ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A091302

RANDOMIZED PHASE II STUDY OF SORAFENIB WITH OR WITHOUT EVEROLIMUS IN PATIENTS WITH RADIOACTIVE IODINE REFRACTORY HÜRTHLE CELL THYROID CANCER

Industry-supplied agent: Everolimus (NSC# 733504)
Commercial agent(s): Sorafenib
IND Exempt Study

ClinicalTrials.gov Identifier: NCT02143726

Study Chair
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Participating Organizations:
ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ ECOG-ACRIN Cancer Research Group
NRG / NRG Oncology
SWOG / SWOG

Study Resources:

Expedited Adverse Event Reporting
[redacted]

Medidata Rave® iMedidata portal
[redacted]

OPEN (Oncology Patient Enrollment Network)
[redacted]

Biospecimen Management System
[redacted]

Protocol Contacts:

A091302 Nursing Contact
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A091302 Pharmacy Contact
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Alliance Biorepository at Ohio State
[redacted]

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

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions at [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted]. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at [redacted]		

RANDOMIZED PHASE II STUDY OF SORAFENIB WITH OR WITHOUT EVEROLIMUS IN PATIENTS WITH RADIOACTIVE IODINE REFRACTORY HÜRTHLE CELL THYROID CANCER

Pre-Registration Eligibility Criteria (see Section 3.2)

Central pathology review submission (see § 3.2.1)

Registration Eligibility Criteria (see § 3.3)

Measurable disease as defined in Section 11.0.

RAI-refractory disease (see § 3.3.2)

Progressive disease defined by RECIST criteria ≤ 14 months as in Section 11.4

Metastatic disease or locally advanced unresectable disease

Prior treatment: radiation therapy ≥ 21 days of registration; RAI therapy ≥ 90 days of registration; Chemotherapy or targeted therapy ≥ 21 days of registration; any number of prior lines of therapy; No prior use of sorafenib or an mTOR inhibitor (see § 3.3.5)

Required Initial Laboratory Values

Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 mg/dL **OR**
Calc. Creatinine Clearance (see Alliance website)	≥ 30 mL/min
Total Bilirubin	≤ 1.5 x ULN
SGOT(AST)	≤ 2.5 x ULN
Fasting Serum Cholesterol	≤ 300 mg/dL
Fasting Triglyceride	≤ 2.5 x ULN

No history of major surgery ≤ 28 days of registration

No history of intracranial brain metastasis

No history of ≤ 6 months of registration: myocardial infarction or unstable angina; New York Heart Association grade III or greater congestive heart failure; cerebrovascular accident; grade 3 or 4 peripheral ischemia or thromboembolic event (see § 3.3.8)

No history of liver disease as in § 3.3.9

No history of gastrointestinal fistula or gastrointestinal perforation < 90 days of registration

No known history of prolonged QT syndrome

No Grade 3 or 4 hypertension that cannot be controlled with medication prior to registration (see § 3.3.12)

Concomitant medications: No chronic concomitant treatment with strong inhibitors of CYP3A4; No chronic concomitant treatment with strong CYP3A4 inducers; Patients requiring anticoagulation must be on stable dose of medication prior to registration (see § 3.3.13)

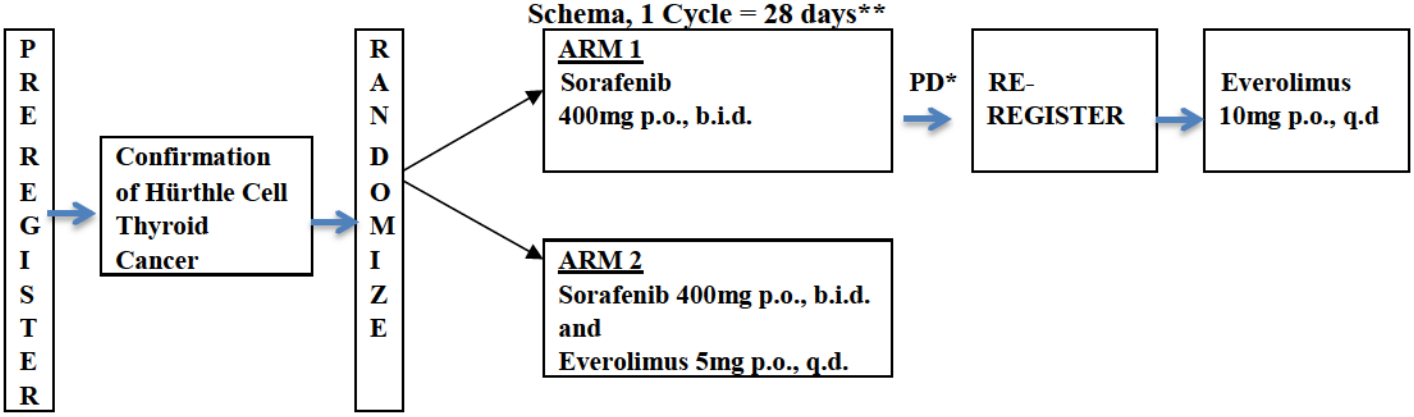
Not pregnant and not nursing (see § 3.3.14)

Age ≥ 18 years

ECOG Performance Status ≤ 2

Eligible patients must have histopathologically confirmed Hürthle cell thyroid cancer by central review

Schema, 1 Cycle = 28 days**



*PD= Progression of Disease

** 28-day cycle for 12 cycles (1 year). Starting with cycle 13, the cycle length will be 56 days.

Treatment is to continue until disease progression or unacceptable adverse event.

Patients will be followed for five years or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Table of Contents

1.0 INTRODUCTION

Thyroid cancers of follicular origin consist of several histologic subtypes with diverse genetic and biologic features that directly influence clinical behavior and response to systematic therapies. Papillary thyroid cancer (PTC), representing 80% of all thyroid cancers, follicular thyroid cancer, and Hürthle cell thyroid cancer make up a group of malignancies known as differentiated thyroid cancer (DTC). DTCs can progress to more aggressive forms of disease categorized pathologically as poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC), a rapidly progressive and fatal disease with less than one year survival in most cases. Medullary thyroid cancers are not derived from follicular cells, but instead the parafollicular C-cells. Hence, medullary thyroid cancer is considered to be different than DTC.

The incidence of new thyroid cancers is the fastest growing among all cancers for both men and women with an estimated 44,670 new cases anticipated for 2010[1]. 10-20% of thyroid patients develop distant metastasis[2,3]. Surgical resection of recurrent and/or metastatic tumors, administration of radioactive iodine (RAI), and treatment with external beam irradiation are palliative therapeutic options for a subset of patients. Once tumors lose the ability to accumulate RAI and are not amenable to locoregional treatments, therapeutic options are quite limited as traditional chemotherapeutic agents are relatively ineffective[4]. Doxorubicin is the only Food and Drug Administration (FDA) approved drug for the treatment of RAI-refractory thyroid cancer based on limited clinical data generated from the 1980s.

Treatment options for patients with recurrent and/or metastatic thyroid carcinoma not amenable to curative surgery or radioactive iodine (RAI) are limited; no effective systemic therapy currently exists. Doxorubicin is the only FDA-approved agent for the treatment of RAI-refractory thyroid cancer, and its efficacy is questionable.

The discovery of exciting insights into the biology of thyroid cancer, including the existence of tumor initiating genetic mutations, has greatly informed the conduct and interpretation of clinical investigations evaluating molecularly targeted therapies for thyroid cancer. The mitogen activated protein kinase (MAPK) signaling pathway is frequently activated in human malignancies. MAPK activation in cancer can result from alterations in upstream regulators such as receptor tyrosine kinases (RTKs), the RAS oncogene, and the RAF serine/threonine kinase. Signaling through these components leads to activation of the MAPK kinase MEK and subsequently the MAPK ERK. 70% of all PTC possess mutually exclusive genetic alterations in the upstream activators of MAPK, including the RTKs *RET* (*RE*arranged during *T*ransfection) and *NTRK* (neurotrophic tyrosine kinase receptor) as well as the signaling molecules *RAS* and *BRAF*[8]. However, there is no evidence that over activation of the MAPK pathway plays a significant role in Hürthle cell thyroid cancer.

Thyroid malignancies are highly vascular tumors. Studies examining the relationship between microvessel density and clinical outcomes have demonstrated that hypervascular tumors correspond to worse disease free survival relative to less vascularized tumors[9,10] . Vascular endothelial growth factor (VEGF) has been identified as a critical activator of angiogenesis in the tumor microenvironment via stimulation of tumor associated endothelial cell growth and survival. Several isoforms of VEGF have been discovered (VEGF-A, B, C, D) as well as several different VEGF specific transmembrane receptor tyrosine kinases (Flt-1, KDR/Flk-1, Flt-4). Multiple studies have reported higher VEGF expression in primary thyroid cancer specimens[11-15] relative to normal thyroid tissue. Both normal and malignant thyroid cells can secrete VEGF into cell culture medium[14,16], and serum VEGF levels are elevated in patients with recurrent or metastatic well differentiated thyroid cancers relative to normal patient controls[17,18]. Higher VEGF expression has been correlated to larger tumor size[11], higher tumorigenic potential[15], metastatic disease[19], and shorter recurrence free survival[20]. Furthermore, overexpression of VEGF in poorly tumorigenic cell lines can enhance tumor formation in nude mice via increased tumor vascularity, while suppression of VEGF expression via an antisense strategy decreased tumorigenic potential in an oncogenically aggressive tumor cell line[21].

Taken together, these data suggest that the high levels of VEGF observed in patients and tumors may be a biologically relevant contributor to oncogenic progression in thyroid cancer.

Consistent with data suggesting a reliance upon VEGF activation for the tumorigenic phenotype, antibodies[17,22,23] and small molecules[24,25] targeting VEGF signaling reduce thyroid tumor cell line growth in xenograft models. In addition to blocking VEGF induced endothelial cell mitogenesis, the antitumor effects of these strategies may also be related to a direct impact upon thyroid cancer cells, which also express VEGF receptors FLT-1 and KDR/FLK-1[26,27]. These data support the clinical hypothesis that VEGF targeted agents may be effective in this disease and most recent clinical studies have focused on this target.

Over the past decade, there have been multiple phase II studies with various targeted therapies such as sorafenib[28,29], axitinib[30], sunitinib[31,32], and pazopanib[33]. All of these agents have shown some activity in the treatment of RAI-refractory thyroid cancer. All of these study have included all subtypes of DTC, and several have reported the results for follicular and Hürthle cell thyroid cancers as a single group instead of separate entities. However, recent work at Memorial Sloan-Kettering Cancer Center (MSKCC) evaluating the genomics of Hürthle cell thyroid cancer has suggested that it is a completely separate entity[34].

While the studies of these targeted therapies were all in "radioactive iodine refractory" thyroid cancer, they likely represent a heterogenous population. Most early studies were inconsistent in either their definition of what makes a thyroid cancer refractory to radioactive iodine or what type of progression, if any, would be required for study entry. The earliest study with axitinib had a response rate of 30% with a median progression-free survival of 18.1 months[30]. Pazopanib was reported to have a response rate of 49% with a median progression-free survival of 11.7 months[33].

1.1 Sorafenib

Sorafenib has been the best studied agent in this disease. Sorafenib is an oral receptor kinase inhibitor that has multiple targets include RAF, VEGFR1-3, and platelet-derived growth factor receptor-β[35]. Partial response rates have been reported to be between 11.5%[29] and 23%[28]. At this point in time, sorafenib is the recommend treatment for RAI-refractory thyroid cancer by the National Comprehensive Cancer Network guidelines [redacted] and is compendium approved for this indication. A phase III study comparing sorafenib to placebo (the DECISION trial) has been completed and it has been announced that it met its primary objective with an improvement in progression-free survival of 5 months compared to placebo. In addition, it showed that sorafenib had a partial response rate of only 12.2% with a disease control rate (complete/partial response or stable disease rate for $\geq$ 6 months) of 54.1% compared to 33.8% for placebo. It is notable that 18.8% of patients who received sorafenib discontinued due to adverse events[40]. In addition, 77% of the patients on the sorafenib arm required a dose modification due to an adverse event, although 30.1% in the placebo arm required the same.

Despite the activity seen with sorafenib in thyroid cancer and other types of cancers, it is not clear which of the molecular targets are responsible for the anticancer effects in each tumor model. Furthermore, both phase II studies with sorafenib included subjects with all thyroid cancer cell types (i.e., papillary, follicular, Hürthle, and poorly differentiated/anaplastic).

Due to this data, National Comprehensive Cancer Network (NCCN) guidelines for the treatment of thyroid cancer specifically states that sorafenib is an acceptable treatment for RAI-refractory thyroid cancer (compendium approved) and is currently the standard of care. The FDA has granted sorafenib priority review for the treatment of RAI-refractory thyroid cancer.

1.2 Everolimus

Everolimus is an orally available inhibitor of the mammalian target of rapamycin (mTOR). Everolimus is a macrolide derivative of rapamycin, a natural compound produced by bacteria.

Everolimus has been formulated for oral administration, and is being developed as an anticancer agent and an immunosuppressant. Everolimus selectively inhibits mTOR, an evolutionarily-conserved intracellular serine/threonine kinase implicated in the control of protein translation[1,2].

Everolimus binds the intracellular 12-kilodalton immunophilin FK506-binding protein (FKBP12) with high affinity; the resulting FKBP12/everolimus complex then inhibits mTOR kinase activity. Phosphatidylinositol 3-kinase (PI3-K) and Akt are well described upstream regulators of mTOR activity, although other mechanisms of mTOR activation have been described. Two well-characterized phosphorylation targets of mTOR are eIF4E-binding protein (4E-BP1) and p70 S6 kinase 1 (S6K1), which regulate translation of proteins required for G1-S phase progression in the cell cycle. TOR inhibitors such as everolimus usually are cytostatic when administered alone, although anti-proliferative and pro-apoptotic effects also have been described[1,2].

At weekly and daily schedules and at various doses explored, everolimus is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with everolimus therapy are manageable. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible.

The initial rationale to evaluating everolimus, an mTOR inhibitor, in thyroid cancer is the belief that in thyroid cells, mTORC1 activity is required for the proliferative effects of TSH in vitro and in vivo. Unpublished work from the Fagin lab at Memorial Sloan-Kettering Cancer Center shows that mTORC1 is also required for the growth promoting effects of the oncoproteins RET/PTC, RAS and BRAF in rat thyroid PCCL3 cells. Rapamycin is the prototypical mTORC1 inhibitor, as it interferes with the association between mTOR and Raptor. Rapamycin has significant growth inhibitory effects in human cell lines harboring endogenous mutations of these oncoproteins. Furthermore, Cowden's syndrome, which is caused by germline mutations in *PTEN*, is associated with a 10% lifetime risk of developing thyroid cancer. The wild-type allele is often inactivated through epigenetic events later in tumor progression. In addition, PTEN deficiency in mouse models is associated with follicular thyroid cancer aggressiveness[36].

1.3 Combination of sorafenib and temsirolimus/everolimus in cancers other than thyroid cancer

Preclinical evidence suggests synergy when both the MAPK and PI3K-mTOR pathways are inhibited[3]. The combination of sorafenib with mTORC1 inhibitors increases cell death in melanomas, where *BRAF* mutations are particularly common[4], and the combination of sorafenib and temsirolimus was evaluated in the treatment of melanoma in a large randomized phase II study through the Southwest Oncology Group[44] and evaluated in the treatment of kidney cancer (by the Eastern Cooperative Oncology Group). It is currently being evaluated in the treatment of glioblastoma multiforme (North Central Cancer Treatment Group). In the phase I study evaluating sorafenib and temsirolimus (another mTOR inhibitor)[5], a partial response was seen in a subject with papillary thyroid cancer. The combination of sorafenib and everolimus has been evaluated in a phase I study for kidney cancer, with the recommended dose of sorafenib 400 mg twice a day with everolimus 5 mg daily[6]. In the phase I study, treatment-related events that occurred greater than 20% of the time included diarrhea, hand-foot syndrome, hypertension, hypophosphatemia, hypothyroidism, and rash. Pharmacokinetic data suggested that everolimus had no effects on sorafenib blood levels. The most common grade 3 toxicity was hypophosphatemia (45%) as well as grade 3 diarrhea (10%). At the MTD, 75% of patients eventually required dose reduction (although this percentage is similar to what is seen with sorafenib alone in the DECISION study).

1.4 Hürthle cell thyroid cancer

Hürthle cell thyroid cancers in general have not been as well studied as other cell types. Evaluation of the SEER database confirms that cancer-specific survival is worse in this subgroup compared to other thyroid cancers[5]. It accounts for about 4% of all thyroid cancers. Characteristically, they are large cells with hyperchromatic nuclei and an abundant granular cytoplasm containing large numbers of mitochondria.

In general, Hürthle cell thyroid cancers usually present with worse prognostic features (older age, larger primary tumors) than other DTC's[6]. Compared to other differentiated thyroid tumors, Hürthle cell thyroid cancers tend to be less responsive to RAI and more typically have distant metastases and a worse survival[7]. Hürthle cell thyroid cancer have often been considered a variant of follicular thyroid cancer, but an extensive analysis of mutations in DTC at Memorial Sloan-Kettering Cancer Center have suggested that Hürthle cell thyroid cancer is a very separate entity[42]. A total of 27 cases with either Hürthle cell adenoma, minimally invasive Hürthle cell thyroid cancer or widely invasive Hürthle cell thyroid cancer were evaluated for somatic mutations. Oncomine analysis of the genes in the widely invasive group showed that B-catenin is intimately involved in the process as well as the presence of a temsirolimus-sensitive signature (genes related to mTOR inhibition sensitivity).

While studies of DTC may include Hürthle cell thyroid cancers, to date there does not seem to be a single study that specifically includes only Hürthle cell subtype. Notably, in the Ohio State phase II study with sorafenib for RAI-refractory thyroid cancer, all of the responses were in the papillary subgroup with no partial responses in the follicular/Hürthle cell subgroups. Furthermore, the median progression-free survival in this latter group was only 4.5 months (compared to 16 months in the treatment-naïve papillary thyroid cancer subgroup)[29].

1.5 Clinical experience of sorafenib and everolimus in RAI-refractory thyroid cancer

We have recently completed a phase II study evaluating the efficacy of sorafenib and everolimus in RAI-refractory thyroid cancer. The phase II study used the recommended dose of sorafenib 400 mg twice a day with everolimus 5 mg daily[37]. In the phase II study of thyroid cancer at Memorial Sloan-Kettering Cancer Center, a total of 41 patients were enrolled onto the study of which 36 are currently eligible for evaluation of the primary endpoint of response. Data updated in September of 2013 (unpublished) now shows nine of these patients had Hürthle cell RAI-refractory thyroid cancer. Of these 9 patients, 7 (78%) had either a confirmed or unconfirmed partial response and 2 had stable disease (both patients with stable disease have remained on study for greater than 1 year). Only 2 of the 9 patients came off study in less than a year (one for progression of disease and one for protocol-defined toxicity). As of September 2013, the median time on study has been 500 days (ranging from 76 to 791 days). Both the response rate and the time on study are impressively higher than reported in the Ohio State study (i.e., 0% partial response rate; median progression free survival of 4.5 months). The reason for this increase in response with the addition of everolimus to sorafenib in the Hürthle Cell subgroup has yet to be elucidated, and further investigations are ongoing at Memorial Sloan-Kettering Cancer Center.

Based on these impressive results in a single arm phase II study, along with the lack of proven efficacious agents for the treatment of Hürthle cell RAI-refractory thyroid cancer, we have decided to proceed with a randomized phase II study in this uncommon cancer.

2.0 OBJECTIVES

2.1 Primary objective

To compare the progression-free survival (PFS) between sorafenib and everolimus vs. sorafenib alone in patients with radioactive iodine refractory Hürthle cell thyroid cancer

2.2 Secondary objective

To compare the confirmed response rate, overall survival (OS), and adverse event rates between sorafenib and everolimus vs. sorafenib alone.

3.0 PATIENT SELECTION

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

3.1 On-Study Guidelines

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

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

Listed below are examples only, and should be modified by the study chair as necessary. NOTE that these guidelines are phrased in the negative; i.e., these are potential participants who should <u>not</u> be enrolled to the study.

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for $\geq$ 3 years.
- Patients who cannot swallow oral formulations of the agent(s).
- Moderate CYP 3A4 inhibitors, moderate PgP inhibitors, and drugs that are metabolized/eliminated by UGT1A1 pathway are to be used with caution while on study.

In addition:

- Women of child-bearing potential (WOCBP). Defined as all women physiologically capable of becoming pregnant, and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Highly effective contraception methods include a combination of any two of the following (a+b, a+c, or b+c). Other appropriate methods of birth control are d or e:

  a. Use of oral, injected or implanted hormonal methods of contraception or;

  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);

c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository;

d. Total abstinence or;

e. Male/female sterilization.

3.2 Pre-Registration Eligibility Criteria

Pre-registration procedures are found in Section 4.1.

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

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

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

___ **3.2.1 Central pathology review submission**

Patients must have 10 representative H&E stained thyroid tissue slides OR tumor block available for submission to central pathology review. This review is mandatory prior to registration to confirm eligibility. If 10 H&E slides are not available, 5 H&E slides will be acceptable with the consent of the PI (Dr. Sherman) although an additional 5 slides may still need to be requested if the central pathologist requires it after reviewing the slides. See Section 4.4 for details on slide/block submission.

3.3 Registration Eligibility Criteria

___ **3.3.1 Measurable disease** as defined in Section 11.0.

Patients must have measurable disease by RECIST criteria, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan; CT must be performed within 28 days of registration.

___ **3.3.2 RAI-refractory disease defined as 1 or more of the following:**

- Patients who have received greater than 600 mCi of radioactive iodine in their lifetime **OR**
- RAI-avid metastatic lesion which remained stable in size or progressed despite RAI treatment within 9 months of RAI treatment **OR**
- 10% or more increase in serum thyroglobulin (on TSH-suppression) within 9 months of RAI treatment **OR**
- Index metastatic lesion non-RAI avid on a diagnostic RAI scan **OR**
- Presence of FDG avid metastatic lesions on PET/CT scan (SUVmax > 5 of any single lesion)

___ **3.3.3 Progressive disease** defined by RECIST criteria ≤ 14 months (as in Section 11.4).

___ **3.3.4 Patients must have metastatic disease or locally advanced unresectable disease.**

___ **3.3.5 Prior Treatment**

- Patients may have received prior radiation therapy to index lesions ≥ 21days prior to registration on this protocol if there has been documented progression by RECIST criteria. Prior radiation therapy to the non-index lesions is allowed if ≥ 21 days prior to registration on this protocol.
- Prior RAI therapy is allowed if ≥ 90 days prior to registration on this protocol and evidence of progression (as defined above) has been documented in the interim (a diagnostic study using <10 mCi of RAI is not considered RAI therapy).
- Prior chemotherapy or targeted therapy is allowed if ≥ 21days prior to registration on this protocol.
- Patient may have received any number of prior lines of therapy.
- No prior use of sorafenib or an mTOR (including PI3k or AKT) inhibitor for the treatment of thyroid cancer.

___ **3.3.6 No history of major surgery** ≤ 28 days of registration.

___ **3.3.7 No history of intracranial brain metastasis.**

___ **3.3.8 Cardiovascular disease**: **No history of any of the following ≤ 6 months of registration:**

- Myocardial infarction or unstable angina
- New York Heart Association grade III or greater congestive heart failure
- Cerebrovascular accident
- Grade 3 or 4 peripheral ischemia.
- Grade 3 or 4 thromboembolic event

___ **3.3.9 Liver disease: No history of the following**:

- Child Pugh Class B or C liver disease
- "Chronic active" hepatitis defined as:
  1. HBsAg is positive > 6 months
  2. Serum HBV DNA 20,000 IU/ml (105copies/ml), lower values 2,000-20,000 IU/ml (104-105 copies/ml) are often seen in HBeAg-negative chronic hepatitis B
  3. Persistent or intermittent elevation in ALT/AST levels
  4. Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation

___ **3.3.10 No history of gastrointestinal fistula or gastrointestinal perforation** < 90 days of registration.

___ **3.3.11 No known history of prolonged QT syndrome**.

___ **3.3.12 No Grade 3 or 4 hypertension** (systolic BP>160 and/or diastolic BP> 100) that cannot be controlled with medication prior to registration.

___ **3.3.13 Concomitant Medications:**

- **Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study.** Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study. See section 7.1 for more information.
- **Chronic concomitant treatment with strong CYP3A4 inducers is not allowed.** Patients must discontinue the drug 14 days prior to the start of study treatment. See section 7.2 for more information.
- **Patients requiring anticoagulation** must be on stable dose of medication prior to registration.

___ **3.3.14 Not pregnant and not nursing,** because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative serum pregnancy test done ≤ 7 days prior to registration is required.

___ **3.3.15 Age ≥ 18 years**

___ **3.3.16 ECOG Performance Status ≤ 2.**

___ **3.3.17 Documentation of Disease:**

Histologic Documentation: Eligible patients must have histopathologically confirmed Hürthle cell thyroid cancer by central review.

___ **3.3.18 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 mg/dL **OR**
Calc. Creatinine Clearance	≥ 30 mL/min
Total Bilirubin	≤ 1.5 x upper limits of normal (ULN)
SGOT (AST)	≤ 2.5 x upper ULN
Fasting Serum Cholesterol	≤ 300 mg/dL
Fasting Triglyceride	≤ 2.5 x ULN

4.0 PATIENT REGISTRATION

4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;

- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

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

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

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at [redacted] For questions, please contact the RCR Help Desk by email at [redacted]

4.2 CTSU Registration Procedures

This study is supported by the NCI CTSU.

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be

accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling [redacted].

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on Protocols in the upper left of your screen
- Enter the protocol number in the search field at the top of the protocol tree, or

- Click on the By Lead Organization folder to expand, then select Alliance, and protocol number A091302;
- Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

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

Checking Your Site's Registration Status:

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

- Log on to the CTSU members' website;
- Click on Regulatory at the top of your screen;
- Click on Site Registration;
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Enrollment

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

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

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

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

4.4 A091302 Pre-registration and Registration Requirements

4.4.1 Pre-registration requirements

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Pre-Registration eligibility criteria**: Patients who meet the pre-registration eligibility criteria will be pre-registered. After the patient has been pre-registered, 10 H&E stained slides OR tumor block from diagnostic biopsy should be sent to the Alliance Biorepository at Ohio State, per Section 6.2. Once the site receives confirmation from the Alliance and the registration criteria have been met the patient can be registered.

4.4.2 Registration requirements

- **Registration Procedures:** The Alliance will notify the pre-registering site, within 5 business days of receipt, whether or not the patient is eligible based on the central pathology review. Patients will then be registered using the OPEN system (registration will occur within 14 days of slide submission). The CRA should enter the ID number obtained at pre-registration into the OPEN system to register the patients. The OPEN system will provide the institution with a printable confirmation of registration. Please print this confirmation for your records.
- Follow the OPEN enrollment procedures as detailed in Section 4.3.

4.5 Re-Registration at Crossover

- Upon confirmation of progression, by the treating investigator, patients who were initially assigned to sorafenib alone will be allowed to cross over to everolimus at 10 mg q.d.
- Follow the OPEN enrollment procedures as detailed in Section 4.3.

4.6 Stratification Factors and Treatment Assignments

This phase 2 randomized study will compare the combination of sorafenib and everolimus vs. sorafenib alone in patients with radioactive iodine refractory Hürthle cell thyroid cancer. A 1:1 randomization will be used, where the Pocock-Simon algorithm[38] will be used to balance the arms with respect to important stratification factors of interest. For this study, the following stratification factors will be used:

- ECOG Performance Status: 0 vs. 1 vs. 2
- Prior systemic treatment for Hürthle thyroid cancer (not including RAI): Yes vs. No

5.0 STUDY CALENDAR

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

Pre-Study Testing Intervals

- To be completed ≤ 16 DAYS before registration: All laboratory studies, history and physical.
- To be completed ≤ 28 DAYS before registration: Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol.

	Prior to Registration	Day 1 and 15 of Cycles 1 and 2*	Day 1 of each cycle starting with Cycle 3** and after Crossover	Post-Treatment Follow-up***	Survival and Disease Status Follow-up Ψ
Tests and Observations					
History and Physical Exam	X	X	X	X	
Adverse Event Assessment	X	X	E	X	
Blood Pressure	X	X	X		
Weight	X	X	X		
Performance status	X	X	X	X	
EKG (as indicated)	X				
Fatigue/Uniscale Assessment	X				
Laboratory Studies					
Triglycerides, cholesterol π	X		X	X	
CBC w/diff, plts	X	X	X	X	
Serum comprehensive Σ	X	X	X	X	
Serologic Hepatitis B Surface Ag and Hepatitis C RNA (physician discretion, not required)	X				
Serum B-HCG	A		A		
Thyroglobulin, Serum	X		B		
Thyrotropin (Thyroid Stimulating Hormone or TSH), Serum	X		C		
Staging					
CT/MRI Tumor measurements	X		D		X

* All evaluations during the first and second cycle may be scheduled for +/- 3 days of the scheduled day.

** Patient may have all evaluations for day +/- 7 days to starting treatment. For the first 2 cycles, evaluation schedule is every 2 weeks (+/- 3 days). Then for 10 cycles, evaluation schedule is every 4 weeks (+/- 7 days). After 12 cycles (48 weeks), evaluation frequency is every 8 weeks (+/- 7 days).

*** Post treatment follow-up between 2-6 weeks after study treatment termination.

A Serum beta human chorionic gonadotropin pregnancy test (in women of childbearing potential) **only** ≤ 7 days before registration and, after crossover, ≤ 7 days prior to starting treatment with everolimus only.

B Serum Thyroglobulin does not need to be drawn if clinically not indicated (e.g., the presence of serum anti-thyroglobulin antibodies) after the baseline is done. Serum Thyroglobulin suggested at cycle 3 (+/- 7 days) and then every 4 cycles (or 16 weeks +/- 8 weeks) from the last time it was drawn.

C Thyrotropin (Thyroid Stimulating Hormone or TSH), Serum every 2 cycles (or every 8 weeks, +/- 2 weeks).

D Every 2 cycles (or every 8 weeks, +/- 2 weeks) for the first 12 cycles. Every 2 cycles (or every 16 weeks, +/- 2 weeks) thereafter. This must include the minimum of the neck and chest CT scan at baseline, although an abdominal and pelvic CT scan are strongly recommended at baseline. Intravenous contrast should be given unless there is indication to omit; as documented by the treating physician. A MRI of the neck may be substituted for a CT of the neck. Documentation (radiologic and pathology report) of the diagnosis scan must be submitted. A PET/CT can be substituted if the index lesions can be measured appropriately per RECIST 1.1.

E Adverse events should be collected Day 1 of every cycle beginning with cycle 3 until year 1. After 12 cycles (1 year) adverse events can be collected every other cycle.

∑ Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium, bilirubin.

π All patients will have baseline lipid profile. Also, if it has been more than 3 months since the last lipid profile, it must be repeated at crossover. It is strongly recommended these patients have a lipid profile after 2 cycles, then every 4 cycles while on everolimus.

Ψ For patients who have come off of treatment for progression, no further scans are needed. For patients who have come off treatment for any other reason, disease status information (i.e. progression status) will be collected every 3 months (+/- 1 month) until progression. It may be done more frequently as per the investigator. It no longer needs to be done if a patient begins other systemic treatment for the thyroid cancer. Documentation (radiologic) must be provided at progression of disease. In addition, survival and disease status information is required approximately every 6 months until 5 years after registration. This does not require that the subject be seen and/or examined. For example, follow-up may be done through a telephone call to the subject or his treating physician.

6.0 DATA AND SPECIMEN SUBMISSION

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to [redacted] for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login [redacted] using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

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

6.1 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.2 Specimen collection and submission

For all patients pre-registered to Alliance A091302: Real-time histopathology review will be conducted using the thyroid tissue from the diagnostic biopsies.

	≤ 3 days from pre-registration	**Submit to:**
Mandatory for all patients registered to A091302:		
10 Representative H&E stained slides OR tumor block	X	Alliance Biorepository at Ohio State

6.2.1 Specimen submission using the Alliance Biospecimen Management System

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

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

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

Shipment of samples

- All samples should be labeled with institutional surgical pathology number (tumor samples), study number, patient ID number patient initials, sample collection date and time and be accompanied by the completed specimen submission shipping manifest which will be generated by BioMS.

  Note for CRA – The following PHI must be removed or blacked out for all specimens or reports: signature, name, date of birth, other identifying information, except initials and study identification number.

- All samples should be shipped to the Alliance Biorepository at Ohio State.

- Specimens may be sent to the Alliance Biorepository at Ohio State on Monday through Thursday for next day delivery. **Shipment on Monday through Thursday by overnight service to assure receipt is encouraged. Do not ship specimens on a Friday or Saturday or the day before a federal holiday.**
- The institution is expected to pay the cost of mailing specimens and will be reimbursed through capitation fees set for each individual study.
- Arrange for express courier pick-up through your usual institutional procedure. Ship specimens to the address below:

Alliance Biorepository at Ohio State

[redacted]

6.2.2 Collection and processing for histopathology review

Consistent and accurate histologic grading is important for this study. Submission of 10 H&E slides OR tumor block from the diagnostic thyroid biopsy, thyroidectomy specimen (preferred), or any pathology specimen containing the thyroid neoplasm is required at pre-registration.

10 H&E slides OR tumor block of the patient's Hürthle cell thyroid cancer diagnosis should be retrieved from the surgical pathology department. Blocks which contain minimal amounts of tissue specimen or that are very thin should not be submitted unless the block is the only representative tissue for the case. A de-identified surgical pathology report should be sent with all specimens. Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report.

When shipping blocks and /or FFPE slides, it is important to avoid extreme heat. If environmental conditions indicate, specimens may be shipped in containers containing cold packs. The diagnostic slide(s) must be appropriately packed to prevent damage (e.g. slides should be placed in appropriate slide container) and placed in an individual plastic bag. It is also important that blocks are shipped in appropriately padded and secure containers to avoid physical damage. Do not wrap blocks or slides in tissue or paper toweling that is in direct contact with the paraffin.

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. The goal of the Alliance is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days of registration. For questions regarding treatment, please see the study contacts page.

This phase II randomized study is comparing sorafenib alone (standard treatment at 400 mg orally twice a day) to the combination of sorafenib (400 mg orally twice a day) and everolimus (5mg orally once a day) in patients with RAI-refractory Hürthle cell thyroid cancer. This would be a 1:1 randomization.

In patients who are randomized to sorafenib alone, we would allow for a crossover to everolimus alone (10 mg orally daily) at time of progression as an exploratory cohort. If a patient does crossover to everolimus alone, everolimus must begin within 6 weeks of the last dose of sorafenib on study. If restaging imaging has not been done within 28 days before treatment with everolimus alone, it must be repeated.

At the time of crossover, pregnancy test must be repeated. Also, if it has been more than 3 months since the last lipid profile, the lipid profile must be repeated at crossover. Other lab tests and observations will be performed per study calendar in Section 5.0.

Patients will remain on treatment as long as there is no progression of disease, excessive toxicity requiring the patient to come off of treatment, or the patient withdraws from treatment.

Arm 1:

Agent	Dose and Route	Frequency	Cycle Length (ReRx)
Sorafenib*	400 mg PO	Twice daily	28 days***

Arm 2:

Agent	Dose and Route	Frequency	Cycle Length (ReRx)
Sorafenib*	400 mg PO	Twice daily	28 days***
Everolimus**	5 mg PO	Once daily	28 days***

Crossover for Arm 1:

Agent	Dose and Route	Frequency	Cycle Length (ReRx)
Everolimus**	10 mg PO	Once daily	28 days***

* Sorafenib should be taken twice daily on an empty stomach one hour before or two hours after eating. This tablet should be swallowed whole and cannot be crushed or chewed.

** Everolimus should be administered once daily at approximately the same time each day with or without food. Tablets should be swallowed whole with a glass of water. The tablets must not be chewed or crushed and grapefruit juice or grapefruit should be avoided.

***After year 1, at the start of cycle 13, the cycle length will be 56 days.

7.1 CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with sorafenib.

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA and/or IUPUI websites, or your local institution's pharmacist.

7.2 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with sorafenib.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA and/or IUPUI websites, or your local institution's pharmacist.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint with the exception of thyroid hormone replacement in order to suppress the TSH.

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

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

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

8.1.5 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day). The following supportive measures are also allowed: hydration, octreotide, and other antidiarrheals.

8.1.6 Palliative radiation therapy may not be administered during active treatment. Patients who require radiation therapy during active treatment will be removed from protocol therapy due to disease progression. However, if the patient is randomized to the sorafenib alone arm, they may receive palliative radiation therapy for a symptomatic lesion prior to the crossover for everolimus if the following conditions are met: (1) there are RECIST 1.1 lesions present outside of the radiation field; (2) Everolimus is started 2 or more weeks after radiation therapy is completed; (3) Everolimus is started within 6 weeks of the last dose of sorafenib.

8.1.7 Alliance Policy Concerning the Use of Growth Factors

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

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

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

1. Filgrastim (G-CSF)/pegfilgrastim and sargramostim (GM-CSF) treatment for patients is discouraged.
2. Filgrastim/pegfilgrastim and sargramostim may be used:
   a. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported. (e.g. on CRFs per protocol requirements)
   b. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

8.1.8 Palmer-plantar erythrodysesthesia (PPE) syndrome

PPE is a common side effect of **sorafenib**. Patients should use moisturizers, avoid heat exposure (direct sun, saunas, etc), treat calluses, and should report rash or symptoms. In order to proactively alleviate PPE, consider using prophylaxis before starting treatment. Examples of prophylaxis include: Moisturizers such as eucerin, urea cream.

8.1.9 Pneumonitis

Refer to the following table for SUGGESTED medical management of the pneumonitis associated with **everolimus**. These are not required and included to provide site guidance for management:

Grade of Pneumonitis	Investigations to utilize	Management of Pneumonitis
Grade 1	CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.	No specific therapy is required
Grade 2	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy *	Symptomatic only. Prescribe corticosteroids if cough is troublesome.
Grade 3	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest.; Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.

*A bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.

8.1.10 Stomatitis

The following are recommendations for stomatitis management associated with **everolimus**, to provide sites with guidance and are not required:

- For mild toxicity (Grade 1), use conservative measures such as **non-alcoholic mouth wash or salt water (0.9%) mouthwash** several times a day until resolution.
- For more severe toxicity (Grade 2 or 3), the suggested treatments are **topical analgesic mouth treatments,** with or without **topical corticosteroids**
- Antifungal and antiviral agents should be avoided due to drug interaction concerns

8.1.11 Hyperglycemia

Patients taking **everolimus** should be treated with appropriate medical therapy for hyperglycemia.

8.1.12 Hyperlipidemia

Patients taking **everolimus** should be treated with appropriate medical therapy for hyperlipidemia and avoiding concomitant medications that interact with study medication.

8.2 Dose Modifications for Sorafenib

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Sorafenib will not be re-escalated once reduced
- If dose reductions beyond dose level -2 is required or sorafenib is held for 4 weeks, sorafenib will be discontinued.
- If more than one of these toxicities apply, use the most stringent criteria (i.e., the greatest dose reduction.)
- If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered.

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

8.2.1 Dose levels

Dose reduction of sorafenib will be performed according to the table below. Sorafenib will be permanently discontinued for patients who require dose interruptions of > 28 days or who experience dose limiting toxicities at dose level -2. Missed doses of sorafenib will not be made up.

Dose Level	Drug Name	Dose
0*	Sorafenib	400mg twice daily
-1	Sorafenib	200mg twice daily
-2	Sorafenib	200mg daily

*Dose level 0 refers to the starting dose.

- If dose reductions beyond the lowest dose level are required discontinue all protocol therapy.
- Doses that have been reduced will not be re-escalated.

8.2.2 Dose Modifications for Hematologic Toxicities

Grade ≥3 neutropenia, thrombocytopenia, or neutropenic fever: Interrupt sorafenib until ≤ grade 2, then resume with one dose level reduction of sorafenib for all subsequent doses.

8.2.3 Dose Modifications for Gastrointestinal Toxicities

• **Grade 2 diarrhea**: Interrupt sorafenib until diarrhea improves to ≤ grade 1, then resume sorafenib at same dose level.

• **Grade ≥ 3 diarrhea:** Interrupt sorafenib until diarrhea improves to ≤ grade 2, then resume sorafenib with one dose level reduction.

• **GI Perforation:** Discontinue sorafenib.

8.2.4 Dose Modifications for Hepatic Dysfunction

• **Grade 2 blood bilirubin increased:** Interrupt sorafenib until improved to grade 1, then resume sorafenib at same dose.

• **Grade 3 blood bilirubin increased:** Interrupt sorafenib until improved to grade 1, then resume sorafenib at 1 dose level reduced.

• **Grade 4 blood bilirubin increased**: Discontinue sorafenib.

• **Grade 3 transaminase increased:** Interrupt sorafenib until improved to grade 1, then resume sorafenib at 1 dose level reduced.

• **Grade 4 transaminase increased**: Discontinue sorafenib.

8.2.5 Dose Modifications for Hypertension

• **For hypertension >140/90 and ≤160/100:** Continue sorafenib. Consider adding or adjusting anti-hypertensive medications (e.g., calcium channel blockers as per institution's guideline for HTN treatment).

• **For persistent (>160/100) or symptomatic hypertension:** Interrupt sorafenib. Resume when blood pressure improves to ≤160/100. If sorafenib is interrupted for > 4 weeks, discontinue sorafenib therapy.

• **Grade 4 hypertension**: Discontinue all sorafenib therapy.

8.2.6 Dose Modifications for Cardiotoxicity

• **Myocardial ischemia**: Discontinue sorafenib.

8.2.7 Dose Modifications for Skin Toxicity (palmar-plantar erythrodysesthesia (PPE) syndrome)

Skin Toxicity	Occurrence	Suggested Dose Modification
Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet relief which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief
Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib dose by one dose level

	4th occurrence	Discontinue sorafenib
Moist desquamation, ulceration, blistering or severe pain the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib until toxicity of resolves to Grade 0-1. When resuming treatment, decrease sorafenib dose by one dose level
	3rd occurrence	Discontinue sorafenib

8.2.8 Dose Modifications for Other Non-hematologic Toxicities

For other clinically significant grade 3/4 non-hematologic toxicities likely related to sorafenib, interrupt sorafenib. Resume sorafenib at 1 dose level reduced when the toxicity resolves to a clinically acceptable level (grade 1/2).

8.3 Dose Modifications for Sorafenib + Everolimus

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Sorafenib or everolimus will not be re-escalated once reduced
- If dose reductions beyond dose lowest dose level is required OR sorafenib or everolimus is held for 4 weeks, sorafenib or everolimus will be discontinued. If 1 agent is discontinued, the patient may remain on the other agent. If sorafenib is discontinued and everolimus has never been dose reduced, the patient may have everolimus dose increased to 10 mg daily. In this scenario, dose level chart for everolimus in section 8.4.1 should be used.
- If more than one of these toxicities apply, use the most stringent criteria (i.e., the greatest dose reduction.).

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

8.3.1 Dose levels

Dose reduction of sorafenib and everolimus will be performed according to the table below. Sorafenib or everolimus will be permanently discontinued for patients who require dose interruptions of > 28 days or who experience dose limiting toxicities at dose level -2. Missed doses of sorafenib or everolimus will not be made up. To clarify, only the dose level of the offending agent needs to be dose reduced as per protocol if it is clear that the other drug did not cause the adverse event (e.g., only sorafenib needs to be dose reduced for hand-foot syndrome). If there are any questions, please discuss with protocol PI (Dr. Eric Sherman).

Dose Level	Drug Name	Dose	Drug Name	Dose
0*	Sorafenib	400 mg twice daily	Everolimus	5mg daily
-1	Sorafenib	200 mg twice daily	Everolimus	2.5mg daily
-2	Sorafenib	200mg daily	Everolimus	2.5mg every other day

*Dose level 0 refers to the starting dose.

8.3.2 Dose Modifications for Hematologic Toxicities

• **Grade 2 thrombocytopenia**: Interrupt sorafenib and everolimus until grade ≤ 1, then resume sorafenib and everolimus at same dose.

• **Grade ≥3 neutropenia, grade ≥3 thrombocytopenia, or neutropenic fever**: Interrupt sorafenib and everolimus until ≤ grade 2, then resume with one dose level reduction of sorafenib and everolimus for all subsequent doses.

8.3.3 Dose Modifications for Gastrointestinal Toxicities

• **Grade 2 diarrhea:** Interrupt sorafenib and everolimus until diarrhea improves to grade ≤ 1 then resume at same dose.

• **Grade ≥ 3 diarrhea:** Interrupt sorafenib and everolimus until diarrhea improves to ≤ grade 2, then resume sorafenib and everolimus with one dose level reduction of both agents.

• **GI Perforation:** Discontinue sorafenib.

• **Grade 3 stomatitis:** Interrupt everolimus until ≤ grade 1 then resume with one dose level reduced.

• **Grade 4 stomatitis:** Discontinue everolimus.

8.3.4 Dose Modifications for Hepatic Dysfunction

• **Grade 2 blood bilirubin increased:** Interrupt sorafenib and everolimus until improved to grade 1, then resume sorafenib and everolimus at same dose.

• **Grade 3 blood bilirubin increased:** Interrupt sorafenib and everolimus until improved to grade 1, then resume sorafenib and everolimus at 1 dose level reduced.

• **Grade 4 blood bilirubin increased**: Discontinue sorafenib and everolimus.

• **Grade 3 transaminase increased:** Interrupt sorafenib and everolimus until improved to grade 1, then resume sorafenib and everolimus at 1 dose level reduced.

• **Grade 4 transaminase increased:** Discontinue sorafenib and everolimus.

8.3.5 Dose Modifications for Hypertension

• **For hypertension >140/90 and ≤160/100:** Continue sorafenib. Consider adding or adjusting anti-hypertensive medications (e.g., calcium channel blockers as per institution's guideline for HTN treatment)).

• **For persistent (>160/100) or symptomatic hypertension:** Interrupt sorafenib. Resume when blood pressure improves to ≤160/100. If sorafenib is interrupted for > 4 weeks, discontinue sorafenib therapy.

• **Grade 4 hypertension**: Discontinue sorafenib

8.3.6 Dose Modifications for Cardiotoxicity

Myocardial ischemia: Discontinue sorafenib.

8.3.7 Dose Modifications for Skin Toxicity

• **Palmar-plantar erythrodysesthesia (PPE) syndrome**

Skin Toxicity	Occurrence	Suggested Dose Modification
Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet relief which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief
Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief. If no improvement within 7 days,

activities		see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib and everolimus dose by one dose level
	4th occurrence	Discontinue sorafenib
Moist desquamation, ulceration, blistering or severe pain the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib until toxicity of resolves to Grade 0-1. When resuming treatment, decrease sorafenib dose by one dose level
	3rd occurrence	Discontinue sorafenib

• **Grade 4 Acneiform Rash:** Interrupt everolimus until grade ≤ 2, then restart at one dose level decreased

• **Grade 3 Maculopapular Rash:** Interrupt sorafenib and everolimus until grade ≤ 2, then restart sorafenib and everolimus at one dose level decreased

8.3.8 Dose Modifications for Pulmonary Toxicity

• **Grade 2 or 3 pneumonitis:** Interrupt everolimus until ≤ grade 1. Resume everolimus at one dose level decreased

• **Grade 4 pneumonitis:** Discontinue everolimus

8.3.9 Dose Modifications for Renal Toxicity

• **Grade 2 increased creatinine:** Interrupt everolimus until grade ≤ 1, then resume with one dose level decreased

• **Grade 3 and 4 increased creatinine**: Discontinue everolimus

8.3.10 Dose Modifications for Metabolism

Grade 4 Hyperglycemia: Interrupt everolimus until grade ≤ 2, then resume at same dose

8.3.11 Dose Modifications for General Disorders

Grade 3 Edema: Interrupt everolimus until ≤ grade 2, then resume at one dose level decreased

8.3.12 Dose Modifications for Other Non-hematologic Toxicities

For other clinically significant grade 3/4 non-hematologic toxicities likely related to sorafenib or everolimus, interrupt sorafenib or everolimus. Resume sorafenib or everolimus at 1 dose level reduced when the toxicity resolves to a clinically acceptable level (grade 1/2).

8.4 Dose Modifications for Everolimus alone (after crossover)

• If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

• Everolimus will not be re-escalated once reduced

• If dose reductions beyond dose level -2 is required or everolimus is held for 4 weeks, everolimus will be discontinued.

• If more than one of these toxicities apply, use the most stringent criteria (i.e., the greatest dose reduction.).

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

8.4.1 Dose levels

Dose reduction of everolimus will be performed according to the table below. Everolimus will be permanently discontinued for patients who require dose interruptions of > 28 days or who experience dose limiting toxicities at dose level -2. Missed doses of everolimus will not be made up.

Dose Level	Drug Name	Dose
0*	Everolimus	10mg daily
-1	Everolimus	5mg daily
-2	Everolimus	2.5mg daily

*Dose level 0 refers to the starting dose.

8.4.2 Dose Modifications for Hematologic Toxicities

Grade ≥3 neutropenia, thrombocytopenia, or neutropenic fever: Interrupt everolimus until ≤ grade 2, then resume with one dose level reduction of everolimus for all subsequent doses.

8.4.3 Dose Modifications for Gastrointestinal Toxicities

• **Grade ≥ 3 diarrhea:** Interrupt everolimus until diarrhea improves to ≤ grade 2, then resume everolimus with one dose level reduction.

• **Grade 3 stomatitis:** Interrupt everolimus until ≤ grade 1 then resume with one dose level reduced.

• **Grade 4 stomatitis:** Discontinue everolimus

8.4.4 Dose Modifications for Hepatic Dysfunction

• **Grade 2 blood bilirubin increased:** Interrupt everolimus until improved to grade 1, then resume everolimus at same dose.

• **Grade 3 blood bilirubin increased:** Interrupt everolimus until improved to grade 1, then resume everolimus at 1 dose level reduced.

• **Grade 4 blood bilirubin increased**: Discontinue everolimus.

• **Grade 3 transaminase increased:** Interrupt everolimus until improved to grade 1, then resume everolimus at 1 dose level reduced.

• **Grade 4 transaminase increased:** Discontinue everolimus.

8.4.5 Dose Modifications for Skin Toxicity

• **Grade 4 Acneiform Rash:** Interrupt everolimus until grade ≤ 2, then restart at one dose level decreased

• **Grade 3 Maculopapular Rash:** Interrupt everolimus until grade ≤ 2, then restart at one dose level decreased

8.4.6 Dose Modifications for Pulmonary Toxicity

• **Grade 2 or 3 pneumonitis:** Interrupt everolimus until ≤ grade 1. Resume everolimus at one dose level decreased

• **Grade 4 pneumonitis:** Discontinue everolimus

8.4.7 Dose Modifications for Renal Toxicity

• **Grade 2 increased creatinine:** Interrupt everolimus until grade ≤ 1, then resume with one dose level decreased

• **Grade 3 and 4 increased creatinine**: Discontinue everolimus

8.4.8 Dose Modifications for Metabolism

Grade 4 Hyperglycemia: Interrupt everolimus until grade ≤ 2, then resume at same dose

8.4.9 Dose Modifications for General Disorders

Grade 3 Edema: Interrupt everolimus until ≤ grade 2, then resume at one dose level decreased

8.4.10 Dose Modifications for Other Non-hematologic Toxicities

For other clinically significant grade 3/4 non-hematologic toxicities likely related to everolimus, interrupt everolimus. Resume everolimus at 1 dose level reduced when the toxicity resolves to a clinically acceptable level (grade 1/2).

9.0 ADVERSE EVENTS

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

9.1 Routine adverse event reporting

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

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

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Neutrophil count decreased	Investigations
Platelet count decreased	Investigations
Hemoglobin decreased	Investigations
Hyperglycemia	Metabolism and nutrition disorders
Hypertension	Vascular disorders
Fatigue	General disorders
Palmar-plantar erythrodysesthesia syndrome	Skin and subcutaneous tissue disorders
Diarrhea	Gastrointestinal disorders
Weight Loss	Investigations

9.2 CTCAE Routine Study Reporting Requirements

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.
b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as below. Alliance investigators are required to notify the Alliance Central Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site [redacted]

The Alliance requires investigators to route all expedited adverse event reports through the Alliance Central Protocol Operations Program Office for Alliance-coordinated studies.

Be sure to read this entire protocol section, as requirements are described in both the table and bullet points following the table. Note that the table below and the additional instructions or exclusions are protocol specific, and in the case of a conflict, the additional instructions or exclusions supersede the table.

9.3.1 Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial ≤ 30 Days of the Last Day of Treatment[1,]

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

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

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

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

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

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes

<table>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td>Not required</td><td>10 Calendar Days</td></tr>
<tr><td colspan="4"><u>Expedited AE reporting timelines are defined as:</u>
o "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
o "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.</td></tr>
<tr><td colspan="4">[1] Serious adverse events that occur more than 30 days after the day of treatment require reporting as follows:
Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:
• All Grade 4, and Grade 5 AEs that are at least possibly related to treatment
Expedited 10 calendar day reports for:
• Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization and that are at least possibly related to treatment
• Grade 3 adverse events and that are at least possibly related to treatment</td></tr>
</table>

Additional Instructions or Exclusions:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Treatment expected adverse events include those listed in Section 10.0, in the package inserts for everolimus and sorafenib, and in the CAEPR for sorafenib. NOTE: The ASAEL column of the sorafenib CAEPR has been replaced with the specific protocol exceptions to expedited reporting (SPEER) list. This list now includes 'expected' severity grades in addition to event terms.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (acute myelogenous leukemia, and in situ tumors. In CTCAE v5.0, secondary malignancies may be reported as one of the following three options: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- All pregnancies and suspected pregnancies occurring in female patients during therapy or within 28 days after completion of treatment on A091302 must be reported via CTEP-AERS. In CTCAE version 5.0, pregnancy loss is defined as "Death in utero," and any pregnancy loss should be reported as "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC (grade 4).
    - o CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities). Fetal deaths should be reported as "Death neonatal" under the General disorders and administration SOC (grade 4).
    - o The CTEP-AERS report should be amended for any neonatal deaths occurring within 28 days of birth considered at least possibly related to treatment. Use the event term "Death neonatal" under the General disorders and administration SOC (grade 4).
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g. cooperative group data reporting.

9.4 CAEPRs

9.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Sorafenib (BAY 43-9006, NSC 724772)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [redacted] for further clarification. *Frequency is provided based on 2571 patients.* Below is the CAEPR for Sorafenib (BAY 43-9006; Nexavar).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.10, June 24, 2020[1]

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
CARDIAC DISORDERS		
	Chest pain - cardiac	
		Heart failure Left ventricular systolic dysfunction
		Myocardial infarction
GASTROINTESTINAL DISORDERS		
Abdominal pain		

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Ascites	
	Constipation	
Diarrhea		
	Gastrointestinal hemorrhage[2]	
		Gastrointestinal perforation[3]
	Mucositis oral	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
Fatigue		
	Fever	
HEPATOBILIARY DISORDERS		
		Hepatic failure
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Injury, poisoning and procedural complications - Other, specify (wound healing complication)
INVESTIGATIONS		
	Activated partial thromboplastin time prolonged	
Alanine aminotransferase increased		
Alkaline phosphatase increased		
Aspartate aminotransferase increased		
Blood bilirubin increased		
Creatinine increased		
		Electrocardiogram QT corrected interval prolonged
	GGT increased	
INR increased		
	Investigations - Other (Bicarbonate-serum low)	
Lipase increased		
Lymphocyte count decreased		
	Neutrophil count decreased	
Platelet count decreased		
Serum amylase increased		
		Thyroid stimulating hormone increased
Weight loss		
White blood cell decreased		

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
	Hypercalcemia	
Hyperglycemia		
	Hyperkalemia	
	Hypernatremia	
Hypoalbuminemia		
Hypocalcemia		
	Hypoglycemia	
	Hypokalemia	
Hyponatremia		
Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Muscle cramp	
	Myalgia	
	Pain in extremity	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
	Treatment related secondary malignancy	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Intracranial hemorrhage
		Reversible posterior leukoencephalopathy syndrome
PSYCHIATRIC DISORDERS		
	Insomnia	
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Respiratory hemorrhage[5]	
	Voice alteration	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia		
	Dry skin	
		Erythema multiforme
Palmar-plantar erythrodysesthesia syndrome		
	Pruritus	
Rash maculo-papular		

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
VASCULAR DISORDERS		
	Hypertension	
		Thromboembolic event

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [redacted]. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage may include Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation may include Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[5]Respiratory hemorrhage may include bronchopulmonary hemorrhage, epistaxis, laryngeal hemorrhage, mediastinal hemorrhage, pharyngeal hemorrhage, and pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[6]Febrile neutropenia is seen mostly in combination with other agents.

Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS
Anemia (Gr 3)
CARDIAC DISORDERS
GASTROINTESTINAL DISORDERS
Abdominal pain (Gr 3)
Constipation (Gr 2)
Diarrhea (Gr 3)
Gastrointestinal hemorrhage[2] (Gr 3)
Nausea (Gr 3)

Specific Protocol Exceptions to Expedited Reporting (SPEER)
Vomiting (Gr 3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Fatigue (Gr 3)
Fever (Gr 2)
HEPATOBILIARY DISORDERS
IMMUNE SYSTEM DISORDERS
INFECTIONS AND INFESTATIONS
INJURY, POISONING AND PROCEDURAL COMPLICATIONS
INVESTIGATIONS
Activated partial thromboplastin time prolonged (Gr 2)
Alanine aminotransferase increased (Gr 3)
Alkaline phosphatase increased (Gr 3)
Aspartate aminotransferase increased (Gr 3)
Blood bilirubin increased (Gr 3)
Creatinine increased (Gr 3)
INR increased (Gr 3)
Lipase increased (Gr 3)
Lymphocyte count decreased (Gr 3)
Neutrophil count decreased (Gr 4)
Platelet count decreased (Gr 4)
Serum amylase increased (Gr 3)
Weight loss (Gr 2)
White blood cell decreased (Gr 4)
METABOLISM AND NUTRITION DISORDERS
Anorexia (Gr 3)
Hyperglycemia (Gr 3)
Hyperkalemia (Gr 3)
Hypoalbuminemia (Gr 3)
Hypocalcemia (Gr 3)
Hypoglycemia (Gr 2)
Hypokalemia (Gr 3)
Hyponatremia (Gr 3)
Hypophosphatemia (Gr 3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
Arthralgia (Gr 3)
Back pain (Gr 3)

Specific Protocol Exceptions to Expedited Reporting (SPEER)
Pain in extremity (Gr 3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)
NERVOUS SYSTEM DISORDERS
Headache (Gr 3)
PSYCHIATRIC DISORDERS
RENAL AND URINARY DISORDERS
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS
Cough (Gr 2)
Dyspnea (Gr 3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Alopecia (Gr 2)
Dry skin (Gr 2)
Palmar-plantar erythrodysesthesia syndrome (Gr 3)
Pruritus (Gr 3)
Rash maculo-papular (Gr 3)
VASCULAR DISORDERS
Hypertension (Gr 3)

Adverse events reported on sorafenib (BAY 43-9006; Nexavar) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that sorafenib (BAY 43-9006, Nexavar) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (Thrombotic microangiopathy (e.g., TTP or HUS)); Febrile neutropenia[6]
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Palpitations; Pericardial effusion; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
ENDOCRINE DISORDERS - Adrenal insufficiency; Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (color vision deficits); Eye disorders - Other (light to dark adaptation); Eye disorders - Other (retinal vein occlusion, bilat); Eye disorders - Other (retinal hemorrhage); Eye disorders - Other (visual field distortion); Flashing lights; Keratitis; Photophobia; Retinal detachment
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fistula; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Colonic ulcer; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophagitis; Flatulence; Gastric ulcer; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (small bowel NOS fistula); Gastrointestinal fistula; Hemorrhoids; Ileal fistula; Ileus; Oral pain; Pancreatitis; Proctitis; Rectal fistula; Rectal mucositis; Rectal obstruction; Rectal pain; Small intestinal obstruction; Stomach pain; Visceral arterial ischemia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Facial pain; Flu like symptoms; Localized edema; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic hemorrhage; Hepatobiliary disorders - Other (biliary obstruction secondary to multiple biliary stones)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Cytokine release syndrome; Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Fall; Fracture; Hip fracture; Vascular access complication; Wound dehiscence
INVESTIGATIONS - CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Ejection fraction decreased; Fibrinogen decreased; Investigations - Other (blood urea nitrogen high)
METABOLISM AND NUTRITION DISORDERS - Acidosis; Alkalosis; Dehydration; Hypermagnesemia; Hypertriglyceridemia; Hyperuricemia; Hypomagnesemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (cramping); Myositis; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Hydrocephalus; Ischemia cerebrovascular; Lethargy; Leukoencephalopathy; Memory impairment; Muscle weakness left-sided; Muscle weakness right-sided; Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Libido decreased; Personality change; Psychosis
RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (focal segmental glomerulosclerosis); Renal and urinary disorders - Other (right ureter rupture); Renal calculi; Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urine discoloration
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Gynecomastia; Hematosalpinx; Menorrhagia; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal fistula; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Bronchospasm; Hiccups; Hoarseness; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fibrosis; Respiratory, thoracic and mediastinal disorders - Other (nasal septal perforation); Tracheal mucositis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythroderma; Hyperhidrosis; Nail loss; Pain of skin; Purpura; Rash acneiform; Scalp pain; Skin and subcutaneous tissue disorders - Other (non-life threatening squamous cell carcinoma of skin: keratocanthomas type); Skin hyperpigmentation; Skin hypopigmentation; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypotension; Phlebitis; Vascular disorders - Other (ruptured aortic aneurysm); Vasculitis

Note: Sorafenib (BAY 43-9006; Nexavar) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.4.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Everolimus (RAD-001, NSC 733504)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted

below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [redacted] for further clarification. Frequency is provided based on 3033 patients. Below is the CAEPR for Everolimus (RAD-001).

Version 2.5, July 3, 2018[1]

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 5.0 Term) [n= 3033]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
Diarrhea[2]		
Mucositis oral[3]		
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
Fatigue		
	Fever	
IMMUNE SYSTEM DISORDERS		
		Allergic reaction
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Wound complication[5]
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased Aspartate aminotransferase increased	
	Cholesterol high	
	Creatinine increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 5.0 Term) [n= 3033]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Anorexia	
	Hyperglycemia[6]	
	Hypertriglyceridemia	
	Hypophosphatemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dysgeusia	
	Headache	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Epistaxis	
	Pneumonitis[7]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
	Pruritus	
Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)[8]

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [redacted] Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.
[2]Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.
[3]Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.
[4]Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.
[5]Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma.
[6]Hyperglycemia may result in either exacerbation of or development of new onset diabetes mellitus.
[7]Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis, pulmonary fibrosis, and restrictive pulmonary disease.
[8]Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema.
[9]Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.

Adverse events reported on everolimus (RAD-001) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that everolimus (RAD-001) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (myocardial abnormality); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
ENDOCRINE DISORDERS - Endocrine disorders - Other (increased blood follicle stimulating hormone [FSH] levels); Endocrine disorders - Other (increased blood luteinizing hormone [LH] levels); Hypothyroidism; Testosterone deficiency
EYE DISORDERS - Blurred vision; Keratitis
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Dieulafoy's lesion); Hemorrhoids; Intra-abdominal hemorrhage; Oral pain; Pancreatitis; Periodontal disease; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema trunk; Flu like symptoms; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (hepatomegaly)
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bicarbonate decreased; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; GGT increased; INR increased; Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia).
METABOLISM AND NUTRITION DISORDERS - Dehydration; Glucose intolerance; Hypercalcemia; Hyperkalemia; Hyperlipidemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (high ammonia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (ovarian cysts)
NERVOUS SYSTEM DISORDERS - Dizziness; Encephalopathy; Hydrocephalus; Lethargy; Paresthesia
PSYCHIATRIC DISORDERS - Agitation; Anxiety[9]; Delirium; Depression; Insomnia; Irritability; Mania
RENAL AND URINARY DISORDERS - Hematuria; Proteinuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dysmenorrhea; Genital edema; Irregular menstruation; Menorrhagia; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (rales); Rhinorrhea; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Rash acneiform; Skin and subcutaneous tissue disorders - Other (nail disorder); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin ulceration
VASCULAR DISORDERS - Flushing; Hypertension; Lymphedema; Phlebitis; Thromboembolic event; Vascular disorders - Other (acute bowel ischemia); Vascular disorders - Other (hemorrhage)

Note: Everolimus (RAD-001) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.4.2.1 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

BLOOD AND LYMPHATIC SYSTEM DISORDERS

- Grade 3 anemia and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

GASTROINTESTINAL DISORDERS

- Grade 3 diarrhea (includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea) and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 3 mucositis oral (includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation) and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 3 nausea, vomiting and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

- Grade 2 edema limbs and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 fatigue and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 fever and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

INFECTIONS AND INFESTATIONS

- Grade 3 infection (infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC) and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

INVESTIGATIONS

- Grade 2 alanine aminotransferase increased and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 alkaline phosphatase increased and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 aspartate aminotransferase increased and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 cholesterol high and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 creatinine increased and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 lymphocyte count decreased and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 4 neutrophil count decreased and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 4 platelet count decreased and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 4 white blood cell decreased and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

METABOLISM AND NUTRITION DISORDERS

- Grade 2 anorexia and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

- Grade 3 hyperglycemia (Hyperglycemia may result in either exacerbation of or development new onset diabetes mellitus) and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 4 hypertriglyceridemia and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 hypophosphatemia and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

NERVOUS SYSTEM DISORDERS

- Grade 2 headache and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

- Grade 2 cough and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 dyspnea and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 2 epistaxis and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

- Grade 2 rash maculo-papular and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

10.0 DRUG INFORMATION

10.1 Sorafenib (Nexavar®, BAY 43-9006)

Procurement

Sorafenib is commercially available.

Formulation

The drug product for supply of clinical studies is an immediate release (IR) 200 mg tablet. The tablets are red in color.

Tablets also contain microcrystalline cellulose, croscarmellose sodium, hydroxypropyl methyl cellulose, magnesium stearate, sodium lauryl sulfate with a film coat containing hydroxypropyl methyl cellulose, polyethylene glycol, titanium dioxide, and red iron oxide.

Preparation, Storage and Stability

The tablets are packaged in high-density polyethylene bottles (climate zones I/II) or alu-alu blisters (climate zones III/IV). They should only be stored in the pack provided. The storage temperature for high density polyethylene bottles should not exceed 25ºC.

Administration

Administer on an empty stomach (1 hour before or 2 hours after eating). When given with a high fat meal, sorafenib absorption is reduced approximately 30% compared with fasting administration.

Drug Interactions

Cytochrome P450 Effect:

Substrate of CYP3A4 (minor), UGT1A1

Inhibits CYP2B6 (moderate), 2C8 (strong), 2C9 (moderate), UGT1A1, UGT1A9

Increased Effect/Toxicity: Sorafenib may increase the levels/effects of carboplatin, docetaxel, doxorubicin, fluorouracil, and irinotecan (and active metabolite SN38). Sorafenib may increase the serum concentration of the active metabolite of dacarbazine. Sorafenib may enhance the

anticoagulant effect of warfarin. Sorafenib may increase the levels/effects of CYP2B6 substrates; example substrates include bupropion, promethazine, propofol, selegiline, and sertraline. Sorafenib may increase levels/effects of CYP2C8 substrates; example substrates include amiodarone, paclitaxel, pioglitazone, repaglinide, and rosiglitazone. Sorafenib may increase levels/effects of CYP2C9 substrates; example substrates include bosentan, dapsone, fluoxetine, glimepiride, glipizide, losartan, montelukast, nateglinide, paclitaxel, phenyton, warfarin, and zafirlukast. The levels/effects of sorafenib may be increased by: bevacizumab; CYP3A4 Inhibitors (Strong); denosumab; pimecrolimus; tacrolimus (topical); trastuzumab.

Decreased Effect: Sorafenib may decrease the absorption of digoxin tablets. Sorafenib may decrease the levels/effects of fluorouracil. Sorafenib may decrease the serum concentration of dacarbazine and BCG. CYP3A4 inducers may decrease the levels/effects of sorafenib; example inducers include aminoglutethimide, carbamazepine, nafcillin, nevirapine, phenobarbital, phenytoin, and rifamycins.

Please see the FDA approved package insert of sorafenib for a detailed description of drug interaction data and recommendations.

Ethanol/Nutrition/Herb Interactions:

Food: Bioavailability is decreased 29% with a high-fat meal (bioavailability is similar to fasting state when administered with a moderate-fat meal).

Herb/Nutraceutical: Avoid St John's wort (may decrease the levels/effects of sorafenib).

Pharmacokinetics

Bioavailability: 38% to 49%, reduced when administered with a high-fat meal.

Protein Binding: 99.5%. Sorafenib is approximately equally distributed between red blood cells and plasma with plasma to blood ratio of 1.33.

Metabolism: Hepatic: via CYP3A4 (primarily oxidated to the pyridine N-oxide; active, minor) and UGT1A9 (glucuronidation)

Half-life elimination: 25-48 hours

Time to peak, plasma: ~3 hours

Excretion: Feces (77%, 51% as unchanged drug); Urine (19%, as metabolites)

Adverse Events

Known potential adverse events: Consult the package insert for the most current and complete information. Frequency listed derived from monotherapy trials.

Common known potential toxicities, > 10%:

Cardiovascular: Hypertension, thromboembolic event

Central nervous system: Fatigue, sensory neuropathy, pain

Dermatologic: Rash/desquamation, hand-foot syndrome, alopecia, pruritus, dry skin, erythema

Endocrine & metabolic: Hypoalbuminemia, hypocalcemia, hypophosphatemia, hyperglycemia, lipase increased, serum amylase increased

Gastrointestinal: Diarrhea, lipase increased, amylase increased, abdominal pain, weight loss, anorexia, nausea, vomiting, constipation

Hematologic: Lymphopenia, thrombocytopenia, INR elevated, neutropenia, hemorrhage, leukopenia, prolonged APTT

Hepatic: Liver dysfunction, alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased

Neuromuscular & skeletal: Muscle pain, weakness

Respiratory: Dyspnea, cough

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

Cardiovascular: Cardiac ischemia/infarction, heart failure, flushing

Central Nervous System: Headache, depression, fever, dizziness, insomnia

Dermatologic: Acne, exfoliative dermatitis

Endocrine & metabolic: Hyperkalemia, hypoglycemia, Cholesterol high, GGT increased, low serum bicarbonate, hypernatremia, hyperuricemia, hypokalemia, hypocalcemia

Hematologic: Anemia, febrile neutropenia

Gastrointestinal: Appetite decreased, dyspepsia, dysphagia, esophageal varices bleeding, glossodynia, mucositis oral, stomatitis, xerostomia, gastrointestinal hemorrhage, anal mucositis, rectal mucositis, small intestinal mucositis, ascites

Genitourinary: Erectile dysfunction

Hepatic: Transaminases increased

Neuromuscular & skeletal: Joint pain, arthralgia, myalgia, back pain, pain in extremity, muscle spasms

Renal: Renal failure, elevated creatinine, hematuria, renal hemorrhage, proteinuria

Reproductive system and breast disorders: Hematosalpinx, ovarian hemorrhage, prostatic hemorrhage, spermatic cord hemorrhage, testicular hemorrhage, uterine hemorrhage, vaginal hemorrhage

Respiratory: Bronchopulmonary hemorrhage, epistaxis, hoarseness, laryngeal mucositis, pharyngeal mucositis, tracheal mucositis

Miscellaneous: Flu-like syndrome, edema limbs, non-cardiac chest pain, infection

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

Acute coronary syndrome, anaphylaxis, left ventricular systolic dysfunction, acute renal failure, alkaline phosphatase increased, aortic dissection, arrhythmia, bilirubin increased, bone pain, cardiac failure, cerebral hemorrhage, cholangitis, cholecystitis, dehydration, eczema, erythema multiforme, folliculitis, gastritis, gastrointestinal perforation, gastrointestinal reflux, gynecomastia, hypersensitivity (skin reaction, urticaria), hypertensive crisis, hyponatremia, hyper/hypothyroidism, jaundice, MI, muscle wasting, myocardial ischemia, nephrotic syndrome, pancreatitis, pleural effusion, preeclampsia-like syndrome (reversible hypertension and proteinuria), respiratory hemorrhage, reversible posterior leukoencephalopathy syndrome (RPLS), Rhinorrhea Interstitial Lung Disease-like events (includes pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis and lung inflammation) skin cancer (squamous cell/keratoacanthomas), Stevens-Johnson syndrome, thromboembolism, tinnitus, toxic epidermal necrolysis, transient ischemic attack, tumor lysis syndrome, tumor pain

Nursing Guidelines

- Drug should be taken with at least 250 cc of water. Should be taken without food (at least 1 hour before or 2 hours after meals). Do not administer with grapefruit juice.
- Patient may experience flu-like symptoms such as fatigue, fever, acetaminophen may be beneficial for these patients.
- Monitor CBC. Instruct patients to report signs and symptoms of infection and excessive bruising or bleeding to the MD.

- Monitor LFT's.
- Patients may experience diarrhea. See section 8.1.5 for management of diarrhea.
- Instruct patient to report severe abdominal pain, as pancreatitis is a possibility.
- May cause anorexia. Encourage patient to consume small frequent meals.
- Monitor for sign/symptoms of hand/foot syndrome. See section 8.2.7 for appropriate management.
- May cause alopecia, instruct patient of this possibility
- Monitor for rash. Toxic epidermal necrolysis is a rare but serious condition. Instruct patient to report any rash to MD.
- Patients on Coumadin should be monitored closely, as dose may need to be adjusted secondary to CYP3A inhibition. As there are many potential drug interactions, instruct patient not to start any new medication (including OTC's or herbal products) without checking with their MD first.
- Monitor blood pressure. Instruct patients who are self-monitoring to report any increase in their blood pressure to the study team.
- Nausea and vomiting may occur. Administer antiemetics as necessary and monitor for their effectiveness.
- Bleeding has been seen (GI, respiratory, CNS). Instruct patient to report any bleeding to the study team immediately. If bleeding is severe, seek out emergency medical attention.
- Numerous electrolyte imbalances may occur (hypernatremia, hypocalcemia, hypokalemia). Monitor chemistry panel and report any abnormalities to the treating physician.

10.2 Everolimus (RAD001, Afinitor®)

Procurement: Drug supply is from Novartis; distribution to sites will be arranged between Novartis and the Alliance, unless drug should become commercially available for this disease.

Formulation: Tablets containing, 5 and 10 mg of everolimus are blister packed under aluminum foil in units of 10 tablets (2.5 mg available). Excipients include: butylhyroxytoluene/butylated hydroxytoluene (BHT), magnesium stearate, lactose, hypromellose/hydroxypropyl methylcellulose, and crospovidone.

Preparation, Storage and Stability: The storage of everolimus is supported by ongoing stability studies. Refer to label for expiration date and storage conditions.

Administration: Everolimus should be administered orally, once daily at the same time each day either consistently with food or consistently without food. Tablets should be swallowed whole. The tablets must not be chewed or crushed and grapefruit or grapefruit juices should be avoided, and all other foods should be avoided that are known to interact with CYP3A4 and PgP inhibitors.

Drug Interactions: Avoid the use of strong CYP3A4 or P-glycoprotein (PgP) inhibitors as these drugs may cause increased everolimus concentrations. Use caution when everolimus co-administered with moderate CYP3A4 and/or PgP inhibitors. Avoid the use of concomitant strong CYP3A4 inducers.

The pharmacokinetic interaction between everolimus and other chemotherapeutic agents is being investigated, and some data is available. See the current Investigator's Brochure for more

comprehensive information as well as recommendations for use with compounds known to interact with everolimus.

Pharmacokinetics:

Absorption: Rapid, but moderate

Protein binding: 74%

Vd: 107 to 342 L

Time to peak, plasma: 1-2 hours

Metabolism: hepatic, principally via CYP3A4. Metabolism involves demethylation, hydroxylation, and ring degradation. There are six main metabolites, which have approximately 100-times less activity than the parent everolimus compound.

Bioavailability: ~30%; system exposure reduce by 22% with a high-fat meal and by 32% with a light-fat meal

Half-life elimination: ~30 hours

Excretion: Feces (~80%); urine (~5% as inactive metabolite)

Adverse Events:

Known potential adverse events: Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:

Cardiovascular: Peripheral edema, hypertension

Central nervous system: Fatigue, fever, headache, seizure, personality change, insomnia, dizziness

Dermatologic: Rash, cellulitis, pruritus, contact dermatitis, excoriation, acne, dry skin, nail disorder

Endocrine & metabolic: Hypercholesterolemia, hypertriglyceridemia, hyperglycemia, hypophosphatemia, hypokalemia, blood lactate dehydrogenase increased

Gastrointestinal: Stomatitis, constipation, diarrhea, nausea, anorexia, vomiting, mucosal inflammation, gastroenteritis, dysgeusia

Genitourinary: none

Hematologic: Anemia, lymphocytopenia, thrombocytopenia, neutropenia (pancytopenia)

Hepatic: AST increased, ALT increased, bilirubin increased

Neuromuscular & skeletal: Weakness, pain in extremity, back pain

Otic: Otitis media

Renal: Creatinine increased, hematuria

Respiratory: Upper respiratory infection, sinusitis, cough, dyspnea, nasal congestion, rhinitis, pharyngitis, pneumonitis, epistaxis, pneumonia

Miscellaneous: weight decreased

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

Cardiovascular: Chest pain, tachycardia, angina, atrial fibrillation, chest discomfort, edema, hypertension, palpitation, syncope, congestive cardiomyopathy, stress cardiopathy, hemorrhage (various locations)

Central nervous system: Chills, agitation, restlessness, anxiety, depression, hallucination, hemiparesis, hyperesthesia, malaise, somnolence

Dermatologic: Palmar-plantar erythrodysesthesia syndrome, erythema, onychoclasis, pityriasis rosea, skin lesions, alopecia, Hirsutism, incision complications, hyperhidrosis, hypertrichosis

Endocrine & metabolic: exacerbation of pre-existing diabetes mellitus, acidosis, Cushingoid syndrome, dehydration, gout, hypercalcemia, hyperparathyroidism, hyperphosphatemia, hyperuricemia, hypoglycemia, hyponatremia, iron deficiency, vitamin B_{12} deficiency

Gastrointestinal: Xerostomia, gastritis, hemorrhoids, dyspepsia, dysphagia, abdominal distention, epigastric discomfort, flatulence, gastroesophageal reflux, gingival hypertrophy, hematemesis, ileus, peritonitis, oral pain, abdominal pain, gastroenteritis viral

Genitourinary: Bladder spasm, erectile dysfunction, ovarian cysts, pollakiuria, polyuria, pyuria, scrotal edema, urinary retention, urinary urgency, urinary tract infection, menorrhagia, vaginal hemorrhage, menstruation delayed, amenorrhea

Hematologic: Hemorrhage, leukocytosis, lymphadenopathy, thrombocythemia

Hepatic: none

Immunologic: Hypersensitivity including anaphylaxis

Neuromuscular & skeletal: Tremor, paresthesia, jaw pain, arthralgia, joint swelling, muscle spasm, musculoskeletal pain, myalgia, osteonecrosis, osteopenia, osteoporosis, spondylitis

Ocular: Eyelid edema, ocular hyperemia, conjunctivitis, blurred vision, cataract

Renal: Renal failure (including acute renal failure), BUN increased, hydronephrosis, interstitial nephritis, proteinuria, renal artery thrombosis, renal impairment, increased daytime urination

Respiratory: Pleural effusion, nasopharyngitis, bronchitis, pharyngolaryngeal pain, rhinorrhea, atelectasis, pulmonary edema, sinus congestion, wheezing, pulmonary embolism, hemoptysis, upper respiratory tract infection

Miscellaneous: BK virus infection, candidiasis, night sweats

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

Cardiovascular: Fluid accumulation, acute cardiopulmonary event, cardiogenic shock, cardio-respiratory arrest, myocardial infarction, embolic stroke, deep vein thrombosis, congestive cardiac failure

Central nervous system: Ageusia

Dermatologic: Wound healing complication, impaired wound healing

Endocrine & metabolic: New onset of diabetes mellitus, testosterone levels decreased

Gastrointestinal: Pancreatitis, duodenal ulcer, esophageal perforation, GI hemorrhage, internal hernia, intestinal perforation, salivary gland calculus

Genitourinary: Azoospermia, oligospermia

Hematologic: Thrombotic microangiopathy/thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TMA/TTP/HUS), neutropenic sepsis, pure red cell aplasia

Hepatic: Hepatic cholestasis, hepatitis B reactivation, hepatic cirrhosis

Immunologic: Dyspnea, flushing chest pain, angioedema

Infection: Aspergillosis, polyoma virus infection, sepsis

Metabolism and Nutrition: none

Neuromuscular & skeletal: Synovitis, bone fissure

Ocular: Papilledema, retinal artery thrombosis, retinal detachment

Respiratory: Acute cardiopulmonary event, acute respiratory distress syndrome, cardio-respiratory arrest, chronic obstructive pulmonary disease, pulmonary hypertension

Miscellaneous: Lymphoma, skin cancer, concomitant disease progression, multi-organ failure. Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

Nursing Guidelines

- Patient may experience headaches. Treat symptomatically with analgesics, and assess for their effectiveness. Instruct patient to report headaches that are not relieved.
- Fatigue: Work with patient in energy conserving lifestyle.
- Aphthous ulcers/oral mucositis: treat symptomatically. Potential treatments are over the counter salt and soda mouthwash, prescriptions such as viscous lidocaine or magic mouthwash (combination benadryl/maalox/lidocaine). Consult with treating provider for best option for your patient.
- Medication should be administered at the same time each day either consistently with food or without food. Tablets should be swallowed whole; they should not be crushed or chewed. Patients should be instructed to follow the requirements for fatty foods as outlined in the specific protocol.
- Patients should be instructed to avoid drinking grapefruit or other citrus juice while taking everolimus.
- Other drugs: Ensure that patients are aware of drug-drug interactions. Assess patients' use of other agents, including OTC (over the counter) agents and herbal supplements. Instruct patients not to start any medications without informing treating physician.
- Nausea: Monitor for nausea and treat symptomatically as required.
- Pneumonitis can be seen in patients taking everolimus. There have been fatal cases of this reported. Instruct patients to report any cough, shortness of breath, fever, chest pain, or any other related symptoms to the healthcare team immediately. Symptoms should be assessed at each visit.
- Diabetic patients may experience fluctuations in their blood sugar. Instruct patients to monitor their blood sugars closely.
- Hyperlipidemia and hypertriglyceridemia are common. Monitor lipid levels closely. Administer lipid lowering agents as ordered and monitor for their effectiveness. Pancreatitis may develop as a of high lipid levels. Instruct patients to report new or unusual abdominal pain to the study team promptly.
- Inform patient of possible rash, pruritis and dry skin. Instruct patient to report these side effects to the study team.
- Monitor LFT's. Report increase LFT's to treating physician.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)[39]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 8 weeks. After 12 cycles (or 48 weeks) of treatment, patients will be reevaluated every 16 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

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

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

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

Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions: Progression of disease per RECIST 1.1 since the completion of radiation therapy.

11.2.2 Non-Measurable Disease

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

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

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

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease:

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- **PET-CT:** If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- **Chest X-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- **Physical Examination:** For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **FDG-PET:** FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

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

     2) If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

     3) If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.3.3 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained within 9 weeks, and not less than 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 8 weeks (see Section 11.4.4).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease if the effusion is significant enough to be safely tapped..
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Target Lesions & Target Lymph Nodes

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

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

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

11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

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

11.4.3 Response Criteria

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

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

11.4.3.2 Evaluation of Target Lesions

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to < 1.0 cm.
- **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

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

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

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

11.4.4 Overall Objective Status

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

For Patients with Measurable Disease

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

* See Section 11.4.3.1

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

11.5 Definitions of analysis variables

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

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

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

12.1.2 Disease Progression: Give a minimum of 6 weeks of therapy. Remove from protocol therapy any patient with disease progression. Document details, including tumor measurements, on data forms.

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

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

12.2 Managing ineligible and canceled patients and major protocol violations

Data must be submitted per Section 5.0 for patients deemed ineligible or canceled. See also the Forms Packet for full details of data submission requirements. If a patient is deemed ineligible, they may be replaced.

12.2.1 Definitions

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

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

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

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

12.2.2 Follow-up Requirements

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

12.3 Extraordinary Medical Circumstances

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

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

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Overview

This randomized Phase II trial will compare the progression-free survival (PFS) of sorafenib and everolimus vs. sorafenib alone in patients with radioactive iodine refractory hürthle cell thyroid cancer. Prior studies have shown that the median PFS is generally around 4.5 months for sorafenib alone in this disease population[29]. It is hoped that the combination of everolimus and sorafenib can increase the median PFS to at least 9 months. In addition to PFS, this trial will also compare the confirmed response rate, overall survival (OS), and adverse event rates between sorafenib and everolimus vs. sorafenib alone.

13.2 Primary Endpoint

The primary endpoint for this study will compare PFS between sorafenib and everolimus vs. sorafenib alone in patients with radioactive iodine refractory hürthle cell thyroid cancer. PFS is defined as the time from randomization to the first of either disease progression or death from any cause, where disease progression will be determined based on RECIST 1.1[39] and will be documented at each enrolling site with no central review planned.

Final Analysis: The primary goal is to compare sorafenib and everolimus vs. sorafenib alone, where the alternative hypothesis is that sorafenib and everolimus has improved PFS compared to sorafenib alone. We will enter 15 evaluable patients to each arm of the study using a 1:1 randomization scheme (30 evaluable patients total), unless the study is stopped early at the time of the interim futility analysis (see below). With 15 evaluable patients per arm, we have 80% power to detect an improvement in the median PFS from 4.5 to 9 months (hazard ratio (HR)=0.50), assuming a 1-sided significance level of 0.20 and an accrual rate of 1 patient per month. The primary analysis will be a comparison of sorafenib and everolimus vs. sorafenib alone using a one-sided log-rank test. This analysis will take place after an approximate 36 ~~14~~ month accrual period, and after 28 total events have occurred across both arms combined (which should happen after about 12 months of follow-up in all evaluable patients). All patients who meet the eligibility criteria, sign the consent form, and are randomized will be considered evaluable for this endpoint.

Interim Futility Analysis: The interim futility analysis will happen after 14 events are observed across both arms combined. The interim futility boundary was selected using EAST software. We selected a Rho family "Beta" spending function with rho parameter "equal" 1.015. To reject the alternative hypothesis at the interim analysis (i.e. reject sorafenib and everolimus as promising), the HR will need to be > 1 for sorafenib and everolimus vs. sorafenib alone, which corresponds to a 1-sided p-value greater than 0.50. If the HR is less than or equal to 1 (1-sided $p <= 0.50$), the study will continue to full accrual and the final analysis will be conducted as discussed above.

13.3 Secondary Endpoints

The following endpoints will be compared between the 2 arms: confirmed response rate, overall survival, and adverse events.

Confirmed Response Rate: A patient will be classified as a confirmed response per the RECIST 1.1 criteria, if they have a partial or complete response for 2 consecutive evaluations at least 4 weeks apart. The proportion of patients with a confirmed response will be calculated and compared between the 2 arms using a Chi-square or Fisher's Exact test.

Overall Survival: Overall survival (OS) is defined as the time from study entry to death from any cause. OS will be estimated using the Kaplan-Meier method, where the log-rank test will be used to compare the 2 treatment arms.

Adverse events: The maximum grade for each type of adverse event will be summarized using CTCAE version 4.0. The frequency and percentage of grade 3+ adverse events will be compared between the 2 treatment arms. Comparisons between arms will be made by using either the Chi-square or Fisher's Exact test.

Crossover patients exploratory analysis: In the crossover group that receives everolimus alone, we will assess both the response rate and progression-free survival as an exploratory analysis.

13.4 Total Sample Size

A maximum of 30 evaluable patients will be accrued onto this randomized phase II study unless the study is closed early for excessive toxicity or lack of efficacy. We anticipate accruing an additional 10% of patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is 34 patients (17 per arm).

13.5 Expected Accrual and Accrual Duration

The expected accrual rate is about 1 patient per month for the Alliance group. With this accrual rate, we expect to finish accrual within about 36 months, assuming we accrue 34 total patients.

13.6 Anticipated time to study completion

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

13.7 AE Stopping Rule

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

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

- If at any time, 3 of the initial 10 treated patients or 30% or more of all patients (i.e. when accrual is greater than 10 patients) have experienced a grade 4 adverse event.
- If at any time, 2 patients have experienced a grade 5 adverse event (not due to progressive disease).

13.8 Accrual Monitoring Stopping Rule

Given the expected accrual rate is around 1 patient per month, it is expected that the study will take around 36 months to fully accrue. We plan to monitor the accrual continually and if we only end up accruing 4 patients or less in the first year (after study activation), we will consider stopping the trial for slow accrual.

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

The primary endpoint is a comparison of PFS between the 2 treatment arms, as discussed in detail in section 13.2. The final analysis is expected to take place around 5 years after the study begins, so we expect that the primary endpoint completion time to be around 5 years after study activation.

13.10 Descriptive Factors

- Metastatic Disease outside the chest: Yes vs. No
- Any prior chemo/TKI regimens: Yes vs. No
  - Prior VEGFR TKI: Yes or No
  - Prior targeted therapy other than VEGFR TKI: Yes or No
  - Prior cytotoxic chemotherapy (e.g., doxorubicin, paclitaxel): Yes or No
  - Prior RAI: Yes or No
  - Prior RAI > 600mCi: Yes or No
  - Prior Thyroidectomy: Yes or no
- Any lesion with SUVmax > 5 (from PET/CT scan in prior 6 months): Yes vs. No

13.11 Inclusion of Women and Minorities

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

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	23	9	32
Ethnic Category: Total of all subjects	24	10	34
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	2	1	3
Black or African American	2	1	3
Native Hawaiian or other Pacific Islander	1	1	2
White	18	6	24
Racial Category: Total of all subjects	24	10	34

Ethnic Categories:

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

Not Hispanic or Latino

Racial Categories:

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

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

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

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

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

14.0 CORRELATIVE AND COMPANION STUDIES

There are no correlative or companion studies available for A091302.

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

There are no credentialing requirements for A091302.

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APPENDIX I REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

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

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

How would you describe:

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

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

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

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

APPENDIX II ALLIANCE A091302 OPTIONAL MEDICATION CALENDARS

PATIENT MEDICATION DIARY – Sorafenib 28-day cycle

Today's date _____ **Agent: Sorafenib**

Patient Name_____ *(initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **sorafenib**.
2. **Sorafenib should be taken twice daily on an empty stomach one hour before or two hours after eating. These tablets should be swallowed whole and cannot be crushed or chewed.**
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily doses(am/pm)		# of capsules taken	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					

Day	Date	Time of daily doses (am/pm)		# of capsules taken	Comments
25					
26					
27					
28					

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of capsules taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

Patient's signature

_____

PATIENT MEDICATION DIARY – Sorafenib 56-day cycle

Today's date _____ **Agent: Sorafenib**

Patient Name_____ *(initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 8 week-period while you take **sorafenib**.
2. **Sorafenib should be taken twice daily on an empty stomach one hour before or two hours after eating. These tablets should be swallowed whole and cannot be crushed or chewed.**
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily doses(am/pm)		# of capsules taken	Comments
1					
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Day	Date	Time of daily doses (am/pm)		# of capsules taken	Comments
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Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of capsules taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____=_____

Patient's signature

_____

PATIENT MEDICATION DIARY – Everolimus 28-day cycle

Today's date _____ **Agent: Everolimus**

Patient Name_____ *(initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **everolimus**.
2. **Everolimus should be administered once daily at approximately the same time each day with or without food. Tablets should be swallowed whole with a glass of water. The tablets must not be chewed or crushed and grapefruit juice or grapefruit should be avoided.**
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of tablets taken	Comments
1				
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24				

Day	Date	Time of daily dose	# of tablets taken	Comments
25				
26				
27				
28				

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of tablet's taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

Patient's signature

_____

PATIENT MEDICATION DIARY – Everolimus 56-day cycle

Today's date _____ **Agent: Everolimus**

Patient Name_____ *(initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 8 week-period while you take **everolimus**.
2. **Everolimus should be administered once daily at approximately the same time each day with or without food. Tablets should be swallowed whole with a glass of water. The tablets must not be chewed or crushed and grapefruit juice or grapefruit should be avoided.**
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of tablets taken	Comments
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Day	Date	Time of daily dose	# of tablets taken	Comments
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Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of tablet's taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

Patient's signature

_____