Schema

Eligibility:

- Advanced RAIR DTC with BRAFV600E mutation
- Measurable disease by RECIST
- Documented radiographic PD (RECIST 1.1) over any time interval on or after first line multi kinase inhibitor
- Patients with 2 cm growth in single lesion within 3 months prior to randomization are excluded
- 1-2 prior multi kinase inhibitors, including lenvatinib and/or sorafenib
- ECOG Performance Status 0-2

Stratification Factors:

- Baseline tumor burden (sum of all target lesions) < or 4 cm.

RANDOMIZATION

Arm A:
Dabrafenib 150 mg PO BID

Trametinib 2 mg PO QD

Arm B:
Cabozantinib 60 mg PO QD

Treatment will continue until disease progression or intolerable toxicity.

Crossover is allowed at time of RECIST progression.

N=240
Randomization 1:1

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

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

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit, and require reporting to the IRB of record as non-compliance.

All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@ecog-acrin.org) or the Group's Regulatory Officer (EA.ExecOfficer@ecog-acrin.org).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have an ECOG Performance Status 0-2.

_____ 3.1.3 Patient must have differentiated thyroid cancer (DTC) with BRAF V600E mutation as determined by local testing, including the following subtypes (Note: results of a previous biopsy will be accepted):

- Papillary thyroid carcinoma including histological variants of PTC such as follicular variant, tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, poorly differentiated.
- Follicular thyroid carcinoma including histological variants of FTC such as Hürthle cell, clear cell, insular, and poorly differentiated.

_____ 3.1.4 Patient must have been previously treated with or deemed ineligible for treatment with Iodine-131 for DTC, and must be receiving thyroxine suppression therapy.

_____ 3.1.5 Patient must have had prior treatment with at least one of the following vascular endothelial growth factor receptors (VEGFR)-

targeting tyrosine kinase inhibitor (TKI) agents for DTC: lenvatinib or sorafenib.

NOTE: Up to two prior VEGFR-targeting TKI agents are allowed including, but not limited to lenvatinib and sorafenib.

_____ 3.1.6 Patient must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1·1 on chest CT (computed tomography) /abdominal/pelvis CT/MRI (magnetic resonance imaging) performed within 4 weeks prior to randomization.

_____ 3.1.7 Patient must have radiographic progression by RECIST 1.1 over any time interval on or after most recent prior systemic treatment.

_____ 3.1.8 Patient must not have any of the following cardiovascular and thromboembolic disorders or medical conditions:

- Congestive heart failure class 3 or 4 as defined by the New York Heart Association, unstable angina pectoris, or serious cardiac arrhythmias.
- Uncontrolled hypertension defined as sustained blood pressure > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.
- Stroke, myocardial infarction, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months prior to randomization. Patients with more recent diagnosis of deep venous thrombosis are allowed if stable and treated with therapeutic anticoagulation for at least 6 weeks prior to randomization.

_____ 3.1.9 Patient must not have any clinically significant hematemesis or haemoptysis of > 0·5 teaspoon (> 2·5 mL) of red blood or history of other significant bleeding within 3 months prior to randomization.

_____ 3.1.10 Patient must not have any cavitating pulmonary lesion(s) or lesions invading major pulmonary blood vessels.

_____ 3.1.11 Patient must not be on any concomitant anticoagulation with oral anticoagulants or platelet inhibitors, except for the following allowed agents:

- Low-dose aspirin for cardioprotection.
- Therapeutic anticoagulation with any agent in patients (1) without known brain metastases, (2) on a stable dose for at least 6 weeks prior to randomization, and (3) with no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

_____ 3.1.12 Patient must not have any gastrointestinal (GI) disorders associated with a high risk of perforation or fistula formation:

- Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.

- Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months prior to randomization.

_____ 3.1.13 Patient must have completed any prior local therapy (e.g., surgery, radiation, ablation) at least 4 weeks prior to randomization, with complete wound healing and resolution of clinically relevant complications from prior local therapy.

_____ 3.1.14 Patient must not have had major surgery (e.g., GI surgery, removal or biopsy of brain metastasis) within 8 weeks prior to randomization. Complete wound healing from major surgery must have occurred 4 weeks prior to randomization and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days prior to randomization.

_____ 3.1.15 Patient must not have any lesion(s) with ≥2cm growth within 3 months or ≥1.5cm growth within 2 months prior to randomization, and must not have documented anaplastic histology at or following cancer recurrence.

_____ 3.1.16 Patient must not have had prior treatment with cabozantinib or any prior BRAF targeted therapy for thyroid cancer.

_____ 3.1.17 Patient must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All patients of childbearing potential must have a blood test or urine study within 14 days prior to randomization to rule out pregnancy.

A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of child bearing potential? _____(Yes or No)

Date of blood test or urine study: _____

_____ 3.1.18 Patients must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in the study and for 2 weeks after the last dose of dabrafenib and 4 months after the last dose of trametinib or cabozantinib. Patients must also not breastfeed while on study treatment and for 2 weeks after the last dose of dabrafenib and for 4 months after the last dose of trametinib or cabozantinib.

NOTE: Patients of childbearing potential who are on hormonal contraceptives may be at risks because Dabrafenib may decrease the efficacy of hormonal contraceptives. An effective non-hormonal contraception should be used during therapy and for 2 weeks following discontinuation of

dabrafenib and at least 4 months following the last dose of trametinib and cabozantinib.

_____ 3.1.19 Patient must have the ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.

_____ 3.1.20 Patient must have adequate organ and marrow function as defined below (these labs must be obtained ≤ 28 days prior to protocol randomization):

_____ Hgb ≥ 8 g/dL

Hgb:_____Date of Test:_____

_____ Leukocytes ≥ 3,000/mcL

Leukocytes:_____Date of Test:_____

_____ Absolute neutrophil count (ANC) ≥ 1,500/mcL

ANC:_____Date of Test:_____

_____ Platelets ≥ 100,000/mcL

Platelets:_____Date of Test:_____

_____ Total Bilirubin ≤ 2.0 x institutional upper limit of normal (ULN)

Total Bilirubin:_____Institutional ULN:_____

Date of Test:_____

_____ AST(SGOT)/ALT(SGPT) ≤ 3.0 × institutional ULN or < 5.0 x ULN with the presence of hepatic metastasis

AST:_____Institutional ULN:_____

Date of Test:_____

ALT: _____Institutional ULN:_____

Hepatic metastases?_____(Yes or No)

_____ Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m²

eGFR_____Date of Test:_____

Urine protein/creatinine (UPC) ratio ≥1

Urine protein:_____Date of Test:_____

Urine protein/creatinine ratio:_____ Date of Test:_____

_____ 3.1.21 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of randomization are eligible for this trial.

_____ 3.1.22 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

_____ 3.1.23 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

_____ 3.1.24 Patients with treated brain metastases are eligible if follow-up brain imaging obtained after central nervous system (CNS)-directed therapy (radiotherapy and/or surgery) shows no evidence of progression. CNS disease must be stable for at least 4 weeks prior to randomization; patients must be neurologically asymptomatic and without corticosteroid treatment at time of randomization.

_____ 3.1.25 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

_____ 3.1.26 Patients must have corrected QT interval calculated by the Fridericia formula (QTcF) ≤ 500 ms obtained within 28 days prior to randomization.

NOTE: If a single electrocardiogram (ECG) shows a QTcF with an absolute value >500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these 3 consecutive results for QTcF will be used to determine eligibility.

_____ 3.1.27 Patient must be English or Spanish speaking to be eligible for the QOL component of the study.

NOTE: Sites cannot translate the associated QOL forms.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.