



PROTOCOL: IMMU-132-01

Phase I/II Study of IMMU-132 in Epithelial Cancers

Protocol Title: A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients with Epithelial Cancer

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PPD

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SYNOPSIS

Protocol Number IMMU-132-01

Protocol Title A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients with Epithelial Cancer

Study Drug IMMU-132 (hRS7-SN38 antibody-drug conjugate) is provided in glass vials as a sterile lyophilized powder **CCI**
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Objectives In Phase I, the primary objective is to evaluate the safety and tolerability of IMMU-132 as a single agent administered in 3-week treatment cycles, in previously treated patients with advanced epithelial cancer. The secondary objectives are to obtain initial data concerning pharmacokinetics, immunogenicity, and efficacy with this dosing regimen. In Phase II, the primary objective is the evaluation of the safety and efficacy of IMMU-132 administered in 3-week treatment cycles at a dose selected in Phase I, while the secondary objectives include pharmacokinetics and immunogenicity.

Scope of Study This is planned as a multi-center study. In Phase II, up to 150 patients (assessable) in each of 5 cancer subtypes [triple-negative and non-triple-negative breast cancer (TNBC, non-TNBC), non-small-cell lung cancer (NSCLC), small cell lung cancer (SCLC), urothelial cancer (UC)] and up to 56 patients (assessable) per other cancer types will be studied at the 10 mg/kg dose.

Study Duration In Phase II, all patients receive IMMU-132 10 mg/kg administered once-weekly for the first 2 weeks of 3-week treatment cycles, to be continued in the absence of unacceptable toxicity or progression of disease requiring termination of further treatment. Patients who have progression of disease assessed for the first time during the study but derive continued clinical benefit from IMMU-132 treatment, may continue to be treated based on physician discretion (with Sponsor approval). After discontinuing treatment, follow-up is then required until resolution or stabilization of any treatment-related toxicity, and patients with stable disease or objective responses must also continue evaluations for up to 2 years or until progression of disease or initiation of other treatment. All patients will be followed for survival every month, which may be by telephone, but no longer than 2 years from final study evaluation.

Background SN-38 is the active metabolite of irinotecan (CPT-11), a highly potent chemotherapeutic agent that is approved as a single agent and is incorporated into combination regimens for the treatment of advanced colorectal cancer, but which has dose-limiting gastrointestinal and hematologic toxicities. hRS7 is a humanized monoclonal antibody which targets the Trop-2 (human trophoblast cell-surface antigen) antigen which is expressed on a variety of human carcinomas and also known as EGP-1 (epithelial glycoprotein-1), GA733-1 (gastric antigen 733-1), and TACSTD2 (tumor-associated calcium signal

transducer). Trop-2 has been associated with more aggressive disease in some cancers and is a promising target for drug delivery with hRS7, since a portion of the antibody internalizes when bound to the antigen on the cell surface. As such, Immunomedics has developed an antibody-drug conjugate (ADC), called IMMU-132, in which SN-38 is conjugated to hRS7 in order to enhance delivery of SN-38 to Trop-2-expressing tumors while reducing systemic toxicity.

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Based upon data from the Phase I portion of this study, a starting dose of 8 or 10 mg/kg, administered on days 1 and 8 of a 21-day cycle was considered acceptable for further evaluation, and 10 mg/kg was subsequently selected for the ongoing Phase II portion of this study. Severe (Grade 3 or higher) toxicities have primarily been limited to neutropenia, diarrhea or febrile neutropenia (see Investigator's Brochure for most recently updated safety profile).

In Phase I & Phase II, there was evidence of efficacy. Partial responses have been observed currently in patients with triple-negative breast cancer, small-cell lung cancer, non-small cell lung cancer, esophageal cancer and urinary bladder and colorectal cancers. Disease stabilization has been observed in many patients. Many patients have continued therapy for periods of months, but with little evidence of evoking antibodies to the drug (SN-38) or antibody (hRS7) of the ADC.

Study Design

This is a Phase I/II, open-label study of IMMU-132 in previously treated patients with advanced epithelial cancers, including ovarian, endometrial, cervical, breast (TNBC and non-TNBC), prostate (hormone refractory), lung (non-small-cell and small-cell), head & neck (squamous cell), esophageal, gastric, hepatocellular, renal (clear cell), papillary thyroid, and urothelial cancers, as well as glioblastoma multiforme. A table of approved or standard or commonly used therapeutic regimens for each of these cancer types is included in [Appendix 1](#). Patients who have not received approved or standard treatment lines for their cancer must be informed that alternatives to receiving IMMU-132 are available prior to their consenting to participate in this trial.

In Phase II, up to 150 patients (assessable) in each of 5 cancer subtypes (TNBC, non-TNBC, NSCLC, SCLC, UC) and up to 56 patients (assessable) per other cancer types will be studied at 10 mg/kg dose.

Baseline evaluations within 4 weeks of the scheduled start of treatment include patient history, physical examination with vital signs and performance evaluation, local histology review to confirm one of the epithelial cancers included, contrast-enhanced CT or MRI scans (chest, abdomen, pelvis with additional imaging of other involved areas), CBC (with differential and platelet count), routine serum chemistries, urinalysis (with microscopic, if needed), PT/PTT, EKG, and serum samples for human anti-human antibody (HAHA). 

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Tumor biomarkers are to be monitored at baseline and at each radiologic response assessment time point whenever possible. 

A single whole-blood sample (purple- or pink-topped tube, 2 mL) will be collected from each registered patient prior to receiving IMMU-132 for determination of UGT1A1 and related genotypes. This sample will be shipped to Sponsor who will perform this assay. The results from this test are NOT required to determine eligibility but will be used retrospectively to assess its utility in predicting toxicity.

 PPD

 Core biopsies that are  fresh-frozen and also formalin-fixed (described above) are also desired at baseline and intervals during therapy whenever possible.

In the ongoing Phase II study, all patients receive IMMU-132 10 mg/kg administered in 3-week treatment cycles with weekly dosing the first two weeks (days 1 and 8 of 21-day cycles) and no dosing the third week. The cycles are to be continued in the absence of unacceptable toxicity or progression of disease requiring termination of further treatment. The first assessment of disease progression per RECIST1.1 does not require discontinuation of study treatment if there is still the potential for patient benefit in the opinion of the investigator and approved by the Sponsor, but treatment must be discontinued if subsequent imaging documents disease progression from that assessment.

All patients are closely monitored over the course of their treatment, and NCI CTCAE v4.0 is used to grade all adverse events and to provide dose reduction, delay or cessation guidelines in the event of treatment-related toxicity. Based on irinotecan and animal testing, the major toxicity of IMMU-132 is expected to be gastrointestinal symptoms and hematologic suppression. Growth factors and other supportive care are allowed when medically necessary any time during treatment with IMMU-132 but should not be given prophylactically before start of treatment with IMMU-132 first dose in cycle 1.

In the current experience in over 200 patients, the major Grade 3 or Grade 4 toxicity has been neutropenia, which is managed with dose delay, dose reduction, or growth factors, if spontaneous remission is not experienced within 7 days.

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Patients who exhibit an excessive cholinergic response to IMMU-132 treatment (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Because of the many clinical sites participating in this trial, the investigators are requested not to consent and start screening a potentially eligible patient before consulting with the Sponsor to determine when such a patient could be accepted into the trial, should the patient prove to be eligible after screening.

Study procedures during treatment include physical examination and vital signs, CBC (with differential and platelet count), routine serum chemistries, PT/PTT, serum samples for PK (to be collected in all patients in Phase II, unless exempted by the Sponsor) and HAHA, concomitant medications and adverse events, and EKG. Starting with the initial dose of IMMU-132, CT or MRI examinations and biomarkers are to be obtained every 8 weeks until the occurrence of progression of disease requiring termination of further treatment. At that time, the patient will undergo an end-of-study evaluation, with additional follow up only required until resolution or stabilization of any treatment-related toxicity. For scans showing stable disease, but with substantial or rapid tumor shrinkage near threshold for a partial response, the 8-week interval for the next scan may be shortened at investigator discretion and if discussed with the medical monitor. Confirmatory CT/MRI scans are to be obtained 4 to 6 weeks after an initial partial response and/or 4 to 6 weeks after an initial complete response. If a

confirmatory scan is performed, the subsequent scans will be scheduled every 8 weeks from the confirmatory scan. Additional scans may be performed at the discretion of the physician to assess disease status as medically indicated. At the discretion of treating physician, patients who have biopsiable lesion(s) and consented to biopsy(ies) will provide during the study as many tumor metastasis core biopsy samples as possible. **CCI**

In addition, SN-38 concentrations will be determined only in specimens that are taken within one day after completion of any IMMU-132 infusion. All specimens should be placed in 10% formalin, without any further processing and shipped to sponsor for analysis, as well as fresh-frozen specimens for determining protein or RNA levels.

In the event of treatment termination due to unacceptable toxicity, the patient will continue on study follow up until there is documentation of progression of disease, at which time an end-of-study evaluation will be performed, with additional follow-up only required until resolution or stabilization of any treatment-related toxicity.

Long-term follow-up will continue in patients with stable disease or an objective response with evaluations performed every 3 months for up to 2 years or until progression of disease or initiation of other treatment. All patients will be followed for survival every month, which may be by telephone, but no longer than 2 years from final study evaluation.

Patients continuing to benefit from treatment at time of study closure may be eligible to enroll in a rollover study, so they may continue to receive treatment.

(See study calendar below for detailed schedule of procedures)

Population

Males or non-pregnant, non-lactating females \geq 18 years of age, able to give signed, written informed consent, may be eligible if they have documented epithelial cancer that involves any of the following tumor types: ovarian, cervical, endometrial, breast (triple-negative and other breast tumors), prostate (hormone refractory), lung (non-small-cell and small-cell), head and neck (squamous cell), esophageal, colorectal, gastric, pancreas, renal (clear cell), papillary thyroid, glioblastoma multiforme, urinary bladder (urothelial), and hepatocellular. Patients must have metastatic disease (except GBM) and have either relapsed after receiving or were refractory to at least one standard chemotherapy (or biological, targeted or hormonal) regimen for their disease.

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All patients must have measurable disease by CT or MRI at the time of treatment, but no single lesion \geq 7 cm in diameter. Patients with any bulky lesions over 7 cm, but otherwise eligible, may be considered for enrollment after discussion and approval by the medical monitor (Sponsor). Patients who have not received all approved or standard treatment lines for their cancer must be informed that these alternatives to receiving IMMU-132 are available prior to consenting to participate in this trial. Patients must be 2 weeks beyond any major surgery, radiation, immunotherapy, endocrine therapy, investigational drugs including small molecular inhibitors, or chemotherapy regimens, and have recovered from any acute toxicities associated with these prior treatment(s) to Grade 1 or less (except alopecia).

Patients must have a life expectancy \geq 6 months, an ECOG performance score of 0 or 1, adequate hematology without ongoing transfusional support (ANC \geq 1.5 x 10⁹/L, platelets \geq 100 x 10⁹/L, hemoglobin $>$ 9 g/dL), no active \geq Grade 2 anorexia, nausea or vomiting or signs of intestinal obstruction, no prior history of clinically significant bleeding, intestinal obstruction, or GI perforation within 6 months, no known history of anaphylactic reaction or \geq Grade 3 GI toxicity to prior irinotecan, no known history of unstable angina, MI, or CHF present within 6 months or clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy, no known history of clinically significant, active COPD, or other moderate to severe chronic respiratory illness present within 6 months, adequate renal (creatinine \leq 2.0 x IULN) and hepatic function (bilirubin \leq 1.5 x IULN, AST and ALT \leq 3 x IULN or 5 x IULN if known liver metastases), and with otherwise all toxicity at study entry $<$ Grade 1 by NCI CTC v4.0 (Patients with \leq Grade 2 neuropathy will be eligible). Patients with Gilbert's disease are excluded. Patients with treated, non-progressive brain metastases, off high-dose steroids (>20 mg prednisone or equivalent) for at least 4 weeks, can be enrolled in the trial.

Patients with successfully treated non-melanoma skin cancer or carcinoma in situ of the cervix are eligible, while patients with other prior malignancies must have had at least a 3-year disease-free interval.

Patients of childbearing potential must be willing to practice birth control during the study until at least 12 weeks after treatment, and women of childbearing potential must have a negative urine or serum pregnancy test to enter the study.

Other exclusion criteria include patients known to be HIV positive, hepatitis B-antigen positive, or hepatitis C positive, infection requiring intravenous antibiotic use within 1 week, use of systemic, high-dose corticosteroids within 2 weeks, and other concurrent medical or psychiatric conditions that, in the investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

Concomitant

Medications	<p>Patients enrolled in this trial will be refractory to or relapsed after one or more chemotherapy regimens, including irinotecan in colorectal cancer patients, or hormonal agents, biologicals or targeted therapeutic agents, and may also have received antibody therapy. All of these treatments must be discontinued for a minimum of 2 weeks prior to starting IMMU-132, and these or other anti-cancer therapies (i.e., drugs, biologics, procedures) are not permitted during this study. Palliative and/or supportive medications and procedures are permitted to be used during the study. Patients who receive palliative and/or supportive medications and procedures should have a washout period of 1 week after the last IMMU-132 dose and 2 weeks prior to resuming the treatment with next IMMU-132 dose, unless otherwise a different washout period is arranged by discussion with medical monitor (Sponsor). The requirement for premedication with acetaminophen, steroids, and diphenhydramine or equivalents is not anticipated; however, these will be employed as clinically indicated to decrease infusion reactions.</p> <p>Antiemetics, anti-diarrheal medications, cytokines or blood transfusions may be administered as clinically indicated. Cytokines or blood transfusions are not permitted prophylactically before start of first IMMU-132 dose in cycle 1. Other supportive care is allowed as medically warranted.</p>
Phase II	<p>In Phase II, up to 150 patients (assessable) in each of 5 cancer subtypes (TNBC, non-TNBC, NSCLC, SCLC, UC) and up to 56 patients (assessable) per cancer type for all other cancers will be studied at the 10 mg/kg dose.</p>
Endpoints	<p>Safety and tolerability will be evaluated from adverse events, standard safety laboratories (CBC with differential and platelet count, serum chemistries, and urinalysis), physical examination, vital signs, and EKG. Adverse events will be classified according to the MedDRA system of preferred terms and system organ class, and all adverse events and abnormal laboratories will be classified for severity using NCI CTCAEv4.0 toxicity grades. Descriptive statistics will be used to characterize adverse events, cytopenias, and other abnormal laboratories.</p> <p>Efficacy will be evaluated from CT scans (or if needed MRI studies), using RECIST 1.1 criteria to classify tumor response, time to onset of objective response, duration of objective response, time to progression and survival. Changes in biomarkers will be evaluated.</p> <p>Pharmacokinetics (PK) will be evaluated from serum samples using an ELISA assay performed by the Sponsor. The results will be characterized by standard PK parameters including peak and trough values, area-under- the-curve (AUC), maximum concentration (Cmax), and half-life (T1/2), if feasible, and summarized using descriptive statistics.</p> <p>Immunogenicity will be determined from serum samples using an ELISA assay performed by the Sponsor for the occurrence of any human antibodies against IMMU-132 (e.g., HAHA). The occurrences of any positive HAHA results will be characterized by descriptive statistics.</p>

**Long-Term
Follow-Up**

After the last treatment dose, follow-up continues for patients who have not progressed with CT studies performed every 3 months for up to 2 years or until progression of disease or initiation of other treatment. Follow-up is also required at least every 3 months until resolution or stabilization for any treatment-related abnormalities that warrant continued monitoring. Adverse events and concomitant medications reported at any follow-up visits will include outcome of any ongoing unresolved events, new events attributed to the study treatment, deaths, hospitalizations, GI toxicity, and infectious episodes requiring prescription or IV anti-infectives. All patients will be followed for survival every month, which may be by telephone with patient or caregiver, for no longer than 2 years from final study evaluation.

Table 2: Study Calendar

PRETREATMENT		TREATMENT (3-Week Treatment Cycles)						POST TREATMENT	
	Within 4 Wks of Entry	Cycle 1			Subsequent Cycles			Final ¹ Study Eval	Long-Term Follow-up Every 1 month
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		
Signed Informed Consent	X								
Patient Eligibility	X								
Histology review	X								
Pregnancy Test	X ³				X ³			X	
Hepatitis B & C Test	X								
Medical/Surgical History	X								
UGT1A1 genotype		X							
Genotype analysis results ¹³		X							
CT/ MRI (chest, abdomen, pelvis; other if needed) and biomarkers ⁴	X							X	
EKG	X				X ¹⁰			X	X ²
Phys. Exam (PE)	X				X ¹¹			X	X ²
CBC (with diff, platelets) ⁵	X	X	X		X	X		X	X ²
Serum Chemistries ⁵	X	X	X		X	X		X	X ²
PT/PTT	X				X ¹¹			X ¹¹	X ²
Urinalysis	X				X ¹¹			X	
Concomitant Medications	X	X	X		X	X		X	X ⁶
CCI									
IMMU-132 infusion		X	X		X	X			
Vital Signs	X	X ⁷	X ⁷		X ⁷	X ⁷		X	X ²
Adverse Event Reporting		X	X		X	X		X	X ⁸
CCI									
CCI	Biopsy Tissue	X ¹²							
Survival status									X
1	Performed 14 days after the last dose of study drug or in event of premature study termination								
2	Otherwise, long-term follow-up required every 3 months for up to 2 years or initiation of other treatment in patients who have not progressed, or only until resolution of any treatment-related abnormalities once patients progresses								
3	Pregnancy test, if applicable, will be performed within 1 week prior to start of treatment, and on Day 1 of every even numbered treatment cycle (2, 4, 6, etc) and at the end of the study								
4	CT or MRI and biomarkers required at 8 week intervals after the start of treatment until the occurrence of progression of disease requiring discontinuation of further treatment CT/MRI scans also to be obtained in any patient within 4 to 6 weeks to confirm complete / partial response assessments Additional CT/MRI can be performed at the discretion of the physician to assess disease status as medically indicated CCI								
5	CCI								
5	Serum chemistries include glucose, creatinine, BUN, total bilirubin, AST, ALT, CCl ¹³ alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, CO ₂ , magnesium and phosphorus More frequent laboratories required in event of \geq Grade-3 toxicity								
6	Only IV or prescription anti-infectives or medications for GI toxicity will be recorded								
7	VS's obtained prior to 1st infusion, every 15 min for the first hour, then every 30 min until completed, at completion, and then 30 min post-infusion In absence of significant changes, may be reduced with subsequent doses to prior to infusion, at 30 min, and then at completion								
8	Ongoing AEs until resolved, new events attributed to test article; otherwise, deaths, hospitalizations, or events requiring IV or prescription anti-infectives or medications related to GI toxicity								
10	CCI								
10	EKG required after completion of day 1 infusion of every even numbered treatment cycle (2, 4, 6, 8, etc) and at the end of the study								
11	PE, Urinalysis, CCI & PT/PTT at baseline, at day 1 of every even numbered treatment cycle (2, 4, 6, 8, etc) and at the end of the study CCI								
12	CCI								
12	Patients who have biopsiable lesion and consented to biopsy will provide as many tumor metastasis biopsy samples as possible								
13	CCI								
<i>NOTE: Unless otherwise specified, collection windows for study time points are nominally within \pm 10% or according to institutional standard procedures. Planned deviations in treatment schedule are allowable up to 7 days due to holidays, vacation or personal reasons.</i>									

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LIST OF ABBREVIATIONS

AE	adverse event
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CCI	
BUN	blood urea nitrogen
CBC	complete blood count
CDC	complementary-dependent cytotoxicity
CDR	complementarity-determining region
CFR	Code of Federal Regulation
CNS	central nervous system
CR	complete response
CRF	case report form
CTCAE	common terminology criteria for adverse events
DLT	dose limiting toxicity
FDA	Food and Drug Administration
GCP	good clinical practice
HAHA	human anti-human antibodies
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IATA	International Air Transport Association
ICH	International Committee on Harmonization
IEC	independent ethics committee
IgG	immunoglobulin G
IND	Investigational New Drug
IRB	institutional review board
IULN	institutional upper limit of normal
CCI	
mAb	monoclonal antibody
MTD	maximum tolerated dose
NSAE	non-serious adverse event
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
OR	Objective Response, OR = CR + PR
PBS	phosphate-buffered saline
PK	pharmacokinetics
PR	partial response
RBC	red blood cell
SAE	serious adverse event
Trop-2	Trophoblastic cell-surface antigen
TPP	time to progression
WBC	white blood cell

1. INTRODUCTION

Over the past 60 years, antibodies have been investigated for their ability to shepherd toxic compounds, such as radioactivity, drugs, or toxins to tumors in an attempt to deliver these agents in a more selective manner for improved anti-tumor effects. While initially finding unconjugated antibodies to be largely ineffective, today there are several antibodies approved for clinical use in a variety of cancers, and there are many more under clinical evaluation.⁽¹⁻⁶⁾ Even though relatively few antibody conjugates have been approved for treating cancer, most antibodies are themselves incapable of eliciting sufficient responses to warrant their use as standalone agents. Instead, most unconjugated antibodies are combined with chemotherapeutic regimens in some way. Thus, it is not surprising that there has been a renewed interest in antibody-drug conjugates, particularly with the recent success of the trastuzumab emtansine, an anti-HER2- maytansine conjugate, in HER2-positive breast cancer patients, even those who were refractory to unconjugated trastuzumab.⁽⁷⁻⁹⁾

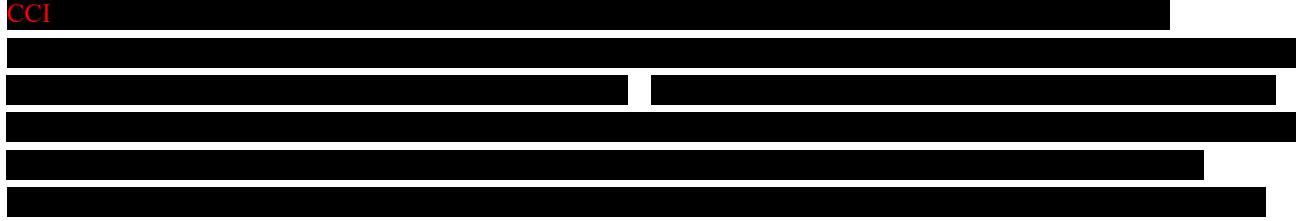
Most of the antibody-drug conjugates (ADC) being explored clinically today use drugs that cannot be given alone because they are too toxic (i.e., ultra-toxic). Conjugating these drugs, such as maytansine, calicheamicin, and auristatin to antibodies detoxifies them, usually by altering their natural pharmacokinetic and biodistribution properties. However, as the decision to remove Mylotarg (gemtuzumab ozogamicin; anti-CD33-calicheamicin conjugate) from marketing suggests, the therapeutic window of these agents can be limited.^(10, 11) For this reason, we have taken a closer look at the various chemotherapeutic agents that already have been tested clinically to determine if any might be suitable for conjugation to antibodies. Since most chemotherapeutics require micromolar concentrations for therapy, they are not suitable for use as antibody conjugates. However, SN-38 is promising because it has activity in the low nanomolar range, which is between the extreme of the ultratoxics that are active in subnanomolar concentrations and most of the other commonly used chemotherapeutics.

SN-38, a topoisomerase I inhibitor, is the active metabolite of the camptothecin CPT-11 (irinotecan), which is approved as a single agent for colorectal cancer and included in treatment regimens such as FOLFIRI.⁽¹²⁻²⁰⁾ SN-38 is not water soluble, and therefore it was derivatized to a water-soluble form, irinotecan, but it must be enzymatically cleaved to the SN-38 form for it to have maximum potency. Unfortunately, at best, only 5% of irinotecan will be converted to the active SN-38 form by esterase activity residing primarily in the liver, albeit there are esterases in the tumor that can cleave irinotecan to SN-38.⁽²¹⁻²⁴⁾ Its catabolism in the liver results in its transport through the bile duct into the intestines, resulting in GI toxicity.

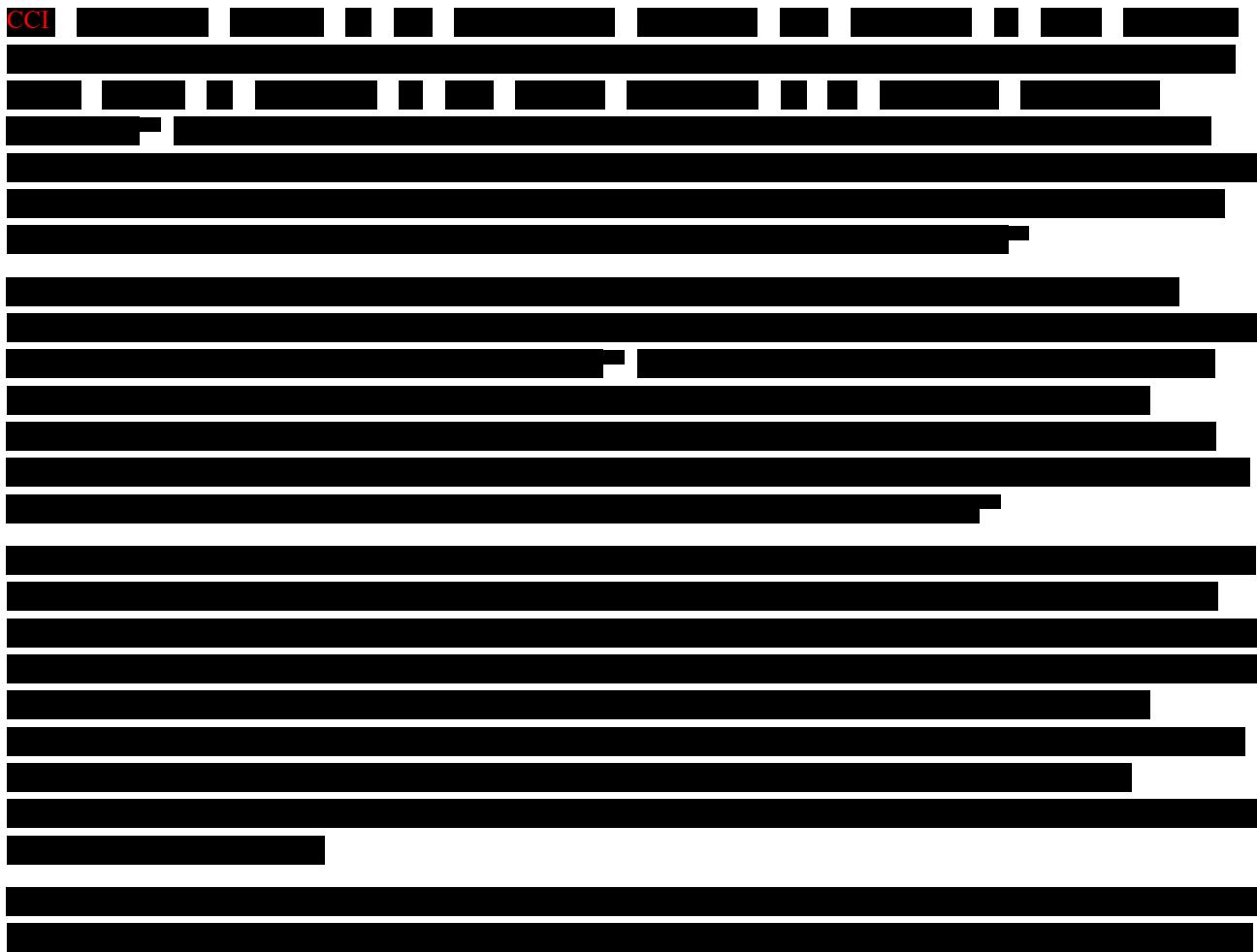
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CCI



Immunomedics is currently pursuing several ADCs based on the SN-38 conjugation technology it developed. In this protocol, a humanized anti-Trop-2 antibody (hRS7) is examined. Trop-2 (trophoblastic cell-surface antigen; also known as EGP-1, epithelial glycoprotein-1), is a cell surface, transmembrane calcium signal transducer glycoprotein belonging to the TACSTD gene family that is highly expressed in many epithelial cancers, particularly metastatic sites⁽²⁷⁾, with much lower expression in normal tissues.⁽²⁸⁾ Trop-2 has been implicated as an important antigen in oncogenesis, often being found in more aggressive tumors⁽²⁹⁻³⁹⁾. The murine RS7 antibody was initially identified as being specific for epithelial glycoprotein-1 (aka, Trop-2)^(40, 41), being found in a number of different epithelial cancers and it was internalized⁽⁴²⁻⁴⁵⁾, a highly desirable property for an antibody-drug conjugate. Indeed, as mentioned above, the initial studies with the SN-38 conjugates used an anti-CEACAM5 antibody that is not readily internalized, yet it was potent *in vivo*, leaving us to hypothesize that local release of the SN-38 from the antibody bound to the tumor provides an important mechanism for that conjugate's activity. However, the hRS7-SN-38 conjugate further benefits from the antibody's ability to internalize.⁽⁴⁶⁾



Horizontal bar chart showing CCI values for 15 countries. The y-axis lists countries: CCI, Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Uruguay, and Venezuela. The x-axis represents the CCI value, with a scale from 0 to 100. Most countries have high CCI values (above 80), while Argentina and Venezuela have lower values (around 60).

Country	CCI
CCI	85
Argentina	60
Brazil	95
Chile	98
Colombia	92
Costa Rica	95
Ecuador	95
El Salvador	95
Guatemala	95
Honduras	95
Mexico	95
Nicaragua	95
Panama	95
Paraguay	95
Uruguay	95
Venezuela	60

Since 8 of the 9 patients treated at 12 mg/kg required dose delays and reductions during the first cycle, that starting dose was considered to have exceeded the maximum acceptable dose for further consideration. In contrast, the initial dose level of 8 mg/kg appears acceptable with 3 additional patients (2 pancreatic, 1 gastric cancer). To establish a maximum acceptable dose level, a final intermediate dose level of 10 mg/kg was evaluated.

Based upon these data from the Phase I portion of this study, starting doses of 8 or 10 mg/kg, administered on days 1 and 8 of a 21-day cycle were considered acceptable for further evaluation, and subsequently 10 mg/kg was selected for the ongoing Phase II portion of this study. Severe (Grade 3 or higher) toxicities have primarily included neutropenia, diarrhea and febrile neutropenia. Adverse events of all causalities (all grades and grade 3/4) are shown below.

Adverse events all grades and all causalities with incidence ≥ 5%.					
Adverse Event Preferred Term	All Doses (N=203)	8 mg/kg (N=82)	10 mg/kg (N=109)	12 mg/kg (N=9)	18 mg/kg (N=3)
Nausea	36%	52%	22%	56%	100%
Diarrhea	35%	48%	19%	67%	67%
Fatigue	35%	54%	17%	89%	67%
Neutropenia	30%	38%	17%	89%	100%
Alopecia	29%	41%	18%	44%	33%
Vomiting	23%	28%	17%	44%	67%
Anemia	20%	34%	7%	33%	33%
Abdominal pain	17%	18%	13%	33%	67%
Constipation	16%	27%	9%	22%	0%
Anorexia	12%	17%	8%	0%	33%
Hypokalemia	10%	13%	6%	33%	33%
Hypomagnesemia	10%	12%	6%	22%	67%
Edema peripheral	10%	16%	4%	22%	33%
Pyrexia	9%	15%	4%	22%	0%
Dizziness	8%	12%	5%	22%	0%
Dyspnea	8%	15%	4%	11%	0%
Headache	7%	13%	4%	0%	0%
Leukopenia	7%	11%	4%	22%	0%

Grade 3 and 4 adverse events all causalities ≥ 1%.					
Adverse Event Preferred Term	All Doses (N=203)	8 mg/kg (N=82)	10 mg/kg (N=109)	12 mg/kg (N=9)	18 mg/kg (N=3)
Neutropenia	22%	29%	13%	56%	67%
Febrile neutropenia	4%	2%	5%	11%	0%
Diarrhea	3%	4%	4%	22%	0%
Anemia	2%	10%	2%	22%	0%
Fatigue	2%	7%	2%	22%	0%
Abdominal pain	2%	2%	1%	0%	67%
Leukopenia	2%	5%	3%	0%	0%
Hypokalemia	1%	2%	1%	11%	0%
Hyponatremia	1%	4%	1%	0%	0%
Lymphopenia	1%	2%	1%	0%	0%
Nausea	1%	1%	1%	0%	0%
Urinary tract infection	1%	1%	1%	0%	0%
Vomiting	1%	1%	1%	0%	0%

In Phase I & Phase II, there was evidence of efficacy. Partial responses have been observed currently in patients with triple-negative breast cancer, small-cell lung cancer, non-small-cell lung cancer, esophageal cancer, urinary bladder, and colorectal cancer. Disease stabilization has been observed in many patients.

2. STUDY OBJECTIVES

This is a first-in-man clinical study with the antibody-drug conjugate, IMMU-132, which uses the humanized antibody hRS7 to deliver the topoisomerase I inhibitor, SN-38, directly to Trop-2-expressing epithelial tumors.

2.1. Primary Objective

The primary objective in Phase I is to evaluate the safety and tolerability of IMMU-132 as a single agent administered in 3-week treatment cycles, in previously treated patients with advanced epithelial cancer. Dose escalation in Phase I (completed) was intended to determine a maximum acceptable dose and select cancer types for continued expanded study in Phase II. Phase II continues enrollment with dose levels and cancers selected based upon Phase I results and preliminary efficacy results. The primary objective in Phase II is the evaluation of the safety and efficacy of IMMU-132 administered in 3-week treatment cycles, at a dose selected in Phase I.

2.2. Secondary Objectives

In Phase I, the secondary objectives are to obtain initial data concerning pharmacokinetics, immunogenicity, and efficacy with this dosing regimen. In Phase II, secondary objectives also include pharmacokinetics and immunogenicity.

3. STUDY DESIGN

This is a Phase I/II, open-label study of IMMU-132 in previously treated patients with the following metastatic epithelial cancers:

- Gastric adenocarcinoma (GC)
- Esophageal cancer (EC)
- Hepatocellular carcinoma (HCC)
- Non-small cell lung cancer (NSCLC)
- Small-cell lung cancer (SCLC)
- Epithelial ovarian cancer (EOC)
- Cervical Cancer
- Papillary thyroid cancer
- Glioblastoma multiforme (GBM)
- Endometrial Cancer
- Triple-negative breast cancer (TNBC)
- Non-triple-negative breast cancer (mBC)
- Hormone-refractory prostate cancer (HRPC)
- Head and neck cancers- squamous cell (SCCHN)
- Renal cell carcinoma (clear cell) (RCC)
- Urothelial cancers, including urinary bladder cancer.

A table of approved or standard therapeutic regimens or regimens in documented clinical trials for each of these cancer types is included in **Appendix 1**. *Patients who have not received all approved or standard treatments for their cancer must be informed that these alternatives to receiving IMMU-132 are available prior to consenting to participate in this trial.*

In Phase II, up to 150 patients (assessable) in each of 5 cancer subtypes (TNBC, non-TNBC, NSCLC, SCLC, UC) and up to 56 patients (assessable) per other cancer types will be studied at the 10 mg/kg dose.

Based upon the Phase I results, the 8 mg/kg and 10 mg/kg dose levels were selected for further evaluation in Phase II, and subsequently the 10 mg/kg dose was selected for the ongoing Phase II study.

Baseline evaluations within 4 weeks of the scheduled start of treatment include patient history, physical examination with vital signs and performance evaluation, local histology review to confirm one of the epithelial cancers listed above, contrast-enhanced CT or MRI scans (chest, abdomen, pelvis with additional imaging of other involved areas), CBC (with differential and platelet count), routine serum chemistries, urinalysis, PT/PTT, EKG, and serum samples for human anti-human antibody (HAHA). **CCI**

CCI

CCI

CCI

A single whole-blood sample (purple or pink-topped tube, 2 mL) will be collected from each registered patient prior to receiving IMMU-132 for determination of *UGT1A1* or other *UGT1* genotype. This sample will be shipped to Sponsor who will perform this assay. The results are not used to establish eligibility but will be used for retrospective assessment of toxicity.

All patients receive two doses of IMMU-132 administered in 3-week treatment cycles with weekly dosing in the first two weeks (days 1 and 8 of 21-day cycles) and no dosing the third week. In the ongoing Phase II portion of the study, all patients receive 10 mg/kg starting doses and the treatment cycles are to be continued in the absence of unacceptable toxicity or progression of disease requiring termination of further treatment. The first determination of disease progression per RECIST1.1 does not require discontinuation of study treatment if there is still the potential for patient benefit in the opinion of the investigator, but treatment must be discontinued if subsequent imaging documents disease progression from that assessment. All patients are closely monitored over the course of their treatment, and NCI CTCAE v4.0 is used to grade all adverse events and to provide dose reduction, delay or cessation guidelines in the event of treatment-related toxicity. Based on irinotecan and animal testing, the major toxicity of IMMU-132 is expected to be gastrointestinal symptoms and hematologic suppression. Growth factors and other supportive care are allowed when medically necessary any time during treatment with IMMU-132, but not prophylactically before start of treatment with the first IMMU-132 dose in cycle 1.

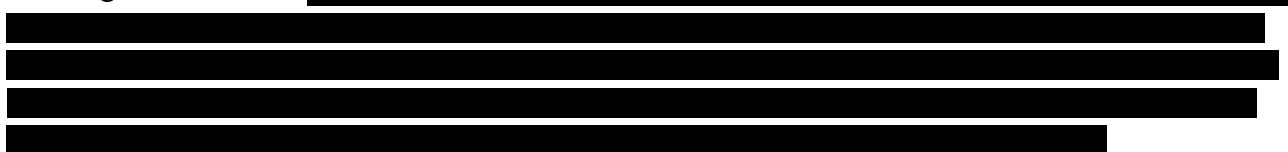
CCI

Patients who exhibit an excessive cholinergic response to IMMU-132 treatment (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., Atropine) for subsequent treatments.

In Phase I, dose guidelines will be followed with a goal of being able to give the first cycle without requiring dose reduction, delay, or discontinuation or cytokine support at the time the second cycle is given.

Study procedures during treatment include physical examination and vital signs, CBC (with differential and platelet count), routine serum chemistries, PT/PTT, serum samples for PK (*to be collected in all patients in the ongoing Phase II study unless an exemption is approved by the Sponsor*) and HAHA, concomitant medications and adverse events, and EKG.

Starting with the initial dose of IMMU-132, CT (or MRI if needed) examinations are to be obtained at 8-week intervals until the occurrence of progression of disease requiring discontinuation of further treatment. For scans showing stable disease, but with substantial or rapid tumor shrinkage near threshold for a partial response, the 8-week interval for the next scan may be shortened at investigator discretion and if discussed with the medical monitor. Confirmatory CT/MRI scans are to be obtained 4 to 6 weeks after an initial partial response and/or 4 to 6 weeks after an initial complete response. If a confirmatory scan is performed the subsequent scans will be scheduled every 8 weeks from the confirmatory scan. Tumor biomarkers are to be obtained at the time of radiologic evaluations. **CCI**



After discontinuing treatment, the patient will undergo an end-of-study evaluation, with additional follow-up only required until resolution or stabilization of any treatment-related toxicity. Additional CT or MRI may be performed at the discretion of the physician to assess disease status as medically indicated.

Long-term follow-up will continue in patients with stable disease or an objective response with evaluations performed every 3 months for up to 2 years or until progression of disease or initiation of other treatment. All patients will be followed every month for survival, which may be by telephone, for no longer than 2 years from final study evaluation.

Patients continuing to benefit from treatment at time of study closure may be eligible to enroll in a rollover study, so they may continue to receive treatment.

(See study calendar for detailed schedule of study procedures)

4. PATIENT POPULATION

The study population comprises previously treated adults with Stage IV (metastatic) epithelial cancers. Eligible patients must satisfy the following entry criteria at time of study entry:

4.1. Inclusion Criteria

- Male or female patients, ≥ 18 years of age, able to understand and give written informed consent.
- Histologically or cytologically confirmed epithelial cancer of one of the following types:
 - Gastric adenocarcinoma (GC)
 - Esophageal cancer (EC)
 - Hepatocellular carcinoma (HCC)
 - Non-small-cell lung cancer (NSCLC) CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
 - Small-cell lung cancer (SCLC)
 - Epithelial ovarian cancer (EOC)
 - Cervical Cancer
 - Endometrial Cancer
 - Triple-negative breast cancer CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
 - Non-triple-negative breast cancer
 - Papillary thyroid cancer (*excludes follicular, medullary, Hurthle cell, and anaplastic thyroid cancer*)
 - Glioblastoma multiforme (GBM)
 - Hormone-refractory prostate cancer (HRPC)
 - Head and neck cancers- squamous cell (SCCHN)
 - Renal cell cancer (clear cell) (RCC)
 - Urothelial cancer CCI [REDACTED]
[REDACTED]
[REDACTED]

CCI

- Stage IV (metastatic) disease (except for patients with GBM).
- Refractory to or relapsed after at least one prior standard therapeutic regimen.

(Appendix 1 lists approved or standard chemotherapeutic agents for each cancer type. Patients who have not received all approved or standard treatments for their cancer must be informed that these alternatives to receiving IMMU-132 are available prior to consenting to participate in this trial.)

- Adequate performance status (ECOG 0 or 1) ([Appendix 2](#)).
- Expected survival \geq 6 months.
- Measurable disease by CT or MRI.
- At least 2 weeks beyond treatment (chemotherapy, investigational drugs including small molecular inhibitors, endocrine therapy, immunotherapy and/or radiation therapy) or major surgery and recovered from all acute toxicities to Grade 1 or less (except alopecia).
- At least 2 weeks beyond high dose systemic corticosteroids (however, low dose corticosteroids < 20 mg prednisone or equivalent daily are permitted).
- Adequate hematology without ongoing transfusional support (hemoglobin > 9 g/dL, ANC $> 1,500$ per mm 3 , platelets $> 100,000$ per mm 3).
- Adequate renal and hepatic function (creatinine $\leq 2.0 \times$ IULN, bilirubin ≤ 1.5 IULN, AST and ALT $\leq 3.0 \times$ IULN or 5 x IULN if know liver metastases).
- Otherwise, all toxicity at study entry \leq Grade 1 by NCI CTCAE v4.0.

4.2. Exclusion Criteria

- Women who are pregnant or lactating.
- Women of childbearing potential and fertile men unwilling to use effective contraception during study until conclusion of 12-week post-treatment evaluation period.
- Patients with Gilbert's disease.
- Patients with brain metastases can be enrolled only if treated, non-progressive brain metastases and off high-dose steroids (> 20 mg prednisone or equivalent) for at least 4 weeks.
- Presence of bulky disease (defined as any single mass > 7 cm in its greatest dimension). Patients with a mass over 7 cm, but otherwise eligible, may be considered for enrollment after discussion and approval with the medical monitor.
- Patients with active \geq grade 2 anorexia, nausea or vomiting, and/or signs of intestinal obstruction.
- Patients with non-melanoma skin cancer or carcinoma *in situ* of the cervix are eligible, while patients with other prior malignancies must have had at least a 3-year disease-free interval.

- Patients known to be HIV positive, hepatitis B positive, or hepatitis C positive.
- Known history of unstable angina, MI, or CHF present within 6 months or clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy.
- Known history of clinically significant active COPD, or other moderate-to-severe chronic respiratory illness present within 6 months.
- Prior history of clinically significant bleeding, intestinal obstruction, or GI perforation within 6 months of initiation of study treatment.
- Infection requiring intravenous antibiotic use within 1 week.
- Patients with a history of an anaphylactic reaction to irinotecan or \geq Grade 3 GI toxicity to prior irinotecan.
- Other concurrent medical or psychiatric conditions that, in the Investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

4.3. Concomitant Medications and Procedures

- Patients enrolled in this trial will be refractory or relapsed after one or more chemotherapy regimens that may have included irinotecan. All of these treatments must be discontinued for a minimum of 2 weeks prior to starting IMMU-132, and these or other anti-cancer therapies (i.e., drugs, biologics, procedures) are not permitted during this study. However, palliative and/or supportive medications and procedures will be allowed at the investigator's discretion. Patients who receive palliative and/or supportive medications and procedures should have a washout period of 1 week after the last IMMU-132 dose and 2 weeks prior to resuming the treatment with nextIMMU-132 dose, unless otherwise a different washout period is arranged by discussion with medical monitor.
- Premedication with acetaminophen, steroids, and diphenhydramine or equivalents is not anticipated; however, it will be employed as clinically indicated to decrease infusion reactions. Patients with a history of infusional reactions to other antibody therapies may be pre-medicated at the discretion of the treating physician.
- Patients who exhibit an excessive cholinergic response to IMMU-132 treatment (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g. Atropine) for subsequent treatments.
- Hematopoietic growth factors or blood transfusions are allowed at physician's discretion, but not prophylactically before the first IMMU-132 dose in Cycle 1.
- High dose systemic corticosteroids are not allowed within 2 weeks of study entry.
- Low dose corticosteroids <20 mg prednisone or equivalent daily are permitted (topical steroids and corticosteroid inhalers are allowed).
- Antiemetics, anti-diarrheal medications, cytokines or blood transfusions may be administered as clinically necessary.
- Other supportive and palliative care is allowed as medically warranted.

CYP3A4 inducers and inhibitors. There is a potential for altered toxicity profile from common medications and foods with possible potent effects on liver metabolism of drugs such as irinotecan and SN38. As such, all patients should be recommended to avoid the following while on study therapy:

CYP 3A4 Inhibitors:

Amiodarone	Indinavir
Amprenavir	Isoniazid
Aprepitant	Itraconazole
Atazanavir	Ketoconazole
Chloramphenicol	Lapatinib
Clarithromycin	Miconazole
Conivaptan	Nefazodone
Cyclosporine	Nelfinavir
Darunavir	Posaconazole
Dasatinib	Ritonavir
Delavirdine	Quinupristin
Diltiazem	Saquinavir
Erythromycin	Tamoxifen
Fluconazole	Telithromycin
Fluoxetine	Troleandomycin
Fluvoxamine	Verapamil
Fosamprenavir	Voriconazole
Grapefruit juice	
Imatinib	

CYP 3A4 Inducers:

Aminoglutethimide	Oxcarbazepine
Bexarotene	Phenobarbital
Bosentan	Phenytoin
Carbamazepine	Primidone
Efavirenz	Rifabutin
Fosphenytoin	Rifampin
Griseofulvin	Rifapentine
Modafinil	St. John's wort
Nafcillin	
Nevirapine	

5. DOSE ESCALATION

Dose escalation phase is now completed.

6. STUDY PROCEDURES

Blood samples obtained for HAHA and antibody / conjugate serum levels and UGT1A1 levels are to be shipped to the Sponsor who will perform these assays. Instructions for shipping these blood samples are given in [Appendix 3](#). Otherwise, all procedures are to be performed locally at each study site.

6.1. Informed Consent

No study procedure or alteration of patient care will be undertaken until informed consent has been obtained from the patient or legal representative. The Investigator will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the patient and/or legally authorized representative.

A table of approved or standard therapeutic regimens for each of these cancer types is included in [Appendix 1](#). *Patients who have not received all approved or standard treatment lines for their cancer must be informed that these alternatives to receiving IMMU-132 are available prior to consenting to participate in this trial.*

If the patient agrees to participate, the informed consent form will be signed, dated, and witnessed, with a copy given to the subject.

6.2. Patient Registration

Since this Phase I /II trial is being performed at multiple institutions and in different cancers, investigators must contact the Clinical Project Manager (Sponsor) or designee in advance of consenting and start screening a patient to determine if or when a patient may be enrolled. This is particularly important because a number of clinical sites are enrolling patients and the Sponsor needs to plan enrollment in specific tumor types relative to product supply.

Eligible patients will be enrolled in the study by calling the Clinical Project Manager or designee at Immunomedics at PPD Monday through Friday, between 8:30 AM and 5:00 PM EST. The screening CRF pages are to be completed and faxed to Immunomedics at PPD or emailed to register the patient at least 48 hours prior to the expected treatment start date.

6.3. Pre-Study/Baseline Evaluations

Required within the 4 weeks prior to treatment:

- Signed informed consent
- Hepatitis B surface antigen test, hepatitis C antibody test

cc:

- Documented histology review to confirm epithelial cancer of one of the following types:
 - Gastric adenocarcinoma (GC)
 - Esophageal cancer (EC)
 - Hepatocellular carcinoma (HCC)
 - Non-small-cell lung cancer (NSCLC)
 - Small-cell lung cancer (SCLC)
 - Epithelial ovarian cancer (EOC)
 - Cervical Cancer
 - Endometrial Cancer
 - Triple-negative breast cancer (TNBC)
 - Non-triple-negative breast cancer
 - Glioblastoma multiforme (GBM)
 - Papillary thyroid cancer
 - Hormone-refractory prostate cancer (HRPC)
 - Head and neck cancers - squamous cell (SCCHN)
 - Renal cell cancer (clear cell) (RCC)
 - Urothelial cancers.
- Medical/surgical history review with treatment history to include treatment response and also time to progression for last therapy regimen
- Concomitant medications review
- Physical examination with vital signs
- Standard 12-lead electrocardiogram (EKG)
- CBC including platelet count, with WBC differential in absolute cell counts
- Routine serum chemistries (*i.e.*, glucose, creatinine, BUN, total bilirubin, AST, ALT, **CCI**, alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, CO₂, magnesium and phosphorus)
- Serum sample for HAHA (frozen, to be shipped to Sponsor for analysis)
- Urinalysis
- PT/PTT
- CT or MRI with contrast (chest, abdomen, pelvis, other regions of known/suspected involvement)*

cc

cc

CC [REDACTED]
CC [REDACTED]
CC [REDACTED]
CC [REDACTED]
CC [REDACTED]
CC [REDACTED]

- A single whole-blood sample (purple or pink-topped tube, 2 mL) to be collected from each registered patient prior to receiving IMMU-132 for determination of UGT1A1 genotype.

** MRI abdomen and pelvis with contrast may be done in situations where a CT with contrast is equivocal or contraindicated. A non-contrast chest CT should be done for patients requiring an MRI of the abdomen and pelvis.*

6.4. 3-Week Treatment Cycle Procedures

Treatment Days [Days 1 & 8 (+/- 1 day) of each cycle]

- IMMU-132 dose preparation and administration
- Vital signs (*Prior to first infusion and every 15 minutes for the first hour then every 30 minutes until completing IV administration, at completion, and then additionally 30 minutes later. In absence of significant changes, may be reduced with subsequent doses to prior to infusion, at 30 minutes, and then at completion.*)
- Blood samples prior to infusion:
 - CBC (with differential and platelet count)
 - Serum chemistry panel (glucose, creatinine, BUN, total bilirubin, AST, ALT, CCI [REDACTED], alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, CO₂, magnesium and phosphorus)
 - PT/PTT [*required only on Day 1 of all even numbered cycles (cycle 2, 4, 6, 8, etc.)*]
- Urinalysis (*required only on Day 1 of all even numbered cycles starting with cycle 2*)
- Physical examination (*required only on Day 1 of all even numbered cycles starting with cycle 2*)
- 12-lead EKG done [*required after completing infusion on Day 1 of all even numbered cycles (cycle 2, 4, 6, 8, etc.)*]
- Concomitant medications (continued, changed)
- Adverse event reporting
- Serum samples for PK analysis: (frozen, to be shipped to Sponsor for analysis). CCI [REDACTED]
[REDACTED]
[REDACTED]

If samples are not collected with the first dose, then all samples should be obtained with the first dose of a subsequent cycle as advised by the Sponsor.

- HAHA sample (frozen, to be shipped to Sponsor for analysis) **CCI** [REDACTED]
- Pregnancy test, if applicable [*required only on Day 1 of all even numbered cycles (cycle 2, 4, 6, 8, etc.)*]

CT or MRI examinations **CCI**

Starting with the initial dose of IMMU-132, **CT or MRI scans** **CCI** [REDACTED] and are to be obtained at 8 week intervals after the first treatment dose until the occurrence of progression of disease requiring discontinuation of further treatment. For scans showing stable disease, but with substantial or rapid tumor shrinkage near threshold for a partial response, the 8-week interval for the next scan may be shortened at investigator discretion and if discussed with the medical monitor. Confirmatory CT/MRI scans are to be obtained in any patient within 4 to 6 weeks of an initial partial response and/or complete response. If a confirmatory scan is performed, then subsequent scans will be scheduled every 8 weeks from the date of confirmatory scan.

Note: MRI abdomen and pelvis with contrast may be done in situations where a CT with contrast is equivocal or contraindicated. A non-contrast chest CT should be done for patients requiring an MRI of the abdomen and pelvis.

CCI

Additional CT or MRI studies may be performed at the discretion of the physician to assess disease status as medically indicated.

If patient does not experience unacceptable toxicity or progression of disease requiring discontinuation of treatment, treatment cycles may be continued. Patients, who have progression of disease assessed for the first time during the study but derive continued clinical benefit from IMMU-132 treatment, may continue to be treated based on physician discretion and approved by Sponsor.

6.5. Pharmacokinetic Evaluations

Serum for PK analysis in the ongoing Phase II study will be obtained in all patients (unless exempted by the Sponsor) with the first dose of cycle 1 (i.e., Cycle 1, Day 1). **CCI** [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

6.6. Final Study Evaluation or Unscheduled/Early Termination Visit

To be conducted 14 days after the last dose of study drug or in the event of premature study termination

- 12-lead electrocardiogram (EKG)
- Physical examination (complete)
- Pregnancy test, if applicable
- Vital signs
- Blood samples
 - CBC (with differential and platelet count)
 - Serum chemistry panel
 - PT/PTT
 - Serum sample for HAHA (frozen, to be shipped to Sponsor for analysis)
- Urinalysis
- Concomitant medications (continued, changed)
- Adverse event reporting

6.7. Long-Term Follow-Up

After completing the final study evaluation, follow-up continues for patients who have not progressed with assessments including CT or MRI studies performed every 3 months for up to 2 years or until progression of disease or initiation of other treatment. Follow-up will also include physical exam, CBC, chemistries, CCI [REDACTED]

(Note: MRI abdomen and pelvis with contrast may be done in situations where a CT with contrast is equivocal or contraindicated. A non-contrast chest CT should be done for patients requiring an MRI of the abdomen and pelvis).

Follow-up is also required at least every 3 months until resolution or stabilization for any treatment-related abnormalities that warrant continued monitoring in patients who progressed and otherwise would have completed the study.

Adverse events and concomitant medications reported at any follow-up visits will include outcome of any ongoing unresolved events, new events attributed to the study treatment, deaths, hospitalizations, and infectious episodes requiring prescription or IV anti-infectives or GI toxicity.

All patients will be followed every month for survival, which may be by telephone. Patients will not be followed beyond 2 years from final study evaluation.

6.8. Criteria for Removal from Protocol Treatment

Patients may be removed from protocol treatment under the following conditions:

- First documentation of progressive disease (Physician discretion and Sponsor approval to continue) or symptomatic deterioration indicating treatment failure.
- Patients who want to continue treatment after radiological documentation of progressive disease should notify the physician who will obtain Sponsor approval before treatment continuation.
- Unacceptable toxicity.
- Treatment delay for any reason > 3 weeks (Treatment delays of up to 3 weeks will be allowed at the investigator's discretion).
- The patient may withdraw from the study at any time for any reason.

7. STUDY DRUG INFORMATION

7.1. Description of Study Drug

hRS7 is a CDR-grafted, humanized monoclonal IgG₁ anti-Trop-2 antibody. The antibody is prepared using cell culture methods by Immunomedics, Inc. (Morris Plains, NJ) in accordance with Food and Drug Administration (FDA) guidelines for the manufacture and testing of monoclonal antibody products for human use. SN-38 (7-ethyl-10-hydroxy-camptothecin) is a small molecule and the active metabolite of the chemotherapeutic agent irinotecan.

IMMU-132 is an antibody drug-conjugate prepared by Immunomedics, Inc. (Morris Plains, NJ) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Complete and detailed drug preparation and storage instructions in addition to the management of drug accountability are provided in the Pharmacy Manual, which should be used as the primary reference for these activities.

7.2. Drug Accountability

All vials of study drug must be stored under refrigeration (monitored at 2-8°C) and protected from light in a locked room that can be accessed only by the pharmacist, the study Investigator, or another duly designated person. The study medications must not be used outside of the context of this protocol. Under no circumstances should the Investigator or other site personnel supply study drug to other Investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from Immunomedics, Inc.

Adequate records documenting receipt, use, return, loss, or other disposition of study drug vials must be kept. A complete drug accountability record, supplied by Immunomedics (or its designee or NCI drug accountability forms), or computer records used by the pharmacy at the investigational site, can be used to provide drug accountability. In all cases, information describing study medication supplies and their disposition, patient-by-patient, must be provided and signed by the Investigator (or the pharmacist or other person who dispensed the drug) and collected by the Study Monitor. Requisite data include relevant dates, quantities, batches or code numbers, and patient identification for patients who received trial product.

At the end of the study, following authorization by study management, study medication may be destroyed at the site as dictated by the appropriate standard operating procedures at the participating institutions. Destruction must be documented. Alternatively, after notification, all unused products will be collected by the Study Monitor and returned to Immunomedics.

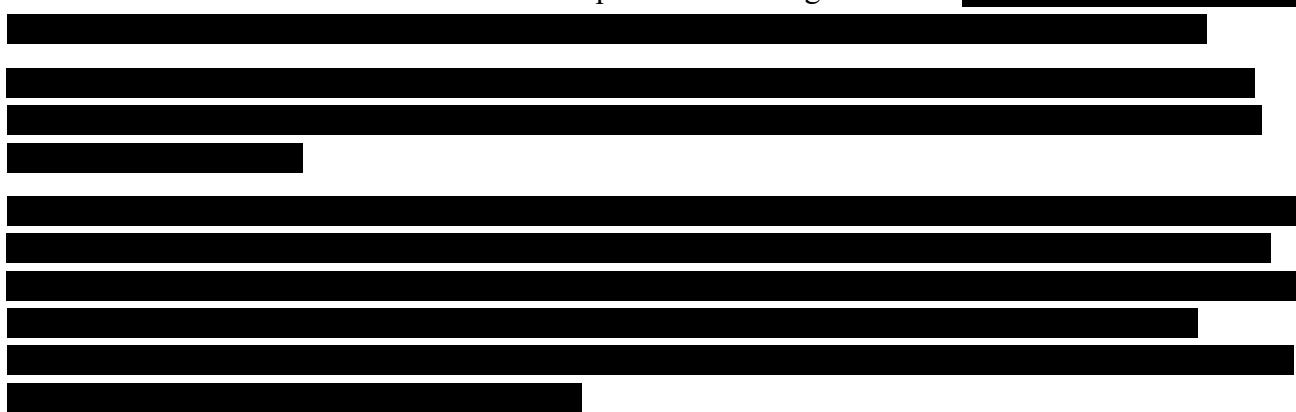
7.4.2. Vital Signs

Vital signs will be assessed prior to first infusion every 15 ± 5 minutes for the first hour and then every 30 minutes until completing IV administration, at completion, and then additionally 30 minutes later. In absence of significant changes, may be reduced with subsequent doses to prior to infusion, at 30 minutes, and then at completion.

7.4.3. Intravenous Administration

Do not administer as an IV push or bolus. IMMU-132 is administered intravenously as a slow infusion as described below.

Intravenous access must be well established prior to initiating infusion. **CCI**



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7.4.4. Managing Infusional Toxicity

Immunomedics, Inc., should be notified within 24 hours in the event of any serious infusion reaction.

NCI CTCAE version 4.0 is used to grade all adverse events and to provide management guidelines for infusional toxicity.

For a serious infusion reaction considered severe or life threatening (NCI toxicity Grade 3 or higher) an infusion must be permanently terminated.

- Examples of such events include: serious or clinically significant cardiopulmonary events, severe allergic (symptomatic bronchospasm) or anaphylactic reactions, or other severe reactions.
- The occurrence of Grade 3 infusion-related reactions (e.g., Prolonged infusion related reactions-not rapidly responsive to symptomatic medication and/or brief interruption of infusion) also require the infusion to be permanently terminated.

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Recommended actions for mild toxicity (Grade 1 events) include slowing the remaining infusion rate.

Any infusional toxicity must have resolved to < Grade 1 prior to a patient receiving the next scheduled infusion.

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A large, bold, red logo consisting of the letters 'CCI' in a sans-serif font, centered on a black rectangular background.

Additional Medications

Patients may be medicated during treatment as indicated in the judgment of the treating physician to control potential infusion or hypersensitivity responses. For anaphylactic reactions, appropriate medical measures (e.g., epinephrine, antihistamines, hydrocortisone, and i.v. fluids) should be taken. Such a subject should not receive additional study drug and should be discontinued from the study.

Nausea, Vomiting and Diarrhea

Gastrointestinal toxicity may be dose limiting with this study agent. Hospital or institutional guidelines may exist and should be consulted for recommended treatment of these conditions in patients received cancer therapy. Several major oncology organizations have also provided comprehensive guidelines for optimal medical management of nausea, vomiting and diarrhea with cancer treatment. As of this writing, guidelines from these organizations are not stratified by toxicity Grade. A partial list of the major medications is provided below, but the hospital/institution guidelines or the references below should be consulted for more detailed information as to management of these conditions.

Patients who exhibit an excessive cholinergic response to IMMU-132 treatment (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g. Atropine) for subsequent treatments.

Table 7: Recommended Medications for Nausea, Vomiting and Diarrhea*

Agent	Dose/Frequency	Route of administration
For Prevention of Acute Emesis:		
Palonosetron	0.075mg	
Decadron	10-20 mg 10 mg every 12 hours	PO or IV PO or IV
Granisetron	1 mg or 0.01 mg/kg 1-2 mg daily	IV PO
Ondansetron	8 mg or 0.15 mg/kg 16-24 mg daily	IV PO
Lorazepam	0.5-2 mg every 4-6 hours	PO or sublingual
Alprazolam	0.5-2 mg every 4-6 hours	PO or sublingual
For Delayed Emesis:		
Aprepitant	125 mg on Day 1 followed by 80 mg on Days 2 & 3	PO
Fosaprepitant	115 mg day 1 only	IV
For Diarrhea:		
Loperamide	4 mg initially followed by 2 mg with every episode for a maximum of 16 mg daily. Discontinue 12 hours after diarrhea resolves and normal diet is resumed.	PO
Octreotide	100-150 mcg three times daily	Subcutaneously
Fluoroquinolones (for diarrhea persisting > 24 hrs., ANC <500 or fever with diarrhea)	(e.g., ciprofloxacin 250-750 mg every 12 hours for 7 days)	PO

* Based on NCCN Antiemesis Guidelines v1.2011; Benson et al (2004) Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 22:2918-26; Kris et al (2006) American Society of Clinical Oncology guidelines for antiemetics in oncology: Update 2006. J Clin Oncol 24:2932-47.

7.4.5. Dosing Schedule

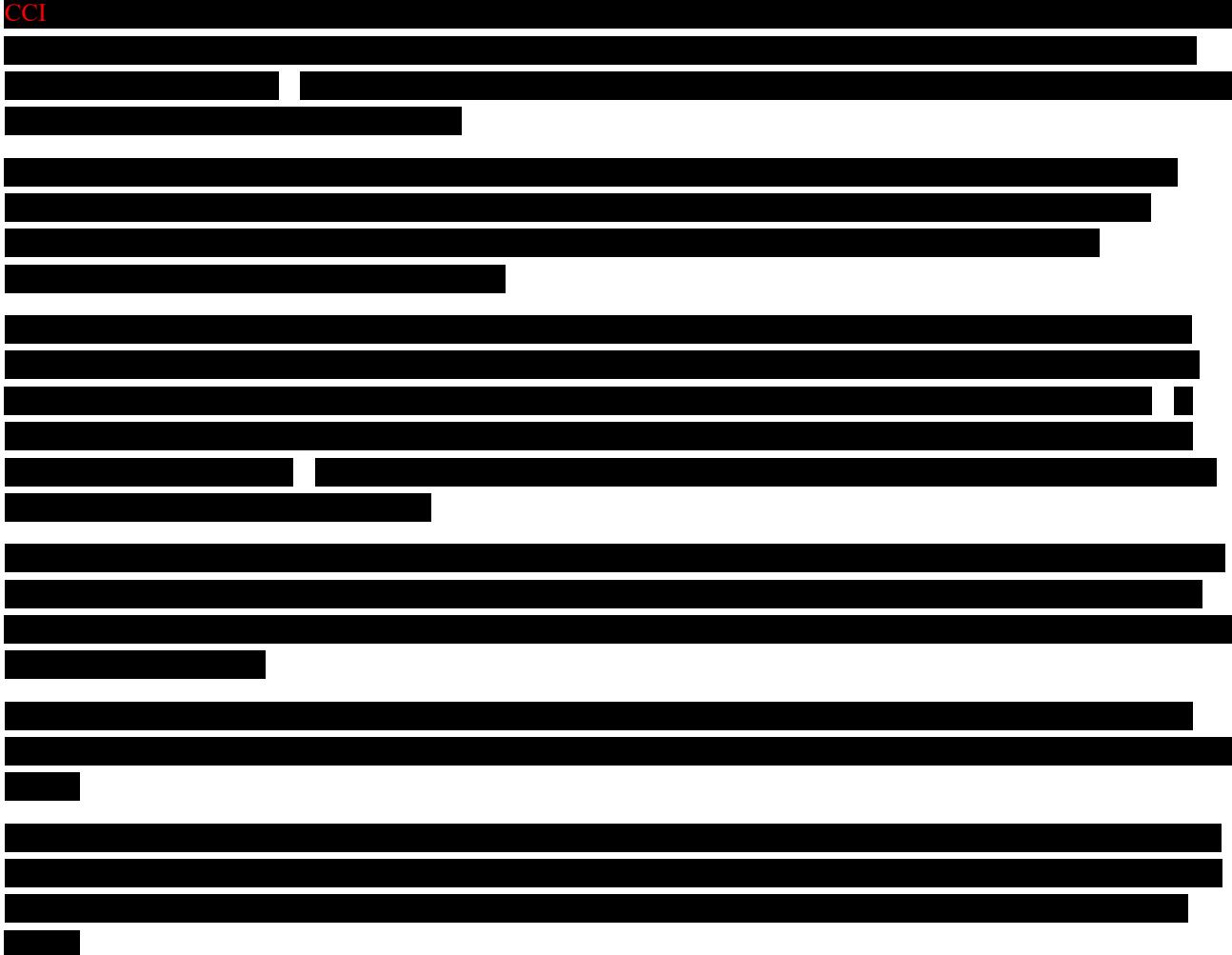
All patients receive IMMU-132 to be administered in the ongoing Phase II study at 10 mg/kg weekly for 2 consecutive weeks (2 weekly doses plus 1 week without treatment represents a single 3 week cycle). Treatment can be continued without a rest period in the absence of progression of disease or unacceptable toxicity. Planned deviations in treatment schedule are allowable up to 7 days due to holidays, vacations or personal reasons.

7.4.6. Dose Reduction and Termination Guidelines

The major toxicities of IMMU-132 are expected to be gastrointestinal symptoms and hematologic suppression. All patients are closely monitored over the course of their treatment. NCI CTCAE v4.0 is used to grade all adverse events and to provide the following dose reduction, delay or cessation guidelines in the event of treatment-related toxicity.

In the ongoing Phase II study, patients will receive 10 mg/kg IMMU-132 once weekly for 2 consecutive weeks followed by 1 week rest in cycles of 21 days, with treatment continued in the absence of progression or unacceptable toxicity. Neutropenia, GI toxicity, and alopecia were the most common toxicities in Phase I testing. All patients will be closely monitored over the course of their treatment, with NCI CTCAE v4.0 used to grade all adverse events and to provide dose reduction, delay or cessation guidelines in the event of toxicity.

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7.4.7. Biopsy specimens

At the discretion of treating physician, patients who have biopsiable lesion(s) and consented to biopsy(ies) will provide before and during the study as many tumor metastasis core biopsy samples (~0.2 to 0.5 cm³) as possible.

Procedure for Handling Core Biopsies

Samples should be shipped to Immunomedics to perform research assays intended to detect a variety of biomarkers, CCI. The purpose of this testing is to develop a database that will be used to assess biomarker status versus anti-tumor response to IMMU-132. Immunomedics recommends investigators participating in the collection of core biopsy samples consult with their institutional Pathology Department for the processing and handling of specimens. While some of the testing can be performed on conventionally preserved specimens (i.e., fixed in 10% buffered formalin), other assays require fresh tissue that should be snap frozen in liquid nitrogen or another suitable method typically used by Pathology Departments to prepare frozen tissues for RNA, protein, and microscopic examination. Thus, Immunomedics is requesting both formalin-fixed and fresh/frozen tissues according to the procedure described below:

If possible, obtain 4-6 core biopsy samples from sites of confirmed cancer. If 4 cores are obtained, 2 should be placed in 10% buffered formalin, the other 2 should be flash frozen (6 cores, split 3+3; 2 cores, split 1+1; odd number cores, process more by flash freezing).

- a. 10% buffered formalin: Place specimens in suitable leak-free container. Add enough formalin to cover completely. Ensure specimen is completely immersed. Sample can be stored at room temperature or in refrigerator prior to shipping. Sample should remain in the fixative at least overnight before shipping. When shipping, the vessel containing the tissue should be filled with formalin as much as possible so that tissue will remain in contact with the formalin.
- b. Flash-frozen: Tissues processed in this manner are best handled by the Pathology/Histology department. The core biopsies should be placed in a small amount of saline to transport. The tissue is then gently blotted dry, placed in a cassette containing a small amount of a cryoprotective embedding media (e.g., OCT compound). The cassette is then partially filled with this compound to cover tissue and then snap-frozen using a freezing spray or liquid nitrogen. Ship to Immunomedics frozen on dry ice.

8. STUDY EVALUATIONS

Safety and tolerability will be evaluated from adverse events, standard safety laboratories (CBC with differential and platelet count, serum chemistries, and urinalysis), physical examination, vital signs, and EKG. Adverse events will be classified according to the MedDRA system of preferred terms and system organ class, and all adverse events and abnormal laboratories will be classified for severity using NCI CTCAE v4.0 toxicity grades. Descriptive statistics will be used to characterize adverse events, cytopenias, and other abnormal laboratories.

Efficacy will be evaluated from CT scans (or MRI studies), using RECIST 1.1 criteria given in [Appendix 4](#) to classify tumor response, time to onset of objective response, duration of objective response, and time to progression. Overall survival will be determined.

Pharmacokinetics (PK) will be evaluated from serum samples using an ELISA assay performed by the Sponsor. The results will be characterized by standard PK parameters including peak and trough values, area-under-the-curve (AUC), maximum concentration (C_{max}), and half-life ($T_{1/2}$), if feasible, and summarized using descriptive statistics.

Immunogenicity will be determined from serum samples using an ELISA assay performed by the Sponsor for the occurrence of HAHA, that is, the presence of any human antibodies against IMMU-132. The occurrences of any positive HAHA results will be characterized by descriptive statistics.

The *UGT1A1* genotype (or another *UGT1* genotype) will be determined at baseline and compared to hematological toxicity (see [Appendix 5](#) for procedure for whole blood sample collection and shipping).

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9. ADVERSE EVENTS

All patients must be carefully monitored for AEs, including clinical laboratory tests. AEs should be assessed in terms of their seriousness, intensity, and relationship to the study drug. For consistency, events are to be graded using the CTCAE version 4.0.

An AE is any untoward medical occurrence; the event does not necessarily have a causal relationship with that treatment or usage. AEs include the following:

1. An exacerbation, or an unexpected increase in frequency or intensity of a pre-existing condition (other than condition under investigation), including intermittent or episodic conditions.
2. Significant or unexpected worsening or exacerbation of the condition/indication under investigation.
3. A suspected drug interaction.
4. An intercurrent illness.
5. Any clinically significant laboratory abnormality.

An AE does not include:

1. Anticipated day-to-day fluctuations of any pre-existing conditions, including the disease under study.
2. Signs and symptoms of the disease under study that do not represent a significant worsening or exacerbation.
3. Expected progression of the disease under investigation.

9.1. Serious Adverse Events

An AE that meets one or more of the following criteria/outcomes is classified as serious:

1. Fatal
2. Life threatening
3. Disabling/incapacitating
4. Results in hospitalization or prolongs a hospital stay
5. A congenital abnormality
6. Other important medical events may also be considered SAEs if they may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions not resulting in inpatient hospitalization, development of drug dependency or drug abuse).

An SAE does not include:

1. Progression of the underlying disease.
2. Hospitalization for a routine clinical procedure as stipulated by the protocol.

Hospitalization for non-medical reasons (i.e., social admissions, hospitalizations for social, convenience or respite care).

9.2. Reporting AEs/SAEs

The Investigator is to report all AEs directly observed or spontaneously reported by patients using concise medical terminology on the appropriate CRF. Each patient will be questioned about AEs at each clinic or evaluation visit, asking, for example, “Since your last clinic visit have you had any health problems?”

The AE reporting period begins with the first dose of study drug and ends with the last scheduled study evaluation or until all drug related toxicities and ongoing AEs have resolved, whichever is later.

All AEs/SAEs or exposure during pregnancy must be reported to Immunomedics or its designee, whether or not considered related to study medication using the appropriate forms/procedure. For SAEs, the Sponsor designated contact is to be notified by the Investigator, using the designated form, **within 24 hours of awareness of the event**. The initial report is to be followed by submission of more detailed SAE information within 5 calendar days of the event.

Clinical Research Department

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Morris Plains, NJ 07950

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Reporting requirements for AEs are summarized in the following table:

Table 8: Reporting Requirements for Adverse Events

	Reporting Time	Type of Report
SERIOUS	Within 24 hours	Initial report on designated SAE form
	Within 5 calendar days	Follow-up/Final report on designated form
NON-SERIOUS	Per CRF submission procedure	Appropriate CRF pages

9.3. Recording Information on AEs

All AEs, whether observed by the Investigator, elicited from, or volunteered by the patient, will be recorded including: duration, severity, relationship to the study medication, treatment, action taken with respect to the study medication and outcome. When possible, all events should be reported in diagnostic terms or the most acceptable medical terms in order to interpret safety information accurately.

The investigator must review all laboratory and test data and record any adverse events. The same format will be used as for other adverse events, regardless whether related to study therapy or not, including event severity grading, attribution, and resolution. A summary listing of all adverse events occurring during the past year on this study will be provided in progress reports reported to regulatory authorities.

The investigator will notify Immunomedics or its designee if he/she becomes aware at any time, during or following the study, of the occurrence of death or new malignancy involving the participant of a clinical trial, even though the event may not appear to be drug related.

9.4. Grading of AE Severity

The severity of AEs will be graded using the CTCAE Version 4.0. For each event, the highest severity grade should be reported. If a CTCAE criterion does not exist, the Investigator should use the grade or adjectives as described in [Table 9](#).

Table 9: Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Does not interfere with patient's usual function
Grade 2	Moderate	Interferes to some extent with patient's usual function
Grade 3	Severe	Interferes significantly with patient's usual function
Grade 4	Life-Threatening	Results in a threat to life or in an incapacitating disability

A severe reaction (e.g., a severe headache) would not be classified as serious unless it met one of the criteria for SAE(s) listed above.

9.5. Pregnancy

The Sponsor must be notified of any patient or partner of a male patient becoming pregnant during the study, and any pregnancy must be followed until completion or termination of pregnancy. In the case of a live birth, the “normality” of the newborn can be assessed at the time of birth. The “normality” of an aborted fetus can be assessed by gross visual inspection unless pre-abortion laboratory findings are suggestive of a congenital anomaly.

9.6. Follow-up of Unresolved AEs

All AEs should be followed until they are resolved, or the Investigator assesses them as chronic or stable or the patient's participation in the trial ends (i.e., until a final report is completed for that patient). Instructions for reporting changes in an ongoing AE during a patient's participation in the trial are provided in the instructions that accompany the AE CRFs.

In addition, all AEs and SAEs assessed by the Investigator as possibly related to the investigational medication/product should continue to be followed even after the patient's participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as “chronic” or “stable.” Resolution of such events is to be documented on the appropriate CRF.

10. STATISTICAL CONSIDERATIONS

10.1. Overview and Study Design

This is an open label, non-randomized Phase I/II study in patients with a variety of refractory/relapsed metastatic epithelial cancers. Prior use of irinotecan or other camptothecin-derived agents (e.g., topotecan) is allowed except when there is a known history of anaphylactic reaction or \geq Grade 3 GI toxicity to prior irinotecan. The primary objectives of Phase I are to evaluate the safety and tolerability of several dose levels of the antibody-drug conjugate IMMU-132 (hRS7-SN-38). The secondary objectives are to obtain preliminary information on efficacy, pharmacokinetics, and immunogenicity. The primary objective in Phase II is the evaluation of the safety and efficacy of IMMU-132 administered in 3-week treatment cycles, at a dose selected in Phase I; secondary objectives also include pharmacokinetics and immunogenicity.

The dose escalating phase has been completed and 12 mg/kg (on Days 1 and 8 of a 21-day cycle identified as the MTD. The Phase II expansion is ongoing at 10 mg/kg dose level, including enrollment currently focusing on 5 expansion cohorts (TNBC, non-TNBC, NSCLC, SCLC, UC).

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10.3. Safety Analysis

In general, all patients administered any dose of study drug will be included in the evaluation of safety.

Dose escalation continued for determination of the MTD, but for the Phase II portion of the protocol, the Sponsor will select 2 dose levels; one where at least 2 of 6 patients can complete the first cycle without \geq Grade 3 toxicity and the other a lower dose level.

The frequency and severity of adverse events (AEs) will be tabulated by MedDRA Preferred Term and System Organ Class (SOC) for each dose group. AEs will be classified using the MedDRA version 10 with severity assessed by NCI CTCAE v4 toxicity grades. The frequency of AEs will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term for each dose group. For this purpose, an AE that occurs more than once within each patient will be counted only once (at the worst CTCAE grade and relationship category). In the same fashion, similar AEs will be consolidated using the worst CTCAE grade and relationship category observed prior to classification into each MedDRA SOC.

AEs leading to death or to discontinuation from treatment, as well as all SAEs will be summarized separately, if appropriate. The reasons for discontinuation will also be summarized for each dose group using frequency distributions.

Both actual and change-from-baseline data on vital signs will be summarized using descriptive statistics by dose group for each study time-point.

Routine safety laboratories, based on hematology and serum chemistry data, will be listed by patient and summarized by descriptive statistics for each dose group, if appropriate. Laboratory test results will be graded according to CTCAE severity grade when applicable. The frequency distribution of the worst CTCAE grade observed will be tabulated in a shift table for each parameter by dose group.

Similarly, data on human anti-hRS7 antibody responses (HAHA) will be listed and summarized by descriptive statistics, if appropriate. In addition, PK data documenting the clearance of SN-38 in a select number of patients will be used to gain preliminary information on the conjugate's clearance properties, focusing on the area under the curve for total SN-38 (IgG-bound and free) and free SN-38. This value potentially could be helpful for assessing toxicity.

Furthermore, the UGT1A1 genotype will be determined at baseline and compared to hematological toxicity.

10.4. Efficacy Analysis

In general, all patients who were treated with at least one complete cycle of study drug and have available response assessment data will constitute the efficacy population and be included in the analysis of efficacy.

The objective response rate (ORR) and duration of response, will be tabulated and summarized by descriptive statistics for patients in each indication. Progression-free survival (PFS) and overall survival (OS) will be summarized, either by tabulation, or, if feasible, by Kaplan-Meier methodology. Other efficacy analysis may be performed as appropriate.

10.5. Other Evaluations

Because of the escalation design, the dose levels and the number of patients entered on each dose level in this study cannot be determined in advance. Pre - and post-dose serum samples for peak and trough drug concentrations will be collected in all patients. Once the MTD level is known, additional patients accrued to that level will have additional serum taken to better define the rate of clearance after each injection. This will provide adequate data to allow for the determination of potential drug accumulation with repeated dosing. Antibody pharmacokinetics will be evaluated in a separate report based on blood levels of IMMU-132 from a subgroup of patients as measured by the

Sponsor in order to characterize concentration levels during treatment (See Study Calendar for time points).

Descriptive statistics will be used to summarize both peak and trough values at each infusion as well as values measured at other time-points. Formal pharmacokinetic analysis based on a non-compartmental model will be performed on patients with adequate serum concentration data, if feasible. Additional analyses may also be performed to evaluate serum levels of SN-38, if feasible, and to study the correlations between IMMU-132 concentrations and various treatment outcomes.

10.6. Interim Analysis

No formal interim analysis is planned during the course of this study.

11. TREATMENT COMPLIANCE

IMMU-132 will be administered at scheduled study centers under the supervision of the Investigator or sub-investigator(s). The pharmacist will maintain records of study drug receipt, preparation, and dispensing, including the applicable lot numbers, patient's height, weight and total drug administered in milligrams. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents and on appropriate CRF.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor has ethical, legal and scientific obligations to follow this study carefully in a detailed and orderly manner in accordance with established research principles and applicable regulations. Monitoring visits to the study site will be conducted periodically during the study to ensure that good clinical practice (GCP) and all aspects of the protocol are followed. The trial site may also be subject to review by the IRB/IEC, to quality assurance audits performed by Immunomedics, and/or to inspection by appropriate regulatory authorities. Investigator(s) and their relevant personnel must agree to be available and participate with visits conducted at a reasonable time in a reasonable manner, and the Investigator/Institution must guarantee direct access to source documents by Immunomedics and its designee, and appropriate regulatory authorities.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs and must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

13. DATA HANDLING AND RECORD KEEPING

13.1. Case Report Forms

A CRF is required and must be completed for each enrolled patient. The completed original CRFs are the sole property of Immunomedics and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Immunomedics.

It is the Investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the Investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true.

At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Patient source documents are the physician's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts. In some cases, a portion of the source documents for a given study site may be the CRFs. The Investigator must agree which items will be recorded in the source documents and for which items the CRF will stand as the source document.

All entries in the CRF should be made legibly with black ballpoint pen. Corrections to the CRF must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect data. The correction must be initialed and dated by the person making the correction (ICH E6 4.9.3).

13.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Immunomedics, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition. The records must be retained by the Investigator until 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, study records may be retained for a longer period if required by local regulations. The Sponsor is responsible for informing the Investigators when these documents need no longer be retained.

If the Investigator relocates, retires, or for any reason withdraws from the study, Immunomedics should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Immunomedics. The Investigator must obtain Immunomedics written permission before disposing of any records.

14. ADMINISTRATIVE REQUIREMENTS

14.1. Good Clinical Practice

The study will be conducted in accordance with the ICH for GCP and the appropriate local and national regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study medications as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files for this study should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

14.2. Ethical Considerations

This study is planned to be conducted both in the North America and in Europe, and European regulatory agencies require that the study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The trial will be performed in accordance with ICH GCP guidelines, the Declaration of Helsinki, 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions (as mandated for European trials), and applicable local regulatory requirements and laws. In the United States, ethical protection is provided by compliance with GCPs as described in ICH and 21 CFR 50 (Protection of Human Subjects).

The Institutional Review Board (IRB) and the Institutional Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The Investigator is responsible for providing their IRB/IEC with any required study documents, progress reports and safety updates and is responsible for notifying the IRB/IEC promptly of all SAEs occurring at the site.

All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Immunomedics or the designee.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC and Immunomedics or its designee in writing within 5 working days after the implementation.

14.3. Patient Information and Consent

It is the responsibility of the Investigator to give each patient (or the patient's acceptable representative) full and adequate verbal and written information regarding the objective and procedures of the trial including the possible risks and benefits involved. Written patient information, approved by the IRB/IEC, must be given to each patient before any trial-related procedure is undertaken. During the consent process, the patient must be informed about their right to withdraw from the trial at any time. The patient must also be given ample time to read the written informed consent form and have all study-related questions answered to the satisfaction of the patient (or the patient's legally acceptable representative). It is the responsibility of the Investigator to obtain a signature from each patient, the patient's legally acceptable representative if applicable, and from the persons conducting the informed consent discussion prior to undertaking any trial-related procedure. The patient (or the patient's legally acceptable representative) must be

given a copy of the signed and dated informed consent form. The Investigator is also responsible for providing the patient (or the patient's legally acceptable representative) with any clinical trial updates that may affect the subject's willingness to continue participation in the study. The informed consent process must be documented in the patient's medical or source chart.

The written patient information must not be changed without prior approval by Immunomedics and the IRB/IEC.

Per ICH E6 4.3.3, it is recommended that the Investigator notify the patient's primary care physician of the subject's participation in the trial if the subject agrees to the Investigator informing the primary care physician.

14.4. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by Immunomedics, and given approval by the IRB/IEC, and the appropriate regulatory authorities.

Modifications to the protocol should not be made without agreement of both the Investigator and the Immunomedics. Changes to the protocol will require written IRB/IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to the patients. The IRB/IEC may provide, if applicable, regulatory authorities permit, expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB/IEC.

Immunomedics will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact Immunomedics, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the patient's CRF and source documentation.

14.5. Site Monitoring and On-Site Audits

Monitoring and auditing procedures developed by Immunomedics or its designee will be followed, in order to comply with GCP guidelines. On-site review of patient's CRFs for completeness and clarity, cross-checking with source documents, and review of regulatory documents will be performed. All available source documents should be obtained by the Investigator and provided to the Sponsor or designee at each monitoring visit.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications.

Regulatory authorities, the IRB/IEC, and/or Immunomedics clinical quality assurance group or designee may request access to all source documents, patients' CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

14.6. Patient Data Protection

Privacy Act Compliance. Information collected in this clinical trial is subject to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) as described in 45 CFR 160 and 45 CFR 164. The study Investigator is responsible for informing patients of their rights under HIPAA and obtaining any necessary HIPAA authorizations. In compliance with the provisions of

that policy, Immunomedics or designee will not collect any protected health information and will only collect de-identified health information. Any clinical study information referred to in this section is understood to be compliant with the provisions of the Privacy Act.

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the conduct of this study will be used by Immunomedics or designee in connection with the development of the study drug. The study Investigator is obliged to provide Immunomedics or designee with complete test results and all data developed in this study. This information may be disclosed to other physicians participating in the study, to the FDA, or to national and local health authorities. To ensure compliance with all current Federal Regulations and the ICH/GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, Immunomedics, designee, and the IRB/EC for each study site.

14.7. Financial Disclosure

In accordance with 21 CFR Part 54, FDA requires that certain financial interests and arrangements between sponsors of clinical investigations be disclosed in marketing applications.

Since the results of this study may eventually be used in a marketing application, compliance with this Federal statute is essential. In order to comply with the provisions of this regulation, Immunomedics requests that every Investigator and sub-Investigator mentioned on FDA Form 1572 fill out a financial disclosure form. Under the provisions of 21 CFR Part 54, the term clinical Investigator includes the spouse and each dependent child of the Investigator.

The provisions of 21 CFR Part 54 specify disclosure of significant equity interests in the Sponsor that exceed \$50,000, or significant payments of other sorts made by the Sponsor to the Investigator that have a monetary value of more than \$25,000, exclusive of the costs of conducting the clinical study or other clinical studies (e.g., grants to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation), during the time the clinical Investigator is carrying out the study or for 1 year following the completion of the study. If a change in financial interest occurs throughout the study, the Investigator is obligated to notify Immunomedics.

To assist Immunomedics in providing the FDA with the required information, please complete the financial disclosure form and return the original signed copy. All information provided in the financial disclosure form will be regarded as strictly confidential and will only be disclosed to the FDA.

14.8. Sponsor Discontinuation Criteria

Immunomedics reserves the right to discontinue the trial at any time but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within a time period set by the Sponsor. As directed by the Sponsor, all study materials will be collected and all CRFs completed to the greatest extent possible.

15. DISSEMINATION AND PUBLICATION OF RESULTS

The conditions regulating dissemination of the information derived from this clinical study are described in the Clinical Trial Agreement.

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APPENDIX 1

List of Standard Treatments for Each Cancer Type

Esophageal cancer	<p>Refractory to or relapsed after at least one chemotherapy regimen containing one or more of the following agents: 5 FU, Cisplatin, Epirubicin, Capecitabine, Irinotecan, Oxaliplatin, Vinorelbine; Commonly used standard regimens in the appropriate lines of treatment are listed below.</p> <p>Epirubicin + Cisplatin + 5-FU (ECF) Epirubicin + Cisplatin + Capecitabine (ECX) Epirubicin + Oxaliplatin + 5-FU (EOF) Epirubicin + Oxaliplatin+ Capecitabine (EOX) Capecitabine + Oxaliplatin (CAPOX, XELOX) Cisplatin / Carboplatin + Paclitaxel Gemcitabine + 5 FU + Leucovorin Liposomal Doxorubicin + Cisplatin + 5 FU 5-FU + Leucovorin + Oxaliplatin 5-FU + Leucovorin + Irinotecan 5-FU + Cisplatin Docetaxel + Cisplatin Docetaxel + Irinotecan Cisplatin + Irinotecan Mitomycin + Irinotecan Paclitaxel / Docetaxel Irinotecan Vinorelbine Etoposide Trastuzumab Erlotinib</p>
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Head and neck cancer

Refractory to or relapsed after at least one chemotherapy regimen containing one or more of the following agents: 5 FU, platinum agents, taxanes, gemcitabine, Epirubicin, ifosfamide, bleomycin, methotrexate, Erlotinib and cetuximab; Commonly used standard regimens in the appropriate lines of treatment are listed below.

Cisplatin or Carboplatin + 5 FU + Cetuximab
Cisplatin or Carboplatin + Cetuximab
Cisplatin or Carboplatin + docetaxel or paclitaxel
Paclitaxel + Cetuximab
Docetaxel + Cisplatin + 5 FU (TPF)
Cisplatin / Carboplatin + 5-FU
5-FU + Cisplatin + Bleomycin
5-FU + Cisplatin + Bleomycin + Epirubicin
5-FU + Cisplatin + Bleomycin + Epirubicin + Mitomycin
Cisplatin + Docetaxel + Erlotinib
Cisplatin + Gemcitabine
Cisplatin + Erlotinib
Cisplatin
Carboplatin
Oxaliplatin
5-FU
Docetaxel
Paclitaxel
Gemcitabine
Ifosfamide,
Bleomycin,
Methotrexate
Cetuximab

Gastric cancer	<p>Refractory to or relapsed after at least one Fluoropyrimidine-based, platinum-based or Taxane-based single agent, doublet or triplet regimen. The chemo regimen may include one or more of the following agents: Epirubicin, Cisplatin, Oxaliplatin, 5FU, Irinotecan, Paclitaxel, Capecitabine, and Methotrexate. Commonly used standard regimens in the appropriate lines of treatment are listed below.</p> <p>Epirubicin + Cisplatin + 5-FU (ECF) Epirubicin + Cisplatin + Capecitabine (ECX) Epirubicin + Oxaliplatin + 5-FU (EOF) Epirubicin + Oxaliplatin + Capecitabine (EOX) Docetaxel + Cisplatin + 5-FU (DCF) Docetaxel + Cisplatin Paclitaxel + Cisplatin 5-FU + Leucovorin + Irinotecan (FOLFIRI) 5-FU + Leucovorin + Oxaliplatin (FLO) 5-FU + Leucovorin + Oxaliplatin (FUFOX) +Cetuximab 5-FU + Doxorubicin + Methotrexate (FAMTX) 5-FU + Cisplatin 5-FU + Leucovorin + Irinotecan Capecitabine Cisplatin + Capecitabine Cisplatin + Irinotecan Irinotecan + Docetaxel + Oxaliplatin</p>
Colon cancer	<p>Refractory to or relapsed after at least one chemotherapy regimen containing one or more of the following agents: 5 FU, Leucovorin, Capecitabine, Irinotecan, Oxaliplatin, Bevacizumab, Cetuximab and Panitumumab; Commonly used standard regimens in the appropriate lines of treatment are listed below.</p> <p>5-FU + Leucovorin + Oxaliplatin (FOLFOX) FOLFOX4 + Bevacizumab /Cetuximab FOLFOX6 + Bevacizumab mFOLFOX6 ± Bevacizumab /Panitumumab 5-FU + Leucovorin + Oxaliplatin (FUFOX) 5-FU + Leucovorin + Irinotecan (FOLFIRI) 5-FU + Leucovorin ± Bevacizumab FOLFIRI + Bevacizumab FOLFIRI + Cetuximab /Panitumumab 5-FU + Leucovorin + Oxaliplatin+ Irinotecan (FOLFOXIRI) Capecitabine + Oxaliplatin (CAPOX, XELOX) Capecitabine + Oxaliplatin Irinotecan (COI) Capecitabine + Irinotecan (XELIRI) Capecitabine + Irinotecan (XELIRI)+ Bevacizumab Capecitabine + Oxaliplatin (XELOX) + Bevacizumab Capecitabine ± Bevacizumab Irinotecan + 5-FU + Leucovorin (IFL) Irinotecan + 5-FU + Leucovorin (IFL) + Bevacizumab Irinotecan + Oxaliplatin (IROX) Irinotecan ± Cetuximab Cetuximab / Panitumumab Cetuximab +Bevacizumab + Irinotecan (CBI) Cetuximab +Bevacizumab (CB) Uracil +Tegafur + Leucovorin</p>

Rectal cancer	<p>Refractory to or relapsed after at least one treatment with the following Fluoropyrimidine-based or Platinum based chemotherapy regimens with or without biological agents or chemo-radiation. Commonly used standard regimens in the appropriate lines of treatment are listed below.</p> <p>5 FU + Leucovorin ± Bevacizumab FOLFOX± Bevacizumab /Panitumumab Capecitabine ± Bevacizumab Capecitabine + Oxaliplatin (CapOX) ± Bevacizumab /Panitumumab FLOX FOLFIRI± Cetuximab /Panitumumab /Bevacizumab FOLFOXIRI Irinotecan Irinotecan + Oxaliplatin (IROX) Irinotecan + Cetuximab /Panitumumab Cetuximab /Panitumumab 5-FU + Leucovorin + Radiation Therapy (RT) 5-FU + Oxaliplatin + RT 5-FU + RT Capecitabine + RT XELOX + RT</p>
Hepato-cellular carcinoma	<p>Refractory to or relapsed after at least one of the following chemotherapeutic/targeted agents and underwent locoregional approaches including trans-arterial chemo-embolization or radio-embolization. Commonly used regimens as the appropriate lines of treatment are listed below:</p> <p>Sorafenib Capecitabine Doxorubicin Bevacizumab 5-FU + Leucovorin Capecitabine + Oxaliplatin (XELOX) Cisplatin + Gemcitabine Gemcitabine + Oxaliplatin + Bevacizumab (GEMOX-B)</p>

Ovarian cancer	<p>Refractory to or relapsed after at least one treatment with platinum based and Taxane based doublets/Pegylated Doxorubicin or Gemcitabine or Topoisomerase inhibitor - based regimen or biological agents. Commonly used regimens as the appropriate lines of treatment are listed below:</p> <p>Carboplatin + Paclitaxel Cisplatin + Paclitaxel Carboplatin + Gemcitabine Pegylated liposomal Doxorubicin Pegylated liposomal Doxorubicin + Gemcitabine, alternating with Cisplatin + Cyclophosphamide Cyclophosphamide + Bevacizumab Topotecan Etoposide Gemcitabine Vinorelbine Ifosfamide 5-FU + Leucovorin Bevacizumab</p>
Non-small cell lung cancer	<p>Refractory to or relapsed after at least one treatment with chemotherapy regimen containing one or more of the following agents: Paclitaxel, Docetaxel, Gemcitabine, Pemetrexed, Vinorelbine, Topotecan, Erlotinib, Sunitinib, Cetuximab and anti-PD-1 antibody. Commonly used regimens include platinum- based doublets, Taxane- based / Pemetrexed, Gemcitabine-based / Vinorelbine-based regimens and targeted agents as listed below.</p> <p>Cisplatin + Paclitaxel Cisplatin + Gemcitabine Cisplatin + Docetaxel Carboplatin + Paclitaxel Carboplatin + Docetaxel Carboplatin + Gemcitabine Cisplatin + Vinorelbine Carboplatin + Vinorelbine Gemcitabine + Docetaxel Gemcitabine + Vinorelbine Carboplatin + Pemetrexed Cisplatin + Pemetrexed Carboplatin + Paclitaxel + Bevacizumab Paclitaxel + Carboplatin + Gemcitabine Cisplatin + Gemcitabine + Bevacizumab Cisplatin + Vinorelbine + Cetuximab Docetaxel + Bevacizumab Pemetrexed + Bevacizumab Erlotinib + Bevacizumab Gefitinib ± platinum doublet chemotherapy</p>

Small cell lung cancer	Refractory to or relapsed after at least one platinum-based chemotherapy regimen or one of the following combinations; Commonly used regimens as the appropriate lines of treatment are listed below: Cisplatin Cisplatin + Etoposide (EP) Carboplatin + Etoposide (EP) Irinotecan + Cisplatin Irinotecan + Carboplatin Cisplatin / Carboplatin + Etoposide + Ifosfamide Cisplatin / Carboplatin + Etoposide + Paclitaxel Cyclophosphamide + Adriamycin + Vincristin (CAV)
Pancreatic cancer	Refractory to or relapsed after at least one Gemcitabine-based or Fluoropyrimidine-based chemotherapy with or without targeted agents. Commonly used regimens as the appropriate lines of treatment are listed below: Gemcitabine Gemcitabine + Capecitabine (GEM-CAP) Gemcitabine + Docetaxel + Capecitabine (GTx) Gemcitabine + Oxaliplatin Gemcitabine + Erlotinib Gemcitabine + Cisplatin Capecitabine + Erlotinib Oxaliplatin + 5-FU + Leucovorin (OFF) 5-FU + Leucovorin + Oxaliplatin+ Irinotecan (FOLFIRINOX) Abraxane (nab-paclitaxel)
Renal Cell Cancer	Refractory to or relapsed after at least one treatment with a regimen containing one or more of the following targeted agents and or immunotherapeutic agents. Commonly used regimens as the appropriate lines of treatment are listed below: Sorafenib Sunitinib Temirolimus Everolimus Interferon α -2b Interleukin-2 Interleukin-2 + Interferon α -2a Bevacizumab Bevacizumab + Interferon α -2a
Urothelial Cancer	Refractory to or relapsed after at least one treatment with a regimen containing one or more of the following chemotherapeutic agents. Commonly used regimens as the appropriate lines of treatment are listed below: Gemcitabine + Cisplatin Methotrexate (MTX) + Vinblastine + Adriamycin+ Cisplatin (MVAC) Carboplatin or Taxane based regimens Cisplatin Cisplatin + RT Cisplatin + 5 Fu Carboplatin + Paclitaxel Gemcitabine + Paclitaxel Gemcitabine + Cisplatin + Paclitaxel Mitomycin + 5 FU Pemetrexed

Triple-Negative Breast cancer

Refractory to or relapsed after at least one chemotherapy regimen containing one or more of the following agents: Doxorubicin, Epirubicin, Pegylated liposomal Doxorubicin, Docetaxel, Paclitaxel, Albumin-bound Paclitaxel (Abraxane), Gemcitabine, Vinorelbine, Vinblastine, Capecitabine, Ixabepilone (Ixempra), Tamoxifen, Goserelin, Anastrozole, Letrozole, Exemestane, Fulvestrant, Trastuzumab and Lapatinib. Commonly used standard regimens in the appropriate lines of treatment are listed below.

AC (Doxorubicin + Cyclophosphamide)
TAC (Docetaxel +Doxorubicin + Cyclophosphamide)
AC followed by Paclitaxel
AC followed by Docetaxel
Dose-dense AC followed by Paclitaxel
TC (Docetaxel + Cyclophosphamide)
FAC or CAF (Fluorouracil + Doxorubicin + Cyclophosphamide)
FEC or CEF (Cyclophosphamide + Epirubicin + Fluorouracil)
CMF (Cyclophosphamide + Methotrexate + Fluorouracil)
A followed by T followed by C (Doxorubicin followed by Paclitaxel followed by Cyclophosphamide)
FEC followed by T (Docetaxel)
EC (Epirubicin +Cyclophosphamide)
AT (Doxorubicin + Paclitaxel / Docetaxel)
EP (Epirubicin + Paclitaxel)
Docetaxel + Capecitabine
GT (Gemcitabine +Paclitaxel)
Ixabepilone + Capecitabine
Paclitaxel + Bevacizumab
Docetaxel + Bevacizumab
Capecitabine + Bevacizumab
Eribulin Tamoxifen + Goserelin,± Zoledronic Acid
Anastrozole + Goserelin ,± Zoledronic Acid
AC→TH AC followed by Paclitaxel+ Trastuzumab
TH Docetaxel + Trastuzumab
TCH Docetaxel + Carboplatin+ Trastuzumab
Trastuzumab + Paclitaxel
Trastuzumab + Anastrozole
TPC Trastuzumab + Paclitaxel + Carboplatin
Trastuzumab +Capecitabine
Trastuzumab +Docetaxel+ Capecitabine
Lapatinib + Capecitabine
Lapatinib+ Paclitaxel

Prostate cancer	Refractory to or relapsed after at least one regimen containing one or more of the following agents: Docetaxel, Mitoxantrone, Cabazitaxel, Sipuleucel-T, Cyclophosphamide, Vinblastine, Vinorelbine, Enzalutamide, Abiraterone Acetate, Radium 223, and Androgen Deprivation Therapy. Commonly used standard regimens in the appropriate lines of treatment are listed below. Docetaxel + Prednisone Docetaxel + Estramustine Mitoxantrone + Prednisone Estramustine + Vinblastine Satraplatin + Prednisone Estramustine + Cyclophosphamide Cabazitaxel + Prednisone Sipuleucel-T Cyclophosphamide Vinblastine Vinorelbine
Cervical Cancer	Cisplatin Cisplatin + 5 FU Cisplatin + Paclitaxel Paclitaxel, Vinorelbine Topotecan Cisplatin + Topotecan Cisplatin + Vinorelbine Cisplatin + Gemcitabine
Endometrial Cancer	Doxorubicin + Cisplatin Cisplatin + Ifosfamide + Mesna (CIM) Megesterol Acetate Tamoxifen Carboplatin Paclitaxel Topotecan Dactinomycin Carboplatin + Paclitaxel Doxorubicin+ Cisplatin+ Paclitaxel Ifosfamide+ Paclitaxel+Mesna

Glioblastoma Multiforme	<p>Refractory to or relapsed after at least one chemotherapy regimen containing one or more of the following agents:</p> <p>Irinotecan, Temozolomide, Bevacizumab, Everolimus, Carmustine, Lomustine, Fotemustine, Procarbazine, Vincristine, Carboplatin and Cisplatin. Commonly used standard regimens in the appropriate lines of treatment are listed below:</p> <p>PCV (Procarbazine, lomustin + Vincristine) Temozolomide +RT Irinotecan + Bevacizumab Carboplatin + Bevacizumab Carboplatin + Teniposide Cisplatin + Etoposide</p>
Thyroid Cancer (Papillary)	<p>Refractory to or relapsed after at least one regimen containing one or more of the following agents: Radioiodine, Sorafenib, Axitinib, Everolimus, Pazopanib, Sunitinib, Vandetanib, Cabozantinib, and Lenvatinib.</p>

Note: The lists include regimens recommended by the NCCN guidelines as well as used in documented clinical trials. Patients who received other treatment combination may also be eligible for enrollment after obtaining approval from the medical monitor.

APPENDIX 2

Performance Status Evaluation

Percent	Karnofsky Performance Status Description	Level	ECOG*
100	Normal; no complaints, no evidence of disease	0	Normal Activity
90	Able to carry on normal activity; minor signs or symptoms of disease		
80	Normal activity with effort; some signs or symptoms of disease	1	Symptoms but ambulatory
70	Cares for self; unable to carry on normal activity or do active work		
60	Requires occasional assistance but is able to care for most needs	2	In bed < 50% of time
50	Requires considerable assistance and frequent medical care		
40	Disabled; requires special care and assistance	3	In bed \geq 50 % of time
30	Severely disabled; hospitalization is indicated although death is not imminent		
20	Very sick; hospitalization is necessary	4	100% bedridden
10	Moribund; fatal processes progressing rapidly		
Abstracted from: Karnofsky DA, et al., Cancer. 1948; 1:634-656		*ECOG: Eastern Cooperative Oncology Group	

APPENDIX 3 **Procedure for Collection, Storage, and Shipment of Serum Samples**

It is important that serum and not plasma be sent

Serum Samples Obtained for Measurement of:	Minimum Required Serum Volume for Each Time-point:	Documentation to be Completed and Sent with Samples:
HAHA (human anti-antibodies)	1.5 mL	HAHA Levels
IMMU-132 serum levels /Free SN38	1.5 mL	PK Levels
Conjugate levels	1.5 mL	PK Levels SN38 conjugate

A. Collection Schedule:

As per protocol.

B. Collection, Labeling, Storage and Shipment:

1. Blood for serum IMMU-132 (PK) and Human Anti-Human Antibody (HAHA) concentrations.
 - a) Four (4) mL of blood will be drawn into a glass vacutainer with a red stopper.
 - b) Allow blood to clot at room temperature.
 - c) Refrigerate clotted sample for 30 minutes at 4°C to contract the clot.
 - d) Centrifuge at 1000 rpm at 4°C for ten minutes to extract additional serum.
 - e) Pipette all serum but not more than 1.5 mL into a 2 mL screw cap cryotube (to be supplied by Immunomedics).
 - f) Label each sample using stickers provided by the Sponsor. They must bear the following information:

Timepoint – Sample

Protocol No.: IMMU-132-01

Patient Initials: _____

Patient No.: _____ - _____

Date Drawn: _____ - _____ - _____

Time Drawn: _____

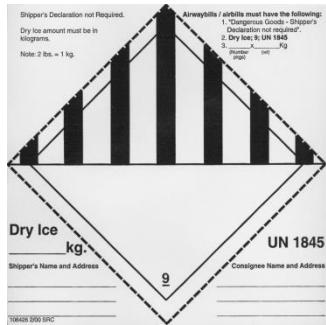
2. Storage

- a) Samples should be stored frozen at -20°C or below until time of shipment.

3. Shipment

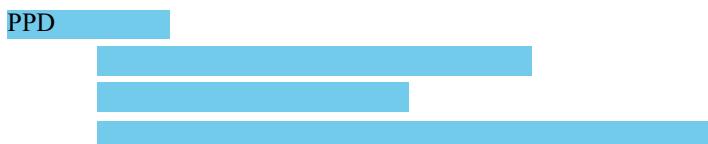
- a) Samples should be accumulated and shipped at appropriate intervals on a Monday or Tuesday.
- b) Log samples in on the appropriate **Serum Pharmacokinetics** and/or **HAHA** Worksheet(s). This paperwork must be included with all specimen shipments.
- c) Labeled cryotubes containing serum samples for HAHA and PK evaluation must be wrapped with enough absorbent material to absorb all liquid completely in case of leakage. Place wrapped vials in a leak resistant clear pouch or sealable pack.
- d) The specimens must be placed in an insulating (primary) container with dry ice. Place the insulated mailer inside a sturdy outer corrugated (secondary) container and write, "DIAGNOSTIC SPECIMEN," on the box.

If using dry ice to ship specimens, International Air Transport Association (IATA) regulations require that the following packaging markings include:



- "Dry Ice"
- "UN 1845"
- Net quantity of dry ice in kilograms
- Name and address of BOTH the shipper and recipient (An air bill does not fulfill this requirement)

Address package with return address to:



- e) Shipments must be made by Federal Express. The airway bill number must be transmitted to the CRA by phone before shipment of specimens.



IMMUNOMEDICS[®], INC.

HAHA Levels Worksheet

Protocol #: IMMU-132-01 **Patient Initials:** **Patient ID #:** -

F M L

(Site #) (Pt #)

Return To: _____ Fax No. _____

PLEASE INCLUDE A COPY OF THIS PAGE WITH EVERY SHIPMENT
RECORD ONLY THOSE SAMPLES INCLUDED IN THE SHIPMENT
[ORIGINAL PAGE(S) SHOULD BE RETAINED IN PATIENT BINDER]

Sampling Times	Collection Date (mm/dd/yy)	Collection Time [as 14:20 = 2:20PM]	Date & Time Sample Frozen (mm/dd/yy)	Shipping date* (mm/dd/yy)
CCI				
* If samples are shipped separately indicate date each sample was shipped in box(es) above. If the multiple samples are shipped on the same date, simply indicate the collection information as required for each sample, check the shipment date box [✓] and record the date of that shipment below:				
Shipment date:	Shipped by:			

Send Specimens
to:

PPD





IMMUNOMEDICS[®], INC.

Antibody IgG and Intact Conjugate PK Levels Worksheet

Protocol #: IMMU-132-01 **Patient Initials:** **Patient ID #:** - -

F M L

(Site #) (Pt #)

Return To: _____ Fax No. _____

Fax No.

PLEASE INCLUDE A COPY OF THIS PAGE WITH EVERY SHIPMENT
RECORD ONLY THOSE SAMPLES INCLUDED IN THE SHIPMENT
[ORIGINAL PAGE(S) SHOULD BE RETAINED IN PATIENT BINDER]

* If samples are shipped separately indicate date each sample was shipped in box(es) above. If the multiple samples are shipped on the same date, simply indicate the collection information as required for each sample, check the shipment date box [✓] and record the date of that shipment below:

Shipment date: _____ Shipped by: _____

Send Specimens to:

PPD

APPENDIX 4

Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

New Response evaluation criteria in Solid tumors: Revised RECIST criteria [EJC 4 (2): 228-247, 2009] are summarized below.

Measurable/Non-Measurable Lesions. Each tumor lesion or site of disease identified at baseline is categorized as either a measurable lesion or a non-measurable lesion according to the following definitions.

Lesion Type	Qualifying Definition
Measurable	<p>Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:</p> <ul style="list-style-type: none">• 10mm by CT scan (CT scan slice thickness no greater than 5 mm.)• 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)• 20mm by chest X-ray. <p>Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15mm 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.</p>
Non-Measurable	All other lesions, including small lesions (longest diameter < 10mm or pathological lymph nodes with 10 to < 15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment: Bone lesions: • Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. • Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable. Cystic lesions: • 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.

Lesions with prior local treatment: • Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. All measurements should be recorded in

metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Target Lesions. Target lesions are selected from measurable lesions at baseline on the basis of their size and suitability for accurate repeated measurements by imaging techniques or clinical judgment. The sum of the longest diameter (LD) for all target lesions provides a quantitative means of characterizing objective tumor response to treatment as follows:

Evaluation Criteria Used for Categorizing Treatment Response of Target Lesions	
Response Category	Definition
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	> 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	> 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Non-Target Lesions. Non-target lesions are other lesions (or sites of disease) not identified as target lesions at baseline. These include both non-measurable lesions as well as measurable lesions exceeding the maximum number allowed per organ or in total. The response of non-target lesions to treatment is evaluated on the basis of their presence or absence as follows:

Evaluation Criteria Used for Categorizing Treatment Response of Non-Target Lesions	
Response Category	Definition
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker levels initially above upper limits of normal
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Incomplete Response/Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

New Lesions. New lesions not present at baseline should be recorded at time of occurrence.

Overall Response. The 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). To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once with a minimum interval of at least 6-8 weeks from study entry

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR*
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD**
Any	PD	Yes or No	PD**
Any	Any	Yes	PD**

*When evaluation of possible CR depends on distinguishing residual disease from normal tissue, fine needle aspirate/biopsy is recommended before confirming the complete response status.

**Patients without objective evidence of disease progression, but with globally deteriorated health status requiring discontinuation of treatment should be classified as having "symptomatic deterioration" at that time, with every effort made to document the objective progression, even after discontinuation of treatment.

Duration of 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). 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.

APPENDIX 5

Procedure for Collection, Storage, and Shipment of Whole-Blood Sample for UGT1A1 Genotyping

Immunomedics will provide shipping boxes with the appropriate materials for collecting the sample and shipping it to Immunomedics. The kit includes:

- (1) Insulated Shipper (Outer Packaging)
- (1) Plastic Shipping Tubes (50 mL secondary containers) + Cap
- (1) Glass Vacutainer Blood Collection tube inside the secondary shipping tube.
- (4) 24-oz Gel Packs (do NOT freeze)
- Bubble Wrap
- Packing List Envelope with instructions and FedEx shipping form and label.

Blood Draw and Packing Instructions:

The day before:

1. Place gel packs from each box to be shipped into a refrigerator overnight.

Day of the blood draw:

1. Draw 1 x 2 mL vacutainer tube per patient on a Cycle 1 Day 1 visit.
2. Label all the tube with Immunomedics study identification number [site ID – patient number]
3. The blood samples can stay at ambient temperatures until loaded into shipping container if shipment takes place on the same day. Samples may be stored in refrigerator up to 7 days until shipped. These samples are NOT to be frozen before or during shipment
4. Multiple samples can be batched together per shipping container if shipped within 7 days. Make sure each sample is labelled appropriately if multiple samples are in a container.
5. Put the cold gel packs back into the shipping container. Do NOT use dry ice.

6. Place the vacutainer tube into the 50 mL secondary container and screw the cap back on tightly.
7. Place the secondary container in a biohazard bag and seal the bag.
8. Place the tube back into the styrofoam holder.
9. Pack in the bubble-wrap around the tubes to hold in place during transport.
10. Seal up the box and fill out the FedEx form for shipping (Immunomedics will be charged for the shipping costs).
11. Send FedEx Priority Overnight.

APPENDIX 6

Tissue Sample Instructions and Worksheet

Procedure for Submitting Samples for Tissue Testing for IMMU-132

1. Tissue testing can be done on paraffin embedded tumor biopsies or other paraffin embedded archival tissue (e.g. lymph nodes). Smears, touch preps or other cytology specimens are NOT acceptable.
2. Send the at least 10 **unstained** histologic sections on positively charged immunohistochemistry slides (preferably Vision Biosystems slides) OR paraffin block. Your hospital's histology lab is familiar with these terms and should be able to provide this material. If paraffin block is sent, any unused sample will be sent back to you. If you have any questions, please call the Clinical Research Department below.
3. ***Label the samples with the patient's study identification # and initials and patient's diagnosis.***
4. Notify your CRA that samples are being shipped. Tissue Sample Shipment forms will be provided, and a copy of this form should be included with the shipment.
5. Ship using Federal Express overnight (airbills provided by Immunomedics).
6. Shippers must also comply with all applicable local, state and federal laws governing packing, marking and labeling of shipments of blood and blood products regardless of whether they are infectious. Blood, urine and Biological Substance, Category B (UN 3373), shipments may not be deposited in a FedEx Express® Drop Box.
7. Refer to: <http://www.fedex.com/us/services/options/dangerousgoods/hidden.html> and download the "how to pack" attachment.
8. **Clinical Samples That Are Dried and Non-infectious: Dried samples such as dried blood, tissue, saliva, hair.** While noninfectious samples of dried blood are not dangerous goods and are not required to meet dangerous-goods regulations, they do require special packaging that meets FedEx guidelines. Dried-blood samples on absorbent pads or cards for diagnostic testing must be enclosed in watertight plastic bags and shipped in a sturdy outer container or commercial envelope. Samples on glass or plastic slides must be adequately cushioned and may be shipped inside a sturdy outer container or flexible-envelope packaging. Use of the FedEx Clinical Pak is optional.
9. Send the samples to:
c/o Clinical Research
Immunomedics, Inc.
300 The American Road
Morris Plains, NJ 07950

PPD

IMMUNOMEDICS[®], INC.

Tissue Sample Worksheet

Protocol #: IMMU-132-01

Patient Initials:

Patient ID #: _____ - _____

F M L

(Site #) (Pt #)

Patient's Diagnosis and Current Stage: _____

Clinical Site to Complete				
Date Sample Taken	Tissue	Sample Sent * (describe the type and amount of sample sent i.e. 5 unstained slides or 1 paraffin block)	Date sent to IMMU	Fed-Ex tracking number

* Paraffin block is preferred; if slides are being sent, it should be at least 10 **unstained** slides.

Results (to be recorded by Immunomedics, Inc.):

Immunomedics Use Only			
Date Received	Date of Analysis	Results	Comments

Send Specimens including a copy of this form to:

c/o Clinical Research Department
Immunomedics, Inc.
300 The American Road
Morris Plains, NJ 07950

Performed By:

Approval Signature:

Date of Approval: - - -

Signature Page for VV-RIM-0003811 v1.0

Approval	PPD
	23-Jan-2020 14:29:46 GMT+0000

Approval	PPD
	23-Jan-2020 15:00:24 GMT+0000

Signature Page for VV-RIM-0003811 v1.0