NCI Protocol #: 7609

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TITLE: Phase II Study of Sorafenib (BAY 43-9006) in Patients with Metastatic Medullary Thyroid Carcinoma

Coordinating Institution: **The Ohio State University (OSU)**

Principal Investigator: **Bhavana Konda, MBBS, MPH**
The Ohio State University
A440 Starling Loving Hall
320 W 10th Avenue
Columbus, OH 43210
Phone: 614-293-8629
Fax: 614-293-3112
Pager: 293-PAGE ext: 3920
Email:*bhavana.konda@osumc.edu*

Participating Institutions:

Washington University School of Medicine
Institutional P.I.: **Jeffrey F. Moley MD**
Professor of Surgery
Washington University School of Medicine
Associate Director, Alvin Siteman Cancer Center
Box 8109
660 S. Euclid
St. Louis MO 63110
Phone: 314-747-0064
Fax: 314-747-1310
Pager: 314-823-2025
Email: moleyj@wustl.edu

Institutional Co-Is.: **Samuel A. Wells, Jr., M.D.**
Professor of Surgery
Phone: 919-668-8435
Fax: 919-668-7123
Email:wells029@surgerytrials.duke.edu

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SCHEMA

Phase II Trial of Sorafenib (BAY 43-9006) in Patients with Metastatic Medullary Thyroid Carcinoma

Arm A: (n=16 or 25)	**Arm B: (n=16 or 25)**
MTC in setting of inherited syndromes (MEN-2A, 2B or FMTC) **plus** **Measurable disease** **Plus** **No prior ZD6474 or AMG 706**	**MTC in setting of sporadic ds** **plus** **Measurable disease** **Plus** **No prior ZD6474 or AMG 706**

Sorafenib (BAY 43-9006) administered orally at 400 mg PO BID on a continuous basis as an outpatient

Correlatives Studies
(Section 7.0 for details as some of these tests are done in a selected group of patients)

- **Serum calcitonin and CEA at pre-therapy, on-therapy and post-therapy.**
- **PET scan at pre-therapy and on-therapy as clinically indicated.**
- **Dynamic contrast enhanced MRI at pre-therapy, on-therapy and post-therapy (Optional per Section 7.3 of protocol).**
- **Pharmacogenomics studies in case clinical responses are observed.**
- **Tumor biopsies for MAPK, AKT phosphorylation and VEGF expression at pre-therapy, at 8-weeks and at post-therapy (Optional per Section 7.5 of protocol).**
- **Obtain formalin-fixed, paraffin-embedded tumor specimen collected any time prior to study for evaluating the presence/type of RET gene defects.**
- **RET mutation studies in peripheral blood obtained pre-study if not been previously tested.**

(n=16 or 25)

Tumor response assessment every 16 weeks

Progressive disease	**Complete Response**	**Stable disease or Partial Response**
No further therapy- off study	**8 more weeks of therapy and off study**	**8 more weeks of therapy and reassess**

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OBJECTIVES

1.1 Primary Objective:

1.1.1 To assess objective response rate of sorafenib (BAY 43-9006) in metastatic medullary thyroid carcinoma in setting of inherited tumor syndromes, such as multiple endocrine neoplasia (MEN) 2A, MEN 2B, or familial medullary thyroid carcinoma (FMTC).
1.1.2 To assess objective response rate of sorafenib (BAY 43-9006) in sporadic metastatic medullary thyroid carcinoma.

1.2 Secondary Objectives:

1.2.1 To assess toxicity of sorafenib (BAY 43-9006) in patients with metastatic medullary thyroid carcinoma.
1.2.2 Measure serum tumor markers calcitonin and carcinoma embryonic antigen (CEA) pre-, during-, and post-treatment to correlate with disease response.
1.2.3 Correlate nuclear medicine functional imaging [F-18 fluorodeoxyglucose positron emission tomography (PET) scan] data obtained at pre-, during- and post-treatment with tumor response.
1.2.4 Correlate dynamic-contrast enhanced magnetic resonance imaging (DCE-MRI) data obtained at pre-, during- and post-treatment with changes in tumor permeability and vascularity with tumor response.
1.2.5 Perform pharmacogenomic studies on procured PBMCs if clinical responses are observed.
1.2.6 To correlate between the degree of Ras-MAPK signaling inhibition and vascular endothelial growth factor (VEGF) expression in the tumor and clinical response.
1.2.7 To correlate between the presence and type of RET gene defects in tumor and clinical response.

2 BACKGROUND

2.1 Metastatic Medullary Thyroid Carcinoma (MTC):

MTC is one of the best characterized solid tumors in regard to its pathologic, biochemical, and molecular genetic properties. MTC derives from the neuroendocrine parafollicular or C cells of the thyroid. Sporadic MTC accounts for about 75-80% of all cases of the disease. The remaining cases consist of inherited tumor syndromes, such as multiple endocrine neoplasia (MEN) 2A, MEN 2B, or familial medullary thyroid carcinoma (FMTC). Because the C cells are predominantly located in the upper portion of each thyroid lobe, patients with sporadic disease typically present with upper pole nodules. The ability of the tumor to secrete measurable quantities of calcitonin, occasionally along with other hormonally active peptides (such as adrenocorticotrophic hormone [ACTH] or calcitonin-gene related peptide [CGRP]) can contribute to the development of diarrhea, Cushing's syndrome, or facial flushing in many patients with advanced disease. Sporadic disease typically presents in the fifth or sixth decade. There may be a slight female preponderance. Sporadic patients typically present with an

asymptomatic mass in the thyroid. Patients with bulky disease with extremely high levels of calcitonin may have severe secretory diarrhea as a principal symptom. Metastatic cervical adenopathy appears in about 50% of patients at initial presentation. Symptoms of upper aerodigestive tract compression or invasion are reported by up to 15% of patients with sporadic disease.

Chemotherapy and external-beam radiation therapy are ineffective against MTC, rendering surgical resection the only definitive therapy (Moley JF *et al*, 1998; Evans DB *et al* 1999). Chemotherapeutics used in treatment of MTC include adriamycin, dacarbazine, streptozocin, and 5-fluorouracil (Schlumberger M *et al*, 1995). Single-agent response rates are poor, with aggressive adriamycin regimens producing 20% to 30% objective responses. A study of combination chemotherapy showed that a regimen of 5-fluorouracil, streptozocin, and dacarbazine produces objective responses in only 15%. Due to failure of chemotherapy and radiation therapy to offer significant benefit for patients with MTC, innovative therapeutic strategies for systemic treatment of MTC need to be developed.

2.2 Tumor markers and imaging studies in MTC:

Serum calcitonin is a reliable prognostic tumor marker in patients with metastatic MTC (Brunt LM. *et al.,* 1987) while reliability of CEA maker in MTC is not well-established. Serum calcitonin is widely used in the clinic to assess the response to therapy as well as to detect the subclinical and/or recurrent disease. FDG-PET has been widely applied in oncology primarily as a staging and restaging tool that can guide patient care. However, because it accurately detects recurrent or residual disease, FDG-PET also has significant potential for assessing therapy response. In this regard, it can improve patient management by identifying responders early, before tumor size is reduced; non-responders could discontinue futile therapy. For example, PET imaging is valuable in assessing tumor response to some tyrosine kinase inhibitors (Gleevec, SU11248) in the patients where conventional imaging studies may reveal stable disease.

Dynamic contrast enhanced MRI has recently been shown to be a valuable tool to assess tumor permeability and vascularity (Stevenson *et al.,* 2003; Morgan *et al.,*, 2003;Galbraith *et al.,*, 2003). Our group has extensive experience in using this imaging tool in the setting of clinical trials.

2.3 Genetics of MTC

The RET protooncogene codes for a cell membrane-associated tyrosine kinase receptor for a glial, cell line-derived neurotrophic factor. Mutations in the RET proto-oncogene are found in at least 95% of kindreds with MEN 2A and 88% of FMTC. Mutations associated with MEN 2A and FMTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13, whereas MEN 2B and some FMTC mutations are found within the intracellular exons 14-16. About 6% of patients with clinically sporadic MTC carry a germline mutation in RET, leading to identification of new kindreds with multiple previously undiagnosed affected individuals.

Somatic mutations in exons 11, 13, and 16 have also been found in at least 25% of sporadic MTC tumors, particularly the codon 918 mutation that activates the tyrosine kinase function of

the receptor and is associated with poorer patient prognosis. The genetic basis of MTC in the other 75% of patients is not well understood. It is possible that genetic defects other than point mutations in RET gene (ie: duplication of chromosome 10) might be present. RET point mutation results in constitutive activation of signaling, thus inhibition of RET signaling has the potential of being a good therapeutic target.

2.4 Sorafenib (BAY 43-9006)

Activation of the *ras* oncogene signaling pathway is considered to be an important mechanism by which human cancer develops. Raf kinase is a protein involved in the Ras signal transduction pathway. Ras regulates several pathways which synergistically induce cellular transformation, including the Raf/Mek/Erk cascade and the rac and rho pathways (Campbell *et al.,* 1998, Chong *et al.,* 2003). In particular, Ras activates the Raf/Mek pathway by first localizing Raf to the plasma membrane, where Raf initiates a mitogenic kinase cascade. Activated Raf phosphorylates and activates Mek which in turn phosphorylates and activates Erk. Activated Erk then translocates from the cytoplasm into the nucleus and modulates gene expression via the phosphorylation of transcription factors. Thus activation of Raf kinase, via activation of Ras, is thought to play an important role in carcinogenesis.

In particular, B-raf, a serine/threonine kinase, has been shown to be activated in a number of human tumor types including melanoma, ovarian and papillary thyroid carcinomas (Davies *et al.*, 2002, Mercer and Pritchard, 2003, Pollock and Meltzer, 2002, Singer *et al.*, 2003, Tannapfel *et al.*, 2003, Cohen *et al.*, 2003). A survey of 43 cancer cell lines showed that all B-raf mutations resided in exons 11 or 15. Remarkably, 80% of these B-raf mutations represent a single nucleotide change of T-A at nucleotide 1796 resulting in a valine to glutamic acid change at residue 599 (V599E, exon 15) in the CR3 domain (ATP binding and substrate recognition) which in turn confers constitutive kinase activity (Davies *et al.*, 2002, Mercer and Pritchard, 2003).

In Vitro Activity

The ability of sorafenib (BAY 43-9006) to inhibit a number of kinases was evaluated (Investigator's Brochure, 2003). The *in vitro* biochemical and cellular profile of sorafenib (BAY 43-9006) is summarized below:

Biochemical Assay	**IC_{50} (μM)**
c-raf[b]	0.002/0.006
b-raf wild-type	0.025
b-raf V599E mutant	0.038
VEGFR-2 (human)	0.090
VEGFR-2 (murine)	0.006
VEGFR-3 (murine)	0.010
PDGFR-β (murine)	0.028
Flt-3	0.058
c-KIT	0.068
FGFR-1	0.580
p38α	0.038

Cellular Mechanism[c]	IC_{50} (μM)
MDA-MB-231 MEK phosphorylation (Human Breast)	0.04
BxPC-3 MEK phosphorylation (Human Pancreatic)	1.00
LOX ERK phosphorylation (Human Melanoma)	0.80
b-raf ER MEK activation (Human Chimera, 3T3 cells)	2.30
VEGFR-2 phosphorylation (Human, 3T3 cells)	0.03
VEGFR-3 phosphorylation (Mouse, 293 cells)	0.10
PDGFR-β phosphorylation (Human, AoSMC)[d]	0.02
Cellular Proliferation	IC_{50} (μM)
MDA-MB-231 (10% FCS)[e]	2.60
MDA-MB-231 (0.1% FCS)	0.10
VEGF-HUVEC (2.0% FCS)[f]	3.00
PDGFR-β AoSMC[d] (0.1% BSA)[g]	0.23

a Recombinant enzyme assay
b Raf kinase activated with Lck (truncated/full length c-raf)
c Mechanistic cellular assays all performed in 0.1% BSA
d Human aortic smooth muscle cells
e Fetal calf serum
f Human umbilical vein endothelial cells
g Bovine serum albumin

In vitro kinase assays demonstrated that sorafenib (BAY 43-9006) is a potent inhibitor of wildtype and mutant (V599E) B-Raf and c-Raf Kinase isoforms in vitro (Investigator's Brochure, 2003). In addition, sorafenib (BAY 43-9006) did not inhibit human EGFR or Her2 kinases at 10 · M. Nor were PKC-α, PKC-β, PKC-γ, and PKA (rat, rabbit and bovine sources) kinase activity inhibited in vitro. sorafenib (BAY 43-9006) demonstrated an IC50 of 780 nM against p59 (bovine) Fyn kinase (Src family of protein tyrosine kinases). In non-kinase targets sorafenib (BAY 43-9006) had moderate potency against the adenosine A3, dopamine D1, and muscarinic M3 receptors with IC50 of 1.6 · M, 2.0 · M, and 3.1 · M, respectively. sorafenib (BAY 43-9006) did not inhibit MEK-1, ERK-1, EGFR, HER2/neu, c-met, PKA, PKB, Cdk-1/cyclin B, pim-1, GSK 3-b, CK-2, PKC-α (r), PKC-β (r), PKC-γ at concentrations as high as 10 μM. In summary, sorafenib (BAY 43-9006) showed ≥100-fold more selectivity for raf kinase relative to other target proteins.

Sorafenib (BAY 43-9006) also inhibited *in vitro* several receptor tyrosine kinases (RTKs) that are involved in tumor progression; human VEGFR-2, murine VEGFR-2, murine VEGFR-3, murine PDGFR-β, Flt-3, c-KIT, and p38α (MAPK family). In cellular assays, sorafenib (BAY 43-9006) was found to be a potent inhibitor of human and murine VEGFR-2, murine VEGFR-3, and murine PDGFR-β receptor phosphorylation (Investigator's Brochure, 2003).

Finally, Santoro et al. has shown that sorafenib (BAY 43-9006) inhibits RET kinase activity *in vitro* (IC50 dose 100 nM) (Carlomagno *et al*, 2006)

In Vivo Activity

Sorafenib (BAY 43-9006) has demonstrated *in vivo* anti-tumor efficacy as a single agent against a broad range of human tumor xenografts as summarized in the following table. The models evaluated include HCT-116 and DLD-1 colon tumor xenografts, MX-1 mammary tumor xenograft, NCI-H460 and A549 NSCLC xenografts, MiaPaCa-2 pancreatic tumor xenografts, and SK-OV-3 ovarian tumor xenografts. In this table, compound efficacy is expressed as percent tumor growth inhibition (TGI) and is calculated as ((1-(T/C)) *100, where T and C represent the mean tumor size in the Treated and Control groups respectively at the first measurement after the end of treatment.

Sorafenib (BAY 43-9006) Demonstrates Broad Spectrum Anti-Tumor Efficacy in Preclinical Xenograft Models

Tumor Type	Model	Dose (mg/kg/dose free base equiv.)[1]	Percent TGI ((1-(T/C))*100)
Colon	HCT-116	10 30 100	45 64 68
Colon	DLD-1	15 30 60	31 66 75
NSCLC	NCI-H460	10 30	27 56
NSCLC	A549	30 60	60 68
Mammary	MX-1	30 60	51 67
Pancreatic	Mia-PaCa-2	10 30 100	45 66 73
Ovarian	SK-OV-3	10 30 100	58 64 81

[1] Compound dosed as sorafenib (BAY 43-9006) or equivalent dose levels of tosylate salt, BAY 54-9085

The majority of the initial anti-tumor efficacy evaluations *in vivo* were conducted in the HCT116 colon tumor model since the tumorigenicity of this cell line was previously shown to be dependent on K-ras activation. Additional studies indicated that prolonged anti-tumor efficacy could be attained by extending the duration of treatment and that, in this tumor model, sorafenib (BAY 43-9006) was able to arrest tumor growth even if therapy was initiated against a substantially greater tumor burden.
Sorafenib (BAY 43-9006) also showed significant oral activity against two additional human tumor xenograft models that contain K-ras mutations: MiaPaCa-2 pancreatic carcinoma and H460 non-small cell lung carcinoma. The anti-tumor efficacy of sorafenib (BAY 43-9006) was also evaluated against the human SKOV-3 ovarian tumor cell line that contains a wild-type Ras

but over-expresses both the EGF and Her2 growth factor receptors. These receptors also signal through the Ras/Raf/Mek pathway.

In human tumor xenografts, MDA-MB-231 (breast) and Colo-205 (colon), there was a dramatic reduction of tumor neo-vascularization (Investigator's Brochure, 2003). Recent data also indicated that inhibition of c-raf may promote cell death in endothelial cells as a downstream event of VEGFR-2 stimulation (Alavi et al., 2003).

Taken together, data suggests that sorafenib (BAY 43-9006) may be of therapeutic value not only in human tumors containing *ras* gene mutations, but also in tumors over-expressing growth factor receptors in the Ras/Raf/Mek pathway, and by inhibiting tumor angiogenesis or neo-vascularization through inhibition of VEGFR-2, VEGFR-3, and/or PDGFR-β.

The ability of sorafenib (BAY 43-9006) (or its tosylate salt, BAY 54-9085) to be combined with paclitaxel, irinotecan, gemcitabine, or cisplatin was evaluated in preclinical *in vivo* models. In these studies, the focus was to evaluate if the co-administration of sorafenib (BAY 43-9006) would adversely affect the tolerance or anti-tumor efficacy of the 'standard of care' agent. The general health of mice was monitored and mortality was recorded daily. Tumor dimensions and body weights were recorded twice a week starting with the first day of treatment. Treatments producing greater than 20% lethality and/or 20% net body weight loss were considered 'toxic'. The results of these combinability analyses are summarized below:

Combinability of Concurrent Treatment with sorafenib (BAY 43-9006) and Clinically Established Agents

Combination Agent	Tumor Model	Combinability Y/N
Paclitaxel	NCI-H460 NSCLC MX-1 Mammary	Ye s
Irinotecan	DLD-1 Colon	Yes
Gemcitabine	MiaPaCa-2 Pancreatic	Yes
Cisplatin	NCI-H23 NSCLC	Yes

Sorafenib (BAY 43-9006) can be safely combined with a variety of standard cytotoxic cancer chemotherapy agents, including paclitaxel, irinotecan, gemcitabine and cisplatin with no significant increase in the toxicity associated with those agents and without diminishing their anti-tumor efficacy in preclinical models.

2.5 Clinical Experience

Sorafenib (BAY 43-9006) has been evaluated in multiple Phase 1 and Phase 2 studies in a variety of tumor types. To date, over 500 patients have been treated with single agent sorafenib (BAY 43-9006). The Phase 1 single agent clinical plan has focused on characterizing the safety and pharmacokinetic profile sorafenib (BAY 43-9006) in several different dosing regimens. All Phase 1 patients had a variety of advanced refractory solid tumors, and some of the patients stayed on trial for more than one year. Four different regimens have been tested: continuous treatment, 4 weeks on/ 1 week off, 3 weeks on /1 week off, and 1 week on/ 1 week off. Patients

have received doses ranging from 50 mg once weekly to 1600 mg daily of sorafenib (BAY 43-9006) on intermittent and continuous schedules. The 800 mg bid continuous administration cohort has exceeded the maximum tolerated dose (MTD) in all tested schedules. The 600 mg bid cohort exceeded the MTD in all but the less dose intensive regimen of 1 week on / 1 week off. The most frequent drug-related adverse events were hand-foot skin reaction, dermatitis, rash, fatigue, anorexia and diarrhea. There was an increase in the number of serious adverse events, discontinuations due to adverse events, and a number of skin toxicities at the higher dose levels ≥ 600 mg bid. Therefore, 400 mg bid was selected as the recommended dose for Phase 2.
In general, sorafenib (BAY 43-9006) at 400 mg PO BID dosing was well tolerated chronically by most patients. The most common drug-related adverse events (>5%) seen at this dose schedule were skin-related findings. The adverse events include hand-foot skin reaction occurring in 11 patients (35.5%), pruritus in 9 patients (29%), dermatology/skin-other in 9 patients (29.0%), alopecia in 8 patients (25.8%), and rash/desquamation in 7 patients (22.6%). Other common adverse events include fatigue in 11 patients (35.5%), anorexia in 7 patients (22.6%), diarrhea in 11 patients (35.5%), and pain-other in 5 patients (16.1%). Liver function abnormalities did occur, with SGOT elevation occurring in 6 patients (19.4%), SGPT elevation in 5 patients (16.1%), and alkaline phosphatase and bilirubin elevation in 4 patients each (12.9%). Of note, unlike most cytotoxic agents, myelosuppression was rarely observed.

Currently, the Phase 2 program includes studies designed to explore anti-tumor efficacy in certain tumor types and to gain additional experience with pharmacokinetics and safety. Thus far, Phase 2 studies have enrolled over 300 patients with a variety of tumor types including colorectal, renal cell, hepatocellular, pancreatic, and thyroid cancer and melanoma as well as several less common tumors.
In general, available information from the ongoing Phase 2 studies reveals toxicities that are similar to the Phase 1 data. Again, the five most frequent drug-related toxicities observed include hand-foot skin reaction, rash, anorexia, diarrhea, and fatigue. When all available data from the various studies/schedules are combined, the incidence of greater than grade 3 treatment emergent skin toxicity (e.g. hand-foot syndrome and "dermatology/skin reaction") for an initial dose of 400 mg bid and 600 mg bid, was 0% and 30%, respectively. Anti-tumor activity was observed in both Phase 1 and 2 studies. In December 2005, Sorafenib Tosylate (BAY 43-9006; NEXAVAR®) was approved by the FDA for the treatment of patients with advanced renal cell carcinoma.

2.6 Rationale

There is no standard systemic therapy for metastatic MTCs. Systemic chemotherapy has extremely limited value and local external beam radiation therapy only may help with palliation of symptoms. A median disease-specific survival in this group of patients is only 3 to 5 years. Targeted therapy for such chemo-resistant tumors is desperately needed.

RET mutation is a hallmark of genetic defect in MTC. Mutations in the RET proto-oncogene are found in at least 95% of kindreds with MEN 2A and 88% of FMTC and in about 25% of patients with sporadic MTC. It is possible that other mechanisms of RET gene defects in MTC are not discovered yet, but play a role in the pathogenesis of sporadic MTC. Sorafenib (BAY 43-9006) inhibits the RET/Ras/Raf/Mek pathway, and may indirectly inhibit the RET/Akt pathway. In addition, it also inhibits tumor angiogenesis or neo-vascularization through inhibition of VEGFR-2, VEGFR-3, and/or PDGFR-β. Sorafenib (BAY 43-9006) is an orally active small

molecule that was generally well tolerated in phase I clinical trials. Thus, sorafenib (BAY 43-9006) targeting the RET signaling pathway represents an excellent oral agent for the possible treatment of patients with metastatic medullary thyroid carcinoma.

3 PATIENT SELECTION

3.1 Eligibility Criteria specific for Arm A: All patients enrolled on Arm A must meet all eligibility criteria outlined in sections 3.1 and 3.3.

3.1.1 Histologically confirmed medullary thyroid carcinoma under the clinical setting of inherited tumor syndromes, such as multiple endocrine neoplasia (MEN) 2A, MEN 2B, or familial medullary thyroid carcinoma (FMTC).

3.2 Eligibility Criteria specific for Arm B: All patients enrolled on Arm B must meet all eligibility criteria outlined in sections 3.2 and 3.3.

3.2.1 Histologically confirmed medullary thyroid carcinoma under the clinical setting of sporadic MTC.

3.3 Eligibility Criteria common for Arms A and B: All patients enrolled on Arm A must meet all eligibility criteria outlined in sections 3.1 and 3.3. All patients enrolled on Arm B must meet all eligibility criteria outlined in sections 3.2 and 3.3.

3.3.1 Patients must have measurable disease as define in section 9.1.1.

3.3.2 Metastatic and/or locally advanced or locally recurrent disease.

3.3.3 Oral or intravenous (IV) bisphosphonates therapy will be allowed for patients with bony metastasis at the investigator's discretion. Bisphosphonate usage should be recorded if used since these agents may have anti-farnesyl transferase activity and may have some therapeutic effect in combination with sorafenib.

3.3.4 Age $\geq$ 18 years. Because no dosing or adverse event data are currently available on the use of sorafenib (BAY 43-9006) in patients <18 years of age, children are excluded from this study.

3.3.5 Life expectancy must be $\geq$ six months.

3.3.6 Patients must have an Eastern Cooperative Oncology Group performance status 0-2 (see Appendix A).

3.3.7 Patients must have normal organ and marrow function as defined below in the 10 days

prior to patient enrollment.

- Leukocytes ≥2,000/μL
- Absolute neutrophil count ≥1,000/μL
- Platelets ≥100,000/μL
- Total bilirubin ≤ within 2 x upper limit of normal
- AST (SGOT)/ALT (SGPT) ≤ within 3 x upper limit of normal
- Serum creatinine within normal institutional limits
  - OR
- Creatinine Clearance > 30 mL/min (by Cockcraft-Gault formula)

3.3.8 The effects of sorafenib (BAY 43-9006) on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because kinase inhibitors are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for at least 30 days after completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

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

3.4 Exclusion Criteria for Arm A and Arm B:

3.4.1 Patients who have had systemic anti-tumor therapy (such as chemotherapy, biologic modifiers or antiangiogenic therapy) within 4 weeks (6 weeks if nitrosourea or mitomycin chemotherapy) prior to study entry.

3.4.2 Patients who have had external beam radiation therapy within 1 week or if the adverse events associated with radiation are not resolved to grade 1 or less prior to study entry.

3.4.3 Prior therapy with sorafenib (BAY 43-9006), ZD 6474 or AMG-706.

3.4.4 Patients currently receiving any other tumor-specific therapy for thyroid cancer or investigational therapy. Patients receiving adjuvant hormonal therapy for a second primary (such as breast cancer or prostate cancer) are allowed to participate as far as there are no known drug interactions.

3.4.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to sorafenib (BAY 43-9006).

3.4.6 Patients unable to swallow sorafenib tablets. (e.g. Any condition that impairs patient's ability to swallow pills)

3.4.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled hypertension, or psychiatric illness/social situations that would limit

compliance with study requirements.

3.4.8 Patients with any evidence of a bleeding diathesis.

3.4.9 Patients actively receiving anticoagulation with therapeutic intent. Prophylactic anticoagulation (i.e. low dose warfarin) or venous or arterial access devices is allowed provided that the PT, INR or PTT are normal.

3.4.10 Pregnant women or women who are breast-feeding are excluded from this study because sorafenib (BAY 43-9006) is an investigational agent and teratogenicity has not been evaluated yet. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with sorafenib (BAY 43-9006), breastfeeding should be discontinued if the mother is treated with sorafenib (BAY 43-9006).

3.4.11 HIV-positive patients receiving combination anti-retroviral therapy because of possible pharmacokinetic interactions with sorafenib (BAY 43-9006). Patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.4.12 Patients taking the cytochrome P450 enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine, or Phenobarbital), rifampin or St. John's Wort due to potential drug interactions with sorafenib.

3.5 Inclusion of Women and Minorities

Entry to this study is open to both men and women, and to all racial and ethnic subgroups. Patients will not be excluded from this study on the basis of a history of known HIV positive status.

4 TREATMENT PLAN

4.1 Sorafenib (BAY 43-9006) Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications for sorafenib (BAY 43-9006) are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat thyroid cancer.
Sorafenib (BAY 43-9006) will be administered at the dose of 400 mg orally twice a day on a continuous basis. Sorafenib (BAY 43-9006) is supplied as 200-mg tablets. Patients are to swallow the tablets whole with approximately 250 ml (8 oz.) of water, each morning and evening (i.e., approximately 12-hourly). When given with a moderate fat meal, bioavailability was similar to that in the fasted state. With a high fat meal, sorafenib (BAY 43-9006) tosylate's bioavailability was reduced by 29% compared to administration in the fasted state. Thus, it is recommended that sorafenib (BAY 43-9006) be taken on an empty stomach (at least 1 hour before or 2 hours after eating).

Patients will be given monthly calendars (patient diaries) to document the time when the sorafenib (BAY 43-9006) pills are taken. At monthly visits, patients will bring back this record.

Hypertension is a known and potentially serious adverse event associated with Sorafebnib (BAY 43-9006) treatment. Patients will have their blood pressure monitored and recorded weekly during the first cycle of therapy, either at the doctor's office or using any calibrated electronic device (such as those found at a local drug store or pharmacy). Patients will be provided with a Blood Pressure Check Diary on which to record the measurements. An increase in blood pressure of > 20 mm Hg (systolic) and 10 mm Hg (diastolic) should be reported to the treating physician immediately. See dose modification guidelines in section 5 in event of drug related hypertension.

Oral or intravenous (IV) bisphosphonates therapy will be allowed for patients with bony metastasis at the investigator's discretion.

Close monitoring is recommended for patients taking BAY 43-9006 tosylate and CYP3A4 inducers. The CYP3A4 inducers such as antiepileptic drugs (phenytoin, carbamazepine, or Phenobarbital), rifampin or St. John's Wort are not permitted on the protocol due to potential drug interactions with sorafenib.

4.2 Supportive Care Guidelines

Prophylactic use of anti-emetics, anti-diarrheal treatment, or growth factors is not recommended. However, anti-emetics, anti-diarrheal treatment or growth factors may be used for acute treatment of toxicities and growth factors may be offered as per the ASCO guidelines.

For patients who develop hand-foot reaction, treatment with topical emollients (such as *Aquaphor*) for symptom relief is recommended. Topical and/or oral steroids or anti-histamine agents may be used. High dose vitamin B6 (pyridoxine; up to 400 mg orally each day) may also be used.

4.3 Duration of Therapy

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

- Progressive Disease and no clinical benefit (Note: patients who have continued clinical benefit such as symptomatic or tumor marker improvement or decreased tumor burden compared to baseline or limited progression in non-target lesion treated with radiation or surgery will be able to continue therapy)
- Completion of 8 weeks of therapy after complete remission
- Off of study drug due to any reason for more than 21 consecutive days
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5 DOSING DELAYS/DOSE MODIFICATIONS

- For delay of treatment due to toxicity for more than 21 days, patient will be removed from the study.

Dose should be modified and/or delayed according to the following guidelines:

In the event of grade 3 or 4 drug-related non-hematologic toxicity, therapy will be held till the toxicity has resolved to baseline or ≤ grade 1. For delay of treatment due to toxicity for more than 21 consecutive days, patient will be removed from the study. Once toxicity is resolved to baseline or ≤ grade 1, sorafenib (BAY 43-9006) should be started at a reduced dose of 200 mg PO BID. If tolerated, the dose can be re-escalated to 600 mg/day given as 400 mg in the AM and 200 mg in the PM. If 600 mg/day dose is tolerated, further re-escalation to the full dose of 400 mg PO BID may be done after discussing with protocol chair.

In the event of grade 2 hand-foot skin reaction or recurrent grade 2 drug-related non-hematologic toxicity, therapy may be held till the toxicity has resolved to baseline or ≤ grade 1. For delay of treatment due to toxicity for more than 21 consecutive days, patient will be removed from the study. Once toxicity is resolved to baseline or ≤ grade 1, sorafenib (BAY 43-9006) should be started at a reduced dose of 200 mg PO BID. If tolerated, the dose can be re-escalated to 600 mg/day given as 400 mg in the AM and 200 mg in the PM. If 600 mg/day dose is tolerated, further re-escalation to the full dose of 400 mg PO BID may be done after discussing with protocol chair.

In the event of GI-Perforation, patient will be removed from the study and followed until adverse event is resolve.

In the event of treatment-emergent Hypertension:

Grade of hypertension Event (CTCAE v.3)	**Management/ Next Dose**
grade 1	Consider increased BP monitoring
grade 2 asymptomatic and diastolic BP < 110 mm Hg	Begin anti-hypertensive therapy and continue agent
grade 2 symptomatic/ persistent OR diastolic BP ≥ 110 mm Hg OR grade 3	1. Agent should be held* until symptoms resolve and diastolic BP ≤ 100 mm Hg; also treat patient with anti-hypertensives and restart at reduced dose of 600 mg/day given as 400 mg in the AM and 200 mg in the PM. Dose can be re-escalated to full dose as tolerated. 2. If diastolic BP not controlled (≤ 100 mm Hg) on therapy, reduce to another dose level with a dose of 400 mg/day given as 200 mg in the AM and 200 mg in the PM. **
grade 4	Discontinue protocol therapy
* Patients requiring a delay of > 3 weeks should go off protocol therapy. ** Patients requiring > 2 dose reductions should go off protocol therapy.	

6 PHAMACEUTICAL INFORMATION

6.1 Sorafenib (BAY 43-9006) (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; Nexavar®.

Molecular Formula: $C_{12}H_{16}ClF_3N_4O_3$ $XC_7H_8O_3S$

M.W.: BAY 43-9006 tosylate: 637 Daltons; BAY 43-9006 (free base): 465 Daltons

Classification: Kinase inhibitor (Raf, VEGF-R, and PDGF-R).

Description: 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. BAY 43-9006 is a potent inhibitor of c-raf, and wild-type and mutant b-raf in vitro. Additionally, further characterization of BAY 43-9006 tosylate 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.

How Supplied: Sorafenib tosylate is supplied by Bayer Healthcare AG and distributed by PMB, CTEP, DCTD, NCI. The tablets are available as 200 mg immediate release tablets. The inactive ingredients are microcrystalline cellulose, croscarmellose sodium, hydroxypropylmethyl cellulose, magnesium stearate, sodium lauryl sulfate, and a film- coat with hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide and red iron oxide.
■ The commercially labeled 200 mg tablets are round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side and packaged in HDPE bottles of 120 tablets.

NOTE: Sorafenib tablets may be repackaged in HDPE pharmacy dispensing bottle other than the original container with expiration date not to exceed 30 days.
Route of Administration: Orally.

Method of Administration: Following oral administration, sorafenib (BAY 43-9006) tosylate's mean relative bioavailability is 38-49%. When given with a moderate fat meal, bioavailability was similar to that in the fasted state. With a high fat meal, BAY 43-9006 tosylate's bioavailability was reduced by 29% compared to administration in the fasted state. Thus, it is recommended that sorafenib (BAY 43-9006) be taken on an empty stomach (at least 1 hour before or 2 hours after eating) and with at least 250 mL of water.

Drug Product Storage: Store intact bottles at controlled room temperature, not to exceed 25ºC.

If a storage temperature excursion is identified, promptly return sorafenib to controlled room temperature (not to exceed 25°C) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Drug Product Stability: Stability studies are ongoing for investigationally-labeled supplies. Refer to package labeling for shelf life of commercially-labeled supplies.

Approximate Solubility: 0.19 mg/100 mL in 0.1 N HCl, 453 mg/100 mL in Ethanol, and 2971 mg/100 mL in PEG 400.

Potential Drug Interactions: Sorafenib metabolizes primarily by CYP3A4 during phase I metabolism (oxidation) and primarily by UGT1A9 in phase II (conjugation). Co-administration of rifampin resulted in sorafenib AUC reduction of approximately 37%. Therefore, use caution when co-administering with strong CYP3A4 inducers, such as St. John's wort, phenytoin, carbamazepine, phenobarbital and dexamethasone as they can reduce sorafenib exposure. CYP3A4 inhibitors are not expected to cause clinically relevant changes to sorafenib exposure.

In vitro, sorafenib is a moderate inhibitor CYP2C19, 2D6, and 3A4 and a strong inhibitor of CYB2B6, 2C8, and 2C9. It also inhibits pathway enzymes UGT1A1 and UGT1A9 in phase II conjugation. Clinical data suggests sorafenib does not increase exposure of other drugs metabolized by CYP pathways and therefore does not appear to be clinically relevant. Use caution when co-administered with sensitive substrates of UGT1A1.

While sorafenib solubility is pH dependent, co-administration with omeprazole did not result in clinically relevant change in sorafenib exposure.

Sorafenib may prolong the QT/QTc interval. Avoid concomitant drugs that may induce the QTc prolongation.

Patient Care Implications: Hand-foot skin rash can be treated with topical emollients, high-potency topical steroids, or keratolytic cream (urea/salicyclic acid).

Females of childbearing potential should avoid becoming pregnant while they or their male partners are taking sorafenib and should use effective contraception during and for at least 30 days after completion of therapy.

Availability:

Sorafenib (BAY 43-9006) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Sorafenib (BAY 43-9006) is provided to the NCI under a Clinical Trials Agreement (CTA) between Bayer Corp./Onyx and the DCTD, NCI (see Section 10.4).

Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the

CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

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

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

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

Version 2.7, November 16, 2015[1]

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006) (CTCAE 4.0 Term) [n= 2571]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome	
	Chest pain - cardiac		
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
GASTROINTESTINAL DISORDERS			
Abdominal pain			***Abdominal pain (Gr 3)***
	Ascites		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Gastrointestinal hemorrhage[2]		***Gastrointestinal hemorrhage[2] (Gr 3)***
		Gastrointestinal perforation[3]	
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic Failure	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INVESTIGATIONS			

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006) (CTCAE 4.0 Term) [n= 2571]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Activated partial thromboplastin time prolonged		***Activated partial thromboplastin time prolonged (Gr 2)***
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 3)***
Alkaline phosphatase increased			***Alkaline phosphatase increased (Gr 3)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increase			***Blood bilirubin increased (Gr 3)***
Creatinine increased			***Creatinine increased (Gr 3)***
	GGT increased	Electrocardiogram QT corrected interval prolonged	
INR increased			***INR increased (Gr 3)***
	Investigations - Other (bicarbonate-serum low)		
Lipase increased			***Lipase increased (Gr 3)***
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 3)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
Serum amylase increased			***Serum amylase increased (Gr 3)***
Weight loss			***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
Hyperglycemia	Hypercalcemia		***Hyperglycemia (Gr 3)***
	Hyperkalemia		***Hyperkalemia (Gr 3)***
	Hypernatremia		
Hypoalbuminemia			***Hypoalbuminemia (Gr 3)***

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006) (CTCAE 4.0 Term) [n= 2571]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Hypocalcemia			***Hypocalcemia (Gr 3)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 3)***
Hyponatremia			***Hyponatremia (Gr 3)***
Hypophosphatemia			***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
	Back pain		***Back pain (Gr 3)***
	Bone pain		
	Musculoskeletal and connective tissue disorder - Other (muscle spasm)		
	Myalgia		
	Pain in extremity		***Pain in extremity (Gr 3)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Treatment related secondary malignancy		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Reversible posterior leukoencephalopathy syndrome	
PSYCHIATRIC DISORDERS			
	Insomnia		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Respiratory hemorrhage[5]		

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006) (CTCAE 4.0 Term) [n= 2571]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Voice alteration		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
Palmar-plantar erythrodysesthesia syndrome		Erythema multiforme	***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
		Stevens-Johnson syndrome Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event	

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

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (Thrombotic microangiopathy [e.g., TTP or HUS]); Febrile neutropenia[6]
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Palpitations; Pericardial effusion; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
ENDOCRINE DISORDERS - Adrenal insufficiency; Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (color vision deficits); Eye disorders - Other (light to dark adaptation); Eye disorders - Other (retinal vein occlusion); Eye disorders - Other (retinal hemorrhage); Eye disorders - Other (visual field distortion); Flashing lights; Keratitis; Photophobia; Retinal detachment
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fistula; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Colonic ulcer; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophagitis; Flatulence; Gastric ulcer; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (small bowel NOS fistula); Gastrointestinal fistula; Hemorrhoids; Ileal fistula; Ileus; Oral pain; Pancreatitis; Proctitis; Rectal fistula; Rectal mucositis; Rectal obstruction; Rectal pain; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Facial pain; Flu like symptoms; Localized edema; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic hemorrhage; Hepatobiliary disorders - Other (biliary obstruction secondary to multiple biliary stones)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Cytokine release syndrome; Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Fall; Fracture; Hip fracture; Vascular access complication; Wound complication; Wound dehiscence
INVESTIGATIONS - CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Ejection fraction decreased; Fibrinogen decreased; Investigations - Other (blood urea nitrogen high)
METABOLISM AND NUTRITION DISORDERS - Acidosis; Alkalosis; Dehydration; Hypermagnesemia; Hypertriglyceridemia; Hyperuricemia; Hypomagnesemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness left-sided; Muscle weakness lower limb; Muscle weakness right-sided; Muscle weakness upper limb; Musculoskeletal and connective tissue disorders - Other (cramping); Myositis; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor

hemorrhage); Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Hydrocephalus; Ischemia cerebrovascular; Lethargy; Leukoencephalopathy; Memory impairment; Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Libido decreased; Personality change; Psychosis
RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Proteinuria; Renal and urinary disorders - Other (focal segmental glomerulosclerosis); Renal and urinary disorders - Other (nephrotic syndrome); Renal and urinary disorders - Other (right ureter rupture); Renal calculi; Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urine discoloration
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Gynecomastia; Hematosalpinx; Menorrhagia; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal fistula; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Bronchospasm; Hiccups; Hoarseness; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fibrosis; Respiratory, thoracic and mediastinal disorders - Other (nasal septal perforation); Tracheal mucositis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythroderma; Hyperhidrosis; Nail loss; Pain of skin; Purpura; Rash acneiform; Scalp pain; Skin and subcutaneous tissue disorders - Other (folliculitis); Skin and subcutaneous tissue disorders - Other (non-life threatening squamous cell carcinoma of skin: keratoacanthoma type); Skin hyperpigmentation; Skin hypopigmentation; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypotension; Phlebitis; Vascular disorders - Other (ruptured aortic aneurysm); Vascular disorders - Other (visceral arterial ischemia); Vasculitis

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

7 CORRELATIVE/SPECIAL STUDIES:

Several studies listed in this section are not necessarily research tests but they have been outlined below as the information obtained from following tests may not be needed to determine objective response (primary endpoint of the study) while they may be helpful in clinical care of the patient. Informed consent must be obtained prior to obtaining research studies [any tissue specimen, biopsies, research blood draws, and DCE-portion of MRI].

7.1 Measure serum tumor markers (calcitonin and CEA) pre-, during-, and post-treatment to correlate with disease response.

This will be done in all the patients participating on the study as it is considered standard of care. This will be done pre-treatment, every 16 weeks during treatment and post-treatment [within 2-4 weeks after last dose of sorafenib (BAY 43-9006)]. All the centers participating in this study perform calcitonin and CEA routinely as a part of standard clinical care.

In addition to drawing samples for serum calcitonin and CEA at the baseline, extra 10-mL of blood (research blood draw) will be drawn in red top tube on ice at pre-study visit. Serum will be separated, aliquoted in 0.5 mL/tube and stored for possible future re-measurement of calcitonin and/or CEA. Such frozen samples will be utilized if clinical laboratory changes the calcitonin and/or CEA assays while patient is on study, to avoid inter-assay variation. In such cases, such baseline sample may be re-run concurrently with specimen drawn during treatment.

7.2 Perform a nuclear medicine functional imaging F-18 fluorodeoxyglucose positron emission tomography (PET) scan] pre-, and during-treatment.

PET scans are not required as a part of this research study. Per protocol, PET scans are not used for response assessment. PET scans may be done in any patient on the study as clinically indicated pre-treatment and every 16 weeks during treatment. This will be determined by the treating physician.

7.3 Perform a dynamic-contrast enhanced magnetic resonance imaging (DCE-MRI) pre-, and during-treatment to correlate change in tumor permeability and vascularity with tumor response.

All the centers participating in this study perform MRI routinely as a part of standard clinical care for the cancer patients. These centers also have capacity to perform DCE-MRI. While DCE-portion of this test is considered research, MRI is considered a standard imaging for patients with medullary thyroid carcinoma. All centers participating in the study will use a standard uniform acquisition protocol for DCE-MRI scan (see Appendix C for the details). Digital images will be transferred to Dr. Knopp's OSU imaging laboratory for central reading. DCE-MRI scans are performed as a part of laboratory correlative studies only and the results will not be used to assess the response.

DCE-MRI scan will be preferred in at least 16 patients entered on the Arm A and at least 16 patients entered on Arm B of the study except under the following circumstances:

Patients who have:

- Cardiac pacemaker
- Other ferromagnetic metal implants not authorized for use in MRI such as some types of cerebral aneurysm clips
- Claustrophobia not helped by pre-medications
- Obesity (exceeding the equipment limits)
- Following circumstances exist:
- In case, MRIs are not suitable for evaluating response per RECIST criteria
- Investigator's disapproval
- Funding for the research part of DCE-MRI is not sufficiently available

DCE-MRI may be performed for the remaining patients enrolled on Arms A and B of the

study per investigator's discretion.

Time points: Performed pre-therapy (within 4 wks prior to treatment), at 8 weeks on therapy. DCE-MRI scans at the time points beyond 8 weeks (at every 8 week interval while on the study and at off study visit time point) may be done per investigator's discretion.

Note: MRI scans will be continued to be utilized to measure response.

7.4 Pharmacogenomic studies:

We will procure PBMCs from all the patients enrolled on the study. Pharmacogenomic studies will be performed in all the patients if any clinical responses are observed on this trial. We will examine for selected polymorphisms of genes influencing sorafenib (BAY 43-9006) metabolism and/or resistance genes that may predict response or toxicity. These changes will be correlated with toxicity and clinical response to therapy.

Blood will be drawn for all the patients enrolled on the study.

Sample collection and shipping: 20 ml peripheral blood in heparinized tube (usually solid green top tubes) will be collected, kept at the room temperature till shipped on the same day of collection (see Appendix B for shipping instructions). Blood specimens will be collected from all patients and PBMCs will be isolated.

Time Points: Performed pre-therapy (within 4 weeks prior to registration).

7.5 Assess the degree of Ras-MAPK signaling inhibition, and vascular endothelial growth factor (VEGF) expression in the tumor and clinical response. (Maximum of 24 patients to participate)

Perform MAP kinase and AKT phosphorylation assay by immunohistochemistry to evaluate the degree of RET-Ras-MAPK signaling inhibition by sorafenib (BAY 43-9006) in tumor biopsies. Given that sorafenib (BAY 43-9006) also inhibits VEGFR, we will evaluate VEGF expression in tumor biopsies to correlate with DCE-MRI parameters and with clinical response when possible.

These tests will be performed in any patients on Arm A or B of the study who has biopsiable disease and is willing to undergo biopsies for research purposes.

Biopsies will not be performed under one of the following circumstances:

- Investigator's disapproval
- Funding for the biopsies is not sufficiently available
- Patient refuses to undergo the procedure.

In such cases biopsies may be performed pre-treatment (within 4 weeks prior to starting treatment) and at 8 wks on treatment. Post-treatment (within 4 wks after last dose of treatment) biopsies in these patients may be performed per investigator's discretion. Please note that the CT or MRI, DCE-MRI, and PET scan that might need to be done at these time points should be done prior to doing biopsy procedure. No specific time interval is necessary between these imaging studies and biopsy.

Sample collection and processing: Fine needle aspiration (FNA) biopsies (using 18-21 gauge needle) of the tumor (ie: either cervical lymph nodes or bulky bony or lung or liver metastasis) will be performed under imaging guidance or blindly depending on the location and size of the tumor.

Fine needle aspirated material will be collected in the tubes containing RPMI media. No direct smears slides will be made from FNA. Using Autocyte PREP system standard protocol, slides will be prepared using CytoRich® Red (Tripath Imaging) cytological preservative. The actual slides used will be PLUS slides; as these are precoated that facilitates the cells staying on the slides during processing. At least 8 unstained slides will be prepared using the standard protocol. Two slides will be stained with PapStain for cytologic diagnosis so that we verify that tumor was indeed present in the FNA specimen.

Principle of Autocyte PREP system: The AutoCyte PREP System converts a liquid suspension of a cell sample into discretely stained, homogenous thin-layer of cells while maintaining diagnostic cell clusters. The process includes cell preservation, randomization, enrichment of diagnostic material, autmated pipetting, sedimentation, and discrete staining portions of the process. The AutoCyte PREP presents a wellpreserved population of stained cells present within a 13mm diameter circle. Using this system, we have been able to perform immunohistochemistry studies on specimens prepared from FNA material in our ongoing CTEP- sponsore d phase II trial (NCI 6609).

All stained and unstained slides will be shipped to Dr. Shah at the OSU (see Appendix B for shipping instructions) who then will transfer batched specimen to Dr. Ringel's laboratory.

Methods: Studies on unstained slides will be processed at Dr. Ringel's laboratory at the OSU. **Immunohistochemical staining** Sections will be dewaxed, soaked in alcohol and after microwave treatment in antigen unmasking solution for 10 min incubated in 3% hydrogen peroxide for 15 min to inactivate endogenous peroxidase activity. Sections will be incubated at 4°C overnight with anti- phospho-Akt (dilution 1:100), with anti-Ret (C-19) (dilution 1:100), with anti-p44/42 MAP kinase (dilution 1:100), with anti VEGF (dilution 1:100). Immunostaining will be performed by use of the Vectastain Universal Quick kit according to the manufacture's instruction. Peroxidase staining will be revealed with 3, 3 - diaminobenzidine. Negative control will be applied by omission of antiserum. Results will be interpreted independently by three blinded investigators and scored for the presence or absence of staining. Scoring will be compared between the three investigators independently and agreement between two of the three investigators will be required for a positive result to be assessed.

7.6 Assess the presence and type of RET gene defects in the tumor to correlate with clinical response.

As the presence of RET gene mutations in patients with metastatic sporadic medullary thyroid carcinoma is highly variable but on average about 25%, we plan to examine the presence and type of such gene defects in our patient population while treating them with sorafenib (BAY 43-9006) that inhibits the downstream signaling pathway for RET.

As patients on Arm A are expected to have germ-line mutations in RET, collection and studies on tumor tissue blocks may not be necessary in those patients. In this group of patients, we will have RET germ-line mutation information available from the genotyping

studies performed in the peripheral blood (see section 7.7).

All patients on Arm B on the study will have this test performed except under the following circumstances:

- Tissue block is not sufficient for research purposes.
- Tissue block is not transferable for research purposes.

Sample collection and shipping: There is no new biopsy performed for this test. The tissue block preserved routinely at clinical pathology laboratory of previously performed thyroid cancer biopsy/surgery will be obtained and shipped to Dr. Shah at the OSU (see Appendix B for shipping instructions).

Time point: Anytime prior to registration on the study.

Methods: Ten micron/slice will be cut from the tumor paraffin tissue block and such 3-4 unstained slides will be used for isolating tumor DNA. H&E slides will be prepared to verify pathologic diagnosis. Tumor DNA will be isolated in Dr. Ringel's laboratory at the OSU. **DNA extraction:** After microdissection of tumor on slides, DNA will be extracted using QI-Amp DNA mini kit (Qiagen SA) according to the manufacturer's instruction. All PCR products will be electrophoresed on 3% agarose gel in TAE buffer and stained with ethidium bromide.

RET mutation studies will be performed in Dr. Thomas Prior's laboratory at the OSU using standard protocol for RET genotyping.

7.7 Assess the presence and type of RET gene defects in the peripheral blood to correlate with clinical response.

RET genotyping in peripheral blood is a clinical test that is standard of care in all patients with medullary thyroid carcinoma. Each participating center will use their clinical laboratories to perform such RET genotyping tests.

This test will be sent out to the clinical laboratory (5 mL blood in one purple top/EDTA tube) in all the patients enrolled on the study during their pre-study visit unless the RET mutation analysis report from previously performed analysis is available.

8 STUDY CALENDAR

	Pre-therapy[a]	Course I (subsequent courses as course I[i,✋])		Off-therapy[c]
		Week 4[b]	Week 8	
Sorafenib (BAY 43-9006)[d]				
Patient diaries		X	X	X
History/Physical Exam	X	X	X	X
Vital signs/Weight	X	X	X	X
Blood pressure monitoring	Once a week till stable or at least for the first 4 weeks.			X
Adverse Event Evaluation		X	X	X
CBC w/diff, platelets	X	X	X	X
Serum chemistry[e]	X[e]	X[e]	X[e]	X[e]
Serum β-HCG[f]	X[f]			
CT or MRI scan of neck/chest/abdomen[g]	X[g]		X[g]	X[g]
Serum Calcitonin and CEA	X		X	X
Following tests may be done in selected group of patients ONLY. See Sec7.0 for the details.				
10-mLblood for procurement of serum (*Section 7.1*)	X			
PET scan (*Section 7.2*)[h]	X		X	X
DCE-MRI scan (*Section 7.3*)	X		X	X[j]
20-mLblood for plasma and PBMCs (*Section 7.4*)	X			
FNA biopsy of the tumor (*Section 7.5*)	X[k]		X[k]	X[j]
Paraffin tumor tissue block (*Section 7.6*)	X			
RET genotyping to clinical lab (*Section 7.6*)	X			

a. Pre-therapy evaluations are to be conducted within 10 days prior to administration of sorafenib (BAY 43-9006) except imaging studies, research blood draws, and tumor biopsies that should be done within 4 weeks prior to the start of therapy.
b: Week 4 evaluations may be done at local doctor's office. However, AE eval must be by research staff via phone interview with the patient and principal investigator must sign off on adverse event data forms within 36 hours of the phone interview.
c. Off-therapy evaluations are to be conducted within 4 weeks after last dose of sorafenib (BAY 43-9006) treatment. Serum calcitonin and CEA, CT/MRI scans will be optional if a patient received sorafenib (BAY 43-9006) for ≤4 weeks.
d: Oral sorafenib (BAY 43-9006) will be given with 250 ml (about 8 ounces) of water at the dose of 400 mg BID.
e: Sodium, Potassium, Chloride, Bicarbonate, Creatinine, BUN, Glucose, Phosphorus, Total protein, Albumin, Total bilirubin, S GOT (AST), SGPT (ALT), Alkaline phosphatase, LDH.
f: Pregnancy test (sensitivity of at least 50 mIU/mL) will be performed for all women of childbearing potential before beginning sorafenib (BAY 43-9006).
g: CT or MRI scans as determined by investigators to assess the response per RECIST criteria.
h: PET scans are performed only as clinically indicated as determined by treating physicians.
i: Research blood draws and tumor biopsies will not be required in subsequent courses.
j: Optional per investigator's discretion.
k: If patient has biopsiable disease and agrees to have biopsies for research purpose.
✋: After six months, we will eliminate week 4 visits and all associated testing at week 4 of the each course. Patients will return to OSU every 16 weeks for an evaluation visit.

9 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every 16 weeks. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

9.1 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 (Therasse *et al.*, 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.

9.1.1 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 or MRI performed with following technique:

MRI images acquired in at least two imaging planes (such as axial and coronal) that give 'in-plane' resolution of at least 2.5 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless the lesion in irradiated area shows progression.

9.1.2 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 or MRI with 'in-plane resolution of 2.5 mm'), 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.

9.1.3 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.

9.1.4 **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.

9.2 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.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless the lesion in irradiated area shows progression.

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 anti-tumor 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.

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.

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.

9.3 Response Criteria for patients with measurable disease:

DCE-portions of MRI scans and PET scans will not be used to assess the response as they are not part of RECIST criteria. Please see section 9.4 for patients who have only assessable disease.

9.3.1 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

9.3.2 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 marker (calcitonin) is initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.3.3 **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 section 9.3.1).

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: 1) 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.
2) 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/biopsy) before confirming the complete response status.

9.4 Confirmatory Measurement/Duration of Response

9.4.1 **Confirmation**

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 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 16 weeks (see section 9.3.3).

9.4.2 **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.

9.4.3 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.

9.5 Response Review

As the primary endpoint for this trial is response rate, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Note: When a review of the radiological images is to take place, it is also recommended that images be free of marks that might obscure the lesions or bias the evaluation of the reviewer(s).

10 REGULATORY AND REPORTING REQUIREMENTS

The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the *CTEP web site* (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting.

All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the *CTEP web site* (http://ctep.cancer.gov/reporting/ctc.html).

10.1 Expedited Adverse Event Reporting

(AE; formerly known as Adverse Drug Reaction)

- Expedited reports are submitted to CTEP via the secure CTEP-AERS application accessed via the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).
- In the rare occurrence when Internet connectivity is lost, an adverse event report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- Those AEs that do not require expedited reporting must be reported in routine (CDUS) study data submissions. AEs reported through CTEP-AERS must **also** be reported in routine study data submissions.

10.1.1 **Expedited Reporting Guidelines** –Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND:

CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

10.1.2 **Expedited Adverse Event Reporting Exclusions**

None.

10.1.3 **Secondary AML/MDS**

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols using the NCI/CTEP Secondary AML/MDS Report Form. *This form can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/index.html).* Second malignancies and non-AML/MDS secondary malignancies (*e.g.*, endometrial cancer in a breast cancer patient receiving tamoxifen) should NOT be reported via CTEP-AERS but should be submitted as part of the study results via routine CDUS reporting.

10.1.4 **Data Safety Monitoring Plan**

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with the sponsors, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report biannually for this Phase II study that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will also be reported to the IRB of record as per the policies of the IRB.

10.2 Data Reporting

The OSU clinical trials' office will be responsible for the submission of the CDUS data to CTEP. This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov/reporting/cdus.html).

10.3 CTEP Multicenter Guidelines

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair: Dr. Bhavana Konda serves as a protocol chair for this multi-center study.

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center: The Ohio State University serves as a coordinating center for this multi-institutional study.

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. The participating institutions must report directly to CTEP with a copy to the Coordinating Center. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.

- The Coordinating Center must be designated on the title page.
- Central registration of patients is required. The procedures for registration must be stated in the protocol.
- Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.

- Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

10.3.1 **Institutional Review Board (IRB)**

A copy of the IRB approval for this protocol must be submitted to the coordinating office along with the approved consent form prior to patient registration. Yearly approvals and revised consent forms must also be submitted to the OSU clinical trials office. Patients will not be registered if the IRB approval date is greater than one year prior to the date of registration. Patients must sign a copy of the current, approved consent form.

10.3.2 **Patient Registration**

All patients will be registered with the OSU clinical trials office from 8:00 am to 4:30 pm Eastern Standard Time, Monday through Friday, excluding holidays, by calling Dr. Shah's office at 614-293-8629 and faxing the registration forms to 614-293-3112. Patients must be registered prior to initiation of treatment.

The following must be faxed to the OSU clinical trials office at 614-293-3112 prior to patient registration:

- Copy of signed informed consent Form
- Eligibility Checklist
- Baseline Pathology Report
- Baseline Radiology Report
- Pre-therapy Laboratory Reports
- History and physical exam note
- Documentation of prior therapy
- Documentation of current medications
- Patient demographics

No patient will be registered in the OSU clinical trials office unless every question on the submitted forms is answered satisfactorily. NO PROTOCOL DEVIATIONS are allowed.

Patients will not begin treatment until a confirmation of registration is received from the OSU clinical trials office. A registration number will be given to each patient and will be used as a

unique identifier on all patient materials and data sheets submitted thereafter.

10.3.3 **Data Forms and Data Submission Guidelines**

Data must be submitted according to the protocol requirements for ALL patients registered whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

10.3.3.1 On Study Data Submission Schedule

Flowsheets : Data to include history, physical exam, vital signs, weight, laboratory values, dose and duration of study drug given, toxicities, concomitant medications will be recorded and must be submitted at the end of each month.

Disease Assessment Form: Lesions identified at baseline must also be assessed and measured at subsequent protocol-specified courses.

10.3.3.2 Off study and follow up Data Submission Schedule

Contact the study protocol chair or the OSU clinical trials office nurse representative to advise them of when patients are deemed to be off study.

Off Study Form: The form should indicate the primary reason the patient is being taken off study. The date of off study determination should also be noted.

Follow up form: Once a patient goes off-therapy due to disease progression or toxicity, the patient will be followed until the toxicity is resolved and for no less than thirty days after the last treatment.

10.3.4 **Auditing**

Patient medical records, study charts, patient scans, protocol regulatory documents, IRB approvals and correspondence, and drug accountability records are subject to periodic audit by the CTEP Quality Assurance and Data Monitoring Committee, the NCI, and the FDA.

10.4 Clinical Trials Agreement (CTA)

The agent sorafenib (BAY 43-9006) supplied by CTEP, DCTD, NCI used in this protocol is provided to the NCI under a Collaborative Agreement (CTA) between Bayer Corp. and Onyx Pharmaceuticals (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to "Collaborator" contained within the terms of award, apply to the use of the sorafenib (BAY 43-9006) in this study:

1. Sorafenib (BAY 43-9006) may not be used for any purpose outside the scope of this protocol, nor can sorafenib (BAY 43-9006) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for sorafenib (BAY 43-9006) are

confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational sorafenib (BAY 43-9006) contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

4. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

5. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstract should be provided to CTEP for forwarding to Fujisawa in sufficient advance to investigator's presentation for allowing Fujisawa to review it and protect intellectual property rights. Copies of abstracts must be provided to

CTEP for forwarding to Collaborator(s) preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: anshers@ctep.nci.hih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborators' confidential/ proprietary information.

11 STATISTICAL CONSIDERATIONS

11.1 Study design/Endpoints:

Arm A and Arm B

The primary endpoint of this phase II study is to assess objective response rate of sorafenib (BAY 43-9006) in metastatic medullary thyroid carcinoma in setting of inherited tumor syndromes as well as in setting of sporadic medullary thyroid cancer.

For this Phase II study, we have chosen the minimax two-stage design of Simon resulting in a trial with two stages with decisions to continue after 16 and 25 response-evaluable patients are accrued to each cohort (Arms A and B) (Simon *et al.*, 1989).

This design minimizes the expected sample size given specified alpha and beta error rates. For example, we will define the true minimum response rate, p_0 . This is a response probability, at which or below, we consider the agent to be clinically unimportant, ineffective, or uninteresting. Associated with this probability is the alpha error rate, the probability of failing to reject an agent with a response rate $\leq p_0$. On the other hand, we will designate 'upper' target response rate, p_1, with its associated error rate, beta. The beta error is the probability of falsely rejecting an agent with a response rate of $\geq p_1$. Using exact binomial probabilities, the Simon design generates two study sample sizes. At the first stage, if r_1 or fewer responses are observed in n_1 patients, the study is terminated. If the number of observed responses is greater than r_1, the study is continued to the maximum sample size, n. If in n patients, r or fewer responses are observed, the agent is considered ineffective and no further study is warranted. For the given p_0, one can calculate the expected sample size, EN (p_0), and the probability of early termination, PET (p_0).

We will consider sorafenib (BAY 43-9006) to be ineffective or uninteresting if the true response [PR+CR using unidimensional RECIST/WHO response criteria] probability is less than 10% (p_0). We will also assume that the regimen is worthy of further study if the true response probability or target response rate is 30% or greater (p_1). These figures result in a two-stage design of 16 and 25 patients, with an alpha of 0.10 and beta of 0.10. If one or no responses are seen in the first 16 response-evaluable patients, the study is terminated early and this regimen is deemed ineffective for this patient population. If two or more patients respond in the first 16, an additional 9 patients are treated for a total of 25. If 5 or more patients respond of the 25, we will recommend that the regimen be studied further. If 25 patients are treated, we will be able to estimate the frequency of response with a 95% confidence interval of not greater than 19.6%.

Similarly, the 25 patients in each of Arms A and B will allow us to estimate the probability of a specific toxicity to within ± 19.6% in each cohort. Any toxicity occurring with at least a 10% probability has a 92.8% chance of being seen at least once in 25 toxicity-evaluable patients.

11.2 Sample Size/Accrual Rate:

For this study of 16 or 25 patients in Arm A and 16 or 25 patients in Arm B, we estimate that we will accrue 3-4 patients per month, and meet our total accrual goal of 50 response-evaluable patients in 12-16 months or less.

11.3 Analysis of secondary endpoints:

- To assess toxicity of sorafenib (BAY 43-9006) in patients with metastatic medullary thyroid carcinoma.
- Measure serum tumor markers calcitonin and carcinoma embryonic antigen (CEA) pre-, during-, and post-treatment to correlate with disease response.
- Correlate nuclear medicine functional imaging [F-18 fluorodeoxyglucose positron emission tomography (PET) scan] data obtained at pre-, during- and post-treatment with tumor response.
- Correlate dynamic-contrast enhanced magnetic resonance imaging (DCE-MRI) data obtained at pre-, during- and post-treatment with changes in tumor permeability and vascularity with tumor response.
- Perform pharmacogenomic studies on procured PBMCs if clinical responses are observed.
- To correlate between the degree of Ras-MAPK signaling inhibition and vascular endothelial growth factor (VEGF) expression in the tumor and clinical response.
- To correlate between the presence and type of RET gene defects in tumor and clinical response.

With little preliminary data on the biological variability of tumor markers, VEGF expression, ERK phosphorylation, RAS-MAPK signaling pathway inhibition, DCE-MRI parameters, or their assay variation in our laboratories, it is difficult to provide the usual sample size estimates given specified levels of significance and power. Our normal procedure is to use preliminary data of variation coupled with clinically based definitions of reasonable differences to be evaluated to arrive at objective sample size estimates. The 16-patient estimate for estimating a confidence interval for the objective response rate may be insufficient for comparisons of biological correlates.

To address this concern, we will perform an initial analysis of data for secondary endpoints from the first eight patients. This analysis will be done solely to estimate variance and to compute formal sample size estimates based on these findings. While we assume that the 16 patients will provide a sample size sufficient to give general indications of the effect of sorafenib (BAY 43-9006) in cohorts for Arms A and B, our interim assessment will allow us to refine the overall sample size estimate. Depending on biological and experimental variation, we will adjust our definition of a clinically important difference using specified levels of significance and power.

11.4 Reporting and Exclusions

11.4.1 **Evaluation of toxicity:** All patients will be evaluable for toxicity from the time of their first treatment with sorafenib (BAY 43-9006).

11.4.2 **Evaluation of response:**

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

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APPENDIX A

Performance Status Criteria

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

APPENDIX B

Sample Shipping Instructions

a) Research peripheral blood (Section 7.4)

- All samples must have a label that includes subject no, name of the institution, date/time of collection, and 'NCI 7609'.
- All samples must be shipped on the same day of collection.
- Ship on Monday-Friday only.
- Notify the technician of impending arrival of the sample.
- Ship at room temperature to the following address by overnight mail for AM delivery.

Shipping Address:
Manisha Shah, M.D./Attention: Donna Bucci
The Ohio State University
James Cancer Hospital Lobby
300 West 10th Avenue
Columbus, OH 43210
Phone: 614-293-3300

b) For slides of FNA biopsies (Section 7.5) or tissue blocks (Section 7.6)

- All samples must have a label that includes subject no, name of the institution, date of collection, and 'NCI study no'.
- Sample may be shipped as soon as available or in a batch.
- Ship on Monday-Thursday only.
- Notify the technician of impending arrival of sample.
- Ship at room temperature to following address by overnight mail for AM delivery.

Shipping Address

Manisha H. Shah, M.D.
The Ohio State University
A438 Starling Loving Hall
320 West 10th Ave
Columbus, OH 43210
Phone: 614-293-8629

For questions or notifying impending arrival contact:
Ms. Beth Scholl/Dr. Manisha Shah
Phone: 614-293-8629
Fax: 614-293-3112

APPENDIX C

Confidential

SITE MANUAL for DCE - MRI Imaging Procedures

Drug: Sorafenib (BAY 43-9006)

Protocol Title:
Phase II Study of Sorafenib (BAY 43-9006) in Patients with Metastatic Medullary Thyroid Carcinoma

Document type: Protocol – Appendix C

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without the consent of the Division of Imaging Research of the Ohio State University

Table of Content

Introduction:

The purpose of this site manual is to document the standard imaging procedure, serve as a handy reference in case of questions and as an information resource.

This document will be subject to revisions, so please make sure that you have the most recent manual.

This document does not supersede any trial document or IRB (Internal Review Board or local Ethics committee) guidelines or requirements.

In case of any **questions**, do not hesitate to contact the protocol chair, the Study Imaging expert and copy the Imaging Trial Lab. All appropriate information is found in the *Contact Section* of this document.

Please inform the Imaging Corelab of any changes in equipment and procedures, and use the *Equipment and Procedure Checklist Section* check list for guidance. If you are unsure about any topic or question, please contact the above resources with details in the *Contact Section* of this document.

Dynamic contrast enhanced MRI (DCE-MRI) will provide data revealing the changes in the vascular perfusion and permeability characteristics of tumors. Successful biologic inhibition will reduce both vascular perfusion and permeability causing a decrease in the peak and rate of contrast enhancement. Dynamic MRI therefore offers a more direct biologic 'in vivo' assessment of therapeutic efficacy.

Contacts:

Protocol Chair:
Bhavana Konda, MBBS, MPH
Bhavana.konda@osumc.edu

Imaging Expert:
Michael V. Knopp, MD, PhD
knopp.16@osu.edu

Imaging Core Lab / Central Image Analysis Laboratory (CIAL)
The Ohio State Research Foundation-
Image Analysis Lab -Wright Center of Innovation in Biomedical Imaging

The lab has the following generic E-Mail which is automatically forwarded to the staff in charge: E-mail: XXXXX@imagingcorelab.com (XXXXX) will be the assigned name of the opened protocol and will be specified prior to start up.

This e-mail address should be included in all correspondence and will be read and accessible to all relevant staff at OSU.

Administrative Director:
Robert McKenney, PhD
Department of Radiology
The Ohio State University
University Hospitals
659 Means Hall
1654 Upham Drive
Columbus, Ohio 43210-1228

Office Phone: 614-293-7165
Fax: 614-293-9275
E-Mail: mckenney.1@osu.edu

Lab Manager:
Steffen Sammet, M.D., Ph.D.
Department of Radiology
The Ohio State University
University Hospitals
647 Means Hall
1654 Upham Drive
Columbus, Ohio 43210-1228

Office Phone: 614-293-2929
Fax: 614-293-9275
E-Mail: sammet.5@osu.edu
OSU Data Management – IMRES Project Leader
Guang Jia

Department of Radiology
The Ohio State University
University Hospitals
646 Means Hall
1654 Upham Drive
Columbus, Ohio 43210-1228

Office Phone: 614-293-9151
Fax: 614-293-9275
E-Mail: jia.11@osu.edu

OSU Data Analysis – IMRES Project Leader
Xiangyu Yang
Department of Radiology
The Ohio State University
University Hospitals
646 Means Hall
1654 Upham Drive
Columbus, Ohio 43210-1228

Office Phone: 614-293-9151
Fax: 614-293-9275
E-Mail: yang.367@osu.edu

Director:
Michael V. Knopp, MD, PhD
Chairman and Professor of Radiology
Novartis Chair of Imaging Research
Department of Radiology
The Ohio State University
University Hospitals
657 Means Hall
1654 Upham Drive
Columbus, Ohio 43210-1228, USA

Office Phone: 614-293-9998
Direct Line: 614-293-9227
Fax: 614-293-9275
E-Mail: knopp.16@osu.edu

Imaging relevant components of the overall protocol:

Dynamic contrast enhanced MRI (DCE-MRI) will provide data revealing the changes in the vascular perfusion and permeability characteristics of tumors. DCE-MRI therefore offers a more direct 'in vivo' assessment of efficacy.

Imaging time is estimated at **45-60** minutes per scan.

Standard morphologic MRI sequences (scanning has to cover all tumor areas in at least two planes (such as axial and coronal)) will be used for tumor size determination for all patients undergoing DCE-MRI. These standard sequences (see 1 and 2 below) are performed without contrast; sequences used should be the same at all time points for a given patient. These standard sequences are performed at any time point requiring tumor size measurement. At those time points where DCE-MRI is to be performed, the DCE-MRI protocol is performed after the standard pre-contrast sequences. The standard imaging follows your institutional protocol and should include:

1. T_2 weighted (Fast or turbo spin echo) breath-hold
2. T_1 weighted Fast Multi-planar Gradient Recalled Echo breath-hold

Both sequences will be performed in the plane suitable to the studied body part. Axial will be the standard plane with better than 2.5 mm in plane resolution and 8 mm slice thickness. Further planes may be implemented as appropriate. The same plane and slice thickness must be used for tumor measurements.

Uni- and bi-dimensional measurements of disease will be recorded of all tumors that can be measured and documented. These measurements and the clinical decision-making accompanying the measurements will be made at the site.

At timepoints where DCE-MRI is being performed, prior to imaging, an IV cannula with a long line is inserted into an arm vein (the ante cubital fossa where possible) for contrast injection.

After completion of the standard sequences, the supervising radiologist will then plan a oblique - coronal slice for the dynamic study which will include the target lesion and major artery such as the aorta or iliac artery. This will remain the studied lesion throughout the trial. T_1- and T_2-weighted images should be used to select the target lesion and the position for the dynamic image set. For consistency the slice should traverse the mid-line of the tumor. Where possible highly necrotic tumor lesions should **NOT** be selected for the DCE-MRI.

A T_1-weighted dynamic contrast enhanced sequence (3D spoiled gradient echo) will then be performed.

Three additional measurement series (5 repetitions each) similar to the DCE sequence will be performed with three different low flip angles for normalization of MRI signal data.

A low molecular weight Gd-chelate MRI contrast agent licensed for i.v. use in humans 0.1 mmol/kg body weight will be injected, preferably by power injector. Injection will commence **after** 5^{th} (fifth) measurement in order to allow a steady state to develop and to provide baseline signal intensities. Power injector rate should be 0.6 ml/sec. Contrast injection is followed by a 20 ml saline flush, also injected at the same speed. Contrast agent and injection technique should be the same at each visit for a given patient.

Because the individual measurements are rapid, breath-hold is not required. As the plane of imaging is in a coronal /oblique orientation, quiet breathing has to be encouraged.

From this dynamic imaging sequence, data will be obtained showing an increase in signal intensity in the various areas over time. The area of maximum enhancement of the tumor will be used for the tumor region of interest (ROI). Regions of interest will also be taken from a major arterial vessel such as the aorta.

The signal intensity versus time data for the tumor, and the major artery (aorta, carotid or iliac artery) will be graphed. From these enhancement curves, several parameters will be calculated including the AUC under the contrast enhancement curve, peak enhancement, K_i and K_{trans} (transfer coefficient, a parameter similar to K_i) as well as A [Amplitude] and k_{ep} [exchange rate constant]. Where necessary for calculation, the low flip angle sequences will be used to normalize data. Data will be presented as % of baseline value of a given parameter.

Studies will be stored in the PACS system, on MR manufacturer-specific storage media as an exact copy for trial purposes and will be forward per FTP to the imaging corelab.

Clinical decision-making will be made on the basis of on-site reading of tumor dimensions from the standard MR images. DCE-MRI is done as laboratory correlative study and will not be used to assess objective response per RECIST. An independent central analysis of combined multi-site DCE-MRI data will be performed, but not used for clinical care.

The Imaging Procedure:

The following information details the imaging procedure. Please note that this does not detail information you will need to enter into the Case Report Form. The imaging procedure need to be adhered to, but was designed to be comparable with your local procedures. The most unique feature of this imaging series is the dynamic imaging sequence used to monitor the contrast agent passage.

Upon registration of the patient for the exam please verify that the patient has signed the informed consent form.

Please assign or get a unique trial patient identifier which will be used for identification purposes in the anonymized image assessment.

Please make sure that the patient understands the imaging procedure and that her or his cooperation is essential for best quality. Please explain that multiple imaging sequences will be acquired and that you will be giving instructions and comments via the intercom.

Prior to imaging an i.v. cannula with a long line is inserted into a vein in the arm (the ante cubital fossa where possible) for contrast injection. In the undesirable event that a different route of access has to be chosen, please document it appropriately.

The imaging procedure consists of the following steps:

i. Localizer series
ii. Pre-contrast T2w

iii. Pre-contrast T1w
iv. Pre-contrast low flip angle series (same parameters as the dynamic sequence, flip angles set to 4°, 8° and 12°)
v. Dynamic Series with injection of the contrast agent
vi. Post-contrast imaging as necessary
vii. Image archiving, clinical plus trial copy
viii. Image anonymization and data transfer to the Imaging Core Lab

The overall imaging time is estimated at 45 minutes per procedure. Standard sequence scanning should cover the whole liver including all tumor areas.

For the pre-contrast T_{1w} scan, a T_1-weighted Fast Multi-planar Gradient Recalled Echo or balanced-field echo (FIESTA, TRUEFISP) breath-hold sequence will be used.

For the T_2 weighted image set, a Fast or Turbo Spin Echo breath-hold sequence will be used. Axial imaging will be the standard plane with 8 mm slice thickness. Further planes may be implemented as appropriate. The same plane and slice thickness must be used for tumor measurements in the follow up procedures.

The supervising radiologist will then plan the plane and location of the dynamic study which will remain the **evaluation (target) lesion** throughout the trial for the specific patient. T_1 and T_2 weighted images should be used to select the target lesion volume. For consistency, the mid slice should traverse the mid-line of the tumor. Where possible highly necrotic tumors or tumor regions should **not** be selected.

A pre-contrast set of multi low flip angle **(12, 8 and 4 degrees)** 3D SPGR sequences in the selected plane and location will be performed to aid normalization of MRI signal data (T_1 estimation) immediately prior to the dynamic series.

A T_1-weighted dynamic contrast enhanced sequence (3D SPGR) is then performed with the following scan parameters (see also: *Detailed parameter for the dynamic imaging sequence)*:

14 slices through the representative tumor lesion, 7 mm each with no gap; sequential imaging measurements will be repeated approximately every 10 seconds for about 8 minutes (at least 50 measurements after contrast injection).

A commercially available MR-contrast agent for human use should be used at a dosage of 0.1 mmol/kg body weight.

The preferable method of contrast agent injection is a power injector. Injection is started after the first 5 measurements (data sets) in the continuous dynamic series to allow a steady state to develop and provide baseline signal intensities. Power injector rate should be 0.6 ml/sec. Contrast injection need to be followed by a 20 ml saline flush injected at the same rate. If hand injection is done, it should be performed as a rapid bolus through a long line of tubing which has been filled with the MR contrast agent. Contrast agent and injection technique should be the same at each visit for a given patient.

As the individual measurements are rapid, breath hold is not required. The patient is to be instructed to use shallow breathing. As the plane of imaging should be in a coronal /oblique-coronal orientation, quiet breathing does not move the volume of interest out of the imaging slab.

From this acquisition series, data will be obtained showing an increase in signal intensity due to the contrast agent passage of the various areas over time. The area of maximum enhancement of the tumor will be used for the tumor region of interest (ROI). Regions of interest will also be taken from a major arterial vessel to assess the vascular enhancement and kinetics. From the enhancement curves, several parameters will be calculated. For some quantifications, the T_1 estimation sequence (three low flip angles), will be used to normalize data.

A post-contrast T_{1w} scan can be acquired similar to the pre-contrast T_1-weighted scan.

After completion of the imaging, data storage and data preparation for the off-site, core lab assessment needs to be performed.

Images should be:
A, stored in the same procedure as standard clinical patients at the local site for local patient care and assessment
B, an additional data-backup of the complete imaging set should be done onto CD (preferable) or magneto-optical disk.
C, the complete data set should be anonymized and transferred via secure FTP to the imaging core lab as outlined in the *data transfer section.*

Clinical decision-making will be made on the basis of on-site reading of tumor dimensions from the standard MR images.

An independent central analysis of combined multi-site DCE-MRI data will be performed, but these evaluations will not be used for clinical decision making.

Relative exclusion Criteria to MRI imaging
Patients who have:
1. Cardiac pacemaker
2. Ferromagnetic metal implants not authorized for use in MRI such as some types of cerebral aneurysm clips
3. Claustrophobia not helped by pre-medications
4. Obesity (exceeding the equipment limits)
5. In case, MRIs are not suitable for evaluating response per RECIST criteria

In these patients who have a contraindication to MRI imaging, other radiologic imaging (i.e. CXR and CT scans) must be used to assess response as outlined in the clinical trial protocol.

Detailed parameter for the dynamic imaging sequence will be tailored to the specific MR system used. Below is a generic description for a 1.5T GE MR system:

Parameter for Dynamic Series:

Type:	3D spoiled gradient echo
Repetitions in dynamic series:	at least 50
Averages:	1
Field of view:	about 360 mm
Flip:	16 deg.
Slice Thickness:	7 mm
Spacing (gap):	0 mm
TE:	min
TR:	min
Matrix:	256 x 160 or better
Voxel size (approx.)	2.5 x 2.5 x 7.0 mm^3 or better

Parameter for Dynamic Series (specific example GE protocol at OSU):

Type:	3D SPGR
Repetitions in dynamic series:	50
Averages:	1
Bandwidth:	244 Hz/pixel equals 62.5 kHz
Field of view:	360 mm
Flip:	16 deg.
Slice Thickness:	7 mm
Spacing (gap):	0 mm
TE:	3.092 msec
TR:	10.287 msec
Matrix:	256 x 192
Voxel size (approx.)	1.4 x 1.9 x 7.0 mm^3

For the T_1 estimation acquisition prior to the dynamic series, the flip angle has to be set to 12°, 8° and 4°, everything else including the imaging volume remains the same.

Data Transfer:

Overview:
Imaging data will be stored using the local onsite storage procedure (PACS) and on an additional copy of manufacturer -specific storage media. Electronic storage of data to a common media such as CD or optical disc in DICOM format is the preferred method of secondary storage.

The study data will be transferred to an imaging core lab for off-site analysis. The data transfer should be performed preferably via secure FTP to facilitate rapid review of the imaging studies; if these direct data transfers can not be achieved, then an express shipment of data in a digital format such as CD will be arranged.

The imaging data will be anonymized at the central image analysis laboratory and a secure master file will be generated for cross-referencing. The imaging corelab will review the imaging study for technical and quality control and provide feedback in case of identifiable problems. The imaging corelab will also perform image analysis of the DCE-MRI by placing ROIs and generating signal intensity data, which will then be quantified using different quantitative methods as outlined above. Volumetric data will be quantified whenever possible to allow comparison between dynamic MRI parameters and tumor size changes. The local imaging site will have access via secure web-link to the placed ROIs and source signal intensity plots for review and comment of its own performed cases.

Details:
All data will be handled in DICOM format and all data management will adhere to GCP and other established guidelines. The following information details the data transfer procedure. Please note that this does not detail information you will need to enter into the Case Report Form.

As mentioned in the imaging section, the local site needs to generate safe and secure backups for their local needs including patient care and should generate a CD backup (preferable) or Optical Disk as a second source of data for this trial. These backup data will be collected per request.

Initiation of data transfer:
This procedure is being used until all firewall issues within the local institution are resolved. The recommended software is WS-FTP and a copy was provided during the initial site visit. Copies can be requested form the Imaging Core Lab and copies as well as updates will be placed within the software subdirectory of the FTP account.

Any FTP software can be used to initiate access to the FTP Server of the Imaging Core Lab.

IP address:	140.254.8.48
User / account:	XXXXX@ftp2.IMRES.med.ohio-state.edu
Password:	tobedefined

The secure SSL account will be access after the secure key has been established. The secure access information will not be documented in this manual.

IP address: 140.254.8.48

User / account: Tobesupplied@ftp.IMRES.med.ohio-state.edu
Password: Tobesupplied

Once you have access to be main directory, change to the data directory, create a new directory with the anoymized identifier. You can also use the unique DICOM identifier generate by your PACS system if you so choose. Then just upload or copy your imaging files.

Once the upload is completed, please send an e-mail to McKenney.-1@medctr.osu.edu to inform the imaging core lab, that the study has been completely uploaded from your site, report the patient weight and the place of injection site

The imaging core lab will review the received data and will generate a confirmation e-mail that the data have been received and appear readable. Once the case is analyzed, a detailed report and access information will be send to you local imaging investigator.

Equipment and Procedure Checklist:

As this trial will be performed over a longer time period, equipment and procedure changes could potentially occur and any changes need to be documented and passed on to the Imaging Core Lab. In case of any relevant changes, the Imaging Expert needs to be consulted.

At the time of the first patient inclusion and imaging for this trial study at the local site, the *Initial Equipment and Procedure Checklist Form* needs to be completed. In case of any changes, use the *Equipment and Procedure Update Checklist Form* for documentation.

Initial Equipment and Procedure Checklist Form:

Are you using multiple MRI systems for patient studies?
If yes, ***please fill out each form for every MRI system that is being used in this trial***

Please enter your local description of used MRI bay (e.g. Research Scanner 1. Floor)

_____

Please enter you MRI model

_____

Please enter the type of coil used for the procedures of this type

_____

Please enter the software release you use on your above MRI system

_____

Please enter the type and model of the injector you use to perform the contrast injection

_____

Please enter the MR Contrast Agent you intend to use for this study

_____

Are you using any other software (PACS) system prior to data transfer and storage? If yes, kindly identify the software, version and manufacturer

_____

You will be archiving the image sets on the following media type

(CD –ROM / Magneto-Optical / Tape)

_____

Equipment and Procedure Update Checklist Form:

Are you using multiple MRI systems for patient studies?
If yes, ***please fill out each form for every MRI system that is being used in this trial***

Has there been a major change in MR hardware or software?
If so, please identify and explain:

_____

_____

Please enter your local description of used MRI bay (e.g. Research Scanner 1. Floor)

_____

Has there been a change in type or model of coil used for the procedures of this trial?

_____

Please enter the software release you use on your above MRI system

_____

Please enter the type and model of the injector you use to perform the contrast injection

_____

Please enter the MR Contrast Agent you currently use for this trial

_____

Are you using any other software (PACS) system prior to data transfer and storage? If yes, kindly identify the software, version and manufacturer

_____

You will be changing your archiving of the image sets in the near future? If yes, please explain and does it affect the current procedures?

_____

DCE-MRI Scan Time schedule:

Per section 7.3 in the protocol.

MRI Imaging Site Summary Sheet

- Did the patient sign the informed consent form?
- Assign or get unique trial patient identifier for anonymized image handling
- Place an IV cannula (preferable in the antecubital fossa) for contrast injection
- Record the patient weight for contrast dose calculation and the place of injection site

Imaging procedure (Sample of a 1.5T GE system (will be tailored to site specific system):

1. Localizer
2. Pre-contrast T2- weighted axial images covering the entire neck and upper thorax (according to the standard protocol for thyroid cancer); TR 2450, TE 104.2, Flip 90º, thick: 4 mm, 256x256 .
3. Pre-contrast T1- weighted axial images covering the same volume; TR 400, TE 9.0, Flip 90º, thick: 4 mm, 256x256
4. Identify appropriate target lesion and position the target volume in oblique coronal to have at least one slice through the carotid artery or aorta
5. **Parameter for Dynamic Series:**
   Type: GE, saturation recovery FGRET, PSD Filename: ufgret
   Repetitions in dynamic series: 100
   Averages: 1
   Bandwidth: 244 Hz/pixel equals 62.5 kHz
   Field of view: 500 mm
   Flip: 25 deg.
   Slice Thickness: 8 mm Spacing (gap): 2 mm
   TE: 3.092 msec TR: 10.287 msec
   Matrix: 256 x 256 Voxel size (approx.) 1.8 x 1.8 x 8.0 mm3
6. Pre-contrast T1w image set (5 repetitions, parameters of the dynamic sequence with the saturation pulse turned off. All other dynamic images with pulse turned on)
7. Dynamic Series with injection of the contrast agent (Contrast injection **after the fifth** measurement. Injected volume: 0.1mmol/kg bw followed by 30 ml saline flush. Injection rate is 2.0 ml/sec for contrast and saline injection.)
8. Post-contrast Imaging as necessary (T1-weighted similar to 3.)
9. Image archiving, clinical plus trial copy on separate media
10. Image anonymization and data transfer to the Imaging Core Lab. Send e-mail that study was performed to XXXX@imagingcorelab.com and please report any technical issues, dosage and patient weight.
11. In case of questions, please do not hesitate to contact in addition to your local staff: TBA or Dr. Michael Knopp, at the Imaging Core Lab at OSU knopp.16@osu.edu and cc XXXX@imagingcorelab.com