NCI Protocol #: CITN-06-ALT-803

Local Protocol #: CA-ALT-803-01-13

TITLE: A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, ***Sarcoma, Colon, Non-Hodgkin Lymphoma,*** Non-Small Cell Lung and Squamous Cell Head and Neck Cancer ***and Cutaneous Squamous Cell Cancer***

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The SCCA, Cleveland Clinic Foundation, University of Minnesota and Rutgers University will participate to the dose-escalation phase of the trial. NCI will be added in the expansion phase of the trial.

INVESTIGATOR SIGNATURE PAGE

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Date of Protocol:

Version # 01	April 8, 2013
Version # 02	May 6, 2013
Version # 03	July 26, 2013
Version # 04	December 02, 2013
Version # 05	October 08, 2014
Version # 06	November 20, 2014
Version # 07	January 26, 2015
Version # 08	June 11, 2015
Version # 09	August 5, 2015
Version # 10	April 13, 2016
Version # 11	***August 9, 2016***

Sponsor Contact:

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By my signature below, I hereby attest that I have read, and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol.

Additionally, I will not initiate this study without approval of the appropriate Institutional Review Board (IRB), and I understand that any changes in the protocol must be approved in writing by the sponsor, the IRB, and, in certain cases the FDA, before they can be implemented, except where necessary to eliminate hazards to subjects.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

password, and click on the "accept" link in the upper right corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave accounts will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

This study will be monitored as designated by CTEP and CITN Coordinating Center guidelines.

12.1.2 ***Responsibility for Data Submission***

This study will not report to CDUS.

12.2 CTEP Multicenter Guidelines: N/A

12.3 Collaborative Agreements Language: N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The proposed clinical trial is a phase I, open-label, dose-escalation study of ALT-803 in patients with surgically incurable advanced solid tumors: melanoma, renal cell, ***sarcoma, colon, non-Hodgkin lymphoma,*** non-small cell lung and squamous cell head and neck cancer ***and cutaneous squamous cell cancer***.

In the dose-escalation phase, dose levels to be evaluated will be 0.3, 0.5, 1, 3, and 6 μg/kg administered intravenously, and dose levels 6, 10, 15, 20 μg/kg administered subcutaneously. ***Additional dose escalation cohorts will be added at 10, 15, 20 μg/kg to evaluate intratumoral injection followed by subcutaneous injections.*** The dose of ALT-803 will be increased in increments of 5 μg/kg if a minimum of three patients have been treated at 20 μg/kg, and the Maximum Tolerated Dose (MTD) and Optimum Biological Dose (OBD) have not been identified. Enrollment will continue until the MTD/OBD is identified. A "dose level minus -1" of 0.1 μg/kg will be provided in the unlikely event of encountering DLT in patients at the planned starting dose level of 0.3 μg/kg. Cycle 1 consists of 4 weeks on therapy and 2 weeks off. Patients will receive weekly ***dose*** of ALT-803 for 4 weeks (Days 1, 8, 15, and 22) used for the identification of the OBD and MTD. After a 2-week rest period (Weeks 5 and 6) and recovery of any DTLs to grade 0–1 of Cycle 1, a second 6-week (42-day) cycle (4 weeks on treatment and 2

weeks off) can begin. After a rest period during Weeks 5 and 6 of Cycle 2, stable or benefitting patients assessed at week 8 ± 1 may receive up to 2 additional 6-week cycles (4 weeks on treatment and 2 weeks off).

Treatment Schema				
Agent	**Dose levels*** ***(µg/kg)***	**Route**	**Schedule**	**Cycle Length, Duration of Rx**
ALT-803	0.3 0.5 1 3 6	IV	Weekly, weeks 1–4 (Days 1, 8, 15, 22)	42 days (4 weeks on, 2 weeks off) Up to 4 cycles in the absence of unacceptable toxicity or disease progression
	6 10 15 20	SQ		
	10 + 15 SQ ***15 + 15 SQ*** ***20 + 15 SQ***	***IT followed by SQ***	***Weekly, weeks 1-4*** ***Day 1 (IT)*** ***Days 8, 15, 22 (SQ)***	***42 days*** ***(4 weeks on, 2 weeks off)*** ***With up to 4 cycles in the absence of unacceptable toxicity and disease progression***** ***Cycle 1 only: pre and post treatment biopsy***

***NOTE:** A "dose level minus -1" of 0.1 µg/kg will be provided in the unlikely event of encountering DLT in patients at the planned starting dose level of 0.3 µg/kg.

The dose escalation uses a 3+3 design. Between cohorts and at the end of the study, all clinical and safety data will be analyzed. We plan to identify the OBD defined by phenotypic lymphocyte subsets, if lower than a clinically defined MTD. We plan to perform subsequent trials using ALT-803 as either a single agent or in combinations based on their immunologic and antitumor properties of the agents in appropriately selected cohorts of solid tumor patients.

As a safety precaution, the first patient of each ALT-803 dose level cohort will be observed in the inpatient unit for 24 hours after dosing ***on Cycle 1, Week 1, Day 1,*** and followed for toxicities for an additional 48 hours before administering ALT-803 to other patients at the same dose level.

Subsequent patients in the same dose level cohort will be observed for at least 24 hours after dosing ***on Cycle 1, Week 1, Day 1***. All patients at a dose level cohort will be observed through one full cycle (4 weekly doses followed by 2 weeks rest) before either escalating the dose to the next level, treating 3 additional patients or adding 3 patients at the next lower dose level.

The primary endpoints are safety and efficacy, defined below by the increase in the total number of peripheral lymphocytes during the first cycle. The safety endpoint is the MTD of ALT-803, defined as the dose level below that at which ≥2 of 6 patients experience a DLT. The efficacy endpoint is the OBD, defined as that which produces an ALC ≥25,000/μL and/or a total WBC ≥35,000/μL among 2/3 of patients. For safety, we have also defined an "exceeding OBD" as the occurrence of ALC ≥35,000/μL and/or WBC ≥50,000/μL.

In the expansion phase, after the establishment of a dose that appears to predictably increase the number of T cells and NK cells with an acceptable tolerability and safety profile, additional patients will be treated in an expansion cohort (to total 12 evaluable patients at the optimum dose) to further assess predictability, safety, and efficacy.

13.2 Sample Size/Accrual Rate

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	2	=	4
Not Hispanic or Latino	3	+	5	=	8
Ethnic Category: Total of all subjects	5(A1)	+	7(B1)	=	12(C1)
Racial Category					
American Indian or Alaskan Native		+	1	=	1
Asian	1	+	1	=	2
Black or African American		+		=	
Native Hawaiian or other Pacific Islander		+		=	
White	4	+	5	=	9
Racial Category: Total of all subjects	5(A2)	+	7(B2)	=	12(C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

[redacted]

13.5.3 ***Evaluation of Response***

Only those patients who have measurable disease present at baseline, have received at least one complete cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. Patients who exhibit objective disease progression before the end of cycle 1 will also be considered evaluable.

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: (1) CR, (2) PR, (3) SD, (4) PD, (5) early death from malignant disease, (6) early death from toxicity, (7) early death because of other cause, or (9) unknown (not assessable, insufficient data). [*NOTE*: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4–9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4–9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.,* early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.