

IACUC - Protocol Review

9/7/18, 10:46 AM

Staff Reviewer: Nicole Dias**Committee Reviewer 1:** not assigned**Committee Reviewer 2:** not assigned**Reviewer:** Robert Rebhun - *review completed 07-25-2018*

# Questions: 3	University of California, Davis PROTOCOL FOR ANIMAL CARE & USE	Protocol: 20668
# Questions Sent: 0		Expires:
# Responses: 0		

1. Contacts

[Ask a Question \(section 1\)](#)
[Review Questions/Responses](#)

Primary Investigator		Alternate Contact	
Name:	Robert B Rebhun *	Name:	Robert J Canter
E-mail:	rbrehhun@ucdavis.edu	E-mail:	rjcanter@ucdavis.edu
Department:	VM: Surgical & Radiological Science	Department:	MED: Surgery, Div of Surgical Oncology
Telephone:	530-754-5028	Telephone:	916-734-7044
After Hours:	530-219-5960	After Hours:	215-964-0468

**Primary contact for sick animals*

2. Title

[Ask a Question \(section 2\)](#)
[Review Questions/Responses](#)

ALT-803 Immunotherapy for Treatment of Lung Metastases

Replacement Protocol: No**3. Protocol Type**

[Ask a Question \(section 3\)](#)
[Review Questions/Responses](#)

Research
VMTH Clinical Trial

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[DocUpload-01-86084-\(CTRB Consent form\)_ClinicalTrial.docx](#)

4. Species

[Ask a Question \(section 4\)](#)
[Review Questions/Responses](#)

Common Names	Total Number for Study	Name of Source of the Animals
dog - <i>client-owned dogs</i>	14	VMTH Oncology Service Population

USDA: No**Detrimental Species:** No**5. Brief Summary of Procedures**

[Ask a Question \(section 5\)](#)
[Review Questions/Responses](#)

We propose a phase 1 clinical study to assess the safety and efficacy (secondary endpoint) of ALT-803, an IL-15 superagonist. In brief, dogs with measurable (on radiographs) lung metastases who have exhausted standard treatment options or whose owners have declined such therapy will have up to 20 mLs of blood drawn by venipuncture on days 0,

7, 10, 17, 24, 31, 45, 73, and 101. Dogs will receive once weekly ALT-803 for a total of four treatments. An ultrasound guided fine needle aspirate of one pulmonary mass will be performed on day 0 (prior to starting ALT-803) and again on day 31 of the study if deemed safe to do so based on ultrasound appearance and location. Animals will be monitored for any side effects from treatment, and then followed by a chest x-ray at days 31, 45, 73, 101. After day 101, chest x-rays will be performed every 2-3 months as or as clinically recommended. The trial will formally end at the 101 day radiographs.

6. Animal Location(s)

[Ask a Question \(section 6\)](#)
[Review Questions/Responses](#)

Study Area/Laboratory:

Building - Room	AAALAC
None/Animals Will Not Leave Animal Facility	-

Overnight Housing (vivarium):

Vivarium(s)
VMTH - Small Animal Clinic

Animals will be maintained by:

Vivarium

7. Special Husbandry Requirements:

[Ask a Question \(section 7\)](#)
[Review Questions/Responses](#)

There are no special requirements.

8. Hazardous Materials:

[Ask a Question \(section 8\)](#)
[Review Questions/Responses](#)

No

9. Special Procedures and/or Activities:

[Ask a Question \(section 9\)](#)
[Review Questions/Responses](#)

None - No Special Procedures and/or Activities

10. Funding Source(s):

[Ask a Question \(section 10\)](#)
[Review Questions/Responses](#)

National Cancer Institute

11. Veterinary Care:

[Ask a Question \(section 11\)](#)
[Review Questions/Responses](#)

VMTH Small Animal Service

12. Objectives and Significance:

[Ask a Question \(section 12\)](#)
[Review Questions/Responses](#)

Objectives:

To determine the maximum tolerated dose (MTD) for ALT-803 in dogs with lung metastases. Response to therapy and peripheral immune correlates are secondary endpoints.

Significance:

If successful, this trial will provide important evidence in a large animal, outbred model of spontaneous metastasis that ALT-803 is a safe and potentially effective treatment for dogs with lung metastasis. Dogs with lung metastases have a dismal prognosis and response rates to standard chemotherapy are less than 20-30% for most tumor types. Therefore, these patients are ideal candidates for novel therapies. Future work (Aim 3) related to this grant will build upon these findings by combining this therapy with standard chemotherapy for dogs with osteosarcoma.

13. The 3 R's - Refinement, Replacement, and Reduction:
[Ask a Question \(section 13\)](#)
a) Database Search for Alternatives:
[Review Questions/Responses](#)

1) Does this project involve USDA covered species? **No**

b) Refinement:

Through the use of proper handling, we will minimize any potential pain and distress in the animals

c) Has this study been previously conducted?

No

d) Replacement (Species Rationale):

Dogs are the target species for this therapy. Dogs will also serve as a spontaneous tumor model for future human studies.

e) Reduction (Animal Numbers Justification):

This trial will utilize an accelerated phase 1 study design. We plan to use a 40% dose escalation between single-patient cohorts in the accelerated phase which reverts to a standard 3+3 cohort design when one dose-limiting toxicity (DLT) or two moderate toxicities (excluding minor dermatologic toxicities at injection site) are observed during any cycle. We will start at 30 ug/kg and proceed to 42 ug/kg, 60 ug/kg, 82 ug/kg, 115 ug/kg, and 160 ug/kg. We estimate that up to 14 patients will be enrolled. This is based on the conversion to a 3 + 3 Study design, where up to 5 dogs could be enrolled at the first dose for which a dose limiting toxicity is observed. Assuming a patient fallout rate of 20% (2 dogs), we arrived at an estimate of 14 dogs. This study design is intended to minimize the number of dogs used in the study, while also minimizing the number of dogs exposed to potentially subclinical dosing of ALT-803.

Since an MTD of ALT-803 has not been established in dogs, we will escalate until dose-limiting toxicities (DLTs) are observed. However, we will not escalate past dose level 6 even if MTD is not reached. A DLT will be defined as = grade 3 toxicity in any category (except hematologic) according to the Veterinary Cooperative Oncology Group Common Terminology Criteria for Adverse Events.

In this Phase I trial, the MTD will be defined as the highest dose level at which no more than 1/6 of the subjects develops a DLT.

Dose level escalation will be determined based on DLTs observed during therapy, but DLTs will be monitored after the cessation of treatment, and dose de-escalation may occur if significant late DLTs are observed. Necropsy will be strongly encouraged on all subjects, and careful histologic evaluation will be performed to determine cause of death from cancer progression versus immuno-pathology. The primary objective of this study is to determine the MTD of ALT-803. Up to 14 client-owned clinical dogs with OSA or melanoma pulmonary metastases will be enrolled in this sub-aim. In addition to toxicity, secondary outcome measures of efficacy will be evaluated including response rate, response duration, and median survival time.

14 dogs in this arm should also allow us to evaluate immune correlates.

f) Study Groups and Numbers Table:

Group	Species	Number of Animals	Procedures/Treatments
Dogs with lung metastases	dog - <i>client-owned dogs</i>	14	

14. Procedure Details:
[Ask a Question \(section 14\)](#)

a) Describe the use of animals in your project[Review Questions/Responses](#)

All owners will sign the CTRB approved consent form prior to enrollment. Up to 14 client-owned dogs with pulmonary metastasis greater than 2cm, for which all other reasonable treatment options have been exhausted or declined, will be eligible for entry into the trial. Prior to entry into the trial, the dog will undergo a physical exam and routine hematologic evaluation with a CBC and serum chemistry panel as well as a urinalysis. 2-6 mls of venous blood will be collected from the jugular vein or other peripheral vessel as is standard for clinical patients in the VMTH.

The UCD blood collection policy will be followed. (i.e. 1% of animals body weight can be collected in 24 hours every 14 days) for any samples listed above. Patients less than 10kg will be excluded.

Other analgesics as needed which as assessed by the attending clinician including NSAIDS, tramadol, gabapentin or opioids are allowed but not part of the protocol.

Appropriate sedation protocols for chest x-rays (and fine needle aspirates) may be done on an individual patient basis based upon the recommendations made by a board certified veterinary anesthesiologist from the VMTH Clinical Anesthesia Service, however, this will most commonly be performed with dexmedetomidine and butorphenol. Monitoring under sedation will be standard and as is done for all VMTH clinical patients and at a minimum will include heart rate and respiratory rate monitoring, mucous membrane color, CRT as well as assessing for appropriate depth of sedation. Recovery from sedation will take place under supervision of a VMTH clinical veterinarian or licensed veterinary technician. All compounds given to the animals are pharmaceutical grade.

Prior to therapy, an ultrasound-guided fine needle aspirate of a single pulmonary metastatic lesion will be obtained under sedation when possible and deemed safe to do so.

Day 0- Blood sample obtained for evaluation of peripheral blood mononuclear cells (PBMCs), Fine needle aspirate of pulmonary lesion, chest x-rays Day 3- ALT-803 Day 7- Blood sample for PBMCs, CBC/CHEM Day 10- Blood sample for PBMCs, CBC/CHEM, ALT-803 Day 17 - Blood sample for PBMCs, CBC/CHEM, ALT-803 Day 24 - Blood sample for PBMCs, CBC/CHEM, ALT-803 Day 31- Blood sample obtained for evaluation of peripheral blood mononuclear cells (PBMCs), Fine needle aspirate of pulmonary lesion, chest x-rays Day 42 - Blood sample for PBMCs, CBC/CHEM, chest x-rays Day 70 - Blood sample for PBMCs, CBC/CHEM, chest x-rays Day 98 - Blood sample for PBMCs, CBC/CHEM, chest x-rays

Serial measurements of blood and serum will be obtained weekly to assess for hematologic (WBC, hemoglobin, platelet count, and sub-populations) and biochemical toxicity (serum Na, K, Cl, glucose, alkaline phosphatase, ALT, AST, bilirubin, BUN, creatinine, albumin, and globulin). Blood will be obtained for PBMC evaluation

ALT-803 treatments will be given subcutaneously and all injections will be performed here at the VMTH in order to monitor for any complications. The owners will be informed to look for clinical signs such as dyspnea, tachypnea, hyperemia, anaphylaxis, depression, etc. and advised to call or come in immediately if any clinical signs should be displayed. Blood pressure, heart rate, and temperature will be monitored periodically for 6-8 hours to assess for vasomotor/hemodynamic toxicity on days of injection.

In this Phase I trial, the MTD will be defined as the highest dose level at which no more than 1/6 of the subjects develops a DLT.

This trial will utilize an accelerated phase 1 study design. We plan to use a 40% dose escalation between single-patient cohorts in the accelerated phase which reverts to a standard 3+3 cohort design when one dose-limiting toxicity (DLT) or two moderate toxicities (excluding minor dermatologic toxicities at injection site) are observed during any cycle. We will start at 30 ug/kg and proceed to 42 ug/kg, 60 ug/kg, 82 ug/kg, 115 ug/kg, and 160 ug/kg. We estimate that up to 14 patients will be enrolled. This is based on the conversion to a 3 + 3 Study design, where up to 5 dogs could be enrolled at the first dose for which a dose limiting toxicity is observed. Assuming a patient fallout rate of 20% (2 dogs), we arrived at an estimate of 14 dogs. This study design is intended to minimize the number of dogs used in the study, while also minimizing the number of dogs exposed to potentially subclinical dosing of ALT-803.

Dose level escalation will be determined based on DLTs observed during therapy, but DLTs will be monitored after the cessation of treatment, and dose de-escalation may occur if significant late DLTs are observed. Necropsy will be strongly encouraged on all subjects, and careful histologic evaluation will be performed to determine cause of death from cancer progression versus immuno-pathology.

We do not plan to escalate past dose level 6 even if MTD is not reached. A DLT will be defined as = grade 3 toxicity in any category (except hematologic) according to the Veterinary Cooperative Oncology Group Common Terminology Criteria for Adverse Events (Veterinary Cooperative Oncology Group, 2011).

Previous toxicity studies have been performed in mice and non-human primates, both of which tolerated weekly 100 ug/kg subcutaneous dosing of ALT-803. Human clinical trials are currently underway and toxicity has been found to be acceptable in dosing ranging from 6-30 ug/kg.

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b) All Drugs and Compounds to be Administered to the Animals (except for euthanasia) - anesthetics, analgesics, neuromuscular blocking agents, antibiotics and/or experimental compounds:

Will drugs be used in this study? **Yes**

Species	Drug	Dose	Route	When and how often will it be given?
dog	Atipamazole	0.2-0.4 mg/kg	Intramuscular (IM)	For reversal of dexmedetomidine sedation. Will be administered IM as same volume as dexmedetomidine was used
dog	ALT-803	up to 160 ug/kg	Subcutaneous (SC)	Once weekly for four weeks
dog	butorphanol	0.2 mg/kg	Intravenous (IV)	If needed prior to imaging or aspirates
dog	dexamethasone	0.2 mg/kg	Intravenous (IV)	if needed for anaphylactic reaction
dog	dexmedetomidine	125-375 mg/m squared	Intravenous (IV)	If needed prior to imaging or aspirates
dog	epinephrine	0.01 mg/kg	Intravenous (IV)	once, only in extreme cases. Can be repeated if no improvement.
dog	Diphenhydramine	2-4 mg/kg	Intramuscular (IM)	if needed for anaphylactic reaction

15. Adverse Effects:

[Ask a Question \(section 15\)](#)
[Review Questions/Responses](#)

a. Describe all significant adverse effects that may be encountered during the study.

Due to treatment: anaphylaxis during administration, pulmonary edema, vomiting, diarrhea, anorexia, infection, fever, death. Due to aspirates: bleeding, pneumothorax, respiratory distress, death

b. Describe frequency for monitoring the well-being of animals on the study and criteria for terminating/modifying the procedures(s) if adverse effects are observed.

Serial measurements of blood and serum will be obtained weekly to assess for hematologic (WBC, hemoglobin, platelet count, and sub-populations) and biochemical toxicity (serum Na, K, Cl, glucose, alkaline phosphatase, ALT, AST, bilirubin, BUN, creatinine, albumin, and globulin). In this Phase I trial, the MTD will be defined as the highest dose level at which no more than 1/6 of the subjects develops a DLT. Three patients will be enrolled per dose level, with escalation to the next dose level if no DLT is observed. If one DLT is observed, the dose level will be expanded to a total of 6 patients, and escalation will occur if no more than one DLT is observed among the 6 patients. If 2 or more patients in any cohort experience DLT, this will be defined as the maximally administered dose, and the phase I study will be concluded or dose reduced to the previous dose level (then defined as the MTD). Dose level escalation will be determined based on DLTs observed during therapy, but DLTs will be monitored after the cessation of treatment, and dose de-escalation may occur if significant late DLTs are observed. Necropsy will be strongly encouraged on all subjects, and careful histologic evaluation will be performed to determine cause of death from cancer progression versus immuno-pathology. If an owner elects euthanasia, then it will be allowed. After discharge, the owner will have a number to call if there are any perceived side effects. The patients will be evaluated once weekly per protocol and on an as needed basis by the oncology service.

Adverse event forms are generated for all oncology trials based on VCOG adverse events criteria. Owners will be informed to monitor for signs of fever, lethargy, decreased appetite, respiratory changes, etc. Side effects of inhaled IL-2 have not been seen previously.

c. How will the signs listed above be ameliorated or alleviated?

Serial measurements of blood and serum will be obtained weekly to assess for hematologic (WBC, hemoglobin, platelet count, and sub-populations) and biochemical toxicity (serum Na, K, Cl, glucose, alkaline phosphatase, ALT, AST, bilirubin, BUN, creatinine, albumin, and globulin). In this Phase I trial, the MTD will be defined as the highest dose level at which no more than 1/6 of the subjects develops a DLT. If one DLT is observed, the dose level will be expanded to a total of 6 patients, and escalation will occur if no more than one DLT is observed among the 6 patients. If 2 or more patients in any cohort experience DLT, this will be defined as the maximally administered dose, and the phase I study will be concluded or dose reduced to the previous dose level (then defined as the MTD). Dose level escalation will be determined based on DLTs observed during therapy, but DLTs will be monitored after the cessation of treatment, and dose de-escalation may occur if significant late DLTs are observed. Necropsy will be strongly encouraged on all subjects, and careful histologic evaluation will be performed to determine cause of death from cancer progression versus immuno-pathology.

d. List the criteria to be used to determine when euthanasia is to be performed or the animal will be removed from the study.

If quality of life is considered compromised by the owner, then euthanasia will be performed if requested by the owner. Otherwise, all clinically available palliative care modalities will be used. If the attending clinician feels that the dog's quality of life is compromised while on this trial they can be removed from the trial without the owner's consent. Alternative palliative measures or humane euthanasia will also be offered based on the clinical situation as appropriate. Other study endpoints may include withdrawal by the owner, progression of disease, decreased quality of life, or adverse event profile.

16. Euthanasia:

[Ask a Question \(section 16\)](#)
[Review Questions/Responses](#)

Species	Method	Drug	Dose	Route	Justification for Physical Methods
dog	Overdose	Pentobarbital	100 mg/kg	Intravenous (IV)	N/A

17. Disposition:

[Ask a Question \(section 17\)](#)
[Review Questions/Responses](#)

We do not anticipate that any of these animals will be euthanized as a direct result of therapy. There may be progression of disease (despite therapy) that warrants euthanasia. When the trial period is concluded, patients will remain under the care of veterinarians within the clinical oncology service, and owners will be given further treatment options including palliative care options. All live animals will go home with their owners.

18. Roster:

[Ask a Question \(section 18\)](#)
[Review Questions/Responses](#)

Name	Title/Degree	E-mail	OccHealth Participation		ACU 101 Training	Rodent Survival Surgery Course	Qualifications
			Completion	Renewal			
Burton, Jenna H.	Asst Clin Professor	jburton@ucdavis.edu	04-20-2016	04-20-2019	10-04-2016	Not Found	Dr. Burton is a board certified medical oncologist with extensive clinical trials experience and 8 years experience treating dogs with cancer.
Canter, Robert J.	Associate Professor	rjcanter@ucdavis.edu	09-18-2015	09-16-2018	11-28-2017	10-07-2013	Will be overseeing NK

IACUC - Protocol Review

9/7/18, 10:46 AM

							cell expansion and preparation. Will not be involved in handling animals
Guerrero, Teri A.	Clinical Trials Coord	tguerrero@ucdavis.edu	04-20-2017	04-20-2020	01-12-2016	Not Found	Ms. Guerrero has been working with dogs in a veterinary setting since 1996 and she has an RLAT certification. She has been employed by the veterinary school at UC Davis since 2007 and serves as the clinical trials coordinator, a position that involves patient care, client communication, and SOP development and completion.
Kent, Michael S.	Professor	mskent@ucdavis.edu	04-07-2016	03-31-2019	11-11-2016	Not Found	A board certified veterinarian with over 20 years experience working with dogs.
O'Daniel, Franklin	Staff Research Assoc II	fodaniel@ucdavis.edu	07-12-2017	07-12-2020	05-19-2017	Not Found	12 years animal handling experience including dogs. RVT and CVPM. Efficient in catheter placements, animal handling, venipuncture, anesthesia, drug calculations in dogs.
Rebhun, Robert B.	Associate Professor	rbrebhun@ucdavis.edu	07-24-2018	07-24-2021	04-07-2017	04-29-2013	10 years experience treating dogs as a practicing veterinarian. Completion of residency and board certified in medical oncology. Handling of chemotherapeutic agents was part of the oncology training.
Skorupski, Katherine A.	Assoc Prof	kskorups@ucdavis.edu	04-27-2018	04-27-2020	01-09-2018	Not Found	14 years

IACUC - Protocol Review

9/7/18, 10:46 AM

	of Clin						experience treating dogs as a practicing veterinarian and board certified in Veterinary Medical Oncology.
Willcox, Jennifer	ASST PROF OF CLIN-FY	jwillcox@ucdavis.edu	11-07-2017	11-07-2019	08-01-2018	Not Found	A board certified veterinary oncologist with over 6 years experience treating dogs
Withers, Sita	GSR-FULL FEE REM	sswithers@ucdavis.edu	09-20-2016	09-06-2019	05-02-2017	08-12-2014	Board certified oncologist with over 4 years treating dogs with cancer.

Assurances for the Humane Care and Use of Vertebrate Animals:

I have read and agree to abide by the **UC Davis Policy and Procedure Manual section 290-30** ([Animal Care and Use](#)). This project will be conducted in accordance with the **ILAR Guide for the Care and Use of Laboratory Animals**, and the **UC Davis Animal Welfare Assurance** on file with the US Public Health Service. I will abide by all Federal, State, and local laws and regulations dealing with the use of animals in research.

The activities proposed in this application do not unnecessarily duplicate previous experiments [AWA 2.31(d)(1)(iii)].

I will advise the IACUC in writing of any proposed significant changes in the procedures and wait for IACUC approval prior to implementing the change. I will also advise the IACUC of any changes in personnel involved in this project.

I have read and agree with the above statement.