Phase 2 Consortium
Mayo – Wisconsin – Johns Hopkins
Wash U – CTRG – Metro MN
P2C
Colorado – Iowa – Miami

MC057H – A Phase II Trial of GW786034 in Advanced Thyroid Cancer

P2C Addendum 25 –

CTEP Request for Protocol Amendment dated February 14, 2018:

#	Section	Comments
1.	8.1	**Novartis supplies and the PMB, DCTD, NCI distributes commercially-labeled 200 mg pazopanib tablets (as free base). Gray, film-coated tablets are debossed with "GS JT" on one side and packaged in bottles of 120 tablets.** **Tablet excipients include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, iron oxide black, macrogol/polyethylene glycol 400 and polysorbate 80.** ~~Novartis supplies and the PMB, DCTD, NCI distributes pazopanib as aqueous, film-coated tablets according to the descriptions and availability below.~~

~~Streng~~	~~Description~~	~~Bottle~~	~~Availability~~
~~200 mg~~	~~Oval-shaped, white tablets packaged in investigationally-labeled HDPE induction-sealed bottles with white,~~	~~34~~	~~Transitioning to commercially-labeled supplies around March~~
~~200 mg~~	~~Gray, tablets are debossed with "GS JT" on one side and packaged in commercially-labeled bottles~~	~~120~~	~~Transitioning from investigationally-labeled supplies~~

#	Section	Comments
		~~400 mg~~ ~~Oval-shaped, white tablets packaged in investigationally-labeled HDPE induction-sealed bottles with white,~~ ~~68~~ ~~Not available after March 31, 2018 or when existing supplies are~~ ~~Tablet excipients in all tablet sizes include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, macrogol/polyethylene glycol 400 and polysorbate 80. In addition, the film-coat for commercially-labeled 200 mg tablets contains iron oxide black.~~

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A Phase II Study of GW 786034 (Pazopanib) in Advanced Thyroid Cancer

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DCTD Supplied Investigational Agent(s):
GW786034 (pazopanib; NSC 737754)

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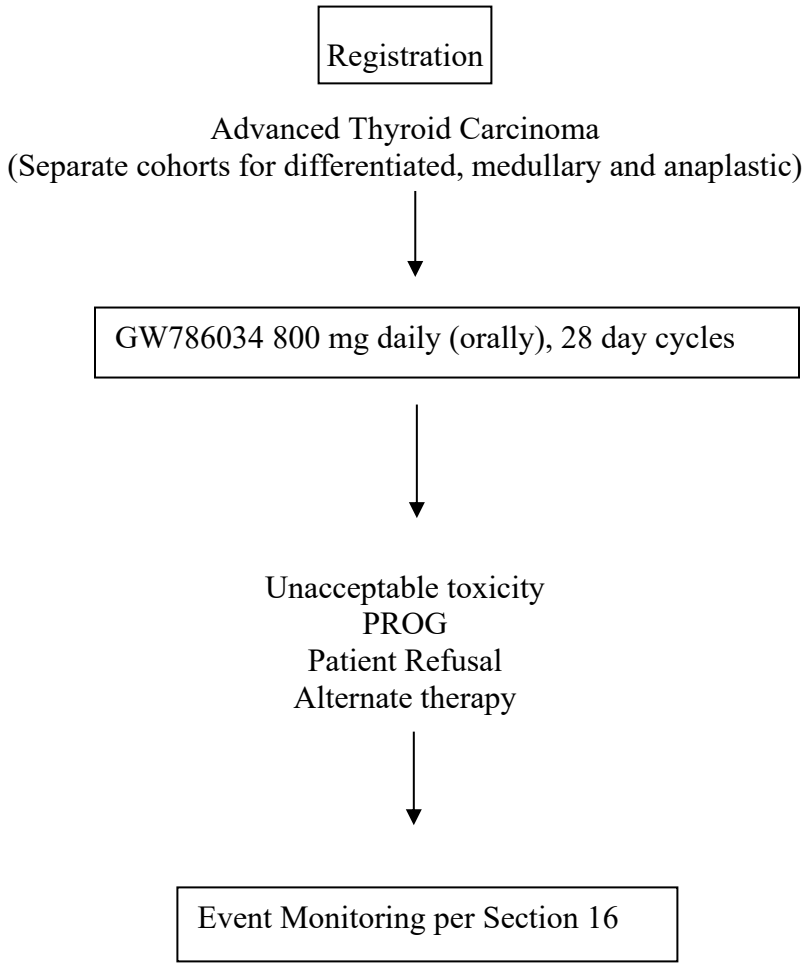

Drug Names/Abbreviations
P2C Name: GW786034
Generic Name: Pazopanib
Mayo Abbreviation: 786034

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1. OBJECTIVES

1.1 Primary Objectives

1.11 The primary objectives of this trial are to establish the safety and efficacy of GW786034 (pazopanib) as a therapeutic in patients afflicted with differentiated, medullary and anaplastic thyroid cancers. Efficacy will be assessed via the primary endpoint of the proportion of patients who incur clinical responses based upon RECIST criteria, and the secondary endpoint of progression free survival (proportion of patients without progression at 6 months for differentiated and medullary, 3 months for anaplastic). Tertiary clinical endpoints include time to treatment failure, overall survival, duration of response, time to subsequent therapy, and biomarker-based measures of response and time to progression.

1.2 Correlative Objectives

1.21 Correlative objectives of the trial include assessment of the impact of therapy with GW786034 on serum/plasma VEGF levels.

1.22 To explore the potential relationship between changes in thyroglobulin levels and tumor response in patients with advanced differentiated thyroid cancer known to be thyroglobulin antibody negative.

2. BACKGROUND

2.1 Thyroid Cancer

Differentiated thyroid carcinoma is the most common endocrine malignancy, with an estimated 25,000 new cases annually, accounting for approximately 1500 deaths each year in the United States (Jemal, Murray et al. 2005) The disease is classified histologically into 5 major groups: Papillary (PTC - representing 80 – 85% of all differentiated thyroid cancer); Follicular (FTC - 5 – 10%) and its Hurthle Cell variant (HCC - 3 – 5%); Medullary carcinoma (MTC - ~5%); and Anaplastic carcinoma (ATC - ~1%) (Hay, Bergstralh et al. 1993).

Papillary, Follicular and Hurthle cell carcinoma.
These three major groups of tumors arise from the thyroid follicular cell, and typically retain some differentiated cell functions, including production of thyroglobulin and some capacity for iodine concentration (Kinder 2003). Amongst older patients and those with more advanced disease at diagnosis, the capacity for iodine concentration is less pronounced and may be absent, which has important implications for treatment, as discussed below (Fernandes, Day et al. 2005). Continued production of thyroglobulin provides a clinically useful marker for disease recurrence, correlating with disease burden, within an individual (Hay, Thompson et al. 2002).

Overall survival for these cancer types is good, with a combined 5-year survival of ~95% at 1 year and 85% at 5 years (Tseng, Lee et al. 1996). However, non-papillary histotypes carry a less favorable prognosis that PTC. Moreover, advanced stage of disease also impacts on survival, with overall 5-year mortality for metastatic FTC and HCC about 50% (Chow, Law et al. 2003). Even amongst PTC patients, 10 year mortality is ~20% in stage III (node positive disease in patients over 45 years), and 5-year mortality approaches 80% in stage IV disease (Hay, Thompson et al. 2002).

Treatment of differentiated thyroid carcinoma of all types relies on surgical resection of the disease along with the normal thyroid gland and any involved cervical lymph nodes, followed by radioactive iodine therapy, administered both to eliminate the normal thyroid remnant and in an effort to eradicate residual or metastatic disease (D'Avanzo, Ituarte et al. 2004). Postoperative suppression of thyrotropin (TSH) may also decrease the risk for recurrence and cause-specific mortality in high-risk patients (Cooper, Specker et al. 1998).

Radioactive iodine is an effective treatment for metastatic thyroid cancer, particularly amongst young patients, in whom control or effective cure, particularly of pulmonary metastases, can sometimes be achieved (Brink, van Heerden et al. 2000). However, not all thyroid cancers concentrate iodine, making this group of tumors unresponsive to radioactive iodine treatment, while some tumors lose iodine avidity over time to become iodine-refractory (Caplan, Wickus et al. 2005). This problem of radioiodine refractory disease affects an estimated 20% of PTC amongst young patients (<45 years), but as many as 70 – 80% of FTC, HCC and PTC amongst older patients. For patients experiencing locally recurrent disease in the neck, following primary surgery and radioactive iodine treatment, external beam irradiation may provide effective control of the disease when further surgical exploration is not a suitable option (Kim, Yang et al. 2003).

Currently, no effective systemic treatment options are available for radioiodine refractory metastatic disease. Palliative intervention may be used to treat symptomatic or pre-symptomatic metastases, including surgical resection and external beam irradiation. Response rates of 10 – 20% have been reported in small series of chemotherapy trials, using doxorubicin and/or cisplatin (Gimm 2001), but no responses were seen in a trial of etoposide treatment in differentiated thyroid cancer of all types (Leaf, Wolf et al. 2000). Occasional patients may exhibit some inhibition of tumor growth in response to octreotide, though this may be restricted to the minority of patients with octreotide-avid disease, and the impact on tumor spread and on survival is, at best, marginal (Alhamarneh, Murphy et al. 2004). Consequently, there is no standard single-agent or combined-agent therapy in routine clinical use at the current time.

In contrast to the lack of effective systemic therapies for differentiated thyroid carcinoma, our understanding of their molecular and genetic underpinnings has

progressed dramatically in the last decade. Identification of activating mutations of ras and B-Raf, and activating rearrangements of the RET proto-oncogene, implicate the ras/raf/MAP-kinase pathway in the pathogenesis of PTC (Salvatore, Giannini et al. 2004). Animal models have confirmed the oncogenic potential of at least some of these identified mutations (Capen and Sagartz 1998). There is also a recognized role in PTC and FTC/HCC of the receptor protein-kinase systems (PKA and PKC) (Fagin 2004), while between 30% and 50% of FTC express an oncoprotein that inhibits PPAR pathways, which has been implicated in oncogenesis (Sahin, Allard et al. 2005). A number of growth factor receptors, including EGF-R, IGF-α, and IGF-1 are also expressed in thyroid cancers (Duh and Grossman 1995), which also exhibit increased telomerase activity, and hTERT gene expression (Zeiger, Smallridge et al. 1999).

Development of novel targeted drugs affecting each of these pathways offers promise of new therapies for patients with advanced thyroid carcinoma, which is currently otherwise untreatable.

Medullary Thyroid Cancer (MTC)
MTC arises from the C-cells of the thyroid gland, of neural crest lineage (Clayman and el-Baradie 2003). These tumors retain the capacity to secrete calcitonin, providing a reliable marker for disease recurrence, progression and response to treatment. MTC occurs either sporadically (~80%) or as one manifestation of a familial cancer predisposition syndrome (~20%). In familial MTC (FMTC) the only phenotype is MTC arising typically in early to mid-adult life (Quayle and Moley 2005). Presentation of MTC typically occurs earlier, and may be more aggressive, in the multiple endocrine neoplasia (MEN) syndromes. In MEN type 2A, MTC is accompanied by a high incidence of pheochromocytoma and hyperparathyroidism, while MEN-2B is associated also with developmental anomalies and multiple benign neurofibromata (Quayle and Moley 2005). The penetrance of MTC in each of these familial syndromes approaches 100% and presentation is earlier and more aggressive in MEN2B than MEN2A, with nodal and distant metastatic spread being the rule, unless these patients are detected by genetic screening.

Treatment of MTC consists of surgical resection of the disease and the disease-bearing thyroid gland, with cervical lymph node dissection. However, nodal metastatic spread affects up to 60% of cases, and the majority of these cases suffer either residual or recurrent disease, which may require further surgical debulking (Cohen and Moley 2003).

Because MTC arises from the C-cell lineage, these tumors do not express the sodium-iodide transporter and do not exhibit iodine-concentrating activity. Consequently, radioactive iodine is not effective in treating this disease. Similarly, the response of MTC to radiation therapy has proven disappointing, though it may prove useful to palliate symptomatic metastases.

Metastatic MTC may cause symptoms directly, by local compression and invasion, or indirectly through the secretion of calcitonin and other neuroactive substances, which cause flushing, diarrhea, anorexia and malaise. Some useful control of these symptoms can be achieved by use of octreotide, which may also slow the growth, at least of octreotide-avid disease. Octreotide is the only accepted standard treatment for metastatic MTC, but its impact on survival is marginal and unproven (Traugott and Moley 2005). Chemotherapeutic combinations have had only limited success in a small number of case reports and consequently, there is no currently accepted systemic therapy for metastatic MTC.

Activating mutations of the RET proto-oncogene, a receptor tyrosine kinase involved in signaling for cell growth and differentiation, are responsible for the familial MTC syndromes, and are also detectable in 50 – 80% of sporadic MTC (Jindrichova, Kodet et al. 2003). Novel agents directed at this and other intracellular signaling cascades offer hope for modulation of this disease.

Anaplastic Thyroid Cancer (ATC)
ATC is a highly aggressive and rapidly progressive form of thyroid cancer, accounting for half of all thyroid cancer deaths despite comprising only 2% of all thyroid cancers (Jemal, Murray et al. 2005). Mortality from ATC exceeds 90% at 1 year, and approaches 95% at 5 years, with a median life expectancy from the time of diagnosis of ~3 months (McIver, Hay et al. 2001).

Although ATC may arise spontaneously in some cases, a majority of cases exhibit co-existing differentiated thyroid cancer, suggesting that ATC may reflect "de-differentiation" of a pre-existing differentiated thyroid cancer (McIver, Hay et al. 2001). Mutations of the p53 tumor suppressor gene may play a role in the aggressive phenotype and chemoresistance of this tumor (Quiros, Ding et al. 2005).

Initial treatment for localized ATC includes primary surgery and lymph node dissection, with consideration given to adjuvant radiotherapy and/or chemotherapy due to its highly aggressive nature. Often, however, the disease presents at a locally advanced stage, precluding surgical resection and requiring radiotherapy, with palliative tracheostomy and gastrostomy tube placement, because of rapidly progressive disease in the neck. Metastatic disease is present at the time of diagnosis in over 50% of all patients and becomes evident in the majority of the remaining patients rapidly thereafter (McIver, Hay et al. 2001).

Palliative therapies in use for advanced or metastatic disease include single agent doxorubicin or paclitaxel, with transient responses to paclitaxel observed in up to 50% of treated patients (Ain, Egorin et al. 2000). However, there is no evidence that such treatment alters the outcome of this near-universally fatal disease (McIver, Hay et al. 2001), for which no effective therapy is currently available.

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 whom 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 which 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 Background and Rationale

TUMOR ANGIOGENESIS

Tumor angiogenesis is the result of a complex sequence of events triggered by several seminal upstream mediators. Activation occurs via vascular endothelial growth factors (VEGFs), fibroblast growth factors (FGFs), and TGFα and –ß-- while inhibition is mediated via thrombospondins, angiostatins, endostatins, and others. The VEGF gene family appears to play a fundamental role in neoangiogenesis (Leung 1989) by inducing proliferation of endothelial cells, stimulating angiogenesis, and increasing vascular permeability. The expression of VEGF is controlled by differentiation, transformation, and oxygen supply.

ANGIOGENESIS IN THYROID CANCER

In the thyroid gland, neoangiogenesis occurs in hyperplastic goiters, Graves disease, thyroiditis, and cancer. Further, Bunone *et al.* (Bunone 1999) reported overexpression of VEGF in thyroid cancers, compared with normal tissue. The authors suggested that factors inducing neoangiogenesis are involved in the neoplastic growth and aggressiveness of thyroid cancers-- and that VEGF might be an initial angiogenic signal, inducing tumor growth and local invasiveness. Recently, it was shown that the intensity of VEGF expression is associated with an increased risk of recurrence and decreased disease-free survival in papillary thyroid carcinomas (Lennard 2001). Mounting evidence demonstrates that VEGF plays a role in thyroid cancer proliferation, as demonstrated by 1) increasing VEGF levels in differentiated thyroid cancer in comparison to control benign thyroid tissue, and 2) the fact that increased VEGF levels in sera/plasma from thyroid cancer patients is a negative prognostic indicator associated with increased risk of distant metastases and disease recurrence (Lin 2003). Furthermore, increased VEGF immunohistochemical staining in tumor specimens is similarly associated with worse patient outcome (Klein 2001; Lennard 2001; Kilicarslan 2003), and interventions targeting VEGF attenuate tumor growth in xenograft models of both differentiated (Soh 2000; Bauer 2003) and anaplastic thyroid cancers (Bauer 2002; Schiff 2004). Collectively, available data therefore implicate VEGF as a potentially important therapeutic molecular target in thyroid cancer.

<u>GW786034 (Pazopanib)</u>

GW786034 (pazopanib) is a novel, orally active small molecule targeting multiple tyrosine kinases including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-alpha and –beta, and c-kit. An antitumor effect due to inhibiting of the VEGF driven angiogenic pathway is well established (package insert). In addition to its effects on VEGF receptors, GW786034 targets additional tyrosine kinases, including PDGF receptors and c-kit that also have established roles in tumorigenesis and oncogenic mutations (Shibuya 1990). Preliminary data from a phase I study of GW786034 in patients with solid tumors demonstrated early evidence of antitumor activity (Terman 1992). Among 43 patients enrolled, a minimal response occurred in 4 patients and stable disease > 6 months was observed in an additional 6 patients. GW786034 was well tolerated at doses up to 2000 mg daily.

DIFFERENTIATION STATUS AND RESPONSE TO RADIOACTIVE IODINE
Differentiated thyroid carcinomas of the follicular and papillary type have an overall excellent prognosis because of their high grade of differentiation and the effective use of therapeutic radioiodine. However, there is a small but significant fraction of patients who ultimately develop radioiodine-resistant cancer and die of their disease. The reason for this appears to be at least partially attributable to progressive dedifferentiation with loss of tumor expression of sodium-iodine symporters. Effective therapeutic options for such patients are presently unavailable. Therefore, new approaches to the treatment of poorly or dedifferentiated thyroid tumors and tumors without iodine uptake are necessary. Various agents including retinoids, inhibitors of histone deacetylation and anti-retrovirals have been tested with promising preclinical effects (Landriscina 2005). However, despite their activity *in vitro*, retinoids, the most study agents in this group, did not show sufficient clinical activity in human trials (Cohelo 2005).

TYROSINE KINASE INHIBITORS IN THYROID CANCER
In xenograft models of several human carcinomas (pancreas, renal cell and colon cancer), VEGF receptor blockade with the tyrosine kinase inhibitor PTK/ZK induced significant inhibition of tumor growth (Drebs 2202; Baker 2002; Ellis 2000; Wood 2000). Similarly, blockade of VEGF receptors by PTK/ZK inhibited growth of xenografts from human thyroid tumor cells of the ML-1 cell line implanted into nude mice, with mean xenograft tumor volume significantly reduced in PTK/ZK-treated mice, compared to control animals.

Based upon these data, we hypothesized that blockade of VEGF function may be a promising target for the treatment of poorly or dedifferentiated thyroid carcinomas. We also hypothesized that protein kinase inhibitor-mediated blockade of the VEGF/VEGF receptor system may result in re-differentiation of thyroid tissue, with re-expression of the NIS gene resulting in induction of iodine uptake ability in the tumor cells-- hopefully thereby leading to restored sensitivity to therapeutic radioiodine.

Hypothesis 1:*GW786034 treatment of patients with thyroid cancers will lead to attenuated tumor growth or tumor regression, as well as to stabilization or reductions in patient tumor markers (e.g. thyroglobulin, calcitonin).* Tumor burden will be serially assessed via patient-appropriate imaging, and relevant tumor markers will be serially evaluated in plasma, to assess the effects of GW786034 on tumor extent and growth rate. In particular, tumor extent will be formally evaluated using standard response criteria (RECIST) and changes in tumor status on treatment will be compared to tumor measurements prior to study entry to capture not only GW786034-induced tumor regression, but also GW786034-induced disease stability. This will be accomplished by requiring that all enrolled patients have evidence of tumor progression in the 6 month period prior to GW786034 initiation, making it possible to compare tumor growth pre- and on-study. Similarly, rates of change of relevant tumor markers (e.g. thyroglobulin, calcitonin, CEA) of patients will be evaluated pre- and on-study to determine whether GW786034 therapy may lead to either reductions, or stabilizations, of these markers. This will be critical, because substantial data suggest that VEGF-targeted agents will likely lead more to disease stabilization than regression.

Hypothesis 2: GW786034 will affect decreased levels of angiogenic markers (over time and in response to treatment), consequently impacting downstream targets of the pathway. Levels of free VEGF and PDGF will be explored in a graphical manner in pre-treatment and multiple on-treatment samples. Results of these assays of circulating VEGF and PDGF, will be used to identify candidate markers of response to pazopanib.

Hypothesis 3: GW786034-induced changes in thyroglobulin levels in patients with advanced differentiated thyroid cancers who are thyroglobulin antibody negative will be predictive of patient objective response and disease progression.

Rationale: Anecdotal experience of investigators enrolling patients on the initial cohort of differentiated thyroid cancer patients on MC057H suggested that induced changes in thyroglobulin seen in thyroglobulin antibody negative patients might be predictive of patient response. Formal retrospective analysis indeed demonstrated that the proportion of patients with at least a 50% decrease in Tg values from pre-treatment levels was 0.50 among the 12 patients with stable or progressive disease and 0.80 among the 6 patients with a PR, suggesting that such an association may exist. We therefore now propose to more rigorously and prospectively examine this association in an expanded DTC patient cohort. This analysis will be important in the design of future pazopanib clinical trials in differentiated thyroid cancer, given its apparent promising clinical activity in DTC, so as to allow optimal use of tumor markers and imaging in the evaluation of further patients receiving the agent.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.11 Histologically or cytologically confirmed differentiated, medullary or anaplastic thyroid cancer that is now advanced or metastatic. NOTE: *Patients with thyroid lymphomas or sarcomas are specifically excluded, as are patients with metastatic disease from other sites of origin to thyroid.*

3.111 As of P2C Addendum 6, patients with confirmed differentiated thyroid cancer to be enrolled in the expanded/additional DTC cohort must be thyroglobulin antibody negative.

3.11a Zero, one or two prior therapeutic regimens (this includes cytotoxic plus non-cytotoxic therapeutic regimens).

3.12 Absence of sensitivity to therapeutic radioiodine (differentiated only).

3.13 Measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with spiral CT scan. See section 11.2 for the evaluation of measurable disease. NOTE: Disease that is measurable by physical examination only is not eligible.

3.14 Age >18 years. NOTE: GW786034 (pazopanib) is contraindicated in the pediatric population due to the potential effect on the epiphyseal growth plates.

3.15 Life expectancy >3 months.

3.16 ECOG performance status (PS) 0, 1 or 2 (Karnofsky ≥60%; see Appendix A).

3.17 Normal/acceptable organ and marrow function as defined below and obtained ≤ 7 days prior to registration:

- Leukocytes > 3,000/mcL
- Absolute neutrophil count > 1,500/mcL
- Platelets >1 00,000/mcL

- Total bilirubin ≤ 1.5 X institutional upper limit of normal (ULN)
  (If there is reason to believe that the patient has Gilbert's Syndrome, the bilirubin can be fractionated. If the fractionated bilirubin is consistent with Gilbert's Syndrome and there is no other possible explanation for the elevated indirect bilirubin, the patient may be eligible for the study if and only if the direct bilirubin is ≤ 1.5 X institutional ULN)

- AST(SGOT) < 2 .5 X institutional ULN
- Creatinine ≤ 1.5 X ULN
- Proteinuria ≤ + on urinalysis (may re-check per exclusion criteria 3.25)
- INR ≤ 1.2 X the ULN

3.18 Blood pressure (BP) <140 mmHg (systolic) and <90 mmHg (diastolic). Initiation or adjustment of BP medication is permitted prior to registration provided that the average of three BP readings at a visit prior to registration is <140/90 mmHg.

3.19a Objective evidence of tumor progression in the 6 month period prior to GW786034 initiation as assessed by unequivocal progression of objectively measured disease on successive appropriate imaging (e.g. CT scan). In cases of uncertainty of tumor progression, the Principal Investigator of the study will be available to assist in decisions.

3.19b Women of child-bearing potential must have a negative serum pregnancy test ≤7 days prior to registration. NOTE: 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 (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician *immediately. Effective contraception is required for all fertile participants in the trial.*

3.19c Ability to understand and the willingness to sign a written informed consent document.

3.19d Willingness to comply with the requirement of the study.

3.19e Willingness to donate blood for correlative marker studies. (Only applicable to sites within the United States)

3.2 Exclusion Criteria

3.21 Anaplastic, Differentiated, Medullary: a total of > 2 prior therapeutic regimens (this total includes cytotoxic plus non-cytotoxic regimens). Note: Enrollment of anaplastic, differentiated, and medullary patients who have had zero, one or two prior therapeutic regimens (cytotoxic plus non-

cytotoxic regimens) is allowed - provided therapy ceased > 21 days prior to registration.

NOTE: The Principal Investigator of the study should be contacted in the event of uncertainty related patient eligibility based upon prior therapies.

3.21b Disease that is measurable by physical examination only.

3.22 Any of the following:

- Radiotherapy ≤ 4 weeks prior to registration.
- Major surgery ≤4 weeks prior to registration
- Radiotherapy to ≥25% of bone marrow
- Concurrent therapy with octreotide unless tumor progression on this therapy has been demonstrated.

3.23 Any other ongoing investigational agents.

3.24 History of allergic reactions attributed to compounds of similar chemical or biologic composition to GW786034 (pazopanib) or other agents used in the study.

3.25 > +1 proteinuria (<30 mg/dL) on two consecutive dipstick or other urine assessments taken at least 1 week apart. NOTE: (In cases where questions arise related to disparate proteinuria measurements, the study PI should be consulted for assistance in determining patient study eligibility.)

3.26 QTc prolongation (defined as a QTc interval ≥480 msecs) or other significant ECG abnormalities (e.g. frequent ventricular ectopy, evidence of ongoing myocardial ischemia). NOTE: The Principal Investigator of the study should be contacted in the event of uncertainty related patient eligibility based upon ECG changes.

3.27 Receiving CYP interactive concomitant medications.
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 B.

3.28 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 GSK786034 (pazopanib).

3.29a Any of the following conditions:

- Serious or non-healing wound, ulcer, or bone fracture
- History of abdominal fistula, gastrointestinal perforation, active diverticulitis, intra-abdominal abscess or gastrointestinal tract bleeding ≤ 28 days of registration
- Any history of cerebrovascular accident (CVA) ≤6 months
- Current use of therapeutic warfarin. Note: Low molecular weight heparin and prophylactic low-dose warfarin (INR<1.2 X ULN) are permitted. PT/PTT must meet the inclusion criteria (Section 3.17)
- 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 C). NOTE: A patient who has a history of Class II heart failure and is asymptomatic on treatment may be considered eligible
- History of bleeding disorder, including patients afflicted with hemophilia, disseminated intravascular coagulation, or any other abnormality of coagulation potentially predisposing patients to bleeding
- Poorly controlled depression or anxiety disorder, or recent (≤6 months) suicidal ideation

3.29b Known active and/or untreated brain metastases and/or brain metastases requiring ongoing therapy (e.g. corticosteroids). NOTE: (Because of the poor prognosis often associated with brain metastases and because of the potential risk of bleeding in active brain metastases associated with multi-targeted tyrosine kinase inhibitor therapy, patients with active and/or untreated brain metastases and/or those with brain metastases requiring ongoing therapy - e.g. corticosteroids - are excluded from trial enrollment. Enrollment will, however, be permitted in cases of patients with longstanding treated and inactive brain metastases not requiring ongoing therapy, providing that stability of brain metastases has been demonstrated for a period of 3 months or greater as assessed by intracranial imaging - and providing that there is no indication of increased vascularity of the treated metastases by MRI imaging conducted ≤14 days prior to registration. When questions arise related to these criteria, the PI of the trial, Dr. Keith Bible, should be contacted for assistance on eligibility.)

3.29c Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would or might reasonably be expected to limit compliance with study requirements.

3.29d Pregnant women. NOTE: (Because GW786034/pazopanib is an antiangiogenic agent which 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.)

3.29e HIV-positive patients on combination antiretroviral therapy. NOTE: (Because of the potential for pharmacokinetic interactions with GW786034/pazopanib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.)

3.29f Receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics of GW786034 (pazopanib). NOTE: The eligibility of patients will be determined following review of their case by the Principal Investigator (see Section 3.27 for further information). Efforts should be made to switch patients who are taking enzyme-inducing anticonvulsant agents to other medications.

3.29g Receiving any concomitant medications that are associated with a risk of QTc prolongation and/or Torsades de Pointes. (Appendix I) NOTE: These medications should be discontinued or replaced with drugs that do not carry these risks, if possible.

4. REGISTRATION PROCEDURES

4.1 Patient Registration

To register a patient, access the Phase 2 Consortium (P2C) web page and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up is available between 8 a.m. and 4:30 p.m. Central Time (Monday through Friday) by phone at (507) 284-2753 or by fax at (507) 284-0885.

The instructions for remote registration are available on the P2C web page and detail the process for completing and confirming patient registration. Prior to

initiation of protocol treatment, this process must be completed in its entirety and a P2C subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the remote system can be confirmed in any of the following ways:

- Contact the P2C Registration Office (507)-284-2753. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.
- In the remote registration application, select the *Show Subject* button to verify that the patient registration data is retrievable.
- Enter the remote data entry system and, using the P2C subject ID, confirm the patient appears in the data entry system.

4.2 Required Regulatory Documents

A signed HHS 310 form, documenting current approval by the investigator's Institutional Review Board), must be on file in the P2C Registration Office before an investigator may register patients. In order to assure timely processing, this documentation must be faxed directly to the P2C Registration Office at (507) 284-0885.

In addition to submitting initial IRB approval documents, ongoing approval documentation must be submitted (no less than annually) to the P2C Registration Office. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

4.3 Required Registration Documents

Prior to accepting the registration/randomization, the remote registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information (USA institutions only)

4.4 Mandatory Translational Research

A mandatory translational research component <u>for blood</u> is part of this study, the Randomization Center will automatically register patients separately to the mandatory translational component of this study (see Section 9.0). (Only applicable to sites within the United States).

4.5 Treatment Allowed Only at P2C Member Institutions

Treatment on this protocol must commence at a P2C member institution under the supervision of a physician, endocrine surgeon, endocrinologist, and/or medical

oncologist investigator registered with NCI Pharmaceutical Management Branch (PMB) and the P2C Coordinating Center.

4.6 Timing of Treatment
Treatment cannot begin prior to registration and must begin ≤7 days after registration.

4.7 Pretreatment Tests
Pretreatment tests must be completed within the guidelines specified on the test schedule.

4.8 Baseline Symptoms
All required baseline symptoms (see Section 7.34) must be documented and graded.

5. TREATMENT PLAN

5.1 GW786034 (Pazopanib) Administration

5.11 Treatment Regimen – One Cycle = 28 days

Agent	Dose	Route	Schedule	Cycle Length
GW786034	800 mg	PO (orally)	Once daily	28 days[+]

[+]Cycle length can be altered in the range of 21 to 35 days on an occasional basis with the specific approval of the study PI so as to accommodate holidays, inclement weather, and other scheduling issues *if a particular patient is tolerating the study drug well*. Cycle length can also be extended to 56±7 days (8 weeks ± 1 week) at treating MD discretion after a patient has been on study >12 cycle/1 year.

- Grouping Factor: DTC, MTC, or ATC
  Patients will be divided into three cohorts based upon the nature of their thyroid cancer: Cohort 1, differentiated thyroid cancers; Cohort 2, medullary thyroid cancer; Cohort 3, anaplastic thyroid cancer. These three cohorts will be evaluated independently for efficacy and toxicity end points.

- 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/day (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 meals. Tablets should be swallowed whole; they must not be chewed, broken, or crushed. Treatment continues until one of the criteria in Section 5.4 applies, provided that the retreatment criteria in Section 5.3 have been met. Missed and/ or withheld doses of pazopanib (whether intentional or unintended) are to be reported in the Medication Diary below, but not made up. Patients will be provided with a Medication Diary for GW786034/pazopanib (Appendix D), 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.

- TSH will be monitored each cycle, and if > 0.1 mIU/L, differentiated thyroid cancer patient's dosage of levothyroxine (Synthroid) should be increased by 0.05 mg (50 micrograms) per day. Dosage of l-thyroxine should not be increased more frequently than every 8 weeks.

5.12 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 antihypertensive therapy is recommended.

Frequent blood pressure (BP) monitoring is important in patients receiving GW786034 (pazopanib) starting on day 8 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 E). 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 F. Home blood pressure monitors can be obtained free of charge from GlaxoSmithKline (GSK)(See Section 17.1).

Renal function (creatinine and urinary protein) should be frequently monitored 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.

The risks of diverticular disease and/or intestinal perforation and/or bleeding appear to be increased in patients receiving pazopanib and related agents. On this basis, patients with active diverticulitis, gastrointestinal tract bleeding and other potentially serious underlying GI conditions within 28 days of enrollment will be specifically excluded from the trial. Moreover, patients receiving pazopanib should be closely monitored and treated aggressively in response to any symptoms deemed suspicious for evolving GI tract pathology. In particular, abdominal pain - especially when accompanied by fever - should be promptly evaluated with CT scan and treated aggressively with empiric antibiotics, with strong consideration of discontinuation of pazopanib. Similarly, any patient presenting with gastrointestinal tract bleeding should be promptly evaluated with endoscopies, with strong consideration given to cessation

of pazopanib. Further, any patient suspected of having GI tract perforation should be subject to prompt surgical evaluation, with cessation of pazopanib until perforation is absolutely excluded.

5.13 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) $\geq 1{,}000/mm^3$ ($1 \times 10^9/L$).
- Platelet count $\geq$ 50,000/mm3 (50 X 109/L).
- Blood pressure, if elevated, should be controlled with antihypertensive medication(s).
- Urine protein < 1+ (30 mg/dL).
- No clinically significant non-hematologic toxicity $\geq$ grade 2.
- No indication of new or active gastrointestinal tract pathology (see section 5.12 above).

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.

Because of the risk of prolonged QTc, Caution should be exercised when administering pazopanib to patients with a history of QTc interval prolongation, in patients taking anti-arrhythmics or other medications that may prolong the QTc interval, and those with relevant pre-existing cardiac disease.

Section 8 provides lists of agents and substances specifically prohibited during GW786034 (pazopanib) administration as well as those which are to be used with caution. Appendix B 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.

Patients with new gastrointestinal tract pathology and/or symptoms should be managed in accord of the guideline provided above in section 5.12.

Repeat EKG must be performed during the week 4, cycle 1 visit. If the QTc interval at 4 weeks is $\geq$ 500 msec, the EKG should be repeated within 7 days and, if the QTc interval remains $\geq$500 msec, the patient should be removed from the study. Additionally, if the QTc interval is increased by 60 msec or more from baseline but the QTc interval remains at < 500 msec, an EKG should be repeated within 7 days. If the repeat EKG again shows a $\geq$ 60 msec increase in the QTc interval from baseline, consideration should be given to removing the patient from the study or increasing monitoring, after discussion with the principal investigator.

5.3 Duration of Therapy

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

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient goes on to alternate therapy,
- 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.

5.4 Duration of Follow Up

- If a patient discontinues treatment due to progression within 3 years of registration, submission of an event monitoring form is required every 6 months thereafter until death or a maximum of 3 years post-registration.
- If a patient discontinues treatment due reasons other than progression or death within 3 years of registration, submission of an event monitoring form is required every 3 months until progression then every 6 months thereafter until death or a maximum of 3 years post-registration.

- If a patient discontinues treatment more than 3 years after registration, submission of an event monitoring report is required 6 months after treatment discontinuation.

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 sponsor (DCTD, NCI) 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)*
-3	200 mg daily
-2	400 mg daily
-1	600 mg daily
1	800 mg daily

*If doses are held, do not make up doses.

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 F.

- 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*

Systolic and Diastolic Categories	Antihypertensive Therapy	Blood Pressure Monitoring	GW786034 (pazopanib) Dose Modification
Category A < 140 mmHg Systolic < 90 mmHg Diastolic	• None • Baseline	• Standard monitoring (BID) •	• No Change

Category B 140-159 mmHg Systolic 90-94 mmHg Diastolic	• Initiate BB **or** Initiate DHP CCB • Increase doses of existing medications until BP controlled or at maximum dose	• Increased frequency of BP monitoring until stabilized	• No Change
Category C 160-179 mmHg Systolic 95-104 mmHg Diastolic	• Initiate BB **or preferably** DHP CCB (may use ACEI **or** Vasodilator **if DHP CCB ineffective)** • Increase dosages or number of medications until BP controlled or at maximum dosages	• Increased frequency of BP monitoring (*e.g.*, every 4-6 hours) until stabilized • 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 antihypertensive drugs, increasing to a maximum dose until hypertension controlled; monitor for hypotension. • Decrease GW786034 (pazopanib) by 1 dose level
Category D ≥ 180 mmHg Systolic ≥ 105 mmHg Diastolic	• Start immediate therapy with 2 drug combination including at least a DHP CCB • Escalate dosages 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 dosages of all drugs	• Increased frequency of BP monitoring (*e.g.*, every 4-6 hours) until stabilized • 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
Category E 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 CTCAEv4.0

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		Initial	Intermediate	Maximum	Hepatic

class	Agent	dose	dose	dose	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 persistently ≥1+ (30 mg/dL) 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+ (30 mg/dL, 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+ (30 mg/dL) 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 treatment

6.3 Management of Other CTCAE Adverse Events

Adverse Event/ CTCAE v3.0 Category	Grade	Treatment Modification	Follow Up
Gastrointestinal Perforation, GI	Grade >1	Discontinue treatment and go to event monitoring	Monitor and treat as clinically indicated.
Diverticulitis/colitis Typhlitis	Grade >1	Hold Pazopanib therapy until resolved, resume at discretion of treating physician after complete resolution	Hold Pazopanib therapy until resolved, treat aggressively with antibiotics and supportive care; hospitalize if fever >101 F or if otherwise clinically indicated.
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.	Monitor as clinically indicated. Follow up per protocol (Section 5.4) if patient is removed from

		If grade 2 or greater hemorrhage/ bleeding recurs following dose reduction, stop GW786034 (pazopanib) and remove patient from study. [1]	the study.
	Grades 3 or 4	Discontinue treatment go to event monitoring. [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 asymptomatic 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.
	Symptomatic Grade 4	Discontinue treatment and go to event monitoring.	Follow up per protocol (see Section 5.4
Thrombocytopenia/ 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 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 sponsor (DCTD, NCI) about continued treatment at 200 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
AE resolves promptly with supportive care	Maintain dose level
1. Grade 3 or higher (non-hematologic or grade 4 (hematologic) AE related to GW786034 (pazopanib) and lasting >5 days that does not resolve to grade 2 or below despite maximum	Reduce one dose level*

supportive care for ≤ 48 hours. 2. Lower grade but related AEs (*e.g.*, abdominal pain)	
AE does not resolve to grade 2 or below after treating patient at the lowest (*i.e.*, 200 mg daily) reduced dose level.	In general, move patient to event monitoring**
* Alternatively and if medically appropriate, investigators may choose to hold dose for up to 21 days or withdraw patient from study. ** After consultation with study PI, Dr. Keith Bible, a dose of 200 mg daily may be considered for patients on study ≥ 3 months who are benefiting from the agent.	

6.5 Management of Potassium, Calcium, Phosphorus and Magnesium.

If, according to **CTCAE version 4** criteria, the potassium level is grade 2 or greater and/or if the calcium, magnesium and/or phosphorous are grade 3 or higher, an EKG must be performed and appropriate action taken based on the results (see below).

Adverse Event	Grade	Treatment Modification	Follow Up
Hypokalemia (< LLN) or Hyperkalemia (>5.5mmol/L)	Grade ≥ 2	Hold Pazopanib therapy until hypokalemia or hyperkalemia is grade 1 or within institutional limits	Even though pazopanib administration is allowed at these lower grades, every effort should be made to correct the abnormal lab values to normal if possible.
Hypocalcemia (<7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9mmol/L;) or Hypercalcemia (>12.5 mg/dL; > 3.1 mmol/L; Ionized calcium > 1.6 mmol/L)	Grade ≥ 3	Hold Pazopanib therapy until hypokalemia or hyperkalemia is grade 2	
Hypophosphatemia (<2.0 mg/dL; <0.6 mmol/L)			
Hypomagnesemia (<0.9- mg/dL; <0.4 mmol/L) or Hypermagnesemia (>3.0 mg/dL; >1.23 mmol/L)			

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 CDUS) reporting.

7.1 CAEPR for Pazopanib

Comprehensive Adverse Events and Potential Risks list (CAEPR) For Pazopanib (GW786034, NSC 737754)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1568 patients.* Below is the CAEPR for pazopanib (GW786034).

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

Version 2.4, April 11, 2012[1]

Adverse Events with Possible Relationship to GW786034 (pazopanib) (CTCAE 4.0 Term) [n= 1568]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
	Hypothyroidism		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
		Gastrointestinal fistula[2]	***Gastrointestinal fistula[2] (Gr 1)***
		Gastrointestinal hemorrhage[3]	
	Gastrointestinal pain		
		Gastrointestinal perforation[4]	***Gastrointestinal perforation[4] (Gr 1)***
	Mucositis oral		

Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
	Non-cardiac chest pain		
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
	Ejection fraction decreased		
		Electrocardiogram QT corrected interval prolonged (accompanied by Torsades de pointes)	
	INR increased		
	Lipase increased		
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
	Serum amylase increased		
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		***Hyperglycemia (Gr 3)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypernatremia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 3)***
	Hypoglycemia		***Hypoglycemia (Gr 3)***
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		***Hyponatremia (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		
NERVOUS SYSTEM DISORDERS			

	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Proteinuria		***Proteinuria (Gr 3)***
		Urinary fistula	***Urinary fistula (Gr 1)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Female genital tract fistula	***Female genital tract fistula (Gr 1)***
		Uterine fistula	***Uterine fistula (Gr 1)***
		Vaginal fistula	***Vaginal fistula (Gr 1)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Respiratory hemorrhage[5]		***Respiratory hemorrhage[5] (Gr 1)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 1)***
		Palmar-plantar erythrodysesthesia syndrome	
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation)			***Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation) (Gr 3)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 1)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
		Thromboembolic event (venous)[6]	
		Vascular disorders - Other (arterial thromboembolic event)[6]	

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

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Enterovesical fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

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

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

[5]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[6]These events can result in life-threatening pulmonary, cardiac, cerebral, and other complications.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac disorders - Other (sinus arrest); Cardiac disorders - Other (supraventricular extra systoles); Pericardial effusion; Supraventricular tachycardia
ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Eye disorders - Other (asthenopia); Eye disorders - Other (eye/retinal hemorrhage); Eye pain; Floaters; Glaucoma
GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Dyspepsia; Dysphagia; Esophagitis; Flatulence; Gastrointestinal disorders - Other (pneumatosis intestinalis); Oral pain; Pancreatitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Malaise; Pain
INFECTIONS AND INFESTATIONS - Infection[7]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Cholesterol high; GGT increased; Investigations - Other (blood TSH increased)
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hypermagnesemia; Hypertriglyceridemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Neck pain; Pain in extremity
NERVOUS SYSTEM DISORDERS - Extrapyramidal disorder; Intracranial hemorrhage; Ischemia cerebrovascular; Paresthesia; Peripheral sensory neuropathy; Stroke; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Confusion; Depression; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Hematuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pharyngolaryngeal pain; Pleuritic pain; Pneumonitis; Pneumothorax; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Pruritus; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes
Note: Pazopanib (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: 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 until September 30, 2010 for AE reporting. CTCAE v4.0 will be utilized for expedited adverse event reporting only, beginning October 1, 2010.All appropriate treatment areas should have access to a copy of the

CTCAE version 4.0. A copy of the CTCAE version 4.0 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

7.31

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. 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 must be entered electronically into AdEERS by the original submitter at the site.

Effective with Addendum 12, and beginning October 1, 2010, expedited AdEERS reporting for this protocol has been updated by the NCI/CTEP to use CTCAE v4.0. Therefore;

1) Events requiring expedited reporting through AdEERS must be reported through the AdEERS system in CTCAE v4.0.

2) The events reported via AdEERS must ALSO be reported through routine reporting (i.e., Case Report Forms) using CTCAE v3.0.

3) Routine data collection via Case Report Forms, including the "Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form", will remain using CTCAE v3.0 for this study.

7.32 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. Addenda 12, 13

7.33 **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 v4.0 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.

SECONDARY MALIGNANCIES (defined as "cancer caused by treatment for previous malignancy," e.g., treatment with radiation or chemotherapy) are to be reported through

AdEERS, as noted in Section 10.22. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

Note: Second Primary malignancy (malignancy not due prior to treatment) should not be reported through AdEERS.

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

7.34 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated in the table below:

Category (CTCAE v3.0)	**Adverse event/Symptoms**	**Baseline**	**Each evaluation**
Cardiac General	Hypertension	X	X
Constitutional Symptoms	Fatigue (lethargy, malaise, asthenia)	X	X
Dermatology/ Skin	Hypopigmentation (Hair and or skin pigmentation change)	X	X
Neurology	Mood alteration – select - Agitation - Anxiety - Depression - Euphoria	X	X
	Neuropathy, sensory	X	X
Gastrointestinal	Anorexia	X	X
	(# of stools per day)	X	
	Diarrhea		X
	Nausea	X	X
	Vomiting	X	X
Blood/Bone Marrow	Hemoglobin	X	X
	Leukocytes (total WBC)	X	X
	Platelets	X	X
	Neutrophils/granulocytes (ANC/AGC)	X	X
Hemorrhage/ Bleeding	Hemorrhage, GI (select)		
	Abdomen NOS		X
	Lower GI NOS		X
	Oral Cavity		X
	Upper GI NOS		X
Metabolic/ Laboratory	AST, SGOT (serum glutamic oxaloacetic transaminase)	X	X

	Proteinuria	X	X

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine (CDUS) study data submissions. **AEs reported through AdEERS must <u>also</u> be reported in routine study data submissions.**

7.41 Submit to the P2C Research Base via the Nadir/AE Log the following AEs experienced by a patient and not specified in Section **7.34**:

7.411 Grade 2 AEs deemed possibly, probably, or definitely related to the study treatment or procedure.

7.412 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

7.413 Grade 5 AEs (Deaths)

7.4131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

7.4132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

7.42 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Study Calendar in Section **10.0**).

7.5 Secondary AML/MDS

Beginning October 1, 2010, AdEERS will only accept CTCAE v4.0 for this study: Report these events using "Neoplasms benign, malignant and unspecified (incl. cysts and polyps) – Other (Specify, _____)."

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.

8.1 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:

Novartis supplies and the PMB, DCTD, NCI distributes commercially-labeled 200 mg pazopanib tablets (as free base). Gray, film-coated tablets are debossed with "GS JT" on one side and packaged in bottles of 120 tablets.

Tablet excipients include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, iron oxide black, macrogol/polyethylene glycol 400 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: Refer to package label for expiration date of commercially-labeled supplies. Repackaging is not allowed and tablets must be dispensed in the original container. If exact quantity must be dispensed, then extra tablets should be removed, documented as waste and destroyed immediately.

Route of Administration: Oral. GW786034 should be taken on an empty stomach either 1 hour before or 2 hours after meals. The tablets should be swallowed whole and cannot be crushed or broken.

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, glimepiride, nateglinide
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- Neuroleptic: pimozide
- Erectile dysfunction agents: sildenafil, tadalafil, vardenafil
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexilitine, amiodarone, quinidine, propafenone
- Immune modulators: cyclosporine, tacrolimus, sirolimus
- Miscellaneous: theophylline, quetiapine, risperidone, tacrine, cloazapine, atomoxetine

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, propanolol, timolol
- Anticonvulsants: phenobarbital, phenytoin, primadone, carbamazepine
- Miscellaneous: codeine, methadone, mifepristone, estrogens and progestins (including oral contraceptives)
- Oral hypoglycemics: pioglitazone, rosiglitazone

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 or its juice

Inducers of CYP3A4:

- Glucocorticoids: cortisone (> 50 mg), hydrocortisone (> 40 mg), prednisone (> 10 mg),, methylprednisolone (> 8 mg), dexamethasone (> 1.5 mg)Anticonvulsants: phenytoin, carbamazepine, Phenobarbital, oxcarbazepine
- HIV: efavirenz, nevirapine
- Antibiotics: rifampin, rifabutin, rifapentine
- Miscellaneous: St. John's wort, modafinil

Availability: Pazopanib is supplied by Novartis Pharmaceuticals and distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Agent Ordering: NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Accountability: The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final

disposition of all agents received from the PMB using the NCI Investigational Agent (Drug) Accountability Record Form (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability: The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts:

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eappsctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eappsctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: IBCoordinator@mail.nih.gov

Nursing Guidelines

- Due to the early investigation nature of this drug, not all adverse effects can be known at this time. Monitor patients closely and report side effects to the MD.

- Hypertension is the most commonly reported side effect. Monitor blood pressure closely per study guidelines. Administer antihypertensives as ordered by MD.

- Nausea and vomiting were also frequently reported in early studies. Administer antiemetics as ordered and assess for the effectiveness.

- Diarrhea was seen in all phase I dosing groups. Assess hydration status, and administer antidiarrheals as ordered. Instruct patient to report an increase in the number of stools or nocturnal diarrhea to the study team.

- Due to the similarity in nature of this agent to other VEGF inhibitors (bevacizumab, VEGF-trap, etc.) monitor for signs of thrombosis and PE. Instruct patient to report any calf tenderness, shortness of breath or chest pain immediately.

9. CORRELATIVE/SPECIAL STUDIES

(Mandatory unless otherwise noted)

Only applicable to sites within the United States

9.1 Hypothesis 1

GW786034 treatment of patients with thyroid cancers will lead to reductions in patient blood tumor markers (e.g. thyroglobulin, calcitonin, CEA). Rates of change of relevant blood tumor markers (thyroglobulin, calcitonin, CEA) of patients will be evaluated pre- and on-study to determine whether GW786034 therapy may lead to either reductions, or stabilizations, of these markers. This will be critical, because substantial data suggest that VEGF-targeted agents will likely lead more to disease stabilization than regression. Relevant markers will be assessed as proscribed in the Section 10.

9.2 Hypothesis 2:

GW786034 will affect decreased levels of angiogenic markers (over time and in response to treatment), consequently impacting downstream targets of the pathway. Levels of free VEGF, free GW786034, and GW786034/VEGF will be explored in a graphical manner in pre and post-treatment samples. Results of these assays, in addition to effects on circulating VEGF, PDGF and other angiogenic marker levels, will be used to identify markers of response in responders versus non-responders. Times of collection of samples for VEGF/PDGF/angiogenic markers assessment are indicated in Section 10. Weekly assessment of VEGF/PDGF/ angiogenic markers will be accomplished cycle 1 only to capture non-sustained/transient induced changes.

9.3 Sample Instructions for Hypothesis 1 & 2:

PLASMA PK SPECIMENS

Blood should be drawn at the following timepoints:

- Pretherapy
- Cycle 1, Week 1
- Cycle 1, Week 2
- Cycle 1, Week 3
- Cycle 1, Week 4
- Retreatment Week 4
- Retreatment Week 8
- Retreatment Week 12
- Retreatment Week 16

• End of treatment

COLLECT: (Lavender)EDTA 3.0 mL

COAGULATE: MIN. 30'/MAX. 60'

PREPARE: CENTRIFUGE AT 4°C MIN. 10' MAX. 15'AT 3000 RPM (approx. 1,000 x g)

TRANSFER WITH A PIPETTE

RETURN: PLASMA (1.8 NuncCryovial)
1.0 mL
PK STORAGE

Do not fill tube completely as liquid will expand when frozen.

STORE IN AN UPRIGHT POSITION AT –20°C ON SITE AND SEND ON DRY ICE ON THE DAY OF COLLECTION.

Kit ordering: Participating site Principal Investigators will be sent starter kits (after confirmation of local IRB approval) directly from Quest Diagnostics with complete instructions on how to order future kits (the protocol identification for Quest is listed under: (Dr. Keith Bible-NCI-7627). Please use the patient number with the "PH" removed when identifying the patient study number.

Shipping information: Quest Diagnostics Clinical Trials, Attn: Specimen Processing for NCI Protocol #7627, 7600 Tyrone Avenue, Van Nuys, CA 91405

10. STUDY CALENDAR

This schedule is based on currently available information regarding the study regimen and specifies the *minimum* procedures, exams, testing, etc., necessary to determine eligibility (baseline) and to evaluate safety and plan dose adjustments at subsequent cycles. The frequency of procedures may be increased or additional procedures performed as clinically indicated at physician discretion.

Tests and procedures	≤7 days prior to registration	Prior to subsequent cycles	End of Treatment
History[10] and exam, wt, PS or Karnofsky score, concomitant medications[11]	X	X	X
Blood Pressure	X	X[6]	
BP and Medication Diaries		X[6]	
Height	X		
Hematology group WBC, ANC, Hgb, PLT	X	X[3]	X
Chemistry group (fasting) [12]: glucose, total and direct bilirubin, creatinine, alkaline phosphatase, AST (SGOT), ALT (SGPT), Na, K, Ca, Mg, phosphorus, cholesterol, triglycerides, lactate, TSH	X	X	X
Tumor Markers (e.g. thyroglobulin, calcitonin, CEA), TSH; as appropriate for involved cancer[7]	X	X	X
INR	X		
VEGF, PDGF, Angiogenic Markers [5, R]	X[9]	X[4]	X
Tumor Measurement/ Evaluation of indicator lesion (CT, MRI, etc.)[2,8,]	X	X[2]	
ECG	X	X[13]	
Urinalysis	X	X	
Serum pregnancy test[1]	X		

1. For women of childbearing potential only.
2. Baseline assessment may be ≤21 days prior to registration. Use the same method throughout the study. Followup scans to be performed every other cycle (8 weeks) for differentiated and medullary cancers, but every cycle (4 weeks) for anaplastic thyroid cancer. If tumor measurement made by physical examination, must document prior to each cycle. Repeat measurements are required 4 weeks following a PR or CR to document sustained response. See Section 11.0 for full RECIST criteria.
3. To be performed weekly (+/- 1 day). Weekly CBC's are optional (physician discretion) after cycle 2.
4. To be performed weekly (+/- 1 day), cycle 1 weeks 1-4, retreatment weeks 4, 8, 12, 16 and End of Treatment.
5. To be assayed off-site by GlaxoSmithKline.
6. Twice daily blood pressure monitoring beginning Day 8 until off treatment (See Section 5.12 & Appendix E-1). Home Blood Pressure monitors can be obtained free of charge from GlaxoSmithKline (See Section 17.1).
7. Papillary, follicular, Hurthle cell: TSH, anti-thyroglobulin antibody and thyroglobulin should be tested, with l-thyroxin dosage adjusted to maintain TSH< 0.1 mIU/L; medullary: CEA and calcitonin should be tested; anaplastic: no specific tumor marker testing required.
8. Baseline imaging of brain metastases, if known, should be accomplished ≤14 days prior to registration using MRI with gadolinium enhancement (see Section 3.29b).
9. Plasma PK samples can be drawn after registration but prior to Day 1 therapy.
10. To be performed ≤28 days prior to study drug administration, patient history of heart disease, prolonged QTc, family history of prolonged QTc and medications associated with prolonged QTc (Appendix I) must be obtain
11 Any concomitant medications that are associated with a risk of QTc prolongation and/or Torsades de Pointes should be discontinued or replaced with drugs that do not carry these risks, if possible. Patients who must take medications with a risk or possible risk of Torsades de Pointes should be watched carefully for symptoms of QTc prolongation, such as syncope. Performing additional EKGs on patients who must take one or more of these medications is not required; however, additional investigations, including EKGs, may be performed as per the treating physician's judgment.
12. If, according to CTCAE version 4 criteria, the potassium level is grade 2 or greater and/or if the calcium, magnesium and/or phosphorous are grade 3 or higher, an EKG must be performed and appropriate action taken. (see section 16.5) and footnote 14 for EKG monitoring
13. Repeat EKG must be performed during the week 4, cycle 1 visit. If the QTc interval at 4 weeks is ≥ 500 msec, the EKG should be repeated within 7 days and, if the QTc interval remains ≥500 msec, the patient should be removed from the study. Additionally, if the QTc interval is increased by 60 msec or more from baseline but the QTc

interval remains at < 500 msec, an EKG should be repeated within 7 days. If the repeat EKG again shows a ≥ 60 msec increase in the QTc interval from baseline, consideration should be given to removing the patient from the study or increasing monitoring, after discussion with the principal investigator.

R. Research funded.

11. MEASUREMENT OF EFFECT

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated by tumor measurement (i.e. scan) every 2 cycles (Differentiated, Medullary), versus every cycle (Anaplastic) (see Section 10.0 for more details).

11.2 Treatment evaluation for patients (MTC or DTC) with measurable disease using RECIST1 Criteria

11.21 Definitions of Measurable and Non-Measurable Disease

11.211 Measurable disease is defined as at least one lesion whose longest diameter can be accurately measured as ≥2.0 cm with conventional techniques or as ≥1.0 cm with spiral CT. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

11.212 All other lesions (or sites of disease), including small lesions (longest diameter <2.0 cm with conventional techniques or as <1.0 cm with spiral CT) are considered non-measurable disease. Bone lesions leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CR or MRI), and cystic lesions are all non-measurable.

11.22 Guidelines for Evaluation of Measurable Disease

11.221 Measurement Methods: All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use spiral CT imaging for both pre- and post-treatment tumor assessments. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.222 Acceptable imaging modalities for measurable disease: CT scan (conventional and spiral), MRI, chest x-ray.

- Conventional CT and MRI should be performed with cuts of 1.0 cm or less in slice thickness contiguously.
- Spiral CT must be performed using a 5 mm contiguous reconstruction algorithm. This specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities require specific procedures.
- Ultrasound (US): is not acceptable to measure tumor lesions that are clinically not easily accessible.
- Color Photography: In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

11.223 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.3 Measurement of Effect

11.31 Target Lesions

All measurable lesions (as defined in Section 11.311) up to a maximum of 10 lesions representative of all involved organs should be identified as target lesions and recorded and measured at baseline. If the protocol specified studies are performed, and there are fewer than 10 lesions identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions. For any one organ, no more than 5 lesions need to be measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive 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 to further characterize the objective tumor response of the measurable dimension of the disease.

11.32 Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed in accord with 11.33.

11.33 Response Criteria

All identified sites of disease must be followed on re-evaluation. Specifically, a change in objective status to either a PR or CR cannot be done without rechecking all identified sites (i.e., target and non-target lesions) of pre-existing disease.

<u>Evaluation of Target Lesions</u>

- Complete Response (CR): Disappearance of all target lesions.
- Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions taking as reference the baseline sum LD.
- Progression (PD): At least a 20% increase in the sum of 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 references the smallest sum LD.

<u>Evaluation of Non-Target Lesions</u>

- Complete Response (CR): Disappearance of all non-target lesions.
- Stable Disease (SD): Persistence of one or more non-target lesions.
- Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

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

11.34 Overall objective status

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Objective Status
CR	CR	No	CR
CR	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

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

11.36 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration:

- Weight loss >10% of body weight
- Worsening of tumor-related symptoms
- Decline in performance status of >1 level on ECOG scale or > 20% on the Karnofsky scale

11.4 Formal Statistical Definitions of Analysis Variables
Formal statistical definition of analysis variables involving response and disease progression are contained in Section 13.0.

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

12.11 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).

12.12 Responsibility for Submissions

Study participants are responsible for submitting CDUS data and/or data forms to the Coordinating Center quarterly to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.11.). For trials monitored by CTMS, the monthly data submission to CTEP from Theradex should be copied to the Coordinating Center.

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 H.

- 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 Collaborator(s)] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator@ (http://ctep.cancer.gov/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

13.11 Study Overview: The primary goal of this phase-II study is to evaluate the efficacy and biological effects of GW786034 treatment in patients with thyroid cancer. Evaluating this treatment regimen in patients with differentiated thyroid carcinoma (DTC) is of primary interest; however, as noted above, we are also interested in evaluating this treatment in medullary thyroid carcinoma (MTC) and anaplastic thyroid carcinoma (ATC). Therefore, we propose to assess clinical and biologic responses as well as tolerability of GW786034 treatment simultaneously and independently in each of these three patient cohorts. Specifically, a one-stage phase-II study design with an interim analysis based on the proportion of patients who have a clinical response (based on RECIST criteria) will be applied to the DTC, ATC, and MTC group to assess efficacy. This study will also assess toxicity, the proportion of patients who have not failed treatment by 6 months (3 months for ATC patients), survival, time to progression, and several biochemical and genetic correlates in each of the groups.

An expanded/additional cohort of 75 patients with confirmed differentiated thyroid cancer who are thyroglobulin antibody negative will be added to the original cohort of DTC patients enrolled on trial in order to prospectively examine a potential/hypothesized correlation between induced changes in thyroglobulin levels and patient response. **Rationale:** Anecdotal experience of investigators enrolling patients on the initial cohort of differentiated thyroid cancer patients on MC057H suggested that induced changes in thyroglobulin seen in thyroglobulin antibody negative patients might be predictive of patient response. Formal retrospective analysis undertaken in response indeed demonstrated that the proportion of patients with at least a 50% decrease in Tg values from pre-treatment levels was 0.50 among the 12 patients with stable or progressive disease and 0.80 among the 6 patients with a PR, suggesting that such an association may exist. We therefore now propose to more rigorously and prospectively examine this association in an expanded DTC patient cohort. This analysis will be important in the design of future pazopanib clinical trials in differentiated thyroid cancer, given its apparent promising clinical activity in DTC, so as to allow optimal use of tumor markers and imaging in the evaluation of further patients receiving the agent.

13.12 Primary Endpoint: The primary efficacy endpoint for each of the groups evaluated in this trial is the proportion of patients who have achieved an objective response to the study agent (RECIST criteria).

13.13 Secondary Endpoints: The secondary efficacy endpoints for each of the groups evaluated in this trial is the proportion of patients who have not failed treatment at 6 months (3 months for ATC), the proportion of patients in which the radioactive iodine scan have changed from "no uptake" to "any uptake", and the proportion of patients achieving a biochemical response in appropriate tumor markers. Any patients who have progressive disease within 6/3 months of study entry will be considered treatment failures and will be included in the denominator of the proportion for efficacy analyses. Note that each of the groups will be using radiographic (i.e. RECIST) criteria only to document progression. In addition, radioactive iodine scan will be used to determine response to GW786034, as will tumor markers. Any patients who discontinue treatment due to adverse reactions, refusal, or who go on to receive alternate therapy within 6/3 months of study entry will be considered treatment failures and will be analyzed in a similar manner. For this measure we will evaluate those patients who are not treatment failures at 6/3 months; i.e. those patients who are progression-free and have not gone off treatment due to adverse reactions, refusal, or have not gone on to receive further alternate therapy and those patients in which the radioactive iodine scan has changed from "negative" to "any uptake".

13.2 Sample Size/Accrual Rate

13.21 Sample Size: The single arm, one stage design with an interim analysis to be used for each patient group (i.e. DTC, MTC, and ATC) is fully described below. The efficacy decision rules require 33 evaluable patients for each patient group. To accommodate potential losses due to ineligibility, cancellation, or major violations, 3 additional patients will be accrued to each group. Thus, a total of 36 patients will be accrued to each group for a maximum of 108 patients overall to this trial, unless undue toxicity is encountered or accrual is stopped early based on the results of the planned interim analysis. An interim analysis will be performed in each patient group (as described below) after the first 14 eligible patients have been accrued to each of the DTC, MTC, and ATC patient groups, have begun treatment, and have been observed for at least 6/3 months. Accrual will not be suspended prior to the interim analysis. We recognize that additional patients will be accrued by the time of these interim analyses; however, given the paucity of treatments available for these patients as well as the relatively small overall sample size for each group, these analyses can be used for interim reporting of results as appropriate.

13.22 Accrual Time and Study Duration: Based upon ongoing accrual to the currently active Mayo P2C thyroid trial, the anticipated accrual rate for the proposed trial is about 1 to 2 patients per month in the cohort of patients with differentiated thyroid cancer (Cohort A). At this accrual rate, it will take approximately 9 months to enroll the 14 patients needed for the interim analysis for Cohort A. Overall accrual to Cohort A is expected to take 24 months. Note that these accrual estimates also include the anticipated over accrual. Accrual to Cohorts B (medullary thyroid cancer) and C (anaplastic thyroid cancer) are expected to be somewhat slower. If accrual is slower than expected, then the study can be opened to accrual at other Phase 2 Consortia.

13.3 Statistical Design to be used for the ATC, DTC, and MTC Patient Groups

13.31 Primary endpoint: This study is designed to also look at the proportion of patients who have a clinical response to treatment as defined by the RECIST criteria. Few prospective clinical studies have been done in these patient populations and little published data exist in these relatively rare patient groups for these kinds of trials, especially for the MTC and ATC groups. Given that this study is focusing on (and hence requiring) patients who have documented disease progression within the 6 months prior to study entry, this translates to a cohort of patients who have more aggressive disease. Therefore, we can assume that only 5% of patients will achieve a response if this therapeutic regimen is not effective in this patient population. If this single agent therapy of GW786034 is truly promising, we would expect that the true response rate would be at least 20% for each of these patient populations. In other words, the fact that we are requiring patients to have documentation of progressive disease within the 6 months prior to study entry (ATC patients excepted), we can assume that the same response rates would be of interest for all three thyroid carcinoma subtype populations.

13.32 Definition of success: As discussed above, a treatment success in this trial will be considered the event that a patient has a clinical response (i.e. a PR or CR by the RECIST criteria). This same definition for success will be used for all three patient groups.

13.33 Decision rule: This decision rule will be applied independently and individually for each of the patient cohorts. The largest success proportion where the proposed treatment regimen would be considered ineffective in this patient population is 5%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 20%. The following Three-Outcome Phase II study design44 is a modification of the Simon Optimal design and uses a maximum of 33 evaluable patients to test the null hypothesis that the true success proportion in the patient population is at most 5%. The following

decision rule will be used for each patient cohort:

"Not promising": This regimen will be classified as not promising with respect to the success rate in this patient population if at most 1 success is observed in a total of 33 evaluable patients.

"Inconclusive": The results of this study will be classified as inconclusive with respect to this regimen demonstrating an improved success rate if 2-3 successes are observed in 33 evaluable patients. In this case, the proportion of patients who have not failed treatment at 6 months (or 3 months for the ATC group), toxicity, and time to progression observed in this study will be used in addition to the rate of patients who responded to treatment in order to make the final determination as to whether or not this treatment is considered promising and worthy of further study in this patient population.

"Promising": This regimen will be classified as promising with respect to increasing the success rate in this patient population if at least 4 successes are observed in 33 evaluable patients. Subsequent larger confirmatory studies may be recommended.

13.34 Interim analyses:

Efficacy: An interim analysis will be performed in each patient group after 14 evaluable patients have been observed for at least 6 months. If in the interim analysis no patients have responded to treatment, we will consider this regimen insufficiently active and accrual may be terminated in this group at this point. It should be noted that unless we observe an unexpected toxicity rate or rapid accrual, we will not suspend accrual between stages to wait to perform the interim analysis.

Toxicity Stopping Rule: The following toxicity stopping rule will be applied independently to each of the patient cohorts in this trial. If at any time 30 % or more patients in a patient group develop ≥grade 4 non-hematologic toxicity (including febrile neutropenia), accrual to that patient group will be suspended to allow for investigation. After consideration by the study team (study chair[s], statistician, P2C Operations Office, etc.) and consultation with CTEP and the primary IRB affiliated with the P2C Operations Office, a decision will be made as to whether accrual can be resumed. CTCAE v3.0 will be used to determine grading for these stopping rules.

13.35 Power and significance level: Assuming that the number of successes is binomially distributed, the significance level for this study design is 0.07. This decision rule has 90% power to detect an effective treatment given

that the true response rate is at least 20% using this treatment.

13.36 Other considerations: Toxicity, incidence and duration of response, and other considerations will be taken into account in any decision process at each step. If more than 33 evaluable patients are accrued, only the first 33 will be used for decision purposes, but the additional patients will be included in the analyses described above.

13.37 Statistical Design to be used for the expanded cohort of patients with DTC who are thyroglobulin antibody negative:

13.371 Primary endpoint: The primary endpoint of this trial is a confirmed tumor response defined as a CR or PR (by the RECIST criteria) noted as the objective status on 2 consecutive evaluations at least 8 weeks apart.

13.372 Overview: The goal of this extended cohort of differentiated thyroid carcinoma (DTC) patients is to examine whether the proportion of patients whose tumor size decreases (PR or CR by the RECIST criteria) tend in parallel to have greater decreases in serum thyroglobulin levels (Tg levels). This analysis will be important in the design of future pazopanib clinical trials, so as to allow optimal use of tumor markers and imaging in evaluation of patients receiving the agent. Among the patients with DTC initially enrolled on MC057H, the proportion of patients with at least a 50% decrease in Tg values from pre-treatment levels was 0.50 among the 12 patients with stable or progressive disease and 0.80 among the 6 patients with a PR, suggesting that such an association may exist.

13.373 Study design: We expect a 2:1 ratio between the number of patients in the stable or progressive disease and the PR groups. A one stage clinical trial design will be used to assess whether the difference in the proportion of patients with at least a 50% decrease in Tg values from pre-treatment levels between patients who response to treatment and those who do not differs by at least 30%. With 45 patients in the stable or progressive disease group and 23 patients in the PR group, a one-sided two sample test of proportions will have a significance level 0.05 and a 80% chance of detecting that difference in the proportion of patients with at least a 50% decrease in Tg values from pre-treatment levels between patients who respond to treatment and those who do not is at least 0.30, when the proportion of patients with at least a 50% decrease in Tg values from pre-treatment levels among patients with stable or progressive disease is 0.50.

To account for ineligibility, cancellation, major treatment violation, or other reasons, we will additionally accrue 7

additional patients - for a total of 75 required. We therefore propose an extended cohort of 75 additional patients to test our hypothesis. Since a phase II trial has been conducted just prior to this extended study, there will be no interim analysis for this cohort, but patients will be closely monitored for toxicity, AE, etc.

Final analysis decision rule: after full accrual, we will conduct a two-sample test for proportions as specified in the design.

13.4 Analysis Plans

The following analyses will be performed for each patient group. All evaluable patients in that group will be used.

13.41 Primary Efficacy Endpoint

Patient evaluability: All patients meeting the eligibility criteria who have signed a consent form and begun treatment will be considered evaluable for estimation of response to treatment

Success probability: The proportion of successes will be estimated by (a) the standard binomial estimator, i.e., the number of successes divided by the total number of evaluable patients, and (b) 90% binomial confidence intervals.

13.42 Analysis of Secondary Endpoints for all 4 Patient Cohorts

Definitions and Analyses of Secondary Endpoints:

Toxicity: As per NCI CTCAE Version 3.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either “unrelated or unlikely to be related” to study treatment in the event of an actual relationship developing.

Proportion of patients who fail treatment at 6 months (3 months for ATC patients): The proportion of patients who have not failed treatment due to disease progression, adverse reactions, refusal for further participation, or who went on to alternate therapy at 6 months (3 months for ATC patients) will be calculated and summarized independently within each of the patient groups. Assuming that the incidence of response is binomially distributed, 90% binomial confidence intervals will also be calculated.

Times to progression and death: The overall survival time is defined as

the time from registration to date of last follow-up or death due to any cause. Similarly, the time to progression is defined as the time from registration to the date of progression or last follow-up, whichever comes first. The distributions of overall survival time and time to progression will be estimated using the method of Kaplan-Meier. In addition, the 6-month progression-free rate will be evaluated using the 6-month rates and associated confidence intervals. In addition, competing risk analyses may be done to evaluate time to progression, allowing for going on to alternate treatment or death prior to progression as competing risks.

Time to treatment failure and time to subsequent therapy: The time to treatment failure is defined as the time from registration to the date the patient discontinues treatment, and its distribution will be estimated using the method of Kaplan-Meier. In addition, the time to subsequent therapy will also be evaluated using a similar approach.

Duration of response: Duration of response will be calculated from the date of documentation of response (PR or CR) until the date of progression or last follow-up (whichever comes first) in the subset of patients with confirmed response.

Biomarker-based response and progression-free survival: Response and progression-free rates based on biomarker-based definitions alone will also be evaluated in each of these patient groups and summarized independently. Specifically, calcitonin-based progression alone will be evaluated for the MTC group and changes in thyroglobulin levels will be evaluated for the DTC group. These rates will be summarized assuming they are binomially distributed, and the biomarker levels themselves will be explored both quantitatively and graphically before and after treatment.

Correlative assay analyses: Given the limited sample sizes available for each of the patient cohorts evaluated in this trial, the following correlative endpoint analyses for each of the groups will be done in an exploratory manner. In addition, we will also evaluate differences between groups and may analyze these endpoints across all three thyroid carcinoma subtypes. In this case, we may also be able to evaluate these relationships quantitatively in addition to the summarization and primary graphical analyses described below.

Blood markers for angiogenesis including levels of free VEGF, free GW786034, and GW786034/VEGF complexes will be evaluated before and during therapy. Changes in these levels will largely be explored in a graphical manner as well as exploring any potential relationships between these levels and clinical outcome such as response or progression-free rate and toxicity incidence.

13.5 Monitoring

The principal investigator and the study statistician will review the study periodically to identify accrual, toxicity, and any endpoint problems that might be developing. In addition, this study will be monitored according to the Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Plan that is currently in place. The MCCC Data Safety Monitoring Board (DSMB) is responsible for reviewing safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

13.6 Data Reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. The coordinating center will submit cumulative CDUS data quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

At the time CTCAE v4.0 became available, this study involved collection of adverse events using CTCAE v3.0. The study continues to collect all routine AE data using CTCAE v3.0; however, all adverse event data submitted via CDUS must use CTCAE v4.0 terminology. CTEP provided mappings will be used to convert v3.0 data to v4.0 prior to submission to CTEP, as agreed upon by NCI and the Mayo Clinic Cancer Center.

13.7 Subset Analyses for Minorities:

This study will be available to all eligible patients, regardless of sex, race or ethnic origin. The planned analyses will look for difference in treatment effect based on racial groupings. The current percentage of ethnic minorities accrued to studies at the P2C sites is approximately 7%. Therefore, it is not expected that more than 5 ethnic minority patients will be accrued to this study. Since there is no evidence currently available that suggests that the effects of therapies studied in this trial would be related to gender or ethnic status, the sample sizes are not increased in order to provide additional power for subset analyses.

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	2	2	0	4
Not Hispanic or Latino	92	92	0	184
Ethnic Category: Total of all subjects*	**94**	**94**	**0**	**188***
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	1	1	0	2
Black or African American	2	2	0	4
Native Hawaiian or other Pacific Islander	0	0	0	0
White	91	91	0	182
Racial Category: Total of all subjects*	**94**	**94**	**0**	**188**

These totals must agree. Enter actual estimates (not percentages**)*

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." **Not Hispanic or Latino**
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. **Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) **Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 DESCRIPTIVE FACTORS

14.1 Baseline Calcitonin Levels
Baseline Thyroglobulin levels

15.0 PATHOLOGY CONSIDERATIONS

Histologic or cytologic confirmation of disease will be the responsibility of each center independently without central review. A copy of the pathology reports is to be sent to the P2C Coordinating Center ≤2 weeks of study entry (see Section 16.5). **NOTE:** At Mayo enrollment sites, molecular markers of thyroid cancer will be assessed to complete histological/cytological studies. (This is normal standard practice at Mayo Clinic).

16. Data SUBMISSION To Coordinating Center

16.1 Data Collection
Data will be collected using protocol-specific forms and the P2C web-based remote data entry system. Data is to be submitted ≤ 2 weeks following each evaluation of the patient and according to the schedule in Section 16.5.
After the patient discontinues treatment, follow–up will continue as specified in the following section(s):

16.2 Cancels
Those patients who cancel participation prior to the start of treatment must provide On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further follow-up is required.

16.3 Ineligible
A patient is deemed *ineligible* if at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, all data up until the point of confirmation

of ineligibility must be submitted. Event monitoring will be required per Section 16.5 of the protocol.

- If the patient never received treatment, On-study materials and the End of Active Treatment/Cancel Notification Form must be submitted. No further follow-up is required.

16.4 Treatment Discontinuation

After a patient discontinues treatment, follow-up data will be collected and entered via the remote data entry system according to schedule outlined below (also see Section 16.5).

- If a patient discontinues treatment due to progression within 3 years of registration, submission of an event monitoring form is required every 6 months thereafter until death or a maximum of 3 years post-registration.

- If a patient discontinues treatment due reasons other than progression or death within 3 years of registration, submission of an event monitoring form is required every 3 months until progression then every 6 months thereafter until death or a maximum of 3 years post-registration.

- If a patient discontinues treatment more than 3 years after registration, submission of an event monitoring report is required 6 months after treatment discontinuation.

Follow-up data will be collected and entered via the remote data entry system according to the schedule in Section 16.5.

16.5 Data Entry/Submission Timetable

Forms/Other	Active-Monitoring Phase (Compliance with Test Schedule)			Event-Monitoring Phase[2] (Completion of Active-Monitoring Phase) PD = Progression (see Section 11.0)				At Each Occurrence		
	Initial Material	Subsequent material								
	≤2 weeks after registration	At each evaluation	At end of treatment	q. 3 months until PD[2]	At PD[2]	After PD q. 6 mos.[2]	Death	All Grade 4/5 AEs All Hospitalizations During Treatment Secondary AML/MDS	New Primary	Late Adverse Event
On-Study Form	X									
Baseline Adverse Events	X									
Concomitant Medication Form	X	X	X							
Measurement Form[4]	X	X[4]	X[4]							
Pathology Report Submission[1]	X									
Event-Monitoring Form				X	X[4]	X	X		X	X
Evaluation/Treatment Form		X	X							
Nadir/Adverse Event Form		X	X							
Endocrine Lab Form	X	X								
Specimen Submission Form (Blood)	X	X[6]								
End of Active Treatment/Cancel Notification Form	X[5]		X							
AE Reporting per Section 7.0								X[3]	X[3]	
CTEP Report Variables Form	X									
Notification Form, Grade 4/5								X		

1. Submit copy of pathology reports via fax or mail to the P2C Coordinating Center, (Attention: QCS for MC057H), 200 First Street SW, Rochester, MN 55905, Fax: (507) 266-7240.
2. If a patient discontinues treatment due to progression within 3 years of registration, submission of an event monitoring form is required every 6 months thereafter until death or a maximum of 3 years post-registration. If a patient discontinues treatment due reasons other than progression or death within 3 years of registration, submission of an event monitoring form is required every 3 months until progression then every 6 months thereafter until death or a maximum of 3 years post-registration. If a patient discontinues treatment more than 3 years after registration, submission of an event monitoring report is required 6 months after treatment discontinuation.
3. Reminder: Adverse events that necessitate expedited reporting are also to be reported via the routine clinical data (i.e. Nadir/Adverse Event Form, etc.) submitted with each evaluation.
4. Submit copy of documentation of response, recurrence, or progression to the P2C Coordinating Center, Attention: QCS for MC057H, Fax (507) 266-7240.
5. Submit this form only if withdrawal/refusal prior to beginning protocol therapy occurs.
6. To be performed (+/-) 1 day. Cycles 1 weeks 1-4, retreatment weeks, 4, 8, 12, and 16 and End of Treatment.

17. FUNDING CONSIDERATIONS

17.1 Costs Charged to Patient

All routine clinical care. GW786034 will be provided by the NCI. The patient or the patient's health plan/insurer will be responsible for charges associated with supplies and procedures necessary for administration of the study drug(s), as well as all other drugs or treatment given to help control adverse events as well as the cost of tests or exams to evaluate possible adverse events. Blood pressure monitors will be provided free of charge and can be obtained by contacting Graham Arnold (garnold@theradex.com), telephone 609-799-7580 Ext 3001.

17.2 Other Budget Concerns

This study is supported by the Phase 2 Consortium (P2C) through its N01 contract with the National Cancer Institute.

17.3 Manufacturer to Supply Drug

The manufacturer of GW786034 will accomplish all VEGF and PDGF analyses at the site of their specification and at their expense.

REFERENCES

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APPENDIX A: Performance Status Criteria

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

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

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 C: 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.

CTEP-assigned Protocol #_____

Local Protocol # _____

APPENDIX D: Patient's Medication Diary

PATIENT'S MEDICATION DIARY - GW786034 (pazopanib)

Today's date _____ **Agent** _____**GW786034 (pazopanib)**_____

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. Take your dose of GW786034 (pazopanib) each day. You should take GW786034 on an empty stomach either 1 hour before or 2 hours after meals. The tablets should be taken with about 1 cup (240mL) 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	What time was dose taken?	# of tablets taken		Comments
			200 mg	400 mg	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
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18					
19					
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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:_____

CTEP-assigned Protocol # _____

Local Protocol # _____

APPENDIX E: Patient's Blood Pressure Diary

Today's date _____

Patient Name_____ Patient Study ID _____

(*initials acceptable)*

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 140 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. 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)
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
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Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

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

APPENDIX F: 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 for the duration of treatment. More frequent monitoring should be considered on a study by study 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:

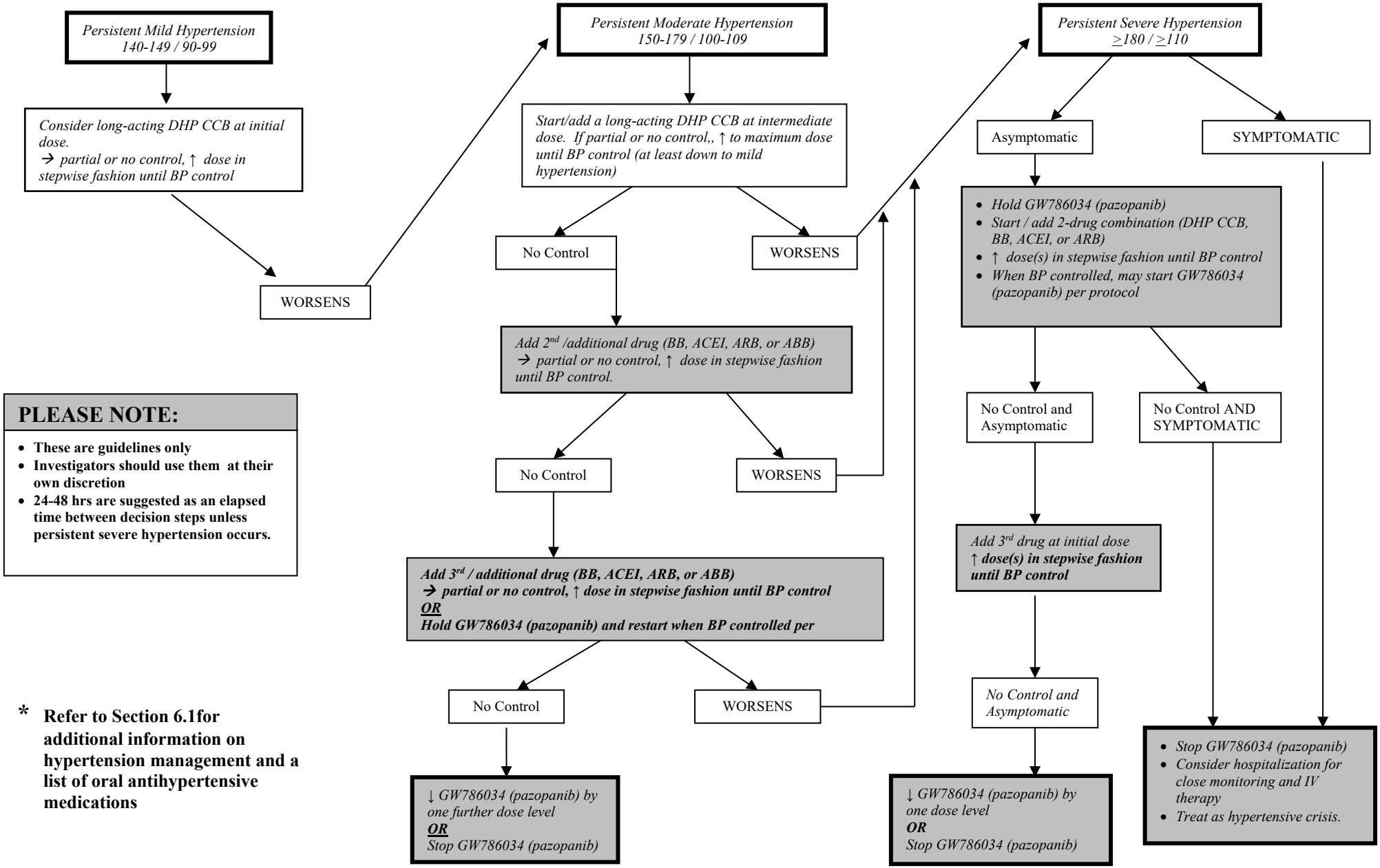
- BP changes from baseline (or from previous assessment) (specify CTCAE v3.0 grade changes)
- Hypertension-related symptoms as reported by patient (*e.g*., headache)
- Other relevant changes associated with development of hypertension (*e.g*., ECG abnormalities)
- Trade name, drug class*, dose, dose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

APPENDIX G: Management of GW786034 (Pazopanib)-Induced Hypertension*



PLEASE NOTE:

- **These are guidelines only**
- **Investigators should use them at their own discretion**
- **24-48 hrs are suggested as an elapsed time between decision steps unless persistent severe hypertension occurs.**

* **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 H: 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.

APPENDIX I: Medications That May Cause QTc Prolongation

The following table presents a list of drugs that prolong, may prolong or are unlikely to prolong the QTc. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: *http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm*.

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	*Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes*	*Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism).*
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine /Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram /Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine /Anafranil®
Bepridil /Vascor®	Chloral hydrate /Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril®	Diphenhydramine /Benadryl®
Chlorpromazine /Thorazine®	Dolasetron /Anzemet®	Diphenhydramine /Nytol®
Cisapride /Propulsid®	Dronedarone /Multaq®	Doxepin /Sinequan®
Clarithromycin /Biaxin®	Felbamate /Felbatrol®	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor®	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx®	Galantamine /Reminyl®
Droperidol /Inapsine®	Gatifloxacin /Tequin®	Imipramine /Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporanox®
Erythromycin /E.E.S.®	Granisetron /Kytril®	Ketoconazole /Nizoral®
Halofantrine /Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil®
Haloperidol /Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl /Orlaam®	Lapatinib /Tyverb®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Levofloxacin /Levaquin®	Sertraline /Zoloft®

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	*Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes*	*Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism).*
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Methadone /Dolophine®	Lithium /Lithobid®	Solifenacin /VESIcare®
Methadone /Methadose®	Lithium /Eskalith®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Moxifloxacin /Avelox®	Trimipramine /Surmontil®
Pimozide /Orap®	Nicardipine /Cardene®	
Probucol /Lorelco®	Nilotinib /Tasigna®	
Procainamide /Pronestyl®	Octreotide /Sandostatin®	
Procainamide /Procan®	Ofloxacin /Floxin®	
Quinidine /Cardioquin®	Ondansetron /Zofran®	
Quinidine /Quinaglute®	Oxytocin /Pitocin®	
Sotalol /Betapace®	Paliperidone /Invega®	
Sparfloxacin /Zagam®	Perflutren lipid microspheres /Definity®	
Terfenadine /Seldane®	Quetiapine /Seroquel®	
Thioridazine /Mellaril®	Ranolazine /Ranexa®	
	Risperidone /Risperdal®	
	Roxithromycin* /Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend®	

	Ziprasidone /Geodon®	