Oregon Health & Science University
OHSU Knight Cancer Institute
IRB Protocol #: 9464

A Phase II Study of Sorafenib with Chemotherapy, Radiation, and Surgery for High-Risk Soft Tissue Sarcomas

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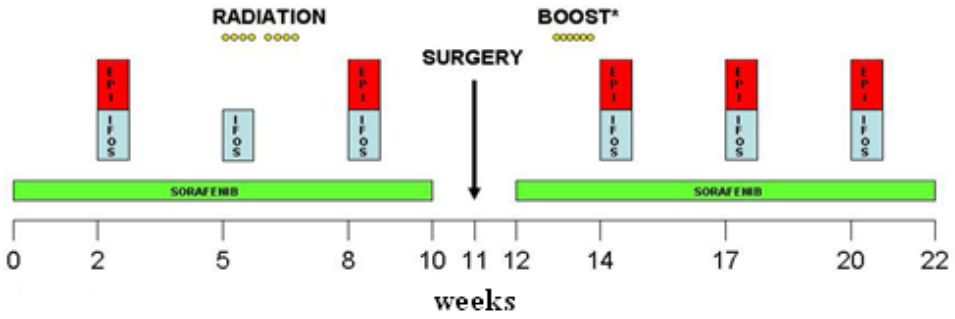
Original Protocol Date: 08 March 2013
Revision Date: 29 December 2015
15 September 2016

SCHEMA



- **Epirubicin:** 30 mg/m^2/day I.V., days 1-3 of each cycle. Epirubicin to be omitted during cycle 2 (concomitant chemoradiation)
- **Ifosfamide:** 2500 mg/m^2/day I.V., days 1-3 of each cycle. Administered with hydration and Mesna.
- **Peg-filgrastim or filgrastim:** S.C. administered after each chemotherapy cycle.
- **Sorafenib:** 400 mg p.o. once daily beginning 2 weeks before first chemotherapy cycle, held 1 week before and after surgery.
- **Radiation:** 28 Gy (350cGy x 8 fractions in 10 days) beginning at the start of cycle 2. *Boost: postoperative boost of 12 Gy (200 cGy x 6 fractions) for patients with positive surgical margins only.

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1. OBJECTIVES

- **Primary objective**
  - To determine the pathologic response rate (≥95% necrosis) after preoperative treatment with sorafenib, epirubicin, ifosfamide, and hypofractionated radiation for high risk soft tissue sarcomas of the extremities or body wall.
- **Secondary objectives**
  - To further characterize the safety of sorafenib plus chemoradiotherapy, including wound complication rate
  - To estimate time-to-event rates, including overall survival, overall disease-free survival, distant disease-free survival, and local disease-free survival in patients with high risk soft tissue sarcomas of the extremities or body wall treated with preoperative sorafenib plus chemoradiotherapy and postoperative sorafenib plus chemotherapy.

2. BACKGROUND

2.1 Soft-Tissue Sarcomas

Soft-tissue sarcomas are a group of heterogeneous, rare tumors that are diagnosed in approximately 8,000 patients per year in the United States. While limb-salvage procedures combining wide excision with radiation therapy achieve local control in up to 90% of patients with extremity soft-tissue sarcomas, approximately half of patients with high-grade, >5 cm, deep tumors will die from metastatic disease.[1-4] The outcome of these patients is unacceptable. Improving the survival of patients diagnosed with such high-risk tumors is a priority.

2.2 Adjuvant Radiotherapy

The ability to perform limb-salvage surgery was facilitated by the introduction of adjunctive radiotherapy. Adjuvant radiotherapy for soft-tissue sarcoma was initially described by Suit and Lindberg, who demonstrated improved local control rates of extremity sarcomas in over 80% of patients.[1,2,5] Preservation of function of the limb was achieved in greater than 90% of cases. Randomized trials have validated the efficacy of the limb-sparing approach in achieving excellent local control rates that have eliminated the need for amputation for the majority of patients. A prospective, randomized clinical trial of limb-sparing surgery plus radiation versus amputation found equivalent recurrence-free survival rates.[6] A randomized study of limb-sparing surgery plus or minus adjuvant radiation showed a significant decrease in local recurrence in those patients receiving radiation.[3] Radiotherapy has clearly demonstrated its utility in improving local control rates and reducing the amputation rate.

Administration of radiation can be performed either pre- or postoperatively. A randomized study showed an increased acute wound complication rate with preoperative radiation compared to postoperative radiation.[7] However, longer follow-up has suggested that postoperative radiation is associated with a greater incidence of long-term complications, such as subcutaneous fibrosis, that tend to be permanent problems and are probably due to the larger field size and higher radiation dose that

are used with postoperative treatment.[8] In terms of efficacy, local control rates are the same whether the radiation is administered pre- or postoperatively.[7] The use of pre- vs. postoperative radiation varies between institutions and is a matter of preference of the surgeon and radiation oncologist. Preoperative administration has been the preference at our institution. Theoretical advantages of preoperative radiation include delivery to undisturbed, well-oxygenated tissue. The field size does not need to be increased as it does in post-operative radiotherapy, allowing for lower radiation doses.[9] Importantly, pathologic examination of the tumor specimen after surgery for necrosis allows assessment of the efficacy of the pre-operative treatment that may correlate with overall survival.[10]

2.3 Adjuvant Chemotherapy

The utility of chemotherapy in treatment of localized sarcomas remains controversial. Theoretically, treatment with drugs active against advanced sarcoma, such as anthracyclines or ifosfamide, may eradicate micro-metastases and thus increase the cure rate over surgery plus radiation alone. The first generation of adjuvant studies included doxorubicin as the key active agent. These small studies reported conflicting results. A meta-analysis using updated data on 1568 patients treated on trials using doxorubicin-based adjuvant therapy was published in 1997,[11] and was subsequently updated with data from additional studies for a total population of 1953 patients.[12] A statistically significant benefit favoring chemotherapy was demonstrated for local, distant, and overall recurrence. The absolute risk reduction for overall recurrence was 10%.[12] A trend towards absolute overall survival benefit of 4% at 10 years was not statistically significant, but did reach statistical significance upon subgroup analysis of extremity sarcomas (P=.029).[11] The studies on which these meta-analyses were based had a number of faults, including heterogeneity of stage and grade, incorporation of non-active chemotherapy drugs into the treatment regimens, and possible under-dosing of doxorubicin.

Randomized, controlled, adjuvant studies containing ifosfamide and using intensified chemotherapy doses with hematopoietic growth factor support were begun in the 1990's. The first to be published was an Italian study that randomized patients with high-risk sarcomas to observation or to post-operative chemotherapy with ifosfamide and epirubicin.[13] This study included only high-risk patients with high-grade, large (≥5 cm) or recurrent sarcomas of the extremities or girdle. One-hundred-four patients were randomized to chemotherapy or to observation, and accrual was halted in 1996 after an interim analysis suggested significant benefit from chemotherapy. Subjects in the treatment group received 5 cycles of epirubicin 60 mg/m^2 days 1 and 2 and ifosfamide 1.8 g/m^2 days 1 through 5, with hydration, mesna, and granulocyte colony-stimulating factor support. The median disease-free survival was 48 months in the treatment group and 16 months in the control group (P =.04) and the median overall survival was 75 months for treated and 46 months for untreated patients (P =.03). The study has been criticized for its small size and early stopping based on recurrence-free survival; indeed, with longer follow-up the overall survival advantage lost statistical significance.[14]

2.4 Neoadjuvant Chemoradiotherapy

There are advantages, both practical and theoretical, to treating high-risk extremity soft tissue sarcomas with pre-operative chemotherapy and radiation. Chemotherapy may act both in the early systemic treatment of micrometastatic disease and as a radiosensitizer for improved local control. In combination with pre-operative radiotherapy, neoadjuvant chemotherapy may improve tumor downsizing and potential resectability. Preoperative radiation has the advantage of delivery to undisturbed, well-oxygenated tissue. The field size does not need to be increased as it does in post-operative radiotherapy, allowing for lower radiation doses.[9] Additionally, preoperative therapy allows evaluation of treatment effect from the surgical specimen: the degree of pathologic necrosis in the surgical specimen after chemoradiation has been associated with improved local control and overall survival in patients with soft-tissue sarcoma. In a study published by Eilber,[10] treatment-induced pathologic necrosis after neoadjuvant treatment with chemotherapy and radiation was found to be an independent predictor of both local recurrence and overall survival for patients with high-grade sarcomas. The 10-year overall survival rate for patients who had achieved ≥ 95% necrosis was 71%, compared with 55% in patients with < 95% necrosis. While combined chemotherapy and radiation prior to surgery has been reported by a number of different groups, there exists no standard regimen. [15-20]

We previously published a 25 patient, phase II study investigating a dose-intense, pre-operative chemoradiotherapy regimen for patients with large, intermediate- and high-grade sarcomas of the extremity or body wall.[20] Intense doses of epirubicin and ifosfamide were given pre- and post-surgery, and 28 Gy of radiation in 8 fractions was given preoperatively, partly in conjunction with ifosfamide. This "hypofractionated" or "rapid fractionation" scheme was based on that previously reported by the UCLA group, a short-course treatment plan that provides for convenient and effective administration of radiation.[15] The rate of ≥95% pathologic necrosis in the resected tumors was 40% (95% C.I. 21%, 59%) and estimates of 2-year overall and disease-free survival were 84% (95% CI, 66% to 100%) and 62% (95% CI, 37% to 86%), respectively. Postoperative wound complications requiring an operative procedure occurred in 20%, within the expected and acceptable range for pre-operative radiotherapy.[7] Due to expected chemotherapy side effects and related patient drop-out, only 64% of patients completed all chemotherapy cycles and the average delivered dose intensity relative to intended therapy was 69%. Notable toxicities included neutropenic fever (40%), ifosfamide encephalopathy (24%), and grade 3-4 anemia (64%). While the toxicity was manageable and expected from the agents utilized, it did impact our ability to deliver the intended dose intensity. The rate of ≥95% pathologic necrosis found in a subsequent analysis of 37 patients treated both on- and off- study was 32%.[21] The high rate of pathologic necrosis with this regimen has been encouraging, and has prompted us to consider alternate methods of augmenting neoadjuvant chemoradiotherapy in soft tissue sarcoma.

2.5 Antiangiogenic Therapies for Sarcoma

Development of new blood vessel formation is critical in the progression of tumors. Folkman's hypothesis[22] of targeting this process as an antineoplastic strategy has

become practical reality three decades later with the advent of antiangiogenic agents now in widespread use based on clinical trials that have shown benefit in combination with chemotherapy[23,24] or as monotherapy in select diseases.[25-27] Common among these treatments is inhibition of the vascular endothelial growth factor (VEGF) activity, a key pathway in tumor angiogenesis.

Soft tissue sarcomas frequently overexpress VEGF[28,29] and elevated circulating levels of the pro-angiogenic factors VEGF and basic fibroblast growth factor (bFGF) are found in patients with soft tissue sarcoma.[30-33] Tumor VEGF concentration has been found to correlate with grade, stage, and prognosis of soft-tissue sarcomas.[29,34]

VEGF-directed therapies have now demonstrated to have activity in a variety of advanced soft tissue sarcomas. Pazopanib, an inhibitor of VEGF-R and multikinase inhibitor was approved by the FDA in 2012 for treatment of advanced soft tissue sarcoma after previous chemotherapy. This approval was based on the results of a phase III study that showed improvement in progression-free survival over placebo control.[35] Several studies have looked at sorafenib, a multi-kinase inhibitor of VEGF receptors, PDGF receptor, Raf/MEK/ERK, and others, as a single-agent in patients with metastatic soft tissue sarcoma. The first of these studies to be reported observed a small number of radiographic responses in subjects with angiosarcoma and leiomyosarcoma, as well as stable disease in these and other sarcoma subtypes.[36] At least 2 other studies of sorafenib in advanced sarcoma have been conducted, including a phase II study by the Southwest Oncology Group in which OHSU led accrual and developed a sizeable pilot experience using the agent for this disease (19 subjects).[37] While no objective radiographic responses were observed in this study, patients with vascular-type sarcomas were noted to have prolonged stable disease.

While the activity of these antiangiogenic agents against soft-tissue sarcomas may appear low when evaluated with the traditional metric of radiographic response rates, this measure is far from optimal in assessing the activity of antiangiogenic agents which typically may not cause rapid involution of tumors. Radiographic disease stabilization as a clinically meaningful effect has been demonstrated in studies with sorafenib in renal carcinoma, in which traditional response rates are low but progression-free survival is improved.[25] Additionally, the use of these agents as monotherapy in the high-disease burden setting of metastatic disease may not reveal their full activity, and studying their use in combination with chemotherapy in the locally advanced, micrometastatic setting may yield greater impact. In a VEGF-overexpressing preclinical sarcoma model, VEGF receptor blockade enhanced chemotherapy responsiveness and decreased development of pulmonary metastases, suggesting that combining anti-VEGF therapy with chemotherapy might be most useful in high VEGF-secreting sarcoma patients at high risk of eventual metastatic spread.[38]

2.6 Sorafenib

Sorafenib (BAY 43-9006) is an oral multi-kinase inhibitor with effects on tumor proliferation and tumor angiogenesis.[39] It was initially selected based on inhibitory activity against the serine/threonine kinases Raf-1 and wild-type B-Raf, which are pivotal components of the Ras/Raf/MEK/ERK signaling pathway. Inhibitory activity was subsequently demonstrated against the tyrosine kinases for vascular endothelial growth factor (VEGF) receptor and platelet-derived growth factor (PDGF) receptor as well as Flt-3 and c-Kit.[39]

The Raf/MEK/ERK pathway is an important mediator of responses to growth factors, and a strong inducer of genes involved in tumorigenesis, angiogenesis, apoptosis, and tumorigenesis.[40] In preclinical studies, sorafenib demonstrated broad-spectrum anti-tumor activity by inducing complete tumor stasis and inhibition of tumor angiogenesis in a variety of tumor types.[39]

The safety and clinical activity of sorafenib, alone [41-44] or in combination[45,46] with chemotherapy, has been examined in a series of phase I studies conducted in patients with solid tumors. Results of a multi-center, randomized, placebo-controlled, double-blind phase III trial of sorafenib in advanced renal cell carcinoma (RCC) were first reported in 2005.[47,48] The co-primary endpoints of the trial were overall survival (OS) and progression-free survival (PFS). Patients with advanced clear cell renal carcinoma with good performance status following one prior systemic therapy were randomized to either sorafenib or blinded placebo with best supportive care. At the time of a per-protocol interim analysis of PFS, 769 of 884 planned patients had been randomized, and 342 PFS events had been reported. Median PFS was 24 weeks for sorafenib versus 12 weeks for placebo (hazard ratio 0.44; $p<0.00001$) and the 12 week progression-free rate was 79% for sorafenib versus 50% for placebo. Based on these results, the study in May 2005 was unblinded and patients in the placebo group were allowed to cross over and receive sorafenib. At the time of cross over, an interim analysis of overall survival was conducted based on 220 events. Median overall survival in the placebo group was 14.7 months and had not been reached in the sorafenib group. The Hazard Ratio (sorafenib over placebo) was 0.72 with a p-value of $p = 0.018$. The threshold for statistical significance for this interim analysis was not reached ($p < 0.0005$). Final analysis of OS was reported at ASCO 2007.[49] Overall survival in the sorafenib group was 17.8 months and 15.2 months in the placebo group (HR 0.88, $p=0.146$). For this study, however, OS was likely confounded by the fact that approximately half of the placebo patients crossed over at the time of unblinding to receive sorafenib. To illustrate that point, overall survival analysis with placebo patients censored at the time of cross over indicated that sorafenib treated patients had a statistically significant 22% reduction in mortality risk compared to placebo patients (OS 17.8 mo vs. 14.3 mo, HR 0.78, $p=0.0287$).

A multi-center, randomized, placebo-controlled, double-blind phase III trial of sorafenib in advanced hepatocellular carcinoma (HCC) was also reported at ASCO in 2007.[26] In this study 602 patients with advanced HCC, Child Pugh class A, having received no prior systemic therapy were randomized to receive either sorafenib (n=299) at 400 mg bid or placebo (n=303). In February 2007, based on a planned interim analysis of overall survival, the DMSB recommended unblinding and closure

of the study. OS in the sorafenib group was 46.3 wks versus 34.4 wks in the placebo-treated group. This represented a 44% increase in relative OS (HR 0.69, p=0.00058). PFS was also significantly increased in the sorafenib group (24 wks) vs. the placebo group (12.3 wks); HR 0.58, p=0.000007.

As mentioned previously, several studies with sorafenib monotherapy have been conducted in soft tissue sarcoma, and activity has been seen in several histologic subtypes including angiosarcoma and leiomyosarcoma.[36]

2.7 Antiangiogenics plus Chemoradiotherapy

Antiangiogenics have been shown to increase the effects of chemotherapy and radiation in pre-clinical and clinical studies. Bevacizumab has been demonstrated to increase overall survival when added to chemotherapy for advanced colorectal cancer and non-small cell lung cancer.[23,24] This may seem counterintuitive, as anti-vascular therapies would be expected to reduce blood flow, thus potentially decreasing delivery of drug and oxygen to the tumor needed for the therapeutic effects of chemotherapy and radiation, respectively. However, tumor vasculature is thought to be abnormal due to an imbalance of pro- and antiangiogenic factors leading to a number of effects that can be a barrier to drug and oxygen delivery including impedance of blood flow and interstitial hypertension.[50] The concept of "normalizing" tumor vasculature with antiangiogenic therapy has been proposed as a method whereby drug delivery and oxygenation are improved and thus can amplify the effect of chemotherapy and radiation.[50] Blockade of VEGF signaling can "prune" immature vessels, helping to normalize the vasculature and tumor microenvironment, thus improving tumor oxygenation and delivery of drugs.[51,52] Early evidence suggests that combined VEGF-blockade and chemoradiotherapy is safe and promising in locally advanced rectal cancer.[52,53] Many phase I-II studies investigating combined antiangiogenic and chemoradiotherapy are ongoing, but to our knowledge none are currently investigating this approach in soft tissue sarcomas.[54]

2.8 Sorafenib with Chemoradiotherapy

Given the early clinical activity observed with antiangiogenic agents in advanced soft tissue sarcomas and given that the greatest effect of antiangiogenics may not be as monotherapy but in their ability to potentiate the effects of chemotherapy and radiotherapy, we have found it compelling to study the effect of combined antiangiogenic therapy with chemoradiotherapy in patients with localized, high-risk, extremity soft tissue sarcomas. We thus conducted a 16 subject phase I study with escalating doses of sorafenib to determine the maximum tolerated dose of sorafenib in combination with a dose-modified version of our previously published regimen of preoperative chemoradiation and postoperative chemotherapy with epirubicin and ifosfamide.[55] At a sorafenib dose of 400 mg twice daily, dose-limiting toxicities included grade 4 neutropenic sepsis in 1 patient and grade 3 hand-foot syndrome in all 3 patients treated. We determined a maximum-tolerated-dose for sorafenib to be 400 mg daily when combined with a regimen of 28 Gy of preoperative hypofractionated radiation and pre- and post-operative chemotherapy (epirubicin 30 mg/m^2/day days 1-3 and ifosfamide 2.5 g/m^2/day days 1-3). At this dose level, toxicity was similar to that seen with chemoradiotherapy alone. Grade 3-4 hematologic toxicity was common including a 50% rate of neutropenic fever and

neutropenic infections. The most common grade 3-4 nonhematologic toxicity was hypophosphatemia, a known side effect of both sorafenib and ifosfamide, which was easily managed with phosphorus replacement and did not lead to any significant sequelae. The rate of wound complications was 38%, which is similar to the 35% that has been reported with preoperative radiation alone.

We observed a promising rate of pathologic response (≥95% necrosis) across all dose levels of 44%. Eleven of the subjects were enrolled in a companion study evaluating DCE-MRI to assess preoperative therapy effect, and results indicate that treatment effect of sorafenib could be detected in some patients after only 2 weeks of sorafenib, and that the change in a novel DCE-MRI biomarker, ΔK^{trans}, at this time point correlated with pathologic necrosis found at the time of eventual surgery (Figure 1).

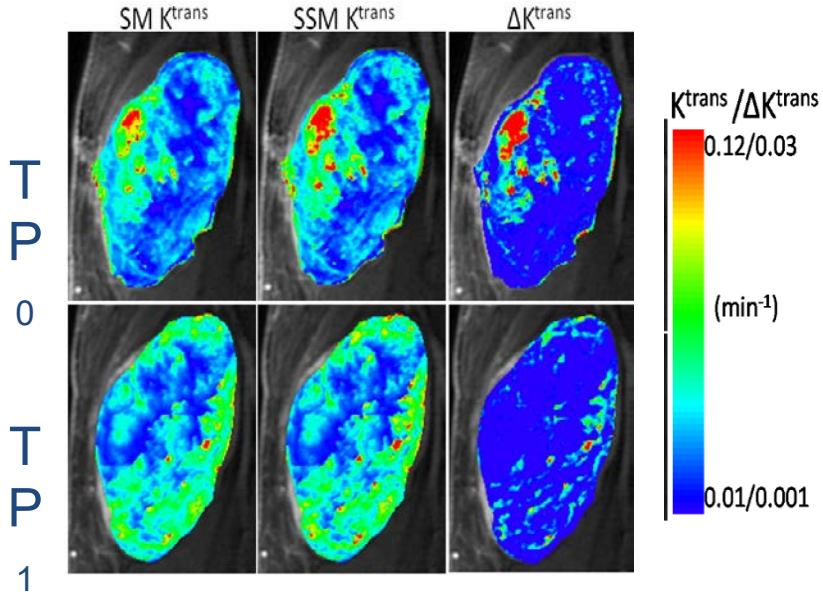

Figure 1: Myxoid round cell liposarcoma of thigh demonstrating change in 3 different DCE-MRI biomarkers (SM K^{trans}, SSM K^{trans}, and ΔK^{trans}) from baseline (TP_0) to 2 weeks after sorafenib treatment (TP_1)

2.9 Study Rationale

The optimal chemoradiotherapy regimen for soft-tissue sarcomas remains undefined. We have extended our neoadjuvant chemoradiotherapy experience by confirming the safety and feasibility of combined treatment with sorafenib in a dose-finding phase I study.[55] We now propose to further study the efficacy and safety of sorafenib 400 mg/daily when combined with chemoradiotherapy (epirubicin, ifosfamide, and hypofractionated radiation) as an adjunct to surgery for extremity soft tissue sarcomas in the setting of a phase II trial.

We hypothesize that this regimen will improve clinical outcome in patients with high-risk disease by potentiating the effects of chemoradiotherapy on the local tumor and enhancing the effects of chemotherapy on micrometastatic disease. Treatment effect will be assessed by the pathologic response rate (≥95% necrosis), and subjects will be followed for local recurrence, distant relapse, and overall survival.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Histologically confirmed, soft-tissue sarcoma: excluding rhabdomyosarcoma (pleomorphic rhabdomyosarcoma patients are eligible), Ewing's, PNET, osteosarcoma, or gastrointestinal stromal tumor

3.1.2 AJCC (7th Edition) Stage IIb, III, or IV patients planned for resection of the primary tumor

- >5 cm in greatest dimension
- Intermediate or High-Grade (see 3.1.4)
- Superficial or Deep

3.1.3 Sarcoma located on upper (includes shoulder) or lower (includes hip) extremities or on body wall

3.1.4 Intermediate or High-Grade: Grades 2 or 3 on scale of 1-3

3.1.5 LVEF ≥ 50%

3.1.6 Required initial laboratory values:

ANC	≥ 1500 /μL
Hgb	≥ 9.0 g/dL
Platelets	≥ 100,000 /μL
Creatinine	≤ 1.5 x ULN
Bilirubin	≤ 1.5 mg/dL
AST/ALT	≤ 1.5 x ULN

3.1.7 INR < 1.5 or a PT/PTT within normal limits. Patients receiving anti-coagulation treatment with an agent such as warfarin or heparin **may** be allowed to participate. For patients on warfarin, the INR should be measured prior to initiation of sorafenib and monitored at least weekly, or as defined by the local standard of care, until INR is stable.

3.1.8 No prior chemotherapy, radiation, or biotherapy

3.1.9 No major surgery within 4 weeks prior to study entry

3.1.10 No contraindications to limb-sparing surgery. Patient should be evaluated by a surgeon who specializes in sarcoma resections prior to study enrollment to ensure pt is a candidate for limb-sparing surgery.

3.1.11 No severe peripheral vascular disease

3.1.12 Adequate contraception must be used and patients must not be pregnant or breastfeeding. Women of childbearing potential and men must

agree to use adequate contraception (barrier method of birth control) prior to study entry and for the duration of study participation. Men and women should use adequate birth control for at least thirty days after the last administration of sorafenib.

3.1.13 Women of childbearing potential must have negative serum pregnancy test performed within 7-days prior to registration.

3.1.14 Age≥18

3.1.15 ECOG PS 0-1

3.1.16 Patient must sign a study-specific consent form prior to registration

3.1.17 Ability to understand and the willingness to sign a written informed consent. A signed informed consent must be obtained prior to any study specific procedures.

3.2 Exclusion Criteria

3.2.1 Patients with known brain metastases. Patients with neurological symptoms must undergo a CT scan/MRI of the brain to exclude brain metastases.

3.2.2 Uncontrolled intercurrent illness including, but not limited to, ongoing or active serious infection >CTCAE Grade 2, symptomatic congestive heart failure, unstable angina pectoris, cardiac ventricular arrhythmia requiring anti-arrhythmic therapy, or psychiatric illness/social situations that would limit compliance with study requirements. Patients must not have unstable angina (angina symptoms at rest) or new onset angina (began within the last 3 months) or myocardial infarction within the past 6 months.

3.2.3 Uncontrolled hypertension defined as systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg, despite optimal medical management.

3.2.4 Known human immunodeficiency virus (HIV) infection or chronic Hepatitis B or C.

3.2.5 Thrombolic or embolic events such as a cerebrovascular accident including transient ischemic attacks within the past 6 months.

3.2.6 Pulmonary hemorrhage/bleeding event ≥ CTCAE Grade 2 within 4 weeks of first dose of study drug.

3.2.7 Any other hemorrhage/bleeding event ≥ CTCAE Grade 3 within 4 weeks of first dose of study drug.

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

3.2.9 Evidence or history of bleeding diathesis or coagulopathy.

3.2.10 Major surgery or significant traumatic injury within 4 weeks of first study drug.

3.2.11 Use of strong CYP3A4 inducers (See Section 4.6).

3.2.12 Known or suspected allergy to sorafenib or any agent given in the course of this trial.

3.2.13 Any condition that impairs patient‘s ability to swallow whole pills.

3.2.14 Any malabsorption problem.

3.2.15 Pregnant or lactating women are excluded from this study because of possible risk to the fetus or infant.

3.2.16 Patients with a "currently active" second malignancy other than non-melanoma skin cancers are not to be registered. Patients are not considered to have a "currently active" malignancy if they have completed therapy and considered by their physician to be at less than 30% risk of relapse.

3.2.17 Any uncontrolled thyroid disease.

3.2.18 Requirement for hemodialysis or peritoneal dialysis

3.3 Removal of Subjects from Study

3.3.1 Criteria for stopping therapy:

- Substantial non-compliance with the requirements of the study.
- Any adverse event which, in the Investigator’s opinion, requires termination of the study medication.
- Disease progression, unless at the discretion of the investigator (in collaboration with Bayer/Onyx) continued treatment with study drug is appropriate.
- The patient would benefit from additional radiation therapy beyond that specified in the protocol.
- Request by the patient or a legal representative/relative to stop the treatment.
- The patient presents with a beta-HCG test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event
- The patient uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.
- The development of a second malignancy that requires treatment, which would interfere with this study.
- The patient is lost to follow-up.
- Interruption in study drug’s administration for greater than 3-week delay. Following surgery, interruption in study drug’s administration is allowed for up to 10-weeks from initial surgery.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a significant degree.

3.3.2 Criteria for study withdrawal:

- Disease progression, unless at the discretion of the investigator (in collaboration with Bayer/Onyx) continued treatment with study drug is

appropriate.

- Study closure,
- Unacceptable adverse event(s),
- Patient decision to withdraw from the study, or
- In the judgment of the investigator, further treatment would not be in the best interest of the patient.

The Investigator will make every reasonable effort to keep each patient in the study unless it is in the patient's best interest to discontinue participation. If a patient is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the patient is willing and able to be assessed. A description of the reason(s) for withdrawal from the study will be recorded on the case report form (CRF). The Investigator should also ensure that all patients are followed up for survival and recurrence after the Final Visit.

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all patients participating in the study, even for a brief period of time. Patients who discontinue following entry will have relevant information completed and recorded on the CRF. All patients who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any patient should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the OHSU IRB and the Bayer representative. The cause of death should be recorded in detail, within 24 hours, on a serious adverse event (SAE) form and reported to the sponsor Drug Safety Unit (refer to Section 10)).

4. TREATMENT PLAN

TX	SORAFENIB RUN-IN	CYCLE 1 DAYS	CYCLE 2 DAYS	CYCLE 3 DAYS	SURGERY	CYCLE 4 DAYS	CYCLE 5 DAYS	CYCLE 6 DAYS
EPI		15-17	OMIT	57-59		99-101	120-122	141-143
IFOS		15-17	36-38*	57-59		99-101	120-122	141-143
MESNA		15-17	36-38*	57-59		99-101	120-122	141-143
SORAFENIB	1-14	15-35	36-56	57-71**	85-98**	99-119	120-140	141-155
PEG-FILGRASTIM♦		18	39	60		102	123	144
RT			36-45*			BOOST***		
SURGERY					78**			

1 cycle = 21 days in length

♦ PEG-Filgrastim should be administered 24-48 hours after completing chemotherapy. 10 days of filgrastim may be substituted.

* Radiation administration will consist of 8 fractions over 10 days, as it is common practice in many centers not to administer radiation therapy on weekends. Whenever possible, both radiation and chemotherapy should be administered together on days 36-38. Initiating chemoradiation on a Monday, Tuesday, or Wednesday for cycle 2 will help ensure concomitant administration during these 3 days prior to the weekend break.

** Sorafenib should be discontinued 1 week before surgery and resumed 1 week after surgery. Note that the timing of surgery and resumption of post-operative chemotherapy presented here are estimations. While adherence to this schedule is a goal, treatment-related complications and other logistical factors may alter scheduled events. In general, surgery should be planned for 2-4 weeks after the initiation of chemotherapy for cycle 3. Deviation from this schedule will be reported in the final analysis. In case of delays, the dates specified above should be appropriately recalculated. If a major wound complication requires additional surgery, reinstitution of chemotherapy (cycle 4) should be initiated only after adequate wound healing has been achieved (a minimum of 2 weeks following the second surgery). Patients who require a delay of greater than 10 weeks since initial surgery due to inadequate wound healing will be removed from further protocol therapy.

*** For patients with positive surgical margins, 12 Gy (200 cGy x 6 fractions) will be given by external beam prior to restarting chemotherapy. Begin radiation 2 weeks after surgery (approximately day 91) assuming wound is healing well.

4.1 Study Drug

Sorafenib will be administered orally 400 mg once daily. Sorafenib will begin 2 weeks before first chemotherapy cycle with epirubicin and ifosfamide. Sorafenib will be held 1 week before and after surgery

4.2 Chemotherapy Dose and Suggested Administration Guidelines (may be modified per institutional standards)

Chemotherapy can be administered on either an inpatient or outpatient basis. No investigational or commercial agents or therapies other than those described in the protocol may be administered with the intent to treat the patient's malignancy. Patients will receive 3 cycles of pre-operative chemotherapy and 3 cycles of post-operative chemotherapy.
Recommended hydration is 0.45 NS + 50 mEq NaHCO3 1L over 2 hours prior to ifosfamide daily.

- Epirubicin: 30 mg/m^2/day I.V., days 1-3 of each cycle. Epirubicin is to be omitted during cycle 2 (concomitant chemoradiation)
- Ifosfamide: 2.5 g/m^2 over 90 minutes I.V., days 1-3 of each cycle. Begin after 1 L hydration

- Mesna: Suggested dosing: 850 mg/m^2 mixed in same bag as ifosfamide, then 850 mg/m^2 I.V. over 15 minutes given 4 hours and 8 hours after start of ifosfamide, days 1-3 of each cycle
- PEG-filgrastim 6 mg administered as a subcutaneous injection starting 24-48 hours after completion of chemotherapy (may substitute filgrastim 5 mcg/kg/day (rounded to nearest vial size) administered as a subcutaneous injection starting 24-48 hours after completion of chemotherapy for 10 days, or until white blood count has recovered after nadir (ANC > 10,000)

4.3 Radiation

Treatment is to consist of one course of external beam radiation therapy (EBRT) coinciding with the start of cycle 2 of chemotherapy. Treatment will consist of a total dose of 28 Gy (350cGy x 8 fractions in 10 days). If treatment falls on a weekend or holiday, treatment can resume the next business day.

The target volume of radiation therapy will include the site of the primary lesion and those tissues suspected of involvement by microscopic disease to a clinically important probability. Physical exam in conjunction with MRI or CT scans obtained during evaluation will be used in defining the target volume. The margins beyond clinically or radiologically-evident sarcoma will be 7 cm. Optimal field arrangement, beam parameters, and shaped blocks will be used to achieve the closest approximation of treatment volume to target volume to minimize irradiation of uninvolved normal tissue. Immobilization devices should be used daily to ensure reproducibility of treatment.

Post-operative EBRT boost will be given for patients with positive margins. The radiation treatment is to be completed by administering 12 Gy in 6 fractions (once a day) to the bed of the residual tumor (including a margin of 1 cm). Boost will not be given for patients with 100% necrosis. EBRT will begin approximately 2 weeks following resection, assuming there is satisfactory healing of the surgical wound. The target volume for the post-operative radiation therapy will be the tumor bed as defined by the operative and pathological findings. Chemotherapy can resume thereafter.

4.4 Surgery

Surgical treatment necessary to resect the tumor with negative margins should be used. All lesions of the trunk and extremities will be treated with conservative resection (minimal wide excision) after pre-operative therapy. Surgical resection should remove as wide a margin of tissue around the tumor as possible without compromising function. Dissection should always be done through grossly normal tissue planes and should be done beyond fascial plane adjacent to the tumor. If the tumor is close to or displaces major vessels or nerves, these need not be removed if the adventitia or perineurium is removed and the margin is not involved pathologically. Frozen section at the time of surgery should be done from the closest margin and should be confirmed as being free of tumor. If postoperative pathology evaluation reveals positive soft-tissue margins other than bone, nerve, or large blood vessels, this margin should be resected if possible. If bone, major blood vessel or nerve is microscopically positive additional radiation should be given as

noted in the protocol. In general, lymph node dissection is not recommended, but a sampling can be performed if the primary tumor is over a major node station. Primary tumors overlying major lymph node stations may best be treated with surgical resection including node dissection. Marker clips (titanium) may be placed to help guide the radiation oncologist. Closed wound suction drainage should be used in all anatomic regions (Davol, Hemavac, etc.) The drains should exit the skin close to the edge of the surgical incision. External compression for extremity resections with ace wraps or compression dressings is advised.

State clearly in the operative note what type of surgical procedure was performed, and from where the frozen section of the margins was taken.

Because all patients will have had radiation, special care must be given to skin flaps. Use of muscle flaps, pedicled myocutaneous flaps, and even free flaps is encouraged to fill dead space and used if there is any concern about the viability of the wound flaps.

In general, the following principles should be followed in post-operative management of these patients:

- Maintain staples or skin sutures per surgeon preference but because of potential delay in wound healing, 3-4 weeks is recommended
- Leave drains until the drainage meets the criteria for surgeon preference for discontinuation
- Begin rehabilitation slowly

Resectability will depend upon the judgment of the operating surgeon. For the extremities, resection must be limb salvage procedure. For other anatomic areas, it must be the judgment of the operating surgeon that he/she may reasonably expect to obtain negative margins. Extremity patients who are not resectable without amputation may be amputated, and should complete chemotherapy per protocol. Unresectable tumors elsewhere may be palliated with additional chemotherapy, per protocol. Patients who would benefit from additional radiation therapy will be withdrawn from protocol therapy.

Note that documentation of wound complications is an integral part of this clinical trial. Wound complications are defined in section 8.5 and must be accurately recorded and reported to the coordinating center.

4.5 Supportive Care Guidelines

Appropriate anti-emetics per institutional standard and at the investigator's discretion should be used with this highly-emetogenic regimen.

Use of erythroid growth factors to support hemoglobin levels are permitted, at the discretion of the investigator.

Prophylactic antibiotics for prevention of neutropenic fever may be used at the discretion of the investigator. Use of prophylactic antibiotics must be recorded in the case report forms.

4.6 Other Concomitant Medications

Sorafenib is metabolized primarily by liver enzymes, in particular CYP3A4. Caution is recommended when administering sorafenib with inducers of the CYP3A4 family.

Concurrent administration of strong CYP3A4 inducers (such as, phenyoin, rifabutin, and rifampin) is not permited. In a clinical interaction study, concurrent administration of sorafenib with rifampin resulted in a 37% decrease in mean sorafenib AUC. Other agents known to moderately induce CYP3A4 should be avoided if possible.

4.7 Duration of Therapy

Treatment should continue until the end of protocol therapy or until one of the following criteria applies:

Disease progression,

The patient would benefit from additional radiation therapy beyond that specified in the protocol,

Intercurrent illness that prevents further administration of treatment,

Unacceptable adverse events(s),

Greater than 3-week delay in therapy due to adverse event

The patient presents with a beta-HCG test consistent with pregnancy.

Patient or legal representative/relative requests to withdraw from the study, or

General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5. DOSE MODIFICATIONS

5.1 Sorafenib Dose Modifications

General Considerations. Sorafenib dosing will be modified for adverse events that are at least in-part *attributable* to sorafenib according to the following dose levels:

Dose Level	Sorafenib
0	400 mg once daily
-1	200 mg once daily
-2*	200 mg every other day

All patients will start treatment at dose level 0.

Patients will be removed from protocol treatment if dose reduction below -2 is indicated.

5.1.1 Dose Modifications for Sorafenib for Hand-Foot Skin Reaction

Grade	Occurrence	Suggested Dose Modification
Grade 1 Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Any	Promptly institute supportive measures such as topical therapy for symptomatic relief and continue sorafenib treatment
Grade 2 Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	First	Promptly institute supportive measures such as topical therapy for symptomatic relief and consider a decrease of sorafenib by one dose level for a minimum of 7 days and up to 28 days • If toxicity resolves to grade 0–1 after dose reduction, increase sorafenib back to previous dose level • If toxicity does not resolve to grade 0-1 despite dose reduction, interrupt sorafenib treatment for a minimum of 7 days and until toxicity has resolved to grade 0–1. ▪ When resuming treatment after dose interruption, resume sorafenib at a one dose level reduction ▪ If toxicity is maintained at grade 0–1 at reduced dose for a minimum of 7 days and up to 28 days, increase back sorafenib to previous dose level
	Second or Third occurrence	As for first occurrence. Upon resuming sorafenib, decrease dose by one dose level. Decision whether to dose re-escalate should be based on clinical judgment and patient preference.
	Fourth occurrence	Decision whether to discontinue sorafenib should be made based on clinical judgment and patient preference
Grade 3 Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	First occurrence	Institute supportive measures such as topical therapy for symptomatic relief and interrupt sorafenib treatment for a minimum of 7 days and until toxicity has resolved to grade 0–1 • When resuming treatment after dose interruption, decrease sorafenib by one dose level • If toxicity is maintained at grade 0–1 at reduced dose for a minimum of 7 days and up to 28 days, increase by one dose level
	Second occurrence	As for first occurrence. Upon resuming sorafenib treatment, decrease dose by one dose level. Decision whether to dose re-escalate should be made based on clinical judgment and patient preference.
	Third occurrence	Decision whether to discontinue sorafenib treatment should be made based on clinical judgement and patient preference.

5.1.2 Dose Modifications for Sorafenib-Associated Hypertension

Hypertension is a known and potentially serious adverse event associated with sorafenib treatment. Patients will have their blood pressure monitored and recorded weekly during the first 6 weeks of therapy, either at the doctor's office or by using any calibrated electronic device (such as those found at a local drug store or pharmacy). Patients will record their weekly blood pressure during the first 6 weeks on their drug diary, a copy of which will remain in the research chart. If the patient's blood pressure is elevated at any time (>150/100), even outside clinic visits, they should contact their treating physician.

Grade (CTCAE v4.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 1	None	Routine	No change
Grade 2	Initiate monotherapy (suggest dihydropyridine calcium-channel blocker)	Increase frequency and monitor (by health professional) every 2 days until stabilized	No change
Grade 3	Add agent(s): Ca^{++} channel blocker (if not already used), K+ channel opener (angiotensin blockers), beta-blocker, thiazide diuretic	Increase frequency and monitor (by health professional) every 2 days until stabilized; continue qod monitoring to stabilization after dosing restarted.	Hold* sorafenib until symptoms resolve and diastolic BP < 100 mm/Hg. Resume treatment at 1 dose level lower
Grade 4			Off protocol therapy
* Patients requiring a delay of > 21 days should go off protocol therapy			
CTCAE v4.0 definitions Grade 1: Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg) Grade 2: Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated. Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated Grade 3: Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated. Pediatric: Same as adult Grade 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated. Pediatric: Same as adult			

5.1.3 Dose Modifications for Other Sorafenib-Associated Toxicity

Toxicity	Grade 1	Grade 2	Grade 3*	Grade 4*
Non-hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1, then resume treatment at the same dose level. If patient experiences a second grade 3 toxicity, withhold dose until toxicity is grade ≤1, then reduce one dose level and resume treatment.	Withhold dose until toxicity is grade ≤1, then reduce one dose level and resume treatment, or discontinue at the discretion of the principal investigator.
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤2, then resume treatment at the same dose level. If patient experiences a second grade 3 toxicity, withhold dose until toxicity is grade ≤2, then reduce one dose level and resume treatment.	Withhold dose until toxicity is grade ≤2, then reduce one dose level and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study supporter.

*Patients who develop grade 3 fever/chills, grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, grade 3 leukopenia, or grade 3/grade 4 lymphopenia may continue study treatment without interruption at the discretion of the investigator.

Because certain grade 3-4 adverse events are common with epirubicin, ifosfamide and radiotherapy, the above table should be modified for these adverse events as defined below (unless the adverse events are definitely attributable only to sorafenib, in which case refer to above table). Attribution to sorafenib at least in-part should be present in order to justify sorafenib dose-reduction:

- Neutropenia – Grade 3 or Grade 4 lasting ≤7 days: no action. Grade 4 lasting >7 days: refer to table above
- Neutropenic Fever – Grade 3 lasting ≤5 days: no action. Grade 3 lasting >5 days or Grade 4: refer to table above
- Leukopenia – No dose reduction
- Thrombocytopenia -- Grade 3: no action. Grade 4 lasting ≤ 5 days: no action, Grade 4 lasting > 5 days: refer to table above. Grade 3-4 thrombocytopenia with clinically significant bleeding: refer to table above.
- Anemia – Grade 3: no action. Grade 4: refer to table above

- Nausea/Vomiting – Per above table, only if persistent Grade 3-4 despite maximal anti-emetic adjustment
- Fatigue – Grade 3: no action. Grade 4: refer to table above.
- Diarrhea – Diarrhea should be initially managed with anti-diarrhea agents including loperamide or Lomotil. If persistent Grade 3- 4 toxicity, refer to table above.
- Hypophosphatemia/Hypokalemia – Grade 3: replacement therapy. Grade 4: refer to above table only if refractory to replacement therapy
- Transaminitis – Grade 3 with ALT and AST: Monitor liver function tests until resolution. Consider dose reduction at investigator's discretion.

5.2 Chemotherapy Dose Modifications

Dose modifications for epirubicin and ifosfamide-related toxicity will be based on the following dose level schema. All patients will start treatment at dose level 0. Patients who require a reduction of dose below Dose Level –3 will be removed from the study.

Dose Level	**Dose Epirubicin (mg/m^2 D1-3)**	**Dose Ifosfamide (mg/m^2 D1-3)**
0	30	2500
-1	22.5	2500
-2	22.5	2000
-3	20	1750

5.2.1 Hematologic Toxicity

5.2.1.1 A treatment cycle may not begin unless the patient's absolute neutrophil count (ANC) is ≥1500/μL and platelet count is ≥75,000/μL (without transfusion).

5.2.1.2 **Grade 4 neutropenic fever, grade 3 neutropenic fever lasting >5 days, or grade 4 neutropenia for >7days:** reduce by one dose level for next and all subsequent cycles

5.2.1.3 **Grade 3-4 thrombocytopenia with clinically significant bleeding or grade 4 thrombocytopenia lasting >5 days:** reduce by one dose level for next and all subsequent cycles

5.2.1.4 **Anemia:** Institution of erythropoietin or darbopoietin at physician's discretion

5.2.2 Non-hematologic Toxicity

Patients who experience Grade 3 or 4 toxicity that is attributable to chemotherapy and not to the underlying disease should have chemotherapy held until the toxicity resolves to ≤ Grade 1. Treatment should then be resumed at a

reduction of one dose level for the next and all subsequent cycles (see exceptions below). Patients who are delayed greater than 3 weeks due to non-resolution of such toxicity will be taken off study.

5.2.2.1 Nausea and Vomiting: Grade 3 or 4 nausea or vomiting should be managed with anti-emetic adjustments (at treating physicians discretion) before a dose-reduction is performed

5.2.2.2 Cardiac Toxicity: Patients who experience a Grade 3 or greater impairment in left ventricular function (decline of ≥ 20% of baseline LVEF or symptomatic congestive heart failure) or Grade 3 or greater left ventricular systolic dysfunction should immediately be removed from protocol therapy.

5.2.2.3 Renal Toxicity: Patients who experience grade 2 or greater Acute Kidney Injury or Hematuria should have therapy held until the toxicity resolves to ≤ Grade 1. Treatment should then be resumed at the next lower dose level that includes a lower dose of ifosfamide (i.e. reduce from dose level 0 or -1 to dose level -2, reduce from dose level -2 to dose level -3) for the next and all subsequent cycles, at the discretion of the treating physician.

5.2.2.4 Electrolyte Wasting: Electrolyte wasting, especially potassium and phosphorous, is a common effect of ifosfamide therapy due to renal tubular effects. Grade 3 or greater hypokalemia and/or hypophosphatemia should be managed with appropriate electrolyte replacement. If electrolyte wasting is refractory to replacement therapy, a dose reduction should be undertaken to the next lower dose level that includes a lower dose of ifosfamide

5.2.2.5 CNS Toxicity: Patients who experience grade 3 or greater Encephalopathy should have therapy held until the toxicity resolves to ≤ Grade 1. Treatment should then be resumed at the next lower dose level that includes a lower dose of ifosfamide (i.e. reduce from dose level 0 or -1 to dose level -2, reduce from dose level -2 to dose level -3) for the next and all subsequent cycles. If a patient is to be removed from study due to reaching the maximum allowable number of dose level reductions, and if these reductions were due to ifosfamide-related CNS toxicity, then the patient will be allowed to continue on treatment with omission of ifosfamide and continuation of epirubicin and sorafenib.

6. AGENT FORMULATION AND PROCUREMENT

6.1 *Sorafenib (Nexavar)*

Availability: Sorafenib will be supplied for this study

Product description: Sorafenib 200 mg is supplied as round, biconvex, red-film-coated tablets, debossed with the 'Bayer cross' on one side and '200' on the other side. The tablets contain sorafenib tosylate equivalent to 200 mg of the free base sorafenib, and the excipients croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, and magnesium stearate. The film-coat consists of

hypromellose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active sorafenib tosylate. Study Drug can be supplied as sorafenib 200 mg commercial tablets in bottles of 140 tablets with a product identification label affixed or as commercial Nexavar in bottles of 120 tablets.

Storage requirements: Do not store above 25°C (77°F). Store in the original package.

Stability: The current shelf life is 36 months.

Route of administration: Orally. Sorafenib should be given on an empty stomach 1 hour before 2 hours after a meal.

Pregnancy: Women should avoid becoming pregnant while on therapy. Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes sever malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity). Sorafenib should not be used during pregnancy. Breastfeeding should be discontinued during sorafenib therapy.

Expected adverse events: The following additional drug-related adverse events and laboratory abnormalities were reported from clinical trials of sorafenib in 1286 cancer patients who received sorafenib as monotherapy (*very common* 10% or greater, *common* 1 to less than10%, *uncommon* 0.1% to less than 1%):

Cardiovascular**:** *Uncommon:* hypertensive crisis, myocardial ischemia and/or infarction

Dermatologic: *Very common:* erythema *Common:* exfoliative dermatitis, acne, flushing *Uncommon:* folliculitis, eczema, erythema multiforme

Digestive: *Very common:* increased lipase, increased amylase *Common:* mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia *Uncommon:* pancreatitis, gastrointestinal reflux, gastritis. Note that elevations in lipase are very common; a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values

General Disorders: *Very common:* asthenia, pain (including mouth pain, bone pain, and muscle pain) *Common:* decreased appetite, influenza-like illness, pyrexia *Uncommon:* infection

Hematologic: *Very common:* leukopenia, lymphopenia *Common:* anemia, neutropenia, thrombocytopenia *Uncommon:* INR abnormal

Hypersensitivity: *Uncommon:* hypersensitivity reactions (including skin reactions and urticaria)

Metabolic and Nutritional**:** *Very common:* hypophosphatemia *Common:* transient increases in transaminases *Uncommon:* dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism

Musculoskeletal: *Common:* arthralgia, myalgia

Nervous System and Psychiatric: *Common:* depression *Uncommon:* tinnitus

Reproductive**:** *Common:* erectile dysfunction *Uncommon:* gynecomastia

Respiratory: *Common:* hoarseness *Uncommon:* rhinorrhea

In addition, the following medically significant adverse events were reported

infrequently during clinical trials of sorafenib: cerebral hemorrhage, transient ischemic attack, cardiac failure, arrhythmia, thromboembolism, acute renal failure. For these events, the causal relationship to sorafenib has not been established.

Effects on fertility: Results from animal studies indicate that sorafenib can impair male and female fertility.

6.2 *Epirubicin (Ellence)*

Availability: Epirubicin is commercially available.

Product description: Epirubicin is available in polypropylene single-use vials containing 2 mg epirubicin hydrochloride per mL as a sterile, preservative-free ready-to-use solution in 50 mg and 200 mg vials.

Solution preparation: Epirubicin is available as a preservative-free, ready-to-use solution.

Storage requirements: Store refrigerated between 2ºC and 8ºC (36ºF and 46ºF). Do not freeze. Protect from light.

Stability*:* Epirubicin should be used within 24 hours of first penetration of the rubber stopper.

Route of administration: Intravenous administration of epirubicin should be performed with caution. It is recommended that epirubicin be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose solution) over a period of 3 to 5 minutes. This technique is intended to minimize the risk of thrombosis or perivenous extravasation, which could lead to severe cellulites, vesication, or tissue necrosis. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Pregnancy: Women should avoid becoming pregnant while on therapy. Breastfeeding should be discontinued during therapy.

Expected adverse events:

Hematologic: A dose-dependent, reversible leukopenia and/or neutropenia is the predominant manifestation of hematologic toxicity. Severe thrombocytopenia and anemia may also occur.

Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis

Dermatologic: Alopecia, flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin.

Extravasation: Infiltration can cause severe inflammation, tissue necrosis, and ulceration. If the drug is infiltrated, consult institutional policy, apply ice to area, and elevate the limb. May require debridement.

Cardiac: Anthracycline-induced cardiac toxicity may be manifested by early or late events. Early cardiac toxicity consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes, but tachyarrhythmias , bradycardia, as well as atrioventricular and bundle-branch block have also been reported. Delayed cardiotoxicity results from a characteristic cardiomyopathy that is manifested by reduced LVEF and/or signs and symptoms of congestive heart failure.

The probability of developing CHF increases with increasing cumulative doses of epirubicin. The risk of developing CHF in the absence of other cardiac risk factors increases steeply after an epirubicin cumulative dose of 900 mg/m^2.

Secondary Leukemia: The occurrence of secondary acute myelogenous leukemia has been reported in patients treated with anthracyclines.

Miscellaneous: Allergic reaction, anaphylaxis.

6.3 *Ifosfamide (Ifex)*

Availability: Ifosfamide is commercially available.

Product description: Ifosfamide is available as a powder for reconstitution in 1 and 3 g vials.

Solution preparation: Dilute powder with SWI or NS to a concentration of 50 mg/mL as follows. **DO NOT USE BACTERIOSTATIC SWI OR NS** - incompatible; solution is stable for 7 days at room temperature and 6 weeks under refrigeration

1 g vial = 20 mL

3 g vial = 60 mL

Storage and Stability: Further dilution in NS, D5W or LR is stable for 7 days at room temperature and 6 weeks under refrigeration. Compatible with mesna in NS for up to 9 days at room temperature. Store intact vials at room temperature or under refrigeration.

Route of administration: Administer ifosfamide IVPB over 90 minutes. Adequate hydration (at least 2 L/day) of the patient during therapy is recommended to minimize the risk of hemorrhagic cystitis. Mesna should be administered concomitantly, 4 hours after and 8 hours after ifosfamide administration.

Pregnancy: Women should avoid becoming pregnant while on therapy. Breastfeeding should be discontinued during therapy.

Expected adverse events:

Central nervous system: Somnolence, confusion, hallucinations in 12% and coma (rare) have occurred and are usually reversible; usually occur with higher doses or in patients with reduced renal function; depressive psychoses, polyneuropathy. **Note:** CNS depression can be reversed with methylene blue (50 mg intravenously) and methylene blue is recommended for prophylaxis for subsequent doses if the patient has CNS manifestations with the first dose.

Dermatologic: Alopecia occurs in 50% to 83% of patients 2-4 weeks after initiation of therapy; may be as high as 100% in combination therapy. Phlebitis, dermatitis, nail ridging, skin hyperpigmentation, impaired wound healing.

Gastrointestinal: Nausea and vomiting in 58% of patients is dose and schedule related (more common with higher doses and after bolus regimens); nausea and vomiting can persist up to 3 days after therapy; also anorexia, diarrhea, constipation, transient increase in LFTs and stomatitis noted.

Genitourinary: Hemorrhagic cystitis has been frequently associated with the use of ifosfamide; a urinalysis prior to each dose should be obtained; **ifosfamide should never be administered without a uroprotective agent (MESNA)**; hematuria has been reported in 6% to 92% of patients; renal toxicity occurs in 6% of patients and is

manifested as an increase in BUN or serum creatinine and is most likely related to tubular damage; renal toxicity, including ARF, may occur more frequently with high-dose ifosfamide; metabolic acidosis may occur in up to 31% of patients.

Endocrine & metabolic: SIADH

Hematologic: Myelosuppression: Leukopenia is mild to moderate, thrombocytopenia and anemia are rare. However, myelosuppression can be severe when used with other chemotherapeutic agents or with high-dose therapy; be cautious with patients with compromised bone marrow reserve

Respiratory: Nasal stuffiness, pulmonary fibrosis

Cardiovascular: Cardiotoxicity

Miscellaneous: Immunosuppression, sterility, possible secondary malignancy, allergic reactions

6.4 *Mesna (Mesnex)*

Availability: Mesna is commercially available.

Product description: Mesna is available as a sterile, preservative-free aqueous 100 mg/mL solution in 200 mg ampules or 1 g multidose vials. Mesna tablets are available as a white, oblong, scored, film coated 400 mg tablet.

Mechanism of action: Mesna is a uroprotecant whose oxidized form dimesna binds to and inactivates acrolein, a urotoxic metabolite of cyclophosphamide and ifosfamide.

Solution preparation: Mesna can be diluted in D5W or NS to a final concentration of 1-20 mg/mL.

Storage and Stability: Diluted solutions are chemically and physically stable for 24 hours at room temperature; polypropylene syringes are stable for 9 days at refrigeration or room temperature; injection diluted for oral administration is stable 24 hours at refrigeration

Route of administration: Mesna may be mixed in same bag as ifosfamide or administered separately IVPB over 15 minutes.

Mesna injection may also be administered orally. For oral administration, injection may be diluted in 1:1, 1:2, 1:10, 1:100 concentrations in carbonated beverages (cola, ginger ale, Pepsi®, Sprite®, Dr Pepper®, etc), juices (apple or orange), or whole milk (chocolate or white), and is stable 24 hours at refrigeration. Mesna tablets should be given orally and absorption is not affected by food. Mesna tablets are approximately 50% bioavailable and are generally dosed at 2 & 6 hours after the first mesna dose, which is usually given intravenously, to account for the delayed absorption with an oral vs. the intravenous product

Pregnancy: Women should avoid becoming pregnant while on therapy. Breastfeeding should be discontinued during therapy.

Expected adverse events:

Cardiovascular: Hypotension

Central nervous system: Malaise, headache

Gastrointestinal: Diarrhea, nausea, vomiting, bad taste in mouth, soft stools

Neuromuscular & skeletal: Limb pain

Dermatologic: Skin rash, itching

6.5 *Pegfilgrastim (Neulasta)*

Availability: Pegfilgrastim is commercially available.

Product Description: Neulasta™ is supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27 gauge, 1/2 inch needle with an UltraSafe® Needle Guard. Neulasta™ is provided in a dispensing pack containing one syringe (NDC 55513-190-01).

Storage and Stability: Neulasta™ should be stored refrigerated at 2° to 8°C (36° to 46°F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, Neulasta™ may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Neulasta™ left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, Neulasta™ should be allowed to thaw in the refrigerator before administration. If frozen a second time, Neulasta™ should be discarded.

Route of Administration: The recommended dosage of Neulasta™ is a single subcutaneous (SC) injection of 6 mg administered once per chemotherapy cycle. Neulasta™ should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy. The 6 mg fixed-dose formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg. Neulasta™ should be visually inspected for discoloration and particulate matter before administration. Neulasta™ should not be administered if discoloration or particulates are observed.

Neulasta™ is supplied in prefilled syringes with UltraSafe® Needle Guards. Following administration of Neulasta™ from the prefilled syringe, the UltraSafe® Needle Guard should be activated to prevent accidental needle sticks. To activate the UltraSafe® Needle Guard, place your hands behind the needle, grasp the guard with one hand, and slide the guard forward until the needle is completely covered and the guard clicks into place. NOTE: If an audible click is not heard, the needle guard may not be completely activated. The prefilled syringe should be disposed of by placing the entire prefilled syringe with guard activated into an approved puncture-proof container.

Pregnancy: Women should avoid becoming pregnant while on therapy. Breastfeeding should be discontinued during therapy.

Expected Adverse Events:

Bone pain was the most frequent adverse event attributable to pegfilgrastim in clinical trials. Hypoxia was observed in one patient. Toxicities associated with the parent compound, filgrastim include:

Central nervous system: Neutropenic fever, fever.

Dermatologic: Alopecia.

Gastrointestinal: Nausea, vomiting, diarrhea, mucositis, splenomegaly (this occurs more commonly in patients with cyclic neutropenia/congenital agranulocytosis who received S.C. injections for a prolonged (>14 days) period of time; ~33% of these

patients experience subclinical splenomegaly; ~3% of these patients experience clinical splenomegaly).

Neuromuscular & skeletal: Medullary bone pain (24% incidence--this occurs most commonly in lower back pain, posterior iliac crest, and sternum and is controlled with non-narcotic analgesics), weakness.

Cardiovascular: Chest pain, fluid retention, transient supraventricular arrhythmia, pericarditis.

Central nervous system: Headache.

Dermatologic: Skin rash.

Gastrointestinal: Anorexia, stomatitis, constipation.

Hematologic: Leukocytosis.

Local: Pain at injection site, thrombophlebitis.

Respiratory: Dyspnea, cough, sore throat.

Miscellaneous: Anaphylactic reaction.

7. CORRELATIVE / SPECIAL STUDIES

7.1 Angiogenic Biomarkers

Plasma will be collected for measurement of tumorigenic and angiogenic markers including p-ERK, VEGF, sVEGFR2, and bFGF at baseline, week 2 (after sorafenib run-in), and then every 3 weeks through completion of treatment. Blood samples (10 mL) will be drawn using venipuncture into a Vacutainer containing potassium EDTA and inverted gently several times to mix with anticoagulant. Within 10-15 minutes after collecting, blood samples will be centrifuged in a refrigerated (4°C) centrifuge for 10 minutes to separate the plasma. If a refrigerated centrifuge is not available, the tubes should be chilled in an ice bath for 5-15 minutes and then placed in a standard centrifuge for 10 minutes to separate the plasma. The plasma will be transferred to polypropylene tubes and frozen at -70°C or lower. The tubes will be labeled with the investigator's name, study number, and subject's study number, and time and date of the sample acquisition.

Fresh tumor tissue will be collected when possible at baseline and at time of resection. Tissue will be immediately frozen with liquid nitrogen and stored at –70°C or lower. Tumor tissue will be mechanically homogenated for 5 minutes on ice in 1 ml of extraction buffer per 100 mg tissue wet weight, and extract obtained after centrifugation for 20 minutes at 4°C will be transferred to polypropylene tubes and frozen at -70°C or lower. The tubes will be labeled with the investigator's name, study number, and subject's study number, and time and date of the sample acquisition.

Quantitative enzyme-linked immunosorbent assays (ELISA) for p-ERK, VEGF, sVEGFR2, and bFGF will be performed on plasma and tumor extracts using commercial kits. Manufacturers' protocols will be followed and samples are to be measured in duplicate.

Paraffin block of the primary tumor biopsy and resected tumor will be obtained. Representative areas from each whole-mount paraffin block chosen as the best composite representation of tumor based on H&E morphology will be placed in

standard-sized tissue cassettes. These will be re-embedded, sectioned at 4 μm, and mounted on poly-L-lysine–coated slides for immunohistochemistry. Sections of paraffin embedded tissue will be deparaffinized and rehydrated. After appropriate antigen retrieval methods, staining with commercial antibodies for p-ERK, VEGF-R2, phospho-VEGF-R2, PDGFR, and phospho-PDGFR will be performed using an automated Dako immunostainer. Staining will be visualized by incubating the slides with 3,3'-diaminobenzidine solution, after which they will be rinsed, counterstained with hematoxylin, dehydrated in a Leica Autostainer XL, coverslipped, and reviewed by a single experienced pathologist who will score the percentage of positively staining cells

8. STUDY PROCEDURES AND SCHEDULE OF EVENTS

8.1 Subject Registration

Written informed consent must be obtained before any study specific medical procedures are performed.

All patients must be registered with the Oregon Health & Science University Cancer Center.

8.2 Baseline Screening

To be completed within 6 weeks of registration:

CT of Chest

CT or MRI of primary disease site

To be completed within 4 week of registration:

History & Physical, including vitals, PS

EKG

MUGA or ECHO

To be completed within 1 week of registration:

Labs, pregnancy test, urinalysis

(Pregnancy test must be repeated prior to dispensing Sorafenib to the patient if completed >7 days before treatment start)

8.3 Study Visits

See table 8.7

Toxicities and adverse experiences will be assessed at each visit using the NCI Common Toxicity Criteria for Adverse Events v4.0 (http://ctep.cancer.gov). Assessment of study drug attribution will be made by an Investigator. **Acute and long-term radiation toxicity will be assessed for the following CTCAE categories: 1) Injury, poisoning and procedural complications: Dermatitis radiation 2) Musculoskeletal and connective tissue disorders: Fibrosis (superficial and/or deep) 3) other appropriate Musculoskeletal and connective tissue disorders AEs appropriate to limb function.**

8.4 Pathology Sample Submission

All pathology slides from the initial diagnostic biopsy and the post-chemoradiation

excision must be submitted for central review at OHSU by a pathologist experienced in sarcoma. For the post therapy excision, the specimen should be sectioned parallel to the long axis of the tumor; a full face of the plane of greatest cross sectional area should be fixed and blocked in, up to 20 sections. If there are central cystic necrotic areas, they can be noted in a specimen diagram and not sampled.

8.5 Assessment of Wound Complications

An accurate assessment of post-operative wound complications is vital for the accurate reporting of toxicity associated with this regimen. Major wound complications will be defined as described by O'Sullivan et. al. in the prospective, randomized study of preoperative vs. postoperative radiation.[7]

A major wound complication is defined as a secondary operation under general or regional anesthesia for wound repair (debridement, operative drainage, and secondary wound closure including rotationplasty, free flaps, or skin grafts), or wound management without secondary operation. Wound management includes an invasive procedure without general or regional anesthesia (such as aspiration of seroma), readmission for wound care such as intravenous antibiotics, or persistent deep packing for 120 days or longer.

8.6 Follow-up

Follow-up for all patients registered on this study, including those who do not receive any protocol therapy, will be required until the patient's death. Follow-up after completion of protocol therapy will be limited to monitoring for 1) development of local tumor recurrence, 2) development of distant metastatic disease, 3) survival, and 4) late toxicity, including limb function impairment and secondary malignancy. Follow-up reports are due every 4 months.

8.7 Schedule of Events

	Prior to Registration	Prior to Day 1 of each cycle*	Time of Pre-Surgical Restaging**	Post Treatment Follow-up
Tests & Observations				
History and Progress Notes	X	X	X	X
Physical Examination	X	X	X	X
Pulse, Blood Pressure###	X	X	X	X
Height/Weight***	X	X		
Performance Status	X	X	X	X
Treatment Toxicity Assessment		F	F	F
Pathology Review	A		A	
Laboratory Studies				
CBC, Differential, Platelets	X	B,C	X	PRN
Serum Chemistries#	X	B,C	X	PRN
Urinalysis	X	C		
Pregnancy Test##	X	X		
INR	X	H		
EKG	X			PRN
MUGA or ECHO	X		X	D
Blood for correlative studies (Section 7.1)	X	X	X	
Staging				
Chest CT	X		X	E
MRI or CT of primary site	G		G	E

* To be performed within 1 week of each chemotherapy cycle

** After completion of cycle 3 of chemoradiotherapy and within 4 weeks of surgery

*** Height only needs to be checked prior to cycle #1 if the patient's height is stable (i.e. not currently in puberty).

\# Electrolytes (including Phos, Mg), BUN, creatinine, bilirubin, AST, ALT, alkaline phosphatase

For women of childbearing potential. Screening pregnancy test does not need to be repeated if within 7 days of start of Sorafenib run-in. Will be repeated prior to each cycle of chemotherapy.

Blood pressure to be monitored weekly during the first 6 weeks of protocol treatment

A Initial diagnostic pathology specimen as well as post-operative specimen must be submitted for central review. Both specimens may be submitted together after surgery

B To be checked once weekly during each cycle or as clinically indicated

C Must be checked within 24 hours prior to each chemotherapy cycle

D As clinically indicated

E Post-treatment imaging studies for disease recurrence is at investigator's discretion. It is suggested that a chest CT or chest X-ray be performed every 4 months for the first 2 years, every 6 months for the 3rd year, and yearly for the 4th and 5th year. It is suggested that MRI or CT of the primary site be obtained yearly for the first 3 years.

F Toxicity assessments per CTCAE v 4.0 (See section 8.3). Long term follow-up for radiation toxicity and limb function required per section 8.3

G An MRI or CT of the primary tumor should be performed within 6 weeks prior to registration and again prior to surgery per standard care decision of the subject's surgeon

H INR should be closely monitored for patients receiving warfarin. INR does not need to be monitored during study for patients not receiving warfarin.

9. MEASUREMENT OF EFFECT

9.1 Pathologic Response

All specimens of primary tumor will be examined for pathologic response at the time of surgery. The study pathologist will estimate the amount of viable tumor, and report the percentage of necrosis. For purpose of analysis, tumors will be classified as either ≥95% necrosis or <95% necrosis.

9.2 Radiographic and Clinical Response

The radiographic and/or clinical response of the primary tumor to preoperative therapy will be evaluated. For subjects with stage IIb or III disease, the primary lesion will serve as the sole target lesion and will be recorded and measured at baseline. For patients with stage IV disease, target lesions will be chosen according to RECIST procedure. The longest diameter (LD) of the target lesions will be measured and reported as the baseline LD. The baseline LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.[56] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

9.3 Response Criteria

9.3.1 Evaluation of target lesions

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

9.3.2 Evaluation of best overall response

The best overall response is the best response achieved prior to surgical resection of the target lesion.

Target Lesions	New Lesions	Overall Response
CR	No	CR
PR	No	PR
SD	No	SD
PD	Yes or No	PD
Any	Yes	PD

Note:
In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, this will be determined at the time of surgical resection.

9.4 Confirmatory Measurement/Duration of Response

9.4.1 Confirmation

Given that the target lesion will be surgically removed after the first evaluation for response, no confirmatory scans will be able to be performed.

9.4.2 Duration of overall response

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

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

9.4.3 Duration of Stable Disease

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

9.5 Time-to-Event Measures

9.5.1 Time to Local Recurrence

Defined as the duration of time from surgical resection of the primary tumor until local recurrence (amputated patients excluded).

9.5.2 Local Disease-Free Survival

Defined as the duration of time from surgical resection of the primary tumor until local recurrence or death, whichever occurs first.

9.5.3 Distant Disease-Free Survival

Defined as the duration of time from registration until development of distant metastatic disease or death, whichever occurs first. Subjects with stage IV disease will be censored from this analysis.

9.5.4 Disease-Free Survival

Defined as the duration of time from surgical resection to local recurrence, distant metastatic disease, or death, whichever occurs first. Subjects with stage IV disease will be censored from this analysis.

9.5.5 Progression-Free Survival

Defined as the duration of time from registration to progressive disease (per RECIST), local recurrence, distant metastatic disease (exclusive of stage IV subjects), or death, whichever occurs first.

9.5.6 Overall Survival

Defined as the interval of time from registration until death from any cause.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (CI) Clinical Research Review Committee (CRRC) and appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

10.2 Informed Consent

Written informed consent will be obtained from all patients, or the legally authorized representative of the patient, participating in this trial, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. If a patient's signature cannot be obtained, and for all patients under the age of 18, the investigator must ensure that the informed consent is signed by the patient's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the patient's medical record.

10.3 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the patient. In that event, the investigator must notify the CRRC and IRB in writing within 10 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol.

10.4 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Research Management. Records must be maintained according to sponsor or FDA requirements.

10.5 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems (UP) and Adverse Events (AE) will be reported to IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site http://www.ohsu.edu/research/rda/irb/policies.shtml.

Fatal and life-threatening UP will be reported to OHSU IRB within 7 days of notification of the event. All other UP reports will be submitted to OHSU IRB no later than 15 days of occurrence or notification of the event. Copies of the report documents will be kept in the study regulatory binder. If any of these require a change (as determined by the PI or the IRB) to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the OHSU IRB.

UP and AE reports are submitted through OHSU e-IRB and will be reviewed by OHSU Knight Cancer Institute and IRB. Monthly accumulative reports will be reviewed by a DSMC Oncologist and forwarded to the CRRC.

10.6 Adverse Event Definitions

10.6.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The adverse event does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An adverse event occurring in the course of the use of a drug product in professional practice.
- An adverse event occurring from an overdose whether accidental or intentional.
- An adverse event occurring from drug abuse.
- An adverse event occurring from drug withdrawal.
- An adverse event where there is a reasonable possibility that the event occurred purely as a result of the subject's participation in the study (e.g. adverse event or serious adverse event due to discontinuation of anti-hypertensive drugs during wash-out phase) must also be reported as an adverse event even if it is not related to the investigational product.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an adverse event as it is already reflected as a data point

captured in the CRF. If, however, the event fulfills any of the criteria for a "serious" adverse event, it must be recorded and reported as such.

10.6.2 Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours.

OR

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study).

OR

- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfil the criteria of 'medically important' and as such may be reportable as a serious adverse event dependant on clinical judgement. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the "WHO Adverse Reaction Terminology – Critical Terms List. These terms either refer to or might be indicative of a serious disease state. Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

10.6.3 Unexpected Adverse Event

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current Package Inserts for Nexavar (sorafenib). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. An event more specific or more severe than described in the package insert would be considered "unexpected".

10.6.4 Relationship of Adverse Event to Investigational Product

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

An assessment of 'No' would include:

- The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.

OR

- Non-Plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of 'Yes' indicates that there is a reasonable suspicion that the adverse event is associated with the use of the investigational drug.

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subjects response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

10.6.5 Intensity (Severity) of the Adverse Event

The intensity or severity of adverse events should be graded according to NCI-CTC version 4.0 criteria.

10.6.6 Adverse Event Documentation

All adverse events occurring after the subject has signed the informed consent must be fully recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

10.7 Reporting of Serious Adverse Events to the Sponsor

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE, unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

All serious adverse events should be reported to Bayer/Onyx within 24 hours. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures. In brief:

The Investigator/Sponsor may report serious adverse drug reactions (SADRs) using either:

An ADEERS form (Adverse Event Expedited Reporting System) available at http://ctep.cancer.gov/reporting/adeers.html

OR

A MedWatch form available at http://www.fda.gov/medwatch/

All reports shall be sent electronically to:

Electronic Mailbox:	DrugSafety.GPV.US@bayer.com
Facsimile:	(973) 709-2185
Address:	Global Pharmacovigilance - USA
Mail only	Bayer HealthCare Pharmaceuticals Inc. P.O. Box 1000 Montville, NJ 07045-1000
Address: **FDX or UPS only**	340 Changebridge Road Pine Brook, NJ 07058

Reports for all Bayer products can also be phoned in via our Clinical Communications Dept:

Phone:	1-888-842-2937

10.8 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each patient treated on this protocol. OHSU Knight Cancer Institute (CI), through the auditing function of the Knight Clinical Trials Office, is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies. The Data and Safety Monitoring Committee (DSMC) is responsible for conducting Quality Assurance audits on CI approved protocols according to the Data and Safety Monitoring Plan policies and procedures
http://ozone.ohsu.edu/cancer/sharedres/kctoresdocs.cfm

Locally initiated studies will be audited by an OHSU Knight CI Auditor. Newly approved studies may be audited any time after enrollment has been initiated. Each OHSU Knight approved treatment protocol will be audited on an annual basis in accordance with the Knight Data and Safety Monitoring Plan. .

10.9 Inclusion of Women, Minorities and Children

10.9.1 Inclusion of Women and Minorities

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied.

Table 1: Population Demographics - Oregon (%)

Ethnic Category	**Sex/Gender**		
	Females	Males	Total
Hispanic or Latino			11.7
Not Hispanic or Latino			88.3
Ethnic Category: Total of all subjects*			100*
Racial Category			
American Indian or Alaskan Native			1.4
Asian			3.7
Black or African American			1.8
Native Hawaiian or other Pacific Islander			0.3
White			83.6

Ethnic Category	Sex/Gender		
	Females	Males	Total
More than one race			3.8
Unknown/Other			5.3
Racial Category: Total of all subjects*			100*
TOTALS	50.4	49.6	100*

Source: Adapted from U.S. Census Bureau, 2000 *Totals may not equal 100 due to rounding

Table 2: Projected Accrual for the Present Study (enter actual estimates, not percentages).

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	1-2	1-2	0	2-3
Not Hispanic or Latino	8-9	8-9	0	17-18
Unknown	0	0	0	0
Ethnic Category: Total of all subjects	10	10	0	20
Racial Category				
American Indian or Alaskan Native	0-1	0-1	0	0-1
Asian	0-1	0-1	0	0-1
Black or African American	0-1	0-1	0	0-1
Native Hawaiian or other Pacific Islander	0-1	0-1	0	0-1
White	8-9	8-9	0	16-17
More than one race	0-1	0-1	0	0-1
Unknown	0-1	0-1	0	0-1
Racial Category: Total of all subjects	10	10	0	20

Source: **Adapted from U.S. Census Bureau, 2010.**

10.9.2 Inclusion of Children

In accordance with NIH guidelines on the inclusion of children as participants in research involving human subjects, children under the age of 18 years must be included in all human subjects' research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them. Therefore, proposals for research involving human subjects must include a description of plans for the inclusion of children.

This protocol does not include children <18 years of age for the following reason: no dosing or adverse event data are currently available on the use of sorafenib in combination with ifosfamide and epirubicin in children, therefore,

children <18 years of age are excluded from this study but will be eligible for future pediatric phase 2 combination trials.

11. STATISTICAL CONSIDERATIONS

This is a single-stage, single-arm phase II clinical trial to determine the pathologic response rate **(≥ 95% necrosis) in the operative specimen.**

11.1 Study endpoints

11.1.1 Primary endpoint

The primary endpoint is the pathologic response rate.

11.1.2 Secondary endpoint

Secondary endpoints include level of toxicity, would complication rate, overall survival, overall disease-free survival, distant disease-free survival and local disease-free survival.

11.2 Statistical analysis plan

Descriptive statistical analysis will be conducted for the primary and secondary endpoints. The proportion with 95% confidence interval will be summarized for the categorical variables. Method of Kaplan-Meier will be used to estimate the survival functions.

We will also conduct exploratory analysis to investigate levels of tumor proliferation and angiogenic markers including p-ERK, VEGF, sVEGFR-2, bFGF in the plasma and tumor tissue at baseline, during, and after treatment with sorafenib plus chemoradiotherapy and to evaluate expression of tumorigenic and angiogenic factors including p-ERK, VEGF-R2 and PDGFR in tumor tissue by immunohistochemical staining. These analyses will be conducted in an exploratory manner with the aim of generating clinically and biologically interesting hypotheses.

11.3 Sample size consideration

This is a single-stage single-arm phase II clinical study. We expect to enroll a total of 20 patient for achieving 80% power at a significance level of 5% using one-sided binomial test. The null hypothesis to be tested is that the pathologic response rate is 25%, and we assume the pathologic response rate after preoperative treatment with sorafenib, epirubicin, ifosfamide and hypofractionated radiation for high risk soft tissue sarcomas is at least 52%.

11.4 Duration of Accrual

This study will be conducted in a single stage. Based on an estimated accrual rate of 1 patient per month, we expect to complete the enrollment within 20 months.

REFERENCES

1. Suit HD, Russell WO, Martin RG: Sarcoma of soft tissue: clinical and histopathologic parameters and response to treatment. Cancer 35:1478-83, 1975
2. Lindberg RD, Martin RG, Romsdahl MM, et al: Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer 47:2391-7, 1981
3. Yang JC, Chang AE, Baker AR, et al: Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 16:197-203, 1998
4. Weitz J, Antonescu CR, Brennan MF: Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. J Clin Oncol 21:2719-25, 2003
5. Suit HD, Mankin HJ, Wood WC, et al: Preoperative, intraoperative, and postoperative radiation in the treatment of primary soft tissue sarcoma. Cancer 55:2659-67, 1985
6. Rosenberg SA, Tepper J, Glatstein E, et al: The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 196:305-15, 1982
7. O'Sullivan B, Davis AM, Turcotte R, et al: Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 359:2235-41, 2002
8. Davis AM, O'Sullivan B, Turcotte R, et al: Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 75:48-53, 2005
9. Suit HD, Proppe KH, Mankin HJ, et al: Preoperative radiation therapy for sarcoma of soft tissue. Cancer 47:2269-74, 1981
10. Eilber FC, Rosen G, Eckardt J, et al: Treatment-induced pathologic necrosis: a predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. J Clin Oncol 19:3203-9, 2001
11. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet 350:1647-54, 1997
12. Pervaiz N, Colterjohn N, Farrokhyar F, et al: A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 113:573-81, 2008
13. Frustaci S, Gherlinzoni F, De Paoli A, et al: Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol 19:1238-47, 2001
14. Frustaci S, De Paoli A, Bidoli E, et al: Ifosfamide in the adjuvant therapy of soft tissue sarcomas. Oncology 65 Suppl 2:80-4, 2003
15. Eilber F, Eckardt J, Rosen G, et al: Preoperative therapy for soft tissue sarcoma. Hematol Oncol Clin North Am 9:817-23, 1995
16. DeLaney TF, Spiro IJ, Suit HD, et al: Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 56:1117-27, 2003
17. Kraybill WG, Harris J, Spiro IJ, et al: Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. J Clin Oncol 24:619-25, 2006
18. Mack LA, Crowe PJ, Yang JL, et al: Preoperative chemoradiotherapy (modified Eilber protocol) provides maximum local control and minimal morbidity in patients with soft

tissue sarcoma. Ann Surg Oncol 12:646-53, 2005

19. Ryan CW, Montag AG, Hosenpud JR, et al: Histologic Response of Dose-Intense Chemotherapy with Preoperative Hypofractionated Radiation for High-Risk Soft Tissue Sarcomas. Cancer, (In Press)

20. Ryan CW, Montag AG, Hosenpud JR, et al: Histologic response of dose-intense chemotherapy with preoperative hypofractionated radiotherapy for patients with high-risk soft tissue sarcomas. Cancer 112:2432-9, 2008

21. Perlewitz KS, hung AY, Koudelka CW, et al: Dose-intense chemotherapy and preoperative hypofractionated radiation for high-risk soft tissue sarcomas: a multi-institutional updated analysis, Connective Tissue Oncology Society 14th Annual Scientific Meeting. London, U.K., 2008, pp (abstr 34866)

22. Folkman J: Tumor angiogenesis: therapeutic implications. N Engl J Med 285:1182-6, 1971

23. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-42, 2004

24. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542-50, 2006

25. Escudier B, Eisen T, Stadler WM, et al: Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356:125-34, 2007

26. Llovet J, Ricci S, Mazzagerro V, et al: Sorafenib improves survival in advanced Hepatocellular Carcinoma (HCC): Results of a Phase III randomized placebo-controlled trial (SHARP trial). Proc Am Soc Clin Oncol 25:18S, 2007

27. Motzer RJ, Hutson TE, Tomczak P, et al: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356:115-24, 2007

28. Potti A, Ganti AK, Tendulkar K, et al: Determination of vascular endothelial growth factor (VEGF) overexpression in soft tissue sarcomas and the role of overexpression in leiomyosarcoma. J Cancer Res Clin Oncol 130:52-6, 2004

29. Chao C, Al-Saleem T, Brooks JJ, et al: Vascular endothelial growth factor and soft tissue sarcomas: tumor expression correlates with grade. Ann Surg Oncol 8:260-7, 2001

30. Graeven U, Andre N, Achilles E, et al: Serum levels of vascular endothelial growth factor and basic fibroblast growth factor in patients with soft-tissue sarcoma. J Cancer Res Clin Oncol 125:577-81, 1999

31. Yoon SS, Segal NH, Olshen AB, et al: Circulating angiogenic factor levels correlate with extent of disease and risk of recurrence in patients with soft tissue sarcoma. Ann Oncol 15:1261-6, 2004

32. Yoon SS, Segal NH, Park PJ, et al: Angiogenic profile of soft tissue sarcomas based on analysis of circulating factors and microarray gene expression. J Surg Res 135:282-90, 2006

33. Hayes AJ, Mostyn-Jones A, Koban MU, et al: Serum vascular endothelial growth factor as a tumour marker in soft tissue sarcoma. Br J Surg 91:242-7, 2004

34. Yudoh K, Kanamori M, Ohmori K, et al: Concentration of vascular endothelial growth factor in the tumour tissue as a prognostic factor of soft tissue sarcomas. Br J Cancer 84:1610-5, 2001

35. van der Graaf WT, Blay JY, Chawla SP, et al: Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 379:1879-86, 2012

36. D'Adamo DR, Keohan M, Scheutze S, et al: Clinical results of a phase II study of

sorafenib in patients (pts) with non-GIST sarcomas (CTEP study #7060). Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I 25:100001, 2007

37. von Mehren M, Rankin C, Goldblum JR, et al: Phase 2 Southwest Oncology Group-directed intergroup trial (S0505) of sorafenib in advanced soft tissue sarcomas. Cancer 118:770-6, 2012

38. Zhang L, Hannay JA, Liu J, et al: Vascular endothelial growth factor overexpression by soft tissue sarcoma cells: implications for tumor growth, metastasis, and chemoresistance. Cancer Res 66:8770-8, 2006

39. Wilhelm SM, Carter C, Tang L, et al: BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 64:7099-109, 2004

40. Hilger RA, Scheulen ME, Strumberg D: The Ras-Raf-MEK-ERK pathway in the treatment of cancer. Onkologie 25:511-8, 2002

41. Strumberg D, Richly H, Hilger RA, et al: Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. J Clin Oncol 23:965-72, 2005

42. Awada A, Hendlisz A, Gil T, et al: Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours. Br J Cancer 92:1855-61, 2005

43. Clark JW, Eder JP, Ryan D, et al: Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors. Clin Cancer Res 11:5472-80, 2005

44. Moore M, Hirte HW, Siu L, et al: Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. Ann Oncol 16:1688-94, 2005

45. Siu LL, Awada A, Takimoto CH, et al: Phase I trial of sorafenib and gemcitabine in advanced solid tumors with an expanded cohort in advanced pancreatic cancer. Clin Cancer Res 12:144-51, 2006

46. Richly H, Henning BF, Kupsch P, et al: Results of a Phase I trial of sorafenib (BAY 43-9006) in combination with doxorubicin in patients with refractory solid tumors. Ann Oncol 17:866-73, 2006

47. Escudier B, Szczylik C, Eisen T, et al: Randomized Phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC). Proc Am Soc Clin Oncol 23:16S, 2005

48. Escudier B, Szczylik C, Eisen T, et al: Randomized Phase III trial of the multi-kinase inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC). ECCO 13. Eur J Cancer 3:226, 2005

49. Bukowski RM, Eisen T, Szczylik C, et al: Final results of the randomized phase III trial of sorafenib in advanced renal cell carcinoma: Survival and biomarker analysis. Proc Am Soc Clin Oncol 25:18S, 2007

50. Jain RK: Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 7:987-9, 2001

51. Jain RK: Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 307:58-62, 2005

52. Willett CG, Boucher Y, di Tomaso E, et al: Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med 10:145-

7, 2004

53. Willett CG, Boucher Y, Duda DG, et al: Surrogate markers for antiangiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: continued experience of a phase I trial in rectal cancer patients. J Clin Oncol 23:8136-9, 2005

54. Duda DG, Jain RK, Willett CG: Antiangiogenics: the potential role of integrating this novel treatment modality with chemoradiation for solid cancers. J Clin Oncol 25:4033-42, 2007

55. Meyer JM, Perlewitz KS, Hayden JB, et al: Phase I study of neoadjuvant chemoradiation (CRT) plus sorafenib (S) for high-risk extremity soft tissue sarcomas (STS). . J Clin Oncol 30, 2012

56. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-16, 2000