ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A091305

A PHASE 2 STUDY OF EFATUTAZONE, AN ORAL PPAR AGONIST, IN COMBINATION WITH PACLITAXEL IN PATIENTS WITH ADVANCED ANAPLASTIC THYROID CANCER

Industry-supplied agent: Efatutazone (IND #121997, NSC #776711);
Commercial agent: Paclitaxel

ClinicalTrials.gov Identifier: NCT02152137

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NRG/NRG Oncology
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Study Resources:

Expedited Adverse Event Reporting
https://eapps-ctep.nci.nih.gov/ctepaers/

Medidata Rave® iMedidata portal
https://login.imedidata.com

OPEN (Oncology Patient Enrollment Network)
https://open.ctsu.org

Biospecimen Management System
http://bioms.allianceforclinicaltrialsinoncology.org

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Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model consent revisions:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Ohio State

<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.

Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at [redacted]</td><td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.</td></tr>
<tr><td colspan="3">For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3">For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
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</table>

A PHASE 2 STUDY OF EFATUTAZONE, AN ORAL PPAR AGONIST, IN COMBINATION WITH PACLITAXEL IN PATIENTS WITH ADVANCED ANAPLASTIC THYROID CANCER

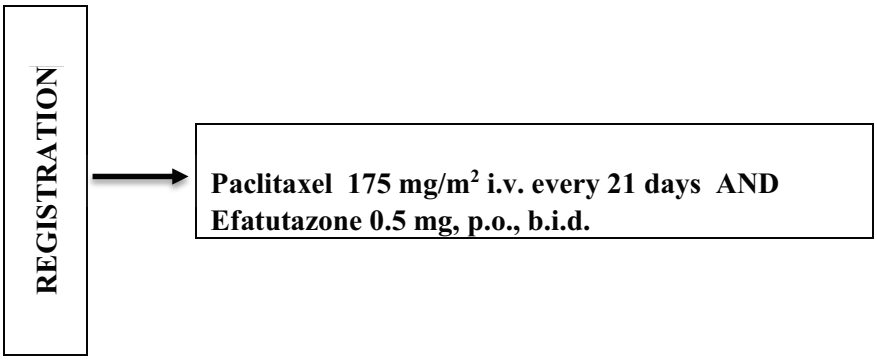
Eligibility Criteria (see Section 3.0)

Histologically or cytologically diagnosed advanced ATC
Measurable disease as defined in Section 11.0.
Patients must have either metastatic or locally advanced unresectable disease
Resolution of toxic effects of prior therapy (except alopecia) to NCI CTCAE, Version 4.0, grade 1
No limit to number of prior lines of treatment
No treatment with chemotherapy, radiation therapy, Immunotherapy, biological therapy, hormonal therapy, or other thiazolidinediones (TZDs) ≤ 21 days of registration
No prior taxane therapy ≤ 6 months except as radiosensitizer
No history of class III or IV CHF, grade 3 or 4 thromboembolic event < 6 months, pericardial effusion ≤ 12 months, pericardial involvement with tumor, or grade 2 or higher pleural effusion ≤ 6 months
No current symptomatic, untreated, or uncontrolled brain metastasis
No major surgery ≤14 days prior to registration
No grade 2 or higher neuropathy
No history of severe hypersensitivity reactions to efatutazone or paclitaxel formulations
Not pregnant and not nursing (see § 3.2.10)
Age ≥ 18 years
Patients with diabetes mellitus requiring concurrent treatment with insulin or TZD oral agents are not eligible
Patients with known hypersensitivity to any TZD oral agents are not eligible.
ECOG Performance Status ≤2

Required Initial Laboratory Values	
Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 x ULN mg/dL
Calc. Creatinine Clearance (see Alliance Web site)	**OR** ≥ 60 mL/min
Total Bilirubin	≤ 1.5 x ULN
AST	≤ 2.5 x ULN

Schema

1 Cycle = 21 Days



NOTE: Effective with Update #02 A091305 will no longer be a randomized study. All patients will be assigned to the same treatment.

Treatment is to continue until disease progression or unacceptable adverse event.
Patients will be followed for two years or until death, whichever comes first.
Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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1.0 BACKGROUND

While thyroid cancer is the most common endocrine malignancy, anaplastic thyroid cancer (ATC) is extremely rare. In 2013, the estimated incidence rate for thyroid cancer in the United States (US) is about 60,220 newly diagnosed cases (1), of which ATC comprises less than 2% (2, 3). ATC is an undifferentiated, highly aggressive tumor with a median survival of 5 months from diagnosis and a 1-year survival of no more than 20%. Patients with ATC die from distant metastases or locoregional disease that obliterates the airway. Median age at diagnosis ranges between 63 and 74 years. ATC affects women more frequently than men (3). Symptoms at diagnosis include hoarseness (due to invasion of the trachea, larynx, or recurrent laryngeal nerve), dysphagia (due to invasion of the esophagus) and dyspnea (3). A diagnosis of ATC frequently follows a prior or concurrent diagnosis of well‐differentiated thyroid cancer or benign nodular thyroid disease, and synchronous pulmonary metastases may be present in up to 50% of patients (3). If detected early, extensive surgery offers the best chance of cure. Combination chemotherapy and hyperfractionated radiotherapy (RT) are used with limited success, but several clinical studies using taxanes have shown benefit (4-7). More effective targeted therapies based on a better understanding of the molecular and signaling pathways that are disrupted in ATC are needed (8-11).

The molecular pathogenesis of thyroid cancer is beginning to be understood, with recent studies describing distinct gene expression patterns (12-20). A progression model from more differentiated papillary and follicular carcinomas to undifferentiated ATC has been suggested (21). Genomic profiling has been performed to identify genes unique to benign versus malignant lesions (22), including 1 study of patients with ATC (23). For ATC, oncogenic mutations and frequencies of mutation have been identified for Ras (20% to 60%) and B‐Raf (0% to 20%) (23, 24).

1.1 Study Rationale

Mechanisms of peroxisome proliferator-activated receptor (PPAR) mediated antitumor activity by thiazolidinediones (TZDs) include induction of cellular differentiation, promotion of cell cycle arrest, antiangiogenic effects, and induction of apoptosis (25). PPAR agonists induce cell cycle arrest via a p53 independent pathway (26-28). In thyroid cancer, PPAR may act as a tumor suppressor gene (28). PPAR agonists are known to antagonize anti‐apoptotic pathways such as survivin, which may account for synergy between PPAR agonists and taxanes, since taxanes upregulate survivin (29-31). Since survivin is highly expressed in poorly differentiated cancers including ATC (26, 32), it is hypothesized that the combination of efatutazone, a PPAR agonist that may antagonize survivin, and paclitaxel may enhance antitumor activity.

Paclitaxel is a potent suppressor of microtubule dynamics. By binding to the paclitaxel site on tubulin, it induces mitotic arrest through polymerization and stabilization of microtubules. Paclitaxel induces cell death by apoptosis (33-36). However, its effectiveness is limited because many tumors develop resistance. One mechanism of resistance is the result of apoptotic blockade due to expression of survivin, which counteracts paclitaxel‐induced apoptosis (37). While undetectable in most normal adult tissues, survivin is highly expressed in poorly differentiated cancers, including ATC. Its expression is associated with carcinogenesis, cancer progression, poor prognosis, drug resistance, and short duration of survival (38). Inhibition of survivin expression and/or function in tumor cells by survivin antisense or dominant‐negative mutants triggers apoptosis as well as a defect in cell division (39-41).

Paclitaxel has been shown to have antineoplastic activity in ATC cells in vitro and in vivo. Enhancement of paclitaxel activity by manumycin is mediated through p21 (42). In a study in ATC cells, Pushkarev et al. (43) examined mechanisms of paclitaxel action in KTC‐2 and KTC‐3 cells and found differential sensitivity with respect to induction of apoptosis. Low doses of paclitaxel phosphorylated Bcl2 (antiapoptotic protein), causing its degradation;

increased Bax (proapoptotic protein) levels; and resulted in accumulation of survivin (antiapoptotic protein) and X chromosome‐linked inhibitor of apoptosis. c‐jun‐NH terminal kinase activation was essential for apoptosis, and Raf/MAPK kinase/ERK and P13K/Akt were survival mechanisms stimulated by paclitaxel. Survivin and c‐IAP‐1 were elevated in ATC cells; silencing of these proteins with siRNA increased ATC cell sensitivity to chemotherapy (26).

1.2 Nonclinical Studies

Copland et al. (25) (published and unpublished data) found that functional PPARγ and retinoid X receptor (RXR) α were present in multiple ATC cell lines, and that efatutazone (formerly RS‐5444; CS-7017) was a high affinity agonist, stimulating the PPAR‐response element and inhibiting cell proliferation and colony formation in ATC cell lines. This efatutazone‐dependent inhibition of ATC cell proliferation was prevented by concomitant use of GW9662 (a pharmacologic PPARγ inhibitor), PPARγ siRNA, or lentiviral shRNA.

Efatutazone upregulates p21WAF1/CIP1 and downregulates cyclin E in vitro and in ATC xenografts implanted in nude mice. Efatutazone also upregulates Ras homolog gene family, member B (RhoB) mRNA and protein in cell culture and in xenografts. Silencing RhoB inhibits the effect of efatutazone on both p21WAFI/CIPI and cell proliferation. These studies led to the current model in which binding of efatutazone to PPARγ:RXR heterodimer up‐regulates transcription of RhoB mRNA and protein, then p21WAFI/CIPI mRNA and protein, and finally inhibits cell cycle progression.

An important observation by Copland et al. (25) was that efatutazone has no direct effect on apoptosis in ATC cells, but synergistically enhances the apoptotic effect of paclitaxel. The synergism is negated by p21 siRNA. When efatutazone and paclitaxel were used as single agents in an ATC xenograft model, they inhibited tumor growth by 63% and 73%, respectively. However, in combination they reduced tumor size by 96%. These studies, in aggregate, have provided preclinical data to support a clinical study using these 2 agents in subjects with ATC.

1.3 Clinical Experience

A Phase 1, open-label, dose-escalation study of oral efatutazone as a single agent given twice daily to 31 patients (27 evaluable) with advanced malignancies determined the recommended phase 2 dose to be 0.5 mg PO twice daily. One patient had a sustained partial response (690 days) and 10 had stable disease for >60 days. There were three episodes of dose limiting toxicity, all related to fluid retention (which was managed by diuretics—furosemide and spironolactone). Common adverse events included peripheral edema (51.6%), weight increase (54.8%), anemia (38.7%), and fatigue (45.2%). Plasma adiponectin increased 6-to 14-fold at doses of 0.10 to 1.15 mg twice daily. The active metabolite R-150033 had a peak plasma level at 2-3 hours, and an apparent half-life from 5.7 to 14 hours. Immunohistochemistry of archived tissue samples showed greater expression of PPAR-gamma and retinoid-x-receptor (RXR) in patients with stable disease for >60 days or a partial response (44).

Several studies have shown activity of taxanes in ATC patients: Ain et al, (4) described a single agent transient response rate of 53% in 19 patients receiving paclitaxel alone. Bhatia et al, (5) had one long term survivor out of six patients receiving paclitaxel and twice daily radiation. In 9 stage IVB patients receiving preoperative paclitaxel, Higashiyama (6) reported a 33% response (with one CR) and 44% one-year survival, while Troch et al, (7) treated six patients with docetaxel and IMRT and had 2 PRs and 4 CRs. Pertinent to the current protocol, study CS7017-A-U103 was a phase 1 study of efatutazone, an oral PPAR agonist, in combination with paclitaxel in subjects with advanced anaplastic thyroid cancer (45). Patients received efatutazone orally BID for one week (run-in phase), followed by a 3 h iv infusion of paclitaxel (175 mg/m2) every 3 weeks in combination with efatutazone BID. Efatutazone doses were

escalated (0.15, 0.3, or 0.5 mg). Tissue biopsies were obtained at baseline and at one and three weeks for immunohistochemistry of PPAR- γ responsive proteins; serum efatutazone PK studies were also performed. Nineteen patients were enrolled, but 4 were not dosed (3 due to progression, 1 ineligible). Seven participated in efatutazone dose levels 1a/1b (0.15 mg BID), six in dose level 2 (0.3 mg BID), and two in dose level 3 (run-in phase only—0.5 mg BID). Of the 15 treated patients, 10 (67%) were women. Median age was 59 years (range: 43-82).

Of 15 patients receiving drug, one had a confirmed partial response (PR) lasting from Day 69 to Day 175, and eight had stable disease (SD) as their best response. Median Time to Progression in 7 patients at Dose Level 1 was 49 days, but 70 days in Dose Level 2 (43% prolongation); corresponding median survival was 99 (0.15 mg BID) vs. 140 days (0.3 mg BID, 42% increase). Median peak efatutazone blood level was 8.6 ng/mL (range: 5.1 to 13.7) for Level 1 and 22.0 ng/mL (17.0 to 31.5) for Dose Level 2. Ten patients had AEs ≥ Grade 3, with two (anemia and localized edema) related to efatutazone. Thirteen events of fluid retention/edema were reported in 8 patients, with only 2 events of CTCAE grade ≥ 3. Eight patients had ≥ one SAE, with one (anemia) due to efatutazone. One SAE (anaphylactic reaction) was related to paclitaxel. No dose-limiting toxicity was observed. Biopsies were available on 7 patients at baseline, in 5 patients at one week of efatutazone and in 2 patients after one cycle of combination therapy. PPAR-γ, RXR-α, RhoB were present in all; angiopoietin-like 4 was induced by efatutazone. Combination therapy with efatutazone and paclitaxel was tolerated and has biologic activity in patients with metastatic anaplastic thyroid carcinoma, with initial exploratory data suggesting a dose-dependent improvement in time to progression and survival in response to escalating efatutazone dosage.

Several recent studies have shown that aggressive multimodal therapy (surgery, if possible; IMRT; plus cytotoxic chemotherapeutics, usually including a taxane) have prolonged survival in ATC patients with Stages IVA and IVB, but not IVC disease (46, 47). The death rate is still high, even in patients with only locoregional disease at presentation, and so different agents need to be tested, based upon preclinical results, to identify drug combinations that will improve outcomes in both the adjuvant and metastatic settings. The current protocol, based on encouraging preclinical data and evidence of biologic activity and acceptable safety in a phase 1 trial, would potentially alter clinical practice if results are positive for efatutazone being used with paclitaxel. Even if negative, the trial will identify members in ALLIANCE with an interest in ATC, and establish a venue for future trials of new agents in this rare, lethal tumor.

2.0 OBJECTIVES

2.1 Primary objective

To determine if the combination of paclitaxel and efatutazone improves the confirmed response rate in patients with advanced anaplastic thyroid cancer.

2.2 Secondary objective

To estimate the overall survival (OS), duration of response, progression-free survival (PFS), and adverse event rates for the combination of paclitaxel and efatutazone.

2.3 Correlative science objective

The association of biomarkers with clinical outcome data will be assessed in an exploratory translational analysis.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Contact Information page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years. There is an **exception for patients with a history of well differentiated thyroid cancer that has progressed to anaplastic thyroid cancer.**
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).
- Efatutazone is metabolized by CYP3A4/5, and inhibits CYP2C8, 2C9, 2C19, and 3A4, and is a substrate of PgP and BCRP. The clinical significance of any drug interactions is unknown to date.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday four weeks later would be considered Day 28.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease:**

Patients must have histologically or cytologically diagnosed advanced ATC.

___ **3.2.2** Patients must have **Measurable disease** as defined in Section 11.0.

___ **3.2.3** Patients must have either metastatic (stage IVC) or locally advanced unresectable disease (stage IVB).

___ **3.2.4 Prior Treatment:**

- Patients should have resolution of any toxic effects of prior therapy (except alopecia) to NCI CTCAE, Version 4.0, grade 1.
- There is no limit to the number of prior lines of treatment a patient has received.
- No treatment with chemotherapy, radiation therapy, immunotherapy, biological therapy, hormonal therapy, or other thiazolidinediones (TZDs) ≤ 21 days before study registration.
- No prior taxane therapy ≤ 6 months, except as a radiosensitizer.

___ **3.2.5 No history of the following:**

- Class III or IV congestive heart failure (CHF).
- Grade 3 or 4 thromboembolic event ≤ 6 months.
- Pericardial effusion ≤ 12 months (any grade).
- Pericardial involvement with tumor.
- Grade 2 or higher pleural effusion ≤ 6 months.

___ **3.2.6** No current symptomatic, untreated, or uncontrolled brain metastases present.

___ **3.2.7** No major surgery ≤ 14 days prior to registration.

___ **3.2.8** No grade 2 or higher neuropathy

___ **3.2.9** No known history of severe hypersensitivity reactions to any of the components of efatutazone or paclitaxel formulations.

___ **3.2.10 Not pregnant and not nursing,** because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects. Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required.

___ **3.2.11 Age ≥ 18 years**

___ **3.2.12 Concomitant Medications:**

- Patients with diabetes mellitus requiring concurrent treatment with insulin or thiazolidinedione (TZD) oral agents are not eligible.
- Patients with known hypersensitivity to any TZD oral agents are not eligible.

___ **3.2.13 ECOG Performance Status ≤2**

___ **3.2.14 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 x ULN mg/dL **OR**
Calc. Creatinine Clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x upper limit of normal (ULN)
AST	≤ 2.5 x upper limit of normal (ULN)

4.0 PATIENT REGISTRATION

4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their

registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR Help Desk by email at [redacted]

4.2 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number

- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the A091305 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand.
- Click on the Alliance link to expand, then select trial protocol #A091305
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for A091305 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org → (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

[redacted]

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at [redacted]

4.4 Registration to Correlative Study A091305-ST1

There is one substudy within Alliance A091305. This correlative science study **must be offered to all patients** enrolled on Alliance A091305 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A091305 is:

- Tissue Biomarkers as Predictors of Response in Paclitaxel +/- Efatutazone Anaplastic Thyroid Carcinoma Protocol, Alliance **A091305-ST1**

If a patient answers "yes" to "I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study described above." Question #1 in the model consent, they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A091305-ST1 at the same time they are registered to the treatment trial (A091305). Samples should be submitted per Section 6.2.

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 16 DAYS before registration: All laboratory studies, history and physical.
- To be completed ≤ 28 DAYS before registration: Any scan of any type which is utilized for tumor measurement per protocol.
- To be completed ≤ 28 DAYS before registration: Any baseline exams used for screening, or any X-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement.

	Prior to Registration*	Day 1 of each cycle (+/- 3 days)	Post treatment follow up**
Tests & Observations			
History and physical, weight, PS***	X	X	X
Height	X		
Pulse, Blood Pressure	X	X	X
ECG (physician discretion, not required)	X		X
Adverse Event Assessment		X	X
Patient Medication Diary		X(1)	
Patient Weight Diary		X(1)	
Registration Fatigue/Uniscale Assessment	X(2)		
Laboratory Studies			
Complete Blood Count, Differential, Platelets,	X	X	X
Serum Creatinine, Na, K, Mg	X	X	X
Calcium, albumin, glucose	X	X	X
AST, ALT, Alk. Phos., Bili	X	X	X
Triglycerides, cholesterol, HDL, LDL (physician discretion, not required)	X		
TSH	X	X(3)	
Thyroglobulin and thyroglobulin antibody	X		
Serum or Urine HCG	X(4)		
Staging			
PET scan	X		
CT or MRI	X(5)	A	
Correlative study A091305-ST1: For patients who consent to participate			
Tissue samples	Slides (or slide and block) from prior surgery/biopsy		

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 72 hours prior to day of treatment.

** Physical examination and staging scans are required ≤ 28 days after the end of treatment, then every 8 weeks until disease progression. Thereafter, survival and disease status information is required every 6 months until 5 years following registration. This does not require that the subject be seen and/or examined. For example, follow-up may be done through a telephone call to the subject or his treating physician. See also Section 12.0.

*** Drug dosages need not be changed unless the calculated dose changes by ≥ 10%.

1 The diaries, found in Appendix II, must begin the day the patient starts taking the medication and must be completed daily per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.

2 To be completed after registration and ≤ 21 days prior to treatment, see Appendix I.

3 TSH every other cycle starting with cycle 3.

4 For women of childbearing potential (see Section 3.2.10). Must be done ≤ 7 days prior to registration.

5 Baseline scans include a PET scan and diagnostic CT, spiral CT, or MRI performed with both IV and oral contrast, and the CT acquired with 5 mm or less slice thickness. Documentation (radiologic and pathology report) of the diagnosis scan must be submitted.

A Every 6 weeks (beginning prior to Cycle 3) until evidence of progression or relapse. Documentation (radiologic) must be provided at progression of disease. Scans may be done up to 7 days prior to beginning a cycle. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline. For partial or complete response, a scan must be performed within 4 weeks to confirm response.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data collection and submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted]

6.2 Specimen collection and submission

For patients registered to substudy A091305-ST1: All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A091305-ST1, although patient participation is optional. Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, tissue will be collected at the following time points for these studies:

	≤ 30 days after registration	**Submit to:**
For patients registered to A091305-ST1, submit the following:		
At least one (two if possible) H&E stained slides with representative tumor from primary and metastatic tumor (if available)	X	OSU
Either a minimum of 10 unstained slides OR 1 paraffin block	X	OSU

6.2.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted]. For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A091305), Alliance patient number, patient's initials and date and type of specimen collected.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

All specimens should be sent to the following address:

[redacted]

6.2.2 Collection of slides and/or paraffin block of archived anaplastic thyroid cancer primary and metastatic tumors

For patients who consent to participate, specimens will be used for the analyses described in Section 14.1.

At least 1 (prefer 2) H&E slides from primary tumor and metastatic tumor (if available) and either a minimum of 10 unstained slides OR 1 paraffin block should also be retrieved from the surgical pathology department. Slides should be cut at 5 μm. A de-identified surgical pathology report should be sent with all blocks and slides. Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report. Specimens should be sent to the Alliance Biorepository at Ohio State (OSU). Please specify the source of the tumor block (primary or metastatic site).

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block.

The goal of the OSU is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All paraffin blocks that are to be stored at the OSU will be vacuum packed to prevent oxidation and will be stored at 4º C to minimize degradation of cellular antigens. For these reasons it is preferred that the OSU bank the block until the study investigator requests thin sections. All blocks will be stored by the appropriate Alliance biorepository but will be returned at the written request of a site.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days following registration.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Protocol therapy will consist of continuous cycles administered every 21 days. Treatment will continue until disease progression, unacceptable adverse event, or a minimum of 2 cycles beyond a complete response (CR).

NOTE: Effective with Update #02 this will no longer be a randomized study. All patients will be assigned to the ARM A treatment. ALL PATIENTS SHOULD BE TREATED WITH PACLITAXEL AND EFATUTAZONE.

A091305 Arm A dose table:

Agent	Dose	Route	Day	Retreatment
Paclitaxel	175mg/m^2	IV	Day 1	every 21 days
Efatutazone	0.5 mg	PO	BID	every 21 days*

* taken continuously with no break between cycles

A091305 Arm B dose table:

Agent	Dose	Route	Day	Retreatment
Paclitaxel	175mg/m^2	IV	Day 1	every 21 days

Treatment cycles will be 21 days in duration. Disease assessments will be performed every 42 days (6 weeks) of study participation. Treatment will continue until disease progression, unacceptable toxicity, or consent withdrawal. There is no limit to the number of treatment cycles that can be administered. After discontinuation from the study treatment, subjects will be followed at 6-month intervals to obtain information about subsequent treatment and survival status.

Patients assigned to arm A will receive both paclitaxel and efatutazone as described in the A091305 Arm A dose table (above). Patients assigned to arm B will receive paclitaxel alone as described in the A091305 Arm B dose table (above). However, please note that with update #2**, arm B is closed** and all patients should receive paclitaxel and efatutazone.

The number of efatutazone tablets required should be calculated and dispensed into a pharmacy bottle with Child Resistant Cap Closure. Efatutazone tablets are to be self-administered PO BID, with or

without food. The intended dosing schedule for efatutazone dosing is every 12 hours. However, dosing may occur within ± 2 hours of the scheduled administration time.

In Arm A, Efatutazone and paclitaxel will be administered as combination treatment. On day 1 of each cycle, administer paclitaxel IV infusion over 3 hours immediately following administration of efatutazone. To prevent severe hypersensitivity reactions, the patient should be premedicated in accordance with institutional standards for paclitaxel (26).

The patient's weight will be measured daily and recorded in the Patient Weight Diary, found in Appendix II. Drug dosages need not be changed unless the calculated dose changes by ≥ 10%.

At each study visit, collect unused efatutazone tablets and determine compliance with dosing regimen using the Patient Medication Diary (Appendix II).

The End of Treatment visit is to occur within 21 to 35 days after the last dose of study drugs. Protocol specified withdrawal procedures are the same as the End of Treatment visit procedures.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., non-TZD oral agents for diabetes); and intermittent use of dexamethasone as an antiemetic.

8.1.4 Antiemetics may be used at the discretion of the attending physician.

8.1.5 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

8.1.6 Palliative radiation therapy: Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.7 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice Guideline. J Clin Oncol 24(19): 3187-3205, 2006.

Darbepoietin or Epoetin (EPO): Use of darbepoietin or epoetin in this protocol is permitted at the discretion of the treating physician.

Filgrastim (G-CSF) and sargramostim (GM-CSF)

Filgrastim/pegfilgrastim and sargramostim may not be used:

a. To avoid dose reductions or delays.
b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported.
c. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

8.1.8 Hyperlipidemia: Elevations of lipids is a known side effect of this medication. The use of medications for hyperlipidemia is permitted at the discretion of the treating physician.

8.1.9 Anemia: Patients have developed anemia associated with efatutazone. Full supportive care should be utilized at the discretion of the treating investigator.

8.1.10 Edema: Edema/fluid retention is a common side effect of this medication. Patients should follow their weight, and should be weighed with all visits. The following is a suggested regimen for fluid retention but is NOT required:

- With weight gain of 5 lbs. or more, start furosemide 20mg daily and spironolactone 25mg daily
- For additional weight gain unresponsive to initial diuretics, increase dose of furosemide to 40mg daily and spironolactone to 50mg daily

8.1.11 Hypersensitivity/infusion reactions: Treat hypersensitivity and infusion reactions to paclitaxel as per institutional standards.

8.2 Dose Modifications

General rules for dose modification:

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Efatutazone and paclitaxel will not be re-escalated once reduced
- If dose reductions beyond dose level -2 is required or efatutazone or paclitaxel is held for 21 days, efatutazone or paclitaxel will be discontinued.

CTEP-AERS reporting may be required for some adverse events (See Section 9.0)

8.2.1 Dose Levels

Dose Level	Drug Name	Dose
0*	Efatutazone	0.5 mg BID
-1	Efatutazone	0.5 mg every morning, 0.25mg every evening
-2	Efatutazone	0.25 BID

*Dose level 0 refers to the starting dose.

Dose Level	Drug Name	Dose
0*	Paclitaxel	175 mg/m2 every 21 days
-1	Paclitaxel	135 mg/m2 every 21 days
-2	Paclitaxel	100 mg/m2 every 21 days

8.2.2 Hematologic Toxicities

- For **grade 3 neutrophil count decreased** on Day 1, delay paclitaxel until grade ≤ 2, then resume paclitaxel at same dose
- For **grade 4 neutrophil count decreased or febrile neutropenia**, delay paclitaxel until grade ≤ 2, then resume paclitaxel with one dose level decreased
- For **grade 2 platelet count decreased**, delay paclitaxel until grade ≤ 1, then resume paclitaxel at same dose
- For **grade 3 or 4 platelet count decreased,** delay paclitaxel until grade ≤ 1, then resume paclitaxel at one dose level decreased

8.2.3 Neurotoxicity

- For **grade 2 neuropathy,** delay paclitaxel until grade ≤ 1, then resume paclitaxel at same dose level
- For **grade 3 neuropathy,** delay paclitaxel until grade ≤ 1, then resume paclitaxel at one dose level decreased. **If grade 3 neuropathy recurs, discontinue paclitaxel**
- For **grade 4 neuropathy**, discontinue paclitaxel

8.2.4 Gastrointestinal Toxicity

- For **grade 3 nausea or vomiting**, delay paclitaxel until grade ≤ 2, then restart paclitaxel at same dose
- For **grade 4 nausea or vomiting**, delay paclitaxel until grade ≤ 2, then restart paclitaxel at one dose decreased
- For **grade 3 diarrhea**, delay paclitaxel until grade ≤ 2, then restart paclitaxel at same dose
- For **grade 4 diarrhea**, delay paclitaxel until grade ≤ 2, then restart paclitaxel at one dose decreased

8.2.5 Hepatobiliary Toxicity

- For **grade 2 or 3 AST or ALT elevated**, delay paclitaxel until grade ≤ 1, then restart paclitaxel at one dose level decreased
- For **grade 4 AST or ALT elevated**, discontinue paclitaxel
- For **grade 2 or 3 bilirubin elevated**, delay paclitaxel until grade ≤ 1, then restart paclitaxel at one dose level decreased
- For **grade 4 bilirubin elevated**, discontinue paclitaxel

8.2.6 Cardiac Toxicity

For **grade 3 or 4 pericardial effusion**, discontinue efatutazone

8.2.7 General disorders

- For **grade 2 edema**, omit efatutazone until grade < 2, then resume efatutazone at same dose
- For **grade 3 edema**, omit efatutazone until grade < 2, then resume efatutazone at one dose level decreased

8.2.8 Pulmonary Toxicity

- For **grade 2 pleural effusion**, omit efatutazone until grade ≤ 1, then resume efatutazone at one dose decreased
- For **grade 3 or 4 pleural effusion**, discontinue efatutazone.

8.2.9 Non-hematologic Toxicities

For all other **grade 3 or 4 non-hematologic toxicities** likely related to paclitaxel and/or efatutazone, omit paclitaxel and/or efatutazone until resolved to ≤ grade 1, then resume paclitaxel and/or efatutazone at one dose decreased

8.2.10 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at http://ctep.cancer.gov/ reporting/ctc.html. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, Rave is used for routine AE reporting.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.-

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Neutrophil count decreased	Investigations
Platelet count decreased	Investigations
Anemia	Blood and lymphatic system disorders
Peripheral sensory neuropathy	Nervous system disorders
Edema limbs	General Disorders
Weight gain	Investigations
Pleural Effusion	Respiratory disorders
Pericardial Effusion	Cardiac disorders
Cholesterol high	Investigations
Hypertriglyceridemia	Metabolism and nutrition disorders

9.2 CTEP Adverse Event Reporting System (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the CTEP Adverse Event Reporting System (CTEP-AERS). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The Alliance requires investigators to route all expedited adverse events through the Alliance Central Protocol Operations Program Office for Alliance-coordinated studies**. Be sure to read this entire protocol section**, as requirements are described in both the table and bullet points following the table. The bullet points (additional instructions or exclusions) are protocol specific and in the case of a conflict, the additional instructions or exclusions supersede the table.

9.2.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Additional Instructions or Exclusions:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Alliance A091305 uses a drug under an Alliance IND. These reporting requirements apply for all agents (any arm) in this trial.
- Grade 3/4 hematosuppression or febrile neutropenia and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results via routine reporting.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Treatment expected adverse events include those listed in Section 10.0, in the IB for efatutazone, and in the package insert for paclitaxel.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplasic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE v5.0, secondary malignancies may be reported as one of the following three options: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- All pregnancies and suspected pregnancies occurring in female during therapy or within 28 days after completion of treatment on A091305 must be reported via CTEP-AERS. In CTCAE version 5.0, pregnancy loss is defined as "Death in utero," and any pregnancy loss should be reported as "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC (grade 4).
    - CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities). Fetal deaths should be reported as "Death neonatal" under the General disorders and administration SOC (grade 4).
    - The CTEP-AERS report should be amended for any neonatal deaths occurring within 28 days of birth considered at least possibly related to treatment. Use the event term "Death neonatal" under the General disorders and administration SOC (grade 4).
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g. cooperative group data reporting.

10.0 DRUG INFORMATION

10.1 General Considerations:

- The total administered dose of paclitaxel may be rounded up or down within a range of 5% of the actual calculated dose.
- It is not necessary to change the doses of paclitaxel due to changes in weight unless the calculated dose changes by ≥10%.

10.2 Efatutazone dihydrochloride monohydrate (CS-7017) (Alliance IND #121997)

Procurement

Efatutazone dihydrochloride monohydrate (Efatutazone) will be provided and distributed by Daiichi Sankyo. Use the order form found on the Alliance A091305 web page (under the supplemental materials tab) or on the A091305 study page on CTSU web page (under the Pharmacy Tab) to order efatutazone. The form must be completed with each order. Sites must have IRB approval before ordering efatutazone. **Note:** No starter supplies are available.

Institutions should complete the top portion of the form, including and up to "Date Drug Supply is Needed at Site." Submit the completed form via email to [redacted]. Questions regarding orders should be directed to [redacted]

Note: Please allow for a 4-5 business day turn-around time to receive drug.

Formulation

Efatutazone is supplied as 0.25 mg tablets. The strength of efatutazone is expressed as the anhydrous free base. Efatutazone is supplied as white uncoated tablets. The inactive ingredients are mannitol, low-substituted hydroxypropyl cellulose, silicon dioxide, and magnesium stearate.

The uncoated tablets are provided in 100ct amber glass bottles. The number of tablets required should be calculated and dispensed into a pharmacy bottle with Child Resistant Cap Closure.

Preparation, Storage and Stability

All drug supplies should be stored in a secure location, at room temperature, up to 25ºC (77ºF), with excursions permitted from up to 30ºC (86ºF).

Administration

Efatutazone should be taken twice daily at the same time each day, approximately 12 hours apart with or without food.

Drug Interactions

CYP3A4/5 is involved in the metabolism of efatutazone. Efatutazone may inhibit CYP2C8, CYP2C9 and CYP3A4. A drug-drug interaction study with CYP3A4 inhibitor ketoconazole has been evaluated in healthy subjects. With concurrent administration of ketoconazole, total exposure of efatutazone increased by approximately 71% without significantly affecting the peak exposure.

Food and gastric pH effect have been evaluated in healthy subjects receiving efatutazone. No clinically significant effect was observed on the oral bioavailability of efatutazone by either food or gastric pH. Therefore, efatutazone can be taken together with food or gastric pH modifiers.

In vitro studies indicate that efatutazone has an inhibitory potential on uptake transporters (OATP1B1, OATP1B3, OAT3, and OCT2) and efflux transporters (P-glycoprotein and BCRP) with IC_{50} values of 0.508 to 16μM. However, these levels of efatutazone are much higher than the exposure observed in humans; therefore drug-drug interaction on these transporters would be unlikely.

Pharmacokinetics

Absorption: Well absorbed and has high oral bioavailability (59-101.8%). The rate of absorption is slightly slower in the fed state compared to the fasted state with respective median tmax values of 3 and 2 hours. The 90% CI for the ratio of Cmax for fed to fasted states was from 79.3% to 89.2% associated with a 15.9% decrease in mean Cmax. Efatutazone may be taken without regard to meals.

Distribution: $V_{d:}$ 16.9 L at 0.5 mg dose

Protein binding in humans is 99.52% and low partitioning into red blood cells.

Metabolism: In rats and monkeys efatutazone was mainly metabolized by O-dearylation followed by sulfation and glucuronidation. In vitro correlation analyses conducted using human liver microsomes and specific antibodies for each P50 isoform suggest that efatutazone is mainly metabolized by CYP3A4/5.

Half-life elimination: 8.37 hours

Excretion: Feces (69.9%); urine (20.2%)

Clearance: 1.45 L/hour

Adverse Events

Final safety data are available from 10 completed studies as of December 8, 2011. Adverse drug reactions which have a reasonable causal relationship to treatment with efatutazone include: edema, facial edema, localized edema, peripheral edema, pitting edema, fluid retention, weight gain, joint swelling, facial swelling, pleural effusions, hypercholesterolemia, hypertriglyceridemia, fatigue, asthenia, dyspnea, nausea, pain in the extremities, and anemia. Neutropenia and febrile neutropenia has been observed when efatutazone was given with FOLFIRI.

Nursing Guidelines

1. Edema and fluid retention have been noted. Instruct patient to report any swelling or weight gain to the study team.

3. Lipid abnormalities have been reported. Monitor lipid panel as per protocol. Instruct patient on appropriate diet.

4. Monitor CBC w/diff. Instruct patients to report any signs/symptoms of infection or bleeding to the study team.

6. Agent may be taken with or without food.

10.3 Paclitaxel (Taxol)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection 6 mg/mL (5 mL, 16.7 mL, 25 mL, and 50 mL) [contains alcohol and purified Cremophor EL (polyoxyethylated castor oil)].

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature and protect from light. Dilute in 250-1000 mL D_5W or 0.9% NaCl to a concentration of 0.3 – 1.2 mg/mL. Solutions in D_5W and 0.9% NaCl are stable for up to 3 days at room temperature. Chemotherapy dispensing devices (e.g., Chemo Dispensing Pin) should not be used to withdraw paclitaxel from the vial.

Paclitaxel should be dispensed in either glass or non-PVC containers (e.g., Excel/PAB). Use nonpolyvinyl (non-PVC) tubing (e.g., polyethylene) to minimize leaching.

Administration

Infuse IV over 3 hours, or per institutional standards. Infuse through a 0.22 micron in-line filter and nonsorbing administration set.

Drug Interactions

Cytochrome P450 Effect: Substrate (major) of CYP2C8, CYP3A4; **Induces** CYP3A4 (weak).

Increased Effect/Toxicity: CYP2C8 inhibitors may increase the levels/effects of paclitaxel. Refer to the package insert or LexiComp[1] for example inhibitors.

Decreased Effect: CYP2C8 inducers may decrease the levels/effects of paclitaxel. Refer to the package insert or LexiComp[1] for example inducers.

Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors. Avoid valerian, St John's wort (may decrease paclitaxel levels), kava kava, gotu kola (may increase CNS depression).

Pharmacokinetics

Distribution: $V_{d:}$ Widely distributed into body fluids and tissues; affected by dose and duration of infusion

V_{dss}: 1- to 6-hour infusion: 67.1 L/m^2

V_{dss}: 24-hour infusion: 227-688 L/m^2

Metabolism: Hepatic via CYP2C8 and 3A4; forms metabolites (primarily 6α-hydroxypaclitaxel).

Half-life elimination: 1- to 6-hour infusion: Mean (beta): 6.4 hours,

3-hour infusion: Mean (terminal): 13.1-20.2 hours

24-hour infusion: Mean (terminal): 15.7-52.7 hours

Excretion: Feces (~70%, 5% as unchanged drug); Urine (14%)

Clearance: Mean: Total body: After 1- and 6-hour infusions: 5.8-16.3 L/hour/m^2; after 24-hour infusions: 14.2-17.2 L/hour/m^2

Adverse Events

Consult the package insert for the most current and complete information. Percentages reported with single-agent therapy. **U.S. Boxed Warning**: Bone marrow suppression is the dose-limiting toxicity; do not administer if baseline absolute neutrophil count (ANC) is <1500 cells/mm^3 (1000 cells/mm^3 for patients with AIDS-related KS); reduce future doses by 20% for severe neutropenia. **U.S. Boxed Warning**: Severe hypersensitivity reactions have been reported.

Common known potential toxicities, > 10%:

Cardiovascular: Flushing, ECG abnormal, edema, hypotension.

Dermatologic: Alopecia, rash.

Gastrointestinal: Nausea/vomiting, diarrhea, mucositis, stomatitis, abdominal pain (with intraperitoneal paclitaxel)

Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, bleeding.

Hepatic: Alkaline phosphatase increased, AST increased.

Local: Injection site reaction (Erythema, tenderness, skin discoloration, swelling).

Neuromuscular & skeletal: Peripheral neuropathy, arthralgia, myalgia, weakness.

Renal: Creatinine increased.

Miscellaneous: Hypersensitivity reaction, infection.

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Bradycardia, tachycardia, hypertension, rhythm abnormalities, syncope, venous thrombosis.

Dermatologic: Nail changes.

Hematologic: Febrile neutropenia.

Hepatic: Bilirubin increased.

Respiratory: Dyspnea.

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Anaphylaxis, ataxia, atrial fibrillation, AV block, back pain, cardiac conduction abnormalities, cellulitis, CHF, chills, conjunctivitis, dehydration, enterocolitis, extravasation recall, hepatic encephalopathy, hepatic necrosis, induration, intestinal obstruction, intestinal perforation, interstitial pneumonia, ischemic colitis, lacrimation increased, maculopapular rash, malaise, MI, necrotic changes and ulceration following extravasation, neuroencephalopathy, neutropenic enterocolitis, ototoxicity, pancreatitis, paralytic ileus, phlebitis, pruritus, pulmonary embolism, pulmonary fibrosis, radiation recall, radiation pneumonitis, pruritus, renal insufficiency, seizure, skin exfoliation, skin fibrosis, skin necrosis, Stevens-Johnson syndrome, supraventricular tachycardia, toxic epidermal necrolysis, ventricular tachycardia (asymptomatic), visual disturbances. Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

Nursing Guidelines

- Premedicate with steroids, antihistamines, and H2 blockers as per institutional guidelines.
- Mix the infusion bag well. Thorough admixture of this drug often prevents a hypersensitivity reaction. An inline filter of <0.22 micron should be used distal to the infusion pump. Filter may need to be changed if infusion is to be prolonged >12 hours. Inspect solution for excessive particulate matter, if present do not use.
- Assess the patient frequently for the first 30 minutes. Paclitaxel hypersensitivity reactions, which may include chest pain, back pain, flushing, diaphoresis, dyspnea, pruritus, hypotension, hypertension, bronchospasm and/or urticaria, usually occur early in the infusion. Have the anaphylaxis tray available.
- If a reaction occurs, stop the infusion immediately. Follow institutional protocol or treating provider orders for management.
- Approximately 60% of patients experience peripheral sensory neuropathy (numbness, tingling, burning pain, fine motor skills impairment, paresthesias, distal sensory loss). Patients receiving higher doses at shorter infusion times are at greater risk. Most cases have been reported at doses >170 mg/m^2/day and with cumulative doses over multiple courses of therapy. The nerve damage may take months to resolve. Nonsteroidal anti-inflammatory agents and opiates have not been effective in treating neuropathic pain. Consult MD about trying tricyclic antidepressants or possibly gabapentin.
- Mucositis can usually be managed with a salt and soda mouthwash (1 tsp. Salt, 1 tsp. Soda and 1 quart boiled water).

- Narcotics and nonsteroidal anti-inflammatory drugs may be used to manage the myalgias.
- Monitor CBC closely. Neutropenia is most severe in patients who have had previous chemotherapy. Instruct patient to report signs or symptoms of infection, unusual bruising or bleeding to the health care team.
- Monitor IV site closely and establish patency before administration. Paclitaxel is an irritant, however rarely rash, radiation recall, and ulceration have occurred with infiltration of drug.
- Monitor liver function tests
- Inform patient about total alopecia.

11.0 MEASUREMENT OF EFFECT

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) guidelines (version 1.1) (50). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 6 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Note: Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions: Disease progression prior to study entry at the same location that was treated with radiation.

11.2.2 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: '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. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease:

- **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.

  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. The lesions should be measured on the same pulse sequence. 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.
- **PET-CT:** If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- **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 scans are preferable.
- **Physical Examination:** For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **FDG-PET:** FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' 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:

     1) If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

     2) If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional

follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

3) 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, it is not classified as 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 has been 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.

11.3.3 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained at least 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be

calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- **The minimum sum of the dimensions (MSD)** is the minimum of the BSD and the PBSD.

11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.4.3.3.

11.4.3 Response Criteria

11.4.3.1 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.4.3.2 Evaluation of Target Lesions

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to < 1.0 cm.
- **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.4.3.3 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
  c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.4.3.1

11.4.5 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.5 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 CR, PR, or SD: Patients who are in CR, PR or SD will continue on therapy indefinitely.

12.1.2 Disease Progression: Remove from protocol therapy any patient with disease progression. Document details, including tumor measurements, on data forms.

After disease progression, patients should be followed for survival per the study calendar (Section 5.0).

12.1.3 Discontinuation of study agent: If the patient discontinues paclitaxel and efatutazone, patients should be followed for survival per the study calendar (Section 5.0).

12.2 Managing ineligible and canceled patients and major protocol violations

Data must be submitted per Section 5.0 for patients deemed ineligible or canceled. See also the Forms Packet for full details of data submission requirements.

12.2.1 Definitions

Cancelled Patient: A study participant who is registered to the trial but never receives study treatment.

Ineligible Patient: A study participant who is registered to the trial but does not meet all of the eligibility criteria at time of registration.

Clinical Follow-up: The follow-up period where the study participant is no longer receiving treatment, but is still following the study calendar for tests, exams, and correlative endpoints (e.g., specimen collection, quality of life, disease assessments as required by the study).

Survival Only Follow-up: The follow-up period where the study participant is monitored for long-term endpoints, is no longer receiving study treatment, and is not required to follow the study calendar for tests, exams, and correlative endpoints (e.g., specimen collection, quality of life, disease assessments as required by the study). In this follow-up period, there is a schedule in which case report forms should be submitted, but the physician visits are based on the standard of care.

12.2.2 Follow-up Requirements

Patients who are deemed ineligible may continue protocol treatment provided the treating physician, study chair, and Executive Officer agree there are no safety concerns. If the patient continues protocol treatment, all scans, tests, data submission will continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

NOTE: THE FIRST 6 PATIENTS WERE ENROLLED AS PART OF THE ORIGINAL RANDOMIZED DESIGN (3 TO EACH ARM). PATIENTS RANDOMIZED TO ARM B WILL NOT BE INCLUDED IN THE NEW SINGLE ARM TRIAL. THE 3 ARM A PATIENTS WILL BE INCLUDED IN THE NEW SINGLE ARM TRIAL.

13.1 Study Overview

This single arm Phase II trial will assess the confirmed response rate of efatutazone in combination with paclitaxel in patients with advanced Anaplastic Thyroid Cancer. In addition to the confirmed response rate, this trial will also estimate the overall survival (OS), duration of response, progression-free survival (PFS), and adverse event rates for the combination of efatutazone and paclitaxel. Finally, the association of biomarkers with clinical outcome data will be assessed in an exploratory translational analysis.

13.2 Primary Endpoint

The primary endpoint for this study will assess the confirmed response rate (by RECIST 1.1) of efatutazone in combination with paclitaxel in patients with advanced Anaplastic Thyroid Cancer. Any confirmed response that occurs during the first 8 cycles of treatment will count as a success (24 weeks). Per RECIST 1.1, responses need to be confirmed (2 consecutive responses at least 4 weeks apart) to count as a response (see Section 11). All eligible patients who are registered and start treatment will be evaluable for response. A Simon's optimal two-stage MinMax design will be utilized (see below). This design has 90% power to detect an improvement in the confirmed response rate from 15% to 50%, with a significance level of 0.10. See 2-stage design details below:

First Stage: Enroll 5 eligible patients (need 2 additional patients after design change to single arm trial) and temporarily close the study. If at least 1 confirmed response is observed in the first 5 eligible patients, we will open the trial to the second stage and continue the study to a full accrual of 12 eligible patients. Otherwise, the study will be permanently closed due to lack of efficacy.

Second Stage: If the trial is a success during the first stage analysis, we will enroll another 7 eligible patients to the second stage (12 eligible total). If at least 4 confirmed responses are observed in the first 12 eligible patients (33%), the combination treatment will be considered worthy of further investigation. Otherwise, the study will be permanently closed due to lack of efficacy.

13.3 Secondary Endpoints

The following endpoints will be assessed as well: overall survival, duration of confirmed response, progression-free survival, and adverse events.

Overall Survival: Overall Survival (OS) is defined as the time from study entry to death from any cause. OS will be estimating using the Kaplan-Meier method.

Duration of Confirmed Response: The duration of confirmed responses will be assessed using the Kaplan-Meier method, where the duration of confirmed response will be defined as the time from the first documented date of confirmed response (CR or PR) to the date at which progression is first documented.

Progression-Free Survival: Progression-free survival (PFS) is defined as the time from study entry to the first of either disease progression or death from any cause, where disease progression will be determined based on RECIST 1.1 criteria. PFS will be estimated using the Kaplan-Meier method.

Adverse events: The maximum grade for each type of adverse event will be summarized using CTCAE version 4.0. The frequency and percentage of grade 3+ adverse events will be estimated.

13.4 Translational Studies

We plan to correlate the tumor markers (PPAR, RXR, RhoB, $p21^{WAF1/CIP1}$, and angiopoietin‐like 4) with clinical endpoints like confirmed response, survival, PFS, and adverse events. Statistical and graphical techniques will be used to evaluate the relationships between tumor markers and clinical data. For time-to-event endpoints, we will use Cox proportional hazards models, and for confirmed response we will use Logistic regression models. In addition, we will use the Chi-square or Fisher's exact tests to test the association between categorical marker data and confirmed response/adverse events. Continuous marker data will be assessed using 2-sample t-tests (or the nonparametric equivalent for non-normal data). Descriptive statistics and graphical techniques will be used to summarize this data by treatment arm. Given the small sample size, all these analyses will be considered hypothesis generating and exploratory.

13.5 Total Sample Size

A maximum of 15 evaluable patients (12 for single arm trial + 3 Arm B patients enrolled during randomized phase II study) will be accrued onto this phase II study unless the study is closed early for excessive toxicity or lack of efficacy. We anticipate accruing an additional 25% of patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is 20 patients.

13.6 Expected Accrual and Accrual Duration

The expected accrual rate is about 0.50 patients per month for the Alliance group. With this accrual rate, we expect to finish accrual within about 4 years, assuming we accrue 20 total patients.

13.7 Anticipated time to study completion

We anticipate that the study will take approximately 5 years to complete. This allows a 12-month follow-up for the final patient enrolled, along with data entry, data clean-up, and analysis.

13.8 AE Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy any of the following criteria:

- If at any time, 2 of the initial 5 treated patients or 40% or more of all patients (i.e. when accrual is greater than 5 patients) have experienced a grade 4 non-hematologic, non-edema adverse
- If at any time, 1 patient has experienced a grade 5 adverse event (non -progressive disease).

13.9 Accrual Monitoring Stopping Rule

Given the expected accrual rate is around 0.50 patients per month, it is expected that the study will take around 4 years to fully accrue. We plan to monitor the accrual continually and if we only end up accruing 3 patients or less in the first year (after study activation), we will consider stopping the trial for slow accrual.

13.10 Primary Endpoint Completion Time Estimation (For clinicaltrails.gov reporting):

The primary endpoint is to assess the confirmed response rate, as discussed in detail in section 13.2. The final analysis is expected to take place around 5 years after the study begins, so we expect that the primary endpoint completion time to be around 5 years after study activation.

13.11 Descriptive Factors

- Prior RT: Yes vs. No
- Prior Surgery: Yes vs. No
- If Yes, Extent of Surgery: R0/R1 vs. R2 resection
- Prior systemic therapy: Yes vs. No
- Stage 4B vs 4C

13.12 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Based on prior studies involving similar disease sites, we expect about 20% of patients will be classified as minorities by race and about 70% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	13	5	18
Ethnic Category: Total of all subjects	14	6	20
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	1	1	2
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0
White	11	5	16
Racial Category: Total of all subjects	14	6	20

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be one substudy and all patients are encouraged to participate.

14.1 Correlative Science

14.1.1 Background

Preclinical data demonstrate that PPARɣ and RXR are necessary for Efatutazone antiproliferative activity (25). It was further discovered that RhoB and p21 mediated the antiproliferative activity of PPARɣ (51). Also shown in this publication was the fact that Efatutazone (a.k.a. CS-7017) in combination with paclitaxel demonstrated antitumor synergy. Thus, genes transcriptionally regulated by PPARɣ:RXR and their protein products may serve as biomarkers for response to Efatutazone therapy. In the Phase 1 clinical trial testing of Efatutazone with paclitaxel in ATC patients, biomarkers were tested using IHC in patients prior to therapy and during therapy. Angiopoietin-like 4 (ANGPTL4), a gene highly upregulated by PPARɣ:RXR was found to be elevated in patient tissues at the protein level (45).

14.1.2 Objectives

The association of biomarkers with clinical outcome data will be compared between the 2 treatment arms as a translational analysis.

14.1.3 Methods

Biopsy or surgical tissue samples obtained prior to treatment will be collected. Tissues analyzed using immunohistochemistry will be mounted on slides from paraffin-embedded blocks and then blocked with Diluent that contained Background Reducing Components (Dakocytomation, Denmark) for 30 minutes and probed for specified antibodies that included: RXR-α, RhoB (Santa Cruz, Santa Cruz, CA), p21 (Dako, Carpintera, CA), ANGPTL4 (Sigma-Aldrich, St Louis, MO), and PPARγ (kind gift from E.A. Thompson, Mayo Clinic Jacksonville). Negative sections will be prepared by incubating the slides in the absence of the primary antibody as controls and cases will be excluded from analyses if there is insufficient tumor tissue.

Stain scoring will be done using algorithms generated with Imagescope software (Aperio) created by a histologist. H-scores will be calculated based upon signal intensity (0–3+) using the formula: [(1+%x1) + (2+%x2) + (3+%x3)], intensity (I)-scores will be calculated by dividing signal intensity by area, and nuclear (N)-scores will be calculated by dividing% positive nuclei by total nuclei examined per area. Cases where insufficient tumor tissue presented are excluded. 20× images will be obtained using Scanscope XT and Imagescope software. Further details can be found in Smallridge et al. (45).

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

There are no credentialing requirements for A091305.

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APPENDIX I REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and recorded on the Registration Fatigue/Uniscale Assessments Form (see Forms Packet).

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX II PATIENT DIARIES

Patient Medication Diary

A091305 "A PHASE 2 STUDY OF EFATUTAZONE, AN ORAL PPAR AGONIST, IN COMBINATION WITH PACLITAXEL IN PATIENTS WITH ADVANCED ANAPLASTIC THYROID CANCER"
Medication: Efatutazone

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

SPECIAL INSTRUCTIONS

Efatutazone should be taken by mouth, twice daily at the same time each day, approximately 12 hours apart with or without food for 21 days with no break between cycles.

Cycle number _____

Date	AM Time	Number of tablets	PM Time	Number of Tablets	Comments

(To be completed by research staff)

Number of Pills Given:_____ Pill Bottle(s) returned: Circle Yes or No
Total Daily Dose:_____
Number of Pills returned:_____
Research Staff signature:_____
Date:_____

Patient Weight Diary

A091305 "A PHASE 2 STUDY OF EFATUTAZONE, AN ORAL PPAR AGONIST, IN COMBINATION WITH PACLITAXEL IN PATIENTS WITH ADVANCED ANAPLASTIC THYROID CANCER"

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

SPECIAL INSTRUCTIONS: Weigh yourself daily and record weight in this diary. If you gain more than 5 lbs, call your treating doctor for instructions.

Cycle number _____

Date	Weight (in pounds)	Comments

(To be completed by research staff)

Research Staff signature:_____
Date:_____