Adaptive Tyrosine Kinase Inhibitor Therapy in Patients with Advanced Progressive Thyroid Cancer

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Adaptive tyrosine kinase inhibitor therapy in patients with advanced progressive thyroid cancer

Protocol Identifying Number: MCC# 19442

Principal Investigator: Christine H. Chung, M.D.

Sponsor: Moffitt Physical Sciences Oncology Center

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IST OF ABBREVIATIONS

AE	Adverse Event
ACT	Cabozantinib adaptive therapy
AT	Adaptive therapy
ALT	Adaptive Lenvatinib therapy
ATT	Adaptive TKI therapy
ANCOVA	Analysis of Covariance
CCT	Conventional Cabozantinib therapy
CLT	Conventional Lenvatinib therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Conventional TKI therapy
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CRO	Contract Research Organization
CT	Conventional therapy
DTC	Differentiated thyroid cancer
eCRF	Electronic Case Report Forms
EOT	End of Treatment
FDA	Food and Drug Administration
MCC	Moffitt Cancer Center
MTC	Medullary thyroid cancer
NCI	National Cancer Institute
NIH	National Institutes of Health
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RAIR	Radioactive Iodine Resistant
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
Tg	Thyroglobulin
Tg AB	Thyroglobulin antibodies
TKI	Thyrosine kinase inhibitors
US	United States

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Moffitt Physical Sciences Oncology Center Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed of their obligation to meet the above commitments.

Principal Investigator: Christie H. Chung Print/Type Name

Signed: _____ Date: _____

STUDY SUMMARY

Title: Adaptive tyrosine kinase inhibitor therapy in patients with advanced progressive thyroid cancer.

Précis: This is a randomized phase II clinical trial to evaluate the efficacy and tolerability of tyrosine kinase inhibitor (TKI) therapy through adaptive (intermittent) versus conventional (continuous) dosing schedule in patients with differentiated thyroid cancer (DTC) or medullary thyroid cancer (MTC).

Objectives:

Primary objective:

- To evaluate the efficacy and tolerability of TKI therapy (Lenvatinib or Sorafenib for DTC; Cabozantinib or Vandetanib for MTC) through adaptive (intermittent) versus conventional (continuous) regimen.

Secondary objective:

- To evaluate response and survival of TKI therapy (Lenvatinib or Sorafenib for DTC; Cabozantinib or Vandetanib for MTC) through adaptive (intermittent) versus conventional (continuous) regimen.

Exploratory objective:

- To determine predictive biomarkers of TKI response.

Endpoint:

Primary endpoint:

- Time to TKI treatment discontinuation due to progressive disease, intolerability, or disease-related death at 2 years.

Secondary endpoints:

- Overall response rate
- Progression free survival
- Overall survival

Exploratory endpoints:

- Determine predictive biomarkers of TKI response

Population: Patients with advanced progressive 131I-refractory DTC or MTC will be enrolled to this study. Forty-five patients responding to TKI therapy (defined as ≥50% drop in tumor marker level within the first two months of treatment) will be randomized to receive TKI therapy either through adaptive (intermittent) or conventional (continuous) regimen.

Phase: Randomized phase II clinical trial

Number of Sites enrolling participants: 1 (Moffitt Cancer Center)

Description of Study Agent:

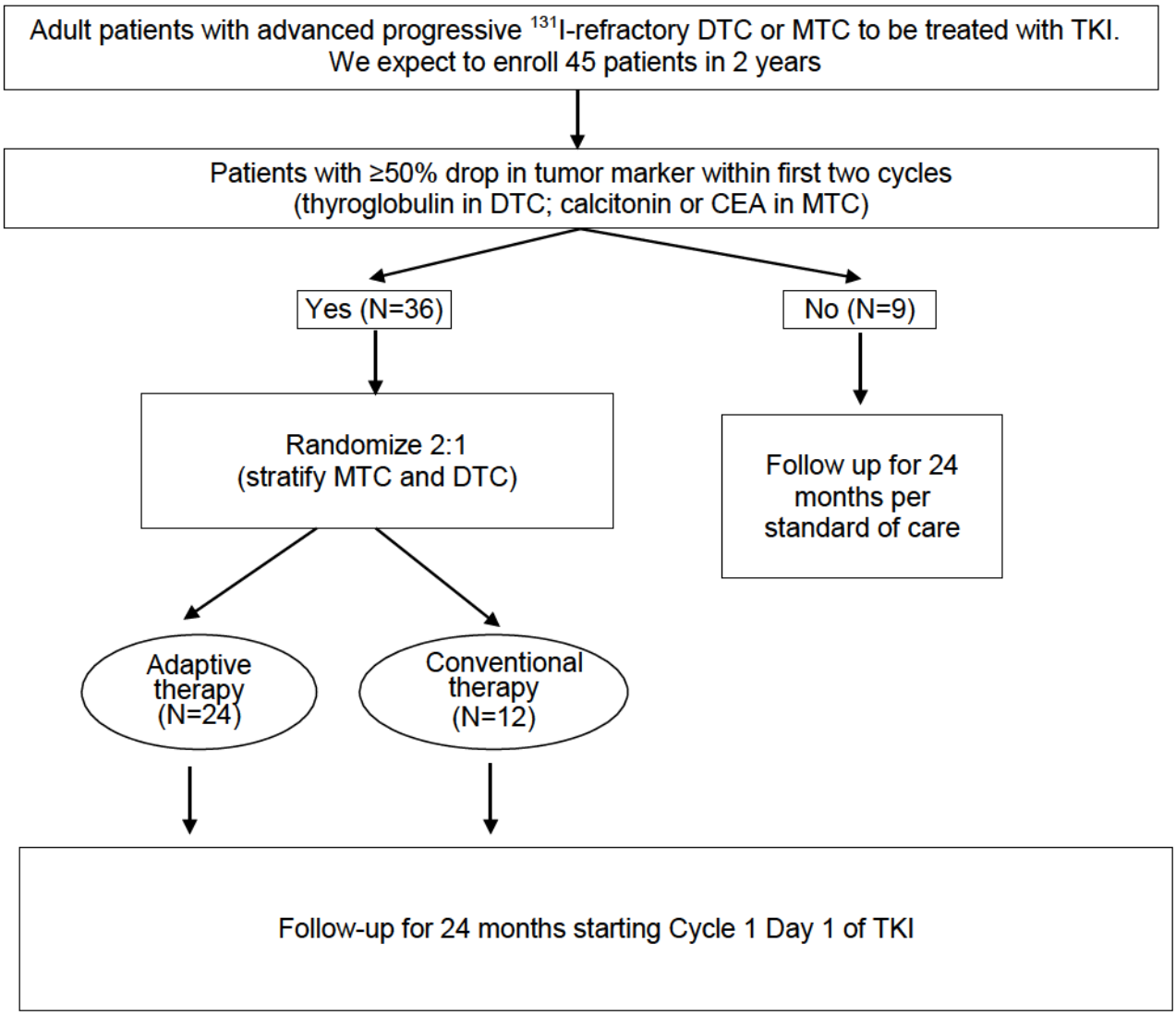
- All patients will start receiving standard of care treatment: Lenvatinib 24 mg daily or Sorafenib 400 mg twice daily with DTC; Cabozantinib 140 mg daily or Vandetanib 300 mg daily with MTC. Doses will be adjusted as needed due to toxicity or drug tolerance in both arms.
- Patients in the conventional therapy regimen will receive continuous treatment at the indicated dose until disease progression or development of intolerability.

- Patients in the adaptive therapy regimen will receive TKI therapy in cycles: continuous treatment at the indicated dose until the patients' tumor marker (thyroglobulin in DTC patients; calcitonin or CEA in MTC patients) drops by ≥50% from the level at the time of enrollment ("baseline" level). Only tumor markers that meet inclusion criteria at baseline can be used for randomization and adaptive therapy purposes. A new cycle of TKI treatment will begin:
-
    - When/if the tumor marker increases to ≧70% of the "baseline" level.
      OR
    - At the discretion of the treating physician if a patient develops worsening disease-related symptoms with rising tumor marker levels indicating disease progression. In the case of resumption for disease-related symptoms, TKI treatment will continue until the symptoms improve at the discretion of the treating physician and the tumor markers are again ≤50% from the level at the time of enrollment.

Study Duration: 48 months

Participant Duration: 48 months

SCHEMATIC OF STUDY DESIGN



1. KEY ROLES

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2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Primary thyroid cancers can be classified into 3 groups according to the cells of origin: 1) follicular-cell derived carcinomas which represent 95% of all thyroid cancers and include differentiated thyroid cancers (DTC) such as papillary, follicular and poorly-differentiated thyroid carcinomas; and undifferentiated or anaplastic thyroid carcinomas; 2) parafollicular or C-cell derived carcinomas, termed medullary thyroid carcinomas (MTC) that represent around 4% of all thyroid cancers; and 3) stromal-cell derived carcinomas that represent <1% of all thyroid cancers and include tumors such as thyroid lymphoma, sarcoma or fibrosarcoma. Presently, thyroid cancer exhibits the most rapidly increasing incidence of all solid tumors in the United States and several other countries; and it is already the fifth most common cancer among women in the United States (1-5). During 2017, it is expected that 56,870 patients will be diagnosed with thyroid cancer (6). Despite this rapid increase in incidence, thyroid cancer-specific mortality has remained stable for the last 50 years and most patients with differentiated thyroid cancer have an excellent prognosis with an estimated five-year survival rate > 98% (6). Nonetheless, the five-year survival rate if distant metastases are present is considerably worse (56%), which has also remained unchanged for several decades (6).

In the last decade our understanding of the underlying genetic alterations of thyroid cancer has improved significantly, leading to the development of new therapies (7, 8). Since 2011, the FDA has approved four novel tyrosine kinase inhibitors (TKI) for the treatment of progressive metastatic thyroid cancer: Lenvatinib and Sorafenib for DTC; and Cabozantinib and Vandetanib for MTC).

Lenvatinib is an inhibitor of the vascular endothelial growth factor receptors (VEGFR) 1-3; the fibroblast growth factor receptors 1-4; the platelet-derived growth factor receptor α; RET; and KIT. In a phase III randomized placebo controlled study (SELECT), Lenvatinib was associated with significant improvements in progression-free survival (18.3 versus 3.6 months) and response rate (64.8% versus 1.5%) (9). Sorafenib is an inhibitor of the VEGFR 1-3, RET, RAF

and platelet-derived growth factor receptor β. In a randomized, double blind, placebo-controlled phase III trial (DECISION), Sorafenib also was associated with a significant increase in progression-free survival (10.8 versus 5.4 months) and response rate (54.1% vs. 33.8%) (10). Cabozantinib, inhibits the hepatocyte growth factor receptor (MET); the vascular endothelial growth factor receptor 2; and RET. In a phase III randomized placebo controlled study (EXAM), Cabozantinib improved the median progression-free survival from 4.0 to 11.2 months (hazard ratio, 0.28 [0.19 to 0.40]); as well as the response rate from 0% to 28% (11). Finally, Vandetanib selectively targets RET, VEGFR and EGFR signaling. In a phase III randomized, double-blind, placebo-controlled study (ZETA), Vandetanib showed to prolong the progression free survival from 19.3 months in the placebo group to 30.5 months in the Vandetanib group (hazard ratio, 0.46 [0.31-0.69]); and to improve the response rate (49% vs 13%) (12). Response to therapy was seen rapidly, at a median of 2 months for radiological response and even earlier for tumor markers in the SELECT study.(9) Most patients on TKI therapy, however, develop resistance to the drug after 12-18 months of treatment, and then tumor restarts progression.(9-12)

TKI therapy has proven to increase the progression free survival; however, their impact on overall survival is still unclear, in part due to the rapid development of tumor resistance. Furthermore, TKI treatment is associated to significant toxicity. Severe (grade 3-4) treatment related adverse events were reported in 76%, 69% and 37% of the patients treated with TKI on the SELECT, EXAM and DECISION studies, respectively, compared to 10%, 33% and 26% in their respective placebo-control groups (9-11). As a consequence of the adverse events, a dose reduction was necessary in 68% of the study participants treated with Lenvatinib, and treatment needed to be interrupted in 82% of patients in the SELECT study (9). Similarly, 64% of the patients required a dose reduction and 66% treatment interruption under Sorafenib treatment in the DECISION trial.(10) In the ZETA study, a significantly higher proportion of patients required dose reduction due to adverse events or QT prolongation in the Vandetanib group than in the placebo group (35% vs. 3%).(12) TKI treatment was permanently discontinued in around 15% of the participants in all studies due to adverse events (9-12).

Finding mechanisms that allow delaying the selection of resistant clones and decreasing the toxicity profile of TKIs in patients with thyroid cancer might improve the progression free survival and could have a positive impact on the overall survival. Adaptive TKI therapy could be one of such mechanisms (13).

2.2 *RATIONALE*

In general, cytotoxic drugs are administered with the assumption that maximum clinical benefit is obtained by killing the greatest possible number of cancer cells. Consistent with this premise, most systemic cancer chemotherapies are applied at the maximum tolerated dose density. This model is being theoretically challenged by an alternative model that views cancer therapy as an evolutionary and ecological process (13, 14). This alternative model rests on three major assumptions. First, phenotypically or environmentally mediated resistant cells are present before treatment. Second, most xenobiotic mechanisms protecting cells from cytotoxic agents do not require mutations, but rather increased expression of molecular machinery already encoded in the genome. Third, cancer populations within a tumor compete with each other for space and substrate. Clearly, in the presence of chemotherapy, resistant cells are better adapted and, thus, fitter (more proliferative) than wild-type cells. However, in the absence of chemotherapy, this fitness difference is typically reversed because of the metabolic cost of the resistance mechanism (synthesis, maintenance, and operation of membrane extrusion pumps). In an environment of limited substrate, this cost requires diversion of resources from proliferation and invasion. In this Darwinian setting, maximum dose density therapy strongly selects for resistant phenotypes and, by removing all competitors, permits

unconstrained proliferation of the resistant populations even when no drug is present—a phenomenon well recognized in evolutionary dynamics as "competitive release".

A recent study applied these evolutionary principles to prolong tumor control in preclinical models of breast cancer (15). In this study, mice with orthotopic implants of breast cancer cells survived longer using a treatment regimen that modulated the dose according to changes in tumor volume than those receiving standard chemotherapy. One of the limitations to translate this into the clinical practice is that tumor volume was evaluated twice a week through MRI. However, in thyroid cancer, there are specific tumor markers (thyroglobulin for DTC and calcitonin for MTC) that have a direct correlation with the burden of disease (16, 17). Therefore, these biomarkers can be used as an indirect reflection of the response to therapy to adjust treatment dose.

2.3 *POTENTIAL RISKS AND BENEFITS*

2.3.1 KNOWN POTENTIAL RISKS

Potential risks for study participants for both adaptive TKI therapy and conventional TKI therapy are related to TKI side effects (See section 8 and Appendix 3).

Additionally, the efficacy of adaptive TKI therapy for the treatment of advance progressive thyroid cancer is currently unknown. Therefore, there is the potential of disease progression. Study participants will be monitored closely with regular clinical examination, tumor marker measurement, and imaging studies so that progression is detected early if present. If it occurs, the treatment will be modified accordingly.

2.3.2 KNOWN POTENTIAL BENEFITS

Lenvatinib and Sorafenib in patients with advanced progressive differentiated thyroid cancer and Cabozantinib, and Vandetanib in patients with advanced progressive medullary thyroid cancer have proven to increase the progression free survival in phase 3 randomized controlled trials *(9-12)*.

3. OBJECTIVES AND PURPOSE

Primary objective:

- To evaluate the efficacy and tolerability of TKI therapy (Lenvatinib or Sorafenib for DTC; Cabozantinib or Vandetanib for MTC) through adaptive (intermittent) versus conventional (continuous) regimen.

Secondary objective:

- To evaluate response and survival of TKI therapy (Lenvatinib or Sorafenib for DTC; Cabozantinib or Vandetanib for MTC) through adaptive (intermittent) versus conventional (continuous) regimen.

Exploratory objective:

- To determine a predictive biomarkers of TKI response.

4. STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a pilot randomized phase 2 clinical trial to evaluate the efficacy and tolerability of TKI therapy through adaptive (intermittent) versus conventional (continuous) regimen in patients with DTC or MTC. Eligible subjects with DTC or MTC will have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and will be randomized 2 to 1 to receive adaptive (intermittent) versus conventional (continuous) therapy when and if the tumor marker drops 50% or more from the baseline level (before initiating TKI treatment) within the first two months of treatment. Randomization will be stratified by cancer types, DTC vs. MTC. Patients in which the tumor marker does not drop by 50% or more within 2 months ("non-responders") will be kept on conventional therapy and used to compare with the patients who drop their tumor markers by 50% or more as an exploratory analysis.

All patients will start receiving standard of care treatments: Lenvatinib 24 mg daily or Sorafenib 400 mg twice daily with DTC; Cabozantinib 140 mg daily or Vandetanib 300 mg daily with MTC. Doses will be adjusted as needed due to toxicity or drug tolerance in both arms (See section 6.1.8).

- Patients in the conventional therapy regimen ("responders" and non-responders") will receive continuous (daily) treatment at the indicated dose.

- Patients in the adaptive therapy regimen will receive TKI therapy in cycles: continuous (daily) treatment at the indicated dose until the patients' tumor marker (thyroglobulin in DTC patients; calcitonin or CEA in MTC patients) drops by ≥50% from the level at the time of enrollment ("baseline" level). ≥70% ofOnly tumor markers that meet inclusion criteria at baseline can be used for randomization and adaptive therapy purposes. A new cycle of TKI treatment will begin:

1. When/if the tumor marker increases to ≥70% of the "baseline" level.

   OR

2. At the discretion of the treating physician, if a patient develops worsening disease-related symptoms with rising tumor marker levels indicating disease progression. In the case of resumption for disease-related symptoms, TKI treatment will continue until the symptoms improve at the discretion of the treating physician and the tumor markers are again ≤50% from the level at the time of enrollment.

All study participants will be followed for at least 24 months after treatment initiation. Patients will continue to receive treatment until confirmed disease progression, development of unacceptable toxicity, withdrawal of consent, or study termination by investigator. After disease progression, subjects will be followed for survival and may be treated according to standards of care, which includes conventional (continuous) TKI treatment for patients in the adaptive therapy arm.

After 24 months, patients in the adaptive therapy arm that remain on TKI therapy and under control will be given the choice to continue with adaptive therapy or to convert to conventional (continuous) regimen, which is the current standard of care.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

The primary endpoint is time to TKI treatment discontinuation due to progressive disease, intolerability (Grade 3 and 4 toxicities refractory to best symptom management that are deemed probably or definitely related to study treatment only), or disease-related death at 2 years. We hypothesize that time on TKI treatment will be significantly longer for patients on the adaptive therapy arm than on the conventional therapy arm because we expect a decrease in drug-associated toxicities and a delay in the selection of resistant clones in the adaptive therapy arm.

4.2.2 SECONDARY ENDPOINTS

We will evaluate overall response rate, progression free survival and overall survival of the adaptive therapy regimen and of the conventional therapy regimen.

4.2.3 EXPLORATORY ENDPOINTS

We will determine predictive biomarkers of TKI response.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Subjects who meet all inclusion criteria will able to participate in the study.

Inclusion criteria:

1. All histologically or cytologically confirmed diagnosis of thyroid cancer, other than anaplastic or stromal-cell derived cancers.
2. **Participants with DTC** must have negative thyroglobulin antibodies.
3. Measurable disease meeting the following criteria and confirmed by central radiographic review:
    - At least 1 lesion of ≥ 1.0 centimeter (cm) in the longest diameter for a non- lymph node or ≥ 1.5 cm in the short-axis diameter for a lymph node which is serially measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI). If there is only one target lesion and it is a non-lymph node, it should have a longest diameter of ≥ 1.5 cm.
    - Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease (substantial size increase of ≥ 20%) within 12 months to be deemed a target lesion.
4. Participants must show evidence of disease progression comparing (a) scan in screening and (b) historical scan obtained within 12 months prior to signing informed consent, according to RECIST 1.1 assessed and confirmed by central radiographic review of CT and/or MRI scans.
5. **Participants with DTC** must not be eligible for possible curative surgery and must be radioiodine (RAI)-refractory / resistant as defined by at least one of the following:
    - One or more measurable lesions that do not demonstrate iodine uptake on any

radioiodine scan
- One or more measurable lesions that has progressed by RECIST 1.1 within 12 months of RAI therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning.
- Disease progression in a patient that has received a cumulative activity of RAI of ≥ 550 millicuries (mCi) (22 gigabecquerels), with the last RAI dose administered at least 6 months prior to study entry.
- Otherwise deemed not a candidate for further RAI therapy by a multidisciplinary tumor board within 60 days of enrollment

6. **Participants with DTC** must be receiving thyroxine suppression therapy and thyroid stimulating hormone (TSH) should not be elevated (TSH should be ≤ 0.1 mU/L).
7. "Measurable" tumor marker (non-stimulated thyroglobulin >10 ng/mL in patients with DTC; or serum basal calcitonin >10 pg/mL or CEA > 10 ng/mL in patients with MTC)
8. Participants may have received prior multi-kinase targeted therapy except the TKI used in this trial. For example, patients getting Lenvatinib on this study may have been previously treated with Sorafenib, Vandetanib, Sunitinib, Pazopanib, etc. Each of the TKI targeted agents will be counted individually, regardless of the duration of its administration.
9. Participants with known brain metastases who have completed whole brain radiotherapy, stereotactic radiosurgery or complete surgical resection, will be eligible if they have remained clinically stable, asymptomatic for 30 days.
10. All chemotherapy or radiation related toxicities must have resolved to < Grade 2 severity per Common Terminology Criteria for Adverse Events (CTCAE v 5.0), except alopecia infertility, anemia (see separate criteria) and any toxicities deemed irreversible by the treating physician.
11. Participants must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 – 2 (See Appendix 2).
12. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤ 150/90 mm Hg at screening and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1
13. Adequate renal function defined as calculated creatinine clearance ≥ 30 mL/min (using Cockcroft/Gault formula)
14. Adequate bone marrow function:
    - Absolute neutrophil count (ANC) ≥ 1500 mm3 (≥ 1.5 × 103/micro liter [µL])
    - Platelets ≥ 100 × 10^9/ L
    - Hemoglobin ≥ 9.0 g/dL
    - Adequate blood coagulation function as evidenced by an INR≤ 1.5
15. Adequate liver function:
    - Bilirubin ≤ 1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome who must have a total bilirubin level of < 3.0 x ULN).
    - Alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if participant has liver metastases).
16. Males or females age ≥ 18 years at the time of informed consent
17. Females must not be breastfeeding or pregnant at Screening or Baseline (as documented by a negative human chorionic gonadotropin [hCG]. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
    All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrhea for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically

(ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

18. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days prior to study entry and must agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the participant must agree to use a double-barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.
19. Male participants must have had a successful vasectomy (confirmed azoospermia) or they and their female partners must meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 30 days after study drug discontinuation). Those with partners using hormonal contraceptives must also be using an additional approved method of contraception, as described previously.
20. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol

5.2 PARTICIPANT EXCLUSION CRITERIA

Subjects who meet at least one exclusion criteria will not be able to participate in the study.

Exclusion criteria:

1. Participants who have received any anticancer treatment (including Chinese herbal medicine specified for the treatment of tumor) within 21 days or any investigational agent within 30 days prior to the first dose of study drug. This does not apply to the use of TSH-suppressive thyroid hormone therapy.
2. Major surgery within 21 days prior to the first dose of study drug.
3. Palliative radiation therapy within 14 days prior to the first dose of study drug.
4. Participants having > 30 mg/dL urine protein on urine dipstick testing (Participants with urine protein < 1 g/24 hour (h) will be eligible).
5. Gastrointestinal malabsorption or any other condition that in the opinion of the investigator might affect the absorption of Lenvatinib, Sorafenib, Cabozantinib, or Vandetanib.
6. Significant cardiovascular impairment: history of (a) congestive heart failure greater than New York Heart association (NYHA) Class II, (b) unstable angina, (c) myocardial infarction, (d) stroke, or (e) cardiac arrhythmia associated with impairment within 6 months of the first dose of study drug.
7. Bleeding or thrombotic disorders (Treatment with low molecular weight heparin is allowed).
8. Radiographic evidence of major blood vessel invasion/infiltration.
9. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 21 days prior to the first dose of study drug.
10. Active infection (any infection requiring systemic treatment).
11. Active malignancy (except for DTC/MTC or definitively treated basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or bladder) within the past 24 months.
12. Known intolerance to any of the study drugs (or any of the excipients).
13. Any medical or other condition which, in the opinion of the investigator, would preclude

participation in a clinical trial.
14. Females who are pregnant or breastfeeding.
15. Participants who are taking prohibited medications outlines in section 7.5.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients with metastatic progressive thyroid cancer (DTC and MTC) referred to medical oncologist clinic for systemic therapy will be screened based on inclusion and exclusion criteria. Subjects who meet inclusion criteria and are willing to participate in the study will be enrolled.

No compensation will be provided for study participation.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate participation in the study in the following circumstances:

- If any treatment-related Grade 4 adverse events (AE) develops during TKIs therapy.
- If any clinically adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interests of the participant
- If the participant meets any exclusion criteria (either newly developed or not previously recognized) that precludes further study participation.
- Extraordinary medical circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, the protocol treatment should be discontinued.
- If patient develops progressive disease, then the patient will discontinue the protocol therapy (See Appendix 4).
- If patient develops unacceptable toxicity, then the patient will discontinue the protocol therapy.

The reason and date for patient removal from the study must be documented in the Case Report Form (CRF).

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems.

Those who discontinue protocol therapy early will be followed for response until progression and for survival for 1 year from the date of withdraw or termination.

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

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated by the investigators. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason for the termination or suspension.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the PI and IRB.

6. STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

Tyrosine kinase inhibitors used in this study, Lenvatinib, Sorafenib, Cabozantinib, and Vandetanib, are FDA- approved and standard of care for DTC and MTC. They will be prescribed through specialty pharmacy or conventional pharmacy depending on the availability. The study participants will be mailed to home or personally pick up the medication depending on the availability.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Lenvatinib is an FDA approved drug for treatment of metastatic progressive differentiated thyroid cancer. Lenvatinib capsules (Lenvima) are produced by Eisai and come in 2 strengths: 10 mg and 4 mg; capsules are supplied in cartons of 6 blister cards. Each cartoon contains a 30 day supply of Lenvatinib capsules.

Sorafenib is an FDA approved drug for treatment of metastatic progressive differentiated thyroid cancer. Sorafenib (Nexavar) is produced by Bayer in 200 mg tablets.

Cabozantinib is an FDA approved drug for treatment of metastatic progressive medullary thyroid cancer. Cabozantinib (Cometriq) is produced by Exelixis as 80 mg and 20 mg gelatin capsules.

Vandetanib is an FDA approved drug for treatment of metastatic progressive medullary thyroid cancer. Vandetanib (Caprelsa) is produced by Sanofi Genzyme in 2 strengths: 100 mg and 300 mg tablets.

6.1.3 PRODUCT STORAGE AND STABILITY

Lenvatinib, Sorafenib, Cabozantinib, and Vandetanib must be stored in accordance with the instructions on the label at room temperature: 68 F to 77 F (20 C to 25 C).

6.1.4 PREPARATION

No specific preparation of study agent is required.

6.1.5 DOSING AND ADMINISTRATION

Study participants with DTC will be taking either:

- **Lenvatinib** (Lenvima) 24 mg in the form of two 10-mg capsules and one 4-mg capsule. Lenvatinib should be taken at the same time each day. If the patient misses a dose and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration. Lenvatinib may be taken in a fasting state or following a meal. Lenvatinib capsules can be swallowed whole. Alternatively, the capsules can be dissolved in one tablespoon of liquid (water or apple juice). Leave the capsule in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture and add another tablespoon of liquid (water or apple juice) to the glass, swirl the contents a few times and swallow the additional liquid.

Or

- **Sorafenib** (Nexavar) 400 mg twice daily in the form of two 200-mg tablets every 12 hours, on empty stomach (at least 1 hour before and 2 hours after a meal). If the patient misses a dose, the next dose should be taken at the regularly scheduled time, and not double the dose.

Study participants with MTC will be taking either:

- **Cabozantinib** (Cometriq) 140 mg once daily in the form of one 80-mg capsule and three 20-mg capsules. Cabozantinib should be taken at the same time each day, on empty stomach (at least 1 hour before and 2 hours after meal) with at least 8 ounces of water. If the patient misses a dose and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Or

- **Vandetanib** (Caprelsa) 300 mg once daily in the form of one 300-mg tablet. Vandetanib should be taken at the same time each day. If the patient misses a dose and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration. Vandetanib may be taken with or without food. Tablets can be dispersed in 2 ounces of water by stirring for approximately 10 minutes (will not dissolve completely). Do not use other liquids for dispersion. Swallow immediately after dispersion and mix any remaining residue with 4 additional ounces of water and shallow.

6.1.6 ROUTE OF ADMINISTRATION

Lenvatinib, Sorafenib, Cabozantinib, and Vandetanib will be taken orally.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

The starting dose of Lenvatinib in patients with DTC is 24 mg/day. This is the maximal dose that study participants will receive.

The starting dose of Sorafenib in patients with DTC is 400 mg twice daily. This is the maximal dose that study participants will receive.

The starting dose of Cabozantinib in patients with MTC is 140 mg/day. This is the maximal dose that study participants will receive. Patients with hepatic impairment will start treatment at 80 mg/day.

The starting dose of Vandetanib in patients with MTC is 300 mg/day. This is the maximal dose

that study participants will receive.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

All patients will start receiving standard of care treatment:

- DTC: Lenvatinib 24 mg daily or Sorafenib 400 mg twice daily
- MTC: Cabozantinib 140 mg daily or Vandetanib 300 mg daily.

Dose will be adjusted as needed due to toxicity or drug tolerance in both arms (See below).

- Patients in the conventional therapy regimen ("responders" and non-responders") will receive continuous (daily) treatment at the indicated dose.

- Patients in the adaptive therapy regimen will receive TKI therapy in cycles: continuous (daily) treatment at the indicated dose until the patients' tumor marker (thyroglobulin in DTC patients; calcitonin or CEA in MTC patients) drops by ≥50% from the level at the time of enrollment ("baseline" level). Only tumor markers that meet inclusion criteria at baseline can be used for randomization and adaptive therapy purposes. A new cycle of TKI treatment will begin:

1. When/if the tumor marker increases to ≥70% of the "baseline" level.
   OR
2. At the discretion of the treating physician if a patient develops worsening disease-related symptoms with rising tumor marker levels indicating disease progression. In the case of resumption for disease-related symptoms, TKI treatment will continue until the symptoms improve at the discretion of the treating physician and the tumor markers are again ≤50% from the level at the time of enrollment.

All study participants will continue to receive treatment until confirmed disease progression, development of unacceptable toxicity, withdrawal of consent, or study termination by investigator.

After disease progression subjects will be followed for survival and may be treated according to standards of care, which includes conventional (continuous) TKI treatment for patients in the adaptive therapy arm.

Held doses will be considered missed and will not be made up so that patients will complete on-study treatment within the anticipated 24 month duration. Treatment may be delayed for toxicity, other palliative treatments (i.e. palliative radiation, palliative surgery, etc.) for a maximum of 4 weeks. Any treatment beyond the 24 months specified herein will be considered off protocol and not subject to the requirements of this protocol.

6.1.8.1 MANAGEMENT OF MOST COMMON GENERAL SIDE EFFECTS OF TKI TREATMENT (NOT AGENT-SPECIFIC)

MANAGEMENT OF HYPERTENSION

- Insure BP ≤ 150/90 mmHg at the time of study entry.
- Discuss preventive measurements.
- Insure that study participants has a BP cuff at home and are willing to measure BP twice a day and report if elevated.

  - Patients will be asked to maintain a diary of these measurements to be reviewed with the treating physician or APP during clinic visits
  - If patient reports 3 consecutive at-home systolic BP measurements of ≥ 140 mmHg and/or diastolic BP measurements of ≥ 90 mmHg, they will be instructed to set up a clinic visit to be assessed for further management. The BP measurements obtained in clinic will be used to manage hypertension as detailed further below.

- Treat SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg with antihypertensive agents individualized to the subject's clinical circumstances based on standards of clinical practice.
- For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred.
- TKI should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (e.g., BP ≥ 160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the blood pressure is controlled, study drug should be resumed as described below.
- If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg persists despite maximal antihypertensive therapy, then study drug administration should be interrupted and restarted at a dose of 20 mg once daily when BP ≤ 150/95 mmHg.
- If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the 20-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at a dose of 14 mg once daily when BP ≤ 150/95 mmHg.
- If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the 14-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at a dose of 10 mg once daily when BP ≤ 150/95 mmHg.
- For Grade 4 hypertension (life- threatening consequences) discontinue study drug.
- Additional dose reduction should be upon medical judgment of PI.

MANAGEMENT OF PROTEINURIA

- Regular assessment for proteinuria should be conducted as specified in study calendar (See Table 8).
- Initial episode of proteinuria: if proteinuria ≥ 2+ is detected on urine dipstick testing study drug will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Withhold TKI for ≥2 grams of proteinuria/24 hours and resume at a reduced dose when proteinuria is <2 grams/24 hours.
- Discontinue TKI for nephrotic syndrome

MANAGEMENT OF DIARRHEA

- Diarrhea is very common with TKIs. The first step in management of diarrhea, however, is to investigate other potential causes including: other medications such as laxatives, stool softeners or antibiotics; lifestyle factors such as excessive dietary fiber or lactose; and infectious causes of diarrhea.
- TKI related diarrhea is usually mild to moderate and early management is essential to prevent dose reduction or discontinuation. Antimotility agents such as loperamide should be initiated on appearance of mild diarrhea, and patients should avoid foods that cause symptoms. Patients should be advise to drink approximately three liters of liquids a day to

minimize the risk of dehydration.
- If diarrhea persists despite up to 20 mg loperamide per day, patients should return to the clinic for further assessment.
- For patients with persistent grade 2-3 diarrhea, interruption of treatment may be considered to allow symptoms to improve. The TKI dose may also be reduced to control diarrhea.
- If diarrhea fails to resolve after dose reductions or discontinuation, octreotide may be considered in some cases.
- For patients with grade 4 diarrhea permanently discontinue treatment despite medical management.

MANAGEMENT OF HAND AND FOOT SYNDROME
- Hand-foot syndrome usually occurs early; and prompt initiation of management can reduce its severity and duration. Patients should be informed to keep their skin moisturized and to notify their physician of early signs of hand-foot syndrome
- For grade 1 (minimal skin changes without pain), maintain TKI dose and keep skin well hydrated.
- For grade 2 (skin changes such as peeling, blisters, bleeding, edema or hyperkeratosis, with pain that limits instrumental activities of daily living), TKI treatment may need to be interrupted in some cases. Hyperkeratosis should be controlled, the skin kept moisturized and discomfort relieved with analgesics.
- For grade 3 (skin changes such as peeling, blisters, bleeding, edema or hyperkeratosis, with pain that limits self-care activities of daily living), TKI treatment need to be interrupted. Keratosis on the pressure points of the feet can be shaved by a podiatrist; and may be reduced with topical creams with salicylic acid or urea. Other treatments directed to reduce symptoms and the impact on patient's quality of life are also recommended, including appropriate analgesics.

MANAGEMENT OF MUCOSITIS
- Before the start of treatment, patients should have an oral hygiene check-up. Patients should be advice to brush their teeth and tongue with a soft-bristled brush in addition to flossing and rinsing with normal saline.
- Patients that develop mucositis in the mouth should rinse their mouth out every two to three hours. Mouthwash or bicarbonate can be useful for grade 1 mucositis. Additionally:
- For grade 1 mucositis (minor symptomatic inflammation of the mouth) maintain TKI dose and apply triamcinolone in dental paste 2–3 times daily as needed.
- For grade 2 mucositis (causes some pain but eating and drinking are tolerable) maintain TKI dose and apply triamcinolone paste two to three times daily as needed AND oral erytrhromycin 250-350mg daily OR minocycline 50 mg daily. Mouthwashes that include corticosteroid are very useful for treating mouth ulcers that may develop.
- For grade 3 mucositis (severe pain that prevents them eating or drinking), temporarily discontinue TKI for 2-4 weeks. Upon improvement to grade 2 or less, reintroduce TKI at a reduced dose (see section 6.1.8 for specific details). If toxicities do not worsen, escalate the dose. If no improvement, discontinue. Apply clobetasol ointment 2–3 times daily as needed AND oral erythromycin 500 mg daily OR minocycline 100 mg daily. Mouthwashes that include corticosteroid are very useful for treating mouth ulcers; and analgesics are necessary to treat pain.

6.1.8.2 MANAGEMENT OF MOST COMMON SIDE EFFECTS SPECIFIC TO EACH TKI AGENT

Dose Reduction and Interruption Instructions for Lenvatinib

Table 1. Adverse Reactions Requiring Dose Modification of Lenvatinib

Adverse Reaction	CTCAE Grade	Action	Dose Reduce and Resume Lenvatinib
Hypertension	Grade 3[1]	Hold	Resolves to Grade 0, 1, or 2
	Grade 4	Discontinue	Do Not Resume
Cardiac Dysfunction	Grade 3	Hold	Resolves to Grade 0, 1, or baseline
	Grade 4	Discontinue	Do Not Resume
Arterial Thrombotic Event	Any Grade	Discontinue	Do Not Resume
Hepatotoxicity	Grade 3 or 4	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
Hepatic Failure	Grade 3 or 4	Discontinue	Do Not Resume
Proteinuria	Greater than or equal to 2 gm/24 hours	Hold	Resolves to less than 2 gm/24 hours
Nephrotic Syndrome	-------	Discontinue	Do Not Resume
Nausea, Vomiting, and Diarrhea[2]	Grade 3	Hold	Resolves to Grade 0, 1, or baseline
Vomiting and Diarrhea[2]	Grade 4	Discontinue	Do Not Resume
Renal Failure or Impairment	Grade 3 or 4	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
GI Perforation	Any Grade	Discontinue	Do Not Resume
Fistula	Grade 3 or 4	Discontinue	Do Not Resume
QTc Prolongation	Greater than 500 ms	Hold	Resolves to less than 480 ms or baseline
Reversible Posterior Leukoencephalopathy syndrome	Any Grade	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0 to 1
Hemorrhage	Grade 3	Hold	Resolves to Grade 0 to 1
	Grade 4	Discontinue	Do Not Resume

1: Grade 3 despite optimal anti-hypertensive therapy
2: Initiate prompt medical management for nausea, vomiting or diarrhea. Permanently discontinue for Grade 4 vomiting and diarrhea despite medical management

Other adverse reactions with Lenvatinib will be managed following the instructions from Table 2:

Table 2. Dose Modifications for Lenvatinib for treatment-related Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities[a]

Adverse Reaction	Modification	Adjusted Dose[b]
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	20 mg (two 10 mg capsules) orally once daily
Second occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsule plus one 4 mg capsule) orally once daily

Third occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily

a: Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of Lenvatinib
b: Reduce dose in succession based on the previous dose level (24 mg, 20 mg, or 14 mg per day)
c: Refers to the same or a different adverse reaction that requires dose modification

Patients with confirmed systolic BP≥140 mmHg or diastolic BP ≥90 mmHg will be administered antihypertensive agents and monitored every 1-2 weeks. In patients with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite optimal management the treatment dose will be reduced. Patients with confirmed proteinuria Grade ≥2 (1.0–3.4 g/24h) will be tested every 2 weeks; and treatment will be interrupted until proteinuria decreases to Grade 0–1 or baseline level at which time, a lower dose will be restarted.

For patients with DTC, the recommended dose of Lenvatinib 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)

Dose Reduction and Interruption Instructions for Sorafenib

Temporary interruption of Sorafenib is recommended in patients undergoing major surgical procedures.
Temporary interruption or permanent discontinuation of Sorafenib may be required for the following:
- Cardiac ischemia or infarction
- Hemorrhage requiring medical intervention
- Severe or persistent hypertension despite adequate anti-hypertensive therapy
- Gastrointestinal perforation
- QTc prolongation
- Severe drug-induced liver injury

Table 3. Recommended Doses for Patients with DTC Requiring Sorafenib Dose Reduction

Dose Reduction	**Sorafenib Dose**	
First Dose Reduction	600 mg daily dose	400 mg and 200 mg 12 hours apart (2 tablets and 1 tablet 12 hours apart – either dose can come first)
Second Dose Reduction	400 mg daily dose	200 mg twice daily (1 tablet twice daily)
Third Dose Reduction	200 mg daily dose	200 mg once daily (1 tablet once daily)

When dose reduction is necessary for dermatologic toxicities, reduce the Sorafenib dose as indicated in Table 4 below.

Table 4. Recommended Sorafenib Dose Modifications for treatment-related Dermatologic Toxicities

Dermatologic Toxicity Grade	**Occurrence**	**Sorafenib Dose Modification**

Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	Continue treatment
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Decrease dose to 600 mg daily If no improvement within 7 days, see below
	No improvement within 7 days at reduced dose *or* 2nd occurrence	Interrupt until resolved or improved to grade 1 If resumed, decrease dose (see Table 3)
	3rd occurrence	Interrupt until resolved or improved to grade 1 If resumed, decrease dose (see Table 3)
	4th occurrence	Discontinue Sorafenib permanently
Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities of daily living	1st occurrence	Interrupt until resolved or improved to grade 1 If resumed, decrease dose by one dose level (see Table 3)
	2nd occurrence	Interrupt until resolved or improved to grade 1 When resumed, decrease dose by 2 dose levels (see Table 3)
	3rd occurrence	Discontinue Sorafenib permanently

Following improvement of Grade 2 or 3 dermatologic toxicity to Grade 0–1 after at least 28 days of treatment on a reduced dose of Sorafenib, the dose of Sorafenib may be increased one dose level from the reduced dose. Approximately 50% of patients requiring a dose reduction for dermatologic toxicity are expected to meet these criteria for resumption of the higher dose and roughly 50% of patients resuming the previous dose are expected to tolerate the higher dose (that is, maintain the higher dose level without recurrent Grade 2 or higher dermatologic toxicity).

Dose Reduction and Interruption Instructions for Cabozantinib

For Adverse Reactions:
Withhold Cabozantinib for treatment-related NCI CTCAE Grade 4 hematologic adverse reactions, Grade 3 or greater non-hematologic adverse reactions or intolerable Grade 2 adverse reactions.
Upon resolution/improvement of the adverse reaction (i.e., return to baseline or resolution to Grade 1), reduce the dose as follows:

Table 5. Recommended Doses for Patients with MTC Requiring Cabozantinib Dose Reduction

Dose Reduction	Sorafenib Dose
First Dose Reduction	100 mg daily dose (one 80-mg and one 20-mg capsule)
Second Dose Reduction	60 mg daily dose (three 20-mg capsules)
Third Dose Reduction	Resume at 60 mg if tolerated, otherwise, discontinue

Permanently discontinue Cabozantinib for any of the following:
- Development of visceral perforation or fistula formation
- Severe hemorrhage
- Serious arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction)
- Nephrotic syndrome
- Malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management
- Osteonecrosis of the jaw
- Reversible posterior leukoencephalopathy syndrome

In Patients Concurrently Taking a Strong CYP3A4 Inhibitor:
Reduce the daily Cabozantinib dose by 40 mg (for example, from 140 mg to 100 mg daily or from 100 mg to 60 mg daily). Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.

In Patients Concurrently Taking a Strong CYP3A4 Inducer:
Increase the daily Cabozanib dose by 40 mg (for example, from 140 mg to 180 mg daily or from 100 mg to 140 mg daily) as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. The daily dose of Cabozantinib should not exceed 180 mg

Dose Reduction and Interruption Instructions for Vandetanib

For treatment-related adverse reactions:
The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets) and then to 100 mg for Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or greater toxicities.
Interrupt Vandetanib for the following:
- Corrected QT interval, Fridericia (QTcF) greater than 500 ms: Resume at a reduced dose when the QTcF returns to less than 450 ms.
- CTCAE Grade 3 or greater toxicity: Resume at a reduced dose when the toxicity resolves or improves to CTCAE Grade 1.

For recurrent toxicities:
Reduce the dose of Vandetanib to 100 mg after resolution or improvement to CTCAE Grade 1 severity, if continued treatment is warranted.
Because of the 19-day half-life, adverse reactions including a prolonged QT interval may not resolve quickly. Monitor appropriately.

For patients with renal impairment:
Reduce the starting dose to 200 mg in patients with moderate (creatinine clearance ³30 to <50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment.

For patients with hepatic impairment:
Vandetanib is not recommended for use in patients with moderate and severe hepatic impairment.

6.1.9 DURATION OF THERAPY

TKIs therapy (Lenvatinib, Sorafenib, Cabozantinib or Vandetanib) will be maintained until radiological disease progression is confirmed or earlier due to toxicity (see section 6.1.8).

6.1.10 TRACKING OF DOSE

Records of treatment compliance for each subject will be kept during the study through a pill diary which will be checked by the treating physicians or APPs at each visit

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

6.2.1 Drug Accountability

Lenvatinib is purchased from Esai as a standard of care. Sorafenib is purchased from Bayer as a standard of care. Vandetinib is purchased from Sanofi Genzyme as standard of care. Cabozantinib is purchased from Exelixis as standard of care.

6.2.2 Treatment Compliance

Records of study medications used, dosages administered, and intervals between visits will be recorded by study personnel.

6.2.3 Biological sample accountability

Record of sample collection and processing will be kept in Moffitt Tissue Core Database and in the separate excel sheet. The database will include storage information in -80^{0}C freezer. The tumor, plasma and PBMC samples will be released or further processed upon separate instructions from the principal investigator.

7. STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY-SPECIFIC PROCEDURES

Study-specific procedures that are not part of standard clinical care include:

- Frequency of thyroglobulin and thyroglobulin antibodies monitoring.
- Tissue biopsy prior to the initiation of the TKI therapy, at 4 months and at 6 months.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

Standard of care procedures obtained during the study:

- Medical history.
- Medication history.
- Physical examination.
- Radiographic or other imaging assessments. State the specific imaging required and, as

appropriate, provide description of what is entailed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion may be described in a separate document such as a MOP or SOP.

- Laboratory evaluations (Table 6).
- Assessment of therapy adherence.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Table 6. Clinical laboratory tests

Category	Tests
Laboratory tests	CBC w/differential (hemoglobin, hematocrit, WBC with differential count, platelet count) CMP (Sodium, potassium, bicarbonate, chloride, BUN, creatinine, total bilirubin, ALT, AST). Magnesium INR (only as part of the screening assessment or if clinically indicated) Amylase, lipase
Pregnancy test	Serum or urine β-hCG (for women of childbearing potential)
Thyroid panel	TSH and free T4 Thyroglobulin and thyroglobulin antibodies (for DTC only) Calcitonin and CEA (for MTC only)
Urine tests	Urine dipstick

ALT= alanine aminotransferase, AST=aspartate aminotransferase, β-hCG = beta-human chorionic gonadotropin, BUN=blood urea nitrogen CBC=complete blood count, CMP=comprehensive metabolic panel, INR = International Normalized Ratio, TSH= thyroid stimulating hormone, T4 = thyroxine, WBC=white blood cells.

[redacted]

[redacted]

[redacted]

[redacted] be processed within 2 hours from collection.

[redacted]

[redacted]

[redacted]

[redacted]

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit (Day -28 to -0)
Before performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all subject candidates and written informed consent will be obtained. Once informed consent has been obtained (within 8 weeks of first dose of study drug), the following procedures and evaluations will be performed:

- Verify inclusion/exclusion criteria (See Sections 5.1-5.2)
- Record demographic data.
- Evaluate ECOG performance status (Appendix 2).
- Establish pTNM staging and diagnosis (Appendix 1).
- Record medical and surgical history.
- Obtain vital signs (systolic and diastolic BP, HR, RR, and body temperature), weight, and height. BP, HR, and RR will be obtained after subjects have been resting for 5 minutes. For subjects with an elevated BP (≥ 140/90 mmHg), confirmation should be obtained by performing 2 assessments 1 hour apart. Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg should be confirmed by repeat measurements after an hour.
- Perform a comprehensive physical examination (including a neurological evaluation).
- Collect blood samples for laboratory testing and thyroid panel and pregnancy test if indicated (See Table 6 for the tests to be performed).
- Collect urine sample for dipstick testing (See Table 6 for the tests to be performed).
- Collect urine sample for β-hCG pregnancy testing from all women of childbearing potential.
- Perform targeted radiologic imaging studies, CT/MRI of head/neck/chest/abdomen/pelvis and other areas of known disease at screening plus any areas of newly suspected disease.
- Record all prior and concomitant medication use (prescription and nonprescription medications as well as transfusions).
- Plan for obtaining tumor tissue.

The screening form must be completed for all subjects screened, providing reasons for screen failure when applicable.

7.3.2 ENROLLMENT/BASELINE

Enrollment/Baseline: Cycle 0 Day -2 to Cycle 1 Day 1 (cycles are considered to last 28 days)

The baseline assessment can be performed on Cycle 1 Day 1 (C1D1), prior to treatment.

Clinical and laboratory assessments are valid if obtained within 72 hours of baseline assessment.

- Obtain informed consent or verify previously obtained during screening signed informed consent form.
- Verify inclusion and exclusion criteria.
- Obtain laboratory tests; urinary dipstick; and thyroid panel.
- Confirm negative urine/serum pregnancy test.
- Obtain demographic information, medical history, medication and social history.
- Evaluate ECOG performance status.
- Obtain vital signs.
- Record all concomitant medication use.
- Perform a comprehensive physical examination.
- Establish new baseline tumor assessments (selection of target and non-target lesions) based upon scans taken (CT and/or MRI) that showed evidence of disease progression (unless performed within 4 weeks).
- Verify that study participant received Lenvatinib/Sorafenib/Cabozantinib/Vandetanib through special pharmacy.
- Educate about potential AEs and SAEs. Encourage early recognition and reporting.
- Obtain tumor tissue (should be done prior to initiation of therapy).

7.3.3 FOLLOW-UP

Follow-up Visits

Study participants will be seen weekly for the first cycle (Cycle 1 Days 8, 15 and 22), every two weeks for the second cycle (Cycle 2 Days 1, 15), every four weeks until cycle 12 (Day 1 of Cycles 3-12); and every 2 cycles thereafter until end of study (Day 1 of cycles 14, 16, 18, 20 and 24). However, when the patient is off the TKI with observation only in the adaptive arm, the patient needs to follow up every 28 days (+/- 7 days) for determination of starting a new cycle.

In each scheduled visit we will:

- Obtain vital signs.
- Record all concomitant medication use.
- Perform a comprehensive physical examination.
- Evaluate ECOG performance status.
- Obtain laboratory tests and urinary dipstick.
- Assess for AEs and SAEs.
- Assess compliance with the medication.
- Assess survival.

Thyroid panel evaluation

Thyroid panel will be assessed every 2 weeks during the first two cycles (Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, and Cycle 3 Day 1). If the tumor marker (thyroglobulin in DTC patients; calcitonin or CEA in MTC patients) drops by ≥50% from baseline (Cycle 1 Day 1) during the first two cycles (analysis of Cycle 3 Day 1 included), the patient will be randomized to receive either standard (continuous) or adaptive (intermittent) therapy. Patients randomized to

the standard therapy arm will then get Thyroid panel checked every 3 cycles (Day 1 of Cycle 6, 9, 12). Patients randomized to the adaptive therapy arm will get Thyroid panel checked every cycle (Day 1) during the first two years. After 24 months, patients in the adaptive therapy regimen who remain on TKI therapy will be given the choice to continue with the adaptive therapy regimen and monitoring of the thyroid panel in every cycle; or to convert to standard (continuous) regimen in which case thyroid panel evaluation will be checked every 3 cycles. In either case, all patients that continue to receive TKI therapy beyond 24 months will be treated off trial. Patients in which the tumor marker does not drop ≥50% within the first two months of TKI therapy will be managed by the standard of care.

Diagnostic imaging

Diagnostic imaging of affected and suspected sites (CT and/or MRI) will be done at Day 1 of cycles 3, 6, 9, 12, 16, 20, 24 in all patients. Diagnostic imaging will continue to be done every 4 months thereafter while the patient remains on TKI therapy or as clinically indicated otherwise.

7.3.4 FINAL STUDY VISIT

Final Study Visit

At the end of the study (at least 24 months after TKI initiation) the following data will be collected:

- Obtain vital signs.
- Record all concomitant medication use.
- Perform a comprehensive physical examination.
- Evaluate ECOG performance status.
- Obtain laboratory tests and urinary dipstick.
- Obtain thyroid panel (if not done within previous 3 weeks)
- Assess for AEs and SAEs.
- Assess compliance with the medication.
- Diagnostic imaging of affected and suspected sites (CT and/or MRI).
- Assess survival.

7.3.5 EARLY TERMINATION VISIT

An End of Treatment (EOT) visit will be performed for all subjects who do not complete the 24 month treatment period for any reason (e.g. disease progression, unacceptable toxicity, withdraw consent, etc.). At the end of treatment (30 days after last TKI dose, or any time within 30 days of being removed from treatment for patients in the adaptive therapy arm) the following data will be collected:

- Obtain vital signs.
- Record all concomitant medication use.
- Perform a comprehensive physical examination.
- Evaluate ECOG performance status.
- Obtain laboratory tests and urinary dipstick.
- Assess for AEs and SAEs.
- Assess compliance with the medication.

- Assess survival.

7.3.6 UNSCHEDULED VISIT

Unscheduled visits may be related but not limited to development of TKI toxicities. In that case the Grade of toxicity will be documented and the medication dose will be adjusted as per protocol (See section 6.1.8, and Appendix 3). All unscheduled visit will be documented in the patients chart.

7.3.7 SCHEDULE OF EVENTS TABLE

Table 8. Schedule of events

Phase	Screen	Experimental phase															
Cycle (28 days)[a]	0	1	1	1	1	2	2	3	4	5	6	9	12	16	20	24	EOT[n]
Day[b]	-28 to -0	1	8	15	22	1	15	1	1	1	1	1	1	1	1	1	30
Assessments																	
Informed consent[c]	X[d]	X[d]															
Inclusion/exclusion	X[d]	X[d]															
Randomization		When/if tumor marker drops ≥50% within first 2 cycles[m]															
Demographic data	X[d]	X[d]															
pTNM staging[e]	X[d]	X[d]															
Medical history	X[d]	X[d]															
ECOG[f]	X[d]	X[d]	X	X	X	X	X	X	Patients on conventional therapy:Q3 cycles (Day 1 of cycles 6, 9, 12, 15, 18, 21, 24) Patients in the adaptive therapy: On TKI: Every day 1 of each cycle for up to 12 cycles, Q2 cycles (Day 1 of cycles 14, 16, 18, 20, 22 and 24). Off TKI: Every day 1 of each cycle until resume TKI.							X
Vital signs[g]	X[d]	X[d]	X	X	X	X	X	X									X
Physical exam	X[d]	X[d]	X	X	X	X	X	X									X
Laboratory tests[h]	X[d]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine dipstick	X[d]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid panel[i]	X[d]	X[d]		X		X	X	X	Patients on conventional therapy: Q3 cycles (Day 1 of cycles 6, 9, 12, 15, 18, 21, 24) Patients in the adaptive therapy: Day 1 of each cycle								X
Pregnancy test[j]	X[d]	X[d]															
Imaging studies (CT/MRI)[k]	X[d]	X[d]						X			X	X	X	X	X	X	
Mandatory research blood collection	X							X			X	X	X			X	X
Tumor collection	Mandatory: - Archival Optional: - Fresh Tissue																Optional: - Fresh Tissue
Concomitant meds	X	Throughout															X
AEs/SAEs[l]		Throughout															X
Survival		Throughout															X

a: Patients in adaptive therapy arm will continue to follow the schedule with TKI withheld as long as their markers continue to be below 70% of the 'baseline' level. Upon resumption of TKI therapy the Cycle number will match that which would be expected based on duration on treatment (ie TKI therapy is omitted, not held).
b: Efforts should be made to conduct study visits on the day scheduled during the first month (± 3 days) and there after ± 5 days. Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures.
c: Informed consent may be taken up to 8 weeks prior to C1D1.
d: The baseline assessment can be performed on Cycle 1 Day (C1D1), prior to treatment. Clinical and laboratory assessments are valid if obtained within 72 hours of baseline assessment.
e: For pTNM Staging see Appendix 1
f: For ECOG assessments see Appendix 2.
g: Assessments will include vital signs (resting BP, HR, RR, and body temperature, weight, and height. Height will be measured at the Screening Visit only. Elevated BP (Systolic BP ≥ 140 mmHg and/or elevated Diastolic BP ≥ 90 mmHg) should be confirmed by 2 assessments 1 hour apart. If systolic BP is ≥ 160 mmHg or diastolic BP ≥100 mmHg, BP should be confirmed by repeat measurements after an hour.
h: Laboratory tests include: CBC w/differential, CMP, ALT, AST, magnesium, amylase, lipase, urine dipstick and if clinically indicated INR (see Table 6).
i: Thyroid panel includes: TSH, free T4, and for patients with DTC thyroglobulin and thyroglobulin antibodies; and for patients with MTC calcitonin and CEA (see Table 6). Thyroid panel results may be collected up to 7 days prior to the first dose on Cycle 1 Day 1. These lab tests should be performed while the patient is in a fasting state.
j: Serum or urine, in women of childbearing potential only.
k: Baseline imagine to include CT/MRI of head /neck/chest/abdomen/pelvis and other areas of known disease. On treatment imagine will include only areas of known disease plus any areas of newly suspected disease.
l: AEs/SAEs will be assessed during each visit clinically and based on laboratory data. Patients will be encouraged to report AEs/SAEs at the earliest recognition via the phone between the visits.
m: Includes the analysis on Cycle 3, day 1. Only a decrease in tumor markers that met inclusion criteria at baseline may be used for randomization purposes.
n: End of Treatment visit is to occur 30 days after the last dose of TKI therapy (or within 30 days of being removed from treatment in the case of adaptive therapy patients) ±7 days. The optional research biopsy may be taken up to 30 days after this visit as scheduling may require. If the subject is unable or unwilling to return to clinic this visit can be conducted via a telephone call.

7.4 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications, over-the-counter medications, and non-prescription medications taken during study participation will be recorded on the case report forms (CRFs). All additional local therapies for metastatic lesions (including, but not limited to EBRT, surgery, embolization, ethanol injections, etc.) will be recorded on CRFs.

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Due to its common use and interference with many thyroid hormone and biomarker assays including thyroglobulin, patients will not be allowed to take supplemental biotin in any form.

For patients treated with Lenvatinib, Sorafenib, Cabozantinib, or Vandetanib treatment, the following concomitant medications will not be permitted unless discussed with, and approved by the clinical instigators.
Lenvatinib: No medications are contraindicated.
- No dose adjustment of LENVIMA is recommended when co-administered with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors and CYP3A and P-gp inducers.

Sorafenib: Sorafenib in combination with carboplatin/paclitaxel is contraindicated in patients with squamous cell lung cancer. In combination with gemcitabine/cisplatin is not recommended in patients with squamous cell lung cancer
- Avoid concomitant use of strong CYP3A4 inducers (such as, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, St. John's wort), when possible, because these drugs can decrease the systemic exposure to Sorafenib.

Cabozantinib: No medications are contraindicated.
- Avoid taking a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) while taking Cabozantinib or reduce the dosage of Cabozantinib if concomitant use with strong CYP3A4 inhibitors cannot be avoided (see section 6.1.8).
- Avoid ingestion of foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 while taking Cabozantinib.
- Avoid chronic co-administration of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort) with Cabozantinib or increase the dosage of Cabozantinib if concomitant use with strong CYP3A4 inducers cannot be avoided.
- Concomitant administration of MRP2 inhibitors may increase the exposure to cabozantinib. Monitor patients for increased toxicity when MRP2 inhibitors (e.g., abacavir, adefovir, cidofovir, furosemide, lamivudine, nevirapine, ritonavir, probenecid, saquinavir, and tenofovir) are coadministered with Cabozantinib.

Vandetanib: No medications are contraindicated.
- Avoid administration of Vandetanib with anti-arrhythmic drugs (including but not limited to amiodarone, disopyramide, procainamide, sotalol, dofetilide) and other drugs that may prolong the QT interval (including but not limited to chloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, and pimozide).
- Avoid concomitant use of known strong CYP3A4 inducers during Vandetanib therapy. Avoid concomitant use of St. John's Wort because it can decrease Vandetanib exposure unpredictably.
- Use caution and closely monitor for toxicities when administering Vandetanib with drugs that are transported by OCT2 like metformin.
- Use caution and closely monitor for toxicities when administering CAPRELSA with digoxin

7.6 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Most common adverse events of Lenvatinib, Sorafenib, Cabozantinib, or Vandetanib therapy will be discussed in detail with the study participant on enrollment/baseline visit. Early recognition and early management of adverse events will be emphasized. The study participant will be provided with the information on the preventive strategies for most common adverse events of TKI therapy.

7.7 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Acute toxicities will be managed as described above in the "dose adjustments / modifications/ delays" section of this protocol.

7.8 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Lenvatinib and Sorafenib, and Cabozantinib and Vandetanib are FDA approved drugs for treatment of progressive metastatic RAI refractory differentiated thyroid cancer and medullary thyroid cancer, respectively. Study participant will receive the medication as per standard of care if indicated upon study closure.

8. ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Study participants will be monitored closely based on clinical, laboratory and imaging studies as outlined in study calendar (Table 8). Lenvatinib, Sorafenib, Cabozantinib and Vandetanib AEs and SAEs have been well described in literature (9-12). Patients will be educated and encouraged to report any AEs and SAEs promptly. Our primary endpoints include evaluation of safety and toxicity of adaptive TKI therapy and its comparison to conventional TKI therapy by measuring incidence of AEs and SAEs and time to its developments in adaptive and conventional therapy arms.

All AEs and SAEs will be graded according to CTCAE v5.0 (Appendix 3) and recorded in patient's charts and CRFs.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relation with this treatment.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is defined as any AE that results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is to be deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.
Patients may be hospitalized for administrative or social reasons during the study (e.g. long distance from home to site). These and other hospitalizations planned at the beginning of the study do not need to be reported as an SAE in case they have been reported at screening visit in the source data and have been performed as planned.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS

Unanticipated adverse therapy effect, any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence or any other unanticipated serious problem associated with the therapy that relates to the rights, safety, or welfare of subjects.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

All AEs will be graded using the CTCAE 5.0 criteria (Appendix 3).
For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Related – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
Not Related – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The study participants will be monitored closely throughout the study for occurrence of AE or SAE. The patients will be educated regarding most comment AEs and SAEs and will be encouraged to report promptly.

If AEs and SAEs occur, information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product, and time of resolution/stabilization of event. All AEs occurring during the study will be documented appropriately, regardless of relationship. All AEs will be followed to adequate resolution.
Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Unanticipated problems will be recorded in the data collection system throughout the study.

Events will be followed for outcome information until resolution or stabilization is achieved.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All AEs occurring prior to initiation of TKI therapy do not need to be reported.

All AEs occurring after first administration of TKI therapy (Lenvatinib, Sorafenib, Cabozantinib, or Vandetanib) and 30 days after last administration of TKIs will be considered as on treatment. All AEs will be collected and graded according to CTCAE v5.0 (Appendix 3), with the exception of Grade 1 laboratory abnormalities which will not be collected. All Grade 2 and above toxicities will be collected and documented by the investigator, but only Grade 3 toxicities deemed possibly, probably or definitely related to the study treatment will be reported on the appropriate CRFs/SAE reporting forms. Only SAEs will be reported to the PI. All AEs, including those persisting after end of study treatment must be followed up until they have resolved or have been sufficiently characterized or the principal investigator decides to not further pursue them.

Serious and non-serious AEs occurring later than 30 days after last administration of trial drugs will only be reported in case they are considered drug-related or trial (procedure) related.

Deaths (unless they are considered drug-related or trial related) will not be reported as SAE when they occur later than 30 days after last administration of the trial.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

All SAEs will be reported to the PI within 48 hours after identification and recorded in OncCore by the investigator. All deaths and immediately life-threatening events, whether related or unrelated to the study agent/procedure, will be recorded on the SAE Form and submitted to the PI within 24 hours of site awareness. All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the adherence to be stable.

8.4.3 UNANTICIPATED PROBLEM REPORTING

The study investigator will report to the PI unanticipated problems and it will be on the discretion of the PI whether to conduct an evaluation of an unanticipated problem and whether to report it to IRB.

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable.

8.4.5 REPORTING OF PREGNANCY

Pregnancy when diagnosed will be reported to the PI and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

8.5 SAFETY OVERSIGHT

Serious Adverse Events: Serious Adverse Events (SAEs) from this protocol will be reported concurrently to the IRB (per IRB reporting guidelines) and to the study sponsor via submission through The Online Collaborative Research Environment (OnCore).

Protocol Monitoring Committee (PMC):
The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

The data and safety plan will define criteria for stopping the trial according to rules set forth by this protocol. This trial will be continuously monitored by the PI and the research team and reviewed at weekly Head and neck-Endocrine Oncology Research Group meetings. Safety and monitoring reports will be submitted to the PMC after completing the first 2 cycles after the randomization of initial 5 patients in each arm or more frequently if requested by the PMC. A final safety and monitoring report including all 45 patients will be submitted to the PMC within three months of completing the study enrollment. This protocol will be subject to periodic internal audits based on risk or as recommended by the PMC.

9. CLINICAL MONITORING

Data will be captured in OnCore, Moffitt's electronic Clinical Trials Database. For each participant enrolled, the electronic CRF must be completed by the assigned data manager or other authorized study staff. Any paper forms should be typed or filled out indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those patients who fail to complete the study. If a patient stops dosing or terminates from the study, the dates and reasons must be noted on the CRF. If a patient terminates from the study because of toxicity, thorough efforts should be made to clearly document the outcome. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Protocol Monitoring Committee.

10. STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

This is a randomized phase II clinical trial with 2:1 randomization to adaptive therapy versus conventional therapy. The primary endpoint is time-to-discontinuation (TTD) of treatment, which is a "survival analysis"-type statistical comparison. We plan to enroll 24 patients on the adaptive therapy and 12 on the conventional therapy arm. Assuming uniform enrollment of patients for 2 years, with a minimum follow-up of 2 years, and a one-sided $\alpha = 0.20$, we will have 82% power to detect a hazard ratio of 0.50, assuming 12 and 24 month median TTD for the conventional and adaptive therapy groups. If the median TTD of the adaptive group is 20 months (HR=0.6), the power is 67%.

We anticipate that 20% of the patients will not have the ≥50% drop in tumor markers needed for study randomization arm of the study. Thus, we anticipate recruiting ~45 patients to have 36 patients for randomization.

The ~9 patients enrolled to the trial not candidates for the randomization will be given conventional therapy as standard of care. As an exploratory analysis, and realizing that the sample sizes are small, we will compare their PFS rates with the 12 patients from the randomized portion of the trial who receive conventional therapy using the log-rank test.

10.2 STATISTICAL HYPOTHESES

We hypothesize that we will prolong time to treatment discontinuation with the adaptive therapy regimen (**experimental group**) compared to the continuous therapy regimen **(control group**). Literature suggests that the median time to discontinuation with standard (continuous) therapy is 12 months. We hypothesize that the median time to discontinuation will increase to 24 months (Hazard ratio 0.50) with the adaptive therapy regimen. The power of the study to detect this difference is 82% for an alpha of 0.20.

10.3 DESCRIPTION OF STATISTICAL METHODS

10.3.1 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is the time-to-discontinuation of treatment.

- The measurement endpoint is the status of a patient 12 months following the start of TKI.
- This is a binary metric. 1 = the patients is still receiving TKI at 12 months; 0 = patient is no longer on TKI due to cancer progression and/or toxicity.
- The results will be described as % patients that remain on TKI at 12 months by experimental and control groups.
- The test statistic will a Fisher's Exact test on a two by two contingency table of patient counts based on all four combinations of whether a patient remains or does not remain on TKI (0 or 1) by treatment group (adaptive therapy or continuous therapy)
- We will begin by comparing the historical control patients with the control patients of the trial. If these two groups do not differ (using a Type I error rate of $p > 0.1$) then they shall be combined to provide the patient counts for the Fisher's Exact Test comparison of the control group to the experimental group of the trial.
- If the historical control patients differ from the control patients of the trial (using a Type I error rate of $p < 0.1$) then they will be compared separately to the experimental group using Fisher Exact test's with a Bonferroni adjusted Type I error rate of $p < 0.05$.

10.3.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

- To estimate overall response rate.

The response rate will be estimated using binomial theory with Wilson's method for the 95% confidence interval.

- To estimate progression-free survival.

The median progression-free survival rates will be estimated from the Kaplan-Meier curve with the 95% confidence interval obtained from Greenwood's formula.

- To estimate overall survival.

The median overall survival rates will be estimated from the Kaplan-Meier curve with the 95% confidence interval obtained from Greenwood's formula.

10.3.3 EXPLORATORY ANALYSES

- To determine a predictive biomarkers of TKI response

Exploratory analysis to assess the association of potential biomarkers with disease response will be made using logistic regression.

10.4 SAMPLE SIZE

The planned study is a randomized clinical trial, with 2:1 randomization to adaptive therapy versus conventional therapy. The primary endpoint is time-to-discontinuation (TTD) of treatment, which is a "survival analysis"-type statistical comparison. We plan to enroll 24 patients on the adaptive therapy and 12 on the conventional therapy arm. Assuming uniform enrollment of patients for 2 years, with a minimum follow-up of 2 years, and a one-sided α = 0.20, we will have 82% power to detect a hazard ratio of 0.50, assuming 12 and 24 month median TTD for the conventional and adaptive therapy groups. If the median TTD of the adaptive group is 20 months (HR=0.6), the power is 67%.

We anticipate that 20% of the patients will not have the ≥50% drop in tumor markers needed for study randomization arm of the study. Thus, we anticipate recruiting ~45 patients to have 36 patients for randomization.

Objective time-to-discontinuation criteria are described in Section 4.2.1. Patients may electively withdraw from treatment at any time and will be counted as a discontinuation event. All randomized patients will be included in the primary analysis. A sensitivity analysis will also be conducted, where the patients who choose to withdraw are considered as censored (non-events) at the time of withdrawal.

10.5 MEASURES TO MINIMIZE BIAS

10.5.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

In order to encourage enrollment of study participants, who may prefer the adaptive therapy arm, patients will be randomized 2:1 ratio to receive TKIs adaptive therapy vs TKIs conventional therapy. All randomized patients will be included in the primary analysis.

The randomization assignments will be made by the Moffitt Biostatistics Core and placed into a web-accessed SRAR system. Researchers consenting the patients will become unblinded upon treatment assignment. The use of variable block sizes makes it more difficult for consenters to guess the treatment randomization assignments in advance of the consent process. Blocking also helps ensure ongoing balance in treatment allocation.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Medical and research records for this trial including but not limited to, hospital records, clinical and office charts, laboratory notes, will be maintained in compliance with regulatory and MCC institutional requirements for the protection of confidentiality of participants.

Investigators of the study will have access to records.

12. QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigators will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research. The investigators agree to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

Information regarding study conduct and progress will be reported to the IRB per Moffitt institutional standards.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to initiation therapy with TKIs (Lenvatinib, Sorafenib, Cabozantinib, and Vandetanib) starting study product.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

An investigator will explain to each participant the nature of the study, its purpose, procedures involved, expected duration, and potential risks and benefits. All patients will be informed that participation in the study is voluntary and that they may withdraw from the study at any time, and that withdrawal of consent will not affect their subsequent medical treatment. This informed consent will be given by means of a standard written statement and will be submitted for IRB approval prior to use. No patient will enter the study before informed consent has been obtained. In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to the patient's medical information, which

includes all hospital records relevant to the study, including the patient's medical history.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

The study participant's contact information will be securely stored at Moffitt during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by Moffitt IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Moffitt. This will not include the participants' contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Moffitt.

All unpublished information that the Coordinating Center gives to the investigator shall be kept confidential and shall not be published or disclosed to.

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to a third party without the prior written consent of the PI (or her designee).

No data collected as part of this study will be utilized in any written work, including publications, without the written consent of the PI. All persons assisting in the performance of this study must be bound by the obligations of confidentiality.

13.5 FUTURE USE OF STORED SPECIMENS

Data collected for this study will be analyzed and stored at the OnCore research database. After the study is completed, the de-identified, archived data will be transmitted to and stored at OnCore under the supervision of the PI. With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the MCC. These samples could be used for future research.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

14. DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be collected by investigators/clinical stuff under supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study.

Clinical data (including AEs and concomitant medications) and clinical laboratory data will be entered into Power Chart, a CFR Part 11-compliant data capture system provided by the Cerner. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 STUDY RECORDS RETENTION

Following closure of the study, MCC will maintain a copy of all site study records in a safe and secure location for a minimum of 10 years after completion of the study.

14.3 PROTOCOL DEVIATIONS

The study protocol will be followed as written. If investigators identify any deviations from the protocol, they will report them in writing to the PI within 1 week or discuss it in the weekly Head and Neck Cancer Clinical Research Meetings. Any change to the protocol requires a written protocol amendment or administrative change will be submitted to IRB. This requirement should in no way prevent any immediate action from being taken by the investigators in the interest of preserving the safety of all subjects included in the study.

14.4 PUBLICATION AND DATA SHARING POLICY

Clinical trial will be registered at ClinicalTrials.gov.

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by primary investigator.

The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study shall be set out in the agreement between all investigators.

15. STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The Principal Investigator is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Taking responsibility for the overall conduct of the study and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE).
- Principal Investigator has the authority to stop the study.

16. CONFLICT OF INTEREST POLICY

None of the participating investigators have conflicts of interests related to the study.

New conflicts of interests developed during the clinical trial will be reported to the PI and

addressed accordingly to the institutional policies.

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APPENDIX

Appendix 1. Thyroid Cancer Tumor-Node-Metastasis Staging System (AJCC 8th edition starting January 2018)

The TNM System (tumor-node-metastasis) is the most widely used system for cancer staging in the world. Created by the American Joint Committee on Cancer (AJCC) (19), a distinguished group of experts from national healthcare organizations and major cancer centers around the country, the system defines cancer stage by describing:

Primary tumor (T)	
Papillary, follicular, poorly differentiated and Hurthle cell thyroid carcinoma	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤1 cm in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Tumor >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumor >4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size
NOTE: All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest tumor determines the classification).	
Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No evidence of locoregional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease.
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis

Appendix 3. Common Terminology Criteria for Adverse Events (v4.0).

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v5.0 published 27 Nov 2017) provides descriptive terminology to be used for adverse event reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE version 5.0 have been correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA®) terms.

CTCAE v5.0 grading refers to the severity of the AE. CTCAE grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Grade	CTCAE Status
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; ntervention not indicated.
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).[a]
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.[b]
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event.

a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v5.0. Available from https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix 4. RECIST criteria (version 1.1).

Tumor response assessments in this clinical trial will utilize Response Evaluation Criteria in Solid Tumors (RECIST 1.1) based on the 2009 article by Eisenhauer et al entitled, New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1) (21).

As required by RECIST 1.1, the protocol states that the minimum duration of stable disease is 7 weeks following the date of first dose of study drug.

Evaluation of target lesions	
Complete Response:	Disappearance of all target lesions
Partial Response :	At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum LD
Progressive Disease:	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease:	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started