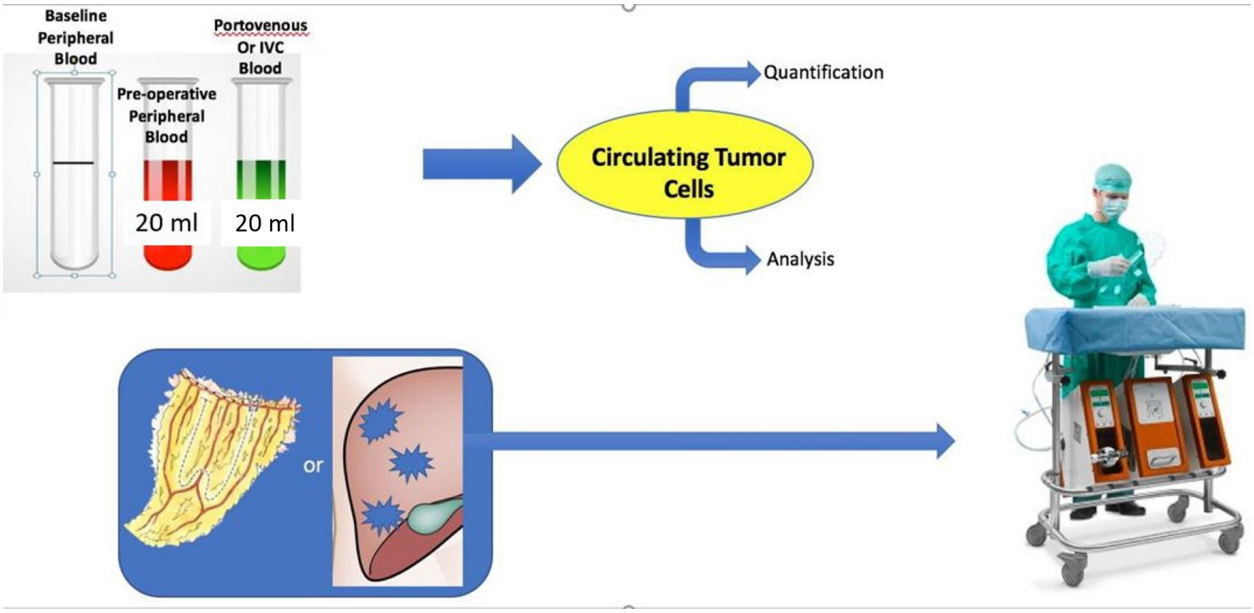

Figure 15: Scientific Endpoints. Evaluation of Circulating Tumor Cells (top) and Ex Vivo Tissue Modeling (bottom)

5.2.5 Circulating Tumor Cell Evaluation

Blood will be collected for circulating tumor cell (CTC) assays to be performed in the Dr. Trepel Laboratory (Developmental Therapeutics Branch, CCR).

Peripheral blood will be drawn from a peripheral vein and the portal or supra-hepatic IVC (intra-op) for enumeration and characterization of CTCs. CTCs will be assessed using ferrofluidic enrichment and multiparameter flow cytometric detection. CTCs will be identified as viable, nucleated cells, that positively express one or more epithelial or tumor markers and are negative for expression of hematopoietic markers. The number of CTCs in peripheral blood will be counted.

In addition to quantification, we will evaluate CTCs for CA 19-9 expression using flow cytometry.

5.2.6 Monocyte Phagocyte System (MPS) Profiling

Blood will be collected for monocyte phagocyte system (MPS) profiling, to be performed in the Zamboni Laboratory – University of North Carolina at Chapel Hill. MPS profiling will be used to evaluate the impact of MVT-5873 therapy on circulating tumor cells.

Coded linked samples will be sent to Dr. Zambroni at the Zamboni Laboratory under MTA (see Section **11.1**):

Zamboni Laboratory – UNC at Chapel Hill
Attn: Andrew Lucas
120 Mason Farm Road
1022A Genetic Medicine Building, CB#7361
Chapel Hill, NC 27599
Lab Phone: (919) 966-1622

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

Tissue samples will be sent to Blood Processing Core (BPC) for barcoding and initial storage until they are distributed to Dr. Hernandez for sample analysis as described in the protocol.

5.3.1 Samples Managed by the Blood Processing Core (BPC)

5.3.1.1 BPC Contact Information

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.3.1.2 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to subjects without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.3.1.3 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80^{0}C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed or returned to the patient, if so requested. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.3.2 Procedures for Storage of Patient Samples in the Laboratory of Dr. Trepel

Contact the Trepel Lab by email (Jane Trepel: trepel@helix.nih.gov; Min-Jung Lee: leemin@mail.nih.gov; Akira Yuno: akira.yuno@nih.gov and Sunmin Lee: lees@pop.nci.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240-760-6330.

A lab member will come to pick up the blood. Please keep blood at ambient temperature. Members of the lab will enter the samples into a secure password protected patient's sample tracking database (Translational Pharmacodynamics Research Group Patient Sample Management System) and process the samples.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol. It is critical that the sample remains coded and linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate with these variables.

Blood samples will be stored initially in the Trepel Lab in the Magnuson Clinical Center. If, at any time, a subject withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested). When a patient withdraws consent the

participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

5.3.3 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not embedded in paraffin is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

5.3.4 Procedures for Storage of Patient Samples in the Laboratory of Dr. Hernandez

Patient samples, collected for the purpose of research under IRB approved protocols where Dr. Hernandez is Principal Investigator, may be archived in the Laboratory of Dr. Hernandez. All data associated with archived clinical research samples is entered into the NCI Labmatrix database. All staff in Dr. Hernandez's laboratory have received updated NIH/CIT training and maintain standards of computer security.

The data recorded for each sample includes the patient ID, trial name/protocol number, date drawn/collected, treatment cycle/time point, cell source (e.g. peripheral blood, marrow, biopsy) as well as box and freezer location. Patient demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI clinical records. All received samples will receive a unique bar code number, which will be added to the sample NCI Labmatrix database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to patients without authorized access to the NCI Labmatrix database.

Samples are stored in freezers at -80°C (sera, plasma, tissue samples) or under liquid nitrogen (cells), according to stability requirements. These freezers are located onsite at Dr. Hernandez's laboratory. Access to samples from a protocol for research purposes will be by permission of the Principal Investigator.

5.3.5 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be transferred to protocol 13C0176.

Subjects will be co-enrolled on protocol 13C0176. Thus, all tissue will be stored, tracked and disposed after transfer as specified in protocol 13C0176.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

5.3.6 A Certificate of Confidentiality

A Certificate of Confidentiality will be obtained for this study.

5.3.7 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory.

5.3.8 Genetic Counseling

If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling with the NCI Genetics Branch to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

For the purposes of the research sample analyses and correlation with clinical outcomes, demographic information, histology, operative and peri-operative interventions, pathologic findings, laboratory and imaging parameters (performed as part of routine or protocol specified patient care) may be collected on this study. The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D and Labmatrix) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day -3, through the last study intervention on Cycle 2 Day 15. Beyond 28 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

End of Study Procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or Destruction of Data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in Section **7.2.1**.

6.1.1 Routine Data Collection

Following enrollment and for the duration of the study, graded adverse events will be described in the source documents, reviewed by the designated research nurse, and captured in C3D unless otherwise indicated below.

Note: No Grade 1 adverse events will be recorded.

6.1.1.1 Concomitant Medications (captured in source documents only)

- Only those medications that the patient is taking at baseline on a routine basis or medications that cause an AE will be captured. (Thus, one time medications, PRN medications, and medications given to treat adverse events will not be captured.)

6.1.1.2 Laboratory Events

Laboratory events that will be described in the source documents and captured in C3D:

- **During hospitalization for the procedure**, only the following labs will be uploaded into C3D:
  - Admission labs,
  - First morning labs drawn after 4:00 AM, and
  - Labs that support the diagnosis of a reportable event.
- **In the immediate post-operative period (7 days)**, only the following values will be captured (including laboratory values obtained at sites other than the NIH Clinical Center):
  - Hemoglobin, total white blood cell count, absolute neutrophil count, platelet count
  - PT, PTT, or INR
  - Creatinine, ALT, AST, total bilirubin

Any unexpected laboratory abnormality ≥ Grade 3 ***AND*** associated with symptoms or an intervention will be reported. We recognize that laboratory abnormalities are the norm for subjects undergoing the procedures as outlined in this study and therefore will exercise PI discretion in reporting of abnormalities outside the reported ULN.

6.1.1.3 Exceptions to Adverse Event Recording

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is not directly attributable to the operation
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Non-laboratory, non-concomitant medication events that will be captured only in the source documents:

- **During hospitalization for surgical resection**
  - ≤ Grade 3 events except **unexpected** events that are possibly or definitely related to the research.
- **Post-operative recovery period (following discharge)**
  - ≤ Grade 3 events except **unexpected** events that are possibly or definitely related to the research.
  - Note: Events that result in hospitalization for convenience will not be reported.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center).
- Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository, clinicaltrials.gov, dbGaP.
- BTRIS (automatic for activities in the Clinical Center).
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.

- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response at C1D1, C1D8, C2D1 and C2D15 (+/- 48 hours) and at EOT.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[1] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with MVT-5873.

Evaluable for Objective Response: Only those patients who have measurable disease present at baseline, have received at least one dose of the monoclonal antibody, undergone a resection and have had their disease re-evaluated will be considered evaluable for DFS response. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least dose of the monoclonal antibody, undergone a resection and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.3.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By chest x-ray: ≥20 mm;
- By CT scan:
  - Scan slice thickness 5 mm or under: as ≥10 mm
  - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete

clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. [2-4] I In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.[5]

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.3.4 Response Criteria

6.3.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.3.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD

Non-Target Lesions	New Lesions	Overall Response
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.3.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3.6 Progression-Free Survival

Intrahepatic PFS is defined as the duration of time from date of operation to the date of first observation of progressive disease within the liver or death, whichever comes first.

Extrahepatic PFS is defined as the duration of time from date of operation to the date of first observation of progressive disease outside of the liver or death, whichever comes first.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 28 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see Section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to Section **6.1**.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in Section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=157942842

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 REPORTING PREGNANCY

8.4.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of

when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (Section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.4.2 Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of MVT-5873.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

8.5 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

10.1.1 Primary Efficacy Endpoints

The primary objectives of this trial are to:

1) Determine if the use of the monoclonal antibody in the immediate perioperative period is safe for subjects undergoing the two main procedures: hepatic resection and pancreatic resection.
2) Determine whether subjects with pancreatic cancer, cholangiocarcinoma, or colorectal cancer metastatic to the liver who undergo a resection and receive the anti-CA 19-9 monoclonal antibody can decrease their 12-month recurrence probability from 50% to 25% for pancreatic cancer, from 40% to 20% for colorectal cancer, and from 40% to 20% for cholangiocarcinoma.

10.1.2 Secondary Efficacy Endpoints

The secondary end-point of disease-free survival, defined as the time of resection (D0) until the time of documented clinical recurrence (radiographically or pathologically) will be determined for each patient on study. In the absence of a knowable time of recurrence, time of death will be used as a surrogate. The data will be compared to data obtained from recent randomized clinical trials with adjuvant therapy, and each cohort will be analyzed separately. We anticipate maturation of this data will take years to complete, and plan an analysis at 3 years from the time of accrual of the last patient in each cohort.

10.2 SAMPLE SIZE DETERMINATION:

Sample sizes are calculated on the basis of 12-month recurrence probability for each of the three histologies accrued in this study (pancreatic cancer, cholangiocarcinoma and colorectal cancer):

1. **Pancreatic cancer:** Data from ESPAC4 indicate that the expected 12-month recurrence probability is ~50%. The goal is to determine if use of the monoclonal antibody will be potentially associated with a decrease to a 25% recurrence probability, 12 months after surgery. As a means of determining the sample size for the study, with 23 evaluable subjects with pancreatic cancer who receive surgery and the monoclonal antibody and are potentially followed for 12 months, there would be 80% power to rule out a 50% recurrence rate in favor of a 25% recurrence rate, with a one-sided 0.10 significance level exact binomial test. In practice, if 23 subjects are treated and if 8/23 (34.8%) have recurred by one year, then the upper one-sided 90% confidence bound on 8/23 is 50.3%, which would indicate a marginally improved recurrence probability compared to a historical 50%. In addition, the lower one-sided 90% confidence bound on 8/23 is 21.4%, which demonstrates that 8/23 could be shown to be consistent with as low as a 25% recurrence rate. In practice,

confidence intervals about the recurrence probabilities will be reported, but no formal hypothesis test will be undertaken.

2. **Cholangiocarcinoma:** Data from the BILCAP trial and single institution series indicate that the expected 12-month recurrence probability is 40%. The goal is to determine if use of the monoclonal antibody will be potentially associated with a decrease to a 20% recurrence probability, 12 months after surgery. As a means of determining the sample size for the study, with 24 evaluable subjects with cholangiocarcinoma who receive surgery and the monoclonal antibody, and are potentially followed for 12 months, there would be 81% power to rule out a 40% recurrence rate in favor of a 20% recurrence rate, with a one-sided 0.10 significance level exact binomial test. In practice, if 24 subjects are treated and if 6/24 (25%) have recurred by one year, then the upper one-sided 90% confidence bound on 6/24 is 39.8%, which would indicate a marginally improved recurrence probability compared to a historical 40%. In addition, the lower one-sided 90% confidence bound on 6/24 is 13.7%, which demonstrates that 6/24 could be shown to be consistent with a 20% recurrence rate. In practice, confidence intervals about the recurrence probabilities will be reported, but no formal hypothesis test will be undertaken.
3. **Colorectal cancer:** Data from MSKCC indicate that the expected 12-month recurrence probability is 40%. The goal is to determine if use of the monoclonal antibody will be potentially associated with a decrease to a 20% recurrence probability, 12 months after surgery. As a means of determining the sample size for the study, with 24 evaluable subjects with colorectal cancer who receive surgery and the monoclonal antibody, and are potentially followed for 12 months, there would be 81% power to rule out a 40% recurrence rate in favor of a 20% recurrence rate, with a one-sided 0.10 significance level exact binomial test. In practice, if 24 subjects are treated and if 6/24 (25%) have recurred by one year, then the upper one-sided 90% confidence bound on 6/24 is 39.8%, which would indicate a marginally improved recurrence probability compared to a historical 40%. In addition, the lower one-sided 90% confidence bound on 6/24 is 13.7%, which demonstrates that 6/24 could be shown to be consistent with a 20% recurrence rate. In practice, confidence intervals about the recurrence probabilities will be reported, but no formal hypothesis test will be undertaken.

This study contains the stratified accrual of two successive safety lead-in cohorts, there is the potential for up to 24 safety lead-in subjects to be enrolled. In addition, 71 (23+24+24) subjects will be enrolled in the expansion cohorts. As safety lean-in subjects treated at the MTD may be evaluated in the expansion cohorts, 83 (24-12+71) evaluable subjects will be required. It is expected that approximately 24-30 subjects per year may enroll onto the study, with approximately 8-10 subjects per year for each of the three histologies. Thus, it is expected that 3-4 years may be required to enroll up to 83 total evaluable subjects. To allow for unevaluable subjects and screening failures, the total accrual ceiling for the trial will be set at 105 subjects.

10.3 POPULATIONS FOR ANALYSIS

Modified intention to treat: all subjects who receive at least one dose of the monoclonal antibody and undergo a resection will be included in the statistical analyses performed.

10.3.1 Evaluable for Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with MVT-5873.

10.3.2 Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one dose of the monoclonal antibody, undergone a resection and have had their disease re-evaluated will be considered evaluable for response. CA 19-9 will be measured for response. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

10.3.3 Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least dose of the monoclonal antibody, undergone a resection and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

Fractions of subjects who recur by 12 months will be reported along with appropriate confidence intervals. Estimates of the fraction experiencing important side effects will be reported along with appropriate confidence intervals.

10.4.2 Analysis of the Primary Efficacy Endpoints

1. Safety: see Section **10.4.4**.
2. Recurrence-free survival at 12 months: see Section **10.4.1**.

10.4.3 Analysis of the Secondary Efficacy Endpoints

Disease Free survival (DFS) is the time from resection to the time of definitive evidence recurrence, defined radiographically or by biopsy

DFS will be determined using the Kaplan-Meier method, along with 80% and 95% two-side confidence intervals at the 12-month time point as well as the median for each of the three histologies. Safety will be evaluated as stated in the next section.

10.4.4 Safety Analyses

AE's will be captured with the first dose of MVT-5873 and continue until 28 days after the last dose of MVT 5873, or the start of additional therapy, whichever comes first.

The primary outcome measure (1 of 2) for this trial is safety of immediate peri-operative MVT-5873. For these reasons, we have stratified accrual based on two successive safety lead-in cohorts, and predicated successive accrual to successful completion of the preceding cohort. For example, if we are unsuccessful accruing subjects to lead-in Cohort 2, the remainder of accrual will only take place with subjects meeting study inclusion criteria and safety lead-in Cohort 1 criteria. As described in Section **3**, the safety lead-in cohorts have been designed as an extra safe

guard to ensure patient safety by accruing subjects with the least amount of transaminase and bilirubin abnormalities first.

However, we also want to ensure that the use of MVT-5873 is not associated with an increase in procedure related complications. For this reason, we have added additional safe guards, which are procedure-related and irrespective of histology:

1. **For Subjects Undergoing a Liver Resection:**

   The fraction of subjects whose treatment results in hepatic insufficiency will be noted and reported along with two-sided 80% and 95% confidence intervals. The general expectation is that up to 10% of subjects undergoing a hepatic resection will experience hepatic insufficiency.

   If after the first 10 evaluable subjects who receive this procedure, there are 3 or more who experience hepatic insufficiency, this will be considered excessive since the one-sided lower 90% confidence interval bound on 3/10 is 11.6%, which would demonstrate potential inconsistency with 10%. T, the fraction of subjects who experience hepatic insufficiency (AST and/or ALT elevation in combination with ascites or altered mental status) will be reported, along with a 95% two-sided confidence interval. In addition, each patient will have slides made from the resected tissue and if a single patient within a cohort is noted to have significant necrosis and/or direct damage to the biliary tree, then no further subjects will be enrolled onto that cohort.

2. **For Subjects Undergoing a Pancreas Resection:**

   For subjects who undergo a pancreatic resection, the fraction of subjects whose treatment results in pancreatic leaks will be noted and reported along with two-sided 80% and 95% confidence intervals. The general expectation is that up to 20% of subjects undergoing a pancreatic resection will end up with a leak.

   If after the first 10 evaluable subjects who receive this procedure, there are 5 or more who experience a leak, this will be considered excessive since the one-sided lower 90% confidence interval bound on 5/10 is 26.7%, which would demonstrate potential inconsistency with 20%.

10.4.5 Baseline Descriptive Statistics

Demographic and baseline clinical characteristics of all subjects will be reported.

10.4.6 Planned Interim Analyses

For the two types of procedures, determination of whether there are excessive side effects after treatment of 10 evaluable subjects receive each type of procedure will take place, as described in the section above.

10.4.7 Exploratory Analyses

The following objectives will be analyzed as indicated for each:

The Kaplan-Meier method will be used to determine OS by disease type for subjects treated with preoperative MVT-5873.

For patients that experience a rise in AST, ALT or Bilirubin prior to surgery, the mechanism(s) of liver function test abnormalities associated with MVT-5873 administration will be determined by having liver tissue evaluated with a battery of immunohistochemical stains at the discretion of the liver pathologist, Dr. David Kleiner.

In order to determine the tumor penetration of MVT-5873 in primary tumors of the pancreas and bile ducts, and in metastatic colorectal cancers to the liver, antibody staining (using an antibody against MVT-5873) will be performed by the Hernandez Laboratory on each tumor sample removed. The samples will be scored for staining positivity.

Evaluation of CTCs obtained before receiving the monoclonal antibody and just prior to surgery will be undertaken in order to determine the impact of MVT-5873 therapy on circulating tumor cells. The difference in the CTC levels between the time points will be determined and tested for significance by a Wilcoxon signed rank test. If multiple statistical tests of these laboratory-based parameters are performed, the results will be reported without any formal correction for multiple comparisons.

Resected tumor-bearing liver and pancreas will be perfused in order to develop *ex vivo* models for pancreatic cancer, cholangiocarcinoma, and metastatic colorectal cancer. A model will be deemed viable if the tissue remains intact and functional for 48 hours and if the transcriptome of the tumor changes less than 10% from baseline during the perfusion.

Ex vivo analysis of peritoneal tumor tissue with resected mesothelial metastases will be performed utilizing the SMART System to support the identification of underpinnings of interventional chemotherapeutic and immunomodulatory agent effects in subjects after undergoing pre-operative MVT-5873 therapy.

11 COLLABORATIVE AGREEMENTS

11.1 MATERIAL TRANSFER AGREEMENT (MTA)

There are MTAs in place with the following, see Section **5.2** for additional information on the information/materials being shared with each:

- Genomic Expression (43208-17).
- Zamboni Laboratory – University of North Carolina at Chapel Hill (pending)

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

Subjects with a diagnosis of colorectal cancer with predominantly hepatic metastases will be eligible for this study, as will subjects with resectable pancreatic cancer and cholangiocarcinoma. Eligibility assessment will be made solely on the patient's medical status. Recruitment of subjects on this study will be through standard CCR mechanisms. The investigational nature and objectives of this trial, the procedure and the treatments involved, the attendant risks and discomforts, potential benefits and potential alternative therapies will be carefully explained to the subjects in

the clinic setting and in the hospital prior to treatment and prior to obtaining a signed informed consent.

12.2 PARTICIPATION OF CHILDREN

Children are excluded from this study because no dosing or adverse event data are currently available on the use of MVT-5873 in subjects < 18 years of age. Since the efficacy of this experimental procedure is unknown, it does not seem reasonable to expose children to this risk without further evidence of benefit. Should results of this study indicate efficacy, which is not responsive to other standard forms of therapy, future research can be conducted in the pediatric population to evaluate potential benefit in that patient population.

12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **12.4**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

12.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The potential benefit is increased likelihood of cure from complete tumor extirpation. Therefore, although this protocol involves greater than minimal risk, it presents the prospect of direct benefit to individual subjects. The major risk is that the use of peri-operative MVT-5873 may increase the likelihood of procedure related complications, although we believe this risk to be small.

Risks and benefits will be carefully discussed with the patient at the time consent is obtained. Patients will be monitored throughout the study in order to limit the consequences of any adverse events.

The risks and benefits of participation for adults who become unable to consent on study are no different than those described for the rest of the study population.

12.4.1 Risks

12.4.1.1 Abdominal Surgery

The risks for this protocol include the risks associated with any abdominal surgery. This includes postoperative bleeding, intra-abdominal infection, wound healing complications including fascial dehiscence, enterocutaneous fistulas, anesthetic mishap and perioperative death. All attempts will

be made to avoid unnecessary enterotomies or a bowel resection where feasible. In the case of intra-abdominal catastrophe after surgery, subjects may require reoperation.

12.4.1.2 Study Drug Risks

The use of peri-operative MVT-5873 may increase the likelihood of procedure related complications, although this risk is believed to be small.

12.4.1.3 Blood Sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

12.4.1.4 Urine Collection

There is no physical risk involved with urine collection.

12.4.1.5 Tissue Collection Risks

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If subjects suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NCI's Clinical Center in Bethesda, MD. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which subjects are entitled under applicable regulations.

Biopsy side effects may include a mild burning sensation when the numbing medicine is injected into the skin, small amounts of bleeding at the biopsy site, and rarely, a small infection at the site. Biopsy sites usually heal very well and with very little scarring.

12.4.1.6 Electrocardiogram (EKG)

This test is safe and side effects are unlikely, but it may be uncomfortable when the electrodes are taken off after the test is completed.

12.4.1.7 Scans and Contrast

The most common discomfort is the length of time a patient must lay still during a scan. Patients may also become uncomfortable with the closed space of the machines.

There is a small risk of reaction in scans involving contrast (including gadolinium). Common reactions include pain in the vein where the contrast was given, a metallic or bitter taste in the mouth, headache, nausea and a warm or flushing feeling that lasts from 1-3 minutes. In very rare cases, severe reactions that affect breathing, heart rhythm or blood pressure have occurred. Gadolinium for research MRI scans will not be given to patients who have impaired kidney function or who received gadolinium within the previous month.

An IV line may need to be inserted for administration of the contrast agent or anesthetic, which may cause pain at the site where the IV is placed and there is a small risk of bruising or infection.

12.4.2 Risks of Exposure to Ionizing Radiation

This research study involves exposure to radiation from CT scans, collected for research purposes only. Subjects will be exposed to approximately 8.5 rem. This amount of radiation is above the

guideline of 5 rem per year, and will expose the subject to the roughly the same amount of radiation as 28.3 years of background radiation.

12.4.3 Non-Physical Risks of Genetic Research

12.4.3.1 Risk of Receiving Unwanted Information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Subjects will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with subjects, family members or health care providers.

12.4.3.2 Risk Related to Possibility that Information May be Released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the subjects, family members or health care providers, this risk will be included in the informed consent document.

12.4.3.3 Risk to Family or Relatives

Family members or relatives may or may not want to be aware of familial tendencies or genetic risks of disease which may cause anxiety about possible future health problems.

12.4.4 Benefits

The potential benefit to subjects undergoing this therapy would be cure, or palliation at a minimum, in terms of preventing or delaying intra-abdominal tumor recurrence and metastases elsewhere which can be a devastating and painful source of symptoms and cause for demise.

12.4.5 Certificate of Confidentiality

As part of study efforts to provide confidentiality of subject information, this study has obtained a Certificate of Confidentiality which helps to prevent forced disclosure of personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality

12.5 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided to the participant or consent designee(s) (e.g., the legally authorized representative [LAR] if participant is an adult unable to consent) for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

12.5.1 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in Section **2.2.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

13 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

13.1 DRUG MVT-5873 (IND # 144112)

13.1.1 Source

MVT-5873, also known as HuMab-5B1, is a monoclonal human IgG1 lambda antibody targeted against sLe^a. MVT-5873 is human derived and has a fully human sequence. MVT-5873 has been shown to bind with high affinity and specificity to sLe^a using in vitro cell-based assays, ELISA, and by glycan microarray analysis. MVT-5873 drug is manufactured by AAIPharma

13.1.2 Toxicity

Based on early clinical data, MVT-5873 appears to demonstrate dose limiting toxicity manifest as increases in liver transaminases and blood bilirubin. When seen, liver toxicity generally occurs early (within a few days of drug administration) and appears to be reversible.

As with other protein based therapeutics, subjects are at risk for infusion reactions during or shortly after completion of an infusion of MVT-5873. The reactions are consistent with infusion reactions reported for other intravenous protein therapeutics and may consist of skin reactions (e.g., urticaria, pruritus, flushing), fever, chills, shortness of breath, and tachycardia. Reactions appear to respond to interruption of the infusion and administration of steroids. In many cases, following resolution of the infusion reactions, infusions may be restated at a lower infusion rate without return of infusion reaction symptoms.

Other side effects related to MVT-5873 are mostly low grade (Grade 1 or 2) and are predominately GI in nature (e.g., constipation, diarrhea, nausea, vomiting), or appear consistent with systemic immune activation (e.g., fever, fatigue, malaise, rash).

13.1.3 Formulation and Preparation

MVT-5873 injection drug product contains 10 mg/mL MVT-5873 as the active ingredient. Each vial contains 3.1 mL of MVT-5873 drug product formulated as a solution for intravenous (IV) delivery. The table below provides a complete list of ingredients and quantitative formulation on a per mL basis.

Ingredient	**Function**	**Unit Formula**	**Quality Standard**
MVT-5873	Active Ingredient	10.0 mg/mL	NA
L-histidine	Buffer	3.88 mg/mL	USP/NF
Hydrochloric Acid	Buffer Modifier[1]	Q.S. to pH 6.0	USP/NF
Sucrose	Stabilizer	3.21 mg/mL	USP/NF
Sodium Chloride	Tonicity Modifier	51.35 mg/mL	USP/NF
Polysorbate 80	Solubilizer	0.2 mg/mL	USP/NF
Water for Injection	Solvent	Q.S. to 1.0 mL	USP
[1] HCl may be added to the formulation buffer to attain the desired pH			

13.1.4 Stability and Storage

MVT-5873 Injection drug product is packaged in clear USP Type I borosilicate glass vials with 20 mm West 4432/5- stoppers (grey colored coated closures) and 20 mm flip-off seals. MVT-5873 Injection drug product is stored at -20ºC.

13.1.5 Administration Procedures

MVT-5873 Injection drug product is provided in clear borosilicate glass vials which contain a sterile solution of 10 mg/mL MVT-5873, 25 mM L-histidine, 55mM sodium chloride, 150 mM sucrose, 0.02% Polysorbate 80, pH 6.0 in a total volume of 3.1 mL and stored at -20ºC. Details of the method of administration are included in the Clinical Protocol and the Study Procedure Manual for each study.

13.1.6 Incompatibilities

MVT-5873 should not be administered to subjects with a history of anaphylactic reaction to human or humanized antibody, or to subjects with known hypersensitivity to any of its components or excipients.

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15 APPENDICES

15.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

15.2 APPENDIX B: TOXICITY TABLES

Adverse events reported by MabVax Therapeutics for their Phase I clinical trial MV-0715-CP-001.01, ClinicalTrials.gov Identifier: NCT02672917 are summarized below in Tables 1 to 5 Table 1 All AEs (related and unrelated); highest grade per subject reported by System Organ Class, Preferred Term, CTCAE Grade (as 15-December-2017)

	Cohort A1: 1mg/kg Q2wk (n=6)					Cohort A2: 3mg/kg Q2wk (n=3)					Cohort A4: 1mg/kg wkly (n=6)					Cohort A5: 2 mg/kg wkly (n=6)					Cohort A6: 3mg/kg wkly (n=6)					Cohort A7: 2.5mg/kg wkly (n=5)					Cohort B0: 0.125mg/kg wkly (n=6)					Cohort B3: 1mg/kg wkly (n=3)				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
System Organ Class Preferred Term																																							
Blood and lymphatic system disorders	1										1	1														2	1				1	4	1				2			
Anaemia	1										1	1														2	1				1	3					2			
Neutropenia																																	1							
Thrombocytopenia																																1								
Cardiac disorders																					2	1														1				
Atrial fibrillation																					1																				
Sinus tachycardia																																				1				
Tachycardia																					1	1																			
Ear and labyrinth disorders																										2	1														
Ear congestion																										1															
Ear discomfort																										1															
Vertigo																											1													

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	Cohort A1: 1mg/kg Q2wk (n=6)					Cohort A2: 3mg/kg Q2wk (n=3)					Cohort A4: 1mg/kg wkly (n=6)					Cohort A5: 2 mg/kg wkly (n=6)					Cohort A6: 3mg/kg wkly (n=6)					Cohort A7: 2.5mg/kg wkly (n=5)					Cohort B0: 0.125mg/kg wkly (n=6)					Cohort B3: 1mg/kg wkly (n=3)				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Endocrine disorders																1																								
Hypothyroidism																1																								
Eye disorders																1										1					1									
Lacrimation increased																1																								
Ocular icterus																										1														
Vision blurred																															1									
Gastrointestinal disorders	6	5				3	2				12	2	4			14	1	1			6					9	3				14	4	1			6	1			
Abdominal discomfort																1															1									
Abdominal distension											1															1														
Abdominal hernia	1																																							
Abdominal pain											3					2					1					2	1				2	2				1				
Abdominal pain upper	1																																							
Ascites		1									1							1									1													
Constipation	2	2									1	1				2										2					3	1				1				
Diarrhoea	1										2					1					2						1				1		1			1				
Dry mouth																					1																			
Dyspepsia											1																					1								
Epigastric discomfort																1																								

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	Cohort A1: 1mg/kg Q2wk (n=6)					Cohort A2: 3mg/kg Q2wk (n=3)					Cohort A4: 1mg/kg wkly (n=6)					Cohort A5: 2 mg/kg wkly (n=6)					Cohort A6: 3mg/kg wkly (n=6)					Cohort A7: 2.5mg/kg wkly (n=5)					Cohort B0: 0.125mg/kg wkly (n=6)					Cohort B3: 1mg/kg wkly (n=3)				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Faeces discoloured																										1														
Flatulence																1															2									
Gastrointestinal haemorrhage													1																										
Gingival bleeding																															1									
Haemorrhoidal haemorrhage																1																								
Impaired gastric emptying																					1																			
Nausea		1				1	1				2		1			4	1									2					3					1	1			
Oral pain											1																												
Stomatitis	1											1																											
Vomiting		1				2	1						2			1					1					1					1					2				
General disorders and administration site conditions	5	5	1				2	1			10	3				4					9	4	1			5		1			11	2				4	1			
Asthenia								1													1										1									
Chest discomfort																										1														
Chest pain	1																														1									
Chills	1										1					1					2	1									2									
Disease progression																																								
Fatigue	1	2					1				2	2				1					1	2	1			3					3					1	1			

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	Cohort A1: 1mg/kg Q2wk (n=6)					Cohort A2: 3mg/kg Q2wk (n=3)					Cohort A4: 1mg/kg wkly (n=6)					Cohort A5: 2 mg/kg wkly (n=6)					Cohort A6: 3mg/kg wkly (n=6)					Cohort A7: 2.5mg/kg wkly (n=5)					Cohort B0: 0.125mg/kg wkly (n=6)					Cohort B3: 1mg/kg wkly (n=3)				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Hernia pain											1																												
Hyperhidrosis	1										1																												
Inflammation																1																							
Localised oedema																																				1				
Malaise		1					1				2																												
Mucosal inflammation																															1									
Oedema peripheral	1		1								1					1					3	1								1									
Pain		1																								1		1				1								
Pyrexia		1									2	1									2										2	1				2				
Hepatobiliary disorders	1		1					1																												1				
Hyperbilirubinaemia			1					1																																
Jaundice	1																																			1				
Immune system disorders		1	1																		1						1												
Infusion related reaction		1	1																		1						1												
Infections and infestations		1				1		1			1	1				2							1			2	2					2								
Candida infection																										1														
Clostridium difficile colitis		1																																						

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Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Folliculitis																																1								
Lung infection																							1									1								
Nail infection						1																																		
Pneumonia								1																																
Rhinitis																											1													
Sinusitis																										1														
Upper respiratory tract infection												1				1																									
Urinary tract infection											1					1											1														
Injury, poisoning and procedural complications	1					2					2																													
Fall	1					1																																		
Incision site inflammation											1																													
Wound						1																																		
Wound complication											1																													
Investigations	5		4					1			6	1	4			1	2	8	1		1	3	4			5	5	10	1		13	8	6			5	5	5	1	
Activated partial thromboplastin time prolonged																											1													

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Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Alanine aminotransferase																																1	1							
Alanine aminotransferase increased	1							1				1						2					1					2	1		2	1	2				1	2		
Aspartate aminotransferase																																2								
Aspartate aminotransferase increased	1										1		1					1					2			1		3			4						2	1		
Blood alkaline phosphatase																											1													
Blood alkaline phosphatase increased	2										3		2					1				1	1			2		2				1					1			
Blood bilirubin increased			2								1						1	3				1				1	2	1			3					1		2		
Blood cholesterol increased																															1									
Blood creatinine increased	1																																							
Blood fibrinogen decreased			1																																					

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Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Blood lactate dehydrogenase increased											1																													
Blood phosphorus decreased																																					1				
International normalised ratio increased			1														1														1									
Lipase increased																			1									1												
Lymphocyte count decreased													1					1										1												
Neutrophil count decreased																											1					1	1						1	
Platelet count decreased																						1									2	1				1				
Weight decreased																1					1									1					1					
White blood cell count decreased																										1							1			1				
Metabolism and nutrition disorders	1		2				1	1			9		5			1	1	1			3					4	2				8	3	3			2	2	1		
Decreased appetite							1				1					1					1					1														

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Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Dehydration											1																												
Hyperglycaemia	1												3				1	1									1					1	2	2				2			
Hyperkalaemia								1																							1									
Hypermagnesaemia																															1									
Hypertriglyceridaemia																															1									
Hypoalbuminaemia			1								2										1						1				1									
Hypocalcaemia																										1					1									
Hypoglycaemia																																	1							
Hypokalaemia																					1										1	1				1		1		
Hypomagnesaemia											2															1					1									
Hyponatraemia			1								1		1																								1			
Hypophosphataemia													1																											
Iron deficiency											1																													
Vitamin B12 deficiency											1																													
Vitamin D deficiency																										1														

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Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Musculoskeletal and connective tissue disorders	1		3			2					2					3					6	2				3					2	2								
Arthralgia																1					2																			
Back pain			1			1										1					3					1					1									
Muscle injury																																1								
Muscle spasms																																1								
Muscular weakness																						1				1														
Musculoskeletal discomfort																															1									
Musculoskeletal pain	1		1																			1																		
Myalgia																1										1														
Neck pain						1					1																													
Pain in extremity			1								1										1																			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)																																								
Malignant neoplasm progression																																								

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Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Nervous system disorders	1	1				2	1									1					2									7	1	2			2				
Balance disorder						1																																	
Confusional state																					1																		
Dizziness						1																									1								
Encephalopathy																																							
Headache							1														1															1				
Neuropathy peripheral																1														4		1			1				
Paraesthesia																														1									
Peripheral sensory neuropathy		1																												1		1							
Somnolence	1																																						
Syncope																														1									
Psychiatric disorders																1					1	1				1					2					2				
Depression																1					1															1				
Disorientation																						1																	
Insomnia																										1					2					1				
Renal and urinary disorders	1										1										1					2	1													
Chromaturia																										2														

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Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Chronic kidney disease											1																													
Pollakiuria	1																				1																			
Proteinuria																											1													
Respiratory, thoracic and mediastinal disorders	2					5					5					1					4	2				4	2				5		3			2				
Cough						1										1										1	1				2		1			1				
Dyspnoea	1					1					1										2					1										1				
Dyspnoea exertional						1																1									1									
Epistaxis											1																				2									
Hiccups	1																					1																		
Nasal congestion											1															1														
Paranasal sinus discomfort						1																																		
Pleural effusion																											1													
Pneumonia																																	1							
Pneumonitis																																	1							
Productive cough											1															1														
Pulmonary congestion																					1																			
Pulmonary embolism																					1																			

Adverse events reported by MabVax Therapeutics for their Phase I clinical trial MV-0715-CP-001.01, ClinicalTrials.gov Identifier: NCT02672917 are summarized below in Tables 1 to 5 Table 1 All AEs (related and unrelated); highest grade per subject reported by System Organ Class, Preferred Term, CTCAE Grade (as 15-December-2017)

	Cohort A1: 1mg/kg Q2wk (n=6)					Cohort A2: 3mg/kg Q2wk (n=3)					Cohort A4: 1mg/kg wkly (n=6)					Cohort A5: 2 mg/kg wkly (n=6)					Cohort A6: 3mg/kg wkly (n=6)					Cohort A7: 2.5mg/kg wkly (n=5)					Cohort B0: 0.125mg/kg wkly (n=6)					Cohort B3: 1mg/kg wkly (n=3)				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Rhinorrhoea						1					1																													
Skin and subcutaneous tissue disorders	1										2					2	1				1					3					5	2				4				
Alopecia																															2	2				1				
Contusion																1																								
Hyperhidrosis											1										1																			
Night sweats																															1									
Pruritus											1															1										1				
Pruritus generalised	1																																							
Rash																															1					2				
Rash maculo-papular																1										2					1									
Urticaria																	1																							
Surgical and medical procedures											1																													
Wound drainage											1																													
Vascular disorders		1	1													1						3					1	1				3	1	1				1			
Deep vein thrombosis																						1					1					1								
Flushing																															1						1			
Hypertension		1														1						1						1			1									
Hypotension			1																			1									1		1							

**Unaudited data as of 15-Dec-2017*

MVT-5873-Related AEs; highest grade per subject reported by System Organ Class, Preferred Term, CTCAE grade (as of 15-December-2017)																																					
	Cohort A1: 1mg/kg Q2wks (n=6)					**Cohort A2: 3 mg/kg Q2wks (n=3)**					**Cohort A4: 1mg/kg wkly (n=6)**					**Cohort A5: 2mg/kg wkly (n=6)**					**Cohort A6: 3mg/kg wkly (n=6)**					**Cohort A7: 2.5mg/kg wkly (n=5)**					**Cohort B0: 0.125mg/kg wkly (n=6)**					**Cohort B3: 1mg/kg wkly (n=3)**				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
System Organ Class Preferred Term																																								
Blood and lymphatic system disorders																										2						1								
Anaemia																										2						1								
Cardiac disorders																						1															1				
Sinus tachycardia																																					1				
Tachycardia																						1																			
Eye disorders																										1														
Ocular icterus																										1														
Gastrointestinal disorders	3	1									3					5										4					3	1				2	1			
Abdominal pain																										1														
Abdominal pain upper	1																																							
Constipation																															1									
Diarrhoea	1										1					1																1								
Faeces discoloured																										1														
Nausea											1					3										1					1					1	1			
Oral pain											1																													
Stomatitis	1																																							

MVT-5873-Related AEs; highest grade per subject reported by System Organ Class, Preferred Term, CTCAE grade (as of 15-December-2017)																																					
	Cohort A1: 1mg/kg Q2wks (n=6)					Cohort A2: 3 mg/kg Q2wks (n=3)					Cohort A4: 1mg/kg wkly (n=6)					Cohort A5: 2mg/kg wkly (n=6)					Cohort A6: 3mg/kg wkly (n=6)					Cohort A7: 2.5mg/kg wkly (n=5)					Cohort B0: 0.125mg/kg wkly (n=6)					Cohort B3: 1mg/kg wkly (n=3)				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Vomiting		1														1										1					1					1				
General disorders and administration site conditions	1	3									3	3				1					3	2								2	1				2				
Chest pain	1																																						
Chills											1					1					2	1								1									
Fatigue		2									1	2										1													1				
Malaise		1									1																												
Pyrexia												1									1									1	1				1				
Hepatobiliary disorders								1																															
Hyperbilirubinaemia								1																															
Immune system disorders		1	1																		1						1											
Infusion related reaction		1	1																		1						1											
Infections and infestations																										1												
Candida infection																										1												
Investigations	3		1					1			1	1	2					8	1			3	3			4	3	9	1		7	4	2			3	5	4		
Alanine aminotransferase																																1	1							
Alanine aminotransferase increased								1				1						2					1					2	1		2	2	1				1	2		

MVT-5873-Related AEs; highest grade per subject reported by System Organ Class, Preferred Term, CTCAE grade (as of 15-December-2017)																																						
	Cohort A1: 1mg/kg Q2wks (n=6)					Cohort A2: 3 mg/kg Q2wks (n=3)					Cohort A4: 1mg/kg wkly (n=6)					Cohort A5: 2mg/kg wkly (n=6)					Cohort A6: 3mg/kg wkly (n=6)					Cohort A7: 2.5mg/kg wkly (n=5)					Cohort B0: 0.125mg/kg wkly (n=6)					Cohort B3: 1mg/kg wkly (n=3)				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Aspartate aminotransferase																																1								
Aspartate aminotransferase increased	1												1					1					2			1		3			3						2	1		
Blood alkaline phosphatase																											1													
Blood alkaline phosphatase increased	1												1					1				1				2		2										1		
Blood bilirubin increased	1		1								1							3				1				1	2	1			1					1		1		
Blood phosphorus decreased																																					1			
International normalised ratio increased																																				1				
Lipase increased																			1																					
Lymphocyte count decreased																		1										1												
Platelet count decreased																						1									1									
White blood cell count decreased																																				1				
Musculoskeletal and connective											1					1					2																			

MVT-5873-Related AEs; highest grade per subject reported by System Organ Class, Preferred Term, CTCAE grade (as of 15-December-2017)																																						
	Cohort A1: 1mg/kg Q2wks (n=6)					Cohort A2: 3 mg/kg Q2wks (n=3)					Cohort A4: 1mg/kg wkly (n=6)					Cohort A5: 2mg/kg wkly (n=6)					Cohort A6: 3mg/kg wkly (n=6)					Cohort A7: 2.5mg/kg wkly (n=5)					Cohort B0: 0.125mg/kg wkly (n=6)					Cohort B3: 1mg/kg wkly (n=3)				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
tissue disorders																																								
Arthralgia																					1																			
Back pain																1					1																			
Neck pain											1																													
Psychiatric disorders																																				1				
Depression																																				1				
Renal and urinary disorders																										2	1														
Chromaturia																										2														
Proteinuria																											1													
Respiratory, thoracic and mediastinal disorders	1																				1												2			1				
Cough																																	1			1				
Dyspnoea	1																				1																			
Pneumonitis																																	1							
Skin and subcutaneous tissue disorders																	1														2				3					
Alopecia																																				1				
Rash																															1					2				
Rash maculo-papular																															1									
Urticaria																	1																							
Vascular disorders		1														1						1																1			
Flushing																																					1			

MVT-5873-Related AEs; highest grade per subject reported by System Organ Class, Preferred Term, CTCAE grade (as of 15-December-2017)																																						
	Cohort A1: 1mg/kg Q2wks (n=6)					Cohort A2: 3 mg/kg Q2wks (n=3)					Cohort A4: 1mg/kg wkly (n=6)					Cohort A5: 2mg/kg wkly (n=6)					Cohort A6: 3mg/kg wkly (n=6)					Cohort A7: 2.5mg/kg wkly (n=5)					Cohort B0: 0.125mg/kg wkly (n=6)					Cohort B3: 1mg/kg wkly (n=3)				
Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Hypertension		1														1						1																		

**Unaudited data as of 15-Dec 2017*

Table 5 Serious Adverse Events Reported as of 15 December 2017

Manufacturing Ctrl No.	Subject ID	Drug	Dose and Frequency	Cycle	Adverse Event (Verbatim Term)	CTCAE Grade	Relationship
MVT5873-2016-001	02-004	MVT-5873	1mg/kg Q2W	1	Hypotension	3 (severe)	Unrelated
MVT5873-2016-002	02-004	MVT-5873	1mg/kg Q2W	1	Hyperbilirubinemia	3 (severe)	Unrelated
MVT5873-2016-003	01-012	MVT-5873	1mg/kg Q2W	1	Fever	2 (moderate)	Unrelated
MVT5873-2016-005	01-012	MVT-5873	1mg/kg Q2W	2	Encephalopathy	5 (death)	Unrelated
MVT5873-2016-006	02-007	MVT-5873	1mg/kg Q2W	4	Lung Infection*	3 (severe)	Unrelated
MVT5873-2016-007	02-002	MVT-5873	1mg/kg Q2W	1	Clinical Progression of Pancreatic Cancer	5 (death)	Unrelated
MVT5873-2016-010	02-028	MVT-5873	3mg/kg QW	1	Clinical Progression of Pancreatic Carcinoma	5 (death)	Unrelated
MVT5873-2016-011	01-025	MVT-5873	3mg/kg QW	2	Progression of Disease	5 (death)	Unrelated
MVT5873-2017-001	02-034	MVT-5873	3mg/kg QW	1	Lung Infection	3 (severe)	Unrelated
MVT5873-2017-002	02-034	MVT-5873	3mg/kg QW	1	Lung Infection	3 (severe)	Unrelated
MVT5873-2017-003	02-006	MVT-5873	3mg/kg Q2W	10	Weakness	3 (severe)	Unrelated

Manufacturing Ctrl No.	Subject ID	Drug	Dose and Frequency	Cycle	Adverse Event (Verbatim Term)	CTCAE Grade	Relationship
MVT5873-2017-005	02-006	MVT-5873	3mg/kg Q2W	10	Headache	2 (moderate)	Unrelated
MVT5873-2017-006	02-006	MVT-5873	3mg/kg Q2W	10	Clinical Disease Progression	5 (death)	Unrelated
MVT5873-2017-009	01-024	MVT-5873	2mg/kg QW	2	Malignant neoplasm progression	5 (death)	Unrelated
MVT5873-2017-010	03-014	MVT-5873	1mg/kg QW	2	Disease Progression	5 (death)	Unrelated
MVT5873-2017-012	01-047	MVT-5873	1mg/kg QW	3	Fever	1 (mild)	Unrelated
MVT5873-2017-013	03-046	MVT-5873	1mg/kg Q2W	5	Upper Gastrointestinal Hemorrhage**	3 (severe)	Unrelated
MVT5873-2017-014	02-016	MVT-5873	1mg/kg QW	13	Gastrointestinal Bleeding***	3 (severe)	Unrelated
MVT5873-2017-015	02-016	MVT-5873	1mg/kg QW	13	Vomiting***	3 (severe)	Unrelated

*Subject 02-007 received a starting dose at 3 mg/kg and then received 6 doses at 1 mg/kg Q2W prior to SAE start date.
**Subject 03-046 received a starting dose at 2mg/kg QW and then received 1mg/kg Q2W beginning on C1D15
***Subject 02-016 dose escalated to 2mg/kg QW starting C6D15 through C7D15 and then dose reduced back to original dose of 1mg/kg QW

15.3 APPENDIX C: INVESTIGATOR AGREEMENT

This form can be used to send to Participating site PIs if the CCR is the coordinating center for the protocol.

I have received and reviewed the Investigator Brochure for (*insert Study Agent)*

I have read this protocol and agree that the study is ethical.

I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title:

Protocol Version Date:

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (printed or typed)