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A Phase I/II Trial of BAY 43-9006 plus Gemcitabine and Capecitabine in the Treatment of Patients with Advanced Renal Cell Carcinoma

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NCI Supplied Agent:

BAY 43-9006 (NSC 724772)

Commercially Supplied Agent: Gemcitabine
Capecitabine

Protocol Version Date: 5/23/11

SCHEMA

1 Cycle = 21 days

	Week 1							Week 2							Week 3						
DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Gemcitabine	X							X													
Capecitabine	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
BAY 43-9006	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Gemcitabine: **750 (mg/m^2) IV over 30 minutes on days 1 and 8.**

Capecitabine: **415 (mg/m^2) p.o. twice daily on days 1-14.**

BAY 43-9006: **200 mg p.o. twice daily will be administered from day 1 until day 21.**

Treatment will be continued until disease progression or unacceptable toxicity. Patients should receive a minimum of three cycles of therapy. Patients may discontinue therapy if a complete response is achieved.

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1. OBJECTIVES

1.1. To determine the Maximum Tolerated Dose (MTD) and Dose Limiting Toxicity (DLT) of BAY 43-9006 administered in combination with gemictabine and capecitabine in patients with advanced renal cell carcinoma.

1.2. To determine the objective response rate for BAY 43-9006 in combination with gemcitabine and capecitabine in patients with advanced renal cell carcinoma.

1.3. To determine the duration of overall survival and progression free survival in these patients.

2. BACKGROUND

2.1 **Renal Cell Carcinoma**

Renal Cell Carcinoma (RCC) accounts for approximately 3% of all malignant adult tumors, with an estimated 35,710 new cases and 12,480 RCC related deaths in the year 2004(1). Immunotherapy with interferon alpha or interleukin-2 has become the mainstay of treatment with low, but reproducible response rates in the 10% to 15% range and complete responses with long term survival in 5% or fewer patients(2). The only therapy that has been demonstrated to improve survival is interferon alpha for which the median survival is approximately 2-3 months(3;4). Novel agents are clearly needed in the treatment of patients with metastatic RCC.

2.2 **BAY 43-9006**

Activation of the *ras* oncogene signaling pathway is considered to be an important mechanism by which human cancer develops. Raf kinase is a protein involved in the Ras signal transduction pathway. Ras regulates several pathways which synergistically induce cellular transformation, including the Raf/Mek/Erk cascade and the rac and rho pathways(5;6). In particular, Ras activates the Raf/Mek pathway by first localizing Raf to the plasma membrane, where Raf initiates a mitogenic kinase cascade. Activated Raf phosphorylates and activates Mek which in turn phosphorylates and activates Erk. Activated Erk then translocates from the cytoplasm into the nucleus and modulates gene expression via the phosphorylation of transcription factors. Thus activation of Raf kinase, via activation of Ras, is thought to play an important role in carcinogenesis.

In particular, B-raf, a serine/threonine kinase, has been shown to be activated in a number of human tumor types including melanoma, ovarian and papillary thyroid carcinomas(7-12). 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 (7;8).

In Vitro Activity

The ability of BAY 43-9006 to inhibit a number of kinases was evaluated (Investigator's Brochure, 2003). 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* (Investigator's Brochure, 2003). 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 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-β receptor phosphorylation (Investigator's Brochure, 2003).

VEGF and PDGF receptors are involved in the mechanism of tumor angiogenesis (13;14). PDGF receptors may also play a role in patients with chronic myeloproliferative cancers (15). Flt-3 is important in acute myelogenous leukemia (16) and c-Kit plays a critical role in gastrointestinal stromal tumors (17).

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	45
		30	64
		100	68
Colon	DLD-1	15	31
		30	66
		60	75
NSCLC	NCI-H460	10	27
		30	56
NSCLC	A549	30	60
		60	68
Mammary	MX-1	30	51
		60	67
Pancreatic	Mia-PaCa-2	10	45
		30	66
		100	73
Ovarian	SK-OV-3	10	58
		30	64
		100	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 and that, 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.

In human tumor xenografts, MDA-MB-231 (breast) and Colo-205 (colon), there was a dramatic reduction of tumor neo-vascularization (Investigator's Brochure, 2003). Recent data also indicated that inhibition of c-raf may promote cell death in endothelial cells as a downstream event of VEGFR-2 stimulation (18).

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	Yes
	MX-1 Mammary	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 500 patients have been treated with single agent BAY 43-9006. The Phase 1 single agent clinical plan has focused on characterizing the safety and pharmacokinetic profile BAY 43-9006 in several different dosing regimens. All Phase 1 patients had a variety of advanced refractory solid tumors, and some of the patients stayed on trial for more than one year. Four different regimens have been tested: continuous treatment, 4 weeks on/ 1 week off, 3 weeks on /1 week off, and 1 week on/ 1 week off. Patients have received doses ranging from 50 mg once weekly to 1600 mg daily of 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.

Currently, the Phase 2 program includes studies designed to explore anti-tumor efficacy in certain tumor types and to gain additional experience with pharmacokinetics and safety. Thus far, Phase 2 studies have enrolled over 300 patients with a variety of tumor types including colorectal, renal cell, hepatocellular, pancreatic, and thyroid cancer and melanoma as well as several less common tumors.

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

2.3 Gemcitabine and Capecitabine

Historically, chemotherapy has been ineffective in the treatment of RCC(19), however, recent trials using gemcitabine in combination with 5-fluorouracil (5-FU) or capecitabine have demonstrated response rates as high as 21%(20;21;27). The Cancer and Leukemia Group B recently completed a phase II study (#90008) of gemcitabine and capecitabine in patients with metastatic RCC(27). Patients were treated with gemcitabine at 1000 mg/m^2 day 1, 8, 15 and

capecitabine at 830 mg/m^2 twice daily, days 1-21 on a 28 day cycle. Partial responses were observed in 8 out of 55 patients for a response rate of 15% with a median duration of response and time to progression of 7.1 and 5.1 months, respectively. Grade 3,4 toxicities included neutropenia (40%) with febrile neutropenia in 1 patient, anemia (15%), thrombocytopenia (6%), nausea (11%), fatigue (7%), diarrhea (7%), and hand/foot syndrome and stomatitis (2% each). Grade 1, 2 toxicities included leukopenia (49%), fatigue (62%), nausea (42%), stomatitis (29%), diarrhea (27%), and hand/foot syndrome (36%). The investigators concluded that the combination of gemcitabine and capecitabine has modest activity in metastatic RCC, however, further evaluation of the regimen would require a dose modification. An evaluation of prognostic factors for survival with gemcitabine plus 5-FU based regimens concluded that although there is not a specific group of patients who are most likely to benefit from this combination, there is a continued suggestion that this regimen provides a modest improvement over past chemotherapy approaches(22).

2.4 **Rationale**

Both gemcitabine and capecitabine have separately been evaluated in combination with BAY 43-9006. A phase I/II trial of BAY 43-9006 and gemcitabine in patients with advanced solid tumors and in advanced pancreatic cancer revealed a lack of pharmacokinetic interaction between the two and non-overlapping clinical toxicities(23). A single-center phase I study of BAY 43-9006 in combination with capecitabine (Bayer Pharmaceuticals). BAY 43-9006 was administered orally (bid) from day 8 until day 21 in cycle 1, and continuously thereafter in doses of: 200 mg bid (Cohort 1), 400 mg bid (Cohort 2), and (for Cohort 3 only) 200 mg bid for the first two cycles, then 400 mg bid for each subsequent cycle. Capecitabine was given orally bid (2100 mg/m^2 per day) from day 1 in a 2 weeks on/1 week off schedule. The most frequent drug-related toxicities were hand/foot syndrome, diarrhea, fatigue, mucositis, and nausea. Dose-limiting toxicities included grade 3 hand/foot syndrome and grade 3 diarrhea in Cohort 1, and grade 3 hand/foot syndrome and grade 3 mucositis in Cohort 2. Treatment is ongoing in Cohort 3. An additional cohort has been added to evaluate BAY 43-9006 400 mg bid and capecitabine 1700 mg/m^2 per day. Preliminary pharmacokinetic analysis of BAY 43-9006 reveals no clinically significant interaction with capecitabine.

Based on the activity of gemcitabine and capecitabine and single agent BAY 43-9006 in metastatic RCC, it is important to investigate this three drug combination.

3. PATIENT SELECTION

3.1 **Eligibility Criteria**

3.1.1 Patients must have histologically or cytologically confirmed renal cell carcinoma that is unresectable and/or metastatic. Patients with collecting duct carcinoma, oncocytomas, or transitional cell carcinoma are not eligible. Patients with sarcomatoid renal cell carcinoma are eligible, but those with pure sarcomas are not. Histologic documentation of metastatic disease is not required. Clinical confirmation, but not pathologic staging, of metastatic disease is required.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See section 9.2 for the evaluation of measurable disease.

3.1.3 Patients may have received one prior immunotherapy based regimen (i.e. interleukin-2 or interferon alpha) ending ≥ 4 weeks prior to enrollment.

3.1.4 Patients may have received up to 2 prior regimens containing MAPK, VEGF pathway inhibitors (e.g. sunitinib or bevacizumab) and/or mTOR inhibitor (e.g. temsirolimus) ending ≥ 4 weeks prior to enrollment.

3.1.5 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of BAY 43-9006 in combination with gemcitabine and capecitabine in patients < 18 years of age, children are excluded from this study but will be eligible for future pediatric phase 2 combination trials.

3.1.6 Life expectancy of greater than 3 months (assessed using MSKCC Criteria, J Clin Oncol 20:289-96, 2002).

3.1.7 ECOG performance status ≤2 (Karnofsky ≥60%; see Appendix A).

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

-	leukocytes	≥3,000/μL
-	absolute neutrophil count	≥1,500/μL
-	platelets	≥100,000/μL
-	total bilirubin	≤1.5 X institutional upper limit of normal
-	AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
-	creatinine	≤1.5 X institutional upper limit of normal
	OR	
-	creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

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

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

3.2 **Exclusion Criteria**

3.2.1 Patients may not have received prior chemotherapy. If patients have had prior definitive or other surgery, prior radiation therapy, they must have fully recovered from the effects of therapy with at least 4 weeks recovery time. For patients who have had a surgical biopsy only, they must have simply recovered.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients with known active brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Previously treated brain metastases are allowed if they show no evidence of progression on CT or MRI at least 8 weeks after completion of surgery and/or radiotherapy

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to BAY 43-9006, gemcitabine and capecitabine.

3.2.5 No concurrent megestrol is permitted. No megestrol therapy within 4 weeks prior to protocol treatment is allowed. No concurrent cytochrome P450 enzyme-inducing antiepileptic drugs (phenytoin, phenobarbitol or carbamazepine), rifampin, or St. John's wort.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, uncontrolled hypertension, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, pulmonary disease including asthma, chronic bronchitis, emphysema with requirements for chronic oxygen use or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study because BAY 43-9006 is a kinase inhibitor agent 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, breastfeeding should be discontinued if the mother is treated with BAY 43-9006. The potential risks may apply to other agents used in this study.

3.2.8 Because patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy, HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with BAY 43-9006,

gemcitabine, or capecitabine administered during the study. Appropriate studies will be undertaken in patients receiving combination ant-retroviral therapy when indicated.

3.2.9 Any swallowing dysfunction leading to difficulty taking the investigational therapy or capecitabine.

3.2.10 Prior treatment with BAY 43-9006 (sorafenib).

3.2.11 Patients with any history or evidence of a bleeding diathesis.

3.2.12 Patients on therapeutic anticoagulation with coumarins (e.g. warfarin). Prophylactic coumarin-based anticoagulation (i.e. low dose warfarin) for venous or arterial access devices is allowed provided that the requirements for PT, INR and/or PTT are met. Prophylactic or therapeutic low molecular weight heparin is allowed. Patients with known brain metastases are excluded (even if treated and stable) if they are also on therapeutic doses of anticoagulation.

3.2.13 Patients with known dihydropyrimidine dehydrogenase deficiency.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4. PHASE I TREATMENT PLAN

4.1 BAY 43-9006, Gemcitabine and Capecitabine Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for BAY 43-9006, gemcitabine and capecitabine are described in Section 7. Appropriate dose modifications for BAY 43-9006, gemcitabine and capecitabine are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

The phase I dose escalation study will be conducted according to the dosing regimen described in the table below.

Cohort	BAY 43-9006	Gemcitabine	Capecitabine
A	200 mg p.o. bid x 21d	750 mg/m^2 IV d1 & 8	415 mg/m^2 p.o. bid x 14d
B	400 mg p.o. bid x 21d	750 mg/m^2 IV d1 & 8	415 mg/m^2 p.o. bid x 14d
C	400 mg p.o. bid x 21d	1000 mg/m^2 IV d1 & 8	415 mg/m^2 p.o. bid x 14d
D	400 mg p.o. bid x 21d	1000 mg/m^2 IV d1 & 8	622 mg/m^2 p.o. bid x 14d

Initially, 3 subjects will be enrolled into the cohort A. Enrollment for the next dose level may begin when 3 of the subjects in cohort A or previous cohort, have completed day 21 of cycle 2 without experiencing a dose limiting toxicity (DLT) as defined in Section 5. A cycle is defined as a 21-day period starting with the administration of BAY 43-9006, gemcitabine and capecitabine on day 1.

If a DLT is observed in 1 of 3 subjects, then a total of 6 subjects will complete 2 cycles prior to opening the next cohort. If < 2 of the 6 subjects experience a DLT, dose escalation can continue. However, if ≥ 2 of 6 subjects experience a DLT, then the maximum tolerated dose (MTD) has been exceeded. The MTD is generally one dose below that at which DLT occurs in > 2 of 6 subjects in any given cohort. Once the MTD is determined, 6 additional subjects will be enrolled at that dose level. If the MTD is not determined after completion of cohort D, 6 additional subjects will be enrolled at a dose level thought by the Investigator to be the recommended dose for the Phase 2 part of the trial. Cohorts will consist of a minimum of 3 subjects and a maximum of 6 subjects excluding the MTD or similar cohort.

Patients should receive a minimum of three 21-day cycles of treatment. Responding patients or those with stable disease may continue to receive treatment until disease progression.

Patients with an objective response or stable disease, who at the discretion of the Principal Investigator, are unable to continue chemotherapy or patients meeting dose modification criteria for stopping chemotherapy as defined in Section 6 may receive BAY 43-9006 alone until disease progression.

After establishing the MTD of BAY 43-9006 in combination with gemcitabine and capecitabine in the phase I trial, an additional 12 to 35 patients will be treated at the MTD regimen.

4.1.1 BAY 43-9006

BAY 43-9006 is supplied as 200-mg tablets and is administered orally. Patients are to swallow the tablets whole with approximately 250 ml (8 oz.) of water, each morning and evening (i.e., 12-hourly). BAY 43-9006 is to be taken on an empty stomach (at least 1 hour before or 2 hours after a meal.

BAY 43-9006 will be administered from day 1 until day 21.

Patients receiving BAY43-9006 should have their blood pressure measured weekly during the first cycle of therapy. Patients can have the blood pressure measurements in their doctor's office, a clinic or using a calibrated machine such as can be found at a supermarket or shopping mall. Patients should record their blood pressure measurements and if they are in the normal range, bring the measurements to the clinic at the time of routine follow-up. If blood pressure readings are abnormal (e.g. ≥150/100) then patients should contact

their doctor promptly.

4.1.2 Gemcitabine

Gemcitabine will be administered intravenously over 30 minutes on days 1 and 8.

4.1.3 Capecitabine

The capecitabine dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. The tablets should be swallowed with water. Patients who take aluminum hydroxide- or magnesium hydroxide- containing antacids should be instructed not to take them within one hour of capecitabine administration. Capecitabine will be administered p.o. bid from days 1-14 of each cycle, followed by a 7 day rest period.

Patients will maintain a medication log to monitor compliance with BAY 43-9006 and capecitabine. The medication diary should be signed and dated by the patient and/or person who completes the diary so that it may serve as source documentation of treatment administration. A copy of the medication diary is included as Appendix B.

4.2 **Supportive Care Guidelines**

4.2.1 General Guidelines

Institutional guidelines and the discretion of the treating physician should be used for decisions regarding transfusions of blood and blood products, erythropoietin (EPO), antibiotics, and antiemetics.

Chemotherapy induced diarrhea should be managed as per ASCO guidelines.

4.2.2 Palliative Radiation Therapy

Palliative radiation therapy may not be administered while patient is on the protocol. The need for palliative radiation indicates progressive disease and the patient should be removed from the protocol treatment. Irradiate any lesion that may produce disability (e.g., unstable femur) prior to study initiation.

4.2.3 Growth Factors

Filgrastim (G-CSF) and sargramostim (GM-CSF) may NOT be used:

a. to avoid dose reductions, delays or to allow for dose escalations specified in the protocol.

b. prophylactically because of concern about myelosuppression from prior therapies.
For the treatment of febrile neutropenia the use of CSF's should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSF's may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSF's in this setting. The use of CSF (filgrastim and sargramostim) must be documented and reported on flow sheets.

4.2.4 Supportive Management of Hand/Foot Syndrome

Patients who develop hand/foot syndrome may receive topical emollients (such as Aquaphor) as well as topical steroids or antihistamine agents if appropriate. Vitamin B6 (pyridoxine 50-150 mg orally daily) may also be used.

4.3 Duration of Therapy

Patients should receive a minimum of 3 cycles of therapy. Patients may discontinue protocol therapy if a complete response is achieved.

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s),
- 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.

Subjects who complete at least 3 cycles of treatment with objective response or stable disease who are deemed poor candidates for continued chemotherapy may continue therapy with BAY 43-9006 at their current dose. The dose of BAY 43-9006 may be escalated at the discretion of the investigator after 3 weeks at the current dose up to a maximum of 400 mg BID. Subjects who continue on BAY 43-9006 alone will continue with weekly follow up until resolution of toxicities attributable to chemotherapy (gemcitabine and capecitabine) to $\leq$ Gr 1. Following resolution of chemotherapy-atributable toxicities to $\leq$ Gr 1, investigators may elect to lengthen the interval between study visits to a maximum of 4 weeks provided that study drug-attributable non-hematologic toxicities are stable at Gr $\leq$1. Other study procedures

should continue, but for those subjects on single-agent sorafenib with disease control past 12 cycles and non-hematologic toxicities stable at Gr ≤1, study procedures may be performed every 4 weeks. Radiographic evaluation should continue every 3 cycles (i.e. for those stable on 4-week cycles, scan should be performed every 12 weeks).

All patients who receive at least one cycle of treatment will be followed until disease progression, or for a maximum of 6 months following termination of treatment.

Following progression of disease, all subjects will be followed until death. Mortality follow up should be performed at least annually, and may be obtained by contacting the subject and/or the referring physician or via medical record review.

5. PHASE I DOSE LIMITING TOXICITY CRITERIA

The current version (3.0) of the NCI Common Terminology Criteria for Adverse Events will be used to grade toxicity (http://ctep.info.nih.gov/).

5.1 Definition of Dose Limiting Toxicity

A dose limiting toxicity is defined as one of the following occurring during the first two cycles of therapy:

1. Treatment Emergent Hypertension as follows:
    a. Any Grade 2 symptomatic/persistant (requiring a treatment delay for > 2 weeks)
    b. Diastolic BP ≥ 110 mm Hg
    c. Any Grade 3 or 4
2. Any Grade 3 or 4 dermatitis or hand/foot syndrome.
3. Any Grade 3 neutropenia or thrombocytopenia.
4. Any Grade 4 neutropenia or thrombocytopenia consisting of:
    a. Febrile neutropenia (defined as temperature ≥ 38.5°C [101°F] sustained for more than one hour concomitant with an ANC < 500/mm^3)
    b. granulocytes < 500/µl
    c. platelets < 10,000/µl
5. Any non-hematologic Grade 3 or 4 toxicity "possibly" or "probably related" to one of, or the combination of the study drugs being evaluated.

At the discretion of the Principal Investigator, patients experiencing DLT may continue to receive treatment using the Phase II dose modifications as defined in Section 6.

6. PHASE II TRIAL

After establishing the MTD of BAY 43-9006 in combination with gemcitabine and capecitabine in the phase I trial, an additional 12 to 35 patients will be treated at the MTD

regimen.

The MTD has been determined in the phase I portion of the trial:

BAY 43-9006 200 mg p.o. BID D1-D21
Gemcitabine 750 mg/m^2 IV D1, D8
Capecitabine 415 mg/m^2 p.o. BID D1-D14

General guidelines and dose modifications for the combination are outlined below:

6.1 General Guidelines

Depending on the type of toxicity, a cycle interrupted may either not be completed or may continue with dose/treatment modification as defined throughout Section 6 below. A new cycle may begin as soon as all laboratory eligibility criteria are met (see Section 3.1.7) and all other toxicity has resolved to baseline or at least grade 1, as long as at least one and not more than three weeks have elapsed since therapy was interrupted i.e. a delay of > 3 weeks in the re-initiation of therapy will result in the removal of the patient from the protocol treatment.

Doses will not be re-escalated.

6.2 Dose Modification Guidelines

Dose modification for BAY 43-9006, gemcitabine and capecitabine will occur as illustrated in the tables below. Due to differences in the toxicity profiles of the individual agents, dose modification may occur for one drug only (section 6.4).

BAY 43-9006 dose modifications will take place according to the table below:

Dose Level	BAY 43-9006
0	200 mg BID
-1	50% reduction (200 mg daily)
-2	STOP BAY 43-9006

Gemcitabine dose modifications will take place according to the table below:

Dose Level	Gemcitabine
0	750 mg/m^2
-1	25% reduction (563 mg/m^2)

-2	50% reduction (375 mg/m^2)
-3	STOP GEMCITABINE

Capecitabine dose modifications will take place according to the table below:

Dose Level	Capecitabine
0	415 mg/m^2
-1	25% dose reduction
-2	STOP CAPECITABINE

Capecitabine is available in two tablet sizes, 500 mg (peach colored) and 150 mg (light peach colored). The following tables display the total daily dose by body surface area and the number of tablets to be taken at each dose.

Capecitabine Dose Calculation According to Body Surface Area

Capecitabine Dose Level 0-1

415 mg/m^2 bid		**Number of tablets to be taken at each dose (morning and evening)**	
Surface area (m^2)	**Total Daily Dose (mg)**	**150 mg**	**500 mg**
≤ 1.29	1000	0	1
1.30-1.47	1000	0	1
1.48-1.68	1300	1	1
1.69-1.89	1600	2	1
1.90-2.07	1600	2	1
2.08-2.28	1900	3	1
≥ 2.29	2000	0	2

Capecitabine Dose Level 1-2

311 mg/m^2 bid		**Number of tablets to be taken at each dose (morning and evening)**	
Surface area (m^2)	**Total Daily Dose (mg)**	**150 mg**	**500 mg**
≤ 1.29	900	3	0
1.30-1.47	900	3	0
1.48-1.68	1000	0	1
1.69-1.89	1000	0	1
1.90-2.07	1200	4	0
2.08-2.28	1300	1	1
≥ 2.29	1600	2	1

6.3 Treatment-emergent Hypertension

With initiation of therapy, monitor BP at least weekly until stable on therapy for at least the first 4 weeks.

Dose modification for BAY 43-9006 will occur for treatment-emergent hypertension as outlined in the table below:

Management of Treatment-emergent Hypertension

Grade of Event (CTCAE v.3)	**Management/ Next Dose**
grade 1	Consider increased BP monitoring
grade 2 asymptomatic and diastolic BP < 110 mm Hg	Begin anti-hypertensive therapy and continue agent
grade 2 symptomatic/ persistent OR diastolic BP ≥ 110 mm Hg OR grade 3	1. Agent should be held* until symptoms resolve and diastolic BP ≤ 100 mm Hg; also treat patient with anti-hypertensives and when agent is restarted, reduce by 1 dose level.** 2. If diastolic BP not controlled (≤ 100) on therapy, reduce another dose level ***
grade 4	Discontinue protocol therapy

* Patients requiring a delay of > 2 weeks should go off protocol therapy.
** May be able to resume full dose later.
*** Patients requiring > 2 dose reductions should go off protocol therapy. Patients who experience treatment-emergent hypertension while receiving BAY 43-9006 200 mg b.i.d. and require > 1 dose reduction should go off protocol therapy.

Current CTCAE definitions used by CTEP:
Grade 1: asymptomatic, transient (< 24 hours) increase by > 20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated
Grade 2: recurrent or persistent (> 24 hours) or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 if previously WNL; monotherapy may be indicated
Grade 3: requiring more than one drug or more intensive therapy than previously
Grade 4: life threatening (e.g. hypertensive crisis)

6.4 Neutropenia/Thrombocytopenia

6.4.1 Grade 3 Neutropenia/Thrombocytopenia

If grade 3 neutropenia or thrombocytopenia develops in any cycle, all therapy should be held with the exception of BAY 43-9006, which may be continued at 200 mg p.o. b.i.d or at current dose.

Therapy should be reinitiated as a new cycle according to the guidelines outlined in Section 6.1. Capecitabine should be decreased by 1 dose level, but gemcitabine can be resumed at the previous dose. If capecitabine has already been discontinued and a patient experiences grade 3 or 4 neutropenia or thrombocytopenia on Day 8 of any given cycle, gemcitabine should be

reduced by 50% for that dose. A full dose of gemcitabine should be resumed with the next cycle. If grade 3 neutropenia or thrombocytopenia reoccurs, a permanent dose-reduction of 25% should be made. In the event that capecitabine must be stopped, at the discretion of the Principal Investigator, patients may continue to receive gemcitabine alone with BAY 43-9006 until disease progression. If both capecitabine and gemcitabine must be stopped, patients may continue on with BAY 43-9006 alone at the discretion of the Principal Investigator.

6.4.2 Grade 4 Neutropenia/Thrombocytopenia

Grade 4 neutropenia or thrombocytopenia includes:

- Febrile neutropenia (defined as temperature ≥ 38.5°C [101°F] sustained for more than one hour concomitant with an ANC < 500/mm^3),
- granulocytes < 500/µl, or
- platelets < 10,000/µl

If grade 4 neutropenia or thrombocytopenia develops in any given cycle, all therapy should be held with the exception of BAY 43-9006, which may be continued at current dose. When therapy is reinitiated according to the guidelines in Section 6.1, the dose of gemcitabine should remain the same and capecitabine should be decreased by 1 dose level. If capecitabine has already been discontinued and a patient experiences grade 3 or 4 neutropenia or thrombocytopenia on Day 8 of any given cycle, gemcitabine should be reduced by 50% for that dose. A full dose of gemcitabine should be resumed with the next cycle. If grade 3 or 4 neutropenia or thrombocytopenia reoccurs, a permanent dose-reduction of 25% should be made. In the event that capecitabine must be stopped, at the discretion of the Principal Investigator, patients may continue to receive gemcitabine alone with BAY 43-9006 until disease progression. If both capecitabine and gemcitabine must be stopped, patients may continue on with BAY 43-9006 alone at the discretion of the Principal Investigator.

6.4.3 Blood Counts on Day 1 of Cycle

As noted in Section 6.1, all blood count eligibility criteria must be met before beginning a new cycle (ANC ≥ 1,500/µl, platelets ≥ 100,000/µl). A delay of > 3 weeks in the re-initiation of therapy will result in the removal of the patient from the protocol treatment.

6.5 **Hepatic Dysfunction**

If grade 3 hepatic toxicity develops in any given cycle, gemcitabine, capecitabine and

BAY 43-9006 should be held and that cycle of therapy considered complete. If therapy is reinitiated according to the guidelines in Section 6.1 (i.e. all laboratory eligibility criteria are met), the dose of gemcitabine should be decreased by 2 dose levels. If grade 3 hepatic toxicity occurs on a subsequent cycle despite these dose reductions or if a 2 dose level reduction would lead to a dose less than Dose Level -2, the patient should be removed from protocol treatment.
A delay of > 3 weeks in the re-initiation of therapy will result in the removal of the patient from the protocol treatment.

If grade 4 hepatic toxicity develops, the patient should be removed from protocol treatment.

6.6 Gastrointestinal Toxicities

6.6.1 Grade 2 mucositis and diarrhea

If grade 2 mucositis or diarrhea develops in a given cycle, capecitabine and gemcitabine therapy should be stopped until resolved to grade 0-1. Patients may continue BAY 43-9006. BAY 43-9006 and gemcitabine may be resumed without dose modification. The dose of capecitabine from that point forward should be decreased by 1 dose level. If dose reduction of capecitabine would lead to a dose less than Dose Level -1, at the discretion of the Principal Investigator, patients may continue to receive gemcitabine alone with BAY 43-9006 until disease progression. A delay of > 3 weeks in the re-initiation of therapy will result in the removal of the patient from the protocol treatment.

6.6.2 Grade 3 mucositis and diarrhea

If grade 3 mucositis or diarrhea develops in a given cycle, all therapy should be held and that cycle of therapy considered complete. When therapy is reinitiated according to the guidelines in Section 6.1, the dose of capecitabine should be decreased by 1 dose level. BAY 43-9006 and gemcitabine may be resumed without dose modification. If grade 3 mucositis or diarrhea occurs on a subsequent cycle despite these dose reductions or if a dose level reduction of capecitabine would lead to a dose less than Dose Level -1, at the discretion of the Principal Investigator, patients may continue to receive gemcitabine alone with BAY 43-9006 until disease progression. A delay of > 3 weeks in the re-initiation of therapy will result in the removal of the patient from the protocol treatment.

6.6.3 Grade 4 mucositis and diarrhea

If grade 4 mucositis or diarrhea develops in a given cycle, all therapy should be held and that cycle of therapy considered complete. Capecitabine should be stopped and at the discretion of the Principal Investigator, patients may continue to receive gemcitabine alone with BAY 43-9006 until disease

progression. A delay of > 3 weeks in the re-initiation of therapy will result in the removal of the patient from the protocol treatment.

6.6.4 GI Perforation (NOS)

If GI perforation occurs, the patient must be taken off therapy completely.

6.7 Skin Toxicity

The following table should be used for grading hand/foot syndrome:

Grade	Clinical Domain	Functional Domain
1	Numbness, dysesthesia/paresthesia, tingling, or painless swelling or erythema	Discomfort which does not disrupt normal activities
2	Painful erythema, with swelling	Discomfort which affects activities of daily living
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living

In the case of a discrepancy between the clinical domain and the functional domain, the assigned grade should correspond to the most important intensity from one domain or the other.

6.7.1 Grade 2 dermatitis or hand/foot syndrome

If grade 2 dermatitis or hand/foot syndrome develops in a given cycle, BAY 43-9006 and capecitabine should be stopped until resolved to grade 0-1. The dose of capecitabine from that point forward should be decreased by 1 dose level. Gemcitabine and BAY 43-9006 may be resumed without dose modification. In the event that capecitabine must be stopped, at the discretion of the Principal Investigator, patients may continue to receive BAY 43-9006 with gemcitabine until disease progression. A delay of > 3 weeks in the re-initiation of therapy will result in the removal of the patient from the protocol treatment

6.7.2 Grade 3 dermatitis or hand/foot syndrome

If grade 3 dermatitis or hand/foot syndrome develops in a given cycle, all therapy should be held and that cycle of therapy considered complete. When therapy is reinitiated according to the guidelines in Section 6.1, the dose of capecitabine should be decreased by 1 dose level. Gemcitabine and BAY 43-9006 may be resumed without dose modification. In the event that capecitabine must be stopped, at the discretion of the Principal Investigator, patients may continue to receive BAY 43-9006 with gemcitabine until disease progression. A delay of > 3 weeks in the re-initiation of therapy will result in the removal of the patient from the protocol treatment

6.7.3 Grade 4 dermatitis

If grade 4 dermatitis develops, the patient should be removed from protocol treatment.

6.8 Pulmonary Toxicity

If a patient develops gemcitabine-induced pulmonary toxicity with ≥ Grade 3 dyspnea, gemcitabine should be discontinued and further protocol therapy terminated.

6.9 Unspecified Grade 3 or 4 Toxicities

For any other grade 3 or 4 non-hematologic, drug-related toxicity not listed in Sections 6.2- 6.8, except for alopecia and isolated anemia, all therapy should be held and that cycle of therapy considered complete. When therapy is reinitiated according to the guidelines in Section 6.1, the doses of BAY 43-9006, gemcitabine and capecitabine should be decreased by 1 dose level. If the same grade 3 or 4 toxicity occurs on a subsequent cycle despite these dose reductions or if a dose level reduction of any agent would lead to a dose **less than** Dose Level –1 for BAY 43-9006. Dose Level -2 for gemcitabine or Dose Level –1 for capecitabine, the patient should be removed from protocol treatment. A delay of > 3 weeks in the re-initiation of therapy will result in the removal of the patient from the protocol treatment

6.10 Dose Modification for Obese Patients

There will be no dose modification for obese patients. All dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without modification unless explicitly described in the protocol.

7. PHARMACEUTICAL INFORMATION

7.1 BAY 43-9006 (NSC 724772)

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

Other Names: BAY 54-9085 is the tosylate salt of BAY 43-9006; sorafenib

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 24 months when stored at controlled room temperature.

Route(s) **of Administration:** Orally

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 AdEERS (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 hemorrhage[2]		***Gastrointestinal 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.

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. 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-9006 tosylate is metabolized by the P450 CYP3A enzyme and has been shown in preclinical studies to inhibit multiple CYP isoforms. Therefore, it is possible that BAY-9006 tosylate may interact with drugs that are metabolized by the P450 CYP isoenzymes or with drugs that inhibit CYP 3A. Close monitoring is recommended for patients taking agents with narrow therapeutic indices and metabolized by the liver, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital,

cyclosporine, and digoxin. Additionally, BAY-9006 tosylate is 97% to 99% protein bound; however, no drug interactions have been reported in studies, thus far.

Availability:

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

BAY 43-9006 is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Bayer Corp./Onyx and the DCTD, NCI (see Section 10.4).

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

Agent Ordering:

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 agents received from DCTD using the NCI Drug Accountability Record Form. *See the CTEP web site for Policy and Guidelines for Accountability and Storage of InvestigationalDrugs(http://ctep.cancer.gov/requisition/storage.html).*

7.2 Gemcitabine

Product description:

Gemcitabine is supplied in Vials: 200 mg white, lyophilized powder in a 10 mL size sterile single use vial (No. 7501) (NDC 0002-7501-01) or 1 g white, lyophilized powder in a 50 mL size sterile single use vial (No. 7502) (NDC 0002-7502-01). store at controlled room temperature (20° to 25°C) (68° to 77°F). The recommended diluent for reconstitution of emcitabine is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum

concentration for gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

Preparation:

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200 mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1 g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200 mg vial or 1.3 mL for the 1 g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted gemcitabine is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

Stability:

When prepared as directed, gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [*See* USP]. Discard unused portion. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur.

The compatibility of gemcitabine with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) [*See* USP].

Caution should be exercised in handling and preparing gemcitabine solutions. The use of gloves is recommended. If gemcitabine solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the

mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, two of three rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. [1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

1. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Printing Office, Washington, DC 20402.
2. Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. *JAMA* 1985;253:1590.
3. National Study Commission on Cytotoxic Exposure—Recommendations for handling cytotoxic agents, 1987. Available from Louis P Jeffrey, ScD, Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Aust* 1983;1:426.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *CA* 1983;33(Sept/Oct): 258.
6. American Society of Hospital Pharmacists: Technical assistance bulletin on handling cytotoxic drugs in hospitals. *Am J Hosp Pharm* 1990;47:1033.
7. Yodaiken RE, Bennet D, OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. *Am J Hosp Pharm* 1988;43:1193-1204.

Availability: Gemcitabine is commercially available.

Solution preparation: Please see the package insert for standard preparation instructions.

Route of administration: Gemcitabine is to be administered as a short intravenous infusion over 30 minutes.

Expected adverse events: See manufacturer's package insert for expected adverse events.

7.3 Capecitabine

Product description: Capecitabine is provided as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine.

Preparation: Instructions regarding the calculation of the number of tablets to achieve the appropriate dosing can be found in Section 4.1.3.

Stability: Capecitabine tablets should be stored at room temperature (25°C

or 77°F).

Availability: Capecitabine is commercially available.

Route of administration: Capecitabine is administered by mouth twice a day. Prior studies of capecitabine have included administration within 30 minutes of food (and safety/efficacy data are based on this schedule), therefore, capecitabine will be administered similarly in this study. The tablets should be swallowed with water.

Expected adverse events: See manufacturer's package insert for expected adverse events.

Drug Interactions: See manufacturer's package insert for information on drug interactions including leucovorin, coumarin derivatives and phenytoin

8. CORRELATIVE/SPECIAL STUDIES

Tissue Analysis for MAPK and VEGFR2 Expression

BAY 43-9006 is a potent inhibitor of wild-type and mutant B-Raf and c-Raf kinase isoforms in vitro, with no effects on EGFR, PKC and HER2/neu kinase activities. Activation of Raf initiates a signaling cascade that results in MAP kinase phosphorylation(24). The effect of BAY 43-9006 on Raf activation and MAP kinase activation in patients receiving the drug has not been well-studied. Specifically, it is unknown if to what extent 1) activation of Raf kinase - MAP kinase signaling axis can predict likelihood of response 2) inhibition of Raf kinase and/or MAP kinase activation is necessary for patients to respond to BAY 43-9006 based therapy; 3) VEGFR2 activation and subsequent correlates with tumor microvessel density and clinical response; and 4) Raf kinase inhibition correlates with phospho-Akt status, a negative upstream regulator of both Raf-kinase isoforms. Therefore, we propose to measure MAP kinase activation in pre- and post-treatment tumor specimens when available.

Pre- and, when available, post-treatment paraffin-embedded tumor tissue specimens will be analyzed using monoclonal antibodies specific for activated MAP kinase, c-raf, VEGFR2(25;26), MEK, PDGF-R, AKT and PCNA. To assess potential role of VEGFR2 blockade on angiogenesis paraffin-embedded sections will be stained for CD31, an endothelial-specific cell marker.

Please send paraffin-embedded tumor tissue samples to:

Scott Tagawa, M.D.
Div. of Hematology & Medical Oncology
New York Presbyterian Hospital/Cornell
525 East 68th Street
New York, NY 10065
Tel 646-962-2072
Fax 646-962-1603

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤ 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Note that for subjects with stable disease or better past cycle 12 who remain on single-agent sorafenib with stable non-hematologic toxicities of Gr ≤ 1, cycles may be moved to q4 weeks with study procedures performed on D1 of each cycle; radiographic evaluation should continue every 3 cycles unless clinically indicated sooner regardless of the length of the cycle.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study[c]
BAY 43-9006		A	A	A	A	A	A	A	A	A	A	A	A	
Gemcitabine		B	B		B	B		B	B		B	B		
Capecitabine		C	C		C	C		C	C		C	C		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------											X	
Physical exam	X	X			X			X			X			X
Vital signs[e]	X	X	X	X	X			X			X			X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine protein/creatinineratio[f]	X	A urine protein/creatinine ratio (UPC ratio) will be done on day 1 of every 3rd cycle for the first 9 cycles. After cycle 9, the UPC ratio will be repeated on day 1 of every cycle.												
EKG (as indicated)	X													
Adverse event evaluation		X----------											X	X
Tumor measurements	X	Tumor measurements are repeated after every 3 cycles. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X[c]
Radiologic evaluation	X	Radiologic measurements should be performed after every 3 cycles.												X[c]
B-HCG	X[b]													

A: *BAY 43-9006*: 200 mg p.o. BID for each cycle (1 cycle = 21 days). Dose modifications will occur if indicated (see Section 5); *BAY 43-9006 will be administered day 1 through day 21, and continuously thereafter.*

B: *Gemcitabine*: 750 mg/m^2 IV over 30 minutes. Dose modifications will occur if indicated (see Section 5)*; Gemcitabine will be administered on days 1 and 8 of each 21-day cycle.*

C: *Capecitabine: 415* mg/m^2 p.o. twice daily. Dose modifications will occur if indicated (see Section 5); *Capecitabine will be administered on days 1-14 of each 21-day cycle.*

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

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

c: Off-study evaluation. **Two consecutive measurements taken 4 weeks apart must be used to document progressive disease if the patient is removed from study for this reason.**

e. Blood pressure monitoring will be conducted weekly for the first treatment cycle.

f. Obtain at least 4ml of a random urine sample in a sterile container (does not need to be 24-hour sample). Determine protein concentration (mg/dl) and creatinine concentration (mg/dl). Divide protein concentration by creatinine concentration for the UPC ratio. If spot urine protein/Cr is $\geq$ 0.2, a 24 hour collection for protein and creatinine should be assessed and the level of proteinuria should be graded per CTCAE.

10. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every 9 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

10.1. Definitions

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

Final determination of response categorization will be determined by independent radiographic review. See section 10.6

10.1.1 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).

10.1.2 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.

10.1.3 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.

10.1.4 **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.

10.2 Guidelines for Evaluation of Measurable Disease

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

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

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 can be useful to confirm complete pathological response when biopsies are obtained.

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

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

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

10.3 Response Criteria

10.3.1 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

10.3.2 **Evaluation of non-target lesions**

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

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

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

10.3.3 **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.

10.4 Confirmatory Measurement/Duration of Response

10.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 9 weeks (see section 9.3.3).

10.4.2 Duration of overall response

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

reference for progressive disease the smallest measurements recorded since the treatment started).

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

10.4.3 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.

10.5 Progression-Free Survival

PFS will be measured from the time of the patient's initial best response (PR or CR) until documented progression.

10.6 Response Review

All objective responses will be evaluated by an independent panel. All radiographs (such as CT, MRI, bone scan) will be sent to Weill Cornell Medical College for central review by the independent study radiologist. Electronic format (e.g. on CD) is preferred, but hard copies are acceptable.

11. REGULATORY AND REPORTING REQUIREMENTS

Expedited adverse event (AE) reporting for this study is via AdEERS (Adverse Event Expedited Reporting System), accessed via the secure CTEP web site https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). The reporting procedures to be followed are presented in the "NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents" which can be downloaded from the *CTEP web site* (http://ctep.cancer.gov/reporting/adeers.html).

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. 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).*

11.1 **Expedited Adverse Event Reporting**

(AE; formerly known as Adverse Drug Reaction)

For this consortium effort, participating institutions will report to the Coordinating Center who in turn will report to CTEP.

Expedited reports are submitted to CTEP via the secure AdEERS application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). Those AEs that do not require expedited reporting must be reported in routine (CDUS) study data submissions. AEs reported through AdEERS must **also** be reported in routine study data submissions.

11.1.1

Phase 1 Trials Utilizing an Agent under a CTEP IND: AdEERS 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]
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 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:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

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

December 15, 2004

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

- Expedited AE reporting timelines defined:

➢ "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.

➢ "10 calendar days" - A complete AdEERS 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 AdEERS 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.

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS 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	Unex-pected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unex-pected	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 <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

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

December 15, 2004

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

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within <u>24 hours</u> of learning of the event followed by a complete AdEERS report within <u>5 calendar days</u> of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within <u>10 calendar days</u> 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 AdEERS 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.

11.1.2 Expedited Adverse Event Reporting Exclusions.

N/A

11.1.3 Secondary AML/MDS

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

11.2 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. 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).*

11.3 CTEP Multicenter Guidelines

Procedures for Central Patient Registration

Registration will be done centrally by the Phase II Coordinating Center. Patients must be screened for eligibility and then registered with the Coordinating Center by calling 718 904-2730 or via fax to 718 822-0335. The first page and the signature page of the Informed Consent will be sent via fax to the Coordinating Center as well as the eligibility criteria and a one page registration form. These documents should be faxed Monday to Friday from 9:00 AM to 5:00 PM. The following information will be obtained or assigned at that time:
Protocol Number
Investigator Identification
Patient Identification (grant number, institution number, sequence number)

Data Collection Forms: All data forms must be sent to the Coordinating Office on a quarterly basis (every 3 months).

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and

Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.

- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

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

Agent Ordering

- Except in very unusual circumstances, each participating institution will

order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

11.4 Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA), hereinafter referred to as Collaborative Agreement:

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 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 participating on the study or patient's family member, 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. All data made available will comply with HIPAA regulations.

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
6130 Executive Boulevard, Suite 7111
Rockville, MD 20852
FAX 301-402-1584
E-mail: 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 Collaborator's confidential/proprietary information.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

The study is a prospective, non-randomized, multi-institutional phase II trial with objective response as the major endpoint. Recent trials using gemcitabine in combination with 5-flurouracil or capecitabine have demonstrated response rates in the range of 15- 21%(20;27). The trial is designed to effectively discriminate between true response rates of no more than 10% and at least 30%. The maximum trial size will be set at 35 evaluable patients. If at least 6 responses (at least 17%) were observed among the 35 evaluable patients, this regimen would be considered worthy of further testing in this disease. If no more than 1 response (no more than 8%) were observed among the initial 12 patients, the study would be terminated early and declared negative. This design yields at least 90% power to detect a true response rate of at least 30%. It yields at least .90 probability of a negative result if the true response rate is no more than 10%, with at least .65 probability of early negative stopping.

12.2 Sample Size/Accrual Rate

The maximum trial size will be set at 35 evaluable patients. If at least 6 responses were observed among the 35 evaluable patients, this regimen would be considered worthy of further testing in this disease. If no more than 1 response were observed among the initial 12 patients, the study would be terminated early and declared negative.

An estimated accrual of 3-4 patients per month is expected with a goal to complete the trial within one year

12.3 Stratification Factors

N/A

12.4 Analysis of Secondary Endpoints

Progression free survival and overall survival will be assessed. Because of the heterogeneity in outcome of patients with advanced renal cell carcinoma, assessment of survival will be limited. Nevertheless, median survival for this group of patients has historically been < 12 months. Improvement over that level will be encouraging. Likewise, PFS > 3 months is suggestive of a durable benefit from the treatment.

The study will be monitored for unacceptable toxicity defined as death or grade 4 toxicity.

When available, pre- and post-treatment paraffin-embedded tumor tissue specimens will be analyzed using monoclonal antibodies specific for total and activated MAP

kinase, VEGFR2 as well as others as defined in Section 8. Although this is a limited analysis, it has the potential to provide preliminary data for future larger scale studies.

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 with BAY 43-9006.

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. REFERENCES

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APPENDIX A

Performance Status Criteria

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

APPENDIX B

Patient Medication Log

Patient's Name _____ Cycle # _____

Day of Cycle	Date	Capecitabine Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	BAY 43-9006 Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
1	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
2	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
3	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
4	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
5	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
6	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
7	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
8	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
9	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
10	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
11	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
12	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
13	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
14	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
15	__/__/__		Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
16	__/__/__		Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
17	__/__/__		Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
18	__/__/__		Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
19	__/__/__		Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
20	__/__/__		Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
21	__/__/__		Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken

APPENDIX C

Patient Medication Log – For subjects who remain on single-agent sorafenib

Day of Cycle	Date	**BAY 43-9006** Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
1	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
2	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
3	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
4	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
5	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
6	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
7	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
8	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
9	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
10	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
11	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
12	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
13	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
14	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
15	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
16	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
17	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
18	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
19	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
20	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
21	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
22	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
23	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
24	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
25	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
26	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
27	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken
28	__/__/__	Time ___:___(AM) ____# pills taken Time ___:___(PM) ____# pills taken