Amendment

Protocol Number: 17C0029-B **Reference Number:** 374341

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Protocol Title: A Phase II Trial of CUDC-907 in Patients with Metastatic and Locally Advanced Thyroid Cancer

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CONCURRENCE

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Aruna Acharyya	AM B	11/28/2017
Signature	Print Name	Date

* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: Expedited

DEC Clearance Date: 10/11/2017

Protocol Version Date: 10/11/2017

Abbreviated Title: CUDC-907 for thyroid cancer

CC Protocol #: 17C0029 B

Version Date: 10/11/2017

NCT number: NCT03002623

Title: A Phase II Trial of CUDC-907 in Patients with Metastatic and Locally Advanced Thyroid Cancer

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A. Obtain information by intervening or interacting with living individuals for research purposes
B. Obtaining identifiable private information about living individuals
C. Obtaining the voluntary informed consent of individuals to be subjects
D. Makes decisions about subject eligibility
E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
G. Some/all research activities performed outside NIH

Investigational Agents:

Drug Name:	CUDC-907
IND Number:	132413
Sponsor:	Center for Cancer Research, NCI
Manufacturer:	Curis Inc.

PRÉCIS

Background:

- There are no standard or effective systemic therapies for metastatic or locally advanced poorly differentiated and undifferentiated thyroid cancer.
- Poorly differentiated and undifferentiated thyroid cancer are aggressive, with high mortality.
- CUDC-907 is a first-in-class dual inhibitor of HDAC and PI3K signaling.
- Approximately 80% of poorly differentiated and undifferentiated thyroid cancers have driver mutations in the PI3K/AKT pathway or activation of the pathway.
- HDAC2 is upregulated in poorly differentiated and undifferentiated thyroid cancer, and aggressive variants of differentiated thyroid cancer, and CUDC-907 treatment reduces HDAC2 levels in thyroid cancer cells.
- CUDC-907 inhibits thyroid cancer cell growth, invasion and migration *in vitro*.
- In addition to inhibiting the PI3K/AKT signaling pathway, CUDC-907 inhibits the EGFR/RAS/RAF/MEK/ERK signaling pathway, which is also activated in poorly differentiated and undifferentiated thyroid cancer.
- CUDC-907 inhibits growth and metastases in a mouse model of metastatic thyroid cancer.
- We hypothesize that CUDC-907 will cause cancer regression in patients with metastatic and locally advanced poorly differentiated and undifferentiated thyroid cancer, and aggressive variants of differentiated thyroid cancer.

Objective:

- To determine response to CUDC-907 treatment by RECIST criteria in patients with locally advanced and metastatic poorly differentiated and undifferentiated thyroid cancer, and aggressive variants of differentiated thyroid cancer.

Eligibility:

- Age $\geq$ 18 years
- Thyroid cancer that is refractory to or relapsed after standard treatment.
- Aggressive thyroid cancer confirmed on histology or cytologic analysis.
- Measurable disease.
- Last dose of chemotherapy or last radiotherapy treatment more than 4 weeks prior to starting treatment with this protocol, except for subjects with anaplastic/undifferentiated thyroid cancer who may enroll immediately after discontinuation of previous therapy.

Design:

- Open label, phase II trial to determine response to CUDC-907 treatment.
- Patients will be given 60 mg of CUDC-907 orally for 5 consecutive days followed by 2 days off (5/2 schedule).
- One cycle is 21 days. Patients may continue on treatment if there is no disease progression.

- Initial anatomic and functional imaging will be performed at enrollment and after 2 cycles of treatment. Thereafter, anatomic imaging will be performed every two cycles of treatment.

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1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

- To determine response to CUDC-907 treatment by RECIST criteria in patients with locally advanced and metastatic poorly differentiated and undifferentiated thyroid cancer and aggressive variants of differentiated thyroid cancer.

1.1.2 Secondary Objectives:

- To determine progression-free survival (PFS) and overall survival (OS) with CUDC-907 treatment as compared to historical control patients.
- To determine if driver mutations status, activation of the PI3K/AKT and EGFR/RAS/RAF/MEK/ERK pathways, and/or HDAC2 and survivin levels in tumor tissue is associated with response to CUDC-907 treatment.

1.2 BACKGROUND AND RATIONALE

Locally advanced and metastatic poorly differentiated and undifferentiated thyroid cancer, and aggressive variants of differentiated thyroid cancer

Patients with stage IV differentiated thyroid cancer have a five-year survival rate of only 25%. In patients with progressive or recurrent differentiated thyroid cancer, one-third of patients develop or have dedifferentiated tumors (loss of differentiation) [1]. Clinically, this results in more aggressive tumors with decreased or absent iodine uptake in the tumor, and tumors which are refractory to conventional treatment. There have been significant advances in targeted therapy for differentiated thyroid cancer with two agents (sorafenib and lenvatinib) showing improved PFS in patients with radioiodine refractory differentiated thyroid cancer and both were recently approved by the U.S. Food and Drug Administration [2, 3]. Unfortunately, no significant advances have occurred in the development of new therapies for poorly differentiated thyroid cancer, aggressive variants of differentiated thyroid cancer (hürthle cell carcinoma, tall-cell variant, sclerosing variant, insular variant), and undifferentiated (anaplastic) thyroid cancer, which account for most of the thyroid cancer-related deaths in the U.S. [4, 5]. Furthermore, there is currently no standard or effective systemic therapy for patients with locally advanced and metastatic poorly differentiated thyroid cancer, the aggressive variants of differentiated thyroid cancer, and anaplastic thyroid cancer.

Anaplastic thyroid cancer is among the deadliest of all human cancers, with a median survival of 4.9 months and a one year survival of less than 20% [6]. Patients with locally advanced poorly differentiated thyroid cancer have a 5-year overall survival rate of only 47% [7]. Patients with hürthle cell carcinoma, and aggressive variant (tall-cell, sclerosing, insular) of differentiated thyroid cancer have a 5-year disease-specific mortality rate of 4-15%, and 18-29%, respectively [8-12]. Thus, the need for effective therapeutics for poorly differentiated and anaplastic thyroid carcinoma, rare and neglected malignancies, is enormous, as well as for the

less common aggressive variant of differentiated thyroid cancer [13]. Survival in patients with poorly differentiated and anaplastic thyroid cancer has not changed in more than 6 decades due primarily to uncontrolled systemic metastases [6, 14].

CUDC-907 in thyroid cancer

CUDC-907 is a first-in-class dual inhibitor of histone deacetylases (HDAC) and phosphatidylinositol 3-kinase (PI3K) signaling. We found CUDC-907 treatment resulted in significant growth inhibition in 6 thyroid cancer cell lines with driver mutations common in poorly differentiated and anaplastic thyroid cancer **(Figure 1)**

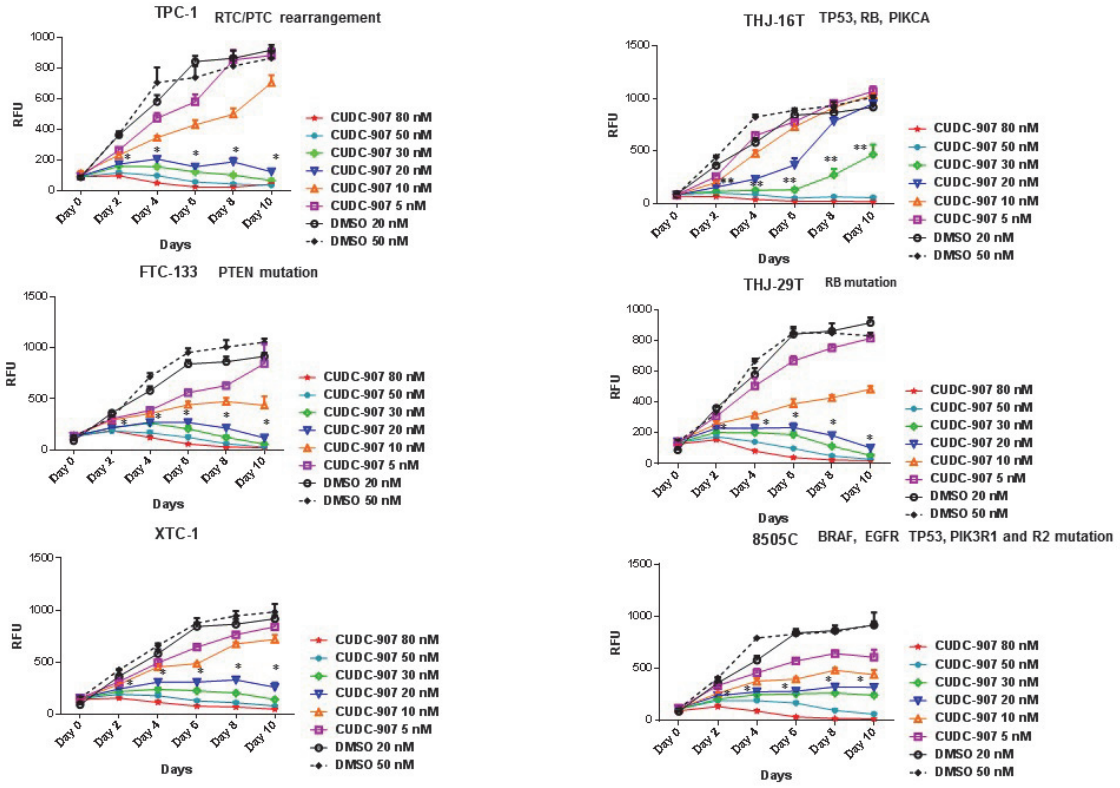


Figure 1 CUDC-907 inhibits cellular proliferation. * $p<0.05$, ** $p<0.01$ for the lowest concentration (20nM) for all cell lines except for THJ16T for which it is 30nM.

As expected CUDC-907 treatment of thyroid cancer cell lines resulted in effective inhibition of the PI3K/AKT pathway and deacetylation of H3 **(Figure 2).** Furthermore, CUDC-907 also inhibited EGFR/RAS/RAF/MEK/ERK signaling in thyroid cancer cell lines with driver activating mutations in this pathway **(Figure 2).**

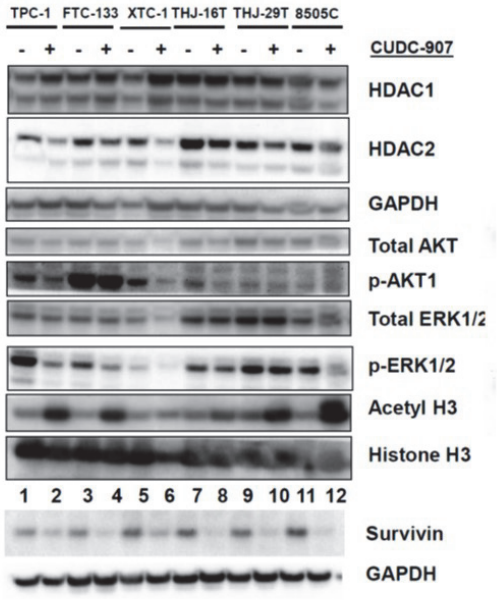


Figure 2

Western blot analysis of proteins altered with CUDC-907 treatment. CUDC-907 inhibits the PI3K/AKT and EGFR/RAS/RAF/ERK/MEK pathways and the deacetylation of H3, and decreases HDAC2 levels.

CUDC-907 treatment also induced caspase-dependent apoptosis and inhibited cellular migration/invasion **(Figure 3).**

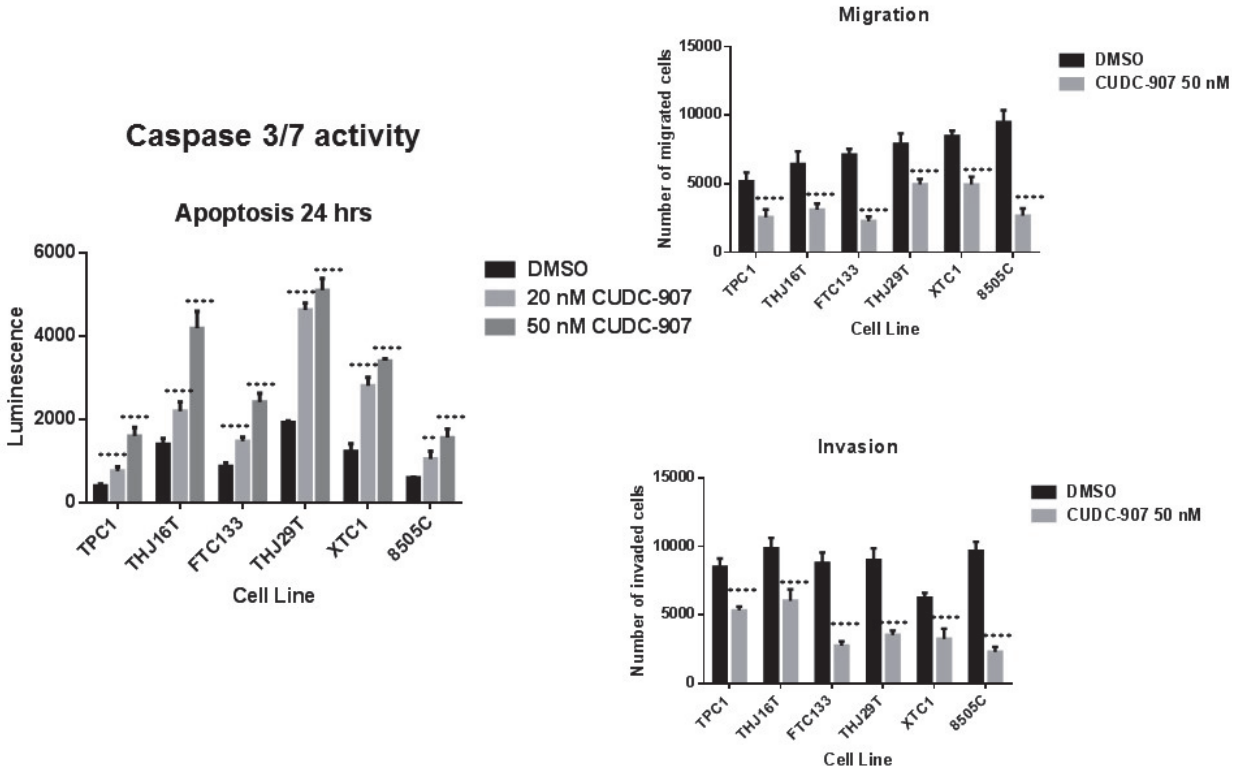


Figure 3

CUDC-907 treatment induces apoptosis and inhibits cellular migration and invasion. ** $p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$.

CUDC-907 treatment in our metastatic model of thyroid cancer that recapitulates the heavy tumor burden seen in patients with poorly differentiated and anaplastic thyroid cancer resulted in significant inhibition of growth and metastases (**Figure 4**).

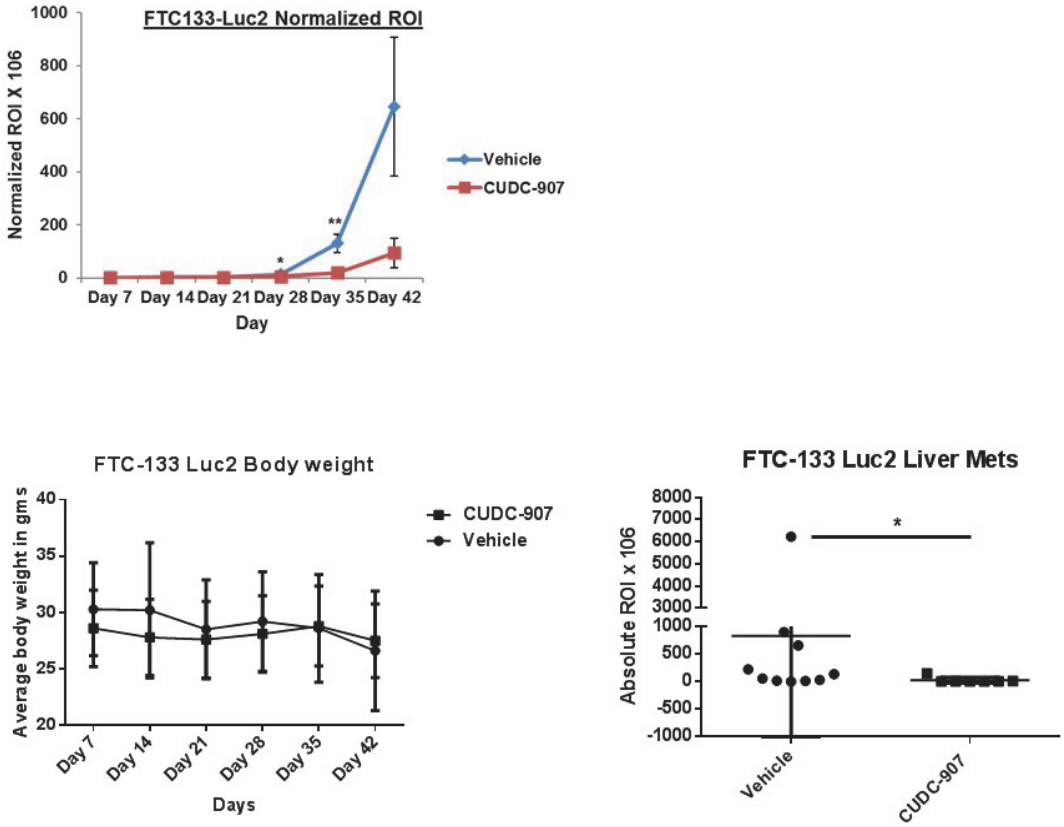
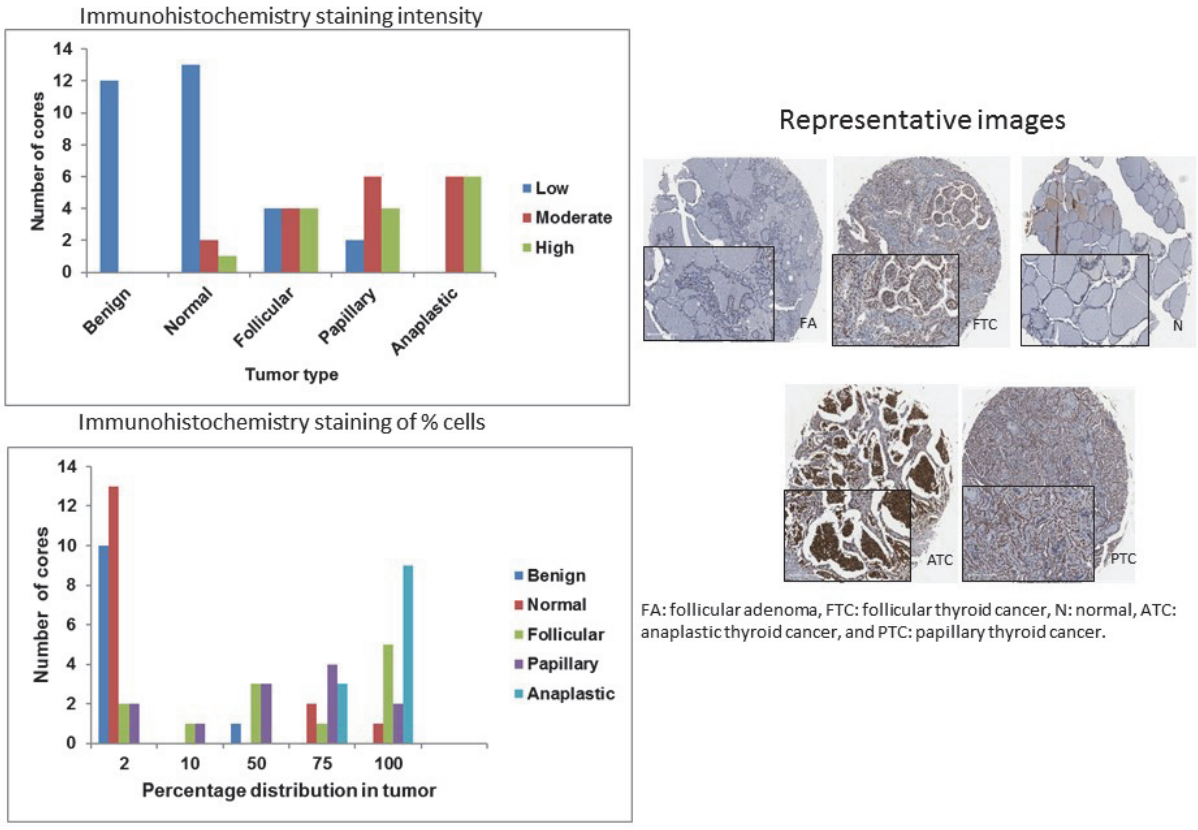


Figure 4 CUDC-907 treatment reduces growth and metastasis in a mouse model of metastatic thyroid cancer. Left top panel shows total body luciferase activity and left bottom panel shows body weight. Bottom right panel shows luciferase activity in liver. *$p < 0.05$, ** $p < 0.02$. Mice received CUDC-907 75 mg/kg by oral gavage for 5 days followed by 2 days of no treatment. No significant difference in body weight was seen with CUDC-907 treatment compared to vehicle control.

CUDC-907 targets genes/pathways commonly altered in poorly differentiated and anaplastic thyroid cancer

Currently, there are 18 known human HDACs and the expression of several of the HDACs have been studied in thyroid cancer [15, 16]. HDAC2, HDAC4 and HDAC6 were found to be overexpressed in thyroid cancer as compared to benign thyroid tumors, and HDAC2 expression was associated with lymphatic and vascular invasion in thyroid cancer [15]. Thus, we evaluated the effect of CUDC-907 treatment on HDAC2, HDAC4 and HDAC6 protein levels in thyroid cancer cells, and found reduction of HDAC2 protein levels (**Figure 2**). We also performed immunohistochemistry for HDAC2 in thyroid tissue samples and found significantly higher levels with mostly nuclear staining in anaplastic thyroid cancer and aggressive variants of thyroid cancer **(Figure 5)** We previously have identified survivin to be a biomarker of treatment response in thyroid cancer cells and CUDC-907 treatment also reduced survivin levels *in vitro* (**Figure 2**). [17-19].



FA: follicular adenoma, FTC: follicular thyroid cancer, N: normal, ATC: anaplastic thyroid cancer, and PTC: papillary thyroid cancer.

Figure 5 HDAC2 is overexpressed in aggressive thyroid cancer. HDAC2 immunohistochemistry and scoring for intensity and percent of positive cells.

The thyroid cancer cell lines used to evaluate the anticancer activity of CUDC-907 have the driver mutations that are present in human poorly differentiated and anaplastic thyroid cancer and that activate the PI3K/AKT and EGFR/RAS/RAF/MEK/ERK signaling pathways that are inhibited by CUDC-907 (**Table 1, Figure 1**).

Table 1 Frequency of common driver mutations present in poorly differentiated and anaplastic thyroid cancer.^

Genes	Anaplastic thyroid cancer (%)	Poorly differentiated thyroid cancer (%)
BRAF	26-45	33
RAS	22-24	28
PTEN	12-15	4
PI3K/PIK3CA/MTOR	17-18	2
TERT	73	8
TP53	55	40

^Data from references [14, 20, 21].

Clinical experience with CUDC-907 treatment in hematologic and solid malignancies

CUDC-907 is being studied in 3 early phase clinical trials for the treatment of hematologic malignancies (IND# 115780) and solid tumors (IND# 123500). Under IND# 115780, Curis is conducting 2 trials, a Phase 1 dose escalation and expansion trial in subjects with lymphoma or multiple myeloma and a Phase 2 trial to evaluate CUDC-907 as monotherapy and in combination with rituximab in subjects with relapsed/refractory MYC-altered diffuse large B-cell lymphoma. As of November 2015, a total of 72 subjects have been treated with CUDC-907. In the completed dose-escalation phase, subjects received CUDC-907 daily (QD, doses: 30 or 60 mg), or intermittently on twice weekly or thrice weekly schedules (doses: 60, 90, 120 or 150 mg), or on a 5 days on, 2 days off (5/2) schedule (dose: 60 mg). CUDC-907 dosed at 60 mg on the 5/2 schedule was determined to be the RP2D. Among 58 response-eligible subjects (defined as having received study medication and undergone at least one post-baseline response assessment) with relapsed/refractory lymphoma or multiple myeloma, 3 have achieved confirmed complete response (CR) and 6 have achieved partial response (PR). Another 30 subjects achieved stable disease (SD) (in some cases, of lengthy duration, such as nearly 3 years

in one subject with multiple myeloma) and 19 have experienced progression of disease (PD). CUDC-907 has also been evaluated in patients with advanced solid tumors in a Phase 1 single-agent clinical trial (CUDC-907-102).

Recently, the results of the phase I study on CUDC-907 safety, tolerability, and preliminary activity was reported in 44 enrolled patients (of whom ten were sequentially assigned to CUDC-907 once-daily (maximum tolerated dose {MTD} 60 mg), 12 to twice-weekly (MTD 150 mg), 15 to three-times-weekly (MTD 150 mg), and seven to the 5/2 dosing schedule (MTD 60 mg) [22]. 37 (84%) patients had discontinued study drug as a result of progressive disease or clinical signs of progressive disease at the data cutoff. Four dose-limiting toxicities (DLTs) occurred in three of 40 DLT-evaluable patients (diarrhea and hyperglycemia in one patient on 60 mg once daily, hyperglycemia in one patient on 150 mg twice weekly, and diarrhea in one patient on 150 mg three times weekly) **(Table 2)**.

Table 2 CUDC-907 therapy-associated toxicity from phase I trial.^

Toxicity	Grade 1–2	Grade 3	Grade 4	Grade 5
Diarrhea	23 (52%)	2 (5%)	0	0
Fatigue	16 (36%)	1 (2%)	0	0
Nausea	11 (25%)	0	0	0
Thrombocytopenia	2 (5%)	7 (16%)	2 (5%)	0
Neutropenia	2 (5%)	2 (5%)	2 (5%)	0
Upper respiratory infection	5 (11%)	1 (2%)	0	0
Constipation	5 (11%)	0	0	0
Cough	5 (11%)	0	0	0
Rash	5 (11%)	0	0	0
Hyperglycemia	0	1 (2%)	2 (5%)	0
Hypokalemia	2 (5%)	1 (2%)	0	0
Hypomagnesemia	2 (5%)	1 (2%)	0	0
Increased blood alkaline phosphatase	2 (5%)	1 (2%)	0	0
Dehydration	1 (2%)	1 (2%)	0	0
Dizziness	1 (2%)	1 (2%)	0	0
Epistaxis	1 (2%)	1 (2%)	0	0
Musculoskeletal pain	1 (2%)	1 (2%)	0	0
Pleural effusion	0	2 (5%)	0	0
Pneumonia	0	2 (5%)	0	0
Hypercalcaemia	0	0	1 (2%)	0
Lymphoma	0	0	0	1 (2%)
Sepsis	0	0	0	1 (2%)
Acute renal failure	0	1 (2%)	0	0
Anemia	0	1 (2%)	0	0
Cardiac tamponade	0	1 (2%)	0	0
Failure to thrive	0	1 (2%)	0	0
Hyperuricemia	0	1 (2%)	0	0
Influenza	0	1 (2%)	0	0

Lymph node pain	0	1 (2%)	0	0
Urosepsis	0	1 (2%)	0	0
Vascular access complications	0	1 (2%)	0	0

^Data from reference 22.

There was no DLTs observed in patients on the 5/2 schedule. Grade 3 or worse adverse events occurred in 19 (43%) of 44 patients. The most common of which were thrombocytopenia (9 of 44 patients [20%]), neutropenia (3 [7%]), and hyperglycemia (3 [7%]). Five (14%) of 37 response-evaluable patients achieved an objective response (two complete responses and three partial responses). All five responses occurred in the subgroup of patients with diffuse large B-cell lymphoma (DLBCL; n=9), and three occurred in those with transformed follicular lymphoma DLBCL (n=5). On the basis of these findings, we selected CUDC-907 60 mg on the 5/2 dosing schedule as the recommended phase 2 dose. As of 29 September 2015, CUDC-907 60 mg 5/2 had been administered to 15 subjects with solid tumors. Among 9 response-evaluable subjects as of data cut-off, there were 5 SDs (3 breast cancer, 1 adenoid cystic, 1 ovarian cancer) and 4 PDs (3 breast cancer, 1 salivary gland cancer). Based on this clinical experience, we will use 60 mg of CUDC-907 with the 5/2 schedule.

Plasma pharmacokinetics of CUDC-907 and the major metabolites were recently reported [22]. A dose-related increase in plasma exposure were observed. In six patients on the 60 mg 5/2 schedule, a low parent drug and metabolite concentrations in 0-24 hours were observed (24-hour plasma average concentration of active M2 metabolite and inactive M1 metabolite being 25 ng/mL and 20 ng/ml, respectively) [22].

Rationale for clinical protocol

There is currently no standard or effective therapy for poorly differentiated and anaplastic thyroid cancer, and aggressive variants of differentiated thyroid cancer. Our preclinical studies suggest that CUDC-907 may be effective in patients with locally advanced and metastatic poorly differentiated and anaplastic thyroid cancer, and aggressive variants of differentiated thyroid cancer. Moreover, the dual targets of CUDC-907 are prevalent in poorly differentiated and anaplastic thyroid cancer, and aggressive variants of differentiated thyroid cancer.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria:

2.1.1.1 Subjects ≥ 18 years of age.

2.1.1.2 Thyroid cancer histology or cytology that is aggressive (anaplastic/undifferentiated thyroid cancer, poorly differentiated thyroid cancer, hürthle cell carcinoma, tall-cell variant of papillary thyroid cancer, sclerosing variant of papillary thyroid cancer).

2.1.1.3 Measurable disease.

2.1.1.4 Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

2.1.1.5 Absolute neutrophil count ≥ 1,000/μL

2.1.1.6 Platelets ≥ 75,000/μL

2.1.1.7 Creatinine ≤ 1.5x upper limit of normal (ULN) or creatinine clearance ≥ 60ml for

patients with creatinine levels 1.5 times above institutional ULN (calculated based on age, weight and sex

2.1.1.8 Total bilirubin ≤ 1.5x ULN; AST/ALT ≤ 2.5x ULN. For subjects with documented liver metastases, the AST/ALT may be ≤ 5x ULN.

2.1.1.9 Recovery to Grade 1 or baseline of any toxicity due to prior anticancer therapies (excluding alopecia).

2.1.1.10 Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to screening CBC or Cycle 1, Day 1 treatment.

2.1.1.11 Women of child bearing potential must have a negative serum pregnancy test.

2.1.1.12 The effects of CUDC-907 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation and for 30 days following the last study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.13 Able to provide written informed consent and to follow protocol requirements.

2.1.2 Exclusion Criteria:

2.1.2.1 Systemic anticancer therapy within 4 weeks of study entry, except for subjects with anaplastic/undifferentiated thyroid cancer who may be enrolled immediately after discontinuation of previous therapy.

2.1.2.2 Other investigational agents within 4 weeks prior to study treatment, except for subjects with anaplastic/undifferentiated thyroid cancer who may be enrolled immediately of discontinuation of previous therapy.

2.1.2.3 Pregnant women are excluded from this study because the potential risk of teratogenic or abortifacient effects of CUDC-907 is unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with CUDC-907, breastfeeding should be discontinued if the mother is treated with CUDC-907. These potential risks may also apply to other agents used in this study.

2.1.2.4 Diabetes mellitus that is not controlled with medication.

2.1.2.5 Serious infection requiring intravenous antibiotic therapy within 14 days prior to study treatment.

2.1.2.6 Evidence of central nervous system metastasis.

2.1.2.7 Uncontrolled or severe cardiovascular disease, including myocardial infarction, unstable angina, or atrial fibrillation (AFib) within 6 months prior to study treatment, New York Heart Association (NYHA) Class II or greater congestive heart failure, serious arrhythmias requiring medication for treatment, clinically significant pericardial disease, cardiac amyloidosis, or QTc with Fridericia's (QTcF) correction that is unmeasurable or ≥ 480 msec on screening ECG. (Note: for QTcF ≥ 480 sec on the screening ECG, the ECG may be repeated twice at least 24 hours apart; the mean QTcF from the three screening ECGs must be < 480 msec in order to meet eligibility for trial participation).

2.1.2.8 Gastrointestinal disease or disorder that could interfere with the swallowing, oral

absorption, or tolerance of CUDC-907. This includes uncontrolled diarrhea (> 1 watery stool/day), major abdominal surgery, significant bowel obstruction and/or gastrointestinal diseases that could alter the assessment of pharmacokinetics or safety, including but not limited to: irritable bowel syndrome, ulcerative colitis, Crohn's disease and hemorrhagic coloproctitis.

2.1.2.9 Unstable or clinically significant concurrent medical condition that would, in the opinion of the investigator, jeopardize the safety of a subject and/or compliance with the protocol.

2.1.2.10 Second primary malignancy within 2 years of study entry other than adequately treated non-melanoma skin or superficial bladder cancer, curatively treated carcinoma in situ of the cervix or other curatively treated solid tumor deemed by the investigator to be at low risk for recurrence.

2.2 SCREENING EVALUATION

2.2.1 At any time prior to initiation of study therapy

- Pathology or cytology slides will be reviewed by NCI Laboratory of Pathology.

2.2.2 Within 4 weeks prior to treatment

- Brain MRI or CT
- CT scan of the neck, chest, abdomen and pelvis (CT C/A/P) or MRI if patient has renal insufficiency
- Bone scan for patients in whom bone metastases are suspected
- 18-F FDG PET scan

2.2.3 Within 2 weeks prior to treatment

- Laboratory Evaluations:
    - CBC with differential and platelets
    - Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein, cortisol, PT/PTT, TSH and thyroglobulin.
    - Urinalysis
- Complete history and physical examination including vital signs, height, weight and ECOG status
- 12 lead ECG

2.2.4 Within 3 days prior to treatment

- Serum or urine beta-HCG (woman of childbearing potential)

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov . After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4 STRATIFICATION PROCEDURES

Patients will be stratified in two groups for whom response by the RECIST criteria will be evaluated separately based on the histologic category of thyroid cancer as the aggressiveness of the disease types are significantly different. Group I will include patients with anaplastic thyroid cancer. Group II will include patients with poorly differentiated thyroid cancer and the aggressive variants of differentiated thyroid cancer. Up to 20 evaluable patients will be enrolled to each cohort using a Simon Minimax two-stage phase II trial design as described in section **8**.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This will be an open label, phase II trial and patients will be given 60 mg of CUDC-907 orally once a day on a five days on and two days off schedule (5/2). One cycle will be 21 days. Patients may continue on treatment if there are no unacceptable adverse events (see Section **3.3**) or disease progression on anatomic imaging. Response to treatment will be assessed after completing two cycles of treatment.

Patients will undergo ultrasound -guided biopsy of their tumor once before treatment if the site of disease is readily accessible without posing a significant risk to the patient. The tissue sample will be used for mutation profiling of common driver mutations and phosphoprotein profiling of commonly activated pathways in poorly differentiated and anaplastic thyroid cancer, and aggressive variants of differentiated thyroid cancer (**Table 1**).

3.2 DRUG ADMINISTRATION

CUDC-907 60 mg (2 × 30 mg capsules) will be given orally once a day 5 days on and 2 days off.

All doses of study drug will be administered with meals (± 30 minutes) at approximately the same time each dosing day, if possible.

Subjects will be given the exact number of study agent until the next study visit.

Patents will complete and return Patient's Diary (**Appendix B)**.

Research team will document study agent compliance on the Patient Self-Administer Study Agent Compliance Log.

3.3 DOSE MODIFICATION

3.3.1 Subjects may continue to receive 21-day cycles of study treatment until disease progression has been documented or other discontinuation criteria have been met.

To continue dosing of CUDC-907, subjects must meet the following criteria:

- ANC > 1,000/μL.
- Platelets ≥ 50,000/μL.
- AST and ALT ≤ 2.5 × ULN (for subjects with documented liver metastases AST and ALT must be ≤ 5 X ULN).
- Total Bilirubin concentration ≤ 1.5 × ULN.
- Creatinine ≤ 1.5 × ULN.
- ≤ Grade 2 diarrhea controlled by antidiarrheal treatment.

3.3.2 Dose Delays and Discontinuation of CUDC-907

In the event that any of the above criteria are not met, study drug dosing will be held until the retreatment criteria are met. Treatment may then resume at the full dose of CUDC-907, as long as none of the criteria in **Table 4** and/or **Table 5** are met. Beyond Cycle 1, subjects held for > 7 days may restart treatment after the subject has met the above criteria at the discretion of the Investigator. Beyond Cycle 2, subjects may have study drug held for up for 1 full cycle (21 days). If beyond 1 full cycle, then the subject will be taken off treatment per section **4.9.2**.

Subjects who experience a DLT-like event will be either discontinued from further study treatment or their dose will be reduced as outlined in **Table 3.** A DLT-like event will be defined as any of the following AEs occurring at any time:

- Non-hematological ≥ Grade 3 AE, other than Grade 3 nausea or Grade 3 vomiting in subjects treated with less than optimal antiemetic therapy.
- An AE resulting in a dose delay of 21 days.
- Grade 4 neutropenia ≥ 7 days, or ≥ Grade 3 neutropenia with fever > 101.3ºF (38.5ºC) or ≥ Grade 3 neutropenia with infection.
- Grade 4 thrombocytopenia ≥ 7 days, or ≥ Grade 3 thrombocytopenia and significant bleeding.

Table 3 CUDC-907 Dose Reduction Steps

Reduction Steps:	**Schedule**	**Dose**
Starting dose	5/2	60 mg
Dose Reductions	**Schedule**	**Dose**
First dose reduction	4/3	60 mg
Second dose reduction	5/2	30 mg
Final dose reduction	4/3	30 mg

4/3 = 4 days on, 3 days off; 5/2 = 5 days on, 2 days off

Dose Adjustments for CUDC-907 Hematologic and Non-hematologic Toxicity

The administration of HDAC and PI3K inhibitors has been associated with predictable bone marrow suppression that is typically transient and reversible.

The administration of HDAC and PI3K inhibitors has also been associated with hyperglycemia. This hyperglycemia does not generally result in severe metabolic complications and typically resolves with therapeutic intervention. The treatment goal for glycemic control is fasting plasma glucose < 160 mg/dL; while making every attempt to avoid hypoglycemia. Dose modifications of CUDC-907 are based on the severity of toxicities.

CUDC-907 dose adjustments for hematologic and non-hematologic toxicities are shown in **Table 4** and **Table 5.**

Table 4 **CUDC-907 Dose Adjustments for Hematologic and Non-Hematologic Toxicities**			
Thrombocytopenia	**Grade 1 or 2** No change in dose	**Grade 3 or 4 (platelets < 50,000/µL)** Hold treatment until platelets ≥ 50,000/µL or baseline, then reduce dose to the next lower dose level (as applicable per **Table 3**).	**Grade 4 thrombocytopenia requiring platelet transfusion** Hold treatment until platelets ≥75,000/µL or baseline, then reduce dose to the next lower dose level (as applicable per **Table 3** **).**
Neutropenia	**Grade 1 or 2** No change in dose	**Grade 3 or 4 (ANC < 1,000/uL)** Hold treatment until ANC ≥ 1000/µL, then reduce dose to the next lower dose level (as applicable per **Table 3**).	**Grade 4 febrile (≥ 38.5° C) neutropenia** Hold treatment until febrile neutropenia resolves and ANC ≥ 1000/µL or baseline, then permanently dose reduce to the next lower dose level (as applicable per **Table 3**).
Anemia	**Grade 1 or 2** No change in dose	**Grade 3 or 4 (hemoglobin < 8 g/dL)** Hold treatment until hemoglobin ≥ 10 g/dL or baseline then reduce dose to the next lower dose level (as applicable per **Table 3**).	**Grade 4 anemia requiring transfusion** Hold treatment until hemoglobin ≥ 10 g/dL or baseline, then permanently dose reduce to the next lower dose level (as applicable per **Table 3**).
Recurrence of Grade 3 or 4 hematologic toxicity will be cause for a second dose modification. **If the starting dose does not permit dose modification, then study drug will be discontinued.**			

Table 4
CUDC-907 Dose Adjustments for Hematologic and Non-Hematologic Toxicities

Non-hematological AEs (excluding hyperglycemia)	**Grade 1 or 2** No change in dose[1]	**Grade 3** • Hold treatment until resolution to ≤ Grade 1 or baseline • If not recovered to ≤ Grade 1 or baseline within 3 weeks, reduce to next lower dose level upon return to ≤ Grade 1 or baseline (as applicable per **Table 3**).	**Grade 4** Discontinue treatment.[2]
Recurrence of Grade 3 non-hematologic toxicity (excluding hyperglycemia) or inability to reduce dose (based on starting dose) will be grounds for discontinuation of study drug.			

Table 5 CUDC-907 Dose Adjustments for Hyperglycemia			
Toxicity	**Management**		
Hyperglycemia	Grade 1/2 or Grade 3 (> 250 – 500 mg/dL) asymptomatic; No change in dose[1]	Grade 3 (> 250 – 500 mg/dL) symptomatic or Grade 4 (> 500 mg/dL) Hold treatment until glucose < 250 mg/dL and asymptomatic; Reduce dose to the next lower dose level (as applicable per **Table 3**).	≥ Grade 3 hyperglycemia not improving despite appropriate treatment for 1 week or symptomatic Grade 4 hyperglycemia (> 500 mg/dL) Hold treatment until glucose < 250 mg/dL and asymptomatic; Reduce dose to the next lower dose level (as applicable per **Table 3**) upon return to ≤ Grade 1 or baseline.
Recurrence of Grade 3 or 4 hyperglycemia will be cause for a second dose modification. If the starting dose does not permit dose modification, then study drug will be discontinued. Recurrence of Grade 3 or 4 hyperglycemia that does not recover to ≤ Grade 1 or baseline within 3 weeks after second modification (as applicable) will be grounds for discontinuation of study drug.			

[1] Transient Grade 1 or 2 hyperglycemia will be monitored per Investigator discretion and medical guidelines.

3.4 EVALUATION DURING TREATMENT

Laboratory evaluations and physical examinations will be performed within two weeks prior to initial treatment and every three weeks (one cycle) while subjects are on therapy.

- CBC with differential and platelets
- Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein, cortisol, PT/PTT, TSH and thyroglobulin.
- Urinalysis

Within three days prior to each treatment cycle.

- Toxicity evaluation
- Vital signs, ECOG status, 12 L ECG

- Limited Physical examination

3.5 STUDY CALENDAR

Procedures	Baseline Screening[6]	Every Cycle (within 3 days)	Every 2 Cycles (within 3 days)	Off Treatment Evaluations (Following Treatment) [5]				
				1 Month	3 Months	6 Months	12 Months	FU
Confirmation of thyroid cancer	X							
Informed Consent	X							
History and PE including height and weight	X							
Limited PE		X		X	X	X	X	
Vital signs	X	X						
Performance Score ECOG	X	X		X	X	X	X	
Toxicity evaluation	→	→	→	→	→	→	→	
12L ECG	X	X				X		
RECIST 1.1 disease assessment	X		X					
Urinalysis	X	X						
CBC with diff and platelets	X	X		X	X	X	X	
Chemistries[1]	X	X		X	X	X	X	
TSH and Thyroglobulin	X	X						
Serum or urine beta-HCG	X							
CT CAP or MRI	X		X	X	X	X	X	
Brain MRI or CT Scan	X							
Bone Scan	X							

Procedures	Baseline Screening[6]	Every Cycle (within 3 days)	Every 2 Cycles (within 3 days)	Off Treatment Evaluations (Following Treatment) [5]				
				1 Month	3 Months	6 Months	12 Months	FU
Tumor Biopsy	X							
FDG PET Scan[2]	X		X					
Phone/Email Evaluation[3]								X
Advance Directives [4]	X							

[1] Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein, cortisol, PT/PTT

[2] 18F FDG PET scan will be performed after 2 cycles of treatment (+/- 3 days), and then annually or when clinical indicated.

[3] Following the 12-month evaluation patients will be followed via phone or e-mail contact every 6 months for survival

[4] Filling out of the advance directives will be offered, but obtaining of it is not required. For details see Section **10.3**

[5] For follow up visits +/- window applies: +/- 1 week for 1 Month, +/- 2 weeks for 3 Month, +/- 4 weeks for 6 and 12 Months.

[6] Evaluations done at screening will be used as Baseline assessments.

3.6 CRITERIA FOR CONTINUED TREATMENT

3.6.1 Prior to each treatment cycle.

- Treatment with CUDC-907 will continue until progression of disease, development of unacceptable toxicity, or withdrawal of consent.
- Adequate hematologic and organ function:
    - Hemoglobin greater than or equal to 8.0 gm/dL; ANC greater than or equal to 1,000/mm^3; Platelets greater than or equal to 75,000/mm^3
    - Creatinine ≤ 1.5x upper limit of normal (ULN)
    - Total bilirubin ≤ 1.5x ULN
    - AST/ALT ≤ 2.5x ULN. For subjects with documented liver metastases, the AST/ALT may be ≤ 5x ULN.

3.7 RESTAGING

Patients will undergo the following evaluations at the end of every 2 cycles of treatment (+/- 3 days).

- CT scan of the chest, abdomen and pelvis (CT C/A/P) or MRI
- ^{18}F FDG PET scan will be performed after 2 cycles of treatment (+/- 3 days), and then annually or when clinical indicated.
- Patients who continue to receive clinical benefit may continue treatment at the discretion of the PI.
- Response will be determined using RECIST 1.1 criteria (please see Section **6.4**)

3.8 OFF TREATMENT EVALUATIONS (FOLLOWING TREATMENT)

3.8.1 3 months

- Physical exam including ECOG status
- CBC with differential
- Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein
- CT scan of the chest, abdomen and pelvis (CT C/A/P) or MRI

3.8.2 6 months

- Physical exam including ECOG status
- CBC with differential
- Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein
- 12L ECG
- CT scan of the chest, abdomen and pelvis (CT C/A/P) or MRI

3.8.3 12 months

- Physical exam including ECOG status
- CBC with differential
- Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein
- CT scan of the chest, abdomen and pelvis (CT C/A/P) or MRI

3.8.4 Following the 12-month evaluation patients will be followed via phone or e-mail contact every 6 months for survival

3.9 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to documenting removal off study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy. The following evaluation will occur:

- Physical exam including ECOG status
- CBC with differential
- Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein
- CT scan of the chest, abdomen and pelvis (CT C/A/P) or MRI

3.9.1 Off Treatment Criteria

- Progressive Disease
- Excessive toxicity as defined in section **3.3**
- Allergic reaction to investigational agent
- The subject becomes pregnant
- PI discretion
- Patient request to be withdrawn from study

3.9.2 Off-study Criteria

- Death
- Patient request to be withdrawn from study
- PI discretion
- Investigator decision to the end the study

3.9.3 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site **(**http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov .

4 SUPPORTIVE CARE

Appropriate supportive care for any side effects or toxicity may be provided by the Endocrine Oncology Branch. Patients may be admitted as necessary to manage issues related to study medication or disease process. Antidiarrheal treatment (e.g., loperamide) will be administered immediately upon the first onset of symptoms. Each subject will be instructed to have loperamide or a comparable anti-diarrheal medication readily available and to begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the subject until diarrhea free. Subjects will be instructed to notify the Investigator if diarrhea occurs and will be evaluated in the clinic for significant dehydration, possible electrolyte imbalance, and/or ongoing losses. If clinically significant dehydration is present, rehydration and electrolyte repletion will be performed. Additionally, subjects will be monitored following rehydration for the risk of recurrence and electrolyte imbalances and advised regarding appropriate fluid management to reduce the likelihood of subsequent dehydration events. Antiemetics will be given prophylactically after the first episode of nausea or vomiting. Growth factor support will be permitted for neutropenia or neutropenic fever.

5 BIOSPECIMEN COLLECTION

Test/assay	Samples	Type of tube	Collection time point	Location of specimen analysis
Direct Sanger Sequencing (for mutations in **Table 1**) and Immunohistochemistry for pERK, pAKT, pS6, HDAC2, survivin.	Tumor tissue sample from biopsy and or archival paraffin block.	Saline	Baseline (within 1 month prior to treatment)	Endocrine Oncology Branch Lab

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

Samples will be collected and sent to the Endocrine Oncology Laboratory as described below.

Contact: Sophie Wang

Pager number: 1211-10873

Endocrine Oncology Branch
National Cancer Institute
CRC Room 4-5840
10 Center Drive, MSC 1201
Bethesda, MD 20892-1201
(301) 496-5049

5.1.1 Direct Sanger Sequencing and Immunohistochemistry

- An ultrasound -guided tumor biopsy will be obtained at baseline if the site of disease is readily accessible without posing a significant risk to the patient. If a tumor biopsy cannot be performed archival paraffin tumor blocks will be used with core biopsy of the tumor sample for direct Sanger sequencing of the driver mutations listed in **Table 1** and for immunohistochemistry for proteins listed above.
- Biopsy samples will be collected, placed on ice and sent immediately to the Endocrine Oncology Branch Laboratory.
- The direct Sanger sequencing and immunohistochemistry will be performed in the Endocrine Oncology Branch laboratory.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be labeled with the date and time of acquisition, the type of tissue and patient study ID. Upon receipt in the lab, samples will be barcoded and logged into the tissue database, LabMatrix. Tissue will be stored in -20°C or -80°C freezers until molecular analysis and those for immunohistochemistry will be fixed in formalin. All freezers are monitored and are on separate emergency generator lines.

- All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NCI IRB as soon as he is made aware of such loss.
- If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data will be collected using the NCI C3D web based data collection system.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

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

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.2 ROUTINE DATA COLLECTION

6.2.1 Following enrollment, all adverse events will be described in the source documents and be reviewed by the designated research nurse, and captured in C3D.

6.2.2 During the follow up period (more than 30 days following the last treatment), only those events that are serious, unexpected, and related to the treatment will be captured in C3D.

6.2.3 Exclusions to Routine Data Collection:

The following Adverse Events will be captured only in the source documents and will not be reported in C3D:

- Laboratory values that do not support the diagnosis of a reportable event
- All grade 1 events

6.2.4 Concomitant medications

Only those medications that the patient is taking at baseline on a routine basis or medications that cause an AE will be captured in C3D. [Thus onetime medications and PRN medications will not be captured in C3D except those used to treat adverse events.]

6.3 HUMAN DATA SHARING PLANS

6.3.1 Human Data Sharing Plan

6.3.1.1 Human data generated in this research will be shared for future research as follows:

- De-identified data in an NIH-funded or approved public repository
- Identified data in BTRIS

6.3.1.2 Data will be shared through:

- An NIH-funded or approved public repository: clinicaltrials.gov
- BTRIS
- Publication and/or public presentations.

6.3.1.3 Data will be shared at the time of publication or shortly thereafter.

6.3.2 Genomic Data Sharing Plan

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

6.4 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 2 cycles (6 weeks, +/- 3 days).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.4.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with CUDC-907.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

6.4.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded

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

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

6.4.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

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

6.4.4 Response Criteria

6.4.4.1 Evaluation of target lesions*

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

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

Progression (PD): At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) or the appearance of one or more new lesions.

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

*All measurable lesions up to a maximum of 5 lesions (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all organs involved, and be suitable for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

6.4.4.2 Evaluation of non-target lesions**

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

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

Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions

All other lesions (or sites of disease), including pathological lymph nodes should be identified as **non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression."

6.4.4.3 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

6.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **6.2**.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **7.3, 7.4.**

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

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

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
  Suggest that the research places subjects or others at a *great risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB AND CLINICAL DIRECTOR (CD) REPORTING

7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and the NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations

- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

   NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.3 IND Sponsor Reporting Criteria

An investigator must **immediately** report to the sponsor, using the mandatory MedWatch form 3500a, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

• All Grade 5 (fatal) events (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.

• All other serious adverse events including deaths due to progressive disease must be reported within one business day

Study endpoints that are serious adverse events (e.g. all-cause mortality) will be reported in accordance with the protocol and study sponsor.

Events will be submitted to the Center for Cancer Research (CCR) at: CCRsafety@mail.nih.gov and to the CCR PI and study coordinator.

7.3.1 Reporting Pregnancy

7.3.1.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately and the pregnancy reported to the Sponsor. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agents (s) should be documented in box B5 of the MedWatch form "Describe Event or Problem".

Pregnancy itself is not regarded as an SAE. However, as patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, the CCR is requesting that pregnancy should be reported in an expedited manner as **Grade 3** "***Pregnancy, puerperium and perinatal conditions - Other (pregnancy)***" under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

If any pregnancy occurs in the course of the study, then the investigator should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all relevant information is provided to the Sponsor within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.3.1.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 30 days after the last dose of CUDC-907.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 30 days after the last dose should, if possible, be followed up and documented.

7.4 Expedited Adverse Event Reporting Criteria To The Pharmaceutical Collaborator (Curis)

All events listed below must be reported in the defined timelines to CCRsafety@mail.nih.gov.

The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below.

The collaborator has engaged Novella Clinical Inc. ("Novella") for centralized safety reporting and pharmacovigilance for the CUDC-907 compound. Novella will be notified and provided information related to any, pregnancy, suspected unexpected serious adverse reaction (*SUSAR*) and serious adverse event ("SAE") related to the Study Product, within twenty-four (24) hours of awareness of the event. Initial report may consist of limited information provided via email to pvgsafety@novellaclinical.com. A full report will be provided within eleven (11) calendar days from the SAE event; such report shall be the same as submitted to the IRB and

FDA, including all SAE information from any Approved Sub-Investigator Site. Sub-investigators must report all SAEs to the Investigator so that the Investigator can meet his/her foregoing reporting obligations to the required regulatory agencies; such information shall be sent by fax to 1-866-761-1274 or email Safety-Inbox@novellaclinical.com .

7.5 DATA AND SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. The principal investigator will be responsible for revising the protocol as needed to maintain safety. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and to the Sponsor.

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

7.5.2 Sponsor Monitoring Plan

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

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

The monitoring program also extends to multi-site research when the CCR is the coordinating center.
This trial will be monitored by personnel employed by an NCI contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

8 STATISTICAL CONSIDERATIONS

The primary objective of this trial is to determine the objective response rate of patients with locally advanced and or metastatic poorly differentiated and anaplastic thyroid cancer, and aggressive variants of differentiated thyroid cancer.

Patients will be enrolled into separate cohorts in order to estimate the response rates in each cohort: 1: Anaplastic thyroid cancer; 2: Poorly differentiated and aggressive variants of

differentiated thyroid cancer. Since there is no reliable information on expected clinical response rates in either cohort, each will be evaluated individually, with the primary objective in each cohort being to determine if using CUDC-907 would rule out a 5% response rate and target a rate of 25%. As such, in each cohort, the trial will be conducted using a Simon Minimax two-stage phase II trial design in order to rule out an unacceptably low partial (PR) + complete response (CR) rate of 5% (p0=0.05) in favor of an improved response rate of 25% (p1=0.25) [18]. With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), this first stage will enroll 13 evaluable patients in a given cohort, and if 0 of the 13 have a clinical response, then no further patients will be accrued to that cohort. If 1 or more of the first 13 patients have a response in that cohort, then accrual would continue until a total of 20 evaluable patients have been treated in that cohort. As it may take up to several months to determine if a patient has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 1 to 2 patients with a response out of 20 patients in a cohort, this would be an uninterestingly low response rate. If there were 3 or more of 20 (15%) who experienced a response, this would be sufficiently interesting to warrant further study in later trials with that cohort. Under the null hypothesis (5% response rate), the probability of early termination in either cohort is 51.3%.

In order to ensure that it remains safe to accrue patients, toxicity will be monitored in all patients. If at any time after 6 or more patients have been accrued in both cohorts combined, the cumulative fraction of patients with DLTs is 1/3 or greater, then no further patients will be enrolled on the trial.

Any secondary evaluations performed will be done in an exploratory fashion, with results presented without any formal adjustment for multiple comparisons.

It is anticipated that approximately 6 to 8 patients per year may enroll onto the trial. Thus, accrual of up to 40 total evaluable patients may be completed in approximately 5 to 7 years. In order to allow for a small number of in evaluable patients, the accrual ceiling will be set to 50 patients.

9 COLLABORATIVE AGREEMENTS

There is a CRADA agreement (03090) in place with Curis who is supporting this study.

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

Patients with metastatic or locally advanced poorly differentiated and anaplastic thyroid cancer will be selected for this study. To date, there is no information which suggests that differences in drug metabolism or disease response would be expected in any one patient group. Patient selection for this protocol will not be based on gender, race or ethnic background.

10.2 PARTICIPATION OF CHILDREN

Children will not be included on this protocol as poorly differentiated and anaplastic thyroid cancer is exceedingly rare in children.

10.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.4**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIHMEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Treatment with CUDC-907 may prove to be more effective treatment than systemic chemotherapy for locally advanced and metastatic poorly differentiated and anaplastic thyroid cancer. Patients with a long history of unresponsiveness to other treatment modalities may experience an actual therapeutic benefit. Risks include those associated with the agent, and standard imaging procedures for this disease entity. Care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will have laboratory tests to monitor for complications. If patients suffer any physical injury as a result of the participation of this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

10.4.1 Specimen Collection Risks

Risks also include those associated with specimen collection include pain, bleeding and the possibility of infection at the sampling site.

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

10.5 RISKS/BENEFITS ANALYSIS

Patients with locally advanced or metastatic poorly differentiated and anaplastic thyroid cancer have limited options available to them. CUDC-907 may provide anticancer activity in patients with advanced and metastatic poorly differentiated and anaplastic thyroid cancer. The potential

benefits outweigh the risks of treatment with CUDC-907. If this study demonstrates a tumor response to CUDC-907 a large, multicenter, trial using CUDC-907 in this population of patients will be considered.

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts, potential benefits and potential alternative therapies will be carefully explained to the patient, and a signed informed consent document will be obtained by the PI, AI or clinical staff fellow.

10.6 Consent and Assent Process and Documentation

All patients who are being considered for this trial will undergo informed consent prior to being enrolled on the trial. The PI or associate investigator will perform the consenting process. Patients and family members when applicable will be asked to read the consent and will be encouraged to ask questions. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. Patients will be enrolled after the consent document has been signed. Separate consents will be obtained for any surgical procedures performed.

10.6.1 Reconsent via phone

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject signature will sign and date the consent.

The original informed consent document will be mailed, via the US Postal Service or FedEx, back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

10.6.2 Informed consent of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, 45 CFR 46.117 (b) (2), (If a study with an IND or IDE, also cite 21 CFR 50.27 (b) (2)). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible,

interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

11 PHARMACEUTICAL INFORMATION

11.1 CUDC-907 MESYLATE

11.1.1 Source

CUDC-907 Mesylate drug product will be provided by Curis Inc. (Lexington, MA) under a research collaborative agreement with NCI.

10.1.2 CUDC-907 Mesylate

CUDC-907 mesylate is a white to off white crystalline powder that melts with decomposition at 230°C.

10.1.3 Chemical Properties

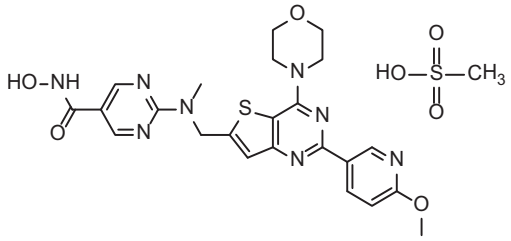
CUDC-907 is a synthetic small molecule inhibitor of HDAC and PI3K. The chemical structure of CUDC-907 integrates the hydroxamic acid moiety of HDAC inhibitors into a morpholinopyrimidine pharmacophore of phosphatidylinositol 3 kinase (PI3K) inhibitors. These two moieties are shared with well-studied, commercially approved or investigational drugs. The hydroxamic moiety is shared with FDA-approved agents such as vorinostat (suberoylanilide hydroxamic acid; SAHA), panobinostat, and belinostat and the morpholinopyrimidine moiety is shared with investigational agents such as PI-103, pictilisib, and BKM-120.

10.1.4 Chemical Name

The chemical name for CUDC-907 mesylate is N-Hydroxy-2-(((2-(6-methoxypyridin-3-yl)-4- morpholinothieno[3,2-d]pyrimidin-6-yl)methyl)(methyl)amino)pyrimidine-5-carboxamide mesylate.

10.1.5 Structural Formula

The chemical structure of CUDC-907 mesylate is shown below:



Chemical Formula: $C_{24}H_{28}N_8O_7S_2$
Molecular Weight: 604.66

10.1.6 Molecular Formula

The molecular formula of CUDC-907 mesylate is $C_{24}H_{28}N_8O_7S_2$

10.1.7 Molecular Weight

The molecular weight of CUDC-907 mesylate is 604.66 g/mol.

10.1.8 Pharmaceutical Properties

CUDC-907 free base showed low solubility but good permeability in early development testing. The solubility of the molecule was increased by the formation of salts, namely the mesylate capsule formulation that has been administered in the clinic to date.
CUDC-907 mesylate has been isolated in three polymorphic forms during early stage development. The form selected is reproducibly manufactured and controlled as assessed by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

10.1.9 Formulations

CUDC-907 mesylate is formulated as a gelatin capsule containing 30 mg CUDC-907. Excipients include silicified microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The capsules are packaged in high-density polyethylene bottles containing 35 capsules each, and appropriately labelled for clinical trial use as per national regulatory requirements. Additional capsule strengths may be made available for clinical trial use as needed

10.1.10 Storage Conditions

CUDC-907 mesylate 30 mg capsules should be stored at room temperature (15–30° or 59–86°F) in a tightly closed container.

11.1.11 Stability Data

CUDC-907 mesylate 30 mg capsules have been shown to be stable for 36 months at real time and six months accelerated conditions. Stability studies are ongoing and retest intervals will be updated periodically.

11.1.12 Toxicity

Study CUDC-907-101

As of the data cut-off of 02 November 2015, the most frequently reported AEs in CUDC-907-101 have been diarrhea, fatigue, nausea thrombocytopenia, and neutropenia. The frequency and severity of AEs on the 60 mg 5/2 schedule appears comparable to those observed in the overall population of subjects dosed with CUDC-907 on this trial. Additionally, this dose and schedule appears to be better tolerated than the QD dosing schedule (30 or 60 mg), during which all subjects experienced Grade 1-3 diarrhea and Grade 1-4 thrombocytopenia as frequent AEs (50% of subjects on the QD schedule). Among 29 subjects enrolled at the 60 mg 5/2 dosing schedule, diarrhea occurred in 63% of those treated and thrombocytopenia occurred in 24%.

Study CUDC-907-102

Similar to the safety results from Study CUDC-907-101, AEs on the CUDC-907-102 study have generally been self-limiting Grade 1 – 2 events of fatigue, nausea, and diarrhea. Adverse events were reported in 71% of subjects with Grade 3 events occurring in 21% of subjects; there were no Grade 4 or 5 events. The most common AEs were fatigue, nausea, decreased appetite, and abdominal pain. No DLTs have been reported to date.

10.1.13 Pregnancy and Lactation

There are no data available on the effect of CUDC-907 on the developing fetus. It is not known whether CUDC-907 is excreted in human milk.

Subjects who are pregnant or who intend to become pregnant during the treatment period should not receive CUDC-907. Men and women of childbearing potential and their partners must use an effective method of contraception during the treatment period and for 30 days following the last study treatment for subjects receiving CUDC-907. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence.

10.1.14 Overdose

No specific information is available on the treatment of over dosage of CUDC-907. In the event of an overdosage, the subject will be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional standards of care.

10.1.15 Missed Dose

Patients will be instructed if they miss a dose of CUDC-907 to take it as soon as possible. However, if it is within 6 hours of the next dose, then they will be instructed to skip the missed dose and go back to their regular dosing schedule. Patients will be instructed to not double their doses.

11.1.16 Incompatibilities

In vitro data suggest that with the exception of CYP3A4, CUDC-907 is a weak inhibitor of cytochrome P450 enzymes, with IC50 values > 10 μM. When tested with certain substrates (larger molecular weight substrates such as testosterone), CUDC-907 was shown to be an inhibitor of CYP3A4 (IC50 = 0.28 μM). The CUDC-907 metabolites M1 and M2 were tested as well. M1 was found to have mild inhibition of CYP2C8 (IC50 = 1.72 μM), but this IC50 is expected to be well above the observed plasma concentrations of the metabolite. In murine distribution studies, CUDC-907 demonstrated higher concentrations in the liver than in plasma. These levels may approach the CUDC-907 IC50 values for CYP3A4 and CYP2C8, thus drugs that interact with CYP3A4 and/or CYP2C8 should be used with caution. There are no available data in humans regarding the effects of CUDC-907 on cytochrome P450 enzymes. Subjects receiving concomitant medications metabolized by these enzymes will be monitored at the discretion of the principal investigator.

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13 APPENDICES

13.1 APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. 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	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13.2 APPENDIX B PATIENT'S DIARY

Patient Name Study ID

Please complete this form and return to the research nurse or doctor every cycle

You will take: CUDC-907 Dose: .

DAY	DATE	TIME TAKEN	COMMENTS (side effects or missed doses)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
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Patient Signature:

INSTITUTE: National Cancer Institute

STUDY NUMBER: 17-C-0029 PRINCIPAL INVESTIGATOR: Electron Kebebew, M.D.

STUDY TITLE: A Phase II Trial of CUDC-907 in Patients with Metastatic and Locally Advanced Thyroid Cancer

Continuing Review Approved by the IRB on 10/30/17

Amendment Approved by the IRB 11/13/17 (B) Date posted to web: 11/29/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This study is being done to find out if CUDC-907 will shrink tumors in persons with advanced thyroid cancer.

CUDC-907 is an investigational drug. "Investigational" means that the drug is being studied or tested. It has not been approved by the United States Food and Drug Administration (FDA) as a

prescription or over-the-counter medicine for any purpose, but it has been tested in clinical research.

Why are you being asked to take part in this study?

You are being asked to participate in this study because you have been diagnosed with locally advanced and metastatic thyroid cancer.

How many people will take part in this study?

Up to 50 subjects may participate in this study.

Description of Research Study

What will happen if you take part in this research study?

Before you begin the study:
If you decide to participate, you will undergo a series of tests to make sure you are eligible, including blood tests, tissue and scans as described below. If you have had some of these tests done recently, they may not need to be repeated.

Screening Tests and Procedures

- A review of any past or current medical conditions, medicines you are taking and cancer history.
- Physical examination, including vital signs, height and weight
- Electrocardiogram (ECG) to evaluate your heart.
- Review of your symptoms and your ability to perform your normal activities.
- Imaging Assessments – either a computed tomographic scan (CT) that produces a picture of your body using a small amount of radiation or magnetic resonance imaging (MRI) that uses a magnetic field to produce an image of your tumor and of your brain
- Bone Scan – if there is concern that you have cancer that has spread to your bones
- FDG PET Scan - to produce an image of your tumor
- You will have blood drawn for routine blood tests to find out if you are anemic, have low blood counts, your blood is clotting normally and if your liver, kidneys, and other organs are working well.

- Routine urine test.
- Pregnancy urine test if you are a woman who can have children.
- You will be asked to provide a sample of your tumor from a previous surgery so that we may confirm your diagnosis.

During the study:

If you are eligible for the study and agree to participate, we will perform a biopsy of the tumor before you have received any study medication to test for changes in a limited number of genes associated with thyroid cancer if it can be done without risk to you or use previously collected tumor samples.

You will be given CUDC-907 in tablet form. You will take it by mouth once a day with meals for 5 days, then take 2 days off (no CUDC-907) and then repeat each week. You should try to take CUDC-907 at the same time each day. You will continue to take the CUDC-907 until your cancer gets worse or if other criteria have been met. Your doctor will explain those criteria to you.

You will be given a Patient's Diary to complete for each cycle. In the diary, you will be asked to record date, time and missing doses. Please bring the diary with you at every study visit.

Ongoing Procedures during each treatment cycle (1 cycle = 3 weeks)

While you are taking CUDC-907, you will have tests done:

- Physical exam
- Electrocardiogram (ECG) to evaluate your heart
- Routine blood tests to find out if you are anemic, have low blood counts, your blood is clotting normally and if your liver, kidneys, and other organs are working well.
- Routine urine test.
- A review of any past or current medical conditions, medicines you are taking and cancer history.
- Review of your symptoms and your ability to perform your normal activities

Every 2 cycles (6 weeks):

- Review of your symptoms and your ability to perform your normal activities

- Imaging Assessments – either a CT scan or MRI of your tumor
- FDG PET Scan - to produce an image of your tumor (once after the first two cycles)

When you are finished taking the drugs (treatment):

At 3, 6 & 12 Months after your last dose of treatment:

- Physical exam, including height and weight
- Electrocardiogram (ECG) to evaluate your heart (at 6 months only).
- Review of your symptoms and your ability to perform your normal activities
- Routine blood tests to find out if you are anemic, have low blood counts, your blood is clotting normally and if your liver, kidneys, and other organs are working well.
- Imaging Assessments – either a CT scan or MRI of your tumor

After 12 Months:

We will contact you by phone or e-mail every 6 months for survival.

Birth Control:

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 30 days after you finish study treatment. In addition, male subjects should not donate sperm during the study and for 30 days after the last dose of study therapy. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

Risks Associated with CUDC-907

CUDC-907 works by inhibiting two enzymes, called HDAC (histone deacetylase) and PI3K (phosphoinositide 3-kinase). Each of these enzymes can cause different types of side effects through different mechanisms.

Studies conducted in animals have shown that CUDC-907 may make you less hungry, lose weight, reduce blood cell levels (especially white blood cells); and/or affect your kidneys, thymus gland, and the gastrointestinal (GI) tract, which may cause vomiting and diarrhea.

Over 90 patients have been treated with CUDC-907. The following potential side effects were reported as serious and/or have occurred in 2 or more patients, or resulted in a patient stopping CUDC-907 dosing:

Likely (Greater than 20% chance that this will happen)

- Diarrhea (loose stools)
- Fatigue (feeling tired)
- Nausea (feeling sick to your stomach)
- Decreased appetite (feeling less hungry)

Less Likely (Between a 4-20% chance that this will happen)

- Low platelet counts, which may increase your risk for bleeding (one patient had a serious nose bleed)
- Cough
- Throat pain
- Muscle spasms
- Low white blood cell counts, which may increase your risk for infection
- Constipation
- High blood sugar levels, which could be from interference in glucose metabolism

- Itchy skin
- Raised body temperature/fever
- Rash
- Sinus Congestion
- Sinus and/or throat infection
- Back pain
- Heartburn
- Difficulty speaking
- Bloody nose
- Numbness
- Decreased levels of potassium in the blood, which can cause irregular heart beat
- Low magnesium, which may result in muscle cramps, weakness, tremors or irregular heartbeat
- Low blood pressure
- Inflammation of the lungs, which can cause shortness of breath and difficulty breathing
- Lung infection
- Dehydration

Allergic Reaction

Sometimes people have allergic reactions to drugs. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction are:

- Rash
- Having a hard time breathing
- Wheezing when you breathe
- Sudden drop in blood pressure
- Swelling around the mouth, throat, or eyes

- Fast pulse
- Sweating

Risks from Study Procedures:

Ultrasound guided biopsy:
The risks associated with ultrasound-guided biopsy include:

Bleeding: Although rare, bleeding can occur and may require surgery to control.

Infection: An infection is possible whenever an object, (such as the needle used in ultrasound-guided biopsy) pierces the skin, even if sterile procedures are always followed during the procedure. This is a very rare complication.

Blood Drawing: Local pain, bruising, bleeding, blood clot formation, and, in rare instances, an infection might occur at the site where blood is drawn. There is also the possibility of dizziness or fainting while your blood is being drawn.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if the study drug, CUDC-907 will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

You should speak with your doctor about any other available treatments.
Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat

the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- Qualified representatives from Curis, the pharmaceutical company who produces CUDC-907.

Controlled access databases:

Your individual genomic data and health information will be put in a controlled-access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to identify you. Researchers approved to access information in the database have agreed not to attempt to identify you.

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time

New Information

During the course of the study, if we receive any important new information about the study drug that might change your mind about continuing in the study, the study doctor or study staff will tell you about it. You are free to withdraw your consent from the study at any time.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you become pregnant
- if you have side effects from the treatment that your doctor thinks are too severe

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Curis or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using a drug developed by Curis through a joint study with your researchers and the company. The company also provides financial support for this study.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Electron Kebebew, M.D., Building 10, Room 4-5952, Telephone: 240-760-6153. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative | Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian | Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian | Date | Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM OCTOBER 30, 2017 THROUGH OCTOBER 29, 2018.

Signature of Investigator | Date

Print Name

Signature of Witness | Date

Print Name