A Phase 2 Study of lenvatinib in combination with radioactive iodine therapy in patients with progressive RAI-sensitive differentiated thyroid cancer	
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Study Agents
Lenvatinib

Standard Therapies:
^{131}I Radioactive iodine therapy

Study Exempt from IND Requirements per 21 CFR 312.2(b).

Protocol Type / Version # / Version Date: *[Original/ Version #2 / December 18, 2019]*
Protocol Type / Version # / Version Date: *[Original/ Version #3 / January 4, 2021]*

Summary of amendment changes made to protocol version #2:

1. Page 1: Update study team members
2. Page 6: Clarify inclusion criteria to include biochemical evidence of disease
3. Page 14: Clarify inclusion criteria to include biochemical evidence of disease
4. Page 41: Update study timeline

Summary of amendment changes made to protocol version #3:

1. Pages 5 & 6: Update inclusion criteria to align with prescribing information for lenvatinib
2. Page 14: Update to inclusion criteria to align with prescribing information for lenvatinib
3. Page 29-30: Update to the schedule of activities to correct mistakes regarding lab draws and baseline echocardiogram

PROTOCOL SYNOPSIS/SCHEMA

Background

Differentiated thyroid cancer consists of papillary and follicular subtypes, which make up 85% and 12% of differentiated thyroid cancer respectively. In 2012, there were an estimated 600,000 people living in the United States with thyroid cancer. The incidence has risen from 4.8 per 100,000 in 1975 to 14.9 per 100,000 in 2012.[1] Perhaps the greatest risk factor for thyroid malignancy is prior radiation exposure.[2] Papillary and follicular thyroid cancer are primarily managed by surgical resection leading to cure in the vast majority of patients. However, patients with incompletely resected or residual disease often manifesting as persistent elevation of thyroglobulin levels following radioactive iodine (RAI) ablation of thyroid remnant and TSH suppression are more likely to recur on long term follow-up.[3]

Radioactive Iodine in Thyroid Cancer:

Follicular thyroid epithelial cells possess a membrane sodium-iodide symporter that enables the uptake and concertation of iodine in these particular cells.[4] This unique ability of thyroid cells informed the use of RAI as a therapeutic strategy, which is the mainstay of treatment for differentiated thyroid cancer.[5] [6] Therapy is generally recommended when patients have gross extrathyroidal extension, a primary tumor greater than 4 cm or post-operative thyroglobulin levels greater than 5 to 10 ng/mL.[3] The utility of empiric RAI in patients with identifiable disease on imaging that has no iodine uptake on a diagnostic whole body scan remains uncertain. One particular study evaluated 27 patients retrospectively, in whom a diagnostic whole body scan was negative, and the post-therapy scan showed RAI-avid metastatic lesions at the time of RAI remnant ablation. RAI therapy was given to 12 of 15 patients with progressive disease and 5 of12 patients with stable lesions. However, this failed to cause any disease regression or even stabilize the disease progression. Therefore, patients with persistent progressive disease despite a positive post-therapy scan should be considered for treatment interventions other than empiric RAI. [7] Studies have shown that RAI sensitive metastatic tumors harbor a different profile of genetic mutations compared to RAI refractory disease. Sabra et al studied tumor samples from 43 patients with differentiated thyroid cancer who had RAI uptake on their initial ^{131}I scan. They found that RAI sensitive disease was more likely to have a RAS mutation; whereas RAI refractory disease harbored a BRAF mutation.[8] This distinction in genetic profile can be harnessed to guide the use of targeted therapies in RAI sensitive disease.

Rationale for tyrosine kinase inhibitors

Several signaling pathways are implicated in the development of advanced differentiated thyroid cancer, the most common mutations are along the Ras-Raf-MEK-ERK pathways, such as RAS and BRAF mutations. Mutations along the PI3K pathway are also common.[9, 10] In addition, VEGF is important for the growth and proliferation of tumor vasculature, and is mediated by tyrosine kinase receptors.[11, 12] Therefore inhibition of the receptor tyrosine kinase can inhibit multiple pathways of thyroid tumor growth.

RAI Refractory Disease

With the advent of tyrosine kinase inhibitors (TKIs), the management of metastatic refractory thyroid cancer has changed substantially. Small molecule tyrosine kinase inhibitors such as lenvatinib demonstrated clinical efficacy leading to improved PFS compared to placebo in RAI refractory thyroid cancer. The pivotal SELECT trial lead to the FDA approval of lenvatinib for

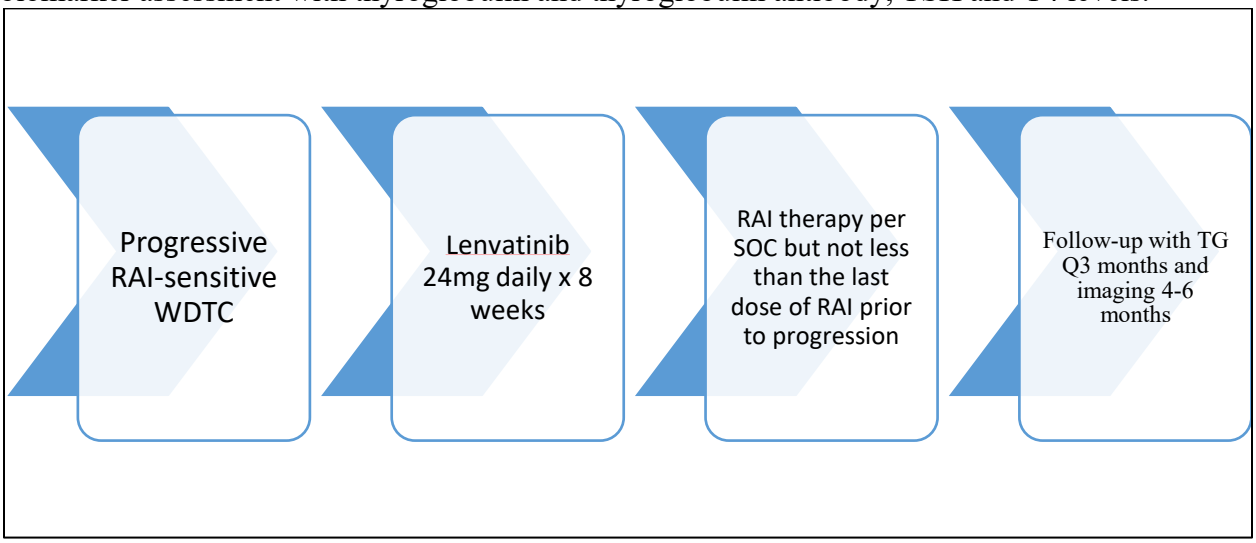
advanced RAI-refractory differentiated thyroid cancer. The trial was a 2:1 randomized two-arm phase III double-blinded multi-center study in advanced iodine refractory thyroid cancer.[13, 14] Two hundred and sixty-one patients received lenvatinib while 131 patients received placebo. PFS was significantly longer in patients who received lenvatinib versus placebo, 18.3 months compared to 3.6 months in the placebo.[15] Posthoc analysis of the result showed that patients with relatively smaller tumor (below the median diameter) derived strong benefit from this agent.[16]

RAI sensitization using kinase inhibitors
The Ras-Raf pathways plays an important role in radioiodine resistant thyroid cancer. Activation of the RAS, RET and BRAF proteins can lead to MAPK signaling, and downstream inhibition of the expression of sodium-iodide symporter. This is in part responsible for iodine uptake in the thyroid epithelial cell. Preclinical studies have shown that this is one of the many pathways involved in development of radioiodine resistance.[17-19] Inhibition of this pathway in mice models has shown reversal of iodine resistance.[20] Based on this preliminary preclinical evidence, Ho et al. studied whether the MEK1/2 inhibitor, selumetinib could resensitize thyroid cancer to radioactive iodine. Twenty patients received selumetinib for an average duration of 4 weeks prior to retreatment with RAI. Selumetinib increased radioiodine uptake in 12 of the 20 patients.[21] Angiogenic targeting agents was shown to be synergistic with ionizing radiation in preclinical cancer models. It is therefore plausible and reasonable to expect that the combination of antiangiogenic agent with RAI will also result in improve benefit of RAI in thyroid cancer. Lenvatinib, a multireceptor tyrosine kinase inhibitor targeting the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1, VEGFR2, and VEGFR3 along with other receptor kinases implicated in cancer growth progression including the FGFR1, 2, 3, and 4; PDGFR alpha, KIT, and RET may also achieve similar effect. [22] Moreover, post hoc analysis of SELECT study data showed that lenvatinib is particularly effective in patients with small volume disease. We therefore aim to test whether the addition of lenvatinib to RAI will result in improved efficacy of RAI in patients with RAI sensitive differentiated thyroid cancer. Since lenvatinib potently inhibits RET, we aim to conduct a study in patients previously treated with RAI, who achieved suboptimal benefit by giving a short course of lenvatinib in order to sensitize the tumor both through increased RAI uptake (RET inhibition) and increased cytotoxicity (angiogenesis inhibition) to iodine and increase radioactive iodine uptake in the tumor cells post-treatment.

Hypothesis
We hypothesize that short course pretreatment with lenvatinib prior to RAI will result in improved efficacy of RAI in patients with iodine sensitive differentiated thyroid cancer
We also hypothesize that tumors with MAPK pathway alteration will be most vulnerable to this therapeutic strategy

Study design and schema –
Single arm phase II study will enroll patients with advanced differentiated thyroid cancer previously treated with RAI and with evidence of anatomic and or biochemical progression within 12 months of the last RAI administration. RAI sensitivity requires demonstrable uptake on delayed whole body scan following the last RAI treatment prior to enrollment on the current study. Consenting and eligible patients will receive lenvatinib at the listed FDA approved dose of 24mg once daily continuously for 8 weeks. Treatment with lenvatinib may continue for up to 12

weeks to accommodate the logistics of RAI treatment and to ensure no break in treatment prior to RAI administration. Patients will receive RAI under appropriate preparation with low dose iodine diet and recombinant TSH (thyrogen) stimulation. Post RAI, patients will undergo delayed whole body scan within 7-10 days of RAI. Subsequent monitoring will include biomarker assessment with thyroglobulin and thyroglobulin antibody, TSH and T4 levels.



Primary Objectives
Evaluate the efficacy of lenvatinib pretreatment along with RAI in patients with previously treated RAI sensitive thyroid cancer

Secondary Objectives –
Demonstrate the safety of this approach
Assess dynamic changes in established serum based biomarkers of DTC activity and putative
Explore the utility of protein and genetic biomarkers to predict treatment efficacy.

Subjects and Centers –
Emory University Winship Cancer Institute

Inclusion Criteria

- Prior treatment with therapeutic dose of radioactive iodine (>50mCi) with evidence of RAI uptake on delayed scan and with progression (biochemical or anatomic) within 12 months of RAI

- Age ≥18 years. Because no dosing or adverse event data are currently available on the use of *lenvatinib* in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

- ECOG performance status 0 or 1 (Karnofsky ≥80%, see Appendix A).

- Patients with acceptable organ and marrow function as defined below:

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin ≤1.5 × institutional upper limit of normal
  AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- creatinine within normal institutional limits
  OR
- creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

- Confirmed diagnosis of differentiated thyroid cancer (Follicular or papillary thyroid cancer and their variants

- Ability and willingness to use appropriate contraception

- The effects of *lenvatinib* on the developing human fetus are unknown. Also, RAI is contraindicated in a pregnant woman. For these reasons and because *kinase inhibitor* agents as well as other therapeutic agents used in this trial may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 2 weeks after completion of *lenvatinib* administration.

- Patients must have biochemical evidence of active disease or measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

- Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

- Patients who have received RAI within 12 weeks of planned retreatment

- Prior receipt of cumulative RAI doses in excess of 1000 mCi.

- Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1)

- Patients who are receiving any other investigational agents.

- Patients with previously untreated and or symptomatic brain metastases are excluded from this clinical trial because of the risk of intracranial bleeding with angiogenic agents and tumoral swelling from RAI.

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to *lenvatinib*

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- Patients with uncontrolled hypertension (requirement for more than 2 BP medications or grade 2 or higher BP elevation while on adequate doses of not more than 2 antihypertensive agents) are excluded from the study because one of the significant adverse events of lenvatinib is worsening hypertension

- QTcF interval prolongation greater than 500 ms

- Recent arterial thromboembolic event within the previous 6 months

- Urine dipstick proteinuria ≥2+ or nephrotic range proteinuria on ≥2gram in 24-hour urine.

- History of gastrointestinal perforation, abscess or fistula

- History of and or medical condition (e.g. diverticular disease; aneurysm) that predisposes to risk of major hemorrhage

- Pregnant women are excluded from this study because *lenvatinib* is a *tyrosine kinase inhibitor* agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with *lenvatinib,* breastfeeding should be discontinued if the mother is treated with *lenvatinib*.

- HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with *lenvatinib.*

Other Therapy
Recombinant TSH (Thyrogen)
^{131}I radioactive iodine therapy

Efficacy Measures
Biochemical response
Anatomic response
Time to progression
Progression free survival (PFS)

Safety Measures
Treatment emergent toxicity will be graded using NCI CTCAE v. 4

Correlative Science
Genomic analysis using TRUsight Illumina platform
Soluble biomarkers
cfDNA profile

Statistical Analysis –
The primary objective of this Phase II trial is to determine the time to progression. We expect that the addition of lenvatinib to RAI will significantly improve the duration of benefit measured as time to treatment failure (anatomic progression or doubling of TG) in patients treated with RAI along with short duration lenvatinib compared to repeat treatment of the same patients with RAI alone.

From previous data, we assume that the enrolled patients without the lenvatinib would have progressed on prior RAI at a median time of 6 months and that the addition of lenvatinib will double the duration of benefit from repeat RAI to a median time of 12 months. We plan the study to have power = 0.90 at the significance level of 0.05 to correctly detect that improvement in median time to progression from 6 moths to 12 months. Since only an improvement in median time-to-progression is of clinical interest, we have a directional hypothesis, and have used a 1-sided alpha. Using a one-sample survival study design, with assumed accrual duration of 12 months and additional follow-up time of 6 months, the minimum sample size requirement is N=30 patients.

The time-to-progression (TTP) will be the primary endpoint for study, and will be determined using all enrolled patients in accordance with the intention to treat (ITT) principle. The censored TTP will be estimated with standard Kaplan-Meier methodology. Both point and 90% confidence interval estimates of the median and other statistics (e.g., 3-month rate, 6-month rate, etc.) from the censored TTP distribution will be calculated. One interim analysis will be conducted after 15 patients have progressed and the trial will stop if the study is significantly better than the null hypothesis at the significance level of 0.0013 according to the O'Brien-Fleming Approach. Otherwise the trial will continue until the targeted sample size is reached.

Patients will be given Lenvatinib 24mg daily by mouth for 60 days followed by standard of care Radioactive Iodine (RAI)

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1. OBJECTIVES

1.1 Primary Objectives

- Evaluate the efficacy of lenvatinib pretreatment along with RAI in patients with previously treated RAI sensitive thyroid cancer

1.2 Secondary Objectives

- Demonstrate the safety of the combination of lenvatinib and RAI in patients with Iodine sensitive DTC
- Assess dynamic changes in established serum based biomarkers of DTC (Tg and Tg antibody)
- Explore the utility of protein and genetic biomarkers to predict treatment efficacy.

2. BACKGROUND

2.1 *Differentiated Thyroid Cancer*

Differentiated thyroid cancer consists of two broad subtypes, papillary and follicular carcinomas, which make up 85% and 12% of differentiated thyroid cancer respectively. In 2012, there were an estimated 600,000 people living in the United States with thyroid cancer. The incidence has risen from 4.8 per 100,000 in 1975 to 14.9 per 100,000 in 2012.[1] Perhaps the best established risk factor for developing this malignancy is prior radiation exposure.[2] Papillary and follicular thyroid cancer are treated similarly, and are primarily a surgical disease. Post-operative management is determined by residual disease, thyroglobulin levels and radioactive iodine (RAI) uptake, and usually consists of ablation of thyroid remnant and TSH suppression.[3]

2.2 Lenvatinib (please refer the FDA prescribing information for full details)

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumor activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signaling in vitro and tumor volume in mouse xenograft models of human renal cell cancer greater than each drug alone.

Absorption:
After oral administration of LENVIMA, time to peak plasma concentration (T_{max}) typically occurred from 1 to 4 hours post-dose. Administration with food did not affect the extent of absorption, but decreased the rate of absorption and delayed the median T_{max} from 2 hours to 4 hours. In patients with solid tumors administered single and multiple doses of LENVIMA once

daily, the maximum lenvatinib plasma concentration (C_{max}) and the area under the concentration-time curve (AUC) increased proportionally over the dose range of 3.2 to 32 mg with a median accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Distribution:
In vitro binding of lenvatinib to human plasma proteins ranged from 98% to 99% (0.3 – 30 µg/mL). In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL). Based on in vitro data, lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, or the bile salt export pump (BSEP).

Elimination:
Plasma concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of lenvatinib was approximately 28 hours.

Metabolism:
CYP3A is one of the main metabolic enzymes of lenvatinib. The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.

Excretion:
Ten days after a single administration of radiolabeled lenvatinib to 6 patients with solid tumors, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

Clinical Experience:
The safety data described below are derived from Study 1 which randomized (2:1) patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) to LENVIMA (n=261) or placebo (n=131) [see Clinical Studies (14.1)]. The median treatment duration was 16.1 months for LENVIMA and 3.9 months for placebo. Among 261 patients who received LENVIMA in Study 1, median age was 64 years, 52% were women, 80% were White, 18% were Asian, and 2% were Black; 4% identified themselves as having Hispanic or Latino ethnicity.
In Study 1, the most common adverse reactions observed in LENVIMA-treated patients (greater than or equal to 30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%). Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA and 5% of patients receiving placebo; 18% of patients discontinued LENVIMA and 5% discontinued placebo for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

2.3 Rationale

Radioactive Iodine in Thyroid Cancer
Thyroid tissue has the unique ability to take up iodine from the blood. Follicular cells have a sodium-iodide symporter in the cell membrane that increase the concentration of iodine in these particular cells. Because of this symporter, the thyroid cancer cell can take up radioactive iodine as well.[4] The first published report of using radioactive iodine was in 1946.[5] Since then, RAI has become of the mainstays of differentiated thyroid cancer treatment and is the primary modality for adjuvant control of disease following surgical resection and also for treating patients with advanced metastatic disease that is sensitive to iodine.[6] Current guideline recommendation supports RAI therapy post-surgery in patients with gross extrathyroidal extension, a primary tumor greater than 4 cm or post-operative thyroglobulin levels greater than 5 to 10 ng/mL.[3] The utility of empiric RAI in patients with identifiable disease on imaging that has no iodine uptake on a diagnostic whole body scan remains uncertain. One particular study evaluated 27 patients retrospectively, in whom a diagnostic whole body scan was negative, and the post-therapy scan showed RAI-avid metastatic lesions at the time of RAI remnant ablation. RAI therapy was given to 12 of 15 patients with progressive disease and 5 of 12 patients with stable lesions. However, this failed to cause any disease regression or even stabilize the disease progression. Therefore, patients with persistent progressive disease despite a positive post-therapy scan should receive treatment other than empiric RAI.[7]

Studies have shown that RAI sensitive metastatic tumors harbor a different profile of genetic mutations compared to RAI refractory disease. Sabra et al conducted a retrospective study where they identified 43 patients with differentiated thyroid cancer who had RAI uptake on their initial ^{131}I scan. The primary tumors were then genotyped for known mutations. They found that RAI sensitive disease was more likely to have a RAS mutation; whereas RAI refractory disease harbored a BRAF mutation.[8] This distinction in genetic profile can perhaps provide benefit to using targeted therapies in RAI sensitive disease.

Rationale for tyrosine kinase inhibitors
As mentioned above, there are several pathways that lead to advanced differentiated thyroid cancer, the most common mutations are along the Ras-Raf-MEK-ERK pathways, such as RAS and BRAF mutations. Mutations in the PI-3K pathway are also common.[9, 10] In addition, VEGF is important for the growth and proliferation of tumor vasculature, and is modulated by receptor coupled kinase enzymes.[11, 12] Therefore inhibition of the receptor tyrosine kinase can inhibit multiple pathways of thyroid tumor growth.

RAI Refractory Disease
With the advent of tyrosine kinase inhibitors (TKIs), the management of metastatic refractory thyroid cancer has changed substantially. Small molecule tyrosine kinase inhibitors such as sorafenib, lenvatinib and pazopanib have shown clinical efficacy and improved PFS compared to placebo in RAI refractory disease. The initial study of sorafenib against placebo in the DECISION trial was the first prospectively acquired data in support of angiogenic agents as salvage therapy in DTC. The pivotal SELECT trial lead to the FDA approval of lenvatinib for advanced thyroid cancer. The trial was a randomized two-arm phase III double-blinded multi-center study for patients with advanced iodine refractory disease.[13, 14] Two hundred and sixty one patients received lenvatinib and 131 patients received placebo. The median PFS was significantly longer in patients who received lenvatinib compared to placebo, 18.3 months versus 3.6 months.[15] Posthoc subset

analysis showed activity of lenvatinib in most patient categories. Particularly relevant to the current study is the stronger efficacy of lenvatinib in patients with small volume disease supporting the use of this agent earlier in the course of the disease.

Kinase inhibitors as a RAI sensitizer
The Ras-Raf pathways plays an important role in thyroid cancer. In particular, activation of the RAS, RET and BRAF proteins can lead to MAPK signaling, and downstream inhibition of the expression of sodium –iodide symporter. This can lead to reduced uptake and limited efficacy of RAI in the thyroid cancer cell. Preclinical studies have shown that this is one of the many pathways involved in development of radioiodine resistance.[17-19] Inhibition of this pathway in mice models resulted in the reversal of iodine resistance.[20] Building on this preclinical data, Ho et al. conducted a study using the MEK1/2 inhibitor selumetinib, as a strategy to resensitize clinically confirmed cases of iodine resistant thyroid cancer to RAI. Twenty patients were given a 4-week pretreatment with selumetinib followed by standard doses of RAI using lesional dosimetry to further optimize the required dose of RAI. Selumetinib increased radioiodine uptake in 12 of the 20 patients. Parallel line of investigation in other tumor types such as colorectal cancer and neurorendocrine tumors also suggests that anti-angiogenic therapy can potentiate the activity of ionizing radiation in part by normalizing the intratumoral blood flow. Indeed, the combination of angiogenic inhibitor and internal radiation was found to be synergistic in preclinical models of pancreatic neuroendocrine tumors.[22] Lenvatinib is a multikinase inhibitor that modulates the angiogenesis pathway in addition to its effect on the MAPK pathway. Moreover, post hoc analysis of SELECT study data showed that lenvatinib is particularly effective in patients with small volume disease. We therefore aim to test whether the addition of lenvatinib to RAI will result in improved efficacy of RAI in patients with RAI sensitive differentiated thyroid cancer. *Given the activity of lenvatinib as an inhibitor of the MAPK pathway and its direct anti-angiogenic activity coupled with established efficacy in RAI resistant tumors, we hypothesize that the combination of lenvatinib and RAI will potentiate clinical efficacy of RAI in iodine sensitive DTC.*
We will conduct a phase II efficacy clinical study of the combination of lenvatinib and RAI in patients with RAI sensitive disease based on clinical definition but where the duration of benefit of RAI was suboptimal. For the purpose of this protocol, suboptimal clinical efficacy of RAI is defined as biochemical or anatomical progression of disease within 6 months of receipt of a therapeutic dose of RAI (not less than 50mCi) in a patient who was adequately prepared for the RAI treatment. Short term administration of lenvatinib for a period of 4-8 weeks will be followed immediately by therapeutic dose of RAI as a way to enhance iodine uptake and clinical efficacy of RAI.[21]

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Prior treatment with therapeutic dose of radioactive iodine (>50mCi) with evidence of RAI uptake on delayed scan, with progression within 12 months of RAI

3.1.2 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of *lenvatinib* in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.3 ECOG performance status 0 or 1 (Karnofsky ≥80%, see Appendix A).

3.1.4 Patients with acceptable organ and marrow function as defined below:

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤1.5 × institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– creatinine	within normal institutional limits

OR

– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.5 Confirmed diagnosis of differentiated thyroid cancer (Follicular or papillary thyroid cancer and their variants

3.1.6 Ability and willingness to use appropriate contraception
The effects of *lenvatinib* on the developing human fetus are unknown. Also, RAI is contraindicated in a pregnant woman. For these reasons and because *kinase inhibitor* agents as well as other therapeutic agents used in this trial may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 2 weeks after completion of *lenvatinib* administration.

3.1.7 Patients must have biochemical evidence of active disease or measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have received RAI within 8 weeks

3.2.2 Prior receipt of cumulative RAI doses in excess of 1000 mCi.

3.2.3 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1)

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 Patients with previously untreated and or symptomatic brain metastases are excluded from this clinical trial because of the risk of intracranial bleeding with angiogenic agents and tumoral swelling from RAI.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to *lenvatinib*

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Patients with uncontrolled hypertension (requirement for more than 2 BP medications or grade 2 or higher BP elevation while on adequate doses of not more than 2 antihypertensive agents) are excluded from the study as one of the adverse events of lenvatinib is worsening hypertension

3.2.9 QTc interval prolongation greater than 500 ms

3.2.10 Recent arterial thromboembolic event within the previous 6 months

3.2.11 Urine dipstick proteinuria ≥2+ or nephrotic range proteinuria on ≥2gram in 24-hour urine.

3.2.12 History of gastrointestinal perforation, abscess or fistula

3.2.13 History of and or medical condition (e.g. diverticular disease; aneurysm) that predisposes to risk of major hemorrhage

3.2.14 Pregnant women are excluded from this study because *lenvatinib* is a *tyrosine kinase inhibitor* agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with *lenvatinib,* breastfeeding should be discontinued if the mother is treated with *lenvatinib*.

3.2.15 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with *lenvatinib.*

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the *Winship Cancer Institute at Emory Univeristy* by the Study Coordinator. Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled and re-screening may be required at the discretion of the study PI. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

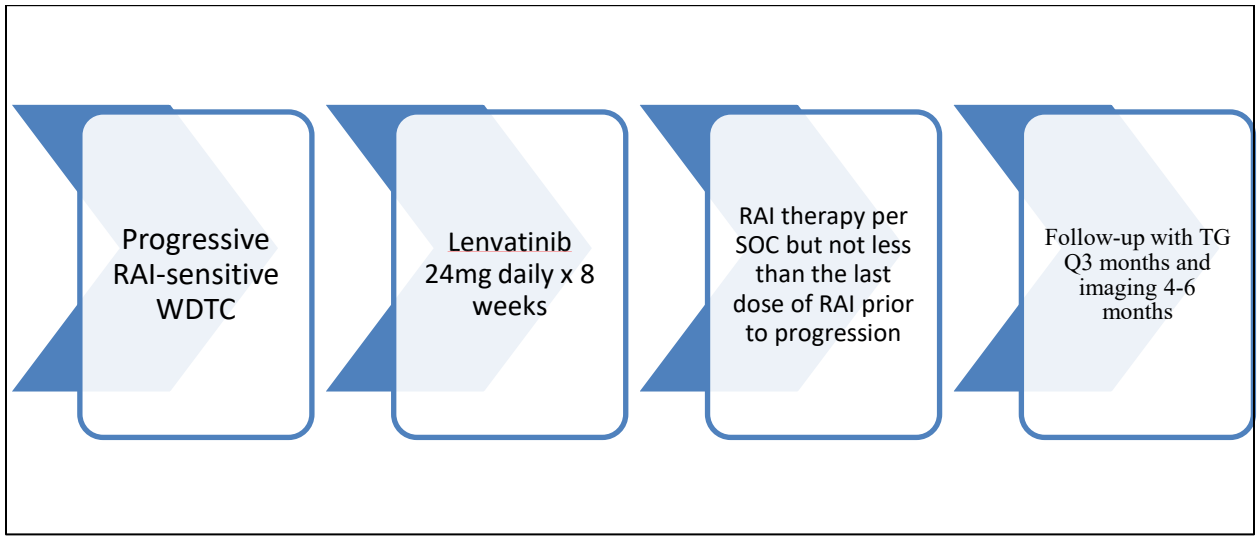
To register a patient, the following documents should be reviewed and verified by the research nurse or Study Coordinator and the PI or designee:

- Copy of required laboratory tests
- Signed patient consent form and HIPAA authorization form
- Eligibility Screening Worksheet
- Register the patient on the study as per Winship Cancer Institute (Winship) standard operating procedures for participant registration.

4.3 Subject ID Number Assignment

All consented patients regardless of whether they meet study eligibility for treatment initiation will be assigned an ID number consisting of an initial "W" indicating Winship and the study number (e.g.W1234) followed by the patients' first and last initials and a 3-digit serial number at enrolment starting at 001 e.g. John Doe, the first patient enrolled on study will have a registration number W1234JD001.

5. TREATMENT PLAN



5.1 Lenvatinib

Treatment will be administered on an *outpatient* basis for lenvatinib and inpatient for RAI unless otherwise cleared by the nuclear medicine physician. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.
Lenvatinib should be taken at the same time every day, with or without food. Capsules should be swallowed whole. Alternatively, the capsules can be dissolved in a small glass of liquid. Measure 1 tablespoon of water or apple juice and put the capsules into the liquid without breaking or crushing them. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add the same amount (1 tablespoon) of water or apple juice to the glass. Swirl the contents a few times and swallow the additional liquid.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Lenvatinib	None	24 mg tablet	Oral*	Once daily	60 days
^{131}I	Thyrogen 0.9mg x 2 doses	100-200 mCi	oral	Once	1 day

**The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.*

5.1.1 *^{131}I Radioactive Iodine*

RAI will be administered as a SOC treatment in patients with progressive but RAI-sensitive thyroid cancer

5.1.2 *Other Agent(s)*

Thyrogen is a lyophilized powder containing 1.1 mg of thyrotropin alfa for single use after reconstitution with Sterile Water for Injection. A two-injection regimen is recommended: THYROGEN 0.9 mg is administered intramuscularly, followed by a second 0.9 mg intramuscular injection 24 hours later. Oral radioiodine should be given 24 hours after the second injection of THYROGEN in both remnant ablation and diagnostic scanning. The activity of 131I is carefully selected at the discretion of the nuclear medicine physician.

Outline of the thyrogen administration protocol.

Low iodine diet for at least two weeks prior to the first thyrogen dose.

Day 1:

- Baseline TSH, Thyroglobulin, and Thyroglobulin antibodies drawn.
  Labs to be drawn prior to receiving first thyrogen injection.
- First thyrogen injection (Thyrogen 0.9 mg intramuscularly (IM).

Day 2

- Second thyrogen injection (Thyrogen 0.9 mg intramuscularly (IM).

Day 3

- Post thyrogen lab draw for TSH, Thyroglobulin and beta HCG drawn prior to reporting to Nuclear Medicine department for radioiodine dosing and scan.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of *lenvatinib* with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. *[For example, the potential targets for drug interaction can involve, but are not limited to CYP450, glucuronidation, P-glycoprotein, protein binding, or reduced absorption from proton-pump inhibitors. Check the study agent Investigator's Brochure for potential sources of drug interactions]*. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment with lenvatinib will continue

for 8 weeks and *up to 12 weeks* or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of RAI
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.4 Duration of Follow Up

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

If a dose is missed and cannot be taken within 12 hours, that dose should be skipped and the next dose should be taken at the usual time of administration.

For patients with DTC, the recommended dose of LENVIMA is 14 mg taken orally once daily in patients with severe renal impairment (creatinine clearance [CLcr] less than 30 mL/min calculated by the Cockcroft-Gault equation) or severe hepatic impairment (Child-Pugh C)

Nausea	**Management/Next Dose for *Lenvatinib***
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.

Nausea	**Management/Next Dose for *Lenvatinib***
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Vomiting	**Management/Next Dose for *Lenvatinib***
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Diarrhea	**Management/Next Dose for *Lenvatinib***
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Neutropenia	**Management/Next Dose for *Lenvatinib***
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Insert any recommended management guidelines, if appropriate.	

Thrombocytopenia	**Management/Next Dose for *Lenvatinib***
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**

Thrombocytopenia	**Management/Next Dose for *Lenvatinib***
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Hypertension	**Management/Next Dose for *Lenvatinib***
≤ Grade 1*	*No dose change (initiate antihypertensive if not previously on BP meds)*
Grade 2*	No dose change (optimize antihypertensive regimen)
Grade 3**	Hold until ≤ Grade 1. Resume treatment with one dose level reduction e.g. 20 mg if previously on 24 mg.
Grade 4	Discontinue.
* Start anti-hypertensive therapy **Despite optimal anti-hypertensive therapy	

Cardiac Dysfunction	**Management/Next Dose for *Lenvatinib***
≤ Grade 1*	*No dose change*
Grade 2*	No dose change
Grade 3*	Hold until < Grade 2. Resume at 20 mg.
Grade 4	Discontinue.
* Start optimal cardiac therapy	

Arterial Thrombotic Event	**Management/Next Dose for *Lenvatinib***
≤ Grade 1	*Discontinue*
Grade 2	*Discontinue*
Grade 3	*Discontinue*
Grade 4	Discontinue.
Do not resume.	

Hepatotoxicity	**Management/Next Dose for *Lenvatinib***
≤ Grade 1	*No dose change*
Grade 2	*No dose change*
Grade 3	*Hold or discontinue. Consider resuming with 1 level dose*

Hepatotoxicity	**Management/Next Dose for *Lenvatinib***
	reduction if resolves to ≤ Grade 1 *or baseline.*
Grade 4	Discontinue.
For hepatic failure- discontinue and do not resume.	

Proteinuria	**Management/Next Dose for *Lenvatinib***
Greater than or equal to 2 gm/24 hours	*Hold until resolves, then reduce by 1 dose level*
For nephrotic syndrome, discontinue permanently.	

Renal Failure	**Management/Next Dose for *Lenvatinib***
≤ Grade 1	*No dose change*
Grade 2	*No dose change*
Grade 3	*Hold or discontinue. Consider resuming 1 dose level reduction if resolves to* ≤ Grade 1 *or baseline.*
Grade 4	*Hold or discontinue. Consider resuming at 1 dose level reduction if resolves to* ≤ Grade 1 *or baseline.*

GI perforation	**Management/Next Dose for *Lenvatinib***
Any grade	*Discontinue*
Immediate medical attention necessary.	

Fistula	**Management/Next Dose for *Lenvatinib***
Grade 3 or 4	*Discontinue*
Immediate medical attention necessary.	

QT prolongation	**Management/Next Dose for *Lenvatinib***
Greater than 500 ms	*Hold until resolves to less than 480 ms then dose reduce to 20 mg*
Immediate medical attention necessary.	

Reversible Posterior Leukoencephalopathy Syndrome	**Management/Next Dose for *Lenvatinib***
Any grade	*Hold, consider resuming at 20 mg*

Reversible Posterior Leukoencephalopathy Syndrome	**Management/Next Dose for *Lenvatinib***
	if resolves to Grade 0 or 1
Immediate medical attention necessary.	

Hemorrhage	**Management/Next Dose for *Lenvatinib***
Grade 3	*Hold, consider resuming at 20 mg if resolves to Grade 0 or 1*
Grade 4	*Discontinue*

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The type of AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting to the IRB and Eisai Inc. **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

Please refer PI for lenvatinib and ^{131}I

7.1.1 CAEPR for *Lenvatinib*

In DTC, the most common adverse reactions (incidence greater than or equal to 30%) for lenvatinib are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia.
Please refer to the package insert for a complete list of adverse events.

7.1.2 CAEPR for RAI (adapted from Tala and Turtle; Clinical Oncology Volume 22, Issue 6, August 2010, Pages 419-429)

Second malignancies:

- Leukemia RR: 2.5 (95% CI: 1.3–5.53) / Dose related: 0.8 extra cases/GBq/10.000 person-years.
- Solid tumors RR: 1.19 (95% CI: 1.04–1.36) / Dose related: 14.4 extra cases/GBq/10.000 person-years. Effects appear after cumulative dose of 200 mCi for soft tissue and bone cancer.

Salivary glands damage:

- Transitory (Occur in about 39%; dose dependent).
  Taste alteration that could last some months.
  Salivary glands swelling/tenderness that could last some months.

- Permanent (occur in < 5%; dose dependent).
  Persistent salivary gland swelling and pain.

Dry mouth (difficulty swallowing).
Persistent taste alterations.
Gum disease and dental cavities

- Nasolacrimal duct obstruction (occurs in approximately 2.5% with doses >100 mCi)

Reproductive problems

- Women –
  Temporary Amenorrhea/oligomenorrhea (occurs in 20–27%)
  No established long-term effect on infertility, miscarriage, and fetal malformation.

- Men
  Temporary reduction in sperm counts and rise in levels.
  No fertility, miscarriage or congenital abnormalities if RAI <200 mCi
  Persistent increase of FSH if cumulative activities >500 mCi.

Bone Marrow Dose related side effects

At low doses of approximately 100 mCi, associated with a significant but mild decline in white blood cells and platelet counts that persists for at least 1 year after ablation

7.2 Serious Adverse Event (SAE) Reporting

All SAE's that are considered as possibly related to Lenvatinib will be reported to Eisai, without any exceptions. Please send report of SAE to ESI Safety

Eisai Product Safety
100 Tice Blvd.
Woodcliff Lake, NJ 07677
Tel: 1-888-274-2378
Fax: -1-732-791-1111
Email: ESI_Safety@eisai.com

Timing of Report to Emory IRB of Protocol Deviations, Serious Adverse events, Deaths and Non Compliance*

Type of Events	**Reporting requirement**
Protocol Deviations	Promptly**: if substantive deviation from protocol and affects rights, safety or welfare of subjects, their willingness to continue in study or the integrity of the research data. •Never: if they do not affect any of the above.
Serious Adverse Events	•Promptly **: if unanticipated, related and involving risk to participant or others or if happening at increased frequency, duration or intensity than previously anticipated. •Periodically ***: if related to study participation. •Never: If not related to study participation.
Internal Deaths	•Promptly**: if related to study participation. •Periodically ***: If not related to study participation.

Non Compliance	Promptly**: The IRB compliance review (CoRe) team will assess if event is possibly serious and/or continuing; if so, Full Board (Committee Q) will review.
(*) This applies to internal events, and external events from sites of Emory sponsor-investigator studies. (**) Promptly: 10 business days from the date the PI first learned about the event (***)Periodically: at continuing review	

7.2.1 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting but must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	**Adverse Event**	**Grade**	**≥24h Hospitalization[a]**
Vascular Disorders	Hypertension	1 or 2	No
Cardiac Disorders	Cardiac Dysfunction	1 or 2	No
Gastrointestinal Disorders	Nausea	1 or 2	No
Gastrointestinal Disorders	Vomiting	1 or 2	No

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

7.3 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously must also be reported in routine study data submissions.**

7.4 Pregnancy

Pregnancy as well as its outcome must be documented. Any reported pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)

- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Study Agents

8.1.1 *Lenvatinib*

Availability

Lenvatinib is the investigational agent employed in this study. It is supplied to investigators by Eisai Inc.

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all study agents.

8.2 Standard of Care Treatment with Radioactive Iodine)

Product description: RAI to be administered per standard protocol in the Nuclear Medicine Division of Emory University.

Solution preparation: Standard preparation with low iodine diet for at least 2 weeks along with thyrogen stimulation or withdrawal as applicable

Route of administration: Orally administered.

Agent Ordering: Per standard nuclear medicine ordering process from commercial vendor.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Genomic analysis using TRUsight Illumina platform using archival tumor samples
Soluble biomarkers of angiogenesis using LUMINEX platform

9.1 Exploratory/Ancillary Correlative Studies

9.1.1 *Genomic analysis using TRUsight Illumina platform using archival tumor samples*
9.1.1.1 Collect archival samples from the Emory or outside facility pathology department
9.1.1.2 Site(s) Performing Correlative Study: Emory Integrated Genomics Core

9.1.2 *Soluble biomarkers of angiogenesis and immune modulation using LUMINEX platform*
9.1.2.1 Collect peripheral blood sample in heparinized tube for plasma separation and storage
9.1.2.2 Handling of Specimens(s) - Store at -80o
9.1.2.3 Site(s) Performing Correlative Study - Stanford Immune Monitoring Lab

10. STUDY CALENDAR

Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate.

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy otherwise, baseline samples obtained within 7 days of starting treatment do not need to be repeated.
Unless otherwise specified, events may occur within a window of ±2 days, ±1 week or a ±1 month as applicable.

	Baseline	Cycle 1				Cycle 2				Cycle 3[i]					
	Pre-Study	Wk 1	Wk 2	Wk 3[h]	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Follow-up[j]	Off Study[c]
Informed consent	X														
Demographics	X														
Medical history	X					X								X	
Physical exam	X	X				X				X				X	X
Height	X														
Weight	X	X				X				X					
Performance status	X	X				X				X				X	X
CBC	X	X				X				X				X	X
Serum chemistry[a]	X	X				X				X				X	X
TG, TG Ab, TSH, Free T4	X													X	
Stimulated TG/Tg Ab	X									X				X[d]	
Urinalysis	X					X									
Pregnancy Test	X[b]					X[b]				X[b]					
Thyrogen Administration	X									X				X[d]	
Archival tissue sample	X														
Echocardiogram*	X														
Peripheral blood for biomarker analysis	X									X				X[k]	
Lenvatinib		X	X	X	X	X	X	X	X	X					
Pill Diary		X				X				X					
Quality of Life Questionnaire	X					X								X	
Nuclear Medicine Consult	X[f]														
Radioactive Iodine Therapy										X					
Adverse event evaluation		X----------X												X	X
Response Assessments	X	Tumor measurements are done at 3 and 6 months post RAI and then Q3-6 months												X	X

		thereafter as clinically indicated.		
Radiologic evaluation	X	Radiologic measurements include a post-therapy scan 7-10 days after RAI and CT scans, (without contrast) MRI or neck ultrasound as clinically indicated for patients with measurable disease every 3 *months* after completion of RAI for up to 1 year then Q 4-6 months thereafter as clinically necessary.		X
Biochemical Response[g]		X[g]	X[g]	

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum or urine pregnancy test (for women of childbearing potential).
c: Off-study evaluation.
d. Stimulated TG to be obtained at baseline (not required if obtained within 3 months of enrolment), with RAI treatment and at 6 months and 12 months post RAI
e. Paired plasma sample to be collected in heparinized tubes at baseline and at the end of treatment with lenvatinib
f. Referral to nuclear medicine for consultation and scheduling of RAI treatment should occur no later than 4 weeks prior to planned RAI treatment
g. Biochemical response will be assessed using suppressed and stimulated thyroglobulin, thyroglobulin antibody. Thyroglobulin and thyroglobulin antibody will be checked at baseline and post RAI every 3 months for 12 months and every 4-6 months thereafter as clinically indicated. Stimulated thyroglobulin obtained at baseline, prior to RAI, at 3 months, 6 months and 12 months post RAI will be used to define biochemical response. Unstimualte Tg levels may be used if unable to obtain stimulated Tg
h. May be conducted by phone if necessary due to logistical reasons
i. Required only if lenvatinib extends beyond 8 weeks due to logistical needs for RAI treatment
j. Regular follow-up within 6 weeks post RAI treatment and every 3 months for 1 year and thereafter per standard of care
k. Optional sample collection
* As clinically indicated

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Biochemical Response: Biochemical response will be assessed using suppressed and stimulated thyroglobulin, thyroglobulin antibody. Thyroglobulin and thyroglobulin antibody will be checked at baseline and post RAI every 3 months for 12 months and every 4-6 months thereafter as clinically indicated. Stimulated thyroglobulin obtained at baseline, prior to RAI, at 3 months, 6 months and 12 months post RAI will be used to define biochemical response.
Response will be classified as previously defined[23] using the stimulated TG/TG Ab levels at baseline as reference point:

- Excellent response: no clinical, biochemical, or structural evidence of disease
- Biochemical incomplete response: abnormal thyroglobulin (Tg) or rising anti-thyroglobulin antibody levels in the absence of localizable disease
- Structural incomplete response: persistent or newly identified locoregional or distant metastases
- Indeterminate response: non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant.

For the purposes of this study, patients should be evaluated for response with a post-therapy scan 5-10 days after RAI and with cross sectional imaging at 3 and *6 months* and Q4 months through 1 year post RAI. Thereafter, imaging will be obtained per standard clinical requirements approximately, every 4-6 months as indicated.

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

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with *lenvatinib.*

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

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at

least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short

axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.1.3 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, 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. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. In addition, thyroglobulin and thyroglobulin anti-body should be checked simultaneously.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT,

additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance

of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

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

11.1.5 *Biochemical Response*:

Thyroglobulin and thyroglobulin antibody will be checked at 6 weeks, 3 months, 6 months after RAI and every 3-6 months thereafter as clinically indicated. Biochemical response will be assessed using suppressed and stimulated thyroglobulin, thyroglobulin antibody. Response will be classified as previously defined using the stimulated TG/TG Ab levels at baseline as reference point.[23]

- Excellent response: no clinical, biochemical, or structural evidence of disease
- Major Biochemical Response: a reduction in TG levels of ≥50% over baseline
- Minor Biochemical Response: a reduction in TG levels of < 50% over baseline
- Biochemical incomplete response: abnormal thyroglobulin (Tg) or rising anti-thyroglobulin antibody levels in the absence of localizable disease
- Structural incomplete response: persistent or newly identified locoregional or distant metastases
- Indeterminate response: non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.7 Time to Progression

Treatment failure leading to disease progression will be defined according to RECIST 1.1 criteria for anatomically defined lesions.
Biochemical progression will be defined as a 50% increase in thyroglobulin levels (either stimulated or unstimulated) over baseline or nadir, whichever is lower; or a minimum of 10% increase in thyroglobulin levels on each of three consecutive measurements if each measurement is obtained at least 12 weeks apart.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Institutional Review Board

The study will be performed in accordance with ethical principles as enshrined in the Declaration of Helsinki and consistent with ICH/Good Clinical Practice as adopted by the FDA in the Federal regulations, and applicable regulatory requirements for subject data protection. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.
The Emory University Institutional Review Board (IRB) will have oversight responsibility and must approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The protocol will be re-approved by the IRB annually or at any other interval deemed appropriate by the IRB.
The study sponsor will provide Regulatory Authorities, IRBs and Investigators with safety updates or reports according to local requirements. Eisai will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

12.2 Informed consent

Each subject (or legally authorized representative) must receive adequate information regarding the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician.
The informed consent should be given by means of a standard written statement, written in non-technical language. The subject should have adequate amount of time to read and consider the consent document before signing and should be given a copy of the signed document. No patient can enter the study before his/her informed consent has been obtained.

12.3 Amendment to the protocol and informed consent form

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Eisai before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB.
Examples of amendments requiring such approval are:

- Increases in drug dose or duration of exposure of subjects,

- Significant changes in the study design (e.g. addition or deletion of a control group)
- Increases in the number of invasive procedures
- Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Eisai will be notified and the IRB must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.
Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

- Changes in the staff used to monitor trials
- Minor changes in the packaging or labeling of study drug.

12.4 Data Collection and Management

Data will be collected using an institutional electronic data recording system, Oncore. Electronic case report forms and study calendar will be generated prior to study activation. Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The Investigator will permit study-related audits by Eisai or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.
The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available so that the accuracy and completeness may be checked.

12.4.1 Disclosure and confidentiality

The investigator will keep all information provided by Eisai in strict confidence and will request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Eisai (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided to the investigator may not be disclosed to others without direct written authorization from Eisai, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.
All study participant information will be kept in a confidential manner by the assigning of a unique random number to each study participant. All data will be kept confidential as per institutional guidelines and policies. Any breach of confidentiality is a serious matter and conflicts with institutional policies and will be reported to the IRB.

12.4.2 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes;

memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval).

12.5 Training of study site personnel

The study PI (sponsor-investigator) will provide training as appropriate to the delegated responsibility to all staffs involved in the conduct of the study. Before the first patient is enrolled in the study, study staff and co-investigators will review and discuss the requirements of the clinical study protocol and related documents including getting trained in any study-specific procedures and electronic data capture systems to be utilized.
The Sponsor-Investigator will ensure that appropriate training relevant to the study is given to all of these staff and any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

12.6 Study oversight and data monitoring

12.6.1 Source data and documents

In accord with section 1.51 of the ICH E6 document all information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.
Case Report Forms (CRFs): Source data may be collected in the source documents or entered directly onto the case report forms.

12.6.2 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur

in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

12.7 Study site and timeline

12.7.1 Number of patients & centers

The maximum number of patients enrolled depends on the overall toxicity and DLT experience on study. We project a minimum of 15 patients and maximum of 30 patients depending on whether o not the study was stopped after the planned interim analysis or proceed to full accrual. This is a single center study to be conducted at the Emory University Winship Cancer Institute, an NCI-designated comprehensive cancer center.

12.7.2 Population

Patients with advanced differentiated thyroid cancer who have been previously treated with therapeutic doses of RAI and who are candidates for further RAI treatment will be enrolled to the study.

12.7.3 Study duration/timelines:

Total accrual duration: 36 months
Study start (FPFV): 04/01/2018
Recruitment end (LPFV): 03/31/2021
End of Study (LPLV): 09/30/2021
Completion of study report (CSR) - 03/31/2022
Publication date -06/30/2022

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary objective of this Phase II trial is to determine the time to treatment failure. We expect that the addition of lenvatinib to RAI will significantly improve the duration of benefit measured as time to treatment failure (anatomic progression or doubling of TG) in patients treated with RAI along with short duration lenvatinib compared to repeat treatment of the same patients with RAI alone.

From previous data, we assume that the enrolled patients without the lenvatinib would have progressed on prior RAI at a median time of 6 months and that the addition of lenvatinib will double the duration of benefit from repeat RAI to a median time of 12 months. We wish to have power = 0.90 at the significance level of 0.05 to correctly detect that improvement in median time to progression from 6 moths to 12 months. Since only an improvement in median time to progression is of clinical interest, we have a directional hypothesis, and have used a 1-sided alpha. Using a one-sample survival study design, with assumed accrual duration of 12 months and additional follow-up time of 6 months, the minimum sample size requirement is N=30 patients.

The time-to-progression will be the primary endpoint for study, and will be determined using all enrolled patients in accordance with the intention to treat (ITT) principle. The censored time-to-treatment failure will be estimated with standard Kaplan-Meier methodology. Both point and 90% confidence interval estimates of the median and other statistics (e.g., 3-month rate, 6-month rate, etc.) from the censored time-to-treatment failure distribution will be calculated. One interim analysis will be conducted after 15 patients have treatment failure and the trial will stop if the study is significantly better than the null hypothesis at the significance level of 0.0013 according to the O'Brien-Fleming Approach. Otherwise the trial will continue until the targeted sample size of 30 patients is reached.

13.2 Sample Size/Accrual Rate

Patient sample size is 30. Accrual rate is 2-3 per month.

13.3 Analysis of Secondary Endpoints

Demographic and other baseline data will be summarized descriptively. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented (i.e., mean, median, standard deviation, minimum, maximum).
in the expansion phase for each arm of the study.

13.3.1 Analysis of Response Endpoints

Efficacy evaluable population - Response will be analyzed in the following patient groups:

- All patients who received any amount of the investigational agent
- Patients who completed at least 2 cycles of therapy and have a baseline and restaging scans performed
- All patients enrolled in the expansion cohort treated at the RP2D.

Summaries of the number of patients with best objective response in each of the following

categories will be provided:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Non-Evaluable (NE)
- Disease Control (DC = CR+PR+SD)

Objective response rate and disease control rate will be summarized. For the expansion cohorts, objective response rate will be presented along with 95% exact confidence intervals.
Demonstrate the safety of this approach
Assess dynamic changes in established serum based biomarkers of DTC activity and putative
Explore the utility of protein and genetic biomarkers to predict treatment efficacy.

13.4 Reporting and Exclusions

13.4.1 Evaluation of Toxicity
All patients who received any amount of the investigational agent will be evaluable for toxicity assessment.

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

In addition, biochemical response will be assessed as follows:[23]

- Excellent response: no clinical, biochemical, or structural evidence of disease
- Biochemical incomplete response: abnormal thyroglobulin (Tg) or rising anti-thyroglobulin antibody levels in the absence of localizable disease
- Structural incomplete response: persistent or newly identified locoregional or distant metastases
- Indeterminate response: non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant.

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

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

REFERENCES

1. SEER Stat Fact Sheet: Thyroid Cancer Available from URL: http://seer.cancer.gov/statfacts/html/thyro.html [accessed October 20, 2016].
2. Schneider AB, Sarne DH. Long-term risks for thyroid cancer and other neoplasms after exposure to radiation. Nat Clin Pract Endocrinol Metab. 2005;1: 82-91.
3. Haddad R, et al. . NCCN Guidelines Thyroid Carcinoma. National Comprehensive Cancer Network. 2016;Version 1.2016.
4. Spitzweg C, Harrington KJ, Pinke LA, Vile RG, Morris JC. Clinical review 132: The sodium iodide symporter and its potential role in cancer therapy. J Clin Endocrinol Metab. 2001;86: 3327-3335.
5. Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. J Am Med Assoc. 1946;132: 838-847.
6. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26: 1-133.
7. Sabra MM, Grewal RK, Tala H, Larson SM, Tuttle RM. Clinical outcomes following empiric radioiodine therapy in patients with structurally identifiable metastatic follicular cell-derived thyroid carcinoma with negative diagnostic but positive post-therapy 131I whole-body scans. Thyroid. 2012;22: 877-883.
8. Sabra MM, Dominguez JM, Grewal RK, et al. Clinical outcomes and molecular profile of differentiated thyroid cancers with radioiodine-avid distant metastases. J Clin Endocrinol Metab. 2013;98: E829-836.
9. Haugen BR, Sherman SI. Evolving approaches to patients with advanced differentiated thyroid cancer. Endocr Rev. 2013;34: 439-455.
10. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159: 676-690.
11. Zeng H, Dvorak HF, Mukhopadhyay D. Vascular permeability factor (VPF)/vascular endothelial growth factor (VEGF) peceptor-1 down-modulates VPF/VEGF receptor-2-mediated endothelial cell proliferation, but not migration, through phosphatidylinositol 3-kinase-dependent pathways. J Biol Chem. 2001;276: 26969-26979.
12. Wedge SR, Ogilvie DJ, Dukes M, et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res. 2002;62: 4645-4655.
13. Mitsutake N, Knauf JA, Mitsutake S, Mesa C, Jr., Zhang L, Fagin JA. Conditional BRAFV600E expression induces DNA synthesis, apoptosis, dedifferentiation, and chromosomal instability in thyroid PCCL3 cells. Cancer Res. 2005;65: 2465-2473.
14. Riesco-Eizaguirre G, Gutierrez-Martinez P, Garcia-Cabezas MA, Nistal M, Santisteban P. The oncogene BRAF V600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Na+/I- targeting to the membrane. Endocr Relat Cancer. 2006;13: 257-269.
15. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372: 621-630.
16. Robinson B, Schlumberger M, Wirth LJ, et al. Characterization of Tumor Size Changes Over Time From the Phase 3 Study of Lenvatinib in Thyroid Cancer. J Clin Endocrinol Metab. 2016;101: 4103-4109.

17. Durante C, Puxeddu E, Ferretti E, et al. BRAF mutations in papillary thyroid carcinomas inhibit genes involved in iodine metabolism. J Clin Endocrinol Metab. 2007;92: 2840-2843.
18. Knauf JA, Kuroda H, Basu S, Fagin JA. RET/PTC-induced dedifferentiation of thyroid cells is mediated through Y1062 signaling through SHC-RAS-MAP kinase. Oncogene. 2003;22: 4406-4412.
19. Liu D, Hu S, Hou P, Jiang D, Condouris S, Xing M. Suppression of BRAF/MEK/MAP kinase pathway restores expression of iodide-metabolizing genes in thyroid cells expressing the V600E BRAF mutant. Clin Cancer Res. 2007;13: 1341-1349.
20. Chakravarty D, Santos E, Ryder M, et al. Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation. J Clin Invest. 2011;121: 4700-4711.
21. Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer. New England Journal of Medicine. 2013;368: 623-632.
22. Wicki A, Wild D, Pretre V, et al. Synergism of peptide receptor-targeted Auger electron radiation therapy with anti-angiogenic compounds in a mouse model of neuroendocrine tumors. EJNMMI Res. 2014;4: 9.
23. Tuttle RM. Optimal management of a biochemical incomplete response to therapy in differentiated thyroid cancer: aggressive treatment or cautious observation? Endocrine. 2014;46: 363-364.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

[Note to authors: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***[****insert study drug name****]***. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Lenvatinib interacts with *the heart's electrical activity (QTc prolongation)*.

- The heart's electrical activity may be affected by lenvatinib. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.
- This drug can cause elevated blood pressure. The study doctor may be concerned about the removal of any anti-blood pressure medications from the patient's medication regimen.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Lenvatinib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Lenvatinib must be used very carefully in patients with high blood pressure. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review

any medicines and herbal supplements that are considered part of your blood pressure regimen.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is Taofeek K. Owonikoko, MD, PhD and he or she can be contacted at 404-778-1900.

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug **Lenvatinib.** This clinical trial is sponsored by Taofeek Owonikoko, MD, PhD. **Lenvatinib** may interact with drugs that are ***[processed by your liver, or use certain transport proteins in your body or affects the electrical activity of your heart]***. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that you may take. ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is Taofeek K. Owonikoko, MD, PhD and can be contacted at 404-778-1900.

APPENDIX C PILL DIARY AND BP RECORD

Study Title	A PHASE 2 STUDY OF LENVATINIB IN COMBINATION WITH RADIOACTIVE IODINE THERAPY IN PATIENTS WITH PROGRESSIVE RAI-SENSITIVE DIFFERENTIATED THYROID CANCER	
Lenvatinib Pill Diary		
Subject Initials		
Subject ID		
Cycle #		
Research Coordinator Name: Phone: Pager:		
Cohort#	Original Lenvatinib Dose ……	BP - Baseline
# of Dose Reductions	Current Lenvatinib Dose :……..	Current BP ……

Instructions:

1. Please take the prescribed pills as instructed

2. Please record the date and time you take your medications. On visit days, medications should be taken in the clinic unless otherwise instructed

3. Please bring medication and pill diary to each study visit.

Day	Date	Lenvatinib (Y/N)	BP AM/PM
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			

23			
24			
25			
26			
27			
28			

I attest that I received the study medications listed on this pill diary.

Patient Signature

……

Date: ……

This section to be completed by a Research Personnel (Investigator, CRN/CRC)

Dosing Cycle Start Date:	Dosing Cycle End Date:	
Lenvatinib Lot Number: ……	# of Bottles / # of Tablets Dispensed : ____4mg ____10mg	Any Interruptions? (Yes/No)…….
Length of Dose Interruption:		
Reason for Interruption:		
Reason for Dose Reduction:		
Additional Comments:		