Amendment

Protocol Number: 10C0041-D **Reference Number:** 346736

Principal Investigator: Electron Kebebew, MD NCI EOB 301.496.5049 Electron.Kebebew@nih.gov

(NIH Employee Name, Institute/Branch, Telephone and e-mail)

Protocol Title: A Phase II Trial of Valproic Acid in Patients with Advanced Thyroid Cancers of Follicular Origin

SIGNATURES

Principal Investigator (*):
Electron Kebebew, MD - applied signature on 04/21/2015 7:56 AM EDT

Accountable Investigator:
PI is the Accountable Investigator

Branch Chief/CC Department Head (**):
Electron Kebebew, MD - applied signature on 04/21/2015 7:57 AM EDT

Medical Advisory Investigator (if applicable):
N/A

Lead Associate Investigator signature:
N/A

Referral Contact signatures:
N/A

Associate Investigators signatures:
N/A

For Institute/Center Scientific Review Committee:
N/A

Other IC Clinical Director signatures:
N/A

APPROVALS

IRB Chair:
Michael Hamilton - applied signature on 04/24/2015 7:32 AM EDT

Clinical Director:
William Dahut - applied signature on 04/22/2015 1:43 PM EDT

CONCURRENCE

OPS Protocol Specialist: C.Bonds-Beeken AM D 05/04/15

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: NA

Protocol Version Date: 04/17/2015

Abbreviated Title: VPA for Advanced Thyroid Cancer

NCI Protocol #: 10-C-0041D
Version Date: 04/17/2015

Title: A Phase II Trial of Valproic Acid in Patients with Advanced Thyroid Cancers of Follicular Origin

Principal Investigator: Electron Kebebew, M.D.
EOB/CCR/NCI
Bldg 10-CRC Room 4-5952
10 Center Drive
Bethesda, MD 20892
(301) 496-5049
kebebewe@mail.nih.gov

Associate Investigators: Naris Nilubol, M.D., EOB/CCR/NCI
Monica Skarulis, M.D., DEOB/CES/NIDDK
Craig Cochran, R.N., DEOB/CES/NIDDK

James Reynolds, M.D., NMD/CC/NIH
Seth Steinberg, Ph.D., BDMS/OCD/CCR/NCI
Marina Zemskova, M.D., DEOB/CES/NIDDK
Dan Zlott, PharmD, PHARM/CC/NIH
Samira Sadowski, M.D., EOB/CCR/NCI
Dhaval Patel, M.D., EOB/CCR/NCI

Vladimir Neychev, M.D., EOB/CCR/NCI
Roxanne Merkel, R.N., OCD/CCR/NCI
Rachel Aufforth, M.D., EOB/CCR/NCI

Referral Contacts:
Roxanne Merkel, R.N., OCD/CCR/NCI

PRECIS

Background:

- Patients who have advanced differentiated thyroid cancers (Stage IV) have a five-year survival of only 25%. Clinically this results in more aggressive growth, metastasis, decreased or loss of iodine uptake in the tumor, and tumors that may be refractory to conventional treatment: surgical resection, radioactive iodine treatment and thyroid hormone for TSH suppression.
- In thyroid cancer, valproic acid, at clinically achievable concentrations, has an antiproliferative and differentiating effect.
- We hypothesize that valproic acid may inhibit proliferation and induce differentiation in thyroid cancer cells so that 131-I may detect residual disease and be more effective for radioiodine ablation of thyroid cancer cells of follicular cell origin.

Objectives:

- The primary goal of this study is to determine if valproic acid will have an antineoplastic and differentiation effect in patients with advanced and or metastatic thyroid cancer of follicular cell origin.

Eligibility:

- Unresectable advanced and or poorly differentiated thyroid cancers of follicular cell origin (excluding anaplastic and medullary thyroid cancer) that have no uptake (<1%) on radioiodine scan or are unresponsive to radioiodine therapy.
- Elevated serum thyroglobulin (Tg) level (>100ng/ml on thyroid hormone; >10ng/ml off thyroid hormone).

Design:

- This will be an open label phase II study to assess the efficacy of valproic acid therapy as an antiproliferative and differentiation agent in patients with incurable differentiated thyroid cancer (unresponsive and/or radioiodine negative and unresectable).
- Oral valproic acid will be administered to reach a therapeutic serum level (50 to 100 μg/ml).
- The number of patients to be enrolled is 25 with an interim analysis of response once 13 patients are evaluable for response. It is anticipated that five patients may be enrolled per year.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 To determine if valproic acid will inhibit thyroid cancer growth, as evidenced by a decrease in thyroglobulin level, and tumor size.

1.1.2 To determine if valproic acid therapy will induce differentiation of thyroid cancer cells and therefore increase uptake of radioactive iodine by the tumor cells.

1.1.3 To determine the effect of valproic acid on differentiation markers of thyroid cancer and global gene expression in thyroid tumor tissue.

1.2 BACKGROUND AND RATIONALE

Thyroid cancer is the fastest growing cancer diagnosis in the U.S.[1]. Approximately 10-15% of patients present with aggressive disease and have about a 30% mortality rate at 5-10 years following initial treatment [2]. Patients with stage IV differentiated thyroid cancer have a five-year survival of only 25%. In patients with progressive or recurrent differentiated thyroid cancer, one-third of patients develop or have dedifferentiated tumors (loss of differentiation) [3]. Clinically this results in more aggressive growth, metastasis, decreased or loss of iodine uptake in the tumor, and tumors that may be refractory to conventional treatment: surgical resection, radioactive iodine (RAI) treatment and thyroid hormone for TSH suppression. In addition, up to 20% of patients with differentiated thyroid cancer have evidence of residual disease as indicated by detectable serum thyroglobulin levels but have negative RAI scans[4]. Patients with differentiated thyroid cancer are usually treated after total or near total thyroidectomy with RAI (I-131) in order to ablate any residual thyroid tissue and/or cancer. Loss of iodine uptake makes RAI ablation therapy ineffective. Further dedifferentiation of thyroid cancers of follicular cell origin, in about 1% of patients, leads to the formation of anaplastic thyroid carcinoma, which is uniformly lethal.

Valproic acid, a histone deacetylase (HDAC) inhibitor, has long been used as an anticonvulsant to treat seizures in patients with epilepsy. It has also been used to treat bipolar disorder. Recent studies have shown that this class of drugs has promising effects in the treatment of cancer by inhibiting cancer cell proliferation, inducing apoptosis, cell cycle arrest and differentiation in brain, hematologic, endometrial, ovarian and prostate cancers [5-8]. Preclinical studies also suggest that valproic acid has a similar antiproliferative and differentiating effect in human thyroid cancer cells [9-14].

Valproic acid interacts with the catalytic site of histone acetyltransferases to disrupt its activity. The post-translational modification process of acetylation is critical to gene transcription, with increased acetylation resulting in increased gene transcription. Because acetylation affects chromatin structure and nucleosomal packaging, it affects gene expression through this

mechanism. Approximately 2-5% of transcribed genes are significantly affected after treatment with HDAC inhibitors.

In thyroid cancer, valproic acid, at concentrations clinically achievable, has an antiproliferative and differentiating effect. At concentrations of 0.5 to 2.0mM, valproic acid inhibited growth by 55 to 80% [9-14]. Valproic acid also upregulates sodium-iodine symporter (NIS) gene expression in dedifferentiated thyroid cancer cells[12-14]. The NIS gene encodes the Na+/I- symporter, located on the basolateral membrane of follicular thyroid cells and is responsible for iodide uptake. Downregulated NIS expression is the predominant mechanism of dedifferentiation in thyroid cancer cells of follicular cell origin that makes RAI ablation therapy ineffective. Treatment with valproic acid increases iodide accumulation in poorly differentiated thyroid cancer cells by increasing the expression of the NIS gene.

Patients with differentiated thyroid cancers are routinely followed with serial thyroglobulin (Tg) levels, ultrasonography and RAI scans. Recurrent or metastatic thyroid cancer of follicular cell origin is suspected by elevated serum Tg in the absence of RAI uptake on a diagnostic scan. Such "false negative" RAI scans occur in up to 20% of diagnostic RAI scans in patients with detectable Tg levels following thyroid ablation and positron emission tomography (PET) is helpful in only a subset of cases for detecting residual disease. The prognosis for patients with thyroid cancer is related to the ability of the cancer to accumulate RAI, since well-differentiated thyroid cancers usually respond to treatment with RAI.

We hypothesize that valproic acid may inhibit proliferation and induce differentiation in thyroid cancer cells so that 131-I may detect residual disease and be more effective for radioiodine ablation of thyroid cancer cells of follicular cell origin *(excluding anaplastic and medullary thyroid cancer)*. If our study demonstrates a tumor response to valproic acid by decreased tumor size and/or decreased thyroglobulin and/or increased radioiodine uptake in patients who are otherwise no longer amenable to conventional therapy, we will have data to support conducting a large, multicenter, trial using valproic acid.

We will also perform correlative studies in tumor tissue biopsy samples to directly determine an effect of valproic acid on differentiation markers, cell cycle and apoptosis regulatory genes, and genome-wide gene expression analysis.

1.3 STUDY DESIGN

This will be an open label phase II study to assess the efficacy of valproic acid therapy as an antiproliferative and differentiation agent in patients with incurable differentiated thyroid cancer (unresponsive and/or radioiodine negative and unresectable). Patients with advanced thyroid cancers of follicular cell origin who have failed conventional therapy (including total thyroidectomy, I-131 ablation, with or without external radiation) who are thyroglobulin-positive/radioiodine-unresponsive will be eligible to enroll in this study. The intervention plan will be to administer valproic acid to all patients and then to compare serum thyroglobulin levels, radioiodine uptake and tumor size, by imaging studies, before and after therapy, as well as, perform correlative tumor tissue studies.

Valproic acid will be administered at an initial dose of 500 mg daily, titrating to 1500 mg daily by week 2 and continuing for 10 weeks. Patients will then undergo imaging for response. Depending on the response, patients will proceed to ablation, continue with an increased dose of valproic acid or be removed from treatment. This dose and dosing schedule was chosen to obtain a concentration level known to have an antineoplastic effect based on the fact that an oral dose of 500 mg twice daily should achieve plasma concentrations of valproic acid typically ranging from 0.4-0.6mM. Valproic acid serum trough levels will be obtained for all patients at the beginning of week 2 and then weekly thereafter to assess compliance, possible drug toxicity and to ensure plasma concentration is 50 to 100 μg/ml.

We will perform tumor tissue biopsy of the target lesions in patients with tumor that is accessible to percutaneous biopsy by ultrasound or CT scan guidance. This will allow us to determine if valproic acid has effects on differentiation, cell cycle and apoptosis regulatory genes, as well as, genome-wide gene expression profile with valproic acid treatment. The correlative studies will then be evaluated based on response and therapeutic serum valproic acid levels. (Study Schema Appendix 1)

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Advanced/poorly differentiated thyroid cancers of follicular cell origin that have no uptake (<1%) on radioiodine scan or are unresponsive to radioiodine therapy. Unresponsiveness to radioiodine therapy is defined as a patient's thyroglobulin not falling to less than 2ng/ml within 6 months after previous radioiodine ablative treatment.

2.1.1.2 Extensive (invasive) loco-regional tumor mass and/or metastatic spread, rendering patient inoperable

2.1.1.3 Thyroglobulin (Tg) levels greater than or equal to 100 ng/ml in the absence of Tg antibodies. Patients who are Tg-antibody (Tg-Ab) positive may be included despite a lower Tg level if they have detectable disease on cross sectional imaging. (The presence of Tg-Ab may lead to falsely low Tg levels and therefore render the Tg a less sensitive marker of disease. However, Tg-Ab has been shown to also act as a tumor marker, and will be used as an endpoint for the study in patients who are Tg-Ab positive.)

2.1.1.4 Within 18 months of enrollment, patients must have had an RAI scan, showing no or therapeutically insignificant RAI uptake (≤1%).

2.1.1.5 Initial therapy must have included total/near-total thyroidectomy and RAI ablation therapy.

2.1.1.6 Patients must have had no chemotherapy, radiotherapy, or biologic therapy for their malignancy in the month prior to treatment and must have recovered from all side effects of therapeutic and diagnostic interventions.

2.1.1.7 Greater than or equal to 18 years of age

2.1.1.8 Must be able to understand and sign the Informed Consent Document

2.1.1.9 Clinical performance status of ECOG less than or equal to 1

2.1.1.10 Life expectancy of greater than three months

2.1.1.11 Women of childbearing potential must have a negative serum beta-HCG within 72 hours prior to study entry and must be willing to practice effective birth control to prevent pregnancy while receiving treatment and for three months after treatment is discontinued. All males of child fathering potential must also be willing to practice effective birth control.

2.1.1.12 Laboratory results must be within the following parameters before entry:

- Absolute Neutrophil Count > 750 cells/mm3
- Hemoglobin > 8.0 gm/dl
- Platelet count > 75000/mm3
- Creatinine < 1.5 times ULN
- Total protein > 6.4.
- Total bilirubin should be < 1.5 times ULN.
- AST (SGOT), ALT (SGPT) < 1.5 times ULN.
- Amylase < 1.5 times ULN
- Ammonia < 1.5 times ULN

2.1.2 Exclusion Criteria

2.1.2.1 Allergy to valproic acid.

2.1.2.2 Current coexisting malignancy other than basal cell carcinoma.

2.1.2.3 Women of child-bearing potential who are pregnant or breastfeeding. Valproic acid is a known teratogen, causing primary neural tube defects, facial abnormalities, and skeletal malformation; therefore pregnant women will be excluded. Additionally, patients that become pregnant while on study protocol will be discontinued immediately.

2.1.2.4 Active systemic infections, coagulation disorders or other major medical illnesses

2.1.2.5 Patients taking tolbutamide, warfarin, zidovudine, benzodiazapines, clonazepam, diazepam

2.1.2.6 Seizure disorder

2.1.2.7 Patients with brain metastases

2.2 RESEARCH ELIGIBILITY EVALUATION

Within 4 weeks prior to treatment

- Ultrasound of the neck
- MRI or CT of the Chest
- Bone scan for patients in whom bone metastases are suspected
- FDG PET scan
- Health Related Quality of Life HRQOL) form completion
- MRI of the brain

Within 2 weeks prior to treatment

- Laboratory Evaluations
  - Thyroid Stimulating Hormone (TSH)
  - Thyroglobulin (Tg)
  - CBC with differential and platelets
  - BUN, creatinine, total protein, total bilirubin, ALT, AST ALKP, amylase, ammonia, albumin
  - 24 hour urinary iodine level
  - Tumor biopsy
- Thyrogen (recombinant TSH) RAI scan (for radioiodine uptake and TSH stimulated thyroglobulin levels. See section 3.4)
- Complete history and physical examination including Height, Weight and ECOG status
- Tumor tissue biopsy of any accessible lesions

Within 3 days prior to treatment

- Serum or urine beta-HCG (if applicable)

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 faxed to 301-480-0757. 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.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

Current conventional therapy for patients with thyroid cancers of follicular cell origin after thyroidectomy and ablative treatment with 131-I involves only thyroid hormone for TSH suppression. In this study, patients will receive TSH suppression therapy with valproic acid for 16 weeks.

The total study period will be 18 weeks, with a one year follow up. Patients who respond to treatment as evidenced by decreased Tg level, RAI uptake or decreased tumor size will continue treatment of valproic acid for 1 year.

3.2 PHASE 1 – WEEKS 1-10

3.2.1 Drug Administration {all doses are given orally}

- Week 1
  - (Days 1-3): Valproic acid - 500 mg every evening
  - (Day 4-7): Valproic acid - 500 mg twice daily (morning and evening)
- Weeks 2 through 10
  - Valproic acid – 500 mg every morning and 1000 mg every evening

Drug will be dispensed at each clinic visit and include the number of capsules necessary to be administered through the next scheduled clinic visit plus 4 days. Patients will be instructed to take the medications at the same time each day, with or without food. Prior to discharge from the clinic, the research nurse will review the following information with the patient:

- The toxicities of the agent and how to treat/prevent them
- The signs and symptoms to report to the study team
- How to complete the patient diary

3.2.2 Valproic acid levels

Blood samples will be collected prior to dosing (trough levels) weekly from weeks 2 to 10 and week 12 for patients on Schedule 2. The patient will be asked to refrain from taking the morning dose of valproic acid and will be instructed to bring in the morning dose along with the rest of valproic acid pills for a pill count.

3.2.3 Dose Modification

Based on the serum valproic acid trough level, the dose of valproic acid will be titrated as noted below to maintain serum trough levels between 50 and 100 μg/ml. Any change of the dose of valproic acid will require repeat serum trough levels within 3 days as described above.

- If the serum trough level is > 100 μg/ml, the dose will be reduced by 125 to 500 mg depending on the serum level
- If the serum trough level is < 50 μg/ml, the dose will be increased by 125 to 500 mg depending on the serum level
- For persistent grade 2 toxicities, the dose will be adjusted at the discretion of the PI
- For grade 3 or greater toxicities, the dose will be held until the toxicity has resolved to grade 1 or baseline. Following resolution, the dose will be reduced

3.2.4 Protocol stopping rules

If more that 15% of patients withdraw from the study due to grade3 toxicity, a safety endpoint will be reached and the study will be closed to accrual. The stopping rule applies to all subjects during the entire treatment and follow up period of the study.

3.3 EVALUATIONS WEEKS 1-10 {ALL EVALUATIONS ARE +/- 3 DAYS}

- Week 2-10:
  - Serum valproic acid levels may be performed weekly on all patients for at least the first 4 weeks of treatment.
  - Reports from all evaluations performed at outside institutions will be faxed to:

    Candice Cottle-Delisle, RN or Roxanne Merkel, RN
    301-402-1788

    This includes lab values, physical exams, patient diaries, etc.

- Week 2 (Day 10):
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Toxicity assessment, pill count, and review of diary

- Week 4 – may be performed by their primary physicians
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Toxicity assessment, pill count, and review of diary

- Week 6:
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Toxicity assessment, pill count, and review of diary

- Week 8 - may be performed by their primary physicians
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Toxicity assessment, pill count, and review of diary

- Week 10:
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Serum valproic acid levels.
  - Toxicity assessment, pill count, and review of diary
  - Tg, TSH
  - Thyrogen Scan
  - Health Related Quality of Life HRQOL) form completion
  - Tumor tissue biopsy of any accessible lesions (Section 3.7)
  - 24 hour urinary iodine level

3.4 THYROGEN RAI SCAN

All patients will undergo a Thyrogen® (thyrotropin alfa for injection) RAI scan at entry to the study and after completion of 10 weeks of valproic acid treatment. Depending on the results of the scan, patients will continue valproic acid and prepare for an ablation, or will continue with valproic acid.

Procedure:

- Low iodine diet for 2 weeks
- Thyrogen 0.9mg intramuscularly (in the buttocks) every 24 hours x 2 doses
- 123-I radioiodine 24 hours following the last dose of Thyrogen
- Serum Tg and TSH **immediately** prior to the scan
- Scan 48 hours after radioiodine administration (72 hours after thyrogen administration)

3.5 PHASE 2 WEEKS 11-16

3.5.1 **Schedule 1** - Patients who exhibit an increased radioiodine uptake on Thyrogen scan post valproic acid therapy at week 10.

- Week 11:
  - Discontinue Levothyroxine
  - Begin Cytomel for 4 weeks (25 micrograms twice a day)
  - Continue valproic acid for a total of 16 weeks

  Note: medication will be dispensed following review of Thyrogen scan

- Week 12 - may be performed by their primary physicians
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Toxicity assessment, pill count, and review of diary

- Week 14: may be performed by their primary physicians
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Toxicity assessment, pill count, and review of diary
  - Stop Taking Cytomel.
  - Begin low iodine diet.

- Week 16:
  - Measure TSH, Tg and 24 hour urinary iodine.
  - I-131 Ablative treatment {refer to Section 3.6}.
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Toxicity assessment, pill count, and review of diary

- Week 17:
  - Post ablation RAI scan {5 days (+/- 2 days) following administration of 131-I}.
    - Ultrasound of the neck
    - MRI or CT of the neck and chest
    - FDG-PET scan
  - Resume Levothyroxine (pre study dose) .

- Stop valproic acid end of week 17
- Toxicity assessment, pill count, and review of diary
- Health Related Quality of Life HRQOL) form completion

3.5.2 **Schedule 2** – patients who do not exhibit an increased radioiodine uptake on Thyrogen scan post valproic acid therapy at week 10

- Week 11:
  - Maintain valproic acid dose

  Note: medication will be dispensed following review of the Thyrogen scan.
- Week 12:
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Serum valproic acid levels.
  - Toxicity assessment and review of diary

- Week 14: may be performed by local physician
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Toxicity assessment and review of diary

- Week 16:
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin and b-HCG (if applicable).
  - Tg, TSH
  - Toxicity assessment and review of diary
  - Ultrasound of the neck and mediastinum
  - MRI or CT of the neck and chest
  - FDG-PET scan
  - Health Related Quality of Life HRQOL) form completion

- Weeks 17-52
  - Patients who show a response by RECIST criteria or have a decreased thyroglobulin level from Day 1 of the treatment (registered as a partial response to the treatment) will continue on valproic acid at their current dose for a total of 52 weeks.

- Stop valproic acid if no response
- Sixteen weeks or 4 months is significant amount of time to measure response to treatment and therefore, if there is a response, a patient's thyroglobulin levels should have decreased by then, as well as, by RECIST criteria.
- Patients who show no response, patients will stop valproic acid treatment and continue with routine follow up.

3.6 RAI ABLATIVE TREATMENT

Activity of 131-I will be determined by dosimetry performed during diagnostic study. The therapeutic dose will not exceed 600 miCu.

3.7 RESEARCH EVALUATIONS

3.7.1 Tumor tissue biopsy samples

3.7.1.1 Patients who have locoregional or metastatic disease that is amenable to ultrasound guided and or CT scan guided needle biopsy will have this done of the target lesion. This will be performed at study entry and at week 10.

3.7.1.2 These samples will be processed as described in Section 5.4.

3.8 FOLLOW UP FOR ALL PATIENTS {FROM WEEK 17}

- 3 months
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin.
  - CT and/or MRI of the chest
  - Health Related Quality of Life HRQOL) form completion
  - Ultrasound of the neck as indicated
  - Tg, TSH
- 6 months
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin..
  - Tg, TSH
  - Health Related Quality of Life HRQOL) form completion
- 9 months - for patients continuing on valproic acid only-
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin.
  - Tg, TSH
  - Health Related Quality of Life HRQOL) form completion

- 12 months
  - Physical exam including ECOG status
  - CBC with differential, platelets, BUN, creatinine, total protein, total bilirubin, ALT, AST, ALKP, amylase, ammonia, albumin.
  - CT and/or MRI of the chest
  - Ultrasound of the and neck
  - Tg, TSH
  - Health Related Quality of Life HRQOL) form completion

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.9.1 Criteria for removal from protocol therapy

- Patient request
- PI discretion, if the PI feels it is not in the best interest of the patient to remain on treatment
- Liver Dysfunction (enzyme levels above 1.5 times ULN)
- Platelet < 50,000
- Ammonia levels > 65 mol/l
- Progressive disease
- Pregnancy
- Pancreatitis (amylase level above 1.5 ULN)
- Alcohol consumption
- Other unacceptable toxicities as determined by the PI

3.9.2 Off-study Criteria

- Completion of the follow up period
- Patient request
- PI discretion ,if the PI feels it is not in the best interest of the patient to remain on treatment
  Note: Patients must remain on study until all study related adverse events have resolved to grade 2 or less or baseline.

3.9.3 Off –Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and faxed to 301-480-0757.

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.

5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

Data will be collected using the NCI C3D web based data collection system.
All data will be kept secure. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number.

5.1.1 Routine Data Collection

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

- For laboratory values obtained at sites other than the NIH Clinical Center: only the following values (highest grade per cycle) will be captured in C3D:
  - Hemoglobin, total white blood cell count, absolute neutrophil count, platelet count
  - Creatinine, ALT, AST, Total bilirubin, Total protein, Albumin, Alkaline phosphatase, Amylase, Ammonia and b-HCG (+/-) if appropriate.
  - Any unexpected laboratory abnormality ≥ grade 2 possibly, probably or definitely related to the research

- 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.

5.1.2 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

5.1.3 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, PRN medications, and medications given to treat adverse events will not be captured in C3D.}

5.2 RESPONSE CRITERIA

RAI uptake and Tg level will be compared pre- and post-valproic acid treatment. The nuclear medicine radiologists using a planar technique will measure the RAI scan uptake. The post-valproic acid scan will then be compared side-to-side with the pre-valproic acid scan, using the planar technique, and will then be scored as "increased" or "unchanged" compared to zero/minimal (<1%) uptake seen on the pre-valproic acid scan. We will define 4 categories of response:

1. Complete response: increased RAI uptake on post-valproic acid therapy at week 10, AND a decrease in Tg level to less than 2 ng/ml (or a decrease in Tg-Ab level to less than 2.0 IU/ml) at 10 weeks AND disappearance of all lesions at 16 weeks.
2. Partial response: increased RAI uptake on post-valproic acid scan at week 10, OR a decreased Tg level (or a decrease in Tg-Ab level by more than 20%) at 10 weeks AND 30% decrease in target lesion at 16 weeks.
3. Stable disease: no change in RAI uptake AND Tg levels (or Tg-Ab level) AND no significant change of lesions 16 weeks.
4. Progressive disease: tumor mass increases OR Tg levels (or Tg-Ab levels) increases over 10 weeks OR at least 20% increase in target lesion at 16 weeks.

Target lesions will be evaluated according to the RECIST response criteria outlined below.

5.2.1 Response Criteria RECIST 1.1

5.2.1.1 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.*

5.2.1.2 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 tumour 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."

5.2.1.3 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
Nor all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

5.3 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).

5.4 SAMPLE STORAGE, TRACKING, AND DISPOSITION

Tumor tissue biopsy samples

Patients who have locoregional or metastatic disease that is amenable to ultrasound guided and or CT scan guided needle biopsy will have this done of the target lesion. This will be performed at study entry and at 10 weeks.

Immediate cytopathologic review will be performed to confirm the presence of tumor cells. The samples will then be stored in -80°C until the immunohistochemistry studies and genome-wide gene expression analysis.

The Na/I symporter expression level will be determined by quantitative RT PCR and immunohistochemistry (11-14). Gene expression levels (differentiation *markers, cell cycle and apoptosis regulatory genes)* changes with valproic acid treatment will be determine by using pathway specific gene expression arrays (12,13).

Blood samples

The laboratory studies will be blinded to the response of patients to therapy.

Samples will be sent to the Endocrine Oncology Laboratory for processing:

NCI Endocrine Oncology Branch Laboratory
CRC Room 4-5840
10 Center Drive, MSC 1201
Bethesda, MD 20892-1201
(301) 435-7891

At the completion of the protocol, the investigator will dispose of all specimens in accordance with the environmental protection laws, regulations and guidelines of the Federal Government

and the State of Maryland. Any unintentional loss or destruction of the tissue will be reported to the IRB.

6 STATISTICAL CONSIDERATIONS

6.1 RATES AND TYPES OF RESPONSES

Rates and types of responses will be determined and presented with 95% confidence intervals. Patient characteristics (demographic and clinical) will be tabulated. Overall survival will be summarized using Kaplan-Meier curves. Toxicities will be tabulated by grade and organ system. Summary responses to the quality of life instrument at selected time points will be tabulated; to aid in the interpretation of temporal changes in quality of life items, change scores will be evaluated using the Wilcoxon signed rank test or McNemar's test as appropriate.

6.2 SAMPLE SIZE AND POWER ANALYSIS

This is a phase II study aimed at measuring the impact of valproic acid on iodine uptake and on tumor response. Response will be defined as complete or partial response as outlined in section 5.2. The study uses a two-stage Simon optimal design with an interim analysis planned when 13 patients are evaluable for response. If no complete/partial responses are seen at that time the study will close to accrual. The study will proceed to stage II if at least one response is seen among the first 13 patients. At the end of study, if the cumulative number of responses among the 20 evaluable patients is 3 or more, valproic acid will be considered efficacious, while this will not be the case if 1-2 responses are noted. Under the null hypothesis of a true response rate that does not exceed 5% (p0=0.05) , the two-stage design will control type I error (alpha) to be no more than 7.4% , and when the true response rate is at least 25% (p1=0.25), the study has at least 90% power (beta=0.10). The probability of triggering early stopping is at least 51% if the true response rate is 5% or less, and less than 2.5% if the true response rate is 25% or more. If the accrual is stopped at the first stage due to futility, the upper bound of a 95% confidence interval for the response rate will be less than 25%. We will plan to enroll up to 25 patients with the expectation that 20 patients (80%) will be evaluable for response.

The stopping rule for Grade 3 toxicity is set at 15% as the acceptable toxicity rate because the study is designed to detect a treatment efficacy rate of 15% or higher. Therefore, if the acceptable toxicity rate is higher than the expected efficacy rate the study will be stopped.

7 HUMAN SUBJECTS PROTECTIONS

7.1 RATIONALE FOR SUBJECT SELECTION

Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information which suggests that differences in drug metabolism or disease response would be expected in any one patient group. As advanced

thyroid cancers are rare in the pediatric population, study will not include patients < 18 years of age.

7.2 PARTICIPATION OF CHILDREN

As noted above, children under the age of 18 will not be enrolled.

7.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Treatment with valproic acid may prove to be more effective than current conventional therapy (thyroid hormone suppression) for advanced differentiated thyroid cancers. Patients with a long history of unresponsiveness to other treatment modalities (surgical debulking, thyroid hormone suppression, radioactive iodine, external beam radiation) 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.

7.4 RISKS/BENEFITS ANALYSIS

Patients with differentiated thyroid cancer of follicular cell origin have limited options available to them. Valproic acid is an approved agent for other indications and the toxicities have been well established. The potential benefits of increased ability to diagnosis and treat residual malignancies in this patient population outweigh the risks of treatment with valproic acid. If this study demonstrates a tumor response to valproic acid and/or increased radioiodine uptake in patients who are otherwise no longer amenable to conventional therapy, a large, multicenter, trial using valproic acid in this population of patients will be considered.

7.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

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.

8 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

8.1 DEFINITIONS

8.1.1 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, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. 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 section **8.2.**

8.1.2 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.

8.1.3 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.

8.1.4 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.

8.1.5 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.

8.1.6 Disability

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

8.1.7 Life threatening Adverse Drug Reaction

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.

8.1.8 Protocol Deviation (NIH Definition)

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

8.1.9 Protocol 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.

8.1.10 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**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized

8.2 NCI-IRB REPORTING

8.2.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths:

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All serious non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

8.2.2 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.

8.3 DATA AND SAFETY MONITORING PLAN

Clinical Trial Monitoring Plan

Data will be entered in C3D by the data manager assigned to the protocol. The research nurse will verify 100% of the e-CRFs for one of the first 3 patients enrolled. Subsequent monitoring will be conducted by the Research Nurse as described in the table below. Any significant discrepancies will be discussed with the PI and the study team and a corrective action plan will be drafted and shared with the team. AEs on all patients are discussed at the weekly team meeting to assess over all safety and to ensure that all reporting requirements are met.

*Based on expected accrual, 25% of enrolled patients will be monitored.

Time of year	Evaluation	# of records monitored
Quarterly	Compare all fields of the following e-CRFs to the source documentation: Eligibility, Surgical Procedure, Course Assessment, Adverse Events, Off Treatment	3-5 study patients

Careful evaluation to ascertain the toxicity and clinical response will be performed. The principal investigator will monitor the data and toxicities to identify trends quarterly. The principal investigator will be responsible for revising the protocol as needed to maintain safety.

9 PHARMACEUTICAL INFORMATION

9.1 VALPROIC ACID - DEPAKOTE

Refer to package insert for additional information

9.1.1 Source

Valproic acid will be purchased from commercial sources by the NIH Clinical Center Pharmacy.

9.1.2 Formulation and preparation

Valproic Acid tablets are for oral administration. Valproic acid tablets are supplied in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg, or 500 mg of valproic acid.

9.1.3 **Stability and storage**

Store tablets below 86°F (30°C).

9.1.4 **Administration procedures**

Valproic acid will be given orally, twice daily with or without food

9.1.5 **Incompatibilities** - Potentially significant drug interactions have been reported with Amitriptyline/Nortriptyline, Carbamazepine/carbamazepine, Clonazepam, Diazepam, Ethosuximide, Lamotrigine, Phenobarbital, Primidone, Phenytoin, Tolbutamide, Warfarin, and Zidovudine.

9.1.6 Toxicity

- Hepatotoxicity
- Teratogenicity in the fetus of pregnant women. At high doses (>90mg/kg/day), valproic acid has been shown to reduce spermatogenesis and induce testicular atrophy in dogs.
- Hyperammonemia has been reported independent of abnormal liver function tests.
- CNS depression and somnolence. Because of the potential interactions of valproic acid with other CNS depressants, alcohol will be prohibited while patients are on the study. If a patient does drink alcohol, he or she will be removed from the study.
- Nausea, vomiting, anorexia, increases appetite and indigestion
- Thrombocytopenia
- Pancreatitis

9.2 LIOTHYRONINE SODIUM, CYTOMEL

Refer to package insert for additional information

9.2.1 Source

Cytomel will be purchased from commercial sources by the NIH Clinical Center Pharmacy.

9.2.2 Formulation and preparation

Cytomel tablets are for oral administration. Cytomel tablets are supplied in three dosage strengths 5 mg, 25 mg, or 50 mg.

9.2.3 Stability and storage

Store tablets between Store between 15° and 30°C (59° and 86°F).

9.2.4 Administration procedures

Cytomel will be given orally, once daily with or without food

9.2.5 Incompatibilities

Potential drug interactions have been reported with the drugs listed below. While administration of these are drugs is not an exclusion criteria, care will be taken to carefully monitor patients who are taking any of these medications.

- Oral Anticoagulants
- Insulin or Oral Hypoglycemics
- Cholestyramine
- Estrogen, Oral Contraceptives
- Tricyclic Antidepressants
- Digitalis
- Ketamine
- Vasopressors

9.2.6 Toxicity

Adverse reactions, other than those indicative of hyperthyroidism because of therapeutic overdosage, either initially or during the maintenance period are rare (see OVERDOSAGE).

In rare instances, allergic skin reactions have been reported with Cytomel (liothyronine sodium) Tablets.

10 REFERENCES

1. Davies, L. and H.G. Welch, *Increasing incidence of thyroid cancer in the United States, 1973-2002.* JAMA, 2006. 295(18): p. 2164-7.
2. Hundahl, S.A., et al., *A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see commetns].* Cancer, 1998. 83(12): p. 2638-48.
3. Goretzki, P.E., et al., *Surgical reintervention for differentiated thyroid cancer.* Br J Surg, 1993. 80(8): p. 1009-12.
4. Ma, C., J. Xie, and A. Kuang, *Is empiric 131I therapy justified for patients with positive thyroglobulin and negative 131I whole-body scanning results?* J Nucl Med, 2005. 46(7): p. 1164-70.
5. Munster, P., et al., *Clinical and biological effects of valproic acid as a histone deacetylase inhibitor on tumor and surrogate tissues: phase I/II trial of valproic acid and epirubicin/FEC.* Clin Cancer Res, 2009. 15(7): p. 2488-96.
6. Rocca, A., et al., *A phase I-II study of the histone deacetylase inhibitor valproic acid plus chemoimmunotherapy in patients with advanced melanoma.* Br J Cancer, 2009. 100(1): p. 28-36.
7. Duenas-Gonzalez, A., et al., *Valproic acid as epigenetic cancer drug: preclinical, clinical and transcriptional effects on solid tumors.* Cancer Treat Rev, 2008. 34(3): p. 206-22.
8. Michaelis, M., H.W. Doerr, and J. Cinatl, Jr., *Valproic acid as anti-cancer drug.* Curr Pharm Des, 2007. 13(33): p. 3378-93.
9. Catalano, M.G., et al., *Effects of the histone deacetylase inhibitor valproic acid on the sensitivity of anaplastic thyroid cancer cell lines to imatinib.* Oncol Rep, 2009. 21(2): p. 515-21.
10. de Vries, L., et al., *Endocrine effects of valproate in adolescent girls with epilepsy.* Epilepsia, 2007. 48(3): p. 470-7.
11. Catalano, M.G., et al., *Valproic acid, a histone deacetylase inhibitor, enhances sensitivity to doxorubicin in anaplastic thyroid cancer cells.* J Endocrinol, 2006. 191(2): p. 465-72.
12. Shen, W.T., et al., *Valproic acid inhibits growth, induces apoptosis, and modulates apoptosis-regulatory and differentiation gene expression in human thyroid cancer cells.* Surgery, 2005. 138(6): p. 979-84; discussion 984-5.
13. Catalano, M.G., et al., *Valproic acid induces apoptosis and cell cycle arrest in poorly differentiated thyroid cancer cells.* J Clin Endocrinol Metab, 2005. 90(3): p. 1383-9.
14. Fortunati, N., et al., *Valproic acid induces the expression of the Na+/I- symporter and iodine uptake in poorly differentiated thyroid cancer cells.* J Clin Endocrinol Metab, 2004. 89(2): p. 1006-9.

INSTITUTE: National Cancer Institute

STUDY NUMBER: 10-C-0041

PRINCIPAL INVESTIGATOR: Electron Kebebew, M.D.

STUDY TITLE: A Phase II Trial of Valproic Acid in Patients with Advanced Thyroid Cancers of Follicular Origin

Continuing Review Approved by the IRB on 06/09/14
Amendment Approved by the IRB on 04/24/15 (D) Date Posted to Web: 05/05/15
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?

The purpose of this study is to see whether valproic acid can inhibit tumor growth and/or induce tumor cell death and/or make tumor cells take up radioiodine. Although valproic acid is already approved by the FDA to treat epilepsy, it is not approved for thyroid cancer and is therefore an investigational drug for research purposes.

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

You are being asked to take part in this study because you have thyroid cancer that is either unresponsive or fails to absorb radioiodine.

How many people will take part in this study?

About 25 people will take part in this study.

Description of Research Study

Stage	Timeframe	Location	Events
Work up	1-2 weeks	Out patient	Scans, x-rays, labs, Thyrogen scan, other tests as needed
Phase 1	Weeks 1-10	Clinical Center Out-patient clinic and home endocrinologist	Continue thyroid hormone suppression therapy, begin valproic acid, physician visits, lab draws, complete diary Thyrogen Scan
Schedule 1 – patients who have increased uptake on thyrogen scan	Weeks 11-16	Clinical Center Out-patient clinic and home endocrinologist	Continue valproic acid, stop long acting thyroid suppression medication, add short acting medications, physician visits, lab draws, scans, complete diary
I-131 ablative treatment	Weeks 16-17	Clinical Center Out-patient clinic and Nuclear Medicine Department	I-131 ablative treatment Scans Stop valproic acid, resume long acting thyroid medication
Schedule 2 - patients who do NOT have increased uptake on thyrogen scan	Weeks 11-16	Clinical Center Out-patient clinic and home endocrinologist	Continue valproic acid physician visit, lab draws, scans, complete diary. Scans
Follow up	Through week 52	Clinical Center Out-patient clinic	Physician visit, lab draws, scans as indicated. Valproic acid for patients in Schedule 2 who respond to therapy.

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

Phase 1

Once we have determined that it is safe for you to participate in this trial you will be seen in clinic and will begin the first phase of this study. You will continue on your thyroid hormone suppression therapy and you will begin valproic acid. You will start at a small dose and then increase the dose twice over the first week. You will then have blood drawn to see if the amount of valproic acid in your blood is within the correct limits. The research nurse will give you a diary to complete – this will include the doses of the medications you will be taking as well as a section to write down any side effects and a form for you to complete about how you are feeling. You will then be seen every 2 weeks for a total of 10 weeks. On weeks 4 and 8 you may be seen by your local physician if that is more convenient. At each clinic visit (both at home and at the NIH Clinical Center) you will have a physical exam, lab work and your diary will be reviewed and collected. On weeks 1, 2, 6, you will have additional blood drawn to check the amount of valproic acid in your blood and you will receive the valproic acid pills.

On week 10, you will have another Thyrogen® Scan done to measure radioiodine uptake after valproic acid therapy. Pending the results of the Thyrogen® Scan, you will follow one of two schedules. Because valproic acid depresses the nervous system, **you may not drink ANY alcohol while you are on this study.**

Research Samples

If your tumor is easy to biopsy, we would like to take a biopsy and a blood sample before you begin treatment and again at week 10 to see if certain characteristics your tumor are changing in response to the valproic acid. A biopsy involves inserting a thin needle into your tumor while under an X-ray or ultrasound machine and removing a small sample of the tissue. Your doctor will explain the procedure to you and ask you to sign a separate consent. If you do not want to have this biopsy done, you may still participate in this study.

Schedule 1

If there is increased radioiodine uptake on the post valproic acid Thyrogen ® Scan, you will receive treatment on Schedule 1 as described below.

You will be prepared for radioiodine ablation therapy. This is the same procedure which you have had in the past. Your doctor will explain the procedure in detail and you will be asked to sign a separate consent. Prior to the treatment you will stop your long acting thyroid hormone and begin a short acting thyroid hormone. After 4 weeks, you will stop the short acting thyroid hormone and begin a low iodine diet. Foods to avoid in a low-iodine diet include milk and other dairy products, commercial baked products (including most breads), seafood, red food dye #3, and salt which has iodine added to it. Your research nurse or dietitian will give you additional information about this diet. During this period, you will be seen every 2 weeks either here at the

Clinical Center or by your home physician; the same as during the first 10 weeks of the study. After 2 weeks off of thyroid medication and a low iodine diet, you will receive radioiodine ablation therapy. One week after therapy you will have a post radioiodine scan. All the necessary blood work to prepare you for the radioiodine ablation therapy will be performed, including measuring your urine iodine and a pregnancy test. After the scan, you will start back on thyroid hormone therapy at your previous dose.

Schedule 2:

If there is no increased uptake on the post valproic acid Thyrogen ® Scan, you will receive treatment on Schedule 2 as described below.

You will continue on valproic acid for 7 more weeks. During this period, you will be seen every 2 weeks either here at the Clinical Center or by your home physician. Following 16 weeks of treatment, your thyroglobulin and TSH will be measured and you will have scans performed. If you your thyroglobulin levels have decreased or the scans indicate that your tumor has shrunk, you will remain on the valproic acid for 8 additional months.

Follow up:

At 3, 6, 9 (for patients continuing on valproic acid only) and 12 months, you will have imaging studies done (an ultrasound, a CT and/or a MRI scan and PET scan), lab work and a physical exam. This is considered standard follow up care for thyroid cancer.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because valproic acid may cause harm to your unborn child and valproic acid is excreted in breast milk. 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 3 months after you finish study treatment. 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

Alternative Approaches or Treatments

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

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.

Risks or Discomforts of Participation

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

The risks of valproic acid are listed in the table below. The risk of somnolence and depression of your central nervous system increase greatly if you drink alcohol. Therefore, **you may not consume any alcohol while you are taking valproic acid.** While you are on this study, you should consult Dr. Kebebew or the research nurse before taking any prescription or over the counter medications.

Likely	Less Likely	Rare but Serious
• Sleepiness • Nausea • Headache	• Vomiting • Anorexia • Dizziness • Indigestion • Muscle weakness • Rash • Abdominal pain	• Liver toxicity which could be mild to severe

Biopsy

The risks of a biopsy include bruising and discomfort at the biopsy site and rarely bleeding and infection.

Radiation

In addition, this research study involves exposure to radiation from 2 CT guided biopsies. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 0.290 REM which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask

the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will make your tumor able to respond to radioactive iodine therapy or to shrink. 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.

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 the pharmaceutical company who produces Valproic Acid.

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.

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 have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

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 the manufacturer of the study drug or their 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.

Optional Biopsy

The biopsy to be performed is exclusively for research purposes and will not benefit you (refer to page 3). It might help other people in the future. Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read the sentence below and think about your choice. After reading the sentence, circle and initial the answer that is right for you. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

I agree to have the tumor biopsy for the research tests in this study.

Yes No Initials_____

Optional Studies

We would like to keep some of the specimens and data that are collected for future research. These specimens and data will be identified by a number and not your name. The use of your specimens and data will be 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 decide now that your specimens and data can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens and/or data. Then any specimens that remain will be destroyed and your data will not be used for future research.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My specimens and data may be kept for use in research to learn about, prevent, or treat cancer or other health problems.

Yes No Initials_____

2. Someone may contact me in the future to ask permission to use my specimen(s) and/or data in new research not included in this consent.

Yes No Initials_____

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 for 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: 301-496-5049. 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: 301-496-4251.

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 JUNE 9, 2014 THROUGH JUNE 8, 2015. _____ _____ _____ _____ Signature of Investigator Date Signature of Witness Date _____ _____ Print Name Print Name	