THE LANCET Oncology

Supplementary appendix

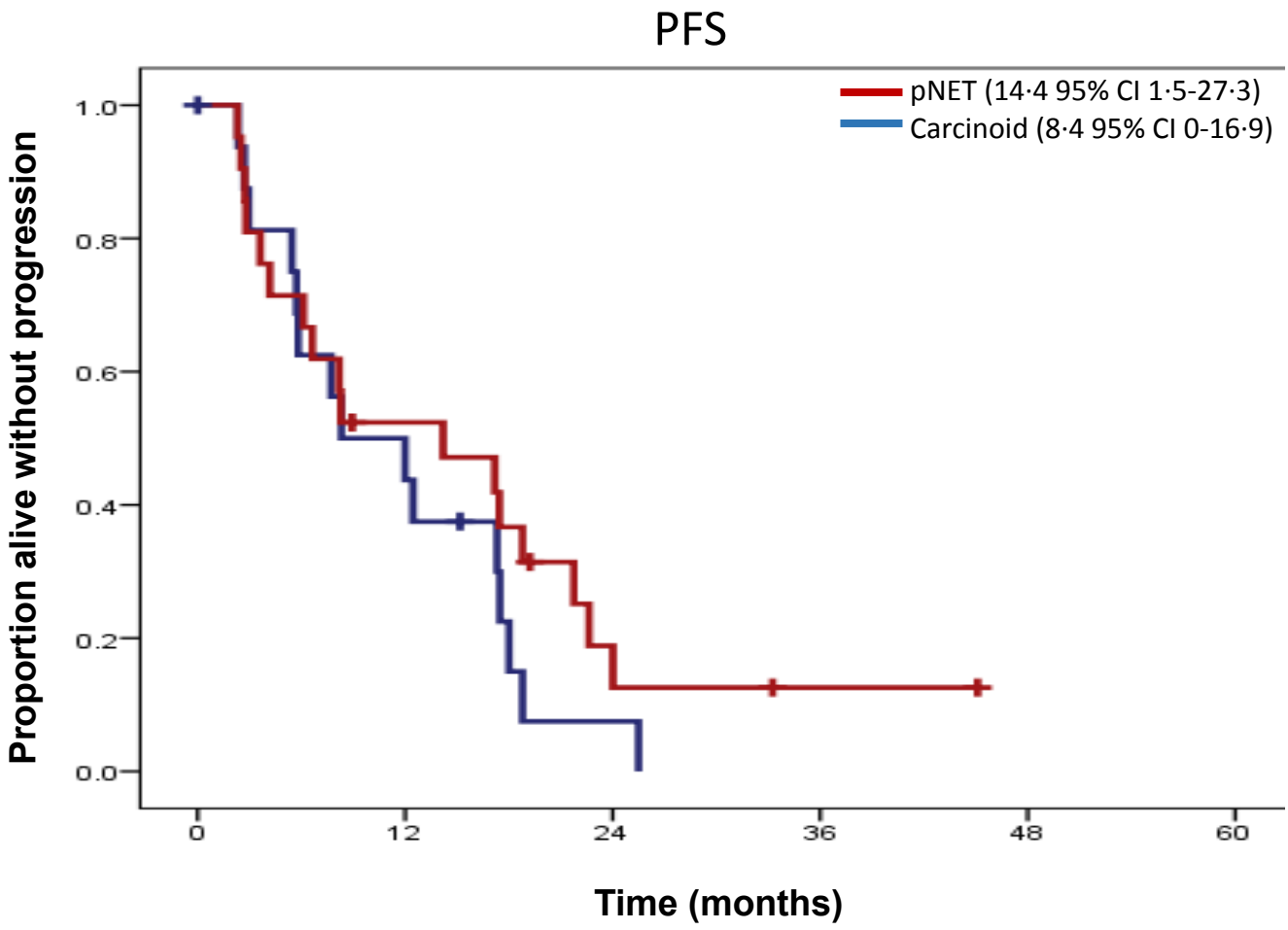
This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Phan AT, Halperin DM, Chan JA, et al. Pazopanib and depot octreotide in advanced, well-differentiated neuroendocrine tumours: a multicentre, single-group, phase 2 study. *Lancet Oncol* 2015; published online May 6. http://dx.doi.org/10.1016/S1470-2045(15)70136-1

Online Supplement

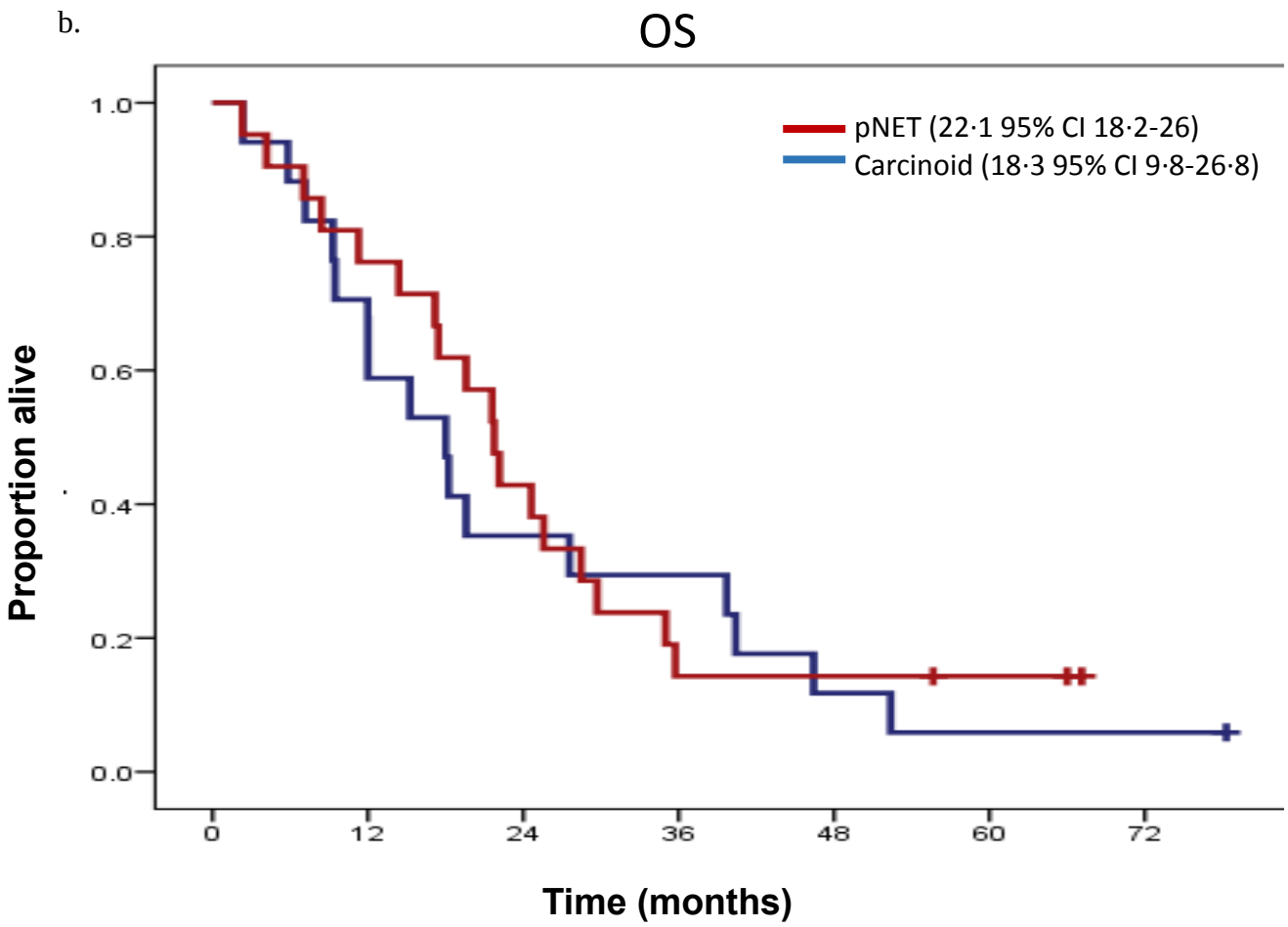
eFigure 1. PFS (a) and OS (b) by cohort for the subset of patients exhibiting progressive disease on study entry. 95% confidence interval is centered about the median.

a.



pNET	21	10	3	1	0	0
Carcinoid	17	7	1	0	0	0

b.



pNET	21	16	9	3	3	2	0
Carcinoid	17	11	6	5	2	1	1

NCI Protocol #: 7650

Local Protocol #: MDACC 2006-0077

TITLE: A Phase 2 Study of GW786034 (Pazopanib) in Advanced Low-grade Neuroendocrine Carcinoma

Coordinating Center: University of Texas M. D. Anderson Cancer Center

***Principal Investigator:** James C. Yao, MD - Unit 426
1515 Holcombe Blvd
Houston, Texas 77030
Telephone: (713) 792-2828
Fax: (713) 563-0539
jyao@mdanderson.org

Participating Center: Dana Farber Cancer Center

Co-Investigators: Matthew Kulke, MD
44 Binney St. – Rm 1220
Boston, MA 02115
Phone: (617) 632-5136
Fax: (617) 632-5424
matthew_kulke@dfci.harvard.edu

Statistician: Kenneth Hess - Unit 447
1515 Holcombe Blvd
Houston, Texas 77030
Phone: 713-794-4157
Fax: 713/563-4243
khess@mdanderson.org

Responsible Research Nurse: Diane Gravel, R.N. - Unit 426
1515 Holcombe Blvd
Houston, Texas 77030
Phone 713-7924-5373
Fax 713-792-0247
dgravel@mdanderson.org

NCI Supplied Agent: GW786034 (pazopanib; NSC 737754)

SCHEMA

Screening for eligibility

Pre-study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4
Screening Consent Labs CT's	----------GW786034 800mg daily----------											
	Cycle 1				Cycle 2				Cycle 3			
				Labs				Labs				Labs CT's

TABLE OF CONTENTS

1. OBJECTIVES

1.1. Primary objective

To determine the objective response rate (ORR) (complete response and partial response) of GW786034 800mg administered orally once daily in patients with low grade neuroendocrine carcinoma.

1.2 Secondary objectives

1.2.1 To determine the progression free survival (PFS) duration of GW786034 800mg administered orally once daily in patients with low grade neuroendocrine carcinoma.

1.2.2 To determine the safety and tolerability of GW786034 800mg administered orally once daily in patients with low grade neuroendocrine carcinoma.

1.2.3 To explore the effect on tumor blood flow as determined by functional CT of GW786034 800 mg orally once daily in patients with low grade neuroendocrine carcinoma.

1.2.4 To assess the trough level of GW786034 800 mg orally once daily in patients with low grade neuroendocrine carcinoma.

2. BACKGROUND

2.1 **Low grade neuroendocrine carcinoma**

Low grade neuroendocrine carcinoma consists of carcinoid and pancreatic endocrine tumors (islet cell carcinomas). Recent increases in the incidence of carcinoid tumors have been detected in the Surveillance, Epidemiology, and End Results (SEER) database. These tumors originate from the neuroendocrine cells throughout the body and are capable of producing various peptides. Their clinical course is often indolent but can also be highly aggressive and resistant to therapy. Current treatments for bulky metastatic tumors have either low biologic activity, highly unfavorable toxicity profiles or both.

For carcinoid, despite the many cytotoxic chemotherapy trials that have been conducted, no regimen has demonstrated a response rate of more than 20% using the criterion of a 50% reduction of bidimensionally measurable disease.[1] In the more recently reported ECOG phase III study of chemotherapy in carcinoid tumors (E1281), patients were randomly assigned to treatment with 5-fluorouracil (5FU) plus doxorubicin or 5FU plus streptozocin.[2] The median progression free survival durations were disappointing. They were 4.5 months in the 5FU plus doxorubicin arm and 5.3 months in the 5FU plus streptozocin arm. Overall survival durations recorded in the trial were also suboptimal at 15 and 24 months respectively. There is no clear survival benefit for cytotoxic chemotherapy.

Octreotide, a somatostatin analogue, is a peptide approved for the management of carcinoid syndrome. While it has significant activity in inhibiting hormonal output from carcinoid tumors, it has not resulted in objective tumor responses. We pooled the data from trials using octreotide for which the number of patients with measurable disease and the number of patients with objective tumor responses were documented. Among a total of 182 patients assessable for tumor response, only 3 partial responses (2%) were documented.[1]

Somatostatin analogues have been reported to have antiangiogenic properties.[3-13] The described cytostatic activity of somatostatin analogues on carcinoid tumors may be mediated through its anti-angiogenic effects. Decrease in plasma vascular endothelial growth factor (VEGF) and insulin like growth factor (IGF-1) have been observed in one colon cancer study and another non-endocrine tumors study.[3,6] In a human xenograft model of hindgut neuroendocrine tumor, treatment with somatostatin analogue resulted in decreased plasma VEGF and bFGF as well as micro vessel density.[10] In addition, octreotide has also been described to inhibit endothelial proliferation through somatostatin receptors present on endothelial cells.[14]

Interferon-α has also been widely studied in this disease. Pooling the data from patients with carcinoid involved in these trials, only 37 (12%) of 309 had objective tumor responses.[1] While octreotide has a role in the management of carcinoid syndrome, objective tumor responses are rare. Similarly, in a recent randomized trial, lanreotide was compared with interferon and with the combination of lanreotide and interferon. The objective response rates for the three groups were 4%, 4% and 7%.[15]

For pancreatic endocrine tumors, there is considerable controversy on the role of systemic chemotherapy in the management of advanced islet cell carcinoma. A number of agents have been reported to have single agent activity in pancreatic endocrine carcinoma.

Chemotherapy agents with known activity include streptozocin, doxorubicin, and dacarbazine. Activity of streptozocin in islet cell carcinoma was first reported in 1973 by Broder and Carter.[16] Of 52 patients with pancreatic endocrine carcinoma treated in that study, a response rate of 50% was observed. Moertel et al treated 42 patients with single agent streptozocin in one arm of a randomized trial.[17] A response rate of 36% was observed. Doxorubicin studied in a single-arm phase II trial induced response in 4 of 20 patients (20%).[18] Chlorozotocin demonstrated clinical activity in two single-agent clinical trials.[19 20] However, chlorozotocin is not commercially available at this time. Dacarbazine was also studied in a phase II trial that included 42 patients with pancreatic endocrine carcinoma. A 33% response rate was observed.[21] Temozolomide, a new oral imidazole tetrazinone, also appears promising.[22]

The combinations of 5FU plus streptozocin and 5-fluorouracil plus doxorubicin achieve response rates ranging from 27% to 69%.[17,20,23-25] However, in a retrospective study of 16 patients who received streptozocin and doxorubicin at Memorial Sloan-Kettering Cancer Center, only one response (6%) was observed.[26] Similarity, a retrospective review of 16 patients treated with streptozocin and

doxorubicin at Dana Faber found only one objective response (6%).[27] Triplet chemotherapy consisting of all three drugs has reported response rates of 40% and 55% in 2 small series.[28,29] We recently reviewed the records of 84 consecutive patients with pancreatic endocrine carcinoma treated with fluorouracil, doxorubicin, and streptozocin (FAS, Table 1).[30] Using the criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee (RECIST), a response rate of 39% was observed. Second-line options for pancreatic endocrine tumors are lacking.[26]

2.2 **GW786034 (pazopanib)**

GW786034 (pazopanib) is a potent and selective, orally available, small molecule inhibitor of VEGFR-1, -2, and -3, PDGF-α, PDGF-β, and c-kit tyrosine kinases (TKs) [Pazopanib (GW786034) Investigator's Brochure, 2005]. The agent selectively inhibits proliferation of endothelial cells stimulated with VEGF but not with basic fibroblast growth factor. In non-clinical angiogenesis models, GW786034 (pazopanib) inhibited VEGF-dependent angiogenesis in a dose-dependent manner and in xenograft tumor models, twice-daily administration of GW786034 (pazopanib) significantly inhibited tumor growth in mice implanted with various human tumor cells. Upon chronic oral dosing, GW786034 (pazopanib) is expected to inhibit VEGF-driven angiogenesis and as a consequence, limit solid tumor growth. Because angiogenesis is necessary for the growth and metastasis of solid tumors, and VEGF is believed to have a pivotal role in this process, GW786034 (pazopanib) treatment may have broad-spectrum clinical utility.

Mechanism of Action

Tumor VEGF expression has been associated clinically with disease prognosis in many different types of malignancies. Expression of VEGF is elevated by diverse stimuli, including proto-oncogene activation and hypoxia, the latter effect frequently arising in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature, an effect that can also contribute to tumor progression. A leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor cell intravasation during metastasis. Two high-affinity receptors for VEGF with associated TK activity have been identified on human vascular endothelium, VEGFR-1 (fms-like TK-1, or Flt-1) and VEGFR-2 (kinase insert domain-containing receptor, or KDR). Although the relative contributions of VEGFR-1 and VEGFR-2 signaling in mediating tumor progression have not been elucidated, a number of studies suggest that VEGFR-2 performs a predominant role.

In addition to VEGF receptor signaling, increasing evidence implicates platelet-derived growth factor receptor (PDGFR) signaling in tumor angiogenesis. PDGF is a critical regulator of pericyte recruitment to tumor vessels. Pericytes surround the endothelial cells and play a key role in vascular development, stabilization, maturation, and remodeling. Pericytes express PDGFR-β, and pericyte abnormalities in tumors are consistent with alterations in PDGF signaling pathways. Recent nonclinical evidence suggests that inhibition of PDGFR signaling augments the

antitumor and antiangiogenic effects of VEGFR inhibitors by destabilizing pericytes. In addition, PDGF signaling is implicated in the autocrine growth of tumor cells, and in the recruitment and regulation of tumor fibroblasts.

In vitro experiments have shown that GW786034 (pazopanib) inhibited the TK activity of human VEGFR-1, -2, and -3 with IC_{50} values of 10, 30, and 47 nM, respectively. The agent also potently inhibited mouse, rat, and dog VEGFR-2 with IC_{50} values of 42, 17, and 17 nM, respectively. Compared to 23 other tested kinases, GW786034 (pazopanib) was 3- to 400-fold more selective for VEGF receptors. These studies also demonstrated that the agent inhibited PDGFR-α and -β, and c-kit TKs with IC_{50} values of 71, 84, and 74 nM, respectively.

In addition to its ability to inhibit TK activity, GW786034 (pazopanib) selectively inhibited proliferation of human umbilical vein endothelial cells (HUVEC) stimulated with VEGF (IC_{50}=21 nM) compared to its effect on HUVEC proliferation stimulated by basic fibroblast growth factor (bFGF; IC_{50}=721 nM). Further evidence of the agent's potential effect on angiogenic activity is shown by its inhibition of VEGF-induced tyrosine phosphorylation of VEGFR-2 in HUVEC in a dose-dependent manner (IC_{50}=7 nM). GW786034 (pazopanib) does not act directly on tumor cell proliferation as shown by its failure to inhibit the proliferation of human cell lines HT-29 (colon), MDA-MB-468 (breast), PC3 (prostate), or A375P (melanoma). However, when the experiment evaluated the agent's effect on angiogenic processes, GW786034 (pazopanib) was >1400-fold selective for VEGF-induced HUVEC proliferation relative to all four tumor cell lines and 48-fold more selective relative to human foreskin fibroblast (HFF) proliferation.

Nonclinical Efficacy

In contrast to *in vitro* proliferation studies, *in vivo* administration of GW786034 (pazopanib) produced marked growth inhibition of a variety of human tumor xenografts in mice. When GW786034 (pazopanib) was administered at 100 mg/kg twice daily for 21 days to mice bearing HT29 (colon) or HN5 (head and neck carcinoma) xenografts, tumor growth was inhibited by 82% and 101%, respectively. A375P and PC3 xenografts were less sensitive to GW786034 (pazopanib).

The inhibitory effect of GW786034 (pazopanib) on bFGF- and VEGF-induced angiogenesis has been demonstrated in two different mouse models of angiogenesis, the Matrigel™ plug assay, and the cornea micropocket model. In the Matrigel™ plug assay, a Matrigel™ plug containing bFGF is implanted subcutaneously in female Swiss nu/nu mice, resulting in new blood vessel growth into the plug that is highly dependent on VEGFR-2 signaling. When GW786034 (pazopanib) was administered either once or twice daily for 5 days in this model system, a dose-dependent inhibition of angiogenesis resulted: 82-86% (100-200 mg/kg per day), 57-58% (30-60 mg/kg per day), and 32% (10 mg/kg administered twice daily). A once-daily dose of 10 mg/kg was ineffective. The ED_{50} (dose producing 50% of the maximal effect) values were 29.4 mg/kg for once-daily dosing and 20.3 mg/kg for twice-daily dosing. In the cornea micropocket model, VEGF or bFGF is formulated into sucralsulfate

micropellets, then implanted in the normally avascular cornea of female Swiss nu/nu mice. Angiogenic endpoints are quantified by measuring the degree of vascularization at the cornea-limbus interface (clock hours) and maximum blood vessel length. Using this model, administration of oral GW786034 (pazopanib) at 100 mg/kg twice daily for 5 days inhibited vascularization by 71% (bFGF) and 100% (VEGF), and the maximum blood vessel length was reduced by 97% (bFGF) and 135% (VEGF).

GW786034 (pazopanib) has been evaluated in combination with other TK inhibitors and with various chemotherapeutic agents. The combined antitumor activity of GW786034 (pazopanib) and lapatanib (an EGFR/ErbB2 TK inhibitor) was examined in breast adenocarcinoma BT474 and in nonsmall cell lung cancer NCI-H322 tumor xenografts in SCID mice. GW786034 (pazopanib) administered alone at 30 or 100 mg/kg/day produced dose-dependent inhibition of both tumor xenografts. When combined with lapatanib, there was a modest increase in antitumor activity against both tumor xenografts compared to either agent alone; however, the differences were not statistically significant. GW786034 (pazopanib) has also been evaluated in combination with various other chemotherapeutic agents (topotecan, irinotecan, 5-fluorouracil, oxaliplatin, or docetaxel) against HT29 tumor xenografts. While GW786034 (pazopanib) alone administered at 30 or 100 mg/kg/day produced dose-dependent inhibition of HT29 tumor growth and all of the chemotherapeutic agents alone have demonstrated activity against this xenograft model, the effect of any of the combinations on tumor growth was not significantly different from that of either agent alone.

Follow up studies were done with GW786034 (pazopanib) and docetaxel with an endpoint of time to reach 2 tumor doublings. GW786034 (pazopanib) was administered orally (PO) at 100 mg/kg daily and docetaxel was administered intraperitoneally (IP) at 50 mg/kg once weekly (Q7D) for three weeks. In two independent experiments, the median time to reach two tumor doublings was longest in mice treated with both GW786034 (pazopanib) and docetaxel concomitantly. These results clearly show an advantage of combining GW786034 (pazopanib) with docetaxel (and likely other chemotherapeutic agents) for better tumor control.

Nonclinical Pharmacology and Toxicology

In safety pharmacology studies, there were no GW876034 (pazopanib)-related central and peripheral nervous system, respiratory, or cardiovascular effects in rats or monkeys given single oral doses of up to 300 mg/kg and 500 mg/kg, respectively. There were also no treatment-related effects on action-potential duration or other action-potential parameters when dog Purkinje fibers were incubated with up to 80 nM GW786034 (pazopanib). There was no detectable effect on β-andrenergic control of the cardiovascular system in the rat following IV treatment with up to 10 mg/kg GW786034 (pazopanib). In rats, drug-related effects after 1 month of dosing were limited to slight liver enzyme increases and pharmacologically mediated changes due to VEGFR-2 inhibition in bone and bone marrow (doses ≥ 100 mg/kg/day) and in teeth (incisors; doses ≥ 30 mg/kg/day). All drug-related effects

had reversed or were resolving by the end of a 10-week recovery period. After 6 months of GW786034 (pazopanib) dosing at 3 mg/kg/day in rats where systemic exposure (AUC) was approximately 90 mcg•hour/mL, there were significant agent-related findings in the trachea, kidney, adrenals, and pituitary glands. Additional target organ effects occurred in the pancreas and nail and nail bed in rats given 30 mg/kg/day.

Extended dosing in monkeys resulted in severe gastrointestinal signs in some animals, which may have been secondary to precipitation of the drug in the intestinal lamina propia. These events resulted in termination of the animals in the 500 mg/kg/day dose group after 9 months of dosing. The 12-month no observed adverse effect level (NOAEL) in the monkey has not been determined; however, a dose of 50 mg/kg/day (AUC 100 mcg•hour/mL in the 1-month study) was well tolerated.

Nonclinical reproductive toxicology studies indicate reduced female fertility, fetal teratogenic effects, and reduced fetal body weight in pregnant rats and/or rabbits given GW786034 (pazopanib). In rats, GW786034 (pazopanib) caused a reduction in the number of stage I-V round spermatids at ≥ 300 mg/kg/day, resulted in female reproductive tract target organs effects at 300 mg/kg/day, and caused early embryo resorptions. The agent was found to be non-mutagenic and non-clastogenic in a range of genetic toxicity tests.

Nonclinical Pharmacokinetics and Drug Metabolism

GW786034 (pazopanib) has good oral bioavailability in both rodent and non-rodent species. Following oral administration of radiolabeled GW786034 (pazopanib) to rats and monkeys, excretion of drug-related material was rapid and essentially complete. The majority of the dose was excreted via feces in both species with lesser amounts in the urine. Biliary excretion accounted for a significant portion of the radioactivity ultimately found in the feces. GW786034 (pazopanib) is highly (>99.9%) protein bound in mouse, rat, dog, monkey, and human plasma. Preliminary *in vitro* data indicate that GW786034 (pazopanib) is highly permeable across membranes and is a substrate for the P-glycoprotein (Pgp) transporter.

Clinical Experience

The company-sponsored phase 1 dose-escalation study of orally administered GW786034 (pazopanib) has completed enrollment of 63 patients with a variety of solid tumor types. Doses administered ranged from 50 mg three times per week to 2000 mg once daily. The maximally tolerated dose was not defined in this trial. Tumor shrinkage (1 partial and 4 minimal responses) or stable disease (2 cases) has been observed in all seven patients with renal cell carcinoma (RCC) treated at ≥ 800 mg once daily (n=5) and 300 mg bid (n=2). Tumor shrinkage was also seen in patients with Hurthel cell and neuroendocrine tumors, as well as chondrosarcoma. In all, 15 patients, including those with RCC, Hurthel cell, carcinoid, GIST, neuroendocrine, sarcoma, melanoma, and lung cancer tumors, have remained on study for 6 months or longer.

Safety

The most common adverse events (AEs) seen in this phase 1 trial regardless of causality were all grade 1 or 2 (except as noted). These AEs (in decreasing order of frequency) include nausea (49%), diarrhea (45%), hypertension (35%), fatigue (33%), anorexia (29%) and vomiting (27%). One of three patients treated with 2000 mg daily of GW786034 (pazopanib) developed dose-limiting toxicity of grade 3 fatigue (Hurwitz *et al.*, 2005). Hair depigmentation (indicative of c-kit and, potentially, VEGFR modulation) was seen in 12 patients, all of who were treated at doses ≥ 800 mg. One of three patients dosed at 2000 mg once daily experienced grade 3 fatigue that resolved upon dose reduction to 800 mg.

As seen with many of the other agents that block VEGF signaling, grade 1-3 hypertension that could be controlled with antihypertensive medication as well as proteinuria have been observed in this ongoing GW786034 (pazopanib) monotherapy phase 1 study. In addition, there have been single events of gastrointestinal bleeding, pulmonary thrombosis, and deep vein thrombosis. No effect of GW786034 (pazopanib) on QTc has been seen. Grade 3 hemoptysis, coagulopathy, thrombosis, and hemorrhage have been reported with other angiogenesis inhibitors and could potentially occur with GW786034 (pazopanib). The use of GW786034 (pazopanib) in pediatric patients is contraindicated due to the potential effect on epiphyseal growth plates.

The pathogenesis of hypertension induced by angiogenesis inhibitors is likely to be multifactorial. VEGF and VEGFR-2 are involved in the proper maintenance, differentiation, and function of endothelial cells. Arterial hypertension is characterized by reduced nitric oxide (NO) biosynthesis, activation of the Renin-Angiotensin-Aldosterone-System (RAAS), increased vasoconstriction, and microvascular rarefaction of arterioles and capillaries. Microvascular rarefaction in hypertension is partly due to impaired angiogenesis.

Hypertension observed with angiogenesis inhibitors is thought to be due to reduced endothelium-derived NO bioavailability. This situation would effectively lead to NO deficiency, which would limit NO-dependent signal transduction pathways to the detriment of normal cellular function. In addition to being a potent vasodilator, NO is required for angiogenesis, although the cellular signaling mechanisms by which NO affects angiogenesis are not yet well characterized. Angiogenic growth factors such as VEGF and FGF induce NO. NO upregulates VEGF leading to increased vascular permeability and angiogenesis. The RAAS also affects angiogenesis. Angiotensin II (Ang II), a main effector molecule of the RAAS, acts as an angiogenic factor. Ang II induces targeted migration of endothelial cells and pericytes. However, the exact mechanisms by which Ang II induces angiogenesis are not fully elucidated yet.

Clinical Pharmacokinetics and Pharmacology

Pharmacokinetic (PK) data have been collected on 51 patients who received oral GW786034 (pazopanib) at doses ranging from 50 mg 3 times weekly to 2000 mg daily while enrolled in the company-sponsored phase 1 trial. In a preliminary report on results from 43 patients, data showed a mean $t_{1/2}$ of 35 hours (Hurwitz *et al*., 2005). Mean C_{max} and AUC_{0-24} values increased after single doses of 50-800 mg, but the increases in these parameters were neither consistent nor proportional to the increase in dose at all dose levels. Maximal exposure (trough concentrations >18 mcg/mL) was observed at doses ≥ 800 mg daily. Daily administration resulted in an approximate 1.5- to 3-fold accumulation of GW786034 (pazopanib) in the plasma in most patients across all dose cohorts, and there were no obvious time-dependent changes in GW786034 (pazopanib) PK values. Updated PK information from this trial indicates that the greatest mean AUC_{0-24} and mean C_{24} (plasma concentration at 24 hr) values on Day 22 were observed in the 800 mg and 1000 mg/day cohorts (Company Communication). Cohorts with daily doses greater than 1000 mg had similar or lower mean Cmax, AUC_{0-24}, and C_{24} values compared to those of the 800 mg cohort. GW786034 (pazopanib) administered at 300 mg or 400 mg twice daily (BID) resulted in an approximately 4- to 7-fold accumulation in plasma [based on AUC_{0-12}] on Day 22 in most patients. Mean C_{max} values on Day 22 in the 300 mg BID and 400 mg BID dose groups were similar, and both values were less than the mean C_{max} values in the 800 mg and 1000 mg once daily cohorts. However, mean C_{24} values on Day 22 were similar all 4 dosing regimens. There were no obvious time-dependent changes in GW786034 (pazopanib) PK after 22 days of 300 mg BID or 400 mg BID dosing.

Potential Drug Interactions

In vitro data indicate that GW786034 (pazopanib) causes a marked to moderate inhibition of cytochrome P450 enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1. Due to the early phase of development, human experience with GW786034 (pazopanib) is limited, and definitive information on the metabolism and drug interaction profile of GW786034 (pazopanib) is not available. However, GW786034 (pazopanib) has the potential to alter the metabolism of medications, which are substrates for cytochrome P450 enzymes. GW786034 (pazopanib) should not be coadministered with medications that are substrates for cytochrome P450 enzymes (*i.e.*, CYP2C9) and which have the potential to cause serious and/or life-threatening adverse events. Because the *in vitro* data also suggest that GW786034 (pazopanib) is a substrate for CYP3A4, medications that induce or inhibit CYP3A4 may alter the pharmacologic effects of GW786034 (pazopanib). Due to the potential for drug interactions with certain anti-hypertensive therapies and other frequently used medications, the prohibited and cautionary medications list should be reviewed prior to initiating treatment (see Section 8).

Dose Selection

The 800 mg daily dose of oral GW786034 (pazopanib) to be tested in this study is supported by both nonclinical and clinical data. Animal models (mice with human tumor xenografts and the Matrigel plug model of angiogenesis) using an osmotic pump to maintain a steady-state plasma concentration of GW786034 (pazopanib)

suggest that a concentration of > 40 mcM (> 17,500 ng/mL) was required for optimal *in vivo* activity. These results were further supported by studies showing that the inhibition of VEGF-stimulated receptor phosphorylation in mouse lungs also required similar plasma GW786034 (pazopanib) concentrations for reproducible activity. The activity of GW786034 (pazopanib) against human and mouse VEGFR-2 kinase is similar (IC_{50} of 23 and 9 nM against human and mouse VEGFR-2, respectively); therefore, similar effective concentrations are expected in humans. *In vitro* and *in vivo* results, taken together, suggest that steady-state plasma GW786034 (pazopanib) concentrations of at least 17,500 – 22,000 ng/mL (40 to 50 mcM) were required to optimally inhibit VEGFR-2 activity.

Doses ranging from 50 mg three times weekly to 2000 mg QD were evaluated clinically in the phase 1 dose-escalation study (VEG10003). Mean plasma GW786034 (pazopanib) concentrations were maintained above 20,000 ng/mL (46 mcM) over the entire dosing interval with 800 mg QD dosing (geometric mean C_{24} ~ 33,000 ng/mL [75 mcM]) or 300 mg BID dosing (geometric mean C_{24} ~ 27,000 ng/mL [62 mcM]). These results suggest that GW786034 (pazopanib) 800 mg QD or 300 mg BID dosing is required to maintain plasma GW786034 (pazopanib) concentrations at levels required for optimal activity in preclinical models for the entire dosing interval.

Evidence of biological activity associated with VEGFR inhibition was observed in cancer subjects in study VEG10003 at plasma GW786034 (pazopanib) concentrations similar to those required for optimal biologic effect in preclinical models. The probability of an increase in blood pressure requiring a modification of antihypertensive therapy increased markedly when plasma GW786034 (pazopanib) concentrations were maintained above 20,000 ng/mL (46 mcM) over the entire dosing interval. Preliminary DCE-MRI data indicate that doses of 800 mg QD or 300 mg BID affect the $IAUGC_{60}$, which is consistent with a decrease in tumor perfusion. In addition, preliminary data indicate inhibition of phospho-VEGFR2 in the over-biopsy samples of the wound healing assay at doses ≥ 800 mg QD.

Evidence of clinical activity after GW786034 (pazopanib) treatment has been observed in subjects with metastatic RCC. In study VEG10003, twelve subjects with metastatic RCC who had failed prior treatments were enrolled into the study. Tumor reductions, as assessed by RECIST criteria, were observed in all 7 subjects in whom the trough concentrations were ≥ 40 mcM (300mg BID, n=2; ≥ 800mg QD, n=5). One of these seven subjects achieved a PR, and the other six had tumor reductions that were less than a PR. In contrast, no tumor reductions were observed in the 5 RCC subjects dosed at 400 mg or less (100mg three times a week, n=1; 50mg QD, n=2; 400mg QD, n=2), and all of these 5 subjects had trough plasma GW786034 (pazopanib) concentrations of <40 mcM.

In the phase 1 study (VEG10003), 800mg daily dosing was relatively well tolerated and C_{24} concentrations were maintained above 40 mcM in subjects who were treated at this dose. No consistent increase in exposure was observed when the dose was

increased from 800 mg daily up to 2000 mg daily, and no MTD was established in this study. Data from definitive studies comparing 800mg daily and 300mg twice daily dosing will not be available in a time frame that can affect dose selection in this trial. Thus, a dose of GW786034 (pazopanib) of 800 mg daily was selected as the dose to be tested in this trial.

2.3 **Octreotide acetate (Sandostatin LAR ® Depot)**

DESCRIPTION

Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide is known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxy-methyl) propyl]-, cyclic (2®7)-disulfide; [R-(R*,R*)].

Octreotide LAR depot (octreotide acetate for injectable suspension) is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres that are made of a biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability. Octreotide LAR depot is available as: sterile 5 mL vials in 3 strengths delivering 10 mg, 20 mg or 30 mg octreotide free peptide.

Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

By virtue of these pharmacological actions, octreotide has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea). Octreotide substantially reduces and in many cases can normalize growth hormone and/or IGF-1 (somatomedin C) levels in patients with acromegaly. Single doses of Sandostatin ® Injection given subcutaneously have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials the incidence of gallstone or biliary sludge formation was markedly increased. Octreotide may cause clinically significant suppression of thyroid stimulating hormone (TSH).

TOXICOLOGY

Octreotide is generally well tolerated in patients with carcinoid tumors. Toxicities may include **Gastrointestinal:** Diarrhea, abdominal pain or discomfort, flatulence, constipation, nausea, vomiting, biliary sludge, gallstone. **Endocrine**: hypoglycemia,

hyperglycemia. **Cardiac**: bradycardia

PHARMACOLOGY

Kinetics:

After a single IM injection of the long-acting depot dosage form Octreotide LAR depot in healthy volunteer subjects, the serum octreotide concentration reached a transient initial peak of about 0.03 ng/mL/mg within 1 hour after administration progressively declining over the following 3 to 5 days to a nadir of <0.01 ng/mL/mg, then slowly increasing and reaching a plateau about two to three weeks post injection. Plateau concentrations were maintained over a period of nearly 2-3 weeks, showing dose proportional peak concentrations of about 0.07 ng/mL/mg. After about 6 weeks post injection, octreotide concentration slowly decreased, to <0.01 ng/mL/mg by weeks 12 to 13, concomitant with the terminal degradation phase of the polymer matrix of the dosage form. The relative bioavailability of the long-acting release Octreotide LAR depot compared to immediate-release Sandostatin ® Injection solution given subcutaneously was 60 - 63%.

In patients with acromegaly, the octreotide concentrations after single doses of 10 mg, 20 mg, and 30 mg Octreotide LAR depot were dose proportional. The transient day 1 peak, amounting to 0.3 ng/mL, 0.8 ng/mL, and 1.3 ng/mL, respectively, was followed by plateau concentrations of 0.5 ng/mL, 1.3 ng/mL, and 2.0 ng/mL, respectively, achieved about 3 weeks post injection. These plateau concentrations were maintained for nearly two weeks.

Following multiple doses of Octreotide LAR depot given every 4 weeks, steady-state octreotide serum concentrations were achieved after the third injection. Concentrations were dose proportional and higher by a factor of approximately 1.6 to 2.0 compared to the concentrations after a single dose. The steady-state octreotide concentrations were 1.2 ng/mL and 2.1 ng/mL, respectively, at trough and 1.6 ng/mL and 2.6 ng/mL, respectively, at peak with 20 mg and 30 mg Octreotide LAR depot given every 4 weeks. No accumulation of octreotide beyond that expected from the overlapping release profiles occurred over a duration of up to 28 monthly injections of Octreotide LAR depot. With the long-acting depot formulation Octreotide LAR depot administered IM every 4 weeks the peak-to-trough variation in octreotide concentrations ranged from 44 to 68%, compared to the 163 to 209% variation encountered with the daily subcutaneous t.i.d. regimen of Sandostatin ® Injection solution.

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg, and 30 mg Octreotide LAR depot administered by IM injection every four weeks were 1.2 ng/mL, 2.5 ng/mL, and 4.2 ng/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after two

injections of 20 and 30 mg and after three injections of 10 mg.

Octreotide LAR depot has not been studied in patients with renal impairment. Octreotide LAR depot has not been studied in patients with hepatic impairment.

Formulation: Octreotide LAR depot (octreotide acetate for injectable suspension) is available in single use kits containing a 5 mL vial of 10 mg, 20 mg or 30 mg strength, a 2 mL vial of diluent, a 5 mL sterile plastic syringe, two sterile 1½" 19 gauge needles, and three alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit. Please see current Prescribing Information packaged with the Sandostatin LAR kit for additional information.

Storage: For prolonged storage, Octreotide LAR depot should be stored at refrigerated temperatures 2°C - 8°C (36°F - 46°F) and protected from light until the time of use. Octreotide LAR depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered.

Administration: Octreotide LAR Depot is administered as an intramuscular (intragluteal) injection. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

Supplier: Octreotide LAR Depot is commercially available and should be purchased through a third party. This drug will not be supplied by the NCI.

2.4 **Rationale**

Carcinoid tumors are vascular tumors with often accompanying desmoplastic reaction. Various investigators have performed studies into the roles of various growth factors in carcinoid tumors and tumor stroma. Vascular endothelial growth factor (VEGF) expression has been demonstrated in both gastrointestinal and pulmonary carcinoid. Cecal transplantations using cells obtained from liver metastasis of human duodenal carcinoid have been performed in mice. In this model, compared to no treatment controls, treatment with VEGF monoclonal antibody resulted in significant tumor growth inhibition and reduction in number of liver metastases.[31] Further, recent studies have demonstrated the expression of VEGFR-FLK, and VEGFR-FLT1 on carcinoid tumor cells (Table 1).

Table 1: VEGF and VEGFR expression in pancreatic endocrine and carcinoid tumors (Kulke, unpublished data)

Tumor Type	VEGF	VEGFR
Carcinoid (n=67)	74%	68%
Appendiceal (n=5)	60%	80%
Small Intestine (n=27)	54%	57%
Rectal (n=1)	100%	100%
Typical Pulmonary (n=24)	91%	78%
Atypical Pulmonary (n=10)	90%	80%
Pancreatic Neuroendocrine (n=16)	100%	88%

Our centers have extensive experience with the use of VEGF inhibitors in neuroendocrine carcinomas. M. D. Anderson completed a phase II study of bevacizumab in carcinoid tumors showing improved progression free survival rate at week 18 among patients treated with bevacizumab compared to those receiving peg interferon (96% vs. 68%, P = 0.02).[31] Dana Farber participated in a multi-institutional phase II study of SU11248, a novel tyrosine kinase inhibitor with activity against VEGFR, c-Kit, and PDGFR in patients with advanced neuroendocrine tumors. In this study, treatment with SU11248 was associated with an overall radiologic response rate of 10% and an 81% rate of stable disease.[32] These studies suggest that VEGF inhibition may be a useful therapeutic strategy in this disease.

It is recognized that carcinoid tumors and pancreatic endocrine carcinoma have similar histologic appearance and biologic behavior. However, they may have molecular differences and may respond differently to certain types of therapy. In a prior trial with SU11248, objective responses were observed in 13% of islet cell patients and only 2% of carcinoid patients.[32] Therefore, we will study carcinoid and pancreatic endocrine carcinoma patients in two separate cohorts.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed low or intermediate grade neuroendocrine carcinoma. Patient with neuroendocrine tumors associated with MEN1 syndrome will be eligible.

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 $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan. See section 11.2 for the evaluation of measurable disease.

3.1.3 Patients may have received 0, or 1 prior cytotoxic therapy. Chemotherapy used as a radiosensitizer will be considered one prior chemotherapy regimen.

Patient must not have received prior bevacizumab or any other therapy targeting VEGF or VEGF receptors (i.e., SU11248, PTK787/ZK222584, Sorafinib, GW786034).

3.1.4 Patients must be on a stable dose of somatostatin analogue for 2 months prior to start of protocol. Octreotide dose not count toward prior therapy.

3.1.5 Prior radiation therapy is permitted. A recovery period of at least 4 weeks after completion of radiotherapy is required prior to enrollment.

3.1.6 Patients may have received prior interferon (not counted toward prior cytotoxic chemotherapy).

3.1.7 Patients may have received prior therapy targeting c-kit, abl, PDGFR, or EGFR (imatinib, gefitanib, erlotinib, cetuximab; not counted toward prior cytotoxic chemotherapy).

3.1.8 Age ≥18 years. GW786034 (pazopanib) is contraindicated in the pediatric population due to the potential effect on the epiphyseal growth plates.

3.1.9 Patients must have unresectable or metastatic disease.

3.1.10 ECOG performance status of 0, or 1 (Karnofsky ≥ 70%; see Appendix I).

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

• leukocytes	≥3,000/mcL
• absolute neutrophil count	≥1,500/mcL
• platelets	≥120,000 /mcL
• total bilirubin	within normal institutional limits
• AST(SGOT)/ALT(SGPT)	≤3.0 X institutional upper limit of normal
• creatinine	≤2.0
OR	
• creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

3.1.12 Patients must have PT/INR/PTT within 1.2 X the upper limit of normal.

3.1.13 Patients must have resting blood pressure (BP) no greater than 150 mmHg (systolic) or 90 mmHg (diastolic) for eligibility. Initiation or adjustment of BP medication is permitted prior to study entry.

3.1.14 The effects of GW786034 (pazopanib) on the developing human fetus are unknown. However, teratogenic effects and reduced fetal body weight have

been seen in pregnant rats and/or rabbits given GW786034 (pazopanib). For this reason and because antiangiogenic 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 prior to study entry and for the duration of study participation. Women of child-bearing potential must have a negative pregnancy test prior to study entry. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Women who have had menses within the past 2 years, who have not had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy are considered to be of child-bearing potential.

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

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks prior to study enrollment. At least 4 weeks must have elapsed since any surgery prior to study enrollment.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients with greater than +1 (>/= 100 mg/dl) proteinuria on two consecutive routine urinalysis taken at least 1 week apart are ineligible.

3.2.4 Certain medications that act through the CYP450 system are specifically prohibited in patients receiving GW786034 (pazopanib) because *in vitro* data indicate that the agent has the potential to interact with the cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Certain other agents should be used with caution. A list of medications that are specifically prohibited or that should be used with caution during this trial of GW786034 (pazopanib) can be found in Section 8. Comprehensive lists of agents that could affect GW786034 (pazopanib) through the cytochrome P450 system can be found in Appendix II.

3.2.5 Patients with any condition (*e.g.*, gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, or active peptic ulcer disease) that impairs their ability to swallow and retain GW786034 (pazopanib) tablets are excluded.

3.2.6 Patients with any of the following conditions are excluded:

- Serious or non-healing wound, ulcer, or bone fracture.
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment.

- Any history of cerebrovascular accident (CVA) within the last 6 months.
- Current use of therapeutic warfarin. Note: Low molecular weight heparin and prophylactic low-dose warfarin are permitted. PT/PTT must meet the inclusion criteria (Section 3.1.12).
- History of myocardial infarction, cardiac arrhythmia, admission for unstable angina, cardiac angioplasty or stenting within the last 12 weeks.
- History of venous thrombosis in last 12 weeks.
- Class III or IV heart failure as defined by the NYHA functional classification system (see Appendix III). A patient who has a history of Class II heart failure and is asymptomatic on treatment may be considered eligible.

3.2.7 Patients with known 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.

3.2.8 No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, or any other cancer from which the patient has been disease free for five years.

3.2.10 Pregnant women are excluded from this study because GW786034 (pazopanib) is an antiangiogenic agent that has produced teratogenic effects and reduced fetal body weight in pregnant rats and/or rabbits, and therefore has the potential for teratogenic or abortifacient effects in humans. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with GW786034 (pazopanib), breastfeeding should be discontinued if the mother is treated with GW786034 (pazopanib). These potential risks may also apply to other agents used in this study.

3.2.11 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with GW786034 (pazopanib).

3.2.12 Uncontrolled diarrhea (8 or more bowel movements per day)

3.3 Inclusion of Women and Minorities

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

3.4 Good Medical Practice

The following should be assessed within 28 days prior to registration in accordance with good medical practice. These items do not determine eligibility and minor deviations would be acceptable if they do not affect patient safety in the clinical judgment of treating physician. The principal investigator should be contacted if there are significant deviations.

- Unless medically necessary, patients should avoid receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics of GW786034 (pazopanib; see Section 3.2.7 for further information).

- Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics at the time of study enrollment should not be enrolled. Patient should not have psychiatric disorders rendering them incapable of complying with the requirements of the protocol.

- Patients with known QTc prolongation (defined as a QTc interval equal to or greater than 500 msecs) should have ECG performed before start of treatment. Additional ECG should be performed as deemed needed by treating physician.

- The following labs should be obtained at baseline and as often as deemed needed by treating physician: Albumin, calcium, glucose, alkaline phosphatase, LDH, electrolytes (Na, K, Cl, CO2, Mg)

4. REGISTRATION PROCEDURES

4.1 General Guidelines

The Study Coordinator will enter eligible patients on study centrally at the University of Texas M. D. Anderson Cancer Center.

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. 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 (PIO@ctep.nci.nih.gov).

4.2 Registration Process

To register a patient, the following documents should be completed by the research nurse or data manager and faxed to the Data Management Center at M.D. Anderson Cancer Center at (713) 563-4318:

- Copy of required laboratory tests
- Signed patient consent form
- HIPAA authorization form
- Source documentation for all eligibility criteria

The research nurse or data manager at the participating site will then call the Data Management Center at M.D. Anderson Cancer Center verify eligibility. To complete the registration process, the Data Management Center at M.D. Anderson Cancer Center will

- assign a patient study number
- register the patient on the study
- fax or e-mail the patient study number and dose to the participating site
- call the research nurse or data manager at the participating site and verbally confirm registration.

5. TREATMENT PLAN

5.1 **GW786034** (Pazopanib) **Administration**

5.1.1 Treatment Regimen

- Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for GW786034 (pazopanib) 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.

- Patients receive GW786034 (pazopanib) on an outpatient basis at a dose of 800 mg once daily (two 400-mg tablets; dose modification will be accomplished by combining 400-mg and 200-mg tablets as necessary). Patients are instructed to swallow tablets once a day (preferably in the morning) on an empty stomach, either 1 hour before or 2 hours after food with about 1 cup (240 mL) water. Tablets should be swallowed whole; they must not be chewed, broken, or crushed. Each cycle is 28 days. Treatment continues until one of the criteria in Section 5.4 applies, provided that the retreatment criteria in Section 5.3 have been met.

- Patients will be provided with a Medication Diary for GW786034 (pazopanib)

(Appendix IV), instructed in its use, and asked to bring the diary with them to each appointment. A new copy of the Medication Diary will be given to patients whose dose is reduced due to adverse events.

- All patients will continue octreotide at the same dose as prior to study entry without interruption The dose of depot octreotide (sandostatin LAR ®) should not exceed 30 mg every 3 weeks.

- All prescription and over-the-counter medications as well as alternative medicines that have been taken within 4 weeks prior to the first dose of GW786034 (pazopanib) must be fully documented in the Case Report Form (CRF; indication, dose information and dates of administration). The Principal Investigator must be informed as soon as possible about any new medication taken from the time of screening until the end of the clinical phase of the study (final laboratory sample); these new medications will be fully documented in the CRF (indication, dose information, and dates of administration).

- All concomitant medications taken during the study will be recorded in the CRF with indication, dose information, and dates of administration.

5.1.2 Precautions/Warnings

- Medical personnel must refer to the list of **prohibited** and **"use with caution"** agents in Section 8 prior to administering treatment.

  Substances that are prohibited cannot be taken from prior to the administration of the first dose of GW786034 (pazopanib) until 1-2 weeks after discontinuation from the study. The length of the pre-study prohibition will be at the discretion of the clinician based on the pharmacokinetic properties of the agents involved.

  Patients taking medications that are listed as "use with caution" should be closely monitored for adverse events. In some instances of treatment for hypertension, a lower dose of the medication may be sufficient to provide the required antihypertensive control. In other instances, the standard dose of such a medication may be associated with adverse events because of increased exposure. Alternatively, the investigator may choose to replace the medication with another in the same pharmacologic class that is less likely to interact with GW786034 (pazopanib). If such a medication is discontinued and replaced, the transition period should occur no less than 7 days prior to the first dose of GW786034 (pazopanib). Based on prior clinical experience with GW786034 (pazopanib), the use of calcium channel blockers (dihydropyridine category) and ACE inhibitors as first-line and second-line therapy is recommended.

- Frequent **blood pressure (BP) monitoring** is important in patients receiving GW786034 (pazopanib) starting on day 8 (+/- 2 days) and continuing until patient is off study. Experience to date suggests that increases in BP may occur following dosing with GW786034 (pazopanib) for a number of weeks and that these increases may occur relatively quickly. It is imperative that the investigator institute appropriate measures to control BP. This may necessitate changes to existing antihypertensive medication, addition of new medication(s) and/or interruption/withdrawal of GW786034 (pazopanib). Section 6 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

  Patients will be provided with a diary in which to record their twice-daily BP readings (see Appendix V). The two daily readings should be taken at least 1 to 4 hours apart. If two successive systolic readings are $\geq$140 mmHg OR two successive diastolic readings are $\geq$90 mmHg OR any combination of elevated systolic and diastolic readings, patients will be instructed to contact their physician as soon as possible. Patients should seek medical advice if their BP exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and should also be encouraged to contact their physician if they are concerned about any symptoms that may be associated with high BP (*e.g.*, headache). Recommendations for the monitoring and recording of BP readings as well as a flow chart for event management are presented in Appendix VI.

- **Renal function** (creatinine and urinary protein) should be monitored once per cycle (or more frequently if clinically indicated) as suggested by the pathologic changes noted in animal studies and evidence from studies of other antiangiogenic agents. Specific guidelines for management of proteinuria and elevated creatinine are presented in Section 6.

5.1.3 Criteria for Continuing Treatment

- Patients will be evaluated at each clinic visit during the treatment period to determine if continued treatment is appropriate. If, at any time during treatment the evaluation criteria are not met, GW786034 (pazopanib) will be held or the dose adjusted according to the dose modification criteria stated in Section 6. To continue therapy, subjects must meet the following criteria:

  - Absolute neutrophil count (ANC) $\geq$ 1,000/mm^3 (1 X 10^9/L).
  - Platelet count $\geq$ 50,000/mm^3 (50 X 10^9/L).
  - Blood pressure, if elevated, should be controlled with antihypertensive medication(s).
  - Urine Protein Creatinine (UPC) ratio < 1+.
  - No clinically significant non-hematologic toxicity $\geq$ grade 2.

- Medical judgment should be exercised in deciding whether an adverse event of greater than or equal to grade 2 requires dose interruption or modification (see Section 6 for Dose Modification guidelines).

5.2 General Concomitant Medication and Supportive Care Guidelines

- Because GW786034 (pazopanib) is known to interact with other concomitantly administered drugs through the cytochrome P450 (CYP450) system, the CRF must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

- Section 8 provides lists of agents and substances specifically prohibited during GW786034 (pazopanib) administration as well as those that are to be used with caution. Appendix II provides comprehensive lists of agents and substances that are known or which may have the potential to interact with GW786034 (pazopanib) through CYP450 isoenzymes. The Principal Investigator should be alerted if the patient is taking any agent on these lists.

- Patients should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, anti-emetics, anti-diarrheals, analgesics, erythropoietin, or bisphosphonates, when appropriate.

- The use of interferon for control of carcinoid syndrome is not allowed. Other medications used for the supportive therapy of carcinoid syndrome are allowed. Specifically, short acting octreotide may be used for control of carcinoid syndrome. Other medications for diarrhea may be used on an as needed basis. Steatorrhea due to somatostatin analogue may be managed by the usage of pancrealipase. Diarrhea due to short gut syndrome should be managed with cholestyramine.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 12 cycles or until one of the following criteria applies:

- Disease progression,

- Intercurrent illness that prevents further administration of treatment,

- Unacceptable adverse event(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.

Principal investigator may grant exception to the 12-cycle rule and allow continuation of therapy if patient is deemed to continue to benefit from treatment, study drug is not commercially available, and study otherwise remains open.

5.4 Duration of Follow Up

Patients removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Follow-up for progression free survival after a patient is off treatment will be per telephone contact, or physician visit contact, approximately every 90 days for 18 months from date of study entry or until closure of protocol following final study report (whichever is earlier). If the patient has started any new treatment, even without objective documentation of progression of disease, follow for progression free survival will also stop. Patients who are deemed inevaluable will not be followed after removal from study.

6. DOSING DELAYS/DOSE MODIFICATIONS

Appropriate dose modifications for GW786034 (pazopanib)-related adverse events are outlined in the following subsections. If treatment has been held for more than 21 days to allow for resolution of an adverse event, the investigator should contact the PI to review the subject's condition prior to resuming the patient's treatment except for delays due to hypertension (see Section 6.1 below). Dose level reductions follow:

Dose level	GW786034 (pazopanib)
-2	400 mg daily
-1	600 mg daily
1	800 mg daily

6.1 Management of Hypertension

Increases in blood pressure (BP) and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following GW786034 (pazopanib) treatment has been seen in animal studies as well as clinical trials. Specific guidelines for management of this adverse event are provided below; additional suggestions for BP management can be found in the flow chart in Appendix VI.

- While patients are receiving treatment with GW786034 (pazopanib), the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.

- Decisions to hold or decrease the GW786034 (pazopanib) dose during treatment must be based on BP readings taken in the clinic by a medical professional.

Hypertension Monitoring and Management*

	Antihypertensive Therapy	Blood Pressure Monitoring	GW786034 (pazopanib) Dose Modification
Normal < 140 mmHg Systolic < 90 mmHg Diastolic	• None • Baseline	• Standard monitoring • Consider diuretics	• No Change
Mild hypertension ≥ 140 mmHg Systolic ≥ 90 mmHg Diastolic	• Initiate BB **or** Initiate DHP CCB **&/or** • Increase doses of existing medications until BP controlled or at maximum dose	• Increased frequency of monitoring until stabilized	• No Change
Persistent moderate hypertension ≥ 140 mmHg Systolic ≥ 90 mmHg Diastolic	• Initiate BB **or** Initiate DHP CCB **or** ACEI **or** Vasodilator **&/or** • Increase doses or number of medications until BP controlled or at maximum dose	• Increased frequency of monitoring until stabilized (*e.g.*, every 48 hours) • Supervised by healthcare professional	• If partial or no control and BP still in a moderate range for 24-48 hours, hold GW786034 (pazopanib) and add additional drugs, increasing to a maximum dose until hypertension controlled; monitor for hypotension. • Decrease GW786034 (pazopanib) by 1 dose level
Severe hypertension ≥ 180 mmHg Systolic ≥ 105 mmHg Diastolic	• Start immediate therapy with 2 drug combination including at least a DHP CCB • Escalate doses to achieve optimal control of BP, up to the maximum dose • If partial or no BP control, add additional drugs up to 4; increase to optimal or maximum doses of all drugs	• Increased frequency of monitoring until stabilized (*e.g.*, every 48 hours) • Supervised by healthcare professional	• Hold GW786034 (pazopanib); if control of BP in the Mild range, restart GW786034 (pazopanib) at the next lower dose level • If partial or no control, decrease GW786034 (pazopanib) by another dose level or discontinue therapy per investigator • Stop GW786034 (pazopanib) if hypertension is symptomatic, and hospitalize patient for management of BP
CTC Grade 4 Hypertensive Crisis	• Optimal management with intensive IV support in ICU	• Hospitalize patient for management	• Off protocol therapy, discontinue GW786034 (pazopanib), and monitor closely for **hypo**tension

Abbreviations: Dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB)

- *See table below for suggested antihypertensive medications by class
- If patients require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- If patients require >2 dose reductions, discontinue protocol therapy
- Patients may have up to 2 drugs for management of hypertension prior to any dose reduction in GW786034 (pazopanib)
- 24-48 hours should elapse between modifications of antihypertensive therapy
- Hypertension should be graded using the NCI CTCAEv3.0

Oral Antihypertensive Medications

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with GW786034 (pazopanib) through CYP450.

Agent class	Agent	Initial dose	Intermediate dose	Maximum Dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**

α and β Blocker	labetolol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

6.2 Management of Proteinuria

Although patients with ≥1+ proteinuria at entry are ineligible, increases in proteinuria may occur during treatment and should be managed as follows:

Management of Proteinuria

Proteinuria value	Monitoring	Dose modification
≥1+ (dipstick or equivalent routine laboratory analysis)	Perform the following tests: • 24-hour urine collection for total protein and creatinine • microscopic examination of fresh urine • urine protein electrophoresis (at first occurrence of >1+ proteinuria only)	See below
Based on results of the 24-hour urine collection:		
<1g protein (24-hour collection)	Continue dipstick or equivalent routine laboratory analysis	Continue planned dose
≥1 g but ≤ 2g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4w) until total protein is <500 mg/24 hours	Decrease one dose level; continue treatment
>2 g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) weekly until proteinuria is <2 g	Hold GW786034 (pazopanib) When protein is <2 g/24 hours, resume treatment at one lower dose level
	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4w)	Continue until patient is off study

6.3 Management of Other Adverse Events

Adverse Event	Grade	Treatment Modification	Follow Up
Hemorrhage/ Bleeding/ Coagulopathy	Grade 1	No interruption in treatment; maintain current dose.	Monitor as clinically indicated.
	Grade 2	Hold GW786034 (pazopanib) until resolved to ≤ grade 1; reduce dose to next lower dose level, and continue treatment. If grade 2 or greater hemorrhage/ bleeding recurs following dose reduction, stop GW786034 (pazopanib) and remove patient from study. [1]	Monitor as clinically indicated. Follow up per protocol (Section 5.4) if patient is removed from the study.
	Grades 3 or 4	Discontinue treatment and withdraw subject from study. [1]	Follow up per protocol (see Section 5.4).
Vascular/ Thrombosis	Grade 2	No interruption in treatment; maintain current dose.	Monitor as clinically indicated.
	Grade 3 or asymp-tomatic Grade 4	Hold GW786034 (pazopanib) until patient is receiving a stable dose of Low Molecular Weight Heparin (LMWH). (Coumadin® is a prohibited medication.) Treatment may resume during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must be on a stable dose of LMWH for treatment. • The subject must not have had a >grade 2 hemorrhagic event while on anticoagulation.	Monitor as clinically indicated.
	Symptom-atic Grade 4	Discontinue treatment and remove patient from study.	Follow up per protocol (see Section 5.4
Thrombo-cytopenia/ Neutropenia/ Anemia [2]	Grades 1 or 2	No interruption in treatment; maintain current dose.	Monitor as clinically indicated.
	Grade 3 or 4	Interrupt treatment until toxicity is ≤ Grade 2; reduce dose to 400 mg. If event recurs following dose reduction, discontinue treatment and remove patient from study. If patient is benefiting from therapy, contact the PI and the sponsor (DCTD, NCI) to discuss course of action.	Monitor as clinically indicated. If subject is withdrawn from study, follow up per protocol (see Section 5.4).

[1] If recurrent event has no clearly associated clinical consequences, consult with the PI about continued treatment at 400 mg per day for patients who are benefiting from GW786034 (pazopanib).

[2] Patients with anemia due to hemorrhage/bleeding should be managed according to Hemorrhage/Bleeding/Coagulopathy section of this table.

6.4 Management of Other Clinically Significant Non-Hematologic Toxicities not specifically addressed above.

Observation	Action
Grade 1 or 2 non-hematologic AE related to GW786034	Continue treatment at current dose
Grade 3 or 4 non-hematologic AE related to GW786034	Hold GW786034 until patient recovers to ≤ grade 1(except for grade 2 alopecia and fatigue) then Reduce one dose level* **
* Treatment may be held for up to 21 days. If toxicity does not recover, patient will be removed from study treatment.. ** After consultation with PI, a dose of 400 mg daily may be considered for patients on study ≥ 3 months who are benefiting from the agent.	

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited (via AdEERS) reporting **in addition** to routine (via CTMS or CDUS) reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete 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 Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (the ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (http://ctep.cancer.gov/reporting/adeers.html) for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for GW786034 (pazopanib).

Version 1.1, October 27, 2005[1]

Category (Body System)	Adverse Events with Possible Relationship to GW786034 (CTCAE v3.0 Term)	Agent Specific Adverse Event List (ASAEL)
CARDIAC GENERAL		
	Hypertension	
CONSTITUTIONAL SYMPTOMS		
	Fatigue (asthenia, lethargy, malaise)	
DERMATOLOGY/SKIN		
	Hypopigmentation (hair depigmentation)	
GASTROINTESTINAL		
	Anorexia	
	Diarrhea	
	Nausea	
	Vomiting	
METABOLIC/LABORATORY		
	ALT, SGPT (serum glutamic pyruvic transaminase)	
	AST, SGOT (serum glutamic oxaloacetic transaminase)	
	Proteinuria	
PAIN		
	Pain - abdomen NOS	

[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 ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on GW786034 trials but with the relationship to GW786034 still undetermined:

Blood/Bone Marrow - hemoglobin
Cardiac Arrhythmia - sinus bradycardia
Dermatology/Skin - rash
Hemorrhage/Bleeding - GI hemorrhage
Neurology - extrapyramidal/involuntary movement
Vascular - thrombosis/thrombus/embolism

Animal Data: The following toxicities have been observed in animal studies with GW786034

Rat: bone/bone marrow changes (trabecular atrophy; periosteal chondroid change and hyperplasia of epiphyseal growth plate, bone marrow hypercellularity); teeth

changes (periodontal edema, enamel degeneration, dental pulp necrosis); nail/nailbed dyskeratosis; hematology changes (decreased red blood cells and hemoglobin, increased white blood cells); blood chemistry changes (increased AST, ALT, alkaline phosphatase, total bile acids, urea nitrogen, and cholesterol; decreased albumin, and albumin/globulin ratio); increased urine protein and urine protein/creatinine ratio; acinar atrophy of pancreas; adrenal angiectasis, hemorrhage, and necrosis; exacerbation of age-related nephropathy; pituitary hypertrophy; decreased tracheal globule leukocytes; atrophy of ovaries with vaginal mucification; atrophy and degeneration of testes; at high doses – birefringent crystalline GW786034 in villi of small intestine.

Monkey: severe gastrointestinal effects (persistent diarrhea; inappetence, decreased activity, weight loss); at high doses - birefringent crystalline GW786034 in villi of small intestine.

Note: GW786034 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **"Expectedness"**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1.1).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These

requirements are briefly outlined in the table below (Section 7.3.3).

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

7.3.2 AdEERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. AdEERS provides a copy feature for other e-mail recipients.

7.3.3 **Expedited Reporting Guidelines** – AdEERS Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials

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

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
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 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 Accession number assigned during trial registration on all reports.

7.3.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

- For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (*i.e.*, AdEERS). The following AEs must be reported through the routine reporting mechanism (Section 7.4):

CTCAE Category	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
GI	Diarrhea	3, 4	Yes	Possible	Common for disease

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine (CTMS or CDUS) study data submissions. **AEs reported through AdEERS must also be reported in routine study data submissions.**

7.5 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). Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (available at http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

GW786034 (NSC 737754)

Other Names: Pazopanib HCl, GW786034B (the suffix B denotes the monohydrochloride salt).

Classification: VEGFR tyrosine kinase inhibitor

Mechanism of Action: GW786034 is a highly potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3). Vascular endothelial growth factor receptor inhibition may block VEGF driven angiogenesis and, as a consequence, constrain tumor growth.

Molecular Formula: $C_{21}H_{23}N_7O_2S$-HCl **M.W.:** 474.0 (monohydrate salt)
437.5 (free base)

Chemical Name: 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride

Approximate Solubility: The monohydrochloride salt is very slightly soluble in 0.1 M HCl (0.65 mg/mL), and is practically insoluble in pH 7.0 phosphate buffer (0.00005 mg/mL), and in pH 11 piperidine buffer (0.0002 mg/mL).

How Supplied: GW786034 monohydrochloride is supplied as a series of aqueous film-coated tablets containing 200 mg and 400 mg of the free base:

- 200 mg, oval-shaped, white, packaged in bottles containing 34 tablets each
- 400 mg, oval-shaped, white, packaged in bottles containing 68 tablets each

Tablet excipients in all tablet sizes include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists

of titanium dioxide, hypromellose, polyethylene glycol, and polysorbate 80.

Storage: The intact bottles should be stored at controlled room temperature [20°C - 25°C (68°F - 77°F)]. Excursions are permitted between 15°C and 30°C.

Stability: Stability studies are ongoing.

Route of Administration: Oral. The tablets cannot be crushed or broken.

Method of Administration: Patients should fast for 2 hours before and 1 hour after each GW786034 dose.

Potential Drug Interactions:

In vitro data indicate that GW786034 is an inhibitor for CYP2C9, CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. In animal studies, there were no GW786034-related effects on the activities of CYP1A, CYP2B, CYP2E, CYP3A, and CYP4A.

In vitro, the most potent inhibition was seen for the isoenzyme CYP2C9. Accordingly, the following medications, which are substrates for CYP2C9, are PROHIBITED in subjects receiving GW786034 (the washout period is at the discretion of the clinician based on the pharmacokinetic properties of each individual agent):

- Anticoagulants: warfarin (therapeutic doses only)
- Oral hypoglycemics: glipizide, glyburide, tolbutamide
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- Neuroleptic: pimozide
- Erectile dysfunction agents: sildenafil, tadalafil, vardenafil
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexilitine, amiodarone, quinidine
- Immune modulators: cyclosporine, tacrolimus, sirolimus
- Miscellaneous: theophylline, quetiapine, risperidone

Certain medications should be used with CAUTION due to the potential for alterations in the pharmacologic effects or increased adverse events secondary to the inhibition of multiple CYP enzymes by GW786034. These medications include (but are not limited to):

- Antidepressants: amitriptyline, buproprion, fluoxetine, fluvoxamine, imipramine
- HMG co-reductase inhibitors: atorvastatin, fluvastatin, lovastatin, simvastatin
- Benzodiazepines: alprazolam, midazolam, triazolam, clorazepate, diazepam, flurazepam

- Calcium channel blockers: diltiazem, felodipine, nifedipine, nicardipine, nimodipine, nitrendipine, verapamil, amlodipine, nisoldipine, isradipine
- Angiotensin II blockers: losartan, irbesartan
- Beta blockers: carvedilol, metoprolol, propafenone, propanolol, timolol
- Anticonvulsants: phenobarbital, phenytoin, primadone, carbamazepine
- Miscellaneous: codeine, methadone, mifepristone, estrogens and progestins (including oral contraceptives)

In vitro data also suggest that GW786034 is a substrate for CYP3A4. Therefore, substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of GW786034 and should be used with CAUTION. These medications include (but are not limited to):

Inhibitors of CYP3A4:

- Antibiotics: clarithromycin, erythromycin, troleandomycin
- HIV: anti-retrovirals (delaviridine), protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconazole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone, fluvoxaine
- Calcium channel blockers: verapamil, diltiazem
- GI: cimetidine, aprepitant
- Miscellaneous: grapefruit juice

Inducers of CYP3A4:

- Glucocorticoids: dexamethasone
- Anticonvulsants: phenytoin, carbamazepine
- HIV: efavirenz, nevirapine
- Antibiotics: rifampin, rifabutin, rifapentine
- Miscellaneous: St. John's wort, modafinil

Availability

GW786034 (pazopanib) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

GW786034 (pazopanib) is provided to the NCI under a Collaborative Agreement between GlaxoSmithKline and the DCTD, NCI (see Section 12.3).

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 Investigational Drugs (http://ctep.cancer.gov/requisition/storage.html).*

9. CORRELATIVE/SPECIAL STUDIES

9.1 Functional CT

Background

Various traditional imaging modalities are available for the detection of the primary carcinoid tumor, the assessment of metastatic disease, and the evaluation of tumor response to treatment. These include angiography, ultrasound, computed tomography (CT), positron emission tomography (PET), and scintography with In-111 labeled somatostatin receptors. CT is useful in the detection of metastatic disease to the liver or lymph nodes. More commonly, the CT is used to evaluate tumor response by monitoring a change in size of the lesion. This proves difficult especially when the change is slow.

Recent technical advances in computerized tomography (CT) have yielded an improvement in temporal and spatial resolution in data acquisition. This has permitted the development of functional CT imaging that can gather consecutive image data with high temporal resolution. Among these novel techniques in functional CT (fCT) is a non-invasive method to quantify angiogenic activity known as CT perfusion. CT perfusion refers to functional CT data acquisition by a cine-CT mode and the application of the software developed by Tim-Yim Lee for the calculation of tissue blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability surface (PS). The mathematical models to calculate these parameters have been tested and validated in various animal models and more recently has been applied to clinical trials at our institution.

In a phase II clinical trial of Thalidomide (an antiangiogenic agent for patients with metastatic renal carcinoma) we have demonstrated a decrease in BV, and PS area products by mean values of 23%, and 27%, respectively, after 12 weeks of treatment, but the BF did not significantly change. However, after 24 weeks of treatment those with a decrease in BF in addition to a decrease in BV and PS had a better outcome.

We also have extensive experience with functional imaging for monitoring of antiangiogenic therapy in carcinoid patients treated with agents targeting VEGF. Our

bevacizumab study showed rapid and sustained drops in BF, BV, PS among carcinoid patients. The change is relative to baseline parameters (approximate a 40% decrease).

Imaging Plan

We plan to perform post-treatment functional CT at week 12 just prior to that day's dose of GW786034. This will help to establish whether there is suppression of tumor blood flow throughout the dosing interval. This optional procedure will only be performed at M.D. Anderson Cancer Center. Patients at the Dana Farber site will not participate due to this procedure is not currently available at this site.

Lesion selection
Staff radiologist in the body section of the Diagnostic Imaging Department will review A CT evaluation of the chest, abdomen, and pelvis. The radiologist will select a metastatic lesion that is larger than 2 cm. If multiple lesions are present, the lesion with the least sensitivity to misregistration due to breathing artifact will be selected.

Functional CT protocol
Intravenous contrast enhancement technique
An 18 G needle will be placed in the anticubital fossa. 30cc of intravenous (IV) contrast material (non-ionic, 320mg Iodine/100mL) will be delivered by an automatic injector at 7 cc/sec. The rate of injection will be adjusted if a smaller 20g needle to 4-5 cc/sec.

Scanning Techniques fCT
All scans will be performed on a helical CT unit with multi-detector row. An un-enhanced CT evaluation will be performed to localize the lesion. A radiologist will select a solid portion of the tumor. The lesion should be at least 2cm in craniocaudal extension. The images will be acquired at 5mm slice thickness (4 images for a 2 cm area). The scan will be obtained with a delay time of 5 to 10 secs. The delay time for lesions in the chest or upper abdomen will be 5 sec. The delay for lesions in the pelvis or thigh will be 7-10 sec. The selected level will be scanned with a CINE-mode for a period of 30-40 seconds with a single breath-hold for lesions that will be affected by respiratory motion or without breath-hold. The scanning parameters will be 120 kVp and 90 mAs, and 1 second per scanning rotation. The data from the scan is saved. The image data will be reconstructed by segmentation every half seconds.

Image Data Analysis

The image data will be transferred to an Advantage workstation for image processing. For each patient a pre-treatment and post-treatment fCT acquisitions will be performed. For each fCT acquisition, four axial anatomic locations, slices, will be evaluated. The metastatic mass will be identified on each of the four axial images. For each slice, functional maps will be generated using the CT perfusion II software developed by Ting-Yim Lee. The whole tumor blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability surface (PS) maps will be generated. For each map, a region of interest will be placed over the entire mass in each anatomic location and an average

value for each parameter (BF, PS, BV, and MTT) will be obtained. The data will be compared at pre-treatment and at 12 weeks. The pre-treatment and 12 week scans will be obtained in conjunction with staging CT evaluation of the chest abdomen and pelvis. The results will be compared to clinical response and change in tumor size. We expect a response to treatment to demonstrate a 40% reduction in BF. This will be similar to our results with Bevacizumab trial.

9.2 Pharmacokinetics

Blood sampling for clinical pharmacokinetics analysis will be performed as follows:

Cycle 1- Days 1, and 28: Pre-dose
Cycle 3 and every third cycle thereafter - Day 28: Pre-dose

Plasma will be isolated from patients' blood specimens drawn at these time points. Determination of GW7856034 concentration will be made by GlaxoSmithKline. See Appendix VII.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to administration of protocol therapy. Scans and x-rays must be done within 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.

	Pre-study	Cycle 1		Cycle 2 onward	Every 3 cycles	End of Study [e]	Follow-up [$]
		Day 1 [d]	Day 28	Day 1	Day 28		
GW786034		----------Daily Dosing----------					
Consent	X						
Medical History	X						
Physical Exam	X	X		X		X	
Vital Signs	X	X		X		X	
Height	X						
Weight		X		X		X	
Performance Status	X			X		X	
Serum B-HCG (female patients)	X	X					
Concurrent meds	X----------Continuous Evaluation----------X						
Adverse event		X----------Continuous Evaluation----------X					
EKG (as indicated)	X						
CBC w diff, plt [a]	X			X		X	
Serum chemistry, PT, PTT [a b]	X			X		X	
Urine protein	X	X		X		X	
CT/MRI	X				X [#]	X	
Tumor Markers [c]	X	X	X		X	X	
Functional CT's [%]	X				X [%]		
PK**		X	X		X		
Follow-up							X

a: May be obtained up to 72 hours prior to dosing on day 1 of cycle 2 onward.
b: Serum Chemistries include: total bilirubin, BUN, creatinine, SGOT[AST], SGPT[ALT], sodium.
c Tumor markers include: Chromogranin A, neuron specific enolase, pancreatic polypeptide, gastrin, glucagon, VIP, 5HIAA. In patients with insulinoma, Insulin, pro insulin and c-peptide will also be obtained.
d: These tests do not need to be repeated if completed within 1 week prior to dosing.
e: These evaluations will be completed within 40 days after last dose of study drug.
%: Functional CT's will be obtained at baseline, and up to 72 hours prior to dosing of cycle 4 day 1.
: Restaging CT's will be obtained at baseline and every 3 cycles (may be obtained up to 72 hours prior to dosing of next cycle)
**: Cycle 1, Days 1 and 28 - Pre-dose; Cycle 3 and every third cycle (at time of response evaluation) thereafter Day 28 - Pre-dose
$: See section 5.4 for follow-up specifics and duration

11. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 12 weeks following initial documentation of objective response.

11.1 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.

11.1.1 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).

11.1.2 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.

11.1.3 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.

11.1.4 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.

11.2 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 only be considered measurable if there has been growth since the completion of radiation.

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

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

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

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

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

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific

context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

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 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.

11.3 Response Criteria

11.3.1 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

11.3.2 **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.

11.3.3 **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 Sections 11.3.1 and 11.4.1).

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.

11.4 Confirmatory Measurement/Duration of Response

11.4.1 Confirmation

To be assigned a status of confirmed PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 12 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 12 weeks (see section 11.3.3).

11.4.2 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.

11.4.3 **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.

11.5 **Progression-Free Survival**

PFS is defined as the duration of time from start of treatment to time of progression or death.

12. DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 **Data Reporting**

12.1.1 Method

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).

12.1.2 Responsibility for Submissions

Study participants are responsible for submitting CDUS data and/or data forms to the Coordinating Center to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.1.1.).

The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix VIII.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. 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 (*PIO@ctep.nci.nih.gov*) except for Group studies.

12.3 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agent(s), supplied by CTEP, DCTD, NCI, used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) [hereinafter referred to as ACollaborator(s)@] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the AIntellectual Property Option to Collaborator@ (http://ctep.cancer.gov/industry) 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 and unless additional disclosure is required by law or court order.–Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to

presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
6130 Executive Boulevard, Suite 7111
Rockville, MD 20892
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.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

It is recognized that carcinoid tumors and islet cell carcinoma have similar histologic appearance and biologic behavior. However, they may have molecular differences and may respond differently to certain types of therapy. Therefore, they will be enrolled into 2 separate cohorts.

For the islet cell cohort:

A true response (CR + PR) rate less than 10% will be considered unacceptable activity for this treatment, whereas a true response rate of at least 30% will be considered acceptable. A two-stage design will be used to test whether there is sufficient evidence that the treatment could be a candidate for further study, with early stopping allowed for poor results. For p0 = 10% and p1 = 30%, we propose a two-stage design enrolling 20 patients in the first stage, continuing if more than 3 patients respond, for a total of 30 patients and declaring the treatment promising if more than 4 patients respond. This design has a 10% chance (type I error rate) of accepting the treatment for further testing if the true response rate is less than 10% and a 89% chance (power) of accepting the treatment for further testing if the true response rate is at least 30%. The probability of early termination is 87%.

For the carcinoid cohort:

A true response (CR + PR) rate less than 5% will be considered unacceptable activity for this treatment, whereas a true response rate of at least 20% will be considered acceptable. A two-stage design will be used to test whether there is sufficient evidence that the treatment could be a candidate for further study, with early stopping allowed for poor results. For p0 = 5% and p1 = 20%, we propose a two-stage design

enrolling 20 patients in the first stage, continuing if more than 1 patient responds, for a total of 30 patients and declaring the treatment promising if more than 3 patients respond. This design has a 5% chance (type I error rate) of accepting the treatment for further testing if the true response rate is less than 5% and a 86% chance (power) of accepting the treatment for further testing if the true response rate is at least 20%. The probability of early termination is 74%.

13.2 Sample Size/Accrual Rate

The maximal number of patients to be accrued is 60 patients. The estimated accrual rate is 6 patients per months.

13.3 Stratification Factors

The data will be analyzed jointly for all patients enrolled and as two separate cohorts (carcinoid versus pancreatic endocrine tumors). Analyses will stratify by primary site.

13.4 Analysis of Secondary Endpoints

We plan integrated analyses of all correlative studies to maximize information gained from data obtained. Plasma trough level of GW786034 will be measured. These will be correlated with changes in tumor markers, functional imaging parameters as well as objective response and progression free survival. Tumor blood flow at baseline, following treatment, and percentage decrease will be correlated with objective response and progression free survival.

13.5 Reporting and Exclusions

13.5.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with GW786034.

13.5.2 **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 to have a treatment failure (disease progression). Thus, an

incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

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

REFERENCES

1. Schnirer II, Yao JC, Ajani JA: Carcinoid: A comprehensive review. Acta Oncol 42:672-692, 2003
2. Sun W, Lipsitz S, Catalano P, et al: Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol 23:4897-904, 2005
3. Cascinu S, Del Ferro E, Ligi M, et al: Inhibition of vascular endothelial growth factor by octreotide in colorectal cancer patients. Cancer Investigation 19:8-12, 2001
4. Danesi R, Benelli U, Del Bianchi S, et al: Octreotide inhibits endothelial cell proliferation and angiogenesis in the chick chorioallantoic membrane and in the rat cornea (Meeting abstract), Proc Annu Meet Am Assoc Cancer Res, 1993, pp A2109
5. Danesi R, Agen C, Benelli U, et al: Inhibition of experimental angiogenesis by the somatostatin analogue octreotide acetate (SMS 201-995). Clinical Cancer Research 3:265-72, 1997
6. Pollak MN, Polychronakos C, Guyda H: Somatostatin analogue SMS 201-995 reduces serum IGF-I levels in patients with neoplasms potentially dependent on IGF-I. Anticancer Research 9:889-91, 1989
7. Reubi JC, Horisberger U, Laissue J: High density of somatostatin receptors in veins surrounding human cancer tissue: role in tumor-host interaction? International Journal of Cancer 56:681-8, 1994
8. Wang C, Tang C: [Inhibition of human gastric cancer metastasis by ocreotide in vitro and in vivo]. Zhonghua Yi Xue Za Zhi 82:19-22, 2002
9. Jia WD, Xu GL, Xu RN, et al: Octreotide acts as an antitumor angiogenesis compound and suppresses tumor growth in nude mice bearing human hepatocellular carcinoma xenografts. Journal of Cancer Research & Clinical Oncology 129:327-34, 2003
10. Koizumi M, Onda M, Tanaka N, et al: Antiangiogenic effect of octreotide inhibits the growth of human rectal neuroendocrine carcinoma. Digestion 65:200-6, 2002
11. Mentlein R, Eichler O, Forstreuter F, et al: Somatostatin inhibits the production of vascular endothelial growth factor in human glioma cells. International Journal of Cancer 92:545-50, 2001
12. Lawnicka H, Stepien H, Wyczolkowska J, et al: Effect of somatostatin and octreotide on proliferation and vascular endothelial growth factor secretion from murine endothelial cell line (HECa10) culture. Biochemical & Biophysical Research Communications 268:567-71, 2000
13. Buscail L, Vernejoul F, Faure P, et al: Controle de la proliferation cellulaire par la somatostatine. Annales d Endocrinologie 63:2S13-8, 2002
14. Adams RL, Adams IP, Lindow SW, et al: Somatostatin receptors 2 and 5 are preferentially expressed in proliferating endothelium. Br J Cancer 92:1493-8, 2005
15. Faiss S, Pape UF, Bohmig M, et al: Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors--the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 21:2689-96, 2003
16. Broder LE, Carter SK: Pancreatic islet cell carcinoma. II. Results of therapy with streptozotocin in 52 patients. Ann Intern Med 79:108-18, 1973
17. Moertel CG, Hanley JA, Johnson LA: Streptozocin alone compared with streptozocin

plus fluorouracil in the treatment of advanced islet-cell carcinoma. New England Journal of Medicine 303:1189-94, 1980
18. Moertel CG, Lavin PT, Hahn RG: Phase II trial of doxorubicin therapy for advanced islet cell carcinoma. Cancer Treatment Reports 66:1567-9, 1982
19. Bukowski RM, McCracken JD, Balcerzak SP, et al: Phase II study of chlorozotocin in islet cell carcinoma. A southwest Oncology Group study. Cancer Chemotherapy & Pharmacology 11:48-50, 1983
20. Moertel CG, Lefkopoulo M, Lipsitz S, et al: Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma.[comment]. New England Journal of Medicine 326:519-23, 1992
21. Ramanathan RK, Cnaan A, Hahn RG, et al: Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282. Annals of Oncology 12:1139-43, 2001
22. FIne R, Fogelman D, Schreibman S: Effective treatment of neuroendocrine tumors with temozolomide and capecitabine. Journal of Clinical Oncology 23:361s, 2005
23. Chernicoff D, Bukowski RM, Groppe CW, Jr., et al: Combination chemotherapy for islet cell carcinoma and metastatic carcinoid tumors with 5-fluorouracil and streptozotocin. Cancer Treatment Reports 63:795-6, 1979
24. Eriksson B, Oberg K: An update of the medical treatment of malignant endocrine pancreatic tumors. Acta Oncologica 32:203-8, 1993
25. Eriksson B, Skogseid B, Lundqvist G, et al: Medical treatment and long-term survival in a prospective study of 84 patients with endocrine pancreatic tumors. Cancer 65:1883-90, 1990
26. Cheng PN, Saltz LB: Failure to confirm major objective antitumor activity for streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. Cancer 86:944-8, 1999
27. McCollum AD, Kulke MH, Ryan DP, et al: Lack of efficacy of streptozocin and doxorubicin in patients with advanced pancreatic endocrine tumors. Am J Clin Oncol 27:485-8, 2004
28. von Schrenck T, Howard JM, Doppman JL, et al: Prospective study of chemotherapy in patients with metastatic gastrinoma. Gastroenterology 94:1326-34, 1988
29. Rivera E, Ajani JA: Doxorubicin, streptozocin, and 5-fluorouracil chemotherapy for patients with metastatic islet-cell carcinoma. American Journal of Clinical Oncology 21:36-8, 1998
30. Kouvaraki MA, Ajani JA, Hoff P, et al: Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 22:4762-71, 2004
31. Konno H, Arai T, Tanaka T, et al: Antitumor effect of a neutralizing antibody to vascular endothelial growth factor on liver metastasis of endocrine neoplasm. Japanese Journal of Cancer Research 89:933-9, 1998
32. Kulke MH, Lenz HJ, Meropol NJ, et al: A phase 2 study to evaluate the efficacy and safety of SU11248 in patients (pts) with unresectable neuroendocrine tumors (NETs). J Clin Oncol 23:310s, 2005

Hurwitz, H., A. Dowlati, S. Savage, *et al*. (2005). Safety, tolerability and pharmacokinetics of oral administration of GW786034 in pts with solid tumors. *Proc Am Soc Clin Oncol.* 23:A3012.

Pazopanib (GW786034) Investigator's Brochure, Version 3 (December 2005). GlaxoSmith Kline, Collegeville, PA.

APPENDIX I

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 II

Drugs Known to be Metabolized by Selected CYP450 Isoenzymes

Selected drugs known to be metabolized by CYP450 isoenzymes

CYP2C8/9

SUBSTRATES		INHIBITORS		INDUCERS	
Generic Name	**Trade Name**	**Generic Name**	**Trade Name**	**Generic Name**	**Trade Name**
Antibiotics: *e.g.*		Antifungals: *e.g.*		Sedatives: *e.g.*	
Rifampin	Rifadin	Fluconazole	Diflucan	Phenobarbiatl	Luminal
Sulfadiazine	--	Ketoconazole	Nizoral	Primidone	Mysoline
		Miconazole	Lotramin		
		Tioconazole	Monistat		
Misc. CV agents: *e.g.*		Antimalarials: *e.g.*		Anticonvulsants: *e.g.*	
Amiodarone	Cordarone	Pyrimethamine	Daraprim	Carbamazapine	Tegretol
Carvedilol	Coreg	Quinine	Legatrin	Phenobarbital	Luminal
				Phenytoin	Dilantin
Anti-asthmatics: *e.g.*		Anti-hyperlipidemics: *e.g.*		Antibiotics: *e.g.*	
Montelukast	Singulair	Fluvastatin	Lescol	Rifapentine	Priftin
Zafirlukast	Accolate	Gemfibrozil	Lopid	Rifampin	Rifadin
Antidepressants: *e.g.*		Antibiotics: *e.g.*			
Fluoxetine	Prozac	Isoniazid	INH, Nydrazid		
Sertraline	Zoloft	Sulfadiazine	--		
		Sulfamethoxazole	Bactrim, Septra		
		Trimethoprim	Primsol		
Anticonvulsants: *e.g.*		Analgesics: *e.g.*			
Fosphenytoin	Cerebyx	Flurbiprofen	Ansaid		
Phenytoin	Dilantin	Ibuprofen	Advil, Motrin		
		Indomethacin	Indocin		
		Mefenamic acid	Ponstel		
Anesthetics: *e.g.*		Anti-ulceratives: *e.g.*			
Ketamine	Ketalar	Omeprazole	Prilosec		
Propofol	Diprivan	Pantoprazole	Pantoloc		
Anti-diabetics: *e.g.*		Antihypertensives: *e.g.*			
Glimepiride	Amaryl	Irbesartan	Avapro		
Rosiglitazone	Avandia	Losartan	Cozaar		
		Nicardipine	Cardene		
Antihypertensives: *e.g.*					
Losartan	Cozaar				
Bosentan	Tracleer				
Paclitaxel	Taxol	Anti-diabetics: *e.g.*			
		Pioglitazone	Actos		
		Rosiglitazone	Avandia		
Alosetron	Lotronex	Amiodarone	Cordarone		
Torsemide	Demadex	Delavirdine	Rescriptor		
		Piroxicam	Feldene		
		Warfarin	Coumadin		
		Zafirlukast	Accolate		

When drugs classified as 'substrates' are co-administered with ***(Study Agent)***, there is the potential for higher concentrations of the 'substrate'. When ***(Study Agent)*** is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of ***(Study Agent)*** is the potential outcome. The coadministration of 'inducers' would potentially lower plasma ***(Study Agent)*** concentrations.

Comprehensive list of drugs that may have potential interactions

CYP2C8/9

Substrates			
Alosetron	Losartan	Rifampin	Tolbutamide
Amiodarone	Mephenytoin	Rosiglitazone	Torsemide
Bosentan	Mestranol	Selegiline	Trimethoprim
Carvedilol	Montelukast	Sertraline	Voriconazole
Fluoxetine	Nateglinide	Sulfadiazine	Warfarin
Fosphenytoin	Paclitaxel	Sulfamethoxazole	Zafirlukast
Glimepiride	Phenytoin	Sulfinpyrazone	Zopiclone
Glipizide	Pioglitazone	Sulfisoxazole	
Ketamine	Propofol	Tamoxifen	

Inhibitors			
Amiodarone	Felodipine	Modafinil	Sertraline
Amitryptiline	Fluconazole	Montelukast	Sildenafil
Amlodipine	Fluoxetine	Nateglinide	Simvastatin
Anastrozole	Fluphenazine	Nelfinavir	Sulconazole
Aprepitant	Flurbiprofen	Nicardipine	Sulfadiazine
Atazanavir	Fluvastatin	Nifedipine	Sulfamethoxazole
Azelastine	Fluvoxamine	Olanzapine	Sulfinpyrazone
Bortezomib	Gemfibrozil	Omeprazole	Sulfisoxazole
Candesartan	Ibuprofen	Ondansetron	Tamoxifen
Chloramphenicol	Imatinib	Orphenadrine	Teniposide
Cholecalciferol (Vitamin D_3)	Indinavir	Pantoprazole	Thioridazine
Cimetidine	Indomethacin	Paroxetine	Ticlopidine
Clopidogrel	Irbesartan	Pentamidine	Tioconazole
Clotrimazole	Isoniazid	Pioglitizone	Tolbutamide
Clozapine	Ketoconazole	Piroxicam	Tolcapone
Cyclosporine	Ketoprofen	Pravastatin	Tranylcypromine
Delavirdine	Lansoprazole	Progesterone	Tretinoin
Dexmedetomidine	Leflunomide	Propafenone	Triazolam
Diclofenac	Losartan	Propofol	Trimethoprim
Diltiazem	Lovastatin	Propoxyphene	Valdecoxib
Dimethyl sulfoxide	Mefenamic acid	Pyrimethamine	Valproic acid
Disulfiram	Meloxicam	Quinidine	Valsartan
Drospirenone	Methimazole	Quinine	Verapamil
Efavirenz	Methoxsalen	Ritonavir	Voriconazole
Entacapone	Metronidazole	Rosiglitazone	Warfarin
Eprosartan	Miconazole	Saquinavir	Zafirlukast
Etoposide	Midazolam	Selegiline	

Inducers			
Carbamazepine	Phenobarbital	Primidone	Rifapentine
Fosphenytoin	Phenytoin	Rifampin	Secobarbital

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.)

Selected Potential Cytochrome P450 (CYP) Drug Interactions

CYP3A4

SUBSTRATES		INHIBITORS		INDUCERS	
Generic Name	**Trade Name**	**Generic Name**	**Trade Name**	**Generic Name**	**Trade Name**
Anti-neoplastics: *e.g.*		Anti-arrhythmics: *e.g.*		Aminoglutethimide	Cytadren
Docetaxel	Taxotere	Amiodarone	Cordarone, Pacerone		
Gefitinib	Iressa	Diltiazem	Cardizem, Dilacor XR		
Irinotecan	Camptosar	Quinidine	Cardioquin		
Anti-virals: *e.g.*		Anti-virals: *e.g.*		Antibiotics: *e.g.*	
Amprenivir	Agenerase	Amprenavir	Agenerase	Rifabutin	Rifadin
Rifampin	Rifadin	Indinavir	Crixivan	Rifampin	Mycobutin
		Nelfinavir	Viracept		
		Ritonavir	Norvir		
Anxiolytics: *e.g.*		Cimetadine	Tagamet	Anticonvulsants: *e.g.*	
Diazepam	Valium			Carbamazapine	Tegretol
Sertraline	Zoloft			Phenytoin	Dilantin
				Pentobarbital	Nembutal
				Phenobarbital	Luminal
Cyclosporine	Sandimmune	Cyclosporine	Sandimmune	*Hypericum perforatum* (2)	St. John's Wort
Anti-infectives: *e.g.*		Antibiotics: *e.g.*			
Erythromycin	Erythrocin	Ciprofloxacin	Cipro, Ciloxan		
Tetracycline	Sumycin	Clarithromycin	Biaxin		
		Doxycycline	Adoxa, Periostat		
		Enoxacin	Penetrex		
		Isoniazid	Nydrazid, INH		
		Telithromycin	Ketek		
Steroids: *e.g.*		Imatinib	Gleevec		
Estrogens, conjugated	Premarin				
Estradiol	Climara				
Progesterone	Crinone				
Haloperidol	Haldol	Haloperidol	Haldol		
Cardiovascular agents: *e.g.*		Diclofenac	Cataflam, Voltaren		
Digitoxin	Crystodigin				
Quinidine	Cardioquin				
Anti-hypertensives: *e.g.*		Vasodilators: *e.g.*			
Nicardipine	Cardene	Nicardipine	Cardene		
Verapamil	Calan, Chronovera	Verapamil	Calan, Chronovera		
Anesthetics: *e.g.*		Anesthetics: *e.g.*			
Ketamine	Xylocaine	Lidocaine	Xylocaine		
Lidocaine	Diprivan	Propofol	Diprivan		
Nefazodone	Serzone	Anti-depressants: *e.g.*			
		Nefazodone	Serzone		
		Sertraline	Zoloft		
Cocaine		Anti-fungals: *e.g.*			
		Itraconazole	Sporanox		
		Ketoconazole	Nizoral		
		Miconazole	Lotrimin, Monistat		
Ketoconazole	Nizoral	Caffeine			
Sildenafil	Viagra	Grapefruit juice (1)			
Albuterol	Ventolin				
Carbamazapine	Tegretol				
Lovastatin	Mevacor				

When drugs classified as 'substrates' are co-administered with ***(Study Agent)***, there is the potential for higher concentrations of the 'substrate'. When ***(Study Agent)*** is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of ***(Study Agent)*** is the potential outcome. The coadministration of 'inducers' would potentially lower plasma ***(Study Agent)*** concentrations.

Comprehensive List of Drugs That May Have Potential Interactions

CYP3A4

Substrates			
Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate	Repaglinide
Amprenavir	Efavirenz	hydrochloride	Rifabutin
Aprepitant	Eletriptan	Levonorgestrel	Rifampin
Aripiprazole	Enalapril	Lidocaine	Ritonavir
Atazanavir	Eplerenone	Losartan	Saquinavir
Atorvastatin	Ergoloid mesylates	Lovastatin	Sertraline
Benzphetamine	Ergonovine	Medroxyprogesterone	Sibutramine
Bisoprolol	Ergotamine	Mefloquine	Sildenafil
Bortezomib	Erythromycin	Mestranol	Simvastatin
Bosentan	Escitalopram	Methadone	Sirolimus
Bromazepam	Estradiol	Methylergonovine	Sufentanil
Bromocriptine	Estrogens, conj., synthetic	Methysergide	Tacrolimus
Buprenorphine	Estrogens, conj., equine	Miconazole	Tamoxifen
Buspirone	Estrogens, conj., esterified	Midazolam	Tamsulosin
Busulfan	Estrone	Miglustat	Telithromycin
Carbamazapine	Estropipate	Mirtazapine	Teniposide
Cerivastatin	Ethinyl estradiol	Modafinil	Terbinafine
Chlordiazepoxide	Ethosuximide	Montelukast	Tetracycline
Chloroquine	Etoposide	Moricizine	Theophylline
Chlorpheniramine	Felbamate	Nateglinide	Tiagabine
Cisapride	Felodipine	Nefazodone	Ticlopidine
Citalopram	Fentanyl	Nelfinavir	Tolterodine
Clarithromycin	Flurazepam	Nevirapine	Toremifene
Clobazam	Flutamide	Nicardipine	Trazodone
Clonazepam	Fosamprenavir	Nifedipine	Triazolam
Clorazepate	Fulvestrant	Nimodipine	Trimethoprim
Cocaine	Gefitinib	Nisoldipine	Trimipramine
Colchicine	Halofantrine	Nitrendipine	Troleandomycin
Cyclophosphamide	Haloperidol	Norethindrone	Vardenafil
Cyclosporine	Ifosfamide	Norgestrel	Venlafaxine
Dantrolene	Imatinib	Ondansetron	Verapamil
Dapsone	Indinavir	Paclitaxel	Vinblastine
Delavirdine	Irinotecan	Pergolide	Vincristine
Diazepam	Isosorbide dinitrate	Phencyclidine	Vinorelbine
Digitoxin	Isosorbide mononitrate	Pimozide	Zolpidem
Dihydroergotamine	Isradipine	Pioglitazone	Zonisamide
Diltiazem	Itraconazole	Primaquine	Zopiclone
Disopyramide	Ketamine	Progesterone	

CYP3A4

Inhibitors			
Acetominophen	Diltiazem	Lovastatin	Progesterone
Acetazolamide	Disulfiram	Mefloquine	Propofol
Amioderone	Docetaxel	Mestranol	Propoxyphene
Amlodipine	Doxorubicin	Methadone	Quinidine
Amprenavir	Doxycycline	Methimazole	Quinine
Anastrozole	Drospirenone	Methoxsalen	Quinupristin
Aprepitant	Efavirenz	Methylprednisolone	Rabeprazole
Atazanavir	Enoxacin	Metronidazole	Risperidone
Atorvastatin	Entacapone	Miconazole	Ritonavir
Azelastine	Ergotamine	Midazolam	Saquinavir
Azithromycin	Erythromycin	Mifepristone	Selegiline
Betamethasone	Ethinyl estradiol	Mirtazapine	Sertraline
Bortezomib	Etoposide	Mitoxantrone	Sildenafil
Bromocriptine	Felodipine	Modafinil	Sirolimus
Caffiene	Fentanyl	Nefazodone	Sulconazole
Cerivastatin	Fluconazole	Nelfinavir	Tacrolimus
Chloramphenicol	Fluoxetine	Nevirapine	Tamoxifen
Chlorzoxazone	Fluvastatin	Nicardipine	Telithromycin
Cimetadine	Fluvoxamine	Nifedipine	Teniposide
Ciprofloxacin	Fosamprenavir	Nisoldipine	Testosterone
Cisapride	Glyburide	Nitrendipine	Tetracycline
Clarithromycin	Grapefruit juice	Nizatidine	Ticlopidine
Clemastine	Haloperidol	Norfloxacin	Tranylcypromine
Clofazimine	Hydralazine	Olanzapine	Trazodone
Clotrimazole	Ifosfamide	Omeprazole	Troleandomycin
Clozapine	Imatinib	Orphenadrine	Valproic acid
Cocaine	Indinavir	Oxybutynin	Venlafaxine
Cyclophosphamide	Irbesartan	Paroxetine	Verapimil
Cyclosporine	Isoniazid	Pentamidine	Vinblastine
Danazol	Isradapine	Pergolide	Vincristine
Delavirdine	Itraconazole	Phencyclidine	Vinorelbine
Desipramine	Ketoconazole	Pilocarpine	Zafirlukast
Dexmedetomidine	Lansoprazole	Pimozide	Ziprasidone
Diazepam	Lidocaine	Pravastatin	
Diclofenac	Lomustine	Prednisolone	
Dihydroergotamine	Losartan	Primaquine	

Inducers			
Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazapine	Oxcarbazepine	Primidone	
Fosphenytoin	Pentobarbital	Rifabutin	
St. John's wort	Phenobarbital	Rifampin	

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.)

(1) Malhorta *et al*. (2000). Clin Pharmacol Ther. 69:14-23

(2) Mathijssen *et al*. (2002). J Natl Cancer Inst. 94:1247-1249
Frye *et al*. (2004). Clin Pharmacol Ther. 76:323-329

APPENDIX III

New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

APPENDIX IV

Patient's Medication Diary

Patient Name_____**ID#** _____**Today's date** _____**Agent GW786034**

PATIENT MEDICATION DIARY

Instruction to the Patient:

1. Complete one form for each month.
2. Take your dose of GW786034 (pazopanib) each day in the morning either 1 hour before or 2 hours after you eat with about 1cup (240 mL) of water. You will take _____**200** mg tablets and _____ **400** mg tablets every day. You should swallow the tablets whole. **Do not chew, crush, or break the tablets.**
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return the forms to your physician when you go for your next appointment.

Day	Date	Time dose taken	Number of tablets taken		Comments
			200 mg	400 mg	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					
29					
30					
31					

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of pills taken this month (each size)_____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature:_____

APPENDIX V

Patient's Blood Pressure Diary

CTEP-assigned Protocol # 7650

PATIENT'S BLOOD PRESSURE DIARY

Today's date _____

Patient Name_____ Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, 110/85).
2. Record the date, then record your blood pressure twice each day using a home blood pressure monitor:
   - each morning while you are resting or reading (not while you are active: dressing, making breakfast, etc.)
   - each evening at bedtime or while you are relaxing during the evening
3. If you take your blood pressure at other times of the day, please record the numbers and time under "Other readings".
4. Normal blood pressure is usually considered to be 120/80 mmHg. If your systolic pressure is greater than 150 or your diastolic blood pressure is greater than 90 when you measure your blood pressure two times at least 1 to 4 hours apart on the same day, please contact your doctor's office at _____ for instructions.
5. You should seek medical advice if your BP exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and should also contact your physician if you are concerned about any symptoms that may be associated with high BP (*e.g.*, headache).
6. Please bring this form to every clinic visit or appointment.

Date	AM readings	PM readings	Other readings (include time of day)	Date	AM readings	PM readings	Other readings (include time of day)
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

_____ _____

Date of this clinic visit Physician/Nurse/Data Manager's Signature

APPENDIX VI

Blood Pressure – Recommendations

for Data Collection/Recording and Event Management

Collection/Recording of Blood Pressure Information

1.0 General Guidelines

1.1 Frequency of monitoring. Blood pressure (BP) should be monitored at least every 2 weeks (patient monitoring is acceptable) for the duration of treatment. More frequent monitoring should be considered on a patient-by-patient basis, particularly during the first two cycles of GW786034 (pazopanib) therapy.

1.2 Data recording. All required data should be recorded in the appropriate CRF or on the patient's blood pressure monitoring diary, as appropriate. **The following data are required at baseline and at each subsequent assessment**:

- Assessment date and time
- Pulse
- Systolic and diastolic BP (2 readings/assessment taken 5 minutes apart while patient sitting)

1.3 Risk factors for hypertension (assess and record data in baseline history/physical CRF)

- Diabetes (type 1 or type 2)
- Renal disease (specify on CRF)
- Endocrine condition associated with HTN (specify on CRF)
- Use of steroids or NSAIDs (specify all concomitant meds)
- Underlying cardiovascular condition – specify (*i.e.*, ischemic heart disease)

2.0 Baseline data collection (at study entry)

2.1 All patients

- Current BP
- Proteinuria, if present

2.2 Patients with preexisting hypertension (*i.e.*, those for whom "hypertension" is entered as a concomitant condition at study entry, or those who are currently receiving therapy with antihypertensive medication) – also record:

- Date of HTN diagnosis (original)
- Type HTN (essential or secondary)
- CTCAE v3.0 grade of HTN (at time of study entry)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of the following:
  - Antihypertensive agents taken at study entry
  - Antihypertensive agents taken in past (e.g., discontinued for toxicity, lack of efficacy)

3.0 Follow up BP data collection (during study)

3.1 All patients (at each clinic visit)

- Current BP
- Proteinuria, if present

3.2 Patients with treatment-emergent hypertension [defined as BP increase of >20 mmHg (diastolic) OR BP >150/100 (if previously within normal limits)] – record at time of hypertension diagnosis and at all subsequent clinic visits:

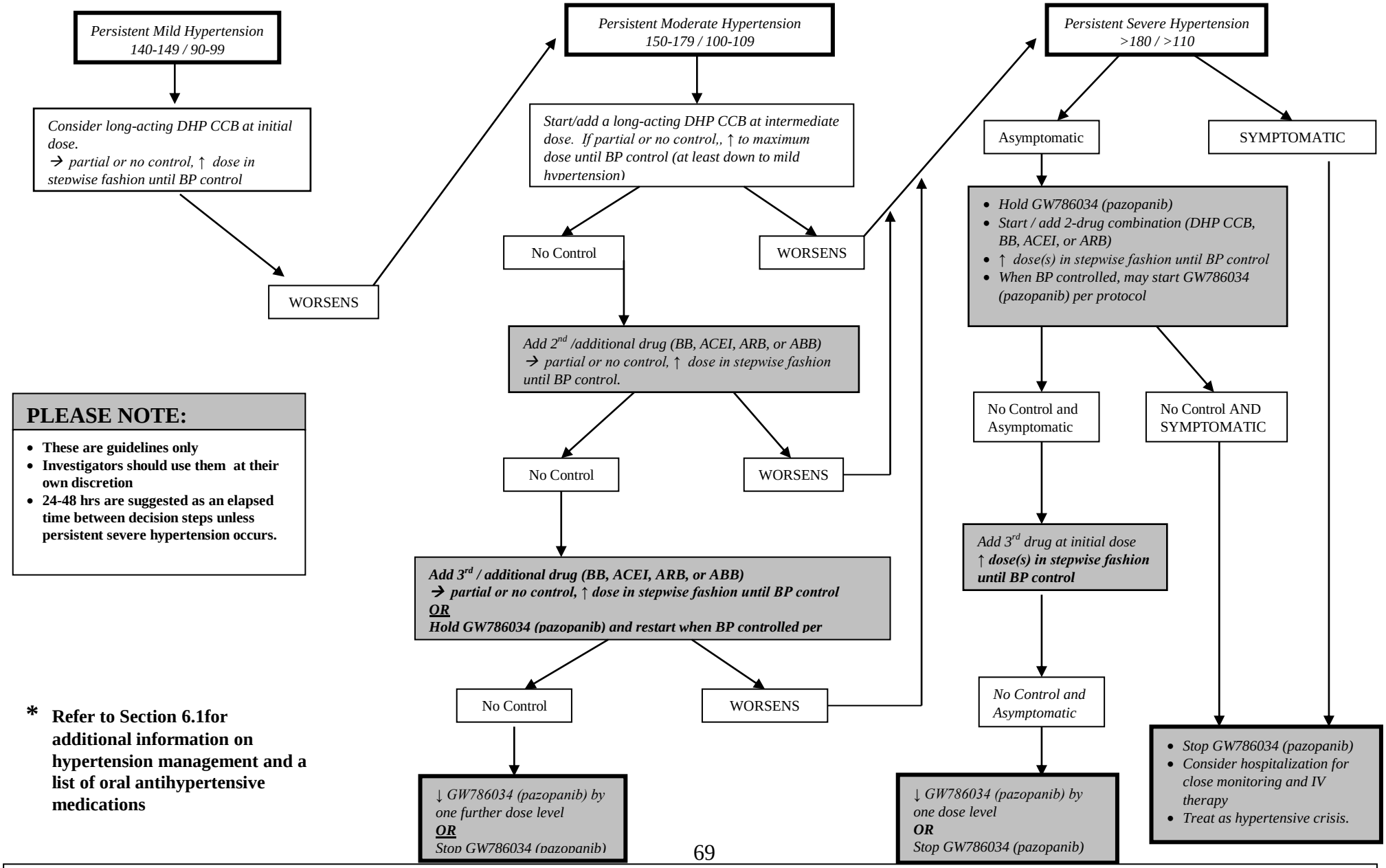
- BP changes from baseline (or from previous assessment) (specify CTCAE v3.0 grade changes)
- Hypertension-related symptoms as reported by patient (*e.g.*, headache)
- Other relevant changes associated with development of hypertension (*e.g.*, ECG abnormalities)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of currently prescribed antihypertensive agents

3.3 Patients with preexisting hypertension at study entry – record at each clinic visit

- BP changes from previous clinic visit (specify CTCAE v3.0 grade changes)
- Hypertension-related symptoms reported by patient (*e.g.*, headache)
- Other relevant changes associated with development of hypertension (*e.g.*, ECG abnormalities)
- Changes in antihypertensive medications since last assessment (*e.g.*, dose change, add/discontinue drug)

Classes of antihypertensive drugs include ACE inhibitors, calcium channel blockers, alpha blockers, beta blockers, diuretics, angiotension II receptor antagonists.

Management of GW786034 (Pazopanib)-Induced Hypertension*



* **Refer to Section 6.1for additional information on hypertension management and a list of oral antihypertensive medications**

DHP CCB (Dihydropyridine Calcium-Channel Blockers); BB (selective Beta blockers); ACEIs (Angiotensin Converting Enzyme Inhibitors); ARBs (Angiotensin II Receptor Blockers); ABB (alpha and beta blocker)

APPENDIX VII

Pharmacokinetic (PK) Procedures

Each whole blood pharmacokinetic sample should be collected as close as possible to the planned time relative to dosing. Blood sampling for clinical pharmacokinetics analysis will be performed as follows:

Cycle 1- Days 1, and 28: Pre-dose
Cycle 3 and every third cycle thereafter - Day 28: Pre-dose

Plasma will be isolated from patients' blood specimens drawn at these time points and determination of GW7856034. The actual time of each blood sample will be recorded on the case report form.

The 2-ml blood samples will be collected into a tube containing EDTA as the anticoagulant, centrifuged to produce plasma, frozen and maintained in a freezer at -20°C until being shipped to the laboratory for analysis by a validated LC/MS method. All samples must be shipped with adequate amounts of dry ice. Further details of the sample handling, labeling, and shipping directions will be provided in the Study Reference Manual.

APPENDIX VIII

CTEP MULTICENTER GUIDELINES

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

Responsibility of the Protocol Chair

- 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.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. 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.