Treatment of Immune Related Adverse Events with CD24Fc (TIRAEC)

Protocol Number:	UCDCC#292 CD24Fc-006 NCT04552704
Indication:	Patients with advanced solid tumors who have treatment interruption due to grade 2 or 3 irAEs from immune check point inhibitors (ICIs)
Phase:	I/II
Funding Source:	UCDCCC, OncoImmune, Inc.
Agent:	Immunomodulator
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Participating Center(s):	UC Davis Comprehensive Cancer Center
Protocol History:	Version 1.5 / October 20, 2020
IND #:	[redacted]
IND Sponsor:	OncoImmune, Inc.

PROTOCOL SIGNATURE PAGE

Protocol Number: UCDCC#292, CD24Fc-006, NCT04552704

Protocol Title: Treatment of Immune Related Adverse Events with CD24Fc (TIRAEC)

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

Tianhong Li, MD PhD

_____
Investigator Name (print)

_____
Investigator Signature

_____
Date

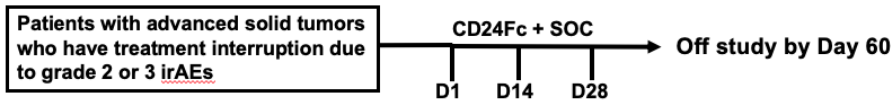
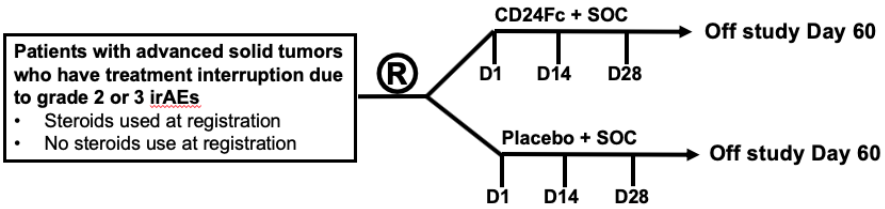
_____
Signature of Chief Medical Officer

Dr. Pan Zheng
Name

_____
Date

PROTOCOL SYNOPSIS

Study Title:	Treatment of Immune Related Adverse Events with CD24Fc (TIRAEC)
Protocol No.:	UCDCC#292, CD24Fc-006, NCT04552704
Phase of Development:	Phase I/II
Investigational Product, Dosage Form, Route, and Dose Regimen	CD24Fc: 480 mg on day 1; then 240 mg on day 14 and day 28 i.v. (a total course of 28 days).
Primary Objective:	Phase I study: To determine the safety and tolerability of CD24Fc in patients with advanced solid tumors who have treatment interruption due to grade 2 or 3 irAEs (by NCI CTCAEv5.0) from immune check point inhibitors (ICIs). Phase II randomized double-blind placebo controlled study: To determine if CD24Fc shortens the recovery time and increases recovery rate of irAEs in cancer patients with grade 2 or 3 irAEs.
Secondary Objectives	Phase I study: Time to irAE reduction by at least 1 grade from CD24Fc. To estimate the time to all irAEs reduced to grade ≤1. Time to resume ICI treatment from the initiation of CD24Fc. To estimate the recovery rate as defined by reduction on irAE by at least one grade. To determine if CD24Fc treatment changes the levels of inflammatory markers in the plasma. Phase II study: To estimate the time to all irAEs reduced to grade ≤1. To record the use of steroids (drug, dose, duration) and other treatment for irAE. To estimate the preliminary overall response rate (ORR), progression free survival (PFS), and 1-year overall survival (OS) after treatment with or without CD24Fc. To determine if CD24Fc treatment changes the levels of inflammatory markers in the plasma
Study Design and Investigational Plan / Methodology:	Phase I study: Patients with advanced solid tumors who have treatment interruption due to grade 2 or 3 irAEs from ICI will be treated with CD24Fc along with standard of care (SOC) treatment for irAE.Phase II randomized double blind placebo controlled study: Patient with advanced solid tumors who have treatment interruption due to grade 2 or 3 irAEs will be randomized (1:1) to receive CD24 Fc vs placebo in addition to SOC treatment for irAE. Patient will be stratified randomized by study statistician based on whether steroid was used for irAE at enrollment. Placebo is 100 ml normal saline, which is used to dilute CD24Fc.

Study Schema: **Phase I**	
Study Schema: **Phase II**	
Study Population and Sample Size:	Cancer patients who have treatment interruption due to grade 2 or 3 irAEs on ICI therapy. Phase I: n=6; Phase II: n=72
Eligibility Criteria:	Patients who developed grade 2-3 irAEs to ICI for treatment of metastatic or unresectable solid tumor leading to therapy hold. Patients should be naïve to CD24Fc therapy. Patients who have grade 4 irAEs or any grade 4 toxicity based on CTCAE v5.0 will be excluded. The detailed inclusion and exclusion criteria are listed in Section 5.0.
Endpoints:	Phase I study: Primary endpoint: Any new AE of ≥grade 3 that are outside the spectrum of irAEs when CD24Fc is given in cancer patients who developed grade 2-3 irAEs. Secondary endpoints: 1) time to irAE reduction by at least 1 grade; 2) time to all irAEs reduced to ≤1 (by NCI CTCAEv5.0); 3) time to resume ICI treatment; 4) recovery rate (as defined by reduction of irAE by one grade) at D42. Phase II randomized study: Co-primary endpoints: 1). Recovery rate (as defined by reduction of irAE by one grade) at D42 2). Kaplan Meier Estimate of time to recovery from grade 2 or 3 irAE (as defined by reduction of irAE by at least one grade in severity). Secondary endpoints: 1) Time to all irAEs reduced to ≤1 after treatment with CD24Fc; 2) the use of steroids and other drugs (drug, dose, duration) as SOC for irAEs; 3) time to resume ICI treatment; 4) ORR; 5) PFS; and 6) 1-year OS

Statistical Considerations	**Statistical Analysis** Demographic and background characteristics obtained at enrollment will be listed and summarized. Descriptive statistics will be used to summarize changes of biomarkers from baseline in clinical laboratory parameters for this cohort, and use of steroids (drug, dose, duration) and other treatment for irAE. To assess toxicity: Toxicity is evaluated by NCI CTCAEv5.0. The type, grade, frequency and proportion of toxicities noted during the treatment period will be reported, along with associated 95% confidence interval of proportion. All adverse events noted by the investigator will be tabulated according to the affected body system. In phase I lead-in study, dose limiting toxicity is defined as any new AE of ≥grade 3 that are outside the spectrum of irAEs. To assess time to recovery from irAE (time to reduction of irAE by at least one grade), time to all irAEs reduced to ≤1, and time to resume ICI treatment: The date of staring treatment (i.e., Day 1) will be used for all time events in the study. Kaplan-Meier plots and confidence intervals will be used to summarize outcomes. Medians and associated 95% confidence intervals will be calculated, and comparisons between groups will be performed by log-rank tests. Cox proportional hazard models will be used to explore association between covariates and outcomes. To assess recovery rate of irAE by CD24Fc (reduction of irAE by one grade) at D42 and response rate of ICI: The fractions will be reported along with 95% two-sided confidence intervals. Comparisons between arms will be performed by Fisher's Exact tests. We will also characterize the proportion who remain that either respond or have stable disease, compared to those who progress. To assess PFS and OS: Kaplan-Meier plots and confidence intervals will be used to summarize PFS, and OS; 1-year OS rate will be reported; medians and associated 95% confidence intervals will be calculated, and comparisons between groups will be performed by log-rank tests. Cox PH models will be used to explore association between outcomes and covariates. As exploratory analysis, we will summarize descriptively the relationship of response rates to tumor type (lung, GI, melanoma, breast, prostate) and to cellular immune response and explore the relationship using logistic regression.

	The possibility of bias from missing data will be addressed. Missing pattern and mechanism will be evaluated, and sensitivity analyses will be performed using imputation methods for use of steroid, irAE type, cancer type, etc., if such might affect point estimates and study conclusions. Sample Size Justification Phase I study: We plan to enroll 6 patients in the phase I study. The objective of this phase I study is to confirm the safety of CD24Fc in ICI-treated cancer patients who have treatment interruption due to grade 2 or 3 irAEs and to estimate the median time to recovery and resumption of ICI after treatment interruption due to irAE. The primary endpoint is new AE of ≥grade 3 that are outside the spectrum of irAEs when CD24Fc is given to treat irAEs. We expect the rate of this event will be less than 33.3%. With a sample size of 6 patients, we would have 74-91% chance to observe at least one occurrence if the true event rate is 20-30%. Hence the sample size is adequate for this pilot study for safety. Randomized phase II study: Previous studies suggested that response rate at 42 days for control group will be about 50%. We hypothesize CD24Fc will increase recovery rate from 50% to 80 %. A sample size of 72 patients (36 in each arm) will have 81% power to detect an increase of recovery rate from 50% of control group to 80% of CD24Fc group. This result is based on one-sided Fisher's Exact test and significance level of 0.05. Group-sequential design will be used with interim analysis to monitor the trial by a cohort size of 24 (12 in each group), with maximum sample size of 72, average sample size of 46 if null hypothesis is true, and 58 if alternative hypothesis is true. Steroids is the most commonly used SOC therapy for irAEs. It affects the severity and duration of irAE, which are the key endpoints of this study. We thus will stratify the subjects based on the status of steroids use at registration and will adjust steroids use in analyses. Few patients might start on steroids as SOC before starting the study treatment, and the patients will be moved to the steroid stratum.
Estimated Accrual/Enrollment Period:	Six patients in the phase I study and 72 patients in phase II randomized study. Of about 50 cancer patients received ICI per month at UCD, 8 patients (15%) develops grade 2 and 3 irAE that require treatment interruption. We estimate 4-5 patients will be enrolled each month.

Estimated Study Duration: Estimated Duration of Participation:	Total duration of the study is estimated to be approximately 3 months for phase I, 18 months for phase II, and 3 months for follow-up, data collection, and analysis.
Anticipated FPFV / LPLV:	
Correlatives:	To evaluate tissue damage-associated molecular pattern (DAMP) signaling contributes to the pathogenesis of irAEs, we will explore the association of pretreatment plasma HMGB1 level with the grade of irAE from all study patients. To test if CD24Fc ameliorates inflammatory response to DAMPs, we will compare plasma levels of inflammatory cytokines in the placebo and the CD24Fc arms.

Figure 1: Phase I Study Schema

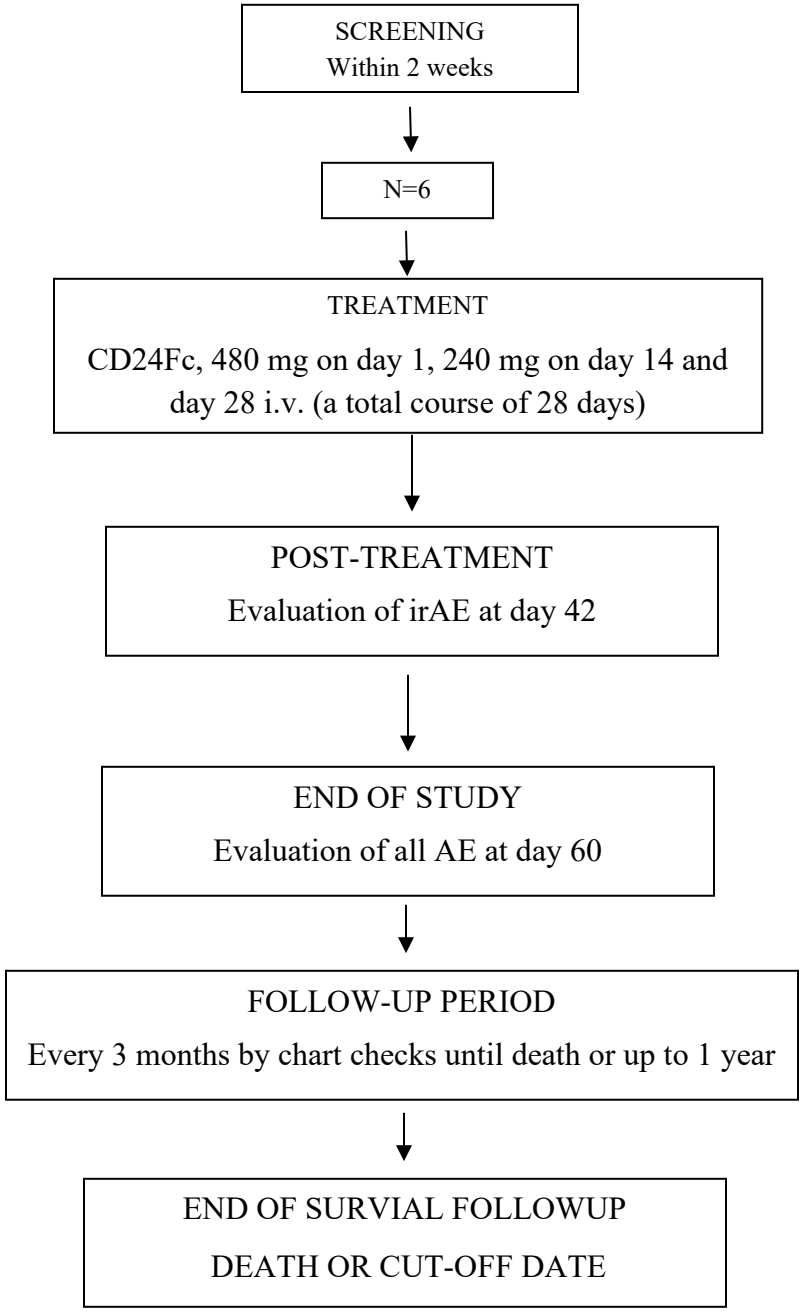


Table 1. Flow Chart for Phase I Study

CD24Fc 480 mg on day 1, 240 mg on day 14, and 240 mg on day 28 i.v. (a total course=28 days)							
Trial Period	Screening	Treatments			Post-Treatment	End of Study	Post-Study
Dose/Treatment Number		1	2	3	2-week Evaluation	Safety Follow Up	Survival Follow Up
Day	-14 to -1	1	14 ± 3	28 ± 3	42 ± 3	60 ± 3	Every 3 months to 1 year[1]
Drug Dispensation							
CD24Fc		X	X	X			
Administrative Procedures							
Eligibility evaluation, informed consent, medical history	X						
Medication review	X	X	X	X	X	X	X
Post-study status, survival status							X
Clinical Procedures							
Full physical exam	X				X	X	
Directed physical exam		X	X	X			
ECOG PS, vital signs, EKG[2], acute AE monitoring[3]	X	X	X	X	X	X	
Evaluation for ICI retreatment					X		
Toxicity assessment (NCI CTCAE V5.0)	X	X	X	X	X	X	X[4]
Laboratory Procedure/Assessment							
CBC with differential, CMP	X	X[5]	X[5]	X[5]	X	X	
Pharmacokinetics/Pharmacodynamics, ADA, correlative blood sample collection[6]		X[6]	X[6]	X[6]	X	X	
Pregnancy test (urine or serum b-HCG)[7]	X						

1. Frequency of follow-up office visits at the discretion of treating physician. Chart check every 3 months for post treatment and survival status. To continue until death or up to 1 year after completion of the study.
2. On days of CD24Fc administration, vitals and EKG will be obtained prior to and post infusion of study drug.
3. All patients will be monitored for 1-hour post infusion with are registered nurse or nurse practitioner within immediate proximity.
4. If irAE has not resolved to ≤grade 1 at day 60, check on primary oncologist's document for the grade of AE at every visit until resolution.
5. CBC and CMP blood draw should be within 3 days prior to CD24 Fc administration
6. The PK/PD, ADA, correlative blood sample collection: 2x 10ml EDTA samples at each time point. The samples should be collected pre-dosing and 30±10 min after each IV infusion. Sample collection must be from the opposite arm to that used for study drug infusion.
7. Women of childbearing age only

Figure 2: Phase II Randomized, Placebo Controlled Study Schema

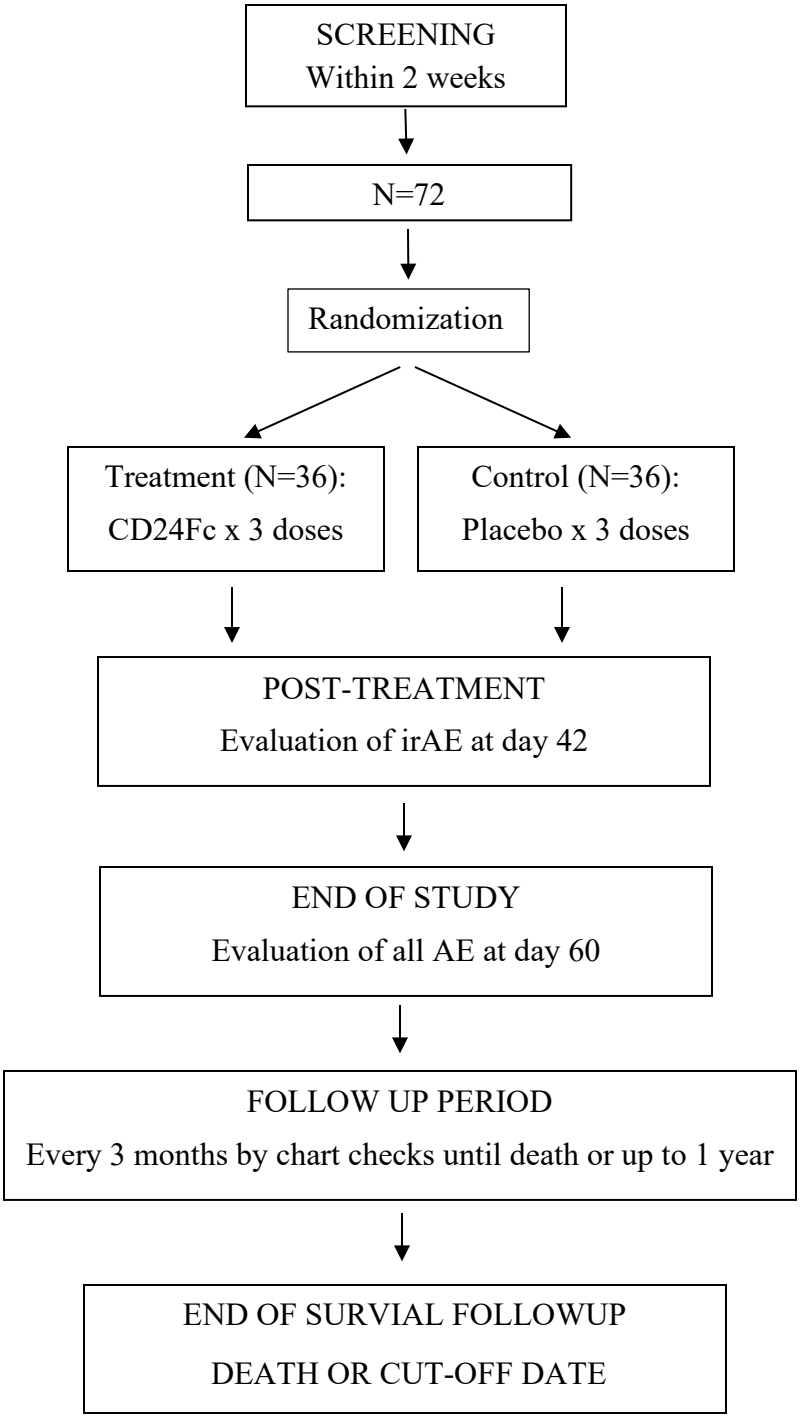


Table 2. Flow Chart for Phase II Study (CD24Fc Group vs Placebo Group)

CD24Fc 480 mg on day 1, 240 mg on day 14, and 240 mg on day 28 i.v. (a total course=28 days)							
Trial Period	Screening	Treatments			Post-Treatment	End of Study	Post-Study
Dose/Treatment Number		1	2	3	2-week Evaluation	Safety Follow Up	Survival Follow Up
Day	-14 to -1	1	14 ± 3	28 ± 3	42 ± 3	60 ± 3	Every 3 months to 1 year[1]
Drug Dispensation							
CD24Fc		X	X	X			
Placebo		X	X	X			
Administrative Procedures							
Eligibility evaluation, informed consent, medical history	X						
Medication review	X	X	X	X	X	X	X
Post-study status, survival status							X
Clinical Procedures							
Full physical exam	X				X	X	
Directed physical exam		X	X	X			
ECOG PS, vital signs, EKG[2], acute AE monitoring[3]	X	X	X	X	X	X	
Evaluation for ICI retreatment					X		
Toxicity assessment (NCI CTCAE V5.0)	X	X	X	X	X	X	X[4]
Laboratory Procedure/Assessment							
CBC with differential, CMP	X	X[5]	X[5]	X[5]	X	X	
Correlative blood and plasma sample collection, PK/ADA samples[6]		X[6]	X[6]	X[6]	X	X	
Pregnancy test (urine or serum b-HCG)[7]	X						

1. Frequency of follow-up office visits at the discretion of treating physician. Chart check every 3 months for post treatment and survival status. To continue until death or up to 1 year after completion of the study.
2. On days of CD24Fc administration, vitals and EKG will be obtained prior to and post infusion of study drug.
3. All patients will be monitored for 1-hour post infusion with are registered nurse or nurse practitioner within immediate proximity.
4. If irAE has not resolved to ≤grade 1 at day 60, check on primary oncologist's document for the grade of AE at every visit until resolution.
5. CBC and CMP blood draw should be within 3 days prior to CD24 Fc administration
6. The PK/PD, ADA, correlative blood sample collection: 2x 8 ml EDTA samples at each time point. For all infusions, the samples should be collected pre-dosing and 30±10 min after IV infusion and the end of study visit. Sample collection must be from the opposite arm to that used for study drug infusion.
7. Women of childbearing age only

LIST OF ABBREVIATIONS AND TERMS

Abbreviation/ Term	Definition
°C	Degrees Celsius
ACVP	American College of Veterinary Pathologists
ADA	Anti-drug antibodies
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
APC	Antigen-presenting cell
AST	aspartate transaminase
AUC0-∞	Area under the plasma drug concentration-time curve from 0 to infinity
AUC0-t	Area under the plasma drug concentration-time curve from time 0 to last measurable time
CD24Fc	CD24 IgG1 Fc fusion protein
cGMP	Current Good Manufacturing Practices
CL	Plasma clearance
Cmax	Maximum plasma concentration
CNS	Central nervous system
CPU	Clinical Pharmacology Unit
CR	complete response
CRA	Clinical Research Associate
CRC	clinical research coordinator
CRF	case report form
CRF	Case report form
CT	computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
DAMP	Danger-associated molecular pattern
DC	Dendritic cell
DLT	dose-limiting toxicity
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice

GVHD	Graft vs host diseases
HBsAg	Hepatitis B virus surface antigen
HCT	Hematopoietic stem cell transplantation
HED	Human equivalent dose
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
ICH	International Conference on Harmonization
IEC	independent ethics committee
IND	Investigational New Drug
irAE	immune related adverse event
irAE	Immune-related adverse events
IRB	institutional review board
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	intravenous
IV	Intravenous
Kel	Elimination rate of constant
KLH	Keyhole limpet hemocyanin
LDH	lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mM	micromolar
MRI	magnetic resonance imaging
MRSD	Maximum recommended starting dose
MS	Multiple sclerosis
MTD	maximum tolerated dose
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NOAEL	No observed adverse event level
OCR	Office of Clinical Research
OS	overall survival
PAMP	Pathogen-associated molecular pattern
PBML	Peripheral blood mononuclear leukocytes
PD	progressive disease
PD	Pharmacodynamics
PET	positron emission tomography
PI	principal investigator
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PPB	Plasma protein binding

PR	partial response
QD	Once daily
RA	Rheumatoid Arthritis
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase II dose
SAE	serious adverse event
SAE	Serious adverse event
SOC	Standard of Care
SOP	Standard operation procedures
SRC	Scientific Review Committee
$t_{1/2}$	Elimination half life
TBI	Total body irradiation
TEAE	Treatment-emergent adverse event
tmax	Time to maximum plasma concentration
UCD	University of California, Davis (UC Davis)
UCDCCC	UC Davis Comprehensive Cancer Center
US	United States
WHO	World Health Organization

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0. OBJECTIVES

0.0 Phase I study:

0.0.0 Primary Objective:

To determine the safety and tolerability of CD24Fc in patients with advanced solid tumors who developed debilitating irAEs from immune check point inhibitors (ICIs)

0.0.1 Secondary Objectives:

1) time to irAE reduction by at least 1 grade
2) time to all irAEs reduced to grade ≤1
3) time to resume ICI treatment
4) recovery rate (as defined by reduction of irAE by one grade) at D42

0.1 Randomized phase II study:

0.1.0 Primary Objective:

To determine if CD24Fc shortens the recovery time of irAE and increases the recovery rate of irAE in cancer patients with G2 or 3 irAEs

0.1.1 Secondary Objectives:

1) To estimate the time to all irAEs reduced to ≤1
2) To record the use of steroids (drug, dose, duration) and other treatment for irAE
3) To record the time to resume ICI treatment
4) To estimate the preliminary overall response rate (ORR), progression free survival (PFS), and 1-year overall survival (OS) after treatment with or without CD24Fc
5) To determine if CD24Fc treatment changes the levels of inflammatory markers in the plasma

1. BACKGROUND

1.0 Overview for immune-related adverse events (irAE)

First-generation immune checkpoint inhibitors (ICIs) targeting programed cell death protein 1 (PD-1) or its ligand PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways have become the most potent and durable cancer immunotherapy for patients with many cancer types. Currently, FDA-approved ICIs include the anti-PD-1 monoclonal antibodies (mAbs) nivolumab and pembrolizumab; the anti-PD-L1 mAbs atezolizumab, durvalumab and avelumab; and the anti-CTLA-4 mAb ipilimumab [1-6]. These ICIs have been approved as first-line, second-line or consolidation treatment for patients with non-small cell lung cancer (NSCLC), first-line therapy for patients with metastatic small cell lung cancer (SCLC), melanoma [7-10] and is promising for mesothelioma [11, 12].

However, immune-related adverse events (irAEs) due to the ICIs, especially combinational regimens, are frequent and potentially severe and even fatal, leading to early treatment discontinuation in ~18% of NSCLC patients [6]. Clinical data showed that greater than 50% of melanoma patients with combination of anti-CTLA4 and anti-PD-1 therapy developed grade 3 and 4 toxicity and many patients could not complete the therapy due to these serious toxicities [9, 10]. Even with the less toxic single anti-PD1/L1

therapy, rare but life-threatening complications have been described [13, 14]. A systematic review including 5,744 NSCLC patients from 23 studies treated with PD-1 or PD-L1 ICIs reported a global incidence of AEs of 64% (14% grade ≥3) with anti-PD-1 and 66% (21% grade ≥3) with anti-PD-L1 mAbs [15]. The incidence of grade 3 or 4 toxicity with the combination was increased compared with either single agent (59 versus 21 and 28 percent, respectively, for nivolumab and ipilimumab) in cancer patients [16, 17]. These irAEs can affect any organ (Figure 3), which including but not limited to skin, gastrointestinal tracts, lung, liver, heart, bone marrow, have unique features and require new management strategies that are distinct from those of chemotherapy and molecularly targeted therapy [18]. Of note, those patients who develop severe irAEs might benefit the most from ICIs [19, 20]. Among all irAEs captured in the largest World Health Organization (WHO) database VigiBase (N=24,079), pneumonitis and colitis are the most common observed irAEs with median time of irAE onset (IQR) of 48 (16-114) and 51 (24-105) days, respectively [21]. Little is known at this point regarding the safety and efficacy of retreatment with immunotherapy after an irAE. Much of the information available is based on retrospective studies [22-24]. In the largest observational WHO database VigiBase (N=6123), 28.8% of the initial irAE leading to the discontinuation of ICI therapy were observed again after a rechallenge with the same ICI [21]. In a rechallenge, colitis, hepatitis, and pneumonitis had higher recurrence rates compared with other irAEs. Thus, irAE represents a major hurdle in the clinical application of ICIs. For many patients this could mean delay, and potentially discontinuation, from life-prolonging treatment. Success in reducing irAE could make a transformative impact in the outcome of cancer immunotherapy, however, the mechanism of irAE related to ICIs is still not well understood, hinders the development of strategies to treat and prevent these toxicities.

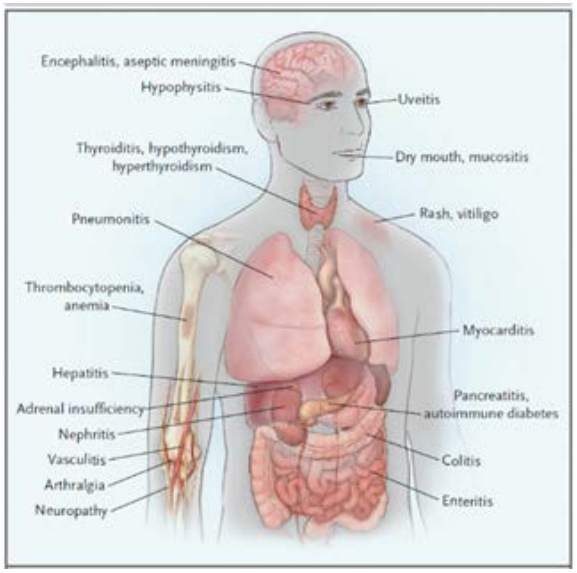


Figure 3: Immune-related adverse events (irAE) associated with cancer immunotherapy with immune checkpoint inhibitors.

1.1 Treatment for immune-related adverse events

Several professional societies have established the practice guidelines for the diagnosis and management of irAEs (NCCN, SITC, and ASCO) [25-27]. Standard of care for the treatment of irAE at this time is limited to high dose steroids, and infliximab for refractory disease [26]. Use of steroids and withholding ICI is considered standard of care for most irAEs though timing intervention varies from grade and site of AE. In general, most guidelines recommend withholding ICI for irAE greater than grade 2 (colitis, pneumonitis, uveitis, episcleritis, transaminitis, pancreatitis). Some organ specific irAE allow for continuation of ICI up until grade 3 (rash, pruritis, inflammatory arthritis). Early recognition of initiation of ICI is heavily emphasized in these guidelines. First line treatment involves initiation of high dose corticosteroids at 0.5-1mg/kg with long taper, over 4-8 weeks [26]. The immunosuppressive effect of steroids is the main mechanism for treating irAE although the exact mechanisms are unknown [28, 29]. However, high dose glucocorticoids for the treatment of irAE has been associated with decreased survival in patients with melanoma [30]. In addition, prolonged steroid use can result in significant morbidity including infection, adrenal suppression, osteoporosis, psychosis, and hyperglycemia. Thus, there is unmet need to explore new treatment option to replace or reduce the steroids use. The objective of this study is to

determine safety and tolerability of CD24Fc, a novel therapy with the intent to reduce the severity and duration of irAE. A 28-day course of 3 CD24Fc treatment will reduce the treatment duration and side effects of steroids.

1.2 Host Defense to Tissue Damage

Danger associated molecular patterns (DAMPs) play an important role in regulating tissue damages. Autoimmunity occurs when disruption in immune tolerance, triggered by aberrant innate and adaptive immune cell activation, results in tissue degradation and organ failure [31]. Innate immune response is initiated by pattern recognition receptors (PRR) such as Toll or Toll-like receptors (TLRs), that respond to injured cells (DAMPs) or pathogens (pathogen-associated molecular patterns, PAMPs) [32, 33]. The classic DAMP high-mobility group box 1 (HMGB1) has been shown to trigger inflammation and exacerbate autoimmune diseases [34]. Tissue necrosis is associated with cancer development and cancer therapy, resulting in release of DAMPs. Studies have shown that attenuating host response to DAMPs may not negatively affect development of cancer immunity, as deletion of DAMPs gp96 in macrophages reduced tumor in a colitis- associated colon cancer model [35].

Siglec-CD24 signaling pathway suppresses inflammation triggered by DAMPs but not PAMPs. Previous work by our groups indicated that sialic-acid–binding immunoglobulin-like lectins (Siglec) is a distinct class of PRR that down regulate innate immunity [36], and have immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their intracellular domains [37]. DAMPs such as HMGB1, HSP70 and -90 are presented to Siglec by binding to their high affinity ligand CD24, which leads to activation of the ITIM Siglec10 (human) / G (mouse) and subsequent abrogation of inflammatory cytokine signals through blockade of NF-κB activation [38], including suppression of TNF-α, IL-1β and IL-6 (Figure 4). CD24 also binds to several DAMPs and represses host response to these DAMPs. Siglec-G deletion in mice (Siglec-G−/−) exacerbated the production of inflammatory cytokines and acute organ failure in response to DAMPs [39, 40], but not PAMPs. Loss of CD24 in the context of exogenously introduced insult resulted in an HMGB1-driven dendritic cell (DC) inflammatory response. The CD24 inflammatory axis is specific to signaling initiated by DAMPs, as the PAMP LPS response did not differ between CD24 knockout (KO) and wild-type (WT) cells [39]. CD24 has been shown to be essential for the development of experimental autoimmune encephalomyelitis in the mice [41, 42], and is associated with a number of autoimmune diseases [43-48]. CD24 deletion in gp96 lupus prone mice reduces the lupus like disease by expansion of myeloid-derived suppressor cells (MDSC) [49]. Recently, in mouse models of graft-versus-host disease

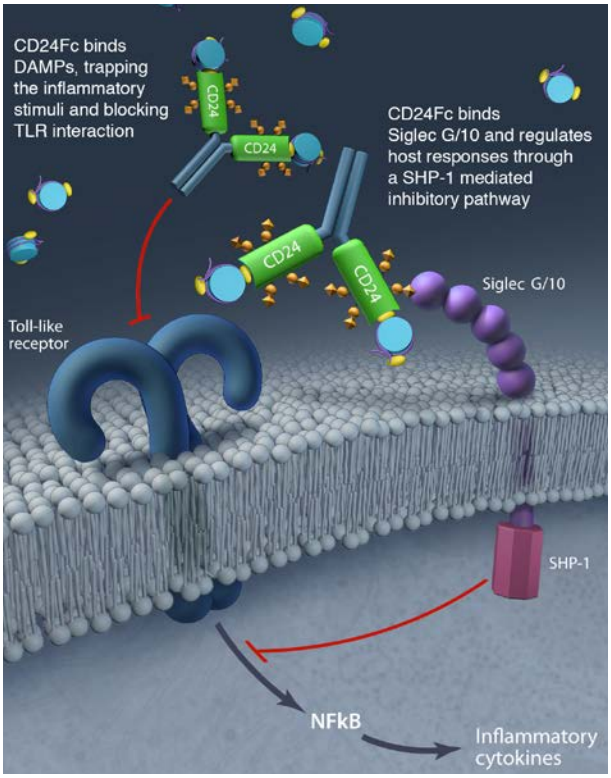


Figure 4: Mechanisms of the Siglec-CD24 pathway and CD24Fc in suppressing the DAMPs triggered innate immune response

(GVHD), Siglec-G expression on host APCs, specifically on hematopoietic cells, was found to negatively regulate GVHD, and rescue experiments with novel CD24 fusion protein (CD24Fc) demonstrate that enhancing the interaction between Siglec-G on host APCs with CD24 on donor T cells attenuates GVHD [50]. These data suggest that enhancing this interaction may represent a novel strategy for mitigating GVHD.

1.3 Preclinical studies on irAEs

1.3.0 A preclinical mouse model to recapitulate irAEs reported in human experience

Our collaborators have developed the human CTLA-4 knock in mouse model to study the irAE. Very young mice (10 days post birth) are given ipilimumab (clinical approved anti-CTLA 4 antibody drug) together with anti-mouse PD-1 antibody. The model can successfully recapitulate a large spectrum of irAEs that have been reported in human clinical trials and real-world experience. Table 3 listed the irAEs in the model and in human experience.

Table 3: Clinical observations recapitulated in *Ctla*$^{h/h}$ mouse model

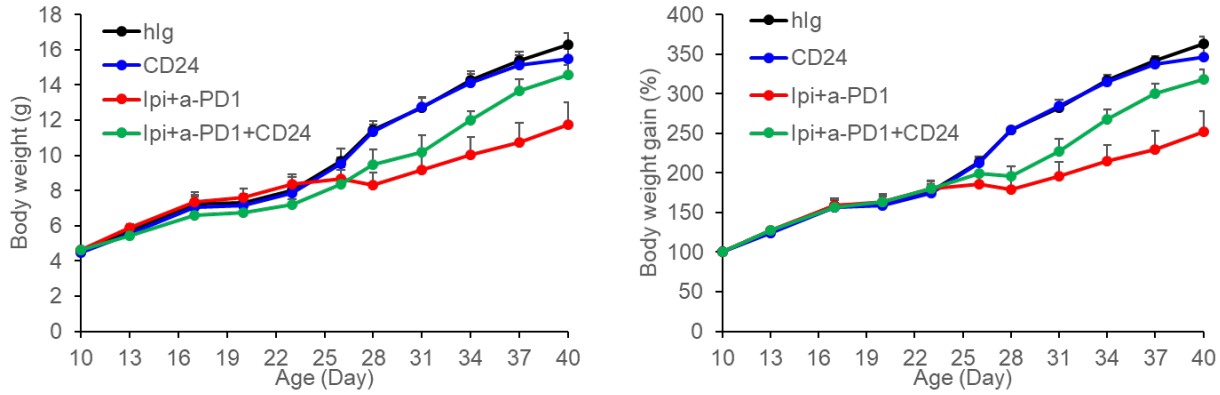
Gastrointestinal select AEs	Diarrhea, ulceration, inflammation	inflammation in mucosal layers mild ulceration
Hepatic select AEs	ALT/AST increase inflammation	ALT increase Inflammation
Pulmonary select AEs	Pneumonitis (CT)	severe inflammation
Renal select AEs	Creatinine increase, swelling (CT), inflammation	No function damage, Inflammation
Heart select AEs	Myocarditis T cell infiltration	Myocarditis, Organ Morphology T cell infiltration
Hematologic select AEs	Hemolytic Anemia, Pure Red-Cell Aplasia	Anemia, BM failure
Sicca syndrome	dry mouth symptoms severe salivary hypofunction	Sever inflammation pathologic structural damage in SG
Skin select AEs	Rash, Pruritus	No rash, hair loss or scratch, slight inflammatory cells infiltration
Endocrine select AEs	Hypothyroidism, Adrenal insufficiency, hypophysitis	ACTH increase, delayed adrenal development
Ovary abnormal	No report	Less mature follicles, hypogonadism

Our collaborators have tested whether CD24Fc could be applied to prevent or treat irAE without affecting T cell anti-tumor function upon immunotherapy. The emphasis was on the effect of short term CD24Fc administration on the long term irAE prevention. They have published our mouse model for irAE with confidence that giving young mice anti-CTLA 4 (Ipilimumab) and anti-PD-1 antibodies can reliably induce growth retardation and irAE in different organs[51].

1.3.1 CD24Fc Reduces irAE by Ipilimumab and Anti-PD-1 Antibody

The young 10-days old *CTLA4*$^{h/h}$ mice were treated with the following four regimen, intraperitoneal injection, at day 10, 13, 16, and 19 for total four injections of 100 µg/mouse/injection for each reagent. (1). Human IgG-Fc. (2). CD24Fc. (3). Ipilimumab + anti-PD-1 (clone RMP 1-14, from Bio-X Cell, Inc.) + human IgG-Fc; (4). Ipilimumab + anti-PD-1 + CD24Fc. We monitored the growth closely with body weight measurement every three days. The mice in group 1 and 2 have body weight increase as expected for normal mice. On day 40 after birth, the body weight of the mice increased from 4.5 – 5.0 grams to 15 to 16 grams. In contrast, the mice in group 3 with Ipilimumab and anti-PD-1 antibody injections had growth retardation starting from day 22 after birth (3 days after last injection). At day 40 after birth, the average body weights for this group of mice were 11.0 grams, significantly lower than the group 1 and 2. Group 4 mice were injected with Ipilimumab and anti-PD-1, plus CD24Fc, rescued mice with accelerated growth from day 30 to day 40 to reach the body weights of 14 grams (60-70% recovery) (Figure 5).

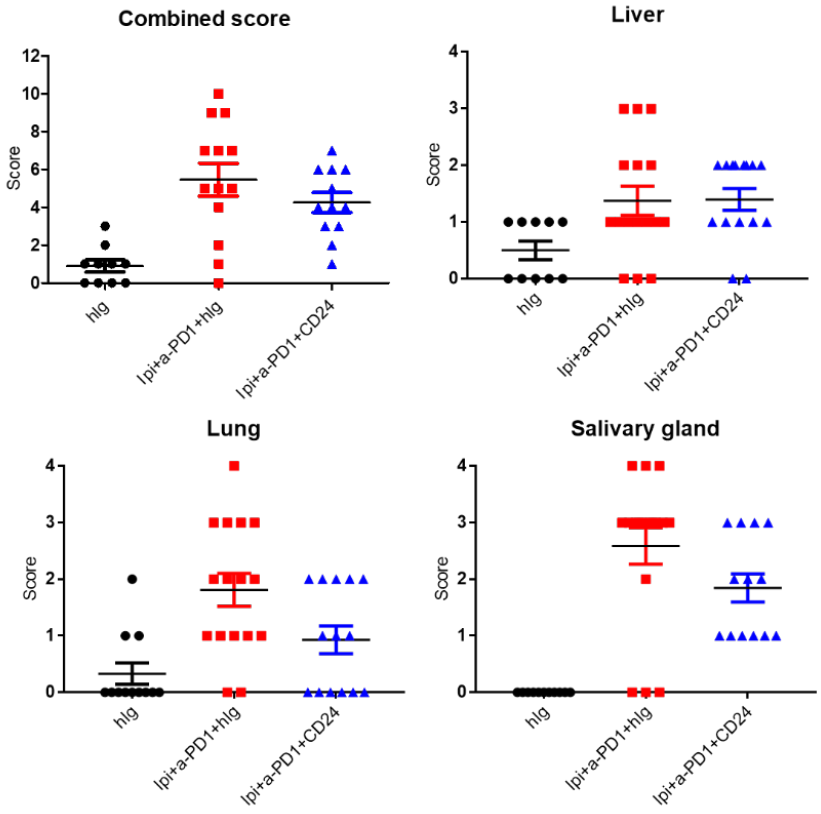
Figure 5: Immunotherapy related AE presented as growth retardation in mouse model.
C57BL/6 Ctla4$^{h/h}$ mice were treated, respectively, with control human IgG-Fc, CD24Fc, anti-PD-1 + Ipilimumab + hIgG-Fc or anti-PD-1 + Ipilimumab + CD24Fc at a dose of 100 µg/mouse/injection on days 10, 13, 16 and 19. The left panel is the body weight measurement. The right panel is the percent change the body weights before first injection at day 10 after birth.



The Complete Blood Counts (CBC) were measured on Day 41. As our collaborators showed in their recent publication [51] Ipilimumab + anti-PD-1 induced hematological abnormalities. These abnormalities were confirmed here with decreased RBC number, HCT and Hb. Surprisingly, the lymphocyte numbers were also significantly reduced. Adding CD24Fc completely reversed the hematological abnormalities.

They examined three different organs for lymphocyte infiltration and tissue destruction for irAE scoring. The scoring system was described in previous paper. The H&E sections from liver, lung and salivary glands are examined and scored (Figure 6). Ipilimumab + anti-PD-1 combination induced more severe inflammation and lymphocyte infiltrations. CD24Fc reduced the severity of the irAE in all three organs.

Figure 6: CD24Fc reduces immunotherapy related adverse events (irAE) in mouse model.
C57BL/6 Ctla4$^{h/h}$ mice were treated with different combination drugs, and the organs and tissues were taken on Day 42 for histology examination.



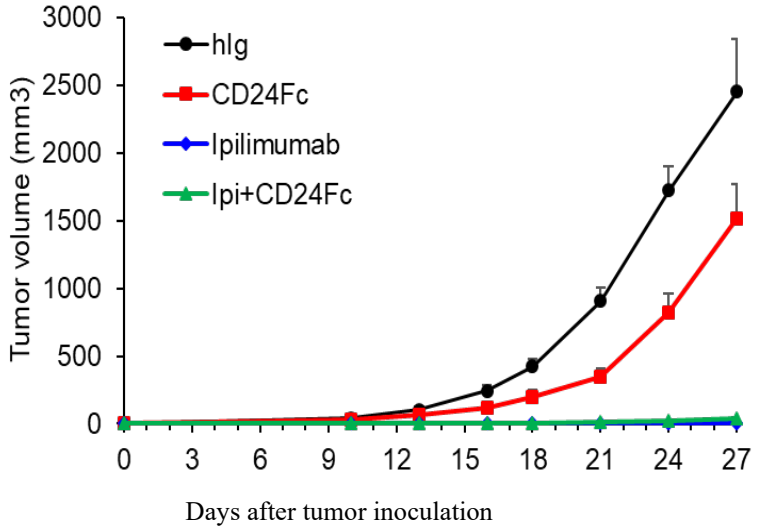
1.3.2 The impact of CD24Fc in immunotherapy anti-tumor efficacy.

It has been reported by our group and others that B16 melanoma in mice are difficult to treat. Figure 7 shows that 4 injections of 10 – 30 µg/mouse/injection of Ipilimumab could reject MC38 colon cancer in *Ctla4$^{h/m}$* mice, and 100 – 150 µg/mouse/injection of Ipilimumab could reject CT26 colon cancer in *Ctla4$^{h/m}$* mice. However, for B16 melanoma, the dose of Ipilimumab had to increase to 250 µg/mouse/injection for 4 injections to induce tumor rejection, which would be 12.5 mg/kg, a dose that was much higher than clinical human dosing of 3 mg/kg or 1mg/kg (Figure 7).

The investigators next performed the tumor rejection experiment with B16F1 tumor cell line adding the groups with CD24Fc. The Ipilimumab dose was the same as before using 250 µg/mouse/injection for 3 injections to induce tumor rejection. CD24Fc dose was 100 µg/mouse/injection for 3 injections. The antibody and CD24Fc were given three days after tumor inoculation. The experiment groups are as follows. (1). Human IgG-Fc. (100 µg/mouse/injection); (2). CD24Fc. (100 µg/mouse/injection); (3). Ipilimumab (250 µg/mouse/injection) + human IgG-Fc (100 µg/mouse/injection); (4). Ipilimumab (250 µg/mouse/injection) + CD24Fc (100 µg/mouse/injection).

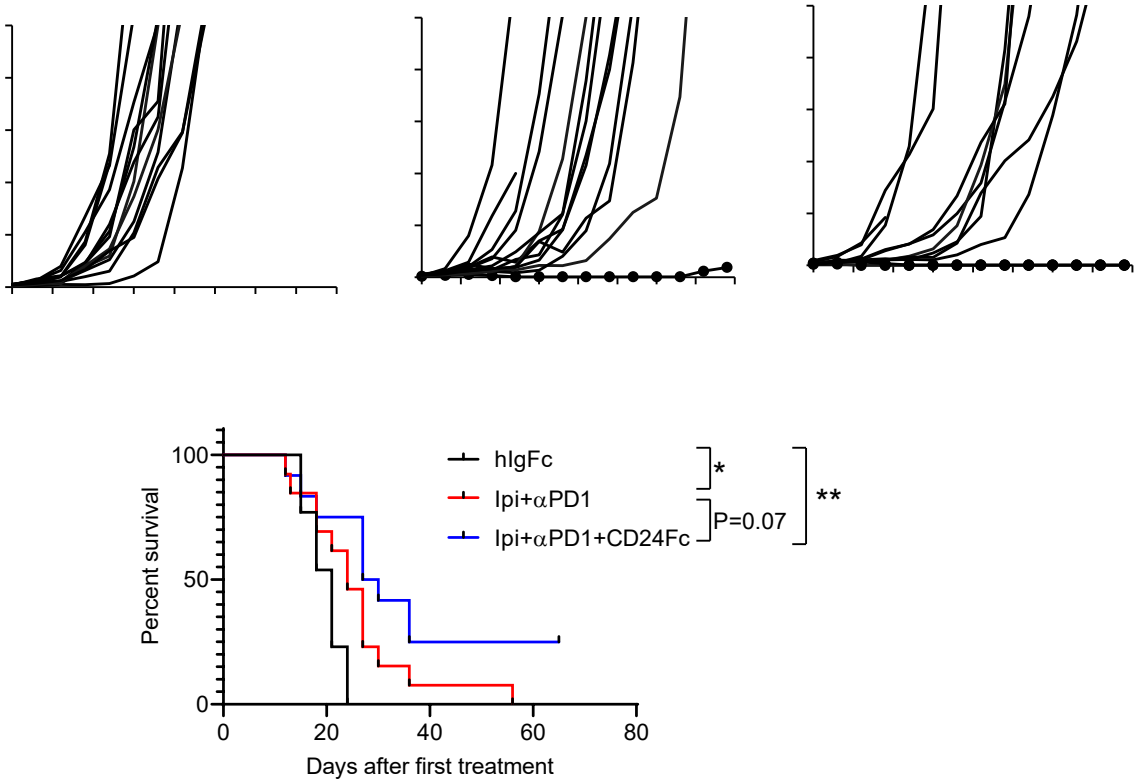
As expected, high dose of Ipilimumab given earlier (day 3, 6, 9) prevented the B16 tumor formation. Adding CD24Fc to Ipilimumab did not affect the anti-tumor efficacy of Ipilimumab. Of note, CD24Fc alone reduced the tumor size considerably (Figure 7). This is unexpected as growing tumor cells in the culture medium containing CD24Fc in vitro had not shown anti-tumor effect by CD24Fc.

Figure 7: CD24Fc has synergistic anti-tumor effect with ipilimumab in melanoma model.
1x10^5 B16-F1 tumor cells were injected (s.c.) into Ctla4h/h mice (n=6), and treated (i.p.) with 100 µg control hIgGFc or CD24Fc, 250 µg Ipilimumab plus 100 µg human IgGFc or CD24Fc, on days 3, 6, and 9. Data represent mean ± S.E.M. of 6 mice per group.



To determine the effect of CD24Fc on combination therapy with anti-PD-1 and anti-CTLA-4 antibodies, we treated B16-F1 tumor-bearing Ctla4$^{h/h}$ mice with control IgG1 Fc, IgG1 Fc+anti-mouse PD-1+Ipilimumab, or CD24Fc+anti-mouse PD-1+Ipilimumab and followed tumor growth kinetics and mouse survival. As shown in Figure 8, CD24Fc promoted therapeutic effect of anti-PD-1+anti-CTLA-4 immunotherapy, as it reduced tumor growth and promoted mouse survival.

Figure 8: CD24Fc enhance therapeutic effect of anti-PD-1+anti-CTLA-4.
1x10^5 B16-F1 tumor cells were injected (s.c.) on *Ctla4$^{h/h}$* mice (n=12-13), and treated (i.p.) with 200 µg Ipilimumab plus 200 µg αPD-1 (RMP1-14) together with 200 µg of hIgFc or CD24Fc on day 8, 11 and 14.. Tumor growth kinetics or 4 weeks and mouse survival curve over 60 days (B) are shown. Data shown were pooled from two independent experiments. Survival endpoints are defined as tumor volume reaching 2000 mm^3, death or moribund per institutional guidelines.



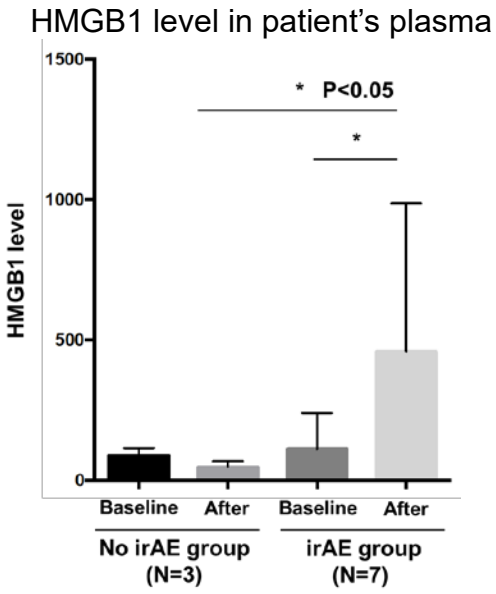
These results support clinical testing of CD24Fc in combination with Ipilimumab + anti-PD-1, not only for reduction of irAE, but also the synergistic anti-tumor effects.

1.3.3 High plasma HMGB1 level in NSCLC Patients with irAEs

HBGB1 is a representative DAMP. HMGB1 is a multifunctional redox sensitive protein with various roles in different cellular compartments. In the nucleus is one of the major chromatin-associated non-histone proteins and acts as a DNA chaperone involved in replication, transcription, chromatin remodeling, V(D)J recombination, DNA repair and genome stability. HMGB1 promotes host inflammatory response to sterile and infectious signals and is involved in the coordination and integration of innate and adaptive immune responses. HMGB1 contribute to the pathogenesis of various chronic inflammatory and autoimmune diseases, and cancer. High serum levels are found in several inflammatory events including sepsis, rheumatoid arthritis, atherosclerosis, chronic kidney disease, systemic lupus erythematosus (SLE)[52].

Using banked serum samples from NSCLC patients who received ICI treatment, we established the ELISA to measure the HMGB1 protein levels in the plasma samples (Figure 9). Our preliminary data showed that patients with irAEs had relatively higher plasma HMGB1 level compared to those patients who did not have irAEs. Further study is warranted to verify this finding and correlate the level of plasma HBGB1 with the severity of irAE.

Figure 9: Plasma HMGB1 levels in NSCLC patients who underwent and responded to immunotherapy.
There are 7 patients with irAEs and 3 patients without irAEs during treatment period.



1.3.4 Rationale to allow COVID-19 infected cancer patients to receive CD24Fc

The COVID-19 pandemic has presented unprecedent challenges and learning opportunities to the global community and all health care providers to patients, especially elderly cancer patients on active treatment with compromised immune systems. A small retrospective analysis showed the cancer patients with COVID-19 infection have much higher death rate than those infected but without cancer diagnoses. It also suggested that the cancer survivors are more vulnerable than the general population [53]. With the ongoing COVID-19 pandemic and accumulation of asymptomatic carriers in the general population, we expect to see more cancer patients tested positive for SARS-CoV-2 infection. At this time, no specific recommendations can be made by professional societies such as American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) [54, 55] for delaying life-saving cancer directed therapy such as immune checkpoint inhibitor therapy in patients who are asymptomatic or recovered from SARS-CoV2 infection.

Preclinical and clinical studies have demonstrated that CD24Fc effectively address the major challenges associated with COVID-19. First, a Phase I clinical trial on heathy volunteers not only demonstrated safety of CD24Fc, but also demonstrated its biological activity in suppressing expression of multiple inflammatory cytokines. Second, in Phase II clinical trial in leukemia patients undergoing hematopoietic stem cell transplantation (HCT), three doses of CD24Fc effectively eliminated severe (Grade 3-4) acute graft vs host diseases (GVHD), which is caused by transplanted T cells attacking recipient target tissues. Third, in preclinical models of HIV/SIV infections, CD24Fc ameliorated production of multiple inflammatory cytokines, reversed the loss of T lymphocytes as well as functional T cell exhaustion and reduced the leukocyte infiltration of multiple organs. It is particularly noteworthy that CD24Fc reduced the rate of pneumonia in SIV-infected Chinese rhesus monkey from 83% to 33%. Therefore, CD24Fc maybe a prime candidate for non-antiviral biological modifier for COVID-19 therapy. On April 8, 2020, OncoImmune received FDA approval for conducting a Phase III clinical trial for the treatment of severe COVID-19

patients (NCT04317040). The first interim analysis of 71 subjects on safety and futility demonstrated that the overall 14-day mortality rate is remarkably low in 4% (3/71) in this Phase III randomized double blind placebo controlled clinical trial for severe and critical COVID-19 patients. The drug is safe without any adverse events directly related to it. There is no infusion reaction or allergic reaction to the drug. With the increasing testing ability for SARS-CoV2 infection and immunity at UC Davis Health, we anticipate identifying cancer patients who have recovered from COVID-19 or are asymptomatic carriers for SARS-CoV2 virus. Since CD24Fc are being evaluated as a non-antiviral-based immune modulator to treat patients with COVID-19, we will allow cancer patients who have recovered from COVID-19 or who are asymptomatic carriers for SARS-CoV2 virus in this protocol after they are cleared by infectious disease physicians for transmission risk.

1.4 Clinical Experience of CD24Fc in Humans

1.4.0 Phase I Summary:

OncoImmune Inc. has developed and manufactured clinical grade CD24Fc for use in humans. CD24Fc has been tested in a Phase I clinical trial in healthy human subjects, and this study showed preliminary safety of single dose CD24Fc by IV administration. A total of 40 subjects were randomized in 5 cohorts of 8 subjects, and 39 subjects completed the study. CD24Fc was administered via IV infusion over 1 hour at doses ranging from 10 to 240 mg, and the subjects were followed over a six-week period. A MTD was not encountered.

In general, adverse events were mild to moderate in severity. The most common AEs were headache (6 [15.0%] subjects), burns second degree (3 [7.5%] subjects), non-sustained ventricular tachycardia (2 [5.0%] subjects), and upper respiratory tract infection (2 [5.0%] subjects). The rates of the AEs were similar in the placebo control group. The SAE of ventricular tachycardia was considered mild in severity by the investigator and did not lead to discontinuation of the subject from the study. This SAE was considered to be drug related due to its close temporal proximity to dosing, though similar short, isolated episodes of non-sustained ventricular tachycardia may be seen in up to 4% of normal, healthy populations. No deaths or adverse events leading to discontinuation occurred during the study.

1.4.1 Phase IIa Summary:

A Phase IIa prospective randomized double-blind clinical trial of CD24Fc for acute GVHD prophylaxis in myeloablative matched unrelated donor HCT was initiated in July 2016. The first patient was enrolled in Sept 2016. A total of 24 patients were enrolled in three cohorts, 240mg single dose given at day -1, 480mg single dose at day -1, 480-240-240mg multi-dose given on day -1, day 14 and day 28, with 6 patients receiving CD24Fc and 2 patients receiving placebo in each cohort. The last patient was enrolled in Dec 2017. The last patient reached 100 days post-HCT on Apr. 5, 2018. Data was locked and unblinded on May 17, 2018. In total there are 18 patients in the CD24Fc group and 6 patients in the placebo group (3:1 randomization). All planned dosages were delivered on schedule.

Subjects between the ages of 18-70 years old undergoing matched unrelated donor allogeneic HCT for a malignant hematologic condition (AML, ALL, CML, CMML, MDS) with a Karnofsky performance score ≥70% were eligible for the trial. An 8/8 HLA allelic match between the unrelated donor and the recipient at HLA-A, HLA-B, HLA-C, and HLA-DRB1 was required. All subjects received myeloablative conditioning and standard of care GVHD prophylaxis with methotrexate and tacrolimus per the Phase IIa protocol. Patients received a myeloablative conditioning regimen consisting of either fludarabine and busulfan (Flu/Bu) or cyclophosphamide and total body irradiation (Cy/TBI), as decided by the treating physician, followed by an infusion of stem cells on day 0. The source of donor stem cells was either peripheral blood stem cells (PBSC) or bone marrow (BM). GVHD prophylaxis was administered to all

subjects and consisted of tacrolimus (initiated Day -3 before transplant) and methotrexate (initiated Day +1 after transplant) in combination with CD24Fc in the treatment arms, and tacrolimus/methotrexate plus saline solution in the placebo arm. In the absence of GVHD, tacrolimus tapering started on day +100.

Overall, CD24Fc was well tolerated in the Phase IIa study. There were no infusion-related toxicities. There was one possible drug related treatment emergent adverse event (TEAE) of grade III-IV hyperglycemia in the 480 mg CD24Fc group, which was managed with insulin. One dose-limiting toxicity (DLT) was observed in the placebo group, and no DLTs were observed in the CD24Fc group. There were no adverse events leading to death in subjects administered CD24Fc within the 180 days. There was one adverse event of pneumonia that led to the death of a subject at Day 48 in the placebo group. The development of anti-drug antibodies (ADA) were not detected in any of the 24 subjects at any point out to day 100 after HCT.

The most common TEAEs grade III-IV (> 10%) included a decrease in platelet counts (83.3% placebo and 94.4% CD24Fc), decrease in WBC counts (66.7% placebo and 88.9% CD24Fc), decrease in neutrophil counts (50% placebo and 83.3% CD24Fc), decrease in lymphocyte counts (50% placebo and 77.8% CD24Fc), anemia (50% placebo and 66.7% CD24Fc), stomatitis (83.3% placebo and 50% CD24Fc), and nausea (0% placebo and 11.1% CD24Fc). These are expected SAEs were anticipated as they were hematologic in nature and were otherwise considered related to the myeloablative conditioning regimen of HCT.

In the Phase 2a study, compared to placebo, treatment with CD24Fc resulted in trends toward:

1. Higher Grade III to IV acute GFS rate at Day 180 (94.4% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.1),
2. Higher DFS rate at 1 year (83.3% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.2),
3. Better OS rate at 1 year (83.3% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.2),
4. Higher Grade III to IV acute GRFS rate at Day 180 (83.3% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.2),
5. Lower incidence of Grade III-IV acute GVHD by Day 180 (5.6% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.1),
6. Lower cumulative incidence of leukemia relapse at 1 year (11.1% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.3),
7. Lower incidence of non-relapse mortality at 1 year (5.6% in CD24Fc treatment group, 16.7% in placebo) (hazard ratio = 0.3),
8. Higher cumulative incidence of Grade II to IV acute GVHD by Day 100 (38.9% in CD24Fc treatment group, 16.7% in placebo) (hazard ratio = 2.6),
9. Slightly higher Grade II to IV acute GFS rate at Day 180 (61.1% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.8),
10. Slightly higher 1 year GRFS (Grade III-IV acute GVHD / chronic GVHD requiring systemic immunosuppressive treatment /relapse free survival) (32.4% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.7),
11. Higher cumulative incidence of all grade chronic GVHD at 1 year (63.3% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 2.1).

An open label single arm Phase II expansion cohort with 20 subjects was initiated in June 2019. The study completed the enrollment of 20 patients in Dec. 2019. The dosing schedule is 480-240-240 mg at Day -1, Day 14 and Day 28 post-hematopoietic cell transplantation. All patients had the first dosing of 480 mg CD24Fc. There was no infusion reaction. There was no adverse event that can be attributed to CD24Fc. All subjects have completed the 180-day primary endpoint follow up time on June 16, 2020. There are no Grade

III-IV acute GVHD in this cohort. The preliminary outcome data is in consistent with the Phase IIa results, confirming the efficacy of CD24Fc in reduction of acute GVHD, reduction of leukemia relapse.

In summary, the preclinical data and the human clinical trial experience on CD24Fc have provided solid scientific foundation for the proposed Phase Ib/II clinical trial. Based on the reported phase I and phase II data, the CD24Fc regimen to be tested in this study is 480 mg on day 1, 240 mg on day 14 and day 28 i.v. (a total course of 28 days).

1.5 Rationale

We hypothesize that tissue damage-associated molecular pattern (DAMP) signaling contributes to the pathogenesis of irAEs. CD24Fc binds to DAMPs such as HMGB1, HSP70, and HSP90, preventing them from associating with TLRs to activate downstream NF-κB. In addition, CD24Fc binds to and activates murine Siglec-10 (Siglec-G in humans), whose signaling also results in suppression of NF-κB. Both actions inhibit NF-κB-mediated aspects of the DAMP response, such as secretion of inflammatory cytokines. Thus, CD24Fc given to patients developed irAEs to ICI could selectively reduce autoimmunity triggered by tissue damage and ameliorate irAEs, without interference to the mechanistically distinct, anti-tumor action of ICIs. Of note, there are paradoxical effect of steroids on the PRR signaling. Low concentrations of endogenous glucocorticoids sensitize the innate immune system by upregulating PRRs, cytokine receptors and complement factors, thus allowing for rapid responses to danger signals. High concentrations of glucocorticoids, by contrast, suppress signals that are mediated by PRRs and cytokine receptors, thereby preventing excessive and/or prolonged immune responses [29].

This pilot, phase I/II trial aims to obtain preliminary safety and efficacy data of CD24Fc for treating grade 2 or 3 irAEs in patients with advanced/metastatic solid tumors who required treatment interruption on ICIs. Based on the reported phase I and phase II data, the CD24Fc regimen is 480 mg on day 1, 240 mg on day 14 and day 28 i.v. (a total course of 28 days).

The knowledge gained from this pilot project will support further investigation of the mechanism of irAEs and provide the basis for a phase III clinical trial to formally evaluate the efficacy and safety of CD24Fc in treating irAEs in patients with advanced/metastatic solid tumors who required treatment interruption on ICIs and allowing the patients to resume the ICI treatment safely.

2. SAFETY IN HUMANS

2.0.0 Phase 1 Safety Data

A Phase I, randomized, double-blind, placebo-controlled, single ascending dose study to assess the safety, tolerability, and PK of CD24Fc in healthy male and female adult subjects was conducted. Details are also provided in section 3.8 A total of 40 subjects were randomized in 5 cohorts of 8 subjects each, and 39 subjects completed the study. CD24Fc was administered via IV infusion over 1 hour. In total, 18 (45.0%) subjects had a treatment-emergent adverse event (TEAE) during the study: 6 (60.0%) subjects in the placebo group, 2 (33.3%) subjects in the CD24Fc 10 mg group, 3 (50.0%) subjects in the CD24Fc 30 mg group, 2 (33.3%) subjects in the CD24Fc 60 mg group, 3 (50.0%) subjects in the CD24Fc 120 mg group, and 2 (33.3%) subjects in the CD24Fc 240 mg group.

All TEAEs in the study were considered mild to moderate in severity by the Investigator except for 1 subject in the placebo group who experienced a severe headache. The most common TEAEs were headache (6 [15.0%] subjects), burns second degree (3 [7.5%] subjects), non-sustained ventricular tachycardia (2 [5.0%] subjects), and upper respiratory tract infection (2 [5.0%] subjects).

Overall, 5 (12.5%) subjects had a study drug-related TEAE: 1 (10.0%) subject in the placebo group, 2 (33.3%) subjects in the CD24Fc 10 mg group, 1 (16.7%) subject in the CD24Fc 30 mg group, and 1 (16.7%) subject in the CD24Fc 60 mg group. The study drug-related TEAEs during the study were headache (4 [10.0%] subjects) and ventricular tachycardia (1 [2.5%] subject). A drug-related SAE of ventricular tachycardia was experienced by 1 (16.7%) subject in the CD24Fc 60 mg group. This SAE occurred at a rate comparable with normal populations, was considered mild by the Investigator, and did not lead to discontinuation from the study. No subjects died during the study and no subjects discontinued from the study due to an adverse event. There were no clinically meaningful changes from baseline in laboratory parameters, vital signs, ECGs, or physical exams during the study.

2.0.1 Phase IIa safety Data

The number of subjects with TEAEs from Day -1 to 30 or 60 days after the last dosing was the same between all treatment groups: 6 (100.0%) patients in the 240 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480/240/240 mg multiple dose cohort, and 6 (100.0%) patients who received placebo experienced TEAEs.

The most common TEAEs were stomatitis (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 6 [100.0%] patients who received placebo); platelet count decreased (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 5 [83.3%] patients who received placebo); white blood cell count decreased (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 4 [66.7%] patients who received placebo). Severe stomatitis (≥Grade 3) occurred in 3 (50.0%) patients in the 240 mg CD24Fc single dose cohort, 4 (66.7%) patients in the 480 mg CD24Fc single dose cohort, 2 (33.3%) patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 5 (83.3%) patients who received placebo, with a clear inverse correlation between CD24Fc doses and duration of severe stomatitis.

One (16.7%) patient in the 480 mg CD24Fc single dose cohort and 2 (33.3%) patients who received placebo experienced a study drug-related TEAE. The most common study drug-related TEAE was diarrhea (1 [16.7%] patient in the 480 mg CD24Fc single dose cohort and 2 [33.3%] patients who received placebo). No patients in other cohorts experienced a study drug-related TEAE.

The incidence of Grade 3/4/5 TEAEs was the same between all treatments: 6 (100.0%) patients in the 240 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480 mg single dose cohort, 6 (100.0%) patients in the 480/240/240 mg multiple dose cohort, and 6 (100.0%) patients who received placebo. One (16.7%) patient in the 480 mg CD24Fc single dose cohort experienced hyperglycemia that was considered a study drug-related Grade 3/4/5 TEAE.

No patients receiving CD24Fc experienced a DLT during the study. One dose-limiting toxicity (DLT) was observed in the placebo group

In total, 1 (4.2%) patient died during the study. Patient 103-001 received placebo and experienced Grade 4 pneumomediastinum and Grade 5 pneumonia TEAEs that resulted in death. Per the Investigator, it was considered unlikely that these TEAEs were related to study drug.

2.0.2 Treatment Emergent SAEs (TESAEs)

In total, 9 (37.5%) patients experienced TESAEs from Day -1 to 30/60 days after the last dosing: 2 (33.3%) patients in the 240 mg CD24Fc single dose cohort (30 days), 1 (16.7%) patient in the 480 mg CD24Fc single dose cohort (30 days), 4 (66.7%) patients in the 480/240/240 mg CD24Fc multiple dose cohort (60

days), and 2 (33.3%) patients who received placebo (30, 30, 60 days). Treatment-emergent SAEs reported for patients who received CD24Fc (some patients had more than one condition) were nausea (2), stomatitis (1), abdominal pain (1), dehydration (1), decreased appetite (1), device related infection (1), pain (1), weight decreased (1), arthritis (1), cognitive disorder (1), and embolism (1). No patients experienced a study drug-related treatment-emergent SAE.

In total, 1 patient experienced a TEAE that led to discontinuation of study drug: this patient received placebo. Patient 103-001 experienced a Grade 4 pneumonia TEAE that led to discontinuation of study drug (ie, placebo). Per the Investigator, it was considered unlikely that this TEAE was related to study drug.

In Chemistry laboratory tests, the incidence of TEAEs of alanine aminotransferase increased or blood alkaline phosphatase increased were similar between patients who received CD24Fc and patients who received placebo (ALT: 44% vs 50%; ALP 22% vs 17%). The incidence of TEAEs of aspartate aminotransferase increased was higher for patients who received CD24Fc compared to patients who received placebo (28% vs 18%). TEAEs of blood cholesterol increased were only reported by patients in the 480/240/240 mg CD24Fc multiple dose cohort (11%). Treatment-emergent adverse events of blood creatinine increased were only reported by patients who received placebo (33.3%). A TEAE of blood bilirubin increased was reported by 1 (16.7%) patient who received placebo. In general, TEAEs were consistent with toxicities normally associated with HCT conditioning and did not appear associated with investigational therapy or placebo.

Hematologic Effects:

In total, the incidence of TEAEs of white blood cell count decreased, lymphocyte count decreased, and neutrophil count decreased were higher in patients who received CD24Fc compared to patients who received placebo (white blood cells decrease 94% vs 67%, lymphocyte decrease 83% vs 50%, neutrophil decrease 89% vs 50%). The incidence of TEAEs of platelet count decreased was similar between patients who received CD24Fc and patients who received placebo (94% vs 83%).

No patient had a laboratory abnormality that was considered an SAE or resulted in discontinuation of study drug.

No patients who received either single or multiple dosing of CD24Fc had positive ADA results at any time point sampled pre- or post-infusion.

A TEAE of weight increased was reported by 1 (16.7%) patient who received placebo and a TEAE of weight decreased was reported by 3 (16.7%) patients who received CD24Fc. A TEAE of ECG QT prolonged was reported by 1 (16.7%) patient who received placebo.

Donor Cell Engraftment and Chimerism:

In total, 18 (100.0%) patients who received CD24Fc and 6 (100.0%) patients who received placebo experienced neutrophil engraftment. The median time to neutrophil engraftment was 13.5 days for patients in the 240 mg CD24Fc single dose cohort, 13.5 days for patients in the 480 mg CD24Fc single dose cohort, 13.0 days for patients in the 480/240/240 mg CD24Fc multi-dose cohort, and 15.5 days for patients who received placebo.

In total, 18 (100.0%) patients who received CD24Fc and 5 (83.3%) patients who received placebo experienced platelet engraftment. The median time to platelet engraftment was 15.5 days for patients in the 240 mg CD24Fc single dose cohort, 13.0 days for patients in the 480 mg CD24Fc single dose cohort, 12.0 days for patients in 480/240/240 mg CD24Fc multiple dose cohort, and 15.0 days for patients who received placebo. No patients experienced primary engraftment failure.

The mean CD3 cell chimerism on Day 28/Day 30 was 73.0% donor cells for patients who received CD24Fc and 77.4% donor cells for patients who received placebo. The mean CD3 cell chimerism on Day 100 was

80.9% donor cells for patients who received CD24Fc and 73.8% donor cells for patients who received placebo.

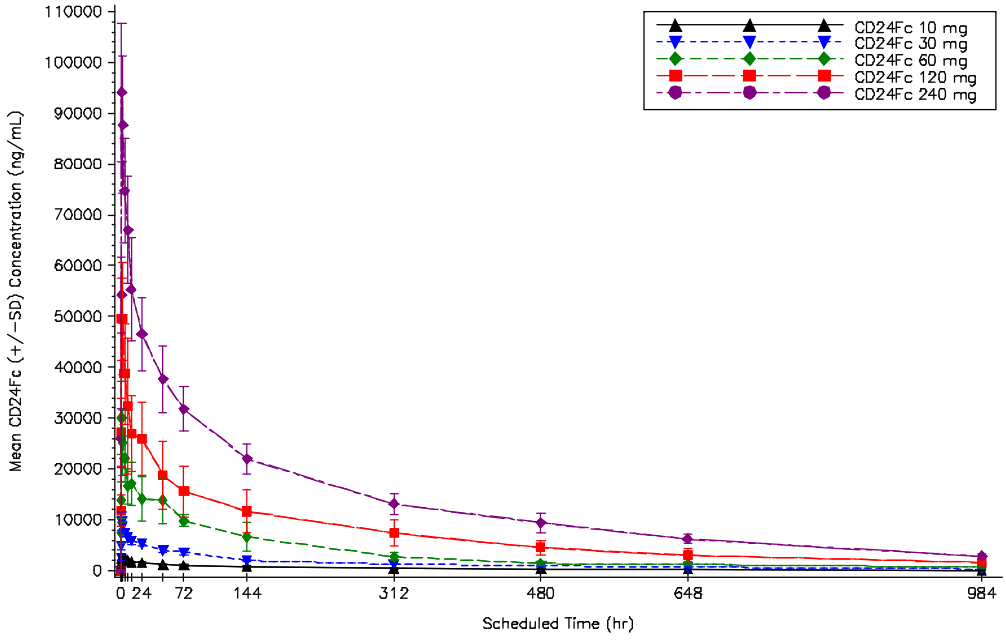
The mean CD33 cell chimerism on Day 28/Day 30 was 100.0% donor cells for patients who received CD24Fc and 100.0% donor cells for patients who received placebo. The mean CD33 cell chimerism on Day 100 was 99.4% donor cells for patients who received CD24Fc and 96.6% donor cells for patients who received placebo.

2.1 Pharmacokinetics in Humans

2.1.0 Phase I PK

The PK of CD24Fc in healthy human subjects was determined from the single dose Phase 1 study. The mean plasma concentration of CD24Fc increased proportionally to the dose of CD24Fc administered (Figure 10). For all dose groups except 120 mg, the maximum mean plasma concentration of CD24Fc was reached at 1 hour post-dose. The maximum mean plasma concentration of CD24Fc for the 120 mg group was reached at 2 hours post-dose. By Day 42 (984 hours), the mean plasma concentration of CD24Fc for all groups had decreased to between 2% and 4% of the maximum mean plasma concentration. The plasma CD24Fc reached Tmax at 1.34 hours. The t½ of plasma CD24Fc range was 280.83 to 327.10 hours.

Figure 10: Plot of Mean (±SD) Plasma CD24Fc Concentration by Treatment – PK Evaluable Population



PK = pharmacokinetic; SD = standard deviation.
Source: Investigators Brochure.

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2.1.1 Phase IIa PK

The PK of CD24Fc in human subjects undergoing HCT has been determined from the Phase IIa study from the two single dose cohorts and one multi-dose cohort. With the 240 mg single dose, the mean plasma concentration of CD24Fc is similar to the 120 mg single dose in Phase I human volunteers. The 480 mg dose shows a proportional increase of CD24Fc at all time points (Figure 11, upper panel). The 480/240/240 mg multi-dose maintains the CD24Fc plasma concentration over 10,000 ng/ml over the period of Day-1 to Day 42 post-HCT (Figure 11, lower panel).

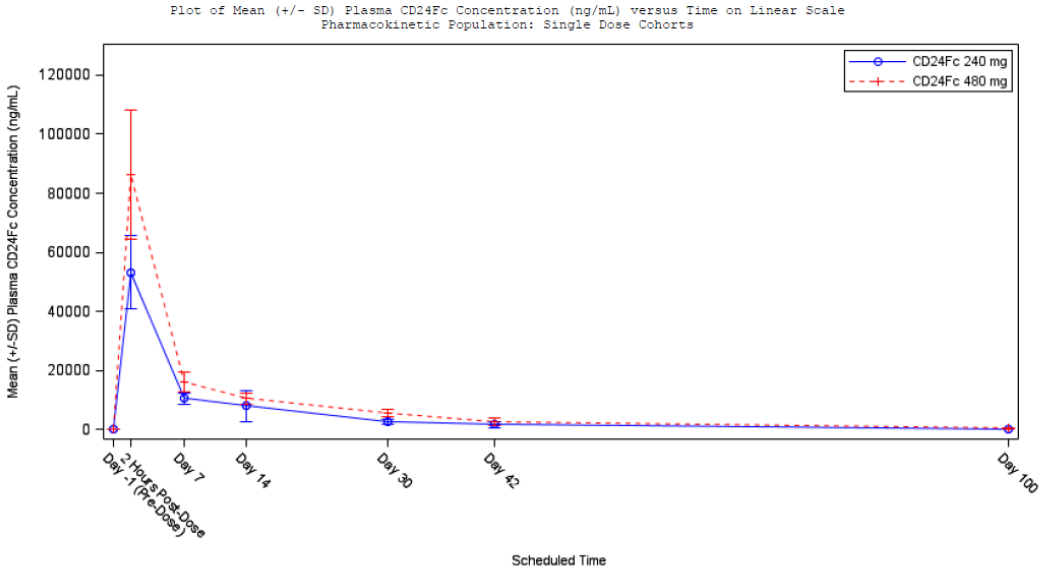
Following a single IV administration of CD24Fc (240 and 480 mg CD24Fc single dose cohorts), the geometric mean plasma exposure ($C_{max,-1d}$, AUC_{0-42d}, and AUC_{0-inf}) increased with increasing CD24Fc doses. The mean $t_{½}$ and λ_z were similar between the 240 and 480 mg doses of CD24Fc. The mean values of $t_{½}$ were 414.739 and 406.648 h and the mean values of λ_z were 0.0018 and 0.0017 h^{-1} for the 240 and 480 mg CD24Fc single dose cohorts, respectively. Additionally, there was an increase in the mean V_z and CL between the 240 and 480 mg doses of CD24Fc.

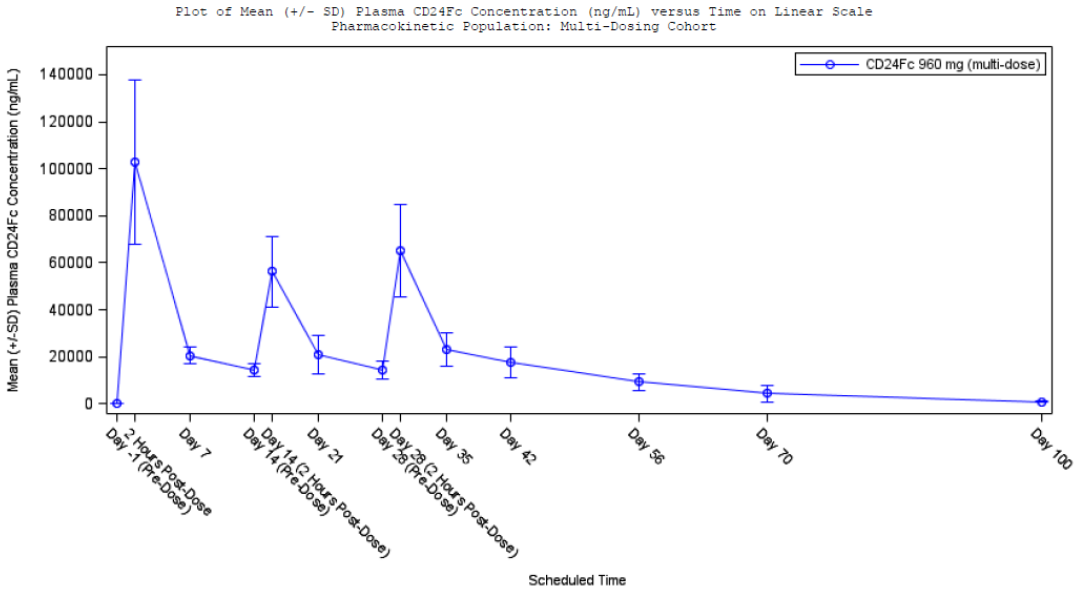
Following multiple IV administrations of CD24Fc (480/240/240 mg CD24Fc multi-dose cohort), the exposure of CD24Fc was sustained over time. Additionally, the mean plasma CD24Fc concentration on Day 100 was higher for the 480/240/240 mg CD24Fc multi-dose cohort (850.84 ng/mL) compared to the single dose cohorts (216.38 ng/mL and 330.96 ng/mL for the 240 and 480 mg CD24Fc single dose cohorts, respectively). Furthermore, the geometric mean $AUC_{0-last,overall}$ value was higher for the 480/240/240 mg CD24Fc multi-dose cohort (37,363,953.5 ng·h/mL) compared to the single dose cohorts (10,156,549.9 ng·h/mL and 15,522,686.2 ng·h/mL for the 240 and 480 mg CD24Fc single dose cohorts, respectively).

The median $t_{max,-1d}$ (2.10 h for both the 240 and 480 mg CD24Fc single dose cohorts and 2.13 h for the 480/240/240 mg CD24Fc multiple dose cohort) remained consistent across all of the CD24Fc doses. For the 480/240/240 mg CD24Fc cohort, the median $t_{max,-1d}$ and $t_{max,28d}$ were similar (2.13 and 2.52 h, respectively).

Figure 11: Plot of Mean (±SD) Plasma CD24Fc Concentration by Treatment – PK Evaluable Population.

(Upper). Single dose cohorts, 240mg (n=6); 480mg (n=6). (lower). multi-dose cohort. 480-240-240mg (n=6).





2.2 Immunogenicity in Humans

2.2.0 Phase 1 ADA

Serum samples in the Phase I study were screened for anti-drug antibodies. Anti-CD24Fc antibodies were detectable at Day 28 and Day 42 in 1 subject in each of the 5 dose cohorts; however, for the subject in the CD24Fc 120 mg group and the subject in the CD24Fc 240 mg group, anti-CD24Fc antibodies were also detectable pre-dose at levels higher than post-dose levels. Except for those subjects with significant pre-dose anti-CD24Fc antibody levels, all post-dose anti-CD24Fc antibody levels were modest. No deviations in PK were found in any subjects with detectable anti-CD24Fc antibody levels.

2.2.1 Phase IIa ADA

In the Phase IIa allogeneic HCT context, given the immunoablation and immunosuppression of host immunity at time of CD24Fc administration, ADA responses were monitored but unlikely to be elicited.

For the two single dose cohorts, the samples were collected at 7 time points from Day-1 to Day 100. For the multi-dose cohort, the samples were collected at 13 time points from Day-1 to Day 100. All samples are negative for ADA in the Phase IIa study.

3. STUDY MEDICATION

3.0 Study drug: CD24Fc or CD24 IgG (OncoImmune, Inc.) and placebo

CD24Fc (CD24 IgG) is a fusion protein consisting of the extracellular domain of mature human CD24 linked to the human immunoglobulin G1 (IgG1) Fc domain.

The placebo is 0.9% Sodium Chloride Solution for IV infusion.

3.0.0 Molecular Formula and Formulation

The complete molecular formula of CD24Fc has not been determined at this time. The mature protein is 261 amino acids long and each CD24Fc molecule includes the 30 amino acid CD24 extracellular domain. CD24Fc forms a disulfide-linked homodimer with a predicted mass of 57.7 kilodaltons (kDa) based on the homodimer amino acid sequence. However, the apparent molecular weight of the intact dimer is approximately 80 KDa based on non-reduced SDS-PAGE. The CD24 domain is highly glycosylated with both N-linked and O-linked oligosaccharides, which comprise approximately 80% of the mass of the CD24 domain.

Name	CD24Fc for IV infusion.
Vial content	120mg/12mL
Formulation	Liquid formulation for IV infusion.
Route	IV Infusion
Storage	-20°C, avoid light.
Manufacturer	Catalent, Inc.
Provider	OncoImmune, Inc

3.0.1 Packaging, Ordering, and Inventory Management

CD24Fc is supplied in clear borosilicate glass vials with chlorobutyl rubber stoppers and aluminum flip off seals. Drug product vials are stored at OncoImmune's clinical distribution site, ALMAC Clinical

Services, at 25 Fretz Road, Souderton, PA. Study site (UCDCC) IDX pharmacy will order the drug for onsite storage after the study activation.

Availability, Storage and Stability

CD24Fc is supplied as a sterile, clear, colorless, preservative-free aqueous solution for parenteral administration. CD24Fc will be stored at -20° C until removed for use. Remove the CD24Fc vials from the freezer and thaw immediately prior to dose preparation. The CD24Fc infusion should begin within 3 hours after reconstitution.

3.0.2 Administration

CD24Fc at doses of 480 mg or 240 mg will be prepared in a diluent comprising 0.9% Sodium Chloride in a volume of 100 ml and be administrated by intravenous infusion over a minimum of 60 minutes as specified in Section 6.2

3.0.3 Disposal and Destruction

Responsibility for drug accountability is on the investigator and the assigned pharmacist or designee. Drug supply will be disposed of according to institutional standard operating procedures. Accurate records of all investigational product received at and dispensed from the study site should be recorded on the Drug Log.

4. TOXICITIES MONITERED

4.0 Treatment-Related Toxicities

The toxicity scale, definitions, and specific criteria for each toxicity level will be those as outlined in the guidelines defined by the NCI CTCAE version 5.0. (Appendix 4). If the patient develops any grade 3 or greater hematologic or non-hematologic toxicity that is possibly, probably, or definitely related to the CD24Fc, no further drug administration will be given to that patient and the patient will be removed from protocol therapy (see Section 4.1). Treatment delay within 3 scheduled days is allowed. Dose modification based on the renal and hepatic function values and hematologic laboratory values (see Section 6.4).

4.1 Phase I Dose Limiting Toxicities

1) Grade 4 non-hematologic toxicity (not laboratory).
2) Grade 4 hematologic toxicity including Grade 4 neutrophil count decrease, Grade 4 platelet count decrease or Grade 4 anemia regardless of duration.
3) Grade 3 Neutrophil count decrease lasting > 1 week, or febrile neutropenia.
4) Grade 3 Platelet count decrease lasting > 1 week, or Grade 3+ thrombocytopenia with bleeding.
5) Grade 3 non-hematologic toxicity (not laboratory) will be considered a DLT with the following exceptions: grade 3 fatigue, Grade 3 nausea, vomiting, or diarrhea lasting < 72 hours, (Grade 3 nausea, vomiting, or diarrhea lasting >72 hours despite optimal supportive care is a DLT).
6) Any Grade 3 non-hematologic laboratory value if:
   - Associated with clinical symptoms or signs, or
   - Medical intervention is required to treat the patient, or
   - The abnormality leads to hospitalization, or
   - The abnormality persists for >1 week.
7) AST and/or ALT elevation >20 x ULN with concurrent total bilirubin elevation to >5 x ULN

without initial evidence of cholestasis.

8) Grade 5 toxicity (i.e., death).

The treatment related toxicities should be evaluated as CD24Fc treatment emergent AE that is not associated to irAEs defined in enrollment. The DLT monitoring period is the 14 days after the first dose of CD24Fc at 480 mg. If DLT occurred in 2 patients during the first dose of CD24Fc dosing in the 14-day period, CD24Fc will be reduced to 240 mg as first dose, or 120 mg until no more than 1/6 patients developed DLT. The study will be terminated if >2 patients have DLT at this reduced dosing. In Phase I, patients will be dosed at least two hours apart and no more than two patients will be enrolled in the same day.

4.2 Managing Infusion Reactions

Although infusion reactions were not observed in the Phase 1 and Phase IIa clinical trials, there is a theoretical potential for CD24Fc to result in infusion reaction. CD24Fc, which includes a human portion IgG1 may induce FcγR cross-linking, which has been associated with infusion reactions for some therapeutics.

Supportive care and vitals monitoring (including but not limited to supplemental oxygen, diphenhydramine, acetaminophen, ibuprofen, steroids and fluids) in the event of infusion reaction will be allowed and be dictated per institutional standards and policies. Depending on the severity of the infusion reactions, patient might be resumed the study drug at the discrepancy of the treatment physician. Patient will be permanently discontinued from the study if infusion reactions recur despite of pre-medications.

4.3 Ventricular Tachycardia

In the phase 1 first in human clinical trial a SAE of ventricular tachycardia was observed in one healthy individual that received 60mg of CD24Fc. Though this was considered mild in severity by the investigator and did not result in discontinuation of the subject from study, patient undergoing CD24Fc will be closely monitored for cardiac SAE.

Vital signs will be checked at immediately before and after each infusion of CD24Fc. EKG will be done before and after receiving CD24Fc. If at any time an episode of arrythmia develops during treatment, study drug should be held until resolution of SAE. If the reaction is considered severe (e.g. symptomatic, hypotension requiring urgent intervention) study drug should be discontinued.

5. SUBJECT SELECTION

Subjects with advanced/metastatic or recurrent solid tumors (stage IV) of any primary site, with emphasis on non-small cell lung cancer, melanoma, bladder, and breast cancer that is incurable with available therapies will be recruited from the UC Davis Comprehensive Cancer Center (Appendix 5).

5.0 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry.

1) Ability to understand and willingness to sign an informed consent form.
2) At least 18 years of age.
3) Histologically confirmed advanced solid tumors.

4) Patients must have grade 2 or 3 irAEs from at least one ICI-containing regimen. Both newly emerging and persistent irAEs are allowed. Systemic steroid therapy or any other form of immunosuppressive therapy for irAEs is allowed. The specific irAEs are:
    a. Grade 2-3 Diarrhea/Colitis: Patients with ≥4 stools per day or moderate-severe increase in ostomy output compared to baseline but not life-threatening diarrhea;
    b. Grade 2-3 Pneumonitis: Mild to moderate (grade 2) or severe (grade 3) symptoms (including hypoxia, shortness of breath, requiring oxygen) but not life-threatening respiratory compromise requiring urgent intervention (e.g., tracheostomy or intubation)
    c. Grade 2-3 Renal irAE: Creatine increased between 1.6-6.0 x ULN or ≤3.0 x baseline if baseline was abnormal, eGFR or creatinine clearance ≥15 ml/min/1.73m^2 but not life-threatening consequences or requiring dialysis.
    d. Grade 2-3 Hepatic irAE: AST/ALT/ALP levels 3-20 x ULN, and T bilirubin increased ≤5 x ULN
    e. Grade 2-3 Skin Rash: moderate (10-30% body surface area, BSA) to severe (>30% BSA) but not life-threatening skin lesions or Stevens-Johnson syndrome.
5) ECOG performance status <2. (Appendix 1).
6) Life expectancy of ≥ 3 months at the time of enrollment.
7) All patients must have a pretreatment absolute neutrophil count (ANC) ≥ 1,000 /μL, hemoglobin ≥ 8 gm/dL and a pretreatment platelet count of ≥ 75,000 /μL obtained within 14 days prior to 1st dose of treatment.
8) Female subjects who are of non-reproductive potential (i.e., post-menopausal by history – no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Or, female subjects of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to the first study drug administration.
9) Male and female subjects who agree to use highly effective method of birth control (e.g., implants, injectables, birth control pills with two hormones, intrauterine devices [IUDs], complete abstinence or sterilized partner, and female sterilization) and a barrier method (e.g., condoms, vaginal ring, sponge, etc.) during the period of therapy and for 90 days after the last dose of study drug.

5.1 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

1) Prior CD24Fc Therapy.
2) Any known active hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, including patients who have an active infection requiring systemic therapy. History of COVID-19 or known asymptomatic carrier of SARS-CoV-2 virus is allowed.
3) Pregnant or lactating women.
4) Any medical condition including additional laboratory abnormalities, or psychiatric illness that would, in the opinion of the investigator, prevent the subject from participating and adhering to study related procedures.
5) Any known severe bacterial, fungal, or viral infection that in the opinion of the investigator would interfere with patient safety or compliance on trial within 2 weeks prior to enrollment.

6) Patients with concomitant proarrhythmic medications. (Appendix 6).
7) Patients with heart failure in NY Heart Association class IV.
8) Any grade 4 irAE symptoms and CTCAE v5.0 grade 4 toxicity. (Appendix 4)
9) Renal, liver and cardiac toxicities as defined below:

Hepatic	AST, ALT, GGT, or ALP	>20.0 x ULN regardless of baseline
	Blood Bilirubin	>5.0 x ULN regardless of baseline
Renal	Creatinine	> 6.0 x ULN or creatinine clearance <15 ml/min/1.73m2
	Urine: Anuria	<140 ml in 24 hours
Electrolytes	Hyponatremia, sodium	<120 mmol/L
	Hypokalemia, potassium	<2.5 mmol/L
Cardiac	CPK	>10.0 ULN
	ECG	Prolonged QT interval ≥480mS, corrected by Fridericia's formula. Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrythmia.

6. STUDY DESIGN AND RULES FOR INFUSION SERIES CONTINUATION

This is a study at the University of California, Davis Comprehensive Cancer Center (UCDCCC). Registration and assignment to the repeated infusions will be done centrally at UCD. (Appendix 2 and Appendix 3).

Rules for dosage/infusion continuation and termination are given below.

6.0 Screening Phase

All patients being considered for this trial will be pre-screened prior to protocol therapy for the following:

Patients who meet the above criteria (in addition to those outlined in section 3.0) will be deemed eligible for protocol therapy.

6.1 Treatment Phase

This is a phase I/II study to determine the safety, tolerability, and efficacy of CD24Fc in patients who needed treatment interruption from irAE with ICI. This study will be divided into two studies. Phase I study is to evaluate safety and tolerability of CD24Fc for treatment of irAE. Phase II consists of a randomized control study evaluating efficacy of CD24Fc in reducing duration of irAE and rate of recovery from irAE.

6.1.0 Phase I Safety Study

In the Phase I study, patients with unresectable or metastatic solid tumors who developed grade 2-3 irAEs and treatment interruption to immunotherapy will be selected for treatment. Once enrolled, CD24Fc will be administered every 2 weeks along with standard of care (i.e., steroids per treating physician and best supportive care) for 3 treatments. All 6 patients shall complete 3 treatments. For treatment dosing and schedule see Table 1 and Figure 1. Patients may receive steroids at the discretion of the treating physician prior to and during treatment with CD24Fc. Two weeks after completing dose 3 of CD24Fc (Day 42) patients will be re-evaluated for resolution of irAE. At the discretion of the treating physician patient can be evaluated for retreatment with ICI at this time. Patient will undergo end of study evaluation on day 60. Post study irAE and survival follow up will consists of chart check every 3 months for up to 1 year.

6.1.1 Phase II Randomized Double Blind Placebo Controlled Study

Phase II study will consist of a randomized double blind placebo controlled study involving patients who have treatment interruption due to grade 2 or 3 irAEs. Patients may receive steroids at the discretion of the treating physician prior to and during treatment with CD24Fc. As the steroids is the most commonly used SOC therapy for irAEs and it affects the severity and duration of irAE, we will separate the subjects into two groups based on the status of steroids use at registration. Each group of patients will be randomized (1:1) to receive CD24Fc vs placebo in addition to SOC treatment for irAE. Patients who are randomized to treatment with CD24Fc will receive treatment every 2 weeks for total of three treatments. Placebo group will receive 100 mL of normal saline every 2 weeks for total of three treatments. Refer to Table 2 and Figure 2 for treatment schedule. All patients shall complete 3 treatments.

Two weeks after completing the third treatment dose, patients will be re-evaluated for retreatment with ICI at the discretion of the treating physician and post treatment re-evaluation. Thereafter, patients will continue to end of treatment safety follow up on day 60. After the end of treatment, we will follow patients with irAE and survival by chart check every 3 months for up to 1 year.

6.2 Serum Sample Collection

During active treatment with CD24Fc CBC and CMP will be collected based on schedule see Tables 1 and 2.

6.3 Drug Administration and Monitoring

CD24Fc or placebo will be administrated by intravenous infusion over 60 minutes.

Vital sign monitoring before the dosing, during and 1-hour post infusion by registered nurse per institutional standard.

If the patient misses a dose, an infusion would be rescheduled within 3 days. Otherwise, the dose will be omitted.

6.4 Dose modification based on laboratory values

6.4.0 Renal Function

If estimated GFR is less than 15 mL/min on the scheduled day of dosing, then the dose be held. If GFR recovers to greater than 15 mL/min within the protocol defined treatment period window (up to day +3), then CD24Fc may be resumed.

6.4.1 Hepatic Function

CD24Fc will be administered on the scheduled day if AST or ALT is ≤20x ULN and total bilirubin is ≤ 5x ULN.

6.4.2 Hematologic laboratory values

CD24Fc will be administered on the scheduled day if absolute neutrophil count (ANC) ≥ 1,000 /μL, hemoglobin ≥ 8 gm/dL and a pretreatment platelet count of ≥ 75,000 /μL.

6.4.3 Dose adjustment

There should be a one level dose reduction (i.e., CD24Fc 240 mg on day 1, 120 mg on day 14, and 120 mg on day 28 i.v.) if any ≥G3 hematologic due to CD24Fc that requires < 2 week to recover to grade 1 or less. There will be no dose reduction according to irAEs.

6.5 Concomitant Therapy

Concomitant ICI and chemotherapies are not allowed during the study period.

Patients may receive ongoing supportive and palliative care (e.g., nutritional support, pain control) as clinically indicated throughout the study. Bisphosphonate therapy is allowed as part of supportive care before or after the study. Steroids are permitted in the study as outline in section 6.2. Patients enrolled to the study will receive steroid treatment as well as other recommended treatment for a given irAE if recommended per the treating physician. Patients who develop urgent complications in previously documented sites of disease may receive palliative radiation therapy. Continuation on the protocol therapy will be determined by discussions with the sponsor and the investigator, if medically appropriate.

6.6 Toxicity

A brief written summary documenting the toxicity or adverse reactions after the 6th patient (phase I study) has received his/her 3th dose will be prepared with input from the UCD clinical PI. The brief report will summarize and define if the study should continue or be terminated. At the end of Phase II study, a summary will likewise be completed to address the same issues. A recommendation whether to continue onto a Phase II clinical trial will also be included.

Toxicity assessments will be done by the treating physician or their licensed representative (such as nurse practitioner) on the days of therapy.

Patients with progressive disease will be counseled as to the option of exiting the study. They will be advised on their disease progress and future options, and their response, if any, to the therapy.

6.7 Criteria for Removal from Protocol Treatment

- Unacceptable toxicity (as determined by the treating physician and/or the patient), or toxicity requiring discontinuation of treatment (See sections 4.0 and 4.1).
- Elevation in AST or ALT >20x ULN on bloodwork prior to CD24Fc treatment.
- Elevation of total bilirubin >5x ULN on bloodwork prior to CD24Fc treatment.
- If the recovery of any ≥G3 hematologic or non-hematological toxicity due to CD24Fc to grade 1 or less requires > 2 weeks.
- Patients may choose to withdraw from the study at any time for any reason.
- Patients may be withdrawn from the protocol at the investigator's discretion if the investigator feels that continuation is not in the patient's best medical interest or if the patient is non-compliant with treatment.
- Completion of treatment CD24Fc.
- All reasons for discontinuation of treatment must be documented in the case report forms.
- Therapy after Protocol Treatment is stopped: If patients fail to respond to the protocol treatment and/or are removed from the therapy because of toxic effects or "disease progression", further treatment, if any, is at the discretion of the investigator.

Follow-up off Protocol Treatment: After removal from protocol treatment, all patients will be followed for late toxicities. Patients will be seen 4 weeks, 4 months and 7 months after coming off therapy. If ongoing toxicities have not resolved to ≤ grade 1 within the first 4 weeks, patients are to be seen every month until toxicity resolves to ≤ grade 1. No new toxicities after the 4-week follow-up will be re-ported unless considered related to protocol treatment by the investigator.

6.8 Replacement of Removed Patients

Additional patients are allowed to replace patients who choose to withdraw from the study before or within 28-day course of drug administration or patients who were withdrawn from the study at the investigator's discretion. Patients who are removed due to CD24Fc related DLT will not be replaced.

6.9 Criteria for Premature Study Termination for Phase II Study

Patients will be enrolled on the study as outlined above. If, at any time during the study, there is sufficient evidence suggesting an excessive Grade 3 or Grade 4 toxicity rate related to treatment, the study will be terminated. An excessive Grade 3 toxicity rate will be taken to be 20% (or 4 patients) and an excessive Grade 4 toxicity rate will be taken to be 10% (or 2 patients) of the patients enrolled to that date. Evidence that the toxicity rate is excessive will be considered sufficient if the lower limit of the 90% one-sided confidence interval for the estimate of the toxicity rate exceeds the appropriate limit (20% for Grade 3, 10% for Grade 4).

7. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to 1st infusion unless otherwise noted. Please see Tables 1 and 2.

8. CRITERIA FOR EVALUATION AND ENDPOINTS DEFINITIONS

8.0 Definitions

8.0.0 Evaluable For Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with CD24Fc up to 30 days after completion of last dose of treatment.

8.0.1 Acute Toxicity

All patients will be evaluable for toxicity from the drug. All patients will be monitored for 1-hour post infusion with are registered nurse or nurse practitioner within immediate proximity.

8.0.2 Evaluable For Response

8.0.2.0 Tumor Evaluation

All patients will be considered evaluable for response according to RECIST 1.1. For this study, PSA-only disease is included in Non-Measurable disease.

8.1 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the new international criteria proposed by RECIST committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

8.1.0 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (PE, CT, XR, MRI) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

8.1.1 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) are considered non-measurable disease. Bone lesion, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory beast disease, abdominal masses (not followed by CT or MRI) and cystic lesions are all non-measurable. Prostate cancer patients may also have PSA-only disease.

8.1.2 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as target lesions and be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease. If there are > 10 measurable lesions, those not selected as target lesions will be considered together with non-measurable disease as non-target lesions (see section 10.2.4).

8.1.3 Non-Target Lesions

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 10 listed as target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent". The exception for this requirement is the serial evaluation of prostate specific antigen (PSA) levels in the serum. Although PSA values constitute "non-target" disease, in this study which includes a population of patients with hormone refractory prostate cancer, PSA levels are expected to be the principal measure of disease activity and response to therapy, if any.

8.1.4 Response

All patients will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR): disappearance of all clinical and radiological evidence of tumor (both target and non-target).

Partial Response (PR): at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD. Patients may not demonstrate clinical or radiographic evidence of progression of measurable or non-measurable disease during this time period.

Stable Disease (SD): steady state disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD): at least a 20% increase in the sum of LD of measured lesions taking as reference the smallest LD recorded since the treatment started or the appearance of one or more new lesions.

In exceptional circumstances unequivocal progression of non-target lesions may be accepted as evidence of disease progression.

Table 4: Evaluation for tumor response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response For This Category Also Requires
CR	CR	No	CR	≥ 4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 weeks confirmation
PR	Non-PD	No	PR	≥ 4 weeks confirmation
SD	Non-PD	No	SD	Documented at least ≥ 4 weeks from baseline; ≥ 8 weeks for PSA-only disease
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD	Yes or No	PD	No prior SD, PR, or CR
Any	Any	Yes	PD	No prior SD, PR, or CR

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

8.1.4.0 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.

8.1.4.1 Stable Disease Duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.1.4.2 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

9. SPECIAL INSTRUCTIONS

A blood sample of 20-30 ml is to be drawn as outlined in study flow charts (Table 1 and Table 2). Each sample will be collected into a non-heparinized vacutainer with a 20 g or larger needle. Blood samples will be shipped at room temperature until processed to separate the plasma. Serological studies will be performed in all patients during the course of this study to assess the changes in HMGB1 level before, during and after the treatment. The sample should be sent to for on-site processing and storage:

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[redacted]

10. STATISTICAL CONSIDERATIONS

10.0 Endpoints

10.0.0 Primary Endpoints

Phase I: Event of new AE of ⩾grade 3 that are outside the spectrum of irAEs when CD24Fc is given in cancer patients who developed grade 2-3 irAEs.

Phase II: Co-primary endpoints:

- Recovery rate (as defined by reduction of irAE by one grade) at Day 42.
- Time to recovery from grade 2 or 3 irAE (as defined by reduction of at least 1 grade in irAE severity) from the initiation of CD24Fc treatment. Patients who have not been documented to have event (reduction of at least 1 grade) will be censored at the date of the latest clinical assessment that documented as being free of event.

10.0.1 Secondary Endpoints

Phase I:

- Time to irAE reduction by at least 1 grade from the initiation of CD24Fc treatment.

- Time to all irAEs reduced to ⩽1 (by NCI CTCAEv5.0) from the initiation of CD24Fc treatment.
- Time to resume ICI treatment from the initiation of CD24Fc treatment.
- Recovery rate (reduction of irAE by one grade) at D42.

Patients who have not been documented to have above events will be censored at the date of the latest clinical assessment that documented as being free of events.

Phase II:

- Time to all irAEs reduced to ≤1 (by NCI CTCAEv5.0) from the initiation of CD24Fc treatment. Patients who have not been documented to have the event will be censored at the date of the latest clinical assessment that documented as being free of event.
- The use of steroids and other drugs (drug, dose, duration).
- Overall response rate (ORR) after retreatment with ICI with or without CD24Fc after resolution of irAE.
- Progression free survival (PFS) will be calculated as the time from initiation of ICI to first documented evidence of disease progression or death, whichever comes first. Alive patients who have not been documented to have progression will be censored at the date of the latest clinical assessment that documented as being free of progression.
- Overall survival (OS) will be calculated as the time from diagnosis to death. Alive patients will be censored at the date of the latest follow-up visit.

10.1 Randomization for Phase II Study

Steroids is the most commonly used SOC therapy for irAEs. It affects the severity and duration of irAE, which are the key endpoints of this study. We thus will stratify the subjects based on the status of steroids use at registration, Stratified block randomization will be used. Randomization codes will be generated in a permuted block design, stratified by the status of steroids use at registration. The block size will be balanced within each block to maintain a 1:1 ratio between the two groups. For patient who have no steroids use at registration but start on steroids before starting CD24Fc treatment, the patient will be moved to the steroid stratum. If a subject withdraws from participation in the study or changed to steroids use group, his or her randomization code will not be re-used.

10.2 Statistical Analysis

Demographic and background characteristics obtained at enrollment will be listed and summarized. Descriptive statistics will be used to summarize changes of biomarkers from baseline in clinical laboratory parameters for this cohort, and use of steroids (drug, dose, duration) and other treatment for irAE. We will adjust steroids use in analyses. Subgroup analyses will be performed separately by the status of Steroids use.

To assess toxicity: Toxicity is evaluated by NCI CTCAEv5.0. The type, grade, frequency and proportion of toxicities noted during the treatment period will be reported, along with associated 95% confidence interval of proportion. All adverse events noted by the investigator will be tabulated according to the affected body system. In phase I lead-in study, dose limiting toxicity is defined as any new AE of ⩾grade 3 that are outside the spectrum of irAEs.

To assess time to recovery from irAE (time to reduction of irAE by at least one grade), time to all irAEs reduced to ⩽1, and time to resume ICI treatment: All time points will be started from Day 1 of CD24Fc treatment. Kaplan-Meier plots and confidence intervals will be used to summarize outcomes. Medians and associated 95% confidence intervals will be calculated, and comparisons between groups will be

performed by log-rank tests. Cox proportional hazard models will be used to explore association between covariates and outcomes.

To assess recovery rate of CD24Fc (reduction of irAE by at least one grade) at D42 and response rate of ICI: The fraction of patients who experience a PR or CR will be determined by dividing the number of responders by the total evaluable patients. The fraction will be reported along with 95% two-sided confidence intervals. Comparisons between groups will be performed by Fisher's Exact tests. We will also characterize the proportion who remain that either respond or have stable disease, compared to those who progress.

To assess PFS and OS: Kaplan-Meier plots and confidence intervals will be used to summarize PFS, and OS; 1-year OS rate will be reported; medians and associated 95% confidence intervals will be calculated, and comparisons between groups will be performed by log-rank tests. Cox PH models will be used to explore association between outcomes and covariates.

As exploratory analysis, we will summarize descriptively the relationship of response rates to tumor type (lung, breast, prostate) and to cellular immune response, and explore the relationship using logistic regression.

The possibility of bias from missing data will be addressed. Missing pattern and mechanism will be evaluated, and sensitivity analyses will be performed using imputation methods for use of steroid, irAE type, cancer type, etc., if such might affect point estimates and study conclusions.

The study design in the Phase II portion allows steroids and other systemic treatments prior to and during study enrollment. CD24Fc/placebo will be added in addition to standard of care. We will perform a sensitivity test for data from the Phase II study. We will consider isolating the effect of CD24Fc in the future Phase III clinical study.

10.3 Sample Size Justification

Phase I study: We plan to enroll 6 patients in the phase I study. The objective of this phase I study is to confirm the safety of CD24Fc in ICI-treated cancer patients who have treatment interruption due to grade 2 or 3 irAEs and to estimate the median time to recovery and resumption of ICI after treatment interruption due to irAE. The primary endpoint is new AE of ⩾grade 3 that are outside the spectrum of irAEs when CD24Fc is given to treat irAEs. We expect the rate of this event will be less than 33.3%. With a sample size of 6 patients, we would have 74-91% chance to observe at least one occurrence if the true event rate is 20-30%. Hence the sample size is adequate for this pilot study for safety.

Randomized phase II study: Previous studies suggested that recovery rate at 42 days for control group will be about 50% [22, 56]. We hypothesize CD24Fc will increase recovery rate from 50% to 80 %. A sample size of 72 patients (36 in each arm) will have 81% power to detect an increase of response rate from 50% of control group to 80% of CD24Fc group. This result is based on one-sided Fisher's Exact test and significance level of 0.05.

10.4 Safety Monitoring and Stopping Rule

The Phase II study is a randomized, double blind, placebo-controlled study. To ensure the safety of the patients enrolled in the Phase II study, Bayesian stopping boundaries are used to allow early stopping at any given time in the combined population. The objective response rate (ORR) and toxicity of CD24Fc during the whole study will be monitored simultaneously using the Bayesian stopping boundaries calculated based on beta-binomial distribution. Toxicity is defined as new AE of ⩾grade 3 that are

outside the spectrum of irAEs. ORR is defined as partial response and complete response by RECIST V1.1 after retreatment with ICI.
The regimen will be considered safe if the ORR is at least 20% in all patients in both arms and the toxicity rate is maintained at most 33.3% for the CD24Fc arm. Previous studies for controls suggested the ORR after retreatment with ICI is about 20-40%, and therefore we consider a response rate <20% in all patients in both arms as unacceptable, which will indicate an effect of CD24Fc on promoting tumor growth. The prior probabilities of response and toxicity for the regimen are modeled by beta distributions [Beta(0.8, 1.2) and Beta(0.3, 1.7), respectively], and response and toxicity are assumed to be independent. Denoting the probabilities of response for both arms and toxicity for CD24Fc arm by $\{\theta_{RES}, \theta_{TOX}\}$, and they are compared to fixed targets of response and toxicity rates. The following decision criteria will be applied:

1) stop if Prob$\{ \theta_{RES} < 0.2 \mid \text{data}\} > 0.97$, and
2) stop if Prob$\{ \theta_{TOX} > 0.333 \mid \text{data}\} > 0.97$

We will have randomization box of 6 patients and thus ensure that 3 patients have been dosed for each 6 subjects enrolled. Patients will be monitored by a cohort size of 6 patients (3 for the CD24Fc arm and 3 for the placebo arm) according to the following stopping boundary for toxicity during the whole study. To be conservative, we attribute all AEs to CD24Fc.

Number of Patients Evaluated in All Enrolled Patients (half control and half CD24Fc)	**Stop if Number of ORR Observed**	**Stop if Number of AE Observed**
6	Never stop with these many patients	Never stop with these many patients
12	Never stop with these many patients	≥5
18	0	≥7
24	≤1	≥8
30	≤2	≥10
36	≤2	≥11
42	≤3	≥12
48	≤4	≥14
54	≤5	≥15
60	≤6	≥16
66	≤7	≥17
72	Always stop with this number of patients	

10.5 Emergency Unblinding

In situations where the Investigator believes that knowledge of the subject's treatment assignment is required to select appropriate continuing therapy for the disease under study, the Investigator may unblind

the patient's treatment assignment. The Investigator should make every effort to contact the medical monitor before unblinding a patient's treatment assignment unless the urgency of the case requires immediate action. All other members of the study team should remain blinded to treatment assignment.

11. SAFETY AND REPORTING REQUIREMENTS

11.0 Adverse Events

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

11.0.0 Severity of Adverse Events

The severity of an AE is graded based on the NCI CTCAE version 5.0. The guideline is as follows:

Grade 1 (Mild):	Asymptomatic or mild symptoms. Requires clinical or diagnostic observations only. Intervention not indicated.
Grade 2 (Moderate):	Moderate symptoms. Minimal, local or non-invasive intervention indicated. Limits age-appropriate activities of daily living.
Grade 3 (Severe):	Severe or medically significant symptoms, but not life-threatening. Limits self-care activities of daily living. Requires hospitalization or prolongation of hospitalization.
Grade 4 (Life-threatening):	Life-threatening consequences. Requires urgent intervention.
Grade 5 (Fatal):	The event caused death.

11.0.1 Causality (Attribution) of Adverse Events

The investigator is to assess the causal relation of all AEs (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related: Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.

Unlikely: The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

Probably Related: The AE is likely related to investigational product.

Related: The AE is clearly related to use of the investigational product.

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

11.0.2 Serious Adverse Events

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening** (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction. It does not refer to an event/reaction which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization**
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event or reaction**. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

11.1 Procedures for Reporting Adverse Events

11.1.0 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the IRB and to the FDA in accordance with CFR 312.32 (IND Safety Reports).

11.1.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins at initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Investigators are not obligated to actively seek information regarding the occurrence of new SAEs beginning after the 30-day post last dose period. However, if the investigator learns of such an SAE and that event is deemed relevant to the use of study treatment, he/she should promptly document and report the event. A longer reporting period applies in the case of pregnancy.

11.1.2 Procedures for SAE Reporting

11.1.2.0 Reporting to the FDA

Sponsor of studies conducted under an IND are required to report all serious, unexpected, and related adverse events directly to the FDA on a MedWatch Form FDA 3500A within 7 (if fatal or life-threatening) or 15 calendar days of first awareness, as described below.

Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction
- Serious
- Unexpected

The Sponsor will notify the FDA according to the following timelines:

within **7 calendar days** of any unexpected fatal or life-threatening adverse event with possible relationship to study drug;

within **15 calendar days** of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

FDA fax number for IND Safety Reports: **(800) FDA-0178** or **(800) 332-0178**

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report to the FDA. For adverse events that are either serious but don't meet the criteria for expedited reporting or are not serious, the FDA will be notified at the time of the IND Annual Report.

MedWatch Form FDA 3500A Reporting Guidelines

In addition to completing appropriate demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch Form FDA 3500A:

- Treatment regimen (dosing, frequency, combination therapy)
- Protocol description (include number if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive diagnostic and laboratory results
- Investigator's assessment of the relationship of the SAE to each investigational product and suspect medication
- Follow-up information:
- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch Form FDA 3500A and submitting it as follow-up
- Adding supplementary summary information and submitting it as follow-up with the original MedWatch Form FDA 3500A

- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e., DOB, initials, subject number), protocol description and number, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted

11.1.2.1 Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Comprehensive Cancer Center's (UCDCCC) Office of Clinical Research (OCR) policies. The UC Davis IRB can be reached at (916) 703-9151.

Participating site(s) will report adverse events per institution's IRB guidelines.

12. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

12.0 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

12.1 Institutional Review Board

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board (IRB).

12.2 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record or per the participating site's policies.

12.3 Patient Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCD CCC OCR or at the participating institutions. Medical records of patients will be maintained in strict confidence according to legal requirements. The patient's

confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.4 Study Registration

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to UCD Office of Clinical Research (OCR) policy. To register a patient, the data manager or designee must complete the Eligibility Checklist and the Patient Registration Form. After verifying the eligibility, the OCR coordinator will register the patient onto the study and assign a patient accession. Administration of study drug may not be initiated until the patient is registered (See Appendix Registration Guidelines).

12.5 Protocol Compliance and Deviations

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center OCR policies and the participating site's IRB policies. Any departures from the protocol must be fully documented in the source documents.

12.6 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

12.7 Quality Assurance and Control

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Comprehensive Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan. Quality control will be maintained by the OCR Quality Assurance team according to OCR policy.

13. OVERSITE AND MONITORING

13.0 Data and Safety Monitoring

In addition to the requirements for adverse event reporting, this protocol is also subject to the UC Davis Comprehensive Cancer Center (UCDCCC) Data and Safety Monitoring Plan. The UCDCCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCCC to fulfill its mission in conducting high quality clinical cancer research.

As per UCDCCC Office of Clinical Research (OCR) standard operating procedures the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events, and to determine if dose escalation is warranted, when applicable.

According to the UCDCCC Data and Safety Monitoring Plan (DSMP), UCDCCC Data and Safety Monitoring Committee (DSMC) monitors all at risk studies, including this study, being conducted at the UCDCCC. The DSMC is responsible for reviewing study accrual logs, adverse event information, and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines. The DSMC meets monthly. All serious adverse events experienced by study subjects will be discussed and appropriate action taken. If serious adverse events occur between these standing meetings and/or calls, all investigators will be informed by email. The UCDCCC Scientific Review Committee (SRC) determines if an additional Data and Safety Monitoring Board (DSMB) is required for a study. If required, the DSMC will appoint an additional DSMB.

13.1 Investigator Monitoring Guidelines

Investigators will conduct continuous review of patient safety. Patients will be monitored bi-weekly during the study. All patients on active treatment will be discussed at weekly conferences that are held at the University of California, Davis

14. PATHOLOGY REVIEW

Not applicable.

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16. APPENDICES

Appendix 1. ECOG and Karnofsky Performance Status Scores[1,2]

http://ecog-acrin.org/resources/ecog-performance-status

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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Appendix 2. Study Registration

Once signed, informed consent has been obtained; patients will be entered on study. To register a patient, the study coordinator must complete the Eligibility Checklist. The study coordinator will register the patient onto the study and assign a unique patient number.

Appendix 3. Data Collection Forms

All data will be collected using UC Davis data collection forms. Any and all source documentation shall be maintained.

Appendix 4. NCI CTCAE Version 5.0

Toxicity will be scored using NCI CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the NCI CTCAE Version 5.0 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE version.

Appendix 5: List of Proarrhymic Drugs

Konstantopoulou A, et al, World J Cardiol 2013 June 26; 5(6): 175-185.

Category	Drugs			
Antianginal	Bepridil			
Antiarrhythmic	Disopyramide, propafenone, dronedarone, azimilide,	procainamide, flecainide, bretylium, ajmaline	quinidine, d,l-sotalol, dofetilide,	mexiletine, amiodarone, ibutilide,
Anticancer	Tamoxifen, arsenic trioxide	lapatinib,	vandetanib,	nilotinib,
Antifungal	Itraconazole,	ketoconazole,	fluconazole,	voriconazole
Antimicrobial	Erythromycin, spiramycin, sparfloxacin, gemifloxacin, pentamidine, mefloquine,	clarithromycin, telithromycin, gatifloxacin, ofloxacin, quinine, halofantrine	azithromycin, levofloxacin, grepafloxacin, trimethoprim-sulfamethoxazole, chloroquine,	moxifloxacin,
Antiviral	Foscarnet			
Antihistamine	Astemizole, hydroxyzine	diphenhydramine,	ebastine,	terfenadine,
Antidepressant	Doxepin, imipramine, citalopram,	venlafaxine, clomipramine, escitalopram	fluoxetine, paroxetine,	desipramine, sertraline,
Antipsychotic	Chlorpromazine, fluphenazine, thioridazine, risperidone, chloral hydrate zimeldine,	prochlorperazine, felbamate, droperidol, quetiapine, pericycline, maprotiline,	trifluoperazine, haloperidol, mesoridazine, ziprasidone, sertindole, tiapride	pimozide, lithium, sultopride,
Antimigraine	Naratriptan,	sumatriptan,	zolmitriptan	
Bronchodilators	Albuterol,	salmeterol		
Diuretics	Indapamide,	thiazide,	furosemide	
Gastrointestinal stimulants	Cisapride,	metoclopramide,	domperidone	
Hormones	Octreotide,	vasopressin		
Others	Probucol, veratridine, tizanidine,	methadone, vincamine, aconitine	cocaine, terodiline, organophosphorus compounds	amantadine, budipine,

17. SUMMARY OF CHANGES

Substantive changes to the Protocol are outlined in the Table below. In cases where the change involves the insertion or deletion of one or a few words, the text may be underlined for ease of reviewing. Additional typographical corrections or edits may also be made throughout the Protocol but not detailed in the Table.

Section of the document	**Revision and Justification**
Title page and header (all pages)	Protocol version number updated to 1.5, dated October 20, 2020.
Page 1 and Page 4	Add the clinicaltrial.gov registration number as a protocol number: NCT04552704
Table 1 and 2	Clarify the window of study visit, and blood draw schedule and amount.
Section 6.4	Clarify dose modification criteria.
Administrative changes	Several grammatical changes that were lost between the different versions.