**Abbreviated Title:** Phase II trial of Sorafenib+Bevacizumab in Ovary

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# A Phase II Study of Sorafenib and Bevacizumab in Epithelial Ovarian, Fallopian, and Peritoneal Cancer


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**Investigator Roles**

A. *Obtain information by intervening or interacting with living individuals for research purposes*
B. *Obtaining identifiable private information about living individuals*
C. *Obtaining the voluntary informed consent of individuals to be subjects*
D. *Makes decisions about subject eligibility*
E. *Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes*
F. *Studying, interpreting, or analyzing coded (linked) data or specimens for research purposes*
G. *Some/all research activities performed outside NIH*

**Commercial Agents:** none

**Investigational Agents:**

| | | |
|---|---|---|
| Drug Name: | BAY 43-9006 | Bevacizumab |
| IND Number: | 69896 | 7,921 |
| Sponsor: | CTEP *(complete 09/04/14)* | CTEP *(complete 09/04/14)* |
| Manufacturer: | Bayer Health Care Corporation | Genentech |

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## PRÈCIS

### Background:

- Sorafenib is an inhibitor of wild-type and mutant B-Raf and c-Raf kinase isoforms in vitro, but it also inhibits p38, c-kit, VEGFR-2 and PDGFR-β affecting tumor growth as well as possibly promoting apoptosis by events downstream of c-Raf.
- Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human vascular endothelial growth factor (VEGF, or VEGF-A) with high affinity ($k_d$ = 1.1nM)
- Phase I trial of sorafenib and bevacizumab administered concurrently showed activity of the combination in patients with refractory ovarian cancer

### Objectives:

- Determine the activity and tolerability of the combination bevacizumab and sorafenib in patients with refractory or recurrent epithelial ovarian, fallopian, or peritoneal cancer in patients who are bevacizumab-naïve or bevacizumab-resistant

### Eligibility:

- Adults with histologically documented refractory or recurrent epithelial ovarian, fallopian, or peritoneal cancer
- Patients must be off prior chemotherapy, radiation therapy, hormonal therapy, or biological therapy for at least 4 weeks.
- Patients must have an ECOG of 1 or less.
- Patients must have disease that is amenable to biopsy
- Patients must have not been previously treated with bevacizumab or must have progressed on prior bevacizumab-based therapy

### Design:

- Patients will be stratified on entrance to the trial based on their previous exposure to bevacizumab to either strata A (bevacizumab-naïve patients) or strata B (patients previously treated with bevacizumab).
- Patients will receive oral sorafenib 200 mg twice daily 5 out of 7 days each week and intravenous bevacizumab 5 mg/kg every two weeks
- Tumor biopsies will be obtained from patients before treatment and six weeks into therapy. DCE-MRI and FDG-PET will be obtained from patients before treatment, on day 3 of treatment, and six weeks into therapy.
- Patients will be evaluated for response every 8 weeks using the RECIST criteria.
- Approximately 74 patients will be needed to achieve the objectives of the trial.

# 1. OBJECTIVES

## 1.1 Primary Objective

Determine the objective response rate of the combination of sorafenib (BAY 43-9006) and bevacizumab in patients with relapsed or refractory epithelial ovarian cancer (EOC), primary peritoneal cancer or fallopian tube cancer in patients who are bevacizumab-naïve or bevacizumab-resistant.

## 1.2 Secondary Objectives

- Determine progression-free survival
- Determine biochemical changes in the Ras-Raf-MAPK and VEGF signal transduction pathways in tumor and stromal cells in EOC in response to treatment with sorafenib and bevacizumab.
- Characterize the toxicity of the combination of sorafenib and bevacizumab in patients with epithelial ovarian cancer
- Evaluate correlations between biochemical pathway alterations and clinical events.
- Examine genetic mutations in raf in EOC and evaluate correlations with clinical events.
- Measure changes in VEGF and other angiogenic cytokines in plasma and fluids (when available) and evaluate correlation with clinical outcomes.
- Apply DCE-MRI and FDG-PET technology to determine changes in tumor vascularity and metabolism during treatment.
- Evaluate Quality of Life during treatment.

# 2. BACKGROUND

## 2.1 Sorafenib (BAY 43-9006)

Sorafenib represents a novel class of anticancer agents known as bi-aryl ureas. It is a potent inhibitor of wild-type and mutant B-Raf and c-Raf kinase isoforms in vitro. In addition, this agent also inhibits p38, c-kit, VEGFR-2 and PDGFR-β affecting tumor growth and possibly promotes apoptosis by events downstream of c-Raf. At this time, over 500 patients have been treated with this drug with tolerable side effects [**1**].

Activation of the *Ras* oncogenic signaling pathway is considered to be an important mechanism by which human cancer develops. Raf kinase is a protein involved in the Ras signal transduction pathway. Ras regulates several pathways which synergistically induce cellular transformation, including the Raf/MEK/ERK cascade and the Rac and Rho pathways [2, 3]. The Ras pathway has multiple activators, including the EGFR tyrosine kinases. In turn, Ras activates the Raf/MEK pathway by first localizing Raf to the plasma membrane, where Raf initiates a mitogen activated kinase cascade. Activated Raf phosphorylates and activates MEK which in turn phosphorylates and activates ERK. Activated ERK then translocates from the cytoplasm into the nucleus and modulates gene expression via the phosphorylation of transcription factors. Thus activation of Raf kinase, via activation of Ras, is thought to play an important role in carcinogenesis.

B-Raf, a serine/threonine kinase, has been shown to be activated in a number of human tumor types including melanoma, ovarian and papillary thyroid carcinomas [1, 4-9]. A survey of 43 cancer cell lines showed that all B-Raf mutations resided in exons 11 or 15. Remarkably, 80% of these B-Raf mutations represent a single nucleotide change of T-A at nucleotide 1796 resulting in a valine to glutamic acid change at residue 599 (V599E, exon 15) in the CR3 domain (ATP binding and substrate recognition) which in turn confers constitutive kinase activity [5, 6].

### *In Vitro* Activity

The ability of BAY 43-9006 to inhibit a number of kinases was evaluated [1]. The *in vitro* biochemical and cellular profile of BAY 43-9006 is summarized below:

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

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

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

*In vitro* kinase assays demonstrated that BAY 43-9006 is a potent inhibitor of wildtype and mutant (V599E) B-Raf and c-Raf Kinase isoforms *in vitro* [1]. In addition, BAY 43-9006 did not inhibit human EGFR or Her2 kinases at 10 μM. Nor were PKC-α, PKC-β, PKC-γ, and PKA (rat, rabbit and bovine sources) kinase activity inhibited *in vitro*. BAY 43-9006 demonstrated an $IC_{50}$ of 780 nM against p59 (bovine) Fyn kinase (Src family of protein tyrosine kinases). In non-kinase targets BAY 43-9006 had moderate potency against the adenosine A3, dopamine D1, and muscarinic M3 receptors with $IC_{50}$ of 1.6 μM, 2.0 μM, and 3.1 μM, respectively. BAY 43-9006 did not directly inhibit MEK-1, ERK-1, EGFR, HER2/neu, c-met, PKA, PKB, Cdk-1/cyclin B, pim-1, GSK 3-b, CK-2, PKC-α (r), PKC-β (r), PKC-γ at concentrations as high as 10 μM.
In summary, BAY 43-9006 showed ≥100-fold more selectivity for Raf kinase relative to other target proteins. BAY 43-9006 also inhibited *in vitro* several receptor tyrosine kinases (RTKs) that are involved in tumor progression; human VEGFR-2, murine VEGFR-2, murine VEGFR-3,

murine PDGFR-β, Flt-3, c-KIT, and p38α (MAPK family). In cellular assays, BAY 43-9006 was found to be a potent inhibitor of human and murine VEGFR-2, murine VEGFR-3, and murine PDGFR-α receptor phosphorylation [**1**].

VEGF and PDGF receptors are involved in the mechanism of tumor angiogenesis [**10**, **11**]. PDGF receptors may also play a role in patients with chronic myeloproliferative cancers [**12**]. Flt-3 is important in acute myelogenous leukemia [**8**] and c-Kit plays a critical role in gastrointestinal stromal tumors [**13**].

### *In Vivo* Activity

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

**BAY 43-9006 Demonstrates Broad Spectrum Anti-Tumor Efficacy in Preclinical Xenograft Models**

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

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

The majority of the initial anti-tumor efficacy evaluations *in vivo* were conducted in the HCT116 colon tumor model since the tumorigenicity of this cell line was previously shown to be dependent on K-Ras activation. Additional studies indicated that prolonged anti-tumor efficacy could be attained by extending the duration of treatment. In this tumor model, BAY 43-9006 was able to arrest tumor growth even if therapy was initiated against a substantially greater tumor burden.

BAY 43-9006 also showed significant oral activity against two additional human tumor xenograft models that contain K-Ras mutations: MiaPaCa-2 pancreatic carcinoma and H460 non-small cell lung carcinoma. The anti-tumor efficacy of BAY 43-9006 was also evaluated against the human SKOV-3 ovarian tumor cell line that contains a wild-type Ras but over-expresses both the EGF and Her2 growth factor receptors. These receptors also signal through the Ras/Raf/MEK pathway. Bay 43-9006 was shown to inhibit tumor growth in that ovarian cell line as well.

In human tumor xenografts, MDA-MB-231 (breast) and Colo-205 (colon), there was a dramatic reduction of tumor neo-vascularization [**1**]. Recent data also indicated that inhibition of c-Raf may promote cell death in endothelial cells as a downstream event of VEGFR-2 stimulation [**14**].

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

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

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

| **Combination Agent** | **Tumor Model** | **Combinability Y/N** |
|---|---|---|
| Paclitaxel | NCI-H460 NSCLC<br>MX-1 Mammary | Yes<br>Yes |
| Irinotecan | DLD-1 Colon | Yes |
| Gemcitabine | MiaPaCa-2 Pancreatic | Yes |
| Cisplatin | NCI-H23 NSCLC | Yes |

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

## Clinical Experience

BAY 43-9006 has been evaluated in multiple Phase 1 and Phase 2 studies in a variety of tumor types. To date, over 750 patients have been treated with single agent BAY 43-9006. The Phase 1 single agent clinical plan focused on characterizing the safety and pharmacokinetic profile BAY 43-9006 in several different dosing regimens. All completed Phase 1 trial patients (197 patients) had a variety of advanced refractory solid tumors, and some of the patients stayed on trial for more than one year. Four different regimens have been tested: continuous treatment, 4 weeks on/ 1 week off, 3 weeks on /1 week off, and 1 week on/ 1 week off. Patients have received doses ranging from 50 mg once weekly to 1600 mg daily of BAY 43-9006 on intermittent and continuous schedules. The 800 mg bid continuous administration cohort has exceeded maximum tolerated dose (MTD) in all tested schedules. The 600 mg bid cohort exceeded the MTD in all but the less dose intensive regimen of 1 week on / 1 week off. The most frequent drug-related adverse events were hand-foot skin reaction, dermatitis, rash, fatigue, anorexia and diarrhea. There was an increase in the number of serious adverse events, discontinuations due to adverse events, and a number of skin toxicities at the higher dose levels ≥ 600 mg bid. Therefore, 400 mg bid was selected as the recommended dose for Phase 2.

In general, available information from the ongoing Phase 2 studies reveals toxicities that are similar to the Phase 1 data. Again, the five most frequent drug-related toxicities observed include hand-foot skin reaction, rash, anorexia, diarrhea, and fatigue. When all available data from the various studies/schedules are combined, the incidence of greater than grade 3 treatment emergent skin toxicity (e.g. hand-foot syndrome and “dermatology/skin reaction”) for an initial dose of 400 mg bid and 600 mg bid, was 0% and 30%, respectively.

Hypertension has also been an observed toxicity for BAY 43-9006. In the phase II trial of sorafenib in renal cell carcinoma, only 5% of patients receiving multiple cycles required dose reduction due to toxicity [**37**]. The phase III trial of sorafenib in renal cell carcinoma presented at ASCO at the annual meeting in 2005 had 25% of patients being dose-reduced, 78% of these due to toxicity [**38**].

A recent study designed to track the incidence of hypertension in 20 patients treated with sorafenib 400 mg po bid found a median increase of systolic blood pressure (SBP) of 20 mmHG,

with 60% of patients having an increase in SBP of 20 mmHg and 75% having an increase in SBP by 10 mmHg. Two patients (10%) required new or increased BP medication [**41**].

Anti-tumor activity was observed in both Phase 1 and 2 studies. Phase 2 results in renal cell carcinoma have shown a 50% progression-free survival at 24 weeks compared to 18% on the placebo arm. Phase 3 studies are proceeding using sorafenib in hepatocellular and renal cell carcinomas [**37**]. On interim reporting, phase 3 data in renal cell carcinoma showed a progression –free survival of 79% versus 50% on the placebo arm [**38**].

**Pharmacokinetics**

Pharmacokinetic studies in humans shows that BAY 43-9006 undergoes metabolism to a few primary metabolites, some of which may be active [1]. No data are available at this writing to describe the pharmacokinetics of repetitive dosing of BAY 43-9006 in patients**.** However, up to 36 hours after a single dose, BAY 43-9006 continues to be the predominant species detected. In vitro liver microsomal degradation studies data indicate that BAY 43-90006 is primarily metabolized by CYP 3A4. Ongoing studies are being pursued by the Sponsor to evaluate drug-drug interaction potential of BAY 43-9006 with agents that alter function of CYP2C19, CYP2D6, and CYP3A4.

## 2.2 Bevacizumab (rhuMAb)

*Background*

Bevacizumab (rhuMAb) is a recombinant humanized anti-VEGF monoclonal antibody composed of human IgG1 framework regions and antigen-binding complementarity-determining regions from a murine monoclonal antibody (muMAb VEGF A.4.6.1) which blocks the binding of human VEGF to its receptors. Approximately 93% of the amino acid sequence, including most of the antibody framework, is derived from human $IgG_1$, and ~7% of the sequence is derived from the murine antibody.

*Preclinical data*

In cynomolgus monkeys, twice weekly IV treatments with bevacizumab (doses of 2, 10 and 50 mg/kg) for 4, 13 or 26 weeks were well tolerated, with no overt signs of acute toxicity [**15**, **16**].

Animals with open growth plates showed physeal dysplasia as well as focal to diffuse chondroid necrosis and linear fissuring of the cartilaginous growth plate. Females treated with 10-50mg/kg twice weekly had decreased ovarian and uterine weights, which were associated with absence of corpora lutea. These findings were expected, considering the known role of VEGF in formation of the corpora lutea and of the growing bone [**17**]. A further study using a similar treatment regimen, in the recovery period the physeal dysplasia and ovarian and uterine changes induced by rhuMAb VEGF were partially reversible. No antibodies against bevacizumab were detected.

*Phase I Clinical studies*

Two phase I studies have been performed. Study AVF0737g was a dose escalation trial of single and multiple intravenous (IV) administration of rhuMAb in patients with advanced malignancies. Five dose levels were evaluated (0.1, 0.3, 1.0, 3.0, and 10mg/kg). rhuMAb VEGF was administered as a 90-minute infusion on days 0, 28, 35 and 42 [**18**]. The second study, AVF0761g, evaluated multiple doses of rhuMAb VEGF 3 mg/kg weekly for up to 8 weeks in combination with one of three cytotoxic chemotherapy regimens (5-fluorouracil/leucovorin, carboplatin/paclitaxel, or doxorubicin) in subjects with advanced solid malignancies [**19**]. rhuMAb VEGF was administered weekly at 3mg/kg for eight doses.

In both studies, rhuMAb VEGF appeared to be well tolerated. In AVF0737g, 3 of 25 patients treated experienced tumor-related hemorrhagic events, possibly related to the administration of rhuMAb VEGF. In two cases the event was considered serious: an intracranial hemorrhage (at an occult cerebral metastasis) in a patient with hepatocellular carcinoma and bleeding at the tumor site in a 38-year-old woman with a slowly progressing sarcoma of the thigh. No patient in AVF0761g reported serious bleeding. No dose limiting toxicity was reached in either study. No antibodies to rhuMAb VEGF were detected after therapy in either study.

*Pharmacokinetics*

In study AVF0737g, the pharmacokinetics of rhuMAb VEGF appeared to be linear for doses ≥ 1mg/kg with a half-life of approximately 15-21 days. Comparable pharmacokinetic data was seen in study AVF0761g. Co-administration of rhuMAb and cytotoxic chemotherapy did not appear to result in a change in the systemic concentration of the cytotoxic agents.

*Phase II Clinical Studies*

Bevacizumab has been shown to be effective in the therapy of metastatic renal cell carcinoma. Yang et al. [**20**] completed a randomized, double-blind, phase 2 trial comparing placebo to bevacizumab at doses of 3 and 10 mg/kg given every 2 weeks. There was a statistically significant increase in time to progression with the high-dose group compared to placebo.

Study AVF0776g is an ongoing Phase II trial in patients with metastatic breast cancer who have progressed following at least one conventional cytotoxic chemotherapy regimen for metastatic disease. Eighteen patients have enrolled in the 3mg/kg dose level every other week and 41 patients at the 10mg/kg every other week dose level. All 59 patients have completed the study and 16 subjects have recently been enrolled at the 20mg/kg dose level. Twenty patients have experienced a total of 25 serious adverse events; 5 of 18 at 3mg/kg, 9 of 41 at 10mg/kg and 6 of 16 at 20mg/kg. Nine patients experienced serious adverse events that were considered possibly or probably related to rhuMAb VEGF. One patient developed hypertension and nephrotic syndrome within one month of starting therapy. Four additional subjects (1 at 3mg/kg, 2 at 10mg/kg and 1 at 20mg/kg) developed hypertension which was reported as a serious adverse event but was easily treated and did not require discontinuation of rhuMAb VEGF therapy. Four patients treated at 20mg/kg developed headache, nausea and vomiting, which resulted in study discontinuation for one patient. Hypertension has been reported as an adverse event in an additional 9 subjects (2 at 3mg/kg, 7 at 10mg/kg; non-serious adverse events at 20mg/kg are not available). Proteinuria has resulted in a study discontinuation for 3 patients (one at each dose level). One patient has developed a deep venous thrombosis; there have been no significant bleeding episodes.

Tumor assessment available for 3mg/kg and 10mg/kg dose groups include 1 partial response in a cervical lymph node in the 3mg/kg group and 4 objective responses (One complete response in a supraclavicular node and three partial responses in lymph node, skin and liver disease). Eight of 41 patients (20%) had either stable disease or an ongoing response at the final tumor assessment at Day 154.

In Study AVF0757g, rhuMAb VEGF administered at a dose of 15mg/kg every 3 weeks in combination with carboplatin and paclitaxel showed a non-significant trend towards increased

response rates and time to progression compared with chemotherapy alone. There was no significant difference in either parameter between chemotherapy and rhuMAb VEGF 7.5mg/kg and chemotherapy alone.

In Study AVF0780g, patients with metastatic colon cancer were treated with either 5-FU/leucovorin (500mg/$m^2$ 5-FU and 500mg/$m^2$ leucovorin administered weekly for six weeks, with courses repeated every eight weeks) alone or in combination with rhuMAb VEGF 5mg/kg or 10mg/kg every two weeks. Response rates were 17%, 40% (p=. 03) and 24%(p=. 23), respectively. A prolonged time to disease progression was seen in patients treated with rhuMAb VEGF 5mg/kg in combination with chemotherapy (9.0 months p=. 005) compared with those who received rhuMAb VEGF 10mg/kg (7.2 months p= .217) or chemotherapy alone (5.2 months).

The GOG phase 2 trial of bevacizumab treated patients with recurrent ovarian or peritoneal cancer and < 3 prior therapies with bevacizumab (15 mg/kg q3wks). The trial found a 38.8% 6 month progression-free survival and a 17% response rate [**39**]. In the California Cancer Consortium phase 2 trial of low-dose oral cyclophosphamide (50 mg po qd) and bevacizumab (20 mg/kg qwk x 3 then q2wk), interim analysis has shown a 47% progression-free survival in patients with recurrent ovarian or peritoneal cancer [**40**].

*Toxicities*

Life threatening toxicities seen in clinical trials to date with rhuMAb VEGF have included hemorrhage, thrombosis, and gastrointestinal perforation. Less severe toxicities have included proteinuria, hypertension, fever, chills, rash, headache, infection, epistaxis and mouth ulceration.

a) Hemorrhage - Life threatening hemorrhage was seen in a Phase I trial (AVF0737g) in the form of an intracranial hemorrhage (at an occult cerebral metastasis) in a patient with hepatocellular carcinoma and in the Phase II study (AVF0757g) in the form of massive hemoptysis or hematemesis. There were 6 life-threatening hemorrhages among 66 patients receiving rhuMAb VEGF-treated patients of which four of these events were fatal. An analysis of possible risk factors for life-threatening bleeding identified squamous cell histology as a risk factor (4 of 6

bleeds occurred in patients with squamous cell histology whereas only 13 of 66 rhuMAb VEGF-treated patients had squamous histology). A number of investigations were performed on two of the patients with pulmonary hemorrhage and in eight patients in AVF0780g receiving rhuMAb VEGF including platelet count, prothrombin time, activated prothrombin time, fibrinogen, bleeding time, euglobulin clot lysis, d-dimer, alpha2-antiplasmin, PFA-100 (a platelet function assay) and these were all within normal range (Novotny,W. Genentech Inc personal communication).

b) Thrombosis- In Study AVF0780g in metastatic colorectal cancer, venous and arterial thrombosis were seen more frequently than in patients treated with rhuMAb VEGF plus 5-FU/leucovorin than in patients treated with 5-FU/leucovorin alone: 3 of 35 patients in the control arm, 9 of 35 patients in the 5mg/kg rhuMAb VEGF arm and 4 of 32 patients in the 10mg/kg rhuMAb VEGF arm. One event was fatal (a pulmonary embolism in the 10mg/kg arm) and three events required study discontinuation (a pulmonary embolism and a superior mesenteric vein occlusion in the 5mg/kg arm and a cerebrovascular event in the 10mg/kg arm). Cancer patients are known to be at high risk for thromboembolism owing to a number of factors including intrinsic tumor pro-coagulant activity, immobilization, indwelling catheters and the pro-thrombotic effects of chemotherapy. The incidence of thrombosis among patients with breast cancer receiving chemotherapy is approximately 5-10% being higher in patients on tamoxifen and in patients with metastatic disease [**21**]. In the first 59 patients with metastatic breast cancer treated with rhuMAb VEGF monotherapy, two patients have developed a subclavian/axillary deep venous thrombosis on the side of the indwelling central line.

In the AVF2107 study, there was a 1% incidence of arterial thromboembolic (TE) events (which include myocardial infarction, transient ischemic attack, cerebrovascular accident/stroke, and angina/unstable angina) in the IFL + placebo arm versus 3% in the ILF + bevacizumab arm. A pooled analysis of the rate of arterial TE events from 5 randomized studies showed that treatment with bevacizumab increased the risk of these events two- to three- fold (up to 5%). Furthermore, certain baseline characteristics, specifically age > 65 years and prior arterial TE event, conferred additional risk.

c) Hypertension- Hypertension has been seen in all rhuMAb VEGF clinical trials to date. There has been one reported case of hypertensive encephalopathy in a patient receiving 3mg/kg of rhuMAb VEGF on Study AVF0776g. In addition, 12 other patients have developed either new hypertension (7 patients) or worsening existing hypertension (5 patients) for which 10 of these patients required medical therapy (3 patients in 3mg/kg rhuMAb arm (n=18) and 7 in the 10mg/kg (n=41), no data available from 20mg/kg arm).
After 10 weeks of treatment, the mean change in blood pressure for all subjects compared with baseline was as follows (mean systolic change/mean diastolic change); 3mg/kg rhuMAb VEGF +10.5mmHg/+8.5mmHg and 10mg/kg rhuMAb VEGF +18.5mmHg/+8.2mmHg. In Study AVF0780g (colorectal cancer), using NCI-CTC Grade 3 or 4 events, there were four events in the control arm (n=35), four events between 2 patients in the 5mg/kg rhuMAb VEGF (n=35) and nine-events among 5 subjects in the 10mg/kg rhuMAb VEGF (n=32). The most commonly used therapies to treat this hypertension have been angiotensin converting enzyme inhibitors and calcium channel blockers.

VEGF has been shown to induce nitric oxide-mediated vasodilatation and hypotension [**22**]. In a recent study, VEGF has been shown to govern endothelial nitric oxide synthase expression via a KDR/flk-1 receptor and protein kinase C signaling pathway, which suggests a possible mechanism for rhuMAb VEGFs induction of hypertension [**23**].

d) Proteinuria - Proteinuria by dipstick analysis has been seen in all rhuMAb VEGF clinical trials and has ranged in severity from clinically silent trace proteinuria to nephrotic syndrome. In study AVF0776g, 8 of 59 (12%) subjects treated with 3mg/kg or 10mg/kg have developed some degree of proteinuria (detected by dipstick) during the study to date. Three of these patients have also developed hypertension. Two patients were discontinued from study because of proteinuria; one patient (10mg/kg arm) had >2.5g/24 hr which decreased to 0.7mg/24 hr within 4 weeks with a normal serum creatinine and a second patient in the 20mg/kg arm who developed >5g/24hr. Another patient (3mg/kg arm) developed hypertensive encephalopathy, which was followed by the development of nephrotic syndrome (5g/24hr). This patient died of progressive disease soon thereafter and renal biopsy was not performed. A recent study has shown that VEGF mediates

glomerular repair, which suggested a possible mechanism for rhuMAb VEGF-associated proteinuria [**24**].

e) Congestive Heart Failure- Two patients with metastatic breast cancer in study AVF0776g who had been treated previously with doxorubicin developed congestive heart failure while on rhuMAb VEGF, one patient after one year at 10 mg/kg and the second patient after two doses at 20 mg/kg.

f) Dyspnea/hypoxia- In study AVF2107g, an ongoing trial with bevacizumab with 5FU/leucovorin in metastatic colon cancer, one patient on this study developed dyspnea and pneumonitis requiring intubation eleven days after receiving her fifth infusion of bevacizumab with irinotecan and 5-FU. Two other patients on this study also developed grade IV respiratory failure felt to be related to end-of-life events and not directly related to the drug. In study AVF0757g, for stage IIIb and IV non-small cell lung cancer, 3 patients had grade IV dyspnea events, the etiology of which is unclear but at least partially attributable to their underlying disease. No other grade IV dyspnea events were reported in other trials.

There has been a recent report of an ovarian cancer patient who developed hypoxia of unclear etiology while on the phase II Bevacizumab in Ovarian Cancer study. Twenty-three incidences of hypoxia have been reported out of 6031 patients enrolled on NCI-sponsored IND trials using bevacizumab.

g) Perforation – The Genentech sponsored trial of bevacizumab in recurrent ovarian cancer was terminated early due to a greater than expected incidence of bowel perforations (11%). Patients were dosed at 15mg/kg q3wks as compared to our likely dosing of 5 mg/kg q2wks. Previous studies of bevacizumab in colon cancer had an incidence of bowel perforation of between 4-6%. At the recent January 2006 GOG meeting, an analysis of all ovarian cancer patients receiving bevacizumab in CTEP sponsored trials, approximately 150 patients, had only a 4.8% perforation/fistula rate, much closer approximating the incidence seen in colon cancer. Further analysis is ongoing to ascertain the true risk of bowel perforation in ovarian cancer patients receiving bevacizumab.

h) Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome – RPLS or clinical syndromes related to vasogenic edema of the white matter have rarely been reported with bevacizumab therapy (<1%). Clinical presentations are variable and may include altered mental status, seizure, and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained altered mental status change, visual disturbances, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of blood pressure and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

### 2.3 Epithelial Ovarian Cancer (EOC)

Ovarian cancer is the fifth leading cause of death from cancer in American women and is the most common cause of death from a gynecologic malignancy in the United States [6]. Although over 70% of women with advanced disease respond to optimal debulking surgery followed by platinum-taxane based chemotherapy, duration of response is short and relapse is common [7]. In the GOG 158 trial, median progression free survival for newly diagnosed optimally debulked stage III ovarian cancer treated with carboplatin/paclitaxel was 20 months [42]. Only 20-30% of relapsing patients have long unmaintained remissions because their tumors become resistant to chemotherapy [7]. Several recent studies have suggested that the median length of remission, based on the extent of disease at the start of initial chemotherapy, ranges between 15 and 24 months but subsequent responses are less than 6 months [8]. At relapse, patients are considered platinum sensitive if their relapse is >6 months from their last platinum treatment. The standard of care in these patients consists of a platinum-containing doublet per the sentinel ICON4 trial and median progression-free survival is 13 months [43]. In platinum-resistant ovarian cancer, many other agents have minimal efficacy with response rates in the <10% range, including taxanes, gemcitabine, liposomal doxorubicin, etoposide, topotecan, and hormonal agents; they

can be administered in any order. Sorafenib/bevacizumab can be considered by all relapsed/refractory patients.

### 2.3.1 EOC and molecular targets

Raf-kinase is important in cellular differentiation and proliferation. Recently, attention has been given to the role of Raf in ovarian cancer. Increased levels of c-Raf were found in a majority of EOC tumor samples in one series and had a significant correlation with poor survival (p=0.002) Antisense oligodeoxynucleotides to c-Raf reduced its levels and inhibited cellular proliferation, suggesting a possible therapeutic benefit in targeting Raf in EOC [**31**]. VEGF and VEGFR have been found to be upregulated in ovarian cancer than in benign and normal ovarian tissue [32], making that pathway a reasonable target in EOC as well. Sorafenib is also an inhibitor of VEGFR and PDGFR. Our hypothesis behind combining it with bevacizumab includes sequential targeting of the VEGF pathway.

### 2.3.2 Sorafenib and EOC

Sorafenib targets Raf-kinase affecting the Ras-Raf-MAPK pathway which is recognized as important for tumor cell proliferation and differentiation. It also inhibits other tyrosine kinases involved in angiogenesis and tumor progression including VEGFR-2, VEGFR-3, PDGFR-β, Flt3, c-kit, p38-α. Mutations in key signaling molecules in the Ras-Raf-MAPK pathway, particularly K-Ras and B-Raf mutations, are known to be important in tumor development in a variety of cancer types [**33**]. These mutations have a high incidence in borderline serous neoplasms and low grade serous malignancies in the ovary but are relatively rare in high grade ovarian serous carcinomas [**34**]. However, even in the absence of genetic mutations, this Ras-Raf-MAPK pathway is activated by the overexpression and activation of upstream growth factors and their receptors, including EGFR. Phase I trials of BAY 43-9006 have included patients with epithelial ovarian cancer, showing some activity [**35**]. The Gynecologic Oncology Group (GOG) has opened a phase II trial of sorafenib (GOG 0170F) in ovarian cancer that has not been analyzed yet.

### 2.3.3 Bevacizumab and EOC

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody which blocks the binding of human VEGF to its receptors. VEGF is upregulated in most human tumors and is produced by both

tumor cells and stroma [17]. Increased levels of VEGF are seen in ovarian cancer cells when compared to both normal ovary and benign ovarian disease [32]. Clinically, high serum VEGF levels in ovarian cancer patients are associated with a poor prognosis and may be a marker for persistent disease [36]. Therefore, inhibiting VEGF and angiogenesis is a logical strategy to target ovarian cancer. Because both sorafenib and bevacizumab affect the VEGF-VEGFR pathway, overlapping clinical activity is expected. The GOG has completed a phase II study of bevacizumab describing an 18% response rates in recurrent ovarian cancer patients [39]. The Genetech trial of ovarian cancer was suspended after the development of perforations in multiple patients, as described in section 2.2. Bevacizumab has also been studied in ovarian cancer patients in combination with oral cyclophosphamide (50 mg po qd) and a response rate of 21% and median PFS of 5.8 months was observed [40].

## 2.4 Combination of Sorafenib and Bevacizumab

Despite the promise of signal transduction and angiogenesis inhibitors, these drugs have met with mixed results in clinical trials. While these drugs clearly have activity in certain tumors models, they are only rarely effective as single agents. We propose that inhibition of multiple targets may be necessary for more significant clinical effects. Sorafenib and bevacizumab inhibit two pathways that are commonly activated in ovarian cancer and related malignancies. There are significant interactions of these signaling pathways in both tumor cells and endothelial cells.

### 2.4.1 Overlapping activity of sorafenib and bevacizumab

BAY 43-9006 was designed to inhibit Raf and is also known to inhibit other kinases including VEGFR2, VEGFR3, PDGFR-β, Flt3, c-KIT, and p38α [1]. Moreover, BAY 43-9006 appears to have antiangiogenic properties which may be mediated through the direct inhibition of these kinases. The drug may also downregulate the VEGF pathway via blockade of Raf kinase which leads to decreased VEGF production. Thus targeting of the VEGF pathway as a component effect of BAY 43-9006 may be important in its clinical activity and is an important testable molecular event.

VEGF is one of the most potent and specific angiogenic factors identified. VEGF is upregulated in most human tumors and is produced by both tumor cells and stroma [25]. Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody which blocks the binding of human

VEGF to its receptors. Recent findings using bevacizumab suggest some overlap in clinical activity with BAY 43-9006. Bevacizumab has been shown to delay progression in renal cell carcinoma as a single agent and increase survival in colon cancer in combination with chemotherapy [**20**, **26**]. These findings support the preclinical data of complementary mechanisms. This also argues that combining these drugs is a promising strategy.

Interestingly, there is notable interaction between the Ras-Raf-MAPK pathway and VEGF. The VEGF mitogenic signal in endothelial cells utilizes Ras-Raf-MAPK [**25**]. In addition, activation of the Ras-Raf-MAPK pathway induces VEGF expression. Thus, inhibition of Raf kinase may block the VEGF angiogenic stimulus in two independent ways. As a result, BAY 43-9006 may augment the antiangiogenic effects of bevacizumab.

### 2.4.2 Clinical experience combining sorafenib and bevacizumab

There is limited clinical experience with the combination of sorafenib and bevacizumab. At this time, our group is completing a phase I trial of sorafenib and bevacizumab in solid tumors (05-C-0022**)**. Thus far, 48 patients have been treated for greater than 344 cycles with each cycle lasting 4 weeks. Nineteen of these patients are ovarian cancer patients. Dose level 1 (DL1) consisted of treatment with sorafenib 200 mg by mouth twice daily with bevacizumab 5 mg/kg IV q2wk. DL1 was the MTD and administered in cohort 2 (N=27). Dose-limiting toxicity in DL2 was grade 3 proteinuria and thrombocytopenia. Dose level 2 (DL2) consisted of sorafenib 200 mg bid with bevacizumab increased to 10 mg/kg IV q2wk. A single DLT was seen at DL1 in a patient with extensive intrabdominal tumor masses who had also undergone multiple bowel resections. With rapid tumor shrinkage, the patient developed an enterocutaneous fistula and fluid collection that appeared to be an abscess. The most common DL1 adverse events (AEs) that were ≥ grade 2 were hypertension (6/6) and hand-foot syndrome (HFS; 4/6). Infection was a late grade 3 AE on DL1. Its attribution to drug remains unclear. DLT was reached at DL2 when 2/6 patients developed grade 3 proteinuria (4, 5 gm/24 hr) and one grade 3 thrombocytopenia. Dose reduction of bevacizumab to 5 mg/kg q2weeks on DL2 was not associated with recurrence of the proteinuria or the thrombocytopenia. Several DL2 patients later had sorafenib dose reduction for HFS. Dose reduction on daily sorafenib (DL1 and DL2) occurred for 11/12 pts at a median of 2 cycles.

Preliminary data were published in the Journal of Clinical Oncology (Azad et al. 2008 [**44**]).

Table of Grade 2 to 5 Toxicity by Maximum Grade per Patient (N=39)*

| | Toxicity Grade (No. of Patients) | | | | | |
|---|---|---|---|---|---|---|
| | Grade 2 | | Grade 3 | | Grade 4 | |
| Toxicity | DL1 | DL2 | DL1 | DL2 | DL1 | DL2 |
| Diarrhea | 1 | 1 | 4 | 1 | 0 | 0 |
| Fatigue | 10 | 2 | 3 | 0 | 0 | 0 |
| Fistula | 1 | 1 | 0 | 0 | 0 | 0 |
| Hand-foot syndrome | 18† | 4 | 0 | 1 | 0 | 0 |
| Hypertension | 12 | 1 | 8 | 4 | 1 | 0 |
| Perforation | 0 | 0 | 1 | 0 | 0 | 0 |
| Proteinuria | 3 | 1 | 0 | 2‡ | 0 | 0 |
| Thrombocytopenia | 1 | 0 | 0 | 1‡ | 0 | 0 |
| Thrombosis | 0 | 0 | 2 | 0 | 1 | 0 |
| Transaminitis | 9 | 0 | 3 | 0 | 1 | 0 |

*Cohort 2 (translational) patients enrolled on DL1 dosage (N=24).
†Recurrent grade 2 hand-foot syndrome was the DLT in DL1.
‡DLT in DL2.

Gastrointestinal fistulae occurred in two ovarian cancer patients, occurring within 4 weeks of initiation of therapy, all in areas of measurable tumor regression. One patient with cervical cancer experienced a rectovaginal fistula after 18 weeks of therapy, in an area of previous radiation therapy. One patient with melanoma was taken off trial after presenting with a perforated appendix that possibly could be attributed to bevacizumab. Toxicities did not appear to be cumulative.

DLTs did occur on DL4, an intermittent dosing schedule of sorafenib 200 mg by mouth twice daily on days 1-5 each week with bevacizumab 5 mg/kg IV on day 1 then every other week, has completed accrual. DL4 was determined to be the MTD. 3/7 patients required dose reduction on the intermittent schedule (DL4) and they were delayed.

DL5A, sorafenib 200 mg by mouth twice daily on days 1-5 each week with bevacizumab 10 mg/kg IV on day 1 every other week, and DL5B, sorafenib 400 mg by mouth twice daily on days 1-5 each week with bevacizumab 5 mg/kg IV on day 1 every other week were added.

Four of the 6 patients treated on DL1, 3 of 6 patients on DL2, and 3 of 7 patients on DL4, 2 of 5 on DL5A, and 1 of 5 on DL5B are ovarian cancer (EOC) patients. In addition, five of the patients on the expansion cohort have EOC. Even at dose level 1, we observed sufficient clinical activity in all 4 patients with EOC leading us to believe that this combinatorial strategy may be efficacious. Responses were seen despite our patients being heavily pre-treated with cytotoxic agents with minimal responses.

Seven of 19 patients (36%) with EOC have been on treatment for greater than 6 months. Six of 19 patients (31.5%) have a PR and 15 of 19 (79%) have SD or PR (duration of treatment ranges from 4 to 37 months. From this group we have 6 PRs by RECIST criteria and one with a 20% tumor shrinkage after 2 cycles. All patients report at least subjective benefit from therapy. Although this is a small cohort of ovarian cancer patients, the results are sufficiently encouraging to warrant investigation of these agents in a larger cohort of patients with ovarian cancer.

One other combination study is a phase 1/2 trial in renal cell carcinoma out of Vanderbilt University, based on the 1/12/06 CTEP meeting detailing the 63 NCI sponsored sorafenib studies. That study administers the sorafenib daily at 200-400 mg bid and bevacizumab 5-10 mg/kg q2wks. It is focusing on maximizing doses of both agents whereas our focus is minimum therapeutic dosing of both agents. Data are too early to report.

# 3. PATIENT SELECTION

## 3.1 Eligibility Criteria

3.1.1 Histopathologically documented recurrent/refractory epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer from a previous biopsy verified by the Laboratory of Pathology, NCI.

3.1.2 Recurrent/refractory disease defined as progression within 6 months of upfront platinum-containing therapy or progression after subsequent therapy in previously relapsed patients.

3.1.3 Disease amenable to percutaneous or skin biopsy as determined by an associate investigator and a member of the interventional team.

3.1.4 Patient willingness to have biopsies performed.

3.1.5 Measurable disease defined as tumor ≥ 1 cm.

3.1.6 Age ≥ 18 years.

3.1.7 Life expectancy of more than 3 months.

3.1.8 Performance status of 0 to 1 according to the ECOG criteria.

3.1.9 Adequate organ function as defined below:

| Laboratory Test | **Required value** |
|---|---|
| Leukocytes | ≥3,000/μL |
| Absolute neutrophil count | ≥1,200/μL |
| Platelets | ≥100,000/μL |
| total bilirubin | ≤1.5 X institutional upper limits of normal |
| AST(SGOT) and ALT(SGPT) | ≤2.5 X institutional upper limit of normal |
| creatinine<br>OR<br>Creatinine clearance | ≤1.5 mg/dL<br><br>≥45 mL/min/1.73 $m^2$ for patients with creatinine levels above institutional normal. |
| Activated partial thromboplastin time (PTT) | < 1.5 x institutional upper limits of normal |
| Prothrombin Time (PT)/INR | < 1.5 x institutional upper limits of normal |
| Amylase and Lipase | Less than institutional upper limits of normal |

3.1.10 Patients must have a urine protein/creatinine ratio (UPC) < 1.0 for enrollment

3.1.11 No surgery, radiation therapy, chemotherapy, immunotherapy, biotherapy, or hormonal therapy (exception raloxifene for bone health) within four weeks (6 weeks for mitomycin C, carboplatin, or nitrosoureas);

3.1.12 No metabolically active complimentary or alternative therapy for at least 1 week, defined as any ingested or administered chemical substances including herbal medications, but not including acupuncture, hypnosis, meditation, or other non-chemical treatments.

3.1.13 No monoclonal antibody therapy for at least 6 weeks.

3.1.14 Patients must have recovered from any acute toxicity related to prior therapy, including surgery. Toxicity should be ≤ grade 1 (as defined by CTCAE v4) or returned to baseline. Peripheral neuropathy ≤ grade 2 will be allowed as this patient population has universally been treated with platinum-based chemotherapy with residual neuropathy being a common occurrence.

3.1.15 No other invasive malignancies within the past two years (with the exception of non-melanoma skin cancers, non-invasive bladder cancer, stage I endometrial cancer or cervical cancer synchronous to the ovarian cancer diagnosis and cured by surgical resection).

3.1.16 Ability to understand and sign an informed consent form.

3.1.17 Patients who require hematopoietic growth factor support (e.g. epogen, darbepoetin), NSAIDs, and other maintenance medications prior to study entry will be allowed to continue their supportive therapies.

3.1.18 Ability to tolerate orally administered medications.

3.1.19 Contraception is not a consideration as these patients have all had surgical removal of their reproductive organs. Pregnant women are excluded from this study because BAY 43-9006 and bevacizumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with BAY 43-9006 and/or bevacizumab, breastfeeding should be discontinued if the mother is treated with BAY 43-9006 and/or bevacizumab.

3.1.20 There is no limit on the number of prior regimens with which a patient has been treated

3.1.21 Patients who have been treated with bevacizumab previously are eligible for the trial if they have progressed while on bevacizumab-based therapy

3.1.21.1 Disease progression on bevacizumab therapy will be defined as documented increase in disease based on imaging while the patient is receiving bevacizumab or within six months of their last dose of bevacizumab.

3.1.21.2 Patients must be at least 6 weeks from their last dose of bevacizumab prior to being enrolled on study

3.1.21.3 Patients who have a healed fistula greater than 28 days prior to enrollment are eligible (refer to section **3.2.15** for patients who have had prior bevacizumab)

## 3.2 Exclusion Criteria

3.2.1 Serious non-healing wounds (including wounds healing by secondary intention), acute or non-healing ulcers, or bone fractures within 3 months of enrollment.

3.2.2 Moderate or massive hemoptysis or surgery within 28 days of enrollment

3.2.3 Ongoing treatment with any other investigational agents.

3.2.4 Brain metastases

3.2.4.1 Patients with CNS metastases within the past 2 years are ineligible. Patients who have had CNS disease curatively treated and without recurrence for 2 years may be eligible. but any CNS disease that has not undergone curative therapy with radiation, gamma knife, and/or surgical therapy are ineligible

3.2.4.2 CNS imaging will not be mandated for all patients. However, if there is clinical suspicion of CNS involvement, a contrast CT or MRI of the brain will be required.

3.2.4.3 Patients with CNS metastases may not be on steroids for the purpose of CNS disease or edema control

3.2.4.4 Patients with CNS disease must be on an anti-seizure medication and that medication cannot be a CYPP4503A modulating agent

3.2.5 Thrombotic or embolic events within the past 6 months such as a cerebrovascular accident (including transient ischemic attacks), pulmonary embolism, unstable angina, or myocardial infarction. Fully treated deep vein thrombosis no longer requiring anticoagulation will be allowed.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (AHA Class II or worse), unstable

angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6.1 Patients with evidence of active infection will become eligible for reconsideration 7 days after completing antibiotic therapy.

3.2.7 HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with sorafenib, bevacizumab, and/or the combination.

3.2.8 Hypertension defined as systolic blood pressure >150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management.

3.2.9 Therapeutic anticoagulation with coumadin, heparins, or heparinoids.

3.2.10 Evidence of a bleeding diathesis.

3.2.11 History of high grade varices or arteriovenous malformations.

3.2.12 Patients previously treated with sorafenib will not be eligible for this trial.

3.2.13 Fistula or bowel obstruction or perforation in the 28 days prior to enrollment

3.2.14 Patients must not be taking the CYP450 enzyme-inducing drugs phenytoin, carbamazepine, phenobarbital, St. John's wort, or rifampin.

3.2.15 For patients who have been previously treated with bevacizumab, any severe toxicity associated with bevacizumab while the patient was being treated with the agent will make the patient ineligible for the trial. This includes bevacizumab-induced hypertensive crisis, arterial thromboembolic events (including cardiac ischemia or cerebrovascular ischemia or other arterial thrombosis), nephrotic syndrome, gastrointestinal perforation, serious hemorrhage, and fistulas (unless the fistula completely resolved while the patient was still on bevacizumab or it has been surgically corrected).

## 3.3 Inclusion of women and minorities

Women of all races and ethnic groups are eligible for this trial.

## 3.4 Baseline evaluation

3.4.1 Complete history and physical examination (including height, weight, vital signs including blood pressure, and ECOG performance score) with documentation of 1) measurable disease, detailed sites of tumor, 2) narcotic use and pain assessment and 3) prior therapies (hormonal, surgical, radio therapeutic and cytotoxic) 4) prior bowel perforations, obstructions, or fistulas will be conducted prior to starting therapy. A complete medication history will be obtained prior to starting including over the counter medications, homeopathic remedies, vitamins, and alternative therapies

3.4.2 Medically Indicated Imaging Studies (Baseline) - Every patient must have a baseline CT scan of chest, abdomen and pelvis areas of known or suspected disease involvement prior to receiving treatment to be used to monitor response. In some patients an MRI, PET, or ultrasound may be more appropriate and may be ordered or requested in addition the baseline CT scan. This must be completed within 16 days prior to enrollment.

3.4.3 An EKG should be obtained within 16 days prior to enrollment.

3.4.4 Laboratory Evaluation [baseline is to be obtained within 4 days prior to enrollment.

3.4.4.1 Hematological Profile: CBC with differential and platelet count, prothrombin time, activated partial thromboplastin time

3.4.4.2 Biochemical Profile: electrolytes, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin, calcium, phosphorous, albumin, magnesium, amylase, lipase

3.4.4.3 CA-125 and TSH within 4 days prior to enrollment.

3.4.4.4 Serum beta-hCG for female patients of childbearing age and anatomic ability. For those women who have undergone hysterectomy this will not be a requirement.

3.4.4.5 Urinalysis and Spot UPC for protein and creatinine.

3.4.4.6 A block of primary tissue (or 10 unstained sections on charged slides) from the time of diagnosis will be required from each patient. Tissue blocks from a known recurrence will be accepted if original tumor samples are unavailable.

3.4.5 Baseline blood pressure will be documented on physical exam on initial screening and confirmed by blood pressure reading on the day of starting therapy.

3.4.6 Baseline quality of life assessment using FACT-O tool (see **APPENDIX E**: FACT-O QUALITY OF LIFE TOOL).

### 3.5 Patient Registration

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and faxed to 301-480-0757.

## 4. TREATMENT PLAN

The doses on this trial will be bevacizumab 5 mg/kg IV every 2 weeks and sorafenib 200 mg PO twice daily for five days of every seven for a cycle length of 28 (+/- 2-3 days to allow for clinic and scheduling variations around holidays or availability of biopsy or imaging facilities), which is based on the results of our phase I study.

At the outset of the study, the patient may be admitted to the inpatient service to complete research studies including biopsies. Otherwise, treatment will be administered on an outpatient basis. For cycle 1, dosing of sorafenib and bevacizumab will not begin until after the completion

of the biopsy and pre-treatment imaging. This cycle may be foreshortened to 25 days due to this scheduling.

## 4.1 Drug administration

### 4.1.1 Sorafenib administration

Treatment will be administered on an outpatient basis with the exception of admissions for the purpose of facilitating research studies. Reported adverse events and potential risks are described in Section **6**. Appropriate dose modifications for sorafenib and bevacizumab are described in Section **5**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Sorafenib is supplied as 200-mg tablets. Patients will self-administer one tablet orally twice a day on days 1-5 of 7 each week (except for cycle 1 week 1, treatment may be less than 5 days for facilitation of biopsies and imaging studies). Patients are to swallow the tablets whole with approximately 250 ml (8 oz.) of water, each morning and evening (i.e., 12-hourly). Cycles will be 28 days long. Patients will be asked to administer the drug at approximately 08:00 and 20:00 hours. When sorafenib is given with a moderate fat meal, bioavailability was similar to that in the fasted state. With a high fat meal, sorafenib's bioavailability was reduced by 29% compared to administration in the fasted state. Thus, it is recommended that BAY 43-9006 be taken on an empty stomach (at least 1 hour before or 2 hours after eating). Patients will be asked to maintain a diary to document consumption of sorafenib as outlined in sections **6** and **4.1.1**.

### 4.1.2 Bevacizumab administration

4.1.2.1 On the day of bevacizumab administration, a review of systems pertinent to bleeding and thrombosis, a spot urine protein/creatinine ratio, and a measurement of blood pressure should be performed. Dose timing adjustments are listed in Section **5**

4.1.2.2 Bevacizumab will be administered intravenously every 2 weeks (+/- 2 days) on an outpatient basis with the exception of admissions for the purpose of facilitating research studies. The dose of bevacizumab to be given is 5 mg/kg (to be adjusted as our phase I study matures).

4.1.2.3 Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection. Administration will be as a continuous IV infusion. The initial bevacizumab dose will be delivered over 90 ± 10 minutes as a continuous IV infusion. If the first infusion is tolerated without infusion-associated adverse events (fevers and/or chills), the second infusion maybe delivered over 60 ± 10 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions maybe delivered over 30 minutes.

4.1.2.4 In the event of an infusion-related event, the infusion of bevacizumab should be stopped and held until resolution of acute symptoms. The PI or AI will be notified of the infusion-related event at the time of the occurrence. Upon resolution, the infusion should be restarted at a rate to increase the total infusion time by 30 minutes beyond the current time. For example, if an infusion related event occurs when the dose is planned to run for 60 minutes (i.e. a rate of 1.7 cc/hr), the drug should be held. When the event is resolved, the rate should be lowered to 1.1 cc/hr.

## 4.2 Supportive Care Guidelines

4.2.1 Patients will be allowed continued use of erythropoietin or analogs initiated prior to entry.

4.2.2 No concomitant use of alternative, complementary therapies or over-the-counter agents will be allowed without prior approval of the PI.

4.2.3 Treatment Plan: Patients who have experienced substantial clinical benefit in the form of tumor reduction resulting in manageable, but increased toxicity that would otherwise require cessation of therapy, will be allowed to continue on therapy at the discretion of the associate investigator physician or PI, after approval by CTEP/sponsors as described in section **5**. The patients will remain officially on study and their responses will be analyzed as such.

4.2.4 Management of toxicities that are likely relating to the investigational agents are found in section **5**.

## 4.3 Duration of Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s). Specifically, CTC toxicity grades 3 or 4 that do not resolve to grade 1 or baseline with a maximum of 3 weeks drug holiday. Bevacizumab may be held for up to 8 weeks for proteinuria.
- Gastrointestinal perforation
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Subject death

Serious noncompliance with sorafenib, supportive care agents, or explicit health care-related instructions, as determined by the judgment of the investigator.

## 4.4 Reassessment

4.4.1 Patients will be seen at least every 4 weeks in clinic. For the first two cycles, patients will be seen every two weeks. A history and physical with vital signs and a review of systems that documents coagulopathy-related events must be charted in the medical record for each visit.

4.4.2 In the absence of intercurrent illness or adverse events, no clinic visit is required for d15 bevacizumab after the first 2 cycles, patients provided that no toxicities attributable to either drug requiring modification of therapy have been encountered.

4.4.3 Medically indicated CT scans will be obtained and reviewed approximately every 8 weeks (or 2 cycles of therapy) to monitor disease response. Measurable disease will be monitored as described below in section **9.3**.

4.4.4 CA-125 should be obtained approximately every 4 weeks; however, no biochemical criteria will be used to describe disease progression.

4.4.5 Routine laboratory studies will be obtained every 4 weeks, to include, but not limited to, CBC with differential and platelet count, and Biochemical Profile: electrolytes, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin, calcium, phosphorous, albumin, magnesium

4.4.6 Treatment for each odd number cycle, starting with cycle 3, cannot be given prior to restaging imaging.

4.4.7 From Cycle 3 onward, the mid-cycle (Day 15) evaluation will include: blood pressure, UPC, and a review of systems focused on bleeding. This will be documented in the electronic medical record.

4.4.8 Blood pressure monitoring will be based on our current and successful experience in our phase 1 trial. Each patient will receive a sphygmomanometer to use to measure blood pressures at home when outside of the clinical center. Blood pressures will be measured daily for the first 8 weeks of therapy (at least once per week in a physician's office, see **APPENDIX F**: BLOOD PRESSURE CHECK FORM). The patient's sphygmomanometer will be calibrated against the clinical center blood pressure machines at each visit. If there is a discrepancy between the measurements from the patient's sphygmomanometer and the clinical center blood pressure machine of greater than or equal to 10 points, it will be documented in the patient's medical record. The manual blood pressure reading with properly sized cuff will be the reading of record from which therapeutic decisions will be made. The PI will be notified for any abnormal measurement (any systolic BP over 160 or diastolic BP > 100). Treatment will be determined by the BP on the clinic visit day surrounding the treatment.

4.4.9 Patients will have their quality of life assessed every two cycles and when they come off study using the FACT-O Quality of Life tool (see **APPENDIX E**: FACT-O QUALITY OF LIFE TOOL).

# 5. DOSING DELAYS/DOSE MODIFICATIONS

Toxicities will be described using CTCAE v4. The following adjustment will only apply if the toxicities reported are attributed by the investigator to be related to sorafenib and/or bevacizumab therapy.

Dose reduction of sorafenib below 200 mg by mouth qd will not be allowed.
Dose reduction of bevacizumab below 3 mg/kg will not be allowed.

Sorafenib dose reductions

| *Grade* | *Occurrence* | *Immediate Action* | *Resumption of Therapy* |
|---|---|---|---|
| 1 | 1st | None | no interruption |
| 2 | 1st | Investigator's discretion to hold therapy until Grade ≤ 1 | No change in dose, but initiate appropriate medical therapy |
| | Subsequent | Hold therapy until Grade ≤ 1 | Reduce sorafenib to 200 mg qd |
| 3 | 1st | Hold therapy until Grade ≤ 1 | Initiate appropriate medical therapy and re-challenge with reduced sorafenib dose (200 mg qd) |
| 4 | 1st | Stop therapy | Terminate therapy with experimental agent(s). Follow patient until resolution/stabilization of toxicity |

Patients experiencing unexpected NCI/CTEP grade 3 or 4 non-hematologic toxicity will have interruption of treatment of the likely offending agent and will be evaluated individually for intervention and resolution of toxicity, and safety for further treatment. Reporting of adverse events will be according to section **10**.

## 5.1 Bevacizumab and sorafenib dosing modifications - Specific adverse events

### 5.1.1 Hypertension

Bevacizumab should be held for systolic BP (SBP) > 160 or diastolic BP (DBP) > 100.
Bevacizumab should be held for symptomatic hypertension of any grade, and should be discontinued for G4 hypertension. If pressure exceeds either of the above parameters, it should

be rechecked no sooner than 30 minutes with a manual sphygmomanometer which has been appropriately calibrated. Bevacizumab should not be administered if the above parameters are exceeded. Antihypertensive therapy should be initiated and/or modified until parameters are met for at least 2 days. After 2 days, therapy may be restarted following the guidelines below.

**Table: Sorafenib adjustments for hypertension**

| Grade of Event (CTCAE v.4) | Antihypertensive Therapy | Blood Pressure Monitoring | Sorafenib Dose Modification |
|---|---|---|---|
| grade 1 | None | Routine | No change |
| grade 2 asymptomatic | Initiate monotherapy (suggest ACE-inhibitors or angiotensin receptor blockers) | Reinstitute daily BP monitoring and qweek by health care professional | No changes |
| grade 2 (symptomatic/ persistent) OR diastolic BP ≥ 110 mm Hg OR grade 3 | Add agents: K+ channel opener, beta-blocker, thiazide diuretic), Ca++ blocker | Increase frequency of monitoring (by health care professional) every 2 days until stabilized; continued q2d monitoring to stabilization after dosing restarted. | Hold sorafenib until symptoms resolved and diastolic BP ≤ 100 mmHg Resume treatment at reduced dose. |
| grade 4 | | | Discontinue protocol therapy |

5.1.2 Hemorrhage/Bleeding

Bevacizumab administration is contingent upon assessment of any persistent bleeding. Active bleeding such as new petechiae, epistaxis, CNS bleed, intermittent minimal hemoptysis or nasal secretions, or other grade 1 or greater bleeding events (excluding dipstick positive urine without red blood cells by microscopic exam) will require additional workup and subsequent risk assessment.

Grade 2 hemorrhage: Bevacizumab will be held for any grade 2 or greater bleeding event until resolution to a grade 0. At that time, reassessment of risk must be made. If bleeding of grade 2 or worse recurs, the patient will be taken off study.

Grade 3 or 4 hemorrhage: The patient will be taken off study without rechallenge.

### 5.1.3 Proteinuria

A spot UPC ratio should be performed prior to each bevacizumab dose. Repeat testing within 24 hours may be performed at the investigator's discretion to rule out spurious results. If the UPC is still elevated (≥ 1), the dose delays/modifications outlined in the table below will be followed.

| UPC ratio | Bevacizumab dose modification |
|---|---|
| <1 | Continue bevacizumab |
| ≥1-3.5 | Hold bevacizumab and recheck UPC in one week. UPC must resolve to < 1.0 in order to resume bevacizumab. |
| >3.5 | Hold bevacizumab. Collect 24 hr urine and recheck UPC in one week. UPC must resolve to < 1.0 in order to resume bevacizumab. When restarted, dose reduction of bevacizumab to 3 mg/kg IV q2weeks will be required |

If bevacizumab is delayed for more than 8 weeks due to proteinuria, discontinue bevacizumab.

Sorafenib will not be held when bevacizumab is held for proteinuria.

### 5.1.4 Surgical or periodontal procedures

If there is need for a major surgical or serious periodontal procedure, bevacizumab should be held for 4 weeks prior to the procedure and must not be resumed before 4 weeks after the surgical procedure. Longer delays may be necessary if clinically indicated in order to insure that adequate healing has taken place prior to bevacizumab resumption. Minor oral or periodontal procedures or surgical procedures may be done with no delay at the discretion of the PI.

### 5.1.5 Thrombosis

#### 5.1.5.1 Arterial Thrombosis

Patients will be taken off study in the event of arterial thrombosis. Arterial thrombosis include CNS ischemia, cardiac ischemia, and any visceral or peripheral artery thrombosis.

#### 5.1.5.2 Venous Thrombosis

For venous thrombosis requiring systemic anticoagulation, the patient may continue on monotherapy with bevacizumab while on systemic anticoagulation (sorafenib must be discontinued). If bevacizumab is continued as a single agent, the following guidelines should be followed regarding bevacizumab and anticoagulation administration:

| | | |
|---|---|---|
| **Venous Thrombosis** | [Note: Patients with lung cancer requiring therapeutic anticoagulation should discontinue bevacizumab] | |
| | Grade 3<br>OR<br>asymptomatic<br>Grade 4 | ▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2weeks, bevacizumab should be held until the full-dose anticoagulation period is over.<br>▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation **IF** <u>all</u> of the criteria below are met:<br>– The subject must have an in-range INR (usually 2-3) on a stable dose of warfarin, or on stable dose of heparin prior to restarting bevacizumab.<br>– The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions)<br>– The subject must not have had hemorrhagic events while on study<br>▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab |
| | Grade 4<br>(symptomatic) | Discontinue bevacizumab |

### 5.1.6 Coagulopathy

Patients with grade 3-4 coagulopathy must hold bevacizumab until the coagulopathy resolves to grade 1 if sorafenib is continuing.

5.1.7 LFT abnormality (SGOT/SGPT, bilirubin)

First appearance of Grade 3 or 4: hold sorafenib until < grade 1 or baseline. If there is no recovery in 3 weeks, discontinue sorafenib.

Recurrent grade 3 or 4: discontinue sorafenib.

5.1.8 Thrombocytopenia (plts < 50,000- grade 3 or greater)

Bevacizumab and sorafenib should be held until platelets are grade 1 or better (>75,000). If held for more than 3 weeks, discontinue therapy.

5.1.9 Allergic reactions and cytokine release syndrome (acute infusion reaction):

Patients who develop grade 2 allergic reactions with bronchospasm or any grade 3/4 allergic/ infusional reactions should have bevacizumab discontinued.

Grade 2/3 cytokine release syndrome can be rechallenged 24 hours later after premedication with methylprednisolone 60 mg IV or dexamethasone 20 mg IV 30 minutes before the infusion. The infusion rate should be increased to 3 hours. If tolerated, the subsequent dose can be given with 50% of the steroid dose and then tapered to 25% of steroid dose with a decreased duration of each infusion from 3 hours→90 minutes→60 minutes→30 minutes.

5.1.10 RPLS

Bevacizumab should be held in patients with signs and symptoms suggestive of reversible posterior leukoencephalopathy syndrome (RPLS), pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.

If bevacizumab is terminated due to toxicity, patients cannot continue on monotherapy with sorafenib.

5.1.11 Hand-Foot Syndrome

Prior to or upon initiating therapy, patients will begin pyridoxine 100 mg by mouth bid. Upon detection of any dryness, redness, or discomfort in the hands or feet, treatment with topical emollients (such as Aquaphor) should begin. These agents should be applied at least 2-4 times daily. In addition, pyridoxine dosage will be increased to a maximum

dosage of 1000 mg a day. Topical steroids agents may be used with PI/AI approval. Use of antihistamine agents is acceptable when appropriate.

5.1.12 Neuropathy

Neuropathy (grade 1 and 2) was a common finding at dose levels 1 and 2 in the phase I study. It is often difficult to distinguish from pain associated with hand foot syndrome. In the setting of discomfort in the hands and feet the associate investigator or PI must make a determination of whether the symptoms are related to hand-foot syndrome or neuropathy as needed. In the setting of neuropathy, therapy with gabapentin 100 mg-300 mg by mouth qHS may be initiated. Doses should be escalated as needed.

5.1.13 Antiemetic therapy

Patients with chemotherapy-induced nausea should be treated initially with a phenothiazine (prochlorperazine 10 mg q8h PO prn or promethazine 25 mg IV q6h prn). If this is inadequate, a benzodiazepine, ondansetron, or steroid should be added until acute nausea is controlled or a steroid may be added (e.g. dexamethasone 4 mg q6h prn). After acute nausea has resolved, consideration should be given to prophylactic therapy. If nausea recurs despite reasonable medical intervention dose reduction should be considered.

5.1.14 Rhinorrhea

Rhinorrhea is an expected toxicity. Use of pseudoephedrine is discouraged due to the likelihood of worsening hypertension. Antihistamine therapy is allowed.

5.1.15 Perforations/Fistulas

Any patient who has a visceral perforation shall be taken off both drugs, and thus off study. If a patient experiences a fistula, bevacizumab will be held pending evaluation of the fistula. If the fistula is non-complicated with no signs or likelihood of perforation based on radiologic appearance and/or consultation with subspecialty services as appropriate, patients may be conservatively managed with watchful waiting and continue on therapy with both drugs.

# 6. PHARMACEUTICAL INFORMATION

## 6.1 BAY 43-9006 (Sorafenib, NSC 724772, IND 69896)

### 6.1.1 Source

The investigational agent BAY 43-9006 will be supplied by the Bayer Health Care Corporation and distributed by CTEP

### 6.1.2 Chemical name and identification

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

**Other Names:** BAY 54-9085 is the tosylate salt of BAY 43-9006; sorafenib, Nexavar®.

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

**Mechanism of Action:** The Ras/Raf signaling pathway is an important mediator of responses to growth signals and angiogenic factors. This pathway is often aberrantly activated in human tumors due to presence of activated Ras, mutant b-Raf, or over expression of growth factor receptors.

BAY 43-9006 is a potent inhibitor of c-Raf, and wild-type and mutant b-Raf in vitro. Additionally, further characterization of BAY 43-9006 tosylate revealed that this agent inhibits several receptor tyrosine kinases (RTKs) that are involved in tumor progression (VEGF-R, PDGF-R, Flt3, and c-KIT) and p38α, a member of the MAPK family.

**Molecular Formula:** $C_{12}H_{16}ClF_3N_4O_3$ X $C_7H_8O_3S$

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

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

**How Supplied:** BAY 43-9006 tosylate is supplied as an immediate-release film-coated, round, and salmon color tablet containing 200 mg of the free base, BAY 43-9006, and the excipients croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium lauryl sulfate, and magnesium stearate. The film-coat consists of hydroxypropylmethyl cellulose, polyethylene glycol, tiranium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active BAY 43-9006 tosylate.

BAY 43-9006 tosylate 200 mg tablets are supplied in bottles of 140 tablets.

**Storage:** Store at controlled room temperature (15ºC – 25ºC). Storage conditions should not exceed 25ºC.

**Stability:** Stability studies with the 200 mg dosage form are ongoing. The current shelf life is 36 months when stored at controlled room temperature.

**Route of Administration:** Oral

**Reported Adverse Events and Potential Risks:**
Full CAEPR listed in section **10.5**

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

**Potential Drug Interactions:** BAY 43-9006 tosylate is neither a clinically meaningful inhibitor nor a clinically meaningful inducer of CYP2C19, CYP2D6 and CYP3A4 isoenzymes and is not expected to significantly increase or decrease the exposure of coadministered compounds metabolized by these pathways. However, concomitant administration of BAY 43-9006 tosylate and CYP3A4 inducers, such as phenytoin, carbamazepine, phenobarbital, rifampin, or St. Johns Wort should be avoided.

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

**Agent Ordering:** NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be

submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN Rm. 7149, Bethesda, MD 20892.

**Agent Accountability:** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from DCTD using the NCI Drug Accountability Record Form (DARF). BAY 43-9006, as an oral self-administered investigational agent, will be properly accounted for, handled, and disposed in accordance with CCR Policy # Clin-1 "Policy on Documenting, Handling and Disposing of Oral Investigational Agents that are Self-Administered by NCI CCR patients." The Standard Operating Procedure # Clin-1 "Standard Operating Procedure for Conducting and Documenting Drug Accountability for Oral Investigational Agents that are Self Administered by Patients at the CCR" identifies all activities associated with drug accountability for orally self administered investigational agents. Study drug may be repackaged by the Clinical Center Pharmacy Dept. and dispensed in light-resistant HDPE containers that contain up to a 28-day supply of BAY 43-9006. Patients will be instructed to document on a study diary the daily intake of BAY 43-9006, including the time the dose is taken, and whether or not any doses are missed. They will bring the study diary and any unused drug to their clinic appointments. Clinic staff will (1) collect all "old" [i.e., empty bottle(s), partial bottle(s) or full bottle(s)] of study drug; (2) perform a pill count and record the results on the approved CCR Pill Count Case Report Form which is to be maintained in the research record; (3) dispense the partial and full bottle(s) of BAY 43-9006 to the patient. Unused study drug is to be returned to the research nurse who will dispose of it according to the SOP.

## 6.2 Bevacizumab

### 6.2.1 Source

Bevacizumab will be supplied by Genentech and distributed by CTEP. The bevacizumab to be supplied for this protocol is intended for clinical trial use only and is not the commercially available Avastin. Investigational bevacizumab and commercially available Avastin may be produced at separate facilities and some difference may exist between the two products, although both are required to meet similar product testing criteria and are expected to be very similar in

safety and activity. For further details and molecule characterization, see the updated bevacizumab Investigator Brochure.

6.2.2 Chemical name and identification

**Chemical Name**:

**Other Names:** Recombinant humanized monoclonal anti-VEGF antibody (rhuMAB VEGF, Avastin®)

**Classification:** Recombinant humanized monoclonal antibody

**Mechanism of Action:** Inhibition of vascular endothelial growth factor (VEGF) resulting in inhibition of angiogenesis.

**How Supplied:** Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in two vial sizes:

- Each 100 mg (25 mg/mL – 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.
- Each 1000 mg (25mg/ml – 40 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

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**Storage:** Upon receipt, bevacizumab should be refrigerated (2 to 8º C). Do not freeze. Do not shake.

**Stability:** Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry.

Once diluted in 0.9% sodium chloride, solutions of bevacizumab must be administered within 8 hours.

**Preparation:** Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.

**Route of Administration:** Intravenous

**Reported Adverse Events and Potential Risks:**
Full CAEPR listed as in section **10.4**

**Method of Administration:** rhuMAb VEGF will be administered intravenously through a secondary IV set piggybacked above the infusion control device (pump) into a primary IV set containing 0.9% NaCl. When the rhuMAb VEGF drug product container is empty, 0.9% NaCl from the primary line should be used to flush the secondary set to complete rhuMAb VEGF delivery. 0.9% NaCl infusion should be continued to flush the primary IV set with a volume of fluid at least equal to the tubing priming volume, thus insuring complete drug delivery. Note that this flush is not included in the infusion times below.

The loading dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that was well tolerated.

## 6.3 Pyridoxine hydrochloride (CAS registry No.58-56-0)

### 6.3.1 Source

Pyridoxine HCl is available generically in a variety of formulations for oral use, including: prompt-release tablets containing 25mg. 50mg, 100mg, 250mg, or 500mg of the active drug. Pyridoxine HCl will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

### 6.3.2 Chemical name and identification

**Chemical Name**:

1) 3,4-pyridinedimethanol, 5-hydroxy,6-methyl-, hydrochloride
2) Pyridoxine hydrochloride

**Other Names:** Vitamin B6

**Pharmacology:** Pyridoxine and two related water-soluble compounds, pyridoxal and pyridoxamine, have equal biologic activity and are collectively known as vitamin $B_6$. They are converted in the liver primarily to pyridoxal phosphate, the active form of the vitamin; some conversion to pyridoxamine phosphate occurs, which is also biologically active.

Pyridoxine is absorbed by passive diffusion in the jejunum and, to a lesser extent, the ileum, and is converted to pyridoxal-5-phosphate in the liver and excreted mostly as 4-pyridoxic acid in the urine (35 – 63%).

Pyridoxal phosphate (pyridoxal 5′-phosphate) is a coenzyme involved in numerous metabolic transformations of proteins and amino acids; is a cofactor for glycogen phosphorylase; is involved in the metabolism of neurotransmitter amines, polyunsaturated fatty acids, and phospholipids; and modulates the actions of steroid hormones via interaction with steroid receptor complexes.

**Storage:** Pyridoxine HCl should be stored at <30°C (<86°F) in well-closed containers and protected from light

**Stability:** Commercial products are labeled with the manufacturer's expiration date.

**Route of Administration:** Oral

**Reported Adverse Events and Potential Risks:**

Nausea and other gastrointestinal complaints have been reported with pharmacologic doses of pyridoxine. Abdominal pain, vomiting, and a loss of appetite have been reported with high doses. Pure sensory axonal neuropathy, with symptoms of numbness, burning, shooting, or tingling pain; perioral numbness, decreased sensation to touch, temperature, and vibration; paresthesia; clumsiness, unstable gait, and ataxia are alleged to occur after chronic daily ingestion of 75 – 300mg pyridoxine. Other neurologic symptoms may include depression, headache, tiredness, and irritability.

Central sensory neuropathy, with ataxia, Romberg's sign, and Lhermitte's symptoms, may also be present and may account for incomplete recovery in some patients. Muscle weakness, fasciculations, and diminished reflexes may accompany sensory changes.The principal effect of pyridoxine overdosage is a sensory axonal neuropathy. Central effects have also been described. Neuropathy has been most commonly reported after chronic ingestion of 200 – 6000 mg/day for months or years. The minimum amount acutely associated with ganglion cell destruction in humans is 10,000 mg in an adult (~140 mg/kg). A reversible skin lesion similar to that of porphyria cutanea tarda may accompany sensory neuropathy.

Transient withdrawal symptoms (nervousness, tremors, abnormal EEG) were described in three of eight adult males following cessation of doses of 200 mg/day for 33 days.Pyridoxine use has been reported to cause photosensitivity.

Maternal supplementation with up to 20 mg pyridoxine daily may decrease lactation. Breast soreness and breast enlargement have been reported rarely with pharmacologic doses of oral pyridoxine during therapy of premenstrual syndrome.

Low serum folic acid concentrations have been reported in patients with homocystinuria who received pyridoxine 500 – 1500 mg daily.

In overuse: Patients who receiving 2000 – 7000 mg/day (or greater than 200 mg/day for >2 months) have developed sensory neuropathy with associated ataxia and numbness of the hands and feet. Symptoms decrease after pyridoxine is discontinued; however, it may take 6 months for sensation to normalize.

**Drug Interactions:** Drugs that may result in vitamin $B_6$ deficiency include the vitamin $B_6$ antagonists: isoniazid, cycloserine, penicillamine, hydralazine, and estrogen. Urinary excretion of 4-pyridoxic acid <0.1 mg/24 hours is suggestive of vitamin $B_6$ deficiency.

Concurrent use of altretamine and pyridoxine should be avoided. Data from a randomized trial evaluating altretamine and cisplatin ± pyridoxine in the treatment of ovarian cancer found that pyridoxine administration adversely affected the duration of response to chemotherapy.

## 7. CORRELATIVE/SPECIAL STUDIES

### 7.1 Tissue and sample acquisition and processing

Table 1: Laboratory studies by techniques

| ***Tissue lysates arrays (TLA)*** | ***Immunohistochemistry (IHC)*** |
|---|---|
| Tumor Biopsies | Archival tissue re-cuts |
| | Tumor biopsies |
| ***Cytokine profiling*** | ***Genotyping*** |
| Serum | Whole blood |
| Plasma | Tumor biopsies |

### 7.1.1 Rationale

In the context of this study, patients will undergo serial biopsies of tumors to characterize the effects that sorafenib and bevacizumab have upon the biology of both the tumor and the stroma. Serial tumor biopsies will be obtained through Interventional Radiology if considered minimal surgical risk.

The two studies during cycles 1 and 2 have specific translational purposes. The pretreatment biopsy is necessary to have baseline analysis of the patients' tumors. The purpose of the day 42 (C2D15) biopsy is to determine long-term post-treatment changes in the tumor and corresponds to biopsy date in the phase I trial, so there will be a large cohort of patient samples biopsied at the same time during their treatment to evaluate the effect of sorafenib/bevacizumab treatment and can be correlated with PET/MRI results. The final biopsy (again completely voluntary) will be to ascertain if patient's tumors change when they become refractory to treatment. Detailed molecular profiling will be used to evaluate target pathways as well as related pathways. Completed and ongoing studies have shown that both sorafenib and bevacizumab affect their intended targets; further detailed molecular analysis of tumor and stroma will lead to an understanding of the mechanisms mediating clinical response, tumor progression, and toxicities. In addition, the combination of these drugs may lead to molecular events that do not occur with either drug alone. Pathway profiling will be done in both tumor and stroma using LCM to selectively procure each. We have extended our tissue lysate arrays to allow assessment of stroma and angiogenesis.

### 7.1.2 Tumor Biopsies

#### 7.1.2.1 Timing

Biopsies will be performed at the following times (the biopsy should be obtained prior to the day's dosing of both sorafenib and bevacizumab- doses should be held if needed):

- after consent, prior to treatment on C1D1
- C2D15 after 1.5 months of treatment if the patient consents (optional)
- Off-study if the patient consents (optional)

Patients who choose not to undergo optional biopsies will remain on study and continue to receive treatment.

7.1.2.2 At least two core biopsies, not less than 18-gauge in diameter and at least 1cm in length will be obtained. Inability to get tissue with a reasonable attempt will not preclude treatment and the patient will remain eligible for all other translational components, including imaging. A reasonable attempt is defined as one attempt prior to the procedure being deemed unsuccessful. The use of imaging to facilitate biopsies will be decided upon by members of the interventional radiology team. Should CT scans be needed for biopsy, a limit of 10 scans for each procedure will be observed to minimize radiation exposure to the patient.

7.1.2.3 The biopsies are to be immediately embedded and frozen on site according to SOP (**APPENDIX B**: NCI/FDA PROTEOMICS PROGRAM STANDARD OPERATING PROCEDURE FOR TISSUE CORE COLLECTION – NEEDLE BIOPSY – CRYOPRESERVATION IN OCT**)**. The schedule for the biopsies will be made with Special Procedures (Dr. Brad Wood) or for surgery with Dr. Steven Libutti. Annunziata's lab (10/B1B40, (301) 496-9336, beeper 102-11155), will be on call to receive and embed biopsies.

7.1.2.4 Each patient sample set will be assigned a unique patient identifier upon receipt and storage in Annunziata's lab. The protocol scientific investigator(s) handling the samples will be blinded as to the patient identification, patient data and outcome. Samples from sets of at least three patients will be grouped for scientific analysis.

7.1.2.5 Frozen biopsies will be sectioned, stained, and subjected to microdissection of tumor cells and stromal cells according to optimized SOP (see **APPENDIX B**: NCI/FDA PROTEOMICS PROGRAM STANDARD OPERATING PROCEDURE FOR TISSUE CORE COLLECTION – NEEDLE BIOPSY – CRYOPRESERVATION IN OCT). Dissected cells will be lysed and tissue

lysates arrays printed for prosecution with a panel of antibodies as described below.

7.1.2.6 If a site is deemed appropriate for biopsy with minimal risk to the patient by agreement between the investigators and interventional radiology, an attempt at biopsy will be made. Minimal risk indicates a biopsy that is deemed safe by the performing service, either interventional radiology, general surgery, or the appropriate subspecialty service performing the procedure (pulmonary, gastroenterology, etc.) If the attempt is unsuccessful, the patient will still be eligible for treatment and other non-biopsy procedures and the subsequent biopsies will be foregone.

7.1.2.7 Biopsy material will be prioritized for tissue proteomics. The remaining tissue will be released for additional testing prioritized to raf-mutation analysis, microvessel density measurements, and immunohistochemistry. The archival material requested at the outset of the study will be used for the remainder of the requested tests

7.1.3 Blood samples: Serum and plasma samples will be collected for cytokine analysis and archived for other lab analyses related to angiogenesis, molecular targets, and signaling targets to be determined as described below. **Note: Blood samples will no longer be collected each cycle after 04/11/14 (Amendment J).**

7.1.3.1 One 7 ml EDTA (purple top) tube will be drawn at the beginning of each cycle, maintained on wet ice and transported to the Annunziata's lab. Plasma will be separated immediately upon receipt and aliquots frozen at $-80^0$C (no greater than 500 μl aliquots). Sample pickup can be requested by paging the Annunziata's Lab at 102-11155.

7.1.3.2 The same unique patient identifier linked to the tumor biopsies will be used to shield the archived blood samples.

7.1.4 Archival material. A block of archival tumor material will be requested from each patient. A recent resection sample or a block of tissue from the original resection are

requested. Where a block cannot be released by the governing Pathology department, 10 x 8um re-cuts on charged slides will be requested.

7.1.5 Samples, and associated data, will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to Dr. Annunziata's laboratory."

7.1.6 The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. a broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Dr. Annunziata's laboratory will report any freezer problems, lost samples or other problems associated with samples to the IRB, the NCI Clinical Director, and the office of the CCR, NCI."

7.1.7 DNA methylation profiling in plasma samples of ovarian cancer patients

We have implemented a pipeline to assess DNA methylation levels at one locus in the human genome, *ZNF154*, which has been identified as a pan-cancer marker (Sanchez-Vega, et al. Epigenetics 2013).

Briefly the protocol involves extracting cell free DNA from plasma samples, bisulfite conversion of the DNA (using 20 ng up to 1 ug), PCR amplification of the target region, annealing adapters and barcodes for sequencing, and sequencing on a MiSeq platform. Subsequent computational analyses will identify the extent and patterns of DNA methylation in the sequencing reads, for characterization of tumor vs normal status. Assays are typically run in a 96 well plate, all samples are run in duplicate and only one locus is examined in the genome. No DNA mutations are assessed in this analysis and the results do not give personally identifiable information.

We will assess samples covering time points over the course of treatment from the same individual, as available. The analysis will address the sensitivity of our assay to detect circulating tumor DNA carrying specific DNA methylation patterns that are

unique to tumor samples, from the data of earliest clinical contact through a treatment regime. We anticipate that the detectable signal will vary over the stage and severity of disease, with decreases in signal reflecting response to treatment. As this is a preliminary project, we anticipate testing the sensitivity and specificity of the method when the diagnosis is known for each plasma sample, rather than a blinded study.

A minimum of 1 mL of plasma is needed per time point, up 2mL. Any unused DNA will be returned to the Annunziata lab. Comparisons will be between time points of the same individual, or across affected vs unaffected individuals, where normal plasma samples can be obtained. These normal samples may ultimately come from a commercial source, matched for age, BMI, smoking history and/or any other patient characteristics that are available. All current assays are being conducted on samples obtained from these commercial sources.

Collaborator:

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Dr. Elnitski identified the *ZNF154* site as a pan-cancer marker and developed the pipeline for bisulfite sequence analysis. She will oversee all aspects of the data analysis. The results will be published as a collaborative effort between Drs. Annunziata and Elnitski.

## 7.2 Pharmacoproteomic analysis

7.2.1 The primary targets of pharmacoproteomic modulation to be measured were defined based upon the preclinical signaling data. They are listed below

| **Survival/Proliferation** | | **Angiogenesis** | | **Apoptosis** | |
|---|---|---|---|---|---|
| AKT | p-AKT | ENOS | p-eNOS | PARP | Cleaved-PARP |
| ERK 1 / 2 | p-ERK 1 / 2 | p-VEGFR-2 | CD31 | Caspase 3 | Cleaved Caspase-3 |
| Cyclin D1 | Myb-1 | | | | |

7.2.2 Should additional tissue or TLA arrays be available, the following targets will be characterized. These will include but are not limited to the following:

| **Survival/Proliferation** | | **Angiogenesis** | | **Apoptosis** | |
|---|---|---|---|---|---|
| mTOR | p-mTOR | □-smooth muscle actin | | p53 | |
| EGFR | p-EGFR | Pyk2 | p-Pyk2 | GSK3ß | p-GSK3ß |
| Src | p-Src | VEGFR-2 | | p-bad | |
| NFkB | p-NFkB | Integrin β3 | | p-Bcl-2/bcl-2 | |
| STAT1 | p-STAT1 | | | Caspase 9 | |
| IkB | p-IkB | | | Cleaved Caspase-9 | |
| p38 | Phospho-p38 | | | | |
| Jak1 | p-Jak1 | | | | |

7.2.3 Provided that the following antibodies be validated for usage and adequate tissue or TLA arrays be available, the following additional targets will be characterized:

| **Survival/Proliferation** | |
|---|---|
| Fos | |
| Raf | |
| Ras | |
| CREB | |
| Jun | p-Jun |

## 7.3 Correlative imaging studies

We will use functional tumor imaging with dynamic contrast enhanced (DCE) MRI and PET to evaluate changes in vascularity and quality of index lesions for research purposes only. These modalities may provide early indications of treatment effect even before changes in size can be perceived on CT. Moreover, they may provide data on the additive effect of BAY 43-9006 and bevacizumab on angiogenesis regulation. PET may provide additional information on tumor metabolism as well as the effects of treatment on GLUT-1 transporter function. Together, these modalities should provide a unique window on the single and combined effects of BAY 43-9006 and bevacizumab.

Index lesions will be selected for serial measurement based on size (at least 1 cm in largest diameter for biopsy and imaging studies at the discretion of the collaborative imager) and relative immobility. The same lesion will be evaluated by Dynamic Contrast Enhanced MRI (DCE-MRI) and PET. Scans will be obtained on the same schedule as the tumor biopsies. They will not be used to assess disease response and continuation on the protocol.

### 7.3.1 DCE-MRI

Patients will undergo DCE-MRI using the following parameters. Conventional T1 and T2 weighted images of the target lesion will be obtained and a T1 map will be generated. This will be followed by a series of 3D gradient echo T1 weighted dynamic sequence which will be acquired before, during and after the administration of 0.1mmol/kg of a gadolinium chelate. Data will be analyzed using a general kinetic model by the Clinical Imaging Processing Service (CIPS) in the Diagnostic Radiology Department. This model generates two parameters K_trans and $k_{ep}$ (permeability terms) which will be used as continuous outcome variables in the analysis. Vascular fraction may also be assessed. Color maps based on these parameters will also be generated.

### 7.3.2 PET

Patients will undergo a FDG PET after fasting for 6 hours (patient may have water and oral medications) on C1d1. Approximately 1 hour following injection of 15 mCi FDG a whole body PET will be obtained. For each patient, we will select and measure one lesion that is greater than 1 cm and is the same mass being analyzed by DCE MRI. Standardized Uptake Values (SUV) will be obtained from the target lesion and used as a continuous outcome variable. On C1d3

andC2d15, repeat PETs following the same procedure listed above will be obtained to ascertain if PET response following treatment is predictive of response. SUV values will be compared between patients and across time for changes in tumor activity, as well as compared with eventual patient tumor response to therapy using standard statistical methods.

## 7.4 Angiogenesis studies

### 7.4.1 Cytokine profiling

Cytokine production has been shown to be regulated by the Ras/Raf/MAPK pathways and downstream of VEGFR signaling. Serial plasma samples will be collected during the course of the study. These will be batched and the analyzed by commercially available ELISA. The following will be measured: VEGF, IL-6. IL-8 or others as indicated by pilot results in phase I Sorafenib/bevacizumab (work in progress).

### 7.4.2 Biopsy analysis/microvessel staining

Re-cuts of tumor biopsies where available and/or archival materials will be stained and analyzed for microvessel density (MVD) using standard immunohistochemical assays. Quantification of MVD will be assessed using the method of Weidner et al. using CD31 expression. Sections will then be screened to determine the most vascular area of the tumor (hot spot). Within the hot spot area, the stained microvessels will be counted as a single high-power (x 400) field.

## 7.5 Ras/Raf mutation identification

It has recently been found that B-Raf is commonly mutated in human tumors. To determine if BAY 43-9006 preferentially inhibits tumors with mutant B-Raf, mutational analysis of B-Raf will be done using the following paradigm:

Initial screening for B-Raf mutation will be executed by protein lysate array analysis. The most frequently observed mutation in B-Raf yields the V599E [29] amino acid substitution. Dr. Meltzer's group in the NCI's Genetics Branch has developed a monoclonal antibody specific to this mutation (unpublished data). Lysate arrays will be optimized with this monoclonal antibody and then will be used to assess expression of this B-Raf mutation. Detection of this protein product will prompt allele specific PCR of the tumor genome using a recut from the tumor biopsies obtained for the protocol. No germline analysis will be done. Additionally, once a

cohort of responders has been identified, genomic DNA will be extracted from tissue blocks for allele specific PCR in the other commonly mutated regions, for which a specific antibody does not yet exist.

## 8. STUDY CALENDAR

***Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate (+/- 2-3 days to allow for clinic and scheduling variations around holidays or availability of biopsy or imaging facilities).***

Baseline physical examinations are to be conducted within 1 week prior to administration of protocol therapy. Laboratory evaluations should be within 48 hours prior to initiation of the next cycle of therapy.

| | Pre-Treatment | C1D1 | C1D3 | C1D15 | C2D1 | C2D15 | C3D1 | Q 2 weeks | Q month | Q 2 months | Off Study[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bevacizumab therapy | | X | | X | X | X | X | X | X | X | |
| Sorafenib therapy | | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | |
| Informed consent | X | | | | | | | | | | |
| Demographics | X | | | | | | | | | | |
| Medical history | X | X | | X | X | X | X | | X | X | X |
| Concurrent meds | X | X | | X | X | X | X | | X | X | X |
| Diary review[f] | | X | | | X | | X | | X | X | X |
| Physical exam | X | X | | X | X | X | X | | X | X | X |
| Daily blood pressure (See **APPENDIX F**: | | X | X | X | X | X | | | | | |
| Vital signs | X | X | | X | X | X | X | X | X | X | X |
| Performance status | X | X | | X | X | X | X | | X | X | X |
| Quality of life | | X | | | | | X | | | X | X |
| CBC w/diff, plts | X | X | | X | X | X | X | | X | X | X |
| Serum chemistry[a] | X | X | | X | X | X | X | | X | X | X |
| PT/PTT | X | | | | | X | | | | | |
| CA 125 | X | X | | | X | | X | | X | X | X |
| TSH | X | | | | X | | X | | X | X | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tumor Measurement | X | | | | | | X | | | X | |
| EKG | X | | | | | | | | | | |
| UPC | X | | | X | X | X | X | X | X | X | |
| Adverse event evaluation | | | | X | X | X | X | | X | X | X |
| B-HCG | X[b] | | | | | | | | | | |
| Research Bloods | | X | | | X | | | | | | X[g] |
| Tumor Biopsy | X[e] | | | | | X[g] | | | | | X[g] |
| FDG-PET | X [e] | | X | | | X | | | | | |
| DCEMRI | X[e] | | X | | | X | | | | | |
| CT Chest/Abdomen/Pelvis | X | | | | | | X | | | X | |

a: electrolytes, BUN, creatinine, glucose, AST (SGOT), ALT (SGPT), bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, amylase, lipase

b: Serum pregnancy test (women of childbearing potential only).

c: Off-study evaluation. If the patient is unable to return to the clinical center for evaluation, a follow-up phone call will be made.

d: prestudy tests should be completed within 4 days of enrollment

e: the initial biopsy and DCEMRI should be performed within a period of 7 days prior to starting drug therapy

f: A study diary will be assigned to each patient. It will be reviewed every cycle with the research nurse to monitor compliance and a copy will be placed in the research record.

g: If patient is willing h: Sorafenib will be taken orally twice daily for 5 days every week

## 9. MEASUREMENT OF EFFECT

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

### 9.1 Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable

using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

#### 9.1.1 Measurable Disease

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

#### 9.1.2 Non-measurable Disease

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

#### 9.1.3 Target Lesions

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

#### 9.1.4 Non-target Lesions

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

## 9.2 Guidelines for Evaluation of Measurable Disease

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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

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

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

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

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

**Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

**Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).
The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

**CA-125**. CA-125 alone will not be used to assess response. If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

### 9.3 Response Criteria

Response will be evaluated by physical exam every four weeks and/or noninvasive imaging using techniques that demonstrate lesions and tumor markers where appropriate. 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 [30]. Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST 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 non-target Lesions

| | |
|---|---|
| Complete Response (CR): | Disappearance of all non-target lesions and normalization of tumor marker level |
| Incomplete Response/ Stable Disease (SD): | Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits |
| Progressive Disease (PD): | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions |

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

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

### 9.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section **9.3.1**).

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

## 9.4 Confirmatory Measurement/Duration of Response

### 9.4.1 Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol see section **9.3.3**

### 9.4.2 Duration of Overall Response

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

### 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. Disease must show an absence of progression for a period of at least 4 weeks as verified by serial CT scans to be classified as stable disease.

### 9.4.4 Reporting of Results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients.
Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol deviations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
The 95% confidence intervals should be provided.

# 10. SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

## 10.1 Definitions

### 10.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

### 10.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### 10.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information

described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

10.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.1.6 Disability

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

10.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

10.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

10.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

10.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**

- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

## 10.2 NCI-IRB and Clinical Director Reporting

10.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

10.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance

3. A tabular summary of the following adverse events:

   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

   **NOTE**: Grade 1 events are not required to be reported.

#### 10.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

### 10.3 Expedited Adverse Event Reporting to Sponsor

Expedited adverse event (AE) reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System ), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section **10.3.1**).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section **6** (Pharmaceutical Information). *A copy of*

*the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).*

Expedited reports are submitted to CTEP via the secure CTEP-AERS application accessed via the CTEP web site (http://ctep.cancer.gov) and to the NCI IRB. Those AEs that do not require expedited reporting must be reported in routine (CDUS) study data submissions. AEs reported through CTEP-AERS must **also** be reported in routine study data submissions.

### 10.3.1 Expedited Reporting Guidelines

**Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent**

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

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

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

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

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

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site
- All expedited AE reports must also be sent to the local IRB according to local IRB policy and procedure

### 10.1 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions. AEs reported through CTEP-AERS must also be reported in routine study data submissions.

### 10.2 Secondary Malignancy

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

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

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

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

## 10.3 Second Malignancy

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

## 10.4 CAEPR for Bevacizumab

**Comprehensive Adverse Events and Potential Risks list (CAEPR)**
**for**
**Bevacizumab (rhuMAb VEGF, NSC 704865)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3540 patients.* Below is the CAEPR for bevacizumab (rhuMAb VEGF).

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

**Version 2.3, August 1, 2013**[1]

| **Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | Anemia | | ***Anemia (Gr 3)*** |
| | | Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy) | |
| | Febrile neutropenia | | ***Febrile neutropenia (Gr 3)*** |
| CARDIAC DISORDERS | | | |
| | | Acute coronary syndrome[2] | |
| | Cardiac disorders - Other (supraventricular arrhythmias)[3] | | ***Cardiac disorders - Other (supraventricular arrhythmias)[3] (Gr 3)*** |
| | | Heart failure | |
| | | Left ventricular systolic dysfunction | |
| | | Myocardial infarction[2] | |
| | | Ventricular arrhythmia | |
| | | Ventricular fibrillation | |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | ***Abdominal pain (Gr 3)*** |
| | Colitis | | ***Colitis (Gr 3)*** |
| | Constipation | | ***Constipation (Gr 3)*** |
| | Diarrhea | | ***Diarrhea (Gr 3)*** |
| | Dyspepsia | | ***Dyspepsia (Gr 2)*** |
| | | Gastrointestinal fistula[4] | |
| | Gastrointestinal hemorrhage[5] | | ***Gastrointestinal hemorrhage[5] (Gr 2)*** |
| | Gastrointestinal obstruction[6] | | |
| | | Gastrointestinal perforation[7] | |
| | | Gastrointestinal ulcer[8] | |
| | Ileus | | |
| | Mucositis oral | | ***Mucositis oral (Gr 3)*** |
| | Nausea | | ***Nausea (Gr 3)*** |
| | Vomiting | | ***Vomiting (Gr 3)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Fatigue | | ***Fatigue (Gr 3)*** |
| | Infusion related reaction | | ***Infusion related reaction (Gr 2)*** |
| | Non-cardiac chest pain | | ***Non-cardiac chest pain (Gr 3)*** |
| | Pain | | ***Pain (Gr 3)*** |
| IMMUNE SYSTEM DISORDERS | | | |
| | Allergic reaction | | ***Allergic reaction (Gr 2)*** |
| | | Anaphylaxis | |
| INFECTIONS AND INFESTATIONS | | | |
| | Infection[9] | | ***Infection[9] (Gr 3)*** |
| | | Infections and infestations - Other (necrotizing fasciitis) | |

| | | | |
|---|---|---|---|
| | Infections and infestations - Other (peri-rectal abscess) | | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | | Injury, poisoning and procedural complications – Other (anastomotic leak)[10] | |
| | Wound complication | | ***Wound complication (Gr 2)*** |
| | Wound dehiscence | | ***Wound dehiscence (Gr 2)*** |
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased | | ***Alanine aminotransferase increased (Gr 3)*** |
| | Alkaline phosphatase increased | | ***Alkaline phosphatase increased (Gr 3)*** |
| | Aspartate aminotransferase increased | | ***Aspartate aminotransferase increased (Gr 3)*** |
| | Blood bilirubin increased | | ***Blood bilirubin increased (Gr 2)*** |
| | Cardiac troponin I increased | | |
| Neutrophil count decreased | | | ***Neutrophil count decreased (Gr 3)*** |
| | Platelet count decreased | | ***Platelet count decreased (Gr 4)*** |
| | Weight loss | | ***Weight loss (Gr 3)*** |
| | White blood cell decreased | | ***White blood cell decreased (Gr 3)*** |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | ***Anorexia (Gr 3)*** |
| | Dehydration | | ***Dehydration (Gr 3)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | ***Arthralgia (Gr 3)*** |
| | Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[11] | | |
| | Myalgia | | ***Myalgia (Gr 3)*** |
| | Osteonecrosis of jaw[12] | | |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dizziness | | ***Dizziness (Gr 2)*** |
| | Headache | | ***Headache (Gr 3)*** |
| | | Intracranial hemorrhage | |
| | | Ischemia cerebrovascular[2] | |
| | Peripheral sensory neuropathy[13] | | |
| | | Reversible posterior leukoencephalopathy syndrome | |
| | Syncope | | |
| RENAL AND URINARY DISORDERS | | | |
| | | Acute kidney injury | |
| | Hematuria | | ***Hematuria (Gr 3)*** |
| | Proteinuria | | ***Proteinuria (Gr 2)*** |
| | | Renal and urinary disorders - Other (Nephrotic Syndrome) | |
| | | Urinary fistula | |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | | |
| Reproductive system and breast disorders - | | | |

| | | | |
|---|---|---|---|
| Other (ovarian failure)[14] | | | |
| | | Vaginal fistula | |
| | Vaginal hemorrhage | | ***Vaginal hemorrhage (Gr 3)*** |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Allergic rhinitis | | ***Allergic rhinitis (Gr 3)*** |
| | | Bronchopleural fistula | |
| | | Bronchopulmonary hemorrhage | |
| | Cough | | ***Cough (Gr 3)*** |
| | Dyspnea | | ***Dyspnea (Gr 2)*** |
| | Epistaxis | | ***Epistaxis (Gr 3)*** |
| | Hoarseness | | ***Hoarseness (Gr 3)*** |
| | | Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation) | |
| | | Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula) | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Pruritus | | ***Pruritus (Gr 2)*** |
| | Rash maculo-papular | | ***Rash maculo-papular (Gr 2)*** |
| | Urticaria | | ***Urticaria (Gr 2)*** |
| VASCULAR DISORDERS | | | |
| Hypertension | | | ***Hypertension (Gr 3)*** |
| | Thromboembolic event | | ***Thromboembolic event (Gr 3)*** |
| | | Vascular disorders - Other (arterial thromboembolic event)[2,15] | |

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

[2]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[3]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

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

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak

[11]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[12]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[13]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[14]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[15]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack and stroke.

**Also reported on bevacizumab (rhuMAb VEGF) trials but with the relationship to bevacizumab (rhuMAb VEGF) still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis
**CARDIAC DISORDERS** - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
**EAR AND LABYRINTH DISORDERS** - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
**ENDOCRINE DISORDERS** - Hyperthyroidism; Hypothyroidism
**EYE DISORDERS** - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (floaters); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye disorders - Other (vitreous hemorrhage); Eye pain; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Watering eyes
**GASTROINTESTINAL DISORDERS** - Ascites; Chelitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis;Typhlitis
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
**HEPATOBILIARY DISORDERS** - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
**INFECTIONS AND INFESTATIONS** - Infections and infestations - Other (aseptic meningitis)
**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture

**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
**METABOLISM AND NUTRITION DISORDERS** - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Generalized muscle weakness; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Tumor pain
**NERVOUS SYSTEM DISORDERS** - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
**PSYCHIATRIC DISORDERS** - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
**RENAL AND URINARY DISORDERS** - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
**VASCULAR DISORDERS** - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

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

## 10.5 CAEPR for Sorafenib

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2157 patients.* Below is the CAEPR for sorafenib (BAY 43-9006).

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

**Version 2.4, December 21, 2011**[1]

| **Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006) (CTCAE 4.0 Term) [n= 2157]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | Anemia | | ***Anemia (Gr 3)*** |
| | Febrile neutropenia | | |
| CARDIAC DISORDERS | | | |
| | | Acute coronary syndrome | |
| | | Left ventricular systolic dysfunction | |
| | | Myocardial infarction | |
| GASTROINTESTINAL DISORDERS | | | |
| Abdominal pain | | | ***Abdominal pain (Gr 3)*** |
| | Anal mucositis | | |
| | Ascites | | |
| | Constipation | | ***Constipation (Gr 2)*** |
| Diarrhea | | | ***Diarrhea (Gr 3)*** |
| | Gastrointestinal | | ***Gastrointestinal hemorrhage***[2] |

| | | | |
|---|---|---|---|
| | hemorrhage[2] | | ***(Gr 3)*** |
| | | Gastrointestinal perforation[3] | |
| | Mucositis oral | | |
| Nausea | | | ***Nausea (Gr 3)*** |
| | Rectal mucositis | | |
| | Small intestinal mucositis | | |
| | Vomiting | | ***Vomiting (Gr 3)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Edema limbs | | |
| Fatigue | | | ***Fatigue (Gr 3)*** |
| | Fever | | ***Fever (Gr 2)*** |
| | Non-cardiac chest pain | | |
| IMMUNE SYSTEM DISORDERS | | | |
| | | Anaphylaxis | |
| INFECTIONS AND INFESTATIONS | | | |
| | Infection[4] | | |
| INVESTIGATIONS | | | |
| | Activated partial thromboplastin time prolonged | | ***Activated partial thromboplastin time prolonged (Gr 2)*** |
| Alanine aminotransferase increased | | | ***Alanine aminotransferase increased (Gr 3)*** |
| Alkaline phosphatase increased | | | ***Alkaline phosphatase increased (Gr 3)*** |
| Aspartate aminotransferase increased | | | ***Aspartate aminotransferase increased (Gr 3)*** |
| Blood bilirubin increased | | | ***Blood bilirubin increased (Gr 3)*** |
| | Cholesterol high | | |
| Creatinine increased | | | ***Creatinine increased (Gr 3)*** |
| | GGT increased | | |
| INR increased | | | ***INR increased (Gr 2)*** |
| | Investigations - Other (bicarbonate, serum-low) | | |
| Lipase increased | | | ***Lipase increased (Gr 3)*** |
| Lymphocyte count decreased | | | ***Lymphocyte count decreased (Gr 3)*** |
| | Neutrophil count decreased | | ***Neutrophil count decreased (Gr 4)*** |
| Platelet count decreased | | | ***Platelet count decreased (Gr 4)*** |
| Serum amylase increased | | | ***Serum amylase increased (Gr 3)*** |
| Weight loss | | | ***Weight loss (Gr 2)*** |
| White blood cell decreased | | | ***White blood cell decreased (Gr 4)*** |
| METABOLISM AND NUTRITION DISORDERS | | | |
| Anorexia | | | ***Anorexia (Gr 3)*** |
| | Hypercalcemia | | |
| Hyperglycemia | | | ***Hyperglycemia (Gr 3)*** |

| | | | |
|---|---|---|---|
| | Hyperkalemia | | ***Hyperkalemia (Gr 3)*** |
| | Hypernatremia | | |
| | Hyperuricemia | | |
| Hypoalbuminemia | | | ***Hypoalbuminemia (Gr 3)*** |
| Hypocalcemia | | | ***Hypocalcemia (Gr 3)*** |
| | Hypoglycemia | | ***Hypoglycemia (Gr2)*** |
| | Hypokalemia | | ***Hypokalemia (Gr 3)*** |
| Hyponatremia | | | ***Hyponatremia (Gr 3)*** |
| Hypophosphatemia | | | ***Hypophosphatemia (Gr 3)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | ***Arthralgia (Gr 3)*** |
| | Back pain | | ***Back pain (Gr 3)*** |
| | Bone pain | | |
| | Musculoskeletal and connective tissue disorder - Other (muscle spasms) | | |
| | Myalgia | | |
| | Pain in extremity | | ***Pain in extremity (Gr 3)*** |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dizziness | | |
| | Headache | | ***Headache (Gr 3)*** |
| | | Intracranial hemorrhage | |
| | Peripheral sensory neuropathy | | |
| | | Reversible posterior leukoencephalopathy syndrome | |
| PSYCHIATRIC DISORDERS | | | |
| | Insomnia | | |
| RENAL AND URINARY DISORDERS | | | |
| | Acute kidney injury | | |
| | Hematuria | | |
| | Renal hemorrhage | | |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | | |
| | Hematosalpinx | | |
| | Ovarian hemorrhage | | |
| | Prostatic hemorrhage | | |
| | Spermatic cord hemorrhage | | |
| | Testicular hemorrhage | | |
| | Uterine hemorrhage | | |
| | Vaginal hemorrhage | | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Bronchopulmonary hemorrhage | | |
| | Cough | | ***Cough (Gr 2)*** |
| | Dyspnea | | ***Dyspnea (Gr 3)*** |
| | Epistaxis | | |

| | | | |
|---|---|---|---|
| | Laryngeal mucositis | | |
| | Pharyngeal mucositis | | |
| | Tracheal mucositis | | |
| | Voice alteration | | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| Alopecia | | | ***Alopecia (Gr 2)*** |
| | Dry skin | | ***Dry skin (Gr 2)*** |
| | | Erythema multiforme | |
| Palmar-plantar erythrodysesthesia syndrome | | | ***Palmar-plantar erythrodysesthesia syndrome (Gr 3)*** |
| | Pruritus | | ***Pruritus (Gr 3)*** |
| Rash maculo-papular | | | ***Rash maculo-papular (Gr 3)*** |
| | | Stevens-Johnson syndrome | |
| VASCULAR DISORDERS | | | |
| | Hypertension | | ***Hypertension (Gr 3)*** |
| | Thromboembolic event | | |

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

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

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

[4]Includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

**Also reported on sorafenib (BAY 43-9006) trials but with the relationship to sorafenib (BAY 43-9006) still undetermined:**

**CARDIAC DISORDERS** - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
**EAR AND LABYRINTH DISORDERS** - Tinnitus
**ENDOCRINE DISORDERS** - Hyperthyroidism; Hypothyroidism
**EYE DISORDERS** - Blurred vision; Cataract; Extraocular muscle paresis
**GASTROINTESTINAL DISORDERS** - Abdominal distension; Dyspepsia; Dysphagia; Flatulence; Ileus; Pancreatitis; Rectal fistula; Small intestinal obstruction
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema face; Flu like symptoms; Pain
**IMMUNE SYSTEM DISORDERS** - Allergic reaction
**INVESTIGATIONS** - Fibrinogen decreased
**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hypermagnesemia; Hypertriglyceridemia; Hypomagnesemia
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Generalized muscle weakness

**NERVOUS SYSTEM DISORDERS** - Dysgeusia; Encephalopathy; Ischemia cerebrovascular; Memory impairment; Syncope
**PSYCHIATRIC DISORDERS** - Confusion; Depression
**RENAL AND URINARY DISORDERS** - Proteinuria
**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Erectile dysfunction
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Hypoxia; Pleural effusion; Pneumonitis; Pneumothorax
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Hyperhidrosis; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (non-life threatening squamous cell carcinoma of skin: keratoacanthoma type); Skin hypopigmentation
**VASCULAR DISORDERS** - Flushing; Hypotension; Vasculitis

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

### 10.6 Data Reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means (NCI C3D). Reports are due January 31, April 30, July 31, and October 31. *Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov/reporting/cdus.html).*

## 11. COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT [CRADA/CLINICAL TRIALS AGREEMENT (CTA)]

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as Collaborator(s)) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a

confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

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

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

NOTE: The trial was completed with CTEP September 4, 2014.

## 12. STATISTICAL CONSIDERATIONS

### 12.1 Study Design/Endpoints

The primary objective of this study is to determine if the clinical response rate of this combination is sufficiently high to warrant further evaluation in patients with ovarian cancer. The clinical outcome will be defined as complete response (CR) or partial response (PR).

Secondary objectives include evaluation of progression free survival at greater than or equal to 6 cycles, toxicity, as well as a variety of biologic markers to determine if treatment impacts these parameters, and to see if the changes may be associated with clinical outcome. These studies will include characterization of effects on survival/proliferation, apoptotic, and angiogenic signaling cascades; identification of genetic mutations in raf to determine if this is a potentially important factor in disease response, apply real-time assessments of tumor vascularity and metabolism to characterization of response; and assessment of angiogenic effects of this combination.

Eligible patients will be stratified upon enrollment according to whether they have received prior bevacizumab or not.

In patients with no prior exposure to Bevacizumab, a Simon two-stage optimal design (1) will be used to determine whether the combination of bevacizumab and sorafenib is able to rule out a 20% response rate (p0=0.20) in favor of a more desirable 40% response rate (p1=0.40). Using alpha=0.10 and beta=0.10, initially 17 evaluable patients will be enrolled and receive treatment. If there are 0-3 clinical responses (CR+PR), then no further patients will be enrolled onto this arm of the trial, and this combination will be considered insufficiently active for further consideration in this disease. After 17 patients have been enrolled in this stratum, we will halt accrual until this analysis of the first stage is completed. If 4 or more clinical responses are identified in the first 17 patients enrolled in this stratum, then accrual will continue until a total of 37 patients are enrolled. If 3 to 10 clinical responses are noted in 37 patients, then the agents will not be considered sufficiently active in this disease for this stratum, while 11 or greater responses in 37 patients in this stratum will warrant further investigation in subsequent trials. Under the null hypothesis of 20% response rate, the probability of early termination in this stratum is 55%.

In patients with prior exposure to Bevacizumab, a Simon two-stage optimal design (1) will be used to determine whether the combination of bevacizumab and sorafenib is able to rule out a 5% response rate (p0=0.05) in favor of a more desirable 20% response rate (p1=0.20). Using alpha=0.05 and beta=0.10, initially 21 evaluable patients will be enrolled and receive treatment. If there are 0-1 clinical responses (CR+PR), then no

further patients will be enrolled onto this arm of the trial, and this combination will be considered insufficiently active for further consideration in this disease. After 21 patients have been enrolled in this stratum, we will halt accrual until this analysis of the first stage is completed. If 2 or more clinical responses are identified in the first 21 patients enrolled in this stratum, then accrual will continue until a total of 41 patients are enrolled. If 2 to 4 clinical responses are noted in 41 patients, then the agents will not be considered sufficiently active in this disease for this stratum, while 5 or greater responses in 41 patients in this stratum will warrant further investigation in subsequent trials. Under the null hypothesis of 5% response rate, the probability of early termination in this stratum is 72%.

Additional patients will be accrued to replace any patient who is entered on trial but does not complete the 2 cycle time period for evaluation of the primary endpoint, response (i.e. uncontrolled intercurrent illness, voluntary self-withdrawal, toxicity precluding continuation). Demonstration of progressive disease within that period will not require replacement as it is an outcome response. Any and all adverse events that occur during the time of drug exposure will be counted. Three replacement patients per stratum will be allowed.

A variety of markers will be evaluated at baseline as well as at cycle 2, day 1 of treatment. Changes from baseline will be determined in either absolute or relative terms as appropriate, and evaluated for statistical significance, as well as to determine if the changes or the actual values at a time point are associated with clinical response. Paired comparisons with baseline will be done using a paired t-test or Wilcoxon signed rank test as appropriate, and, if accrual is able to continue onto the second stage, the changes will be compared between responders (CR +PR) and non-responders (SD+PD) using a two sample t-test or Wilcoxon rank sum test as appropriate. As a minimum, for a given stratum, even if 10 markers were evaluated compared to baseline, with 20 patients there would be 88% power to declare a given marker change from baseline to be significant at the 0.05 level after adjusting for multiple comparisons by the Bonferroni procedure, although less stringent adjustments may be made in practice as these would be secondary endpoints.

PET and MRI parameters will also be obtained at the same time points, and changes in these parameters will also be compared in a similar fashion, both with respect to the changes themselves and with respect to any association with clinical response. In all such cases, these analyses will be considered exploratory and not formally adjusted for multiple comparisons. However, to ensure proper interpretation in the context of a potentially large number of explorations being performed, only p-values <0.01 will be interpretable as being associated with statistical significance.

Kaplan-Meier curves depicting time to progression on sorafenib + bevacizumab will be provided for both strata. Appropriate 95% confidence intervals will be formed.

Toxicities will be tabulated and the frequency of grade 3 or greater toxicities will be calculated, and appropriate 95% confidence intervals will be formed. As a final exploratory analysis, results from both strata may be pooled if it is determined that the results from both strata are sufficiently similar, that is, if p>0.10 for a test to determine if any set of results differ by stratum. Since patients with prior bevacizumab exposure are expected to potentially have different outcomes than those who do not, this combination of results will be carefully noted to be a secondary evaluation, not necessarily as meaningful as results from within each stratum, and will only be done cautiously if appropriate to do so at all.

For those correlative studies that do not meet criteria for statistical significance, they will be used as exploratory analyses for hypothesis generator (please refer to section **12.4** of the protocol).

### 12.2 Sample Size/Accrual Rate

It is anticipated that 30 patients per year may be enrolled onto the protocol. In order to enroll 78 evaluable patients, an accrual period of up to 3 years is expected.

### 12.3 Stratification Factors

Patients will be stratified based on exposure to bevacizumab.

### 12.4 Analysis of Secondary Endpoints

Proteomic and molecular endpoints will be evaluated on the protocol in all available enrolled patients. These will all be considered exploratory analyses and will not have their statistical results adjusted for multiple comparisons. However, all interesting findings will be carefully interpreted as hypothesis generating.

### 12.5 Reporting and Exclusions

12.5.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment

12.5.2 **Evaluation of response.** All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

## 13. HUMAN SUBJECTS PROTECTIONS

### 13.1 Rationale for subject selection

This study will be open to all women with recurrent epithelial ovarian, fallopian, and peritoneal cancer regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. For safety reasons, only pregnant women and children are excluded from this study. This study will be recruited through internal referral, our local physician referral

base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-888-624-1937).

All individuals with epithelial ovarian, fallopian, and peritoneal cancer that is refractory to standard care are eligible according to the eligibility criteria within section **3**. This is a phase II study to determine the efficacy of this combination for the treatment of these cancers. Patients must have failed therapy of proven efficacy for their disease.

Female patients all racial /ethnic groups are eligible for this study if they meet the eligibility criteria outlined in section **3**. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, accrual may be expanded, or a follow-up study may be written to investigate those differences more fully.

### 13.2 Participation of Children

Epithelial cancer of the ovary, fallopian tubes, or peritoneum in children is a exceedingly rare, reportable disease. Patients under the age of 18 will be excluded from study.

### 13.3 Evaluation of Benefits and Risks/Discomforts:

The potential benefit to a patient who enters study is a reduction in the bulk of her tumor, which may or may not have a favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects that are listed in the pharmaceutical section and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described earlier, including initial eligibility screening prior to enrollment on the protocol.

## 13.4 Risks/Benefits Analysis:

### 13.4.1 Potential Risks

13.4.1.1 Risk of serial biopsies: All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NIH's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

13.4.1.2 Risk of Treatment: Details of the risk of drug therapy are detailed in section **6**.

13.4.1.3 Risks of radiation exposure: This study incorporates serial imaging with radioactive substances related to the PET scans and CT scans for biopsy guidance (where needed) in the study. Patients will receive 3 injections of 15 mCi of F-18 FDG for PET. The total effective dose is less than 5 rem. This study is approved by the NIH Radiation Safety Committee.

## 13.5 Consent and Assent Process and Documentation:

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient at a subsequent visit. A copy of the signed informed consent will be placed in the patient's medical record and the original held in the Protocol Office.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

## 14. DATA AND SAFETY MONITORING PLAN

Patients are reviewed weekly in team meetings and response data will be reviewed on a quarterly basis as well. All unexpected or serious adverse drug reactions will be reported to the NCI Institutional Review Board (IRB) within 10 working days of the date of occurrence. Safety information from patients enrolled onto the study will be gathered and reported. Any unusual toxicity will be explored for possible causative mechanisms. The safety of the repetitive biopsy procedure will also be determined and reported.

Any unanticipated or unknown treatment- or drug-related toxicity(ies) and life-threatening and lethal toxicity(ies) must follow the guidelines described in section **10**. Clinical Associates and/or senior staff should notify the Principal Investigator at 301-402-2726 (Dr. Annunziata's), Bldg.10, Rm 12N226 of the occurrence of such toxicity.

A summary of the ongoing study will be submitted to the NCI's Institutional Review Board at 12 month intervals and a final report will be sent within six months of study completion at the request of the Institutional Review Board using the CTEP study summary form. The status reported will be submitted and presented at upcoming NCI meetings as requested.

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# 16. APPENDIX A: PERFORMANCE STATUS CRITERIA

| **ECOG Performance Status Scale** | |
|---|---|
| Grade | Descriptions |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

# 17. APPENDIX B: NCI/FDA PROTEOMICS PROGRAM STANDARD OPERATING PROCEDURE FOR TISSUE CORE COLLECTION – NEEDLE BIOPSY – CRYOPRESERVATION IN OCT

## Principle:

Core needle biopsies are used to sample tissue from a specific, defined location. These biopsies may consist of normal, pre-malignant and malignant tissue due to the multi-level tissue sample that is obtained. This type of sample is ideal for studying the micro-tumor environment.

Rapid freezing of the sample is required to prevent degradation of the proteins or RNA. Optimal Cutting Temperature (OCT) compound is an alcohol polymer that is liquid at room temperature and a solid at –20ºC. This polymer is used to cryo-protect the tissue and provide a medium for cryo-sectioning.

## Materials:

Cryomolds (Sakura Finetek Ca.t # 4728)

OCT (Sakura Finetek Cat. # 4583)

Dry ice

Ultra cold freezer ($-70^0$ to $-80^0$C)

Needle: 16 or 18 gauge

Permanent marker

Sterile forceps

Sterile Glass slides

Aluminum foil or 50ml Falcon tubes

**Procedure:**

1. Prepare all supplies prior to the biopsy procedure to avoid delay once the specimen has been obtained.
2. Label the handle and the front surface of the cryomold with the sample or patient's identifying information.
3. Receive core needle biopsy.
4. Pick the core from the biopsy needle onto a sterile glass slide.
5. Fill cryomold about 1/3 full with OCT. Place the cryomold in dry ice to partially freeze the OCT. The OCT should be jelly-like, not completely frozen.
6. Carefully lift the core biopsy by both ends with sterile forceps. **Do not stretch the biopsy or it will break.**
7. Lay the biopsy as straight as possible in the OCT. Once the sample touches the OCT, you cannot reposition it or the sample will break apart.
8. Quickly add OCT on top of the biopsy, completely covering the sample.
9. Ensure the sample is level and freeze immediately in dry ice.
10. Store wrapped in aluminum foil or in a 50ml Falcon tube at –70ºC then offload to liquid nitrogen.

**Note:**

Do not lay the biopsy on frozen OCT and cover it with liquid OCT. The OCT will not fuse and will split into two sections when cutting the frozen tissue sections.

Frozen Section Slides

1. Frozen sections for proteomic analysis should be cut at 5-8um on plain, uncoated glass microscope slides.
2. The tissue section should be placed as close as possible to the center of the slide. Do not place the frozen section at the end of the slide.
3. Two tissue sections from the same biopsy may be placed on the same glass slide if space permits.
4. Do not allow the tissue section to air on the slide. Freeze immediately on dry ice or at –80ºC.

## 18. APPENDIX C: STUDY DIARY

Patient Name:_____

| Day | Please note the times and dose of sorafenib (BAY 43-9006) that was taken by mouth. | Record Blood Pressure Daily at home and have BP checked WEEKLY at Dr's Office during Cycles 1 and 2. (Use separate form for Doctor's BP checks). | Please note any side effects you experienced on this day | Do not list your daily medications, but note any other medications you took on this day (both prescription and nonprescription and the reason why taken) |
|---|---|---|---|---|
| Monday | | | | |
| Tuesday | | | | |
| Wednesday | | | | |
| Thursday | | | | |
| Friday | | | | |
| Saturday | | | | |
| Sunday | | | | |

**Record entries daily. Do not record batch entries. If an error is made, draw a line through it and initial.

Patient Signature_____Date_____

# 19. APPENDIX D: CYTOCHROME P450 3A4 METABOLIZED DRUGS

Substrates

| | | | |
|---|---|---|---|
| Acetaminophen | Dapsone | Levobupivicaine | Risperidone |
| Alfentanil | Dehydroepiandrostendione | Lidocaine | Ritonavir** |
| Alosetron | Delavirdine | Loratadine | Salmeterol |
| Alprazolam | Desmethyldiazepam | Losartan | Saquinavir |
| Amiodarone | Dexamethasone | Lovastatin | Sertindole |
| Amitriptyline (minor) | Dextromethorphan (minor) | Methadone | Sertraline |
| Amlodipine | Diazepam (minor) | Mibefradil | Sibutramine |
| Anastrozole | Digitoxin | Miconazole | Sildenafil citrate |
| Androsterone | Diltiazem | Midazolam | Simvastatin |
| Antipyrine | Disopyramide | Mifepristone | Sirolimus |
| Astemizole | Docetaxel | Mirtazapine | Sufentanil |
| Atorvastatin | Dofetilide (minor) | Montelukast | Tacrolimus |
| Benzphetamine | Dolasteron | Navelbine | Tamoxifen |
| Bepridil | Donepezil | Nefazodone | Temazepam |
| Bexarotene | Doxorubicin | Nelfinavir | Teniposide |
| Bromazepam | Doxycycline | Nevirapine | Terfenadine |
| Bromocriptine | Dronabinol | Nicardipine | Testosterone |
| Budesonide | Enalapril | Nifedipine | Tetrahydrocannabinol |
| Bupropion (weak) | Erythromycin | Niludipine | Theophylline |
| Buspirone | Estradiol | Nimodipine | Tiagabine |
| Busulfan | Ethenyl estradiol | Nisoldipine | Tolterodine |
| Caffeine | Ethosuximide | Nitrendipine | Toremifene |
| Cannabinoids | Etoposide | Omeprazole (sulfonation) | Trazodone |
| Carbamazepine | Exemestane | Ondasetron | Tertinoin |
| Cerivastatin | Felodipine | Oral contraceptives | Triazolam |
| Cevimeline | Fentanyl | Orphenadrine | Troglitazone |
| Chlorpromazine | Fexofenadine | Paclitaxel | Troleandomycin |
| Cimetidine | Finasteride | Pantoprazole | Venlafaxine |
| Cisapride | Fluoxetine | Pimozide | Verapamil |
| Citalopram | Flutamide | Pioglitazone | Vinblastine |
| Clarithromycin | Glyburide | Pravastatin | Vincristine |
| Clindamycin | Granisetron | Prednisone | Warfarin |
| Clomipramine | Halofantrine | Progesterone | Yohimbine |
| Clonazepam | Hydrocortisone | Proguanil | Zaleplon (minor) |
| Clozapine | Hydroxyarginine | Propafenone | Zatoestron |
| Cocaine | Ifosfamide | Quercetin | Zileuton |
| Codeine | Imipramine | Quetiapine | Ziprasidone |

| | | | |
|---|---|---|---|
| Cortisol | Indinavir | Quinidine | Zolpidem\ |
| Cortisone | Isradipine | Quinine | Zonisamide |
| Cyclobenzaprine | Itraconazole | Repaglinide | |
| Cyclophosphamide | Ketoconazole | Retinoic acid | |
| Cyclosporine | Lansoprazole (minor) | Rifampin | |

**Inducers**

| | | | |
|---|---|---|---|
| Carbamazepine | Nelfinavir | Primidone | Sulfadimidine |
| Dexamethasone | Nevirapine | Progesterone | Sulfinpyrazone |
| Ethosuximide | Oxcarbazepine | Rifabutin | Troglitazone |
| Glucocorticoids | Phenobarbital | Rifampin | |
| Griseofulvin | Phenylbutazone | Rofecoxib (minor) | |
| Nafcillin | Phenytoin | St. John's Wort | |

**Inhibitors**

| | | | |
|---|---|---|---|
| Amiodarone | Disulfiram | Mibefradil | Ranitidine |
| Anastrozole | Entacapone | Miconazole (moderate) | Ritonavir** |
| Azithromycin | Erythromycin | Nefazodone | Saquinavir |
| Cannabinoids | Ethenyl estradiol | Nelfinavir | Sertindole |
| Cimetidine | Fluconazole (weak) | Nevirapine | Sertraline |
| Clarithromycin | Fluoxetine | Norfloxacin | Troglitazone |
| Clotrimazole | Fluvoxamine | Norfluoxetine | Troleandomycin |
| Cyclosporine | Gestodene | Omeprazole (weak) | Valproic acid (weak) |
| Danazole | Grapefruit Juice | Oxiconazole | Verapamil |
| Delavirdine | Indinavir | Paroxetine (weak) | Zarfirlukast |
| Dexamethasone | Isoniazid | Propoxyphene | Zileuton |
| Dimethyldithiocarbamate | Itraconazole** | Quinidine | |
| Diltiazem | Ketoconazole** | Quinine | |
| Dirithromycin | Metronidazole | Quinupristin and dalfopristin | |

** Contraindications
From Drug Information Handbook 8th Edition

## 20. APPENDIX E: FACT-O QUALITY OF LIFE TOOL

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

| | **PHYSICAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| | **SOCIAL/FAMILY WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

**By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

| | **EMOTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| | **FUNCTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

**By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| O1 | I have swelling in my stomach area | 0 | 1 | 2 | 3 | 4 |
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C3 | I have control of my bowels | 0 | 1 | 2 | 3 | 4 |
| O2 | I have been vomiting | 0 | 1 | 2 | 3 | 4 |
| B5 | I am bothered by hair loss | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| C7 | I like the appearance of my body | 0 | 1 | 2 | 3 | 4 |
| BMT5 | I am able to get around by myself | 0 | 1 | 2 | 3 | 4 |
| B9 | I am able to feel like a woman | 0 | 1 | 2 | 3 | 4 |
| O3 | I have cramps in my stomach area | 0 | 1 | 2 | 3 | 4 |
| BL4 | I am interested in sex | 0 | 1 | 2 | 3 | 4 |
| BMT7 | I have concerns about my ability to have children | 0 | 1 | 2 | 3 | 4 |

## 21. APPENDIX F: BLOOD PRESSURE CHECK FORM

Blood Pressure Check
Cycle 1

Week 1:

Name of Health Care Facility:

Date _____ B/P_____

Done by _____

Week 2:

Name of Health Care Facility_____

Date _____ B/P_____

Done by _____

Week 3:

Name of Health Care Facility_____

Date _____ B/P_____

Done by _____

Week 4:

Name of Health Care Facility_____

Date _____ B/P_____

Done by _____

Blood Pressure Check
Cycle 2

Week 1:

Name of Health Care Facility:

Date _____ B/P_____

Done by _____

Week 2:

Name of Health Care Facility_____

Date _____ B/P_____

Done by _____

Week 3:

Name of Health Care Facility_____

Date _____ B/P_____

Done by _____

Week 4:

Name of Health Care Facility_____

Date _____ B/P_____

Done by _____