ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO A091105

A PHASE III, DOUBLE BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF SORAFENIB IN DESMOID TUMORS OR AGGRESSIVE FIBROMATOSIS (DT/DF)

NCI-supplied agent(s): sorafenib (*NSC # 7247722, IND#116279)*

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Activation
[X] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[ ] Informed Consent changes	[ ] Suspension / temporary closure
[X] Scientific / Statistical Considerations changes	[ ] Reactivation
[ ] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[ ] Other :	

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.

UPDATES TO THE PROTOCOL

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- In the table entitled "Protocol-related questions may be directed as follows," the contact name and email address for questions regarding CTEP-AERS reporting has been updated from Regulatory Affairs Manager to Alliance Pharmacovigilance Inbox and from regulatory@alliancenctn.org to pharmacovigilance@alliancenctn.org, respectively. The phone number previously listed for the Regulatory Affairs Manager has been removed as all questions should be submitted via email.
- The document history table has been removed. This table now appears as a separate document on the protocol landing page on the member side of the Alliance web site.

Section 5.2.1 (CTEP Investigator Registration Procedures)

This section has been updated in its entirety with the revised CTSU verbiage.

Section 5.2.2 (CTEP Associate Registration Procedures/CTEP-IAM Account)

This section has been removed in its entirety to reflect the revised CTSTU verbiage. Subsequent sections have been renumbered. References to the sections have been updated throughout the protocol.

Section 5.2.2 (CTSU Site Registration Procedures)
This section has been revised in its entirety with the revised CTSU verbiage.

Section 5.3 (Patient Registration/Randomization Procedures)
This section has been updated in its entirety with the revised CTSU verbiage.

Section 7.0 (Required Data)
- The header of the third column has been updated.
- After one year of treatment on sorafenib, the frequency of visits has decreased (from every cycle to every other cycle). Footnote C has been added beneath the table to reflect this change. References to footnote C have been added to the table in the third column.
- The frequency of scans beyond year 3 has decreased, therefore footnote A has been updated.

Section 10.1.2 (Methods)
A second paragraph has been added under "Analysis of the data."

Section 10.2.3 (Specific Hypotheses)
A second paragraph has been added to the end of this section.

Section 10.3.2 (Methods)
A second paragraph has been added to the end of this section.

Section 13.1 (Schedule of Evaluations)
The information in this section has been updated based on the revised scan schedule.

Section 13.4.4 (Overall Objective Status)
The "**" has been removed from the "Overall Objective Status Column" of the CR/PR row.

Section 14.1 (Clinical Follow-Up Phase)
A new bullet has been added to describe the follow-up for those patients who crossed over to sorafenib.

Section 15.1 (Primary Endpoint)
A second paragraph has been added to this section.

Section 15.1.1 (Sample Size & Statistical Power)
A new paragraph has been added to the end of this section.

Section 15.1.6 (Evaluability & Assessment of Patients)
A third paragraph has been added to this section.

Section 15.2 (Secondary Endpoints)
A note has been added as the first paragraph of this section.

Section 15.2.2 (Surgical Intervention)
The following sentence has been added to the end of the first paragraph in this section, "See the note at the beginning of Section 15.2."

Section 15.2.3 [Overall Survival (OS)]
The following sentence has been added to the end of the first paragraph in this section, "See the note at the beginning of Section 15.2."

Section 15.2.4 (Tumor Response)
The following sentence has been added to the end of the first paragraph in this section, "See the note at the beginning of Section 15.2."

Section 15.3.1 (Statistical Design-Imaging Study)
The following sentence has been added to the end of the first paragraph in this section, "Data, analyses, and censoring will also follow the note described in Section 15.2."

Section 15.3.3 (Statistical Design for Correlative Study A091105-ST1)
The following sentence has been added as the first sentence in this section, "See the note in Section 15.2, which will apply to all analyses for this section A091105-ST1."

Section 16.2 (Expedited Adverse Event Reporting)
- The last three sentences in the first paragraph have been updated to reflect the use of CTCAE version 5.0 for expedited adverse event reporting purposes.
- The third note in the FDA reporting table which reads, "Deaths clearly due to progressive disease should **NOT** be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS)." has been removed.
- The following changes have been made under "Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND":
  - Five new bullets have been added to describe reporting of death, pregnancy loss, and neonatal death.
  - The now ninth bullet describing reporting of new malignancies has been updated in its entirety.

Appendix VI (A091105 Optional Medication Diary)
- Placebo is no longer used. This has been removed from the diary.
- Beginning with cycle 14 patients are seen every other cycle. This has been reflected in instruction #1. Additional rows have been added to the diary to account for this change.

UPDATES TO THE MODEL CONSENT:
No changes have been made to the model consent form.

A replacement protocol document and model consent form have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A091105

A PHASE III, DOUBLE BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF SORAFENIB IN DESMOID TUMORS OR AGGRESSIVE FIBROMATOSIS (DT/DF)

NCI-supplied agent(s): sorafenib (*NSC # 7247722, IND#116279), IND Holder: CTEP*
ClinicalTrials.gov Identifier: NCT02066181

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Expedited Adverse Event Reporting
https://eapps-ctep.nci.nih.gov/ctepaers/

Medidata Rave® iMedidata portal
https://login.imedidata.com

OPEN (Oncology Patient Enrollment Network)
https://open.ctsu.org

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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, or (where available) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent	Protocol Coordinator
Questions related to IRB review	Regulatory Affairs Manager: *regulatory@alliancenctn.org*
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox *pharmacovigilance@alliancenctn.org*
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository

CONTACT INFORMATION

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For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) *contact the Study PI of the Lead Protocol Organization.*		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

A PHASE III, DOUBLE BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF SORAFENIB IN DESMOID TUMORS OR AGGRESSIVE FIBROMATOSIS (DT/DF)

ELIGIBILITY CRITERIA (see Section 4.0)

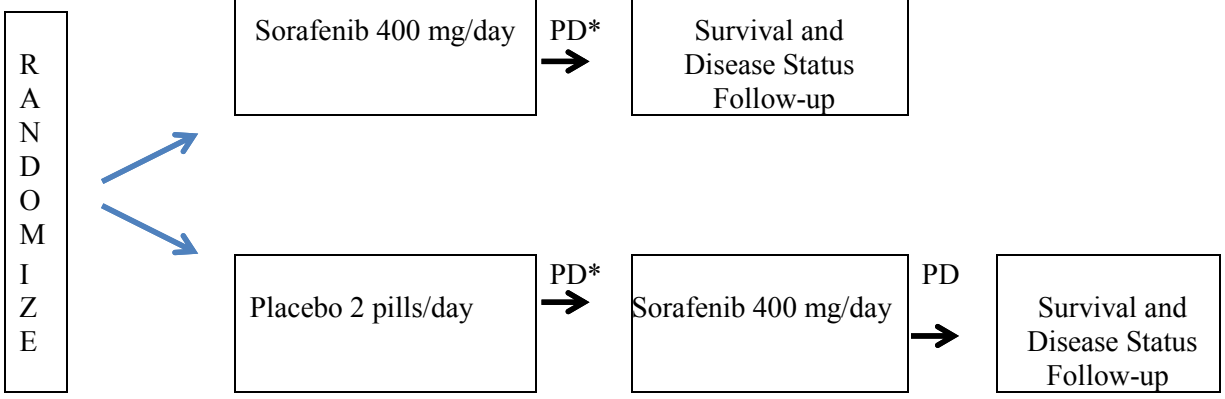
Patients must have confirmation of DT/DF
Patients may have been treated with locoregional therapies completed 4 weeks prior to registration and recovered to < CTCAE grade 2 (see § 4.2.1)
Patients may have been treated with cytotoxic, biologic (antibody), immune or experimental therapy, tyrosine kinase inhibitors, hormone inhibitors or NSAIDs completed 4 weeks prior to registration and recovered to < CTCAE grade 2 (see § 4.2.2)
No prior sorafenib
No concomitant treatment with strong CYP3A4 inhibitors or inducers (see § 4.2.4)
Patients must have measurable disease as defined in Section 13.0.
The patient must meet **one** of the following criteria:

1) Disease determined unresectable or entailing unacceptable morbid surgery based on 1 or more of the following:
   - Multifocal disease
   - Disease in which there is involvement or inadequate plane from neurovascular bundle, bone, skin, or viscera
   - Large size in relationship to location **OR** multicompartment involvement
2) Progression by radiographic imaging (10% increase in size by RECIST 1.1 within 6 months)
3) Patients with symptomatic disease with a BPI score ≥ 3 **AND** 1 of the following:
   - Inability to control pain with NSAIDs and considering the addition of narcotics
   - >30% increase in current use of narcotics **OR**
   - Addition of new opioid narcotic

Age ≥ 18 years
ECOG performance status ≤2
No pregnancy or nursing
No history of cardiac disease as in §4.7.1
No inadequately controlled hypertension (see § 4.7.2)
No clinically significant GI bleeding or bleeding diathesis within 30 days of registration

Required Initial Laboratory Values	
absolute neutrophil count (ANC)	≥ 1500/mm^3
hemoglobin	≥8g/dl
platelets	≥ 75,000/mm^3
total bilirubin	≤ 1.5 x ULN
SGOT(AST) or SGPT(ALT)	≤ 1.5 x ULN
creatinine	Calculated creatinine Clearance ≥50 mL/min

SCHEMA
1 Cycle =28 Days



PD= Progression of Disease

* Patients are unblinded after first incidence of progressive disease

NOTE: Patients discontinuing for reasons other than PD and earlier than 1 year post-randomization must continue in Clinical Follow-up until 1 year post-randomization to capture study endpoints.

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Pathology

Desmoid tumors, also known as deep fibromatosis (DT/DF), are rare fibroblastic sarcomas that arise from musculoaponeurotic stromal elements. Histologically, they have a bland appearance, consisting of small bundles of spindle cells with rare mitosis in an abundant collagenous and fibrous stroma. DT/DF can arise in any location, although the most common sites include extremities, abdominal cavity (root of the mesentery) and retroperitoneum and abdominal wall. The majority of DT/DF are sporadic, however 4–20% are associated with familial adenomatous polyposis (FAP) or Gardner syndrome in which the adenomatosis polyposis coli (APC) gene sustains bi-allelic mutations. Patients with FAP have a high risk of developing colorectal cancer and are recommended prophylactic colectomies. In these cases, surgery appears to be the inciting factor. In FAP patients, there is a ~2% risk of developing DT/DF, a 1000-fold increased risk in comparison to the general population. In addition, there appears to be a weak link between antecedent surgery/ trauma and/or pregnancy and subsequent development of DT/DF. In the majority of patients with sporadic DT/DF, mutations in beta-catenin are commonly observed with dysregulation of the Wnt signaling pathway.

1.2 Epidemiology and Clinical Presentation

DT/DF have an annual incidence of ~1000 in the United States, exhibiting a slight female preponderance and a wide age distribution (15-60 years). DT/DF have a wide range of presentation and have a variable natural history. DT/DF typically exhibit indolent growth, and if asymptomatic may be observed as primary management. In a subset of patients, DT/DF can have a waxing and waning pattern and on rare occasions exhibit spontaneous remission. However, DT/DF can cause significant deformity, loss of function, pain through mass effects requiring narcotics and poor quality of life. Mortality from DT/DF is low and is secondary to compromising vital structures in the abdominal cavity and retroperitoneum resulting in hydronephrosis and/or bowel/bladder obstruction or perforation. Given the low mortality, the prevalence of DT/DF is expected to be much higher.

1.3 Treatment(s)

There is no standard of care for the treatment of DT/DF. To date, case series and small Phase II trials, but no randomized trials inform the role of surgery, radiation or choice of systemic therapies. If asymptomatic, patients may be actively observed. In those patients with symptoms or progressive disease, definite primary treatment involves complete surgical resection with wide margins. Local recurrence rate after surgery range from 19 – 38%. To date, the importance of margin status to predict local recurrence remains controversial. In many patients, limb amputations, deforming surgeries, extensive bowel resections and frequent ureteral stent exchanges remain the only surgical options resulting in profound morbidity in this young population (median age 30 years). Radiation therapy (RT) is used in some patients with high-risk features (e.g. R1 resection) or in recurrent disease not amenable to surgery. However, the long-term consequences of radiation induced secondary cancers must be considered in this young population.

Systemic therapies are typically employed when surgery and radiation therapy are unable to achieve adequate local control. To date, there are no randomized controlled trials to inform initial choice of therapy. Physicians tailor therapy based on patient characteristics, preference and urgency to induce a response. Non-cytotoxic therapies include single agent non-steroidal anti-inflammatory agents (NSAIDs), anti-hormonal therapies or their combinations. In adults, the effectiveness of these agents largely stem from case reports and small case series. The Children's Oncology Group conducted a Phase II trial (ARST0321) evaluating the combination

of sulindac and tamoxifen in advanced, unresectable DT/DF. Duration of therapy was 12 months with evaluation of response every 3 months. 60/70 patients were eligible for evaluation. 40 patients discontinued therapy due to disease recurrence, withdrawal of consent or toxicities. Among the 60 eligible patients, four (4) PRs and one CR were noted for an overall response rate of 8%. The 1-year event free survival (EFS) was estimated to be 44% with three deaths observed. Adverse events included asymptomatic ovarian cysts secondary to tamoxifen in 30% of women. Of note, DT/DF have variable expression of estrogen receptor (ER), in particular ER-beta, however, response to hormonal intervention does not appear to correlate with receptor status.

Cytotoxic chemotherapy is usually reserved for symptomatic and rapidly proliferating disease that is not amenable to surgical or radiation treatment. Doxorubicin or liposomal doxorubicin (Doxil®) has been evaluated in case series of 2 – 12 patients and noted to have prolonged response of 20 – 36% for 7 - 40 months. A small retrospective case series of 12 patients from the Royal Marsden Hospital reported a 36% response rate with liposomal doxorubicin (Doxil®) administered over 6 months. Anthracyclines in combination with decarbazine have slightly higher response rates with expected increase in cardiac, hematologic and mucosal toxicities. A well studied regimen includes vinorelbine/methotrexate and single agent decarbazine or temozolomide or combinations employing one of these agents. The Pediatric Oncology Group conducted a Phase II trial (POG/CCG Intergroup P9650) evaluating vinorelbine and methotrexate in advanced, unresectable DT/DF. Chemotherapy was administered weekly for 26 weeks and then every other week for a total of 52 weeks with minimal toxicities. Imaging was performed every 3 months and in 25 evaluable patients the responses were two CR, five PR, ten SD and 8 PD. One year progression free survival was estimated to be 58%. In a similar Phase II study conducted in 30 adult patients the response rates were 40% PR, 60% SD and at a median follow up of 75 months, the 10 year PFS was 67%.

DT/DF are known to have variable expressions of KIT and PDGFRA/B by IHC and RT-PCR, without any consistent evidence of activating mutations in these genes. Imatinib, an oral tyrosine kinase inhibitor of ABL, ARG, KIT, CSF-1R, PDGFRA and PDGFRB has shown minor activity in this disease. In a large Phase II study of 51 patients with aggressive fibromatosis who received imatinib, 36 patients (80%) reached the primary endpoint of clinical benefit; defined as either complete or partial response at two months, or stable disease at four months. The median time to treatment failure was 6.8 months. Here PDGFRA deletions were found in only 4 of 22 available tumor biopsies. Importantly, there was no correlation to clinical response to expression of KIT or PDGFRA/B. Another Phase II trial evaluated imatinib in 186 patients with advanced cancers (solid and liquid) expressing potential imatinib sensitive tyrosine kinase evaluated a cohort of 20 patients with AF. Objective response in AF was limited to 2 patients with PR and 8 patients with SD. Tumor samples were positive for PDGFRB however not positive for phosphorylated PDGFRA/B or KIT mutations. Again no correlation was drawn between response and mutational status. In a trial of 19 patients with AF evaluated with high dose imatinib, three patients had PR and 4 had SD lasting more than 1 year. Tumors expressed non phosphorylated form of PDGRFB by IHC, but no activating mutations were found in KIT or PDGFRA/B. 16 of 19 patients had mutations in the Wnt (APC, CTNNB1) pathway however no correlation to clinical response was observed.

1.4 Sorafenib in Desmoid Tumors/ Deep Fibromatosis (DT/DF)

Sorafenib, an oral multi-kinase inhibitor, blocks tumor cell proliferation by targeting Raf/MEK/ERK signaling at the level of Raf kinase, and exerts an anti-angiogenic effect by targeting vascular endothelial growth factor receptor-2/-3 (VEGFR-2/-3), and platelet derived growth factor receptor-beta (PDGFR-beta) tyrosine kinases (1). Based on improved survival demonstrated in randomized studies in advanced HCC and RCC, sorafenib is approved by the FDA for these indications. Sorafenib is available for patients and physicians through an

expanded access program. Based on the data with imatinib, an index DT/DF patient evaluated at MSKCC received sorafenib through the expanded access program and was observed to have clinical and radiological benefit with this therapy. This prompted a retrospective review of the collective experience of twenty six DT/DF patients treated with sorafenib. This was presented at ASCO 2010, CTOS 2010 and recently published.

1.5 Methods

Following institutional IRB approval (waiver WA0209-04), medical records of 26 patients from February, 2008 to October, 2010 who received sorafenib for DT/DF was reviewed. The following data was collected: age at the date of diagnosis, presentation status (primary or recurrent), gender, presence of Gardner syndrome, primary site, primary size, radiological appearance (diffuse versus nodular), number and type of surgeries, use of radiation therapy, lines, duration and response on prior therapies (hormonal, cytotoxic and tyrosine kinase inhibitors), reason for treatment discontinuation, time to progression, documentation of progression before initiation of sorafenib, dose and toxicities of sorafenib, overall survival and status. Imaging modalities employed in evaluating this heterogeneous group of patients include: 1) MRI with gadolinium for tumors of the extremities, chest wall, or neck 2) CT with intravenous contrast or oral contrast only for tumors involving mesentery, abdominal wall or thorax.

1.6 Patient and Tumor Characteristics

There were 17 females and 9 males in this cohort. Median age at diagnosis and presentation was 29.5 and 31 years, respectively. At diagnosis, 16 patients underwent surgical resection and 10 patients were deemed surgically unresectable or only resectable with unacceptable deformity (amputation) or morbidity. At the start of sorafenib therapy, all 26 patients had unresectable disease. The histological diagnosis was confirmed at MSKCC. Primary locations included: abdomen/pelvis (12), extremity (6), trunk/chest wall (6) and head and neck (2). Radiological appearance of the tumor was nodular (6) or diffuse/infiltrative (20). The primary tumor size was <5 cm (4), 5–10 cm (11) and >10 cm (11).

1.7 Treatment Characteristics

At initial diagnosis, sixteen patients underwent surgery for resectable disease. Four of 26 patients received adjuvant radiation following primary resection. The use of NSAIDs was not evaluated. Prior systemic therapy included hormonal manipulation, chemotherapy and tyrosine kinase inhibitors. Fifteen patients received a median of 2 prior systemic treatments while 11 patients had sorafenib as first-line treatment. 8/15 patients received hormonal therapy for a median of 8 months before progression. Best response to hormonal treatment included stable disease and one minor response. There was a median of two lines of prior cytotoxic chemotherapy administered for a median of 7 months which consisted of single agents or combinations involving doxorubicin, liposomal doxorubicin, decarbazine, methotrexate and/or cyclophosphamide. Toxicity with anthracyclines included congestive heart failure, alveolar bone loss in the jaw, mucositis, alopecia, nausea and fatigue. Tyrosine kinase inhibitors other than sorafenib had been employed in 6 patients with one minor response as best outcome.

1.8 Sorafenib administration

Sorafenib was initiated when progression was noted on imaging in 23/26 patients while 3/26 patients had RECIST stable disease on chemotherapy, but experienced worsening pain. Sorafenib was started in 15/26 patients after a median of 2 lines of prior systemic and as a first line therapy in 11/26 patients at the time of progression. At the time of this concept submission, 1st and 2nd line patients received sorafenib for a median of 10 months (1–46+) and 15 (2–32) months, respectively. Sorafenib was started at a maximum dose of 400 mg daily and decreased

for toxicity. No patient was treated at 400 mg twice daily, the FDA approved dose in renal cell or hepatocellular carcinoma. The median dose of sorafenib was 200 mg daily. Some patients required further dose reductions for toxicities to 200 mg every other day while others tolerated alternating doses of 400 mg and 200 mg daily (300 mg/day). Sorafenib related toxicities included hand-foot syndrome, fatigue, skin rash, trichodynia, hypertension, mild alopecia and diarrhea. Side effects were well controlled with dose adjustments and inclusion of anti-diarrhea and anti-hypertensive drugs.

1.9 Clinical Outcome on Sorafenib

Median follow up on sorafenib was 12 months (range: 1–46+). Approximately 70% patients (16/22) reported subjective decrease in pain and analgesic use after initiation of sorafenib; these data were not quantitated using a validated pain scale. Some examples of clinical benefit include: (1) A 21 year old male had tumor extending from axilla to brachial artery, median and ulnar nerve which resulted in significant pain, swelling and loss of mobility. Forequarter amputation remained the only option to render the patient disease-free. Within 2 months of sorafenib the patient experienced a RECIST PR, complete resolution of symptoms and thus averting a forequarter amputation; (2) a 24 year old female had a large desmoid tumor displacing her mediastinum and had signs of impending cardiopulmonary collapse despite other systemic therapies. Within one week of sorafenib she had dramatic improvement in orthopnea, dyspnea and lower extremity edema; (3) a 21 year old woman with inoperable cervical spine mass presented with pain and compromised mobility. Therapy did not result in change in tumor size; however there was loss of MRI T2 signal and significant pain relief. Notably, no symptomatic benefit was reported by patients with intra-abdominal desmoids. Three patients stopped sorafenib within 2 months due to abdominal pain, uncontrolled hypertension or visual disturbances. Neither cardiac toxicity nor bleeding was observed.

1.10 Radiological response assessment

Background

MRI is a standard of care in extra-abdominal DT/DF. All patients undergoing MRI as part of their response evaluation will be included in this exploratory study. Response evaluation by RECIST will be performed by ALLIANCE designated central, independent radiology review. For the exploratory study, images of patients treated with sorafenib will be obtained from ALLIANCE Core lab for evaluation by musculoskeletal radiologist Drs. Robert Lefkowitz (Radiology) and Yousef Mazaheri (Medical Physics).

Background #2: The optimal imaging modality to evaluate DT/DF remains undefined[17]. In the study of sorafenib in DT/DF, 6 of 24 patients experienced a RECIST PR and 7/24 had minor response. We noted in our study that patients with changes in T2 signal had described symptomatic improvement without having a RECIST response. We also noted that T2 changes preceded a RECIST response by six months[15]. Studies have shown that areas of desmoid tumor that are hyperintense on T2-weighted and STIR images are associated with active fibroblastic proliferation (Sundaram *et al*, 1987; Vandevenne *et al*, 1997). MRI T2 signal is a unit less number with no intrinsic meaning except for comparative purposes. We therefore developed *a reproducible, quantifiable metric* where the ratio between the T2 intensity of the tumor (C1) and adjacent skeletal muscle (M1) was calculated in pre-treatment and week 12 images (i.e. [C2/M2] / [C1/M1])[15]. A 30% decrease of T2 signal intensity was arbitrarily defined as significant. T2 changes were seen in 12/13 (~90%) patients with extra-abdominal disease and 100% of patients with a RECIST PR (Figure 5). Changes in T2 signal occurred as early as 6 months prior to a RECIST response. In the figure below, patients on the right side had a significantly decreased amount of time on the drug compared to the patients on the left side. The sensitivity and specificity of T2 signal loss as a predictor of RECIST PR was 100% and 12%, respectively. We

hypothesize that T2 signal in extra-abdominal DT/DF is 1) an early predictor of RECIST response and 2) a predictor of clinical benefit in patient with stable disease.

We will also be evaluating diffusion-weighted MR imaging (DW-MRI) in a subset of patients having extra-abdominal disease. DW-MRI is a non-invasive technique that derives its image contrast from differences in the motion of water molecules between tissues. The degree of water diffusion in biologic tissue is inversely correlated to tissue cellularity and the integrity of cell membranes. The motion of water molecules is more restricted in tissues with high cellular density associated with numerous intact cell membranes (e.g., tumor tissue). Quantitative analysis of DW-MRI is achieved by calculation of the apparent diffusion coefficient (ADC). The ADC is calculated for each pixel of the image and is displayed as a parametric map.

RECIST 1.1: Twenty four of 26 patients were evaluable for response. CT or MRI was obtained at a median interval of 4 months. Responses by RECIST 1.1 were: 0/24 complete responses, 6/24 partial responses (25%), 17/24 (70%) with stable disease and 1 patient with progressive disease. Seven patients experienced minor response (defined as 10–29% decrease). Bi-dimensional WHO size measurements were highly correlated (R^2=0.92) with RECIST (not shown). RECIST PR was achieved at a median of 10 months and a minor response (i.e. reduction > 10% by RECIST) was noted at a median of 4 months of starting therapy. PR and SD were mostly seen in extra-abdominal tumors (p=0.03, t-test) and there was no difference between those who received sorafenib as first-line or second-line (p = 0.9, t-test).

Survival: The 26 patients were followed for a median of 50 months (3–209 months) from initial diagnosis. Median follow-up from the start of sorafenib was 12 months (1-46+). Median time to progression was not reached. Five patients progressed despite sorafenib, defined as increasing tumor size (2), symptoms (1) or drug intolerance (2). Twenty-five of 26 patients are alive with disease.

1.11 Registration Fatigue/Uniscale Assessment

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates.

1.12 Inclusion of Women and Minorities

All studies must address the issue of inclusion of women and minorities in clinical research and whether gender or race/ethnicity differences in the intervention effect are to be expected. The statisticians will provide statistical analysis of past phase III studies as well as how the review of the literature will be reflected in the statistical section.

2.0 OBJECTIVES

2.1 Primary Objective

To compare the progression-free survival (PFS) rates of patients with DT/DF who receive either sorafenib or placebo using a double-blinded randomized phase III study.

2.2 Secondary Objective(s)

2.2.1 To assess toxicity.

2.2.2 To assess time to surgical intervention.

2.2.3 To assess tumor response rates and survival.

2.3 Correlative Companion Study Objectives

2.3.1 To evaluate changes in MRI T2 to predict (or correlate) with a biological effect such as tumor growth (by RECIST v1.1), and pain palliation.

2.3.2 The mechanism of action of sorafenib in DT/DF remains unknown. In patients consenting to undergo the paired tumor biopsies (A091105-ST1), treatment induced changes will be quantified by histology, gene expression profiling, proteomic changes and selected interrogation of key pathways by Western blot and RT-PCR.

2.3.3 To collect archival tissue, baseline (tumor, blood) and day 8 (tumor, blood) specimens for basic science research (A091105-ST1).

2.3.4 To assess patient-reported adverse events and quality of life (QOL) as measured by the PRO-CTCAE and the single-item overall LASA (A091105-HO1).

2.3.5 To assess pain palliation measured by the "worst pain" item of the Brief Pain Inventory Short Form (A091105-HO1).

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for $\geq$ 3 years.

In addition,

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).
- Patients must be able to swallow tablets.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

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

4.1 Documentation of Disease

Patients must have confirmation of DT/DF by local pathologist prior to registration.

4.2 Prior Treatment

4.2.1 Patients may have been treated with locoregional therapies such as major surgery, radiation, radiofrequency ablation, or cryosurgery provided this has been completed at least 4 weeks prior to registration and recovered from therapy related toxicity to less than CTCAE grade 2.

4.2.2 Patients may have been treated with cytotoxic, biologic (antibody), immune or experimental therapy, tyrosine kinase inhibitors, hormone inhibitors or NSAIDs provided this has been completed at least 4 weeks prior to registration (6 weeks for mitomycin and nitrosoureas) and recovered from any therapy related toxicity to less than CTCAE grade 2.

4.2.3 Patients with prior or current treatment of sorafenib are excluded.

4.2.4 No concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (*e.g.*, clopidogrel). Low dose aspirin (≤81 mg/day), low-dose warfarin (≤1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted. Please note that drugs that strongly induce or inhibit CYP3A4 or are associated with a risk of Torsades are not allowed. Chronic concomitant treatment of CYP3A4 inducers is not allowed (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort). Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

The following drugs are strong inhibitors of CYP3A4 and are not allowed during the treatment with sorafenib:

- Boceprevir
- Indinavir
- Nelfinavir
- Lopinavir/ritonavir
- Saquinavir
- Telaprevir
- Ritonavir
- Clarithromycin
- Conivaptan
- Itraconazole
- Ketoconazole
- Mibefradil
- Nefazodone

- Posaconazole
- Voriconazole
- Telithromycin

Drugs with possible or conditional risk of torsades should be used with caution knowing that sorafenib could prolong the QT interval. Please see Appendix III for more details.

Chronic daily NSAID use as treatment for controlling desmoid tumors is not allowed, and should be stopped ≥ 3 days prior to registration. NSAIDS are allowed when used for desmoid tumor-related pain or for symptoms that are unrelated to desmoid disease (eg headache, arthritis).

4.3 Measurable Disease

Patients must have measurable disease as defined in Section 13.0.

4.4 Disease Status

Patients have to meet **one** of the following criteria to be eligible:

1. Disease determined unresectable or entailing unacceptably morbid surgery based on 1 or more of the following characteristics:
   - Multifocal disease
   - Disease in which there is involvement or inadequate plane from: neurovascular bundle, bone, skin, or viscera
   - Large size in relationship to location OR multi-compartment involvement
2. Progression by radiographic imaging (10% increase in size by RECIST v1.1 within 6 months of registration)
3. Patients with symptomatic disease which meets the following criteria BPI score greater than or equal to 3 AND **one** of the following:
   - Inability to control pain with NSAIDs and considering addition of narcotics OR
   - >30% increase in current use of narcotics OR
   - Addition of a new opioid narcotic

4.5 Age and performance status

4.5.1 Age ≥ 18 years of age

4.5.2 ECOG Performance Status ≤2

4.6 Pregnancy/nursing status

Patients who are pregnant or nursing are not eligible because of the potential teratogenic/growth inhibitory effects of sorafenib.

4.7 Patient History

4.7.1 No patients with a history of cardiac disease: congestive heart failure > class II New York Heart Association (NYHA); active coronary artery disease (CAD) (myocardial infarction or unstable angina within 6 months prior to study entry)

4.7.2 No patients with inadequately controlled hypertension (defined as a blood pressure of ≥150 mmHg systolic and/or ≥90 mmHg diastolic), or any prior history of hypertensive crisis or hypertensive encephalopathy

4.7.3 No patients with clinically significant gastrointestinal (GI) bleeding or bleeding diathesis within 30 days prior to registration

4.8 Required Initial Laboratory Values:

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

absolute neutrophil count	≥1,500/mm^3
hemoglobin	≥8g/dl
platelets	≥75,000/mm^3
total bilirubin	≤ 1.5 x upper limits of normal (ULN)
SGOT(AST)/SGPT(ALT)	≤1.5 X ULN
creatinine	Calculated creatinine clearance ≥50 mL/min*

* using the Cockcroft-Gault equation

CrCl = (140 - age) x IBW / (Scr x 72) (x 0.85 for females)

5.0 REGISTRATION/RANDOMIZATION AND STRATIFICATION

5.1 Patient Registration Requirements

5.1.1 Informed Consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form are required.

5.1.2 Patient Completed Booklets

Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A091105 CTSU site) and faxing the form to the CTSU data operations center at 1-888-691-8039. Samples of the booklets are found in Appendix II, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

5.2 Registration Procedures

5.2.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

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

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

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

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR Help Desk by email at < RCRHelpDesk@nih.gov >.

5.2.2 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

5.2.2.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A091105 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol # A091105
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided

5.2.2.2 Requirements for A091105 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted).

5.2.2.3 Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website. Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.2.2.4 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable original documents should be mailed to:

CTSU Regulatory Office

1818 Market Street, Suite 3000

Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

5.3 Patient Registration/Randomization Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data {add if a Rave study: and, upon enrollment, initializes the patient in the Rave database.}. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

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

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

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

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

NOTE: The patient should be registered to optional companion studies A091105-HO1 and A091105-ST1 at the same time they are registered to A091105.

5.4 Registration to Companion Studies

5.4.1 Registration to Substudy described in Section 10.2

This companion study **must be offered to all English-speaking patients** enrolled on A091105 (although patients may opt to not participate). The assessments cannot be translated, so patients who do not speak English, may not participate in this substudy. This optional substudy included within A091105 is:

- **A091105-HO1,** "QOL study"

If a patient answers "yes" to "I choose to take part in the Quality of Life study and will fill out these forms:", question #1 in the model consent, they have consented to participate in the substudy described in Section 10.2.

5.4.2 Registration to Substudy described in Section 10.3

This correlative science study **must be offered to all patients** enrolled on A091105 (although patients may opt to not participate). This optional substudy included within A091105 is:

- **A091105-ST1,** "Analysis of archival tissue, and pre-treatment and 8 day tumor biopsy and blood samples"

If a patient answers "yes" to "My coded samples and related coded information **may be used** in the research described above to learn about, prevent, find or treat **cancer**. This may also include research on inherited traits (genes passed on in families)." question #2 in the model consent, they have consented to participate in the substudy described in Section 10.3.

5.5 Re-Registration at the time of crossover to open label sorafenib arm

Upon confirmation of progression, patients will be unblinded to their treatment assignment. Patients who were initially assigned to placebo will be allowed to cross over to the open label sorafenib arm.

Re-registration procedures:

OPEN may be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU website at https://www.ctsu.org, or from the OPEN Registration tab on the Alliance website.

To enroll a patient within OPEN, institution staff must have:

1. A valid and active CTEP-IAM account. This is the same user ID and password used for CTSU's website (for more information see https://www.ctsu.org/public/CTEP-IAM_Factsheet.pdf).
2. Enrollment of patients on Alliance coordinated protocols requires a "Registrar" role in the Alliance roster. Assignment of the "Registrar" role is managed through the Alliance Central Protocol Office via submission of a roster update form signed by the Principal Investigator of the member network.

The OPEN system will provide the registering site with a printable confirmation of re-registration. Please print the confirmation for your records. Further instructional information is provided on the CTSU members' website OPEN tab, or within the OPEN URL. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923, or ctsucontact@westat.com.

5.6 Stratification

Patients will be stratified at randomization by:

1) intra-abdominal disease: yes vs no

2) baseline level of pain (BPI "Worst Pain" Item: 0-<3; 3 – <7 vs 7 – 10). See Appendix V.

We will be using a 2:1 randomization scheme to improve accrual to the study given that is has an observation arm and to also reduce biopsies performed for patients who have been enrolled to the placebo group. The randomization algorithm used by the Alliance Statistics & Data Center uses dynamic allocation procedure[27] which balances the marginal distributions of the stratification factors between treatment regimens.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Medidata Rave®

This study will use Medidata Rave® for remote data capture (RDC) of all study data. The Rave system can be accessed through the iMedidata portal at https://login.imedidata.com. For additional information regarding account setup or training, please visit the training section of the Alliance Web site. Copies of forms and a data submission schedule are also available for download at the Alliance Web site.

Common Terminology Criteria for Adverse Events: This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicity and adverse event reporting.

6.2 A091105-HO1 (QOL) data submission

QOL booklet ordering instructions can be found in Appendix II. For patients who consent to model consent question #1, the assessments in the table below are to be completed at the following timepoints:

Assessment	Within 28 days prior to randomization	Within 28 days prior to treatment	Weeks 4, 8, 12, 16, 20, 24, 28, and 32 of treatment (+/- 3 days) (i.e. Cycles 1-8, Days 22-28)	End of randomized treatment
Brief Pain Inventory Short Form	X		X	X
PRO-CTCAE	X		X	X
Single-item overall LASA	X		X	X
Pain Medication Diary		X*	X	X

* Daily reporting for 7 consecutive days via paper diary prior to treatment. Pain medication diary is not found in QOL booklet.

The Brief Pain Inventory Short Form, PRO-CTCAE and Single-item overall LASA are all contained with the QOL questionnaire booklets (see Appendix II). **Samples of QOL questionnaires found in Appendix II of the protocol document are for reference and IRB submission only. They are not to be used for patient completion.**

The pain medication diary is not part of the QOL Booklet and must be printed. The pain medication diary should be completed during treatment weeks 4, 8, 12, 16, 20, 24, 28, and

32 weeks. Therefore, since a cycle is 28 days, the pain medication diary should be completed the last week of each cycle.

On Day 1 of each cycle site staff should prepare the pain medication diary by listing the pain medication names, routes and strengths in the appropriate columns on the pain medication diary. Site staff must then send the partially completed diary home with the patient and ask that they complete it for the 7 days leading up to the next appointment.

The QOL assessments cannot be translated, therefore, only English-speaking patients may enroll on this substudy.

6.3 Specimen Submission

Specimen	Baseline[3]	Cycle 1, Day 8 (+7 days)	Location
Archival tissue block (FFPE)[1]	X		OSU
Peripheral whole blood[2]	X	X	OSU
Research tumor biopsy[2]	X	X	OSU
Plasma[2]	X	X	OSU

1 Required for all patients registered to A091105. For patients who consent to A091105-ST1, this tissue block will also be used for study described in Section 10.3

2 For patients consenting to optional study A091105-ST1

3 Obtain prior to the start of protocol treatment and between days 8 and 11 of Cycle 1

6.3.1 Formalin Fixed, Paraffin Embedded (FFPE) Tissue

Archival Tissue: All patients must submit an archival tumor specimen block for required retrospective pathology review. This block will be used by the study pathologist to confirm diagnosis of desmoid tumor (DT/DF). For patients who consent to A091105-ST1, this tissue block will also be used for the study described in Section 10.3.

At least 1 adequate-sized archival paraffin block(s) representative of the primary tumor from a diagnostic or therapeutic procedure at time initial diagnosis or subsequently, should be retrieved from the surgical pathology department. Blocks which contain minimal amounts of tissue specimen (less than 0.5 cm2 on the block face) or that are very thin (less than 0.5 cm in depth) should not be submitted unless the block is the only representative tissue for the case. A de-identified surgical pathology report should be sent with all blocks. Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report.

Paraffin blocks retrieved from the surgical pathology department should have a label affixed to them that includes the protocol number, Alliance patient ID, and patient initials. The surgical pathology case number and block identifier should be maintained on the report so that it can be matched with the physical labeling on the block. Paraffin blocks should be shipped within 30 days of starting protocol treatment to Alliance Biorepository at Ohio State (OSU). Upon receipt at OSU, representative H&E slides and/or scanned images will be provided to designated study pathologist for retrospective pathology review. The

pathologist and/or study chair will request block shipping periodically (approximately every 4 months). All blocks will be held by the appropriate Alliance biorepository but will be returned within 30 days of a written request.

In instances where a tissue block cannot be released due to institutional or governmental policy, please contact the Alliance OSU to obtain information about submission of tissue sections as an alternate specimen.

Archival blocks should be requested at time of consent. Blocks should be shipped overnight to Alliance OSU.

6.3.2 Research frozen tumor core biopsy submission (optional study A091105-ST1)

When safe and feasible, according to the treating investigator and proceduralist obtaining biopsy, consenting patients will undergo 2 biopsies (procuring 5 cores for each biopsy) for correlative study A091105-ST1. Depending on tumor location, biopsies can be obtained at the discretion of surgeon or interventional radiology under image guided CT or Ultrasound. Core biopsies should be performed with either 14 (prefer) or 18 gauge needles. When possible, different areas of the tumor should be biopsied. Each core sample will be transferred to individual cryovials. The cryovials containing the 5 research core biopsy specimens should be immediately immersed in liquid nitrogen for 5 minutes. If liquid nitrogen is not available, the specimen may be immersed in a refrigerated cryobath, available in most surgical pathology frozen section rooms. If using a cryobath, one should be certain that the temperature of the bath is at or below -40°C. As a last option, specimens may be frozen by complete immersion in an ethanol / dry-ice bath. Specimens should be left in the cryobath or dry ice bath for at least 15 minutes to ensure complete freezing. **Specimens should not be frozen by placing fresh tissue in a -70°C freezer or inside a cryostat**. Once frozen, tissue may be stored in at least -70°C mechanical freezer or in dry ice until shipping. Once frozen, take extreme care not to let the tissue specimen thaw. Specimens should be shipped on dry ice within 30 days of collection to Alliance OSU. **For sites that do not have -70 C freezer**, tissue should be frozen as described above and shipped within 24 hours of collection according to Section 6.3.6.

6.3.3 Peripheral Whole Blood Submission (optional study A091105-ST1)

Collect 2 vials of 6 mL of peripheral venous whole blood in 9 mL lavender top (EDTA anticoagulant) vacutainer tube(s). Invert tubes approximately 10 times to mix the EDTA. Specimens should be refrigerated within 30 minutes of the blood draw until shipped/transported. The sample should be shipped the same day that the blood is drawn. The specimen should be placed in a biohazard bag and shipped according to IATA guidelines with a cold refrigerant pack by overnight carrier to the Alliance OSU. Shipment on Monday through Thursday by overnight service to assure receipt is encouraged. Do not send specimens on a Friday or Saturday or the day before a federal holiday.

6.3.4 Plasma Specimen Submission (optional study A091105-ST1)

1. For EDTA plasma, draw 6 mL of peripheral blood into 9 mL lavender or purple top vacutainer(s) (K2EDTA anticoagulant). Invert approximately 8 times and centrifuge for 15 minutes at 2500 x g using a refrigerated centrifuge at 2-8^{o} C. Within 15 minutes, transfer the plasma sample into (4) labeled 2 mL cryovials.

2. Label and freeze cryovials at –70°C or colder. Samples should be shipped within 30 days on dry ice by overnight express courier to the Alliance OSU. For sites that do not have -70 C freezer, plasma samples may be temporarily stored at -20^{o} C and shipped within 24 hours of collection.

6.3.5 Specimen Labeling

Research peripheral whole blood, plasma, and frozen tumor specimen tubes must be labeled with the following information (using a Sharpie or Cryopen):

1. Alliance study number (i.e., A091105)
2. Alliance patient ID number
3. Patient's initials
4. Date of specimen procurement
5. Sample type (i.e. whole blood, plasma-EDTA, plasma citrate, urine, marrow aspirate, metastatic site, etc.)

6.3.6 Specimen Shipping

All shipments should follow the International Air Transport Association (IATA) guidelines (http://www.iata.org/whatwedo/cargo/dangerous_goods/Pages/infectious_substances.aspx) including shipment in a biohazard bag and should be sent by overnight shipping service. A shipping service should be selected that is secure and traceable.. Extreme heat precautions should be taken when necessary. The specimens should be sent Monday through Thursday to OSU. Do not send specimens on a Friday or Saturday or the day before a federal holiday.

All samples should be sent to the following address:

Alliance Biorepository at Ohio State

The Ohio State University

Innovation Centre

2001 Polaris Parkway

Columbus, OH 43240

Tel: 614-293-7073 Fax: 614-293-7967

6.3.7 Alliance Biospecimen Management System Instructions

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

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.wustl.edu/bioms using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS.

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

6.4 MR Imaging Data Submission

Once the image acquisition has been completed (at baseline and every 8 weeks), the entire study (complete data sets in digital DICOM format), along with Alliance Adjunctive Data Form (if applicable) and Alliance Image Measurement Form (if applicable), must be

submitted to the ALLIANCE Imaging Core Laboratory within no more than 3 business days. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by the Imaging Core Lab. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number and protocol number. The de-identified digital images may be temporarily burned to a CD or transferred to a PC based system.

Data should be transferred electronically (**recommend**) to the Alliance ICL as follows:

Electronically

1) Web Transfer (http://upload.imagingcorelab.com**)**

Any PCs with internet access and web browser (e.g., Internet Explorer, Mozila Firefox) can be used to web transfer DICOM images and other required files to the Imaging Core Lab. The standard Web Transfer information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

2) **FTP Transfer**

Any FTP software can be used to initiate access to the secure FTP Server of the Imaging Core Laboratory. The standard FTP access information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

Mail/CD Shipment

Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to the Imaging Core Lab. Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of scans, and name of submitting institution.

Submit these data to:

ALLIANCE Imaging Core Lab

Attn: Alliance Trial A091105

The Ohio State University

395 W. 12th Avenue, Suite 414

Columbus, Ohio, 43210

Tel: 614-293-9151

Fax: 614/293-9275

Once the imaging data submission is done, send an e-mail to the Imaging Core Lab at the specific trial email Alliance091105@ImagingCoreLab.com to inform that the study has been submitted from the institution. Please include the basic information of submitted data sets as follows:

1) Alliance patient ID number
2) Scan time point (i.e., baseline)
3) Date of scans
4) Institution name

The ALLIANCE Imaging Core Lab will acknowledge receipt of the imaging data via email confirmation to the institution **within 1 business day** of receipt, and will notify the institution and Alliance imaging committee of the quality check report **within 3 business days.**

7.0 REQUIRED DATA

Pre-Study Testing Intervals

To be completed within 28 DAYS before registration:

- All bloodwork
- History and physical
- CT or MRI of lesion

	Prior to Registration*	Day 1 and 15 (+/- 3 days) of Cycle 1 (Clinical Follow up)**	Day 1 (+/- 3 days) starting with Cycle 2 (Clinical Follow up)**	Survival and Disease Status Follow up***
Tests & Observations				
Physical Examination	X	X	X, C	
Pulse, Blood Pressure	X	X	X, C	
Height	X			
Weight	X			
Performance Status	X	X	X, C	
Tumor Measurements	X (1)		X (1)	B
EKG	PRN		PRN	
Registration Fatigue/Uniscale Assessment	X (2)			
Adverse Event Assessment	X	X	X, C	
Brief Pain Inventory Question #1 (see Appendix II and V)	X(6)			
Laboratory Studies				
CBC with Differential, Platelets	X	X	X, C	
Pregnancy Test (serum) B	X (4)			
Na, K, chloride, bicarb, BUN, creatinine, glucose, Ca, SGOT (AST), SGPT (ALT), bili, total protein, albumin	X	X	X, C	
Staging				
Spiral CT Scan or MRI of lesion	X(7)		A(7)	B
Companion Studies				
QOL Assessments	X (3)	X (3)	X (3)	
Archival Block	X (5)			
Tumor Biopsy and blood†	See Section 6.3			

* Pre-registration labs may be used for day 1 of cycle 1 tests if obtained within 28 days prior to day 1 of Cycle 1.

** For patients discontinuing treatment for reasons other than progressive disease (PD) and prior to 1 year post-randomization, Clinical Follow-up continues at least every 8 weeks after discontinuing treatment until the earliest PD or until 1 year after randomization. Patients on the placebo arm may cross over to the sorafenib arm upon PD, and continue in Clinical Follow-Up. Treatment with sorafenib after crossover must begin within 28 days following documentation of progression.

*** After progression on sorafenib, patient will be followed per. Section 14.1

† For patients who consent to A091105-ST1. Not required for patients who have crossed over to sorafenib.

1 To be performed only for patients with palpable disease. Submit measurements in cm with two dimensions.

2 To be completed within 21 days prior to registration, see Appendix I.

3 Within 28 days prior to randomization, every 4 weeks up to Week 32 while on randomized treatment, and at the end of randomized treatment; see Section 6.2. These items are not required after patients have crossed over to sorafenib.

4 For women of child bearing potential. To be obtained within 3 days prior to day 1 of Cycle 1, **and** after crossover, ≤ 7 days prior to starting treatment with sorafenib.

5 Required for all patients registered to A091105 and will be used for confirmation of diagnosis as described in Section 6.3.1. For patients who consent to A091105-ST1, this tissue block will also be used for study described in Section 10.3.

6 Must be completed within 28 days of registration. Patients who consent to A091105-HO1 will meet this requirement by answering question #1 on baseline QOL assessment (see Appendix II). For patients who do not consent to A091105-HO1, see Appendix V.

7 All MRI images are to be submitted to the Alliance ICL per Section 6.4 and will be analyzed as described in Section 10.1

A Every 2 cycles (i.e. 8 weeks) +/- 7 days after Day 1 of Cycle 1 (i.e. Day 1 of Cycle 3, 5, 7, etc) for the first 3 years. For patients receiving initial treatment beyond 3 years from randomization date; scans may be performed every 4 months through 5 years from randomization, then scans may be performed every 6 months. Patients who crossover must have a scan within 28 days of starting sorafenib. The scan schedule after crossover to sorafenib will be every 2 cycles for three years. For patients receiving crossover treatment beyond 3 years from re-registration; scans may be performed every 4 months through 5 years from re-registration, then scans may be performed every 6 months.

B As clinically indicated per institutional standard of care

C Effective with Update #06, For crossover patients only: Beginning with Cycle 14 (i.e. after 1 year of sorafenib treatment) complete every other cycle.

8.0 TREATMENT PLAN

Protocol treatment is to begin within 14 days of randomization. One cycle is equal to 28 days.

Questions regarding treatment should be directed to the Alliance Study Chair.

8.1 Sorafenib/Placebo

Patients will be randomized to receive either sorafenib 400 mg PO once daily or placebo (two pills) once daily.

Sorafenib/placebo should be taken by mouth once daily on an empty stomach (at least 1 hour before or 2 hours after a meal) and with at least 250 ml of water. Patients should take their daily dose at approximately the same time each day. Patients should use the study pill diary to record their daily dose of sorefenib/placebo. Patients should bring the pill diary with them each time they return for a study follow-up visit.

8.2 Crossover

Upon disease progression, patients treated with placebo will be allowed to crossover to the open label sorafenib arm. Patients who undergo surgical excision of their tumors must start sorafenib within 28 days of surgery. After excision, the patient must have measureable disease (per RECIST v1.1).

8.3 Duration of Treatment

Study treatment is not based on a pre-defined number of cycles. Refer to Section 14.0 for criteria for removal of patients from study treatment.

9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

Should unanticipated circumstances arise that might require minor variances from the prescribed dosing and schedule of the protocol therapy or recommended supportive care, the Study Chair should be contacted in advance for discussion and approval in order to ensure safety and allow patients to continue to receive treatment on study.

9.1 Dose levels

Dose reduction of sorafenib/placebo will be performed according to the table below. Sorafenib/placebo will be permanently discontinued for patients who require dose interruptions of > 28 days or who experience dose limiting toxicities at dose level -1. Missed doses of sorafenib/placebo will not be made up.

Dose level	Sorafenib/placebo
0	400 mg once daily
-1	200 mg once daily

- If dose reductions beyond the lowest dose level are required discontinue all protocol therapy.
- Doses that have been reduced will not be re-escalated, except in the case of skin toxicity.

9.1.1 Dose Modifications for Hematologic Toxicities

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

9.1.2 Dose Modifications for Gastrointestinal Toxicities

- **Grade ≥ 3 diarrhea:** Interrupt sorafenib/placebo until diarrhea improves to ≤ grade 2, then resume sorafenib/placebo with one dose level reduction.
- **GI Perforation:** Discontinue sorafenib/placebo.

9.1.3 Dose Modifications for Hepatic Dysfunction

- **Grade 2 blood bilirubin increased:** Interrupt sorafenib/placebo until improved to grade 1, then resume sorafenib/placebo at same dose.
- **Grade 3 blood bilirubin increased:** Interrupt sorafenib/placebo until improved to grade 1, then resume sorafenib/placebo at 1 dose level reduced.
- **Grade 4 blood bilirubin increased:** Discontinue sorafenib/placebo.
- **Grade 3 transaminase increased:** Interrupt sorafenib/placebo until improved to grade 1, then resume sorafenib/placebo at 1 dose level reduced.
- **Grade 4 transaminase increased:** Discontinue sorafenib/placebo.

9.1.4 Dose Modifications for Hypertension

- **For hypertension >140/90 and ≤160/100:** Continue sorafenib/placebo. Consider adding or adjusting anti-hypertensive medications (e.g., calcium channel blockers).
- **For persistent (>160/100) or symptomatic hypertension:** Interrupt sorafenib/placebo. Resume when blood pressure improves to ≤160/100. If sorafenib/placebo is interrupted for > 4 weeks, discontinue all protocol therapy.
- **Grade 4 hypertension**: Discontinue all protocol therapy.

9.1.5 Dose Modifications for Cardiotoxicity

- **Myocardial ischemia**: Discontinue sorafenib/placebo.

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

Skin Toxicity	Occurrence	Suggested Dose Modification
Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet relief which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib/placebo and consider topical therapy for symptomatic relief
Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Continue treatment with sorafenib/placebo and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib/placebo until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib/placebo dose by one dose level
	4th occurrence	Discontinue sorafenib/placebo
Moist desquamation, ulceration, blistering or severe pain the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib/placebo until toxicity of resolves to Grade 0-1. When resuming treatment, decrease sorafenib/placebo dose by one dose level
	3rd occurrence	Discontinue sorafenib/placebo

9.1.7 Dose Modifications for Other Non-hematologic Toxicities

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

10.0 COMPANION STUDIES

There will be 1 mandatory imaging companion for patients whose disease is being monitored by MRI. There will also be 2 optional sub-studies: A091105-HO1 (Health Outcomes) and A091105-ST1 (Correlative Science). A091105-HO1 and A091105-ST-1 must be offered to all patients for their consent, although patient participation is optional.

10.1 Imaging companion study incorporated within A091105: Evaluation of MRI T2 signal as a novel imaging biomarker in DT/DF treated with sorafenib

10.1.1 Objectives

In a retrospective study, DT/DF patients treated with sorafenib demonstrated decrease in MRI T2 signal intensity suggesting a decrease in cellularity. In this prospective trial, we will undertake exploratory studies to test whether MRI T2 changes can predict (or correlate) with a biological response such as RECIST response, and pain palliation (for patients whose disease is being monitored by MRI).

10.1.2 Methods

Methods Study:

The goal of the MRI portion of this study is to assess the T2-weighted sequences to determine the percentage of the entire tumor volume that is hyperintense relative to normal muscle at baseline compared with follow-up examinations. The patient will undergo an MR examination on a 1.5 T (or greater) whole body scanner located at one of the participating institutions. T2-weighted MR images with fat-saturation will be obtained with standard fast spin-echo pulse sequences with the following sequence parameters: TR = 4000-6600ms, TE = 60-70 ms, echo-train length = 24, number of slices = 30, 4-5 mm thickness, FOV = 320 mm, matrix size = 256x192. If adequate fat saturation cannot be achieved due to the location of the tumor, metal artifacts or patient positioning, the patient will be excluded from T2-signal analysis portion of this study. STIR may be performed but cannot replace T2 with fat saturation in the data analysis for the purpose of this research.

Analysis of the data will be performed in two phases: semi-quantitative and quantitative analysis. All images (DICOM compatible with sensitive patient information de-identified) will be analyzed by two reference radiologists and a physicist from Memorial Sloan-Kettering Cancer Center. In phase one, a reference radiologists will review the images in regions suspicious of desmoid to measure changes in signal intensity for clinical assessment. A region-of-interest (ROI) is drawn to include the entire tumor at its greatest cross-sectional diameter. The ratio of mean ROI tumor signal intensity to the signal intensity of an ROI on the adjacent skeletal muscle is calculated. In the second phase, images will be analyzed to quantify the loss of MRI T2 signal intensity using a histogram analysis.

The Alliance Statistics and Data Center A091105 Statistician will prepare analysis datasets in conjunction with clinical/outcome data. Analyses will be coordinated by the A091105 Statistician and conducted using the analysis datasets used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

DW-MR images will be obtained by using a spin-echo echo-planar imaging (SE-EPI) sequence with a pair of rectangular-shaped gradient pulses along three orthogonal axes. Imaging parameters are TR = 4000-5475ms, TE = 77.6–110.3 ms, FOV = 320 mm, 4-5 mm thickness, no inter-slice gap; b-values were 0, 400, and 700 s/mm^2. The advantage of two non-zero b-values as opposed to one b value is that estimated parameters are less influenced by the choice of b-value and may be more appropriate than ADC for use in multi-institutional studies. The orientation and location prescribed are identical to those prescribed for the transverse T2W images. Four to eight signal averages are obtained for this portion of the exam with an approximate imaging time of 5 - 7 minutes to acquire the two sets of b-values.

Absolute T2-values are obtained with a multi echo (dual echo) fast spin echo imaging sequence at 4 different echo times (TEs). TE values will be: 50, 80,110,150 ms (there is flexibility in the values acquired to within 10 ms). The acquisition parameters are: TR = 6600 ms; FOV = 320 mm; 4-5 mm thickness; number of signal acquired, one; echo train length, 24; matrix, 256 ×192. The images are acquired at the same location, FOV, and coverage and the DW-MR images. Using a dual echo fast spin echo sequence, two echoes are acquired per sequence with a total of two sequences acquired.

Summary of Histogram analysis: Using custom-made software developed in MATLAB environment (version 7.1, Mathworks, Natick, MA) the 25th and 50th (median) percentile values, kurtosis, and skewness of the ROI histograms are computed. Kurtosis provides a quantitative measure of how sharply peaked a histogram is compared with the histogram of a normal distribution. Accordingly, whereas a normal distribution has a kurtosis of 0, a more peaked histogram has a positive kurtosis value. Skewness provides a quantitative measure of the degree of asymmetry of a histogram: a perfectly symmetric histogram has a skewness of 0; a histogram with a long right tail has a positive skewness, whereas a negative skewness is due to the presence of a long left tail.

10.2 QOL Sub-Study-A091105-HO1 (Optional)

There is clinical evidence to suggest that sorafenib improves the quality of life by improving pain and/or decreasing in narcotic drug use. Based on a retrospective review by Gounder et al. (2011)[15], approximately 70% DT/DF patients (16/22) reported subjective decrease in pain and analgesic use after initiation of sorafenib. However, these data were not quantitated using a validated pain scale. Thus, patient-reported outcomes (PRO) will be a key secondary endpoint in this trial, both to assess for improvement in disease-related symptoms/QOL and for impact of sorafenib treatment.

Also, evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates.

10.2.1 Objectives

• To compare pain palliation (primary) and time to pain progression (secondary) between arms using three items from the Brief Pain Inventory Short Form and Pain Medication Diary.

• To compare patient-reported adverse events and QOL between arms as measured by the PRO-CTCAE and the single-item overall LASA.

10.2.2 Methods

The following patient assessments will be included in this study:

Brief Pain Inventory – Short Form: The Brief Pain Inventory (BPI) is a pain assessment tool used with cancer patients to measure both pain intensity (sensory dimension) and pain interference (reactive dimension) in the patient's life[29]. The BPI has been validated in >30 different languages across a range of cancer types. To minimize patient burden, only three items will be used from the BPI, the item assessing "worst pain" severity and two items assessing inference with general activity and sleep.

PRO-CTCAE: Completed on paper at the following time points: prior to randomization; and every 4 weeks up to Week 32 while on randomized treatment; and at end of randomized treatment.

The PRO-CTCAE is a group of items currently being developed by the NCI for direct patient-reporting of adverse symptoms in cancer trials. To date, 78 symptomatic adverse events in the CTCAE have been developed for patient self-reporting via the PRO-CTCAE, and have undergone refinement in a cognitive testing study. A large validation of the PRO-CTCAE has been completed across various cancer types and is expected to provide comprehensive results in support of validation at ASCO 2012 for items selected for this study. In this study, we will administer PRO-CTCAE items for 11 symptoms pertinent to patients in this trial and in this population: insomnia, constipation, pain, fatigue, nausea, vomiting, diarrhea, rash, hand-foot syndrome, decreased appetite, and mouth or throat sores.

Single-item overall LASA: Completed on paper at the following time points: prior to randomization and every 4 weeks up to Week 32 while on randomized treatment; and at end of randomized treatment.

The Linear Analogue Self-Assessment (LASA6) consists of six single-item numeric analogue scales. For this study, we will employ only the one item that measures overall QOL[36,37] on a scale of 0-10. LASA items such as these have been validated as general measures of global QOL dimensional constructs in numerous settings[31,32,34,38]. The LASA has been validated at the Mayo Clinic for use in cancer patients and have been successfully used in numerous clinical trials[28]. The single-item overall LASA has been shown to be prognostic for survival in a range of cancer types[39].

• **Pain Medication Diary:** Daily reporting for 7 consecutive days via paper diary prior to randomization, every 4 weeks through Week 32 while on randomized treatment, and at end of randomized treatment. This pain medication diary will be used to quantify opioid narcotic use for computing pain palliation and pain progression.

10.2.3 Specific hypotheses

Our primary hypothesis is that pain palliation will be improved on the sorafenib arm as compared to the placebo arm as suggested by the retrospective review by Gounder et al. Our secondary hypothesis is that time to pain progression will be extended on the sorafenib arm as compared to the placebo arm, based on our hypothesis that sorafenib will prolong progression-free survival. To understand the impact of the hypothesized pain improvement associated with sorafenib on patients, pain interference on general activity and sleep will also be compared between arms, where we expect interference in both domains to be improved on the sorafenib arm as compared to the placebo arm. In terms of patient-reported adverse events, we hypothesize that pain and insomnia will be improved on the sorfenib arm as compared to the placebo arm; and that fatigue, gastrointestinal toxicity (constipation, nausea, vomiting, diarrhea, decreased appetite, and mouth or throat sores) and skin toxicity (rash, hand-foot syndrome) will be negatively impacted on the sorafenib arm as compared

to the placebo arm given the adverse event profile of sorafenib in other patient populations and based on the adverse events reported in the retrospective review by Gounder et al. Lastly, given the possibility of improved pain and insomnia at the cost of increased treatment toxicity, we will compare overall quality of life between arms and hypothesize that quality of life will be improved on the sorafenib arm as compared to the placebo arm (i.e., that larger improvement in pain will offset the added toxicity of sorafenib treatment).

The Alliance Statistics and Data Center A091105-HO1 Statistician collaborate with the A091105 Statistician to prepare analysis datasets in conjunction with clinical/outcome data. Analyses will be conducted by the A091105-HO1 Statistician, using the analysis datasets used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

10.3 A091105-ST1 "Analysis of archival tissue, and pre-treatment and day 8 tumor biopsy and blood samples" (Optional)

10.3.1 Objectives

• The mechanism of action of sorafenib in DT/DF remains unknown. All patients will undergo treatment tumor biopsies. Treatment induced changes will be quantified by histology, gene expression profiling, proteomic changes and selected interrogation of key pathways by Western blot and RT-PCR.

• To collect archival tissue, pre-treatment biopsies and blood and day 8 biopsies and blood specimens for basic science research.

Three recurrent mutations in beta-catenin gene have been documented and prognosticate risk of local recurrence after surgery. However, there is no study that has attempted to evaluate whether these mutations are predictive biomarkers of response to sorafenib. We will attempt to answer this question in this prospective study.

10.3.2 Methods

All correlative studies will be performed in the laboratory of Mrinal Gounder (correlative chair). From archival FFPE specimen in patients who consent to A091105-ST1, sections (preferably 40 micron x1 or 20 micron rolls x2, cut from blocks with at least 50% tumor content after review by designated study pathologist) will be prepared by OSU and sent to the Schwartz laboratory. DNA sequencing will be performed as previously described by Lazar et al. DNA will be extracted from FFPE material using the QIAamp DNA mini kit DNA isolation kit (Qiagen Valencia, CA). Polymerase chain reaction (PCR) will use primers (*BCAT-DES-F*: 5_-AGTCACTGGCAGCAACAGTC-3_ and *BCAT-DES-R*: 5_-TCTTCCTCAGGATTGCCTT- 3) and under thermocycling conditions previously reported to amplify exon 3 of *CTNNB1* (phosphorylation domain, codons 30 to 48) with appropriate controls. PCR products will be detected by gel electrophoresis in 2% agarose, and amplicon bands further purified using the QIAquick gel extraction kit (Qiagen). Direct sequencing used the above primers (forward and reverse), ABI Prism dye terminator cycle sequencing ready reaction kit, and ABI Prism 3100-Avant genetic analyzer (Applied Biosystems, Foster City, CA). Both strands will be analyzed by the NCBI Blast Alignment Tool (*http://www.ncbi.nlm.nih.gov/blast/Blast.cgi*) to identify mutations.

The Alliance Statistics and Data Center A091105 Statistician will prepare analysis datasets in conjunction with clinical/outcome data. Analyses will be coordinated by the A091105 Statistician and conducted using the analysis datasets used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g.

data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

10.3.3 Specific hypotheses

DT/DF is sporadic (~85%) or arise in the setting of familial adenomatosis polyposis (4 – 20%) with germline mutations in APC[1]. Sporadic desmoids have mutations in the β-catenin gene (CTBNN1) with certain mutations associated with high local recurrance[20,21]. β-catenins function both as a cell adhesion molecule and as a transcriptional activator in the presence of Wnt ligand. Mutations in APC or CTBNN1 result in accumulation of nuclear β-catenin and transcriptional activation of growth signals including Tcf, *c-MYC*, *c-JUN*, and *cyclin D* (Figure 6). Carcinomas that over-express CTNNB are associated with an indolent disease with lack of metastatic ability. Sorafenib is a multi-kinase inhibitor that targets B-Raf, PDGFR-β and VEGFR-2/-3. Both c-KIT and PDGFR-B has been shown to be over-expressed in DT/DF without any underlying mutations. In clinical trials of imatinib in DT/DF, extensive search for tumor or serum biomarkers of response were unsuccessful. Response in DT/DF are thought to involve a shift from fibroblast to collagen deposition and fibrosis[18,19]. We hypothesize that differences in histology, protein and gene expression patterns in paired tumor biopsies identify critical pathways that are transcriptionally upregulated in DT/DF and modulated with sorafenib.

10.3.4 A091105-ST1 Biopsies

Pre- and day 8 (+ 7 days) post-randomization biopsy guidelines

A091105-ST1 must be offered to all patients enrolled on A091105 (although patients may opt to not participate). Patients who consent to A091105-ST1 will undergo 2 biopsies (pre-treatment and day 8 post-randomization).

The following exploratory studies will be performed and analyzed in the laboratory of Mrinal Gounder, correlative chair. Bio-informatics analysis will be provided by MSKCC Bio-informatics core lab. Blood, pre-treatment and day 8 matched <u>tumor</u> biopsies are required elements of this study for patients. Patients will undergo 2 biopsies (procuring 5 cores for each biopsy) by interventional radiology under image guided CT or U/S. Core biopsies will be evaluated for the following studies: 1) one core will be formalin fixed for pathological studies and TMA construction, 2) 1 - 2 cores will be used for gene array expression profiling to determine a sorafenib signature of response, whole exome sequencing, microRNA array and epigenetics 3) one core will be used for a constrained evaluation of phospho-proteomic changes utilizing a Zaptosens reverse protein array of selected pathways identified from genetic studies.

Core sample #1 and #2– Nucleic acid changes

<u>RNA isolation, probe preparation, and expression microarray: Hybridization –Affymetrix platform</u>

Total RNA will be isolated from tissue using the DNA/RNA all prep kit(Qiagen). Quality of RNA will be ensured before labeling by analyzing 2 to 5 ng of each sample using the RNA 6000 NanoAssay and a Bioanalyzer 2100 (Agilent). Samples with a 28S/18S ribosomal peak ratio of 1.8–2.0 and a RIN number >7.0 will be considered suitable for labeling. For samples meeting this standard, 1 to 2 μg of total RNA will be used for cDNA synthesis using an oligo-dT-T7 primer and the SuperScript Double-Stranded cDNA Synthesis Kit (Invitrogen). Synthesis, linear amplification, and labeling of cRNA will be accomplished by in-vitro transcription using the MessageAmp aRNA Kit (Ambion) and biotinylated nucleotides (Enzo Diagnostics). Ten micrograms of labeled and fragmented cRNA will be hybridized to the Human HG-U133A2.0 GeneChip (Affymetrix) at 45 degres

C for 16 h. Post hybridization staining, washing were processed according to manufacturer (Affymetrix). Finally, chips will be scanned with a high-numerical Aperture and flying objective (FOL) lens in the GS3000 scanner (Affymetrix). The image will be quantified using GCOS 1.4 (GeneChip Operating Software, Affymetrix) with the default parameters for the statistical algorithm and all probe set scaling with a target intensity of 500.

Whole exome capture using the Agilent SureSelect platform and Hiseq 2000 sequencing.

DNA capture will be performed on 3 µg of high quality genomic DNA using the 51MB SureSelect Human Exome Target Enrichment kit (Agilent) according to the protocol provided by Agilent. Enriched DNA libraries will then be sequenced on a Hiseq2000 (Illumina), using 75x75 paired end V3 sequencing chemistry. The goal will be to generate 80 to 100 million reads per samples, to reach an average coverage of 100x on 85% of the targeted region.

miRNA profiling on Agilent Human miRNA array

The same QC standards will be applied as for the Affymetrix Gene expression platform. Briefly, samples with a 28S/18S ribosomal peak ratio of 1.8–2.0 and a RIN number >7.0 will be considered suitable for labeling. 200 ng of total RNA will be labeled using the miRNA Complete Labeling and Hybridization Kit (Agilent). Labeled RNA will be hybridized for 20hrs at 20 rpm, 55 ^{o}C. Slides will be washed and scanned according to manufacturer's instructions. Images will be quantified using Feature Extraction 10.4 (Agilent)

Core #3 and #4: Protein expression changes

Evaluate changes in protein phosphorylation in pre -treatment and day 8 tumor tissue biopsies. We will utilize Zeptosens technology to facilitate high-throughput profiling of (phospho-) protein levels in tumor tissue. The system is significantly more sensitive, faster and less expensive than Western blots, requiring much smaller protein amounts. The ZeptoMARK reverse protein array system additionally allows measurement of protein expression and post-translational modifications (phosphorylation, methylation etc.) in signaling pathways. Over 300 validated antibodies in various signaling pathways, including Akt, MAPK, lipid, cAMP, insulin and many others, are available for use on ZeptoMARK reverse arrays. Briefly, treated and control tissue material in an equivalent amount are lysed using ZeptoMARK reverse array lysis buffer as per manufacturer's protocol. The denaturing and enzyme inhibiting properties of the lysis buffer allows the biological processes within the cells to be preserved. Frozen lysates can be stored for long periods of time, if necessary. Further processing is carried out using robotic liquid handling equipment existing at MSKCC Core Facility. Lysates are normalized for further processing based on total protein concentrations. Each normalized sample is diluted in a reverse array spotting buffer in a series of four concentrations and then reformatted from 96 to 384 well plates as the source for spotting. Lysates are spotted in duplicates at 4 concentrations on the ZeptoMARK chip using the array spotter. The chips are coated with a proprietary high absorbance surface. Only per lysate are required per spot, an almost unlimited number of replica arrays can be prepared from about 100µl of lysate solution. The chip is then blocked using ZeptoMARK reverse array blocking buffer in the blocking station. Each chip contains 6 arrays that are probed independently with an antibody specifically binding to a signaling protein or its activated form. The fluorescence markers are introduced by application of a labeled anti-species antibody. Only 20 µL of detection antibody (1:250 - 1:10000 dilution of stock solution) is required per array. Surface confined fluorophores are measured at green or red excitation wavelengths in a wet state in the ZeptoREADER. Signal processing of microarray images taken by the ZeptoREADER is performed with the ZeptoVIEW software, and data is then exported in a standard format for further analysis,

for example bioinformatic pathway analysis. We will specifically evaluate changes in Wnt pathway along with the Notch and Hedgehog pathways. Other pathways to interrogate will include the major and minor targets of sorafenib which include VEGFR2/3, PDGFR-β, RAF, KIT, CDK5, Ephrin[24] (EPHA1-2, EPHB4) and FGFR. Lastly, we will also consider evaluating total and phosphorylated levels of Akt, p-Akt (S473), p-p70-S6K, PTEN, p-Mek and p-Erk.

Core #5

Biopsies will be descriptive and comment on 1) proliferation (Ki-67 expressed as percentage) to assess treatment response (pre-treatment base line and post therapy for drug effect) and expressed as percentage of tumor cells as <10%, 10-25%, 25-50% and >50%, 2) degree of fibrosis, 3) changes in vascularity, 4) necrosis and 5) ratio of nuclear to cytoplasmic beta catenin.

For TMA construction, the techniques are previously well described by Lazar and colleagues. Hematoxylin and eosin (H&E) stained sections will be reviewed to define areas of desmoid tumor; dermal scars, reactive tissue and solitary fibrous tumor will serve as controls. Using an automated TMA apparatus (ATA-27; Beecher Instruments, Sun Prairie, WI), 0.6-mm punch samples (two per case) will be obtained along with controls and formatted into three recipient blocks. H&E-staining of 4-micron TMA sections will be used to verify all samples.

Immunohistochemistry*:* The polymeric biotin-free horseradish peroxide method on a Microsystems Bond Max stainer (Beecher Instruments, Bannockburn, IL) will be used for immunohistochemistry. Four-micron-thick sections will be prepared from formalin-fixed paraffin-embedded tissue blocks and dried in a 60-degree oven for 20 minutes. Sections will be placed in the automated Bond Max stainer, pretreated with enzyme-induced epitope retrieval for 2 minutes followed by incubation with antibodies against beta-catenin (BD Biosciences, San Jose, CA), midkine (Antigenix America, NY), MMP2 (Chemicon, MA) and ADAM12 (Abcam, MA). Additional antibodies may be utilized to interrogate specific pathways identified in micro-array work. Anti-mouse secondary antibody and the Refine polymer detection kit (Leica) will be used for immunostaining, with 3,3-diaminobenzidine serving as chromagen. Positive and negative controls will run in parallel. Labeling intensity grading will be performed by soft tissue pathologist (M.H) as none (_0), weak (_1), moderate (_2), or strong (_3). For the ratio of cellular to nuclear beta catenins, the percentage of positive tumor cells will be estimated from the two paired TMA samples for each case. For nuclear staining, weak (_1) will be defined functionally as having to view nuclei at X400 to confirm nuclear accumulation. Moderate (_2) staining could be viewed at X200 and the blue hematoxylin nuclear counterstain. In strong (_3) staining, the nuclear counterstain will no longer be visible in the majority of nuclei. The staining on the entire array will be performed in the MSKCC clinical immunohistochemistry facility on two occasions and each scored independently.

Plasma and Whole Blood Analysis

DNA will be extracted from whole blood to serve as normal tissue control for tumor studies outlined under: "core sample #1 and #2– Nucleic acid changes". In addition, DNA samples will be analyzed for genetic factors contributing to the subject's response to sorafenib in terms of pharmacodynamics, efficacy and tolerability. Such genetic factors may include genes for drug-metabolizing enzymes, drug transport proteins, genes within the target pathway or other genes believed to be related to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. Plasma specimens will be also be utilized to evaluate known and novel markers (peptides/proteins and drug metabolites) of response and/or resistance to disease.

11.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

11.1 General Considerations

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

11.2 Sorafenib (BAY 43-9006, Nexavar; NSC 724772 / IND #116279) / Placebo

- **Chemical Name** (4-{3-[4-chloro-3-(trifluoromethyl)-phenyl] ureido}-phenoxy)-N2-methylpyridine-2-carboxamide-4-methyl-benzensulfonate.
- **Other Names** BAY 43-9006; Nexavar®; sorafenib; BAY 54-9085 (tosylate salt)
- **Classification** Multi-kinase inhibitor
- **Molecular Formula** $C_{12}H_{16}ClF_3N_4O_3$ X $C_7H_8O_3S$ M.W.: 637 [g/mole]
- **Description** Round, red 10 mm tablets
- **How Supplied** Sorafenib tosylate is supplied by Bayer Healthcare AG and distributed by the DCTD, and available as 200mg coated 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 200 mg tablets are packaged in HDPE bottles containing 140 tablets.

11.2.1 Availability

Sorafenib and matching Placebo will be provided free of charge by Bayer Pharmaceuticals and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Sorafenib and matching Placebo are supplied as an immediate-release, film-coated, round, red-colored tablet for oral administration. Each Sorafenib tablet contains 200 mg of the free base (i.e., BAY 43-9006). The Sorafenib and Placebo tablets contain croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium lauryl sulfate, and magnesium stearate. For Sorafenib and Placebo, the film coat consists of hydroxypropylmethyl cellulose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active sorafenib.

Each tamper-evident, child-resistant, opaque, high-density polyethylene (HDPE) bottle contains 140 tablets of Sorafenib 200 mg or matching Placebo.

No open-label starter supplies will be available for this study. Initial open-label, patient-specific clinical supplies of sorafenib will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient randomization and should arrive within 7 to 10 days of randomization (see Section 11.2.9)

For **BLINDED (sorafenib or placebo) THERAPY**, each bottle will be labeled with…

- the protocol number (i.e., "A091105")
- the bottle number (i.e., "Bottle 1 of 1)
- the number of tablets (i.e., "140 tablets")
- the patient ID number (e.g., "999999", where "999999" represents a unique patient identifier assigned by ALLIANCE at registration).
- the patient initials (i.e., last initial, first initial, middle initial [e.g., "L, FM"])

- the agent identification (i.e., “Sorafenib 200 mg or Placebo”)
- a blank line for the pharmacist to enter the patient’s name
- administration instructions (i.e., “Take ___ tablets once daily.”)
- storage instructions (i.e., “Store at controlled room temperature, not to exceed 25ºC (77ºF).”)
- emergency contact instructions
- a Julian date

For **CROSSOVER (open label sorafenib) THERAPY**, each bottle will be labeled with …

- the protocol number (i.e., “A091105”)
- the bottle number (i.e., “Bottle 1 of 1)
- the number of tablets (i.e., “140 tablets”)
- the patient ID number (e.g., “999999", where “999999” represents a unique patient identifier assigned by ALLIANCE at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., "L, FM"])
- the agent identification (i.e., “Sorafenib 200 mg)
- a blank line for the pharmacist to enter the patient’s name
- administration instructions (i.e., “Take __ tablets once daily.”)
- storage instructions (i.e., “Store at controlled room temperature, not to exceed 25ºC, 77ºF).”)
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2013 = 13, 2014 = 14) and a day count (e.g., January 1 = 001, December 3 = 365). For example, a bottle labeled and shipped on January 1, 2013 would have a Julian date of ‘13001’ and a bottle labeled and shipped on December 31, 2014 would have a Julian date of ‘14365’. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both Sorafenib and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30AM and 4:30PM Eastern Time.

11.2.2 Drug Ordering, transfers, returns, and accountability

NOTE: **No open-label starter supplies will be available for this study. Initial open-label, patient-specific clinical supplies of sorafenib will be shipped from the Pharmaceutical Management Branch to the registering investigator at the time of re-registration and should arrive within seven to ten days (see Section 5.5)**.

BLINDED (Sorafenib or Placebo) THERAPY (Active and Placebo Arms)

No blinded starter supplies will be available for this study. Blinded, patient specific supplies will be sent to the registering investigator at the time of randomization and should arrive within 7 to 10 days. Randomization will be performed by the ALLIANCE Statistics and Data Center. The assigned ALLIANCE patient ID number must be recorded by the registering institution for proper bottle dispersion. Once a patient has been registered with

the ALLIANCE Statistics and Data Center, the ALLIANCE Statistics and Data Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the ALLIANCE Statistics and Data Center the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx Ground (delivery within 5 days). Thus, if a patient is registered on Monday, ALLIANCE would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States sites could expect to receive their order approximately Tuesday or Wednesday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the ALLIANCE Statistics and Data Center at the time the patient is randomized.

The initial request will be for **1 – 140 tablet bottle** (a **2 cycle / 8 week supply** at a dose of 400 mg [2 * 200 mg tablets] orally once daily) of sorafenib or matching placebo. Six (6) weeks after the initial electronic request (i.e., 2 weeks before the next bottle is needed), sites may reorder an additional **1 – 140 tablet bottle** (a **2 cycle / 8 week supply**) by submitting an agent request through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. Once a CTEP IAM account has been established, go to

https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx to access the OAOP application.

The assigned patient ID number (e.g., "44444") and the patient initials (e.g., "L, FM") should be entered in the "Patient or Special Code" field.

All drug orders will be shipped directly to the registering physician at the shipping address provided on their current Supplemental Investigator Data Form (IDF) on file with CTEP. The registering investigator must maintain an active investigator registration status with CTEP, DCTD through the annual submission of an FDA Form 1572 (Statement of Investigator), a Curriculum Vitae, a Supplemental Investigator Data Form (IDF), and a Financial Disclosure Form (FDF).

For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

NOTE: At the time of disease progression, ALL remaining clinical supplies of blinded sorafenib / placebo should be returned to PMB (see "Drug Returns" below).

CROSSOVER (open label sorafenib) THERAPY (Placebo Arm Only)

At the time of disease progression all patients randomized to placebo will cross over to open label sorafenib. This crossover will require a second registration (see Section 5.5 for re-registration instructions).

No open label starter supplies will be available for this study. Open-label, patient-specific clinical supplies will be sent to the registering investigator at the time the patient is unblinded. This unblinding will be performed by the ALLIANCE Statistics and Data Center. **The patient ID number will NOT change.** Once the patient has been unblinded, the ALLIANCE Statistics and Data Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the ALLIANCE Statistics and Data Center the day the patient is unblinded and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx Ground (generally a five day delivery). Thus, if a patient is

unblinded on Monday, ALLIANCE would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States sites could expect to receive their order approximately Tuesday or Wednesday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the ALLIANCE Statistics and Data Center at the time the patient is unblinded.

The initial request will be for 1 – 140 tablet bottle (an 8 week supply at a dose of two tablets daily) of open label Sorafenib. Six (6) weeks after the initial electronic request (i.e., 2 weeks before the next bottle is needed), sites may reorder an additional 1 – 140 tablet bottle (an 8 week supply at a dose of two tablets daily) through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. Once a CTEP IAM account has been established, go to

https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx to access the OAOP application.

The assigned patient ID number (e.g., “44444”) and the patient initials (e.g., "L, FM") should be entered in the "Patient or Special Code" field.

All drug orders will be shipped directly to the registering physician at the shipping address provided on their current Supplemental Investigator Data Form (IDF) on file with CTEP. The registering investigator must maintain an active investigator registration status with CTEP, DCTD through the annual submission of an FDA Form 1572 (Statement of Investigator), a Curriculum Vitae, a Supplemental Investigator Data Form (IDF), and a Financial Disclosure Form (FDF).

For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

NOTE: At the time of disease progression, ALL remaining clinical supplies of open-label sorafenib should be returned to PMB (see “Drug Returns” below).

Drug Transfers

Bottles MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "999999"') and the patient initials (e.g., "L,FM") must be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "A091105").

Drug Returns

Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "999999") and the patient initials (e.g., "L,FM") should be entered in the "Lot Number" field. A separate line item is required for each patient ID number (e.g., "999999") AND for each phase (i.e. blinded/open label) being returned.

Dispensed bottles with remaining tablets should be documented in the patient-specific NCI Investigational Agent Accountability Record (i.e., logged is as "returned by patient" and logged out as "destroyed on site") and destroyed on site in accordance with institutional policy.

Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "999999") AND for each phase (i.e., blinded/open label) on this protocol.

11.2.3 Storage and Stability

Store intact bottles at controlled room temperature, not to exceed 25ºC. Stability studies are ongoing.

11.2.4 Administration

Sorafenib will be administered orally once daily on an empty stomach (at least 1 hour before or 2 hours after a meal) and with at least 250 ml of water according to the treatment plan (sorafenib absorption was reduced by 29% compared with fasting when administered with high fat meals). Patients should take their daily dose at approximately the same time each day.

Sorafenib undergoes metabolism by hepatic CYP3A4. Inducers of CYP3A4 activity can decrease the systemic exposure of sorafenib. Concomitant administration of sorafenib and CYP3A4 inducers, such as phenytoin, carbamazepine, phenobarbital, rifampin, or St. Johns Wort are not allowed.

11.2.5 Toxicity

The most common adverse events for sorafenib are diarrhea (49.7%), fatigue (39.2%), rash (31.6%), hand-foot syndrome (30.5%), nausea (26.9.1%), anorexia (26.9%), alopecia (26.1%) weight decrease (22.3%), and constipation (20.7%). The vast majority of the reported toxicities were of Grade 1 & 2 in severity.

Gastrointestinal perforation has been reported as an uncommon event in patients taking sorafenib (reported in less than 1% of patients taking sorafenib). In some cases this was not associated with apparent intra-abdominal tumor. Sorafenib therapy should be discontinued in the event of such an event.

Hypertension usually mild-to-moderate early in the course of treatment, may occur and is amenable to management with standard antihypertensive therapy. Blood pressure should be checked within the first two to three weeks of starting sorafenib therapy and then monitored and treated, if required, in accordance with standard medical practice.

Reversible posterior leukoencephalopathy (RPLS) has been reported as an uncommon event in single patients taking sorafenib.

Increases in lipase and amylase have been observed in patients treated with sorafenib. The findings in the single agent pool indicate that 11.8% of all patients had CTC Grade 3 and additional 3.2% had CTC Grade 4 lipase elevations. Amylase was increased to CTC Grade 3 and CTC Grade 4 in 3.3% respectively 0.6% of the patients. In most cases, these elevations were asymptomatic. Hypophosphatemia appears to be associated with sorafenib therapy. There were no instances of severe hypophosphatemia, defined as a serum phosphate value

below 1.0 mg/dL, and there were no clinical manifestations associated with hypophosphatemia.

Sorafenib was infrequently associated with peripheral neuropathy. The timing of these events suggests an inflammatory process rather than a cumulative neurotoxic effect.

11.2.6 Unblinding Procedures

Unblinding can be done only at the time of first disease progression or in the case of an emergency.

Emergency unblinding will be available 24 hours a day, every day, according to the criteria below. Please note that, if treatment is unblinded due to an emergency, the patient must permanently discontinue all protocol therapy.

Unblinding procedures upon progression

CROSSOVER (open label sorafenib) THERAPY (Placebo Arm Only)

1. Site physician deems that the patient has had radiographic or clinical progression.
2. Site staff contacts the Alliance Registration Office at (507) 284-0661 during regular business hours for treatment assignment.
3. If patient was on placebo, site may offer crossover to the patient.
4. Site must enter data within 14 days of unblinding for quality assurance purposes.
5. Site re-registers patient in OPEN (See Section 5.5 for re-registration instructions)
6 Alliance SDC orders drug and site receives open label drug from the Protocol Management Branch (See Section 11.2.2).

Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling 773-702-6800, pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., "A091105")
- Alliance patient ID number (e.g., "999999")
- Patient initials (e.g., "L,FM")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation.

After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

11.3 Nursing Guidelines

11.3.1 Drug should be taken with at least 250 cc of water. Should be taken without food (at least 1 hour before or 2 hours after meals).

11.3.2 Patient may experience flu-like symptoms such as fatigue, fever, Tylenol may be beneficial for these patients.

11.3.3 Monitor CBC. Instruct patients to report signs and symptoms of infection and excessive bruising or bleeding to the MD.

11.3.4 Monitor LFT's.

11.3.5 Patients may experience diarrhea. Please ensure patients have been informed of the possibility of diarrhea from sorafenib. They should be prepared by having medication on hand, such as loperamide. It should be stressed with all patients that, with the development of diarrhea, they need to contact their treating physician immediately for management. See Section 9.0.

11.3.6 Instruct patient to report severe abdominal pain, as pancreatitis is a possibility.

11.3.7 May cause anorexia. Encourage patient to consume small frequent meals.

11.3.8 Monitor for sign/symptoms of hand/foot syndrome. See Section 9.0 for appropriate management.

11.3.9 May cause alopecia, instruct patient of this possibility

11.3.10 Monitor for rash. Toxic epidermal necrolysis is a rare but serious condition. Instruct patient to report any rash to MD.

11.3.11 As there are many potential drug interactions, instruct patient not to start any new medication (including OTC's or herbal products) without checking with their MD first.

11.3.12 Monitor blood pressure. Instruct patients who are self-monitoring to report any increase in their blood pressure to the study team.

11.3.13 Nausea and vomiting may occur. Administer antiemetics as necessary and monitor for their effectiveness.

11.3.14 Bleeding has been seen (GI, respiratory, CNS). Instruct patient to report any bleeding to the study team immediately. If bleeding is severe, seek out emergency medical attention.

11.3.15 Numerous electrolyte imbalances may occur (hypernatremia, hypocalcemia, hypokalemia). Monitor chemistry panel and report any abnormalities to the treating physician.

12.0 ANCILLARY THERAPY

12.1 Supportive Care

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, allopurinol, rasburicase etc., when appropriate.

- For patients who experience grade 3 or 4 diarrhea, institute prophylactic anti-diarrheal therapy with agents such as loperamide and/or diphenoxylate/atropine, given around the clock.
- Preventive skin care should be taken to help prevent/decrease the severity of PPE. Patients should use moisturizers, treat calluses, and should report in any rash or symptoms immediately.

12.2 Treatment with other chemotherapeutic agents

Treatment with other chemotherapeutic agents and/or radiation therapy is prohibited while on protocol therapy.

12.3 Palliative radiation therapy

Palliative radiation therapy may not be administered. Irradiate a symptomatic lesion, or one that may produce disability (e.g., unstable femur) prior to study initiation, provided other measurable disease is present.

12.4 Surgery

Patients who require surgery during protocol treatment may proceed as such, unless the surgery involves resection of DT or DF. Sorafenib/placebo should be held prior to and after surgery, for a maximum of 28 days. If the patient requires an interruption of > 28 days, then they will be removed from protocol therapy.

12.5 Alliance Policy Concerning the Use of Growth Factors

The use of colony stimulating factors such as erythropoietin, filgrastim (G-CSF), pegfilgrastim and sargramostim (GM-CSF) is discouraged.

13.0 Criteria For Response, Progression, And Relapse (Solid Tumors)

Treatment Evaluation Using RECIST v1.1 Guideline

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

13.1 Schedule of Evaluations

Refer to the Study Calendar (section 7.0) for timing of disease assessments for this study.

13.2 Definitions of Measurable and Non-Measurable Disease

13.2.1 Measurable Disease

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

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

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

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

13.2.2 Non-Measurable Disease

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

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

13.3 Guidelines for Evaluation of Measurable Disease

13.3.1 Measurement Methods

All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

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

13.3.2 Acceptable Modalities for Measurable Disease

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

As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

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

Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET

scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

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

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

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

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

13.3.3 Measurement at Follow-up Evaluation

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.

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

13.4 Measurement of Effect

13.4.1 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 13.2.1) up to a maximum of 3 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in Section 13.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 3 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

13.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 13.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with Section 13.4.3.

13.4.3 Response Criteria

All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 13.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

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

Evaluation of Target Lesions

Complete Response (CR): All of the following must be true:

a. Disappearance of all target lesions.

b. Each target lymph node must have reduction in short axis to <1.0 cm.

Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 13.4.1).

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 13.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 13.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

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

Complete Response (CR): All of the following must be true:

a. Disappearance of all non-target lesions.

b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (**NOTE:** Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 13.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

13.4.4 Overall Objective Status

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

For Patients with Measurable Disease

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

* See Section 13.4.3

13.4.5 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms in the opinion of the treating physician.
- Decline in performance status of >1 level on ECOG scale.

14.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

14.1 Clinical Follow-Up Phase

- Patients who are in complete response (CR), partial response (PR), or stable disease (SD) will receive treatment indefinitely and until progression (PD) or unacceptable adverse events. Subsequent off-study treatment is at the discretion of their attending physician. See Section 13.4 for the criteria for assessing response.
- Patients who discontinue for non-PD reasons and prior to 1 year post-randomization will remain in Clinical Follow-Up until they have reached 1 year post-randomization. Thereafter, they will begin the Survival and Disease Status Follow-Up Phase.
- Patients on the placebo arm may cross over to the sorafenib arm, upon PD, and continue in Clinical Follow-Up. Patients who undergo surgical excision of their tumors must start sorafenib within 28 days of surgery. After excision, the patient must have measureable disease (per RECIST v1.1). Patients will begin Survival and Disease Status Follow-Up upon subsequent PD.
- Patients on the sorafenib arm will begin Survival and Disease Status Follow-Up upon PD.
- As of Update #06: Patients unblinded following the Alliance Data Safety Monitoring Board release of study data (November 17, 2017) while receiving placebo and prior to PD, may cross over to the sorafenib arm and continue in Clinical Follow-Up. Patients who undergo surgical excision of their tumors must start sorafenib within 28 days of surgery. After excision, the patient must have measurable disease (per RECIST v1.1). Patients will begin Survival and Disease Status Follow-Up upon subsequent PD.

14.2 Survival and Disease Follow-Up Phase

During the Survival and Disease Follow-Up Phase, patients are monitored for off-treatment PD, long-term adverse events, new primaries, and survival. Here, patients should be followed per standard of care. Submit the appropriate form(s), every 6 months until PD. Thereafter, annually until a maximum of 3 years following randomization.

14.3 Managing ineligible and canceled patients and major protocol violations

Data must be submitted per Section 6.0 for patients deemed ineligible or canceled. See also the Forms Packet for full details of data submission requirements.

14.4 Extraordinary Medical Circumstances

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

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on study forms
- Follow the patient for survival or secondary malignancy for a minimum of 3 years following randomization.

15.0 STATISTICAL CONSIDERATIONS

15.1 Primary Endpoint

We are comparing the progression-free survival (PFS) rate of patients will receive either sorafenib or placebo in and using randomized double-blinded placebo controlled phase 3 study design. PFS is defined as the time from randomization to the first occurrence of progression or death due to any cause. If no event exists, the PFS will be censored at the last scheduled disease assessment on study. Patients who have reached their maximum follow-up and have remained progression-free will be censored for progression at the date of their last disease assessment. Data following cross over will be analyzed and summarized separately from the data from the main course of treatment for these patients. Intention to treat principles will be used for analyzing the primary endpoint, excluding patients deemed ineligible due to improper histology having been determined on the basis of information available prior to randomization.

Update #06: Patients enrolled onto this trial were unblinded (November 17, 2017) and those receiving placebo were allowed to crossover to sorafenib, if PD had not yet occurred. This section has been updated to address this for the analysis.

15.1.1 Sample Size & Statistical Power

The placebo (control) arm is expected to have a median PFS of 6 months. We consider improving PFS to a median of 15 months (HR of 0.40, control versus experimental arm) after treatment with sorafenib (experimental arm) to be a significant clinical improvement of PFS in this patient population. We will be using a 1-sided Log-Rank test to determine the whether sorafenib significantly improves the PFS rate. We have designed this study with one planned interim analysis which is designed to stop the trial for "futility" and there is no interim analysis for efficacy. We are also using a 2:1 randomization scheme to increase accrual for the as well as to reduce the number of patients having biopsies while receiving treatment on a placebo arm. There are two stratification factors for randomization and in addition to randomizing membership, namely, Intra- versus Extra-abdominal disease, and Baseline Level of Pain (BPI Item #3: 0 to <3, 3 to <7, versus 7 to 10).

Using 75 patients, we have 90% power at a 1-sided significance level of 0.025 to detect a median PFS 15 months (Ho: median PFS of 15 months for sorafenib) improvement over the placebo arm (Ho: median PFS of 6 months, resulting in a HR=0.40), using a 2:1 randomization favoring the sorafenib arm, assuming we will enroll 4 patients per month, and requiring 12 months of follow-up for all patients. There is 50% chance of terminating the study for futility at the time of the interim analysis if the true median PFS in the sorafenib arm is 6 months. The other type of decision error we could make based on our sample is if we were declare sorafenib as ineffective (ie, "accept" Ho), when in fact the truth is that is effective in our sampling population. In this situation, we have a 1.39% chance of stopping for futility (ie, declaring sorafenib ineffective) at the interim analysis if the median PFS for the sampling population is 15 months.

Decision Rule: We will randomize a total of 75 patients (25-placebo, 50-sorafenib) and observe patients until we have reached 52 PFS events for the efficacy analysis. In the event the median PFS in the control group is larger than expected and long-term follow-up becomes a concern, we will perform the final efficacy analysis after 52 events are observed or after all evaluable patients have been followed for at least 3 years, whichever occurs earlier. If the 1-sided p-value associated with the Log-Rank test is < 0.0255 (corresponding to an observed HR of 0.5776), we will consider sorafenib as having shown promising activity in this population and may recommend it for further testing.

Inefficacy/Futility Analysis: We will evaluate the observed PFS of the arms when 45% of the PFS events required for the final efficacy analysis (i.e., 24) have been observed.

We will terminate the study for futility if the p-value associated with the test statistic from a Log-Rank is at least 0.5025 (corresponding to an observed HR of 1.0027). Otherwise, we will continue to complete full enrollment.

Although the primary endpoint will be evaluated using the first 75 evaluable patients, final efficacy results will further report results (e.g., publication, presentation) using all patients evaluable for determining PFS and so that patient enrolled beyond these 75 may contribute to these estimates.

15.1.2 Maximum Accrual

Maximum accrual is 83 patients, which includes 10% over accrual to replace those patients deemed ineligible due to improper histology having been determined on the basis of information available prior to randomization.

15.1.3 Study Duration

Assuming a rate of 4 patients per month, the anticipated duration of accrual 21 months, (1.7 years). Assuming 12 months of follow-up (with tests required for disease assessment, per the Study Calendar) for every patient to assess the primary endpoint will bring maximum duration to 33 months (2.7 years) after the study opens to accrual, at which time all patients will be evaluable to assess the primary endpoint. This estimate may be adjusted if the study requires suspension for endpoint or toxicity concerns. All patients will be followed for a maximum of 3 years to capture data regarding survival, progression, and late occurring events.

15.1.4 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrails.gov" web site. The Primary and Secondary Endpoints (ie, "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting and as of Update #05, the initial estimated completion date for the Primary Endpoint of this study is 3 years after the study closes to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is the time the last patient registered has been followed for at least 12 months, but may be as high as 3 years, depending on the rate at which the events for the primary endpoint occur and given that the analysis is "event" (vs "time") driven (per 15.1.1).

We note that the PECD may be further adjusted if the study requires suspension for toxicity concerns or re-design due to the planned interim look at the median PFS rate observed in the control arm.

15.1.5 Accrual Monitoring

We will be actively seeking participation from at least one of the other entities in the newly formed National Cancer Trials Network (formerly Cooperative Groups). We will follow the CTEP guidelines for monitoring accrual (http://ctep.cancer.gov/protocolDevelopment/docs/slow_accrual.pdf) for phase III studies. These rules are associated with accrual rates observed at the 5th, 6th, and 8th quarters following activation.

15.1.6 Evaluability & Assessment of Patients

We will perform an intent-to-treat analysis to assess the primary endpoint and all eligible patients will be included in the futility and efficacy analysis for progression-free survival, excluding patients deemed ineligible due to improper histology having been determined on the basis of information available prior to randomization. Given that the central-review of scans and pathology reports will be completed at a later date, we will consider the local review as the factor determining eligibility and evaluability for the progression-free survival endpoint. We will consider performing a secondary analysis, without such cases identified as discordant from the local review and to assess the impact of such cases on the results of the primary endpoint.

Patients on treated on the control/placebo arm are allowed to crossover to the sorafenib upon experiencing progressive disease. We will consider censoring disease assessments at the date of surgical or radiotherapy intervention in patients receiving such care, given that the patients are receiving non-protocol specified therapy (i.e. intervention) which may impact endpoint(s) beyond the treatment effect we are seeking to evaluate.

Patients who were receiving placebo and unblinded prior to progression, effective November 17, 2017, and crossing over to sorafenib, will be censored for the primary endpoint and at their most recent disease assessment prior to initiating crossover treatment.

15.2 Secondary Endpoints

NOTE: All secondary analyses and endpoints (except survival data/analyses) will exclude/censor data for patients (as applicable) receiving crossover treatment, due to the unblinding of study treatment effective November 17, 2017. The summary of data collected during crossover will further separate such patients from those who crossed over upon PD occurring during initial blinded treatment.

15.2.1 Adverse Events

We will use NCI CTCAE v4.0 to assess toxicity. Frequency tables, summary statistics, and categorical analysis will be used to compare the distributions of toxicity for patients treated with sorafenib vs placebo. Data for patients who have crossed over or having received surgical or radiotherapy intervention will be summarized independently from their primary course of study treatment.

Data & Safety Monitoring

The principle investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Alliance Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the Alliance Statistics and Data Center.

Adverse Event Stopping Rules

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

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

- an excessive death rate, defined as 1% or higher mortality attributed to study drug, or
- if 3 or more patients in the first 15 treated patients experience a grade 3 or higher adverse event.
- We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

15.2.2 Surgical Intervention

Surgical excision/amputation is a therapeutic and palliative options for managing this disease. Time to surgical intervention during treatment is defined as time between randomization to the patient undergoing therapeutic surgical resection for this disease. If no event exists, patients will be censored at their date of last treatment for this event. A log rank test will be used to compare the distributions of time to surgical intervention between the two arms using a 2-sided test and alpha=0.05 level of significance. Kaplan-Meier (1958) methodology will be used to estimate various time points (e.g. 1 year rate, 2 year rate, etc.) and 95% Confidence Intervals will be calculated for these estimates. Surgery will be classified by outcome (e.g. complete-macroscopic, complete-microscopic, or partial), type, location (e.g. limb), thereafter analyzed by categorical analysis and descriptive statistics. Non-parametric methods will be used, as appropriate. See the note at the beginning of Section 15.2.

15.2.3 Overall Survival (OS)

Survival will be calculated as the time between the date of randomization to until death. Patients who are alive at the time of the analysis will be censored for survival at the most recent date of the last contact (or lost to follow-up). Kaplan-Meier (1958) methodology and log rank tests will be used to compare OS between the groups at various time points (eg, 1 year rate, 2 year rate, etc) and 95% Confidence Intervals will be calculated for these estimates. Data following crossover will be analyzed and summarized separately from the main course of treatment for these patients. See the note at the beginning of Section 15.2.

15.2.4 Tumor Response

Patients will be classified for disease status according to RECIST v1.1 (see Section 13.0). We will compare best objective status for the two treatment arms and using the Cochran-Mantel-Haenszel test. Duration of response will be calculated as the time between first tumor response and progression. Patients will be censored for duration of response at the date of last assessment if they have reached maximum follow-up without PD (or are lost to follow-up without PD). Kaplan Meier methodology will be used to estimate the distribution of duration of response and the Log-Rank test will be used to test for a difference in duration of response between the two arms. See the note at the beginning of Section 15.2.

15.3 Correlative Companion Study Endpoints

15.3.1 Statistical design- Imaging study

About 50% (38 patients) are expected to have extra-abdominal disease and be evaluated by MRI. Percent change in tumor size by RECIST and percent changes in MRI T2 signal will be calculated at baseline and at response evaluation every 8 weeks. Best RECIST response (ordinal variable) and percent T2 signal change (continuous) will be correlated by Spearman's rho. Careful attention will be paid to patients having received sorafenib after PD on the placebo arm, which may involve censoring or adjusting the patient baseline at the initiation of sorafenib. The percent changes in MRI T2 signal from Week 8 to subsequent imaging will be compared between groups with >30% pain palliation using t-test or a nonparametric alternative (e.g., Wilcoxon rank-sum test). Data, analyses, and censoring will also follow the note described in Section 15.2.

15.3.2 Statistical design- A091105-H01, QOL study

Pain palliation will be defined at each time point as ≥30% decrease from baseline in the worst pain intensity score (BPI-SF "worst pain" item), with neither a concomitant ≥30% increase in average daily use of any opioid narcotic, nor addition of any new opioid narcotic, relative to baseline.

A patient must meet the criteria for pain palliation at both Week 8 and Week 12 to be considered a responder for the primary endpoint. The primary statistical analysis will include all eligible and consented patients who provide baseline pain and pain medication data, have a baseline pain level greater than or equal to 3, and who initiate treatment. Any patient who does not provide pain and pain medication data at Week 8 and Week 12 will be considered a non-responder (i.e., a "failure" for the endpoint but will be included in the denominator).

Pain progression at a given time point is defined as a ≥30% increase compared with baseline in the worst pain intensity score (BPI-SF "worst pain" item) or either a ≥30% increase in the average daily use of any type of opioid narcotic or the addition of a new opioid narcotic compared with baseline. Time to pain progression is defined as the date of randomization to the earliest date that pain progression is observed. Patients not reporting pain progression will be censored at their date of last pain and pain medication data reporting. Time to pain palliation is defined as the date of randomization to the earliest date that confirmed pain palliation is observed. Duration of pain palliation is defined for all patients who experience confirmed pain palliation and is the time from the earliest date that confirmed pain palliation is observed to the earliest date that pain progression is observed. Patients not reporting pain progression will be censored at their date of last pain and pain medication data reporting.

For the primary analysis, the rate of pain palliation at Week 8 confirmed as Week 12 will be compared between arms using a two-sided alpha=0.05 chi-squared tests at the time of the final analysis.

For the exploratory hypotheses, median time to pain palliation, duration of response, and time to pain progression will be estimated for each arm using Kaplan-Meier estimates and will be compared between arms using a log- rank test. All other items/questionnaires will be scored according to published scoring guidelines and statistical analysis will include all eligible and consented patients who provide data for the given outcome and who initiate treatment (i.e., the requirement for baseline pain to be >/=3 is not in effect for the other outcomes). Descriptive statistics will include means, standard deviations, medians, and ranges for each continuous or ordinal scale/subscale/item by group at each time point. Descriptive graphical techniques will include mean plots by group for each continuous or

ordinal scale/subscale/item. Relative frequencies of responses for each ordinal item will also be generated at each time point by group.

Each patient-reported outcome will be compared between arms at each time point using two-sample t-tests followed by analysis of covariance adjusting for the baseline value at each time point. Finally, a linear mixed-effects model with random intercepts and slopes will also be used to compare each continuous/ordinal patient-reported outcome over time between arms. In these linear mixed-effects models, the post-baseline score is the modeled outcome and the predictors are the baseline score of the given patient-reported outcome, arm, time (treated as a continuous variable and measured at the planned week of assessment), and treatment-by-time interaction.

Missing data will be handled in a number of ways. Baseline patient/disease characteristics will be compared between patients who provide data and patients who have missing data for each endpoint. We will also graphically explore patterns of missing data. All analyses will be completed using all available data, followed by analyses completed using imputed data using the arm minimum followed by the arm maximum. Lastly, we will employ pattern mixture models for longitudinal analyses. Output from all analyses will be compared to assess the degree to which missing data impacts study results.

For all statistical analyses, p-values <0.05 will be considered statistically significant. For interpreting the clinical significance of effects, 0.2, 0.5, and 0.8 SD effects will be considered as small, moderate, and large based on Cohen[30] throughout.

Power: We anticipate ~70% of eligible patients who initiate treatment will be evaluable for the primary analysis of this companion study. With 51 patients contributing data for the primary analysis, the primary analysis has 80% power to detect a 40% difference in the rate of pain palliation at Week 8 confirmed at Week 12 between arms (50% pain palliation in the sorafenib arm versus 10% in the placebo arm) using a two-sided alpha=0.05 chi-squared test. Power for a 45% difference (55% pain palliation in the sorafenib arm versus 10% in the placebo arm) is 87%. These power calculations assume 2:1 randomization. This power calculation conservatively assumes that 10% of patients in the placebo arm will experience a "placebo effect" such that patients report improvement in pain despite being treated with a placebo.

15.3.3 Statistical design for correlative study A091105-ST1

See the note in Section 15.2, which will apply to all analyses for this section A091105-ST1.

Statistics for Core #1: Archival FFPE and TMA studies: Associations among the possible predictors of response to sorafenib and CTNNBI mutations will be examined using Fisher's exact test, Kruskal-Wallis test, or Spearman's correlation coefficient as appropriate. Variables considered include *CTNNB1* genotype, tumor size, tumor site, gender, age at initial diagnosis, and primary versus recurrent disease. Strata will be compared by using the log-rank test. Multivariate models will be constructed by introducing all variables aforementioned simultaneously into the model and then eliminating variables using the backward selection method. *P* values will be two-tailed and considered significant at alpha 0.05. Analyses will be conducted using SAS for Windows (release 9.3; SAS Institute, Cary, NC).

Statistics for Core #2: Microarray: A two-sided t-test will be used to identify differentially expressed genes on log transformed data and those with a twofold change. False discovery rate (FDR) will be assessed by permutation testing (n = 1000) of the sample group labels. The selection approach is to first compute two t -tests and fold changes for each comparison between pre- treatment and day 8 versus the normal skin biopsy. Genes that have a nominal p value < 0.01 and fold > 2 for each comparison will be selected. To assess FDR,

permutation testing of the same selection will be performed 1000 times and the sample group labels switched around in each permutation. Java TreeView color maps will be generated. To unravel a treatment-specific gene expression signature, the analysis will identify over- and under-expressed genes in pre- treatment and day 8 biopsies as compared to all control samples (germlineDNA extracted from whole blood). Using Sigterms, sorafenib associated gene signature will search for Gene Ontology (GO) annotation terms, gene sets curated by the Molecular Signature Database (MSigDB, v2.5 and top enriched transcription factor sequence motifs. Enrichment will be assessed by one-sided Fisher's exact test with estimated FDR.

Statistics for Core #3 and 4: For each paired sample, differences in protein levels will be compared by paired t-test. This sample size of 75 patients will allow 93% power to detect 1 standardized difference. Quantitative changes in IHC score of VEGF, PDGFR and β-catenin cytoplasm/nuclear ratio will be correlated with disease status at 1 year by Fishers exact test.

15.3.4 Pain Palliation

See Section 15.3.2 for details**.**

15.4 Inclusion of Women and Minorities

This study will be available to all patients regardless of race, gender, or ethnicity. Total accrual is 83 patients. The newly formed Alliance does not have a history of accrual to sarcoma trials in this population and we are basing our estimates on what has been observed at MSKCC. Here, we expect at least 5% of patients to be Hispanic or Latino, 5% to be African American, and 65% to be female.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	2	0	0	7
White	39	20	5	2	66
More Than One Race	0	0	0	0	0
Total	44	22	5	2	73

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	7	3	0	0	10
More Than One Race	0	0	0	0	0
Total	7	3	0	0	10

Ethnic Categories:

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

Not Hispanic or Latino

Racial Categories:

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

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

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

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

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

16.0 ADVERSE EVENT REPORTING

16.1 Solicited Adverse Events

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

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Fatigue	General disorders
Papulopustular rash	Skin and subcutaneous tissue disorders
Palmar-plantar erythodysesthesia syndrome	Skin and subcutaneous tissue disorders
Diarrhea	Gastrointestinal disorders
Anorexia	Metabolism and nutrition disorders
Nausea	Gastrointestinal disorders
Vomiting	Gastrointestinal disorders
Abdominal pain	Gastrointestinal disorders
Mucositis oral	Gastrointestinal disorders
Hypertension	Vascular disorders
Arthralgia	Gastrointestinal disorders
Myalgia	Gastrointestinal disorders

16.2 Expedited Adverse Event Reporting

Investigators are required by Federal Regulations to report serious adverse events as defined below. Investigators are required to notify the Alliance Protocol Operations Office the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the CTEP Adverse Event Reporting System (CTEP-AERS). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

In the rare event when Internet connectivity is disrupted, a 24 hour notification is to be made to the NCI by telephone at 301-897-7497. An electronic report MUST be submitted upon re-establishment of Internet connection.

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

Be sure to read this entire protocol section, as requirements are described in both the table and bullet points following the table below. Note that the table below and the Additional Instructions or Exclusions may conflict. The Additional Instructions or Exclusions are protocol-specific, and in the case of a conflict, the Additional Instructions or Exclusions supersede the table.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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

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

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

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

- 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 (see below).

• 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.

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

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- A091105 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.
- Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.
- A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

- All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

  Secondary Malignancy:

  A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

  CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy

  Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

  Second Malignancy:

  A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

  Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

  Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

- Treatment expected adverse events include those listed in Section 9.0 and in the package insert.

16.3 CAEPR for Sorafenib

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; Nexavar) (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			
	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 increased			***Blood bilirubin increased (Gr 3)***
Creatinine increased			***Creatinine increased (Gr 3)***
		Electrocardiogram QT corrected interval prolonged	
	GGT increased		
INR increased			***INR increased (Gr 3)***
	Investigations - Other (bicarbonate-serum low)		

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 4.0 Term) [n= 2571]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
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)***
	Hypercalcemia		
Hyperglycemia			***Hyperglycemia (Gr 3)***
	Hyperkalemia		***Hyperkalemia (Gr 3)***
	Hypernatremia		
Hypoalbuminemia			***Hypoalbuminemia (Gr 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; Nexavar) (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)***
		Erythema multiforme	
Palmar-plantar erythrodysesthesia syndrome			***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 reasonable possibility that sorafenib (BAY 43-9006; Nexavar) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (Thrombotic microangiopathy [e.g., TTP or HUS]); Febrile neutropenia[6]

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Palpitations; Pericardial effusion; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
ENDOCRINE DISORDERS - Adrenal insufficiency; Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (color vision deficits); Eye disorders - Other (light to dark adaptation); Eye disorders - Other (retinal vein occlusion); 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**;** Nexavar) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

17.0 REFERENCES

1. Fletcher CDM, Unni KK, Mertens F. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press; 2002. World Health Organization classification of tumours.

2. de Bree E, Keus R, Melissas J, Tsiftsis D, van Coevorden F. Desmoid tumors: need for an individualized approach. Expert Rev Anticancer Ther. 2009 Apr;9(4):525-35. Review.

3. Lewis JJ, Boland PJ, Leung DH, Woodruff JM, Brennan MF. The enigma of desmoid tumors. Ann Surg. 1999 Jun;229(6):866-72; discussion 872-3

4. Smith AJ, Lewis JJ, Merchant NB, Leung DH, Woodruff JM, Brennan MF. Surgical management of intra-abdominal desmoid tumours. Br J Surg. 2000 May;87(5):608-13.

5. Fiore M, Rimareix F, Mariani L, Domont J, Collini P, Le Péchoux C, Casali PG, Le Cesne A, Gronchi A, Bonvalot S. Desmoid-type fibromatosis: a front-line conservative approach to select patients for surgical treatment. Ann Surg Oncol. 2009 Sep;16(9):2587-93. Epub 2009 Jul 1

6. Soft Tissue Sarcoma, National Comprehensive Cancer Network Guidelines, 2011.

7. Interim results of ARST0321: A Phase II Study of Sulindac and Tamoxifen in Patients with Desmoid Tumors that are Recurrent or Not Amenable to Standard Therapy

8. Constantinidou A, Jones RL, Scurr M, Al-Muderis O, Judson I. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. Eur J Cancer. 2009 Nov;45(17):2930-4. Epub 2009 Sep 18.

9. Skapek SX, Ferguson WS, Granowetter L, Devidas M, Perez-Atayde AR, Dehner LP, Hoffer FA, Speights R, Gebhardt MC, Dahl GV, Grier HE; Pediatric Oncology Group. Vinblastine and methotrexate for desmoid fibromatosis in children: results of a Pediatric Oncology Group Phase II Trial. J Clin Oncol. 2007 Feb 10;25(5):501-6.

10. Azzarelli A, Gronchi A, Bertulli R, Tesoro JD, Baratti D, Pennacchioli E, Dileo P, Rasponi A, Ferrari A, Pilotti S, Casali PG Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. Cancer. 2001 Sep 1;92(5):1259-64.

11. van der Hul RL, Seynaeve C, van Geel BN, Verweij J. Low Dose Methotrexate and Vinblastine, Given Weekly to Patients With Desmoid Tumours, is Associated With Major Toxicity. Sarcoma. 2003;7(3-4):153-7

12. Heinrich MC, McArthur GA, Demetri GD, Joensuu H, et. al. Clinical and molecular studies of the effect of imatinib on advanced aggressive fibromatosis (desmoid tumor). J Clin Oncol. 2006 Mar 1;24(7):1195-203.

13. Heinrich MC, Joensuu H, Demetri GD, Corless CL, et. al. Imatinib Target Exploration Consortium Study B2225. Phase II, open-label study evaluating the activity of imatinib in treating life-threatening malignancies known to be associated with imatinib-sensitive tyrosine kinases. Clin Cancer Res. 2008 May 1;14(9):2717-25.

14. Chugh R, Wathen JK, Patel SR, Maki RG, Meyers PA, Schuetze SM, Priebat DA, Thomas DG, Jacobson JA, Samuels BL, Benjamin RS, Baker LH. Efficacy of imatinib in aggressive fibromatosis: results of a phase II multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. Clin Cancer Res. 2010 Aug 19.

15. **Gounder MM**, Lefkowitz RA, Keohan ML, D'Adamo DR, Hameed M, Antonescu CR, Singer S, Stout K, Ahn L, Maki RG. Activity of Sorafenib against Desmoid Tumor/Deep Fibromatosis.Clin Cancer Res. 2011 Jun 15;17(12):4082-90. Epub 2011 Mar 29

16. Cleeland CS, Sloan JA; ASCPRO Organizing Group. Assessing the Symptoms of Cancer Using Patient-Reported Outcomes (ASCPRO): searching for standards. J Pain Symptom Manage. 2010 Jun;39(6):1077-85. Review.

17. Guglielmi G, Cifaratti A, Scalzo G, Magarelli N. Imaging of superficial and deep fibromatosis. Radiol Med. 2009 Dec;114(8):1292-307. Epub 2009 Sep 30.

18. Sundaram M, McGuire MH, Schajowicz F. Soft-tissue masses: histologic basis for decreased signal (short T2) on T2-weighted MR images. AJR Am J Roentgenol. 1987 Jun;148(6):1247-50.

19. McCarville MB, Hoffer FA, Adelman CS, Khoury JD, Li C, Skapek SX. MRI and biologic behavior of desmoid tumors in children. AJR Am J Roentgenol. 2007 Sep;189(3):633-40.

20. Lazar AJ, Hajibashi S, Lev D. Desmoid tumor: from surgical extirpation to molecular dissection. Curr Opin Oncol. 2009 Jul;21(4):352-9. Review.

21. Alman BA, Li C, Pajerski ME, Diaz-Cano S, Wolfe HJ (1997) Increased beta-catenin protein and somatic APC mutations in sporadic aggressive fibromatoses (desmoid tumors). Am J Pathol 151: 329-334.

22. W. A. Messersmith, P. LoRusso, J. M. Cleary, A. Dasari, X. Zhang, M. N. Shaik, R. D. Courtney, S. Randolph, G. ShapiroA phase I dose-escalation study of the novel gamma secretase inhibitor PF-03084014 in patients (pts) with advanced solid tumors. J Clin Oncol 29: 2011 (suppl; abstr 3100)

23. Dodge ME, Lum L. Drugging the cancer stem cell compartment: lessons learned from the hedgehog and Wnt signal transduction pathways. Annu Rev Pharmacol Toxicol. 2011 Feb 10;51:289-310. Review

24. Birgit Mosch, Bettina Reissenweber, Christin Neuber, and Jens Pietzsch. Eph Receptors and Ephrin Ligands: Important Players in Angiogenesis and Tumor Angiogenesis. Journal of Oncology Volume 2010 (2010)

25. Vandevenne JE, De Schepper AM, De Beuckeleer L, Van Marck E, Aparisi F, Bloem JL, Erkorkmaz Z, Brijs S (1997) New concepts in understanding evolution of desmoid tumors: MR imaging of 30 lesions. *European radiology* 7(7): 1013-9

26. Koh DM, Collins DJ (2007) Diffusion-weighted MRI in the body: applications and challenges in oncology. *Ajr* 188(6): 1622-35

27. Pocock SL, Simon JR: Sequential treatment assignment with balancing for prognostic factors in the controlled clincal trial. Biometrics 31:103-115, 1975.

28. Bretscher M, Rummans T, Sloan J, et al. Quality of life in hospice patients: a pilot study. Psychosomatics. 1999; 40:309-313.

29. Cleeland CS, Ryan KM (1994 March). Pain Assessement: Global Use of the Brief Pain Inventory. Ann Acad Med. 23(2): 129-38.

30. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 1988.

31. Grunberg SM, Groshen S, Steingass S, Zaretsky S, Meyerowitz B. Comparison of conditional quality of life terminology and visual analogue scale measurements. Quality of Life Res. 1996; 5:65-72.

32. Gudex C, Dolan P, Kind P, Williams A. Health state valuations from the general public using the visual analogue scale. Quality of Life Res. 1996; 5:521-531.

33. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR; Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002; 77(4):371-83.

34. Hyland ME, Sodergren SC. Development of a new type of global quality of life scale and comparison and preference for 12 global scales. Quality of Life Res. 1996; 5:469-480.

35. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16(1):139-44.

36. Sloan JA, Mahoney MR, Sargent DJ, et al. Was it worth it (WIWI)? Patient satisfaction with clinical trial participation: Results from North Central Cancer Treatment Group (NCCTG) phase III trial N0147. J Clin Oncol 29: 2011 (suppl; abstr 6122)

37. Sloan JA, O'Fallon JR, Suman VJ, Sargent DJ. Incorporating quality of life measurement into oncology clinical trials. Proc Am Stat Assoc. 1998:282-287.

38. Sriwantanakul K, Kelvie W, Lasagna L, Calimlim JF, Weis OF, Mehta G. Studies with different types of visual analog scales for measurement of pain. Clin Pharmacol Ther. 1983; 34:234-239.

39. Tan AD, Novotny PJ, Kaur JS, Buckner JC, Schaefer PL, Stella PJ, Kuebler JP, Sloan JA. A patient-level meta-analytic investigation of the prognostic significance of baseline quality of life (QOL) for overall survival (OS) among 3,704 patients participating in 24 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center (MC) oncology clinical trials. J Clin Oncol. 2008; 26(May 20 suppl; abstr 9515).

40. Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 45(2): 228-247, 2009.

41. Sloan JA, Liu H, Sargent DJ, Satele D, Schaefer PL, Halyard MY, Grothey A, Garces YI, Brown PD, Loprinzi CL, Buckner JC. A patient-level pooled analysis of the prognostic significance of baseline fatigue for overall survival (OS) among 3,915 patients participating in 43 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center (MC) oncology clinical trials. J Clin Oncol 2009; 27(507s)

APPENDIX I- REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

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

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

A translator may be used to administer the assessment. Additionally, since NCIC is participating in A091105, a French version of the assessment has been provided on the following page.

How would you describe:

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

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

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

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

Fatigue/Uniscale Évaluation

Instructions: S'il vous plaît, pour chaque article ci-dessous, encerclez le numéro (0-10) qui vous décrit le mieux.

Comment décririez-vous :

1. Votre niveau de fatigue moyen au cours de la dernière semaine, aujourd'hui inclus?

0	1	2	3	4	5	6	7	8	9	10
Aucune fatigue										La pire fatigue possible

2. Votre qualité de vie globale dans la semaine écoulée, y compris aujourd'hui?

0	1	2	3	4	5	6	7	8	9	10
Aussi mauvaise que possible										Aussi bonne que possible

APPENDIX II- QOL QUESTIONNAIRE

QOL booklets can be ordered by sites through the CTSU Help Desk. CTSU ask sites to allow 7-10 business days for the processing and mailing of supply requests. CTSU only send booklets via US Mail, unless the site provides a FedEx account number.

CTSU Help Desk
1600 Research Blvd, WB384S
Rockville, MD 20850-3195
(240) 453-5641

Sites in need of QOL booklets must submit a Supplier Request Form to CTSU Help Desk operations. That form can be accessed in the CTSU protocol folder document folder under site registration. Completed Supplier Request forms can be faxed (888 691 8039) or emailed (ctsucontact@westat.com) to CTSU.

Patient Information Sheet

Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. The booklet contains 3 sets of questions:
    a. Brief Pain Inventory Short Form (3 questions)
    b. PRO-CTCAE (19 questions)
    c. LASA Overall Quality of Life Item (1 question)

2. Directions on how to complete each set of questions are written on the top of each set.

3. If you were given this booklet during a clinical visit, please complete the booklet during your clinical visit and return it to your physician.

4. If you received this booklet in the mail, please return the completed booklet in the provided envelope.

5. It is very important that you return the booklet to us, whether you finish the study or not.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

Thank you for taking the time to help us.

Please answer the following questions about your symptoms and quality of life:

(Brief Pain Inventory Short Form questions)

1. Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain As Bad As You Can Imagine

2. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes

B. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

(PRO-CTCAE questions)

In the past 7 days…

3. What was the SEVERITY of your **insomnia (including difficulty falling asleep, staying asleep, or waking up early)** at its WORST?

- □ None
- □ Mild
- □ Moderate
- □ Severe
- □ Very Severe

In the past 7 days…

4. How much did **insomnia (including difficulty falling asleep, staying asleep, or waking up early)** INTERFERE with your usual or daily activities?

- □ Not at all
- □ A little bit
- □ Somewhat
- □ Quite a bit
- □ Very much

5. What was the SEVERITY of your **constipation** at its WORST?

- □ None
- □ Mild
- □ Moderate
- □ Severe
- □ Very Severe

6. How OFTEN did you have **pain**?

- □ Never
- □ Rarely
- □ Occasionally
- □ Frequently
- □ Almost Constantly

7. What was the SEVERITY of your **pain** at its WORST?

- □ None
- □ Mild
- □ Moderate
- □ Severe
- □ Very Severe

8. How much did **pain** INTERFERE with your usual or daily activities?

- □ Not at all
- □ A little bit
- □ Somewhat
- □ Quite a bit
- □ Very much

In the past 7 days…

9. What was the SEVERITY of your **fatigue, tiredness, or lack of energy** at its WORST?

□ None
□ Mild
□ Moderate
□ Severe
□ Very Severe

10. How much did **fatigue, tiredness, or lack of energy** INTERFERE with your usual or daily activities?

□ Not at all
□ A little bit
□ Somewhat
□ Quite a bit
□ Very much

11. How OFTEN did you have **nausea**?

□ Never
□ Rarely
□ Occasionally
□ Frequently
□ Almost Constantly

12. What was the SEVERITY of your **nausea** at its WORST?

□ None
□ Mild
□ Moderate
□ Severe
□ Very Severe

13. How OFTEN did you have **vomiting**?

□ Never
□ Rarely
□ Occasionally
□ Frequently
□ Almost Constantly

In the past 7 days…

14. What was the SEVERITY of your **vomiting** at its WORST?

- None
- Mild
- Moderate
- Severe
- Very Severe

15. How OFTEN did you have **loose or watery stools** (diarrhea)?

- Never
- Rarely
- Occasionally
- Frequently
- Almost Constantly

16. Did you have any **rash**?

- No
- Yes

17. What was the SEVERITY of your **hand-foot syndrome (a rash of the hands or feet that can cause cracking, peeling, redness, or pain)** at its WORST?

- None
- Mild
- Moderate
- Severe
- Very Severe

18. In the past 7 days, how much did **hand-foot syndrome (a rash of the hands or feet that can cause cracking, peeling, redness, or pain)** INTERFERE with your usual or daily activities?

- Not at all
- A little bit
- Somewhat
- Quite a bit
- Very much

In the past 7 days…

19. What was the SEVERITY of your **decreased appetite** at its WORST?

□ None
□ Mild
□ Moderate
□ Severe
□ Very Severe

20. How much did **decreased appetite** INTERFERE with your usual or daily activities?

□ Not at all
□ A little bit
□ Somewhat
□ Quite a bit
□ Very much

21. What was the SEVERITY of your **mouth or throat sores** at their WORST?

□ None
□ Mild
□ Moderate
□ Severe
□ Very Severe

(LASA Overall Quality of Life Item)

Please check the number (0-10) best reflecting your response to the following that describes your feelings during the past week, including today.

How would you describe:

22. Your overall **Quality of Life?**

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

Pain Medication Diary

Subject Name: _____

To be completed by study site

Subject ID: __ __ __ __ Assessment Period: __ __ Research Staff Signature: _____ Date:_____

Study Site Staff: Prior to each 7-day period, write in pain medication names, routes, and strengths in the columns below.

- List only one type of medication on each row. Include all medications the patient is taking for pain or that may alleviate pain symptoms
- Please write in the dates where indicated (Month/Day/Year).

Study Participant: Please record the number of units you have taken of each medication over the prior 24 hours. If you are wearing a patch, mark a "1" for every day the patch is worn.

During this 7-day period, if you start a new medication for pain or change the strength of the pills, write the new information on a new row. (Do not change the information about the medication you have already taken.)

Medication Name (write in name)	**Route** (check one box)	**Strength** (example:50 mg)	**Date:** ___/___/___ *(mm/dd/yy)* **# Taken**	**Date:** ___/___/___ *(mm/dd/yy)* **# Taken**	**Date:** ___/___/___ *(mm/dd/yy)* **# Taken**	**Date:** ___/___/___ *(mm/dd/yy)* **# Taken**	**Date:** ___/___/___ *(mm/dd/yy)* **# Taken**	**Date:** ___/___/___ *(mm/dd/yy)* **# Taken**	**Date:** ___/___/___ *(mm/dd/yy)* **# Taken**
	☐ Oral ☐ Patch ☐ Other								
	☐ Oral ☐ Patch ☐ Other								
	☐ Oral ☐ Patch ☐ Other								
	☐ Oral ☐ Patch ☐ Other								
	☐ Oral ☐ Patch ☐ Other								
	☐ Oral ☐ Patch ☐ Other								
	☐ Oral ☐ Patch ☐ Other								

APPENDIX III- DRUGS WITH RISK OF TORSADES DE POINTES

This list contains medications that are generally accepted (and documented in published data) as having an increased risk of QT prolongation and/or torsades de pointes. Concomitant administration of sorafenib and a medication on this list is **prohibited**.

Generic Name	Brand Name	Comments
Amiodarone	Cordarone®, Pacerone®	Low risk torsades de pointes
Arsenic trioxide	Trisenox®	Torsades de pointes
Bepridil	Vasocor®	
Chloroquine	Aralen®	
Chlorpromazine	Thorazine®	
Cisapride	Propulsid®	Restricted availability in U.S.
Clarithromycin	Biaxin®	
Disopyramide	Norpace®	Torsades de pointes
Dofetilide	Tikosyn®	Torsades de pointes
Dolasetron	Anzemet®	
Droperidol	Inapsine®	Torsades de pointes
Erythromycin	Erythrocin®, E.E.S. ®	IV > PO
Halofantrine	Halfan®	
Haloperidol	Haldol®	IV > PO, high doses increase QT prolongation and torsades de pointes
Ibutilide	Corvert®	Torsades de pointes, female > male, non-Caucasian > Caucasian

Levomethadyl	Orlaam®	
Mesoridazine	Serentil®	
Methadone	Dolophine®, Methadose®	
Pentamidine	Pentam®, Nebupent®	
Pimozide	Orap®	
Procainamide	Pronestyl®, Procan®, Procanbid®	N-acetylprocainamide causes torsade de pointes, not parent compound
Quinidine	Cardioquin®, Quinaglute®	Torsades de pointes
Sotalol	Betapace®	Torsade de pointes female > male
Sparfloxacin	Zagam®	
Thioridazine	Mellaril®	

Note: the above list is not all-inclusive.

Drugs with Possible or Conditional Risk of Torsades de Pointes

This list contains medications that, in some reports, have been associated or weakly associated with causing torsades de pointes and/or QT prolongation. There is insufficient data that these medications alone may cause torsades de pointes and/or QT prolongation, however when sorafenib is given concomitantly with a medication on this list (or other risk factors are present such as bradycardia, electrolyte disturbances, congenital long QT syndrome, or concomitant drugs that inhibit metabolism), there may be possible or conditional risk of torsades de pointes and/or QT prolongation. Extreme caution and careful monitoring should be instituted with concomitant administration of sorafenib and a medication on this list.

Generic Name	**Brand Name**	**Comments**
Alfuzosin	Uroxatral®	
Amantadine	Symmetrel®	Low

Amitriptyline	Elavil®	Nonspecific ECG changes reported.
Atazanavir	Reyataz®	
Azithromycin	Zithromax®	
Chloral hydrate	Noctec®	
Ciprofloxacin	Cipro®	
Citalopram	Celexa®	
Clomipramine	Anafranil®	
Desipramine	Pertofrane®	QT prolongation, VF/sudden death reported
Diphenhydramine	Benadryl®, Nytol®	
Dolasetron	Anzemet®	Granisetron < Ondansetron < Dolasetron
Doxepin	Sinequan®	
Dronedarone	Multaq®	
Escitalopram	Lexapro®, Cipralex®	
Felbamate	Felbatrol®	
Flecainide	Tambocor®	
Foscarnet	Foscavir®	
Fosphenytoin	Cerebyx®	
Fluconazole	Diflucan®	IV > PO
Fluoxetine	Prozac®, Sarafem®	1 in 10,000 ventricular arrhythmias reported

Galantamine	Reminyl®	
Gatifloxacin	Tequin®	
Gemifloxacin	Factive®	
Granisetron	Kytril®	Granisetron < Ondansetron < Dolasetron
Imipramine	Norfranil®	Nonspecific arrhythmias reported
Indapamide	Lozol®	
Isradipine	Dynacirc®	
Itraconazole	Sporanox®	
Ketoconazole	Nizoral®	
Lapatinib	Tykerb®	
Levofloxacin	Levaquin®	Lower risk than that of similar agents
Lithium	Lithobid®, Eskalith®	
Moexipril/HCTZ	Uniretic®	
Moxifloxacin	Avelox®	
Nicardipine	Cardene®	
Nilotinib	Tasigna®	
Nortriptyline	Pamelor®	Nonspecific arrhythmias reported
Octreotide	Sandostatin®	
Ofloxacin	Floxin®	
Ondansetron	Zofran®	Granisetron < Ondansetron <

		Dolasetron
Oxytocin	Pitocin®	
Paliperidone	Invega®	
Paroxetine	Paxel®	Lower risk than TCA's
Perflutren lipid microspheres	Definity®	
Protriptyline	Vivactil®	
Quetiapine	Seroquel®	QT prolongation
Ranolazine	Ranexa®	
Risperidone	Risperdal®	QT prolongation, sudden death reported
Ritonavir	Norvir®	
Sertraline	Zoloft®	Lower risk than TCA's
Solifenacin	VESIcare®	
Sunitinib	Sutent®	
Tacrolimus	Prograf®	
Tamoxifen	Nolvadex®	
Telithromycin	Ketek®	
Tizanidine	Zanaflex®	
Trazodone	Desyrel®	
Trimethoprim-Sulfa	Sulfa®, Bactrim®, Bactrim DS®	Low
Trimipramine	Surmontil®	
Vardenafil	Levitra®	
Venlafaxine	Effexor®	1 :1000 risk of arrhythmia

		reported
Voriconazole	VFend®	
Ziprasidone	Geodon®	QT prolongation, 1:1000 risk of arrhythmia

Note: The above list is not all-inclusive.

References:

1. Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What Clinicians Should Know About the QT Interval. *Journal of the American Medical Association* 2003;289:2120-2127.
2. Crouch MA, Limon L, Cassano AT. Clinical Relevance and Management of Drug-Related QT Interval Prolongation. *Pharmacotherapy* 2003;23:887-908.
3. Kies SJ, Pabelick CM et al. Anesthesia for Patients with Congenital Long QT Syndrome. *Anesthesiology* 2005;102:204-210
4. Li EC, Esterly JS, Pohl S, Scott SC, McBride BF. Drug-Incuded QT-Interval Prolongation: Considerations for Clinicans. *Pharmacotherapy* 2010;30:684-701.
5. Roden DM. Drug-Induced Prolongation of the QT Interval. *The New England Journal of Medicine* 2004;350:1013-1022.
6. Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What Clinicians Should Know About the QT Interval. *Journal of the American Medical Association* 2003;289:2120-2127.
7. Crouch MA, Limon L, Cassano AT. Clinical Relevance and Management of Drug-Related QT Interval Prolongation. *Pharmacotherapy* 2003;23:887-908.
8. Kies SJ, Pabelick CM et al. Anesthesia for Patients with Congenital Long QT Syndrome. *Anesthesiology* 2005;102:204-210
9. Li EC, Esterly JS, Pohl S, Scott SC, McBride BF. Drug-Incuded QT-Interval Prolongation: Considerations for Clinicans. *Pharmacotherapy* 2010;30:684-701.
10. Roden DM. Drug-Induced Prolongation of the QT Interval. *The New England Journal of Medicine* 2004;350:1013-1022.

APPENDIX IV- AGENT ACCOUNTABILITY

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as Collaborator(s) 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" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents 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 will 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 as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). 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.

4. 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.

5. 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.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies 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 abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and 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: ncicteppubs@mail.nih.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 Collaborator(s) confidential/ proprietary information.

APPENDIX V- BRIEF PAIN INVENTORY QUESTION #1 FOR STRATIFICATION

All patients are stratified according to baseline level of pain.

- For patients who consented to the A091105-HO1 study: The baseline level of pain question already appears as question #1 in the QOL questionnaire booklet (see Appendix II). Therefore, you do not need to administer this Appendix, and will enter the value circled for question #1 onto the OPEN Registration Form (Step 1).
- For patients who do not consent to the A091105-HO1 study: Administer this appendix within 28 days prior to registration. The baseline level of pain may also be administered verbally as long as a source document is maintained at the institution. French and Spanish versions of the question are provided on the following page.

Baseline Level of Pain

1. Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10	
No Pain											Pain As Bad As You Can Imagine

Español

Clasifique su dolor hacienda un cículo alrededor del número que mejor describe la intensidad máxima de dolor sentido en las últimas 24 horas.

0	1	2	3	4	5	6	7	8	9	10
Ningún Dolor										El Peor Dolor Imaginable

Français

SVP, entourez d'un cercle le chiffre qui décrit le mieux la douleur la plus intense que vous ayez ressentie pendant les dernières 24 heures.

0	1	2	3	4	5	6	7	8	9	10
Pas de douleur										Douleur la plus horrible que vous puissiez imaginer

APPENDIX VI – A091105 OPTIONAL MEDICATION DIARY

PATIENT MEDICATION DIARY – Sorafenib

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

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **sorafenib**. After cycle 14 you will complete one form for each 8 week period.
2. **Sorafenib should be taken once daily on an empty stomach one hour before or two hours after eating. These tablets should be swallowed whole and cannot be crushed or chewed.**
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. If you miss a dose of sorafenib, you should take it as soon as you remember, as long as it is on the same day.
6. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose		# of capsules taken	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					

Day	Date	Time of daily dose		# of capsules taken	Comments
23					
24					
25					
26					
27					
28					
Beginning with Cycle 14 (i.e. after 1 year of treatment)					
29					
30					
31					
32					
33					
34					
35					
36					
37					
38					
39					
40					
41					
42					
43					
44					
45					
46					
47					
48					
49					
50					
51					
52					
53					
54					
55					
56					

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____

3. Total number of capsules taken this month (each size)
   _____

4. Physician/Nurse/Data Manager's Signature
   _____

Patient's signature

_____