MEMORIAL SLOAN-KETTERING CANCER CENTER

IRB PROTOCOL

IRB#: 09-148 A(10)

Phase II Study Evaluating the Combination of Temsirolimus and Sorafenib in the Treatment of Radioactive Iodine Refractory Thyroid Cancer

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Eric Sherman MD	Medicine
Co-Principal Investigator(s)/Department:	James Fagin MD	Medicine
	David Pfister MD	Medicine

Memorial Sloan-Kettering Cancer Center
1275 York Ave.
New York, NY 10021

Amended: 05/12/15

Investigator(s)/Department:		
	Alan Ho MD	Medicine
	Robert Michael Tuttle MD	Medicine
	Shrujal Baxi, MD	Medicine
	Nicole Leonhart NP	Medicine
	Hilda Stambuk MD	Radiology
	Eric Lis MD	Radiology
	Sofia Haque MD	Radiology
	Sasan Karimi MD	Radiology
	John Lyo, MD	Radiology
	Vaios Hatzoglou, MD	Radiology
	Tunc Iyriboz, MD	Radiology
	Ronald Ghossein MD	Pathology
	Nora Katabi MD	Pathology
	Camelia Sima MD MS	Biostatistics
	Michelle Boyar, MD	Medicine – Phelps
	Philip Caron, MD	Medicine – Phelps
	Nancy Mills, MD	Medicine – Phelps
	Stephanie Smith-Marrone, MD	Medicine – Phelps
	Carolyn Wasserheit-Leiblich, MD	Medicine – Phelps
	Michael Fanucchi, MD	Medicine – Phelps
	Arlyn Apollo, MD	Medicine – Mercy
	Pamela Drullinsky, MD	Medicine – Mercy
	Zoe Goldberg, MD	Medicine – Mercy
	Kenneth Ng, MD	Medicine – Mercy
	Tiffany Troso-Sandoval, MD	Medicine – Mercy
	Deena Atieh-Graham, MD	Medicine - Basking Ridge
	Ephraim Casper, MD	Medicine - Basking Ridge
	Audrey Hamilton, MD	Medicine - Basking Ridge
	Mila Gorsky, MD	Medicine - Basking Ridge
	Han Xiao, MD	Medicine - Basking Ridge
	Shilen Patel, MD	Medicine - Basking Ridge
	Tina M. Passalaris, MD	Medicine – Basking Ridge
	Asma Latif, MD	Medicine – Basking Ridge
	Afsheen Iqbal, MD	Medicine – Basking Ridge
	Stefan Berger, MD	Medicine – Commack
	Julie Fasano, MD John	Medicine – Commack
	J Fiore, MD Stuart	Medicine – Commack
	Lichtman, MD Philip	Medicine – Commack
	Schulman, MD Steven	Medicine – Commack
	Sugarman, MD	Medicine – Commack
	Marni Sheren-Manoff, MD	Medicine – Commack
	Marisa F Siebel	Medicine – Commack
	Frank Tsai, MD	Medicine – Commack

Consenting Professional(s)/Department:	
Eric Sherman MD	Medicine
David Pfister MD	Medicine
Alan Ho MD	Medicine
Robert Michael Tuttle MD	Medicine
Shrujal Baxi, MD	Medicine
Stephanie Smith-Marrone, MD	Medicine – Phelps
Carolyn Wasserheit-Leiblich, MD	Medicine – Phelps
Philip Caron, MD	Medicine – Phelps
Nancy Mills, MD	Medicine – Phelps
Michael Fanucchi, MD	Medicine – Phelps
Michelle Boyar, MD	Medicine – Mercy
Zoe Goldberg, MD	Medicine – Mercy
Kenneth Ng, MD	Medicine – Mercy
Pamela Drullinsky, MD	Medicine – Mercy
Arlyn Apollo, MD	Medicine – Mercy
Tiffany Troso-Sandoval, MD	Medicine - Basking Ridge
Ephraim Casper, MD	Medicine - Basking Ridge
Audrey Hamilton, MD	Medicine - Basking Ridge
Mila Gorsky, MD	Medicine - Basking Ridge
Han Xiao, MD	Medicine - Basking Ridge
Deena Atieh-Graham, MD	Medicine - Basking Ridge
Tina M. Passalaris, MD	Medicine – Basking Ridge
Asma Latif, MD	Medicine - Basking Ridge
Afsheen Iqbal, MD	Medicine – Basking Ridge
Shilen Patel, MD	Medicine – Commack
Steven Sugarman, MD	Medicine – Commack
John J Fiore, MD	Medicine – Commack
Philip Schulman, MD	Medicine – Commack
Stefan Berger, MD	Medicine – Commack
Marni Sheren-Manoff, MD	Medicine – Commack
Julie Fasano, MD	Medicine – Commack
Marisa F Siebel	Medicine – Commack
Frank Tsai, MD	Medicine – Commack
Stuart Lichtman, MD	

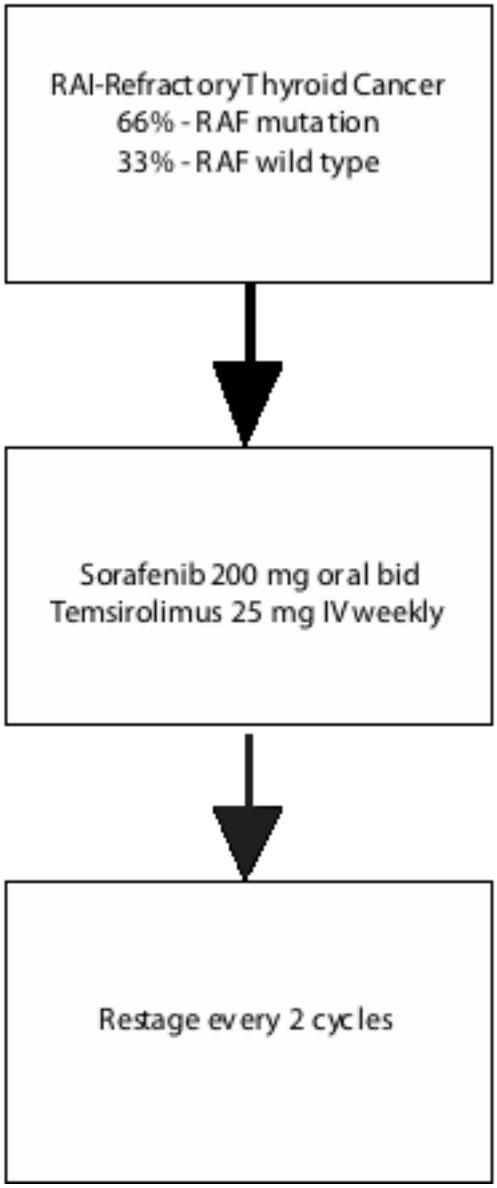
Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

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.

This is a proposed phase II study to evaluate the efficacy of sorafenib and temsirolimus in combination, in the treatment of recurrent and/or metastatic thyroid cancer.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- Determine the objective response rate of the combination sorafenib and temsirolimus in I-131 refractory thyroid cancer.

Secondary Objective

- Evaluate if the presence of *BRAF* mutations, with or without concomitant mutations in the PI3K AKT, mTOR pathway, predict response to therapy.
- Determine progression-free survival under the combination sorafenib and temsirolimus in I-131 refractory thyroid cancer.
- Evaluate safety and tolerability for the combination sorafenib and temsirolimus in I-131 refractory thyroid cancer.

3.0 BACKGROUND AND RATIONALE

3.1 Thyroid Cancer

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. Prior to 2005, there were no abstracts presented at the American Society of Clinical Oncology annual meeting describing prospective chemotherapy studies for thyroid cancer. However, during the past several meetings, there have been multiple phase II studies evaluating targeted therapies such as sorafenib[1,2], axitinib[3], sutinib[4], gefitinib[5], and lenalidomide[6].

Thyroid carcinomas of follicular cell origin are believed to represent a continuous and progressive spectrum of disease. Two current models of progression currently exist. The conventional model postulates that thyroid carcinomas develop in mature follicular thyrocytes and dedifferentiate through progressive genetic damage from the differentiated thyroid carcinomas (e.g., papillary, follicular) into more high grade thyroid carcinomas (e.g., poorly differentiated and anaplastic). The alternative model proposes that thyroid carcinogenesis does not result from transformation of mature follicular thyrocytes, but from developing follicular thyrocytes, with the more immature cells developing into high grade thyroid carcinomas, and the more mature follicular thyrocytes transforming into differentiated thyroid carcinomas. Regardless of which model is embraced, both models agree that there are strong genetic-pathological correlations in all sub-types of thyroid carcinomas of follicular cell origin, be it one of progressive genetic damage as proposed by the former, or a developmental one as proposed by the latter.

3.2 MAPK Pathway

The RAS/RAF/MEK/ERK cascade (classical MAPK pathway) transduces growth factor-initiated signals that regulate cell proliferation and survival. In human cancer, MAPK pathway activation is often the result of mutations in *RAS*, *BRAF* and upstream receptor tyrosine kinases (RTK).

Tumors in which MAP kinase is activated by mutations upstream of *BRAF* (*RAS*, RTKs) are typically less sensitive or resistant to MEK inhibition. These data suggest that MEK inhibitors may be particularly effective in tumors with *BRAF* mutations, and perhaps less so in some tumors with mutant *RAS*[7,8].

The MAPK pathway seems particularly important in thyroid cancers. BRaf is the predominant Raf isoform seen in thyroid follicular cells. BRaf has a higher affinity for MEK1 and MEK2 than CRaf or ARaf, and is more efficient in phosphorylating MEKs than other Raf isoforms[9]. *BRAF* mutations are the most common genetic abnormality in papillary thyroid cancers (36-69%)[10-13]. They are mutually exclusive with mutations of *RAS* genes and with mutations in the receptor kinase receptors *RET* and *NTRK*[12,13] . These genes encode for effectors in the MAPK signaling pathway, hence providing compelling genetic evidence for the significance of MAPK dysregulation in thyroid tumorigenesis. *BRAF* mutations are thought to occur early in the development of papillary thyroid cancers, and are found most commonly in aggressive tumors[14]. Studies have shown that *BRAF* mutations are found commonly in thyroid cancers with poor prognostic features such as the tall cell variant of papillary thyroid cancer (PTC), in tumors associated with extrathyroidal extension, and in anaplastic carcinomas arising from PTC[15]. Moreover, a recent study from our institution shows that recurrent and metastatic PTC and poorly differentiated thyroid cancers (PDTC) that are radioiodine refractory and/or FDG-PET positive are markedly enriched for *BRAF* mutations, often found in association with mutations of *PIK3CA* or *AKT1* (Ricarte Filho JC et al. Cancer Research. 2009. in press).

3.2 mTOR

The mTOR kinase is considered to be important in cancer, as it integrates responses to growth factors, particularly those transduced via the RAF-MEK-MAPK pathway, and the phosphoinositol-3-kinase (PI3K)-AKT pathways. mTOR assembles into two holoenzyme complexes: with Raptor, to form mTORC1, and with Rictor, to form mTORC2. In thyroid cells, mTORC1 activity is required for the proliferative effects of TSH in vitro and in vivo. Unpublished work from the Fagin lab 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, combined treatment with MEK inhibitors and rapamycin shows cooperative growth inhibitory effects in a subset of cell lines with *BRAF* mutations.

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[16]. mTORC1 inhibitors are active in PTEN-deficient tumors[17-19]. In other cancers, concomitant loss of PTEN may decrease the response to specific tyrosine kinase inhibitors: i.e. EGFR kinase inhibitors in glioblastomas (Melinghoff IK. Clin Canc Res 2007). . Hence, it is possible that partial refractoriness to monotherapy with RAF or MEK inhibitors in thyroid cancers with ***BRAF*** mutations may be accounted for in part by concomitant activation of PI3K-mTOR signaling.

3.3 Sorafenib for the treatment of thyroid cancer

Sorafenib is an orally active multi-tyrosine kinase inhibitor of multiple targets, including BRAF, VEGFR1, and VEGFR2[20]. It has already been approved by the US FDA for the treatment of renal cell carcinoma and hepatocellular carcinoma. A phase II study at the University of Pennsylvania has shown a partial response rate of 23% with stable disease present in 53% of patients with thyroid cancer [21]. Median progression-free survival was 79 weeks. No difference was seen between patients with papillary and follicular thyroid cancer. Overall, sorafenib was felt to be an effective agent in the treatment of thyroid cancer. What is less clear is whether it works mainly through inhibiting VEGF action, the RAF-MEK-MAPK pathway, or both. Activity of sorafenib in melanoma is not dependent on BRAF mutational status[22]. We do not know if this is true for thyroid cancer, although activity was seen in follicular and Hurthle cell thyroid cancers, which would not have BRAF mutations.

It also needs to be noted that a phase II study with sorafenib at Ohio State showed only a 15% response rate (5 out of 33 patients) with 57% stable disease rate in patients with papillary thyroid cancer who were treatment naïve[23]. Median progression free survival was 16 months. No responses were seen in the 15 subjects (4 with anaplastic thyroid cancer) who had nonpapillary thyroid cancer. In the non anaplastic thyroid cancer group, the total response rate was 11.5%.
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.

3.4 Combination of sorafenib and temsirolimus

Preclinical evidence suggests synergy when both the MAPK and PI3K-mTOR pathways are inhibited[24]. The combination of sorafenib with mTORC1 inhibitors increases cell death in melanomas, where *BRAF* mutations are particularly common[25], and the combination of sorafenib and temsirolimus is currently being evaluated in the treatment of melanoma in a large randomized phase II study through the Southwest Oncology Group. The doses used in this study are sorafenib 200 mg orally twice a day and temsirolimus 25 mg intravenously weekly. Furthermore, this combination is being evaluated in the treatment of kidney cancer (by the Eastern Cooperative Oncology Group) and glioblastoma multiforme (North Central Cancer Treatment Group). In the phase I study evaluating this combination[26], a partial response was seen in a subject with papillary thyroid cancer.
As noted above, sorafenib is an inhibitor of multiple targets. At this time, it is unclear which targets are meaningful clinically. Multiple phase II studies have suggested that VEGF is an important target in the treatment of thyroid cancer. Despite the importance of the RAF-MEK-MAPK pathway as a target in the treatment of thyroid cancer in the laboratory, it is still unknown whether (1) the target is important clinically and (2) sorafenib exerts any clinical effect in the treatment of thyroid cancer by targeting this pathway. There is little doubt from the phase II study at the University of Pennsylvania that sorafenib is active in tumors without BRAF mutations since responses were seen in tumors known not to have this mutations (i.e., Hurthle cell, follicular)[21]. It will be important to determine if activation of the RAF-MEK-MAPK pathway is important in conferring sensitivity to this drug, in order to refine the design of future studies with sorafenib and

other agents and to determine optimal combinations. In addition, it may help determine which subset of thyroid cancer patients would most benefit with the combination of a RAF inhibitor (sorafenib) and mTORC1 inhibitors such as (tesirolimus).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

We propose a phase II study to evaluate the efficacy of the combination sorafenib with temsirolimus in patients with thyroid cancer of follicular cell origin (e.g., papillary, follicular, Hurthle cell). A maximum of 36 subjects will be evaluated during the study. Restaging scans, with evaluation of response, will be done every 2 cycles (8 weeks of treatment). Treatment will continue until clinical disease progression, unacceptable toxicity, treatment delay > 4 weeks, or at the discretion of the treating physician or patient. Regardless of the duration of treatment, objective response rate will be based on the response within the first 4 cycles of treatment.

A secondary hypothesis will evaluate how the *BRAF* status affects response to therapy. Therefore, all subjects will be required to have tissue (archival is acceptable) for genetic testing at enrollment.

4.2 Intervention

Treatment will be with sorafenib 200 mg orally twice a day and temsirolimus 25 mg intravenous weekly. A cycle will be equivalent to 4 weeks of treatment. These are the doses being used for SWOG protocol 0438 (a randomized phase II study in melanoma). A phase I study recommended this dose level and felt using the full dose of sorafenib (400 mg twice a day) was too toxic[26].

4.3 Tumor Genotyping

In order to determine the *BRAF* mutational status, the DNA from the original tumor and/or of the metastatic lesion (when available) will be genotyped for $BRAF^{T1799A}$ mutation by mass spectrometry. Tumor genomic DNA from all patients will be genotyped more comprehensively for all known mutations of the 3 *RAS* genes, *PIK3CA*, *AKT1* by Sequenom mass spectrometry which has already been optimized in the Fagin lab, to investigate other markers potentially conferring responsiveness to the study agents. The Sequenom assay allows all these genes to be screened simultaneously in 384 well plates. Six multiplexed wells are required for each tumor sample, and the entire assay can be performed in 72h, thus allowing us to enroll patients based on their genotype (BRAF status).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 BAY 43-9006 (sorafenib; NSC-724772)

Chemical Name : 4–{4-[3-(4-chloro-3-trifluoromethyl-phenyl)ureido]-phenoxy}-pyridine-2 carboxylic acid methylamide-4-methylbenzensulfonate.

Other Names: BAY 54-9085 is the tosylate salt of BAY 43-9006; sorafenib
Classification: Kinase inhibitor (Raf, VEGF-R, and PDGF-R)
Mechanism of Action: The ras/raf signaling pathway is an important mediator of responses to growth signals and angiogenic factors. This pathway is often aberrantly activated in human tumors due to presence of activated ras, mutant b-raf, or over expression of growth factor receptors. Sorafenib is a potent inhibitor of c-raf, and wild-type and mutant braf in vitro. Additionally, further characterization of sorafenib revealed that this agent inhibits several receptor tyrosine kinases (RTKs) that are involved in tumor progression (VEGF-R, PDGF-R, Flt3, and c-KIT) and p38α, a member of the MAPK family.
Molecular Formula: $C_{12}H_{16}ClF_3N_4O_3 \cdot C_7H_8O_3S$
M.W.: Sorafenib tosylate: 637 Daltons; free base: 465 Daltons
Approximate Solubility: 0.19 mg/100 mL in 0.1 N HCl, 453 mg/100 mL in Ethanol, and 2971 mg/100 mL in PEG400.
How Supplied: BAY 43-9006 sorafenib 200 mg is supplied as round, biconvex, red-film-coated tablets, debossed with the 'Bayer cross' on one side and '200' on the other side. The tablets contain BAY 43-9006 tosylate equivalent to 200 mg of the free base BAY 43-9006, and the excipients croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium laurylsulfate, and magnesium stearate. The film-coat consists of hypromellose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active BAY 43-9006 tosylate. Study Drug can be supplied as BAY 43-9006 sorafenib 200 mg commercial tablets in bottles of 140 tablets with a product identification label affixed or as commercial Sorafenib in bottles of 120 tablets.
Storage: Do not store above 25°C (77°F). Store in the original package.
Stability: The current shelf life is 36 months.
Route(s) of Administration: Orally
Method of Administration: The recommended daily dose of SORAFENIB is 200 mg (1 x 200 mg tablets) taken twice daily, without food (at least 1 hour before or 2 hours after eating).
Potential Drug Interactions: Sorafenib is metabolized by the P450 CYP3A enzyme and has been shown in preclinical studies to inhibit multiple CYP isoforms. Therefore, it is possible that sorafenib may interact with drugs that are metabolized by the P450 CYP isoenzymes or with drugs that inhibit CYP 3A. Close monitoring is recommended for patients taking agents with narrow therapeutic indices and metabolized by the liver, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin. Additionally, sorafenib is 97% to 99% protein bound; however, no drug interactions have been reported in studies, thus far.

Adverse Events:

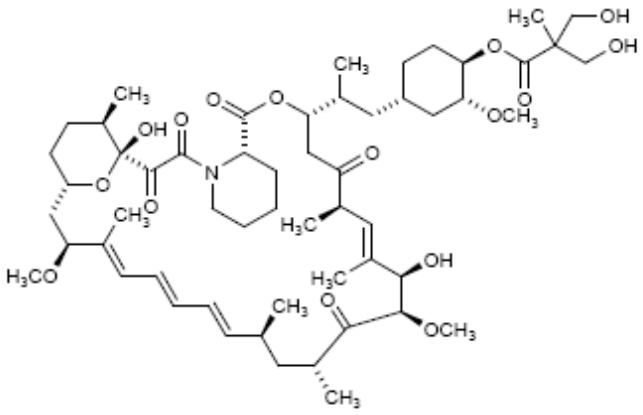
Refer to current version of Sorafenib Package Insert for complete listing of adverse reactions for sorafenib.

1. *Hematologic:* neutropenia, thrombocytopenia, anemia, leukopenia
2. *Body as a whole:* fatigue, flu-like syndromes, fever, arthralgia, pain (including bone pain, joint pain, muscle pain, mouth pain, abdominal pain, tumor pain, and headache)
3. *Cardiac:* hypertension, myocardial infarction, congestive heart failure
4. *Dermatology/Skin:* hand-foot skin reaction, characterized by palmar and plantar erythema; rash/desquamation, hypersensitivity reactions, dry skin, alopecia, nail changes, vitiligo, pruritis, exfoliative dermatitis
5. *Gastrointestinal:* diarrhea; pancreatitis, elevated amylase/lipase, abdominal

pain/cramping, nausea, flatulence, dyspepsia, ascites, constipation, dehydration, dysphagia, mucositis/stomatitis, vomiting, gastrointestinal perforation
6. *Genitourinary:* renal failure
7. *Hemorrhage/Bleeding:* hemorrhage (including gastrointestinal hemorrhage, respiratory tract hemorrhage, cerebral hemorrhage, epistaxis, mouth hemorrhage, rectal hemorrhage, nail bed bleeding, and hematoma)
8. *Hepatic:* increased bilirubin, ALT, AST, GGT, LDH, and alkaline phosphatase
9. *Infection:* febrile neutropenia, infection
10. *Metabolic and Nutritional:* anorexia, albumin, hyperglycemia, hypophosphatemia, decreased weight
11. *Neurologic:* peripheral sensory neuropathy, RPLS
12. *Pulmonary/Upper Respiratory:* hypoxia, pleural effusion, pneumonitis/pulmonary infiltrates, pneumothorax
13. *Other:* Depression

5.2 Temsirolimus (CCI-779; Torisol)

Chemical Name : Rapamycin 42-[2,2-bis(hydroxymethyl)propionate]



Classification: mTOR inhibitor. (Raf, VEGF-R, and PDGF-R)
Mechanism of Action: Temsirolimus (CCI-779) is a structural analog of sirolimus (Rapamycin®) that has been formulated for IV or oral administration for the treatment of various malignancies. Sirolimus was shown to have potent immunosuppressive as well as antifungal and antitumor properties. Its mechanism of action results in part from binding to an intracellular cytoplasmic protein, FKBP-12. The complex of sirolimus bound to FKBP-12 blocks the activity of mTOR, which regulates a signaling cascade that controls growth factor-induced cell proliferation. The net effect of this class of compounds on cells is to block the G1 to S phase transition of the cell cycle. The activity of sirolimus and temsirolimus in vitro can be blocked by a competitive inhibitor (ascomycin) for FKBP-12 binding, suggesting that the 2 compounds have the same mechanism of action. The mechanism of action of temsirolimus, that is binding to FKBP-12 and subsequent inhibition of growth factor-mediated mTOR signaling, is novel for an anticancer drug. Inasmuch as human tumors are partly regulated by growth factors, temsirolimus is expected to inhibit proliferation across a broad range of human tumors. In addition to directly inhibiting tumor cell growth, supportive elements of the tumor microenvironment that require growth factors, such as tumor stroma development and

angiogenesis, may also be inhibited by temsirolimus. Another tumor suppressor gene frequently mutated in human cancer that regulates mTOR pathway is phosphatase related to tensin (PTEN). Loss of PTEN results in increased activation of phosphatidylinositol-3 kinase (PI3K) and its downstream targets Akt and mTOR. Tumors with PTEN loss and or Akt activation respond well to temsirolimus.

Molecular Formula: C56H87NO16

M.W.: 1030.30

Approximate Solubility at 25°C: 514.9 mg/mL in Ethanol (anhydrous), and 27.3 mg/mL in PEG 400.

How Supplied: 25 mg/ ml vials [redacted]

Storage:

Concentrate for Injection should be stored refrigerated (2kinase (PI3K) and its downstream targets Akt and mTOR. Tumors with PTEN los

The active product and diluent must be allowed to warm to room temperature for approximately 1 hour before dilution. Dilution of Temsirolimus Concentrate for Injection in Diluent for Temsirolimus Concentrate for Injection must be followed by further dilution into an infusion bag or bottle of 0.9% sodium chloride injection.

The drug-diluent mixture is stable for up to 24 hours at controlled room temperature. The final diluted infusion solution (drug-diluent in sodium chloride injection) should be stored in a secured, clean environment, at room temperature, and administered within 6 hours from the time that the concentrate-diluent mixture is added to the 0.9% sodium chloride injection. Admixtures of temsirolimus are stable under ordinary fluorescent room light, but should be protected from excessive light, such as sunlight.

Stability: The drug-diluent mixture is stable for up to 24 hours at controlled room temperature. The final diluted infusion solution (drug-diluent in sodium chloride injection) should be stored in a secured, clean environment, at room temperature, and administered within 6 hours from the time that the concentrate-diluent mixture is added to the 0.9% sodium chloride injection. Admixtures of temsirolimus are stable under ordinary fluorescent room light, but should be protected from excessive light, such as sunlight.

Route(s) of Administration: Intravenous. Dilutions of Temsirolimus Concentrate for Injection must be carried out in glass or polyolefin administration devices. Infusion bags and sets containing polyvinyl chloride should not be used to administer this product to avoid leaching of plasticizer. In addition, an in- [redacted] Concentrate for Injectio

Potential Drug Interactions: The primary oxidative metabolism is via CYP3A4, indicating that inhibitors and inducers of CYP3A4 enzyme system may alter the metabolism of temsirolimus, although temsirolimus does not induce CYP3A4. Temsirolimus may inhibit the metabolic clearance of substrates of CYP3A4/5 or CYP2D6 but not CYP2C9 or CYP2C8. However, a clinical study to assess the ability of temsirolimus to inhibit disposition of desipramine, a sensitive CYP2D6 substrate, was negative. This finding indicates that the effect of temsirolimus on other agents metabolized by either CYP2D6 or CYP3A4/5 is expected to be low. In vitro studies showed that temsirolimus is subject to P-gp-mediated efflux; in addition, temsirolimus inhibited the transport of digoxin, a P-gp substrate. The clinical relevance of these in vitro determined P-gp data is currently unknown.

The drug interaction potential of temsirolimus was evaluated in phase 1 drug-interaction studies. Coadministration of IV temsirolimus with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus C_{max} and AUC but increased the major metabolite sirolimus C_{max} by

2.2-fold and AUC by 3.1-fold compared to temsirolimus treatment alone. Caution should be used when administering strong CYP3A4 inhibitors with temsirolimus IV. For subjects with MCL, coadministration of CYP3A4 inhibitors with temsirolimus should be avoided. Coadministration of temsirolimus with rifampin, a potent CYP3A4 inducer, had no significant effect on temsirolimus C_{max} and AUC after IV administration, but decreased sirolimus C_{max} by 65% and sirolimus AUC by 56% compared with temsirolimus treatment alone. It is recommended that caution be used when administering strong CYP3A4 inducers with temsirolimus.

Adverse Events:
Serious:
Hypersensitivity Reactions, Hyperglycemia, Interstitial Lung Disease, Bowel Perforation, and Renal Failure

Common:
Rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities observed with TORISEL are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.

Less Common but >10%:
Pain, Pyrexia, weight loss, headaches, chest pain, chills, diarrhea, abdominal pain, constipation, vomiting, infections, urinary tract infections, pharyngitis, rhinitis, back pain, arthralgia, dyspnea, cough epistaxis, pruritis, nail disorder, dry skin, acne, dysgeusia, insomnia.

The following selected adverse reactions were reported less frequently (<10%):
Gastrointestinal Disorders – Fatal bowel perforation occurred in 1 patient (1%).
Eye Disorders - Conjunctivitis (including lacrimation disorder) occurred in 15 patients (7%).
Immune System - Allergic/Hypersensitivity reactions occurred in 18 patients (9%).
Angioneurotic edema-type reactions have been observed in some patients who received temsirolimus and ACE inhibitors concomitantly.
Infections - Pneumonia occurred in 17 patients (8%); upper respiratory tract infection occurred in 14 patients (7%).
General Disorders and Administration Site Conditions - Impaired wound healing occurred in 3 patients (1%).
Respiratory, Thoracic and Mediastinal Disorders – Interstitial lung disease occurred in 5 patients (2%), including rare fatalities.
Vascular - Hypertension occurred in 14 patients (7%); venous thromboembolism (including deep vein thrombosis and pulmonary embolus) occurred in 5 patients (2%); thrombophlebitis occurred in 2 patients (1%).

5.2.3 Source of Temsirolimus

The supply of Temsirolimus will come from Pfizer. All requests for drug need to be sent to Benedetta Campanelli. Contact information is:

Benedetta Campanelli
Global IIR Senior Associate
Pfizer, Inc.
235 East 42 Street, MS 219/02/01
Office 219/02/98
New York, NY 10017
Benedetta.Campanelli@pfizer.com

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Patients must have histopathologically confirmed at MSKCC thyroid carcinoma of follicular cell origin (D-TC-FCO), which includes papillary, follicular, Hürthle cell histology, or anaplastic, along with their respective variants.
- Available pathology for RAF mutational testing (e.g., paraffin block or 5-10 unstained slides). It is not required that mutational testing be completed before starting the clinical study.

- Patients must have surgically inoperable and/or recurrent/metastatic disease.

- Patients must have a PET scan prior to the protocol start date and have at least one FDG-avid lesion that has not been removed surgically or radiated (unless it has progressed by RECIST criteria after the completion of radiation therapy and is still FDG-avid). FDG-avidity will be defined as any focus of increased FDG uptake greater than normal activity with SUV maximum levels greater than or equal to 3. PET scan can have been done at any time prior to the start of therapy, although it is recommended that it be done within 3 months prior to the start of therapy.

- 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; performed ≤ 4 weeks of protocol start date.

- Patients must have progressive disease defined by at least <u>one</u> of the following occurring during or after previous treatment (including RAI treatment):

    - The presence of new or progressive lesions on CT/MRI.

    - New lesions on bone scan or PET scan.

    - Rising thyroglobulin level (documented by a minimum of three consecutive rises, with an interval of > 1 week between each determination).

- Prior RAI therapy is allowed if > 3 months prior to initiation of therapy 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.

- Patients may have received prior external beam radiation therapy to index lesions ≥ 4 weeks prior to initiation of therapy on this protocol if there has been documented progression by RECIST criteria. Prior external beam radiation therapy to the non-index lesions is allowed if ≥ 4 weeks prior to initiation of therapy on this protocol.

- ECOG p performance status [redacted].

- Patients must have normal organ and marrow function as defined below:

    - Absolute neutrophil count ≥1,500/mcL

    - Platelets ≥100,000/mcL

    - Total bilirubin ≤ 1.5 X institutional ULN*

    - AST(SGOT)/ALT(SGPT) ≤ 2.5 X institutional ULN**

    - Creatinine ≤ 1.5 X institutional ULN

      OR

      Creatinine clearance ≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above 1.5 X institutional ULN [in this circumstance, either of a measured level based on a 24 hour urine collection, or a calculated level using the Cockcroft and Gault equation: (140 – age in years) X (weight in kg) X (0.85 if female)/72 X serum Cr may be used].

    - International normalized ratio (INR) ≤ 1.5 (or in range INR, usually between 2 and 3, if patient is on a stable dose of therapeutic warfarin).

  *ULN = upper limit of normal

  **unless liver metastasis present in which AST/ALT should be ≤ 5 x ULN.

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

- Age 21 years old or older.

6.2 Subject Exclusion Criteria

- Patients may not be receiving any other investigational agents.

- Patients with known history of active intraparenchymal brain metastasis within previous 3 months.

- Serious or non-healing wound, ulcer, or bone fracture.

- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment.

- Patients with a reported history of clinically active diverticulosis or diverticulitis in the prior 3 years.

- Patients with clinically significant cardiovascular disease as defined by the following:

    - History of CVA within past 6 months

    - Myocardial infarction, CABG or unstable angina within past 6 months

    - New York Heart Association grade III or greater congestive heart failure or Canadian Cardiovascular Class grade III or greater angina within past 6 months (Appendices B&C)

    - Clinically significant peripheral vascular disease within past 6 months

    - Pulmonary embolism, DVT, or other thromboembolic event within past 6 months

    - Uncontrolled coronary artery disease, angina, congestive heart failure, or ventricular arrhythmia requiring acute medical management within past 6 months

    - History of myocardial infarct, cerebrovascular accident, or transient ischemic event within the past 6 months

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

- While the use of Angiotensin-Converting Enzyme (ACE) inhibitors is not absolutely excluded, efforts should be made to see if patients on ACE inhibitors can be taken off the medication or switched to another medication.

- Pregnant women will be ineligible; breastfeeding should be discontinued if the mother is treated with study drugs.

- The use of agents that inhibit or induce CYP3A metabolism is not strictly prohibited, but should be avoided if possible. Potential CYP3A inducing agents include carbamazepine, phenytoin, barbiturates, rifabutin, rifampicin, and St. John's Wort. Potential CYP3A inhibitors include protease inhibitors, antifungals, macrolide antibiotics, nefazodone, and selective serotonin inhibitors.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records

for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC or collaborating institution(s) in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study and is not enrolled, the research staff will destroy all information collected on the patient during the initial conversation and medical records review.

8.0 PRETREATMENT EVALUATION

Within 30 days of starting treatment, the following tests need to be done:

- History and Physical Examination
- Vital signs, including blood pressure and weight
- Performance Status (ECOG or Karnofsky Performance Status)
- Radiology studies for disease assessment
- Electrocardiogram (may be done within 60 days of starting treatment)
- Signed Consent Form

Within 14 days of starting treatment, the following tests need to be done:

- Complete Blood Count (including platelets)
- Prothrombin Time (PT)
- Comprehensive including liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase)
- Triglycerides, cholesterol
- Serum thyroid stimulating hormone (TSH)
- Serum thyroglobulin and thyroglobulin antibodies (results do not need to be back before the start of treatment)
- Pregnancy test in women of child-bearing potential.

A PET scan is required as part of inclusion criteria; however, it may be done any time prior to the start of therapy. It is recommended, but not required, that the PET scan be done within 3 months of starting therapy.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Treatment

Note: cycle length is 28 days. Cycle is delayed only if both drugs (sorafenib and temsirolimus) are held for $\geq$ 1 week. Temsirolimus dose may be skipped without a violation due to patient related events (such as weather, family emergency, or hospitalization). Reason for skipping a dose must by documented by the treating physician and approved by the study PI (Sherman).

Agent	Dose	Route	Days (+/- 2 days)	Interval
Diphenhydramine (or similar antihistamine)	25-50 mg	IV/PO		Approximately 30 minutes prior to temsirolimus infusion
Temsirolimus	25 mg	IV over 30 minutes	1, 8, 15, 22	Weekly dosing
Sorafenib	200 mg twice a day (total dose of 400 mg per day)	Oral	1-28	Daily dosing

9.2 Diary

Subjects will be required to complete a diary concerning their use of sorafenib every 28 days.

9.3 Treatment Discontinuation

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies.

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as defined in Section 11,
- Patient noncompliance as determined by the judgment of the investigator that would make further treatment potentially unsafe or make outcomes of the trial difficult to interpret,
- Arterial thromboembolic events including cerebrovascular accidents, myocardial infarctions, transient ischemic attacks, new onset or worsening of pre-existing angina.
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Base-line [a]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9[k]	Wk 10	Wk 11	Wk 12	Off Study[d]
Sorafenib (taken daily)		X	X	X	X	X	X	X	X	X	X	X	X	
Temsirolimus		X	X	X	X	X	X	X	X[j]	X	X	X	X[j]	
Informed consent	X													
Obtain pathology specimen for BRAF mutation testing.	X													
History and Physical Exam	X													
Concurrent meds[g]	X	X——————————————————————————————————X												
Physical exam (symptom-and disease-directed)		X	X	X	X	X		X[i]		X		X[i]		X
Vital signs	X	X	X	X	X	X		X[i]		X		X[i]		X
Blood Pressure	X	X	X	X	X	X		X[i]		X		X[i]		X
Weight	X	X				X				X				X
Performance status	X					X				X				X
Triglycerides, cholesterol	X					X				X				X
CBC w/diff, plts	X	X		X		X		X[i]		X		X[i]		X
Serum comprehensive [b]	X	X		X		X		X[i]		X		X[i]		X
EKG	X													
Adverse event evaluation[g]		X ——————————————————————————————————X												X
Radiologic Tumor measurements	X[f]	Tumor measurements are repeated after every 2 cycles (i.e., anytime between the end of the 1st and the end of the 2nd cycle) while on study[h]. Documentation must be provided for patients removed from study for progressive disease.												
Pregnancy test [c]	X													
Serum thyroglobulin	X									X				X
PT/INR	X													
										X				

Amended: 05/12/15

Serum TSH	**X**													
FDG-PET [e]	**X**													

a: See Section 8.0 for timing prior to the start of therapy.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, , potassium, total protein, SGOT [AST], SGPT [ALT], sodium, bilirubin.
c: Serum beta human chorionic gonadotropin pregnancy test (in women of childbearing potential).
d: Off-study evaluation between 4-8 weeks after study termination.. In addition, follow-up for disease status (e.g., alive with disease) should continue at least for 1 year after treatment is complete. 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.
e: [18-F] fluorodeoxyglucose (FDG)-PET. Baseline FDG-PET to be done any time prior to the start of therapy. No other FDG-PET scans required. It is recommended, but not required, that it be done within 3 months of starting therapy.
f Baseline evaluations, including radiographic studies, are to be conducted ≤ 30 days prior to start of protocol therapy.
g: Concurrent medication and adverse event evaluations will only be done on days of physician visits, although they will include all data from between visits.
h: Restaging studies may be done within 2 weeks before the scheduled start of the cycle. A delay in starting the cycle will not require that the restaging studies need to be repeated. However, a subject cannot go more than 2 cycles without restaging during the first 12 cycles of treatment. After 12 cycles, restaging study only need to be done every 3 cycles (or up to 2 weeks before the 3rd cycle).
i: After 4 cycles of treatment are completed, these tests/procedures can be eliminated.
J: After 6 cycles of treatment are completed, week 4 of temsirolimus will be optional for the patient.
k: Weeks 9-12 should be repeated for all cycles ≥ 4 except where otherwise noted. TSH and Thyroglobulin only need to be checked every 2 cycles.

11.0 TOXICITIES/SIDE EFFECTS

11.1 This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). Please see sections 5.1 and 5.2 for list of expected toxicities.

11.2 General Dose Modification Instructions

Additional cycles of therapy may be administered provided that the patient meets the following criteria for each cycle:

- ANC ≥ 1,000/μl
- Platelets ≥ 75,000/μl
- Non-hematologic toxicity recovered to ≤ Grade 1 (or tolerable Grade 2)
- No evidence of progressive disease

11.2.1 If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.
11.2.2 Patients who experience toxicities that may be due to either agent, may have one agent reduced or both agents reduced depending on the nature/severity of the toxicity.
11.2.3 Patients in whom one agent is delayed or discontinued may continue to receive the other agent if, in the opinion of the treating physician, the patient may continue to benefit from treatment.
11.2.4 Patients requiring dose reductions should not have the dose re-escalated with subsequent treatments.
11.2.5 Patients with toxicities that are manageable with supportive therapy may not require dose reductions (e.g., hyperlipidemia may be treated with statins, such as Lipitor™,

nausea/vomiting may be treated with antiemetics, diarrhea may be treated with loperamide rather than by dose reduction).

11.2.6 In general, patients will be removed from protocol treatment if they do not recover to CTC Grade 0-1 or tolerable Grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related toxicity within 4 weeks (unless otherwise specified below) OR they experience agent-related toxicities at the lowest allowable dose unless in the opinion of the treating physician (after obtaining approval from the PI) the patient would benefit from continuing on protocol treatment.

11.3 Dose Reductions

Sorafenib

Agent	Dose Level	Dose
Sorafenib	Full Dose	200 mg bid (400 mg total dose daily)
	-1 Level	200 mg daily
	-2 Level	200 mg every other day

Up to two dose reductions due to unacceptable toxicity per patient is allowed per the table above. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

NOTE: If a dose or doses are missed, the reason(s) and the number of doses not taken should be noted and recorded in the patient's chart.

Management of Hypertension

Toxicity	Grade	Action to be taken
Hypertension	(A) Asymptomatic and persistent SBP of ≥ 140 and < 170 mmHg, or DBP ≥ 90 or < 110 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg)	Step 1. Continue study treatment at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
	(B). Asymptomatic SBP ≥ 170 mmHg, or DBP ≥ 110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1. Consider reducing or interrupting sorafenib, as clinically indicated. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. If sorafenib was interrupted > 1 week, it can be resumed with dose-reduced by 1 level once BP is well-controlled.
	(C). Symptomatic hypertension or recurring SBP ≥ 170 mmHg, or DBP ≥ 110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt sorafenib. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. Step 4. Sorafenib can be resumed with dose-reduced by 1 level once BP is well-controlled if sorafenib interrupted > 1 week or at the investigator's discretion.
	(D). Grade 4 or Refractory hypertension unresponsive to above interventions	Seek cardiologist opinion, and permanently discontinue sorafenib.

- Abbreviations: SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure
- Blood Pressure Medication suggestions: dihydropyridine calcium-channel blockers (DHP-CCB; Norvasc 2.5 mg and titrate up to 10mg), selective beta blockers (BB; Toprol 12.5 mg and titrate), , additionally Angiotensin II Receptor Blockers (ARB) and central alpha blockers may be used in conjunction with a cardiologist.
- If patients require a delay of > 3 weeks for management of hypertension, discontinue protocol therapy
- If patients require > 2 dose reductions, discontinue protocol therapy
- Patients may have up to 2 drugs (in addition to baseline drugs prior to therapy) for management of hypertension prior to any dose reduction in Sorafenib.
- 24-48 hour should elapse between modifications of antihypertensive therapy
- Hypertension should be graded using the NCI CTCAEv4.0
- If BP is elevated and it is felt by the investigator that this is secondary to an external event (e.g., pain), the investigator may (after documenting reason) delay adjusting hypertension medications for up to 2 working days and have the blood pressure rechecked by a health care professional.

Dose Delays/Dose Modifications for sorafenib

Adverse Event	Treatment Modifications
Cardiac General	
Hypertension	Refer to table in 11.3
Dermatology/Skin	
Grade 2 & 3 Hand/foot skin reaction	Hold dose. Re-evaluate at least weekly until toxicity resolves to ≤ Grade 1 or tolerable Grade 2. Re-treat at a one dose level reduction. If toxicity persists at grade 3 or intolerable at grade 2 for > 2 weeks, then stop sorafenib. Patients with Grade 4 toxicity related to sorafenib may be removed from sorafenib and continue temsirolimus at the discretion of the treating physician after obtaining approval from the PI.
Grade 3 Rash-acne/acneiform	Hold dose. • If toxicity has not resolved to ≤ Grade 1 or tolerable Grade 2 within 2 weeks, discontinue sorafenib treatment. • If < Grade 2, re-treat at one dose level reduction. • If toxicity persists > 3 weeks, remove patient from both sorafenib and temsirolimus treatment. • Patients with Grade 4 toxicities related to sorafenib may be removed from sorafenib treatment and continue temsirolimus at the discretion of the treating physician after obtaining approval from the PI.
All other non-hematologic adverse events	
Grade 0-2	Grade 2 toxicities that are persistent and intolerable (i.e., stomatitis) can result in dose delays or dose reductions to the next lower dose level.
Grade 3-4	Hold dose if possibly related to sorafenib. • Re-evaluate until toxicity resolves to ≤ Grade 1 (or tolerable Grade 2). • If toxicity persists > 2 weeks and is felt to be possible, probably or definitely related to sorafenib, remove patient from sorafenib treatment and continue temsirolimus. • Patients with Grade 4 toxicities related to sorafenib may be removed fiom sorafenib treatment and continue temsirolimus at the discretion of the treating physician after obtaining approval from the PI.
GI Perforation	In the event of a GI perforation, patients must be removed from protocol treatment.

If toxicities are not listed in the table, doses may be reduced or held at the discretion of the treating physician for the patient's safety; however, this should not be without the consent of the Principal Investigator (Eric Sherman), or, if absent/unavailable, the surrogate to the PI. If the PI is unavailable, the surrogate may be either co-PI (David Pfister or James Fagin). In addition, if there is an unforeseen event such as a surgical procedure (i.e. tooth extraction), at the investigator's discretion, sorafenib may be held for up to 2 weeks.

Temsirolimus

Agent	Dose Level	Dose
Temsirolimus	Full Dose	25 mg/week
	-1 Level	15 mg/week
	-2 Level	10 mg/week

All patients should be monitored while receiving temsirolimus infusion and health care personnel must be readily available to respond to hypersensitivity reactions or other emergencies. If the patient begins to develop a hypersensitivity reaction despite pretreatment with diphenhydramine, the infusion should be stopped for at least 30 – 60 minutes, depending upon the severity of the reaction. The infusion may be resumed by administering a histamine H2-receptor antagonist approximately 30 minutes before restarting the temsirolimus infusion. Famotidine 20 mg IV or ranitidine 50 mg IV are recommended rather than cimetidine because of the lack of likely metabolic/pharmacologic interactions with the former drugs. The rate of the temsirolimus infusion may also be slowed from 30 minutes to over an hour.

In the event of toxicity, the dose of CCI-779 (temsirolimus) will be adjusted according to the guidelines in the table below. If toxicities are not listed in the table, doses may be reduced or held at the discretion of the treating physician for the patient'ssafety; however, this should not be without the consent of the Principal Investigator (Eric Sherman), or, if absent/unavailable, the surrogate to the PI. If the PI is unavailable, the surrogate may be either co-PI (David Pfister or James Fagin). Dose adjustments for hematological toxicity are based on the blood counts obtained in preparation for the day of treatment.

Patients who experience toxicities due to CCI-779 (temsirolimus) but with an unrelated or unlikely relationship to the other agent should have their treatment modified according to the directions in the table below. If a dose reduction is required, the dose of CCI-779 (temsirolimus) should be reduced, but the dose of the other agent should remain at the current level.

A dose of temsirolimus may be missed due to certain patient-related (e.g., family emergency), weather-related (e.g., snow storm), or hospital-related (e.g., holiday) events. If possible, subjects should be rescheduled to receive the temsirolimus within 2 days of the event. If not, the dose of temsirolimus may be missed, but the subject should continue taking the sorafenib as per protocol.

Dose Delays/Dose Modifications for temsirolimus

Adverse Event	Treatment Modifications
Blood/Bone Marrow	
Grade 3 Neutrophils ANC 500-999 Platelets 50,000-75,000	Delay temsirolimus and sorafenib until recovery to both ANC >= 1000 and platelets > 75,000. Retreat at one dose level reduction for the temsirolimus if delay causes more than 1 dose of temsirolimus to be held consecutively. If this has occurred more than 1 time during the same cycle, also reduce temsirolimus by 1 dose level. If this has occurred more than 1 time during the protocol, it is the investigator's decision whether to reduce temsirolimus by 1 dose level. If temsirolimus has been decreased 1 dose level previously, decrease either temsirolimus or sorafenib by 1 dose level (investigator's decision). If recovery requires > 2 doses of temsirolimus to be held consecutively, discontinue temsirolimus and continue sorafenib.
Grade 4 Neutrophils ANC <500 Platelets <50,000	Delay temsirolimus and sorafenib until recovery to ≤ Grade 2. Retreat at one dose level reduction for the temsirolimus. If temsirolimus has been decreased 1 dose level, decrease either temsirolimus or sorafenib by 1 dose level (investigator's decision).If recovery requires > 2 weeks, discontinue temsirolimus and continue sorafenib.
Pulmonary/Upper Respiratory	
Pneumonitis (cough, dyspnea, fever)	Discontinue temsirolimus pending investigation. If diagnosis is confirmed and events are considered at least possibly due to temsirolimus, the patient should be removed from temsirolimus treatment and may continue sorafenib.
All other non-hematologic adverse events	
Grade 0-2	Grade 2 toxicities that are persistent and intolerable (i.e., stomatitis) can result in dose delays or dose reductions to the next lower dose level.
Grade 3-4	Hold dose if possibly related to temsirolimus. • Re-evaluate until toxicity resolves to ≤ Grade 1 (or tolerable Grade 2). • If toxicity persists >2 weeks and is felt to be possible, probably or definitely related to temsirolimus, remove patient from temsirolimus treatment and continue sorafenib. • Patients with Grade 4 toxicities related to temsirolimus may be removed from temsirolimus treatment and continue sorafenib at the discretion of the treating physician.
Grade 3: Hyperlipidemia	Treat with antihyperlipidemics and continue temsirolimus as long as hyperlipidemia can be maintained at ≤ Grade 2.

If toxicities are not listed in the table, doses may be reduced or held at the discretion of the treating physician for the patient's safety; however, this should not be without the consent of the Principal Investigator (Eric Sherman), or, if absent/unavailable, the surrogate to the PI. If the PI is unavailable, the surrogate may be either co-PI (David Pfister or James Fagin).

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the purposes of this study, patients should be reevaluated for response every 2 cycles. In addition to a baseline scan, confirmatory scans should also be obtained 4-8 weeks following initial documentation of objective response.

12.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

12.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

12.1.3 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

12.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.2 Guidelines for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific

context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.3 Response Criteria

12.3.1 Evaluation of target lesions

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

12.3.2 Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Incomplete Response / Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

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

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

12.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Sections 12.3.1 and 12.4.1).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD

Any	**PD**	**Yes or No**	**PD**
Any	**Any**	**Yes**	**PD**

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate) before confirming the complete response status.

12.4 Confirmatory Measurement/Duration of Response

12.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed a minimum of 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see section 12.3.3).

12.4.2 Duration of overall response

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

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

12.4.3 Duration of Stable Disease

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

12.4.4 Treatment failure

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) and are evaluable should be included in the main analysis of the response rate, even if there are major protocol treatment deviations. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]. Patients in response categories 4-7 should be considered to have a treatment failure (disease progression) at the time of the event and as progression of disease for response rate if occurs before second restaging imaging.. Category 9 will count as disease progression if it occurs before a second restaging scan after the initiation of treatment unless subject is ineligible or inevaluable. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

12.4.5 Definition of ineligible/inevaluable

A subject is considered ineligible for analysis if it is found after the start of treatment that the subject did not meet the eligibility criteria unless a deviation has been approved by the IRB or the only deviation is lack of RECIST criteria lesion (see next paragraph).

A subject will be classified as inevaluable for response if it is determined after the initiation of therapy that the subject did not have any lesions that met RECIST criteria unless a new lesion appears by the end of 2 cycles in which case the subject will be classified as PD.

12.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from day 1 of treatment to time of disease progression, or death from any cause, whichever comes first. For this trial, the primary PFS endpoint will be at the 1 year time point.

12.6 Response Review

All radiologic studies performed to establish RECIST baseline tumor measurements and for subsequent response assessment purposes will be reviewed by an institutional reference radiologist.

13.0 CRITERIA FOR REMOVAL FROM STUDY

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies.

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient noncompliance as determined by the judgment of the investigator that would make further treatment potentially unsafe or make outcomes of the trial difficult to interpret,
- Arterial thromboembolic events including cerebrovascular accidents, myocardial infarctions, transient ischemic attacks, new onset or worsening of pre-existing angina.
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

14.0 BIOSTATISTICS

14.1 Study Design/Endpoints

An exact one stage Phase II design will be employed to assess the primary endpoint of radiographic response rate (partial response or complete response, by RECIST criteria) of the combination sorafenib and temsirolimus within 4 months since the start of therapy. A 15% response-rate within 4 months is considered not promising (based on previous two studies evaluating sorafenib as a single agent in the treatment of thyroid cancer, which reported response rates of 23%[21] and 11.5%[23]), a 34% response rate is considered promising, and the probabilities of a Type I error (falsely accepting a non-promising therapy) and Type II error (falsely rejecting a promising therapy) are set to 0.1 and 0.1, respectively. We will evaluate a total of 36 patients. If 9 or more of the 36 patients evaluated will have a response, the regimen will be considered worthy of further investigation.

14.2 Sample Size/Accrual Rate

Thirty-six patients will need to be evaluated for this trial. We anticipate 10% of the patients enrolled to become ineligible/inevaluable during the study, so we are prepared to accrue a maximum of 40 patients. There are approximately 200 patients per year who are referred to MSKCC for thyroidectomies; approximately 60% of these cases are patients with well-

differentiated thyroid cancer. An additional equivalent number of cases are referred to the MSKCC department of Endocrinology for recommendation of treatment options on an annual basis. About 25-50% are expected to develop RAI-refractory recurrent or metastatic disease over the next year. In our most recent clinical study with this treatment population, 21 patients were accrued to the study in under 5 months. From this information, we anticipate accruing a minimum of 3 patients per month, thereby finishing accrual to the clinical study within maximum 14 months.

14.3 Analysis of Secondary Endpoints

Progression-free survival curves will be generated using Kaplan-Meier methodology, with time origin at the start of the treatment. Reported data from the phase II study at Ohio State suggested an approximate 1-year disease free survival rate of 47% under Sorafenib monotherapy. All patients enrolled and evaluable who receive at least one dose of the treatment will be included in this analysis. With 36 evaluable patients, we will have 80% power to detect an increase of 18% in PFS at 1 year, at a level $\alpha = 0.1$.

Analysis of BRAF mutation, with or without concomitant mutations in the PI3K AKT, mTOR pathway, will be exploratory and hypothesis generating. We will compare the two BRAF groups, as well as subgroups determined by concomitant mutations, with respect to response rates (using logistic regression) and to PFS (using Cox proportional-hazards regression).

The safety population will comprise all patients who receive at least 1 dose of study treatment. Safety and tolerability will be assessed in terms of AEs, laboratory data and vital sign data, which will be collected for all patients. Appropriate summaries of these data will be presented. AEs (by CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by CTCAE grade.

14.4 Evaluation of response

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) and are evaluable should be included in the main analysis of the response rate, even if there are major protocol treatment deviations. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]. Patients in response categories 4-7 should be considered to have a treatment failure (disease progression) at the time of the event and as progression of disease for response rate if occurs before second restaging imaging.. Category 9 will count as disease progression if it occurs before a second restaging scan after the initiation of treatment unless subject is ineligible or inevaluable. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

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

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Registration reports will be generated to monitor patient's accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study and potential problems will be brought to the attention of the study team for discussion.

Random-Sample data quality and protocol compliance audits may be conducted by the study team, at a minimum of once a year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

17.0.1 Risks, Benefits, Toxicities/side effects

Potential risks to human subjects include drug related toxicity, pain and discomfort associated with mucositis, sorafenib and temsirolimus, placement of IV catheters (if necessary), phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan). The side effects and potential toxicities of sorafenib and temsirolimus are described in Section 5. All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests.

If an adverse medical event occurs, the patient will first contact the primary oncologist or the Principal Investigator. At nights and on weekends, there is an oncology physician on call at all

times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded.

17.0.2 Alternatives/options

Patients other choices may include taking part in another study or getting treatment without being in a study. Participation in this trial is voluntary.

Depending on the specific details of the situation, patient options without being in a study might include:

Doxorubicin or other cytotoxic chemotherapy
Sorafenib

At MSKCC, the standard radiation treatment outside of a clinical trial for patients with RAI refractory thyroid cancer would be either doxorubicin or sorafenib.

17.0.3 Financial Costs/Burdens

The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (third party insurer) will include the cost of sorafenib, hospitalizations, routine blood tests, diagnostic studies, office visits, baseline EKG, and doctor's fees.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

17.2.1 Serious Adverse Event Reporting to Pfizer and the NCCN

Reporting of Serious Adverse Events: Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), Principal Investigator will report to Pfizer and NCCN by facsimile certain Serious Adverse Events ("SAEs," as defined below) for which reporting is required under this provision (as described below). Such SAEs are to be reported for (1) Study subjects who are assigned or, in the case of a blinded Study, possibly assigned to receive the Study Drug or (2) individuals otherwise exposed to the Study Drug as described below. Principal Investigator should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available.

(a) Reporting Forms. Principal Investigator will submit reportable SAEs using one of the following forms: (1) a reporting form approved by the local regulatory authority, (2) a CIOMS form, (3) a Pfizer-provided Investigator-Initiated Research Serious Adverse Event Form, or (4) any other form prospectively approved by Pfizer. The Reportable Event Fax Cover Sheet provided by Pfizer must also be included with each SAE submitted (Appendix A). Such reports shall be directed to NCCN via fax at 215-358-7699 or e-mailed to ORPReports@nccn.org and to the Pfizer U.S. Clinical Trial Department at 1-866-997-8322:

(b) SAE Definition. An SAE is any adverse event, without regard to causality, that is life-threatening (i.e., causes an immediate risk of death) or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity (i.e., substantial disruption of the ability to conduct normal life functions); or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

(c) Subset of SAEs Reportable for this Study. Because the Study Drug used in this Study is a mature marketed product with a well-established safety profile, only SAEs that fit into any of the

following categories need to be reported to Pfizer and NCCN: (1) a death, regardless of whether it is considered related to treatment with the Study Drug, (2) a non-fatal SAE that occurs during the reporting period and that is assessed by the Principal Investigator as both related to treatment with the Study Drug and unexpected for that product, (3) an SAE assessed by the Principal Investigator as related to the Study Drug that occurs after the SAE reporting period, or (4) an otherwise reportable event as described in Section d, below. An event should be considered "related" to the Study Drug if a relationship is at least a reasonable possibility, and "unexpectedness" should be based upon a single safety reference document identified by the Principal Investigator and documented in association with the study.

(d) Exposure During Pregnancy, Exposure During Lactation, Occupational Exposure, and Lack Of Effect. Even though there may not be an associated SAE, exposure to the Study Drug during pregnancy, exposure to the Study Drug during lactation, and occupational exposure to the Study Drug are reportable, and lack of effect of the Study Drug may also be reportable. These requirements are further explained in the training material provided by Pfizer (see Pfizer-Provided Training, below). As used in this Agreement, the term SAE will be understood to include exposure during pregnancy, exposure during lactation, occupational exposure, and reportable instances of lack of effect.

(e) SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Study Drug through 28 days after discontinuation of the Study Drug, or longer if so specified in the Protocol. In addition, if Principal Investigator becomes aware of an SAE occurring any time after the administration of the last dose of the Study Drug, Principal Investigator should report that SAE to Pfizer and NCCN if the Principal Investigator suspects a causal relationship between the Study Drug and the SAE.

(f) Follow-Up Information. Institution will assist Pfizer in investigating any SAE and will provide any follow-up information reasonably requested by Pfizer.

(g) Regulatory Reporting. Reporting an SAE to Pfizer and NCCN does not relieve Institution of responsibility for reporting it to appropriate regulatory authorities, if such reporting is required.

(h) Pfizer-Provided Training. Pfizer will make available training material that provides information about the SAE reporting requirements for IIR studies. Principal Investigator will review this material and share it with any Study staff engaged in the reporting of SAEs.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an

IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCE(S)

1. Brose MS, Nellore A, Paziana K, et al: A phase II study of sorafenib in metastatic thyroid carcinoma. J Clin Oncol (Meeting Abstracts) 26:6026-, 2008

2. Ahmed M, Barbachano Y, Riddell AM, et al: Preliminary results of an open labelled phase 2 study evaluating the safety and efficacy of sorafenib in metastatic advanced thyroid cancer. J Clin Oncol (Meeting Abstracts) 26:6060-, 2008

3. Cohen EE, Vokes EE, Rosen LS, et al: A phase II study of axitinib (AG-013736 [AG]) in patients (pts) with advanced thyroid cancers. J Clin Oncol (Meeting Abstracts) 25:6008-, 2007

4. Cohen EE, Needles BM, Cullen KJ, et al: Phase 2 study of sunitinib in refractory thyroid cancer. J Clin Oncol (Meeting Abstracts) 26:6025-, 2008

5. Pennell NA, Daniels GH, Haddad RI, et al: A phase II study of gefitinib in patients with advanced thyroid cancer. J Clin Oncol (Meeting Abstracts) 25:6020-, 2007

6. Ain KB, Lee C, Holbrook KM, et al: Phase II study of lenalidomide in distantly metastatic, rapidly progressive, and radioiodine-unresponsive thyroid carcinomas: preliminary results. J Clin Oncol (Meeting Abstracts) 26:6027-, 2008

7. Ouyang B, Knauf JA, Smith EP, et al: Inhibitors of Raf kinase activity block growth of thyroid cancer cells with RET/PTC or BRAF mutations in vitro and in vivo. Clin Cancer Res 12:1785-93, 2006

8. Ball DW, Jin N, Rosen DM, et al: Selective Growth Inhibition in BRAF Mutant Thyroid Cancer by the Mitogen-Activated Protein Kinase Kinase 1/2 Inhibitor AZD6244. J Clin Endocrinol Metab 92:4712-4718, 2007

9. Peyssonnaux C, Eychene A: The Raf/MEK/ERK pathway: new concepts of activation. Biol Cell 93:53-62, 2001

10. Cohen Y, Xing M, Mambo E, et al: BRAF mutation in papillary thyroid carcinoma. J Natl Cancer Inst 95:625-7, 2003

11. Fukushima T, Suzuki S, Mashiko M, et al: BRAF mutations in papillary carcinomas of the thyroid. Oncogene 22:6455-7, 2003

12. Kimura ET, Nikiforova MN, Zhu Z, et al: High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. Cancer Res 63:1454-7, 2003

13. Soares P, Trovisco V, Rocha AS, et al: BRAF mutations and RET/PTC rearrangements are alternative events in the etiopathogenesis of PTC. Oncogene 22:4578-80, 2003

14. Fagin JA: Genetics of papillary thyroid cancer initiation: implications for therapy. Trans Am Clin Climatol Assoc 116:259-69; discussion 269-71, 2005

15. Nikiforova MN, Kimura ET, Gandhi M, et al: BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab 88:5399-404, 2003

16. Guigon CJ, Zhao L, Willingham MC, et al: PTEN deficiency accelerates tumour progression in a mouse model of thyroid cancer. Oncogene, 2008

17. Cloughesy TF, Yoshimoto K, Nghiemphu P, et al: Antitumor activity of rapamycin in a Phase I trial for patients with recurrent PTEN-deficient glioblastoma. PLoS Med 5:e8, 2008

18. Hu X, Pandolfi PP, Li Y, et al: mTOR promotes survival and astrocytic characteristics induced by Pten/AKT signaling in glioblastoma. Neoplasia 7:356-68, 2005

19. Wu L, Birle DC, Tannock IF: Effects of the Mammalian Target of Rapamycin Inhibitor CCI-779 Used Alone or with Chemotherapy on Human Prostate Cancer Cells and Xenografts. Cancer Res 65:2825-2831, 2005

20. Wilhelm SM, Carter C, Tang L, et al: BAY 43-9006 Exhibits Broad Spectrum

Oral Antitumor Activity and Targets the RAF/MEK/ERK Pathway and Receptor Tyrosine Kinases Involved in Tumor Progression and Angiogenesis. Cancer Res 64:7099-7109, 2004

21. Gupta-Abramson V, Troxel AB, Nellore A, et al: Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol 26:4714-9, 2008

22. Flaherty KT: Chemotherapy and targeted therapy combinations in advanced melanoma. Clin Cancer Res 12:2366s-2370s, 2006

23. Kloos RT, Ringel MD, Knopp MV, et al: Phase II Trial of Sorafenib in Metastatic Thyroid Cancer. J Clin Oncol:JCO.2008.18.2717, 2009

24. Molhoek KR, Brautigan DL, Slingluff CL, Jr.: Synergistic inhibition of human melanoma proliferation by combination treatment with B-Raf inhibitor BAY43-9006 and mTOR inhibitor Rapamycin. J Transl Med 3:39, 2005

25. Lasithiotakis KG, Sinnberg TW, Schittek B, et al: Combined Inhibition of MAPK and mTOR Signaling Inhibits Growth, Induces Cell Death, and Abrogates Invasive Growth of Melanoma Cells. J Invest Dermatol 128:2013-2023, 2008

26. Patnaik A, Ricart A, Cooper J, et al: A phase I, pharmacokinetic and pharmacodynamic study of sorafenib (S), a multi-targeted kinase inhibitor in combination with temsirolimus (T), an mTOR inhibitor in patients with advanced solid malignancies. J Clin Oncol (Meeting Abstracts) 25:3512-, 2007

20.0 APPENDICES

Appendix A: SAE Fax Cover Sheet
Appendix B: Canadian Cardiovascular Society Classification System
Appendix C: New York Heart Association Classifications
Appendix D: Sample Pill Diary

APPENDIX A
SAE FAX COVER SHEET

Investigator-Initiated Research
Reportable Event Fax Cover Sheet

Use this fax cover sheet to fax a Reportable Event for Investigator-Initiated Research studies.

Include with this form the completed Pfizer Investigator-Initiated Research Serious Adverse Event (IIR SAE) form, MedWatch Form FDA 3500A-Mandatory Reporting, which can be obtained from the FDA website: www.fda.gov/medwatch/getforms.htm, or other Pfizer agreed-upon form for SAE reporting.

If you are using the MedWatch Form to report, the following information should be included in block 5 of the Adverse Events section:

- **The complete clinical course of the patient receiving Pfizer drug**
- **The causality assessment for each Reportable Event**
- **The action taken for each study drug and for each Reportable Event**
- **The outcome for each Reportable Event**

This cover sheet MUST be provided with each completed SAE form. Do not substitute forms/reports or submit additional documentation other than what is required.

Do not fax these forms to any additional fax numbers other than the one listed below.

TO:	*Pfizer U.S. Clinical Trial Department*		
FAX:	*1-866-997-8322*		
FROM:		DATE:	
TELEPHONE:		FAX:	
NUMBER OF PAGES (INCLUDING COVER SHEET):			
PRODUCT	Torisel (temsirolimus)		
PFIZER REFERENCE NUMBER	WS717358-11	EXTERNAL REFERENCE NUMBER	PLEASE PROVIDE
STUDY TITLE	*Phase II Study Evaluating the Combination of Temsirolimus and Sorafenib in the Treatment of Radioactive Iodine Refractory Thyroid Cancer*		
PATIENT NUMBER			
INVESTIGATOR			

Confidentiality Notice: The documents accompanying this telecopy transmission contain information belonging to Pfizer, which is intended only for the use of the addressee. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for the return of the original documents to us. Thank you.

APPENDIX B

Grading of angina pectoris by the Canadian Cardiovascular Society classification system

Class	Description
Class I	Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina [occurs] with strenuous, rapid, or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.
Class III	Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort -- angina symptoms may be present at rest.

Reference: Campeau L. Grading of angina pectoris [letter]. Circulation, 54:522-523, 1976.

APPENDIX C
New York Heart Association Classifications

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to work**
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

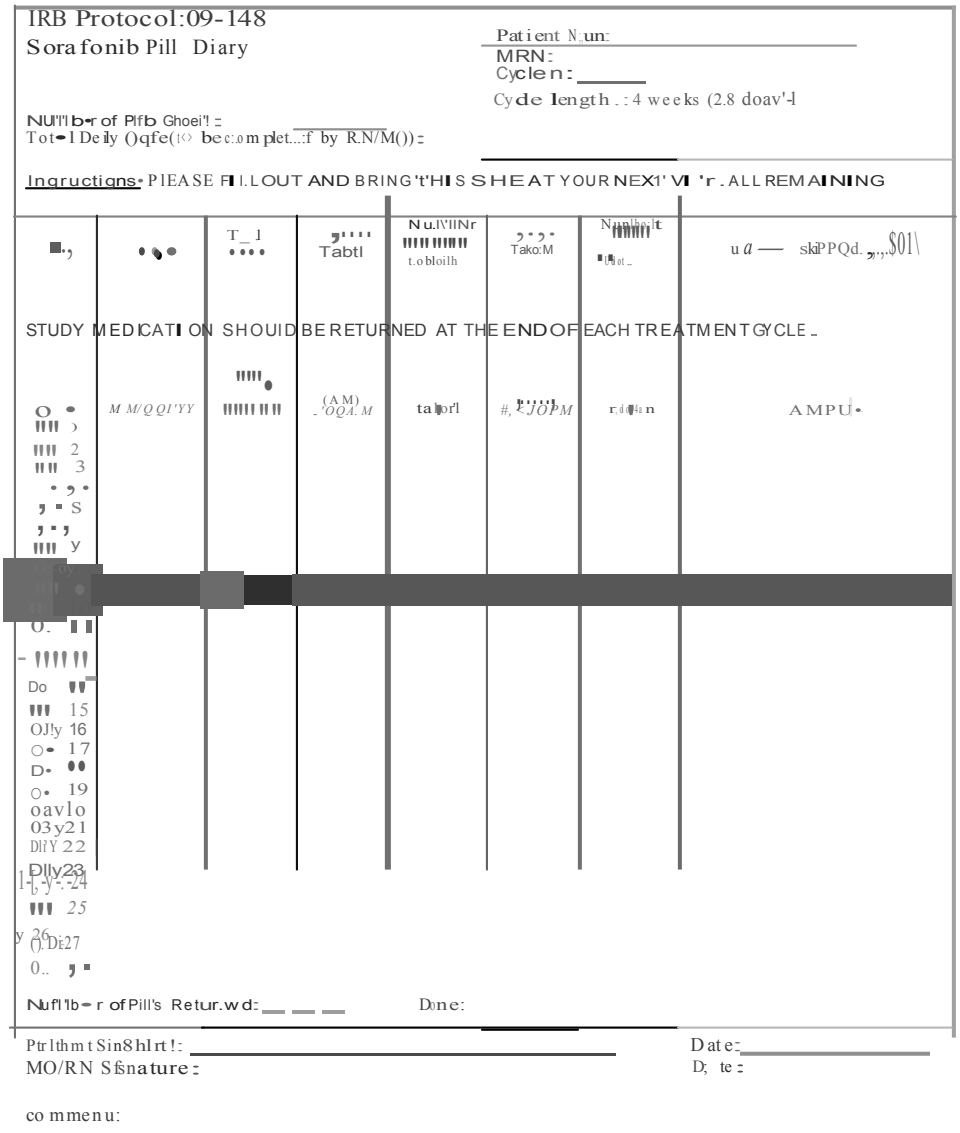
* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

Reference: Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953).

APPENDIXD

Sample Pill DiaJY



IRB Protocol:09-148
Sorafonib Pill Diary

Patient N,un:
MRN:
Cyclen:_____
Cyde length .:4 weeks (2.8 doav'-l

NUl'l'lb-r of Pifb Ghoei'l :
Tot-l Deily ()qfe(1<> bec:.omplet...:f by R.N/M()):

Ingructigns- PIEASE FI I.LOUT AND BRING 't'HI S SHEAT YOUR NEX1' VI 'r . ALL REMAINING

STUDY MEDICATI ON SHOUID BE RETURNED AT THE END OF EACH TREATMENT GYCLE .

Tabtl
Tako:M
AMPU-

Nufl1b-r of Pill's Retur.wd:_ _ _ Done:

Ptrlthmt Sin8hlrt!:
MO/RN Sfsnature:
Date:
D; te:

commenu:

Amended: 05/12/15